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Authors

Wei, Jie
Hunter, David
Lane, Nancy E
et al.

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Weight Loss Induced by Antiobesity Medications and All-Cause Mortality Among Patients With Knee or Hip Osteoarthritis

Jie Wei,[1] David Hunter,[2] Nancy E. Lane,[3] Jing Wu,[4] Chao Zeng,[5] Guanghua Lei,[5] and Yuqing Zhang[6]

Objective. The current guidelines recommend weight loss for patients with overweight or obesity and knee or hip osteoarthritis (OA); however, there is a paucity of data on the relation of weight loss to death among patients with OA. We aimed to examine the relation of the rate of weight loss induced by antiobesity medications over one year to all-cause mortality among patients with overweight or obesity and knee or hip OA.

Methods. Using the IQVIA Medical Research Database, we identified people with overweight or obesity and knee or hip OA. We emulated analyses of a hypothetical target trial to assess the effect of slow-to-moderate (2%–10%) or fast (≥10%) weight loss induced by the initiation of antiobesity medications within one year on all-cause mortality and secondary outcomes over five years' follow-up.

Results. Among 6,524 participants, the five-year all-cause mortality rates were 5.3%, 4.0%, and 5.4% for weight gain or stable, slow-to-moderate weight loss, and fast weight loss arms, respectively. Compared with the weight gain or stable arm, hazard ratios of all-cause mortality were 0.72 (95% confidence interval [CI] 0.56–0.92) for the slow-to-moderate weight loss arm and 0.99 (95% CI 0.67–1.44) for the fast weight loss arm. We found dose–response protective effects of weight loss on incident hypertension, type 2 diabetes, and venous thromboembolism but a slightly higher risk of cardiovascular disease, albeit not statistically significant, in the fast rate of weight loss arm than in the weight gain or stable arm and no significant relations of weight loss to the risk of cancer.

Conclusion. In this population-based study, a slow-to-moderate, but not fast, rate of weight loss induced by antiobesity medications is associated with a lower risk of all-cause mortality in people with overweight or obesity and knee or hip OA.

INTRODUCTION

Osteoarthritis (OA) is a common joint disorder and affects more than 500 million people worldwide.[1] With an aging and increasingly overweight and obese population, this already burdensome syndrome is becoming even more prevalent.[1] Besides its significant impact on disability, symptomatic OA is associated with an increased risk of all-cause mortality.[2,3] To date, there is

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[1]Jie Wei, PhD: Department of Orthopaedics, Xiangya Hospital, Central South University, Key Laboratory of Aging-related Bone and Joint Diseases Prevention and Treatment, Ministry of Education, Xiangya Hospital, Central South University, Hunan Key Laboratory of Joint Degeneration and Injury, and Department of Epidemiology and Health Statistics, Xiangya School of Public Health, Central South University, Changsha, China; [2]David Hunter, MBBS, MSc, PhD: Sydney Musculoskeletal Health, Kolling Institute, University of Sydney and Rheumatology Department, Royal North Shore Hospital, Sydney, Australia; [3]Nancy E. Lane, MD: Center for Musculoskeletal Health and Department of Medicine, University of California School of Medicine, Sacramento, California; [4]Jing Wu, MS: Key Laboratory of Aging-related Bone and Joint Diseases Prevention and Treatment, Ministry of Education, Xiangya Hospital, Central South University and Hunan Key Laboratory of Joint Degeneration and Injury, Changsha, China; [5]Chao Zeng, MD, PhD, Guanghua Lei, MD, PhD: Department of Orthopaedics, Xiangya Hospital, Central South University, Key Laboratory of Aging-related Bone and Joint Diseases Prevention and Treatment, Ministry of Education, Xiangya Hospital, Central South University, Hunan Key Laboratory of Joint Degeneration and Injury, and National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, China; [6]Yuqing Zhang, DSc: Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School and The Mongan Institute, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.

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Address correspondence via email to Guanghua Lei, MD, PhD, at lei_guanghua@csu.edu.cn; Chao Zeng, MD, PhD, at zengchao@csu.edu.cn; or to Yuqing Zhang, DSc, at yzhang108@mgh.harvard.edu.

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no cure for OA, and the main goals of contemporary management of the disease continue to be pain control and improvement in function and health-related quality of life.[4]

Overweight and obesity is an important risk factor for OA.[5] Previous studies have found a significant dose–response relationship between the percentage of weight loss and improvement of pain and function in patients with knee OA.[6–10] There is consensus among international guidelines that weight loss is one of the core treatments for patients with knee and/or hip OA who are overweight or obese.[11–13] The results from the Arthritis, Diet, and Activity Promotion Trial revealed that intentional weight loss (achieved through dietary counseling and lifestyle modification) within 18 months reduced all-cause mortality among the patients with overweight or obesity and knee OA; however, such a beneficial effect was not observed among the participants with a fast rate of weight loss (ie, the percentage of weight loss above the median value of all participants or loss of more than 5% of baseline weight).[14] To date, there is a paucity of evidence on the relationship between the rate of weight loss and all-cause mortality among patients with OA.

We conducted a population-based cohort study emulating a randomized controlled trial (RCT) to examine the relation of the rate of weight loss induced by antiobesity medications over one year to all-cause mortality and risk of several secondary outcomes (eg, hypertension, type 2 diabetes [T2DM], venous thromboembolism [VTE], cardiovascular disease [CVD], and cancer) among patients with overweight or obesity and knee or hip OA.

