Contributions of the Framingham Heart Study to Stroke and Dementia Epidemiologic Research at 60 Years

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The Framingham Heart Study, the longest-running prospective epidemiologic study in history, was initiated in 1948 in response to the rising toll of coronary heart disease and hypertension. During the ensuing decades, the study of other diseases, notably stroke and dementia, was added. In 1971, 5124 offspring of the original cohort of 5209 men and women were added, and a third generation of 4095 men and women were added in 2002. The 3-generation structure was used to relate a host of risk factors measured in mid and late life to the subsequent development of stroke, dementia, and cognitive decline. It has also facilitated studies of family occurrence of disease over generations particularly for genomic research. Dementia and Alzheimer disease research has proceeded from the determination of risk factors for at least moderately severe Alzheimer disease in the first generation to mild cognitive impairment and mild Alzheimer disease in the offspring and to studies of the third generation for detection of pre–mild cognitive impairment and indicators of cognitive decline in mid life. These research efforts have been facilitated by genome-wide association studies, biomarkers, and multiple measures of subclinical vascular disease. The tempo of decline has been documented by serial quantitative measures of brain structure on magnetic resonance imaging and cognitive performance by neuropsychological testing. Clinical correlation with systematic neuropathological examinations of more than 150 brains has provided important confirmation of cerebrovascular and brain tissue indices of disease. Identification of persons at heightened risk for stroke, mild cognitive impairment, Alzheimer disease, and cognitive decline years prior to disease onset may facilitate delay in disease onset and prevention.


The Framingham Heart Study (FHS), the longest-running prospective study of chronic disease in a population, has been in operation for more than 60 years. Designed shortly after the end of World War II, the study was initiated in response to the rapid increase in cardiovascular disease death, which was twice as frequent as cancer, the second-leading cause of death. At the time, coronary heart disease accounted for 1 in 3 deaths in men younger than 60 years. One of 6 coronary attacks was manifested as sudden death, which accounted for half of all coronary deaths and was often the initial symptom of the disease. The FHS represented one of the earliest modern applications of epidemiologic research to chronic disease.

CONDUCT OF THE STUDY

FHS was planned as a 20-year study to identify factors predisposing people to cardiovascular disease and hypertension. The study was subsequently continued and expanded. Details of the history of the study, significant contributions, personnel, and
It is key to highlight a number of important features of the design of the FHS that have unique pertinence for the study of neurologic diseases. Despite the focus on coronary heart disease and its impact on men younger than 60 years, women were invited to participate in the FHS in part to encourage their husbands to join. Women aged 30 to 60 years accounted for approximately half of the 5209 subjects in the original cohort in 1948. This resulted in large numbers of spouse pairs and extended families in this population of uniformly white individuals of European descent (Figure 1). To enhance the study of familial factors, particularly blood lipids and blood pressure, and to capitalize on the large number of spouse pairs, an offspring cohort (n=5124) was recruited in 1971. These children of the original cohort along with their spouses provided 2 generations of subjects for the study of familial and genetic influences on disease and phenotype occurrence. The recruitment of families was extremely fortunate and resulted from an appreciation of clustering of cardiovascular and hypertensive disease in families. In this way, disease occurrence in parents in the original cohort could be related to disease or predisposing factors in their children in the offspring cohort. The advent of noninvasive testing including physiologic measures (eg, ankle-brachial index, imaging of the heart and carotid arteries) permitted identification of subclinical vascular disease in different arterial beds. Recruitment of 4095 children of the offspring cohort in 2002 has provided a further opportunity to explore genetic factors and identify earlier evidence of disease and premonitory factors of subclinical disease. This has important implications for our understanding of precursors of neurologic diseases and aging, which occur over decades and manifest in later life as stroke, dementia, and cognitive decline. The subjects in these 3 cohorts have shown allegiance to the study and cooperated with frequent telephone and in-person surveillance and examinations over decades. Participants of the original cohort have been examined every 2 years, with annual telephone health history follow-up, for 62 years; the offspring cohort participants have been examined approximately every 4 years during 4 decades of follow-up. Detailed and prolonged surveillance, standardized and quality-controlled measurements, and systematic and criteria-based disease reviews have permitted the study of risk factors, disease incidence, secular trends, and genetic studies of disease.

FIGURE 1. Timeline of studies of cognitive performance and magnetic resonance imaging evaluating dementia and cognitive decline in 3 generations of participants in the Framingham Heart Study.

