In the past half-century, longitudinal studies have proven themselves to be powerful tools for research on aging and its attendant diseases. These projects track the health of a group of subjects for years, observing factors that might predict the incidence of age-related diseases or influence processes commonly associated with normal aging, such as fading eyesight and hearing loss. Huge investments in these expensive, big-team, delayed-gratification enterprises have paid off handsomely. They have revealed risk factors for heart disease, cancer, and Alzheimer’s disease, among others, and in some cases they’ve forced experts to rethink dogma on how to avoid illness. This tour highlights the strengths, weaknesses, quirks, and likely futures of some of the most important longitudinal studies.

Some questions have no quick answers. When it comes to studying aging and age-related diseases, researchers on some of the most successful projects practice exceptional patience. They conduct longitudinal studies, which document the health and habits of a cohort of subjects for decades, in search of behaviors, biological markers, or socioeconomic factors that influence how people age.

No one undertakes a longitudinal trial lightly. They’re expensive and require years of cooperation among huge numbers of researchers, some of whom will retire or move on before the study generates publishable data. Most important, longitudinal studies rely on thousands of volunteers willing to be poked and prodded and asked a bunch of nosy questions for years on end.

Despite these obstacles, scores of longitudinal studies are rewarding investigators with tantalizing findings, some of which have overturned conventional wisdom about diseases of old age. For instance, in the early 1960s, many doctors hesitated to treat high blood pressure for fear of boosting a patient’s risk of Alzheimer’s disease, says Tamara Harris, a geriatrician at the National Institute on Aging (NIA) in Bethesda, Maryland. Such worries arose from studies showing that Alzheimer’s patients had lower blood pressure than their nondemented peers. But comparing people with disease to those without it can miss important landmarks on the path to disease, Harris says. Longitudinal studies have since shown that high blood pressure in midlife correlates with Alzheimer’s disease in old age. This correlation can get lost by the time Alzheimer’s is diagnosed, in part because people tend to lose weight as the disease develops, which reduces blood pressure. “If you just look at the time of the diagnosis, you miss the life trajectory that led to the [disease’s] development,” says Harris.

In the past 50 years, longitudinal studies have illuminated risk factors for everything from heart disease to dementia to cancer, guiding public health recommendations along the way. They’ve also helped untangle the differences between aging-related diseases and what many experts would consider normal aging processes. With more than 50 longitudinal studies currently analyzing and collecting data, these programs will undoubtedly produce many more landmark findings. Knowing the strengths and weaknesses of some of the studies helps in evaluating their sometimes conflicting findings—and deciding which ones to watch for answers to burning questions such as what symptoms predict Alzheimer’s disease and whether wine can stave off heart disease (see “Six Other Longitudinal Studies to Keep an Eye On” in addition to the ones described below).

First in Class: The Framingham Heart Study

Heart disease put the small town of Framingham, Massachusetts, on the medical map. The exhaustive study of its residents began in 1948, when rates of coronary heart disease and stroke were soaring in the United States and no one knew why, says Philip Wolf, a Boston University epidemiologist and principal investigator of the study. Under the auspices of the National Institutes of Health (NIH), the Framingham Heart Study set out to identify factors...
Six Other Longitudinal Studies to Keep an Eye On

The Betula Project www.psy.umu.se/memory/Betula.html
Start date: 1988
Study population: 4000 residents of Umeå, Sweden, who were aged 35 to 80 when the study began
The Betula Project is providing clues about how memory changes with age, and researchers hope that brain-imaging data and genetic information collected from some of the subjects will help them detect early markers of impending dementia.

The Atherosclerosis Risk in Communities Study (ARIC) www.cscuc.unc.edu/aric
Start date: 1987
Study population: 15,792 people aged 45 to 64 from four U.S. communities
The ARIC study is tracking cardiovascular disease. It includes a greater proportion of minorities than do Framingham and other studies. The study should allow researchers to discover whether known risk factors for cardiovascular disease apply across different ethnic groups.

The Cardiovascular Health Study (CHS) 128.208.129.3/chs
Start date: 1989
Study population: 5201 people aged 65 and up from four U.S. communities, including more than 687 African Americans
CHS is a population-based study of coronary heart disease and stroke. Its researchers hope to quantify the importance of known cardiovascular risk factors in elderly adults as well as identify new markers that could predict future risk and direct prevention efforts.

