



NHS NEWS

Sugar-Sweetened Beverages and Health

Sugar-sweetened beverages (SSBs), including carbonated and non-carbonated soft drinks, fruit drinks and sports drinks, are the largest source of added sugar in the diet. Although consumption of SSBs in the US has decreased in recent years, more than half of the population still consumes at least one SSB a day. A typical 12 oz. serving of soda contains 140-150 calories and approximately 35-37 grams of sugar, which is close to the recommended daily limit for all added sugar according to the Dietary Guidelines for Americans, of no more than 10% of total calories.

Over recent decades, research from the Nurses' Health Studies (NHS and NHS II) and Health Professionals Follow-Up Study (HPFS) has provided strong and consistent scientific evidence linking intake of SSBs with long-term weight gain and risk of type 2 diabetes, coronary heart disease and other cardiometabolic conditions. Most recently, we showed that SSBs also contribute to a higher risk of premature death.

Higher intake of SSBs was associated with higher risk of death from any cause, with a stronger association among women than men. Compared with drinking SSBs less than once per month, drinking two or more SSBs per day was linked with a 21% higher risk. The association was particularly strong for death from cardiovascular disease, with a modest increase for death from cancer, mostly due to colon and breast cancer.

These recent findings build on our SSB research in the cohorts over the past 15 years. In the NHS II, we found that women who increased their SSB consumption and then maintained a high level of intake gained ~17 lbs, while women who decreased their intake and then maintained a low level of intake gained only ~6 lbs. Two subsequent analyses in the 3 cohorts provide additional evidence for a link between SSB intake and long-term weight gain.

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NURSES' HEALTH STUDY PRINCIPAL INVESTIGATOR REUNION

In September 2018 we celebrated the 50th anniversary of the Channing Laboratory with a day of research presentations and talks from many of our esteemed colleagues. The day also brought NHS Principal Investigators, past and present, together for a special photo.



(L to R) Frank Speizer, MD; Susan Hankinson, RN, ScD; Graham Colditz, MD; Bernard Rosner, PhD (our Senior Bio-statistician, who has been with NHS since the beginning) and Francine Grodstein, ScD.

Recent Findings



Health Benefits of Nut Consumption

Three recent studies from the NHS, NHS II, and the HPFS have found beneficial associations of nut consumption with cardiovascular health and healthy aging.

Eating one serving of nuts (1 ounce, about a handful) five or more times a week was associated with a lower risk of coronary heart disease among both women and men. All types of nuts appeared to be beneficial. Moreover, among individuals with type 2 diabetes, greater consumption of nuts, especially tree nuts, was associated with lower cardiovascular disease incidence and mortality. This is of particular importance given that diabetes increases risk of cardiovascular disease. Additionally, in NHS, women consuming nuts (walnuts in particular) during midlife had better health and well-being as they aged.

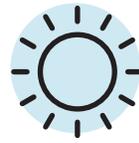
Despite nuts being an energy-dense food, nut consumption has been associated with lower weight gain and lower risk of obesity.

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What might explain these health benefits of nuts? Nuts are high in unsaturated fat, dietary fiber, vitamins (such as vitamin E and folate), minerals (such as calcium, potassium, and magnesium), and phytochemicals (such as flavonoids and phytosterols), which may in part explain

their health benefits. Accumulating evidence has shown that nuts have beneficial effects on many risk factors of chronic diseases, including improving blood lipid levels, while having anti-inflammatory and anti-diabetic effects. Finally, nuts can increase satiety and fullness, especially when consumed in place of unhealthy snacks.

Overall, Nurses' Health Studies findings indicate that frequent intake of nuts is beneficial. Incorporating nuts into your daily diet is a healthy habit!



Vitamin D and Colon Cancer

People living in sunny Southern regions of the US have lower rates of colorectal cancer than people who live in Northern areas. Because exposure of the skin to the sun produces vitamin D, it was thought that higher circulating vitamin D might be protective against colorectal cancers.

