Diabetes and Cardiovascular Disease: Insights from the Framingham Heart Study

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SUMMARY

The role of diabetes in the pathogenesis of cardiovascular disease was unclear until 1979 when Kannel and McGee used data from the Framingham Heart Study to identify diabetes as a major cardiovascular risk factor. It was among the first studies to demonstrate the higher risk of cardiovascular disease in women with diabetes than in men with diabetes. Since then, multiple studies have been done to recognize and curtail cardiovascular risk factors such as smoking, obesity, hypertension, hyperlipidemia, and insulin resistance. This review will examine the contribution of the Kannel and McGee paper and subsequent studies in defining the contribution of several risk factors on cardiovascular disease.

In 1949, it was noted that "the proper control of diabetes is obviously desirable even though there is *uncertainty* as to whether coronary atherosclerosis is more frequent or severe in the uncontrolled diabetic" [1]. The role of diabetes in cardiovascular disease (CVD) had been uncertain until the prominent paper published by Kannel and McGee in 1979 [2] identified it as a major risk factor based on evidence from the Framingham Heart Study (FHS), the seminal prospective study of CVD and its determinants. This study provided an update to the FHS, using data that had been collected for 20 years. The results, hence, changed the way healthcare providers thought about diabetes and paved the way for its establishment as a major cardiovascular risk factor. The Kannel and McGee paper is briefly discussed here with its major implications and contributions to subsequent studies.

DETERMINANTS OF CVD FROM FHS

Kannel and McGee studied the Framingham cohort of men and women 45 to 74 years of age at the time of the study who had been followed biennially over a 20-year period. At each biennial examination, participants diagnosed with the defined cardiovascular endpoints were identified. The diagnosis of diabetes in this study was made based on either a history of treatment with oral hypoglycemic agents or insulin, or a random blood glucose level >150 on 2 separate occasions; participants with these characteristics and an abnormal glucose tolerance test were classified as having diabetes. Selection was performed at each biennial examination based on age, status of diabetes, and other characteristics of interest. At each subsequent biennial examination, incidence of cardiovascular events was documented and the participants were then reclassified.

The investigators looked at 3 variables to determine the effect of diabetes on the incidence of CVD: 1) absolute rate at which CVD develops; 2) relative risk of developing CVD; and 3) the attributable fraction, which is defined as the percent decrease in the incidence of disease that would occur if the risk factor were not present. Attributable fraction minimizes the effect of rare conditions and, therefore, identifies risk factors for a particular disease that, if curtailed, would be of significant importance to the population as a whole.

In the 20 years of follow-up, there were 957 cases of CVD, which included 732 cases of coronary artery disease (CAD), 138 strokes, 179 cases of intermittent claudication, and 219 cases of congestive heart failure (CHF). Looking at the results comprehensively, men had a higher incidence of CVD than did women. Furthermore, comparing the various risk factors, diabetes and left ventricular hypertrophy based on electrocardiographic abnormalities were the least prevalent risk factors when compared with smoking and hypertension.

Diabetes was then individually examined as a risk factor for CVD. First, the relative risk of CVD was examined for those with and without diabetes. Diabetes seemed to double the risk of total CVD in men and triple it in women (Fig. 1). Furthermore, after age-adjustment, relative risks were higher for women than for men for every endpoint that the investigators had considered in the study (CHF, intermittent claudication, stroke, coronary heart disease, CVD, and CVD deaths) (Fig. 1). More significantly, the risks of CHF and of CVD death were doubled for men and tripled for women with diabetes even after adjustment (Fig. 1) [2].

When comparing sex differences, the incidence was greater for men without diabetes than for women without diabetes for every endpoint considered. However, women with diabetes had a higher incidence than did men without diabetes, and for CHF and stroke, women with diabetes had a higher incidence than did men with diabetes [2].