PATIENTS AND METHODS

Data source. We used data from the IQVIA Medical Research Database (IMRD) (incorporating data from The Health Improvement Network, a Cegedim database), an electronic health records database from general practitioners (GPs) in the UK. The computerized information includes sociodemographics, anthropometric characteristics, lifestyle factors, and details from visits to GPs (eg, prescriptions, diagnoses from specialist referrals, hospital admissions, and results of laboratory tests). The Read classification system is used to code specific diagnoses, whereas a dictionary based on the Multilex classification system is used to code drugs. The validity of the IMRD for clinical and epidemiologic research has been demonstrated in previous studies.[15,16] The scientific review committee for the IMRD and the institutional review board at Xiangya Hospital approved this study, with a waiver of informed consent. This study followed the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology initiative for reporting observational studies in epidemiology.

Study design and cohort definition. Participants were eligible for the current analysis if they were 40 to 90 years old, had knee or hip OA, and had at least one year of continuous enrollment with GPs before entering the study between January 1, 2000, and March 31, 2022. We used Read codes to define knee or hip OA according to previous studies using the IMRD.[16,17] Of them, we identified initiators of antiobesity medications (eg, orlistat, sibutramine, and rimonabant)[18,19] based on the first record of antiobesity medication prescription after the diagnosis of the knee or hip OA. The date of initial prescription of antiobesity medications was assigned as the index date for each participant. Participants were excluded if they had cancer, had bariatric surgery, did not have a body mass index (BMI) measurement, or had the nearest BMI less than 25 before the index date.

The treatment strategy in our study is the rate of weight change within one year after initiation of antiobesity medications (ie, a duration of a treatment). We applied a cloning, censoring, and weighting approach to emulate a target trial.[20,21] Cloning makes the comparison groups compatible with their observed data at time zero and minimizes the immortal time bias, especially when a treatment strategy is a duration of treatment. If the participants deviated from their assigned treatment strategy, we censored the patients and used weighting (ie, inverse probability weighting [IPW]) to account for potential selection bias from the censoring. Specifically, as shown in Figure 1A, we created three copies for each initiator at the index date and assigned the three replicates to one of three weight change intervention arms (weight gain or stable [weight loss < 2% or weight gain], slow-to-moderate rate of weight loss [2% ≤ weight loss < 10%], or fast rate of weight loss [weight loss ≥ 10%]) within one year after initiation of antiobesity medications,[22,23] which equates to the random assignment in a real RCT.

The rate of weight change was calculated as the difference of the latest measured weight during the one year after initiation of antiobesity medication from the baseline weight and divided by the baseline weight. We gave the replicates a one-year grace period to reach their target rate of weight change after initiating antiobesity medication.[24] Replicates were censored if they deviated from the assigned treatment within the one-year grace period. For example, patient A lost ≥10% of weight within one year after initiating antiobesity medications (Figure 1B). The copy of patient A assigned to the fast rate of weight loss intervention arm was adhered to their assignment and would not be censored. However, the other two copies of patient A assigned to the weight gain/stable and slow-to-moderate rate of weight loss intervention arms deviated from their assigned arms and thus would be censored when the weight change was measured. Thus, the death outcome was counted only in the copy of patient A who was assigned to the fast rate of weight loss treatment. During the grace period, if an individual died before reaching the target rate of weight change (eg, patient E in Figure 1B), that person was considered adhering to their assignment in all arms (or clones), and the death outcome was counted in each of the assigned arms. Because censoring may introduce selection bias, we used IPW to account for censoring.[20] The denominator of the IPW was the probability that a replicate adhered to their assigned

