



the **nurses'**
health

We don't know who they are, exactly. years, 121,701 nurses have helped lifestyle affects our health. **This is**

study

by John Sedgwick

Every other year since 1976, nurse Linda Vader has been getting a questionnaire in the mail. She always fills it out, often puzzling over why anyone would want to know how many tortillas she has eaten in the past month; sometimes struggling to figure out how many natural teeth she still has. But she answers every question, and because she, and 121,700 other nurses, have willingly opened their lives to scrutiny, American women know a good deal more about the impact lifestyle choices can have on their health.

Vader is part of a vast project called the Nurses' Health Study (NHS). The hundreds of questions she has answered about tortillas and smoking and contraceptive use and fat consumption were designed to bring the rigor of the scientific method to discovering the health consequences of such ordinary, everyday decisions as whether to have a salad or a hamburger, whether to drive or to walk, whether to have children or not. The information gleaned from the nurses' lives has helped resolve many of the thorny medical issues of the day.

The NHS is not the first study to examine these questions, but it is arguably the best, largely because of the questionnaires that lie at the heart of its design. It is a prospective epidemiological study, which means scientists try to discover which factors account for different health outcomes in a population. Why, for example, do some people get lung cancer and others don't? Could tobacco play a role? The standard scientific method is to use the classic double-blind design, but when dealing with potentially dire health consequences, there are inevitably some ethical constraints to this approach. One could not very well have a thousand women smoke tobacco for five years while another thousand puffed away on a placebo, and then blithely tally up the corpses. Epidemiologists get around this by simply recording the medical consequences of the nurses' own, freely made choices. If they want to smoke, fine; the NHS simply keeps track of them over a period of time and compares their health with the health of those in the study who don't smoke.

It's also possible to collect the data retrospectively. Researchers could round up a thousand women with lung cancer, say, then find a thousand similar women who are free of the disease and ask how many in each group smoked. That may sound a lot quicker than following a group of subjects for years, but NHS researchers generally scoff at this

But for the past 20
us understand how
their story.

approach for the simple reason that most people are considerably better at describing the present, as they do in a prospective study, than at trying to dredge up hazy recollections of their past, as they do for a retrospective one. For instance, one current retrospective study is seeking to determine the relationship between stress and breast cancer by asking breast cancer patients how much stress they've had in their lives. "How is someone who is under the stress of a breast cancer diagnosis supposed to recall clearly how much stress she used to have?" asks Graham A. Colditz, M.D., a major investigator with the NHS. "Not a great design."

As it approaches its twentieth anniversary, the NHS has attained near-legendary status among its peers. There are larger projects, such as the ongoing 1.2 million-subject American Cancer Society investigation into the effects of smoking, and there are more expensive ones, like the \$600 million Women's Health Initiative. But no other survey combines the

investigators an extraordinary opportunity to match behavioral causes with medical effects. As the information expands, the rate of published studies is growing exponentially. Although the NHS has historically generated about one paper a month, it now produces one a week. "The study is expanding in all directions," Dr. Willett says. "Time, money, personnel, everything."

The results have transformed American life. In 1987, alcohol consumption took a hit when the NHS revealed an unexpected link between breast cancer and "moderate" alcohol intake. Between 1988 and 1993, it put to rest the illusion that smoking was less dangerous for women than for men when it reported, in the careful language of epidemiology, that smoking is for women a "strong predictor" of lung cancer, cataracts, stroke and—surprisingly—suicide; it is also the "dominant cause" of heart disease, which is the major killer of women. The NHS paved the way for the widespread use of hormone replacement



The nurses are 97 percent white and considerably more affluent than the average American female. Because of their profession, they are also a great deal more health-conscious.

massive scale of the NHS—both in the length of time and the number of subjects—with such talented researchers and such rigorous attention to detail. As a result, in a statistical realm that seems to be even more impressionistic and changeable than presidential polling data, the NHS remains exceptionally productive. "It has probably made more contributions to the understanding of women's health than any other single study over the past 20 years," says Noel S. Weiss, M.D., a professor of epidemiology at the University of Washington.

