

NHS NEWS



Dear Colleagues,

We are pleased to announce that we recently received an additional five years of funding for the Nurses' Health Study II from the National Institutes of Health. Securing this funding in such challenging economic times is a testament to the importance of the research and to your contributions. Nurses'



Health Study I has funding in place until 2010. We have submitted a new five-year grant proposal which is currently under review.

This is a landmark year for the Nurses' Health Studies. We are celebrating the 20th anniversaries of the Nurses' Health Study II and the Nurses' Health Study blood cohort, and we have dedicated this year's newsletter to providing updates and historical perspectives on both. See pages 4 and 5 for a summary of some of our findings over the past 33 years.

Thanks to your continued support and participation, the Nurses' Health Studies have remained the largest long-term studies regarding women's health, offering vital information about the effects of diet and lifestyle choices on a variety of diseases. We extend our gratitude to all of you, and look forward to the exciting new research to come.

Best regards,

Susan E. Hankinson, Sc.D, R.N.
Principal Investigator,
Nurses' Health Study

Walter C. Willett, M.D., Dr.P.H.
Principal Investigator,
Nurses' Health Study II

20th Anniversary of the Nurses' Health Study II

THIS YEAR IS AN IMPORTANT MILESTONE for two reasons: it marks the 20th anniversaries of both the Nurses' Health Study II and the blood sample collections in the original Nurses' Health Study (NHS). Both began in 1989, thirteen years after the inception of the NHS in 1976. This effort to recruit participants into the NHS II and into the blood cohort was aided by the success of the original NHS.

NHS II

Twenty years ago, 116,686 women joined this investigation. 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.

NHS II is unique because at the start of the study in 1989 women were younger—25 to 42 years of age—than in any other large cohort investigation. This has provided insight about the effects of diet and other factors during a time of life that has not been investigated until now. Additional information has been provided by a large portion of the NHS II participants about their diet and activity patterns during high school years, and many of the mothers have completed questionnaires about their pregnancies with their NHS II member. Collecting information about earlier life events expands our understanding of events acting throughout the life cycle, not just the later years. Some of our recent findings about these early life factors are described on page 3 in this newsletter.

In recognition of the accomplishments of the NHS II and its potential to add further unique information about the cause and prevention of such diseases as breast cancer, the National Institutes of Health recently renewed five years of funding that supports this research. Our grant proposal was given one of the highest possible ratings.

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Blood Sample Collections

In addition to the 20th anniversary of NHS II, we are also celebrating the 20th anniversary of blood sample collections among NHS participants. Over the past twenty years, these samples have contributed enormously to a wide range of projects. By studying levels of vitamin D in the blood, for example, we have found that low vitamin D levels are associated with an increased risk of colon and possibly breast cancers, as well as hypertension.

In another study, we used plasma from women who developed breast cancer as well as a subset of women who did not. We found that higher estrogen and testosterone levels are associated with an increased risk of breast cancer. We are now assessing whether these analyses might be useful in helping women decide whether or not to use chemoprevention (e.g., tamoxifen) to decrease their risk of breast cancer.

Blood samples have also been used to help us determine how genetic variation, as well as the combination of genetic make-up and a person's lifestyle, can influence risk of chronic diseases such as cancer and heart disease.

In addition, the second set of samples provided ten years ago will allow us to assess any specific blood marker twice over the course of many years to see when in life it may be most strongly associated with disease risk. Without the use of these blood samples our research would certainly be limited.



Research Assistant Cristian Jimenez removes a rack of frozen blood samples from the liquid nitrogen freezer.

Thank you

This anniversary is a time for celebration; every member should feel proud about what she has contributed to the knowledge gained from the study, because it benefits countless women and their daughters around the globe. None of this work would have been possible without your incredible commitment to participating in these studies. Further, your contributions will multiply as our understanding of ways to promote health and well-being continues to unfold in the coming years. 

STUDY UPDATES

NHS III

As we described last year, we are planning to start a new phase of the Nurses' Health Studies by enrolling a new cohort of RNs and LPNs between the ages of 22 and 42 years: the Nurses' Health Study III. We have been testing multiple strategies to reach nurses who might be eligible to join this study in order to maximize the impact of our recruitment efforts. Some of you helped us in our last pilot evaluation by personally inviting other nurses who might be interested in joining the new study. This has been the most successful strategy for enrolling new participants, and will be a big part of our recruitment efforts when we begin full-scale enrollment later in 2009. We'll let you know when we are ready to ask for your help. For now, we have one final pilot under way and after that we hope to be ready to start enrolling new participants in this primarily web-based study.

