



NHS NEWS



Back row: S. Hankinson, W. Willett, F. Speizer
Front row: M. Stampfer, F. Grodstein

Dear Colleagues,

We are happy to share some exciting news: First, we recently received a perfect score on a grant to support the Nurses' Health Study from the National Institutes of Health (NIH). This funding will cover infrastructure costs and allow us to continue the Nurses' Health Study for another five years. Second, we are also excited to celebrate the 25th anniversary of the Nurses' Health Study II. Dr. Willett shares his thoughts on this milestone on page 8.

In this year's newsletter, our feature article highlights the differences between cancer subtypes. Technology has allowed us to better pinpoint these subtypes, and we have been able to study how individual cancer tumor types are related to dietary, behavioral, and lifestyle factors, as well as disease prognosis.

We also share interesting new research on how stress is related to chronic disease risk, as well as the health benefits of nut consumption.

Many thanks for your continued participation in our studies. We look forward to many more new and exciting discoveries!

Best regards,

The Nurses' Health Study Senior Team
Susan Hankinson, RN, ScD
Walter Willett, MD, DrPH
Meir Stampfer, MD, DrPH
Francine Grodstein, ScD
Frank E. Speizer, MD

NOT JUST ONE DISEASE

Cancer. This one word encompasses not just a singular disease but, as we are increasingly appreciating, a "constellation" of diseases. Over the past few decades, our collective mindset has shifted to reflect this new and broader way of viewing cancer.

The underlying molecular features of tumors have allowed us to more finely classify cancers into different subtypes. As scientists home in on these subtypes, modern medicine is becoming better at identifying, treating, and preventing various cancers.

BREAST CANCER

Historically, we have considered breast cancer as a single disease in our research studies. Many of the well-established risk factors for breast cancer are related to hormonal mechanisms of cancer cell formation. This is not surprising given that approximately 70-80 percent of breast tumors are hormone receptor positive—that is, the tumor exhibits estrogen (ER) and/or progesterone (PR) receptors, which it needs to grow.

Today, most women diagnosed with breast cancer will be tested for ER, PR and HER2 (a human epidermal growth protein) status. These markers provide information on prognosis and help physicians identify appropriate treatment.

Among postmenopausal women in the Nurses' Health Studies (NHS and NHS II), higher circulating estrogen levels are associated most strongly with higher risk of ER-positive breast cancers, while there are no or only modest associations with ER-negative breast cancers. This indicates that we must search in different places for causes of ER-negative breast cancers, which are currently more difficult to treat than the ER-positive cancers.

Our most recent data suggest that carotenoid intake is associated with a reduced risk of ER-negative breast cancers. Specifically, intakes of α -carotene, β -carotene, and lutein/zeaxanthin were inversely associated with the risk of ER-negative breast cancers, but not ER-positive breast cancers. These results are supported by a large project we led, where we combined data from the NHS and seven other large studies, which compared circulating blood levels of carotenoids and breast cancer risk.

Continued on page 6



RECENT FINDINGS

YOGA, WEIGHT TRAINING, AND REDUCED RISK OF DIABETES

We and other researchers have shown that regular aerobic physical activity, such as walking and running, provides protection against type 2 diabetes. However, we wondered if muscle-strengthening activities offered similar protection. In the NHS, regular engagement in resistance exercise and other muscle-strengthening activities such as yoga, stretching, and toning was associated with a lower risk of type 2 diabetes, independent of other health and lifestyle factors (such as diet or weight).

Compared to women who did not engage in these activities, individuals who spent 1 to 2.5 hours per week on these activities had a 25 percent lower risk of diabetes; women who spent more than 2.5 hours per week had a 40 percent lower risk. Women who engaged in both muscle-strengthening exercise and aerobic activity (at least 150 minutes per week of moderate aerobic activity) had about a 70 percent lower risk of diabetes compared to inactive women. Our findings suggest that adding two or more days per week of muscle-strengthening activity to moderate/vigorous activities provides the best protection against diabetes. (Grøntved A et al. *PLoS Med.* 2014;11(1):e1001587)

“OBESITY PARADOX” REFUTED

Previous studies of body weight and mortality among patients with type 2 diabetes have reported conflicting findings, with some suggesting a survival advantage for those who were overweight or obese at the time of their

diabetes diagnosis. A recent analysis among the NHS and the Health Professionals Follow-Up Study (HPFS) indicated that there was no such advantage to being overweight or obese.

