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Invited Commentary

Invited Commentary: The Framingham Offspring Study—A Pioneering Investigation Into Familial Aggregation of Cardiovascular Risk

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Launched in 1948, the Framingham Heart Study was a seminal prospective cohort study of 5,209 adult residents of Framingham, Massachusetts, that was designed to uncover the determinants and natural history of coronary heart disease. Data from this original cohort established the cardiac threat posed by high blood pressure, high cholesterol, smoking, obesity, physical inactivity, diabetes, and other factors. In the late 1960s, investigators conceived the innovative idea of assembling a second cohort that comprised the adult children of the original study population (and these children's spouses). From 1971 to 1975, a total of 5,124 individuals were recruited to form the Offspring Cohort. Studying successive generations in this fashion provided an efficient method for examining secular trends in cardiovascular disease and its risk factors, as well as an opportunity to assess familial aggregation of risk without the threat of recall bias. In a paper published in the September 1979 issue of the *Journal*, then study director William Kannel et al. (*Am J Epidemiol*. 1979;110(3):281–290) described the sampling design of the Offspring Study and presented selected baseline characteristics of the cohort. The scientific questions addressed by this research provided the impetus for a decades-long effort—still in full force today both within the Framingham Study itself and in the broader cardiovascular epidemiologic community—to quantify the independent and synergistic effects of genetic, lifestyle, and other environmental factors on cardiovascular outcomes.

cohort study; coronary heart disease; familial aggregation; Framingham; genetics; study design

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; GWAS, genome-wide association study.

Launched in 1948, the original Framingham Heart Study was a groundbreaking long-term prospective cohort study designed to uncover the determinants and natural history of coronary heart disease (CHD), with the aim of providing an evidence base to inform public-health prevention guidelines. From 1948 to 1953, the study enrolled 5,209 adult residents of the eastern Massachusetts town of Framingham and then followed them via biennial clinical examinations that were initially slated to last 20 years but that ultimately continued throughout the participants' lifespans (1). Starting in the late 1950s and 1960s, studies of this original cohort were among the first to provide clear evidence of the threats to heart health posed by high blood pressure (2), high blood cholesterol (2), cigarette smoking (2), obesity (3), physical inactivity (4), diabetes (5), and other key "risk factors" (a term coined by Framingham investigators in a seminal 1961 paper (2)). Among one of the more striking clinical misconceptions dispelled by the Framingham findings was the belief that rising blood pressure in older adults (so-called benign essential hypertension) was a normal compensatory response to force blood through aging arteries (6, 7). Investigators in the Framingham Study also clarified the natural history and prognosis of specific cardiovascular disease (CVD) subtypes, including myocardial infarction (8, 9), stroke (10, 11), atrial fibrillation (12), peripheral arterial disease (13), and heart failure (14). This historic study (see a timeline of achievements in Table 1) served as the foundation for the emerging field of cardiovascular epidemiology and—as noted in 2005 by current study director Daniel Levy in his aptly named book *A Change of Heart: How the People of Framingham, Massachusetts Helped Unravel the Mysteries of Cardiovascular Disease*—was widely credited with "alter[ing] the slant of [cardiovascular] medicine from

Table 1. Timeline of Achievements[a]

