Mortality Risk by Body Weight and Weight Change in People With NIDDM

The WHO Multinational Study of Vascular Disease in Diabetes

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OBJECTIVE — Care guidelines for people with non-insulin-dependent diabetes mellitus (NIDDM) emphasize the importance of weight loss in reducing mortality risk. However, existing evidence regarding the relationship between weight and mortality and the effects of weight change is conflicting. We examined these relationships in the World Health Organization Multinational Study of Vascular Disease in Diabetes.

RESEARCH DESIGN AND METHODS — This was a cohort study of 1,416 men and 1,544 women. Baseline examinations were performed in 1975 through 1977, a morbidity follow-up was performed in 1983, and a mortality follow-up continued until 1988. Data were analyzed according to geographical groups: Europeans, East Asians, and Native Americans. The relationship between weight change and mortality was analyzed for Europeans only.

RESULTS — Generally, body mass index (BMI) was positively associated with age, blood pressure, and cholesterol but was negatively associated with duration of diabetes, prevalence of retinopathy, and use of insulin. There was no clear relationship between BMI and mortality across the geographical groups. In Europeans, weight loss in the leanest subjects at baseline (BMI < 26 kg/m^2) was associated with a threefold increase in mortality risk compared with those who had maintained a steady weight (relative risk [RR] 3.05, 95% confidence interval [CI] 1.26–7.36). Only in the most obese group was weight loss associated with a reduction in mortality risk (BMI > 29 kg/m^2, RR 0.84, 95% CI 0.40–1.74).

CONCLUSIONS — The positive association of BMI with age, blood pressure, and cholesterol and the negative association with duration of diabetes, retinopathy, and use of insulin may explain why there is no strong relationship between BMI and mortality in NIDDM. Weight loss, particularly in the relatively lean diabetic person, may be associated with an increased mortality risk.

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BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; ECG, electrocardiogram; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes; RR, relative risk; UGDP, University Group Diabetes Project; WHO MSVDD, World Health Organization Multinational Study of Vascular Disease in Diabetes.

There is a well-documented excess mortality in people with non-insulin-dependent diabetes mellitus (NIDDM) compared with the general population (1,2). Deaths from cardiovascular disease (CVD) account for a large proportion of this excess. A major challenge in diabetes management is reducing unfavorable risk factors to ameliorate the high rates of cardiovascular morbidity and mortality.

The reasons for the increased risk of CVD in people with NIDDM are not entirely clear, but obesity is one modifiable cardiovascular risk factor that is far more prevalent in those individuals with NIDDM than in the general population (3). A consensus statement from the American Diabetes Association has identified weight loss as one of the key interventions that should be promoted to reduce the high rates of CVD in people with NIDDM (4). Efforts to encourage weight loss in people with NIDDM should, however, be supported by scientific evidence that clearly shows that obesity is predictive of increased mortality risk and that weight loss is associated with a reduction in that risk.

But even in the general population, there is a lack of consensus as to the role of weight in determining mortality risk, and evidence of the effects of weight loss on mortality risk is even less clear (5). However, findings in the general population may not necessarily be applicable to people with diabetes because risk factor relationships are known not to be the same (1,6). Few studies have examined the relationship between body weight and mortality in people with diabetes, and again, those that have examined the relationship produced conflicting findings (7–10). These inconsistencies may be due to the choice of a biased sample, inadequate study power, and incomplete adjustment for confounders; when adequate account is taken of confounders, body mass index (BMI) does not appear to be an independent risk factor for mortality (7).

Resolution of this question has important implications for the health education advice given to people with diabetes. We therefore examined the relationship between both body weight and weight change with mortality in a large multinational cohort study of people with NIDDM.

RESEARCH DESIGN AND METHODS

— The data used for these analyses were collected for the World Health Organization Multinational Study of Vascular Disease in Diabetes (WHO MSVDD). A brief description of the methods used for this study follows; fuller details have been published elsewhere (11).

Fourteen centers took part in the original cross-sectional study. Of these, 10 centers also participated fully in a mortality follow-up, and 9 of these will be considered further. These centers were divided into three geographical groups: European, which included the London, Switzerland, Berlin, Warsaw, and Zagreb centers; East Asian, which included the Hong Kong and Tokyo centers; and Native American, which included the Arizona and Oklahoma centers. These groups were chosen to ensure within-group homogeneity in BMI and mortality risks. All participants were aged between 35 and 55 years at baseline, and a random, stratified sampling technique from a list of all clinic attenders in a 1-year period was used in as many centers as possible to ensure that participants were representative of people with diabetes. Some centers departed from this sampling technique and used population-based registers (Switzerland, Arizona, and Oklahoma). Insulin-dependent diabetes mellitus (IDDM) was defined as that which required treatment with insulin within 1 year of diagnosis. The remainder of the patients were then classified as having NIDDM.

