Published in final edited form as:
Am Heart J. 2011 July ; 162(1): 184–192.e3. doi:10.1016/j.ahj.2011.03.019.

BMI and Health Status in the Bypass Angioplasty Revascularization Investigation 2 Diabetes Trial (BARI 2D)

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Abstract

BACKGROUND—The longitudinal association between obesity, weight variability and health status outcomes is important for patients with coronary disease and diabetes.

METHODS—The Bypass Angioplasty Revascularization Investigation 2 Diabetes trial (BARI 2D) was a multi-center randomized clinical trial to evaluate the best treatment strategy for patients with both documented stable ischemic heart disease and type 2 diabetes. We examined BARI 2D participants for four years to study how BMI was associated with health status outcomes. Health status was evaluated by the Duke Activity Status Index (DASI), RAND Energy/fatigue, Health Distress, and Self-rated health. BMI was measured quarterly throughout follow-up years, and health status was assessed at each annual follow-up visit. Variation in BMI measures was separated into between-person and within-person change in longitudinal analysis.

RESULTS—Higher mean BMI over follow-up years (the between-person BMI) was associated with poorer health status outcomes. Decreasing BMI (the within-person BMI change) was associated with better Self-rated health. The relationships between BMI variability and DASI or Energy appeared to be curvilinear, and differed by baseline obesity status. Decreasing BMI was associated with better outcomes if patients were obese at baseline, but was associated with poorer DASI and Energy outcomes if patients were non-obese at baseline.

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ClinicalTrials.gov Number: NCT00006305

CONCLUSIONS—For patients with stable ischemic heart disease and diabetes, weight gain was associated with poorer health status outcomes, independent of obesity-related comobidities. Weight reduction is associated with better functional capacity and perceived energy for obese patients but not for non-obese patients at baseline.

Keywords

BMI; obesity; coronary disease; diabetes mellitus; health status

BACKGROUND

The prevalence of obesity has risen in recent decades,[1] and more than half of American adults are estimated to be overweight or obese[2]. Obesity increases the risk for both coronary artery disease and type 2 diabetes,[3] as excessive adipose tissue secretes more adipokines, which may lead to systemic inflammation and insulin resistance. [4, 5] Inflammatory factors are associated with greater risk of sarcopenia, bone loss, and anemia,[6, 7] and undermine functional capacity and health status of an individual.[8] Previous studies have shown that being overweight or obese contributes to lower health-related quality of life.[9] However, previous data were primarily cross-sectional, and about the longitudinal relationship between obesity and health status remains uncertain.

Apart from obesity, weight fluctuation also is a known risk factor for mortality and adverse cardiovascular events.[10, 11] However, little is known about the relationship between weight variability and health status measures, and whether such associations differ by obesity status.

The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) was a multi-center international randomized clinical trial evaluating the treatment strategies for patients with documented stable ischemic heart disease and type 2 diabetes.[12] Baseline results of BARI 2D demonstrated that obesity was inversely associated with desirable health status outcomes, and the relationship was independent of baseline co-morbidities and treatment.[13] To investigate the longitudinal relationship between body mass index (BMI) and health status outcomes, we tested the following hypotheses in the present study: 1) higher BMI is associated with lower health status outcomes during follow-up, 2) individual BMI change is associated with change in health status outcomes, and 3) the association between BMI fluctuation and health status differs by baseline obesity status.

METHODS

Setting

The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) is a NIH sponsored randomized clinical trial. A 2-by-2 factorial design was used to compare treatment strategies for patients with both stable ischemic heart disease and type 2 diabetes. The baseline characteristics and primary findings of BARI 2D have been reported. [14] Briefly, patients were eligible for BARI 2D if they had type 2 diabetes, documented myocardial ischemia, and angiographically documented coronary heart disease suitable for revascularization. Consented patients were randomized to receive one of the two randomized heart disease strategies—prompt revascularization or medical therapy with delayed revascularization when necessary, and simultaneously randomized to receive one of the two glycemic strategies, either insulin-sensitizing or insulin-providing drugs to achieve a serum Hemoglobin A1c level of less than 7.0%. A total of 2,368 patients were enrolled between January 2001 and March 2005, and clinical follow-up ended on November 30, 2008. The average patient follow-up was 5.3 years.