Perhaps the best measure of the study's value is the care with which the data are guarded. The original questionnaires are stored in four different sites, duplicated on microfilm and entered into a computer system that is itself backed up three different ways at two separate locations. Asked to place a dollar value on the NHS data, Walter C. Willett, M.D., the prominent Harvard School of Public Health epidemiologist who is one of the study's major investigators, finds himself uncharacteristically lost for words. "You can't," he says. "It simply is not reproducible."

One reason for its value is the sheer length of time over which the data have been collected. Instead of the usual isolated statistical snapshots, the NHS offers a kind of continuing health documentary of more than 120,000 lives, allowing

therapy (HRT) in 1991 with its announcement that estrogen cut the risk of heart disease, and then caused a round of second thoughts with a troubling follow-up study in which HRT was found to boost the likelihood of breast cancer by as much as 70 percent. The list goes on, year after year, culminating in last year's blockbuster finding that even moderate weight gains of 15 pounds by midlife increased the chance of premature death. (For a fuller accounting, see the chart, *opposite*.)

Frank E. Speizer, M.D., had much more modest goals in mind for the study when he first proposed it in the early 1970s. Prompted by the alarming reports that the birth-control pill led to strokes, he wanted to track the long-term health effects of oral contraceptives. An early practitioner of the then-young specialty of epidemiology, he had done some work with Oxford University's Sir Richard Doll, M.D., whose pathbreaking British Doctors Study used a novel strategy for tracking the health consequences of smoking—questionnaires. Dr. Doll mailed out 60,000 of them to doctors and then tabulated the responses he received. In the U.S., the standard way to do epidemiological research was in the manner of the famous Framingham Heart Study, whose investigators conducted physical examinations of and interviewed 5,209 citizens of Framingham, Massachusetts. The in-person approach was reliable, but

What we've learned from the NHS

1. Hormone replacement therapy cuts the risk of heart disease (1991). HRT may also boost the likelihood of breast cancer by as much as 70 percent (1995).
2. Being slightly overweight increases the likelihood of premature death (1995).
3. Alcohol is associated with an increased risk of breast cancer (1995).
4. Smoking is a strong predictor of lung cancer, cataracts, stroke and suicide. It is the dominant cause of heart disease, the major killer of women. These effects are completely reversible (1987-1993).
5. Trans-fatty acids found in margarine and store-bought muffins drive up the risk of coronary heart disease in women (1992).
6. Vitamin E helps prevent heart disease (1993).
7. Hair dye does not cause cancer (1987).
8. Tubal ligation may prevent ovarian cancer (1993).
9. Current use of birth-control pills increases the risk of heart disease for women in their forties (1988).
10. Family history accounts for 6 percent of all breast cancers (1993).
11. Physical exercise protects against diabetes (1991).
12. Eating too few vegetables is associated with increased breast cancer risk (1993).
13. Obesity leads to coronary heart disease, gallstones and diabetes (1989-1990).
14. Use of oral contraceptives at any time in a woman's life decreases the risk of ovarian cancer by about 35 percent (1995).

it was so expensive that it necessarily restricted the number of subjects to a few thousand. Mailed questionnaires allowed the study to reach a much larger number, a critical factor in dealing with diseases like heart disease and breast cancer that, even if common, would generate only a small number of cases over the limited period of a study.

For the first round of questionnaires, Dr. Spitzer selected a few thousand doctors' wives as his sample, but the mailing flopped. "It was awful," says Meir Stampfer, M.D., one of the NHS investigators. "The women just didn't respond." Then Spitzer tried nurses. After a successful test run, he sent out 170,000 questionnaires to married nurses between the ages of 30 and 55 in 11 large states. He knew immediately that he had struck gold.

