

Burden and Rates of Treatment and Control of Cardiovascular Disease Risk Factors in Obesity

The Framingham Heart Study

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OBJECTIVE — Obesity is associated with an increased risk for cardiovascular disease (CVD). We sought to determine rates of treatment and control of CVD risk factors among normal weight, overweight, and obese individuals in a community-based cohort.

RESEARCH DESIGN AND METHODS — Participants free of CVD ($n = 6,801$; mean age 49 years; 54% women) from the Framingham Offspring and Third Generation cohorts who attended the seventh Offspring examination (1998–2001) or first Third Generation (2002–2005) examination were studied.

RESULTS — Obese participants with hypertension were more likely to receive antihypertensive treatment (62.3%) than normal weight (58.7%) or overweight (59.0%) individuals ($P = 0.002$), but no differences in hypertension control across BMI subgroups among participants with hypertension were observed (36.7% [normal weight], 37.3% [overweight], and 39.4% [obese]; $P = 0.48$). Rates of lipid-lowering treatment were higher among obese participants with elevated LDL cholesterol (39.5%) compared with normal weight (34.2%) or overweight (36.4%) participants ($P = 0.02$), but control rates among those with elevated LDL cholesterol did not differ across BMI categories (26.7% [normal weight], 26.0% [overweight], and 29.2% [obese]; $P = 0.11$). There were no differences in diabetes treatment among participants with diabetes across BMI groups (69.2% [normal weight], 50.0% [overweight], 55.0% [obese]; $P = 0.54$), but obese participants with diabetes were less likely to have fasting blood glucose <126 mg/dl (15.7%) compared with normal weight (30.4%) or overweight (20.7%) participants ($P = 0.02$).

CONCLUSIONS — These findings emphasize the suboptimal rates of treatment and control of CVD risk factors among overweight and obese individuals.

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Obesity affects more than one-third of the adult population in the U.S. Excess weight is associated with multiple cardiovascular disease (CVD) risk factors, including hypertension, dys-

lipidemia, diabetes, and the metabolic syndrome.

Although the incidence and mortality of CVD have declined markedly during the past decades, some studies suggested

that the increasing prevalence of obesity and diabetes may have slowed this rate of decline (1). In addition, recent data suggest that the prevalence of chronic kidney disease is increasing, in part because of the increasing rates of diabetes (2). Unfortunately, the efficacy of current therapies for obesity, including lifestyle and pharmacological interventions, is limited (3). Although bariatric surgery is an effective method of weight loss among severely obese individuals, eligibility criteria limit its use to only the most significantly affected patients.

Given the current limitations of effective weight loss therapies, minimizing the risk of complications of obesity and diabetes due to CVD risk factors is essential. Few studies have focused on a comprehensive approach to CVD risk factor burden, treatment, and control among obese individuals. Therefore, the aim of this study was to examine the burden of CVD risk factors as well as rates of treatment and control among normal weight, overweight, and obese individuals in an unselected population-based cohort. As abdominal fat accumulation is strongly associated with metabolic and CVD risk factors, and as recent guidelines have emphasized the importance of measuring waist circumference as part of clinical cardiovascular risk assessment, we also studied individuals with and without abdominal obesity.

RESEARCH DESIGN AND METHODS

— The Framingham Heart Study is a population-based prospective cohort study that commenced in 1948 and consisted of 5,209 men and women in the original cohort. In 1971, 5,124 men and women were enrolled into the Framingham Heart Study Offspring cohort, including the children of the original cohort and their spouses. Starting in 2002, 4,095 participants who had at least one parent in the Offspring cohort were enrolled into the Framingham Heart Third Generation Study. Approximately every 4 years Offspring participants underwent examinations; the de-

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sign and methodology of the Offspring and Third Generation cohort studies have been previously described (4,5).

For the current study, the study sample consisted of Offspring and Third Generation participants who attended the seventh (1998–2001) and first (2002–2005) examination cycle, respectively. Of 7,634 participants (3,539 Offspring and 4,095 Third Generation), we excluded those with prevalent CVD ($n = 463$), BMI $< 18.5 \text{ kg/m}^2$ or incomplete BMI data ($n = 196$), type I diabetes ($n = 15$), missing waist circumference values ($n = 105$), and missing covariate data ($n = 54$), resulting in 6,801 eligible participants.

The study protocol was approved by the institutional review boards of the Boston University Medical Center. All subjects provided written informed consent.