The Seattle Longitudinal Study geron.psu.edu/sls
Start date: 1965
Study population: more than 6000 people aged 22 to 95
from Washington state
The Seattle Longitudinal Study focuses on psychological development and cognitive ability. It has linked both a flexible personality style at midlife and an intellectually stimulating environment to a reduced risk of cognitive decline. It has also suggested that cognitive training can delay or reverse slides in reasoning and spatial orientation. The study has expanded to include data from siblings, adult children, and, in some cases, grandchildren of primary cohort members.

Honolulu-Asia Aging Study (HAAS) [no link available]
Start date: 1991
Study population: More than 3700 Japanese-American men from Oahu, Hawaii, aged 71 to 93 years
HAAS is examining risk factors for dementia. It was one of the first to show that higher blood pressure in midlife is associated with dementia later. The study includes an autopsy component and tests for Parkinson’s as well as Alzheimer’s and other dementias.

Age, Gene/Environment Susceptibility Study: The Reykjavik Study of Healthy Aging for the New Millennium (AGES) www.hjarta.is/en
Start date: 2001
Study population: 12,000 participants aged 67 and up
AGES is a follow-up to the Reykjavik longitudinal study, which tracked heart disease in more than 20,000 Iceland residents from 1967 to 1994. “We went to the Reykjavik study, because they had all of this early-life data we can use to look at the trajectory of health in old age,” says study investigator Tamara Harris, a geriatrician at the National Institute on Aging in Bethesda, Maryland. AGES has tracked a wide range of aging-related issues, including sarcopenia, osteoporosis, diabetes, osteoarthritis, and dementia. Researchers plan to collect DNA from participants, and they are using computerized tomography to examine coronary arteries and magnetic resonance imaging for brain imaging studies.

contributing to cardiovascular disease by tracking a cohort of volunteers over time. Researchers enrolled 5209 men and women between the ages of 30 and 62—including many spousal pairs—and gave them thorough physical exams in addition to quizzing them about their diets, exercise habits, and other lifestyle choices. Since then, participants have returned every 2 years for follow-up interviews and medical tests. In 1971, researchers recruited 5124 of the original participants’ adult children and their spouses—the so-called offspring cohort—to join the study, and Wolf and his colleagues are currently enrolling a third-generation group, the offspring of the offspring.

Over the years, the study has helped finger cardiovascular risk factors such as high blood pressure, smoking, obesity, diabetes, elevated cholesterol, high homocysteine concentrations, and sedentary lifestyle. More than 1000 peer-reviewed papers have come out of its massive data sets. The study was originally intended to end after 20 years, but by then it had become so successful that no one wanted to see it die, least of all the participants. “They’ve taken this as their contribution to humankind—they’re very devoted,” says Wolf.

The study has branched out from its original heart disease focus to examine other aging-related conditions such as dementia and osteoarthritis. Its researchers now collect DNA from participants, and once they have analyzed it from the third-generation group, they’ll have genetic information on about 7000 people from 700 of the study’s largest families, along with the participants’ health histories and family trees.

Although the Framingham study has continued to grow and adapt, it suffers from a few limitations. For instance, the participants come from a single town and do not reflect the racial and economic diversity of the general population. Still, at the time of its inception, Framingham was a bold experiment, and its success paved the way for later studies.

Ambitious as it is, the Framingham study initially focused on just one type of aging-related disease. The Baltimore Longitudinal Study of Aging, on the other hand, aimed from the start to examine an array of aging-related diseases and phenomena, says E. Jeffrey Metter, a gerontologist and BLSA investigator at...
the NIA branch in Baltimore. For instance, physicians knew that kidney function often declines with age, but the BLSA uncovered a group of people whose kidney health remained unchanged. "So it gave clues about what you could do to maintain renal functions," says Harris. Launched in 1958, the BLSA has enrolled more than 3000 adults of all ages.

The study was concocted by NIH gerontologist Nathan Shock at the suggestion of William Peter, then a recently retired government scientist. "Dr. Peter went out and recruited his friends, and his friends brought in their friends, and that's how the study recruited," says Metter. The result was a group of volunteers packed with highly educated people—about three-quarters have some college education.

Volunteers came to the lab every 2 years until 1998. Then the follow-ups switched to yearly for those older than 80 and every 5 years for the others. In addition to imaging brains and doing other tests, the study autop-sies those who provide consent.

The BLSA has shown that many changes seen in elderly people result from disease rather than the aging process itself, says Harris. For instance, the BLSA allowed researchers to track symptoms that they later discovered were subtle signs of early kidney disease.

