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Cardiovascular Disease Risk Factors, Type 2 Diabetes Mellitus, and the Framingham Heart Study

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Abstract

Type 2 diabetes is a common disorder and an important risk factor for cardiovascular disease (CVD). The Framingham Heart Study (FHS) is a population-based epidemiologic study that has contributed to our knowledge of CVD and its risk factors. This review will focus on the contemporary contributions of the FHS to the field of diabetes epidemiology, including data on diabetes trends, genetics, and future advances in population-based studies.

1.0 Description of the current state of knowledge

Diabetes mellitus (DM), defined as elevated fasting or post-prandial blood sugar or more recently the hemoglobin A1c, is increasing in prevalence both in the United States and world-wide. Current estimates of diabetes prevalence by 2030 include 439 million adults world-wide affected.¹ Diabetes is associated with increased morbidity and mortality, specifically due to complications, including diabetic retinopathy, neuropathy, nephropathy, and cardiovascular disease (CVD). CVD accounts for the primary cause of death of all patients with diabetes.² Despite major advances in primary and secondary prevention of the past 50 years, patients with diabetes still are at increased risks of CVD relative to those without diabetes. While two forms of diabetes mellitus exist, type 2 diabetes accounts for the majority of all cases of diabetes. Thus, this review will focus on type 2 diabetes mellitus.

The Framingham Heart Study (FHS) is a population-based prospective family study that began in Framingham, MA in 1948 with the recruitment of the Original Cohort.³ In 1971, children of the Original Cohort, called the Offspring cohort, were enrolled.⁴ Finally, in 2002, the grandchildren of the Original cohort were enrolled (the Third Generation),⁵ making the FHS the longest running family-based study in history. For the past 62 years, investigators at the FHS have collected data related to CVD and its risk factors. Owing to the long duration of follow-up and the rich and carefully-collected phenotypic data, the FHS is an ideal place to study the evolution of CVD risk factors. This review will focus on the contributions of the FHS to diabetes and CVD.

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2.0 Contributions of FHS past

Diabetes was recognized as a CVD risk factor very early on in the exploration of CVD risk factors in the Framingham Heart Study. Here, diabetes was found to be associated with a 2-4 fold increased risk of myocardial infarction,⁶ congestive heart failure,⁷ peripheral arterial disease,⁸ stroke,⁶ and increased mortality.⁶ Moreover, diabetes was consistently found to be a stronger risk factor for CVD in women as compared to men.⁶ Results from the FHS in this regard have been observed in multiple different settings, underscoring the generalizability of these findings. An exhaustive review of the literature in this regard will not be performed here.

3.0 Contributions of FHS present

The FHS continues to provide insights into the relationships between CVD risk factors, diabetes, and cardiovascular disease, in part owing to 60 years of data, which makes the FHS an ideal setting to study disease trends over time, long-term outcomes, and the natural history of disease. This section will briefly review key contributions of the FHS in this area.

3.1. Trends in DM as a CVD Risk Factor

The FHS is well-equipped to study diabetes as outcome. Because the definition of diabetes has changed over time, the ability to update the working definition of diabetes is an important aspect of epidemiology trends data, particularly as compared to self-reported diabetes status that many large surveys use.

The prevalence of diabetes is increasing, and this has been well-recognized from multiple data sources, particularly the NHANES and BRFSS surveys.^{9,10} However, most surveys rely on unique waves of prevalence data over time. The prevalence of a condition may increase if either the rate of new cases of the disease increases, or if survival among those affected increases. The determination of incidence rates can provide insight into this situation. Because the FHS has followed the same individuals over time, we are able to calculate incidence rates. We studied 3104 participants between the ages of 40-55 years old who were free of diabetes between the 1970s and the 1990s. Indeed, we demonstrated a doubling of the incidence of diabetes between the 1970s and the 1990s, which was most prominent among obese individuals (Figure 1).¹¹ However, from this work alone, it is unclear how increases in the incidence of diabetes will affect the rates of CVD.

In order to understand how increasing diabetes incidence may impact rates of CVD, we first explored the rates of CVD among FHS participants with and without diabetes who were examined in the FHS clinic between 1950-1995. While we observed a 50% reduction in the rates of CVD events among participants with diabetes, the relative risk of diabetes as a CVD risk factor remained unchanged.¹²

In concert with the impact of increasing diabetes incidence with the unchanged relative risk of diabetes as a CVD risk factor, we sought to understand the proportion of CVD due (or attributable) to diabetes over time. This concept, known as attributable risk, is a statistical metric that allows for the determination of the impact of a given risk factor on a disease outcome. We found that the attributable risk of CVD due to diabetes increased from 5.4% between the years 1952-1974 to 8.7% between the years 1975-1998.¹³ This resulted in an attributable risk ratio (which is a ratio of attributable risk in two time periods) of 1.62 (Figure 2). In contrast, the attributable risk of other key CVD risk factors either decreased (as in the case of hypertension) or remained stable (see Figure 2). These findings highlight the importance of increasing diabetes incidence on the burden of CVD, and underscore the need to prevent DM, as well as to aggressively treat CVD risk factors in DM.