Summary of key variables

BMI and health status were measured concurrently at baseline for each BARI 2D participant. During follow-up years, BMI was measured quarterly, while health status was measured annually. BMI was calculated as weight (in kilograms) divided by height squared (in meters). Health status was assessed by four self-administrated instruments—the Duke Activity Status Index (DASI),[15] RAND Medical Outcome Study Energy/fatigue,[16] Health Distress scales,[17] and Self-rated health.[18] The DASI score ranged from 0 (worst) to 58.2 (best). The RAND Energy/fatigue scale (hereafter referred to as Energy) included 5 items reporting the amount of time in the past month the participant felt energetic or tired. The modified RAND Health Distress scale (hereafter referred as Health Distress) quantified how often the participant felt distressed about health. A sample question was "were you discouraged by your health problems?". The Self-rated Health score asked the participant to rate his/her health in general as excellent, very good, good, fair, or poor. We transformed the raw scores of the Energy, Health Distress and Self-rated Health to 0–100 scales for comparison. Higher scores indicated more Energy, better Self-rated Health, and worse Health Distress. The health status measures have been validated in populations with different chronic conditions,[15,16, 19] and used frequently in randomized clinical trials for patients with cardiovascular diseases.[20,21,22]

Statistical Analysis

Data were truncated at year 4 because an increasing proportion of patients did not have a year 5 clinical visit due to late enrollment. Only patients with at least one follow-up health status measure were included in the analysis. Baseline demographic, clinical, and health status profiles were summarized by BMI categories of normal ($BMI<25$), overweight ($25\leq BMI<30$), class I obesity ($30\leq BMI<35$), and class II/III obesity ($BMI\geq 35$). Continuous variables were compared with Spearman rank correlation and categorical variables with Mantel-Haenszel chi-square test for trend. Population means for health status and BMI were summarized at baseline and each follow-up year. The total variability in repeated health status and BMI measures were separated into the between-person and within-person variance components. [23] Nonparametric lowess smoothing was used to examine the relationship between health status and BMI.

For longitudinal analysis, multilevel modeling under the structure of linear mixed models was used. [24] We obtained BMI and health status measured concurrently at each annual follow-up visit, with baseline values as covariates. We separated the change in BMI during follow-up into between-person and within-person differences. The between-person BMI value was determined as the mean BMI over follow-up years for each participant. The within-person change was calculated by subtracting the person-specific mean BMI from the BMI value measured at each follow-up year.[25,26,27] This modeling strategy enabled us to test simultaneously the associations between health status and mean BMI as well as change in BMI, with additional benefit that the assumption of homogeneous variance in the linear mixed effect model was relaxed. [28] The model strategies are summarized in Appendices A-1 and A-2 of the report.

To control for confounding, we assessed the association between BMI and health status outcomes using multivariate models. We tested for quadratic BMI and effect modification between BMI and covariates reported to interact with BMI in previous studies, such as baseline obesity,[13] age and sex.[26] To account for multiple comparisons, we set a two-sided alpha of 0.01 as the significance level for polynomials and effect modification. Model fit was examined by residual and random effect plots.[24] Analyses were performed with SAS statistical software (version 9.1; SAS Institute Inc, Cary, NC).

BARI 2D was funded by the National Heart, Lung, and Blood Institute and the National Institute of Diabetes and Digestive and Kidney Diseases and received support from the pharmaceutical companies listed on the cover page. The study investigators are solely responsible for the design and conduct of this study, and the authors are responsible for all analyses, the drafting and editing of the paper, and its final contents.

RESULTS

Baseline Characteristics

The analysis included 2,163 of the 2,368 (91.3%) BARI 2D participants with one or more follow-up health status measures. At baseline, 1,219 (56.6%) participants were obese. Participants in higher baseline BMI categories were more likely to be African American and from the United States. At baseline, obesity was associated with higher prevalence of insulin use, history of congestive heart failure and chronic renal dysfunction, and inversely associated with smoking and history of myocardial infarction. The baseline distributions of duration of diabetes, serum Hemoglobin A1c, and clinical history of angina, neuropathy, non-coronary artery disease or stroke were similar across BMI categories (Table 1).

