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# Trends in All-Cause and Cardiovascular Disease Mortality Among Women and Men With and Without Diabetes Mellitus in the Framingham Heart Study, 1950 to 2005

Sarah Rosner Preis, ScD, MPH; Shih-Jen Hwang, PhD; Sean Coady, MA; Michael J. Pencina, PhD; Ralph B. D'Agostino, Sr, PhD; Peter J. Savage, MD; Daniel Levy, MD; Caroline S. Fox, MD, MPH

**Background**—Despite population declines in all-cause mortality, women with diabetes mellitus may have experienced an increase in mortality rates compared with men.

**Methods and Results**—We examined change in all-cause, cardiovascular, and non-cardiovascular disease mortality rates among Framingham Heart Study participants who attended examinations during an “earlier” (1950 to 1975; n=930 deaths) and a “later” (1976 to 2001; n=773 deaths) time period. Diabetes mellitus was defined as casual glucose  $\geq 200$  mg/dL, fasting plasma glucose  $\geq 126$  mg/dL, or treatment. Among women, the hazard ratios (HRs) for all-cause mortality in the later versus the earlier time period were 0.59 (95% confidence interval, 0.50 to 0.70;  $P < 0.0001$ ) for those without diabetes mellitus and 0.48 (95% confidence interval, 0.32 to 0.71;  $P = 0.002$ ) for those with diabetes mellitus. Similar results were observed in men. Among women and men, the HR of cardiovascular disease mortality declined among those with and without diabetes mellitus. Non-cardiovascular disease mortality declined among women without diabetes mellitus (HR, 0.76;  $P = 0.01$ ), whereas no change was observed among women with diabetes mellitus or among men with or without diabetes mellitus. Individuals with versus those without diabetes mellitus were at increased risk of all-cause mortality in the earlier (HR, 2.44;  $P < 0.0001$ ) and later (HR, 1.95;  $P < 0.0001$ ) time periods.

**Conclusions**—Reductions in all-cause mortality among women and men with diabetes mellitus have occurred over time. However, mortality rates among individuals with diabetes mellitus remain  $\approx 2$ -fold higher compared with individuals without diabetes mellitus. (*Circulation*. 2009;119:1728-1735.)

**Key Words:** diabetes mellitus ■ mortality ■ men ■ trends ■ women

Over the past several decades, mortality from cardiovascular disease (CVD) has shown a marked decline.<sup>1,2</sup> Despite this decline, diabetes mellitus remains a key risk factor for CVD and is associated with a 2- to 4-fold higher risk of CVD, as well as an increased risk of mortality by up to 3-fold.<sup>3-5</sup> Rising rates of obesity and diabetes mellitus may be increasing the burden of CVD caused by diabetes mellitus, highlighting the need to better understand the morbidity and mortality related to diabetes.<sup>6,7</sup> Declines in mortality rates over time have been observed in people with and without diabetes mellitus.<sup>8-11</sup> However, a recent analysis of national trends data from the National Health and Nutrition Examination Survey (NHANES) suggested that declines in all-cause mortality have occurred among men with diabetes mellitus but not women.<sup>4</sup> Furthermore, these findings suggested that

women may have had an increase in mortality related to diabetes mellitus over time.

## Clinical Perspective p 1735

These conflicting findings may be due to differences in study methodology. Prior studies examining trends in diabetes mortality are limited by the use of self-reported diabetes status or death certificates, increasing the possibility of misclassification.<sup>4,5</sup> Prior work in the Framingham Heart Study has shown that CVD event rates have declined among those with and without diabetes mellitus.<sup>3</sup> As an extension to this prior work, the purpose of the present study is to assess time-period trends in all-cause mortality among women and men with and without diabetes mellitus in the Framingham Heart Study, in which diabetes status has been routinely

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screened for and all deaths have been adjudicated. We also secondarily examined CVD and non-CVD mortality rates over time among men and women with diabetes mellitus.

## Methods

### Study Sample

The Framingham Heart Study and the Framingham Offspring Cohort Study have been previously described.<sup>12–14</sup> Briefly, the Framingham Heart Study is an ongoing prospective cohort study that began in 1948 with the enrollment of 5209 men and women 28 to 62 years of age.<sup>12,13</sup> The participants underwent an examination every 2 years that included a medical history interview, physical examination, and laboratory tests. The Framingham Offspring Cohort Study began in 1971 when 5124 offspring of the original participants and their spouses were enrolled.<sup>14</sup> The offspring cohort underwent examinations every ≈4 years. All subjects provided written informed consent, and the study has been approved by the Institutional Review Board at Boston Medical Center.

