JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 77, NO. 21, 2021

JACC FOCUS SEMINAR

Framingham Heart Study

JACC Focus Seminar, 1/8

Charlotte Andersson, MD, PhD,[a,b] Matthew Nayor, MD, MPH,[a,c] Connie W. Tsao, MD, MPH,[a,d] Daniel Levy, MD,[a] Ramachandran S. Vasan, MD[a,e]

ABSTRACT

The Framingham Heart Study is the longest-running cardiovascular epidemiological study, starting in 1948. This paper gives an overview of the various cohorts, collected data, and most important research findings to date. In brief, the Framingham Heart Study, funded by the National Institutes of Health and managed by Boston University, spans 3 generations of well phenotyped White persons and 2 cohorts comprised of racial and ethnic minority groups. These cohorts are densely phenotyped, with extensive longitudinal follow-up, and they continue to provide us with important information on human cardiovascular and noncardiovascular physiology over the lifespan, as well as to identify major risk factors for cardiovascular disease. This paper also summarizes some of the more recent progress in molecular epidemiology and discusses the future of the study. (J Am Coll Cardiol 2021;77:2680–92) © 2021 Published by Elsevier on behalf of the American College of Cardiology Foundation.

Before antibiotics and vaccines were developed during the first half of the 20th century, communicable diseases were the predominant cause of death in the United States. Indeed, only one-fourth of all deaths in the United States around the year 1900 were attributable to cancer, renal disease, or cardiovascular disease combined (1). However, by the 1940s, the national landscape of cause-specific mortality patterns had changed dramatically, with rapidly declining case-fatality rates being noted for most infectious diseases, such as tuberculosis, rheumatic fever, and pneumonia. By the 1950s, chronic noncommunicable diseases, exemplified by cancer, renal disease, or cardiovascular disease, had emerged as the leading causes of death in the United States, with 68% of all deaths being attributable to these 3 diseases in 1950 (1). In particular, coronary heart disease (CHD) had become a common cause of morbidity and mortality in the mid 1900s, which motivated the U.S. Public Health Service to set up a study aiming to investigate the etiology and natural history of CHD in the community. At that time, very little was understood about the origins of heart diseases and its prevention (2). Given its prior successful completion of public health programs (particularly the 1917 to 1923 Framingham Health and Tuberculosis Demonstration Study) and its proximal location to the leading universities and hospitals in Boston, Massachusetts, the town of Framingham, located approximately 22 miles west of Boston, with a population of approximately 28,000 individuals in the 1940s, was selected for the first large

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

From the [a]National Heart, Lung, and Blood Institute and Boston University's Framingham Heart Study, Framingham, Massachusetts, USA; [b]Department of Medicine, Section of Cardiovascular Medicine, Boston Medical Center, Boston University School of Medicine, Boston, Massachusetts, USA; [c]Cardiology Division, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA; [d]Cardiovascular Division, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts, USA; and the [e]Section of Preventive Medicine and Epidemiology and Cardiovascular Medicine, Departments of Medicine and Epidemiology, Boston University Schools of Medicine and Public Health, Boston, Massachusetts, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received October 14, 2020; revised manuscript received January 4, 2021, accepted January 20, 2021.

ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2021.01.059

HIGHLIGHTS

- The FHS is the longest-running cardiovascular epidemiological study, starting in 1948.
- FHS spans 3 generations of well phenotyped White persons and 2 cohorts comprised of racial and ethnic minority groups.
- Major risk factors for cardiovascular disease in the community have been identified through the FHS.

ABBREVIATIONS AND ACRONYMS

CHD = coronary heart disease

CVD = cardiovascular disease

FHS = Framingham Heart Study

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

LV = left ventricular

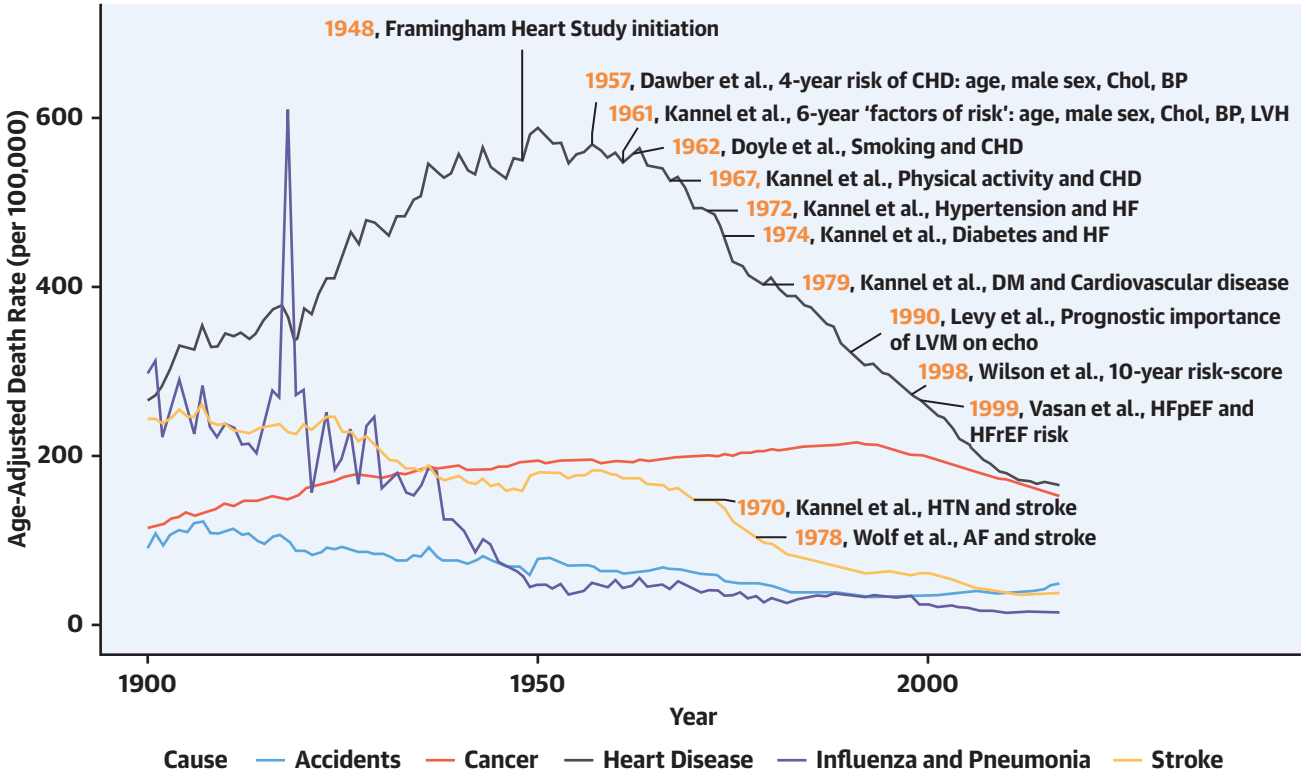
epidemiological study of cardiovascular disease (3). Framingham represented a typical middle-class American community at that time, with a stable population in terms of in- versus out-migration. In one of their first publications describing the aims of the Framingham Heart Study (FHS), Dr. Thomas Royal Dawber, the first FHS principal investigator, and his colleagues stated, "of the epidemiology of hypertensive or arteriosclerotic cardiovascular disease, almost nothing is known" (2). At that time, Dawber et al. (2) hypothesized that there was not one cause of CHD, but rather that multiple causes work slowly within the individual to cause the disease over time, a premise that argued strongly for designing an epidemiological study that is based on "populations of normal composition, including both the sick and the well as they are found in the community." The temporal trends in mortality rates due to the main causes of death in the United States throughout the 1900s and early 2000s, along with examples of landmark scientific contributions from the FHS, are depicted in the **Central Illustration**. The landmark scientific contributions are also outlined in **Table 1**.

Beginning in 1948, 5,209 adult men and women (approximately 19% of the entire population of the town of Framingham) who were free from overt cardiovascular disease (CVD) at study inclusion (termed "normals" by the initial investigators) were invited and agreed to participate in the FHS, with the first individual entering the Heart Study building for a comprehensive clinical examination on September 29, 1948. The age distribution of the study cohort at the time of study entry and throughout follow-up can be seen in **Figure 1**. An executive committee, comprising 15 town residents, was assembled to oversee the study and argued that families should not be divided during sampling. Hence, the initial study sample represented an oversampling of families (i.e., spouse pairs), which facilitated studies of the familial aggregation of various risk factors and diseases, as well as future genetic association studies. Another noteworthy advantage of this approach was that more than 50% of all enrolled participants were women, which was unusual at that time for any scientific investigation of chronic disease.