Year	Achievement
1948	The FHS begins.
1952	First examination of the Original Cohort is completed.
1957	The FHS investigators publish their first paper on CHD incidence, summarizing findings from 4 years of follow-up of the Original Cohort.
1961	High blood pressure, high cholesterol levels, and electrocardiographic abnormalities are found to be CHD risk factors.
1971	The FHS Offspring Cohort is established.
1976	The FHS develops its first CHD risk score.
1983	Different electrocardiography criteria used to diagnose left ventricular hypertrophy are shown to be associated with different levels of CVD.
1989	Parental history of CHD death is shown to be a significant predictor of CHD in offspring.
1990	Echocardiography is found to have important prognostic value for CVD incidence, CVD mortality, and all-cause mortality.
1998	The Framingham CHD risk score is simplified by omitting left ventricular hypertrophy and using a point-scoring strategy for blood pressure and cholesterol values.
2002	The FHS Third Generation Cohort is established.
2007	The FHS investigators publish their first series of GWAS papers, reporting the results for genomic analyses of 987 clinical phenotypes.
2007	The FHS launches the SHARe Project to analyze associations between common genetic polymorphisms and clinical traits in 9,300 FHS participants.
2008	The FHS and 4 other cohort studies establish the CHARGE Consortium.
2009	The FHS investigators publish the first 30-year CVD risk calculator, improving long-term CVD risk assessment.
2013	The FHS conducts a CHD case-control study focused on associations of CHD with differential levels of gene expression and microRNA expression.
2014	The FHS pools its data as part of the Risk Assessment Work Group to develop sex- and race-specific CHD risk models.
2015	The FHS performs whole genome sequencing on 4,200 FHS participants as part of the larger TOPMed Initiative.
2015	The FHS runs an eHealth pilot study as part of the Health eHeart Study, using smartphones and wearable digital technology for data collection integral to investigating CVD and its risk factors.
2016	The third examination cycle of the Third Generation Cohort begins, with an eHealth component included.

Abbreviations: CHARGE, Cohorts for Heart and Aging Research in Genetic Epidemiology; CHD, coronary heart disease; CVD, cardiovascular disease; FHS, Framingham Heart Study; GWAS, genome-wide association study; SNP, single nucleotide polymorphism; SHARe, SNP Health Association Resource; TOPMed, Trans-Omics for Precision Medicine.

[a] Adapted from Chen and Levy (34), with permission from the American Medical Association.

treatment toward prevention" (15, p. 102). The early findings of the Framingham Study not only highlighted the importance of a healthy lifestyle (avoidance of smoking, obesity, and physical inactivity) but also led to the conduct of clinical trials in which it was shown that interventions to lower blood pressure and low-density lipoprotein cholesterol levels were effective for CHD risk reduction—key strategies that remain the cornerstone of CVD prevention to this day (16, 17). Indeed, the dramatic declines in mortality from CHD and stroke in the second half of the 20th century (18) resulted in no small part from insights from the Framingham Heart Study.

However, in the late 1960s, the Framingham Heart Study as originally designed could not provide new insight into a topic of emerging interest: the role of family history and genetics in the development of CVD. Thus, the investigators conceived the brilliant and innovative idea of assembling a second cohort that consisted of the adult children of the original study population. Long-term follow-up of this new cohort would allow researchers to build upon the wealth of cardiovascular data already gathered in the Original Cohort to confirm existing hypotheses and test new ones—in particular, those related to the familial clustering of disease. From 1971 to 1975, a total of 5,124 individuals—approximately 70% of whom were the sons and daughters of members of the Original Cohort and 30% of whom were the spouses of these children—were recruited to form the Offspring Cohort, members of which undergo follow-up clinical examinations approximately every 4 years. (As with the Original Cohort, these examinations are continuing throughout the participants' lifespans.) The launch of the Offspring Study, one of the earliest second-generation epidemiologic investigations, occurred within 2 decades of the 1953 discovery of the structure of DNA and within only a few

years of the 1968 publication of the influential book *The Double Helix* (19). In 1975, Feinleib et al. (20) provided preliminary data on this new undertaking, but it was a series of 4 reports (21–24) in the September 1979 issue of the *American Journal of Epidemiology* that presented the definitive description of the Offspring Cohort, along with the first of many key findings regarding risk factor correlations between parents and their children. The lead paper by then study director William Kannel et al. (21)—that is, the paper that inspired this commentary—set the stage for the 3 accompanying results papers (22–24) by describing the sampling design of the Offspring Study and presenting selected baseline characteristics of the cohort (with the focus on 2,656 offspring of 1,202 of the 1,644 husband-wife pairs who were members of the Original Cohort). Importantly, the study was designed to facilitate comparison of the data between parents and children by using similar standardized examination protocols for both generations and by first examining the children at roughly the age that their parents had been at first examination. As clearly demonstrated in the initial results papers, studying successive generations in this fashion provides not only an innovative and efficient method for examining long-term secular trends in CVD and its risk factors (22) but also a unique opportunity to assess familial aggregation of risk without the threat of recall bias (23, 24). (Indeed, even today, many epidemiologic studies of familial factors in CVD rely on adult participants' (sometimes faulty) retrospective reporting of their parents' medical histories.) For blood pressure (23) and lipids (24), stronger associations were seen between parents and offspring than between offspring and their spouses, a pattern that supports the influence of hereditary factors on these characteristics.

