Increasing Cardiovascular Disease Burden Due to Diabetes Mellitus

The Framingham Heart Study

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Background—Marked reductions in cardiovascular disease (CVD) morbidity and mortality have occurred in the United States over the last 50 years. We tested the hypothesis that the relative burden of CVD attributable to diabetes mellitus (DM) has increased over the past 5 decades.

Methods and Results—Participants aged 45 to 64 years from the Framingham Heart Study, who attended examinations in an “early” time period (1952 to 1974), were compared with those who attended examinations in a later time period (1975 to 1998). The risk of CVD events (n=133 among those with and 1093 among those without DM) attributable to DM in the 2 time periods was assessed with Cox proportional hazards models; population attributable risk of DM as a CVD risk factor was calculated for each time period. The age- and sex-adjusted hazard ratio for DM as a CVD risk factor was 3.0 (95% CI, 2.3 to 3.9) in the earlier time period and 2.5 (95% CI, 1.9 to 3.2) in the later time period. The population attributable risk for DM as a CVD risk factor increased from 5.4% (95% CI, 3.8% to 6.9%) in the earlier time period to 8.7% (95% CI, 5.9% to 11.4%) in the later time period (P for attributable risk ratio=0.04), although multivariable adjustment resulted in attenuation of these findings (P=0.12); most of these observations were found among men.

Conclusions—The proportion of CVD attributable to DM has increased over the past 50 years in Framingham. These findings emphasize the need for increased efforts to prevent DM and to aggressively treat and control CVD risk factors among those with DM. (Circulation. 2007;115:1544-1550.)

Key Words: diabetes mellitus ■ cardiovascular diseases ■ epidemiology ■ risk factors

There is controversy regarding whether adults with diabetes mellitus (DM) have experienced similar declines in cardiovascular disease (CVD) mortality as those without DM. Although some studies have shown that individuals with DM have not achieved similar reductions in risk, in previous work, we have shown that individuals with DM followed up in the Framingham Heart Study have had similar relative declines in CVD incidence rates as those without DM.

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Despite the observed declines in CVD incidence among individuals with and without DM, the relative risk of DM as a CVD risk factor does not appear to have changed. These observations occur in the setting of several epidemiological reports that suggest a rising prevalence and incidence of DM, likely in response to increasing rates of overweight and obesity and other factors such as a more sedentary lifestyle. The increase in the prevalence of DM, along with the observation that the relative risk of CVD associated with DM has not declined, could threaten to slow or even reverse the 50% reduction in coronary heart disease mortality that has occurred over the past 50 years.

There is a paucity of information regarding the potential change over time in the contribution of DM to the burden of CVD in the community. Knowledge of this is essential for efforts to predict trends in CVD and for optimal allocation of resources toward the prevention and treatment of CVD. Because the Framingham Heart Study has followed up individuals for more than 50 years, it is well-suited to assess long-term CVD.
TABLE 1. Age- and Sex-Adjusted Characteristics of Subjects Aged 45 to 64 Years With and Without DM, by Time Period

<table>
<thead>
<tr>
<th></th>
<th>No DM</th>
<th>DM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1952–1974 (n=4418)</td>
<td>1975–1998 (n=4590)</td>
</tr>
<tr>
<td></td>
<td>1952–1974 (n=181)</td>
<td>1975–1998 (n=351)</td>
</tr>
<tr>
<td>Age, y</td>
<td>54±5</td>
<td>55±6</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>57</td>
<td>54</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>135±21</td>
<td>127±17</td>
</tr>
<tr>
<td>Hypertension</td>
<td>41</td>
<td>33</td>
</tr>
<tr>
<td>Hypertension treatment</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>Current smoking</td>
<td>44</td>
<td>25</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>241±44</td>
<td>214±39</td>
</tr>
<tr>
<td>Cholesterol-lowering medications*</td>
<td>0.6</td>
<td>3</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.0±4.0</td>
<td>26.7±4.6</td>
</tr>
<tr>
<td>Obesity†</td>
<td>14</td>
<td>20</td>
</tr>
</tbody>
</table>

Values are mean±SD or percent.
*Cholesterol-lowering medications not available for the 1952–1954 examination.
†Body mass index ≥30 kg/m².