STUDYING DIABETES AS A RISK FACTOR FOR CVD: USING DATA FROM THE FHS

Trends in diabetes

Multiple studies have followed the original Kannel and McGee publication in 1979 to better define the role of

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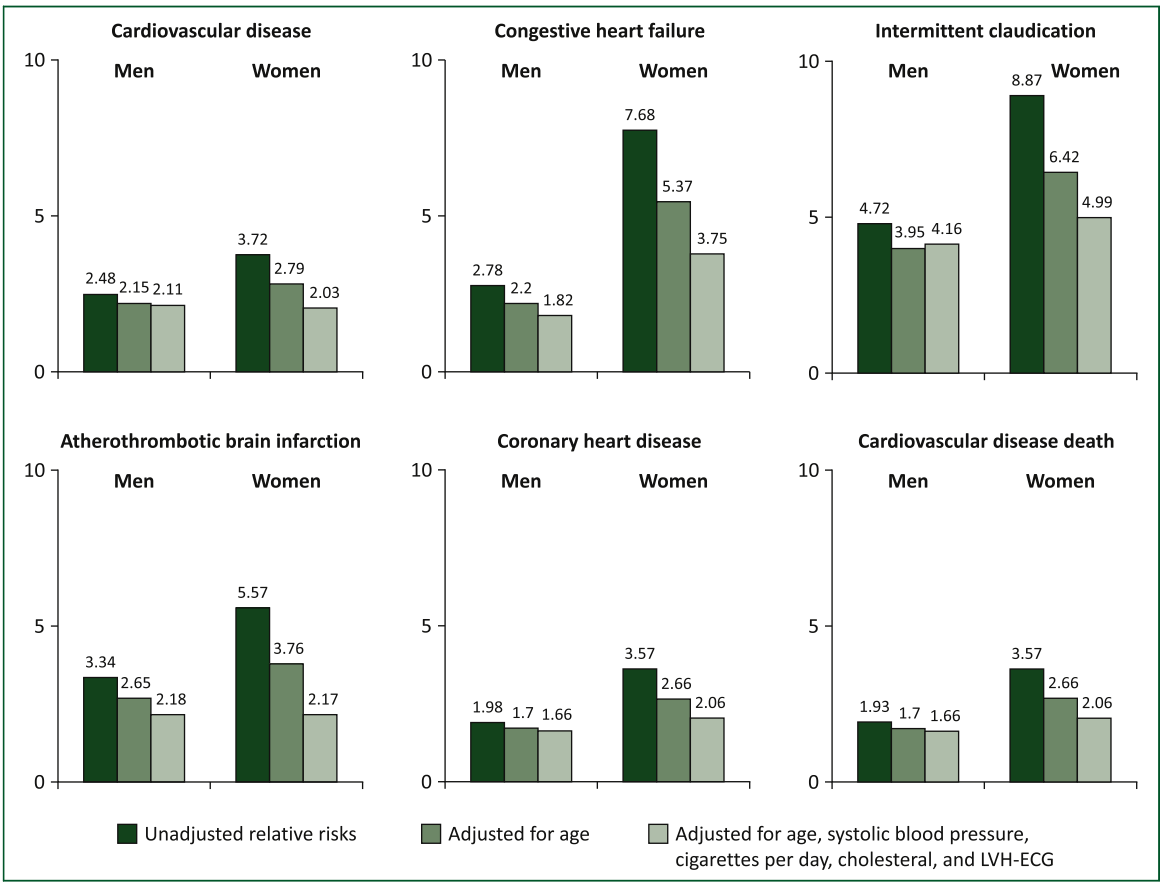

FIGURE 1. Adjusted and unadjusted relative risks of specified events in 2 years for diabetics versus nondiabetics ages 45 to 74 years at time of examination. Reprinted, with permission, from Kannel and McGee [2]. ECG, electrocardiogram; LVH, left ventricular hypertrophy.

diabetes as a risk factor in CVD. Re-examination of the contribution of diabetes is especially important because the definition of diabetes has changed since the publication of the original study, and the prevalence of diabetes has increased dramatically [3]. In 2006, Fox et al. [4] showed that the incidence of diabetes almost doubled between 1970 and 1990. Furthermore, even though there has been a 50% reduction in the rate of CVD among participants with diabetes from the FHS, the relative risk of diabetes as a risk factor for CVD has been unchanged [5].