For the present study, we selected individuals 45 to 74 years of age from 10 serial original cohort examinations, taken 4 years apart and occurring from 1950 to 1990, and from all 7 serial offspring examinations, taken roughly 4 years apart and occurring from 1971 to 2001. The participants were followed up for death in 4-year windows until December 31, 2005. Participants were able to contribute information at >1 examination provided that they survived to the following examination and were 45 to 74 years of age at their next examination. For example, an individual who attended an examination in 1971 would be followed up until death or 1975 (4-year follow-up window), whichever occurred first. The 4-year follow-up window was used so that diabetes status could be updated at each examination that the participant attended. The 4-year risk periods were pooled for each individual, making this approach equivalent to a long-term Cox model with age and diabetes status as time-dependent variables.<sup>15</sup>

We divided the study sample into two 25-year time periods according to the calendar year of examinations, with the “earlier period” for examinations occurring from 1950 to 1975 and the “later period” for examinations occurring from 1976 to 2001. The total follow-up period for death was 1950 to 1979 (1975+4-year follow-up window) for participants attending examinations during the earlier time period and 1976 to 2005 (2001+4-year follow-up window) for participants attending examinations during the later period. In the earlier period, 78 156 person-years were included and 930 deaths occurred, and 79 000 person-years and 773 deaths in the later period.

### Outcome Assessment

The primary outcome of interest was all-cause mortality. We secondarily examined mortality from CVD and non-CVD causes. All deaths were adjudicated by a panel of 3 investigators using previously described criteria.<sup>16</sup> Information on cause of death was obtained from death certificates, hospital admission records, medical records, and family members. CVD was identified as the cause of death if any of the following conditions were responsible for the death: coronary heart disease, intermittent claudication, congestive heart failure, stroke, or transient ischemic attack.

### Diabetes Status Assessment

Participants were considered to have diabetes mellitus if they had a fasting plasma glucose level  $\geq 126$  mg/dL (for the offspring cohort) or a casual plasma glucose level  $\geq 200$  mg/dL (for the original cohort) or if they reported treatment with insulin or an oral hypoglycemic agent. All participants with type 1 diabetes mellitus, as identified by chart review, were excluded from analysis.

### Statistical Methods

A Cox proportional-hazards model using pooled repeated observations was fit to estimate hazard ratios (HRs) and 95% confidence intervals, with follow-up time used as the time scale. Four-year

mortality rates were calculated as the total number of deaths divided by the total number of person-years of follow-up. Mortality rates for the total study sample were directly adjusted for age (in 5-year age groups) and sex. In the primary analysis, separate models were fit for those with and without diabetes mellitus for the total study sample and for men and women separately. All models were adjusted for age; the models for the total study sample were additionally adjusted for sex. The primary comparison of interest was the HR comparing all-cause mortality in the later period with the earlier period among both those with diabetes mellitus and those without diabetes mellitus. A dichotomous variable for time period was entered into the Cox model, and its significance was assessed by a 1-*df* Wald test. To assess the interaction between time period and sex, a cross-product term for time period by sex was entered into each model, and its significance was assessed by a 1-*df* likelihood ratio test.

We also compared the HR of all-cause mortality for individuals with diabetes mellitus to those without diabetes mellitus within each time period. Models were fit separately for the earlier time period and the later time period for the total study sample and for men and women separately. The interaction between diabetes status and sex within each time period was assessed. In secondary analyses, we stratified all-cause mortality into its components and separately examined trends in CVD and non-CVD mortality over time.

In a secondary analysis, we redesigned our analysis to compare our main results with a prior analysis conducted using NHANES data.<sup>4</sup> The NHANES analysis compared 3 different time periods ranging from 1971 to 1994 (1971 to 1975, 1976 to 1980, 1988 to 1994). Because of the overlapping nature of the NHANES follow-up periods (which is possible because they have a different cohort of individuals at each time period), we were not able to construct 3 separate time periods using our data. However, we constructed 2 periods that are equivalent in calendar time to the first (1971 to 1975) and third (1988 to 1994) NHANES surveys, which was the main comparison of interest. We also used a 12-year follow-up period instead of the 4-year follow-up window in our primary analysis and included 35 to 74 years of age to match the NHANES study design more closely.

Because the original and offspring Framingham cohorts used different definitions for assessing diabetes status, we performed a sensitivity analysis to examine the effect of changing the original cohort's definition of diabetes mellitus (casual plasma glucose  $\geq 200$  mg/dL or diabetes treatment). Models were fit that changed the cohort diabetes definition from  $\geq 200$  to  $\geq 150$  mg/dL by decrements of 10 mg/dL.

A value of  $P < 0.05$  was considered statistically significant. All analyses were performed with SAS version 8.1 (SAS Institute, Inc, Cary, NC). The proportional-hazards assumption was assessed graphically with log-log plots from PROC LIFETEST in SAS and was met for all variables considered.

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

### Study Sample Characteristics

In the earlier period, 3.5% of women and 4.5% of men had diabetes mellitus; in the later period, 7.0% of women and 11.2% of men had diabetes mellitus (Table 1). Additional characteristics of the study sample are presented in Table 1.