The original aim of the study was to follow the enrolled participants for the development of CHD for 20 years (i.e., until the end of 1960s). Information that was gained during this initial 20-year period resulted in the first description of the 4-year risk of developing CHD (published in 1957), demonstrating that high blood pressure, high cholesterol levels, and overweight were significantly associated with the development of new-onset CHD (4). Four years later, in 1961, Kannel et al. (5) published a seminal paper on "factors of risk" for the development of CHD, based on the first 6 years of follow-up, showing that high blood pressure and elevated cholesterol levels, as well as left ventricular (LV) hypertrophy on an electrocardiogram, were strong predictors of the risk for developing subsequent CHD (5). Shortly thereafter, smoking and physical inactivity were reported to be strongly associated with CHD risk prospectively (6–8). In 1967, multivariable risk modeling was also applied for the first time, which has several benefits over traditional stratification approaches, including the ability to investigate the relations between several variables simultaneously in a large study cohort (9).

Beginning in 1971, funding for the Heart Study beyond the initially planned 20-year period was secured via a contract between the National Heart Institute (later known as the National Heart, Lung, and Blood Institute) and Boston University that provided the FHS with continued federal support for its ongoing research program. At this point, the FHS was expanded with the addition of an Offspring cohort (established in 1971), comprising children whose parents were enrolled in the Original cohort and the spouses of the children (10). Further expansion of the transgenerational FHS design was facilitated with the recruitment of the Third Generation cohort in 2002, comprising the children of the Offspring cohort participants (i.e., enrollment of the grandchildren of those in the Original cohort) (11). The goals of adding the Offspring and Third Generation cohorts to the FHS included studying temporal trends in CHD risk factors (including birth cohort effects), investigating familial aggregation patterns, and evaluating the

CENTRAL ILLUSTRATION **Age-Adjusted Death Rates for the Leading Causes of Death in the United States and the Framingham Heart Study**



Andersson, C. et al. J Am Coll Cardiol. 2021;77(21):2680–92.

Data are from the Centers for Disease Control and Prevention (156). The highlighted studies are described in Table 1. AF = atrial fibrillation; BP = blood pressure; CHD = coronary heart disease; Chol = cholesterol; DM = diabetes mellitus; echo = echocardiography; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HTN = hypertension; LVH = left ventricular hypertrophy; LVM = left ventricular mass.

genetic determinants of CHD and its risk factors (10). The age distributions at the time of inclusion of the Offspring and Third Generation cohorts were similar to that of the Original cohort (Figure 1). To reflect the changing demographic characteristics of the greater Framingham community, the FHS additionally recruited and enrolled 2 cohorts comprised of racial and ethnic minority groups, termed Omni-1 and Omni-2, (n = 506 and 410, respectively) in 1995 and 2002, respectively. These cohorts included individuals of African American, Hispanic, Asian, Indian, Native American, and Pacific Islander descent.

DATA COLLECTION

In-person visits at the FHS research center have taken place every 2 years for the Original cohort and approximately every 4 to 7 years for the Offspring, Third Generation, and Omni cohorts. During each of these participant visits, a comprehensive interview is performed using standardized medical questionnaires, along with a cardiovascular-focused physical examination, electrocardiogram, biosample collection (blood and urine), and lifestyle-related questionnaires. Additionally, examination-specific tests have been performed at each FHS visit, as outlined in Figure 1. The FHS cohorts are among the most densely phenotyped contemporary cardiovascular epidemiological cohorts. Ongoing surveillance of cardiovascular and noncardiovascular endpoints is accomplished by ongoing review of medical records and participant interviews to ensure timely updated data on key outcome events that constitute FHS clinical endpoints. All potential endpoints are adjudicated by review panels comprising internists and cardiologists (for cardiovascular endpoints) and neurologists (for stroke/dementia endpoints), which enhances their validity.

TABLE 1 Description of the 10 Studies Outlined in Figure 1

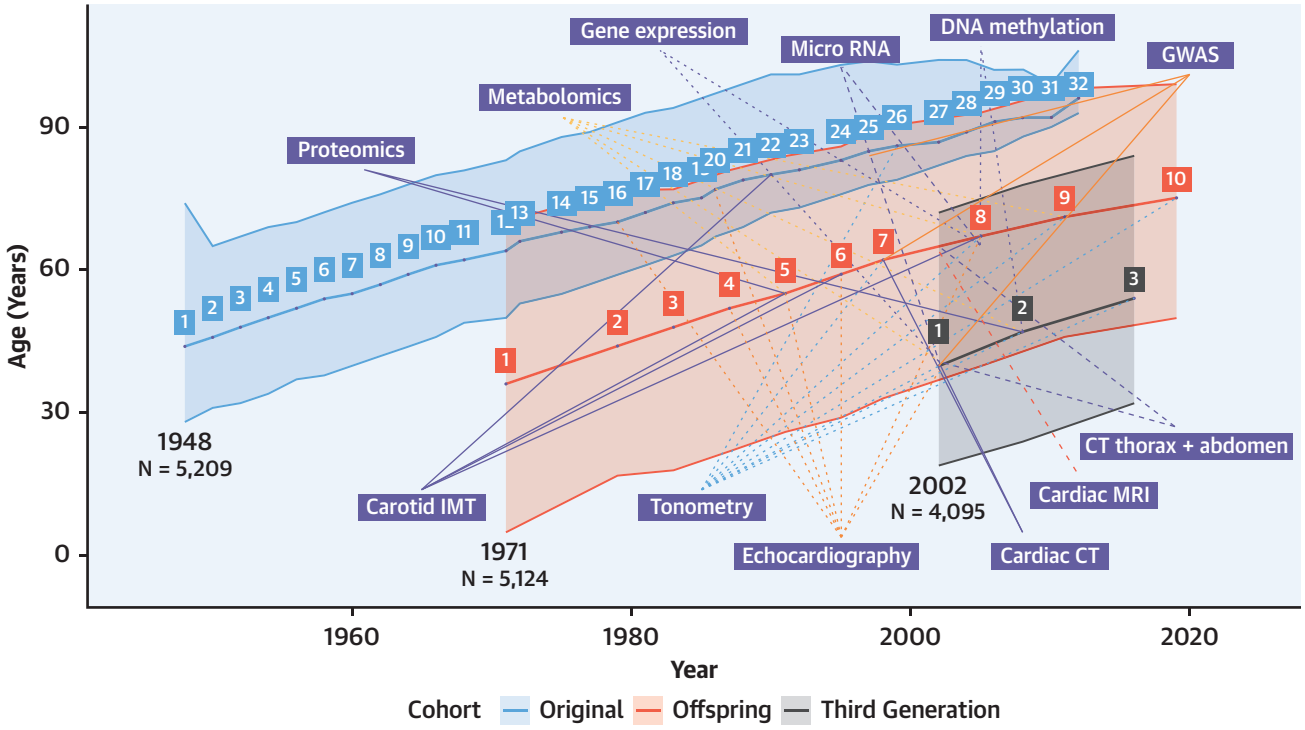
Year	First Author (Ref. #)	Title	Description
1957	Dawber et al. (4)	"Coronary Heart Disease in the Framingham Study"	An early paper reporting on the 4-year risk of developing coronary heart disease. It demonstrated that high blood pressure, high cholesterol levels, and being overweight were significantly associated with the development of new-onset coronary heart disease.
1961	Kannel et al. (5)	"Factors of Risk in the Development of Coronary Heart Disease—Six Year Follow-Up Experience"	The term "factors of risk" for the development of coronary heart disease was used in this follow-up paper, based on data from the first 6 years of follow-up. High blood pressure and elevated cholesterol levels, as well as left ventricular hypertrophy on the electrocardiogram, were strong predictors of the risk for developing subsequent coronary heart disease.
1962	Doyle et al. (6)	"Cigarette Smoking and Coronary Heart Disease. Combined Experience of the Albany and Framingham Studies"	An early study showing that smoking increased the risk of coronary heart disease.
1967	Kannel (8)	"Habitual Level of Physical Activity and Risk of Coronary Heart Disease: The Framingham Study"	Physical inactivity was shown to be a risk factor for coronary heart disease.
1972	Kannel et al. (14)	"Role of Blood Pressure in the Development of Congestive Heart Failure. The Framingham Study"	High blood pressure was reported to increase the risk of developing congestive heart failure.
1974	Kannel et al. (35)	"Role of Diabetes in Congestive Heart Failure: The Framingham Study"	Diabetes was reported to increase the risk of developing congestive heart failure.
1979	Kannel et al. (23)	"Diabetes and Cardiovascular Disease. The Framingham Study"	Diabetes was reported to increase the risk of clinical atherosclerotic events.
1990	Levy et al. (79)	"Prognostic Implications of Echocardiographically Determined Left Ventricular Mass in the Framingham Heart Study"	Increased left ventricular mass was reported to be a strong, independent risk factor for incident cardiovascular disease in asymptomatic individuals.
1998	Wilson et al. (26)	"Prediction of Coronary Heart Disease Using Risk Factor Categories"	During a 12-year follow-up using risk factor categories for cholesterol subfractions, blood pressures, age, sex, diabetes, and smoking, the 10-year absolute risk of coronary heart disease could be effectively predicted among 2,856 women and 2,489 men ages 30 to 74 years (of whom 227 [8%] of women and 383 [15%] of men developed coronary heart disease).
1999	Vasan et al. (40)	"Congestive Heart Failure in Subjects With Normal Versus Reduced Left Ventricular Ejection Fraction: Prevalence and Mortality in a Population-Based Cohort"	One-half of all individuals with prevalent heart failure were reported to have heart failure with a preserved left ventricular ejection fraction—and the prognosis was poor for heart failure with reduced and preserved ejection fraction, with adjusted hazards ratios (for mortality) of 4 for both heart failure subtypes, compared with age- and sex-matched control individuals.

