NHSNEWS

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

Dear Colleagues,
We are happy to share some exciting news: the Nurses' Health Study and the Nurses' Health Study II both recently received grants from the National Institutes of Health (NIH) to continue our important research on cancers—especially breast, ovarian, and colorectal cancers—in women. This work will address many new areas in cancer, including metabolomics research (see "Cutting Edge Research" on page 3).

Much of this newsletter focuses on recent contributions of Nurses' Health Study data to diet research. For example, our feature article highlights a free, online tool we developed to help users learn how to reduce risk of cardiovascular disease through diet and lifestyle. We hope that tools such as this will improve health here and abroad.

We also summarize changes to this year's Dietary Guidelines Report, which includes many findings from the Nurses' Health Studies. Also included are updates on many other issues, such as saturated fat intake and our genetic research.

Please accept our sincerest thanks for your continued participation in our studies. We look forward to many more 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
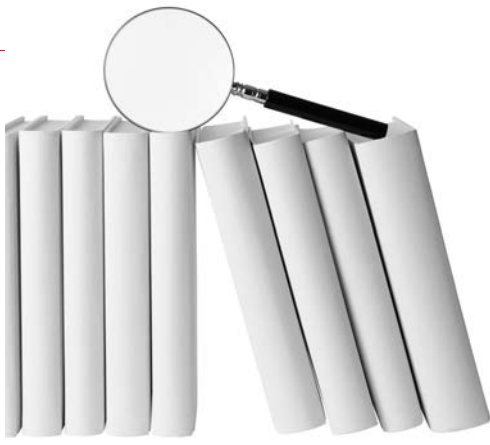
DESIRE A HEALTHY HEART?

Cardiovascular disease (CVD), notably heart attack and stroke, remains the leading cause of death among men and women in the U.S., despite an overall decline in mortality in recent years. Prevention is key—premature occurrence of these conditions may be largely avoided with a healthy diet and lifestyle.

As part of our research efforts, we have developed an online calculator called the Healthy Heart Score (**www.healthyheartscore.com**), which is open to everyone. This calculator estimates long-term risk of developing CVD based on lifestyle habits. By answering the questions posed in the quiz, individuals can learn how their lifestyle habits affect their risk of heart attack and stroke, and determine which lifestyle habits to maintain—and which to improve.

BASED ON ORIGINAL RESEARCH

We developed the Healthy Heart Score using the best available evidence from all sources; a large part of this from your participation in the Nurses' Health Study (NHS) and from men in the Health Professionals Follow-Up Study (HPFS). These studies, with their large numbers of participants and decades of data on diet and lifestyle, proved to be ideal populations to work with in developing this prediction model for CVD.

RECENT FINDINGS

COFFEE CONSUMPTION AND DIABETES

Previous studies have found that higher coffee intake is associated with a lower risk for type 2 diabetes, but no studies have examined how changes in coffee consumption habits influence subsequent risk of diabetes.

Using data from the NHS, NHS II, and HPFS, we found that participants who increased their coffee consumption by more than one cup per day over a four-year period had an 11 percent lower risk of type 2 diabetes in the subsequent four years compared to those who made no changes in consumption. Those who lowered their daily coffee consumption by more than one cup had a 17 percent higher risk of diabetes. Changes in consumption of decaffeinated coffee and caffeinated tea were not associated with changes in risk for type 2 diabetes. (Bhupathiraju et al. *Diabetologia.* 2014 Jul;57(7):1346-54)

MEDITERRANEAN DIET AND TELOMERE LENGTH

The traditional Mediterranean diet—characterized by high intake of vegetables, fruits, nuts, legumes, whole grains, fish, and olive oil—has been consistently linked with an array of health benefits, including decreased risk of chronic disease and cancer.

We recently found that greater adherence to the Mediterranean diet was associated with longer telomeres, which are repetitive DNA sequences at the ends of chromosomes. Telomeres are considered biomarkers of aging. They get shorter every time a cell divides, and shorter telomeres have been associated with decreased life expectancy and increased risk of age-related diseases.