### Trends in All-Cause Mortality

The age- and sex-adjusted all-cause mortality rates (per 1000 person-years) decreased from 12.8 to 7.7 among those without diabetes mellitus and from 33.1 to 15.8 among those with diabetes mellitus, corresponding to a 40% and a 48% reduced risk of death, respectively (Table 2). The results in the sex-specific analysis for all-cause mortality paralleled those in the total study sample. Both women and men with and

**Table 1. Characteristics of the Study Sample by Sex and Time Period in the Framingham Heart Study**

Characteristics	Earlier Period (1950–1975)	Later Period (1976–2001)
<b>Women</b>		
Person-y	43 992	42 592
Age, mean (SD), y	56.9 (7.6)	59.7 (8.3)
Diabetes mellitus,* %	3.5	7.0
Prevalent CVD† at index exam, %	2.5	3.7
<b>Men</b>		
Person-y	34 164	36 409
Age, mean (SD), y	56.5 (7.5)	59.4 (8.1)
Diabetes mellitus,* %	4.5	11.2
Prevalent CVD† at index exam, %	5.5	9.5

\*In total, 399 individuals had diabetes mellitus in the earlier period and 679 individuals had diabetes mellitus in the later period.

†Defined as myocardial infarction, stroke, or congestive heart failure.

without diabetes mellitus had a significantly decreased risk of all-cause mortality in the later period compared with the earlier period (the Figure, Table 2).

The association between diabetes status and risk of mortality by time period is presented in Table 3. In both the earlier and later time periods, participants with diabetes mellitus had a 2-fold increased risk of all-cause mortality compared with those without diabetes mellitus. In sex-specific analyses, women had an  $\approx$ 3-fold increased risk of mortality associated with diabetes mellitus, whereas men had an  $\approx$ 2-fold increased risk (Table 3). The *P* values for the interaction between sex and diabetes status were 0.05 for the earlier period and 0.20 for the later period.

### Trends in CVD Mortality

The results for CVD mortality were similar to those for all-cause mortality. Among the total study sample, participants without diabetes mellitus had a 62% decline in CVD mortality, and participants with diabetes mellitus had a 69% decline (Table 2). Similar magnitudes of decline in CVD mortality were observed when the analysis was performed separately by sex.

When diabetes mellitus was compared with nondiabetes in the total study sample, participants with diabetes mellitus had nearly a 4-fold increased risk of CVD mortality in the earlier time period and nearly a 3-fold increased risk in the later time period (Table 3). In the earlier time period, a comparison of those with diabetes mellitus and those without diabetes mellitus gave an HR for CVD mortality of 5.08 ( $P<0.0001$ ) for women and 2.95 ( $P<0.0001$ ) for men. In the later time period, the HRs of CVD mortality were 3.49 ( $P<0.0001$ ) for women and 2.35 ( $P<0.0001$ ) for men. A statistically significant interaction for CVD mortality was found between sex and diabetes status in the earlier time period (*P* for interaction=0.02).

### Trends in Non-CVD Mortality

In the total study sample, individuals without diabetes mellitus had a 19% decrease in non-CVD mortality rates,

whereas individuals with diabetes mellitus had no change in mortality rates ( $P=0.95$ ) in comparisons of the earlier and later time periods (Table 2). In sex-specific analyses, only women without diabetes mellitus, but not men without diabetes mellitus, had a statistically significantly reduced risk of non-CVD mortality between the 2 time periods. Both women and men with diabetes mellitus had no change in the rates of non-CVD mortality between the earlier and later periods.

In sex-specific analyses, as shown in Table 3, women with diabetes mellitus were at increased risk of non-CVD mortality compared with those without diabetes mellitus in both the earlier (HR, 1.76; 95% confidence interval, 1.02 to 3.05;  $P=0.04$ ) and later (HR, 1.81; 95% confidence interval, 1.17 to 2.78;  $P=0.007$ ) time periods. Among men, no difference was found in the risk of non-CVD mortality comparing those with diabetes mellitus and those without diabetes mellitus in the earlier time period. However, in the later period, men with diabetes mellitus appeared to be at increased risk of non-CVD mortality relative to those without diabetes mellitus, although the difference was not statistically significant ( $P=0.06$ ). The interaction between sex and diabetes status was not statistically significant in either the earlier or later time period ( $P=0.21$  for earlier period;  $P=0.38$  for later period).

### Secondary Analyses

One of our goals was to compare our results with a prior published analysis that used NHANES data.<sup>4</sup> Because the NHANES analysis compared different time periods and had a wider age range and a longer follow-up window than our primary analysis, we restructured our primary analysis to be comparable. Some notable differences emerged between our primary analysis (presented in Table 2) and our restructured analysis (presented in Table 4). Among the total study sample, the magnitude of decline in all-cause mortality was less prominent when the earlier and later time periods were compared, especially among individuals with diabetes mellitus. Among women with and without diabetes mellitus, the difference between the earlier and later periods was not as pronounced compared with our primary analysis (diabetes mellitus: HR, 0.76 versus 0.48; no diabetes mellitus: HR, 0.74 versus 0.59). Furthermore, the HR for all-cause mortality among women with diabetes mellitus was no longer statistically significant ( $P=0.24$ ), although the magnitude of the HR was similar for women with and without diabetes mellitus (HR, 0.76 versus 0.74), likely because of fewer deaths among women with diabetes mellitus in the restructured analysis. For CVD mortality, we did not observe any differences between our restructured analysis and our primary analysis (diabetes mellitus: HR, 0.38 versus 0.29; no diabetes mellitus: HR, 0.38 versus 0.35). For non-CVD mortality, in our restructured analysis, we did not observe a decline in mortality among individuals without diabetes mellitus among men and women combined as we did in our primary analysis. Additionally, among women, we did not observe a decline in non-CVD mortality among those without diabetes mellitus in the restructured analysis as we did in our primary analysis. Among women with diabetes mellitus, a suggestion of an



