

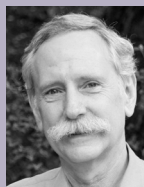


NHS NEWS



DEAR COLLEAGUES,

This year marks the 35th anniversary of the Nurses' Health Study (NHS), and we have had a busy year!



This year's lead article discusses "healthy aging" and explains which biological and lifestyle factors may affect the aging process. Notably, certain factors at middle age may have profound effects

on healthy survival into the later years.

We also review major advances in studying how genes and other biological markers influence risk of disease. For example, the genetics update (page 7) highlights our recent ability to decode the entire genome of many individuals and the amazing new research opportunities that this enables.

On page 3, we describe how the information you have provided influenced the newly released *Dietary Guidelines for Americans, 2010*. In addition, we summarize several recently completed projects, and provide updates on existing and new sub-studies.

Your tireless support and dedication allow us to continue our vital research on factors that influence women's health, such as diet, lifestyle changes, and a range of biomarkers. Please accept our gratitude for this continued and critical effort.

Best regards,

Susan E. Hankinson, ScD, RN
Principal Investigator,
Nurses' Health Study

Walter C. Willett, MD, DrPH
Principal Investigator,
Nurses' Health Study II

Healthy Aging



A MAJOR FOCUS OF OUR RESEARCH involves evaluating how women may achieve overall "healthy aging." While the exact components of healthy aging are debatable, the general definition is survival past age 70, without any major chronic diseases or major impairments in memory, mental health, or physical abilities (such as being able to lift groceries or climb stairs). Specifically, there

is increasing interest in lengthening not just the lifespan, but also the "healthspan" – defined as longevity accompanied by general health, vigor, and quality of life.

Over the last few years, the Nurses' Health Studies have contributed substantially to research on aging. In 2011, the women in the original NHS will all be aged 65 or older. Recently, we have explored how lifestyle and biological factors at mid-life (ages 30 to 55) determine healthy aging later in life. Several factors, such as weight maintenance, physical activity, and telomere length, have especially stood out in this research.

Body Mass Index

Body mass index (BMI) is an important factor in many aspects of health, but we have never before specifically addressed its influence on the aging process. When we examined women's BMI at mid-life and how it relates to healthy aging at ages 70 and older, the results were striking. Of the women who survived until at least age 70, increased BMI at mid-life was significantly associated with reduced chance of healthy survival. For example, obese women (with BMI of 30 or greater) had an 80 percent lower chance of healthy survival compared to their leaner counterparts (with BMI between 18.5 and 22.9). In addition, the more weight a woman

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Frequently Asked Questions

Q: The questionnaire always asks about illnesses that were diagnosed in the past two years, yet there is also a column for "date of diagnosis" that is more than two years old. This is confusing. Do I need to report old illnesses?

A: For most study participants, we are looking to update the information they provided on the last questionnaire (two years earlier). Some members of the study occasionally miss a cycle of the questionnaire, perhaps because they were sick. We definitely want to learn about any major diagnoses that they have had since we last heard from them. Thus, we provide a space for "older" diagnoses. If you have previously reported an illness, it is not necessary to

tell us about it again. If you are not sure if you told us, it never hurts to report it.

Q: Can you explain the difference between Nurses' Health Study 1, 2, and 3? How old are the nurses in each study? Do I always stay in the same study that I started in?

A: With three studies, it can get confusing. You are a member only of the Nurses' Health Study into which you first enrolled. The original NHS began in 1976 with 121,701 RNs who are now between 65 and 90 years old. NHS II started in 1989 with 116,608 RNs who are now 47 to 65 years old. We are presently enrolling RNs and LPNs between ages 22 to 45 into NHS3. We hope to enroll 100,000 or more women in NHS3.

STUDY UPDATES

Lifestyle Validation Study

The Lifestyle Validation Study (LVS) comprises 780 women selected from the NHS and NHS II. We finished enrollment in February 2011 and hope to complete the study in early 2012. We are now investigating ways to improve our methods of measuring dietary intake and physical activity.