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Within the Nurses' Health Study, we have conducted numerous studies using different methods to assess vitamin D status, including measuring blood levels, assessing the amount consumed via diet and supplements, and an integrated measure of different vitamin D exposures. The overall findings of these studies

all support a beneficial association between higher vitamin D levels and lower risk of colorectal cancer. However, because colorectal cancer develops slowly over time, this apparent benefit may take a decade or more to manifest. Moreover, we found that the benefit of vitamin D may depend on the local tumor immune environment, and thus the benefits could be specific to certain subtypes of colorectal cancers. These findings suggest that the potential protection of vitamin D in colorectal cancer may involve the immune system. In addition, in the Nurses' Health Study, there was a suggestion that the benefit of vitamin D may also extend to later stages of cancer progression. Women with high vitamin D levels prior to diagnosis of colorectal cancer demonstrated substantially better survival after cancer diagnosis than those with low vitamin D levels. Similar findings have been observed in other studies

Fats, Carbohydrates, and Health

The high-fat/low-carbohydrate ketogenic diet (aka Keto) is one of most trending diets these days. The general principle of this diet is to limit carbohydrate-rich foods (e.g., grains, pasta, starchy foods) in favor of fat-rich foods. Its ability to induce weight loss in the short term explains why it has become so popular. However, the long-term effects of this diet have received very little examination.

In 2018, researchers pooled data from seven multinational prospective studies, including the Nurses’ Health Study, to evaluate the association of carbohydrate intake and risk of mortality. We found that the association between low-carbohydrate diets and mortality risk varied by the kind of fats which replaced carbohydrates. Low carbohydrate diets, with mostly animal-derived fat sources (e.g., red meat

and butter), were associated with higher mortality, whereas those with more plant-based fat intake (e.g., vegetables, nuts and whole-grains), were associated with lower mortality. So, anyone following a Keto diet should be cognizant of the fat types they are eating, and emphasize plant-based fats.

Just as the quality of fat is important, so too is the quality of carbohydrates. Replacing highly processed carbohydrates (refined grains, potato products, and sugars) with unprocessed carbohydrates (non-starchy vegetables, whole fruits, legumes and whole or minimally processed grains) provides health benefits.

In line with these results, Dr. Walter Willett, Principal Investigator of the Nurses’ Health Study II, and other nutrition experts highlighted in a special section on diet and health in *Science* published in November 2018 that “current evidence indicates that no specific carbohydrate-to-fat ratio in the diet is best.” Instead, it is the quality of the fats and carbohydrates that is important.



WOMEN’S LIFESTYLE VALIDATION STUDY

A publication from the Nurses’ Health Study analyzing the validity of dietary questionnaires was recognized as one of last year’s Top Papers in the *American Journal of Epidemiology*!

Over the years, participants have completed many dietary questionnaires within the Nurses’ Health Study. In the early 1980’s we conducted special studies to assess the validity of these questionnaires by comparing responses to NHS dietary questionnaires with detailed recordings of food intake (including weighing each serving of food for a week) and levels of nutrients in blood and fat. The results provided important documentation of the validity of these food questionnaires.

Because the U.S. food supply and eating habits have changed since the 1980’s, between 2009 and 2012 we conducted the Women’s Lifestyle Validation Study (WLVS), a far larger and more detailed validation study. In this study, 627 women completed dietary assessments using the standard questionnaires, weighed recordings of their diets, and repeated recalls of foods consumed in the previous 24 hours. Multiple blood and urine samples were also collected. The findings, published in 2018 (Yuan C. et al. *American Journal of Epidemiology*, May 2018) provided strong evidence that the dietary questionnaires continue to provide high quality information about diet. Because of the unprecedented wealth of information from the WLVS, the *American Journal of Epidemiology* recognized this report as one of their top ten papers of 2018. We owe a huge thank you to our nurse participants as this was possible only because of their amazing commitment in completing this intensive study.