Change in BMI and Health Status over Time

Among BARI 2D participants, the mean BMI increased from 31.8 at baseline to 32.0 at year 2 and 32.2 at year 4. Health status measures significantly improved from baseline to the year one visit and then gradually declined during follow-up years (Figure 1). The average between-person BMI values were 32.1 for all participants, 35.7 for participants who were obese at baseline and 27.3 for participants who were non-obese at baseline.

For non-obese patients at baseline, those with stable BMI had highest mean DASI over follow-up years. For obese patients at baseline, there was an inverse association between increased BMI category and functional capacity (Table 2). A majority of participants remained in the same BMI category throughout the study. One third of normal or under weight participants became overweight during follow-up, while 155 (21%) overweight participants at baseline became class I obese over time. Fifteen percent (15%) of obese participants shifted down one obesity category during follow-up (Table 2).

Non-linear Association between BMI and Health Status

We observed a nonlinear association between DASI or Energy and BMI. Using DASI as an example, the highest mean DASI score was observed at a BMI between 26 and 30, and for obese participants (BMI > 30), higher BMI was linearly associated with lower DASI. When the change in repeated BMI measures were partitioned into between- and within-person components, the association between DASI and within-person BMI change was curvilinear ($p<0.001$, Figure 2).

After adjustment for confounding, a higher mean BMI during follow-up was significantly associated with lower health status outcomes. A 10 unit difference in mean follow-up BMI was associated with a disparity of 2.7 points in DASI, 3.2 points lower in Energy, 3.2 points more distress and 4.1 points lower in self-rated health ($p <0.001$, Table 3).

The curvilinear relationships between DASI or Energy and within-person BMI change differed by baseline obesity status (Table 3). Patients whose BMI increased during follow-up had worse DASI and Energy scores. Patients whose BMI decreased had better DASI and Energy scores only if they were obese at baseline (Figure 3a and 3b). The interactions between baseline obesity status and individual BMI change on health status were significant. Using DASI as an example, the interaction p value was 0.01 for baseline obesity and BMI

change, and <0.001 for baseline obesity and quadratic BMI change. In Figure 3a, 1) by comparing the height of the two curves at x=0 (no change in BMI), we infer that the mean DASI score is higher for non-obese patients compared with obese patients, and 2) by analyzing the slope of the curves from x=0, we conclude that for patients who were obese at baseline, weight gain during BARI 2D was associated with declining DASI and weight loss was associated with improving DASI, whereas for patients who were not obese at baseline a positive or a negative change in BMI was associated with a decline in DASI. The estimation functions from multivariate models for BMI and health status are summarized and interpreted in Appendix A-3. In order to test whether the observed association between decreasing BMI and decreasing health status (DASI and Energy) among the non-obese patients could be explained by clinical events occurring during follow-up, the diagnosis of cancer and the occurrence of myocardial infarction, stroke, or subsequent procedures during follow-up were included as covariates in longitudinal models; however, the significance of the interaction terms and the estimated results from the multivariate models remained similar with additional control for these time-dependent confounders (Appendix A-4).

For self-rated health, increasing within-person BMI was linearly associated with lower averaged score, regardless of baseline obesity status (Figure 3c). The inverse association was statistically significant (p=0.02). Within-person BMI change was not significantly associated with perceived health distress in study participants.

DISCUSSION

Our study showed that for patients with both stable coronary heart disease and type 2 diabetes, both differences in BMI between patients as well as changes in BMI over time within a patient were important determinants of health status. Higher between-patient BMI associated with lower health status outcomes. Increment in BMI over time was associated with lower health status for all patients, while decrease in BMI over time was associated with better functional capacity and perceived energy outcomes for patients who were obese, but not necessarily for those who were non-obese at baseline. The associations were independent of the effects of demographic factors and obesity-associated morbidity.

To interpret the main finding of the study, we can use the following example: if we compared a non-obese patient with a mean follow-up BMI of 27 to an obese patient with a mean follow-up BMI of 37, the 10 unit difference in mean follow-up BMI resulted in a 2.7 point higher DASI, 3.2 point higher Energy, 3.2 point less health distress and 4.1 point higher self-rated health experienced by the non-obese patient. These differences were of clinical significance, as a 3 point difference for DASI, and a 5 point difference for other health status measures were considered clinically meaningful.[15,21] If we assumed constant height for participants during follow-up years, within-person BMI change could be corresponding to weight change during follow-up years. According to the study finding, weight gain was associated with poorer health status, while weight loss was associated with better functional capacity and perceived Energy for obese patients but not for non-obese patients at baseline.

