JAMA Internal Medicine | Original Investigation

Risks of Myocardial Infarction, Death, and Diabetes in Identical Twin Pairs With Different Body Mass Indexes

Peter Nordström, PhD; Nancy L. Pedersen, PhD; Yngve Gustafson, PhD; Karl Michaëlsson, PhD; Anna Nordström, PhD

IMPORTANCE Observational studies have shown that obesity is a major risk factor for cardiovascular disease and death. The extent of genetic confounding in these associations is unclear.

OBJECTIVE To compare the risk of myocardial infarction (MI), type 2 diabetes, and death in monozygotic (MZ) twin pairs discordant for body mass index (BMI).

DESIGN, SETTING, AND PARTICIPANTS A cohort of 4046 MZ twin pairs with discordant BMIs (difference >0.01) was identified using the nationwide Swedish twin registry. The study was conducted from March 17, 1998, to January 16, 2003, with follow-up regarding incident outcomes until December 31, 2013.

MAIN OUTCOMES AND MEASURES The combined primary end point of death or MI and the secondary end point of incident diabetes were evaluated in heavier compared with leaner twins in a co-twin control analysis using multivariable conditional logistic regression.

RESULTS Mean (SD) baseline age for both cohorts was 57.6 (9.5) years (range, 41.9-91.8 years). During a mean follow-up period of 12.4 (2.5) years, 203 MIs (5.0%) and 550 deaths (13.6%) occurred among heavier twins (mean [SD] BMI, 25.9 [3.6] [calculated as weight in kilograms divided by height in meters squared]) compared with 209 MIs (5.2%) and 633 deaths (15.6%) among leaner twins (mean [SD] BMI, 23.9 [3.1]; combined multivariable adjusted odds ratio [OR], 0.75; 95% CI, 0.63-0.91). Even in twin pairs with BMI discordance of 7.0 or more (mean [SE], 9.3 [0.7]), where the heavier twin had a BMI of 30.0 or more (n = 65 pairs), the risk of MI or death was not greater in heavier twins (OR, 0.42; 95% CI, 0.15-1.18). In contrast, in the total cohort of twins, the risk of incident diabetes was greater in heavier twins (OR, 2.14; 95% CI, 1.61-2.84). Finally, increases in BMI since 30 years before baseline were not associated with the later risk of MI or death (OR, 0.97; 95% CI, 0.89-1.05) but were associated with the risk of incident diabetes (OR, 1.13; 95% CI, 1.01-1.26).

CONCLUSIONS AND RELEVANCE In MZ twin pairs, higher BMI was not associated with an increased risk of MI or death but was associated with the onset of diabetes. These results may suggest that lifestyle interventions to reduce obesity are more effective in decreasing the risk of diabetes than the risk of cardiovascular disease or death.

Invited Commentary

Supplemental content at jamainternalmedicine.com

Author Affiliations: Section of Geriatrics, Department of Community Medicine and Rehabilitation, Umeå University, Umeå, Sweden (P. Nordström, Gustafson); Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden (Pedersen); Section of Orthopedics, Department of Surgical Sciences, Uppsala University, Uppsala, Sweden (Michaëlsson); Public Health and Clinical Medicine, Occupational and Environmental Medicine, Umeå University, Umeå, Sweden (A. Nordström).

Corresponding Author: Peter Nordström, PhD, Section of Geriatrics, Department of Community Medicine and Rehabilitation, 90187 Umeå University, Umeå, Sweden (peter.nordstrom@germed.umu.se).

JAMA Intern Med. doi:10.1001/jamainternmed.2016.4104
Published online August 1, 2016.

During the past decades, the prevalence of overweight and obesity in the Western world has increased by 30% to 50%,[1,2] leading to what has been described as a global epidemic.[3] The significance of obesity involves the associated risks of diabetes, cardiovascular disease (CVD), stroke, and death.[4,5] High body mass index (BMI) contributed to a theoretically estimated 3.4 million deaths in 2010—an increase of 70% in 2 decades.[6,7] In contrast to these estimates, data suggest[8] that the rates of death and myocardial infarction (MI) are decreasing while the prevalence of obesity increases; this trend is not explained by preventive medicine alone.[9,10] These results are supported by other studies that suggest that the association between obesity and CVD and death are more complex. In a meta-analysis,[11] higher rates of death were observed in normal-weight individuals compared with overweight individuals, with normal weight referring to a BMI of 18.5 to 24.9 (calculated as weight in kilograms divided by height in meters squared) according to the World Health Organization definition.[7] A higher risk of death has also been observed in normal-weight patients with CVD[12,13] and patients with type 2 diabetes[14] than in overweight or obese individuals with these diseases.