Currently, participants provide detailed information on diet and physical activity through Web-based recalls and meal-by-meal diet recordings. Additionally, participants provide multiple blood, urine, and saliva samples.

The nurses have faced many challenges, but as always, provide excellent information. Our staff has truly enjoyed working with this group of nurses, and we have been continually impressed by their selfless investment and dedication to the study. Our heartfelt thanks go out to the LVS participants who have provided these exciting new data that we will put to use for years to come.

nhs3.org

Nurses' Health Study 3

The enrollment phase for the new NHS3 is ongoing. To date, over 12,000 RNs and LPNs between the ages of 22 and 45 have joined. We hope you will act as our ambassador and encourage your colleagues to join this new study. To help us spread the word, you can:



- Encourage your colleagues to visit www.nhs3.org and join the study
- Print out and distribute information from www.nhs3.org about how to join the study
- Reach out through nursing groups and organizations in which you are involved, as well as in your online communities, like email lists, Facebook, Twitter, or other social network sites

Your encouragement will go a long way to help explain how a commitment to a study like this is of extraordinary value.

GUTS - Never Too Old for the Growing Up Today Study

"My children are too old for GUTS now." Some nurses have gotten in touch with us to express similar sentiments – that their adult children are now off at college, live on their own, have their own families, or are just too busy to complete the questionnaire. However, just like in the Nurses' Health Studies, responses from GUTS participants become only more valuable over the years! By continuing to participate, your sons and daughters are helping us examine how lifestyle factors, such as diet and physical activity, in adolescence and young adulthood affect health later in life. Therefore, despite the "Growing Up Today" name, we indeed still want to hear from them. As always, your help is greatly appreciated!

SENDING GUTS UPDATES:

 www.nhs2survey.org/nhs2/gutsmoms
 guts@channing.harvard.edu


In Brief

For Your Health: Updated Vitamin D Recommendations

After a recent review of the literature on vitamin D and health, the Institute of Medicine increased the recommended vitamin D intake from 400 to 600 international units (IU) a day for most adults, and to 800 IU a day for those ages 70 and older. The upper daily limit was increased from 2000 IU to 4000 IU. Although these increases are welcomed, mounting evidence suggests that most individuals may benefit from even higher vitamin D intakes. In the NHS, we continue to see strong benefits for colorectal cancer and suggestive benefits for cancers of the breast, pancreas, and ovary – although these require further study. An individual's actual vitamin D requirement will depend on certain lifestyle factors, especially the amount of sun exposure he or she receives. Consult your doctor about the ideal amount of vitamin D for your health. (Wei MY and Giovannucci EL. *Mol Nutr Food Res.* 2010; 54(8):1114-26)

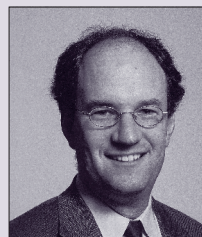
Not Vets Yet: US Cadet Nurse Corps of WWII Update

Although the 2009 HR Bill did not pass out of committee, there will be a new bill. All over the country former US Cadet Nurses are being featured in newspaper articles and honored as WWII veterans; many are NHS participants.

Meanwhile, if you were a US Cadet Nurse or know someone who was, and are not yet registered with The Women in Military Service for America Memorial Foundation, please register now by phone 1-800-222-2294 or online www.womensmemorial.org. To get on the mailing list for news about the Cadet Nurses, contact: Shirley Harrow, 65 Gladstone St., Quincy MA 02171 or saharrow@verizon.net. Thanks to the NHS Newsletter and the grapevine effect, more people are helping every day. 



2010 Dietary Guidelines



Eric Rimm, ScD

EVERY FIVE YEARS, the US Department of Agriculture and the US Department of Health and Human Services collaborate to review dietary research and provide up-

dated evidence-based nutrition information in the *Dietary Guidelines for Americans*. These guidelines inform the development of federal policy and educational tools, such as updated Food Pyramids for the classroom and new Web-based resources for teachers, food service directors, and dietitians.