Statistical Analysis
We performed a proportional hazards analysis using pooled repeated observations. Hazards ratios for DM as a risk factor for CVD were examined with Cox proportional hazards regression. Models were age- and sex-adjusted and then further adjusted for hypertension, current smoking, high cholesterol (total cholesterol ≥200 mg/dL or lipid treatment), and obesity (body mass index ≥30 kg/m²). Population attributable risk (PAR) of DM as a CVD risk factor was calculated in each time period with the following formula: PAR = prevalence × [(HR−1)/HR], where prevalence refers to the prevalence of DM among the cases and the hazard ratio (HR) is the age- and sex-adjusted or multivariable-adjusted hazard ratio for DM relative to nondiabetes. The attributable risk ratio (ARR) was calculated in age- and sex-adjusted models for hypertension, high cholesterol (total cholesterol ≥200 mg/dL or lipid treatment), smoking, and obesity. The ARR was calculated as the ratio of the PAR in the later time period divided by the PAR in the earlier time period. An ARR >1.0 indicates that the PAR of the risk factor had increased in the later versus the earlier time period. The ARR allows for comparisons between risk factors. Ninety-five percent CIs around the PAR and ARR estimates were generated by the bootstrap bias-corrected method from 2000 resamples. A 2-tailed probability value <0.05 was considered significant.

Because DM was defined differently in the offspring and original Framingham cohorts (a necessity because of the data collected during different examination periods), a sensitivity analysis was performed to examine the effect of changing the cohort DM definition (casual glucose ≥200 mg/dL) to ≥160 mg/dL, in 10-mg/dL increments. To minimize the influence of aging in the present study sample and to ensure overlapping age distributions across all decades examined, we restricted our analysis to participants between 45 and 64 years of age at the index examinations.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
The earlier time period consisted of 4418 nondiabetic participants and 181 participants with DM, whereas the later time period consisted of 4590 nondiabetic participants and 351 diabetic participants. Participants with DM were slightly older, tended to have higher blood pressure, and were more likely to be obese (Table 1). In the later versus the earlier time period, there was a trend toward greater changes in mean values for age, systolic blood pressure, body mass index, and cholesterol levels among diabetic participants. DM was diagnosed either by fasting plasma glucose ≥126 mg/dL (7.0 mmol/L; offspring examinations), nonfasting plasma glucose ≥200 mg/dL (11.1 mmol/L; cohort examinations), or treatment with an oral hypoglycemic agent. Subjects with a history of ketoacidosis or with DM age of onset <30 years old were excluded (n=16).

Diabetes Diagnosis
DM was diagnosed either by fasting plasma glucose ≥126 mg/dL (7.0 mmol/L; offspring examinations), nonfasting plasma glucose ≥200 mg/dL (11.1 mmol/L; cohort examinations), or treatment with an oral hypoglycemic agent. Subjects with a history of ketoacidosis or with DM age of onset <30 years old were excluded (n=16).

Trends due to DM. We hypothesized that the relative burden of CVD due to DM has increased over the past 5 decades.

Study Design
Participants for the present study were drawn from the Framingham Heart Study. Selection criteria and study design have been described previously. The standard clinic examination included an interview, physical examination, and laboratory tests. Cardiovascular events were documented throughout follow up by daily hospital and death surveillance.

We selected participants aged 45 to 64 years from serial original cohort examinations, 4 years apart, from 1952 to 1974 and from offspring examinations, also 4 years apart, from 1979 to 1998. Participants could contribute information at more than 1 examination (examinations attended from 1952 to 1974) and a later period formed the basis for comparison of CVD hazards ratios among participants and without DM. Participants were monitored for CVD events in 4-year windows. The early time period contributed 4599 participants (12 962 person-examinations of follow up), and the later time period contributed 4941 participants (11 485 person-examinations of follow up). CVD events were collected up to December 31, 2004.

Outcome Ascertainment
CVD events included recognized fatal and nonfatal myocardial infarction, coronary heart disease death, stroke, transient ischemic attack, angina, coronary insufficiency, claudication, congestive heart failure, and unrecognized myocardial infarction. To establish a diagnosis, a panel of 3 physicians reviewed each cardiovascular event according to preestablished criteria.

Diabetes Diagnosis
DM was diagnosed either by fasting plasma glucose ≥126 mg/dL (7.0 mmol/L; offspring examinations), nonfasting plasma glucose ≥200 mg/dL (11.1 mmol/L; cohort examinations), or treatment with insulin or an oral hypoglycemic agent. Subjects with a history of ketoacidosis or with DM age of onset <30 years old were excluded (n=16).
period, participants with and without DM had lower systolic blood pressure and serum total cholesterol levels.

In the earlier time period, the age- and sex-adjusted prevalence of DM was 2.9%, whereas it was 4.7% in the later time period. Time-period specific hazard ratios for DM as a CVD risk factor were computed, and age- and sex-adjusted and multivariable-adjusted hazard ratios are shown (Table 2). The age- and sex-adjusted PAR of DM for CVD was 5.4% in the earlier time period and 8.7% in the later time period, with an ARR of 1.62 (95% CI, 1.05–2.48). The multivariable-adjusted attributable risk of DM for CVD in the earlier time period was 5.2%, which increased to 7.8% in the later time period, with an ARR of 1.50 (95% CI, 0.89–2.37).

