Body Mass Index, Change in Weight, Body Weight Variability and Outcomes in Type 2 Diabetes Mellitus (from the ACCORD Trial)

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Weight management is highly recommended to patients with diabetes mellitus. However, this prescription is often characterized by weight fluctuations. It remains unclear the effects of weight fluctuations on outcomes in diabetes mellitus. We used the public use dataset from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial to assess the effects of baseline weight, change in weight, and body weight variability (BWV) on outcomes. The ACCORD trial participant's weights were documented annually during the trial. Our primary predictor variables were baseline weight, change in body weight (Initial − final) and BWV defined as average successive variability in weight (average absolute difference between successive values) during the trial. Cox proportional hazards model was used. Out of the 10,251 ACCORD participants, 911(8.9%), 2985(29.1%), and 6355(62%) were normal weight, overweight, and obese. After a mean of 3.5 years of follow-up, 10.2% had the primary outcome (nonfatal MI or nonfatal stroke or CV death), 4.3% had heart failure, 7% died, and 60.7% reported a microvascular complication. BWV was associated with the primary outcome, heart failure, death, and microvascular events in our full models which included BMI [HR (95%CI): 1.25(1.15 to 1.36), 1.59(1.45 to 1.75), 1.74(1.63 to 1.85) and 1.18(1.13 to 1.22), p < 0.0001 respectively). Participants who died were in the quartile that gained the most weight. In this post hoc analysis of ACCORD trial, body weight variability was significantly associated with poor outcomes independent of CVD risk factors and BMI. Our study is consistent with significant risk associated with weight fluctuations in patients with diabetes mellitus. **(Am J Cardiol 2019;123:576−581)**

Obesity has been associated with increased mortality and morbidity in our society.[1,2] Despite current research and efforts, the average weight of populations continues to rise. According to data from the National Health and Nutrition Examination Survey, two of three American adults is either overweight or obese.[3,4] Obesity has been associated with the development of type 2 diabetes mellitus.[5] It has also been shown that about 30% of overweight adults have diabetes and about 85% of patients with type 2 diabetes mellitus are overweight. Therefore weight loss has been recommended as part of the effort not only to reduce the prevalence of diabetes but also help manage the disease and to reduce complications. The prescription of weight loss to patients is often characterized but weight fluctuations (recycling). While in general weight loss has been associated with better outcomes, the effects of the accompanying fluctuations in weight on outcomes have been less studied especially in patients with diabetes mellitus and have produced mixed results.[6−9] In this report, we use the public-use data of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial to assess the effects of baseline weight, change in weight, and body weight variability (BWV) on micro and macrovascular complications in patients with type 2 diabetes mellitus.

Methods

We conducted a post hoc analysis of the data from the ACCORD trial, a multicenter factorial randomized controlled trial that compared intensive blood pressure, glycemic and lipid treatment with standard care in patients with diabetes mellitus. Details of the aims, design and principal results of the ACCORD trial has been published.[10−14] In all 10,251 participants with type 2 diabetes were randomized to intensive and standard treatment of the aforementioned risk factors in 77 North American centers between 2001 and 2005. The inclusion criteria were: type 2 diabetes mellitus, hemoglobin A1C ≥7.5%, age 40 to 79 with CAD or 55 to 79 years with: anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy or ≥2 cardiovascular risk factors (dyslipidemia, hypertension, current smoking, and obesity). The exclusion criteria of the ACCORD trial were frequent or recent serious hypoglycemic events, unwillingness to perform home glucose monitoring or insulin injections, BMI > 45, serum creatinine > 1.5 mg/dL and serious illness. The ACCORD trial was stopped after the safety

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See page 580 for disclosure information.

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0002-9149/
https://doi.org/10.1016/j.amjcard.2018.11.016

committee recommended discontinuation of intensive therapy. This analysis was done with the public-use data of the ACCORD trial.