GUTS

The Growing Up Today Study (GUTS) has had another productive year. Six articles were published and two more are currently in press. The topics of those papers range from weight gain to alcohol, acne, and disordered eating. In addition, projects on food allergies, asthma, stress response, and genetics are currently ongoing. This broad range of topics reflects the ability of GUTS to address many of the important health issues of adolescents and young adults. GUTS has become a unique database, like the Nurses' Health Studies, that can capture trends in behaviors and exposures over time and can link these to later onset of disease.

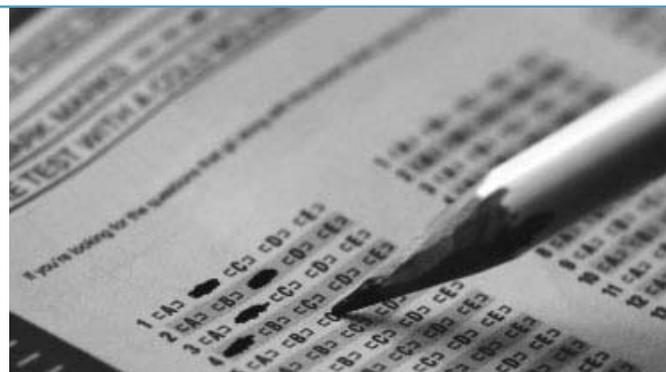
This year almost 80% of GUTS questionnaires were completed online, highlighting the need for us to make sure we have current e-mail addresses for our participants. The rates for completing the

questionnaire online are much lower in GUTS II, due to challenges maintaining current e-mail addresses for many of the GUTS II participants. As ever, we appreciate your help in keeping our databases current. And we appreciate your continued encouragement on our behalf, helping your children understand the long-term payoff of completing their questionnaires.

Shift Work Assessment

With research indicating the possible carcinogenicity of night shift work, the World Health Organization is convening a group of experts to help provide occupational advice for night workers. As part of this effort, we will include a detailed lifetime shift work history assessment on our 2009 Nurses' Health Study II questionnaire, and hope that many of you will help us with our further studies by completing these questions as thoroughly as possible. 

To search for publications discussed in these articles, or any paper that has been published from the Nurses' Health Studies, use the search box in our publications list at www.NursesHealthStudy.org (Click on General Information » Publication Archive).



Pilot Food Frequency Questionnaires

Have you ever wondered how we keep the NHS food frequency questionnaires (FFQ) up-to-date with all the latest changes in the marketplace? New and reformulated foods are constantly being introduced. To keep up with these changes, a team of Harvard research dietitians develop a pilot FFQ to track new foods consumed by nurses.

Every four years, 800 Nurses' Health Study and NHS II participants are randomly selected to take part in the pilot study. The pilot questionnaire we send to you is updated each cycle; we start that process by visiting grocery stores to assess the new products on the market and the new ingredients being added to foods. We look at the amount of shelf space used for these items and then conduct further market research on the product's top brands. We then create a pilot FFQ with questions related to the foods that we would like more information about. For example, the most recent pilot questionnaire asked about new dairy products with added fiber, omega-3 whole grain-added food items, and many other foods and beverages we plan to study.

When we receive the pilot questionnaires, we then analyze the frequency of consumption and the reported serving sizes. We use these results to define the nutrient profiles of food items on the most recently answered NHS FFQ to represent what women are actually eating. This helps us to make behind-the-scenes programming changes to more accurately define the nutrient intake reported on the questionnaires. The results are also used in the development of the next FFQ, to add important new items and remove existing foods that are no longer widely used. [NHS](#)