Prolonged follow-up from mid life to disease and ultimately to death has permitted the computation of a useful statistic, the mortality-adjusted residual or remaining lifetime risk of developing a disease during the remaining years of life in a man or woman at a specific age. This statistic serves to alert physicians, patients, and public health planners to the likelihood and importance of a specific disease or diseases. For example, at age 65 years, the residual lifetime risk of developing either stroke or dementia is 1 in 3 in men and 1 in 2 in women. The residual or remaining lifetime risk is an easily understood portrayal of the high likelihood of developing either or both of these neurologic diseases and may provide an impetus for using preventive measures.

STROKE

The initial FHS publication on stroke in 1965 identified elevated blood pressure, systolic no less importantly than diastolic, as the premier risk factor for stroke, infarction, and hemorrhage. Clinical observation of study subjects hospitalized for stroke provided validation of the diagnoses before imaging became widely available in 1978. With increasing age, systolic blood pressure (SBP) continues to increase while the diastolic component peaks in people aged 50 to 60 years and then decreases, leading to isolated systolic hypertension in persons older than 65 years. Isolated systolic hypertension (ie, SBP ≥160 mm Hg) along with a diastolic blood pressure less than 90 mm Hg was not innocuous as had been commonly taught, but instead was an important and frequent precursor of cardiovascular disease, particularly stroke. These observations led to a series of key clinical trials demonstrating the substantial benefit of SBP reduction on stroke incidence and severity. These trials continue with ever-lower targets and increasingly elderly subjects, demonstrating the benefit of blood pressure reduction even for those older than 80 years. The 40 years of antihypertensive therapy trials, from a Veterans Administration trial of severely hypertensive patients in 1967 to the Hypertension in the Very Elderly Trial nearly 40 years later, represent a remarkable application in clinical trials of the benefits derived from observational studies including the FHS.

A particular contribution of the FHS to stroke epidemiologic research is the documentation of the importance of nonrheumatic chronic atrial fibrillation (AF) to stroke incidence in 1978. While stroke clinicians had associated chronic AF with increased stroke risk and particularly dire clinical outcomes, many physicians, in-
including cardiologists, were skeptical. The demonstration of the importance of AF as an important stroke risk factor in the FHS and of its particular importance in elderly individuals was key to demonstrating the benefit of warfarin anticoagulation in a series of clinical trials. Furthermore, the increasing prevalence of AF with age, which in part was a result of the improved survival of patients with acute myocardial infarction and congestive heart failure, resulted in the growing importance of AF in stroke occurrence in elderly individuals. A risk profile developed in the FHS permits the estimation of the probability of stroke or death in persons with chronic AF.

Other FHS contributions include the application of a number of statistical developments to assist in risk prediction, notably the development of a quantitative scale to estimate the probability of developing a stroke during a specific period. The Framingham Stroke Risk Profile has been widely used as a clinical tool for estimating stroke probability by applying patient data available to an office-based health care professional. Secular trends in the prevalence and impact of the risk factors as well as more recent findings such as familial occurrence of stroke are currently being incorporated into an updated modification of the Framingham Stroke Risk Profile.

DEMENTIA, ALZHEIMER DISEASE, AND COGNITIVE DECLINE

It has been increasingly apparent that atherosclerotic cardiovascular disease and cardiovascular risk factors are contributors to the development of dementia and cognitive decline and play a role in clinical manifestations of vascular cognitive impairment and Alzheimer disease (AD). Systematic assessment of cardiovascular risk factors, subclinical disease, and clinical disease in mid life for more than 60 years in the FHS has provided an opportunity to link them to late-life cognitive decline and dementia. Complementing the extensive accumulated cardiovascular disease data was the systemic assessment of cognitive function dating back to 1975. This battery led to the establishment of a dementia-free (and stroke-free) cohort for study of incidence and risk factors for dementia. The Mini-Mental State Examination was administered routinely on biennial exams until 1989 when a National Institute on Aging grant supported administration of a more extensive battery and neurologic follow-up of participants of the original cohort. Subjects suspected of having dementia were evaluated with neurologic and neurocognitive tests and application of standard criteria for dementia diagnosis and classification. The neurologic, cognitive, and functional statuses of the original cohort participants are monitored with annual health history updates, home and nursing home visits, and biennial clinic visits. Participants of the offspring cohort have been screened with Mini-Mental State Examinations since the 1970s and with more comprehensive testing since 1989. Dementia has been documented in more than 600 subjects from both cohorts. Criteria for amnestic and nonamnestic mild cognitive impairment were fulfilled in more than 225 offspring cohort subjects who continue to be followed up. A brain donation program is in place; to date, more than 150 brains from subjects whose cognitive status was known have been studied. The availability of brain specimens from nondemented and demented subjects has permitted identification of AD pathologic changes in visual association Brodmann area 19 in all AD cases as well as in 52% of cognitively intact elderly subjects, suggesting that this area is particularly vulnerable to these changes and is an early site of AD pathology.