Research in Brief

Fruit and Vegetable Intake and the Risk of Breast Cancer

With the wealth of information you have given us over many years, we are able to look in close detail at specific aspects of diet and their influence on health. In a recent analysis from the Nurses' Health Studies we found that women who ate more than 5 servings per day of fruits and vegetables, compared with those who ate fewer than 3 servings per day, had an overall 11% lower risk of breast cancer. Specific vegetables associated with lower risk included green leafy vegetables, cruciferous vegetables (like broccoli) and yellow and orange vegetables (like winter squash, carrots and peppers).

The inverse association with fruits and vegetables was stronger for more aggressive breast cancer sub-types that are not hormonally responsive. For estrogen receptor negative tumors, each additional 2 servings per day of fruits and vegetables was associated with a 12% lower risk. Lower risk of estrogen receptor negative tumors was seen with consumption of blueberries, strawberries, carrots, winter squash, broccoli and cauliflower. Fruits and vegetables include many bioactive components that could be contributing to this observed association. Carotenoids, such as alpha- and beta-carotene, are antioxidants that are important for the body's response to oxidative stress that may contribute to tumor initiation. Cruciferous vegetables are rich in phytochemicals that, in experimental studies, block tumor formation.

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Eating more, and more colorful, fruits and vegetables has many health benefits, and reducing

the risk of aggressive breast cancer may be one more reason to fill your plate with color.



Coffee and Health

Coffee has received much scrutiny regarding its potential health effects, good and bad. Many studies have been conducted, including in the Nurses' Health Study, and the verdict is now clear – overall, coffee appears beneficial for health. Remarkably, coffee has been associated with lower risk of diabetes, heart disease, gallstones, Parkinson's disease and some cancers, including liver and endometrial cancers, as well as with survival from colorectal cancer. These benefits are mostly not related to caffeine, and are similar for regular and decaffeinated coffee.

All of these effects add up to a lower total mortality rate in coffee drinkers. In the Nurses' Health Study, we recently published that coffee intake is associated with a healthier biomarker profile for inflammation, metabolic health and hormones, which may contribute to coffee's health effects. Despite this evidence, in 2018, California proposed to issue warning labels for coffee products based on the presumed carcinogenicity of acrylamide, a chemical found in coffee that is formed when the beans are roasted. This concern was based largely on extremely high doses given to rodents. Data from the Nurses' Health Study indicate that higher intake or blood levels of acrylamide, even in frequent coffee consumers, appear to be safe. Recently, California reversed its plan for warning labels.



GOING ELECTRONIC

In recent years, over 60,000 participants in the NHS and NHS II have switched from paper questionnaires to completing their surveys online. This switch is extremely helpful as it speeds the data processing, diminishes environmental impact, reduces errors and saves money, enabling use of precious funds for scientific discovery instead of processing paper forms. Filling out the forms online is simple, secure and easy.

If possible, we will be most grateful if you complete future questionnaires online.

“Research in Brief” continued from page 4

Vaginal Estrogen Use and Chronic Disease Risk

Many postmenopausal women experience a range of chronic genital, sexual and urinary symptoms, which have recently been labeled Genitourinary Syndrome of Menopause or GSM. Low-dose vaginal

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estrogen therapy is the most effective treatment for GSM, but it is underutilized owing to perceived risks associated with systemic menopausal hormone therapy. The FDA-issued black-box warning on low-dose vaginal estrogen discourages clinicians from prescribing the product and women from using it. However, these warnings stem from evidence generated from studies of systemic hormone therapy with much higher doses of estrogen. In

NHS, with over 18 years of follow-up, we found that vaginal estrogen use was not associated with a higher risk of cardiovascular disease or cancer. Our findings lend support to the safety of vaginal estrogen use, a highly effective treatment for GSM.

Obstructive Sleep Apnea and Diabetes Risk

Obstructive sleep apnea (OSA) is a potentially serious disorder characterized by repeated pauses in breathing during sleep. This condition is associated with common diabetes risk factors, including obesity, inflammation and insulin resistance. A recent study involving over 140,000 participants from NHS, NHS II and HPFS suggests that there may be a vicious cycle between OSA and diabetes. Participants diagnosed with OSA had about 40% increased risk of developing diabetes even after accounting for obesity. The increased diabetes risk was highest among participants with both OSA and daytime sleepiness. Conversely, participants with diabetes also had an increased risk for OSA. Given that both OSA and diabetes are highly common but often remain clinically undiagnosed, understanding the bidirectional link between them may have important clinical and public health implications for screening and co-management of both disorders.