### Sex-Specific Analyses

Sex-specific analyses were performed (Table 3). Most of the increase in ARR was observed among men only (age-adjusted ARR 2.20; 95% CI, 1.22 to 4.59; multivariable-adjusted ARR 1.88; 95% CI, 0.99 to 3.77), likely due to the higher observed increase in DM prevalence among the cases observed in the 2 time periods.

### Comparison With Other CVD Risk Factors

The age- and sex-adjusted prevalence of DM among CVD cases in the early versus the later time period was compared with the other available CVD risk factors, including hypertension, smoking, high cholesterol, and obesity (Figure 1). Significant declines were observed for hypertension ($P=0.02$), smoking ($P=0.002$), and elevated cholesterol ($P=0.008$). There was an increase in obesity among the cases ($P=0.02$), and the prevalence of DM increased by almost 2-fold among CVD cases (8.1% versus 14.6%, $P=0.0009$).
The age- and sex-adjusted ARRs of hypertension, smoking, high cholesterol, and DM are presented in Figure 2. Whereas the ARR for DM increased (1.62), significant declines were only observed for hypertension.

**Sensitivity Analysis**

Sensitivity analyses were conducted in which the definition of DM was adjusted down by 10 mg/dL from 200 mg/dL to 160 mg/dL in the original cohort sample (Figure 3). This minimally altered the PAR for CVD in the earlier versus the later time period.

**Discussion**

The proportion of CVD attributable to DM has increased over the past 50 years in the Framingham Heart Study. There has been a significant increase in the prevalence of DM and obesity among individuals with CVD in the later compared with the earlier time period. Compared with hypertension, high cholesterol, smoking, and obesity, only DM demonstrated an increase in the PAR over the 2 time periods.

To the best of our knowledge, these are among the first estimates in the United States to document that the PAR for CVD due to DM has increased. Previous work from Rochester, Minn, suggested that this phenomenon might be occurring. Using cause of death as ascertained from death certificates, investigators demonstrated that the number of cases of individuals dying with DM increased nearly 50% from 1970 to 1994, possibly because of a lesser mortality reduction among individuals with as compared with those without DM, although trends in changes of DM ascertainment over time may have contributed to these findings. Data from England and Wales suggest similar trends. Using population-based demographic data and national statistics, Unal et al. found that between 1981 and 2000, the number of coronary heart disease deaths in England and Wales attributed to obesity, physical activity, and DM increased, whereas deaths from smoking, blood pressure, and cholesterol levels declined. In Beijing, the increase in coronary heart disease mortality between 1984 to 1999 has been attributed to increases in serum cholesterol, obesity, and DM. Using New York death certificate data and information regarding hospital discharges, Fang and Alderman showed that the percent of myocardial infarctions among individuals with DM increased from 21% to 36% from 1990 to 2000. Although these findings are subject to changes in DM diagnostic criteria, they nonetheless support the observations we have made in the Framingham Heart Study.

The increased importance of DM as a CVD risk factor is likely due to the relative risk of DM as a CVD risk factor that is not declining, combined with increasing rates of
DM. Prior studies in the United States have consistently demonstrated the increasing prevalence of DM. Compared with the Second National Health and Nutrition Examination Survey (NHANES II; 1976 to 1980), the prevalence of DM increased by >50% in NHANES 1999 to 2000.25 We have previously shown that the incidence of DM has doubled over the last 30 years.12 Less clear is why the relative risk of DM as a CVD risk factor has not changed. Clinical trial data for CVD risk factor control suggest that individuals with DM have higher absolute reductions in CVD outcomes than nondiabetic individuals when treated for hypertension26 and dyslipidemia.27,28 However, in the setting of acute coronary syndrome, individuals with DM fare worse than individuals without DM.29–31 Individuals with DM are more likely to fail thrombolytic therapy,32 and PTCA is not as effective as CABG among individuals with treated DM.33 Among individuals treated with newer therapies such as drug-eluting stents, DM is an independent predictor of stent thrombosis,34 and diabetic individuals in a substudy of the SIRIUS trial (SIRIUS-eluting stent in de novo native coronary lesions) were more likely than nondiabetics to require revascularization.35 Therefore, to narrow the CVD gap between those with and without DM, newer therapies need to be developed that have more impact on individuals with DM. Efforts to prevent or postpone the onset of type 2 DM may also be a key strategy to reduce DM-associated CVD morbidity and mortality.

