Obesity and Overweight in Relation to Mortality in Men With and Without Type 2 Diabetes/Impaired Glucose Tolerance

The original Whitehall Study

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In studies of apparently healthy individuals, overweight and obesity, typically assessed using BMI, have been consistently associated with an increased risk of all-cause mortality, cardiovascular disease (CVD), and select cancers (1–4). However, extrapolating these results to individuals with type 2 diabetes is complex and perhaps inappropriate. Studies of the influence of obesity and overweight on mortality risk in individuals with type 2 diabetes reveal highly inconsistent findings. With all-cause mortality, obesity shows inverse (5,6), positive (7–10), null (11–16), and "J-" or "U-" shaped (17–19) associations; similarly discrepant results are apparent with coronary heart disease (CHD) (10,12,20,21). This discordance may be at least partially explained by methodological limitations in some studies, such as a modest sample size, a differential categorization of weight across studies, a tendency not to separate diabetes into its two main subtypes, and a failure to adjust for potentially important mediating and confounding variables. Using an extended follow-up of a U.K. prospective cohort study, we addressed this paucity of evidence and methodological shortcomings.

RESEARCH DESIGN AND METHODS

— In the Whitehall Study, data were collected on 19,019 male government employees aged 40–69 years when examined between 1967 and 1970, representing a 74% response (22). Height and weight were measured using standard protocols, and BMI was computed (weight [kg]/height^2 [m^2]) and categorized according to current guidelines (23): normal weight (18.5 to <25.0), over weight (25.0–29.99), and obesity (≥30.0 kg/m^2).

After an overnight fast, capillary blood samples were drawn 2 h after consumption of a glucose preparation equivalent to 50 g anhydrous dextrose, and blood glucose concentration was estimated using the ferricyanide reduction micromethod on an autoanalyzer (Technicon method N-9a) (22). Using categories previously utilized in the Whitehall Study (24–26), diabetes was defined as blood glucose ≥11.1 mmol/l (≥200 mg/100 ml) and/or a positive response to the questionnaire enquiry "Are you, or have you been, diabetic?" Impaired glucose tolerance (IGT) was defined as 5.4–11.0 mmol/l (96–199 mg/100 ml). All other men were denoted normoglycemic. We excluded 48 men who reported that their diabetes was controlled by insulin medication (type 1 diabetes) and 135 whose status could not be ascertained due to missing data.

Preliminary analyses showed that the weight-mortality gradient in men with IGT (n = 1,030) and in those with type 2 diabetes (n = 195) was very similar. That is, there was no suggestion that the all-cause weight-mortality relation differed between the IGT (hazard ratio [HR] per increase in weight category 1.12 [95% CI 1.00–1.25]) and diabetes group (1.19 [0.94–1.49], P = 0.64 for difference in gradient between groups). Similar results were apparent when CVD was the outcome of interest (P = 0.98). Therefore, we combined the IGT and type 2 diabetes groups, an approach we have taken elsewhere (26).

A total of 18,863 men (99.2% of participants in baseline survey) were traced using the National Health Service Central Registry until 30 September 2005. The present analyses are based on 18,360 individuals with complete data (679 men with missing continuous data had values imputed) (27). HRs and accompanying CIs were computed using Cox's proportional hazards regression model, with the follow-up period as the time scale (28).

RESULTS

— Relative to the normoglycemic group, there was an elevated risk of death from all-cause mortality (fully adjusted HR 1.26 [95% CI 1.18–1.35]), CVD (1.28 [1.17–1.41]), and, particularly, CHD (1.35 [1.20–1.50]) in men with diabetes/IGT. In examining the relation of BMI with mortality experience in men with diabetes/IGT (Table 1), the greatest age-adjusted risk of all-cause (1.61 [1.28–2.02]), CVD (1.92 [1.43–2.59]), and CHD (2.20 [1.57–3.14]) mortality was apparent in obese individuals. There was also an incremental effect across the weight groups ($P \leq 0.008$, for trend). Control for a range of confounding and mediating factors led to some attenuation of these gradients. Very similar overweight/obesity-mortality relations were seen in men without type 2 diabetes/IGT ($P \geq 0.45$, for interaction for gradients by diabetes status).

To explore the effect of unmeasured comorbidity at study induction, we related weight to mortality experience after

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Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease; IGT, impaired glucose tolerance.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Mortality rates and hazard ratios (95% CIs) for selected mortality outcomes in relation to obesity and overweight in men with and without type 2 diabetes/IGT in the original Whitehall Study*