UNIQUE CONTRIBUTIONS OF THE FHS

Cognitive evaluation of the participants of the original cohort in the mid 1970s when they were aged 55 to 85 years permitted designation of study subjects demonstrated (not just presumed) to be free of dementia and stroke, which is a key step in a cohort study of a disease (Figure 1). There has been longstanding interest in the relationship between blood pressure and cognition. The availability of the Kaplan-Albert neuropsychological battery, designed by the late Edith Kaplan, PhD, and Martin Albert, MD, PhD, administered on biennial examinations 14 and 15 to nearly 3000 surviving original cohort participants, could be related to blood pressure measured during a prior 10-year period. Effective antihypertensive therapy had not yet become available; therefore, this provided an opportunity to relate untreated chronic high blood pressure to cognitive performance. The odds of having a significantly poorer performance (eg, the lowest quartile on logical memory-delayed recall score) increased with age and with increasing SBP. A 40-mm Hg increase in SBP (eg, from 120 to 160 mm Hg) was associated with the performance equivalent to a person 10 years older. Thus, a higher SBP may be associated with cognitive performance on this test of a person whose brain was 10 years older than the chronological age. Subsequent follow-up also disclosed an inverse relationship of performance on this baseline cognitive battery with an increased incidence of AD after 22 years. Poorer performance on the logical memory-delayed testing was associated with an approximately 50% greater incidence of AD even after persons developing AD 5 and 10 years following testing were excluded, providing support for the chronicity of the AD process. We examined this association of poorer performance on the Kaplan-Albert battery in 1976 and incidence of AD after 32 years of follow-up and this robust relationship persists.

In the 1970s, the diagnosis of dementia was made only if it was moderate or severe; mild and possible dementia were not designated as cases. Over time as interest in mild dementia and then predementia or mild cognitive impairment increased, we re-reviewed all potential mild cases and applied contemporary criteria and nosologic research, yielding substantially higher incidence, prevalence, and residual lifetime risk (adjusting for mortality due to competing causes) of these conditions (Table). Detection of subjects with mild cognitive impairment and their categorization as having amnestic and nonamnestic mild cognitive impairment followed. Late-onset AD likely represents the end stage of a prolonged process; therefore, we have used the third-generation cohort (mean age, 45 years) to try to identify persons at increased risk while in a preclinical stage.
diagnose clinical dementia.

RISK FACTORS FOR AD

It has been accepted for many years that clinical stroke is followed by dementia. We found a doubling of the incidence of dementia, largely vascular in type, following clinical stroke. Once computed tomographic scans became available, it became apparent that approximately 12% of initial strokes in persons clinically presumed to be stroke free had computed tomographic evidence of a prior unsuspected stroke. Stroke risk factors that have been related to the incidence of dementia and AD include diabetes mellitus, elevated plasma homocysteine levels, low levels of physical activity, and the presence of plasma phosphatidylcholine docosahexaenoic acid.11

OFFSPRING COHORT AND NEUROCOGNITIVE MARKERS

In 1999, quantitative brain magnetic resonance scans and a comprehensive neuropsychological battery were obtained on nearly 3000 offspring cohort participants (Figure 2). We related previously measured cardiovascular risk factors and markers to these morphologic and cognitive measures. As a starting point, the Framingham Stroke Risk Profile, which was developed for determining the probability of stroke in the FHS and validated in many other populations, was related to supratentorial brain volume as a percentage of the intracranial volume, a ratio we call the total cerebral brain volume (TCBV) and to neuropsychological test performance on tests of executive function and visuomotor indices who were also hypertensive had the poorest performance; brain volume, particularly hippocampal volume; and white matter hyperintensity levels.13 All were related to significantly reduced TCBV. Diabetes and hemoglobin A1c levels were inversely related to hippocampal volume. Total cerebral brain volume was lower in persons with high fasting insulin levels; this was true even in people without diabetes. This lower TCBV was equivalent to 8 years of structural brain aging. Executive function was also inversely related to these indices of metabolic dysregulation.