Obesity was common among our study participants. The high prevalence may largely be due to the risk profile of patients with both heart disease and diabetes. At study entry, the mean age of participants was 62.3 years, and increase in BMI was expected as a result of the natural shift of body composition.[29] Although BARI 2D patients were counseled about weight loss and exercise, we still observed an increasing mean BMI over time. It was not unexpected, as diabetes treatment is known to be associated with weight gain.[30] BMI is a modifiable risk factor of morbidity, and lifestyle intervention programs often use percent weight change as a primary goal for overweight and obese patients. In the present study, one

unit reduction from individual mean follow-up BMI was significantly associated with a small increase in self-rated health for all participants, and a small increase in DASI and Energy for patients who were obese at baseline. Our results support that weight reduction is desirable for obese patients.

For patients who were not obese at baseline, either increase or decrease in within-person BMI was associated with decline in DASI and Energy. Normal weight individuals with metabolic abnormality have been shown to have a higher risk of cardiovascular risk; treatment strategies to attenuate adverse disease outcomes included diet, exercise and medication for insulin resistance.[31] Our results suggested weight reduction may not be the optimal strategy for such patients to achieve better functional capacity. As weight gain in adulthood was primarily resulted from increase in fat mass,[32] older individuals with weight loss were prone to nutritional deficiency and sarcopenia. [33] The decrease in the lean body mass of muscle and bone, which is essential to buffer the low caloric intake during acute illness and wasting in chronic conditions, can subsequently increase the risk of frailty and compromise the individual's ability to perform daily activities.[33] Our results showed that a stable BMI was associated with better functional capacity and perceived Energy outcomes for non-obese patients with heart disease and diabetes.

Due to the shift in body composition and adiposity, waist circumference is another effective measure of abdominal obesity. [34] BMI and waist circumference were highly correlated in the present study, and change in BMI had a stronger association than did waist circumference with health status outcomes. Considering that BMI was more sensitive to changes in health status, and waist circumference was more susceptible to measurement error, we selected BMI for the present study.

In the investigation of the longitudinal relationship between BMI and health status, we also examined the association between preceding health status and subsequent BMI using lagged variables. The relationship between preceding BMI and subsequent health status was stronger than that between preceding health status and subsequent BMI. Similar observations have been reported in the literature, as changes in BMI on health trajectories were more significant than changes in health status on BMI trajectory.[26] Thus, the use of a single direction model for the longitudinal association between BMI and health status outcomes seems to be appropriate.

As a limitation of the study, there is a concern that the occurrence of adverse clinical events during follow-up may have confounded the association between BMI and health status. For example, the diagnosis of cancer or the occurrence of a myocardial infarction or stroke during follow-up may have been related to a decline in both BMI and health status outcomes. The results with or without adjusting for these time-dependent factors were consistent, suggesting that the confounding by these adverse clinical events did not substantially alter the study results. However, it is possible that other clinical factors, not measured in this study, partially explain the observed association between a reduction in BMI and worsening DASI and Energy among non-obese participants. There is also concern about survivor effects; for example, whether participants available in the latter period of the study were likely to report better health status results. In the present study, the association between health status and BMI were similar at each follow-up time, indicating a minor survivor effect. In addition, the multivariate analysis includes terms for missing data patterns to adjust for non-random missing data within the structure of mixed model, and thus, the BMI estimates presented in this manuscript account for missing data.

Compared to previous research, the strength of the present study lies in the investigation of longitudinal relationship between BMI and health status outcomes, where the subtlety of

weight change dynamics over time are captured. This study suggests that BMI management for patients with both heart disease and type 2 diabetes can have a positive impact on health status.

CONCLUSION

For patients with both documented stable coronary heart disease and type 2 diabetes. Weight gain was associated with a decrease in health status outcomes. Weight reduction over time was associated with improvement in functional capacity and perceived energy outcomes for patients who were obese, but not necessarily for those who were non-obese at study entry. The associations were independent of clinical history, treatment and obesity-associated diseases.