Investigations

The majority of baseline investigations were completed between 1975 and 1977. Participants completed a questionnaire that included items on medical history and health-related behaviors. Resting blood pressure was measured once using a standard mercury sphygmomanometer. Height and weight were recorded without shoes and outdoor clothing. Pupils were dilated and funduscopy was performed by trained investigators, comparing the lesions they observed with a set of standard photographs. The findings from the most severely affected eye were used in the analyses. A 12-lead electrocardiogram (ECG) was performed and coded according to the Minnesota code (12). Nonfasting blood samples were taken for estimation of total cholesterol and measured centrally (U.S. Public Health Service Centers for Disease Control and Prevention, Atlanta, GA). Two of the centers (Berlin and Warsaw) performed cholesterol estimations locally. Fasting plasma glucose estimations were performed in seven of the centers (Arizona, London, Oklahoma, Switzerland, Tokyo, Warsaw, and Berlin) that were also involved in the mortality follow-up.

Mortality follow-up

Mortality follow-up continued until 1 January 1988 (1 January 1983 for Hong Kong) and was 95% complete. Information from death certificates, hospital records, and postmortem records was used.

Morbidity follow-up

All patients who were alive on 1 January 1983 were invited to participate in the second morbidity follow-up, performed between 1983 and 1988. Height and weight were again measured using the original protocol.

Statistical analysis

BMI, calculated as weight (in kilograms) divided by the square of the height (in meters), was used as a marker of obesity. The distribution of BMI for each geographical group was divided into approximate tertiles. Analyses were repeated using sex-specific categories of BMI within each geographical group; the results were qualitatively similar to those presented here. Mean age-adjusted continuous variables were calculated by tertile of BMI within each sex/geographical group by least-squares regression models, with the age variable held at its mean value. Prevalence rates were directly standardized to the age and, when relevant, to the duration of diabetes distribution of the whole study NIDDM population by geographical group.

Crude and adjusted mortality rates for all-cause mortality were examined by tertile of BMI using Poisson regression models. Analyses were repeated using proportional hazards models; the results were similar to those presented here. Only participants with complete data on mortality and associated variables (systolic blood pressure, age, duration of diabetes, serum cholesterol, smoking status [never, ex-smoker, current 1–14/day, current 15–24/day, and current ≥25/day], presence of retinopathy, and whether or not receiving insulin therapy) were used in these latter analyses. Smoking status was not included in the mortality analyses for East Asian women because the number of smokers was too small. All subjects with ECG evidence of a previous myocardial infarction (major q waves, i.e., Minnesota codes 1–1 and 1–2) and all deaths in the first year of follow-up were excluded from these analyses. This resulted in the exclusion of 24 and 51 participants, respectively. Both of these categories of participants may have already lost weight at the time of the baseline investigations due to illness, and their inclusion in the analyses may result in a falsely high estimation of mortality in the leanest groups. Analyses were performed using the SAS (SAS, Cary, NC) and EGRET (Epidemiological Resources, Seattle, WA) statistical packages (13,14). Analyses examining mortality by change in BMI were performed for the European group only because there were insufficient deaths in the other groups to provide meaningful results.

Table 1—*Age-adjusted and age-standardized values by BMI in Europeans with NIDDM*

	Tertile of BMI (kg/m^2)			
	<26	26 to <29	≥29	*P* value
Men				
n	319	235	210	—
Age (years)	46 ± 0.3	48 ± 0.4	48 ± 0.4	0.0003
Duration (years)	8 ± 0.3	7 ± 0.4	7 ± 0.4	0.002
Cholesterol (mg/dl)	233 ± 3	245 ± 4	241 ± 4	0.05
Systolic blood pressure (mmHg)	132 (130–135)	142 (140–146)	149 (144–154)	0.0001
Blood glucose (mmol/l)	8.6 ± 0.3	8.9 ± 0.3	9.2 ± 0.3	0.4
Current smokers (%)	42 ± 3	39 ± 3	41 ± 3	0.9
Any retinopathy (%)	30 ± 3	21 ± 3	23 ± 3	0.1
Insulin therapy (%)	31 ± 3	19 ± 3	15 ± 3	0.0001
Women				
n	195	176	331	—
Age (years)	47 ± 0.4	48 ± 0.4	48 ± 0.3	0.2
Duration (years)	9 ± 0.4	8 ± 0.4	7 ± 0.3	0.009
Cholesterol (mg/dl)	244 ± 5	242 ± 5	238 ± 4	0.6
Systolic blood pressure (mmHg)	140 (136–142)	148 (142–156)	152 (148–158)	0.0001
Blood glucose (mmol/l)	9.0 ± 0.4	8.9 ± 0.4	9.8 ± 0.3	0.1
Current smokers (%)	28 ± 3	18 ± 3	20 ± 3	0.02
Any retinopathy (%)	28 ± 3	23 ± 3	24 ± 3	0.8
Insulin therapy (%)	39 ± 4	31 ± 4	29 ± 4	0.03

Data are means ± SE of baseline variables and medians (95% CI for blood pressure). Data for cholesterol, systolic blood pressure, and blood glucose are age-adjusted. Values for current smokers and any retinopathy are age-standardized.