Greater degrees of obesity (eg, body mass index, waist circumference, and waist to hip ratio) were also generally associated with smaller TCBV with a striking interaction between obesity and hypertension. Persons in the uppermost quartile of waist to hip ratio but not body mass index who were also hypertensive had the poorest performance on tests of executive function and visuomotor skills but not on tests of memory. A number of other biomarkers have also been shown to relate to these endophenotypes.

PARENTAL AD AND ENDPHENOTYPES IN OFFSPRING

Rather than having to rely on a history of dementia or AD in the parents of subjects, the FHS used more than 30 years of surveillance, neurologic and cognitive evaluations, and structured case reviews of subjects to determine whether criteria for AD and/or dementia were fulfilled. We could thereby relate subjects fulfilling standard criteria for probable AD in the original cohort to cognitive performance and brain structure in their children.

Table. Comparing the Cumulative Incidences and 25-Year and 40-Year Residual Lifetime Risks of Persons Developing Alzheimer Dementia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Follow-up Period</th>
<th></th>
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<tbody>
<tr>
<td>Outcome used</td>
<td>Age at onset</td>
<td>Age at diagnosis</td>
<td>Age at diagnosis</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>Moderate</td>
<td>Mild</td>
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<tr>
<td>Patients with dementia,</td>
<td>141</td>
<td>353</td>
<td>388</td>
</tr>
<tr>
<td>No.</td>
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<td>Cumulative incidence, %</td>
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<tr>
<td>25 y</td>
<td>14.4</td>
<td>12.2</td>
<td>20.9</td>
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<tr>
<td>40 y</td>
<td>29.9</td>
<td>62.3</td>
<td>66.6</td>
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<tr>
<td>Residual lifetime risk, %</td>
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<tr>
<td>25 y</td>
<td>8.9</td>
<td>8.7</td>
<td>11.1</td>
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<tr>
<td>40 y</td>
<td>11.8</td>
<td>13.5</td>
<td>15.3</td>
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4 Adapted with permission from Elsevier. The cumulative incidences are adjusted for mortality due to competing causes. The patients were cognitively intact at age 65 years based on variation in severity required to diagnose clinical dementia.

Figure 2. Spectrum of measures available for the study of dementia and cognitive decline in 3 generations of participants in the Framingham Heart Study, including risk factors, genome-wide association studies, biomarkers, preclinical indicators and changes in cognitive function and brain morphology, and neuropsychological examination. Neuro indicates neurological examination; NP, neuropsychological battery; and MR, magnetic resonance.
In APOE ε4 carriers only, parental dementia and parental AD were associated with poorer scores on tests of verbal memory and visuospatial memory tasks in their offspring (mean age, 59 years). These APOE ε4 carriers also showed greater brain atrophy rates during 6 years of follow-up on serial brain magnetic resonance imaging. There was worsening performance in executive function among the offspring of parents with AD regardless of APOE ε4 status.

GENETIC STUDIES

In addition to APOE ε4, a number of variants associated with stroke and AD have been identified as a result of genome-wide association studies and extensive collaborations among investigative teams including those from the FHS. It seems likely there will continue to be rapid advances made in the understanding of the genetic influences on late-onset AD. The FHS formed working groups, including the Neurology Traits Working Group, to collaborate with their counterparts in several other prospective epidemiologic studies. The Cohorts for Heart and Aging Research in Genomic Epidemiology consortium was formed to share our data with the AD community, resulting in a recent significant publication. Access to all FHS genome-wide association study data are made available simultaneously to all other non-FHS investigators on the Database of Genotypes and Phenotypes Web site (http://www.ncbi.nlm.nih.gov/gap) as the SNP Health Association Resource.

A comprehensive biomarker initiative called the Systems Approach to Biomarker Research National Heart, Lung, and Blood Institute Biomarker Initiative is under way and is expected to provide thousands of biomarkers for future investigative efforts. These efforts during more than 60 years are because of the steadfast support of the original FHS participants, their children, and their grandchildren. Their allegiance and dedication have made a landmark study such as the FHS possible.

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REFERENCES