**Table 2. HRs of Mortality Comparing the Later and Earlier Periods\* by Diabetes Status in the Framingham Heart Study**

	Earlier Period (1950–1975)			Later Period (1976–2001)			HR (95% CI) for Later vs Earlier	P
	Deaths, n	Person-y	Mortality Rate per 1000 Person-y	Deaths, n	Person-y	Mortality Rate per 1000 Person-y		
Women and men combined†								
All-cause mortality‡								
No diabetes mellitus	821	75 200	12.8	614	72 131	7.7	0.60 (0.54–0.66)	<0.0001
Diabetes mellitus	109	2956	33.1	159	6869	15.8	0.52 (0.41–0.67)	<0.0001
CVD mortality§								
No diabetes mellitus	400	75 200	6.3	193	72 131	2.4	0.38 (0.32–0.45)	<0.0001
Diabetes mellitus	81	2956	24.1	70	6869	6.8	0.31 (0.22–0.43)	<0.0001
Non-CVD mortality								
No diabetes mellitus	383	75 200	5.9	379	72 131	4.8	0.81 (0.70–0.93)	0.004
Diabetes mellitus	26	2956	8.5	73	6869	7.6	1.01 (0.65–1.60)	0.95
Women¶								
All-cause mortality								
No diabetes mellitus	328	42 505	8.8	238	39 708	5.2	0.59 (0.50–0.70)	<0.0001
Diabetes mellitus	49	1487	30.8	50	2884	12.3	0.48 (0.32–0.71)	0.002
CVD mortality								
No diabetes mellitus	135	42 505	3.7	64	39 708	1.3	0.35 (0.26–0.47)	<0.0001
Diabetes mellitus	35	1487	21.0	22	2884	5.3	0.29 (0.17–0.50)	<0.0001
Non-CVD mortality								
No diabetes mellitus	177	42 505	4.6	153	39 708	3.5	0.76 (0.61–0.95)	0.01
Diabetes mellitus	14	1487	9.7	24	2884	6.1	0.80 (0.41–1.56)	0.52
Men¶								
All-cause mortality								
No diabetes mellitus	493	32 695	17.7	376	32 424	10.8	0.60 (0.52–0.69)	<0.0001
Diabetes mellitus	60	1469	36.1	109	3985	20.1	0.55 (0.40–0.76)	0.0002
CVD mortality								
No diabetes mellitus	265	32 695	9.4	129	32 424	3.7	0.39 (0.31–0.48)	<0.0001
Diabetes mellitus	46	1469	27.8	48	3985	8.5	0.32 (0.21–0.47)	<0.0001
Non-CVD mortality								
No diabetes mellitus	206	32 695	7.5	226	32 424	6.5	0.85 (0.70–1.03)	0.09
Diabetes mellitus	12	1469	7.1	49	3985	9.5	1.23 (0.65–2.33)	0.52

CVD deaths and non-CVD deaths do not sum to all-cause deaths because of the presence of deaths of unknown cause in the all-cause mortality group.

\*Total follow-up period is 1950 to 1979 for earlier period and 1976 to 2005 for later period.

†Mortality rates and HRs are adjusted for age and sex.

‡Likelihood ratio test for sex-by-time-period interaction:  $P=0.92$  for non-diabetes mellitus, 0.50 for diabetes mellitus.

§Likelihood ratio test for sex-by-time-period interaction:  $P=0.95$  for non-diabetes mellitus, 0.75 for diabetes mellitus.

||Likelihood ratio test for sex-by-time-period interaction:  $P=0.17$  for non-diabetes mellitus, 0.32 for diabetes mellitus.

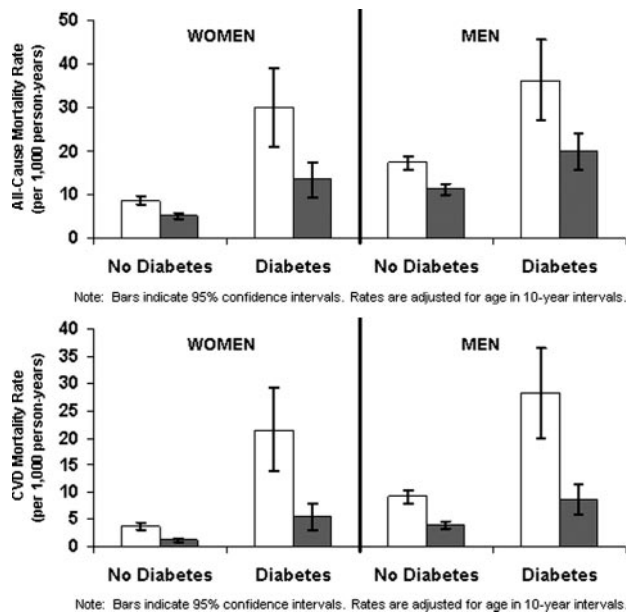
¶Mortality rates and HRs are adjusted for age.

increased risk of non-CVD mortality was found, although the HR was not statistically significant.