RESULTS— Baseline morbidity data were available for 1,416 men and 1,544 women. For both men and women, BMI was highest in Native Americans and lowest in East Asians. In men, age-adjusted mean BMI was 32.0 kg/m^2 in Oklahoma and 22.5 kg/m^2 in Tokyo. In women, mean age-adjusted BMI was 33.2 kg/m^2 in Oklahoma and 23.5 kg/m^2 in Tokyo.

Increasing BMI was positively associated with both age and systolic blood pressure in men and women for all geographical groups, except Native Americans for age and Native American men for blood pressure (Tables 1, 2, and 3). In contrast, the leanest subjects generally had had diabetes longer, were more likely to be receiving insulin therapy, and had a higher prevalence of any retinopathy than the most obese subjects. There was no clear relationship between BMI and smoking in the six sex/geographical groups.

Complete data on mortality and associated risk factors, including blood pressure, cholesterol, smoking, retinopathy status, and whether or not treated with insulin, were available for 1,298 men and 1,442 women. In total, there were 301 deaths of men and 243 deaths of women. Of these deaths, 53% (160) of men and 49% (118) of women were due to circulatory disease.

In the unadjusted analyses, increasing BMI was positively associated with mortality in European men, a U-shaped relationship was observed for Native American men and East Asian men and women, and an inverted U-shaped relationship was observed for European women and Native American men (Fig. 1). In all sex/geographical groups, raised blood pressure and cholesterol, smoking, treatment with insulin, and the presence of retinopathy were generally associated with an increased mortality risk. Adjustment for these variables did not qualitatively alter the relationship between BMI and mortality (Table 4), and interaction terms with smoking showed no consistent relationship between BMI and mortality. Additional analyses adjusting for plasma glucose in those participants who had this test performed also did not qualitatively alter these relationships. Similar relationships between BMI and mortality were observed when deaths from circulatory disease were examined.

Data on BMI for the baseline and follow-up morbidity examinations were available for 503 European men and 489 European women. The relationship between weight change and mortality varied by baseline measures of body weight (Table 5). Thus, weight loss in people who had a BMI of ≤29 kg/m^2 at baseline was associated with a two- to threefold increase in mortality risk compared with those who maintained their weight. In the most obese people at baseline (BMI >29 kg/m^2), weight loss was associated with a nonsignificant reduction in mortality

Table 2—*Age-adjusted and age-standardized values by BMI in Native Americans with NIDDM*

	Tertile of BMI (kg/m^2)			
	<29	29 to <34	≥34	*P* value
Men				
n	123	108	85	—
Age (years)	47 ± 0.5	47 ± 0.5	45 ± 0.6	0.004
Duration (years)	8 ± 0.5	6 ± 0.5	5 ± 0.6	0.004
Cholesterol (mg/dl)	212 ± 6	194 ± 7	205 ± 7	0.1
Systolic blood pressure (mmHg)	138 (130–144)	132 (130–138)	144 (134–152)	0.2
Blood glucose (mmol/l)	11.4 ± 0.4	10.3 ± 0.4	9.5 ± 0.5	0.007
Current smokers (%)	54 ± 5	48 ± 5	51 ± 5	0.2
Any retinopathy (%)	41 ± 5	25 ± 4	18 ± 4	0.001
Insulin therapy (%)	20 ± 4	16 ± 4	7 ± 3	0.1
Women				
n	148	158	193	—
Age (years)	47 ± 0.5	47 ± 0.4	46 ± 0.4	0.1
Duration (years)	9 ± 0.5	8 ± 0.5	5 ± 0.4	0.0001
Cholesterol (mg/dl)	211 ± 5	207 ± 4	194 ± 4	0.01
Systolic blood pressure (mmHg)	126 (122–134)	132 (130–142)	142 (138–146)	0.002
Blood glucose (mmol/l)	12.0 ± 0.4	12.4 ± 0.4	11.5 ± 0.3	0.2
Current smokers (%)	31 ± 5	36 ± 5	28 ± 5	0.2
Any retinopathy (%)	35 ± 5	27 ± 4	17 ± 4	0.0001
Insulin therapy (%)	23 ± 4	28 ± 4	20 ± 3	0.4

Data are means ± SE of baseline variables and medians (95% CI for blood pressure). Data for cholesterol, systolic blood pressure, and blood glucose are age-adjusted. Data for current smokers and any retinopathy are age-standardized.

risk. Only in the most obese group at baseline was weight gain associated with an increase in mortality risk (1.74, 95% confidence interval [CI] 0.74–4.06).