Additionally, since the Kannel and McGee paper other studies have also looked at how the attributable risk has changed over time for diabetes and CVD. The attributable risk for diabetes as a risk factor for CVD has increased from 5.4% between 1952 and 1974 to 8.7% between 1975 and 1998 [6]. The importance of this finding is highlighted when other factors are observed as well; the attributable risk for other factors has either decreased or remained stable (Fig. 2) [6].

Examination of these findings underscores the large contribution of diabetes to CVD. Using data from the FHS, Preis et al. [7] examined 4,195 participants at 50 years of age and 3,495 participants at 60 years of age from 1970 to 2005. Participants with diabetes, as compared to those without diabetes, had a greater increase in body mass index, a larger decrease in low-density lipoprotein, and a decline in their systolic blood pressure [7]. However, only 14% of participants with diabetes from the FHS had their hypertension optimally controlled and 23.1% had low-density lipoprotein within goal range for those with diabetes [7]. These findings highlight the fact that improvements in risk factor control for CVD that have occurred in the last 3 decades are measureable but not sufficient to meet the goals set for participants with diabetes, therefore leading to a persistently elevated CVD risk in this population.

Diabetes duration was also suggested as an important factor in assessing risk for CVD. In 2004, Fox et al. [8] looked at the effect that the duration of diabetes had on CVD by using data from the original FHS cohort as well as their offspring. The results showed that after adjusting for age, CAD risk factors, and sex for every 10 years of diabetes, the risk of CAD event was 1.38× higher and the risk of CAD-related death was 1.86× higher. This study was important as it showed that CAD and CAD-related deaths

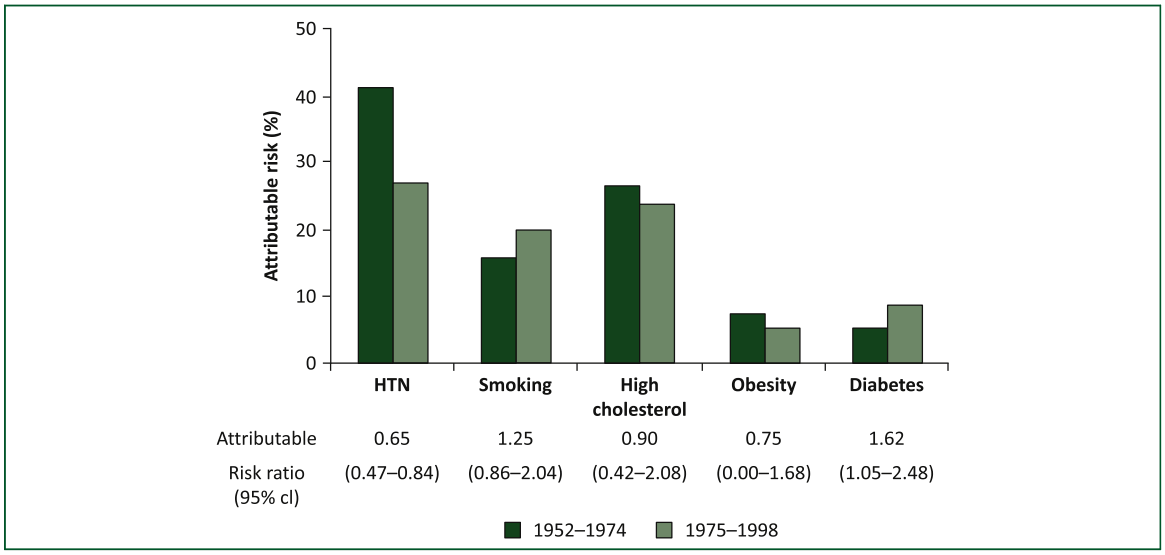

FIGURE 2. Age- and sex-adjusted population attributable risk for diabetes as compared with other standard cardiovascular disease risk factors from the Framingham Heart Study. Reprinted, with permission, from Fox et al. [6]. CI, confidence interval; HTN, hypertension.

are directly related to the duration of diabetes [8]. This study has important implications for primary prevention of diabetes mellitus to delay or stop its onset and, in effect, decrease CAD and CAD-related deaths.