The research questions concerning familial aggregation of CVD risk factors addressed in these early papers from the Framingham Offspring Study provided the impetus for a decades-long effort—still in full force today—to quantify the independent effects of genetic, lifestyle, and other environmental factors on cardiovascular outcomes. Over the years, Framingham investigators have shown that parental histories of CHD (25), stroke (26), diabetes (27), total CVD (28), atrial fibrillation (29), heart failure (30), intermittent claudication (31), and metabolic syndrome (32) significantly predict these outcomes in offspring, and they have also provided heritability estimates for many traits related to CVD and aging (33). To elucidate the genetic basis for such inheritance, Framingham investigators in the late 1980s began to extract DNA from the blood samples provided by members of the Original Cohort, the Offspring Cohort, and later the Third Generation Cohort (see below), and in the 2000s, they began to carry out genome-wide genotyping and genome-wide association studies (GWAS) to explore relationships between common genetic polymorphisms and CVD-related traits (33, 34). (Although family-based studies are not strictly necessary for GWAS analyses, biostatistical research has shown that they facilitate and strengthen interpretation of GWAS results (35).) In stand-alone and collaborative analyses, Framingham data have contributed to the identification of many genetic variants—as well as the creation of composite genetic risk scores—related to clinical and subclinical CVD indices and to blood pressure, cholesterol, body mass index, diabetes, and other major cardiovascular risk factors (concise overviews of this work for nongeneticists are provided by Tsao and Vasan (1) and by Chen and Levy (34)). Most recently, Framingham investigators have also begun to focus on "omics" research, including transcriptomics (36, 37), metabolomics (38, 39), and proteomics (40), in order to elucidate the molecular mechanisms underlying CVD, with the ultimate goal of developing highly individualized prevention and treatment strategies (34, 41).

Apart from furthering knowledge of familial patterns and of the genetics/genomics of CVD, data from the Offspring Cohort have also been used alone and in conjunction with those from the Original Cohort to yield many other contributions to the cardiovascular literature (1, 7, 34, 42). Among the most prominent of these contributions is the development of the Framingham Risk Score to predict 10-year risk of CHD (43), as well as risk scores for prediction of the 10-year (44) and 30-year (45) risks of CVD. Most recently, data from the Original and Offspring Cohorts, together with those from 3 racially and geographically diverse cohorts (from the Atherosclerosis Risk in Communities (ARIC) Study, the Cardiovascular Health Study (CHS), and the Coronary Artery Risk Development in Young Adults (CARDIA) Study), contributed to the development of the Atherosclerotic Cardiovascular Disease Risk Algorithm, released in 2013 by the American College of Cardiology and the American Heart Association (46). This algorithm features race- and sex-specific equations for predicting 10-year risk of CVD. (A lifetime risk score is also available (47).) The Offspring Study has also provided valuable documentation of long-term trends in cardiovascular risk factors and outcomes, including dyslipidemia (48), obesity (49), type 2 diabetes mellitus (50), myocardial infarction (51), CHD mortality (52), heart failure after myocardial infarction (53), stroke (54), atrial fibrillation (55), and intermittent claudication (56). With its pioneering and careful application of epidemiologic principles, including the use of systematic sampling, standardized examination protocols, endpoint adjudication procedures, and (at the time) cutting-edge multivariable statistics, the Framingham Study has also served as a model for the design, conduct, and analysis of many long-term prospective cohort studies. (The detailed analyses presented in the paper by Kannel et al. (21) to assess volunteer bias in the Offspring Study are illustrative of the epidemiologic rigor routinely applied by Framingham investigators to data interpretation. The investigators found few significant differences in CHD risk factors or CHD rates between Original Cohort members whose children had enrolled in the Offspring Study and those whose children had not.) Moreover, early integration of ancillary investigations of noncardiovascular outcomes—including osteoporosis, cancer, cognitive function, arthritis, and hearing and vision disorders (15)—in the Framingham Heart Study allowed for cost- and logistically efficient advances in scientific understanding of these conditions. Finally, the study's multigenerational approach to cohort assembly was an early example of highly efficient recruiting because it capitalized on potential participants' familiarity with, and trust in, the study. As current director Daniel Levy has noted, "Enrolling the 5,124 second-generation participants was nothing like the effort to get their parents involved" (15, p. 127). A similar approach has since been used by other investigators. One large-scale example is the Growing Up Today Study (GUTS) (57), which in 1996 and 2004 enrolled nearly 28,000 nine- to 14-year-old