In addition to secondary prevention, it remains to be determined whether the risk factor profile associated with DM is changing over time relative to individuals without DM. Between 1970 and 1989, obesity among individuals with DM increased by 50%.36 In the present study, the prevalence of obesity among those with DM increased from 27% to 44%. Whether this may fuel the development of a more adverse CVD risk factor profile is uncertain. An analysis of risk factor control among individuals with DM from NHANES III (1988 to 1994) compared with NHANES 1999 to 2000 revealed that the prevalence of individuals with DM who achieved recommended levels of blood pressure, lipid, and hemoglobin A1c control did not change.37 Therefore, more efforts are needed to optimize the control of CVD risk factors among individuals with DM.

The findings in the present study were primarily observed among men and not women. Indeed, we have previously shown that the increase in DM incidence among women is less pronounced than among men.12 In the present work, the hazard ratio for DM as a CVD risk factor among women declined more than that for men in the later compared with the earlier time period. These 2 factors may contribute to the disparate findings in women and men.

There are several strengths to the present study design. Participants have been routinely screened for DM since the inception of the study. CVD events are routinely ascertained, and we do not depend on death certificate review to identify fatal cases. Furthermore, we have >50 years of prospective data on which to base our findings.

Some limitations do exist in our data. The present study sample is primarily white and therefore neither nationally representative nor ethnically diverse. It is possible that the change in attributable risk of CVD associated with DM may be even greater in nonwhite populations with a higher prevalence of DM. Our definition of DM was not uniform in the early and late time periods, because the early time period consisted primarily of casual glucose samples, whereas the later time period consisted of both casual and fasting glucose samples. We have tried to overcome this issue with our sensitivity analysis. Because this did not yield different results, it is unlikely that differences in the definition of DM between the 2 time periods can fully account for the present findings. We were also unable to fully account for differences in DM treatment over time; however, even if individuals with DM were more likely to be treated for their DM in the later time period, we still show in our results that the attributable risk of DM as a CVD risk factor is increasing, which suggests that our inability to fully capture differences in treatment may lead to an underestimation in the increase in attributable risk. We were unable to adjust for HDL cholesterol, diet, or physical activity because these parameters were not measured at all the examination cycles. We were unable to account for differences in diagnostic criteria that have occurred over time. In particular, the advent of more sensitive biomarkers of myocardial damage has led to increases in the diagnosis of myocardial infarction.38 Despite this, we have shown that the absolute incidence rate of CVD events has decreased, not increased, over time.5,15 Therefore, we do not think that this accounts for the present findings. Furthermore, the present study focused on the comparison of the risk of CVD among individuals with versus those without DM; therefore, any impact of changes in diagnostic criteria would occur in
both those with and without DM. Because there is no reason why individuals with versus those without DM should be subject to differential diagnostic classification over time, we do not believe this affects the present findings. Lastly, the study lacked power to definitively assess whether there was a significant change in the multivariable-adjusted PAR over time. Whereas results from a multivariable-adjusted model may provide insight into potential mechanisms, the age- and sex-adjusted model allows for assessment of the overall increasing burden of CVD due to DM.

The relative risk for CVD associated with DM has remained relatively constant over the past 50 years in Framingham. The increased prevalence of DM has increased the proportion of CVD attributable to DM. These findings emphasize the need for increased efforts to prevent DM, as well as efforts to aggressively treat and control CVD risk factors among those with DM.

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Disclosures
Dr Meigs is supported by an American Diabetes Association Career Development Award and currently has research grants from GlaxoSmithKline, Wyeth, and Sanofi-Aventis and serves on safety or advisory boards for GlaxoSmithKline, Merck, and Lilly.

References


CLINICAL PERSPECTIVE
Marked reductions in cardiovascular disease (CVD) morbidity and mortality have occurred in the United States over the last 50 years; however, the increasing prevalence of diabetes mellitus (DM) threatens to slow this decline, especially if the increased risk of CVD associated with DM remains constant over time. Knowledge of this is essential for efforts to predict trends in CVD and for optimal allocation of resources toward the prevention and treatment of CVD. We tested the hypothesis that the relative burden of CVD attributable to DM has increased over the past 5 decades by comparing participants from the Framingham Heart Study who attended examinations in an early time period (1952 to 1974) and those who attended in a later time period (1975 to 1998). The population attributable risk for DM as a CVD risk factor increased from 5.4% (95% CI, 3.8% to 6.9%) in the earlier time period to 8.7% (95% CI, 5.9% to 11.4%) in the later time period (P for attributable risk ratio = 0.04), although multivariable adjustment resulted in attenuation of these findings (P = 0.12). Compared with hypertension, high cholesterol, smoking, and obesity, only DM demonstrated an increase in the population attributable risk over the 2 time periods. The proportion of CVD attributable to DM has increased over the past 50 years in Framingham. These findings emphasize the need for increased efforts to prevent DM and to aggressively treat and control CVD risk factors among those with DM.

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