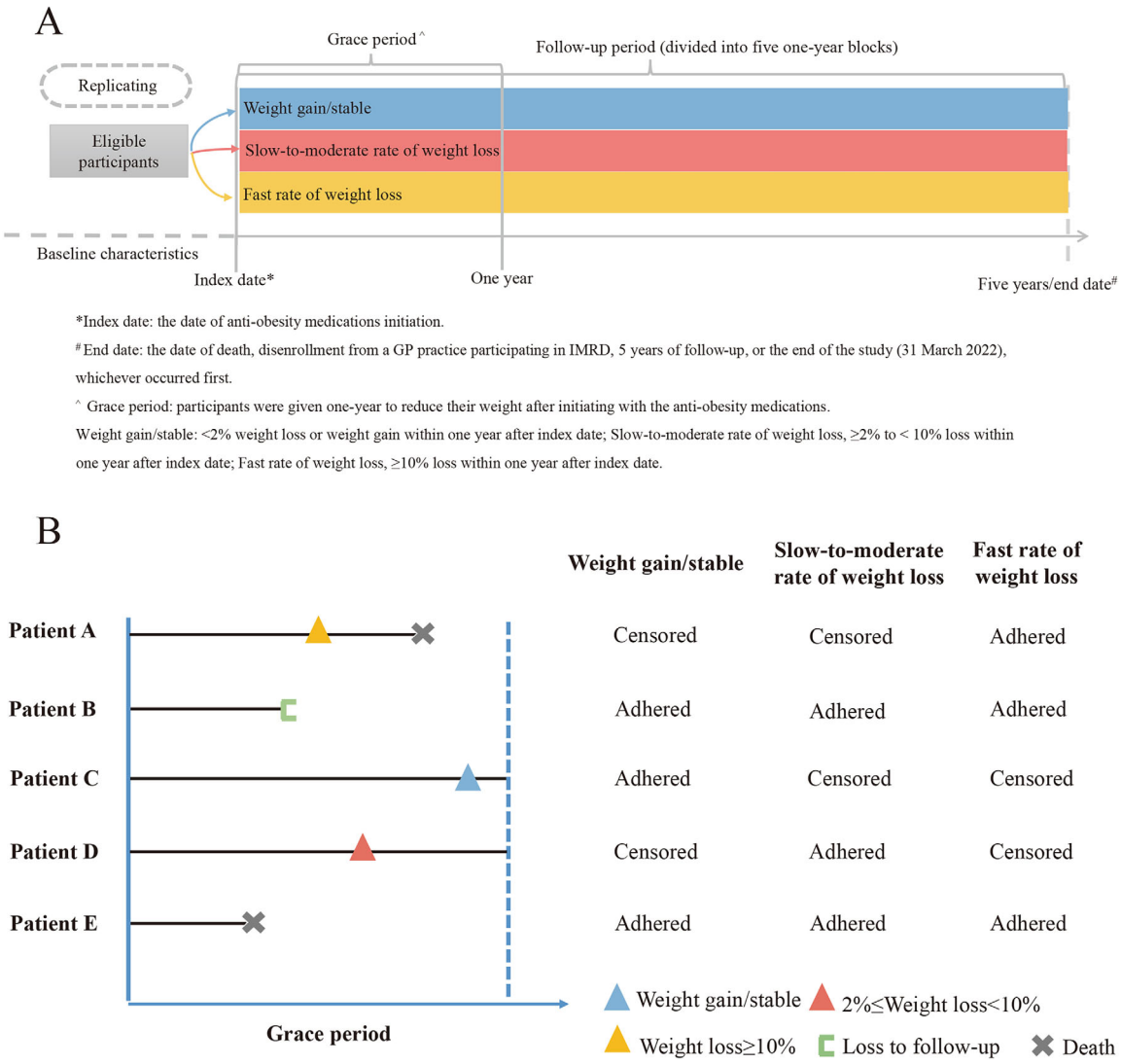


Figure 1. (A) Study design of a hypothetical randomized controlled trial (target trial) on which we modeled our observational data analysis. (B) Cloning and censoring in five hypothetical patients. GP, general practitioner; IMRD, IQVIA Medical Research Database.

intervention arm using the logistic regression, which consisted of the baseline covariates (see Assessment of covariates). The key protocol components are shown in Supplementary Table 1.

Assessment of outcomes. The primary outcome was all-cause mortality over the five-year follow-up after initiation of anti-obesity medication. The death date recorded in the IMRD is linked to the NHS; thus, a change in vital status to "dead" is immediately updated in the person's electronic health record. The secondary outcomes were incident hypertension,[25] T2DM,[26] VTE (pulmonary embolism and deep vein thrombosis), CVD (myocardial infarction [MI] and stroke),[27] and any cancer (lung, breast, colorectal, prostate, head and neck, and other cancers)[28] identified by Read codes during the five-year follow-up period. VTE was defined as a recorded Read code of VTE with a prescription of anticoagulant medication. In addition, because VTE is potentially fatal and some individuals might have died before receiving anticoagulation therapy, we also included individuals with a recorded code of VTE but without a prescription for anticoagulant medication if there was a fatal outcome within one month of the VTE diagnosis.[29]

Assessment of covariates. Sociodemographics (age, sex, and socioeconomic deprivation index score), anthropometric characteristics (BMI and weight), lifestyle factors (smoking status and drinking status), OA duration, comorbidities (hypertension, MI, stroke, heart failure, VTE, hyperlipidemia, depression, chronic obstructive pulmonary disease, falls, osteoporosis, pneumonia or infection, fracture, chronic kidney disease, diabetes, diabetic complications, and liver disease) before the index date were obtained from the IMRD. Health care use (number of hospitalizations, general practice visits, and referrals from specialists) and medication use (antihypertensives, antidiabetics, glucocorticoids,

statins, anticoagulants, aspirin, nonsteroidal anti-inflammatory drugs, opioids, thiazide diuretics, and estrogen) were ascertained during one year before the index date.

Statistical analysis. For the primary outcome, participants were observed until death, disenrollment from a GP practice participating in the IMRD, five years of follow-up, or the end of the study (March 31, 2022), whichever occurred first. We divided the follow-up time into five one-year time blocks starting from initiation of antiobesity medication. We compared the risk of all-cause mortality between three weighted comparison groups using a pooled logistic regression including an indicator for rate of weight loss and adjusting for the year of follow-up (linear and quadratic term) and baseline confounders in the weighted population.[30] The odds ratio generated from this model approximated the hazard ratio (HR) because the outcome is rare.[30] We used a robust SE to compute 95% confidence interval (CI) for HR estimates. We estimated the absolute risk difference of all-cause mortality over five years by fitting the pooled logistic models with product terms between the rate of weight loss indicator and the year of follow-up variables. We used a nonparametric bootstrap analysis with 100 samples to compute the 95% CI for absolute estimates.

