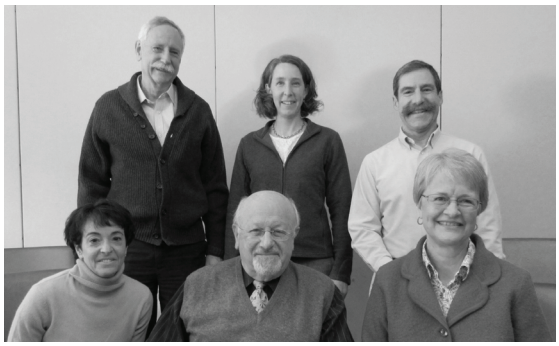
NURSES' HEALTH STUDY NEWSLETTER | VOLUME 25, 2017

NHS NEWS



Back row: Walter Willett, Heather Eliassen , Meir Stampfer
Front row: Francine Grodstein, Frank Speizer, Susan Hankinson

Dear Colleagues,

We are excited to report on a new expansion in the kinds of research possible in the Nurses' Health Studies. We were recently awarded a substantial grant from the Massachusetts Life Sciences Center which will enable us to do cutting edge research on the microbiome (the bacteria of the gut). This new grant allows us to collect stool and saliva samples from tens of thousands of women in Nurses' Health Study II, beginning later this year.

This year's feature article describes the expansive opportunities that lie ahead in the study of the human microbiome.

In other areas, we have had a very productive year, publishing papers on topics as varied as hearing loss, genetics, the importance of physical activity, as well as several looking at cancer risk factors.

Please accept our sincere gratitude for your continued participation in our studies. We look forward to many more exciting discoveries!

Best Regards,
The Nurses' Health Study Senior Team

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THE HUMAN MICROBIOME

One of the world's most underexplored ecosystems

There are more bacteria living in your intestines than there are people in the world.

Humans are covered in huge numbers of microorganisms, including viruses, bacteria and yeasts. In fact, the human body contains ten times more microorganism cells than human cells! Collectively, the ecosystem of microorganisms living on and in us is called the microbiome.

For the past 100 years, scientists have been asking:

- Does the microbiome affect human health?
- Are we able to alter the composition of the microbiome?

The answer to both questions is yes.

We have all experienced, or know someone who has experienced food poisoning. Most food poisoning cases occur when a person eats food that is contaminated with disease-causing microorganisms. When these microorganisms reach our intestines, they release toxins and cause an acute inflammatory response. This small change in the composition of the microbiome causes the symptoms (such as fever, nausea, and cramps) that are observed during food poisoning.

However, it's not all negative. The microbiome can have positive impacts on human health as well. The microbiome is essential for normal immune system development. Specific microorganisms in the large intestine help to break down foods that humans are otherwise unable to digest.

Despite having some understanding of the microbiome, many important questions remain unanswered. Given the tremendous potential for the microbiome to impact human health, it is

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Recent Findings

Physical Activity and Heart Disease in Younger Women

Middle-aged and older women who are more physically active have substantially lower rates of coronary heart disease (CHD). Few studies have examined the possible benefits of leisure-time physical activity in young women. In the NHS II we found that the most active women were less likely to develop CHD when compared with the least active women. In addition, this association was not modified by weight, emphasizing that physical activity is important for all women, whether they were normal weight, overweight or obese. And we don't have to run a marathon to see results. Women who walked briskly for at least 2.5 hours per week saw a 35% lower risk of developing CHD.

NSAIDs and acetaminophen may increase risk of hearing loss in women

> ***"We found that approximately 5.5% of the cases of hearing loss in our cohort of older women could potentially be attributable to NSAIDS and acetaminophen use."***

Two-thirds of women in their sixties suffer from hearing loss. In the NHS II we previously found that regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen was linked to a slightly greater risk of hearing loss in young women. Given the high prevalence of hearing loss in older women, we looked at this association and long durations of regular analgesic use in women from the Nurses' Health Study.