Acknowledgments

Funding: The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) is funded by the National Heart, Lung and Blood Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, Nos. U01 HL061744, U01 HL061746, U01 HL061748, and U01 HL063804. Significant supplemental funding is provided by GlaxoSmithKline, Collegeville, PA, Bristol-Myers Squibb Medical Imaging, Inc., North Billerica, MA, Astellas Pharma US, Inc., Deerfield, IL, Merck & Co., Inc., Whitehouse Station, NJ, Abbott Laboratories, Inc., Abbott Park, IL, and Pfizer, Inc, New York, NY. Generous support is given by Abbott Laboratories Ltd., MediSense Products, Mississauga, Canada, Bayer Diagnostics, Tarrytown, NY, Becton, Dickinson and Company, Franklin Lakes, NJ, J. R. Carlson Labs, Arlington Hts., IL, Centocor, Inc., Malvern, PA, Eli Lilly and Company, Indianapolis, IN, LipoScience, Inc., Raleigh, NC, Merck Sante, Lyon, France, Novartis Pharmaceuticals Corporation, East Hanover, NJ, and Novo Nordisk, Inc. Princeton, NJ.

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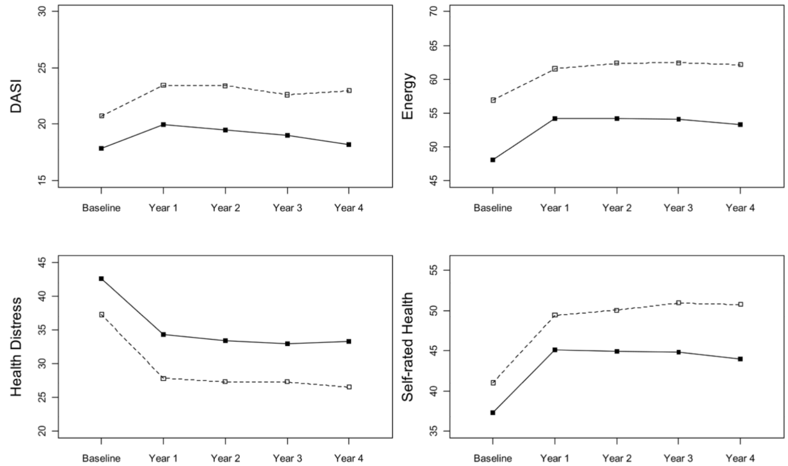

Figure 1.

Mean health status by baseline obesity status.

*Points indicate mean scores in each group. Obese (BMI ≥ 30) (solid symbol: ■ and solid line: ———); non-obese (BMI<30) (open symbols: □ and dashed line: -------).

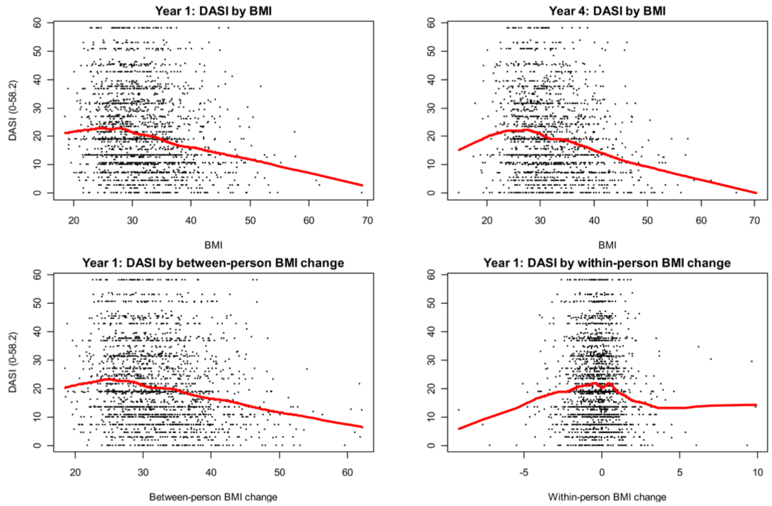

Figure 2.
Lowess smooth of DASI by BMI at year 1 and at year 4; DASI by between-person and within-person BMI change at year 1.