We analyzed data from over 11,000 women and men who had type 2 diabetes. The “normal weight” group (body mass index, or BMI, 18-25 kg/m²) includes lean and healthy participants, as well as smokers and patients with existing or undiagnosed illnesses (both of which can lead to weight loss). This can make the group including “normal” weight individuals appear worse off than overweight or obese individuals in terms of survival. However, after accounting for smoking and underlying health in our study, it was clear that having a body weight within the normal range at time of diabetes diagnosis was associated with the best survival.

We concluded that having a healthy weight not only predicts better survival from diabetes but also lowers the risk of developing diabetes in the first place. (Tobias et al. *N Engl J Med.* 2014;370(3):233-44)

ADOLESCENT MILK CONSUMPTION AND HIP FRACTURE

For years, drinking milk during childhood and adolescence has been recommended to maximize bone mass and thus offset the expected bone loss at older ages that can eventually result in osteoporosis. But does higher milk consumption in early life lead to lower risk of osteoporotic hip fractures?



In postmenopausal women in the NHS and in older men in the HPFS, we found that risk of hip fracture was *not* lower in those who drank milk four or more times per day during their teenage years compared with those who rarely drank milk. In fact, in men, hip fracture risk was *higher* in the teenage milk drinkers, increasing by 9 percent for each additional glass of milk per day.

One explanation for these findings is that milk consumption at young ages promotes greater height; each additional inch of attained height was associated with a 12 percent higher risk of hip fracture. (Feskanich et al. *JAMA Pediatr.* 2014;168(1):54-60)

KIDNEY STONES AND HEART DISEASE

Kidney stones are on the rise among men and women. In the U.S., nearly 9 percent of individuals have had a kidney stone, and men are more than twice as likely as women to get one. Kidney stones can cause severe pain while passing, but have not traditionally been seen as a critical risk to long-term health.

Using data from the NHS and HPFS, we found that women with a history of kidney stones were about 30 percent more likely to develop heart disease, have a heart attack, or undergo a procedure to open blocked heart arteries. No increased risk was seen among men with a history of kidney stones.

The underlying cause of this increased risk is still unclear. Even though we took into account known shared risk factors including dietary intake, obesity, hypertension, and diabetes, there may exist a shared predisposition to the increased risk.

This study does suggest that a kidney stone may be a marker for future risk of heart disease, though more research is needed. (Ferraro et al. *JAMA.* 2013;310(4):408-15)

GENETIC UPDATE

GENETIC RISK SCORES: UNDERSTANDING COMPLEX DISEASES

Over the past decade, genetic studies have identified many differences in DNA that may affect disease risk. One of these differences is known technically as a single nucleotide polymorphism, or “SNP.” Individual SNPs tend to be only very modestly associated with diseases. Because many individual genes work together to contribute to complex diseases, scientists are interested in examining SNPs in combination. For that reason, we have started to combine individual SNPs into *genetic risk scores*. These risk scores sum the number of mutations in relevant genes and give a fuller picture of the total genetic contribution to disease.

Indeed, studies that include genetic risk scores are useful for studying a variety of complex diseases, such as asthma, coronary heart disease, bladder cancer, and type 2 diabetes. For example, risk scores have been more strongly associated with type 2 diabetes than each individual SNP alone.

Genetic risk scores may be more broadly important too. For example, in the NHS and HPFS we found that a higher type 2 diabetes genetic risk score also is linked to higher cardiovascular disease risk. (Qi Q et al. *Diabetes Care.* 2013;36(3):737-9) This result suggests that genetic risk scores could be helpful in discovering common genetic connections between different diseases that have been overlooked. Eventually, this may lead to new means of prevention or cure.

Genetic risk scores hold promise for future clinical practice, even though the improvement in risk assessment has been small so far, because they may help clinicians to better assess a patient’s risk of certain diseases. Ultimately, exploring genetic risk scores in complex diseases may advance basic and clinical research.

IN BRIEF

THE STUDY OF STRESS

Stress is a common part of the human experience. Chronic stress can alter human biology and may influence risk of certain diseases, including heart disease.

Chronic stress is difficult to study. Researchers must capture all aspects of the stress experience, which include the stressful event itself, the person's perception of and emotional response to that event, and coping skills. It is also challenging to measure stress using blood or other biologic samples because stress hormones fluctuate throughout the day.

To solve this problem, we recently started a special research project to explore and test better ways of measuring stress using questionnaires and biologic specimens. We developed the Mind Body Study, which includes over 230 women from the NHS II. In this study, participants provide blood, urine, saliva, toenail, hair, and stool samples over one year. They also complete an extensive questionnaire about different aspects of stress.