For each of the secondary outcomes, we first excluded the participants with a history of the disease and then took a similar approach to assess the effect of the rate of weight loss induced by antiobesity medication on the risk of the incident case of that disease. To control the competing risk of death, we performed a

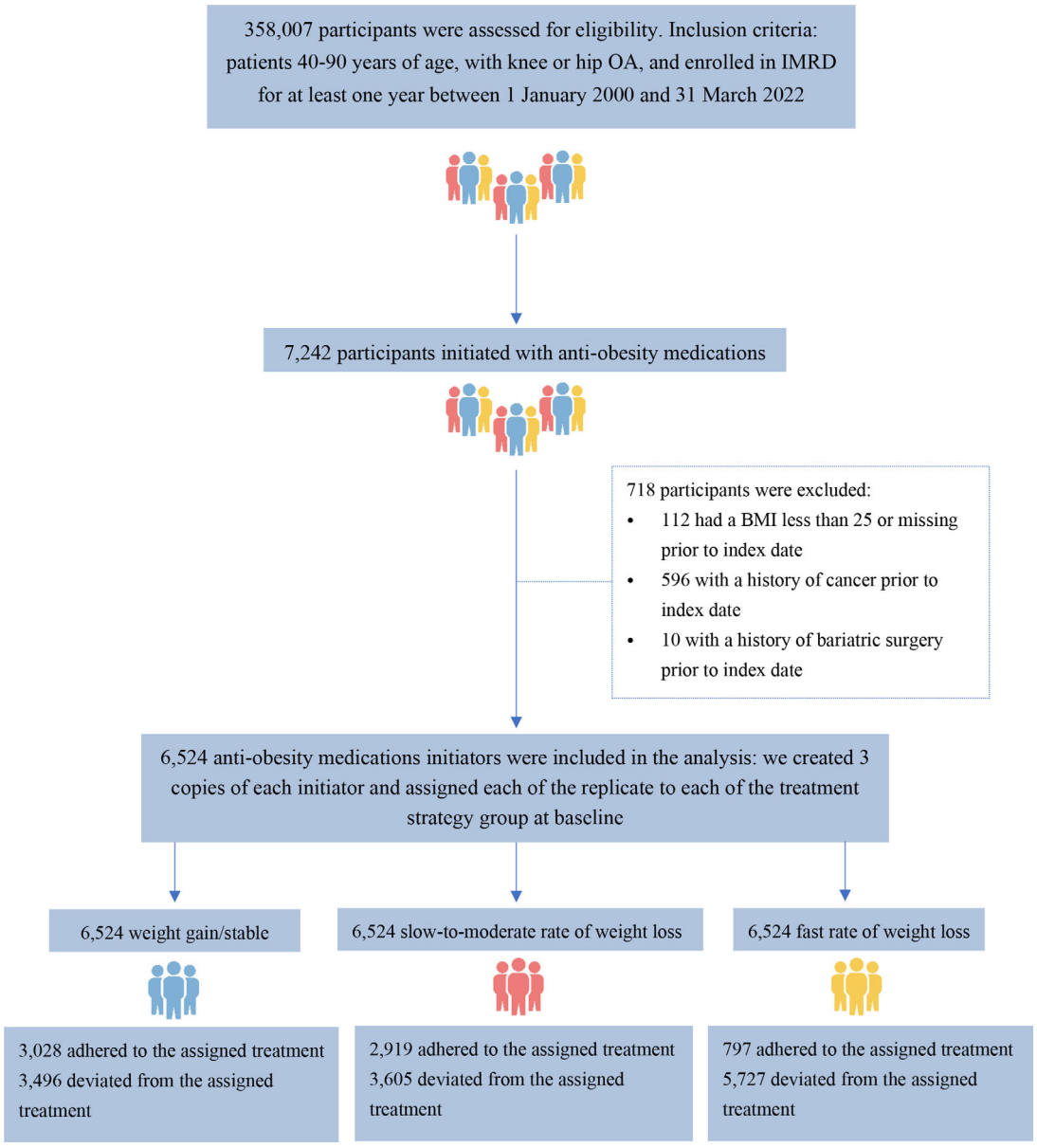


Figure 2. Selection process of the included participants. BMI, body mass index; IMRD, IQVIA Medical Research Database; OA, osteoarthritis.

cross-sectional pooling analysis to estimate the effect size and related 95% CI.[31] We performed three sensitivity analyses to assess the robustness of the study findings. First, we performed an analysis among patients with obesity (BMI ≥ 30). Second, we exclusively analyzed participants initiating orlistat. Third, we included the glucagon-like peptide 1 receptor agonist (GLP-1 RA), which also has a weight loss effect, in the list of antiobesity medications and repeated the analysis. All analyses were conducted using SAS software, version 9.4 (SAS Institute, Inc), and a two-sided *P* value ≤0.05 was considered statistically significant for all tests.