Measurements and definitions

Height and weight were measured directly using a standardized protocol. BMI was calculated by dividing weight in kilograms by the square of the height in meters. General obesity was defined according to the World Health Organization/National Institutes of Health classification scheme. Waist circumference was measured at the level of the umbilicus. Abdominal obesity was defined as a waist circumference $\geq 88 \text{ cm}$ (women) and 102 cm (men).

CVD risk factor assessment

Assessment of CVD risk factors (including fasting blood testing) was based on measurements obtained during a single examination. Hypertension was defined as systolic blood pressure of at least 140 mmHg or diastolic blood pressure of at least 90 mmHg (based on the average of two readings) or current use of antihypertensive medication. Serum cholesterol levels were measured in a fasting state. Participants with elevated LDL cholesterol levels according to their CVD risk level as classified by the National Cholesterol Education Program Adult Treatment Panel III algorithm or those receiving lipid-lowering agents were defined as having elevated LDL cholesterol levels. Type 2 diabetes was defined as a fasting blood glucose level of at least 126 mg/dl (7.0 mmol/l) or current use of insulin and/or hypoglycemic treatment for diabetes. High-performance liquid chromatography was used to measure H1C levels with an assay coefficient of variation of $< 2.5\%$.

Treatment and control of CVD risk factors

To determine rates of treatment, the number of participants receiving medication for each individual condition was divided by the number of all participants with the condition. Rates of control were determined by dividing the number of participants classified as having control by the total number of individuals with the condition. Control of hypertension was defined as either a blood pressure of $< 140/90 \text{ mmHg}$ or $130/80 \text{ mmHg}$ for participants with diabetes (6). Control of LDL cholesterol levels was determined using the participant's specified treatment goal according to the National Cholesterol Education Program Adult Treatment Panel III algorithm. Diabetes control rates were assessed by dividing the number of individuals with fasting blood glucose $< 126 \text{ mg/dl}$ by the number of all participants with diabetes. An A1C level of $< 7.0\%$ was also used to calculate rates of glycemic control in the Offspring cohort only.

Statistical analysis

Prevalence and rates of treatment and control of CVD risk factors were compared among individuals in the three BMI categories. For each risk factor, the age- and sex-adjusted proportion of participants with the condition who were treated and achieved control was calculated; 95% CIs were abstracted from the logistic regression models. In all analyses, the global P values were obtained from models using the generalized estimation equation (GEE) to account for familial correlation, except for analyses for which sample sizes were too small to permit the GEE. In this case, ANOVA P values were calculated. Low HDL cholesterol levels were defined as $< 50 \text{ mg/dl}$ (1.29 mmol/l) in women and $< 40 \text{ mg/dl}$ (1.03 mmol/l) in men or current use of lipid-lowering agents. Rates of dual control of hypertension and elevated LDL C levels and triple control of hypertension, elevated LDL C, and fasting blood glucose were calculated and compared across the three BMI categories.

The following secondary analyses were performed. Participants were stratified by abdominal obesity. In addition, general obesity was further categorized as stage I (BMI 30 to $< 35 \text{ kg/m}^2$) and stage II or higher (BMI $\geq 35 \text{ kg/m}^2$) obesity; the latter is indicated in the text simply as stage II obesity. Participants were also

stratified by age (< 50 years or ≥ 50 years) and sex.

Statistical analyses were performed using SAS statistical software (version 8; SAS Institute, Cary, NC). Two-tailed $P < 0.05$ and $P < 0.01$ were considered statistically significant for primary and secondary analyses, respectively.

RESULTS— Overall, 36.1% of the study participants (mean \pm SD age 49 ± 13 years; 54% women) were normal weight, 38.2% were overweight, and 25.7% were obese; 47.7% had abdominal obesity. The characteristics of the study participants are displayed in Table 1.

Hypertension

The prevalence of hypertension increased significantly with increasing BMI category ($P < 0.001$) (Table 2). Among those with hypertension, obese participants were more likely to be treated (62.3%) than normal weight (58.7%) or overweight (59.0%) participants ($P = 0.002$). However, control rates were uniformly poor and did not differ by BMI category (36.7% [normal weight], 37.3% [overweight], and 39.4% [obese]; $P = 0.48$).

Elevated LDL cholesterol

Elevated LDL cholesterol increased with increasing BMI categories ($P < 0.001$) (Table 2). Obese participants with elevated LDL cholesterol were more likely to be treated with lipid-lowering agents (39.5%) than normal weight (34.2%) or overweight (36.4%) participants ($P = 0.02$). LDL cholesterol was controlled in less than one-third of the participants, and rates of control did not differ by BMI category ($P = 0.11$).