We will use this information to test new biological measures of stress (such as stress hormones in toenails and hair) and to identify the best set of questions that capture the full stress experience. We hope to use this information to study the relationship between stress and the risk of various chronic diseases.

PTSD LINKED TO OBESITY RISK IN WOMEN

New research from the NHS II suggests women with post-traumatic stress disorder (PTSD) gain weight more rapidly and are more likely to be obese than women without the disorder.

PTSD is a mental disorder that occurs following a traumatic event. The disorder is characterized by re-experiencing the traumatic event, avoiding reminders of the event, numbing feelings, and being in a state of hyperarousal (which is similar to a chronic state of "fight or flight"). One in nine women will have PTSD at some point over the course of their lifetime, which is double the risk in men.

We analyzed data collected from 50,504 NHS II women to study the relationship between PTSD and obesity over time (the first study of this kind). Women who initially were of moderate weight when they developed PTSD had 36 percent higher odds of becoming overweight or obese during the 20-year study period compared with women who experienced trauma but developed no symptoms of PTSD.

How does PTSD lead to weight gain? PTSD may upset the hypothalamic-pituitary-adrenal axis, which controls reactions to stress and regulates body processes, including digestion. Ongoing research is also looking at whether PTSD increases women's preference for certain foods (such as processed, high-calorie foods) and/or decreases their likelihood of exercising.

NUTS FOR HEALTH

Nuts used to be considered bad for you because they are high in fats. Yet people who eat nuts on a daily basis may live longer than those who do not. In a recent study in the NHS and HPFS, we found that one daily serving of nuts was associated with a 20 percent lower mortality rate.



The benefit was also observed for most major causes of death. People who ate nuts five or more times a week had a 29 percent reduction in deaths from heart disease, and an 11 percent reduction in deaths from cancer. Our findings are consistent with a wealth of existing data to support health benefits of nuts on many chronic diseases.

We now appreciate that the specific fat types (unsaturated fats) and other nutrients in nuts (such as fiber, vitamins, minerals, and phytosterols) are beneficial. These benefits confer cardioprotective, anticarcinogenic, anti-inflammatory, and antioxidant properties.

Interestingly, in a subsequent study of women in the NHS II and their children in the Growing Up Today Study (GUTS), we found that increased nut consumption by pregnant mothers (who weren't themselves nut-allergic) was associated with lower risk of nut allergy in their children. This finding may help to alleviate the widespread worry that eating nuts during pregnancy will cause the child to develop a nut allergy.

STUDY UPDATES



NURSES' HEALTH STUDY 3

When the NHS began in 1976, there were 48 women for every man in nursing. Today, 1 in 10 nurses are male. Starting this fall, we are pleased to announce that **men will be able to join the Nurses' Health Studies as participants in the NHS3**. If you know a male nurse between the ages of 19 and 46, please let him know about this exciting change!

Most of the nurses who have joined the NHS3 during the last year learned about the study directly from current participants like you; others saw study flyers in a nurses' station at their jobs. With nearly 40,000 nurses already enrolled, we will continue recruiting RNs, LPNs, and nursing students with the goal of enrolling at least 100,000 women and 20,000 men. We hope you will continue encouraging your colleagues to join this new study by visiting www.nhs3.org. With your help, we hope to make the NHS3 a success!

GROWING UP TODAY STUDY (GUTS)

The Growing Up Today Study (GUTS) began in 1996, and comprises offspring of women in the NHS II. Since then, nearly 100 articles about its findings have been published. Among the most exciting of those published this past year is an article on diet during pregnancy and nut allergies in offspring (see "Nuts for Health" on the previous page for more information).

Another recent finding which garnered national media attention is the correlation between vegetable protein and fat intake and the occurrence of benign breast disease (BBD). GUTS research shows that girls who regularly consume vegetable protein, peanut butter, or nuts may significantly reduce their risk of developing BBD as young women.

If your children are part of GUTS, we hope you will let them know about these exciting new findings and continue to encourage them to participate.

In 2013, we introduced a shorter questionnaire to help GUTS participants find time in their busy lives to provide regular updates. We are also wrapping up our saliva collection project, and are pleased to report that we have received samples from nearly 2,000 participants. For more information on recent study findings and other GUTS news, please visit www.gutsweb.org.