That first questionnaire was just one sheet of paper, with questions on both sides. It concentrated on the Pill question, asking respondents to specify which type of oral contraceptive they used and when they had used it, and to report any health problems they'd had. There was a little space left over when he'd finished, so Spitzer threw in one more question. It was, oddly enough, about the use of hair dyes—tests on rats had led to speculation that dyes caused breast cancer. (The study showed no harmful effect.)

As it happened, the NHS research never did settle the Pill question. It found that there is an increased risk of breast cancer and heart disease among women over 40 who were using the Pill. For reasons that NHS researchers themselves have difficulty explaining, women who had taken the contraceptive in the past but were not currently using it had no increased risk. More puzzling still, Pill use does not correlate with an increase in overall mortality rates. "There were a lot of questions about the health risks of using the Pill when we started," says Ichiro Kawachi, M.D., an NHS researcher at the Harvard School of Public Health, "and there still are."

Spitzer had, however, proven the power of the research method, and as word spread, the NHS started to attract other researchers. Foremost among them were the flamboyant Willert, who introduced two pages of dietary questions in the 1980 mailing, and the coolly analytical cancer researcher Dr. Colditz, who saw the NHS as a way to investigate the etiology of breast cancer. "NHS is a bit like a coral reef," explains Dr. Kawachi. "It just keeps building up."

To accommodate the growing number of researchers, the questionnaire has expanded from two pages to six. Each nurse probably spends a total of about an hour answering questions like "How much bodily pain have you had during the past four weeks?" and "How many bagels did you eat last month?" and "Were you breast-fed?" Still, the additional pages haven't eased the competition among scientists to get some of the precious space for

Which study should you believe?

There must be a law of Newtonian physics that each epidemiological study be balanced by an equal and opposite one. How else to explain why epidemiologists so rarely speak with one voice on the major environmental or dietary risks of the day? Take the two conflicting studies last summer on the perplexing topic of the relationship of HRT to breast cancer. In June, the *New England Journal of Medicine (NEJM)* published a well-publicized report from the Nurses' Health Study suggesting that HRT increased the risk of breast cancer by 30 percent to 70 percent. In July, the *Journal of the American Medical Association (JAMA)* ran an equally well-publicized article arguing just the opposite: that, if anything, HRT decreased the risk of breast cancer. What gives?

"That was an unfortunate juxtaposition in time," says Walter C. Willett, M.D., a lead investigator of the Nurses' Health Study. He points to some important differences between the two studies that might account for their different outcomes. First of all, the *JAMA* study was a retrospective study of women with breast cancer, who were asked to recall their past estrogen use and may not have been able to do so accurately. The Nurses' Health Study in the *NEJM*, by contrast, was a long-term prospective study that recorded estrogen use as it happened. Secondly, the *JAMA* study only enrolled women under 65, while the Nurses' Health Study has women up to age 72, and Dr. Willett believes the greatest effects are found in the later years of life.

But there is the more important conflict behind the confusion that such dueling studies invariably generate, and that involves the split between the essential principles of journalism and those of epidemiology. Journalism seizes on the new, while epidemiology endorses the old. The first epidemiological study is not confirmed in any useful sense until it has been reproduced by a fair number of later ones. "It's the old news that is more likely to be true than the new news," says Michael Thun, M.D., statistical analyst for the American Cancer Society. But journalists don't care about old news. So the first dramatic finding—whether true or not—gets their attention. Then they jump on the first dramatic counter finding, and away we go. Unfortunately, it is simply too soon to tell definitively whether either the *NEJM* or the *JAMA* article is "right" about the connection between HRT and breast cancer, agonizing as that may be for women to hear. It is worth noting that the greatest risks emerge most clearly in epidemiological data. If studies continue to swing wildly back and forth on a particular question, the risk is probably not severe.

their questions. The research team meets for three hours every other week to hash things out. It can take months of fiddling to finalize the exact wording, and the fight over some questions has gone on for years. To introduce a new topic, a researcher has to show that the issue is unresolved, poses a significant public health hazard and has a measurable biological effect.