Early Life Factors and Risk of Breast Cancer

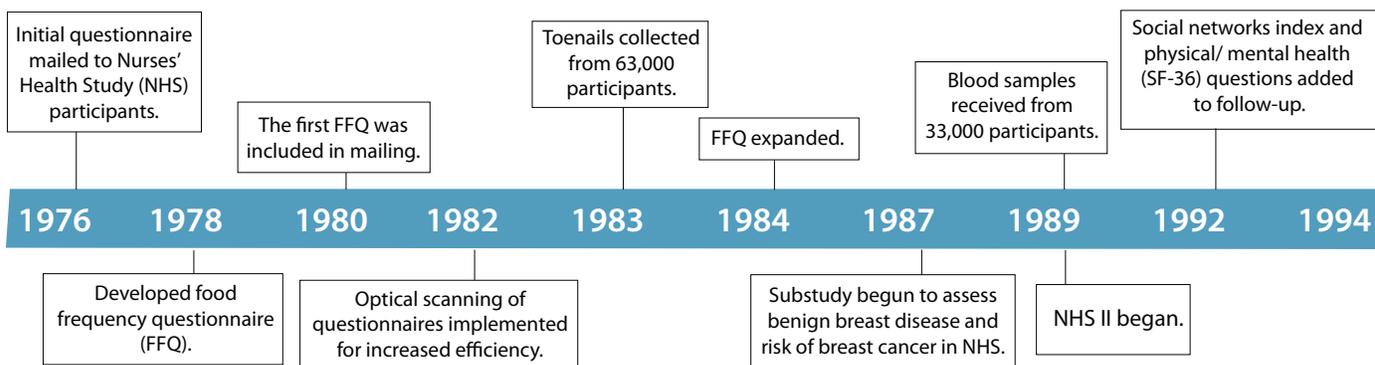
Epidemiologic investigations conducted by our group and others have suggested that during childhood and early adult life breast tissue is particularly sensitive to factors that influence the likelihood of developing cancer many years later. For example, if the breast is exposed to multiple x-rays or other types of radiation during this early period, the risk of breast cancer rises steadily with higher doses, but after age 40 radiation has little effect. Also, we have seen that being overweight before age 20 is paradoxically associated with a reduced risk of breast cancer for the rest of a woman's life, although subsequent weight gain and becoming overweight after menopause increases risk of breast cancer in these later years. These findings led us to develop sets of questions focusing on diet and physical activity during the high school years. We included these in our 1997/1998 NHS questionnaires. In addition, to assess the validity of the recalled dietary data, we invited a sample of mothers of NHS II participants to also complete a questionnaire about the high school diets of their NHS II daughters; strong correlation between the mother-daughter reports supported the validity of our dietary data.

We have now begun to examine the relation of high school diet and activity patterns to subsequent risk of breast cancer. We have seen that higher intake of red meat during the high school years is related to a greater risk of premenopausal breast cancer. Also, higher levels of physical activity during high school were associated with lower risk of breast cancer before menopause. This is particularly important, as many schools do not include regular physical activity in the curriculum, and many girls are now quite inactive during these years. During the continuation of the NHS II we plan to examine the relationships of high school diet and physical activity in greater detail as our findings to date support this as a particularly critical period of life for the prevention of breast cancer. [NHS](#)

Major Findings from the Nurses'