Vitals signs including body weight were documented yearly in ACCORD participants for up to 7 years (Mean of 3.7 years). Of note, even though weight management was not part of the design of the ACCORD trial, disproportionate weight gain was recorded between the groups.[10] Funding, medications, equipment, and supplies were provided by NIH grants from the NHLBI, other NIH departments, the CDC, General Clinical Research Centers, Abbott Laboratories, Amylin Pharmaceutical, AstraZeneca, Bayer HealthCare, Closer Healthcare, GlaxoSmithKline, King Pharmaceuticals, Merck, Novartis, Novo Nordisk, Omron Healthcare, Sanofi-Aventis, and Schering-Plough. The institutional review boards of participating centers approved the trial, and written informed consent was obtained from each participant. We included all ACCORD trial participants with at least 2 recorded weights in this analysis.

Our predictor variables for this analysis were baseline weight, change in weight, and body weight variability. Change in weight was calculated as baseline weight minus exit /final weight (kg). We calculated body weight variability using prior defined formula.[9] Body weight variability was defined as intraindividual variability in body weight between visits. We used average successive variability, which was defined as the absolute difference between successive values, as the primary body weight variability measurement. In general, baseline covariates were adjusted for in our models. However, average blood pressure, HbA1C and lipid levels recorded throughout the trial were used to account for the difference in intensities of treatment in the ACCORD trial.

The outcomes considered in our analysis included the primary outcome of the ACCORD trial: nonfatal MI or nonfatal stroke or CV death; congestive heart failure, total death and microvascular events defined as nephropathy, neuropathy or retinopathy. The event adjudication process of the ACCORD trial has already been published.[11–13] The total ACCORD trial cohort was first classified as normal weight (BMI > 25), overweight (BMI 25 to 30) and obese (BMI >30) based on their baseline body mass index defined as weight (kg) divided by height $(m)^2$. The baseline demographic, risk factors, and clinical characteristics was assessed per weight category. Mean and standard deviation or percent were reported for continuous and categorical variables, respectively.

Cox proportional hazards analysis was used to assess the association between baseline BMI, change in weight and body weight variability and our outcomes of interest adjusting for age, gender, race (binary), arm of the trial, statin use, GFR, mean SBP, mean DBP, mean LDL, mean HDL, mean HBA1C, years of diabetes, cigarette smoking status, antihypertensive medication use, baseline cardiovascular disease status. Time between initial and final weight measurement was also adjusted for in the full models with body weight variability and change in weight as the predictor variable. Our predictor variables were introduced into our models as both continuous and categorical variable (quartiles). Quartiles (Q) of change in weight were as follows: Q1: quarter that gained the most weight Q1: quarter that gained the most weight (gained > 4.1 Kg); Q2: quarter that gained mild weight (gained between zero and 4.1kg); Q3: quarter with mild weight lost (0-3.8kg) and Q4: quarter that lost the most weight (> 3.8kg). > 4.1 Kg); Q2: quarter that gained mild weight (gain between zero and 4.1kg); Q3: quarter with mild weight lost (0-3.8kg) and Q4: quarter that lost the most weight (> 3.8kg). We also compared the risk of outcomes in participants with normal weight but highest quartile of body weight variability with those obese at baseline but had lowest quartile of body weight variability. All analyses were performed with the use of SAS software 9.2 (SAS Institute, Cary NC) and excel spreadsheet.

Results

Of the 10,251 total ACCORD participants, 911 (8.9%) had normal weight, 2985 (29.1%) were overweight and 6355 (62%) were obese. Obese participants were more likely to be females, white and less likely to be cigarette smokers (Table 1). After a mean of 3.7 years of follow-up, 10.2%, 4.3%, 7.0%, and 39% were adjudicated as having the primary outcome, congestive heart failure, total death, and microvascular event respectively. The mean baseline BMI, the mean change in body weight, and body weight variability throughout the ACCORD trial (mean± SD) were 32.2± 5.4 kg/m^2, 0.1± 7.6 Kg and 3.4 ±2.4 respectively. Baseline BMI was associated with CHF, total death, and microvascular events but not with the primary outcome in our fully adjusted Cox models (Table 2).

