



NHS NEWS



L-R: F. Speizer, S. Hankinson, W. Willett, F. Grodstein, M. Stampfer

Dear Colleagues,

We have recently expanded our leadership team in the Nurses' Health Studies (NHS) to include several longtime contributors. Together we hope to continue working with you to pursue critical public health issues.

Our lead article this year reviews NHS research on trans fatty acids and health. These findings were pivotal for changing dietary recommendations for trans fat intake, and creating regulations that required food labeling of trans fat content.

We also summarize our research on walking for health. The NHS is a premiere resource for understanding how regular walking may benefit many aspects of health.

We continue to be thankful and amazed by your unwavering dedication to the Nurses' Health Studies. Your commitment and enthusiasm over the years have truly changed public health and improved the lives of women around the world! We look forward to many more years of collaboration.

Best regards,

The Nurses' Health Study Senior Team

Susan Hankinson, RN, ScD

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Trans Fats: From Scientific Discovery To Public Policy

In 1980, when the NHS began to ask about dietary intake, we became one of the first studies to evaluate how dietary habits relate to the future development of coronary heart disease (such as heart attacks) in women. One of the landmark findings from the NHS was the link between higher consumption of trans fatty acids (TFAs) and a higher risk of heart attacks and mortality from coronary heart disease (CHD). (Willett et al. *Lancet*. 1993;341:581-5) This link between TFAs and heart disease was so novel that the results were initially met with considerable skepticism. But other similar studies soon followed – including from our companion study of men, the Health Professionals Follow-Up Study (HPFS) – and the findings were confirmed repeatedly.

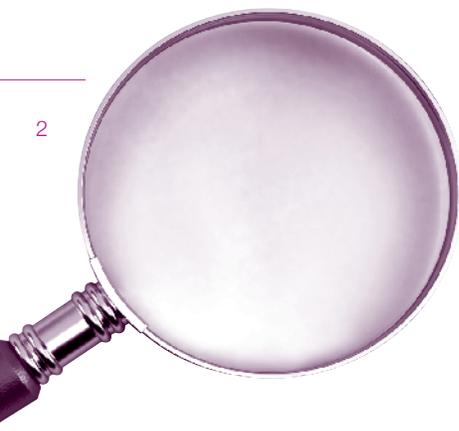


What are Trans Fatty Acids (TFAs)?

Trans fatty acids are created when vegetable oils are partially hydrogenated, a process that converts a large proportion of the naturally occurring “cis” unsaturated double

bonds in vegetable oil fatty acids into “trans” unsaturated double bonds.

A simple change from the “cis” (or “same side”) configuration of the hydrogen atom to the “trans” (or “opposite side”) configuration yields a fatty acid with very different properties. Foods with TFAs are attractive to food manufacturers because the liquid vegetable oil converts into a solid or semi-solid fat at room temperature, which is attractive for many cooking applications. Partial hydrogenation also destroys omega-3 fatty acids, so that vegetable oils are less likely to become rancid, resulting in a longer shelf life. The use of partially hydrogenated vegetable oils skyrocketed from the 1950s to the 1980s because of these commercial advantages and as a consequence of public health recommendations to replace saturated fats (e.g., butter and lard) with allegedly more healthful alternatives.



Recent Findings

Red or Processed Meats and Mortality

Studies have linked intake of red or processed meats to the development of chronic diseases, but their relation to mortality is unclear. We recently reported that one daily serving of unprocessed red meat as well as one daily serving of processed red meat were each associated with a 13 percent and 20 percent, respectively, increased risk of mortality. Red meat contains high amounts of heme iron, saturated fat, and cholesterol, which may increase risk of chronic disease. In addition, high amounts of sodium and nitrites in processed red meat have been found to increase high blood pressure, insulin resistance, and carcinogen production. Fortunately, we found that women who chose more healthful protein sources in place of red meat (e.g., fish, unprocessed poultry, nuts, legumes, low-fat dairy, and whole grains) had lower risk of mortality. (Pan et al. *Arch Intern Med.* 2012; [Epub ahead of print])

Night Shift Work and Type 2 Diabetes

The adverse effects of night shift work on women's health are gaining recognition. In our recent NHS study, we found a modestly higher (24 percent) risk of type 2 diabetes among night shift workers, compared to women without any night work. This is consistent with recent findings from the NHS II, which reported an elevated risk of developing hypertension among night shift workers, suggesting an important role of circadian disruption on their health. We also found that for every five years of night shift work, women tended to gain about 1 pound, suggesting that weight gain may partially explain the increased risk in diabetes.