One of our NHS investigators, Dr. Eric Rimm, participated on the 13-person panel that spent two years shaping the 450-page advisory document, which served as the basis for the *Dietary Guidelines for Americans, 2010* (www.DietaryGuidelines.gov). This evidence-based information was built upon findings from many studies, including the Nurses' Health Study. Dr. Rimm enjoyed the opportunity to translate twenty years of hard work in the NHS into important messages for health and nutrition:

"There were so many occasions where results from the NHS were instrumental in decisions we made. For example, the guidelines this time gave much clearer goals for dietary patterns, rather than just the individual components of the diet such as saturated fat or vitamin B6. The results from our studies on diabetes and coronary heart disease were very important in decisions we made about the different approaches to an optimal diet. We gave very strong messages that sugar-sweetened beverages and sports drinks should be reduced or eliminated, and that one's diet should have plenty of fruits, vegetables, fish, and whole grains. I hope the participants in the NHS feel equally as proud to have contributed to such an important effort."



Recent Findings

Mercury and Cardiovascular Disease

Research shows that eating fish, which is rich in beneficial omega-3 fatty acids, is associated with lower risk of cardiovascular disease (CVD). However, some prior studies suggest that mercury exposure from fish consumption may be linked to higher risk of CVD. We evaluated the association between mercury levels and CVD risk in nearly 7,000 participants from the NHS and our companion study of men, the Health Professionals Follow-Up Study (HPFS). We assessed mercury concentrations in stored toenail clippings, which are excellent biomarkers of long-term mercury exposure. We saw no association between mercury exposure and higher risk of CVD. Actually, we observed trends toward lower risk with higher mercury levels, likely related to other beneficial effects of fish consumption. These findings suggest that mercury exposure may not cause cardiovascular harm. However, public health efforts to reduce mercury in the environment should continue, as mercury exposure may have other harmful effects. (Mozaffarian et al. *N Engl J Med*. 2011 Mar 24; [Epub ahead of print])

Ibuprofen and Parkinson's Disease

In another recent study comprising participants from the NHS and HPFS, we found that adults who regularly take ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), had approximately one-third lower risk of developing Parkinson's disease (PD) compared with non-users. In contrast, aspirin, other NSAIDs, and acetaminophen did not appear beneficial against PD. These findings suggest that ibuprofen, a common and inexpensive over-the-counter drug, could potentially protect the brain's neurons against damage. Future research will study whether ibuprofen can slow disease progression among people already diagnosed with Parkinson's disease. (Gao et al. *Neurology*. 2011; 76:863-869)

Folate Intake and Colorectal Cancer

We previously reported in the NHS that higher folate intakes may lower risk of developing colorectal cancer; however, this association has been inconsistent across other studies. In the NHS and HPFS we addressed one possible reason for this discrepancy among studies: the timing of folate intake. Through the multiple food frequency questionnaires that you have completed over the years, we assessed the relation between long- and short-term folate intake and risk of cancer. When we assessed folate

levels 12 to 16 years before diagnosis, individuals with higher folate intakes (more than 800 micrograms a day) had a 31 percent lower risk of colorectal cancer compared to those with lower folate intakes (less than 250 micrograms a day). Folate intake over a shorter period of time (less than 12 years before diagnosis) was unassociated with risk. This finding suggests that folate affects early pre-cancerous stages and it may take some time for a benefit to emerge. (Lee et al. *Am J Clin Nutr*. 2011; [Epub ahead of print])

Genetics of Age-Related Macular Degeneration


Age-related macular degeneration (AMD) is the leading cause of blindness in the US. While both genetic and lifestyle factors influence AMD, we recently focused on its genetic predictors in the NHS and HPFS. We found that the more common variation of a particular gene (*RORA*) was associated with developing AMD. Compared with participants who possessed only the less common variant of this gene, participants with two copies of the common variant had a three-fold higher risk of the most severe form of AMD, known as the "wet" form. This gene appears to be involved in 45 percent of AMD cases that develop in the US. Eventually, we hope to identify those people who are at highest risk of AMD so that they can be followed-up closely and

Biological Samples Update

ONE OF THE WAYS we use nurses' biological samples (blood, urine, and saliva) is through the study of biomarkers. Presence of a certain hormone or a specific DNA sequence – both biomarkers – may influence disease development. Current research indicates that the timing of a biomarker's measurement may help us determine the risk of diseases that involve multi-step processes (such as cancer), since the level of certain biomarkers within the body can change substantially over time, while others remain stable. Understanding these changes may help us establish how often to measure a specific biomarker when predicting a woman's disease risk.