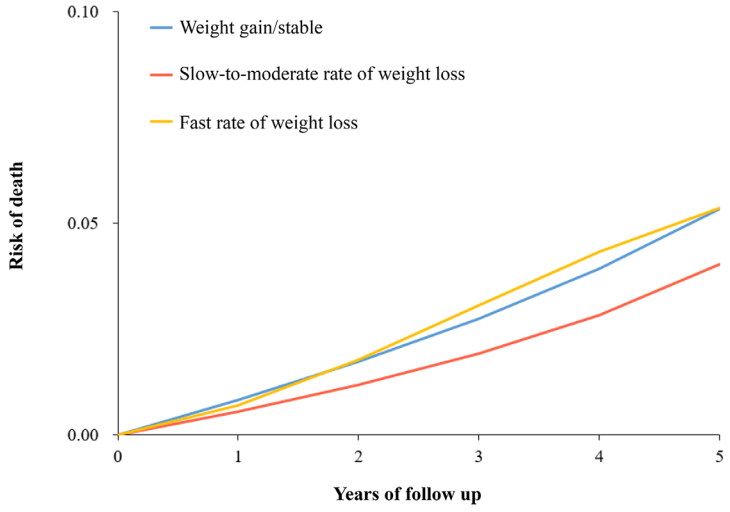
Patient and public involvement. No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or the writing of results. Dissemination of the findings to participants is not possible owing to the use of an anonymized dataset. This study was approved by the IMRD Scientific Review Committee (21SRC005_A1). This study received approval from the Medical Ethical Committee of Xiangya Hospital (2018091077), with a waiver of informed consent.

RESULTS

We identified 6,524 eligible participants for the current analyses (Figure 2). Of these participants, 5,916 initiated orlistat, 488 initiated sibutramine, and 120 initiated rimonabant. The mean age was 60.9 years, and 70.2% were women. The mean BMI was 38.1, and the mean weight was 104.5 kg. The baseline characteristics of the participants are shown in Supplementary Tables 2 and 3.

Of 6,524 replicates who were assigned to either the weight gain or stable, slow-to-moderate rate of weight loss, or fast rate of weight loss arms, 3,028, 2,919, and 797, respectively, adhered to their assigned rate of weight loss within one year after initiation of antiobesity medications. As shown in Figure 3, the slow-to-moderate rate of weight loss arm had a lower five-year risk of all-cause mortality than the weight gain/stable arm (4.0% vs 5.3%); however, no apparent difference was observed between the fast rate of weight loss arm (5.4%) and the weight gain or stable arm (5.3%). Compared with the weight gain or stable arm, the five-year risk differences of all-cause mortality were −1.3% (95% CI −2.1% to −0.5%) for the slow-to-moderate rate of weight loss arm and 0.1% (95% CI −2.0% to 1.3%) for the fast rate of weight loss arm (Table 1). The HRs of all-cause mortality for the slow-to-moderate rate of weight loss arm and the fast rate of weight loss arm were 0.72 (95% CI 0.56–0.92) and 0.99 (95% CI 0.67–1.44) compared with the weight gain/stable arm. Sensitivity analyses conducted among patients with obesity, those initiating orlistat, those initiating antiobesity medications, including GLP-1 RA, did not change the results materially (Table 1).

Results of the secondary outcomes are shown in Figure 4 and Table 2. Compared with the weight gain or stable arm, we



Number at risk

Weight gain/stable	6524	2837	2654	2469	2254	2026
Slow-to-moderate rate of weight loss	6524	2716	2547	2367	2216	2029
Fast rate of weight loss	6524	677	639	596	553	495

Figure 3. Five-year risk of all-cause mortality between weight gain or stable, slow-to-moderate rate of weight loss, and fast rate of weight loss among patients with overweight or obesity and knee or hip osteoarthritis initiating antiobesity medications.

Table 1. Relations of weight reduction induced by antiobesity medications within one year to all-cause mortality in patients with overweight or obesity and knee or hip OA*

	Weight gain and stable[a]	Slow-to-moderate rate of weight loss[a]	Fast rate of weight loss[a]
Patients with overweight or obesity			
Number	6,524	6,524	6,524
Weighted death, n	286	237	271
Weighted risk over five years, %	5.3	4.0	5.4
Weighted risk difference, % (95% CI)	0.0 (reference)	−1.3 (−2.1 to −0.5)	0.1 (−2.0 to 1.3)
Weighted HR (95% CI)	1.00 (reference)	0.72 (0.56 to 0.92)	0.99 (0.67 to 1.44)
Sensitivity analysis			
Patients with obesity, HR (95% CI)	1.00 (reference)	0.72 (0.55 to 0.93)	0.99 (0.67 to 1.46)
Initiating orlistat, HR (95% CI)	1.00 (reference)	0.77 (0.59 to 1.00)	1.03 (0.69 to 1.54)
Including the GLP-1 RA, HR (95% CI)	1.00 (reference)	0.76 (0.61 to 0.94)	0.93 (0.66 to 1.32)

* 95% CI, 95% confidence interval; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HR, hazard ratio; OA, osteoarthritis.
[a] Weight gain or stable: weight loss < 2% or weight gain; slow-to-moderate rate of weight loss: 2% ≤ weight loss < 10%; fast rate of weight loss: weight loss ≥ 10%.

found a dose–response protective effect of weight loss on the risk of incident hypertension (HR 0.76 [95% CI 0.66–0.87] for the slow-to-moderate rate of weight loss arm; HR 0.74 [95% CI 0.60–0.91] for the fast rate of weight loss arm), T2DM (HR 0.78 [95% CI 0.67–0.90] for the slow-to-moderate rate of weight loss arm; HR 0.48 [95% CI 0.38–0.62] for the fast rate of weight loss arm), and VTE (HR 0.68 [95% CI 0.50–0.92] for the slow-to-moderate rate of weight loss arm; HR 0.46 [95% CI 0.27–0.79] for the fast rate of weight loss arm). However, compared with the weight gain or stable arm, albeit not statistically significant, the risk of incident CVD was lower in the slow-to-moderate rate of weight loss arm