These findings also highlight the importance of CVD risk factor levels among participants with and without diabetes. In an effort to understand the role of CVD risk factor level changes among participants with and without diabetes, we examined 4195 participants at 50 years of age and 3495 participants at 60 years of age during the time period of 1970 to 2005. We found that compared to FHS participants without diabetes, those with diabetes had a larger increase in body mass index (BMI; Figure 3A), a greater decrease in LDL cholesterol (Figure 3B), and a similar decline in systolic blood pressure (Figure 3C).¹⁴ Further, among FHS participants with diabetes at a mean age of 50 years, only 14% had their hypertension optimally controlled, 23.1% had their LDL cholesterol optimally controlled, 17.1% were still smoking cigarettes, and 61.8% were obese.¹⁴ These findings point out how individuals with diabetes have not had the necessary risk factor reductions as compared to their non-diabetic counterparts in order to overcome the increased risk of CVD that is associated with diabetes.

Finally, as a way to integrate this information, we explored the trends in all-cause and cardiovascular mortality among FHS participants with and without diabetes. We compared two time periods: an earlier time period (1950-1975), and a more contemporary time period (1976-2001). Similar to our findings with CVD events in the setting of diabetes, we observed a decline in both all-cause and CVD mortality among participants with and without diabetes. However, we found that mortality rates and participants with diabetes still remained twice as high as compared to participants without diabetes.¹⁵

In aggregate, these findings from the FHS make several important points. First, the incidence rate of diabetes is increasing. Second, because the relative risk of diabetes as a CVD risk factor has remained constant over time, the relative importance of diabetes with respect to CVD has increased. Finally, individuals with diabetes remain inadequately managed with regard to CVD risk factor levels. These findings highlight the importance of early identification of diabetes and a means to identify diabetes early in the life course to promote the early aggressive management of CVD risk factors.

3.2 Earlier Identification of Diabetes

The importance of the early identification of diabetes is supported by recent data from a screening model program, which highlights the cost-effectiveness of the early identification of diabetes.¹⁶ In the FHS, we have shown that diabetes duration is a risk factor for coronary heart disease mortality,¹⁷

Within the FHS, the importance of pre-diabetes, or subclinical dysglycemia, has been evaluated recently. Because the definition of impaired fasting glucose changed recently from a fasting plasma glucose of 110-125 mg/dl to a fasting plasma glucose of 100-125 mg/dl in the absence of diabetes treatment,¹⁸ we evaluated the impact of this changing definition on CVD risk. In doing so, we uncovered striking gender differences in the relationship between pre-diabetes and incident CVD. In women, both definitions of pre-diabetes conferred an increased risk of coronary heart disease (hazard ratio of 2.2 [old definition], 1.7 [new definition]).¹⁹ However, in men, we observed no increased risk of CVD events by either definition, suggesting that pre-diabetes may be uniquely associated with increased CVD in women.

Understanding risk factors for diabetes is therefore critical to its early diagnosis. Key risk factors for diabetes include obesity^{9,20} and pre-diabetes. A fasting blood sugar well into the “normal range” has been shown to be a risk factor for diabetes.²¹ Indeed, we have shown that the 4-year risk of diabetes among participants in the FHS with pre-diabetes ranges from a 12.7-fold increase (in men) to a 22.3-fold increase (in women).¹⁹ The metabolic syndrome, a constellation of metabolic risk factors that have been observed to cluster with each other

more than would be expected by chance,²² was formally acknowledged as a syndrome involving the fulfillment of at least 3 criteria, including elevated waist circumference, impaired fasting glucose, elevated blood sugar, elevated triglycerides, or low HDL cholesterol.²³ The presence of the metabolic syndrome is a strong risk factor for the subsequent development of diabetes, conferring risks as a nearly 7-fold increased risk among those with as compared to without the metabolic syndrome.²⁴ As a means of better trying to identify who is at early risk for diabetes, a prediction equation for incident diabetes was developed in the Framingham Heart Study.²⁵ A “simple clinical model” was derived, which includes parental history of diabetes, obesity, hypertension, low HDL cholesterol, elevated triglyceride levels, and impaired fasting glucose; the c-statistic for this model was robust at 0.85. Importantly, more complex models with variables such as waist circumference, insulin resistance, 2-hour post-prandial glucose derived from an oral glucose tolerance test, and C-reactive protein, were not independent predictors of diabetes. This prediction model highlights how simple clinical variables that are readily available can be used to identify individuals at high risk for developing diabetes even before they have evidence for disease.