Because everyone involved takes such pains, one might think that the Nurses' Health Study is uniquely positioned to obtain the deepest truths about women's health, but of course, truth in epidemiology is extremely hard to come by. The researchers are always very careful to qualify their findings. The study on alcohol and breast cancer, for example, states only that there is an "association" between the drinking of alcohol and an increased likelihood of getting breast cancer; it scrupulously do not say that the alcohol consumption "causes" breast cancer. Only in newspaper headlines do lifestyle choices ever cause illnesses. The sad truth is, no epidemiologist ever knows for sure what accounts for what. In the language of the trade, there are too many "confounding variables"—other unknown factors that may bollix up an analysis. Alcohol consumption and breast cancer may both correlate with some third factor, like smoking, coffee drinking, meat eating or—who knows?—disco dancing, that is actually responsible for the outcome. Analysts invariably try to account for as many of these other factors as they can, but they can never be sure they've gotten them all.

And the nurses themselves are hardly typical members of the female public. They are 97 percent white and, because of their profession and marital status, considerably more affluent than the average American female. Nurses are also a great deal more health-conscious than the average. The NHS researchers insist that the similarities among their subjects give the study a kind of concentrated power, since the results are not watered down by too many of those confounding factors. Nevertheless, health information culled from 121,000 fairly well-to-do white women may not have much predictive power for inner-city Hispanics or suburban Laotians.

Epidemiology, as with so many other branches of science, relies on the accumulated findings of many studies on the same issue to build validity. Most researchers would call a first round of results "preliminary" until they have been replicated by other research. Epidemiology, in that sense, is a group effort. Even critics of the NHS acknowledge that the study's record of having its findings repeated in later research is impressive. The moderate alcohol/breast cancer findings, for example, were considered highly questionable when they were first published, but as the NHS researchers cheerfully observe, the results have since been supported by 60 other studies.

In the end, though, the strength of the NHS lies largely in its data. Women are always better at answering questionnaires than men, but female nurses are probably the best of the women when it comes to health questions, because they have a professional appreciation of the information being sought. "We can ask about amyotrophic lateral sclerosis and not have to explain what it is," says Kawachi, referring to the condition better known as Lou Gehrig's disease. "Plus, as health professionals, they are especially motivated to help." A whopping 90 percent of the nurses fill out each questionnaire, and about half as many have gone along with requests to provide vials of blood (for DNA samples) and even toenail clippings (they're used to measure the body's absorption of the element selenium, which had been thought to contribute to breast cancer, but the current NHS data show no correlation).

The researchers don't simply rely on the dedication of their

confirming the thousand or so deaths that occur each year. "That's a truly thankless job," Chase says. "You have to deal with a lot of grieving families."

At peak season in midsummer for the even-numbered years when the questionnaire goes out, as many as 12,000 responses a day arrive at the office. The envelopes are opened and the questionnaires checked over by a dozen college students on their summer break. The first task is to eyeball the responses to see if any stand out as particularly unusual. Was the nurse who reported that her weight went from 114 pounds to 216 suffering from what Chase calls "a real crisis" or was it merely a slip of the pencil? And how should they tabulate all the odd dietary products on the market? How, for example, to classify I Can't Believe It's Not Butter spray-on cooking oil? True to its name, it's not butter. Nor is it margarine, or even an oil. So what is it? "We decided it was nothing and zeroed it out on the forms,"

The world has changed since the study began and so have the nurses. Questions about hours spent digging in the garden have given way to queries about hours spent on a stationary bicycle.



subjects, however. They are dogged in their efforts to get as much information out of the nurses as they can. They have permission to check the nurses' responses against actual medical records, and they do it. Knowing that the questionnaires they don't get back represent the most valuable information of all (because the missing subject may have died or become ill), they send out five to seven rounds of follow-up letters to any nonrespondents. That amounts to hundreds of thousands of letters. In addition, there are usually 4,000 questionnaires that come back from the post office with no forwarding address. NHS investigators track these missing women like detectives, consulting the new residents of the old address, family members, friends and coworkers, and finally the National Death Index.