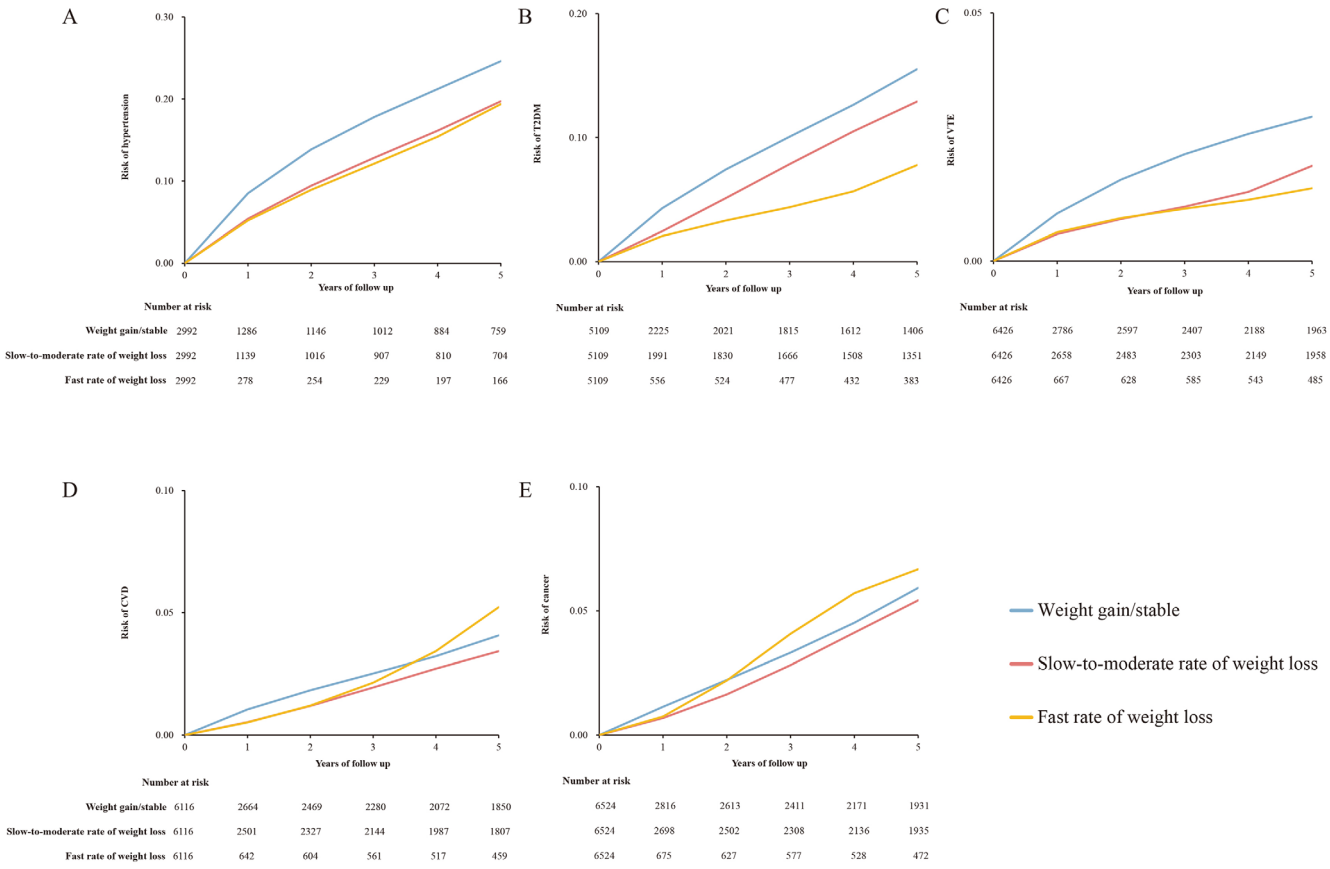


Figure 4. Five-year risk of (A) incident hypertension, (B) T2DM, (C) VTE, (D) CVD, and (E) cancer between weight gain or stable, slow-to-moderate rate of weight loss, and fast rate of weight loss among patients with overweight or obesity and knee or hip osteoarthritis initiating anti-obesity medications. CVD, cardiovascular disease; T2DM, type 2 diabetes; VTE, venous thromboembolism.