Chronic circadian disruption has been associated with increases in circulating glucose and insulin, as well as decreases in leptin (a hormone that controls appetite), which may help explain the weight gain. Variable meal times and chronic sleep deprivation may also underlie a higher diabetes risk in night shift workers. (Pan et al. *PLoS Med.* 2011;8(12):e1001141)

Coffee, Caffeine, and Depression

In a recent study in the NHS, we found that women who regularly drank caffeinated coffee were less likely to develop depression, compared with women who drank one cup or less per week. Women who drank four or more cups per day were 20 percent less likely to develop depression and those drinking two to three cups of caffeinated coffee each day were 15 percent less likely to develop depression. In contrast, drinking decaffeinated coffee was not related to depression risk. Coffee drinking is the most common source of caffeine, and in our study we found no association between caffeine from non-coffee sources. These findings suggest that caffeinated coffee – one of

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U.S. Cadet Nurse Corps Update:

Former U.S. Cadet Nurse Shirley Harrow received more than 600 emails and letters from 28 states in response to the article in the 2011 NHS Newsletter. Ms. Harrow reports there is a new bill, *HR 1718: The U.S. Cadet Nurse Corps Equity Act of 2009*; a new Web site: www.uscadetnurse.org and a Facebook page. For more information, contact Shirley Harrow via the above Web site, or write to her at 65 Gladstone St., Quincy MA 02171.

the most widely consumed psychoactive substances in the world – could provide protective benefits for mood. (Lucas et al. *Arch Intern Med.* 2011; 171(17):1571-1578)

Memory Complaints and Cognitive Function

The ability to think and remember things is called cognitive function, and it is usually measured objectively with formal neuropsychological tests. In our recent NHS study, we found that women who had subjective complaints about their memory also scored lower on neuropsychological tests. Women with specific complaints – those who said they had a recent change in their memory, and those who said they had other memory difficulties (e.g., remembering a short list or following a group conversation) – were slightly more likely to have low scores on the neuropsychological assessments. Interestingly, the complaint of forgetting things from one second to the next – generally considered a part of normal aging – was not related to the objectively-determined tests, and thus may not be a major cause for concern. These findings suggest that some aspects of self-perceived memory may be meaningful reflections of

cognitive function, and women and their healthcare providers should not ignore any of their memory concerns. (Amariglio et al. *J Am Geriatr Soc.* 2011;59:1612-1617)

Alcohol and Breast Cancer Risk

Although studies have linked higher alcohol consumption to increased breast cancer risk, the role of light to moderate drinking is unclear. In the NHS, we recently found a modest increased risk of breast cancer among women who consumed as little as 5.0-9.9 grams of alcohol per day (approximately 3-6 glasses of wine per week). Risk increased with greater alcohol use – regardless of the type of alcohol (beer, wine, or liquor) consumed. In addition, alcohol intake both earlier in adult life (ages 18-40) and later (after age 40) contribute to breast cancer risk, meaning that cumulative intake averaged over time provided the most accurate way to measure risk. Moreover, a woman will need to weigh the modest risks of light to moderate alcohol use on breast cancer against its beneficial effects on heart disease to make the best personal choice regarding alcohol consumption. (Chen et al. *JAMA.* 2011;306:1884-90)

Obtaining Medicare Information

We are exploring the possibility of obtaining Medicare information on costs, diagnoses, and treatments to expand the kinds of analyses we can do in the Nurses' Health Study. To be clear, we will not be sharing any information about you with Medicare and the information we receive would be held in the same secure and confidential manner as the data you have provided to us directly. We hope to use this information to better identify optimal prevention strategies and ways to reduce health care costs. For example, for women who eat a healthier diet, is the cost of their health-care less expensive over time? If you have questions about these Medicare studies, or wish to withdraw from them in

the future, please send an email to nhsmedicare@channing.harvard.edu or write us at Medicare Studies, 181 Longwood Avenue, Boston, MA 02115.

Our Apologies

The story in the 2011 NHS newsletter about the attempts to recognize women from the WWII Cadet Nurse Corps incorrectly featured a historical recruiting poster for the Army Nurse Corp. Many nurses called and wrote to point out our error and to note that the Cadet Nurses uniform featured a beret, not the cap and tie as worn by the Army nurses. We apologize for our error.

In Brief



NHS Researcher Rulla Tamimi shows one of the mammograms submitted for analysis.