Several explanations for this obesity paradox have been suggested, including selection bias.[15,16] Genetic confounding might be another important source of bias (ie, genetic factors shared by obesity and CVD may account for the association), as also indicated by previous studies.[17,18] Monozygotic (MZ) twins are genetically identical and provide a unique tool for the evaluation of the risk associated with obesity independent of genetic factors. This evaluation can be accomplished by comparing the risk of disease in twin pairs that are discordant for obesity. Any differences between the twin pairs with respect to the outcome of interest would then be independent of genetic predisposition. Accordingly, we used a cohort of BMI-discordant MZ twin pairs to estimate the effects of lifestyle-acquired high BMI on mortality and risk of MI. A secondary aim was to evaluate the risk of incident diabetes in this cohort.

Key Points

Question Does genetic confounding influence the association between obesity, diabetes, and cardiovascular disease?

Findings In this cohort study of monozygotic twin pairs with different body mass indexes, the heavier twin did not have a higher risk for myocardial infarction or death than the leaner twin. In contrast, the heavier twin had a lower risk of incident diabetes.

Meaning Lifestyle interventions to reduce obesity may be more effective in reducing the risk of diabetes than the risk of cardiovascular disease or death.

Methods

Study Population

The study cohort originated from the Swedish twin registry and the Screening Across Lifespan Twin (SALT) study,[19] conducted from 1998 to 2002 with the purpose of screening all twins in Sweden born before 1958 for common complex diseases. Information, including body weight and height, was collected using a computer-assisted telephone interview with up to 600 items; the study details have been described elsewhere.[19] In total, data from 44 820 twins were collected, with a response rate of 74%. In this cohort there were 4357 MZ twin pairs and 4102 MZ twin pairs in which both twins had reported weight and height for estimation of BMI. For the present study, we selected all MZ twin pairs (4046 pairs; 2283 female and 1763 male pairs) with discordant (difference >0.01) self-reported BMIs. To determine the impact of longitudinal changes in BMI before baseline, data were extended to include questionnaire information that was distributed in 1972-1973 in 3245 MZ twin pairs[20] that later were also included in the SALT study. The regional ethics board in the Umeå, Sweden, National Board of Health and Welfare and Statistics Sweden approved this study, and all participants provided written informed consent. The study was conducted from March 17, 1998, to January 16, 2003.

Selection of Diagnoses and Other Covariates of Interest

Diagnoses were collected from the National Patient Register (NPR) maintained by the National Board of Health and Welfare (http://www.socialstyrelsen.se). The NPR has covered all inpatient care in Sweden since 1987 and all outpatient specialist care since 2001. Diagnoses recorded between 1987 and December 31, 2013, were identified using appropriate *International Classification of Diseases, Ninth Revision* (*ICD-9*) and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) codes, including MI (*ICD-9* code, 410; *ICD-10*, I21), ischemic stroke (*ICD-9*, 434; *ICD-10*, I63 and I64), cancer (all diagnoses), diabetes (*ICD-9*, 250; *ICD-10*, E10 and E11), and alcohol abuse (*ICD-9*, 303; *ICD-D*, F10). The NPR has been validated, with positive predictive values of 85% to 95%.[21,22] Prescriptions for antidiabetic drugs could also be captured from the Swedish drug registry from 2005 and later, and information about death and causes thereof was collected from the National Causes of Death Register (http://www.socialstyrelsen.se). Data on each participant's social status, income, early disability pension, and educational level were retrieved from the Statistics Sweden (http://www.scb.se) database in the year before the SALT study. Civil status was classified as married, cohabitant, divorced, widow or widower, single, and living apart. Educational level was classified as elementary school only, 2 years of secondary high school, more than 2 years of secondary high school, and university education. Data on income, early disability pension, and educational level were missing for 0, 3, and 32 individuals in the MZ cohort, respectively. Information about marital status, birth order, birth weight, physical activity, and smoking habit was retrieved from SALT questionnaire data. Physical activity was classified as little or none, not a lot, or rather much or very much. Smoking habit was classified as never smoked, previous smoking, or currently smoking, and pack-years of smoking were estimated. In addition, we included questionnaire information reflecting unhealthy drinking habits and diabetes. Data on smoking, physical activity, birth weight,