Cardiovascular mortality related to diabetes and diabetes as a CAD equivalent

There have been multiple studies looking at the effect of diabetes on cardiovascular mortality since the Kannel and McGee study, which was able to show an increase in mortality from CVD in participants with diabetes versus those without diabetes. With more emphasis on preventive medicine and better understanding of treatment of diabetes, there has been a decline in cardiovascular mortality in patients with diabetes over the last few decades [9]. However, diabetes continues to be a strong risk factor for CVD and with a 4-fold increase in mortality [6,10]. In 2004, Fox et al. [5] were able to show that there had been a decrease in the rate of CVD both among those with and without diabetes, and multiple other studies have shown decreased mortality rates in both subgroups as well [11,12]. Upon further exploration, the NHANES (National Health and Nutrition Examination Survey) study found that this decrease in mortality is mostly for men and does not apply to women; there was, in fact, an increase in mortality in women with diabetes [10]. All of these studies presented conflicting evidence about changes in cardiovascular mortality, especially among the fraction of the population with diabetes.

Preis et al. [7] were able to use data from the FHS from 1950 to 2005 to look at trends in all-cause and CVD mortality in both men and women with and without diabetes. In contrast to the NHANES study, this study showed a decline in all-cause and CVD mortality in both men and women with diabetes. It also showed that men and women with diabetes continued to be at higher risk of CVD and all-cause mortality than those without diabetes [7]. These findings have been supported and replicated in other studies as well, showing a decrease in CVD mortality in men and women with diabetes (Fig. 3) [7,12].

In 1998, Haffner et al. [13] were able to show that diabetic patients without a prior myocardial infarction were at a similar risk of developing myocardial infarction as were those patients without diabetes and a history of myocardial infarction [13]. Furthermore, in 2005, Whiteley et al. [14] were able to show that middle-aged men and women with diabetes but no CAD were at a lifetime vascular risk as high as individuals with CAD but no diabetes were. However, one of the most important studies identifying diabetes as a CAD risk-equivalent was conducted by Schramm et al. [15] in 3.3 million Danish residents, which showed that patients with diabetes had a CVD risk comparable to those individuals without diabetes. All of these studies highlighted the notion that diabetes should be considered a CAD risk-equivalent.

FRAMINGHAM OFFSPRING STUDY: RISK FACTORS AND SURROGATE MARKERS FOR CVD

The Framingham Offspring Study (FOS) have also provided further insight into insulin resistance as well as diabetes as CVD risk factors. In 2002, Meigs et al. [16] examined 3,370 subjects from the Framingham offspring cohort and found post-challenge hyperglycemia as an independent risk factor for CVD. This is especially