Among 55,850 women from the Conservation of Hearing Study (CHEARS), a special NHS sub-study, longer durations of NSAID use (> 6 years) and acetaminophen use (> 6 years) were associated with a 10% and 9% increased risk, respectively. There was also a 7% higher risk of hearing loss among women who reported regular NSAID or acetaminophen use (≥2 days/ week). Duration of aspirin use was not associated with hearing loss, suggesting there may be a difference between NSAIDs, acetaminophen, and aspirin. In this study, we found that approximately 5.5% of the cases of hearing loss in our cohort of older women could potentially be attributable to NSAIDS and acetaminophen use. Although the increase in risk for an individual was small, more research is needed in this area.

Physical activity before first pregnancy and risk of breast cancer

Women's breast tissue is particularly susceptible to harmful exposures prior to first pregnancy. A longer interval between the first period (menarche) and their first pregnancy is associated with elevated breast cancer risk. In NHS II, among women whose first pregnancy happened 20+ years after her periods began, physical activity prior to pregnancy was associated with 27% lower breast cancer risk. Physical activity during this time period may offset breast cancer risk, particularly for those with a longer interval between menarche to first pregnancy.

Diet Quality and Physical Functioning

Physical function – the ability to perform basic activities of daily living – is integral to healthy aging and independent living in older adults and is a strong predictor of mortality. We compared women in NHS

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who had the healthiest diets to those with less healthy diets, as measured by our Alternative Healthy Eating Index-2010, to see if those with better diets were more likely to retain their physical function as they age. We found that the healthiest eaters were 13% less likely to develop physical impairment. Higher intake of vegetables and fruits; lower intake of sugar-sweetened beverages, trans fats, and sodium; and moderate alcohol intake were each significantly associated with reduced rates of developing physical impairment. Among individual foods, the strongest relations were found for increased intakes of oranges, orange juice, apples, pears, romaine or leaf lettuce, and walnuts. According to NHS Director Dr. Francine Grodstein, "The simple message from this study is that eating an overall healthy diet, including certain foods, such as fruits and nuts and other whole foods, may help women maintain the ability to do key everyday tasks as they age, like carrying groceries or dressing themselves."

Focus on our Research Team

We have a wonderful variety of people from all over the world who work on the Nurses' Health Study. We would like to introduce three of our young scientists who each moved to Boston to join our team.

Mingyang Song, MD, ScD is from Shandong Province in northern China, which is known as the birthplace of Confucius. His research is focused on understanding the role of nutritional and lifestyle factors in cancer prevention and treatment, especially as it relates to colorectal cancer.

Céline Vetter, PhD comes to us from Munich, Germany. She is a circadian work-hours scientist. Her research seeks to understand how we can design employment schedules to better protect and enhance the health of workers.

Tianyi Huang, ScD, also from China, comes from Sichuan Province which is famous for their spicy food and their natural habitat for pandas. He is developing a research program to identify risk factors for and health effects of sleep apnea.

We asked each of them what it is that inspires them in their work:

Mingyang: The belief that my work can help address one of the biggest health problems (i.e., cancer) afflicting tens of millions of people all around the world really motivates me.

Céline: I believe strongly in the power of translational chronobiology – our body, our physiology is rhythmic and embedded in the 24hour light-dark cycle. Understanding which aspects of work schedules interfere most with an individual's circadian system will allow us to design strategies to reduce the health burden for everybody who has to work schedules outside of the typical 9-5 timeframe, such as night and early morning shifts. On a personal level, I have a number of family members who work in health care and who work shifts and have worked night shifts during my studies, so I can also relate to the challenge that shift work poses.

Tianyi: I'm convinced that alterations in sleep, which is essential for rejuvenation of the human body, plays a central role in human health. Therefore, I am interested in studying how sleep and sleep disorders could influence health and well-being. By finding ways to improve sleep and avoid sleep disorders, we may learn how to prevent sleep-related chronic diseases and enhance people's quality of life.