Mammographic Density

On a mammogram, the appearance of the breast varies depending on its composition: While fat appears dark, glandular tissue appears light

and is considered to be “mammographically dense.” There are a number of ways to measure mammographic (i.e., breast) density. In the NHS, we have been collecting film mammograms from participants and using a computer-assisted technique to measure mammographic density. (Following analyses, original films are returned to the lending facility within two to four weeks.) These collections are ongoing and we thank all of you who have participated in this sub-study!

Using information from these films, we have observed that mammographic density is one of the strongest predictors of breast cancer risk: Women in the highest category of mammographic density have a four- to six-fold increased risk of breast cancer, compared to women in the lowest category of risk. (Note that our measure of density is used only for research purposes and is not being used clinically.) Our current research focuses on determining exactly how mammographic density increases breast cancer risk. In addition, we are working to identify factors that may influence mammographic density in order to better understand its relationship with breast cancer.

In the NHS, for instance, we found that although high hormone levels were not associated with mammographic density in postmenopausal women, women who had both high mammographic density and high levels of the hormone estradiol were at the highest risk of breast cancer. In addition, high mammographic density was more strongly associated with more aggressive types of tumors.

Understanding predictors of mammographic density has important public health implications. For example, by identifying women with the highest risk of breast cancer, regular screening and prevention could be targeted to those who would most benefit from these strategies.

Genetic Research Update

In previous newsletters, we described our discoveries from genome-wide association studies (GWAS). Using DNA samples provided by NHS participants, these studies have uncovered potential links between hundreds of genetic regions and a range of health-related traits – from genetic factors associated with coffee and cigarette use to various cancers and other chronic diseases.

These studies have focused on common genetic variants, shared by more than 5 percent of the population. However, evidence suggests there are yet-to-be-identified rare variants associated with chronic disease.

To identify rare variants, NHS investigators are using several new technologies, that measure all of the DNA in an individual’s genome. Because this approach remains expensive, we currently are using it only in pilot projects involving several dozen participants.

Another technology called an “exome chip” measures genetic changes specifically in the regions of DNA that code for proteins. Along with other collaborators, the NHS is currently using exome chips to study endometrial cancer and type 2 diabetes, as well as hormone levels. In addition, we have proposed to use these chips to study nearly 40,000 women across different studies – half with breast cancer and half without.

Large studies will be the key to the success of these efforts. This highlights the importance of collaboration and careful data sharing with appropriate safeguards on participant confidentiality. Indeed, 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).

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



Walk for Health

Walking is the most common physical activity in older women—and likely younger women as well—and comes with a whole host of health benefits. See the table below for a summary of our research findings about walking:

WALKING AND... WHAT NHS RESEARCH SAYS:

MEMORY

Women who walked at least 1.5 hours per week better maintained their memory over time than those who did not— the walkers' memory skills were similar to women two years younger.

HEALTHY AGING

"Healthy aging" is a composite of longevity with good memory, good physical abilities, good mental health and no major chronic diseases.

Walking for approximately 1.5 hours per week increased the likelihood of healthy aging by about 15 to 20 percent compared to women who did not exercise.

OBESITY

Each hour per day of brisk walking (at least 3 mph) was associated with a 24 percent reduction in risk of obesity.

Two hours per day of standing or walking around at home was associated with a 9 percent reduction in risk of obesity.

Women who walked briskly 30 minutes per day lost 3-4 pounds six years later.

TYPE 2 DIABETES

Each hour per day of brisk walking reduced risk of diabetes by 34 percent.

Standing or walking around at home 2 hours per day was associated with a 12 percent reduction in risk of diabetes.

Sedentary behaviors such as sitting at work, driving, or prolonged TV watching were associated with increased diabetes risk.

CARDIOVASCULAR DISEASE: CORONARY HEART DISEASE AND STROKE

Among women who did not perform vigorous exercise, brisk walking for at least 3 hours per week was associated with a 35 percent reduction in risk of coronary heart disease.

Women who walked at least 3 hours per week had a 34 percent reduction in risk of stroke.

CARDIOVASCULAR DISEASE: TYPE 2 DIABETES

Diabetic women who spent at least 4 hours per week on moderate/vigorous exercise (including brisk walking) had approximately 40 percent lower risk of cardiovascular disease (CVD).

Faster walking pace was associated with a greater reduction in risk of CVD in diabetic women.

NEIGHBORHOOD DENSITY AND ACCESSIBILITY

Women tended to walk more when: they lived in residentially denser counties; they had positive perceptions of neighborhood aesthetics; they believed that their neighborhood traffic was safe; they felt their street network was well-connected.

BENIGN BREAST DISEASE

Each hour of walking per week was associated with a 9 percent reduction in risk of benign breast disease (one of the first steps in the progression to breast cancer).