Change in weight experienced by participants throughout the ACCORD trial ranged from −30.4 kg to 50.6 kg. Participants who gained most weight (Q1) had higher CVD events (primary outcome), CHF events, and total mortality (Figure 1). Of note all those who died during the ACCORD trial were in Q1 (quarter that gained the most weight) (Figure 1). As shown in Table 3 body weight variability(continuous) was associated with the primary outcome, CHF, total death, and microvascular events in both the univariate and multivariable models which included baseline BMI and the time between initial and final weight measurement . As shown in Figure 1, increasing quartiles of body weight variability was associated with increasing number of CHF and microvascular events. However, for the primary outcome and total mortality, those with the least (Q1) and most (Q4) body weight variability appears to have high risk albeit the percentage of events were significantly higher in those with the highest body weight variability(Q4). Supplemental Figure (A to C) illustrates the association between the primary outcome, CHF, total death and quartiles of body weight variability within those classified as normal weight, overweight, and obese at the baseline ACCORD examination. For the primary outcome (supplemental Figure A), increasing quartiles of BWV were associated with increasing percentage of events within each weight category. Increasing percent CHF was observed with increasing quartiles of body weight variability within each weight category (supplemental Figure B). The highest percentage of total deaths appears to be concentrated in those with lowest (Q1) and highest (Q4) quartiles of body weight variability within each weight category (Supplemental Figure C). Participants with normal weight at baseline but were in the highest quartile of body

Table 1
Demographic and risk factor profile of ACCORD participants

Variable	Total cohort (N = 10,251) Mean± SD	Body mass index ≤25 (N = 911) Mean± SD	Body mass index = 25-30 (N = 2985) Mean± SD	Body mass index > 30 (N = 6355) Mean ±SD
Age (Years)	62.8 ± 6.6	64.0 ± 7.5	63.9 ± 6.9	62.0 ± 6.3
Women	38.5%	35.7%	31.6%	42.2%
White	62.4%	41.8%	57.6%	67.5%
Non-White	37.6%	58.2%	42.4%	32.5%
Body mass index (Kg/m^2)	32.2 ± 5.4	23.5 ± 1.3	27.7 ± 1.4	35.5 ± 3.9
Change in weight (Kg)	0.1 ± 7.6	−0.8 ± 4.8	−0.4 ± 6.0	0.4 ± 8.5
Body weight variability	3.4 ± 2.4	2.3 ± 2.0	2.8 ±1.9	3.8 ± 2.5
Duration of diabetes (Years)	10.8 ± 7.6	11.8 ± 7.9	11.6 ± 8.0	10.3 ± 7.3
Cholesterol (mg/dL)*				
Total	171.6 ± 32.7	172.8 ± 33.3	170.5 ± 32.8	171.9 ± 32.6
Low density lipoprotein	95.4 ± 25.8	97.0 ± 26.0	95.3 ± 25.2	95.2 ± 26.1
High density lipoprotein	42.8 ± 10.7	47.1 ± 12.3	43.1 ± 10.6	42.1 ± 10.4
Triglycerides	169.3 ± 92.5	142.7 ± 83.5	162.7 ± 94.2	176.1 ± 92.1
Very low density lipoprotein	32.9 ± 16.4	27.9 ± 14.9	31.7 ± 16.7	34.2 ± 16.2
Blood pressure (mm Hg)*				
Systolic	129.0 ± 11.6	128.9 ± 12.0	129.3 ± 11.3	128.8 ± 11.5
Diastolic	69.4 ± 8.0	67.7 ± 7.9	68.4 ± 8.2	70.1 ± 7.8
Hemoglobin A1C*	8.3 ± 1.0	8.3 ± 1.1	8.3 ± 1.0	8.2 ± 1.0
Glomerular filtration rate	90.2 ± 22.6	91.6 ± 24.3	89.5 ± 22.1	90.2 ± 22.5
ACE-I/ARB Use	71.0%	60.9%	68.8%	73.4%
Statin use	63.7%	59.5%	65.1%	63.6%
Heart rate (bpm)	71.6 ± 9.2	71.1 ± 8.7	70.8 ± 9.2	72.0 ± 9.3
Current smoking	13.9%	21.0%	15.7%	12.1%
Prior cardiovascular disease	35.2%	32.8%	37.1%	34.7%
Outcomes				
Composite	10.2%	11.8%	10.8%	9.7%
Congestive heart failure	4.3%	3.0%	3.9%	4.7%
Total mortality	7.0%	6.6%	7.3%	6.9%
Microvascular	39.0%	35.3%	38.4%	39.9%