CONSERVATION OF HEARING STUDY (CHEARS)

According to the World Health Organization, 360 million people have disabling hearing loss, a condition often considered unavoidable in some people with increasing age. However, our research findings from the NHS Conservation of Hearing Study (CHEARS) have identified potentially modifiable dietary and lifestyle factors that may help prevent the onset of hearing loss and/or delay its progression. Our investigators found that a higher BMI and a larger waist circumference are associated with a higher risk of hearing loss in women. Likewise, a higher level of physical activity—even walking 2 hours/week or more—is associated with a lower risk.

Detailed information for CHEARS is being collected with the Hearing Study Supplementary Questionnaire, and over 2,000 NHS II nurses out of the planned 3,300 have had their hearing tested nationwide as part of this study. To learn more about CHEARS, please visit www.chearsstudy.org.

Recent research studies suggest that there are at least four major breast cancer subtypes: luminal A and B (these are ER-positive tumors), HER2-overexpressing, and basal-like tumors. These subtypes are associated with differing prognoses (that is, some are more aggressive than others) and are believed to vary in their causes and their growth characteristics in the body. In addition to our work with ER-positive and ER-negative cancers, our research continues to explore how risk factor associations may differ by these more recently recognized subtypes.

“It is not, for example, a ‘war on cancer’ as a single enemy. It is many different diseases with common themes that can cause different kinds of disorders in many of our organs.”

HAROLD VARMUS, M.D., DIRECTOR, NATIONAL CANCER INSTITUTE

OVARIAN CANCER

Recently, scientists have discovered that as many as half of ovarian cancers actually start in the fallopian tube rather than the ovaries. The cancerous cells from the fallopian tube “slough off” the tube and attach to the ovary or in the peritoneal cavity; these cells then grow to become the most aggressive types of ovarian cancer.

This tumor subtype has specific genetic mutations and is associated with shorter survival. Hospitals and doctors usually do not collect information about these mutations, so to investigate this subtype, we recently began classifying ovarian cancers in two ways when examining cancer causes:

1. Is the tumor primarily on one side of the body? (Tumors on one side often start in the ovary.) Or is the tumor spread more evenly across the right and left side of the body? (Tumors that are spread evenly often start in the fallopian tube.)
2. Did the patient die of the disease within three years of diagnosis? (These are the most aggressive tumors, which most likely start in the fallopian tube.)

In our research on ovarian cancer subtypes, we have observed in the NHS that a greater number of pregnancies and a history of tubal ligation seem to reduce risk of less aggressive tumors that start in the

ovary (but do not affect the more aggressive tumors). Factors like oral contraceptive use seem to reduce risk of aggressive tumors that start in the fallopian tube.

COLORECTAL CANCER

Colorectal cancers are often categorized based on location in the large intestine, specifically proximal (ascending colon), distal (descending colon), and rectum. In the NHS, we have shown that the underlying genetic mutations and molecular defects vary by these subtypes, and causative factors could differ for the subtypes as well.

For example, a large proportion of proximal tumors belong to a category called CIMP+. These tumors have specific changes to markers attached to the DNA that make the tumors more aggressive. Smoking had been a controversial risk factor for colorectal cancer, but we found that smoking is associated only with CIMP+ cancers, which make up about 20 percent of all colorectal cancers. This year, the Surgeon General’s Report—based largely on our work—finally recognized colorectal cancer as a smoking-related cancer for the CIMP+ subtype.

In addition, we have shown that aspirin use improves survival in colorectal cancer patients and this is now proven in randomized trials. However, because of potential side effects, the use of aspirin has not been indicated for all patients. We discovered a subtype of colorectal cancer that would most likely benefit from aspirin use, which may allow physicians to target aspirin therapy more appropriately. We are in the process of confirming the clinical implications of this finding.

CONCLUSION

We no longer think of cancer as a single disease, but rather as a range of conditions with different developmental pathways and different prognoses. Decades of research have yielded important results in identifying, treating, and preventing various types of cancers, and we are constantly looking for new ways to expand that knowledge. In addition to the cancers discussed here, we hope to learn more about some of the rarer cancers and their subtypes as the NHS continues.

As always, we are incredibly grateful for all your support throughout the years. Your contributions make this research possible, and we cannot thank you enough.

FOCUS ON OUR RESEARCH TEAM:

DISEASE FOLLOW-UP

Over the years, the data collected through the Nurses' Health Studies have taught us a great deal about everything from cancer and heart disease to diabetes and Parkinson's Disease. Though the questionnaires remain our primary source of information, the bulk of our information about diseases comes from the efforts of our disease follow-up team. This 14-person team, led by Senior Project Manager Barbara Egan, is tasked with obtaining permission from participants and then collecting, reviewing, and coding medical records on a variety of diseases for use by our researchers.



