



# NHS NEWS



Dear Colleagues,

We have had another busy and productive year at the Nurses' Health Studies. As always, this work was only possible because of your tremendous support and ongoing participation in the Nurses' Health Studies.



This year our lead article focuses on vitamin D. Recent research suggests that vitamin D likely has a much broader role in maintaining health than previously realized. Your efforts have contributed significantly to this knowledge – in fact, Nurses' Health Study analyses of circulating vitamin D levels in relation to colon cancer, published in the *Journal of the National Cancer Institute*, were cited by *Time Magazine* as one of the "Top 10 Medical Breakthroughs" of 2007.

It has been 32 years since the Nurses' Health Study began and 19 years since the Nurses' Health Study II began, yet your data continue to provide important information for women's health. No matter what your age or profession, you continue to be vital to this study, and we look forward to collaborating with you for years to come.

Best regards,

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

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

## Vitamin D and Cancer



KNOWN AS THE "SUNSHINE VITAMIN," vitamin D has become a popular topic in health-related news over the past few years, in part due to the ongoing debate about potential benefits and optimum levels of this important vitamin. Evidence from the Nurses' Health Studies and the other Harvard cohorts has been especially important in our understanding of the role of vitamin D in cancer.

### Benefits

A well-known role of vitamin D is the prevention of rickets in infants and children. This benefit is largely due to vitamin D's assistance in regulating levels of calcium and phosphorus in the body. In adults, adequate vitamin D is important for bone health and in reducing risk of osteoporosis. In the past several decades, many studies – including the Nurses' Health Studies – have evaluated other roles of vitamin D as well. Vitamin D may be important in reducing the risk of cancer, cardiovascular disease, glucose intolerance, high blood pressure, asthma, some infectious diseases, multiple sclerosis, and type 2 diabetes. While these potential benefits are not definitive, an impressive and growing body of evidence supports that they are valid.

The evidence linking vitamin D with cancer is most consistent for colorectal cancer; women with blood levels of vitamin D above 30 ng/ml (what many experts consider to be the minimum acceptable level) have about half the risk of those with levels below 15 ng/ml. There is also suggestive evidence of a modest benefit on breast cancer. After lung cancer, these are the two most common fatal cancers in women. There may be benefits on other cancers, including ovarian and pancreatic cancers, but these are not definitive and much more work is needed.

A number of researchers are beginning to believe that increasing vitamin D intake may correct a deficiency caused primarily by a lack of the natural

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# Study Updates

## Fundraising for the Nurses' Health Studies

TWO RECENT INITIATIVES have helped support some of the cancer-related research being conducted in the Nurses' Health Studies. We are most appreciative of this support, particularly now when government funding of research has substantially decreased.

### Conquer Cancer Coalition of Massachusetts



This coalition was started by Susan Zuker, in memory of her husband who died of lung cancer. The group developed a "Conquer Cancer" license plate that is now being sold in Massachusetts. Proceeds from these sales are going to

several cancer-related education, treatment, and research activities; the cancer prevention research component supports our activities in this arena. To learn more visit [www.conquercancer.org](http://www.conquercancer.org)

### Support Cancer Research: Top Cause on Facebook



Facebook started as an Internet-based social network site for college students. It has now grown to include millions of members in various age groups. Facebook members are able to support *Causes* that are important to them and to invite other members to join and contribute financially.

Dr. Eric Ding, an epidemiologist and

current medical student, started the "Support Cancer Research" Cause to maintain cancer research in the NHS. This Cause has the largest membership on Facebook with over three million members to date, and has raised over \$60,000! To learn more visit: [http://apps.facebook.com/causes/view\\_cause/210](http://apps.facebook.com/causes/view_cause/210)

We are strongly committed to maintaining funding for the Nurses' Health Studies. To do this, we seek grants from major foundations and government institutes as well as support from private donors. If you or someone you know is interested in contributing to the study, please contact Drs. Sue Hankinson, Frank Speizer, or Walter Willett at (617) 525-2258, or visit [www.nurseshealthstudy.org](http://www.nurseshealthstudy.org) and click the "Donate" link. 