We calculated a Mediterranean Diet score, indicating extent of adherence to a traditional Mediterranean diet, among 4,676 women in the NHS. The difference in telomere length for each one-point change in the diet score was comparable, on average, to the difference in telomere length between women 1.5 years apart in age—meaning greater adherence to the Mediterranean diet may promote health and longevity. (Crous-Bou et al. *BMJ.* 2014;349:g6674)

DIET, HEARING LOSS, AND TINNITUS

Hearing impairment and tinnitus, a ringing or buzzing sound in the ear that can be severely disabling, are both common in adults. Hearing impairment affects almost 48 million Americans, and nearly 25 million people in the U.S. experience tinnitus. Recent findings in the Nurses' Health Studies' Conservation of Hearing Study (CHEARS) identify potentially modifiable dietary factors that may help prevent or mitigate these conditions.

We found that women who ate two or more servings per week of any type of fish or shellfish had a 20 percent lower risk of hearing loss compared with those who rarely consumed fish. In addition, we found that compared with women who consumed the least amount of caffeine (less than one cup of coffee per day), those who consumed the equivalent of three to four cups of coffee per day had a 15 percent lower risk of tinnitus. (Curhan et al. *Am J Clin Nutr.* 2014;100(5):1371-1377. Glicksman et al. *Am J Med.* 2014:127(8):739-743)

EARLY LIFE DIET AND BREAST CANCER

Recent research in the NHS II suggests that red meat consumption in adolescence and early adulthood—but not necessarily in midlife and later—may increase breast cancer risk. Mammary glands may be particularly vulnerable to cancer development during early life due to rapid growth and division of cells. Other evidence suggests exposures that occur between menarche and first pregnancy may play a role in breast cancer development.

Among NHS II women, we found that each additional serving per day of red meat during adolescence was associated with a 21 percent increase in risk of premenopausal breast cancer; an additional daily serving of red meat during early adulthood increased risk by 12 percent. Substituting red meat with fish, chicken, nuts, and legumes during adolescence and early adulthood appeared to lower risk of breast cancer.

Several mechanisms may explain adverse associations with red meat, including carcinogenic byproducts created during high-temperature cooking; animal fat and heme iron from red meat; and growth hormone residues in beef. (Farvid et al. *BMJ*. 2014;348:g3437. Farvid et al. *Int J Cancer*. 2015;136(8):1909-20)

CUTTING EDGE RESEARCH
USING METABOLOMICS TO UNCOVER EARLY SIGNS OF DISEASE

When proteins in your body metabolize food, they create substances (such as amino acids) used for cell functions called *metabolites*. The emerging field of metabolomics involves the study of alterations in these metabolites caused by disease.

Unlike a traditional assay that measures a single biological marker, a metabolomics assay simultaneously measures hundreds or thousands of metabolites. Studies utilizing blood samples or other biospecimens donated before disease development compare metabolite levels between individuals who did and did not go on to develop a particular health condition. Metabolites that differ between groups are considered candidate markers of early disease. Simply put, do the metabolites in the blood of healthy people look different from those who later get sick and if they do, what does it mean?

We recently initiated metabolomics research by combining data from the NHS and three other studies to examine whether pancreatic cancer, a cancer often diagnosed in an advanced stage, produces metabolic changes before diagnosis. The study found that elevated levels of certain essential amino acids were associated with a greater than twofold increased risk of future pancreatic cancer diagnosis. Thus, elevated levels of these amino acids may help facilitate earlier diagnosis of this difficult cancer. (Mayers et al. *Nat Med.* 2014;20(10):1193-8)

By incorporating metabolomics into NHS research, we hope to discover additional markers of early disease development and thus boost prevention and treatment strategies. Recently funded grants in the NHS and NHS II will use metabolomics to study early markers of breast, colon, and ovarian cancer; type 2 diabetes; amyotrophic lateral sclerosis (ALS); and rheumatoid arthritis.

IN BRIEF

DIETARY GUIDELINES REPORT FOR 2015

Earlier this year, the 2015 Dietary Guidelines Advisory Committee published a comprehensive report on the newest nutrition recommendations. The recommendations, which will inform the development of the national 2015 *Dietary Guidelines for Americans* policy later this year, are based on decades of research and include many findings from the Nurses' Health Studies.

As in previous years, the committee stressed healthy eating—more fruits, vegetables, whole grains, low-fat and nonfat dairy, legumes, nuts, and seafood; less sugar, salt, refined grains, red and processed meats, and saturated fats. The report continues to recommend minimizing consumption of artificial trans fat.