Figure 3a

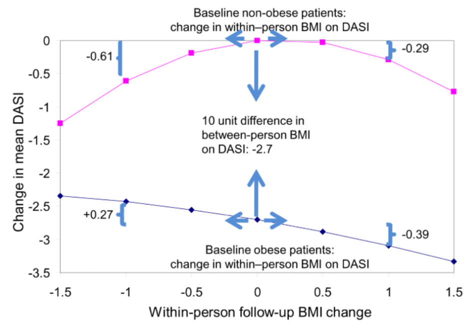

Figure 3b

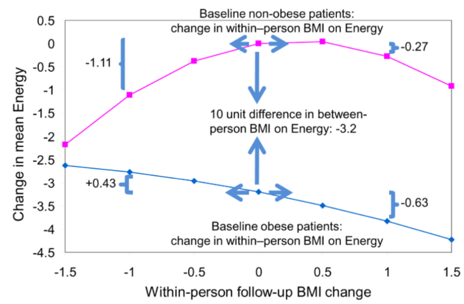

Figure 3c

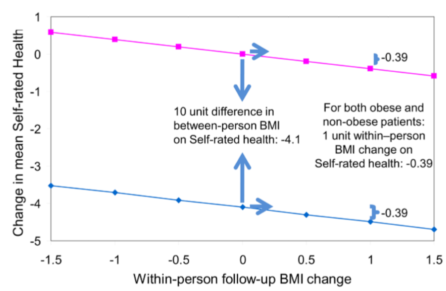

Figure 3.

Interpretation of averaged association of follow-up BMI and health status outcomes.

*Assume mean follow-up BMI is 35 for participant who were obese at baseline, and 25 for participants who were non-obese at baseline.

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Table 1

Baseline characteristics by BMI categories for the 2,163 BARI 2D participants included in the analysis.*

Characteristic	Under/normal (N=192)	Overweight (N=743)	Class 1 obesity (N=694)	Class 2/3 obesity (N=525)	p-value
Age at study entry, mean, SD	61.7, 8.3	63.3, 8.8	62.9, 8.6	60.1, 8.9	<0.001
Male, %	71.4	75.4	72.2	61.9	<0.001
Region of World, %					<0.001
USA	44.8	50.2	65.7	78.1	
Canada	14.6	18.6	15.9	12.0	
Mexico	12.0	6.1	1.2	0.8	
Brazil	26.0	21.7	14.0	6.9	
Czech Republic/Austria	2.6	3.5	3.3	2.3	
Race/Ethnicity, %					<0.001
White non Hispanic	52.1	65.3	69.5	68.4	
Black non Hispanic	13.5	14.0	17.3	20.0	
Hispanic	23.4	13.2	11.0	9.5	
Other non Hispanic	10.9	7.5	2.3	2.1	
Current cigarette smoking	17.7	12.7	11.2	10.9	0.026
Number of years smoked, mean, SD	29.0, 13.9	28.1, 14.1	27.4, 13.6	25.4, 14.3	0.002
Insulin use at baseline, %	18.2	22.7	28.5	36.6	<0.001
Duration of diabetes, mean, SD	10.8, 8.4	10.3, 8.5	10.3, 8.6	10.2, 8.7	0.38
Hemoglobin A1c %, mean, SD	7.8, 1.7	7.6, 1.6	7.6, 1.6	7.7, 1.6	>0.99
History of myocardial infarction, %	37.7	34.4	29.9	27.4	0.001
History of congestive heart failure, %	5.2	4.3	5.8	9.6	<0.001
Baseline angina categories					0.58
None/Angina equivalent only	38.7	38.0	43.2	37.9	
Stable CCS1/CCS2[†]	45.5	45.1	41.1	41.7	
Stable CCS3/CCS4/Unstable	15.7	17.0	15.7	20.4	
Clinical neuropathy (MNSI[‡] ≥ 2), %	47.9	48.5	51.7	51.6	0.18
Non-coronary artery disease, %	26.0	22.6	23.5	23.6	0.88

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Characteristic	Under/normal (N=192)	Overweight (N=743)	Class 1 obesity (N=694)	Class 2/3 obesity (N=525)	p-value
Stroke, %	9.9	9.6	9.7	9.2	0.76
Chronic renal dysfunction, %	0.5	2.0	3.2	4.6	<0.001

* 9 individuals excluded due to missing baseline BMI data.