### Growing Up Today Study

In 1996, the Growing Up Today Study (GUTS) was initiated to study diet, activity, and weight among 9-14-year-olds. In 2004, another 10,000 children (many the younger siblings of GUTS participants) were enrolled in GUTS II. This year has been very productive with 10 articles published on a wide array of topics. Additionally, we expanded the focus of the study to include questions about stressful experiences like losing someone close to you or being involved in a motor vehicle accident. This was done at the specific request of many GUTS participants who asked that we address these sensitive topics.

Keeping up-to-date contact information for GUTS participants

continues to be one of our biggest challenges. If your participating children have new email or postal addresses or new phone numbers, please contact us (see box below) so we can update our records.

As always, we greatly appreciate your continued encouragement to your children on our behalf. Their information continues to make GUTS and GUTS II two of the most important studies of adolescent and young adult health in the U.S.

#### SENDING GUTS UPDATES:



[guts@channing.harvard.edu](mailto:guts@channing.harvard.edu)



(617) 525-2279



[www.nhs2.org/update](http://www.nhs2.org/update)

### Nurses' Health Study III

As we informed you in our 2007 Newsletter, we are piloting a new web-based cohort study, the Nurses' Health Study III, among RNs and LPNs 22-42 years old. We wish to examine how recent changes in hormone preparations, dietary patterns, and nursing occupational exposures influence women's health. Prominent new features will include a closer look at fertility and pregnancy and a greater focus on adolescent diet and breast cancer risk. If the pilot is successful, we hope to launch the full study later this year. 

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source of vitamin D found in sun exposure. Numerous cellular functions require vitamin D to regulate gene expression. For example, vitamin D appears to be important in the regulation of cell proliferation and differentiation; thus, deficiencies could contribute to the formation of cancers. In addition, studies have shown vitamin D to be critical to the immune system, and thus deficiency could contribute to some autoimmune diseases and infections.

## Adequate levels

Although more research is necessary to establish vitamin D levels required for optimal health, an increasing number of experts have concluded that the current levels of vitamin D in many people are inadequate. The history of our species may help explain this inadequacy. Our ancestors first lived in tropical regions, where sunshine was abundant year-round and clothing was minimal due to the warm climate. Moreover, our ancestors did not spend as much time indoors as most of us do! Under these conditions, some have estimated that the vitamin D levels ranged from 50 to 90 ng/ml. It is difficult to determine if there are additional benefits conferred with such high levels of vitamin D, since this is so rare in modern societies. Levels below 10 or 15 ng/ml are not uncommon now, and typically suggest a vitamin D deficiency.

Chronic diseases such as cancer are asymptomatic when they are developing, and sustained vitamin D levels below 30 ng/ml may predispose one to developing cancer. People at especially high risk for deficiency are those that are darker skinned, obese, elderly, or simply avoid sun exposure. For those living in northern climates, sunlight during winter months is too weak to make appreciable amounts of vitamin D, making it difficult to maintain a healthy level.

## Diet

Are the recommended intakes of approximately 400 IU/day enough? Curiously, the recommended intake is the same for a six-pound infant and a 300-pound adult. Consider also that 100 IU of vitamin D daily (the amount in a glass of milk) will raise vitamin D levels by such a small amount that a person with a low level would have to drink roughly 20 glasses of milk per day to reach an adequate level. We do not recommend this! While it may

be useful to get some amount of vitamin D through the diet, it is difficult to raise these levels substantially.

## Supplements

We believe a much better way to increase vitamin D levels is through supplements of vitamin D3 (also called cholecalciferol). Daily intakes of 1000 to 1500 IU/day from supplements, especially during the winter months in northern climates, may be warranted for many individuals. It is recommended not to exceed 2000 IU/day, although there is still much debate about the intake levels that may put one at risk for hypercalcemia, the major consideration for vitamin D toxicity.

### SOURCES OF VITAMIN D

SOURCE	VITAMIN D/ SERVING
Sunlight	N/A
Supplements	400-1000 IU
Fortified milk (1 cup)	98 IU
Cooked salmon (3.5 ounces)	360 IU
Canned tuna (3 ounces)	200 IU
Fortified cereals (3/4 to 1 cup)	40 IU

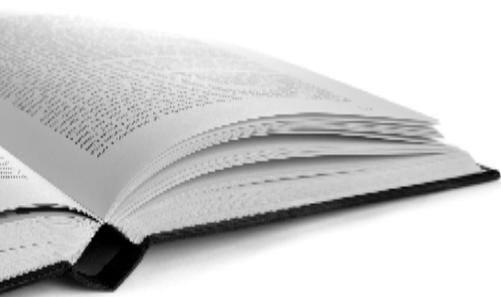
Food sources: <http://dietary-supplements.info.nih.gov/factsheets/vitaminD.asp>