In Brief

Gluten-Free Diets

Gluten-free diets have grown in popularity over the years due to concerns about celiac disease and gluten allergies. However, little research has explored the impact of gluten-free diets in people without celiac disease. Two recent studies from the Nurses' Heath Studies and Health Professionals Follow-up Study (HPFS) investigated the health consequences of gluten consumption in people without celiac disease. We found that eating foods high in gluten, if they are whole grains, can be beneficial to health.

First, in NHS, NHS II, and HPFS, we found that men and women with the highest levels of gluten intake had 20% lower risk of developing type 2 diabetes compared with those with the lowest gluten intake.

In the second study, even after adjusting for intake of refined grains, the risk of coronary heart disease was 15% lower in people with the highest gluten intake vs lowest intake of gluten. Further, gluten intake did not lead to weight gain in people under 65.

> ***A major source of gluten is whole grains, which ... was associated with lower risk of several chronic diseases.***

What explains these health benefits of gluten? A major source of gluten is from whole grains, which we previously found are associated with lower risk of several chronic diseases, including heart disease and stroke. Also, as a plant-based protein, gluten may be used by people to replace protein from beef, which is less healthy. Thus, overall, our research suggests that gluten in the form of whole grains can be an important component of a healthy lifestyle among individuals without celiac disease or gluten sensitivity.

Maintaining a healthy weight

Many of us gain weight slowly and steadily over time. This phenomenon is concerning because considerable evidence—including research from the NHS and NHS II—show that overweight and obesity increase risk of hypertension, type 2 diabetes, stroke, cancer, and heart disease, as well as premature death. Because weight loss can be challenging to attain and maintain long-term, NHS researchers have focused on understanding how to prevent insidious weight gain in the first place. Here, we highlight results from several recent studies that evaluated the impact of changes in diet on weight change in the Nurses' Health Studies and in the HPFS.

Specific foods

We examined associations between changes in intake of specific foods and weight change within 4-year increments in the 3 cohorts. Our analyses accounted for other simultaneous changes in lifestyle (like changes in other aspects of diet, physical activity, and smoking) to help isolate the impact of specific foods.

Overall, we observed several dietary changes associated with less weight gain, including increasing intake of fruits, non-starchy vegetables, and replacing sugar-sweetened beverage or fruit juice intake with water or coffee (see table on page 5).

Overall diet quality

An alternative approach to focusing on individual foods is studying overall eating patterns, especially patterns that emphasize higher intake of vegetables, fruits, nuts, legumes, and whole grains, and lower intake of red and processed meat, sodium, and sweets (e.g., the Mediterranean diet and the Dietary Approaches to Stop Hypertension [DASH] diet). Women and men who improved their diet quality over 4 years gained less weight than those whose diet quality did not change. We found similar results among women with a history of gestational diabetes, who are at an especially increased risk of developing obesity and type 2 diabetes.

"Maintaining a Health Weight" continued from page 4

Dietary changes and their association with weight gain

LESS WEIGHT GAIN	**MORE** WEIGHT GAIN
Tofu and soy	Unprocessed red meat, including regular and lean hamburger
Plain or artificially sweetened yogurt	Corn
Seafood	Processed meats
Fruit, especially blueberries, prunes, apples, pears, strawberries, grapefruit, and avocados	Peas
Chicken without skin	Chicken with skin
Replacing 1 serving/day of sugar-sweetened beverage with coffee or water	Sugar-sweetened beverages
Vegetables, especially cauliflower, summer squash, string beans, broccoli, and green leafy vegetables	Baked, boiled, or mashed potatoes
Replacing 1 serving/day of fruit juice with coffee or water	Fruit juice
Nuts, including peanut butter, peanuts, and walnuts	Regular, full-fat cheese