We performed a sensitivity analysis to examine the effect of changing the original cohort's definition of diabetes mellitus of nonfasting plasma glucose of  $\geq 200$  to  $\geq 160$  mg/dL by 10-mg/dL units (Figure I of the online-only Data Supplement). Overall, changing the diabetes definition for the cohort minimally affected the HR estimates. Excluding those with prevalent CVD at the index examination resulted in findings similar to our main analysis (online-only Data Supplement Table).

## Discussion

Our findings from an analysis of mortality trends among participants with and without diabetes mellitus in the Framingham Heart Study are 3-fold. First, contrary to recent NHANES findings, we observed a decline in all-cause mortality rates among both men and women with and without diabetes mellitus when comparing the earlier and later time periods. We also observed a decline in CVD mortality between the earlier and later time periods. Second, no change was found in non-CVD mortality rates among women or men with diabetes mellitus over time, and women with diabetes



**Figure.** Age-adjusted all-cause (top) and CVD (bottom) mortality rates among participants with and without diabetes mellitus by sex and time period. White bars represent earlier time period (1950 to 1975); gray bars represent later time period (1976 to 2001).

mellitus had an ≈2-fold higher risk of death resulting from non-CVD causes than women without diabetes mellitus in both the earlier and later time periods. Finally, we observed that men and women with diabetes mellitus continue to remain at a higher risk of all-cause and CVD mortality than their counterparts without diabetes mellitus.

Several factors may explain the decrease in mortality rates over time among those with and without diabetes mellitus. In recent decades, there have been improvements in major CVD risk factors, including reductions in smoking prevalence, total cholesterol, and systolic blood pressure levels.<sup>6</sup> Additionally, recent advances in secondary prevention therapies have occurred that may have contributed to the decline.<sup>6</sup> Decreases in incidence rates of CVD events have been observed among individuals both with and without diabetes mellitus.<sup>3</sup> These substantial declines in mortality rates among individuals with diabetes mellitus over time are especially important to consider in light of the recent clinical trials that failed to find benefit of intensive compared with standard glucose-lowering regimens<sup>17,18</sup> and emphasize the continued importance of primary and secondary prevention in the overall reduction of mortality in individuals with diabetes mellitus over time.

We observed that non-CVD mortality was higher in both time periods in women with diabetes mellitus compared with women without diabetes mellitus, although the number of events was small. Nonetheless, these findings are supported by a prior examination of trends in non-CVD mortality among people with diabetes mellitus, which noted a significant increase in cancer mortality in the period from 1970 to 1994.<sup>9</sup>

**In the Context of the Current Literature**

A recent analysis of mortality trends among people with diabetes mellitus conducted using NHANES data showed that men with and without diabetes mellitus had a significant

**Table 3. HRs of Mortality Comparing Participants With Diabetes Mellitus and Those Without Diabetes Mellitus by Time Period\* in the Framingham Heart Study**

	HR of Diabetes Mellitus (95% CI)	P
Women and men combined†		
All-cause mortality‡		
Earlier period	2.44 (1.99–2.98)	<0.0001
Later period	1.95 (1.64–2.33)	<0.0001
CVD mortality§		
Earlier period	3.61 (2.84–4.60)	<0.0001
Later period	2.61 (1.98–3.45)	<0.0001
Non-CVD mortality		
Earlier period	1.28 (0.86–1.90)	0.23
Later period	1.49 (1.16–1.92)	0.002
Women¶		
All-cause mortality		
Earlier period	3.13 (2.31–4.25)	<0.0001
Later period	2.29 (1.69–3.12)	<0.0001
CVD mortality		
Earlier period	5.08 (3.48–7.41)	<0.0001
Later period	3.49 (2.15–5.67)	<0.0001
Non-CVD mortality		
Earlier period	1.76 (1.02–3.05)	0.04
Later period	1.81 (1.17–2.78)	0.007
Men¶		
All-cause mortality		
Earlier period	2.05 (1.57–2.69)	<0.0001
Later period	1.81 (1.46–2.25)	<0.0001
CVD mortality		
Earlier period	2.95 (2.15–4.05)	<0.0001
Later period	2.35 (1.68–3.28)	<0.0001
Non-CVD mortality		
Earlier period	0.96 (0.54–1.72)	0.89
Later period	1.35 (0.99–1.84)	0.06

CVD deaths and non-CVD deaths do not sum to all-cause deaths because of the presence of deaths of unknown cause in the all-cause mortality group.

\*Earlier period consists of examinations attended in 1950 to 1975 (total follow-up period is 1950 to 1979); later period consists of examinations attended in 1976 to 2001 (total follow-up period is 1976 to 2005).