Table 1. Baseline Characteristics of the Monozygotic Twin Cohort

Characteristic	Monozygotic Twin Pairs, No. (%) (n = 4046)		*P* Value
	Heavier Twin	Leaner Twin	
Age, mean (SD), y	57.6 (9.5)	57.6 (9.5)	.90
Social status			
Married	2607 (64.4)	2590 (64.0)	.08
Cohabitant	460 (11.4)	402 (9.9)	
Divorced	340 (8.4)	371 (9.2)	
Widow/widowed	232 (5.7)	264 (6.5)	
Single	353 (8.7)	378 (9.3)	
Living apart	54 (1.3)	41 (1.0)	
Weight, mean (SD), kg	75.1 (13.4)	69.3 (12.4)	<.001
Birthweight, mean (SD), g	2435 (624)	2414 (624)	.27
Born first	1912 (47.3)	1935 (47.8)	.56
Height, mean (SD), cm	170 (9)	170 (9)	.16
BMI, mean (SD)	25.9 (3.6)	23.9 (3.1)	
Overweight, 25.0-29.9	1796 (44.4)	1153 (28.5)	<.001
Obese, ≥30.0	498 (12.3)	151 (3.7)	
BMI in 1972[a]	21.7 (2.8)	21.3 (2.6)	<.001
Changes in BMI from 1973, mean (SD)[a]	4.3 (2.9)	2.6 (2.6)	<.001
Smoking			
Never	1698 (42.0)	1628 (40.2)	<.001
Previous	1357 (33.5)	1188 (29.4)	
Current	619 (15.3)	841 (20.8)	
Physical activity			
Little or none	1059 (26.3)	917 (22.8)	<.001
Not a lot	1094 (27.2)	1081 (26.8)	
Rather much or very much	1870 (46.5)	2029 (50.4)	
Highest educational level			
Elementary school only	1183 (29.2)	1230 (30.4)	.24
2 y of secondary high school	1307 (32.3)	1247 (30.8)	
>2 y of secondary high school	439 (10.9)	479 (11.8)	
University	1097 (27.1)	1078 (26.6)	
Income, 1000th US$, mean (SD)[b]	17 (21)	17 (18)	.56
Disability pension	325 (8.0)	290 (7.2)	.14
Diagnoses at baseline			
Myocardial infarction	90 (2.2)	70 (1.7)	.11
Stroke	37 (0.9)	38 (0.9)	.91
Diabetes	198 (4.9)	169 (4.2)	.12
Cancer	335 (8.3)	331 (8.1)	.87
Alcohol abuse	303 (7.5)	283 (7.0)	.39

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] Data available on BMI in 1973 for both twins in 3245 twin pairs from the total cohort.

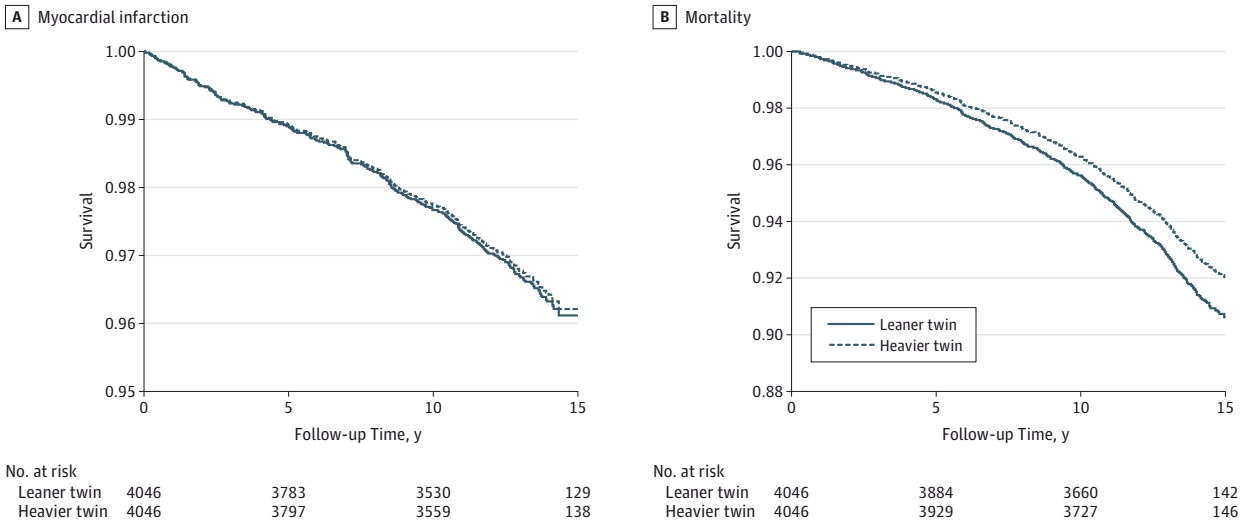
[b] $1 equals 8.47 Swedish krona.

and birth order were missing for 1108 (13.7%), 643 (7.9%), 3719 (46.0%), and 304 (3.8%) people, respectively, for the MZ cohort. All data were linked to cohort individuals using the unique personal identification numbers assigned to all Swedish citizens.

Statistical Analysis

Kaplan-Meier curves were constructed for twins with lower and higher BMIs from each pair, with the primary end point of incident MI or death. No imputations for missing data were performed, and only complete cases were analyzed. Conditional logistic regression analysis was used to compare the odds of any end point in the twin cohort. The first model was unadjusted (age- and sex-adjusted by design); the second model was adjusted for physical activity, never/past/current smoking, and pack-years of smoking; the third model was additionally adjusted for social status, income, educational level, disability pension, alcohol abuse, and birth order; and the final model was additionally adjusted for previous diagnoses (**Table 1**). To evaluate whether the risk of death or MI in the BMI-discordant twins was dependent on follow-up time, a flexible parametric model was used with time-dependent effects and 3 degrees of freedom.[23] To evaluate the association between BMI and the primary end point in the total cohort of MZ twins in a nonpairwise fashion, a Cox proportional hazards regression model with restricted cubic splines and 3 knots at de-

Figure 1. Risks of Myocardial Infarction and Death



Risks of myocardial infarction (A) and death (B) in twin pairs with higher vs lower body mass index with increasing follow-up time.