THE 10 MOST IMPORTANT FINDINGS

The FHS has played an important role in several scientific domains. First, it has contributed to the identification and our current understanding of the major risk factors for CHD, heart failure, atrial fibrillation, stroke and dementia, and vascular disease. Second, the FHS has played an important role in the development and application of modern statistical and epidemiological approaches, including the estimation of lifetime risk, risk prediction scores, and risk reclassification metrics to elucidate the incremental utility of risk factors. Third, the FHS cohorts have undergone an in-depth phenotypic characterization that is unique and have facilitated our understanding of human physiology, vascular biology, and subclinical cardiovascular remodeling. Fourth, the FHS has been at the forefront of cardiovascular and noncardiovascular molecular epidemiology. In the next section, we describe some of the seminal papers in each of 10 main cardiovascular domains. It should be acknowledged, however, that our description does not fully or adequately capture the depth and breadth of the study's legacy—there are many more areas where the FHS has contributed important insights such as environmental exposures; endocrine, renal, and pulmonary health and disease; bone and osteoarthritis; eye health; hearing; and longevity and aging research, to name just a few.

HYPERTENSION. Hypertension, a critical risk factor for CVD in the United States and worldwide (12), has been a main focus for the FHS since its early days. At the time of the initiation of the FHS, the consequences of high blood pressure on adverse cardiovascular remodeling and CHD/CVD risk were not well recognized. A common belief before the FHS was, indeed, that higher blood pressure in the elderly represented a compensatory mechanism to maintain normal organ perfusion with aging. The FHS has contributed several landmark papers that have transformed our understanding of the development and importance of hypertension. In one of the first papers, hypertension was shown to be one of the most important risk factors for the development of CHD. During the early 1970s, data from the FHS established the importance of hypertension as a premier risk factor for stroke and congestive heart failure (13–15). Notably, FHS data from the very outset identified the primacy of systolic blood pressure (relative to diastolic blood pressure) in terms of contributions to CVD risk; the recognition and widespread acceptance of systolic pressure as a treatable risk factor for CVD and stroke pathogenesis evolved

FIGURE 1 Age Span of the 3-Generation Cohorts of the Framingham Heart Study by Calendar Period and Examination Cycle



Number refers to examination cycle. Some of the cardiovascular-specific tests are also outlined, as are molecular data collection times. **Dots** represent mean age, and **shaded areas** show minimum to maximum ages for each examination cycle. In addition to the 3 generations of participants outlined, the FHS includes 2 Omni cohorts, which include participants of parallel ages to those in the Offspring and Third Generation cohorts and include similar phenotypic measures. CT = computed tomography; GWAS = genome-wide association studies; IMT = intima-media thickness; MRI = magnetic resonance imaging.

over several subsequent decades. Factors for the short-term risk of developing hypertension were later outlined (16), and it was shown that the lifetime risk of developing hypertension was exceedingly high (90%) (17). Clinically important data from the FHS have also shown that exaggerated blood pressure response during exercise and higher serum aldosterone levels are important risk factors for the development of overt hypertension (18,19). Data from the FHS have also provided important insights into the rates of progression from optimal blood pressure levels to hypertension in the community (20). More recently, we clarified the long-term relations between aortic stiffness and hypertension by demonstrating that most often, higher arterial stiffness preceded the onset of systolic hypertension rather than the other way around (21). Such a temporal association (between arterial stiffness and elevated blood pressure) was supported subsequently by observations demonstrating that parental hypertension was associated with increased vascular stiffness in their nonhypertensive offspring (i.e., before the onset of hypertension) (22).

CORONARY HEART DISEASE. Some of the first and most impactful studies underlying our understanding of the causes of CHD originated from the FHS. Early reports established that habitual levels of physical exercise (8), cigarette smoking (8), diabetes (23), blood cholesterol levels (24), and obesity were risk factors for CHD (25). The initial description of "factors of risk" for CHD (5) that were later incorporated into 10- and 30-year risk scores for the development of CHD also emerged from the FHS (26,27). The FHS 10-year CHD risk calculator was for many years incorporated into the National Cholesterol for Education Adult Treatment Panel III and determined recommendations for lipid-lowering treatment in primary prevention settings (28). The CHD risk equation was subsequently expanded to a more general CVD risk equation (29). The FHS cohort has also been part of the more recent efforts of estimating the 10-year risk of developing

atherosclerotic cardiovascular disease in the American Heart Association/American College of Cardiology pooled-cohort atherosclerotic cardiovascular disease equation that is the basis of current national recommendations for the initiation of lipid-lowering therapy (30). One of the first studies to highlight the importance of parental CHD as an independent risk factor for disease risk in Offspring was conducted in the FHS (31). Finally, the FHS has provided estimates on the lifetime risk of CHD in the community (32).

HEART FAILURE. The FHS was one of the first studies to illuminate the epidemiology of heart failure in the community (33,34). Major risk factors for heart failure, that is, diabetes (34,35), obesity (36), hypertension (14,15), and parental heart failure (37), were identified in the Original and Offspring FHS cohorts, and later, integrated risk scores estimating the risk of developing heart failure were published based on serial observations (38). The lifetime risk of heart failure in the FHS has been estimated at 20% (39). The FHS has also contributed with seminal work to our current understanding of the epidemiology of heart failure with preserved (HFpEF) versus reduced (HFrEF) LV ejection fraction. As one of the first landmark papers on the topic, FHS data demonstrated that approximately 50% of all individuals in the community who developed clinical heart failure had a preserved LV ejection fraction, and this group of participants with HFpEF experienced a high long-term mortality compared to age-matched control individuals (40). Over time, the proportion of all heart failure cases with a preserved ejection fraction has increased in the FHS, partly reflective of better treatment of select risk factors for HFrEF, such as coronary artery disease and hypertension (41,42). More recently, FHS data demonstrated that heart failure subtype (i.e., HFpEF vs. HFrEF) by itself was not a good discriminant of the risk of hospitalizations and causes of hospitalizations (43). In contrast, among participants with overt heart failure, their comorbidity burden and hospitalization for a specific cause led to frequent recurrent hospitalizations due to the same cause (43).

ATRIAL FIBRILLATION. The FHS was one of the first studies to report the major risk factors for atrial fibrillation (valvular heart disease, heart failure, diabetes, male sex, and advancing age) (34,44), and later, an integrated risk function was developed to estimate the risk of developing the condition (variables included electrocardiographic PR interval, age, sex, systolic blood pressure, treatment for hypertension, valvular heart disease, and heart failure) (45). The initial atrial fibrillation risk function has been expanded more recently into the CHARGE-AF (Cohorts for Heart and Aging Research in Genomic Epidemiology-atrial fibrillation) risk score, in which the FHS is one of many contributing studies (46). The FHS was also one of the initial studies to show that atrial fibrillation increases the risks of developing stroke, heart failure, and all-cause mortality in the community, with the first report being published in 1978 (47–49). Moreover, the FHS has contributed with estimates of the lifetime risks of developing atrial fibrillation (with most recent estimates ranging between 23% and 39%, depending on risk factor profiles) (50). FHS investigators have reported that atrial fibrillation is associated not only with clinical stroke but also with impaired cognitive performance and longitudinal cognitive decline (51,52).