†Mortality rates and HRs are adjusted for age and sex.

‡Likelihood ratio test for sex-by-diabetes interaction: P=0.05 for earlier period, 0.20 for later period.

§Likelihood ratio test for sex-by-diabetes interaction: P=0.02 for earlier period, 0.10 for later period.

||Likelihood ratio test for sex-by-diabetes interaction: P=0.21 for earlier period, 0.38 for later period.

¶Mortality rates and HRs are adjusted for age.

decline in all-cause mortality in comparisons of the time periods of 1971 to 1986 and 1988 to 2000.<sup>4</sup> However, women with and without diabetes mellitus did not have similar declines in the rates of all-cause mortality over the same time period. Among women, the absolute difference in all-cause mortality rates between those with and without diabetes mellitus more than doubled between 1971 to 1986 and 1988

**Table 4. HRs of Mortality Comparing the Later and Earlier Periods by Diabetes Status Using the Analysis Strategy From a Prior NHANES Analysis\* in the Framingham Heart Study**

	Earlier Period (1971-1974)			Later Period (1988-1994)			HR (95% CI) for Later vs Earlier	P
	Deaths, n	Person-y	Mortality Rate per 1000 Person-y	Deaths, n	Person-y	Mortality Rate per 1000 Person-y		
Women and men combined†								
All-cause mortality‡								
No diabetes mellitus	747	63 372	13.1	520	50 435	11.9	0.70 (0.63–0.79)	<0.0001
Diabetes mellitus	114	2805	32.7	124	3299	26.2	0.77 (0.60–1.00)	0.05
CVD mortality§								
No diabetes mellitus	302	63 372	5.4	123	50 435	2.9	0.40 (0.33–0.50)	<0.0001
Diabetes mellitus	73	2805	21.5	44	3299	10.0	0.42 (0.29–0.61)	<0.0001
Non-CVD mortality								
No diabetes mellitus	395	63 372	6.9	366	50 435	8.3	0.95 (0.82–1.10)	0.49
Diabetes mellitus	34	2805	9.3	66	3299	13.7	1.40 (0.92–2.12)	0.12
Women¶								
All-cause mortality								
No diabetes mellitus	316	34 668	9.9	225	27 721	8.8	0.74 (0.62–0.88)	0.0006
Diabetes mellitus	43	1218	25.4	35	1353	19.2	0.76 (0.49–1.20)	0.24
CVD mortality								
No diabetes mellitus	108	34 668	3.5	44	27 721	1.7	0.38 (0.27–0.54)	<0.0001
Diabetes mellitus	30	1218	18.8	12	1353	6.6	0.38 (0.19–0.74)	0.005
Non-CVD mortality								
No diabetes mellitus	179	34 668	5.5	166	27 721	6.5	1.00 (0.81–1.24)	0.99
Diabetes mellitus	10	1218	5.6	21	1353	11.6	1.94 (0.91–4.11)	0.09
Men¶								
All-cause mortality								
No diabetes mellitus	431	28 704	16.8	295	22 714	15.3	0.68 (0.59–0.79)	<0.0001
Diabetes mellitus	71	1587	41.2	89	1946	34.2	0.77 (0.56–1.06)	0.10
CVD mortality								
No diabetes mellitus	194	28 704	7.6	79	22 714	4.1	0.41 (0.32–0.53)	<0.0001
Diabetes mellitus	43	1587	24.6	32	1946	13.8	0.44 (0.27–0.70)	0.0005
Non-CVD mortality								
No diabetes mellitus	216	28 704	8.4	200	22 714	10.4	0.91 (0.75–1.11)	0.34
Diabetes mellitus	24	1587	13.5	45	1946	16.2	1.15 (0.70–1.91)	0.58

CVD deaths and non-CVD deaths do not sum to all-cause deaths because of the presence of deaths of unknown cause in the all-cause mortality group.

\*This analysis was structured to parallel that found in a prior study done using NHANES data.<sup>4</sup> The changes from our main analysis include (1) expanding the age range at the index exam to 35 to 74 years, (2) increasing the follow-up window from 4 to 12 years, and (3) using exams occurring from 1971 to 1974 for the earlier period and 1988 to 1994 for the later period. A total of 119 911 person-years and 1505 deaths were included in the analysis.

†Mortality rates and HRs are adjusted for age and sex.

‡Likelihood ratio test for sex-by-time-period interaction:  $P=0.48$  for non-diabetes mellitus, 0.96 for diabetes mellitus.

§Likelihood ratio test for sex-by-time-period interaction:  $P=0.84$  for non-diabetes mellitus, 0.71 for diabetes mellitus.

||Likelihood ratio test for sex-by-time-period interaction:  $P=0.77$  for non-diabetes mellitus, 0.27 for diabetes mellitus.