## Sun Exposure

A light-skinned person sunbathing for 15-20 minutes can make up to 20,000 IU of vitamin D. No case of sun-induced vitamin D toxicity has ever been documented in history. A darker-skinned person can also make similar amounts of vitamin D, but would require more time in the sun. Efforts to avoid excessive sun exposure remain important, especially among lightly pigmented pre-adults, but the extreme avoidance of sun exposure may have inadvertently contributed to widespread vitamin D deficiencies.

## Conclusion

There appear to be many health benefits associated with adequate intake of vitamin D, including suggestive evidence with colorectal and breast cancers. While the available data are promising, we need to learn a lot more about vitamin D and its potential health effects. We plan continued study of this remarkable nutrient, which will help resolve the many remaining questions. 



# Recent Findings

## Smoking and Breast Cancer Mortality

We wondered whether women diagnosed with breast cancer were more likely to have their breast cancer spread (particularly to the lungs) if they smoked. We also wanted to examine whether they would be at greater risk of dying from breast cancer than women who had never smoked. To find out, we analyzed data from over 5,000 women with early stage breast cancer.

We found that a history of smoking did not increase the women's chances of recurrence or death from breast cancer. However, among these breast cancer survivors, smokers were 43% more likely than non-smokers to die from diseases such as lung cancer and emphysema. As modern treatments help women live long and healthy lives after a breast cancer diagnosis, it is important to remember that they are still prone to the same smoking-related diseases as women without breast cancer. (Holmes MD et al. *Int J Cancer* 2007; 120: 2672-7)

## Trans fat and weight gain

Trans fats, or partially hydrogenated oils, are created to preserve shelf life and maintain flavor in many food items, such as packaged baked goods, vegetable shortenings, and margarine. There is ongoing debate

about the role fat plays in weight gain, but experts agree that trans fats are bad for your heart health.

Overall, we found that there was little association between total fat intake and weight gain. However, there was a stronger association between trans fats and weight gain. We measured the percentage of calories from trans fat for each woman at the start of the study and again eight years later. For every one percent increase in trans fat, women gained an average of 1.7 pounds more than women who did not increase their consumption of trans fat. The association between trans fat intake and weight gain was strongest among women who were overweight at the start of the study. (Field AE et al. *Obesity* 2007; 15(4):967-76)

## Diet and fertility

What you eat seems to be important for many aspects of health, but can diet choices affect fertility? In the Nurses' Health Study II, several dietary factors were associated with lower chances of infertility due to ovulation problems.

We found that a diet that may help women to conceive includes daily multivitamins, low glycemic carbohydrates, and adequate iron from plant sources and supplements. We also found that a diet favoring unsaturated fats over trans fats, vegetable over animal sources of protein, and, surprisingly, low levels of high-fat over low-fat dairy also increased the likelihood of conception. In addition, we confirmed

our earlier findings that a BMI between 20 and 25 and vigorous physical activity confer protection against ovulation-related infertility. Women following five or more of these low-risk dietary and lifestyle habits (as opposed to none) were substantially less likely to experience infertility due to ovulation problems. (Chavarro et al. *Obstet Gynecol* 2007; 110: 1050-1058)

## Air Pollution and Mortality

We have recently started to investigate the impact of residential locations on health. Many studies have shown increases in mortality in areas with higher levels of air pollution. The U.S. Environmental Protection Agency (EPA) monitors outdoor particulate air pollution around the country, and we have used these data to assess mortality and air pollution based on home addresses from 1988 through 2002.