* indicates mean values during the ACCORD trial.

weight variability during the ACCORD trial (n = 90) were at a higher risk of CVD events (primary outcome) compared with those who were obese at baseline and were in the lowest quartile of body weight variability(n = 1305) in the univariate [HR(95%CI): 1.78(1.07 to 2.95), p = 0.02] and full models [HR(95%CI): 2.91(1.35 to 6.28), p = 0.007)

Discussion

The goal of this post hoc analysis was to assess the risk associated with body weight fluctuations often seen in patients with diabetes mellitus. Our study used the publicly available data of the ACCORD trial to show that while obesity is a risk factor for complications in persons with diabetes mellitus, the fluctuation of body weight (body weight variability) which often accompanies weight loss prescription may even be associated with a higher risk for macrovascular and microvascular complications. Our study supports additional recommendations to minimize weight fluctuations during weight loss in diabetes mellitus as part of the weight loss prescription.

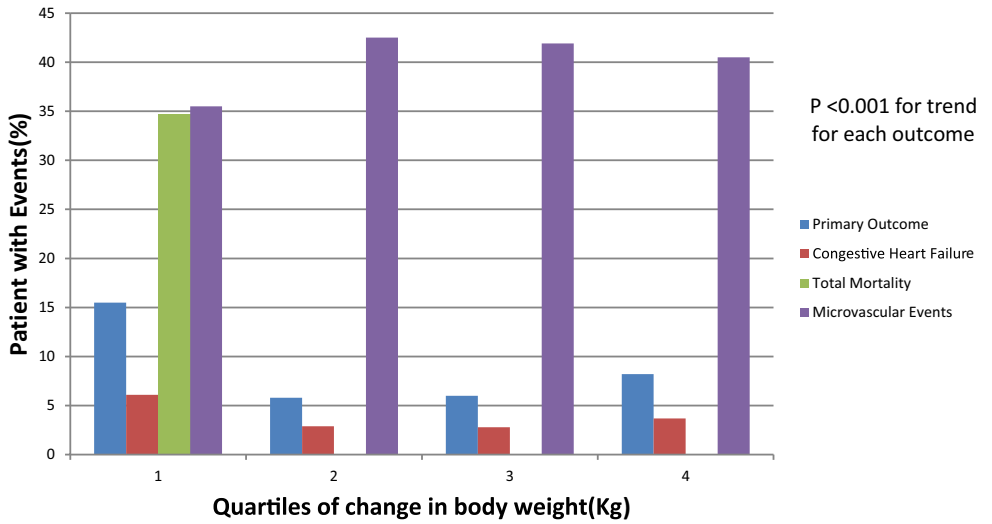
Obesity is an independent risk factor for morbidities and mortality.[14,15] The risk posed by obesity and the benefit gained by weight loss in the general population has both been documented in prospective cohort studies and in clinical trials.[16–19] However, data on the effects of weight fluctuations which often accompanies the weight loss prescription on outcomes have been limited particularly in persons with diabetes mellitus and has shown mixed results.[6–8] Wannamethee et al in a prospective study of