Connections between intestinal microorganisms, diet, and colorectal cancer

How microorganisms in our large intestine affect cancer risk is one of our newest areas for study. Intestinal bacteria can act in concert with diet to reduce or increase the risk of certain types of colorectal cancer. We tested 1019 colon and rectal cancer tumor samples from participants in NHS and HPFS for the presence of *F. nucleatum* bacteria. Among participants with prudent diets (rich in whole grains and dietary fiber), the risk of developing a *F. nucleatum*–positive colorectal cancer was reduced, as compared with the general study population. Study co-senior authors Shuji Ogino, MD, PhD and Andrew Chan, MD noted, "These data are among the first in humans that show a connection between long-term dietary intake and the bacteria in tumor tissue. This supports earlier studies that show some gut bacteria can directly cause the development of cancers in animals." This is an area in which much more research is needed and we plan to be at the forefront of these new discoveries.

Going Electronic

In recent years, over 60,000 participants in the NHS and NHS II have switched from paper questionnaires to completing their surveys online. This switch is extremely helpful as it speeds the data processing, reduces errors, and saves money, enabling use of precious funds for scientific discovery instead of processing paper forms. Filling out the forms online is simple, secure and easy. **We will be most grateful if you can provide us with an email address on the questionnaires and complete future forms online.**

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. (In fact we are introducing a new, more secure ID number starting this year.) 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.

In short, we protect your answers as we would protect our own private information. We work hard to earn—and maintain—your trust.

Study Updates

guts Growing Up Today Study

In 1996 and again in 2004, NHS II participants were invited to enroll their children in the Growing Up Today Study (GUTS). Today over 27,000 GUTS participants in their twenties and thirties are helping us study young-adult health.

Efforts are currently underway to research some of today's most pressing health topics, including obesity, substance use behaviors, and obstacles to accessing care. By combining GUTS and NHS II data, we also have the unique opportunity to examine how maternal factors may influence health in children as they age.

Long-term research of this kind is only possible thanks to the generous commitment of both GUTS and NHS II participants. If your kid(s) are in GUTS, we ask that you remind them that their continued participation at any point is always important to this exceptional research. Even if it has been a few years since your son or daughter last participated, we'd love to hear from them in 2017!

Participants can complete the online GUTS Questionnaire at **gutsweb.org**. For assistance or to provide updated contact information, please email us at **guts@channing.harvard.edu**.

Nurses' Health Study 3

As NHS3 continues to enroll more nurses (both men and women), our best source of new recruits comes from recommendations by you, the participants in NHS and NHS II. We hope you will continue to act as our ambassador to encourage your colleagues to visit **www.nhs3.org** and join this new study. Specifically we are recruiting male and female RNs, LPNs and nursing students born on or after January 1, 1965. To date, over 40,000 have joined, but we need more. We are particularly interested in adding male nurses to the study, so tell your guy nurse friends that we hope they'll enroll.

What are we investigating in NHS3? Lots of things! One of our first projects looks at specific occupational exposures common in the nursing profession and how they influence the ability to become pregnant. Using information on over 1,700 working women who were trying to become pregnant, NHS3 researchers found that occupational use of high level disinfectants was associated with longer times to pregnancy. Use of protective equipment, however, particularly the use of more than one type of protection, appeared to reduce the adverse effects of this exposure on becoming pregnant. It seems that equipment designed to reduce inhalation and skin contact may be effective in minimizing the health effects of high level disinfectants.

Micro-N

Volumes of critical research have resulted from past collections of specimens (blood, urine, saliva, etc.) from NHS participants. Continuing the strong tradition of cutting edge, specimen-based research, the Massachusetts Life Sciences Center has awarded funds to support the Microbiome in Nurses (Micro-N) study to collect tens of thousands of stool and saliva samples, starting in the Fall of 2017. If you are a member of NHS II, we will ask you to join this effort on the new 2017 questionnaire. The collection process is easy, hygienic and can be done at your convenience, with no special handling required; just drop the completed kit in any mailbox. This exciting new resource promises to reveal untold new research possibilities.