NEUROLOGICAL OUTCOMES (STROKE AND DEMENTIA). The FHS has a comprehensive neuroepidemiology program where all FHS participants are under active surveillance for developing stroke, cognitive impairment, and dementia (including Alzheimer's disease). Early reports from the FHS established hypertension (13), smoking (53), atrial fibrillation (47), and LV hypertrophy as key risk factors for stroke (54). These risk factors were later shown to be related to smaller brain volumes on magnetic resonance imaging and to impaired cognitive function in individuals without a history of stroke (55). The cumulative lifetime risks of stroke and dementia was reported to be 1 in 3 in the FHS (56), and having a parent with stroke was reported to increase the risk of stroke by 3-fold (57). The FHS was also the first study to demonstrate that the risk of dementia increased longitudinally with higher levels of serum homocysteine, which is now a well-acknowledged risk factor for dementia (58,59). As noted for trends in frequencies of heart failure and asymptomatic LV systolic dysfunction, over the past 3 decades, the FHS participants have experienced a decline in the incidence rates of stroke and dementia, partly as a result of improvement of the cardiovascular risk factor profiles over time among study participants (60,61). More recently, because of the generous donation of brains postmortem by participants (who consent when they are alive), the cumulative burden of cardiovascular risk factors at midlife was shown to be associated with cortical and subcortical infarcts but not with overall Alzheimer pathology at late life (62).

SUBCLINICAL AND CLINICAL VASCULAR DISEASE. The FHS was one of the first studies to establish an association of smoking with intermittent claudication (63). In later decades, the FHS cohorts have undergone comprehensive, state-of the-art phenotyping for

subclinical vascular disease and function in a variety of vascular beds that have contributed to our understanding of the pathobiology of atherosclerosis, arteriosclerosis, and endothelial dysfunction, as well as the progression of subclinical vascular disease to hard CVD events. Available measures include aortic size and atherosclerotic and calcification burden in the aorta and aortic and mitral valves; carotid intimal-medial thickness on ultrasonography; and coronary artery calcifications based on computed tomography, echocardiography, and cardiovascular magnetic resonance, as well as tonometry-derived measures of carotid-femoral pulse wave velocity and ultrasound-guided measures of brachial artery flow-mediated dilation. For instance, the FHS data demonstrated that arterial stiffness is a strong, independent risk factor for a first CVD event (64) and that there is a residual risk of cardiovascular events even with well-controlled hypertension because of persistent increased vascular stiffness (65). Arterial stiffness has also been shown to be associated with target end-organ damage, including albuminuria and LV hypertrophy (66), cognitive impairment, subclinical brain damage, and dementia (67–70), as well as with atrial fibrillation (71) and heart failure (72). The prevalence of subclinical aortic atherosclerosis based on cardiovascular magnetic resonance was reported to be high (approximately 50%) in the FHS. Like other population-based studies presented in this theme issue of the *Journal*, data from the FHS have confirmed the ability of coronary calcification scores on computed tomography to reclassify individuals at intermediate risk of CHD and have shown an independent prognostic importance of calcification across the different vascular beds for the future risk of CVD (73). More recently, the FHS data also demonstrated that increased aortic size, a precursor of aortic aneurysms and a risk factor for aortic dissection, is a heritable trait (74).

CARDIAC IMAGING. The FHS was an early adopter of cardiac imaging modalities among community-based cohort studies and introduced echocardiography to its routine participant study visits in the late 1970s. Normal ranges for ventricular mass and risk factors for LV hypertrophy (i.e., advancing age, obesity, and high blood pressure) were established shortly after the introduction of cardiac ultrasonography (75,76), along with normal reference values for LV wall thickness, left atrial dimension, and aortic root size in the community (77,78). The FHS has been important for describing the prognostic importance of LV hypertrophy and other abnormal sonographic findings in asymptomatic individuals in the community (79). The FHS also highlighted the adverse prognostic significance of asymptomatic LV systolic dysfunction and dilation by documenting an increased long-term risk of developing overt heart failure (80,81). Given its longitudinal design with repeated echocardiographic measures, the FHS has also described how cardiac remodeling occurs over the adult life course and with normal aging. LV systolic ejection fraction, aortic root, and left atrial size increase with age, whereas the LV end-diastolic dimension decreases (82). Further, LV diastolic function tends to worsen with age, but the age-related decrements in LV diastolic function can be partially attenuated by favorable cardiometabolic risk profiles (83). The prevalence of asymptomatic LV systolic dysfunction declined between 1985 and 2014 in the FHS, partly as a result of better risk factor control (lower prevalences of CHD and poorly controlled blood pressures) (41). More recently, the FHS has also contributed reference values for and clinical CVD risks associated with myocardial strain (on speckled tracking echocardiography), left atrial emptying fraction, and left atrial function index (84–88). Finally, the FHS has established normative values of ventricular mass, cavity volumes, and systolic function measures in the general population based on cardiac magnetic resonance imaging (the current gold standard modality to assess ventricular structure) (89).

BIOMARKERS. The FHS has been at the forefront of biomarker research for risk prediction in the community. For instance, some of the early biomarker research showed that a multimarker panel of 10 proteins (plasma natriuretic peptides, C-reactive protein, renin, aldosterone, fibrinogen, D-dimer, plasminogen-activator inhibitor type 1, homocysteine, and urinary albumin-to-creatinine ratio) was associated with the risk of developing major cardiovascular events and deaths but contributed only minimally to incremental prediction of these events beyond standard risk factors (90). Important work based on the FHS also demonstrated a natriuretic handicap associated with obesity and showed that blood natriuretic peptide concentrations were suboptimal to screen for LV systolic dysfunction and LV hypertrophy in the community (91,92).

GENETICS AND GENOMICS OF CVD AND ITS RISK FACTORS. Genetic discovery in the FHS is facilitated by the family-based sampling, which enables analyses of heritability, linkage, and genome-wide association studies for relevant clinical traits. Starting in 2007, FHS participants have been genotyped with array-based genotyping platforms, initially with the 100K Project (100K Affymetrix [Santa Clara,

California]) and, later, with more dense platforms (500K Affymetrix plus 50K Affymetrix supplement), exome sequencing, and whole-genome sequencing platforms, the last of these through the TOP-Med (Trans-Omics for Precision Medicine) project of the National Heart, Lung, and Blood Institute. The FHS cohorts have also undergone high-throughput assays for whole-blood DNA methylation, microRNA, and gene expression profiling. The majority of participants have consented for genetics and genomics analyses, and the numbers of individuals with available biomarkers are available elsewhere (93). These genetic and genomic data have contributed to important insights into the molecular epidemiology of CVD (94,95), blood pressure (96,97), coronary artery disease (98–101), stroke (102), lipid levels (99,103), aortic stenosis (104), atrial fibrillation (105), and body mass index (106), and they have elucidated the genomic architecture of echocardiographic traits and heart failure (107–110). Many of the investigations have been facilitated by multicohort collaborations, including the CHARGE (Cohort of Heart and Aging Research in Genomic Epidemiology), EchoGen (Echo Genetics), DIAGRAM (Diabetes Genetics Replication and Meta-analysis), MAGIC (Meta-analyses of Glucose and Insulin-Related Traits Consortium), CARDIoGRAM (Coronary Artery Disease Genome-Wide Replication and Meta-analysis), and HERMES (Heart Failure Molecular Epidemiology for Therapeutic Targets) consortia (107,111–115). The summary statistics estimates from these and other genome-wide association studies (exemplified by the GRASP [Genome-Wide Repository of Associations Between SNPs and Phenotypes] database compiled by Johnson et al. [116]) (117,118) continue to serve as important tools for exploring causal inference studies based on mendelian randomization principles (119–121).