¶Mortality rates and HRs are adjusted for age.

to 2000. Both women and men without diabetes mellitus had significant declines in CVD mortality, but significant declines were not observed in either men or women with diabetes mellitus. In contrast, in our primary analysis, we observed strong and significant declines in all-cause and CVD mortality among both men and women with and without diabetes mellitus. However, in our analysis that was restructured to match the NHANES analysis, we did not observe a statistically significant decline in all-cause mortality among either

men or women with diabetes mellitus, although substantial declines were observed among individuals with diabetes mellitus for CVD mortality. Importantly, we did not observe an increase in all-cause mortality among women in any of our analyses, as was observed in the prior analysis of NHANES data.

Potential differences in study design may explain the discrepancy in our results. Most likely, the breadth of the time period examined in the Framingham Heart Study compared

with the NHANES data could explain the disparate findings for all-cause mortality. The NHANES study period covered a narrower and more contemporary time period (1971 to 2000) than our primary analysis (1950 to 2005). For CVD mortality, additional methodologic factors may explain our disparate findings. First, NHANES relied on self-reported diabetes status, whereas in the Framingham Heart Study, diabetes mellitus was routinely screened for with glucose measurements and medication use. A study using NHANES data revealed that the percentage of individuals with undiagnosed diabetes mellitus was 38% in 1976 to 1980, 36% in 1988 to 1994, and 29% in 1999 to 2000.<sup>19</sup> A recent study showed that the sensitivity of self-reported diabetes mellitus was only 49.3% for women and 67.1% for men.<sup>20</sup> If women are less likely to report their diabetes status correctly, it is possible that only the most severe cases of diabetes mellitus are identified through self-report. Additionally, the NHANES analysis ascertained mortality from death certificates, an approach that has been shown to overestimate CVD as a cause of death,<sup>21</sup> whereas all deaths in the Framingham Heart Study were adjudicated by a panel of 3 physicians. Therefore, misclassification of both exposure and outcome could have occurred within the NHANES analysis. Finally, it is possible that the NHANES results differed from ours as a result of either the geographic variability or the high proportion ( $\approx 20\%$ ) of nonwhite participants in their study sample. The Framingham Heart Study is predominantly white and may not be as representative of the general US population as the NHANES population.

In contrast to the NHANES study, the majority of studies of mortality trends among people with diabetes mellitus have shown decreases in mortality rates over time. Three studies have been conducted in predominantly white populations, similar to the racial composition of the Framingham Heart Study. In a population-based study in Rochester, Minn, in which the diagnosis of diabetes mellitus was based on hospital records and cause of death information was obtained from death certificates, all-cause mortality decreased by 13.8% among those with diabetes mellitus and by 21.4% in those without diabetes mellitus between 1970 and 1994.<sup>9</sup> Similarly, an examination of North Dakota death certificate data showed that the mortality rate among persons with diabetes mellitus (as identified on the death certificate) declined by 35% between 1997 and 2002 and that sex-specific rates showed a trend similar to those for the total population.<sup>10</sup> In a study of nearly 75 000 individuals from Norway in which diabetes status was self-reported and cause of death was identified from a national death registry, statistically significant declines in CHD mortality were observed in both men and women with diabetes mellitus from 1984 to 1997.<sup>11</sup>

Trends in mortality rates among people with diabetes mellitus have also been conducted among in multiethnic study samples. For example, a recent study from Ontario, Canada, reported a 25% decline in all-cause mortality in both women and men with diabetes mellitus from 1995 to 2005.<sup>8</sup> Therefore, differences in the ethnic composition of our study sample compared with NHANES are unlikely to fully account for differences in the findings.

## Study Strengths and Limitations

Strengths of this analysis include the routine screening for diabetes mellitus with glucose measurements to define diabetes status in our study sample instead of relying on either self-reported diabetes status or diabetes status from hospital admission records. Self-reported diabetes status can result in misclassification because nearly one third of total diabetes cases are undiagnosed.<sup>22</sup> Furthermore, self-reported diabetes status would have identified only the most severe cases in the earlier years, whereas in the later years, there are fewer undiagnosed cases. Reliance on hospital admission records to define diabetes status only confirms a positive diabetes diagnosis among those who have been admitted to the hospital. Therefore, the use of blood glucose measurements in our study is a more sensitive and specific way of defining those with and without diabetes mellitus. Another strength of our study is the broad time period of observation, which enabled us to elucidate long-term trends.

The results of this analysis should be interpreted in light of its limitations. Our study sample is predominantly white; thus, the results may not be generalizable to other ethnic or racial groups in which disparities in health care may exist. Additionally, we had a small number of deaths among the diabetes group in the sex-specific analyses; therefore, the power to detect a modest effect may be limited. We used different diabetes definitions in the original and offspring cohorts. However, a sensitivity analysis revealed that this is unlikely to account for our findings.

## Conclusions

We observed a decline in all-cause and CVD mortality rates among both men and women with and without diabetes mellitus over the period of 1950 to 2005. Both men and women with diabetes mellitus continue to remain at a higher risk of all-cause and CVD mortality than those without diabetes mellitus. Whether the lack of decrease in non-CVD mortality rates over time among individuals with diabetes mellitus is observed in other studies warrants further investigation.

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## Disclosures

None.