Type 2 diabetes

Despite higher prevalence rates of diabetes with increasing BMI ($P < 0.001$) (Table 2), there were no differences in hypoglycemic treatment (69.2% [normal weight], 50.0% [overweight], and 55.0% [obese]; $P = 0.54$) or in the prevalence of optimal H1C levels across BMI categories in the Offspring cohort (50.0% [normal weight], 58.8% [overweight], and 47.7% [obese]; $P = 0.26$) among participants with diabetes. Obese participants were less likely to have fasting blood glucose $< 126 \text{ mg/dl}$ (15.7%) than normal weight (30.4%) or overweight (20.7%) participants ($P = 0.02$).

Table 1—Characteristics of study participants within different BMI categories

	BMI 18.5 to <25 kg/m ²	BMI 25 to <30 kg/m ²	BMI ≥30 kg/m ²	P value*
n	2,458	2,596	1,747	
Age (years)	46 ± 14	50 ± 13	51 ± 13	<0.001
Sex (% female)	1727 (70.3)	1093 (42.1)	866 (49.6)	<0.001
Systolic blood pressure (mmHg)	115 ± 16	122 ± 16	127 ± 16	<0.001
Diastolic blood pressure (mmHg)	71 ± 9	76 ± 9	79 ± 9	<0.001
Fasting blood glucose (mg/dl)	91 ± 12	98 ± 17	107 ± 29	<0.001
Total cholesterol (mg/dl)	187 ± 34	199 ± 37	198 ± 35	<0.001
LDL cholesterol (mg/dl)	107 ± 31	122 ± 32	120 ± 31	<0.001
HDL cholesterol (mg/dl)	61 ± 17	52 ± 15	48 ± 14	<0.001
Triglycerides, median (25/75 percentiles) (mg/dl)	78 (58/109)	109 (76/161)	131 (93/184)	<0.001
BMI (kg/m ²)	22.5 ± 1.6	27.3 ± 1.4	34.6 ± 4.5	<0.001
Waist circumference (cm)	82.6 ± 7.6	96.6 ± 7.2	113.7 ± 12.0	<0.001
Current smoker (%)	407 (16.6)	386 (14.9)	247 (14.1)	0.14

Data are means ± SD for continuous variables and n (%) for dichotomous variables. SI conversion factors: to convert glucose to millimoles per liter, multiply milligrams per deciliter values by 0.0555; to convert total, LDL, and HDL cholesterol to millimoles per liter, multiply milligrams per deciliter values by 0.0259; and to convert triglycerides to millimoles per liter, multiply milligrams per deciliter values by 0.0113. *Global GEE age- and sex-adjusted P value, except for age, which is sex adjusted, and sex, which is age adjusted.

Combinations of risk factors

The number of CVD risk factors among BMI categories is displayed in Fig. 1 of the online appendix (available at <http://dx.doi.org/10.2337/dc07-2413>); only 6.0% of obese participants had no CVD risk factors. Dual control of hypertension and elevated LDL cholesterol was uniformly low and did not differ by BMI category (19.1% [95% CI 12.6–27.0, normal weight], 12.1% [9.0–15.8, overweight], and 16.0% [12.7–19.8, obese]; $P = 0.94$). Rates of triple control of hypertension, LDL cholesterol, and diabetes were low and showed no differences by BMI category ($P = 0.15$): none of the normal weight participants with hypertension, elevated LDL cholesterol, and

diabetes ($n = 17$) achieved optimal triple control (0% [0–0]), and only 3 of 52 overweight participants (5.9% [1.2–16.2]) and 2 of 131 obese individuals achieved optimal triple control (1.6% [0.2–5.5]).

Secondary analyses

When results were stratified by abdominal obesity, findings were not materially different (Table 1 of the online appendix). In analyses stratified by age, among older participants, obese individuals with hypertension were more likely to receive antihypertensive treatment (74.1%) than those with normal weight (67.4%) and overweight (67.5%) ($P = 0.006$) (Table 2 of the online appendix), whereas hypertension

treatment rates among participants <50 years were uniformly lower and similar across BMI categories ($P = 0.26$). Age-stratified analyses of hypoglycemic treatment demonstrated that in participants aged <50 years, obese individuals with diabetes were less likely to receive treatment (39.3%) than overweight individuals with diabetes (50.0%) ($P = 0.006$) (Table 2 of the online appendix).