CONCLUSIONS — The current emphasis on the importance of weight reduction in people with diabetes implies that there is a strong positive relationship between BMI and mortality risk. However, we find that BMI has no clear effect on mortality, even when adjusted for confounders such as smoking, insulin treatment, and the presence of retinopathy, or for variables that may be influenced by weight to increase mortality risk, such as blood pressure and cholesterol.

The distribution of predictors of mortality in these geographical groups by BMI may partially explain why there is no clear or consistent relationship between BMI and mortality. More obese subjects in each sex/geographical subgroup were generally older and had a higher systolic blood pressure; systolic blood pressure was 17 mmHg higher in the most obese European men compared with the leanest. These factors may act to increase mortality risk. However, these subjects generally had had diabetes for a shorter time, were less likely to be receiving insulin therapy, and had a lower prevalence of retinopathy than the leanest groups. These factors would tend to reduce mortality risk in more obese people. These conflicting relationships may, therefore, explain why we find little relationship between BMI and mortality.

There was little overlap in BMI distribution between the three geographical groups. Thus, BMIs that were found to be particularly protective in the East Asian group (22 to <25 kg/m^2) simply were not represented in the other two geographical groups.

The evidence that obesity confers an increased risk of mortality is conflicting, even in studies of nondiabetic populations. Some studies show an increase in mortality with increasing obesity (15–18), although this association may only be observed after several years of follow-up (19). Others, however, show no relationship (20,21) or one that is very weak (22,23). In some cases, obesity is thought to be protective and improve survival (24). Yet others suggest that there is a J- or U-shaped relationship between obesity and mortality (25–27). Studies examining the relationship between weight change and mortality are even more scarce and equally conflicting (5).

With the degree of conflict in studies of the general population, it is unsurprising that little is known about the association between obesity and mortality in people with NIDDM. It might be assumed that the association between risk factors and mortality should be the same for people with and without diabetes, but this is not the case. In a comparison of diabetic and nondiabetic subjects, both

Table 3—*Age-adjusted and age-standardized values by BMI in East Asians with NIDDM*

	Tertile of BMI (kg/m^2)			
	<22	22 to <25	≥25	*P* value
Men				
n	126	128	82	—
Age (years)	47 ± 0.5	48 ± 0.5	48 ± 0.6	0.3
Duration (years)	9 ± 0.5	8 ± 0.5	6 ± 0.6	0.004
Cholesterol (mg/dl)	192 ± 4	197 ± 4	201 ± 5	0.4
Systolic blood pressure (mmHg)	130 (122–132)	132 (130–138)	150 (140–144)	0.0001
Blood glucose (mmol/l)	8.8 ± 0.4	8.0 ± 0.4	8.7 ± 0.6	0.4
Current smokers (%)	57 ± 5	65 ± 5	52 ± 6	0.06
Any retinopathy (%)	48 ± 5	32 ± 4	27 ± 5	0.004
Insulin therapy (%)	23 ± 4	20 ± 4	13 ± 4	0.1
Women				
n	107	92	144	—
Age (years)	46 ± 0.6	49 ± 0.6	48 ± 0.5	0.04
Duration (years)	9 ± 0.5	7 ± 0.6	6 ± 0.4	0.0001
Cholesterol (mg/dl)	206 ± 5	198 ± 5	211 ± 4	0.2
Systolic blood pressure (mmHg)	124 (120–132)	136 (130–148)	140 (132–148)	0.009
Blood glucose (mmol/l)	8.8 ± 0.4	8.2 ± 0.4	9.6 ± 0.5	0.1
Current smokers (%)	15 ± 5	11 ± 5	18 ± 6	0.5
Any retinopathy (%)	42 ± 5	39 ± 4	30 ± 5	0.2
Insulin therapy (%)	32 ± 5	19 ± 5	9 ± 3	0.0001

Data are means ± SE of baseline variables and medians (95% CI for blood pressure). Data for cholesterol, systolic blood pressure, and blood glucose are age-adjusted. Data for current smokers and any retinopathy are age-standardized.

groups showed no association between obesity and all-cause mortality. However, only nondiabetic patients had an increased risk of death from ischemic heart disease with obesity; this relationship was not observed in those with diabetes (6). A cohort study of people with diabetes showed no association between BMI and mortality (7). In contrast, both the Rochester and University Group Diabetes Project (UGDP) studies showed that obese people with diabetes had a better survival experience than did nonobese subjects (8,9). In both male and female Pima Indians with diabetes, the lowest mortality risk was found in people with a BMI between 35 and 40 kg/m^2, with higher mortality rates being observed at BMIs above and below this level (10).