† CCS: Canadian Cardiovascular Society Functional Classification of Angina.

‡ MNSI: Michigan Neuropathy Screening Instrument.

Table 2

Mean health status during follow-up by baseline and follow-up BMI categories.†

	Follow-up BMI categories*			
	Under/normal	**Overweight**	**Class 1 obesity**	**Class 2/3 obesity**
Distribution (Number of patients)				
Baseline BMI categories				
Under/normal (n=190)	**123**	64	3	0
Overweight (n=741)	63	**521**	155	2
Class 1 obesity (n=693)	0	119	**440**	134
Class 2/3 obesity (n=525)	0	3	63	**459**
DASI (0–58.2)				
Under/normal	**24.6**	21.2	9.7	N/A
Overweight	22.0	**23.6**	21.1	17.5
Class 1 obesity	N/A	20.6	**20.9**	18.9
Class 2/3 obesity	N/A	14.4	17.9	**16.6**
Energy (0–100)				
Under/normal	**63.8**	57.7	55.0	N/A
Overweight	67.2	**62.8**	56.1	60.4
Class 1 obesity	N/A	62.2	**56.3**	51.4
Class 2/3 obesity	N/A	58.8	59.3	**48.6**
Health distress (0(better)–100)				
Under/normal	**26.1**	30.1	28.6	N/A
Overweight	23.6	**26.1**	33.5	50.0
Class 1 obesity	N/A	24.7	**31.4**	35.8
Class 2/3 obesity	N/A	38.5	29.6	**39.3**
Self-rated health (0–100)				
Under/normal	**50.8**	44.6	45.8	N/A
Overweight	53.7	**50.9**	46.2	37.5
Class 1 obesity	N/A	49.6	**47.9**	41.9
Class 2/3 obesity	N/A	49.0	48.4	**40.0**

*Averaged BMI during follow-up years.

†9 individuals with missing baseline BMI, 5 with missing follow-up mean BMI.

Table 3

Adjusted association between obesity and health status outcomes (N=2,163).

Effect	DASI		Energy		Health distress		Self-rated health	
	Estimate	p	Estimate	p	Estimate	p	Estimate	p
One unit increase in mean follow-up BMI (Between-person BMI difference, β_{BS}BMI)	−0.27	<0.001	−0.32	<0.001	0.32	<0.001	−0.41	<0.001
Within a person, one unit difference in each follow-up BMI measure from mean follow-up BMI (Within-person BMI difference, β_{WS}BMI)					−0.027	0.88	−0.39	0.020
β_{WS}BMI for baseline obese patients	−0.33	<0.001	−0.53	<0.001				
Quadratic β_{WS}BMI for baseline obese patients	−0.058	0.034	−0.10	0.017				
β_{WS}BMI for baseline non-obese patients	0.16	0.36	0.42	0.13				
Quadratic β_{WS}BMI for baseline non- obese patients	−0.45	<0.001	−0.69	<0.001				
IS versus IP	0.52	0.18	−0.36	0.54	−0.44	0.51	0.80	0.21
REV versus MED	1.35	<0.001	1.34	0.022	−0.57	0.39	1.84	0.0042
CABG stratum	0.47	0.29	1.67	0.013	−1.96	0.011	3.15	<.0001
Follow-up year (continuous)	−0.61	<0.001	−0.19	0.19	−0.22	0.20	−0.094	0.56
Baseline health status measure	0.49	<0.001	0.42	<0.001	0.40	<0.001	0.38	<.0001
Baseline obesity (BMI ≥ 30)	0.57	0.30	1.10	0.19	−1.40	0.14	1.44	0.11

[1] P value for (1) quadratic within-person BMI change:<0.001 for DASI and <0.001 for Energy; (2) baseline obesity and within-person BMI change: 0.010 for DASI and 0.0034 for Energy; (3) baseline obesity and quadratic within-person BMI change:< 0.001 for DASI and 0.0012 for Energy.

[2] Models control for age, sex, race, geographic region, smoking, physical activity, angina, insulin use, history of hypertension, myocardial infarction, congestive heart failure, stroke, non-coronary artery disease, renal dysfunction, clinical neuropathy and missing data pattern.