We found that a slight increase in outdoor particulate levels was associated with a 1.5% greater risk of dying, after controlling for known risk factors. The risk was highest for death from cardiovascular disease. We are continuing to explore the role of different pollutants and to identify personal characteristics that may place individuals at higher risk. (Puett R et al. *Am J Respir Crit Care Med* 2007;175:A959)

## Prolactin and breast cancer

Prolactin is a hormone involved in breast tissue development, and some studies have suggested that it could

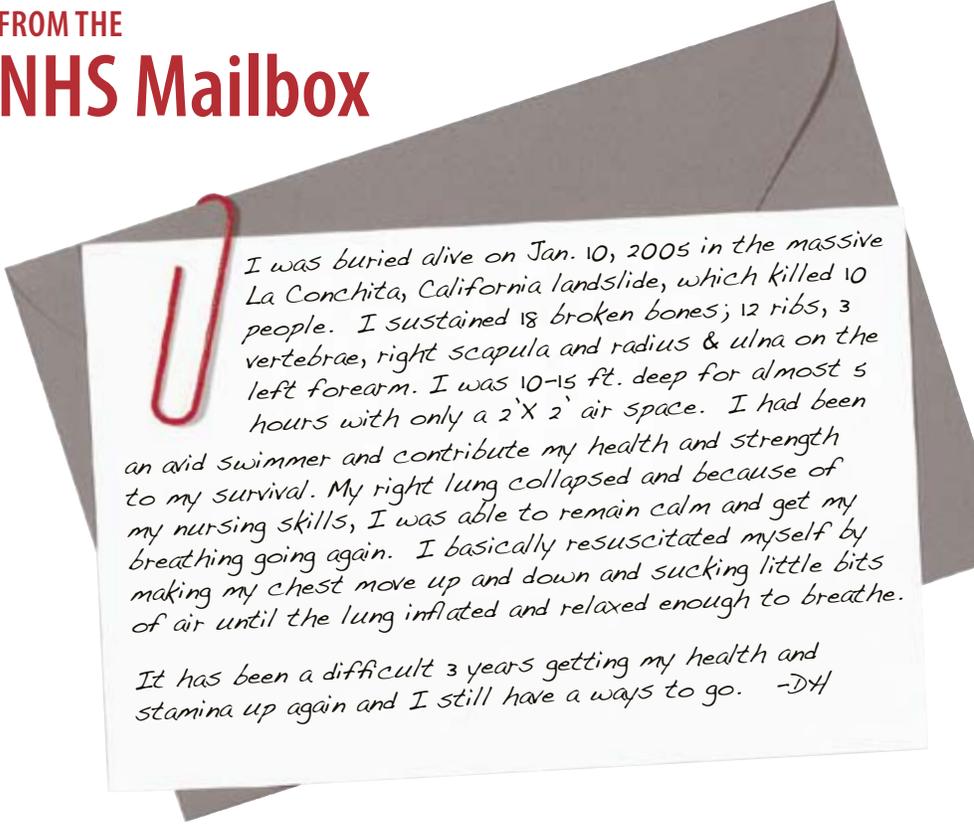
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influence breast cancer. Could high levels of this hormone increase a woman's risk for breast cancer? We measured prolactin in blood samples from nearly 5,000 women in the Nurses' Health Studies.

We found that women with high prolactin levels had a moderately higher risk of breast cancer compared with women with low levels. Specifically, these women had a high risk of estrogen receptor-positive breast cancer (in which the tumor has estrogen receptors on the surface). In the future, we plan to examine whether changes in prolactin levels over 10 years are related to breast cancer risk as well as identify lifestyle choices that may help women lower their prolactin levels. (Tworoger S et al. *J Clin Oncol* 2007; 25(12):1482-8). 

## FROM THE NHS Mailbox



*I was buried alive on Jan. 10, 2005 in the massive La Conchita, California landslide, which killed 10 people. I sustained 18 broken bones; 12 ribs, 3 vertebrae, right scapula and radius & ulna on the left forearm. I was 10-15 ft. deep for almost 5 hours with only a 2'X 2' air space. I had been an avid swimmer and contribute my health and strength to my survival. My right lung collapsed and because of my nursing skills, I was able to remain calm and get my breathing going again. I basically resuscitated myself by making my chest move up and down and sucking little bits of air until the lung inflated and relaxed enough to breathe.*

*It has been a difficult 3 years getting my health and stamina up again and I still have a ways to go. -DH*

## Night Shift Work and Cancer Risk

IN DECEMBER 2007, the World Health Organization classified rotating night shift work as a probable human carcinogen, noting findings from our Nurses' Health Studies regarding an increase in breast cancer risk, as well as findings from other studies. In more recent studies, we found that women who worked these shifts for many years had a 35% increased risk of colorectal cancer and a 47% greater risk of endometrial cancer.