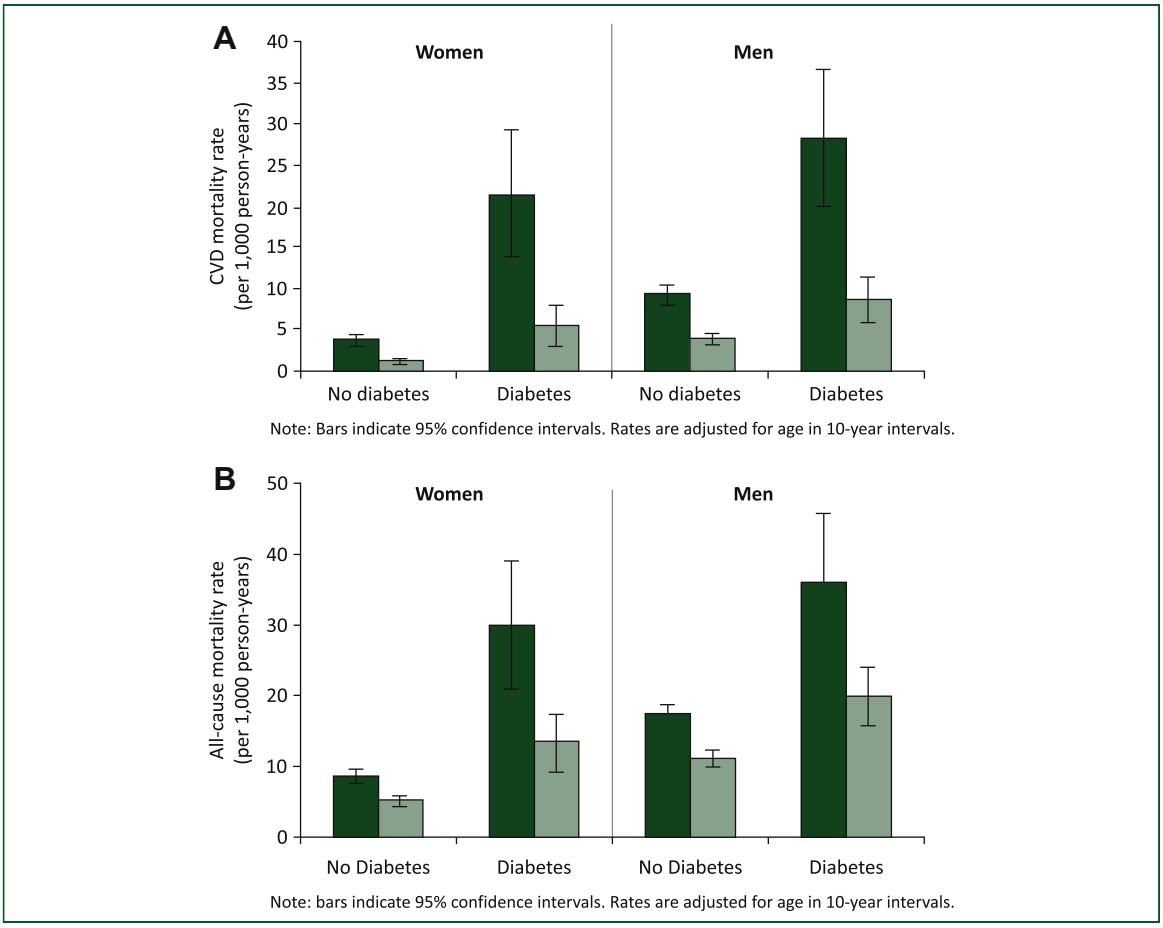

FIGURE 3. Age-adjusted (A) cardiovascular disease (CVD) and (B) all-cause mortality rates among participants with and without diabetes, by sex and time. Reprinted, with permission, from Preis et al. [7].

important because fasting hyperglycemia has largely replaced post-challenge hyperglycemia for diagnosing diabetes [17] and several studies have shown that fasting hyperglycemia overlooks a significant number of people at risk for CVD who are identified using post-challenge hyperglycemia [18,19].

Additionally, other FOS have used data to identify surrogate markers for CVD in diabetics. Meigs et al. [20] found that participants with diabetes had more coronary artery calcification than those without diabetes, indicating a higher burden of subclinical CVD not detected by conventional testing. Similarly, other studies have shown that elevated levels of C-reactive protein [21] and homocysteine [16] are both associated with insulin resistance and an increased risk of CVD.

GLOBAL IMPACT AND OTHER NON-FRAMINGHAM STUDIES FOLLOWING THE KANNEL AND MCGEE ARTICLE

Other studies conducted throughout the world built on the foundation created by the FHS. The INTERHEART (A Study of Risk Factors for First Myocardial Infarction in 52 Countries and Over 27,000 Subjects) collected data from 52 countries and found diabetes, abdominal obesity, and hypertension to be strong risk factors for CAD after smoking and abnormal lipids [22]. Similarly, Stengård et al. [23] were able to show in the Finnish cohort of the Seven Countries Study the role of diabetes in CAD. Hence, the FHS set a precedence for well-designed longitudinal studies around the world that helped our understanding about the role of diabetes in CVD.