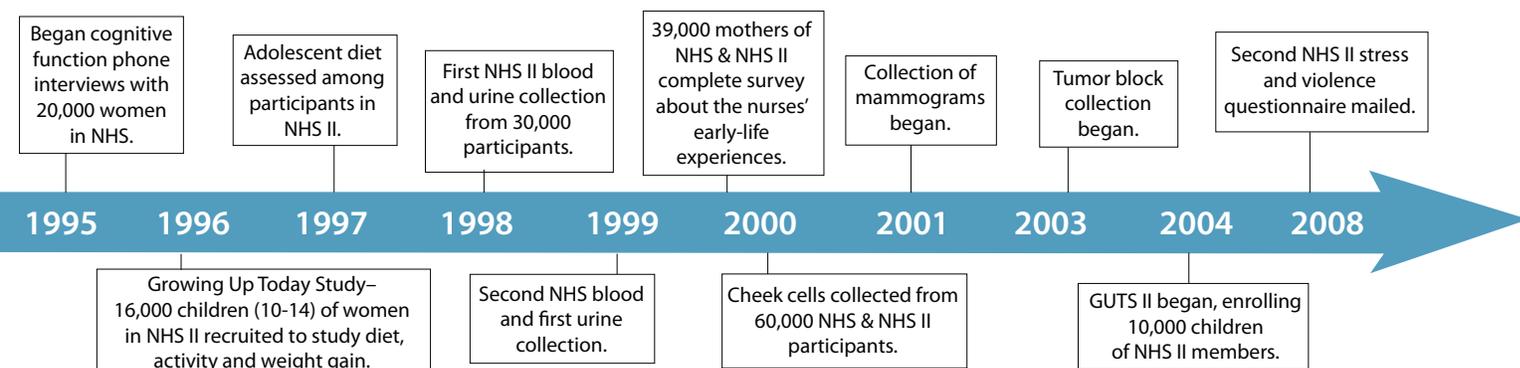
	Breast cancer	Coronary heart disease (CHD)/Stroke	Colon cancer
Smoking	No relation with past or current smoking.	Strong positive association with CHD and stroke; risk reduced within 2-4 years of smoking cessation.	Increases risk of colon cancer.
Oral Contraceptives	Current use increases risk. Past use no association.	Current use increases risk. Past use no association.	Reduces risk of colon cancer.
Postmenopausal Hormones	More than 5 years of estrogen plus progestins increases risk. More than 10 years of estrogen alone increases risk.	Current use increases risk of stroke. Current use among recently menopausal women may reduce the risk of CHD.	Reduces risk of colon cancer.
Obesity	Increases risk among postmenopausal women. Weight loss after menopause is associated with reduced risk.	Strong positive relationship between weight (BMI) and risk of CHD as well as stroke. Weight gain after age 18 increases risk of stroke and CHD.	Increases risk of colon cancer.
Alcohol	One or more drinks per day increases risk.	Moderate alcohol intake reduces the risk of CHD.	Two or more drinks per day increases risk.
Diet	Higher intake of red meat increases risk of premenopausal breast cancer.	A Mediterranean-type diet reduces risk of incident CHD and stroke. Fish intake reduces risk of stroke. Nut and whole-grain consumption reduces risk of CHD. Refined carbohydrates and trans fats increase risk.	Higher intakes of folate, vitamin B6, calcium and vitamin D reduces risk. High intake of red and processed meats increases risk.
Physical Activity	Physical activity (>3 hours/week) reduces risk.	Physical activity, including walking, reduces risk of CHD and stroke.	Physical activity reduces risk.
Other Exposures	Family history of breast cancer, high breast density, high circulating hormone levels, and shift work all increase risk.	Snoring is associated with a modest but significantly increased risk of CHD and stroke.	Aspirin reduces risk after 10 years of use. Family history increases risk up to four-fold for women younger than 50.

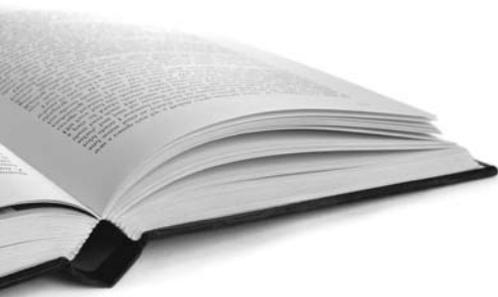
Timeline Evolution of the Nurses' Health Studies



Health Studies 1976-2009

	Hip fracture	Cognitive function	Eye diseases
Smoking	Increases risk of hip fracture for current smokers. Risk increases with greater number of cigarettes smoked per day.	Not examined.	Increases risk of cataracts and "wet" AMD (the most severe form of Age-related Macular Degeneration).
Oral Contraceptives	Not examined.	Not examined.	Reduces risk of "wet" AMD.
Postmenopausal Hormones	Reduces risk of hip fracture for current users.	No relation to cognitive function.	Current use reduces risk of high tension glaucoma and "wet" AMD.
Obesity	Strong protection against hip fracture, in large part due to extra padding around the hips.	Not examined.	Increases risk of cataracts and AMD.
Alcohol	High consumption increases the risk of hip fracture. However, low or moderate consumption is associated with greater bone density.	Moderate intake ($\frac{1}{2}$ – 1 serving per day) reduces risk of cognitive impairment.	No relation to age-related eye diseases.
Diet	Reduction of risk with calcium supplement use among women with low calcium diets; higher dietary calcium intake has no effect. Vitamin D intake reduces risk and retinol intake increases risk.	Higher vegetable intake, especially green leafy vegetables, reduces risk of cognitive impairment.	Some antioxidants reduce risk of cataracts and AMD. Higher intake of fish may reduce risk of cataracts and AMD.
Physical Activity	More physical activity, including walking, reduces risk of hip fracture.	Moderate physical activity reduces risk of cognitive impairment.	No relation to age-related eye diseases.
Other Exposures	Diabetes increases risk of hip fracture. Increasing years spent working rotating night shifts increases risk of hip fracture.	Type 2 diabetes and higher levels of insulin even in women without diabetes increases risk of cognitive impairment.	Diabetes increases risk of glaucoma and cataracts. Positive family history and African heritage increases risk of glaucoma.