BREAST CANCER

Women who walked briskly at least 5 hours per week were at 9 percent lower risk of breast cancer, compared with sedentary women.

Compared to less active women after breast cancer diagnosis, women who walked at least 3-5 hours per week were at 50 percent lower risk of death from this disease.

COLON POLYPS

Women who walked at least 5 hours per week were at approximately 20 percent lower risk of colon adenomas (polyps), compared to the least active women. Faster walking pace was associated with additional reductions in risk.

COLON CANCER

Women who walked more than 1 hour per week were at approximately 30 percent lower risk of colon cancer, compared to inactive women. Faster walking pace was associated with additional reductions in risk.

Study Updates

Big Changes for *guts*

Starting in January 2013, we will be sending one short questionnaire every year to your children enrolled in the Growing Up Today Study (GUTS). Participants in both GUTS I (born 1980-1987) and GUTS II (born 1988-1995) will receive the same questionnaire. We hope this will help participants find the time in their busy lives to give us a regular update. We also plan to refresh our online presence with a new Web site. Stay tuned this summer for more details about these changes!

Additionally, we have a brand new GUTS biorepository, starting with a saliva collection project among a subset of participants. To date we have already received over 400 biological samples! These samples, in conjunction with those contributed by many GUTS moms in the NHS, will allow us to examine genetic and hormonal markers and potentially make exciting discoveries in the future.

Nurses' Health Study **3**

As you may already know, we are now enrolling for the NHS 3, the newest phase of the NHS. More than 25,000 women have already joined! Many of the new participants were encouraged to join after hearing from long-standing members like you. Thank you for sharing with them your experiences as NHS participants. We will continue recruiting female RNs, LPNs and nursing students between the ages of 20 and 46, who are living in the U.S. or Canada, to the new Web-based study. Prominent features of the NHS 3 will include a closer look at fertility and pregnancy; occupational nursing exposures and chronic diseases; and the role of adolescent diet in the development of diseases such as breast cancer, heart disease, and diabetes. We hope you will continue encouraging your colleagues to join this new study by visiting www.nhs3.org. With your help we hope to make this new study a success!



DIABETES & WOMEN'S HEALTH

We recently began the Diabetes & Women's Health Study with the *Eunice Kennedy Shriver* National Institute of Child Health & Human Development (NICHD) and the Danish National Birth Cohort (DNBC). The goal is to investigate the long-term health of women who have had a pregnancy affected by gestational diabetes (GDM).

We have identified 6,500 women in the NHS II and more than 1,400 women from Denmark who have a history of GDM. We will be contacting these women to ask them to provide additional information on pregnancy history, diet, physical activity, and sleeping habits through a supplemental questionnaire. We will also ask them to provide blood, urine, and toenail samples.

Many women who develop GDM have higher risks of developing chronic conditions, including type 2 diabetes and cardiovascular disease. Later in 2012, women in NHS II who have been diagnosed with GDM will be asked to join this new study to help us better understand diabetes risk. If you would like to know more about the study please visit

www.dwhstudy.org or contact us at nhs2dwh@channing.harvard.edu.

ASK NHS

Q: I worry that my Nurses' Health Study answers could get back to my employer or insurance company. Do you sell or give away our answers to anyone who could link them to me?

A: We would never release identifiable information about any NHS member to employers or insurance companies. Your answers were given under a shield of confidentiality and we take that very seriously. Data are always "de-identified" and would never include names, addresses, SSNs or exact birth dates.

FOCUS ON OUR RESEARCH TEAM:

The Women's Lifestyle Validation Study

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The Women's Lifestyle Validation Study (WLVS) collects information on lifestyle factors among a subset of NHS participants to evaluate and calibrate our data collection methods. Participants have provided repeated and detailed information on their diet and physical activity throughout the year using various tools, including Web and paper questionnaires, diet recordings, as well as physical activity monitors. In addition, these participants have provided multiple blood, urine, and saliva samples. We are deeply grateful to all participants who committed their time and efforts to make this important study a success! Every member of the WLVS staff worked hard to ensure the success of the study. Two key members include:



Kate Clowry, MS, RD was one of the first members to join the WLVS staff in October 2009. As study demands grew, so did her administrative responsibilities, and she became research study manager in November

2010. Kate develops study materials, oversees study needs, and manages the day-to-day work flow of the staff. She recently competed in the American Birkebeiner, a 54-kilometer cross-country ski race in her home state of Wisconsin, and she looks forward to competing in her first duathlon this summer.