In sex-specific analyses, obese men were more likely to receive antihypertensive treatment (56.9%) than normal weight men (50.9%) or overweight men (53.5%) ($P = 0.006$) (Table 3 of the online appendix), whereas treatment rates among women were uniformly the same across BMI categories ($P = 0.15$). A sim-

Table 2—Age- and sex-adjusted rates of hypertension, elevated levels of LDL, and type 2 diabetes, as well as treatment and control, among BMI categories

	BMI 18.5 to <25 kg/m ²	BMI 25 to <30 kg/m ²	BMI ≥30 kg/m ²	P value*
n	2,458	2,596	1,747	
Hypertension				
Prevalence	11.5 (10.2–12.9)	22.8 (21.0–24.8)	37.6 (34.5–40.7)	<0.001
Treatment	58.7 (49.8–67.1)	59.0 (52.8–65.0)	62.3 (56.1–68.2)	0.002
Control	36.7 (30.3–43.5)	37.3 (32.7–41.9)	39.4 (34.9–44.0)	0.48
Elevated LDL cholesterol levels				
Prevalence	12.7 (11.3–14.2)	28.2 (26.2–30.4)	35.1 (32.2–38.2)	<0.001
Treatment	34.2 (28.2–40.6)	36.4 (32.3–40.6)	39.5 (34.9–44.4)	0.02
Control	26.7 (21.5–32.4)	26.0 (22.6–29.7)	29.2 (25.3–33.4)	0.11
Diabetes				
Prevalence	1.4 (0.9–1.9)	4.1 (3.4–5.0)	11.9 (10.3–13.6)	<0.001
Treatment	69.2 (38.6–90.9)	50.0 (35.2–64.8)	55.0 (44.7–65.0)	0.54
A1C <7.0%†	50.0 (18.7–81.3)	58.8 (40.7–75.4)	47.7 (35.3–59.4)	0.26
Fasting plasma glucose <126 mg/dl	30.4 (13.2–52.9)	20.7 (12.8–30.7)	15.7 (10.8–21.7)	0.02

Data are % of participants (95% CI). SI conversion factor: To convert fasting plasma glucose to millimoles per liter, multiply milligrams per deciliter values by 0.0555. *Global GEE P value. †Data available for Offspring cohort only.