Recent Findings

Aspirin and Colon Cancer

We have previously shown that aspirin reduces the risk of precancerous colorectal polyps as well as colorectal cancer. Aspirin specifically reduces the risk of a type of colorectal cancer that has an excess of a protein called cyclooxygenase-2 (COX-2). In our most recent work, we extended our findings to assess whether aspirin influences survival after diagnosis with this particular form of colorectal cancer, and if such survival differences varied according to the extent of COX-2 expression. Our results suggest that use of aspirin after diagnosis of colorectal cancer may improve survival from the disease, particularly among those whose primary tumors overexpress COX-2. Thus, aspirin may influence the biology of established colorectal tumors in addition to preventing their occurrence. Ultimately, we hope to determine who may benefit the most from treatment with aspirin. (Chan et al. *N Engl J Med.* 2007;356(21):2131-42)

New Risk Factors for Hypertension

High blood pressure affects over 60 million individuals in the U.S. and is one of the leading causes of preventable death in women. We have studied several new risk factors that predict the development of high blood pressure in the Nurses'

Health Studies, including blood levels of vitamin D, uric acid and fasting insulin, and urine levels of albumin. Nurses with blood levels of vitamin D less than 30 ng/ml (the definition of insufficiency) were 47% more likely to develop high blood pressure; this suggests other roles for vitamin D in addition to bone health. We also measured fasting levels of uric acid, insulin, and albumin excretion in urine in nurses with normal blood pressure. Those women whose levels were in the highest compared to the lowest 25% had a greatly increased risk (approximately 1.5- to 2-fold) of developing high blood pressure. These results suggest that higher levels of certain markers (even within the "normal" range) indicate an increased risk of developing high blood pressure. (Forman et al. *Arch Intern Med.* 2009; 169:155-62. Forman et al. *J Am Soc Nephrol.* 2008; 19:1983-8)

Cognitive Function

One of our areas of continuing interest in the Nurses' Health Study is how to maintain memory during the aging process. We have evaluated several measurable factors in the blood, such as vitamins and insulin, in relation to memory. To do this, we administered memory tests to the oldest participants who had provided a blood sample ten years earlier. We found that, even in women without type 2 diabetes, higher levels of insulin predict worse changes in memory over time. This suggests that perhaps "pre-diabetes" may be harmful to brain health and thus factors that prevent diabetes, such

as exercise and weight maintenance, could be important for memory too. We also examined plasma levels of antioxidant vitamins. However, we found that higher levels of antioxidant vitamins were not related to better memory. (van Oijen M. et al. *Neuroepidemiology.* 2008;30:174-9. Kang JH and Grodstein F. *Neurobiol Aging.* 2008;29:1394-403)

Incontinence in Younger Women

Most people think of urinary incontinence as a condition that affects mainly older women and do not appreciate how common it is among younger women too. Among all participants in NHS II, aged 37-54 years, 43% reported incontinence at least monthly. Two years later, 14% of women who previously had no issues with incontinence reported new onset of incontinence at least monthly. Stress incontinence, occurring mainly with activities such as coughing, sneezing, or laughing, was the most common incontinence type in NHS II participants, and increased with age. Urge incontinence, occurring mainly with a feeling of a sudden need to void, was less common until women got much older. We found that obesity, weight gain in adulthood, and presence of type 2 diabetes were all associated with greater risk of developing incontinence, while long-term, moderate physical activity was associated with lower incontinence risk. (Danforth KN et al. *Am J Obstet Gynecol.* 2006;194:339-45; Townsend MK et al. *Obstet Gynecol.* 2007;110:346-53)

Genome-Wide Association Studies and Data Sharing

In the past year our involvement in genome-wide association studies (GWAS) has led to many exciting findings. In a GWAS, we study at one time many thousands of gene variants to identify chromosomal regions associated with risk of various diseases. Through our partnership with the National Cancer Institute's Cancer Genetic Markers of Susceptibility (CGEMS) initiative, we were the foundational study in the first U.S. GWAS of breast cancer (see Recent Findings article at right for an update on breast cancer risk).