Table 2. Relations of weight reduction induced by antiobesity medications within one year to incident hypertension, T2DM, VTE, CVD, and cancer in patients with overweight or obesity and knee or hip OA*

	Weight gain/ stable[a]	Slow-to-moderate rate of weight loss[a]	Fast rate of weight loss[a]
Hypertension			
Number	2,992	2,992	2,992
Weighted hypertension, n	673	529	412
Weighted risk over five years, %	24.6	19.7	19.4
Weighted risk difference, % (95% CI)	0.0 (reference)	−5.0 (−7.1 to −2.2)	−5.2 (−8.2 to −0.3)
Weighted HR (95% CI)	1.00 (reference)	0.76 (0.66 to 0.87)	0.74 (0.60 to 0.91)
T2DM			
Number	5,109	5,109	5,109
Weighted T2DM, n	678	560	301
Weighted risk over five years, %	15.5	12.9	7.8
Weighted risk difference, % (95% CI)	0.0 (reference)	−2.6 (−4.1 to −1.1)	−7.7 (−9.2 to −5.7)
Weighted HR (95% CI)	1.00 (reference)	0.78 (0.67 to 0.90)	0.48 (0.38 to 0.62)
VTE[b]			
Number	6,426	6,426	6,426
Weighted VTE, n	159	110	70
Weighted risk over five years, %	2.9	1.9	1.5
Weighted risk difference, % (95% CI)	0.0 (reference)	−1.0 (−1.4 to −0.2)	−1.4 (−2.2 to −0.9)
Weighted HR (95% CI)	1.00 (reference)	0.68 (0.50 to 0.92)	0.46 (0.27 to 0.79)
CVD[c]			
Number	6,116	6,116	6,116
Weighted CVD, n	207	189	216
Weighted risk over five years, %	4.1	3.4	5.2
Weighted risk difference, % (95% CI)	0.0 (reference)	−0.6 (−1.3 to 0.2)	1.2 (−0.3 to 2.4)
Weighted HR (95% CI)	1.00 (reference)	0.88 (0.68 to 1.15)	1.20 (0.81 to 1.78)
Cancer[d]			
Number	6,524	6,524	6,524
Weighted cancer, n	332	300	319
Weighted risk over five years, %	5.9	5.4	6.7
Weighted risk difference, % (95% CI)	0.0 (reference)	−0.5 (−1.6 to 0.0)	0.8 (−1.3 to 1.4)
Weighted HR (95% CI)	1.00 (reference)	0.84 (0.68 to 1.05)	1.04 (0.74 to 1.45)

* 95% CI, 95% confidence interval; CVD, cardiovascular disease; HR, hazard ratio; OA, osteoarthritis; T2DM, type 2 diabetes; VTE, venous thromboembolism.
[a] Weight gain or stable: weight loss < 2% or weight gain; slow-to-moderate rate of weight loss: 2% ≤ weight loss < 10%; fast rate of weight loss: weight loss ≥ 10%.
[b] VTE was defined as the combined end point of pulmonary embolism and deep vein thrombosis.
[c] CVD was defined as the combined end point of myocardial infarction and stroke.
[d] Cancer was defined as the combined end point of lung, breast, colorectal, prostate, head and neck, and other cancers.

(HR 0.88, 95% CI 0.68–1.15) and slightly higher in the fast rate of weight loss arm (HR 1.20, 95% CI 0.81–1.78). The results of cancer were similar to all-cause mortality, with HRs being 0.84 (95% CI 0.68–1.05) and 1.04 (95% CI 0.74–1.45) for the slow-to-moderate rate of weight loss arm and the fast rate of weight loss arm compared with the weight gain or stable arm, respectively. We repeated the analyses for secondary outcomes among patients with obesity, those initiating orlistat, or those initiating antiobesity medications, including GLP-1 RA; the results did not change materially (Supplementary Tables 4–6).

DISCUSSION

Emulating a target RCT in individuals with overweight or obesity and knee or hip OA, we showed that the slow-to-moderate (2%–10%), but not the fast (≥10%), rate of weight loss induced by antiobesity medications within one year was associated with lower all-cause mortality compared with weight gain or stable weight. In addition, we found a dose–response protective effect of weight loss induced by antiobesity medications on the risk of incident hypertension, T2DM, and VTE. However, a slightly higher risk of CVD, albeit not statistically significant, was observed in the fast rate of weight loss arm compared with the weight gain or stable arm in individuals with overweight or obesity and knee or hip OA. No apparent difference in the risk of cancer was observed between the fast rate of weight loss arm and the weight gain or stable arm.

Several studies have examined the relation of the rate of intentional weight loss through various interventions to death; the results, however, were inconsistent.[22,32] A post hoc analysis of the Look AHEAD study, an RCT conducted among adults with overweight or obesity and T2DM, showed that the fast rate of weight loss (ie, ≥10%) induced by intensive lifestyle intervention within one year had a lower risk of all-cause mortality than stable weight or weight gain (<2% loss); however, no such a difference

was found between slow-to-moderate rate of weight loss (2%–10%) and stable weight or weight gain (<2% loss).[22] This study applied intensive lifestyle intervention to lose weight, which may be unlikely to result in long-term benefits in a real-world setting because of low adherence to the intervention. Moreover, one cohort study conducted among patients with overweight or obesity and chronic kidney disease failed to show any association between one-year intentional weight loss (either 5%–10% or ≥10%) induced by various interventions and all-cause mortality.[32]

Our study assessed the effect of the rate of weight loss induced by antiobesity medication, which differed from the interventions in previous studies and could be considered an effective strategy for preventing overweight and obesity. In the Sibutramine Cardiovascular Outcomes trial, participants with 5% to 10% weight loss induced by antiobesity medication (ie, sibutramine) within one year had the lowest mortality, whereas those with either weight gain or marked weight loss (>10%) had higher mortality.[33] However, deaths that occurred within the first year after initiation of antiobesity medication were excluded from the analysis; thus, the effect estimates may be susceptible to immortal time bias, which introduces an artificial survival advantage associated with the exposed participants regardless of treatment effectiveness.[34] In the current analyses, we gave each copy a grace period (ie, one year) to reach the target rate of weight change. During the grace period, if an individual died before reaching the target rate of weight change, that person was considered to adhere to their assigned intervention arm, and the death was counted in each of the intervention arms. This approach would eliminate immortal time bias in absolute and relative risk estimates in observational studies.