Sean Sinnott has been a member of the WLVS team since early 2010, and is the study's data manager and programmer. He plays key roles in study recruitment, data collection, and preliminary data analyses. He has worked

extensively with external contractors to produce the Harvard Automated Research Information System (HARIS), which reminds participants to complete study activities on time. Sean is currently pursuing a master's degree through the Harvard Extension School, and spends his free time cooking Indian food, ice-skating, and enthusiastically rooting for the Boston Bruins.

In Brief: Genetic Research Update continued from page 4

recognize that DNA sequence data are potentially 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.

Thanks to the detailed information on lifestyle and diet, and other factors, the NHS is working to understand how genes and the environment act together to influence health. For example, NHS investigators co-led a study on genes, physical activity, and obesity recently featured in the New York Times's "Well" blog (<http://well.blogs.nytimes.com/2011/11/23/when-fat-runs-in-the-family>).

Hearing Loss

Hearing loss is the most common sensory disorder in the U.S., afflicting over 36 million Americans. Identifying ways to prevent or mitigate this prevalent condition is a vital public health issue, but strikingly, there is only limited information on how to do so.

One of the factors most closely associated with hearing loss is, understandably, excess noise. But other potential fac-

tors that may influence risk of hearing loss include older age, analgesics, vitamins, alcohol, menopausal status, and use of postmenopausal hormone therapy.

We recently received a grant from the National Institutes of Health to prospectively examine these issues in over 150,000 participants in the Nurses' Health Studies. The goal of these investigations will be to identify factors that can be modified at an early stage to conserve hearing. To accomplish this, we will examine two different outcomes.

First, we will investigate self-reported hearing loss in all participants. We have already requested this information on previous biennial questionnaires and will continue to do so to identify new cases as they develop. Second, starting this summer, we will invite approximately 3,000 participants in NHS II with either no or mild hearing loss to undergo formal hearing tests at audiology centers near their residences. We will ask those individuals to take a baseline hearing test, followed by another test three years later, so we can assess any potential change in their hearing.

We hope that this study will expand our understanding of risk factors for hearing loss and identify new ways to conserve hearing.

These synthesized molecules are called *industrial* TFAs. Natural TFAs do exist, but are rare in the human diet, and are found mostly in meat and milk from ruminant animals such as cows, sheep, and goats. These natural TFAs are consumed at very low levels in the diet and do not appear to have important health effects. In contrast, industrial TFA consumption from partially hydrogenated vegetable oils is often much higher; they have been present in many common products, such as baked goods, deep-fried foods, packaged snacks, and vegetable shortening.

How Do TFAs Increase the Risk of Coronary Heart Disease?

Consumption of industrial TFAs increases LDL cholesterol (the “bad” cholesterol in the blood) and also lowers HDL cholesterol (the “good” cholesterol). We now know that TFA consumption also causes inflammation in the body and may have harmful effects on insulin sensitivity and even weight gain. These effects are consistent with the observed high risk of heart disease among people who have TFAs in their diets, even at relatively low levels of consumption. In fact, per calorie, the risk of heart disease associated with TFA consumption is much higher than for any other fat, including saturated fat.

Eliminating industrial TFAs is one of the most straightforward public health strategies for improving health. Using data from the NHS and other studies, our research team has estimated that near-elimination of industrially produced TFAs might prevent between 72,000 and 228,000 coronary

heart disease events in the U.S. each year. (Mozaffarian et al. *N Engl J Med.* 2006;354:1601-13)

Public Health Policy Changes

Because of the combined evidence for harm, the U.S. Food and Drug Administration ruled that, effective January 1, 2006, the nutrition labels for all conventional foods and supplements must indicate the content of TFA. This represented the first substantive change to the nutrition facts panel, which lists the key per-serving nutritional information, since 1990. This evidence also directly led to Denmark’s nationwide ban on TFA use, followed more recently by similar bans in New York City and in many other U.S. cities, counties, and states.

This increased public awareness about the harms of TFAs has reduced the average national consumption by about 50 percent between 2000 and 2009, according to estimates by the U.S. Centers for Disease Control. However, work remains to be done. Although many food products have been reformulated to reduce TFAs, many products still contain them, and subsets of the population may still be exposed to high levels from eating these foods. Additionally, TFA consumption remains high in many other countries, which still lack labeling or regulations. Nonetheless, significant progress has been made, and it mostly began with your contributions as a member of the NHS. Whenever you hear about trans fat, you can take pride in knowing that you were a key part in making this important beneficial change in diet all over the world.

Nurses’ Health Study

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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 Web site www.nurseshealthstudy.org and click the “Donate” link.

Letters & feedback are welcome.

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