The waist-to-hip ratio, a marker of central obesity, has been associated with the insulin-resistance syndrome and with an increased risk of mortality (28,29). Unfortunately, no measurements of central obesity were taken in this study; however, geographical differences in body fat distribution and their differing relationships with insulin resistance may help to explain geographical differences in the relationship between obesity and mortality.

Findings of a worse survival experience in those who were relatively lean led some researchers to suggest that leaner people with NIDDM have an increased genetic burden and, therefore, a more severe form of disease and an increased likelihood of complications (30). The leanest participants generally had the highest prevalence of retinopathy and were more likely to be on insulin therapy. This confirms other findings that suggest that retinopathy is more commonly found in leaner subjects (31). An alternative explanation is that in this study, NIDDM was defined on clinical grounds only. Thus, the relatively lean subjects may include a proportion of people with IDDM, who may have a higher mortality risk than people with NIDDM. This is less likely in the Native American group, in which the prevalence of NIDDM is particularly high, but even in this group we do not find a consistent relationship between BMI and mortality.

Relatively lean people with NIDDM who lost weight had a threefold increase in mortality compared with those who maintained a steady weight. Only the most obese subjects appeared to derive some benefit in terms of reduction of mortality risk with weight loss. Weight gain was not associated with a significant increase in mortality. In studies of the general population, weight loss has been associated with both an increase in mortality (32–34) and a decrease in mortality (19), while other studies suggest that both weight loss and weight gain are associated with an increase in mortality (26,35–37). The Framingham study has highlighted the importance of weight cy-

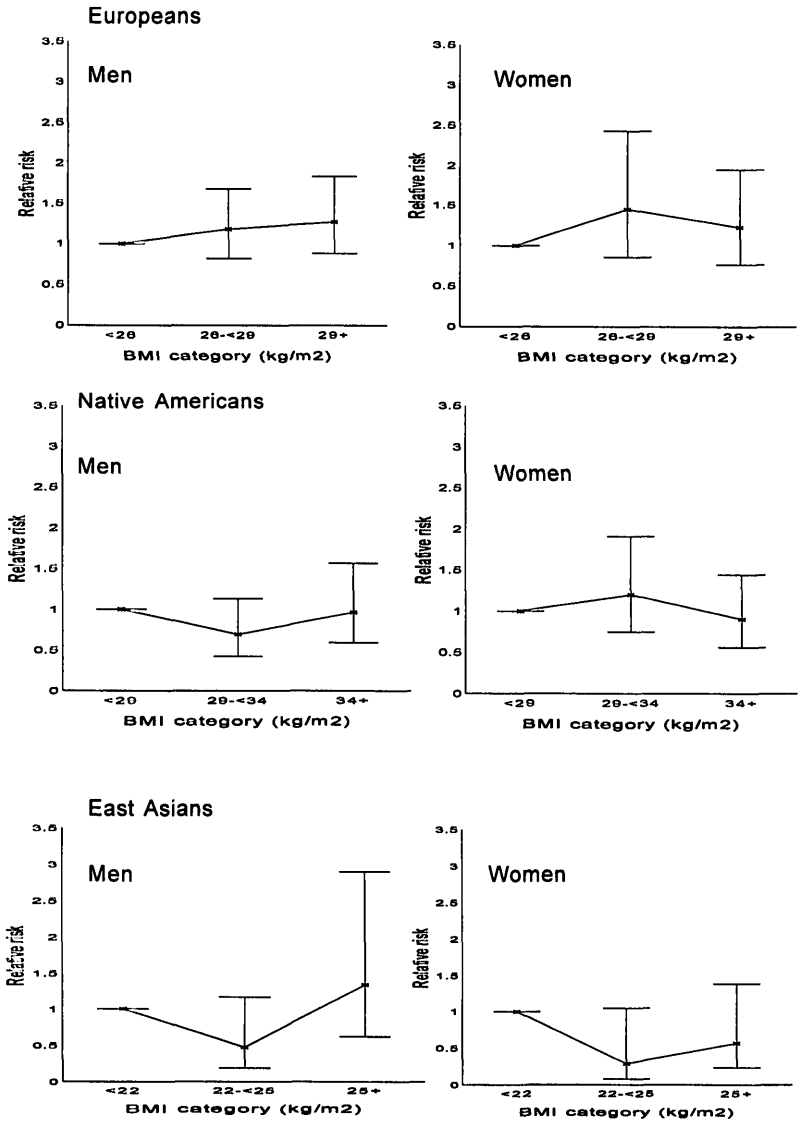

Figure 1—*RR and 95% CI of all-cause mortality in Europeans, Native Americans, and East Asians with NIDDM.*