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### CLINICAL PERSPECTIVE

Over the past several decades, a marked decline has occurred in mortality from cardiovascular disease. Despite this decline, diabetes mellitus remains a key risk factor for cardiovascular disease and is associated with a 2- to 4-fold higher risk of cardiovascular disease, as well as an increased risk of mortality by up to 3-fold. Declines in mortality rates over time have been observed in people with and without diabetes mellitus. However, a recent analysis of national trends data from the National Health and Nutrition Examination Survey suggested that declines in all-cause mortality have occurred among men with diabetes mellitus but not women. In this study, we assessed time-period trends in all-cause mortality among women and men with and without diabetes mellitus in the Framingham Heart Study, in which diabetes status has been routinely screened for and all deaths have been adjudicated. The analysis included participants who attended examinations during an “earlier” (1950 to 1975) and a “later” (1976 to 2001) time period. Our results showed a decline in all-cause and cardiovascular disease mortality rates among both men and women with and without diabetes mellitus over the period of 1950 to 2005. Additionally, both men and women with diabetes mellitus continue to remain at a higher risk of all-cause and cardiovascular disease mortality than those without diabetes mellitus. In summary, reductions in all-cause mortality among both women and men with diabetes mellitus have occurred over time.

## **SUPPLEMENTAL MATERIAL**

**Online Supplemental Table 1.** Hazard ratios of mortality comparing the later to the earlier time period\*, by diabetes status, excluding those with prevalent CVD†, in the Framingham Heart Study.

	Earlier Period (1950-1975)			Later Period (1976-2001)			Later vs. Earlier Hazard Ratio (95% CI)	P Value
	No. Deaths	No. P-Y	Mortality Rate per 1000 P-Y	No. Deaths	No. P-Y	Mortality Rate per 1000 P-Y		
<b>Women and Men Combined‡</b>								
<b>All-cause mortality</b>								
No Diabetes	683	72,811	10.9	500	68,242	6.6	0.61 (0.54, 0.69)	<.0001
Diabetes	71	2,643	23.9	110	5,902	13.1	0.59 (0.43, 0.79)	0.0005
<b>CVD mortality</b>								
No Diabetes	293	72,811	4.8	132	68,242	1.1	0.37 (0.30, 0.45)	<.0001
Diabetes	47	2,643	15.3	38	5,902	4.4	0.30 (0.19, 0.46)	<.0001
<b>Non-CVD mortality</b>								
No Diabetes	355	72,811	5.6	337	68,242	4.5	0.81 (0.69, 0.94)	0.005
Diabetes	23	2,643	8.3	62	5,902	7.6	1.05 (0.65, 1.70)	0.84
<b>Women§</b>								
<b>All-cause mortality</b>								
No Diabetes	289	41,611	7.8	211	38,446	4.7	0.61 (0.51, 0.73)	<.0001
Diabetes	33	1,360	23.8	34	2,615	9.7	0.50 (0.32, 0.80)	0.004
<b>CVD mortality</b>								
No Diabetes	107	41,611	3.0	46	38,446	0.9	0.32 (0.22, 0.45)	<.0001
Diabetes	20	1,360	14.0	11	2,615	3.3	0.26 (0.13, 0.55)	0.002
<b>Non-CVD mortality</b>								
No Diabetes	168	41,611	4.4	146	38,446	3.4	0.78 (0.62, 0.98)	0.03
Diabetes	13	1,360	9.8	21	2,615	5.9	0.78 (0.39, 1.55)	0.47
<b>Men§</b>								
<b>All-cause mortality</b>								
No Diabetes	394	31,200	14.9	289	29,796	9.1	0.61 (0.52, 0.71)	<.0001
Diabetes	38	1,283	24.7	76	3,287	17.8	0.65 (0.44, 0.96)	0.03
<b>CVD mortality</b>								
No Diabetes	186	31,200	7.0	86	29,796	2.8	0.39 (0.30, 0.51)	<.0001
Diabetes	27	1,283	17.4	27	3,287	6.0	0.32 (0.18, 0.54)	<.0001
<b>Non-CVD mortality</b>								
No Diabetes	187	31,200	7.1	191	29,796	6.0	0.83 (0.68, 1.02)	0.08
Diabetes	10	1,283	6.6	41	3,287	10.0	1.38 (0.69, 2.76)	0.37

Abbreviations: CVD, cardiovascular disease; P-Y, person-years; CI, confidence interval

\* Total follow-up period is 1950-1975 for earlier period and 1976-2005 for later period.

† CVD is defined as myocardial infarction, stroke, or congestive heart failure.

‡ Mortality rates and relative risks are adjusted for age (years) and sex.

§ Mortality rates and relative risks are adjusted for age (years).

|| CVD deaths and non-CVD deaths do not sum to all-cause deaths due to the presence of deaths of unknown cause in the all-cause mortality group

**Online Supplemental Figure 1.** Sensitivity analysis using a decreasing glucose threshold to define diabetes (DM) status for the age-adjusted hazard ratio comparing participants in the later versus the earlier time periods, stratified by DM status.