	Normoglycemic (n = 17,135)				Diabetes /IGT (n = 1,225)				
Mortality outcome	Normal weight	Overweight	Obese	P for trend	Normal weight	Overweight	Obese	P for trend	P for interaction‖
n	9,398	7,038	699		568	562	95		
All causes*									
Deaths	6,367	5,169	570		454	453	88		
Mortality rate (age adjusted)†	29.7	31.0	37.2		35.9	35.3	56.8		
Age adjusted	1.0 (ref.)	1.07 (1.03–1.11)	1.43 (1.31–1.56)	<0.001	1.0 (ref.)	1.02 (0.89–1.16)	1.61 (1.28–2.02)	0.008	0.58
Confounder adjusted‡	1.0	1.09 (1.05–1.13)	1.42 (1.30–1.53)	<0.001	1.0	1.06 (0.93–1.21)	1.45 (1.15–1.82)	0.01	0.89
Multiple adjusted§	1.0	1.03 (0.99–1.07)	1.26 (1.16–1.38)	<0.001	1.0	0.99 (0.87–1.13)	1.29 (1.02–1.62)	0.20	0.94
CVD									
Deaths	2,844	2,604	314		225	240	54		
Mortality rate (age adjusted)	13.4	15.7	20.8		17.9	18.8	26.5		
Age adjusted	1.0	1.20 (1.14–1.26)	1.74 (1.55–1.95)	<0.001	1.0	1.08 (0.90–1.30)	1.92 (1.43–2.59)	0.001	0.91
Confounder adjusted	1.0	1.22 (1.15–1.28)	1.71 (1.52–1.92)	<0.001	1.0	1.13 (0.94–1.35)	1.79 (1.33–2.42)	0.001	0.98
Multiple adjusted	1.0	1.09 (1.03–1.15)	1.40 (1.25–1.58)	<0.001	1.0	1.02 (0.85–1.30)	1.53 (1.13–2.07)	0.05	0.85
CHD									
Deaths	1,756	1,670	205		142	167	41		
Mortality rate (age adjusted)	8.2	10.0	13.6		11.3	13.2	20.9		
Age adjusted	1.0	1.25 (1.17–1.33)	1.80 (1.56–2.08)	<0.001	1.0	1.19 (0.95–1.49)	2.20 (1.57–3.14)	<0.001	0.45
Confounder adjusted	1.0	1.26 (1.18–1.35)	1.76 (1.52–2.03)	<0.001	1.0	1.23 (0.99–1.54)	2.10 (1.48–2.97)	<0.001	0.47
Multiple adjusted	1.0	1.14 (1.06–1.22)	1.47 (1.27–1.71)	<0.001	1.0	1.12 (0.89–1.40)	1.83 (1.29–2.59)	0.006	0.38
All cancers									
Deaths	1,854	1,390	128		101	94	16		
Mortality rate (age adjusted)	8.4	8.2	8.3		8.0	7.4	8.6		
Age adjusted	1.0	1.00 (0.93–1.07)	1.10 (0.92–1.31)	0.67	1.0	0.95 (0.72–1.26)	1.28 (0.76–2.18)	0.72	0.82
Confounder adjusted	1.0	1.03 (0.96–1.10)	1.12 (0.94–1.34)	0.23	1.0	0.98 (0.74–1.30)	1.14 (0.67–1.94)	0.81	0.94
Multiple adjusted	1.0	1.02 (0.95–1.10)	1.11 (0.92–1.33)	0.34	1.0	0.98 (0.74–1.29)	1.11 (0.85–1.46)	0.88	0.90

*Forty-three men with unknown cause of death have been excluded from the cause-specific analyses. †Mortality rates are expressed per 1,000 person-years. ‡Confounder-adjusted model adjusted for age, employment grade, physical activity, smoking habit, marital status, disease at entry, and weight loss in the last year. §Multiple-adjusted model adjusted for all potential confounding variables (as above) plus blood pressure–lowering medication, height-adjusted forced expiratory volume in 1 s, systolic and diastolic blood pressure, and plasma cholesterol. ‖Tests of interaction to determine if the linear trend across BMI categories was the same in normoglycemic subjects and men with diabetes/IGT. Disease categories utilized were: deaths due to CVD (ICD8/9, 390–458; ICD10, I00-I99), CHD (ICD8/9, 410–414; ICD10, I20-I25), and all cancers (ICD-8, 140–208; ICD-9, 140–209; ICD-10, 140–208; C00-C97).

dropping data on deaths occurring within the first 10 years of mortality surveillance and after fitting interaction terms for the BMI categories with the logarithm of the follow-up time. In both cases, the weight-mortality relation was somewhat strengthened, particularly for non-CVD outcomes in the latter analyses.

CONCLUSIONS — In men with baseline diabetes/IGT, we found an elevated rate of all-cause, CVD, and CHD mortality in the obese and overweight groups. Our findings of a positive association between weight and all-cause mortality accords with some (6–10) if not all reports (5,6,11–16). (Note: The Verona Diabetes Study [6] found opposing weight-mortality gradients according to age-group [<65 years and ≥65 years].) Similarly, other investigators (10,12,20) have reported an elevated risk of CVD or CHD in men with higher BMI, as we did; again, however, this is not a universal finding (21). The strength of the BMI-mortality gradient was essentially the same in men without diabetes/IGT. We found no strong suggestion of a link between BMI and all cancers in the diabetes/IGT group—to our knowledge, the first time this relation has been examined.

Confounding and selection bias may plausibly explain the associations reported herein. However, we controlled for a range of variables, and loss to follow-up was very low. Study weaknesses should be considered. First, the assessment of obesity and overweight was based on BMI, a widely used index of overall adiposity but one that does not provide an indication of fat distribution. Second, because weight, confounders, and mediators may fluctuate over time, it is preferable to have more than a single baseline measurement. However, in a recent resurvey of surviving members of this cohort (29), there were too few deaths in those with diabetes/IGT to examine this issue.

In conclusion, this study found support for an elevated risk of mortality from all causes, CVD, and CHD in obese or overweight middle-aged men with and without diabetes/IGT at study induction. Overweight or obesity should therefore be avoided in both these groups.

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