"The Human Microbiome" continued from page 1

essential that we better understand: 1) the ways in which the microbiome influences our health; and 2) how lifestyle, environment, diet and early life factors can influence the composition of the microbiome.

We have made important progress towards answering these questions with stool samples provided by men participating in our companion study, the Health Professionals Follow-up Study (HPFS). Significantly, we have validated a collection method that allows study participants to easily collect and mail their stool samples to the study center. This ensures that the collection process is easy, while also providing high quality samples and data.

Using these results, we have begun to make strides in describing and characterizing the microbiome and its metabolic activity. We have also identified parts of the microbiome that are stable over time, and other parts of the microbiome that vary greatly every day. We are currently applying these discoveries to explore how the microbiome is related to risk of chronic diseases (such as colon cancer) and how diet may affect the microbiome.

The overall goal of our microbiome research is to begin to describe what makes up a healthy microbiome and also start to define when it may be unhealthy. Learning how people can alter their microbiome composition may create opportunities to utilize the microbiome to improve human health. To do this, we need your help. If you are in NHS II, we hope you will agree to provide us with a stool sample which will enable us to pursue the factors that may influence the microbiome and identify how the microbiome influences our health. We ask for your willingness to participate in this collection on the 2017 questionnaire.

Genetic Research Update

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 with the goal of being able to identify genetic regions that may be linked to the development of disease.

With this work and results from thousands of other genetic researchers, science is continually moving towards greater use of personalized or "precision" medicine, where the patient's genetic makeup helps to identify the treatments which are most likely to be successful.

We are excited to begin looking at the microbiome, or the millions of bacteria in our intestines. Our goal is to use gene sequencing to catalog the types of bacteria in each stool sample. In addition, we plan to conduct studies to evaluate whether microbiota differ between women with and without specific cancers. We anticipate that this biospecimen resource will allow for future detailed research about the role of the microbiome in many aspects of human health.

This novel collection, starting later in 2017 in NHSII, that will greatly enhance the types of scientific studies that we can conduct.

A Family Affair: Friends of the Nurses' Health Study

It's no secret that we are all getting older. Many participants need a little help to continue their involvement in the Nurses' Health Study. We are so very appreciative of the spouses and adult children who assist our nurses with their biennial questionnaires. While we don't want family members to complete the surveys on their own (only the participating nurse can tell us how they are feeling), it is SO helpful to the study to have the family assist in whatever way is needed.

Many women tell us that they have made sure that their families know that they are long-term participants in the study and to make sure that we are informed if the participant cannot tell us directly about major changes in her health.

Over the years, we have received many thoughtful donations to the Friends of the Nurses' Health Study to support our research. Participants have made gifts, and often donations are made in honor of participants. One participant in NHS II sent us a substantial gift in memory of her mother who was a member of the original Nurses' Health Study. We appreciate these gifts, which truly help to expand the research that we are able to do. In light of decreases in federal research funding, these gifts are especially valuable, particularly to enable younger investigators to continue to make pathbreaking discoveries to enhance women's health. If you would like to make a donation, please contact us at the address below or visit **nurseshealthstudy.org** and click the "Donations" link.

NHS 40th Anniversary Journal Update

As we mentioned in our last newsletter, *The American Journal of Public Health* published a special edition in September 2016 to celebrate the 40th year anniversary of the Nurses' Health Study. That special journal was entirely dedicated to review articles all about the NHS and NHS II. The articles provide an excellent overview of the vast amount of results that have come out of the study over the years. We arranged for free online access to that issue for all NHS participants, and in case you missed it, the issue is still available at **nurseshealthstudy.org/AJPH**

As always, all of this work is only possible because of your participation. Thank YOU for making this study possible!

Staying in touch

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

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