cling (38). People who voluntarily lose weight tend to weight cycle, that is, their weight decreases as dieting is successful, increases as dieting is discontinued, and then decreases as dieting is resumed. These people were found to have particularly high mortality rates. This finding has important implications for care providers for people with diabetes: weight cycling is associated with a high mortality rate and commonly occurs in those wishing to lose weight. Thus, advising people with diabetes to lose weight may actually increase mortality risk. In this study, there are no data to indicate whether weight loss was voluntary or unintentional. However, a recent review found that the only report that compared the effects of voluntary and involuntary weight loss showed that mortality risks were equal for the two groups (5).

Weight loss in people with diabetes is thought to be desirable because it is assumed that weight loss will improve glycemic control, ameliorate symptoms of diabetes, reduce the need for medical treatment, and reduce the rate of complications. These beliefs are not always supported by existing evidence. An intervention study of obese subjects with impaired glucose tolerance did show that those who lost weight were less likely to develop diabetes than those who did not (39). However, others have shown that weight loss has no effect on the subsequent risk of diabetes (40). The UGDP intervention study of NIDDM subjects showed that, although the placebo group lost weight and glycemic control was significantly better in those treated with insulin, mortality was not different in any of the study groups (9). The Mälmo intervention study in impaired glucose-tolerant and NIDDM subjects also showed that weight loss improved glucose tolerance, but only detected a nonsignificant reduction in mortality in those who lost weight. A retrospective study of deceased diabetic patients suggested that weight loss was associated with improved survival, but the design of this study may have biased the outcome (5,41,42). Metabolic responses may explain why weight loss does not have spectacular effects on subsequent mortality. The fat cell shrinks when weight is lost, but body fat distribution remains largely unchanged. If body fat distribution is the more potent risk factor for mortality, this may explain why weight loss may not have a major impact on mortality (43).

We conclude that there is little evidence of a relationship between BMI and mortality in people with NIDDM. We do, however, show that Europeans with an initial BMI of <29 kg/m^2 who lost weight during the follow-up period had a significantly increased mortality risk compared with those whose weight remained the same. Only those in the most obese group (>29 kg/m^2) showed a mild reduction in mortality risk with weight loss. Although these numbers are small, these data provide little evidence to support the hypothesis that weight loss may enhance survival, except in the most obese subjects.

Table 4—*RRs for all deaths according to tertile of BMI by sex in NIDDM patients*

	BMI tertile			Likelihood ratio statistic	*P* value
	Leanest	Middle range	Most obese		
Europeans					
BMI (kg/m^2)	<26	26–<29	≥29	—	—
Men (*n* = 686)					
Deaths/total sample	62/282	59/211	53/188	—	—
RR (1)	1.00	1.06 (0.73–1.51)	1.17 (0.80–1.70)	60.7	<0.001
RR (2)	1.00	0.99 (0.68–1.45)	1.14 (0.77–1.67)	24.4	<0.001
Women (*n* = 640)					
Deaths/total sample	26/172	30/156	52/301	—	—
RR (1)	1.00	1.78 (1.04–3.03)*	1.62 (0.99–2.66)	30.6	<0.001
RR (2)	1.00	1.85 (1.08–3.17)*	1.63 (0.99–2.67)	31.9	<0.001
Native Americans					
BMI (kg/m^2)	<29	29–<34	≥34	—	—
Men (*n* = 312)					
Deaths/total sample	39/122	26/106	29/86	—	—
RR (1)	1.00	0.70 (0.43–1.16)	1.17 (0.71–1.92)	13.8	<0.001
RR (2)	1.00	0.75 (0.45–1.26)	1.22 (0.73–2.03)	7.4	0.3
Women (*n* = 494)					
Deaths/total sample	32/148	39/154	41/196	—	—
RR (1)	1.00	1.36 (0.85–2.18)	1.23 (0.75–2.02)	26.8	<0.001
RR (2)	1.00	1.32 (0.82–2.14)	1.34 (0.80–2.24)	20.5	0.002
East Asians					
BMI (kg/m^2)	<22	22–<25	≥25	—	—
Men (*n* = 309)					
Deaths/total sample	14/112	7/116	12/75	—	—
RR (1)	1.00	0.53 (0.21–1.32)	1.54 (0.70–3.40)	4.7	0.1
RR (2)	1.00	0.61 (0.24–1.57)	1.89 (0.80–4.45)	15.9	0.01
Women (*n* = 318)					
Deaths/total sample	11/92	3/86	9/137	—	—
RR (1)	1.00	0.27 (0.07–0.97)*	0.55 (0.22–1.37)	3.8	0.1
RR (2)	1.00	0.30 (0.08–1.10)	0.56 (0.22–1.42)	1.5	0.5

Data are relative risks (95% CI). RR (1) was adjusted for age and duration (likelihood ratio statistic on 2 df). RR (2) was adjusted for age, duration, systolic blood pressure, cholesterol, smoking, retinopathy, and insulin therapy (likelihood ratio statistic on 8 df). *$P < 0.05$.