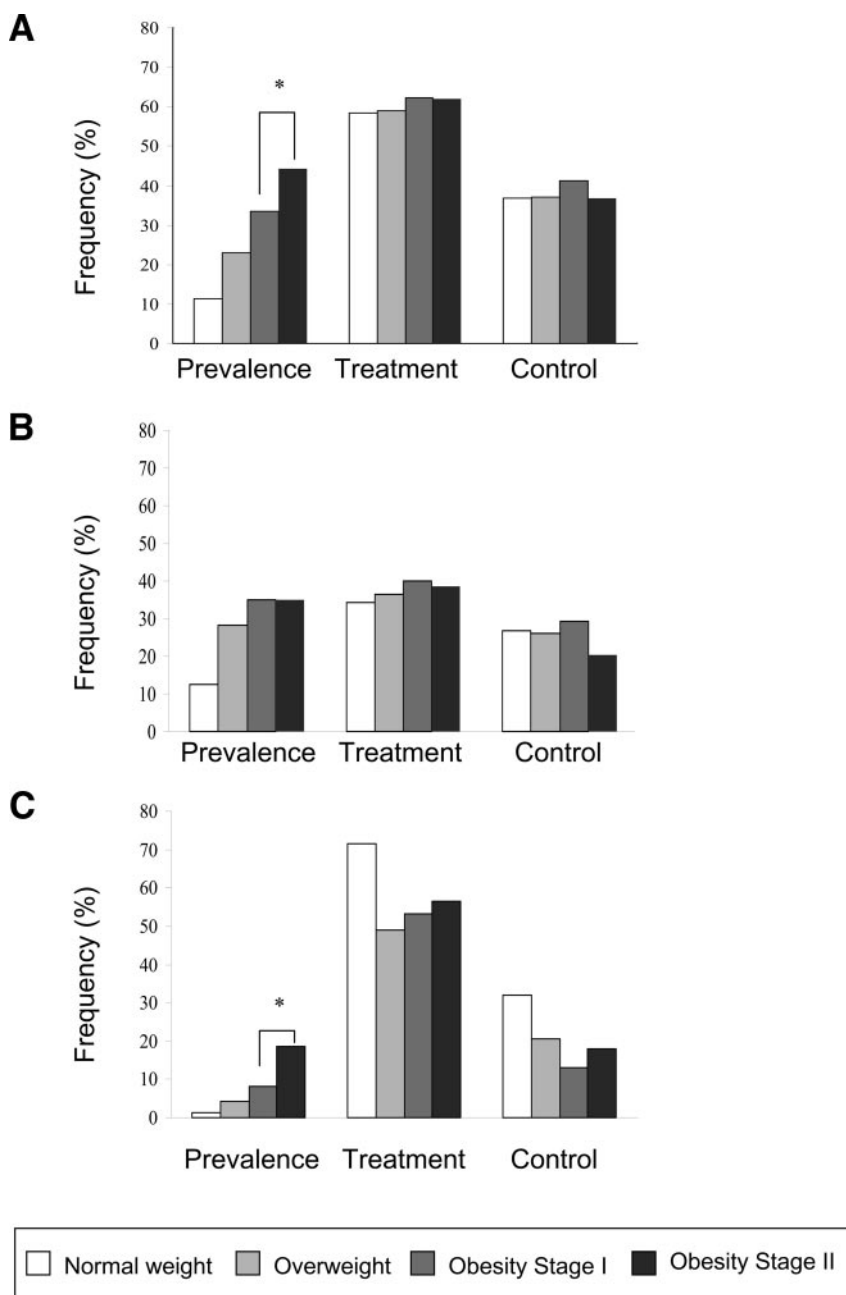


Figure 1—Prevalence and rates of treatment and control of hypertension (A), elevated levels of LDL cholesterol (B), and type 2 diabetes (C) among normal weight, overweight, stage I obese, and stage II obese participants. GEE P values represent stage I obesity versus stage II obesity adjusted for age and sex. * $P < 0.001$.

ilar pattern of sex differences was observed for lipid-lowering treatment and control of elevated LDL cholesterol (Table 3 of the online appendix). Sex-specific analyses of elevated glucose control demonstrated that among women, obese individuals with diabetes were less likely to have fasting blood glucose <126 mg/dl (12.8%) than normal weight (30.8%) or overweight (32.3%) individuals ($P < 0.001$) (Table 3 of the online appendix),

whereas the rates among men were uniformly the same across BMI categories.

When the obesity category was further broken down into stage I versus stage II obesity, no difference in treatment or control of hypertension (Fig. 1A), elevated LDL cholesterol (Fig. 1B), or diabetes (Fig. 1C) was observed despite a higher prevalence of hypertension and diabetes among participants with stage II obesity.

CONCLUSIONS

Principal findings

Despite the higher burden of CVD risk factors among participants with obesity from the Framingham Heart Study, rates of treatment and control of CVD risk factors are suboptimal among overweight and obese individuals. Among participants with obesity, only one in four with hypertension achieved recommended blood pressure levels, less than one-third with elevated LDL cholesterol had optimal control of these values, and only one in six participants with diabetes achieved fasting blood glucose <126 mg/dl. Dual and triple controls of CVD risk factors were uniformly poor across all BMI categories.

Hypertension

High blood pressure is associated with an increased risk of mortality and morbidity from stroke, coronary heart disease, and congestive heart failure (7) and is more frequent in obese individuals than in lean individuals (8). Obese participants were more likely to receive antihypertensive treatment but were not more likely to achieve control. Overall, potential reasons for poor blood pressure control may include unrecognized hypertension, poor adherence to a medication regimen (9), and failure to initiate or intensify therapy when indicated (10). In addition, the pathophysiology of obesity-related hypertension may differ from that of hypertension among nonobese individuals because of the presence of excess adipose tissue. Potential mechanisms that link adipose tissue to hypertension include alterations in the renin-angiotensin system, activation of the sympathetic nervous system, insulin resistance, sodium and volume retention, and renal dysfunction (11). These mechanisms may have important implications for the effectiveness of antihypertensive therapy in obese individuals. Clinical trial data have shown that β -blockers alone (12) or in combination with doxazosin (13) more effectively lower blood pressure in obese than in lean hypertensive individuals. Clinical trials have consistently shown that ACE inhibitors and angiotensin receptor blockers are associated with reductions in the risk of new-onset type 2 diabetes (14), and there is growing evidence that drugs blocking the renin-angiotensin system may be beneficial in the management of hypertension in obese individuals (15). Current treatment guidelines do not pro-

vide specific recommendations for obese individuals regarding blood pressure targets and a particular treatment. This may be due to lack of randomized clinical trials that have focused specifically on this question.