MULTIOMICS STUDIES OF CVD AND ITS RISK FACTORS. The FHS has implemented several initiatives in the fields of molecular epidemiology and is at the forefront of discovering clinical correlates and disorders associated with metabolomic, lipidomic, and proteomic profiling. More recently, the FHS participants have also contributed stool microbiome data, which will be an important resource to understand the influence of the gut microbiome on health and disease risks. Indeed, all of these multiomics data will yield additional important insights into various pathophysiological states in the years to come and have already highlighted biological pathways involved in the development of, for example, diabetes (122–124), high body mass index (125), renal disease (126,127), longevity (128), heart failure (129,130), atrial fibrillation (131), dyslipidemia (99), atherosclerotic disease (132,133), and acute exercise (134). In addition, microbiome data recently solved a long unanswered question, that is, why certain people absorb cholesterol from the intestines, while others do not, by discovering that certain bacteria subtypes metabolize cholesterol to the unabsorbable coprostanol and that individuals whose gut is rich with select bacterial species had higher levels of fecal cholesterol and lower levels of blood cholesterol in the FHS (with the magnitude of variation being comparable to that carried by common genetic variants of lipid homeostasis) (135).

FUTURE RESEARCH DIRECTIONS

FUTURE LEGACY AS AN EPIDEMIOLOGICAL COHORT STUDY. The combination of deep phenotypic measures (many with serial measures over time), familial and transgenerational enrollment structure, and standardized adjudication of outcomes with long-term follow-up over 3 separate generations make the FHS a valuable resource for the scientific community worldwide. In this context, the FHS design is optimal for studying temporal trends in risk factors for CVD, given the standardized measurements of risk factors and consistent use of stringent criteria for the adjudication of key outcome events. However, the advent of modern, large-scale epidemiological studies that use big data, such as the UK Biobank (136), Million Veteran Program (137), and All of Us initiative (138), has complemented findings from smaller-sized cohort studies like the FHS; these large studies offer the ability to study rare diseases, can provide more precise estimates of effect sizes for various associations because of greater statistical power, and may in many cases allow for more refined statistical modeling (e.g., machine learning) because of their larger sample size. However, the precise assessment of risk factors and events is essential for accurate descriptive epidemiology and risk prediction, especially when the associations are modest, and here, the FHS continues to have an important role. In addition, the FHS offers a unique opportunity to study the human physiome over the life course by virtue of the dense phenotyping of its participants, serial and transgenerational measurements, and the use of standardized and reproducible epidemiological methods (with longitudinal tracking of bias, drifts, and intra- and interobserver variability of measurements). The FHS has recently expanded its physiologic profiling even more with cardiopulmonary

exercise testing (hemodynamic and ventilatory gas exchange measures using a metabolic cart and exercise bicycle ergometry) that will help identify clinical correlates, risk factors, and the pathophysiology of impaired exercise tolerance and the relations of these factors to disease, for example, HFpEF risk (134,139). The wealth of biomarker data, together with its rich additional phenotyping, renders the cohort uniquely suitable for refining analyses based on machine learning principles to gain deeper insight into the physiome. In this context, the FHS has a long tradition and will continue to contribute to the development of statistical approaches for modern epidemiological studies, with a focus on the efficient processing of large amounts of data through dimensionality reduction. The FHS will also continue to play an important role in CVD epidemiology and will complement larger-scale studies by providing mechanistic insights into the molecular pathophysiology of subclinical and clinical CVD over the life course in individuals, within families, and across generations. The transgenerational design also makes it ideal to perform several types of genetic and genomics studies (e.g., heritability, family-based association tests, and vertical segregation of disease variants). The continued impact of the FHS in the latter setting is exemplified by recent high-impact publications (74,140–142).

More recently, the FHS has been participating in large collaborative consortia, such as MAGIC, DIAGRAM, and CHARGE; the last of these is a genetic effort that has resulted in more than 700 publications so far. In addition, the FHS is part of the cross-cohort collaboration, which is predominantly for nongenetic projects, and the TOPMed initiative, which is also a National Institutes of Health–funded initiative to enhance genetic and multiomic studies. These and other cross-cohort collaborations will continue.

E-HEALTH. The FHS has begun to collect multiple electronic health data, including continuously measured physical activity levels by wearable devices, and it has launched the e-FHS initiative in which blood pressure, weight, heart rate, and questionnaires are linked to smartphone applications and can be transmitted electronically to an FHS central station. During the COVID-19 epidemic, such digital initiatives were shown to be increasingly important, and the FHS and other initiatives will be important tools to understand how information and digital data can be effectively used to risk stratify ambulatory individuals and predict subclinical and clinical disease. Potential next steps in the digital program may involve home monitoring of biomarkers (e.g., blood biomarkers through finger sticks) and the use of tele-examinations.

TRAINING THE NEXT GENERATION OF RESEARCHERS. The FHS has trained countless epidemiologists and clinical scientists throughout the years. It is an important aim to continue to train and give opportunities for bioinformaticians, biostatisticians, epidemiologists, and clinician-researchers to grow and become independent researchers moving forward. Our current educational and training activities include mentoring of medical residents (via an FHS pathway and an R38 [STaRR (Stimulating Access to Research in Residency)] grant), post-doctoral fellows (T32), and externally funded national and international researchers. Moving forward, we also hope that more investigators from institutions across the United States and worldwide will use the FHS datasets. For instance, there are more than 1.5 million biosamples available in the FHS and thousands of datasets. Importantly, the majority of these data can be accessed at no cost for institutions with appropriate review board approvals and data storage safety measures through dbGap for genetic and genomic studies and BioLincc for nongenetic studies respectively.

CONCLUSIONS

The FHS was the first and one of the most impactful studies of CVD epidemiology in the United States and worldwide. It has had a major impact on our understanding of the natural history of, risk factors for, and temporal trends in CVD, and it has additionally contributed as an inspiration for several other studies in the United States and Europe that have yielded complementary information on the epidemiology of cardiovascular diseases (93,143–155). The FHS has also significantly enhanced our understanding of cardiovascular physiology through its deeply phenotyped participants and the multitude of mechanistic studies that have been conducted. Through continuous surveillance, its transgenerational design, multiple functional and anatomic tests performed at several timepoints, and high-throughput omics, it will continue to serve as an important study in the field of cardiovascular medicine in the years to come.

ACKNOWLEDGMENTS The FHS acknowledges the support of contracts NO1-HC-25195, HHSN26820 1500001I, and 75N92019D00031 from the National Heart, Lung, and Blood Institute. The authors also

acknowledge the dedication of the FHS study participants, without whom this research would not be possible.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr. Nayor is supported by the National Heart, Lung, and Blood Institute (K23-HL138260). Dr. Tsao is supported by the National Institutes of Health (5R03-HL145195). Dr. Levy is supported by the Division of Intramural Research of the National Heart, Lung, and Blood Institute of the National Institutes of Health. Dr. Vasan is supported in part by the Evans Medical Foundation and the Jay and Louis Coffman Endowment from the Department of Medicine, Boston University School of Medicine. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESSES FOR CORRESPONDENCE: Dr. Charlotte Andersson, Section of Cardiovascular Medicine, Department of Medicine, Boston University Schools of Medicine and Public Health, 72 East Concord Street, Boston, Massachusetts 02118, USA. E-mail: ca@heart.dk. OR charlotte.andersson@bmc.org. Twitter: @ca_heart_dk. OR Dr. Ramachandran S. Vasan, Section of Preventive Medicine and Epidemiology and Cardiovascular Medicine, Departments of Medicine and Epidemiology, Boston University Schools of Medicine and Public Health, 72 East Concord Street, Boston, Massachusetts 02118, USA. E-mail: vasan@bu.edu.

REFERENCES

1. Gordon T. Mortality in the United States, 1900-1950. Public Health Rep 1953;68:441–4.

2. Dawber TR, Meadors GF, Moore FE Jr. Epidemiological approaches to heart disease: the Framingham Study. Am J Public Health Nations Health 1951;41:279–81.

3. Mahmood SS, Levy D, Vasan RS, Wang TJ. The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective. Lancet 2014;383:999–1008.

4. Dawber TR, Moore FE, Mann GV. Coronary heart disease in the Framingham study. Am J Public Health Nations Health 1957;47:4–24.

5. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J 3rd. Factors of risk in the development of coronary heart disease—six year follow-up experience. The Framingham Study. Ann Intern Med 1961;55:33–50.

6. Doyle JT, Dawber TR, Kannel WB, Heslin AS, Kahn HA. Cigarette smoking and coronary heart disease. Combined experience of the Albany and Framingham studies. N Engl J Med 1962;266:796–801.