3.3 Genetics of Type 2 Diabetes and Related Glycemic Traits

The introduction of technology into population-based studies, such as the FHS, has brought high-throughput unbiased screens into reality. This has held the most promise thus far in the arena of genetics. It has long-been recognized that parental history contributes to offspring diabetes' risk,²⁶ and fasting glucose was found to be heritable in the FHS.²⁷ Genome-wide association, a high-throughput unbiased approach to genomic locus identification, has identified dozens of genes in association with fasting glucose and type 2 diabetes.²⁸⁻³⁰ The FHS offers the opportunity to test whether knowledge of these genetic loci can improve our ability to detect who will ultimately develop diabetes. To answer this question, we genotyped 18 well-validated single nucleotide polymorphisms (SNPs) that had previously been associated with diabetes in large genetics studies in 2377 participants from the FHS. We found that knowledge of an individual's genotype did not add to information above and beyond the simple clinical model that was previously developed in the FHS.³¹ It is important to acknowledge that current genetics efforts in the Framingham Heart Study have focused on common genetic variants (for e.g., variants that are present in at least 5% of the population). Future efforts will focus on rare genetic variants, which might have stronger effects and hence a potential role in diabetes risk prediction.

4.0 The Future of Diabetes Research in the FHS

The FHS has successfully led to the identification of multiple risk factors for diabetes and for CVD, as well as the interplay between diabetes and CVD. As technology further becomes more common in the FHS and other population-based studies, more unbiased high-throughput screens will be implemented. This is becoming a reality in the Systems Approach to Biomarker Research (SABRe project) in Cardiovascular Disease. This project will take a systems biology approach to CVD and its risk factors, including diabetes. This project will make use of advancing technologies including metabolomics, proteomics, high-throughput immunoassays, gene expression, and microRNA. By integrating information from multiple different data sources with the existing high-quality phenotypic data that have been collected, along with extant genome-wide association data, we will be able to uncover novel biomarkers and mechanisms of diabetes as it relates to CVD.

The SABRe project comes at an important time for diabetes research, as recent clinical trials aiming to reduce CVD risk in patients with diabetes through more aggressive risk factor reduction of standard CVD risk factors including glucose control,³²⁻³⁴ triglycerides,³⁵ and blood pressure³⁶ have not been shown to be effective. It is our hope that unbiased screens

that are currently taking place for genetics, and will soon occur for biomarkers, will have the power to uncover novel mechanisms of disease that will ultimately yield insights into disease pathogenesis and the development of novel therapeutics.

5.0 Questions and Controversies in the Field of Diabetes

One of the major questions and controversies in the field of diabetes as it relates to CVD is the inability to reconcile observational study data with the clinical trial data. Countless studies, including those from Framingham,³⁷ have demonstrated a linear and graded association between increasing hemoglobin A1c, a longer-term marker of glucose levels, and incident CVD. However, nearly all of the clinical trials among patients with type 2 diabetes have failed to show a reduction in CVD events with tighter glucose control, and the ACCORD trial was stopped early owing to an increased risk of cardiovascular mortality among those in the intensive glucose control arm.³²⁻³⁴ The reasons for this are uncertain, and post-hoc analyses of ACCORD have not yet yielded clear insights. The role of epidemiologic studies such as the FHS is evolving, and as such, studies may be able to explore glycemic-related comorbidities, including hypoglycemia, as potential CVD risk factors.

Another major remaining question is why the relative risk for diabetes as a CVD risk factor has failed to decrease over time. As described earlier, the rates of CVD among participants in the FHS have decreased, but this has been outpaced by those without diabetes.¹² In terms of primary prevention, we can aim to reduce the burden of uncontrolled CVD risk factors, including incompletely treated hypertension, dyslipidemia, and participants with diabetes who continue to smoke.¹⁴ Observational studies such as the FHS can help to explore rates of treatment and control for known modifiable risk factors.

6.0 Suggestions for Future Research

Future research in the area of diabetes should focus on high-throughput unbiased screens to uncover novel mechanisms and biology of disease. In addition, research should focus on searching for risk factors for CVD that may be more specific to diabetes, such as hypoglycemia or medication-related co-morbidities.

In conclusion, the FHS has made important contributions to our knowledge in the area of CVD risk factors, diabetes, and incident CVD. Observational studies can highlight trends and treatment gaps. The advent of high-throughput platforms promises to accelerate the rate of discovery.

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Figure 1. Age-sex adjusted 8-year incidence rate of diabetes by body mass index category and decade among participants aged 40-55 years. Error bars represent 95% confidence intervals. Reprinted with permission from *Circulation*.¹¹

Figure 2. Age-and-sex adjusted population attributable risk for diabetes as compared to other standard CVD risk factors from the FHS. Reprinted with permission from *Circulation*.¹³

Figure 3. Risk factors levels among participants aged 50 (left-hand side) and aged 60 (right-hand side) by diabetes (grey) and non-diabetes (black) status for A) BMI; B) Total cholesterol and LDL cholesterol; C) systolic and diastolic blood pressure. Reprinted with permission from *Circulation*.¹⁴