children of more than 116,000 female nurses already participating in the Nurses' Health Study (NHS) II, which has been ongoing since 1989 (58). Following the intergenerational Framingham model, these 2 studies, taken together, represent a powerful resource for informing and advancing the nature-nurture debate.

As mentioned above, the Framingham Heart Study did not close the door to recruitment after establishing the Offspring Cohort. A Third Generation Cohort (59) was enrolled in 2002–2005, with priority given to members of 879 families that already had multiple participants in the study. This cohort consists of 4,095 adults who have at least 1 parent in the Offspring Cohort, along with 103 of their parents who had not previously enrolled in the Offspring Cohort. The 3-generational structure of the Framingham Study will allow it to remain at the forefront of the expansion of knowledge regarding genetic and environmental determinants of CVD for years to come. The Framingham biorepository includes cell lines from participants across the 3 generations—a renewable source of DNA for as-yet-to-be-determined future analyses (1, 41). Because participants in the Original, Offspring, and Third Generation Cohorts are predominantly white and of European ancestry (reflecting the demographics of mid-20th century Framingham), Framingham investigators also recruited nonwhite residents of the town to form the Omni 1 and Omni 2 cohorts in 1994–1998 and 2003–2005, respectively, to broaden understanding of CVD in other racial/ethnic groups.

The quest to pinpoint the independent and synergistic effects of genetic, lifestyle, and environmental factors on cardiovascular outcomes continues today, not only in the Framingham Heart Study but also in the broader epidemiologic research community. Although a review of current work in the area is beyond the scope of this commentary, we wish to close by highlighting a recent report by Khera et al. (60), in which the authors provided a hopeful message to readers who are apprehensive about the seemingly relentless creep of genetic determinism, as well as a cautionary one to those who are enthralled by the promise of genomic medicine. In 3 long-term prospective studies (the Atherosclerosis Risk in Communities Study, the Women's Genome Health Study, and the Malmö Diet and Cancer Study) with a total of more than 50,000 participants, both genetic and lifestyle factors were independent predictors of susceptibility to coronary artery disease. Individuals at high genetic risk (defined as the top quintile of a polygenic risk score derived from analysis of 50 single-nucleotide polymorphisms that had shown a genome-wide significance for association with coronary artery disease in previous studies) were nearly twice as likely to experience a clinical coronary event than were those at low genetic risk (bottom quintile of this score). Nevertheless, at all levels of genetic risk, those with a favorable lifestyle (defined as having at least 3 of the following: no current smoking, no obesity, regular physical activity, and a healthy diet) were nearly 50% less likely to experience such an event than were their counterparts with an unfavorable lifestyle (having no or only 1 healthy lifestyle factor). These results serve as a clear reminder that, even amid the ongoing explosion of genetic/genomic research motivated in part by the establishment of the Framingham Offspring Cohort, lifestyle and other modifiable risk factors first identified long ago in the Original Cohort remain important targets for the prevention and treatment of CVD.

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