Because of the extensive information you have given us over so many years, we can also use this genome-wide data to examine other conditions. For instance, last year we published the discovery of several new genes associated with hair color and skin sensitivity to sunlight based on information you gave us back in 1982. It turns out that these genes are involved in susceptibility to skin cancers. As another example, we have been able to contribute to even larger "meta-analyses" of several such studies that have led to the identification of dozens of new genes associated with weight and height.

Due to the value of pooling data from multiple studies, the National Institutes of Health (NIH) has mandated that data from these studies be deposited in a controlled-access database. Of course, any data we send to this database are completely devoid of any personal identifiers (e.g., your year of birth, address, or zipcode). NIH also restricts access to only qualified researchers who can show an appropriate scientific use for the data, and who commit to maintaining the confidentiality of the de-identified data. If you have questions about these NIH/GWAS studies, or wish to withdraw from them in the future, please send an email to nhsgwas@channing.harvard.edu or write us at NHS NIH/GWAS Studies, 181 Longwood Ave, Boston, MA 02115. One of our researchers can answer any questions you may have.

We are sometimes asked whether the genetic results can be returned to participants. As described when you gave us a blood or cheek cell sample, the tests we do are for research purposes only. The tests are not as tightly controlled as clinical tests, and most of the laboratories doing the testing are not clinically certified to return results to patients. Thus, we cannot return results. We will of course continue to report our latest findings in each annual newsletter. 

For more information regarding GWAS analyses please read "From Darwin's Finches to Canaries in the Coal Mine — Mining the Genome for New Biology" by NHS researcher David Hunter and others, available at <http://content.nejm.org>

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Genes and Breast Cancer

With colleagues, we reported the discovery of two new areas in the genome that are associated with a small increase in risk of breast cancer. Though we presently know little about the first variant, the second variant is located within a gene on chromosome 14 that is involved in DNA repair, called RAD51L1. Though defects in DNA repair are known to underlie some rare familial forms of breast cancer, this is the first time that a common variant in such a gene has been associated with breast cancer.

With discoveries that we and others have made over the past two years there are now 14 common genetic variants that are associated with small increases in breast cancer risk. As more variants are discovered, it may be possible in the future to test for their presence in individual women to obtain a personalized score for inherited genetic risk. In the interim, these genes give us new opportunities to expand our understanding of the biological mechanisms of breast cancer. (Thomas et al. *Nat Gen.* 2009, March 29. Epub ahead of print.) 

Focus On Our Research Team

One of the strengths of our research team is the large number of staff members who have worked on the study for many years. In honor of the twentieth anniversary of NHS II, our focus this year is on the staff members who have worked at the NHS for over twenty years. Thanks to everyone for all their help and to Dr. Speizer for his pioneering work in starting NHS I in 1976.

Back row:

Sue-Wei Chiang – *Computer Programmer*
 Maureen Ireland – *Project Manager for diabetes and eye diseases*
 Sherry Hahn – *Senior Cohort Manager*
 Lisa Dunn – *Project Manager for deceased participants*
 Lori Ward – *Project Manager for cancers*
 Marion McPhee – *Senior Information Systems Programmer/Analyst*
 Steven Stuart – *Software Developer*
 Gary Chase – *Project Manager for data collection*



Front row:

Karen Corsano – *Senior Programmer*
 Cindy Nebolsine – *Administrator to Dr. Frank Speizer*
 Frank Speizer – *Founder of Nurses' Health Study*
 Barbara Egan – *Senior Project Manager for disease follow-up*
 Laura Sampson Kent – *Senior Research Dietician*

Funding the Nurses' Health Studies

We are strongly committed to the Nurses' Health Studies and are doing everything we can to assure their long-term stability. In addition to seeking grants from major foundations and government institutes, we also solicit support from private donors in our effort to sustain the continued operation of the Nurses' Health Studies. As the largest ongoing studies of women's health that include repeated measures of diet, physical activity, and other lifestyle factors related to a broad range of chronic conditions, we are confident we will meet our goal of diversifying the funding base for the NHS.

If you or someone you know is interested in contributing to the study, please contact Dr. Hankinson, Dr. Speizer, or Dr. Willett at (617)525-2258, or visit the web site www.nurseshealthstudy.org and click the "Donate" link.

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 can
 be sent to the Channing Laboratory.