Notable changes to this year's report include easing restrictions on egg consumption, as recent studies indicate dietary cholesterol does not strongly affect blood cholesterol, an important risk factor for heart disease. There is also more evidence that coffee confers many benefits, such as reduced risk of type 2 diabetes and cardiovascular disease. Moreover, the report removes the restriction on total amount of fat in the diet; instead it emphasizes replacing unhealthy fats, such as saturated fat from butter, meats, and high fat dairy, with unsaturated fats from vegetable oils, nuts, seeds, and avocados.

The report provides other big-picture insights into health, including a shift in focus from individual nutrients to whole foods and overall diet patterns; the importance of physical activity; and the positive role plant-based diets play in environmental sustainability, among others. Please visit **www.health.gov/dietaryguidelines/2015-scientific-report** to read the full report.

BUTTER IS NOT BACK

The role of fats in our diet—particularly saturated fats—has stirred up controversial headlines lately. While the media message has been confusing, our research results on fats and how they affect risk of coronary heart disease (CHD) are clear and consistent. Replacing saturated fat (found in butter, red meat) with polyunsaturated fat (found in nuts, vegetable oils) is associated with a lower risk of CHD.

In a recent meta-analysis, we reviewed 13 cohort studies that included more than 310,000 participants. We found that individuals who traded 5 percent of the calories they consumed from saturated fat sources for sources of linoleic acid, a main type of polyunsaturated fat, lowered their risk of CHD by 9 percent. This same group lowered their risk of death from CHD by 13 percent.

One of the reasons this swap from saturated fat to polyunsaturated fat lowers CHD risk has to do with blood cholesterol. Polyunsaturated fats decrease "bad" LDL cholesterol. An increase in "bad" LDL cholesterol may hasten plaque buildup in arterial walls, resulting in CHD.

Since all fats are not created equal, it makes a difference which type is consumed. To achieve a lower risk of CHD, the "swap" component is crucial—such as replacing butter or lard with vegetable oils, such as soybean, olive, canola, and corn oils.
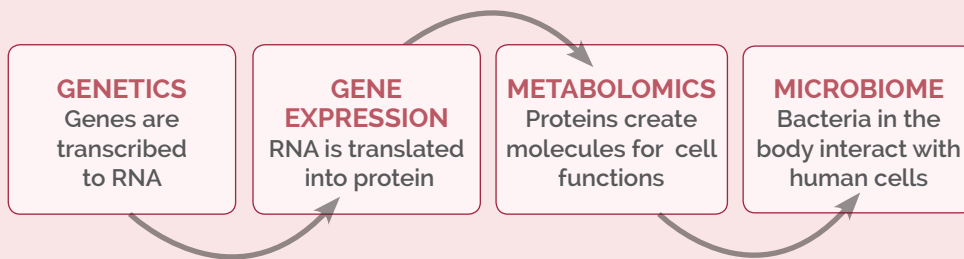
For more information on the role of saturated fats, please read "Is Butter Really Back?" at **www.hsph.harvard.edu/magazine-features/is-butter-really-back**. Another helpful resource is the Nutrition Source at **www.hsph.harvard.edu/nutritionsource.**

GENETIC RESEARCH UPDATE

BEYOND GENETICS

The Nurses' Health Studies have been highly active in researching the roles of genes in complex diseases. We have studied individual variations in DNA called *SNPs* and conducted genome-wide association studies, which look at thousands of SNPs at the same time. We have also completed whole-genome sequencing—which maps the entire genetic code—of several dozen women with and without breast cancer. Although not yet useful to individuals, we hope these data will lead eventually to discovery of new genetic variants associated with breast cancer risk.

GENETICS Genes are transcribed to RNA	**GENE EXPRESSION** RNA is translated into protein	**METABOLOMICS** Proteins create molecules for cell functions	**MICROBIOME** Bacteria in the body interact with human cells

To complement this work, we have initiated research on additional factors which may provide further insight into disease development. For example, after genetic information from DNA is used to assemble proteins, certain proteins metabolize food and create substances, or metabolites, used for cell functions. New metabolomic assays have been developed to measure hundreds of metabolites in blood. As described in "Cutting Edge Research" (see page 3), we are beginning to incorporate this new technology into our research with the goal of discovering new markers in the future to help predict the development of cancer and other diseases.