The BLSA has also provided insights into the aging mind. For example, the study has shown that some types of memory decline with age whereas others, such as vocabulary recall, continue to improve until very late in life (see “All in Your Mind†“). Because BLSA tracks individuals over time, says Metter, researchers can work backward to ask when reliable differences emerge between people who go on to develop dementia and those who don’t. They don’t have a simple answer, but they have found that poor performance on visual-recall tests might predict increased risk of dementia. The study has also uncovered information about heart disease risk factors and metabolic changes across the life span.

Having a highly educated cohort “means you can’t really look at socioeconomic factors and their impact on aging,” says Metter. “But that’s also an advantage because it makes the population more homogeneous,” possibly cutting down on noise to reveal a weak risk factor.

**Sisterhood Is Powerful: The Nurses’ Health Study**

*[www.channing.harvard.edu/nhs](http://www.channing.harvard.edu/nhs)*

The Nurses’ Health Study was the first longitudinal study to focus on women’s health issues. It was inspired in part by the introduction of oral contraceptives in the early 1960s, which meant that “millions of healthy women would be taking a drug for years and nobody knew what the consequences would be,” says Meir Stampfer, an epidemiologist at the Harvard School of Public Health in Boston.

The study enrolled its first participants in 1976: 122,000 married nurses aged 30 to 55 from 11 states. Follow-up questionnaires are sent through the mail every 2 years and include questions about hormone use, physical activity levels, smoking, alcohol consumption, weight, and other health and lifestyle measures. The researchers chose nurses for the project in hopes that they would accurately report about their own health. The designers also assumed that nurses, knowing the value of medical research, would likely stick with the study over the long haul—which has proven to be the case, says Stampfer. Beginning in 1980, researchers also began collecting dietary information from participants. A second arm—the Nurses’ Health Study II—established in 1989, probes the same questions in a new group, women aged 24 to 42 when the study began. “We wanted to look at the impact of young-adult experience on long-term risk of diseases,” says Stampfer.

In addition to plowing through questionnaires, nurses have submitted toenail samples so researchers can accurately gauge their nutrient intakes, and they’ve donated more than 33,000 blood samples for studies of hormones and genetic markers of cardiovascular disease, among other things.

The study has provided a wealth of safety information about birth control pills, such as revealing the increased risk of stroke in smokers who take the pill. It has also contributed to the understanding of age-related diseases such as breast cancer and heart disease. For example, bearing multiple children and having babies at a young age protects from breast cancer—a finding that the Nurses’ Health Study first detected, says Stampfer. Clues that hormone replacement therapy could boost breast cancer risk also first emerged from the study. “People didn’t believe it at first, until [the link was] confirmed in randomized trials,” says Stampfer. Conventional wisdom has been slow to embrace the study’s prescience. “We really got smashed on when we published results showing that women who drank alcohol were at higher risk of breast cancer. Since then there have been three dozen studies that show the same thing.”

The Nurses’ Health Study’s greatest strength is its large sample size. “The Framingham study is extremely valuable, but it’s a few thousand people,” says Stampfer. “There isn’t any other study this large that’s done repeated assessments of diet over time.” Many health food favorites such as sweet potatoes and carrots have received their gold stars from the study, and the apparent ability of an occasional glass of wine or other alcohol to cut heart disease risk also turned up in the Nurses’ Health Study. Nurses’ health consciousness sets them apart from the general population, however. For example, they might be less likely to take multiple drugs that could cause trouble in combination or to shrug off symptoms of disease, which could mean that correlations seen in the study don’t translate to less medically astute people.

**Men Catch Up: The Health Professionals Follow-Up Study**

*[www.hsph.harvard.edu/hfps](http://www.hsph.harvard.edu/hfps)*

With the Nurses’ Health Study churning out so many important findings related to women’s health, Stampfer and his colleague Walter Willett at the Harvard School of Public Health decided to launch a male version in 1986. They enrolled 51,529 male health professionals, such as dentists, pharmacists, podiatrists,
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and veterinarians, all aged 50 and up. They’re using the Nurses’ Health Study methodology to analyze the role of nutrition in diseases such as cancer and cardiovascular disease.

See You at the Pharmacy: The Rotterdam Study
www.epib.nl/ergo.htm

Studies based in Europe sometimes have access to patient data that are difficult to come by in the United States. For instance, computerized pharmacy records in the Netherlands are providing researchers with a rich data set to mine for information about the dangers or neuroprotective effects of a range of medicines.