Table 2. Outcomes for Primary and Secondary End Points[a]

Characteristic	End Point, OR (95% CI)			
	MI or Death (n = 1438)	Death (n = 1183)	MI (n = 375)	Diabetes (n = 569)
Main exposure: heavier vs leaner co-twin	0.80 (0.69-0.93)	0.76 (0.65-0.89)	0.96 (0.78-1.20)	1.95 (1.58-2.42)
Adjusted for				
Smoking and physical activity	0.80 (0.68-0.95)	0.75 (0.62-0.90)	1.03 (0.79-1.35)	1.94 (1.51-2.48)
Social status, income, educational level, disability pension, alcohol abuse, and being born first in the twin pair	0.77 (0.64-0.92)	0.72 (0.59-0.88)	1.03 (0.76-1.38)	2.14 (1.62-2.84)
Previous MI, stroke, cancer, and diabetes	0.75 (0.63-0.91)	0.70 (0.56-0.86)	1.03 (0.76-1.42)	2.14 (1.61-2.84)

Abbreviations: MI, myocardial infarction; OR, odds ratio.

[a] Primary end point (MI or death) and the secondary end point of incident diabetes were evaluated in 4046 body mass index-discordant identical twin pairs using conditional logistic regression.

fault positions was used. $P < .05$ was considered significant, and all presented values are 2-sided. SPSS, version 22 (IBM) and Stata, version 12.1 (StataCorp LP) were used for the analyses. Incident outcomes were determined from March, 17, 2008, until December 31, 2013.

Results

Baseline Characteristics

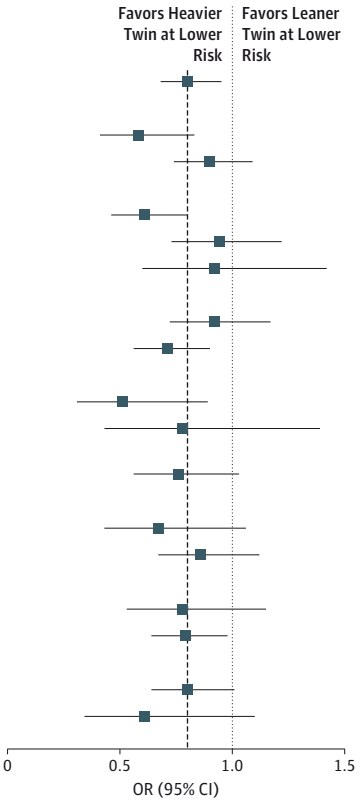
Both MZ twin cohorts had a mean (SD) age of 57.6 (9.5) years (range, 41.9-91.8 years) at baseline (date of the SALT study). Mean baseline BMI in twins with higher and lower BMI within each pair was 25.9 (3.6) and 23.9 (3.1), respectively (Table 1). Among twins with higher BMI, 1796 (44.4%) were overweight and 498 (12.3%) were obese compared with 1153 (28.5%) and 151 (3.7%), respectively, in twins with lower BMI. Twins with higher BMIs were less physically active and fewer were smokers (Table 1) compared with leaner twins from each pair. No other significant differences in baseline characteristics were detected. In a subcohort of 3245 twin pairs, the mean increase in BMI from 1972 until baseline was significantly greater in the heavier compared with the leaner twin (4.3 [2.9] vs 2.6 [2.6]; $P < .001$).

Risk of MI or Death

During a mean follow-up period of 12.4 (2.5) years, 203 MIs (5.0%) and 550 deaths (13.6%) occurred in the heavier twins compared with 209 MIs (5.2%) and 633 deaths (15.6%) in the leaner twins (**Figure 1**). In the fully adjusted model, the odds ratio (OR) for the combined primary end point of MI or death was 0.75 (95% CI, 0.63-0.91) in heavier compared with leaner twins (**Table 2**). The reduced probability of death or MI in heavier twins was most pronounced in a subgroup of those with BMIs of 24.9 or lower at baseline (OR, 0.61; 95% CI, 0.46-0.80) and similar when comparing heavier and leaner twins within the rest of the cohort (OR, 0.99; 95% CI, 0.75-1.31). The odds of death or MI were also not increased significantly in the heavier compared with leaner twins in other subgroups, such as nonsmokers and sedentary twins and in groups stratified on sex (**Figure 2**). In a subcohort of 3245 twin pairs for whom longitudinal data were available, the risk of death or MI was