7. Doyle JT, Dawber TR, Kannel WB, Kinch SH, Kahn HA. The relationship of cigarette smoking to coronary heart disease; the second report of the combined experience of the Albany, NY. and Framingham, Mass. studies. JAMA 1964;190:886–90.

8. Kannel WB. Habitual level of physical activity and risk of coronary heart disease: the Framingham study. Can Med Assoc J 1967;96:811–2.

9. Truett J, Cornfield J, Kannel W. A multivariate analysis of the risk of coronary heart disease in Framingham. J Chronic Dis 1967;20:511–24.

10. Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP. The Framingham offspring study. Design and preliminary data. Prev Med 1975;4:518–25.

11. Splansky GL, Corey D, Yang Q, et al. The Third Generation cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: design, recruitment, and initial examination. Am J Epidemiol 2007;165:1328–35.

12. Bromfield S, Muntner P. High blood pressure: the leading global burden of disease risk factor and the need for worldwide prevention programs. Curr Hypertens Rep 2013;15:134–6.

13. Kannel WB, Wolf PA, Verter J, McNamara PM. Epidemiologic assessment of the role of blood pressure in stroke. The Framingham Study. JAMA 1970;214:301–10.

14. Kannel WB, Castelli WP, McNamara PM, McKee PA, Feinleib M. Role of blood pressure in the development of congestive heart failure. The Framingham Study. N Engl J Med 1972;287:781–7.

15. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA 1996;275:1557–62.

16. Parikh NI, Pencina MJ, Wang TJ, et al. A risk score for predicting near-term incidence of hypertension: the Framingham Heart Study. Ann Intern Med 2008;148:102–10.

17. Vasan RS, Beiser A, Seshadri S, et al. Residual lifetime risk for developing hypertension in middle-aged women and men: the Framingham Heart Study. JAMA 2002;287:1003–10.

18. Morshedi-Meibodi A, Larson MG, Levy D, O'Donnell CJ, Vasan RS. Heart rate recovery after treadmill exercise testing and risk of cardiovascular disease events (the Framingham Heart Study). Am J Cardiol 2002;90:848–52.

19. Vasan RS, Evans JC, Larson MG, et al. Serum aldosterone and the incidence of hypertension in nonhypertensive persons. N Engl J Med 2004;351:33–41.

20. Vasan RS, Larson MG, Leip EP, Kannel WB, Levy D. Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study. Lancet 2001;358:1682–6.

21. Kaess BM, Rong J, Larson MG, et al. Aortic stiffness, blood pressure progression, and incident hypertension. JAMA 2012;308:875–81.

22. Andersson C, Quiroz R, Enserro D, et al. Association of parental hypertension with arterial stiffness in nonhypertensive offspring: the Framingham Heart Study. Hypertension 2016;68:584–9.

23. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham Study. JAMA 1979;241:2035–8.

24. Castelli WP, Abbott RD, McNamara PM. Summary estimates of cholesterol used to predict coronary heart disease. Circulation 1983;67:730–4.

25. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. Circulation 1983;67:968–77.

26. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837–47.

27. Pencina MJ, D'Agostino RB Sr., Larson MG, Massaro JM, Vasan RS. Predicting the 30-year risk of cardiovascular disease: the FRAMINGHAM HEART STUDY. Circulation 2009;119:3078–84.

28. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.

29. D'Agostino RB Sr., Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743–53.

30. Goff DC Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2935–59.

31. Myers RH, Kiely DK, Cupples LA, Kannel WB. Parental history is an independent risk factor for coronary artery disease: the Framingham Study. Am Heart J 1990;120:963–9.

32. Lloyd-Jones DM, Wilson PW, Larson MG, et al. Lifetime risk of coronary heart disease by

cholesterol levels at selected ages. Arch Intern Med 2003;163:1966–72.

33. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. N Engl J Med 1971; 285:1441–6.

34. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol 1993;22:6A-13A.

35. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol 1974;34:29–34.

36. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. N Engl J Med 2002; 347:305–13.

37. Lee DS, Pencina MJ, Benjamin EJ, et al. Association of parental heart failure with risk of heart failure in offspring. N Engl J Med 2006;355: 138–47.

38. Kannel WB, D'Agostino RB, Silbershatz H, Belanger AJ, Wilson PW, Levy D. Profile for estimating risk of heart failure. Arch Intern Med 1999; 159:1197–204.

39. Lloyd-Jones DM, Larson MG, Leip EP, et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. Circulation 2002;106:3068–72.

40. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. J Am Coll Cardiol 1999; 33:1948–55.

41. Vasan RS, Xanthakis V, Lyass A, et al. Epidemiology of left ventricular systolic dysfunction and heart failure in the Framingham Study: an echocardiographic study over 3 decades. J Am Coll Cardiol Img 2018;11:1–11.

42. Tsao CW, Lyass A, Enserro D, et al. Temporal trends in the incidence of and mortality associated with heart failure with preserved and reduced ejection fraction. J Am Coll Cardiol HF 2018;6: 678–85.

43. Velagaleti RS, Larson MG, Enserro D, Song RJ, Vasan RS. Clinical course after a first episode of heart failure: insights from the Framingham Heart Study. Eur J Heart Fail 2020;22:1768–76.

44. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA 1994;271:840–4.

45. Schnabel RB, Sullivan LM, Levy D, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. Lancet 2009;373:739–45.

46. Alonso A, Krijthe BP, Aspelund T, et al. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. J Am Heart Assoc 2013;2:e000102.

47. Wolf PA, Dawber TR, Thomas HE Jr., Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. Neurology 1978;28:973–7.

48. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998;98:946–52.

49. Santhanakrishnan R, Wang N, Larson MG, et al. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. Circulation 2016;133:484–92.

50. Staerk L, Wang B, Preis SR, et al. Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham Heart Study. BMJ 2018;361:k1453.

51. Elias MF, Sullivan LM, Elias PK, et al. Atrial fibrillation is associated with lower cognitive performance in the Framingham offspring men. J Stroke Cerebrovasc Dis 2006;15:214–22.

52. Nishtala A, Piers RJ, Himali JJ, et al. Atrial fibrillation and cognitive decline in the Framingham Heart Study. Heart Rhythm 2018;15:166–72.

53. Wolf PA, D'Agostino RB, Kannel WB, Bonita R, Belanger AJ. Cigarette smoking as a risk factor for stroke. The Framingham Study. JAMA 1988;259: 1025–9.

54. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. Stroke 1991;22: 312–8.

55. Seshadri S, Wolf PA, Beiser A, et al. Stroke risk profile, brain volume, and cognitive function: the Framingham Offspring Study. Neurology 2004;63: 1591–9.

56. Seshadri S, Beiser A, Kelly-Hayes M, et al. The lifetime risk of stroke: estimates from the Framingham Study. Stroke 2006;37:345–50.

57. Seshadri S, Beiser A, Pikula A, et al. Parental occurrence of stroke and risk of stroke in their children: the Framingham study. Circulation 2010; 121:1304–12.

58. Seshadri S, Beiser A, Selhub J, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med 2002;346: 476–83.

59. Smith AD, Refsum H, Bottiglieri T, et al. Homocysteine and dementia: an international consensus statement. J Alzheimers Dis 2018;62: 561–70.

60. Carandang R, Seshadri S, Beiser A, et al. Trends in incidence, lifetime risk, severity, and 30-day mortality of stroke over the past 50 years. JAMA 2006;296:2939–46.

61. Satizabal CL, Beiser AS, Chouraki V, Chene G, Dufouil C, Seshadri S. Incidence of dementia over three decades in the Framingham Heart Study. N Engl J Med 2016;374:523–32.

62. Conner SC, Pase MP, Carneiro H, et al. Mid-life and late-life vascular risk factor burden and neuropathology in old age. Ann Clin Transl Neurol 2019;6:2403–12.

63. Kannel WB, Shurtleff D. The Framingham Study. Cigarettes and the development of intermittent claudication. Geriatrics 1973;28:61–8.

64. Mitchell GF, Hwang SJ, Vasan RS, et al. Arterial stiffness and cardiovascular events: the Framingham Heart Study. Circulation 2010;121: 505–11.

65. Niiranen TJ, Kalesan B, Hamburg NM, Benjamin EJ, Mitchell GF, Vasan RS. Relative contributions of arterial stiffness and hypertension to cardiovascular disease: the Framingham Heart Study. J Am Heart Assoc 2016;5:e004271.