Table 2
Baseline body mass index (BMI) (per unit standard deviation) and risk of outcomes in ACCORD trial

Outcome	Univariate hazard ratio (95%CI)	p value	Multivariable* hazard ratio (95%CI)	p value
Primary outcome	0.97 (0.91 to 1.03)	0.31	1.05 (0.99 to 1.13)	0.13
Congestive heart failure	1.24 (1.14 to 1.36)	<0.0001	1.41 (1.28 to 1.56)	<0.0001
Total death	1.04 (0.97 to 1.12)	0.28	1.20 (1.11 to 1.30)	<0.0001
Microvascular events	1.05 (1.02 to 1.08)	0.0002	1.01 (1.00 to 1.01)	0.02

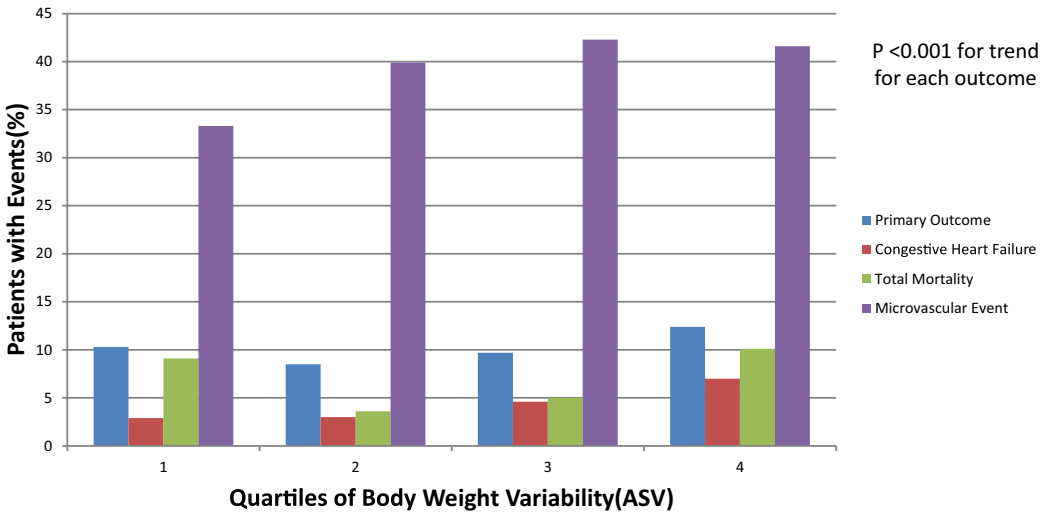
* adjusted for age, gender, race(binary), arm of the trial, statin use, GFR, mean SBP, mean DBP, mean LDL, mean HDL, mean HBA1C, years of diabetes, cigarette smoking status, antihypertensive medication use, baseline cardiovascular disease status.

A



Mean Change Body weight (Kg)	-8.80	-1.98	1.83	9.47
# Outcomes				
PO	628	119	114	168
CHF	248	59	53	76
Death	718	0	0	0
MV events	1433	869	801	830

B



Mean Body weight Variability (Kg)	1.34	2.39	3.48	6.39
#Outcomes				
PO	293	209	240	304
CHF	84	74	114	172
Death	259	89	123	247
MV events	951	984	1045	1022

Figure 1. *(A)* Shows the distribution of the primary outcome, congestive heart failure, total mortality, and microvascular disease events by quartiles of change in weight which occurred in the ACCORD Trial during the follow-up period. *(B)* Shows the distribution of the primary outcome, congestive heart failure, total mortality, and microvascular disease events by quartiles of body weight variability which occurred in the ACCORD Trial during the follow-up period.