We have already collected two samples from NHS women (in 1990 and 2000), and we collected the first sample from premenopausal NHS II women in the mid-1990s. In 2009, we received a grant to collect a second blood and urine sample from the NHS II women, who are now postmenopausal. Matching pre- and postmenopausal samples will allow us to compare the importance of biomarkers measured in these two distinct periods of life to disease risk. So far, more than 78 percent of the NHS II women that we invited to participate have agreed! To date, over 8,500 women have returned blood and urine samples; with your help we hope to more than double that number by the end of 2011. We are extremely thankful for your enthusiasm for this project, which we hope will help us better understand chronic diseases in women.

Gestational Diabetes & Women's Health

WE RECENTLY STARTED COLLABORATING with investigators from the *Eunice Kennedy Shriver* National Institute of Child Health & Human Development (NICHD) and the Danish National Birth Cohort to begin a study on diabetes and women's health. Specifically, we will follow women who have had a pregnancy affected by gestational diabetes to understand its influence on future health. Many women who develop diabetes during pregnancy have higher risks of developing chronic conditions later in life, such as type 2 diabetes and cardiovascular disease. However, little is known about why some women, but not others, develop these conditions following gestational diabetes. We hope to recruit more than 5,000 women from the NHS II and more than 1,000 women from Denmark. This study will be one of the largest to comprehensively investigate long-term health status and its determinants among women with a history of gestational diabetes. If you have been diagnosed with gestational diabetes, watch for this special questionnaire! 

Recent Findings, continued from page 4

receive earlier or more targeted forms of treatment to prevent vision loss. (Schaumberg et al. *Arch Ophthalmol.* 2010; 128(11):1462-71)

Rotating Night Shifts and Skin Cancer

In our 2008 newsletter, we reported that women who worked night shifts for many years had somewhat higher risk of various cancers. Continuing our work to elucidate the effects of night shift work on women's health, we recently examined its relation to skin cancer in the NHS. Compared with women who never worked night shifts, women who worked night shifts for 10 or more years had a 14 percent decreased risk of developing skin cancers – including a 44 percent decreased risk of melanoma. This contrasts with the elevated risk of breast, colon, and endometrial cancer previously observed in nurses who worked night shifts. Conceivably, night workers have less sun exposure because they sleep during the day; however, our data do not support this. Our data were strongest among women with dark hair – raising the possibility of a genetic component that may affect both the extent of melatonin suppression at night and skin cancer risk. (Schernhammer et al. *J Natl Cancer Inst.* 2011; [Epub ahead of print])

Healthy Aging, continued from page 1

gained from age 18 until mid-life, the less likely her chance was for healthy survival after age 70. These findings emphasize the importance of maintaining a healthy weight from early adulthood onward, since mid-life weight gain was strongly related to a reduced likelihood of healthy survival later in life.

Physical Activity

Much research, including from the Nurses' Health Studies, has demonstrated that physical activity can reduce risk of many chronic diseases and premature death. Less clear is whether physical activity can also improve overall health among those who live a long time. We found that higher physical activity levels at mid-life were significantly associated with healthier survival. In particular, the chance of healthy aging improved with even modest activity levels: Women who jogged or cycled about five hours per week almost doubled their chance of healthy aging. Similarly, two or more hours per week of brisk walking, the most common form of activity among older women, increased the chance of healthy aging. These results suggest that higher levels of mid-life physical activity – including brisk walking – can provide health benefits later in life.

Telomeres

There is also much interest in biological aging, or the aging of cells in the body, compared with chronological aging, which simply refers to a person's age in years.