Figure 2. Risk of Myocardial Infarction (MI) or Death

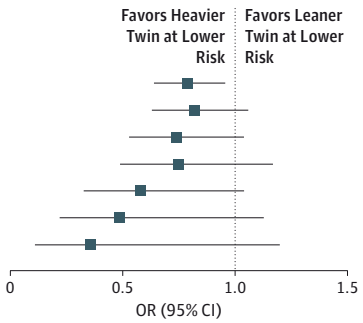
Subgroup	No. of MIs or Deaths (Rate/100 Person-years) Heavier Twin	Leaner Twin	OR (95% CI)
Overall	678 (1.34)	760 (1.52)	0.80 (0.68-0.95)
Age, y			
<56	88 (0.35)	130 (0.52)	0.58 (0.41-0.83)
≥56	590 (2.30)	630 (2.51)	0.90 (0.74-1.09)
BMI in heavier twin at baseline			
<25.0	245 (1.12)	302 (1.40)	0.61 (0.46-0.80)
25.0-29.9	325 (1.45)	351 (1.58)	0.94 (0.73-1.22)
≥30.0	108 (1.76)	107 (1.75)	0.92 (0.60-1.42)
Sex			
Male	351 (1.62)	376 (1.75)	0.92 (0.72-1.17)
Female	327 (1.14)	384 (1.36)	0.71 (0.56-0.90)
Physical activity			
Little or none	179 (1.40)	201 (1.86)	0.51 (0.29-0.89)
Not a lot	223 (1.68)	242 (1.87)	0.78 (0.43-1.39)
Rather much or very much	270 (1.16)	308 (1.23)	0.76 (0.56-1.03)
Smoking habits			
Current	118 (1.56)	207 (2.04)	0.67 (0.43-1.06)
Never	286 (1.33)	294 (1.45)	0.86 (0.67-1.12)
Educational level, y			
≥12	178 (0.92)	194 (1.00)	0.78 (0.53-1.15)
<12	487 (1.57)	557 (1.84)	0.79 (0.64-0.98)
Diagnoses at baseline			
No diagnoses	447 (1.11)	511 (1.25)	0.80 (0.64-1.01)
≥1 Diagnosis	231 (2.25)	249 (2.51)	0.61 (0.34-1.10)



Risks in 4046 monozygotic twin pairs, obtained by comparing those with higher and lower body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) in the total cohort and in specified subgroups. Odds ratios (ORs) and 95% CIs were adjusted for the influences of smoking habits and physical activity. The dashed line indicates the overall effect in the total sample.

Figure 3. Risk of Myocardial Infarction (MI) or Death

Difference in BMI Within Pairs (No.)	Heavier Twin Mean BMI	No. of MIs or Deaths (Rate/100 Person-years)	Leaner Twin Mean BMI	No. of MIs or Deaths (Rate/100 Person-years)	OR (95% CI)
≥1 (2673)	26.6	383 (1.15)	23.7	450 (1.38)	0.79 (0.64-0.96)
≥2 (1655)	27.5	266 (1.29)	23.7	311 (1.55)	0.82 (0.63-1.06)
≥3 (942)	28.4	161 (1.38)	23.6	201 (1.78)	0.74 (0.53-1.04)
≥4 (521)	29.5	87 (1.35)	23.6	117 (1.89)	0.75 (0.49-1.17)
≥5 (324)	30.5	52 (1.30)	23.7	71 (1.85)	0.58 (0.33-1.04)
≥6 (191)	31.5	35 (1.50)	23.8	49 (2.17)	0.49 (0.22-1.13)
≥7 (99)	32.4	20 (1.68)	23.6	25 (2.14)	0.36 (0.11-1.20)



Risks in 4046 monozygotic twin pairs based on body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) differences within pairs. Odds ratios (ORs) and 95% CIs were adjusted for smoking and physical activity.

similar in the heavier and leaner groups (OR, 0.85; 95% CI, 0.66-1.08) after adjustment for physical activity, smoking, and changes in BMI before baseline. Increases in BMI during approximately 30 years before baseline were not associated with the outcome in this model (OR, 0.97; 95% CI, 0.89-1.05). Next, we analyzed the difference in the risk of MI or death in twin pairs based on the extent of BMI dissimilarity in each pair (**Figure 3**). The risk of MI or death did not differ significantly in twin pairs with BMI differences of 1.0 to 7.0 or more before or after adjusting for current smoking habits and physical activity. Finally, 65 twin pairs with BMI differences of 7.0 or more (mean [SE], 9.3 [0.7]), in which the higher BMI was 30.0 or more (mean, 35.0 [SD, 3.9] [SE, 0.5]), were examined. In this subgroup, 10 MIs or deaths occurred during follow-up in heavier twins compared with 17 such events in leaner twins (unadjusted OR, 0.42; 95% CI, 0.15-1.18).