66. Vasan RS, Short MI, Niiranen TJ, et al. Interrelations between arterial stiffness, target organ damage, and cardiovascular disease outcomes. J Am Heart Assoc 2019;8:e012141.

67. Maillard P, Mitchell GF, Himali JJ, et al. Aortic stiffness, increased white matter free water, and altered microstructural integrity: a continuum of injury. Stroke 2017;48:1567–73.

68. Maillard P, Mitchell GF, Himali JJ, et al. Effects of arterial stiffness on brain integrity in young adults from the Framingham Heart Study. Stroke 2016;47:1030–6.

69. Pase MP, Himali JJ, Mitchell GF, et al. Association of aortic stiffness with cognition and brain aging in young and middle-aged adults: the Framingham Third Generation Cohort Study. Hypertension 2016;67:513–9.

70. Pase MP, Beiser A, Himali JJ, et al. Aortic stiffness and the risk of incident mild cognitive impairment and dementia. Stroke 2016;47: 2256–61.

71. Shaikh AY, Wang N, Yin X, et al. Relations of arterial stiffness and brachial flow-mediated dilation with new-onset atrial fibrillation: the Framingham Heart Study. Hypertension 2016;68: 590–6.

72. Tsao CW, Lyass A, Larson MG, et al. Relation of central arterial stiffness to incident heart failure in the community. J Am Heart Assoc 2015;4: e002189.

73. Hoffmann U, Massaro JM, D'Agostino RB Sr., Kathiresan S, Fox CS, O'Donnell CJ. Cardiovascular event prediction and risk reclassification by coronary, aortic, and valvular calcification in the Framingham Heart Study. J Am Heart Assoc 2016;5: e003144.

74. Raunso J, Song RJ, Vasan RS, et al. Familial clustering of aortic size, aneurysms, and dissections in the community. Circulation 2020;142: 920–8.

75. Levy D, Anderson KM, Savage DD, Kannel WB, Christiansen JC, Castelli WP. Echocardiographically detected left ventricular hypertrophy: prevalence and risk factors. The Framingham Heart Study. Ann Intern Med 1988;108:7–13.

76. Levy D, Savage DD, Garrison RJ, Anderson KM, Kannel WB, Castelli WP. Echocardiographic criteria for left ventricular hypertrophy: the Framingham Heart Study. Am J Cardiol 1987;59:956–60.

77. Vasan RS, Larson MG, Levy D, Evans JC, Benjamin EJ. Distribution and categorization of echocardiographic measurements in relation to reference limits: the Framingham Heart Study: formulation of a height- and sex-specific classification and its prospective validation. Circulation 1997;96:1863–73.

78. Vasan RS, Larson MG, Benjamin EJ, Levy D. Echocardiographic reference values for aortic root

size: the Framingham Heart Study. J Am Soc Echocardiogr 1995;8:793–800.

79. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med 1990;322:1561–6.

80. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Levy D. Left ventricular dilatation and the risk of congestive heart failure in people without myocardial infarction. N Engl J Med 1997;336:1350–5.

81. Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS. Natural history of asymptomatic left ventricular systolic dysfunction in the community. Circulation 2003;108:977–82.

82. Cheng S, Xanthakis V, Sullivan LM, et al. Correlates of echocardiographic indices of cardiac remodeling over the adult life course: longitudinal observations from the Framingham Heart Study. Circulation 2010;122:570–8.

83. Nayor M, Enserro DM, Xanthakis V, et al. Comorbidities and cardiometabolic disease: relationship with longitudinal changes in diastolic function. J Am Coll Cardiol HF 2018;6:317–25.

84. von Jeinsen B, Short MI, Larson MG, et al. Prognostic significance of echocardiographic measures of cardiac remodeling. J Am Soc Echocardiogr 2020;33:72–81.

85. Sardana M, Nah G, Tsao CW, et al. Clinical and echocardiographic correlates of left atrial function index: the Framingham Offspring Study. J Am Soc Echocardiogr 2017;30:904–12.

86. Cheng S, Larson MG, McCabe EL, et al. Age- and sex-based reference limits and clinical correlates of myocardial strain and synchrony: the Framingham Heart Study. Circ Cardiovasc Imaging 2013;6:692–9.

87. Sardana M, Lessard D, Tsao CW, et al. Association of left atrial function index with atrial fibrillation and cardiovascular disease: the Framingham Offspring Study. J Am Heart Assoc 2018;7:e008435.

88. Cheng S, McCabe EL, Larson MG, et al. Left ventricular mechanical function: clinical correlates, heritability, and association with parental heart failure. Eur J Heart Fail 2015;17:44–50.

89. Salton CJ, Chuang ML, O'Donnell CJ, et al. Gender differences and normal left ventricular anatomy in an adult population free of hypertension. A cardiovascular magnetic resonance study of the Framingham Heart Study Offspring cohort. J Am Coll Cardiol 2002;39:1055–60.

90. Wang TJ, Gona P, Larson MG, et al. Multiple biomarkers for the prediction of first major cardiovascular events and death. N Engl J Med 2006;355:2631–9.

91. Wang TJ, Larson MG, Levy D, et al. Impact of obesity on plasma natriuretic peptide levels. Circulation 2004;109:594–600.

92. Vasan RS, Benjamin EJ, Larson MG, et al. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: the Framingham heart study. JAMA 2002;288:1252–9.

93. Andersson C, Johnson AD, Benjamin EJ, Levy D, Vasan RS. 70-year legacy of the Framingham Heart Study. Nat Rev Cardiol 2019;16:687–98.

94. Huan T, Joehanes R, Song C, et al. Genome-wide identification of DNA methylation QTLs in whole blood highlights pathways for cardiovascular disease. Nat Commun 2019;10:4267.

95. Yao C, Chen G, Song C, et al. Genome-wide mapping of plasma protein QTLs identifies putatively causal genes and pathways for cardiovascular disease. Nat Commun 2018;9:3268.

96. Evangelou E, Warren HR, Mosen-Ansorena D, et al. Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. Nat Genet 2018;50:1412–25.

97. Huan T, Esko T, Peters MJ, et al. A meta-analysis of gene expression signatures of blood pressure and hypertension. PLoS Genet 2015;11:e1005035.

98. CardiogramplusC4D Consortium, Deloukas P, Kanoni S, et al. Large-scale association analysis identifies new risk loci for coronary artery disease. Nat Genet 2013;45:25–33.

99. Hedman AK, Mendelson MM, Marioni RE, et al. Epigenetic patterns in blood associated with lipid traits predict incident coronary heart disease events and are enriched for results from genome-wide association studies. Circ Cardiovasc Genet 2017;10:e001487.

100. Aslibekyan S, Agha G, Colicino E, et al. Association of methylation signals with incident coronary heart disease in an epigenome-wide assessment of circulating tumor necrosis factor alpha. JAMA Cardiol 2018;3:463–72.

101. Agha G, Mendelson MM, Ward-Caviness CK, et al. Blood leukocyte DNA methylation predicts risk of future myocardial infarction and coronary heart disease. Circulation 2019;140:645–57.

102. Ikram MA, Seshadri S, Bis JC, et al. Genomewide association studies of stroke. N Engl J Med 2009;360:1718–28.

103. Willer CJ, Schmidt EM, Sengupta S, et al. Discovery and refinement of loci associated with lipid levels. Nat Genet 2013;45:1274–83.

104. Thanassoulis G, Campbell CY, Owens DS, et al. Genetic associations with valvular calcification and aortic stenosis. N Engl J Med 2013;368:503–12.

105. Roselli C, Chaffin MD, Weng LC, et al. Multi-ethnic genome-wide association study for atrial fibrillation. Nat Genet 2018;50:1225–33.

106. Mendelson MM, Marioni RE, Joehanes R, et al. Association of body mass index with DNA methylation and gene expression in blood cells and relations to cardiometabolic disease: a mendelian randomization approach. PLoS Med 2017;14:e1002215.

107. Shah S, Henry A, Roselli C, et al. Genome-wide association and mendelian randomisation analysis provide insights into the pathogenesis of heart failure. Nat Commun 2020;11:163.

108. Andersson C, Lin H, Liu C, et al. Integrated multiomics approach to identify genetic underpinnings of heart failure and its echocardiographic precursors: Framingham Heart Study. Circ Genom Precis Med 2019;12:e002489.