Currently, the data collection work goes on in rather dingy temporary quarters on the ground floor of an office building on Brookline Avenue in Boston's celebrated medical district. As directed by project coordinator Gary Chase, the effort resembles a cross between a mail-order operation and a grassroots political campaign. Chase makes a weary gesture toward the shelf full of unforwardable envelopes that hangs over his desk like a bad memory. Three staffers work full-time tracking them. "At any one time, there are about two thousand people we're looking for," he says. "And while we search for them, another thousand get lost." Arduous as that task is, it is better than

says Chase. Because women were having a hard time remembering the brand of birth-control pills they were taking, the study compiled a 32-page booklet illustrating more than a hundred types. "That took one guy a whole year," says Chase.

Once the questionnaires are validated in this way, they go through an electronic scanner, which converts the pencil marks into computerized data for analysis by 10 senior fellows and 40 or so other researchers at the Harvard Medical School, the Harvard School of Public Health, and Brigham and Women's Hospital.

The information processing is so dryly analytic, it is sometimes easy to forget that there are real people out there mailing these things in. (About the only personal detail that the study was willing to reveal about its subjects was that Cheerios was the most popular breakfast cereal.) So it's almost a shock to discover a personal note from a nurse enclosed in her return envelope, as happens occasionally. "I apologize for the chew marks," one woman wrote. "My dog Barney got hold of it." Another regretted that her daughter had spilled orange juice on her questionnaire. And a third made a personal appeal to Gary Chase. "Hey Gary," she asked, "are you married?"

"I think she was kidding," Chase says, blushing.

The NHS jealously guards the names of the study's participants, knowing that the assurance of (continued on page 130)

nurses

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confidentiality is a key ingredient in the nurses' cooperation. But, with more than 100,000 of them out there, it is possible to track them down by other means. Speizer got his original list from nurses' registries, and many of the subjects are still listed. Linda Vader, for example, is now the head nurse at the W. K. Kellogg Eye Center at the University of Michigan. She was the assistant head nurse when she received her first NHS questionnaire in the mail. She didn't hesitate to fill it out. "I thought it was a chance to make a contribution to medicine," she says, "and to the health of future women."

Since then, both her parents have died, she has separated from her husband and gotten reattached to him, taken up racquetball and dropped it, and gone through two pairs of poodles. Through all this, she has done the questionnaire every other year, regular as rain. "It's only a minor nuisance," she says. She has come to regard it as a chance to do the health equivalent of financial planning; the dietary portion, for example, serves as a useful "inventory" of everything she takes into her body, even if it is astounding to contemplate exactly how much breakfast cereal one shovels down every month.

But the study also has an effect on the subjects. Vader has found herself quietly conforming to what she perceives as the researchers' nutritional preferences. Since the NHS reported the hazards of red meat, for example, she has made a point of eating less of it. "I've gotten much more vegetarian in my diet," she says. "And I can show off my improvement by the way I fill out my answers. It seems like an accomplishment."

Vader is deeply committed to the research. She has told her aunt that if she and her husband were to die together—in a plane crash, say—to please send word of the circumstances of her death to the Nurses' Health Study in Boston, Massachusetts.

In the past few years, the study has been edging into the psychosocial realm in pursuit of the root causes of disease. Because a surprising 15 percent of the subjects in another epidemiological study turned out to have significant phobias, Willett has deployed the NHS to investigate the effects of such exaggerated fears on heart disease. There were already a few questions looking into the role of stress—defined as the combination of high demand and low control on the job or at home—in the formation of destructive behaviors like alcoholism and cigarette smoking.

Among the topics that have made their way onto the general questionnaire over the years are fibrocystic disease (which may lead to breast cancer), electric blankets (whose electromagnetic fields may be carcinogenic), lost teeth (which may predict osteoporosis) and left-handedness (because they live in a right-handed world, lefties may be more likely to die from accidents).