We are also looking at the millions of bacteria in our intestines, called the microbiota. We recently completed a pilot stool collection in the NHS II in preparation for a larger study one day that will use gene sequencing to catalog the types of bacteria in each stool sample. We hope to conduct studies to evaluate whether microbiota differ between women with and without specific cancers. We anticipate that this biospecimen resource, albeit sometimes inconvenient or difficult to collect, may allow for future detailed research about the role of the microbiota in many aspects of human health.

DATA SECURITY

Over the years, participants have shared with us their personal and private information. How do we protect that information and how safe is it?

NHS data are never stored on portable devices like phones, laptops, or tablets. The data files we use for analysis contain only study ID numbers. All names, addresses, and social security numbers are stored on a separate computer system that only a small and select group of senior staff can access. As a result, even our investigators do not know the identities of the participants in any given set of data.

What about hackers? For maximum security, we use state-of-the-art digital protection tools to prevent possible intrusions and our internal network is monitored constantly. We have been issued a Certificate of Confidentiality which allows us to refuse to disclose personally identifiable information to anyone. In the 39 years since the Nurses' Health Study began, we have never had a breach of private data.

In short, we protect your answers as we would protect our own private information. Confidentiality is critical to the NHS and we work hard to earn—and maintain—your trust.

STUDY UPDATES

GROWING UP TODAY STUDY

Have you ever wondered how your early life behaviors and lifestyle may have influenced your health and well-being today? Thanks to the dedication of Growing Up Today Study (GUTS) participants—the children of women in the NHS II—we can investigate these relationships as they unfold.

In the last year, we have studied many complex health topics, including binge drinking, hypertension, depression, and obesity. For instance, recent GUTS research shows surprising findings about depression. Previous studies have suggested that girls who experienced an early menarche (first menstrual cycle) have an increased risk of adolescent depression. However, data collected on our questionnaires indicate that this relationship does not persist into the early twenties.

Findings like this are the result of the generous commitment of GUTS participants from across the country. If your children are part of GUTS, thank you for encouraging them to participate and for helping to make these important research activities possible. Even if it has been a few years since your child last participated, we would love to have them participate in the 2015 questionnaire. Please visit **www.gutsweb.org** for more information.

DIABETES AND WOMEN'S HEALTH

Why do some women with a history of gestational diabetes eventually develop type 2 diabetes while others do not? Working in partnership with investigators from the Eunice Kennedy Shriver National Institute of Child Health & Human Development (NICHD), we have enrolled more than 3,000 NHS II participants with a history of gestational diabetes in the Diabetes and Women's Health Study. In addition to supplemental questionnaires, nearly 1,000 participants also provided biological specimens. Over the next year we will be asking this group of women to complete further questionnaires and provide additional biological samples (blood, urine, and saliva). These resources will help us learn what may be done to prevent progression from gestational diabetes to type 2 diabetes in some women. Please visit **www.dwhstudy.org** to read more about the study.

NURSES' HEALTH STUDY 3

Men are a growing part of the nursing world, and now male nurses can be part of our research too! The NHS3 is enrolling both male and female nurses and nursing students between the ages of 19 and 46. The first 100 men have joined already, and we hope to reach 20,000—alongside our goal of 100,000 women.

We're asking for your help in spreading the word about this huge development in the Nurses' Health Study. After all, most of the NHS3 participants have learned about the study from participants like you! We hope you will continue encouraging your nurse colleagues, both male and female, to visit **www.nhs3.org** and join this new study. With your help, we hope to make the NHS3 a success.

CONSERVATION OF HEARING STUDY (CHEARS)

The CHEARS *Audiology Assessment Arm* is a groundbreaking, large-scale assessment of hearing over time. We are thrilled to report that over 3,300 NHS II CHEARS participants have already had their hearing tested by audiologists at 19 major medical centers across the country. These participants will undergo a follow-up hearing test in three years. Our goal is twofold: identify factors that may influence hearing, and detect early-stage changes in hearing, which may prevent further loss.

In addition, over 40,000 participants in the NHS and NHS II have provided detailed hearing-related information for CHEARS by completing the Hearing Study Supplementary Questionnaire. We hope to obtain additional funding so many more participants can have their hearing tested as part of this study. Please visit the CHEARS website at **www.chearsstudy.org** to learn more about the study.

We tracked the development of CVD among healthy participants over a 24-year period, including 61,025 women (of whom 3,775 developed CVD) and 34,478 men (of whom 3,506 developed CVD). Since many factors may contribute to an individual's risk of CVD (by either increasing or decreasing risk), we chose the nine most critical diet and lifestyle factors that best predict CVD development over 20 years (see diagram at right).