Previous studies have shown that intentional weight loss among an overweight or obese population was associated with significant improvements in reducing inflammation, lowering blood pressure, improving insulin sensitivity, and decreasing thrombin generation.[23,35–38] Our results are similar in that both a slow-to-moderate rate of weight loss and a fast rate of weight loss induced by antiobesity medications were associated with lower risk of incident hypertension, T2DM, and VTE. However, several studies also found that intentional rapid weight loss may counteract these benefits. Lack of protein, electrolytes, and micronutrients induced by rapid or major weight loss may contribute to myofibrilla damage in the heart.[39] Indeed, we observed a slightly higher risk of CVD, albeit not statistically significant, in the fast rate of weight loss arm compared with the weight gain or stable arm. In addition, intentional rapid weight loss can escalate the release of potentially harmful lipophilic compounds into the blood circulation,[40] reduce both muscle and fat tissues,[41] and increase the risk of developing metabolic bone disease.[42] Taken together, the discordant findings between the all-cause mortality outcome and each of the other outcomes in the fast rate of weight loss group compared with the reference group might be attributed to the potential drawbacks (eg, myofibrilla damage and increased risk of metabolic bone disease) offsetting the benefits (eg, lowering blood pressure and improving insulin sensitivity) of a fast rate of weight loss induced by antiobesity medications. Nevertheless, we observed a consistent protective effect of the all-cause mortality outcome with each of the other outcomes in the slow-to-moderate rate of weight loss group compared with the reference group, implying that gradual weight loss by antiobesity medications may improve the overall wellness of overweight or obesity patients with knee or hip OA.

Several strengths of our study are noteworthy. First, our study design followed several principles of clinical trials, including a clearly defined intervention strategy (ie, three arms of weight loss [<2%, 2%–10%, and >10%] over one year using the antiobesity medications [eg, orlistat, sibutramine, and rimonabant]), a clearly defined target population (ie, participants with overweight or obesity and knee or hip OA), and well-defined study outcomes (ie, all-cause mortality, hypertension, T2DM, VTE, CVD, and cancer). Second, we started the follow-up from the date of initiation of antiobesity medications, which avoided the potential immortal time bias. Third, we adjusted for potential confounders and used IPW to account for the loss to follow-up. All these measures enhanced the internal validity of the study findings. Potential limitations of our study also deserve comment. First, although we used rigorous approaches to control for confounders, some covariates, such as disease severity, exercise, and diet, may not be well captured by the variables available in the IMRD; thus, we cannot rule out residual confounding. Second, owing to a lack of recent data on cause-specific mortality in IMRD, we could not assess the effect of weight loss on the risk of cause-specific mortality in patients with overweight or obesity and knee or hip OA. Third, previous studies have shown that weight loss has a beneficial effect on pain relief and functional improvement in patients with overweight or obesity and knee or hip OA.[8,9,43,44] We postulate that pain reduction, better function, improved mobility, and better health-related quality of life resulting from weight loss could also lower all-cause mortality. Studies that evaluate whether the effect of weight loss on all-cause mortality is mediated via these benefits among patients with OA are relevant and important. Unfortunately, such data are not systematically collected in the IMRD; therefore, we are unable to address these issues in this study.

Obesity and OA are often comorbid.[5] and weight loss is recommended for patients with overweight or obesity and knee or hip OA.[11–13] In addition to the potential beneficial effect on pain relief and functional improvement in a dose–response relationship manner, there is a paucity of data on all-cause mortality according to the rate of weight loss among patients with overweight or obesity and knee or hip OA. The overall all-cause mortality is critically important because death, regardless of its causes, represents the overall net health impact of various benefits and risks related to any clinical treatment regimen.[45] Although weight loss by intensive lifestyle intervention, such as decreasing caloric intake and

increasing physical activity, has been shown to provide significant benefits for the overweight or obese population, modification of diet and exercise alone is unlikely to result in long-term benefits because of the low adherence to the intervention.[46] Effective pharmacologic therapies could be considered as another strategy for preventing overweight and obesity. Our results provide empirical evidence that a slow-to-moderate rate of weight loss induced by antiobesity medications within one year lowers all-cause mortality. The rate of weight loss is consistent with the guidelines worldwide that gradual weight loss should be recommended for the treatment of obesity.[47–49] Orlistat, accounting for the majority of antiobesity medications in the current study, has been available for treating obesity for two decades and has a good safety profile.[50] Our finding that gradual weight loss by antiobesity medications lowers all-cause mortality, if confirmed by future studies, could guide policy-making and improve the well-being of patients with overweight or obesity and knee or hip OA.

In summary, a slow-to-moderate (2%–10%), but not fast (≥10%), rate of weight loss induced by antiobesity medications within one year is associated with a lower risk of death in people with overweight or obesity and knee or hip OA.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Zeng had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Wei, Hunter, Lane, Zeng, Lei, Zhang.
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