Table 3
Continuous body weight variability (per unit SD) and risk of outcomes

Outcome	Univariate hazard ratio (95%CI)	p value	Multivariable* hazard ratio (95%CI)	p value
Primary Outcome	1.26 (1.16 to 1.36)	<0.0001	1.25 (1.15 to 1.36)	<0.0001
Congestive Heart Failure	1.51 (1.40 to 1.65)	<0.0001	1.59 (1.45 to 1.75)	<0.0001
Total Death	1.66 (1.56 to 1.77)	<0.0001	1.74 (1.63 to 1.85)	<0.0001
Microvascular events	1.18 (1.14 to 1.23)	<0.0001	1.18 (1.13 to 1.22)	<0.0001

* adjusted for age, gender, race(binary), arm of the trial(treatment assignment), baseline BMI, statin use, GFR, mean SBP, mean DBP, mean LDL, mean HDL, mean HBA1C, years of diabetes, cigarette smoking status, antihypertensive medication use, baseline cardiovascular disease status, time between initial and final weight measurement.

middle aged British men showed that the increased risk of mortality associated with weight loss and weight fluctuations is determined to a major extent by disadvantageous lifestyle factors and preexisting diseases.[20] Recently Bangalore et al[9] showed in a post hoc analysis of the Treating to New Targets trial which included patients with coronary artery disease, that fluctuation in body weight was associated with higher mortality and a higher rate of cardiovascular events independent of traditional cardiovascular risk factors. Although these studies included persons with diabetes mellitus, their numbers in these studies were limited and hence limit the generalization of the findings to this uniquely high-risk group. We used the largest cohort which has been studied on this topic to also show that body weight fluctuations are harmful in patients with diabetes mellitus. The risk associated with body weight fluctuations appears to exist in those classified as obese, overweight and even in those with normal weight who are often not recommended weight loss (Supplemental Figure A to C).

In our study, participants who had the most weight gain (Q1: change in weight) had a significantly higher risk of the primary outcome, CHF and total mortality compared with those who lost the most weight (Q4: change in weight) (Figure 1). A higher percentage of participants in our study who had the most weight gain also had a high body weight variability compared with those who had the most weight loss. However, weight loss in diabetes mellitus has been associated with reduced mortality and morbidity, suggesting that the most beneficial way to lose weight in diabetes mellitus maybe through minimal body weight variability. More studies assessing the effects of body weight variability on hard outcomes in patients with diabetes mellitus are needed.

Our study has significant limitations. This is a post hoc analysis of the ACCORD trail and even though we tried to adjust for confounders, our results may still be due to residual confounding. The ACCORD trial was not a weight loss trial and so we are unsure whether the weight change and therefore variability was intentional or unintentional. We adjusted for the mean values of risk factors such as blood pressure, lipid profile, HBAIC, and drug categories such as antihypertensive medication use, statin use, insulin versus noninsulin use in our multivariable models. We were unable to specifically adjust for the use of specific drugs known to be cardioprotective in our models. ACCORD trial recruited only type 2 diabetes, therefore our results may not be extended to other type diabetes mellitus. Our results may also not apply to type 2 diabetes mellitus persons who were in the exclusion criteria of the ACCORD trial.

In conclusion, our study shows a strong and independent associated of BWV with micro and macrovascular complications in persons with type 2 diabetes mellitus. This association was observed within all categories of weight (normal, overweight, and obese) and was independent of BMI. Our study supports the addition of a recommendation to minimize body weight fluctuations in patients with type 2 diabetes mellitus during weight loss.

Funding

The ACCORD Trial was Supported by contracts from the National Heart, Lung, and Blood Institute (N01-HC-95178, N01-HC-95179, N01-HC-95180, N01-HC-95181, N01-HC-95182, N01-HC-95183, N01-HC-95184, and IAA#Y1-HC-9035 and IAA#Y1-HC-1010)

Disclosure

The authors have no conflicts of interest to disclose.

Acknowledgment

The authors would like to thank the investigators, the staff, and the participants of the ACCORD Trial for their valuable contributions.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.amjcard.2018.11.016.

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