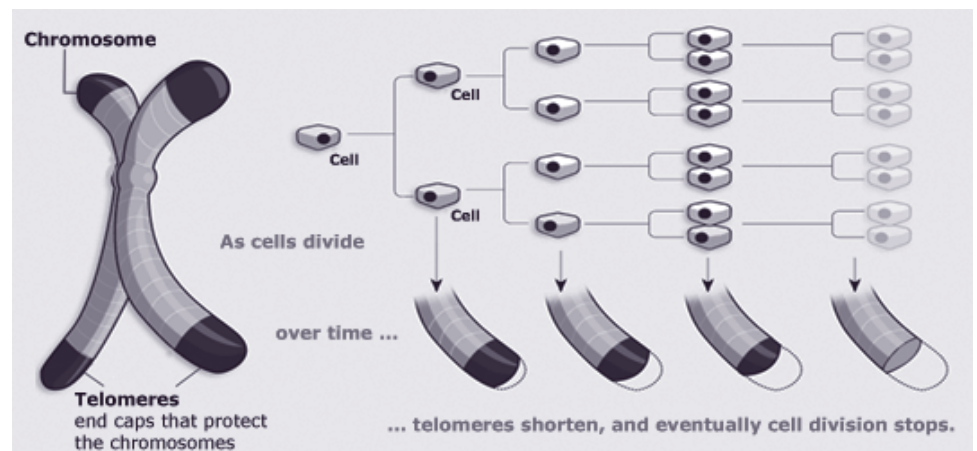


Image courtesy of T.A. Sciences, Inc.


This interest has been sparked by our recent knowledge of telomere biology. Like caps on shoelaces, telomeres are protective regions at the ends of chromosomes that shorten each time the cell divides (see figure above); this is a sign of biological aging. In the NHS, shorter telomeres have been associated with higher risk of certain aging-related diseases, such as bladder cancer and cognitive decline. A number of factors may influence telomere length: In addition to natural biological processes, obesity and smoking can shorten telomeres. In the NHS, we have found that maintaining a healthy body weight, not smoking, and higher physical activity levels may help maintain telomere length.

Future Directions in Research

We are constantly trying to improve our understanding of healthy aging, and your continued participation makes this possible. We recently held a special workshop where we asked government and academic leaders for their guidance in shaping the future of aging research in the NHS. These experts were extremely excited about the possibilities the NHS may offer in helping women

live longer and healthier lives. Some of the topics we will address in the coming years include: physical ability and disabilities, since this is so important for maintaining independence with aging; optimism and resilience – or the ability to recover from physical and emotional injuries; and sleep (including the influence of lifestyle factors on sleep, and how sleep and sleep disorders may influence other health outcomes).

Conclusion

As we age, we strive to better understand how we can maintain our health and well-being. The NHS is a unique resource, allowing us to track how specific factors throughout life may encourage healthy aging among women. 

Genome-Wide Association Studies...and Beyond


OVER THE LAST FEW YEARS we have updated you on the progress of genome-wide association studies (GWAS) conducted in the NHS. These studies measure up to one million DNA variants (specific locations in the genome that contain varying sequences of DNA) in thousands of participants to identify genetic regions associated with common chronic diseases and health-related traits. Over 8,000 NHS participants have had their DNA samples analyzed as part of a GWAS, and these data have helped find hundreds of genetic regions associated with dozens of diseases and traits (see box).

These genetic studies provide valuable clues about disease biology, but many important questions remain. For example, GWAS alone do not pinpoint the particular changes in DNA that influence cell function and thereby contribute to disease, though they do help narrow the search for these changes. Moreover, GWAS are designed to find common genetic markers; they less effectively identify variants that are present in less than 5 percent of the population. For these and other reasons, DNA variants identified by GWAS generally explain a small proportion of the overall variation for a specific disease or trait.

DNA sequencing solves some of these shortcomings. Where GWAS can measure genetic markers in DNA spaced intermittently throughout the genome, DNA sequencing painstakingly measures each letter of DNA code in a region—or, increasingly, each of the 3.3 billion letters in a human genome.