HOW TO USE THE CALCULATOR

The Healthy Heart Score is a simple online quiz that takes just a few minutes to complete. (Participation is anonymous and you may opt out of having your data stored.) Once finished, users receive a snapshot of their overall CVD risk (low, moderate, or high) along with a printable, personalized assessment of recommended lifestyle habits and practical tips for maintaining and improving cardiovascular health. Helpful resources are linked throughout the calculator/quiz for more detailed information.

TARGET AUDIENCE

Anyone can use the online calculator, though the results may be especially useful to women and men who are 40 years or older and who do not have major CVD risk factors, such as hypertension or high cholesterol (which are usually the focus of clinical treatment). Since many adults who develop CVD are not at high risk by "conventional" standards, the Healthy Heart Score hopes to pinpoint this group of otherwise healthy individuals by addressing lifestyle habits *before* harmful risk factors develop.

CRITICAL DIET AND LIFESTYLE FACTORS THAT PREDICT CVD DEVELOPMENT	
Increase Risk of CVD	**Decrease Risk of CVD**
Smoking	Fruits and vegetables
Excess body weight	Exercise
Sugary/sweet beverages	Nuts
Red and processed meat	Whole grains
	Alcohol, in moderation

FUTURE PLANS

The diet and lifestyle factors included in the calculation of the Healthy Heart Score were chosen for their ability to predict CVD development in men and women. However, other factors, particularly those relevant to women, could also be important. For example, the American Heart Association recently recommended that a woman's history of preeclampsia, a common hypertensive disorder of pregnancy, be considered as a risk factor for CVD. We are working now to be the first study to test whether including a history of pregnancy complications will improve the accuracy of the Healthy Heart Score for women.

WHY IT IS SO VALUABLE

The Healthy Heart Score can serve as an important public health screening tool, reaching a broad audience where it can have a major impact for preventing CVD. This is an important way in which you—and the research in which you participate—are helping improve health in this country. (Chiuve et al. *J Am Heart Assoc.* 2014;3:e000954)

Please visit www.healthyheartscore.com to start your own assessment of CVD risk

FOCUS ON OUR
RESEARCH TEAM

When it comes to matters of the heart, Dr. Stephanie Chiuve knows her stuff—she helped develop the Healthy Heart Score, a web-based cardiovascular health calculator (see "Desire a Healthy Heart?" on page 1). She and other researchers are hoping to raise awareness about heart-healthy diets and lifestyle choices through this interactive online quiz, which is based on research from the NHS and HPFS.

Chiuve is a research associate at the Department of Nutrition at the Harvard T.H. Chan School of Public Health and an assistant professor of medicine at Harvard Medical School and Brigham and Women's Hospital. Nutrition has long held her interest, from her childhood days as a competitive figure skater and then in college when she studied the role of diet on chronic disease. Through her first post-college job doing lab work she met Dr. Eric Rimm and other Harvard faculty members, and went on to complete her doctoral degree at the Harvard Chan School.

Outside of work, Chiuve enjoys spending time with her husband, two young children, and dog. She is an avid cook and loves to discover and prepare new heart-healthy recipes for her family. She is also a devoted Boston sports fan—go Red Sox!

FRIENDS OF THE NURSES' HEALTH STUDY

Over the years, many participants and their families have asked how they might help support the NHS and NHS II, beyond the wonderful and generous donation that all participants make of their time and energy. We are deeply grateful for the expressions of support and for donations made to the Friends of the Nurses' Health Study Fund, especially in view of the constraints of federal support for research.

We are particularly grateful to Ernest Crivellone, who has recently provided our largest donation to date. Mr. Crivellone is a friend of one of the members of the Nurses' Health Study team, and was inspired to support the NHS after learning about the remarkable range of research advances yielded by the cohort, especially in the area of breast cancer.

If you wish to make a donation, please contact us at the address below. Alternately, please call us at 617-525-2258 or visit **www.nurseshealthstudy.org** and click the "Donations" link. Donations and bequests help sustain our ongoing research.

STAYING IN TOUCH

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

THE NURSES' HEALTH STUDY
Channing Division of Network Medicine
181 Longwood Avenue
Boston, MA 02115
tel: 617-525-2279 **fax:** 617-525-2008 **email:** nhs@channing.harvard.edu