How then might working night shifts increase the risk of cancer? Light powerfully influences the circadian rhythm, which regulates the normal sleep and wake cycle in humans. Melatonin, which has demonstrated protective effects against cancer, is secreted predominantly in the dark phase of the light-dark cycle; for most

people, this means the hormone levels peak in the middle of the night. Direct light exposure to the eyes at night will immediately suppress melatonin production.

The current Light Study involving women in the Nurses' Health Study II aims to further knowledge of the potential association between cancer risk and night work. In this study, we are evaluating light exposure in rotating shift workers and relating those measures to melatonin levels in urine. We predict that night workers have lower levels of melatonin, and thus an increased risk for certain cancers, when compared with day workers. The participants wear a circadian light meter on a headband to measure light exposure for seven days, as well as provide several urine samples. Since the start of the Light Study in



Photo courtesy of RPI Lighting Research Center

October 2006, an impressive 80% of you have indicated an interest in participating! To date, 130 nurses have completed the study and we will continue enrolling participants until later this summer.

Additional research is needed, and together we are contributing to this effort. In the meanwhile, there are a number of proven ways for women to decrease their cancer risk, such as exercising and maintaining a healthy weight. 

## Nurses' Health Study Data Security

With the many news reports of stolen computers containing personally identifiable information, you may wonder, "How safe is my information at the Nurses' Health Study?" The answer is **very** safe.

NHS data are never stored on laptops. Additionally, these data never contain confidential information like names, addresses, or social security numbers; instead, they are identified by ID number only. As a result, even our analysts do not know the identities of the participants in any given set of data.

All name and address information are stored on a separate computer to which only a select group of senior staff have access. In short, we protect your answers as we would protect our own private information.

Maintaining your trust in the Nurses' Health Study is critically important and we work hard to continue to earn it.

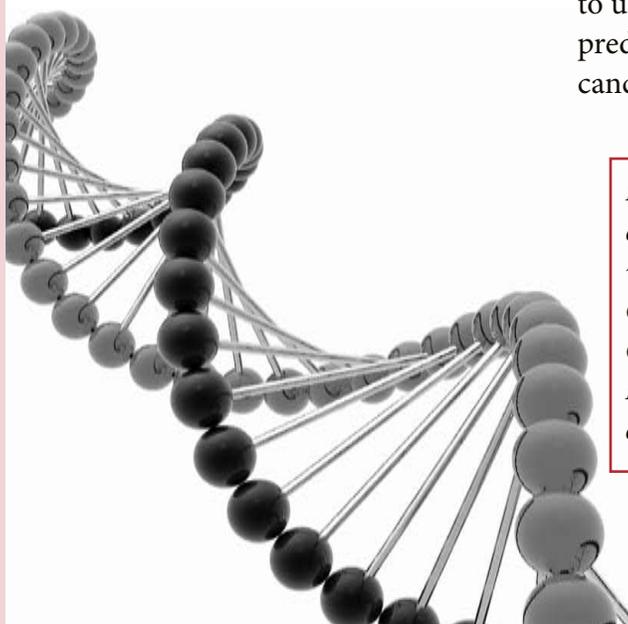
## Genome-wide Association Studies

SINCE THE MAPPING of the human genome began many years ago, genetic research has shed light on a multitude of different diseases. One of the more recent advancements in this field involves the study of "SNPs," which are variations in the sequence of DNA. Genome-wide association studies often use "SNP chips" to look all at once at 500,000 or more gene variants spread across the genome, in order to find chromosomal regions that are associated with risk of various diseases. The Nurses' Health Study has been in the vanguard of these analyses, through our partnership with the National Cancer Institute CGEMS (Cancer Genetic Markers of Susceptibility) initiative.

Together, NHS and CGEMS have focused primarily on the genetic variants involved in breast cancer. Last year we published one of the first successes of SNP chip studies – the finding that variants in the FGFR2 gene are associated with modestly increased risk of breast cancer. These studies provide a window into the spectrum of gene variants that are common in the population (more than 60% of women in the U.S. carry

at least one copy of the FGFR2 "risk" variant), but give rise to far lower risks than those associated with the BRCA1 or BRCA2 genes, which are well documented to increase breast cancer risk. For example, at a young age the risk associated with having a BRCA1 mutation is more than 20-fold, whereas the risk associated with carrying a copy of one of the FGFR2 mutations is less than twofold.