Technological advancements have only recently made these sequencing studies possible. Intriguingly, early DNA sequencing studies estimate that an average person's DNA contains changes that “turn off” over 100 genes, but with few noticeable effects. An important challenge is to understand which DNA changes are tolerable, under which circumstances, and why. To help answer these and other questions, NHS investigators have begun several sequencing projects, including one with over 1,000 NHS participants that sequences regions known to be associated with breast cancer. As always, we will continue sharing our latest findings in each annual newsletter.

The National Institutes of Health (NIH) has mandated that data from these studies be deposited in a controlled-access database. Any data sent to this database will not contain personal identifiers (e.g., your name, date of birth, address, zip code, or any trait information that could identify you). Further, the NIH will give database access only to qualified investigators who commit to maintaining the confidentiality of these data in addition to proposing a scientifically appropriate use for the data. This allows researchers to combine data from many studies, assess the reliability of findings, and better understand health effects (or lack of effects) of rarer DNA variants.

Our participation in this NIH database will greatly contribute to the large international effort to identify the genetic variants underlying the inherited predisposition to cancer, heart disease, diabetes, and other diseases. However, we recognize that DNA sequence data are potentially very sensitive. If you have any questions about these GWAS or sequencing studies, or you wish to withdraw from them in the future, please send an email to nhsgwas@channing.harvard.edu or write to us at NHS NIH/GWAS Studies, 181 Longwood Avenue, Boston MA 02115. 

GWAS Progress to Date

Here is a partial list of traits for which genetic associations have been identified using DNA data from NHS participants:

- breast cancer
- pancreatic cancer
- skin cancer
- bladder cancer
- endometriosis
- type 2 diabetes
- height
- body mass index
- waist-to-hip ratio
- hair color
- age at menarche
- age at menopause
- mammographic density
- smoking behavior

Most of these diseases or traits are best examined in very large collections. A recent study examining body mass index, for example, involved over 240,000 participants! This highlights the importance of collaboration and careful data sharing with appropriate safeguards on participant confidentiality.

Focus On Our Research Team

Fran Grodstein & Olivia Okereke

Two of our NHS investigators, Drs. Fran Grodstein and Olivia Okereke, focus their research on various aspects of the aging process. Their work helps shape the research discussed in the "Healthy Aging" article on the front page.

FRAN GRODSTEIN, ScD, joined the NHS investigative team in 1992 and is currently an associate professor at Harvard's schools of medicine and public health. As part of her earlier research on aging, she initiated the memory study in the 20,000 oldest NHS women, and also started research regarding urinary incontinence in the Nurses' Health Studies. Fran has expanded her work over time, and is presently a leading expert of aging research. She has advised both the NIH and the Centers for Disease Control on their efforts to advance the country's agenda for investigating brain health in aging. Besides her work with the NHS, Fran keeps busy with her family. Her husband is a local orthopedic surgeon at Brigham and Women's Hospital (BWH), and she has two small children who keep her energized.



Fran Grodstein, ScD

OLIVIA OKEREKE, MD, MS, is a board-certified geriatric psychiatrist and an assistant professor at Harvard's schools of medicine and public health. Her work includes examinations of metabolic, lifestyle, and behavioral factors in relation to cognitive aging. Presently, she is co-leading a new initiative on the assessment of aging-related outcomes in the NHS, and is also leading large projects on prevention of depression in older people. In addition, she maintains an outpatient geriatric psychiatry practice at BWH, and is highly involved in community education and service regarding healthy aging-related issues. In her free time she can be heard performing as an alto in the Harvard-Radcliffe Chorus. Olivia feels a special connection to the nurses in the NHS – her mother is a registered nurse who recently retired from a 35-year nursing career!



Olivia Okereke, MD, MS



Susan Hankinson, ScD, RN and Frank Speizer, MD

NHS founding Principal Investigator Frank Speizer and current Principal Investigator Susan Hankinson extend their sincerest thanks to all the nurses as we celebrate 35-years of productive collaboration.

Nurses' Health Study

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Letters & feedback are welcome.

To report name or address changes, visit www.NursesHealthStudy.org

Donations & 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 the website www.nurseshealthstudy.org and click the "Donate" link.