Studying global trends in diabetes, Whiting et al. [24] were able to show that the highest diabetes prevalence for 2011 was for Middle East and North Africa; however, the largest increase in adult diabetes by 2030 would be for African nations. Furthermore, even though China and India already have the highest number of people ages 20 to 79 with diabetes (90 and 61.3 million people, respectively), 48% of the predicted increase of 186 million in people with diabetes from 2011 to 2030 would be in these 2 populous nations [24]. Due to the increased risk of CVD in patients with diabetes as seen in the FHS and other

subsequent studies, these statistics present a difficult challenge to health care and an enormous public health dilemma that needs to be more closely monitored and intercepted.

Since the Kannel and McGee paper, many studies have replicated the increased risk of CAD and CAD mortality in women with diabetes compared with men with diabetes [25,26]. The Strong Heart Study showed a larger impact of diabetes on CV risk factors in women, but the reason for an increased risk in women is still not completely understood [27]. Whereas these studies have replicated most of the findings from the Kannel and McGee paper, our understanding of pathogenesis of CVD due to diabetes has improved significantly, with hyperinsulinemia, insulin resistance [28], and hypercoagulability [29] playing a role in the excess CVD risk in patients with diabetes.

IMPACT OF FHS ON RISK ASSESSMENT, GUIDELINES, AND CLINICAL PRACTICE

Since the inception of the FHS, researchers have tried to devise a score that would help predict the risk of developing CAD based on risk factors. Truett et al. [30] were the first to use data from the FHS to develop a risk score for men and women based on 7 risk factors: age, systolic blood pressure, relative weight, hemoglobin, cigarette smoking, and electrocardiographic evidence of left ventricular hypertrophy. Over time, hemoglobin and left ventricular hypertrophy were removed [31]; glucose intolerance was added; and the American Heart Association published a book of risk tables in 1973 [32]. Eventually, in 1991, a point scoring system was developed to help clinicians risk-stratify patients, [33] and, in 2008, a tool was developed for primary care physicians [34]. Data from the FHS, therefore, were crucial in devising the Framingham Risk Score to determine the 10-year risk of developing CAD [34].

Even though our understanding of the pathogenesis of CVD in patients with diabetes has improved, the incidence and prevalence of diabetes has increased significantly as well. Shaw et al. [35] showed that the burden of diabetes will increase significantly from 2010 to 2030, with a 69% increase in adult diabetes in developing countries, and a 20% increase in developed countries; the associated population increase is expected to be 36% and 2%, respectively. Based on these figures, the diabetes burden will lead to increasing morbidity, mortality, stress on healthcare providers, and healthcare-associated costs. A joint statement by the American Heart Association and American Diabetes Association in 2007 said that a multifaceted approach including risk factor control as well as aggressive lifestyle changes must be employed to prevent the development of diabetes and its complications, most importantly CVD [36]. Using the available data, more individualized plans of action with multifactorial interventions need to be devised to reduce the incidence of CVD as well as CVD-related mortality in patients with diabetes.

CONCLUSIONS

The Kannel and McGee study was among the first to describe diabetes mellitus as a significant risk factor for cardiovascular disease, especially among women. Multiple studies have subsequently examined the role of diabetes as well as other coexisting risk factors and comorbidities that increase the risk of CVD. Current guidelines address target levels of coexisting risk factors in those with diabetes. However, recent studies suggest that there may be different levels of recommended glycemic controls depending on either the duration of diabetes or the presence of comorbidities such as existing CVD. Noninvasive screening techniques such as coronary artery calcium score are also being increasingly used in clinical practice to risk-stratify individuals who need more expensive and invasive screening modalities. The Kannel and McGee paper was seminal in identifying an important risk factor for CVD, and the findings have been paramount in guiding research that followed. Future research needs to be done to look at surrogate markers for CVD and to see how successful individualization of treatment protocols is in preventing CVD.

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