The new generation SNP chip studies are individually very expensive, so the National Institutes of Health (NIH) has mandated that data from these studies be deposited in its database. This allows researchers to cumulate data across studies, and assess the reliability of findings from one study to another. Of course, any data we send to the NIH database is completely devoid of personal identifiers. NIH gives database access only to qualified researchers who go through their application procedure and commit to maintaining the confidentiality of the de-identified data. Our participation with NIH contributes greatly to the large national and international effort to identify the multiple lower-risk genetic variants that are thought to underlie most of the inherited predisposition to breast and other cancers, as well as other diseases. 



For more information regarding SNP-chip analyses, including commercial versions, please read "Letting the Genome Out of the Bottle – Will We Get Our Wish?" by David Hunter, MD, available at: <http://content.nejm.org/cgi/reprint/358/2/105.pdf>

# Focus On Research Team: Lisa Willis

Federal and institutional policy requires that the appropriate Institutional Review Board (IRB) monitor human subjects research to ensure the safety and confidentiality of all participants. The IRBs for the Harvard School of Public Health and Brigham and Women's Hospital also serve as our partners in research and as indispensable sounding boards as the Nurses' Health Studies continue to conduct novel and exciting research.

For the past six years, **Lisa Willis** has acted as a key liaison between Nurses' Health Study researchers and local institutions' IRBs. Over

the past two years, she has worked with the IRBs to pilot a new online IRB submission system and guide researchers in the use of this new paper-reducing and secure technology. She also oversees human subjects training certification, guaranteeing that everyone in our research group maintains current training practices in the protection of participants.

Charged with maintaining approximately 400 IRB protocols related to a wide range of studies (and the number increases daily!), Lisa readily admits that the pace is hectic. However, this self-proclaimed



“workaholic” greatly enjoys working with investigators to help them maintain study IRB approval status in order for them to focus on their research efforts.

Attracted to the wellness field for most of her life, Lisa has worked previously in research, natural foods, and Eastern-based medicine. When she has free time she enjoys dancing, reading, and knitting; through her knitting group, she has had the chance to meet several Nurses' Health Study participants. 

## Keeping us up-to-date

### Authorization for Release of Medical Records

As members of the Nurses' Health Study get older, some will unfortunately develop conditions that make it difficult to respond to future mailings. Should you become disabled, it would greatly help our research if someone could notify us of your health status and subsequently allow your pertinent medical records to be released to us. To help facilitate this process, in 2004 we mailed a copy of our Authorization for Release of Medical Records to every NHS participant. (Copies of that form can also be downloaded at [www.NursesHealthStudy.org](http://www.NursesHealthStudy.org).) While this authorization form will generally not be accepted to release your medical records to us, by keeping it with your will or personal papers, your desire to have someone notify the study about changes in your health status will be known.

### Medical Records Review

Participants who report a new diagnosis in their biennial questionnaires often receive a letter from our study, requesting permission to review their pertinent medical records. This review is important because it allows us to obtain specific information about treatment and diagnosis that only original records can provide. We want to extend a special thank-you to all of the nurses who have helped our work by allowing us to confidentially review their records. We would also like to encourage participants who receive these requests to complete and sign the release forms and then mail them back to us (not directly to the physician). This allows us to keep study information together in an organized and secure manner. 

# Profile of Participants\*

How many participants...	NHS	NHS II
Were smokers at start of study?	33%	14%
Have since quit smoking?	73%	56%
Take a multivitamin?	60%	59%
Take calcium supplements?	47%	38%
Drink 2+ cups of regular coffee/day?	29%	32%
Consume tofu 1+ times/week?	6%	10%
Walk 2+ hours/week for exercise?	35%	29%
Watch TV 20+ hours/week?	18%	7%
Sleep < 6 hours/night?	28%	30%

NHS participants have spread all over the world for a variety of reasons – retirement, healthcare work, better weather, or proximity to family. We enjoy getting their completed surveys from all over the globe!

There are 348 women in the Nurses' Health Studies who live outside the U.S. The three most common countries of residence are Canada (128), UK (29), and Israel (16).



\* Per current NHS Data

## Nurses' Health Study

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 617-525-2279 (tel)  
 617-525-2008 (fax)

Letters & feedback are welcome.  
 To report name or address changes,  
 visit [www.NursesHealthStudy.org](http://www.NursesHealthStudy.org)

Donations & bequests to the Friends  
 of the Nurses' Health Study Fund can  
 be sent to the Channing Laboratory.