Table 5—*All-cause mortality risks with change in BMI from initial BMI in Europeans with NIDDM*

	No change	Lost weight (>2 kg/m^2)	Gained weight (>2 kg/m^2)
Subjects (*n*)	581	252	159
Deaths (*n*)	35	52	14
Baseline tertile of BMI			
<26	1.00	3.05 (1.26–7.36)*	0.78 (0.23–2.67)
26 to <29	1.00	2.02 (1.00–4.08)	0.73 (0.23–2.67)
≥29	1.00	0.84 (0.40–1.74)	1.74 (0.74–4.06)

Data are relative risks (95% CI). * $P < 0.01$, comparing either weight loss or weight gain with no weight change in each initial tertile of BMI, adjusted for age, sex, and duration of diabetes.

Additional good-quality intervention studies of weight loss are required to provide clear scientific evidence of any benefit before further investment is made in persuading people with NIDDM to lose weight.

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References

1. Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 16:434–444, 1993
2. Klienman JC, Donahue RP, Harris MI, Finucane FF, Madans JH, Brock DB: Mortality among diabetics in a national sample. *Am J Epidemiol* 128:389–401, 1988
3. Knowler WC, Pettitt DJ, Savage PJ, Bennett PH: Diabetes incidence in Pima Indians: contributions of obesity and parental diabetes. *Am J Epidemiol* 113:144–156, 1981
4. Colwell JA, Franz MJ, Ginsberg H, Gwynne JT, Landsberg L, Lockwood D, Service FJ, Stern MP, Vinik AI, Weir GC: Role of cardiovascular risk factors in prevention and treatment of macrovascular disease in diabetes: consensus statement of the American Diabetes Association. *Diabetes Care* 12:573–579, 1989
5. Williamson DF, Pamuk ER: The association between weight loss and increased longevity. *Ann Intern Med* 7 (Suppl. 2): 731–736, 1993
6. Fitzgerald AP, Jarrett RJ: Are conventional risk factors for mortality relevant in type 2 diabetes? *Diabetic Med* 8:475–480, 1991
7. Knuiman MW, Welborn TA, Whittall DE: An analysis of excess mortality rates for persons with non-insulin-dependent diabetes mellitus in Western Australia using the Cox proportional hazards regression model. *Am J Epidemiol* 135:638–648, 1992
8. Ballard DJ, Melton LJ: Sources of disparity in incidence and prevalence studies of diabetic retinopathy: influence of selective survival on risk factor assessment.*Diabetes Care* 9:313–315, 1986
9. Knatterud GL, Klimt CR, Goldner MG, Hawkins BS, Weisenfeld S, Kreines K, Haddock L: Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. *Diabetes* 31:1–26, 1982
10. Pettitt DJ, Lisse JR, Knowler WC, Bennett PH: Mortality as a function of obesity and diabetes mellitus. *Am J Epidemiol* 115: 359–366, 1982
11. Jarrett RJ, Keen H, Grabauskas V: The WHO Multinational Study of Vascular Disease in Diabetes. I. General description. *Diabetes Care* 2:175–186, 1979
12. Rose GA, Blackburn H, Gillum RF, Prineas RJ: *Cardiovascular Survey Methods*. Geneva, World Health Organization, 1982
13. SAS: *User's Guide: Statistics. Version 6.03 Edition*. Cary, NC, SAS Inst., 1988
14. Epidemiological Resources: *EGRET: Epidemiological Graphics, Estimation and Testing*. Seattle, WA, Epidemiological Resources, 1991
15. Sonne-Holm S, Sorensen TI, Christensen U: Risk of early death in extremely overweight young men. *Br Med J* 287:795–797, 1983
16. Manson JE, Colditz GA, Stampfer MJ, Willett WC, Rosner B, Monson RR, Speizer FE, Hennekens CH: A prospective study of obesity and risk of coronary heart disease in women. *N Engl J Med* 322: 882–889, 1990
17. Bloom E, Reed D, Katsuhiko Y, MacLean C: Does obesity protect hypertensives against cardiovascular disease? *JAMA* 256:2972–2975, 1986
18. Shinton R, Shipley M, Rose G: Overweight and stroke. *J Epidemiol Community Health* 45:138–142, 1991
19. Hubert HB, Feinleib M, McNamara PM, Castelli WP: Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation* 67: 968–977, 1983
20. Multiple Risk Factor Intervention Trial Research Group: Relationship between baseline risk factors and coronary heart disease and total mortality in the Multiple Risk Factor Intervention Trial. *Prev Med* 15:254–273, 1986
21. Harris TB, Ballard-Barbasch R, Madans J, Makuc DM, Feldman JJ: Overweight, weight loss, and risk of coronary heart disease in older women. *Am J Epidemiol* 137:1318–1327, 1993
22. Fitzgerald AP, Jarrett RJ: Body weight and coronary heart disease mortality: an analysis in relation to age and smoking habit: 15 years follow-up data from the Whitehall Study. *Int J Obes* 16:119–123, 1992
23. Noppa H, Bengtsson C, Wedel H, Wilhelmsen L: Obesity in relation to morbidity and mortality from cardiovascular disease. *Am J Epidemiol* 111:682–692, 1980
24. Mattila K, Haavisto M, Rajala S: Body mass index and mortality in the elderly. *Br Med J* 292:867–868, 1986
25. Tuomilehto J, Salonen JT, Marti B, Jalkanen L, Puska P, Nissinen A, Wolf E: Body weight and risk of myocardial infarction and death in the adult population of eastern Finland. *Br Med J* 295:623–627, 1987
26. Lee IM, Paffenbarger RS: Changes in body weight and longevity. *JAMA* 268:2045–2049, 1992
27. Sorlie P, Gordon T, Kannel WB: Body build and mortality: the Framingham study. *JAMA* 243:1828–1831, 1980
28. Larsson B, Svardsudd K, Welin L, Wilhelmsen L, Bjorntorp P, Tibblin G: Abdominal adipose tissue, obesity and risk of cardiovascular disease and death: a 13-year follow-up of participants in the study of men born in 1913. *Br Med J* 288:1401–1404, 1984
29. McKeigue PM, Shah B, Marmot MG: Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. *Lancet* 337:382–386, 1991
30. Kobberling J: Studies on the genetic heterogeneity of diabetes mellitus. *Diabetologia* 7:46–49, 1971
31. Klein R, Klein BEK, Moss SE: The Wisconsin epidemiological study of diabetic