Risk of Incident Diabetes

During follow-up, 345 incident cases of diabetes occurred in the heavier twins compared with 224 cases in the leaner twins.

After adjustment for physical activity and smoking, the OR of incident diabetes was 1.94 (95% CI, 1.51- 2.48) in the heavier compared with leaner twins (Table 2). The risk of incident diabetes was increased in the heavier twins in most subgroups (eFigure 1 in the Supplement) and rose with increasing BMI dissimilarity within each pair (eFigure 2 in the Supplement). Accordingly, in pairs with BMI discordance of 3.0 or more, the ORs of incident diabetes in heavier twins compared with the ORs in leaner twins was greater than 5.0. In the subcohort of 3245 twin pairs for whom we had access to longitudinal data for BMI, the heavier twin had a higher risk of incident diabetes compared with the leaner twin (OR, 1.55; 95% CI, 1.10-2.19) after adjusting for physical activity, smoking, and changes in BMI from approximately 30 years before baseline. In addition, increases in BMI before baseline were associated with incident diabetes in this model (OR, 1.13; 95% CI, 1.01-1.26).

Sensitivity Analyses

The risk of death or MI in heavier compared with leaner twins was constant during follow-up (eFigure 3 in the Supplement). Thus, the exclusion of twins with less than 1 year of follow-up time did not change the odds of the primary end point (unadjusted OR, 0.80; 95% CI, 0.69-0.92). To evaluate a risk factor that should increase the risk of death and MI independent of genetic confounding, the risk of these outcomes was analyzed in twin pairs discordant for current smoking (n = 658). After adjustment for physical activity level, the twin who was smoking had an increased odds of death (OR, 2.48; 95% CI, 1.65-3.72) and MI (OR, 1.74; 95% CI, 1.04-2.91). In a subcohort and using conditional logistic regression, birth weight was not associated with the risk of death (OR, 0.79; 95% CI, 0.42-1.46 per 1-kg increase) or MI (OR, 0.83; 95% CI, 0.36-1.92).

In an ordinary nonpairwise cohort analysis of the total twin cohort (n = 8092), the association between BMI and the primary end point (death or MI) was j-shaped, with greater risks of death for individuals with low and high BMIs (eFigure 4 in the Supplement). In individuals with BMIs of 24.0 or higher (n = 4626), the risk of MI or death rose by approximately 5% per 1-unit increase in BMI (hazard ratio [HR], 1.05; 95% CI, 1.02-1.08); the rate of MI or death during follow-up was approximately 37% higher in obese individuals (BMI, ≥30.0: HR, 1.37; 95% CI, 1.12-1.69) than in normal-weight individuals (BMI, 18.5-24.9) after adjustment for age, current smoking, and physical activity. The MZ twin cohort analyzed in the present study was similar in characteristics compared with all citizens aged 50 to 70 years living in Sweden on December 31, 2005 (eTable in the Supplement).

Discussion

In the present study, the twin in each pair with the higher BMI at baseline did not have a higher risk of later death or MI than the leaner twin in any of the analyses performed. In contrast, the risk of diabetes was significantly increased in heavier twins. The results also showed that changes in BMI approximately 30 years before baseline were not associated with the risk of MI or death but were associated with the risk of diabetes. The increased risk of diabetes in the heavier twin was also significantly different than the risk associated with MI or death. Together, the results may indicate that interventions performed to promote weight loss are more effective to reduce the incidence of diabetes than to reduce the risk of CVD and death.

Because MZ twin pairs have identical genomes, differences in BMI in the present cohort were the result of environmental and lifestyle factors. Results from a subcohort also indicate that the differences in BMI between the heavier and leaner twins resulted from lifestyle factors in midlife since there were only small differences in BMI approximately 30 years before baseline. Our results show that the risk of death or MI was lower in heavier than in leaner twins overall after taking all available covariates into account. Subgroup analyses indicated that this lower risk was attributable to effects in the subgroup with baseline BMIs of 24.9 or lower (ie, in those with normal BMIs according to the World Health Organization's definition). Explanations could include residual confounding from unknown diseases or general frailty[24] not captured at baseline in leaner twins. Such influences could also result in a decrease in BMI before the baseline assessments and is one explanation put forward to explain the obesity paradox.[16] In the present study, adjustment for changes in BMI before baseline did not influence the risk of MI or mortality when we compared the heavier and leaner twins. Furthermore, when twins with low or normal BMI at baseline were excluded, the odds of MI or death were not higher in subgroups in which the heavier twin was overweight or obese. The results also remained consistent with increasing BMI dissimilarity in twin pairs, including a subgroup in which all high-BMI twins were obese (mean BMI, 35.0). The results of the present study suggest that lifestyle-obtained higher BMI with no genetic contribution, including direct genetic effects and gene-environment interactions, is not causally related to an increased risk of CVD or mortality.