In 1990, Dutch researchers rolled out a study in Ommoord, a suburb of Rotterdam, with the goal of examining disease in senior citizens. They originally enlisted 7983 men and women aged 55 and older, and in 2002 they added another 3011 participants. Interviewers came to the volunteers’ homes and quizzed them on their medical history and socioeconomic background. On follow-up visits at the research center, participants were screened for dementia and a version of the apolipoprotein E gene (ApoE) that increases the risk of Alzheimer’s disease. Additional check-ups occur every 2 to 3 years. The researchers have access to centralized pharmacy records—for example, what drugs were prescribed and how often the prescription was refilled—for an unusually accurate account of medication use.

“Rotterdam was one of the first cross-disciplinary studies,” says Harris. Studies such as Framingham and the Nurses’ Health Study initially focused on a single category of diseases or questions, but Rotterdam, like BLSA, set out from the get-go to investigate a wide range of chronic diseases in elderly people. Its wide net harvests information on dementia, Parkinson’s disease, osteoporosis, arthritis, bone fractures, heart disease, macular degeneration, and glaucoma. Among other discoveries thus far, the study has shored up the finding that nonsteroidal anti-inflammatory drugs (NSAIDs) reduce the risk of developing Alzheimer’s disease and has linked elevated high density lipoprotein cholesterol to age-related macular degeneration. The study has also pointed to a connection between atherosclerosis and depression late in life.

Old as the Hills: Cache County, Utah
[no link available]

The Cache County, Utah, study is famous for the longevity of its study subjects. They beat the national norm by about 10 years, making Cache County one of the longest-lived counties in the United States. What’s more, the people are squeaky clean, which makes for clean data. “About 90% of the population is Mormon, so they don’t drink or smoke, and there’s not much in and out migration,” says Kathleen Welsh-Bohmer, a neuropsychologist at Bryan Alzheimer’s Disease Research Center in Durham, North Carolina, and a study investigator. A rare or subtle risk factor might show up in this homogeneous, healthy population that would be lost in the noise of data from harder-living folks.

The study was designed to “examine the controversy over whether the prevalence of Alzheimer’s continues to rise with age,” says Welsh-Bohmer. It’s also probing the role of environmental and genetic risk factors in the development of Alzheimer’s disease and other dementias. The study’s coordinators aimed to evaluate all people in the county over age 65. They ended up with 5092 participants—more than 85% of those eligible—and the researchers have continued to track these volunteers and test their cognitive abilities since the study began in 1994.

The study’s respectable sample size has allowed it to answer the primary question: “Our initial findings indicated that [Alzheimer’s disease incidence] does indeed continue to rise. It appears to be leveling off at about 90,” says Welsh-Bohmer. The study has also suggested a neuroprotective effect from NSAIDs, as in the Rotterdam study. Clinical trials are now under way to test the drugs’ ability to prevent or delay the disease.

Aside from Alzheimer’s, the project is tracking vascular dementia and mild cognitive impairment, a slightly enfeebled state that often precedes a diagnosis of Alzheimer’s. And it is “now evolving to take up issues of prevention,” says Welsh-Bohmer, by analyzing diet, medication use, and lifestyle factors. There’s no guarantee, however, that a lifestyle factor that appears to protect against dementia in Cache County will work as well in people who drink, spit, and cuss.

Longitudinal Studies’ Long Future

The basic design of longitudinal trials hasn’t changed fundamentally since the people of Framingham began volunteering for service. Nor have the studies become outdated. Longitudinal studies can’t prove that one factor or another slows aging or protects against its companion diseases. Wherever possible, researchers follow up observations from longitudinal trials with the gold standard: clinical trials in which volunteers are randomly assigned to receive a drug or a placebo (see “On Trial”†). But not every risk factor can be randomly assigned—smoking, chowing foods dripping with cholesterol, and forsaking vegetables are well beyond what an Institutional Review Board would allow researchers to request of study subjects.

Future studies will build on previous results to assess how different diseases of aging interact. Many of the first studies performed well in terms of describing a single disease, “but I think we’re going to move away from single-organ studies,” says Harris. Many diseases share common risk factors (both heart disease and diabetes, for instance, are linked to high blood pressure) and, in some cases, even common mechanisms. Longitudinal studies provide a powerful way of observing how these pathways interact, she says. At least for the foreseeable future, volunteers willing to submit to nudging and needles, year after year, will remain indispensable for hunting down secrets of healthy aging.

Christie Aschwanden is a freelance writer in Boulder, Colorado. She is still waiting for studies that link her grandparents’ longevity to their daily scoop of ice cream.

† sageke.sciencemag.org/cgi/genedata/sagekeGdbGene;7
‡ sageke.sciencemag.org/cgi/content/full/2004/24/oa1