Front row: Lisa Dunn, Barbara Egan, Maureen Ireland Johnston, Liz Riley
Back row: Allison Gordon, Rebecca Koumasidis, Lora Wang, Eleni Konstantis, Lori Ward, Ayesha Mohammed

"It's a lot of work and a lot of responsibility," says Egan, who has been with the study since its inception. "There wouldn't be any research without this documentation."

The disease follow-up team works year-round to obtain information from nurses who report various diagnoses on the biennial questionnaires. This additional information helps confirm each diagnosis and supplies detailed information to allow crucial insight on treatment and prevention strategies.

Egan says it has been "the opportunity of a lifetime" to contribute to the study, and commends her team for their hard work and commitment. She's also quick to credit the participants themselves for the success of the NHS.

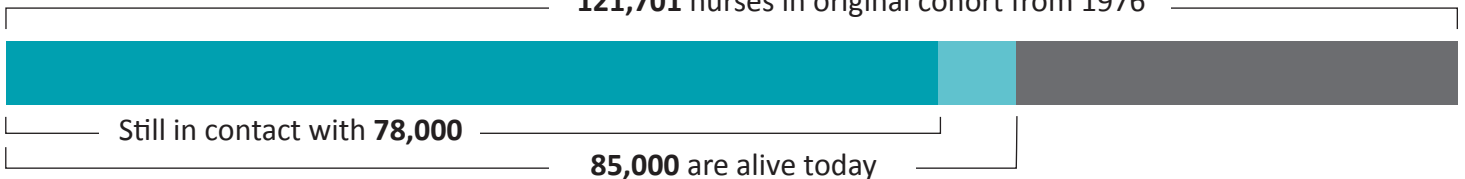
"They've been an amazing group to follow," says Egan. "We couldn't have the study if it wasn't for these nurses. They have been truly dedicated."

BY THE NUMBERS

How many of the original nurses are still participating in the Nurses' Health Studies?

NURSES' HEALTH STUDY

121,701 nurses in original cohort from 1976

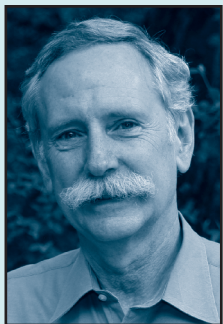


NURSES' HEALTH STUDY II

116,608 nurses in original cohort from 1989



CELEBRATING 25 YEARS OF THE NURSES' HEALTH STUDY II: A MESSAGE FROM WALTER WILLETT



This anniversary is a time for celebration! Twenty-five years ago, 116,608 women joined the NHS II. Like the original NHS, this study provides a framework for women to share their personal experiences with diet, lifestyle factors, and health-related events so that everyone may learn and benefit from this information. At the start of the study in 1989, the participants were 25 to 42 years of age, which makes this study unique because most other cohorts recruited women who were middle aged or older.

Much of our work today links health and lifestyle data from the biennial questionnaires with genetic information gleaned from blood and cheek cell samples provided by the nurses. While many researchers are able to search for genetic markers of disease, our ability to include both biologic and lifestyle data (anything from weight to smoking to physical activity and so much more) makes the NHS II dataset a unique and powerful asset to research. As we move forward there are still many exciting areas where the NHS II can contribute unique and groundbreaking data.

Every member should feel proud of what she has contributed to the study, because the knowledge gained benefits countless women and their daughters around the globe. None of this work would have been possible without your incredible commitment to participating in this study.

FROM THE MAILBAG



When I was 83 years old, my son asked me what I'd do differently in my life if I could. I said 'nothing'—I had a great life always! Then I remembered I never played an instrument. For my next birthday my son bought me a ukulele. I love it and I practice 30-45 minutes each day. I am not great, but I LOVE it.

— B.C.

Being 84 feels just like 50. I drive, bowl, dance and have a highly pleasurable and satisfying sex life. My ancestors provided me with great genes which, in turn, provide wonderful mental and physical health plus a warm and loving spirit that draws people to me. Loving Life!

— L.W.

LETTERS PRINTED WITH PERMISSION

NURSES' HEALTH STUDY

To report name or address changes, please visit www.nurseshealthstudy.org. Letters and feedback are welcome.

CHANNING LABORATORY

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Donations and bequests to the Friends of the Nurses' Health Study Fund help to sustain our continued work.

Donations may be sent to the Channing Laboratory. Alternately, please contact us at 617-525-2258 or visit www.nurseshealthstudy.org and click the "Donations" link.