Based on previous research, the importance of obesity in the development of type 2 diabetes appears to be indisputable. In particular, studies[25] have demonstrated that clinical and laboratory factors are improved or resolved in most patients with type 2 diabetes after bariatric surgery, which often results in a more than 50% weight loss in the first 2 postoperative years.[26] In the present study, the risk of incident diabetes during follow-up was increased markedly in heavier twins compared with leaner twins. This risk also increased in heavier compared with leaner twins with increasing BMI dissimilarity. Higher increases in BMI before baseline also contributed to a higher risk of diabetes independently of baseline BMI. These results suggest a causal link between obesity and the risk of diabetes, independent of genetic influence.

One randomized clinical trial[27] was conducted to evaluate intensive lifestyle interventions with the primary goal of assessing mortality rates after weight loss. A total of 5145 overweight or obese (mean BMI) patients with type 2 diabetes were assigned to an intervention program focusing on weight reduction through caloric restriction and increased physical activity or to a control group. Participants in the intervention group achieved a 9% weight loss during the first year, which was reduced to 6% after 10 years. During the mean follow-up

period of approximately 10 years, the intervention had no significant effect on mortality. The authors'[27] proposed possible explanations for the lack of effect included insufficient weight loss in the intervention group and the consequences of more effective routine medical management of CVD in the control group. Based on the findings of our twin study, the intervention could also have been ineffective due to the primary focus on weight loss.

Several limitations of the present study should be considered. Weight and height were self-reported, but a previous evaluation[28] of data from the twin registry concluded that the use of BMI based on self-reported data would probably not affect the results. Furthermore, in the nonpaired analysis of the twin cohort (ie, without accounting for genetic effects), the j-shaped pattern between self-reported BMI and the risk of MI or death replicates the findings from previous observational studies.[11] In addition, self-reported BMI was linked to the development of diabetes in the present study. Baseline differences in BMI between twins were the result of a combination of environmental and lifestyle factors; thus, no conclusion can be made regarding interventions that may have beneficial effects other than weight loss, such as physical activity.[29] The effects of specific treatment regimens for obesity were not likely captured in the study cohort, including bariatric surgery, for which observational studies[30] also suggest favorable long-term effects on mortality. There was no information about waist circumference, which has been found to be associated with visceral obesity[31] and more strongly related to CVD than BMI.[32] We also lacked information about some potential confounders, such as hypertension and hyperlipidemia. Given that these conditions are related to both obesity and CVD, adjustments would, if anything, reduce the relative risk of CVD and death in the leaner twins. Effective treatment of hypertension and hyperlipidemia could contribute to the similar risk of CVD or death in the twins with higher BMI. Finally, the results demonstrating increased risk of diabetes, but not CVD or death, in the heavier twin with an increasing BMI difference between twin pairs should be interpreted with caution given the relatively small sample sizes.

The strengths of the present study include the unique design used to evaluate causal effects of obesity on disease and death after adjusting for genetic influences and the large cohort of MZ twins with information on multiple covariates. Because MZ twins share familial environmental factors,[33] there is a decreased likelihood of shared environmental confounding in the co-twin analyses. Finally, studies[34] in twins have shown that cumulative risks of late-onset diseases and death do not differ in twins compared with singletons. Characteristics of the present twin cohort were similar to those of the total Swedish population aged 50 to 70 years, suggesting that our results may be valid for the general older population.

Conclusions

The present study was not able to verify that obesity is causally associated with an increased risk of MI or death after consideration of genetic factors. In contrast, the results revealed a significant association between obesity and diabetes after accounting for genetic factors. The association between obesity and diabetes was significantly stronger than the association with CVD and death. This finding may indicate that interventions to promote weight loss are more effective in reducing the risk of diabetes than the risk of CVD and mortality.

ARTICLE INFORMATION

Accepted for Publication: April 28, 2016.

Published Online: August 1, 2016. doi:10.1001/jamainternmed.2016.4104.

Author Contributions: Drs Michaëlsson and A. Nordström contributed equally to the study. Dr P. Nordström had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: P. Nordström, Michaëlsson, A. Nordström.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: P. Nordström, A. Nordström.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: P. Nordström, Michaëlsson, A. Nordström.
Obtained funding: A. Nordström.
Administrative, technical, or material support: P. Nordström, Pedersen, Gustafson, A. Nordström.

Conflict of Interest Disclosures: None reported.

REFERENCES

1. Finucane MM, Stevens GA, Cowan MJ, et al; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Body Mass Index). National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet*. 2011;377(9765):557-567.

2. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2014;384(9945):766-781.

3. Popkin BM, Adair LS, Ng SW. Global nutrition transition and the pandemic of obesity in developing countries. *Nutr Rev*. 2012;70(1):3-21.

4. Pischon T, Boeing H, Hoffmann K, et al. General and abdominal adiposity and risk of death in Europe. *N Engl J Med*. 2008;359(20):2105-2120.

5. Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA*. 2003;289(1):76-79.

6. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2224-2260.

7. Obesity: preventing and managing the global epidemic: report of a WHO consultation. *World Health Organ Tech Rep Ser*. 2000;894:i-xii, 1-253.

8. Schmidt M, Jacobsen JB, Lash TL, Bøtker HE, Sørensen HT. 25 Year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. *BMJ*. 2012;344:e356.

9. Kesteloot H, Sans S, Kromhout D. Dynamics of cardiovascular and all-cause mortality in Western and Eastern Europe between 1970 and 2000. *Eur Heart J*. 2006;27(1):107-113.

10. Odden MC, Pletcher MJ, Coxson PG, et al. Cost-effectiveness and population impact of statins for primary prevention in adults aged 75 years or older in the United States. *Ann Intern Med*. 2015;162(8):533-541.

11. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA*. 2013;309(1):71-82.

12. Gruberg L, Weissman NJ, Waksman R, et al. The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention: the obesity paradox? *J Am Coll Cardiol*. 2002;39(4):578-584.

13. Romero-Corral A, Montori VM, Somers VK, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery

disease: a systematic review of cohort studies. *Lancet*. 2006;368(9536):666-678.

14. Tobias DK, Pan A, Jackson CL, et al. Body-mass index and mortality among adults with incident type 2 diabetes. *N Engl J Med*. 2014;370(3):233-244.

15. Banack HR, Kaufman JS. The "obesity paradox" explained. *Epidemiology*. 2013;24(3):461-462.

16. Strandberg TE, Strandberg AY, Salomaa VV, et al. Explaining the obesity paradox: cardiovascular risk, weight change, and mortality during long-term follow-up in men. *Eur Heart J*. 2009;30(14):1720-1727.

17. Song C, Chang Z, Magnusson PK, Ingelsson E, Pedersen NL. Genetic factors may play a prominent role in the development of coronary heart disease dependent on important environmental factors. *J Intern Med*. 2014;275(6):631-639.

18. Carlsson S, Andersson T, de Faire U, Lichtenstein P, Michaëlsson K, Ahlbom A. Body mass index and mortality: is the association explained by genetic factors? *Epidemiology*. 2011;22(1):98-103.

19. Lichtenstein P, De Faire U, Floderus B, Svartengren M, Svedberg P, Pedersen NL. The Swedish Twin Registry: a unique resource for clinical, epidemiological and genetic studies. *J Intern Med*. 2002;252(3):184-205.

20. Medlund P, Cederlöf R, Flodérus-Myrhed B, Friberg L, Sörensen S. A new Swedish twin registry containing environmental and medical baseline data from about 14,000 same-sexed pairs born 1926-58. *Acta Med Scand Suppl*. 1976;600:1-111.

21. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health*. 2011;11:450.

22. Köster M, Asplund K, Johansson Å, Stegmayr B. Refinement of Swedish administrative registers to monitor stroke events on the national level. *Neuroepidemiology*. 2013;40(4):240-246.

23. Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Stat Med*. 2002;21(15):2175-2197.

24. Fried LP, Tangen CM, Walston J, et al; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146-M156.

25. Buchwald H, Estok R, Fahrbach K, et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med*. 2009;122(3):248-256.e5.

26. Sjöström CD, Lissner L, Wedel H, Sjöström L. Reduction in incidence of diabetes, hypertension and lipid disturbances after intentional weight loss induced by bariatric surgery: the SOS Intervention Study. *Obes Res*. 1999;7(5):477-484.

27. Wing RR, Bolin P, Brancati FL, et al; Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med*. 2013;369(2):145-154.

28. Dahl AK, Hassing LB, Fransson EI, Pedersen NL. Agreement between self-reported and measured height, weight and body mass index in old age—a longitudinal study with 20 years of follow-up. *Age Ageing*. 2010;39(4):445-451.

29. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. *CMAJ*. 2006;174(6):801-809.

30. Sjöström L, Narbro K, Sjöström CD, et al; Swedish Obese Subjects Study. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med*. 2007;357(8):741-752.

31. Gradmark AM, Rydh A, Renström F, et al. Computed tomography–based validation of abdominal adiposity measurements from ultrasonography, dual-energy X-ray absorptiometry and anthropometry. *Br J Nutr*. 2010;104(4):582-588.

32. Yusuf S, Hawken S, Ounpuu S, et al; INTERHEART Study Investigators. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet*. 2005;366(9497):1640-1649.

33. Felson J. What can we learn from twin studies? a comprehensive evaluation of the equal environments assumption. *Soc Sci Res*. 2014;43:184-199.

34. Öberg S, Cnattingius S, Sandin S, Lichtenstein P, Morley R, Iliadou AN. Twinship influence on morbidity and mortality across the lifespan. *Int J Epidemiol*. 2012;41(4):1002-1009.