When the Nurses' Health Study was started, the average age of the respondents was 39. It is now 58. The world has changed, and so have the nurses. Questions about hours spent digging in the garden have given way to queries about hours spent on a stationary bicycle. All but 11,000 of the nurses have passed through menopause by now, and about 7,000 have died. Like Linda Vader, who has cut down on eating meat, the nurses have generally become more health-savvy as the years have rolled along: They were heavier-than-average smokers in 1976; they now quit at the rate of 2 percent a year, twice the national average. Despite such precautions, however, age is catching up with them. In the cold-blooded terms of epidemiological research, the NHS is finally getting to the good part. The women are developing an increasing number of what epidemiologists call "end points." They are getting sick, they are dying, and they are giving the NHS researchers more and more to write about.

Although doubts persist, and always will, the NHS has provided an invaluable service to women, which is why the nurses participate in it so actively. Some have volunteered themselves for additional studies, and they even responded enthusiastically to the proposal of a study to look at their children.

Because of her participation in the NHS, Elizabeth Trought, an associate professor of nursing at the East Carolina School of Nursing, was asked to join the clinical trial of a drug that may have important cardiovascular implications. She does this at no small personal cost. Trought's brother died of a heart attack and her sister recently suffered one, and the research protocol requires that she not take aspirin or beta-carotene, even though she and her doctor husband are convinced that they help ward off heart disease. Trought has decided to take her chances. Why? "I'm doing this for my daughter and for my granddaughter," she says evenly. "If we're going to get any epidemiological information that's valuable, women like me have to cooperate." Ultimately, the strength of the Nurses' Health Study may lie not only in the quality of the data and the power of the analysis, but also in the fierceness of the commitment of these nurses, who are willing to give their lives to the cause. □

murder

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handgun violence, she initiated the gun amnesty program in the city's housing projects. Twenty-four-year-old Garcia was Richmond's Cinco de Mayo queen in 1988, chosen because of her community service; later, she completed her B.A. at the University of California, Berkeley, becoming the first in her immediate family to go to college. After a brief temporary stint at the housing authority, Garcia was hired there as a housing program specialist.

As are other fatal incidents, the one in the Richmond Housing Authority office was allegedly ignited by the disappointment of an employee, a phenomenon Kinney calls "competitive retaliation." The accused killer, Michael Pearson, according to a police report, "was bitter, and felt he had been screwed." Pearson had been hired two months before Garcia, but as an office assistant. He had not worked out. Talley called him in for a termination conference on April 25 at four o'clock. It was the last thing scheduled on her last day of work before she left for a vacation in the Caribbean. But Pearson had other plans. He prepared for his termination conference by buying a pistol at a pawnshop, which he picked up the day before his last day of work. Reportedly, his only display of emotion during his discussion with Talley was moist eyes. Afterward, when he was cleaning out his desk, he took a trip to the restroom. Pearson then knocked at Talley's office and went with her across the hall to the conference room with the gun. He shot Talley, then walked the halls, passing other employees, until he came upon Garcia, hiding in an office. He shot her as well. He was taken by police without resistance, seeming spent and dazed.

In the police station, according to one policeman's account reprinted in the *West County Times*, Pearson said: "I'm shocked at myself. No one is going to understand. My family won't understand. Friends are not going to understand. I know everyone says, 'How can a nice guy do something like that?' I guess I reached my breaking point." Pearson has since pleaded innocent to all charges and is scheduled to go on trial next month.

Pearson's former managers resist psychoanalyzing him publicly, but they have their suspicions. Was he incensed at being fired by a woman? Was he bitter that a female colleague had prospered while he did not? Richmond city council member John Marquez says, "Ms. Garcia comes to work the same time he does, but as a professional with a degree. He's a receptionist. She becomes a specialist, and then he's getting fired." Marquez shrugs, leaving the