Elevated LDL cholesterol

Obese participants with elevated LDL cholesterol were more likely to receive lipid-lowering therapy, but rates of control of LDL cholesterol among affected individuals did not differ across BMI categories. Among all participants with elevated LDL cholesterol, levels were well controlled in less than one-third.

High levels of LDL cholesterol are an important modifiable risk factor in the development of CVD. Many primary and secondary prevention trials have demonstrated the efficacy and safety of statins in reducing CVD risk. Therefore, it is surprising that LDL control was so poor among obese participants. There are several potential reasons for this result. The current National Cholesterol Education Program guidelines do not specifically target obesity as a high-risk condition warranting lower LDL targets for lipid lowering. In addition, few clinical trials have studied the efficacy of statins on intermediate markers of CVD in BMI subgroups to demonstrate increased benefit among obese individuals compared with nonobese individuals or consistent effects across subgroups. Lastly, clinical trials studying the efficacy of statins on cardiovascular outcomes in BMI subgroups are lacking.

Type 2 diabetes

The prevalence of diabetes has increased substantially over the last several decades (16), likely due to increases in obesity, and the prevalence of obesity among individuals with diabetes increased by 50% between 1970 and 1989 (17). Rates of CVD associated with type 2 diabetes are high (18), and recent increases in chronic kidney disease may be due in part to increases in obesity and diabetes (2).

Despite this, we observed similarly low rates of treatment and control of A1C levels across BMI subgroups. There may be several potential reasons for the observed poor glycemic control. First, diabetes may be unrecognized and therefore untreated. Second, clinical trial data demonstrating CVD event reduction in the setting of optimal glycemic control is lacking. However, improved blood glucose control reduces the risk of chronic

kidney disease and diabetic retinopathy (19). Third, patients may not be complying with treatment regimens, including diet and exercise recommendations. Undesirable side effects due to antidiabetic agents, in particular weight gain in the setting of insulin treatment, may limit treatment adherence as well. Last, clinical trials suggest that diabetes is more difficult to control among obese individuals (20).

We have shown that material differences in treatment of diabetes do not exist across BMI categories and that obese individuals are less likely to achieve optimal fasting blood glucose levels. The majority of diabetes occurs in obese individuals. Our results highlight the vast numbers of cases of untreated and uncontrolled diabetes in this subgroup.

Control of combinations of risk factors

Rates of dual and triple control of CVD risk factors were uniformly poor across BMI categories in our study sample. Clustering of metabolic abnormalities contributes cumulatively to CVD risk and complicates treatment (21). These data emphasize the importance of a treatment regimen aimed to control multiple risk factors.

Clinical implications and future research

The suboptimal rates of diabetes treatment and control of CVD risk factors in obese participants in the current study are of particular concern, given the increasing rates of overweight and obesity among U.S. adults. Without substantial improvements in CVD risk factor treatment and control rates among obese individuals, the medical and financial burden of CVD events may grow substantially in the next several decades. There is a paucity of clinical trial data specifically testing interventions in obese subgroups to determine whether more intensive risk factor management or obesity-specific treatment and control guidelines would result in decreased CVD outcomes. Additionally, there is a need for more effective pharmacotherapy for obesity.

Strengths and limitations

Strengths of our study include the examination of a large, population-based sample of women and men with a broad age spectrum and standardized assessment of anthropometric measures and CVD risk factors and treatment. Several limitations

should be acknowledged. We used guidelines for treatment that were not necessarily in place at the time of data collection. However, the aim of current study was to characterize the burden of CVD risk factors using the most contemporary data available. The data collection period spanned from 1998 to 2005, and rates of treatment or control of CVD risk factors may have changed during this period. Participants in the Offspring cohort were followed for several years and may have benefited with respect to risk factor reduction, as the findings of each examination were reviewed and letters were sent to the physician. However, our rates of treatment and control of CVD risk factors are similar to data from national surveys (22), suggesting that the rates of treatment and control mirror national data. Further, the data in the present study from the Third Generation cohort represent their first examination, minimizing this concern. The Framingham Heart Study Offspring and Third Generation cohort participants are primarily white; therefore the generalizability of our findings to other racial groups may be limited. Lastly, we did not examine the reasons for low rates of treatment and control.

In summary, rates of treatment and control of CVD risk factors are suboptimal among overweight and obese individuals in the Framingham Heart Study.

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