109. Vasan RS, Glazer NL, Felix JF, et al. Genetic variants associated with cardiac structure and function: a meta-analysis and replication of genome-wide association data. JAMA 2009;302:168–78.

110. Shah RV, Rong J, Larson MG, et al. Associations of circulating extracellular RNAs with myocardial remodeling and heart failure. JAMA Cardiol 2018;3:871–6.

111. Psaty BM, O'Donnell CJ, Gudnason V, et al. Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium: design of prospective meta-analyses of genome-wide association studies from 5 cohorts. Circ Cardiovasc Genet 2009;2:73–80.

112. Scott RA, Lagou V, Welch RP, et al. Large-scale association analyses identify new loci influencing glycemic traits and provide insight into the underlying biological pathways. Nat Genet 2012;44:991–1005.

113. Wild PS, Felix JF, Schillert A, et al. Large-scale genome-wide analysis identifies genetic variants associated with cardiac structure and function. J Clin Invest 2017;127:1798–812.

114. Schunkert H, Konig IR, Kathiresan S, et al. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. Nat Genet 2011;43:333–8.

115. Morris AP, Voight BF, Teslovich TM, et al. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. Nat Genet 2012;44:981–90.

116. National Heart, Lung, and Blood Institute. GRASP: Genome-Wide Repository of Associations Between SNPs and Phenotypes. Available at: https://grasp.nhlbi.nih.gov. Accessed May 6, 2021.

117. Leslie R, O'Donnell CJ, Johnson AD. GRASP: analysis of genotype-phenotype results from 1390 genome-wide association studies and corresponding open access database. Bioinformatics 2014;30:i185–94.

118. Eicher JD, Landowski C, Stackhouse B, et al. GRASP v2.0: an update on the Genome-Wide Repository of Associations Between SNPs and Phenotypes. Nucleic Acids Res 2015;43:D799–804.

119. Hemani G, Zheng J, Elsworth B, et al. The MR-Base platform supports systematic causal inference across the human phenome. Elife 2018;7.

120. Davies NM, Holmes MV, Davey Smith G. Reading mendelian randomisation studies: a guide, glossary, and checklist for clinicians. BMJ 2018;362:k601.

121. Burgess S, Davey Smith G, Davies NM, et al. Guidelines for performing mendelian randomization investigations. Wellcome Open Res 2019;4:186.

122. Wang TJ, Ngo D, Psychogios N, et al. 2-Aminoadipic acid is a biomarker for diabetes risk. J Clin Invest 2013;123:4309–17.

123. Ho JE, Larson MG, Vasan RS, et al. Metabolite profiles during oral glucose challenge. Diabetes 2013;62:2689–98.

124. Wang TJ, Larson MG, Vasan RS, et al. Metabolite profiles and the risk of developing diabetes. Nat Med 2011;17:448–53.

125. Ho JE, Larson MG, Ghorbani A, et al. Metabolomic profiles of body mass index in the Framingham Heart Study reveal distinct cardiometabolic phenotypes. PLoS One 2016;11:e0148361.

126. Luo S, Coresh J, Tin A, et al. Serum metabolomic alterations associated with proteinuria in CKD. Clin J Am Soc Nephrol 2019;14:342–53.

127. Rhee EP, Clish CB, Ghorbani A, et al. A combined epidemiologic and metabolomic approach improves CKD prediction. J Am Soc Nephrol 2013;24:1330–8.

128. Cheng S, Larson MG, McCabe EL, et al. Distinct metabolomic signatures are associated with longevity in humans. Nat Commun 2015;6:6791.

129. Andersson C, Liu C, Cheng S, et al. Metabolomic signatures of cardiac remodelling and heart failure risk in the community. ESC Heart Fail 2020;7:3707–15.

130. Nayor M, Short MI, Rasheed H, et al. Aptamer-based proteomic platform identifies novel protein predictors of incident heart failure and echocardiographic traits. Circ Heart Fail 2020;13:e006749.

131. Ko D, Benson MD, Ngo D, et al. Proteomics profiling and risk of new-onset atrial fibrillation: Framingham Heart Study. J Am Heart Assoc 2019;8:e010976.

132. Mosley JD, Benson MD, Smith JG, et al. Probing the virtual proteome to identify novel disease biomarkers. Circulation 2018;138:2469–81.

133. Ngo D, Sinha S, Shen D, et al. Aptamer-based proteomic profiling reveals novel candidate biomarkers and pathways in cardiovascular disease. Circulation 2016;134:270–85.

134. Nayor M, Shah RV, Miller PE, et al. Metabolic architecture of acute exercise response in middle-aged adults in the community. Circulation 2020;142:1905–24.

135. Kenny DJ, Plichta DR, Shungin D, et al. Cholesterol metabolism by uncultured human gut bacteria influences host cholesterol level. Cell Host Microbe 2020;28:245–57.

136. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015;12:e1001779.

137. Gaziano JM, Concato J, Brophy M, et al. Million Veteran Program: a mega-biobank to study genetic influences on health and disease. J Clin Epidemiol 2016;70:214–23.

138. All of Us Research Program Investigators, Denny JC, Rutter JL, et al. The "All of Us" Research Program. N Engl J Med 2019;381:668–76.

139. Nayor M, Xanthakis V, Tanguay M, et al. Clinical and hemodynamic associations and prognostic implications of ventilatory efficiency in patients with preserved left ventricular systolic function. Circ Heart Fail 2020;13:e006729.

140. Niiranen TJ, McCabe EL, Larson MG, et al. Heritability and risks associated with early onset hypertension: multigenerational, prospective analysis in the Framingham Heart Study. BMJ 2017;357:j1949.

141. Kaess BM, Andersson C, Duncan MS, et al. Familial clustering of cardiac conduction defects and pacemaker insertion. Circ Arrhythm Electrophysiol 2019;12:e007150.

142. Niiranen TJ, McCabe EL, Larson MG, et al. Risk for hypertension crosses generations in the community: a multi-generational cohort study. Eur Heart J 2017;38:2300–8.

143. ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. Am J Epidemiol 1989;129:687–702.

144. Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. Am J Epidemiol 2002;156:871–81.

145. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. Ann Epidemiol 1991;1:263–76.

146. Taylor HA Jr., Wilson JG, Jones DW, et al. Toward resolution of cardiovascular health disparities in African Americans: design and methods of the Jackson Heart Study. Ethn Dis 2005;15 Suppl 6. S6-4-17.

147. Aguib Y, Al Suwaidi J. The Copenhagen City Heart Study (Østerbroundersøgelsen). Glob Cardiol Sci Pract 2015;2015:33.

148. Volzke H, Alte D, Schmidt CO, et al. Cohort profile: the study of health in Pomerania. Int J Epidemiol 2011;40:294–307.

149. Elliott J, Shepherd P. Cohort profile: 1970 British birth cohort (BCS70). Int J Epidemiol 2006;35:836–43.

150. Power C, Elliott J. Cohort profile: 1958 British birth cohort (National Child Development Study). Int J Epidemiol 2006;35:34–41.

151. Ikram MA, Brusselle G, Ghanbari M, et al. Objectives, design and main findings until 2020 from the Rotterdam Study. Eur J Epidemiol 2020;35:483–517.

152. Rietzschel ER, De Buyzere ML, Bekaert S, et al. Rationale, design, methods and baseline characteristics of the Asklepios Study. Eur J Cardiovasc Prev Rehabil 2007;14:179–91.

153. Borodulin K, Tolonen H, Jousilahti P, et al. Cohort profile: the National FINRISK Study. Int J Epidemiol 2018;47. 696–696i.

154. Krokstad S, Langhammer A, Hveem K, et al. Cohort Profile: the HUNT Study, Norway. Int J Epidemiol 2013;42:968–77.

155. Schmidt R, Lechner H, Fazekas F, et al. Assessment of cerebrovascular risk profiles in healthy persons: definition of research goals and the Austrian Stroke Prevention Study (ASPS). Neuroepidemiology 1994;13:308–13.

156. Centers for Disease Control and Prevention. Age-adjusted death rates for selected major causes of death. Available at: https://data.cdc.gov/NCHS/NCHS-Age-adjusted-Death-Rates-for-Selected-Major-C/6rkc-nb2q. Accessed April 17, 2021.

KEY WORDS cardiovascular epidemiology, Framingham Heart Study, molecular epidemiology, risk factors