retinopathy: a review. *Diabetes Metab Rev* 5:559–570, 1989
32. Sidney S, Friedman GD, Siegelaub AB: Thinness and mortality. *Am J Public Health* 77:317–322, 1987
33. Harris T, Cook EF, Garrison R, Higgins M, Kannel W, Goldman L: Body mass index and mortality among nonsmoking older persons: the Framingham Heart Study. *JAMA* 259:1520–1524, 1988
34. Pamuk ER, Williamson DF, Madans J, Serdula MK, Kleinman JC, Byers T: Weight loss and mortality in a national cohort of adults, 1971–1987. *Am J Epidemiol* 136:686–697, 1992
35. Andres R, Muller DC, Sorkin JD: Long-term effects of change in body weight on all-cause mortality: a review. *Ann Intern Med* 119 (Suppl. 2):737–743, 1993
36. Rhoads GG, Kagan A: The relation of coronary disease, stroke, and mortality to weight in youth and in middle age. *Lancet* i:492–495, 1983
37. Avons P, Ducimetiere P, Rakotovao R: Weight and mortality. *Lancet* i:1104, 1983
38. Lissner L, Odell PM, D'Agostino RB, Stokes J, Kreger BE, Belanger AJ, Brownell KD: Variability of body weight and health outcomes in the Framingham population. *N Engl J Med* 324:1839–1844, 1991
39. Toeller M, Gries FA, Dannehl K: Natural history of glucose in obesity: a ten year observation. *Int J Obes* 6 (Suppl. 1):145–149, 1982
40. Modan M, Karasik A, Halkin H, Fuchs Z, Lusky A, Shitrit A, Modan B: Effect of past and concurrent body mass index on prevalence of glucose intolerance and type 2 (non-insulin-dependent) diabetes and on insulin response: the Israel study of glucose and tolerance, obesity and hypertension. *Diabetologia* 29:82–89, 1986
41. Lean MEJ, Powrie JK, Anderson AS, Garthwaite PH: Obesity, weight loss and prognosis in type 2 diabetes. *Diabetic Med* 7:228–233, 1990
42. Morris RW, Jarrett RJ: Weight loss and survival in type 2 diabetes. *Diabetic Med* 7:841, 1990
43. Kissebah AH, Evans DJ, Peiris A, Wilson CR: Endocrine characteristics in regional obesities: role of sex steroids. In *Metabolic Consequences of Human Obesities*. Vague J, Bjorntorp P, Guy-Grand B, Rebuffe-Scrive M, Vague P, Eds. Amsterdam, Elsevier, 1985, p. 115