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DATA SECURITY AND DATA SHARING

Our questionnaire website is fully encrypted and is hosted on our state-of-the-art secure web server. NHS data are never stored on portable devices. Your stored answers are identified only by study ID number, never by name.

NHS data that could be linked to individual participants are never shared with employers, insurance companies, or governmental agencies.

De-identified data may be shared with other scientists, but never in a way that it can be connected with the person who provided that information.

To help researchers understand NHS data, we developed a training database that will only have data from deceased participants, and include a few lifestyle factors and lung cancer status (no other health variables). All dates are changed, so no individual is identifiable. This training database will be posted publicly for researchers.

Study Updates

MICRO-N

The Microbiome in Nurses (Micro-N) study to collect tens of thousands of stool and saliva samples is well underway. We have been contacting participants of NHS II who indicated their willingness to participate. So far over 4,000 samples have been collected, with over 200 more being returned each week. The collection process is easy, hygienic and can be done at your convenience, with no special handling required. The samples will open a vast new opportunity for scientific study of the human microbiome. We hope if you are contacted that you will agree to participate in this exciting sub-study.

guts GROWING UP TODAY STUDY

The Growing Up Today Study (GUTS) has been following offspring of Nurses' Health Study II participants since 1996. Today, over 27,000 GUTS participants, who are now in their twenties and thirties, are helping us study health through the life course.

If your kid(s) are in GUTS, we hope you'll encourage them to visit gutslogin.org to complete the 2019 GUTS questionnaire. We hope to hear from as many GUTS participants as possible! So far, we have had a great turnout, with over 10,000 GUTS members completing the questionnaire. Long-term research of this kind is only possible thanks to the generous commitment of both GUTS and NHS II participants. Their continued participation is important to studying how factors early in life and between generations can influence health and well-being in adulthood. A list of recent GUTS-related research can be found at our website

nhs2survey.org/gutswordpress

Even if it has been a few years since your son or daughter last participated, we'd love to hear from them in 2019! If you or they have any questions please email us at guts@channing.harvard.edu



NURSES' HEALTH STUDY 3

RECRUITMENT

The Nurses' Health Study 3 (NHS3) team is renewing efforts to boost recruitment of participants in the next generation of the Nurses' Health Study. With the aim of ensuring that the cohort reflects the changing nursing profession, we especially hope to increase participation of men and racial/ethnic minorities. We are almost halfway to our goal of 100,000 NHS3 participants!

Thank you to those in NHS and NHS II who have spread the word for us. Please continue to direct any nurses or nursing students you know who may be interested (and born after 1964) to www.nhs3.org

NEW RESEARCH EFFORTS

Thanks to a number of newly funded grants, NHS3 will be deepening our focus in a few different areas.

We continue to be interested in pregnancy and related life experiences. In the coming year, we will be adding a blood sample collection among women who are pregnant or trying to become pregnant. We are interested in the connections between pre-pregnancy exposures, biomarkers during pregnancy and subsequent pregnancy outcomes.

We were awarded a grant to collect biospecimens from thousands of NHS3 participants, which will make NHS3 an even stronger resource for investigating pulmonary and cardiovascular health. Lastly, we plan to expand our work examining how the environment can impact health.

Like NHS3 on Facebook to see updates on findings, and visit our redesigned website at www.nhs3.org

Expanding research resources to better understand heart and lung diseases



In 2018, Dr. JoAnn E. Manson and Dr. Jorge E. Chavarro leveraged their complementary expertise in women's health to receive a major grant from the National Heart, Lung, and Blood Institute. This new research infrastructure grant will support the documentation of cardiovascular, lung and pregnancy-related disorders in NHS II, GUTS and Nurses' Health Study 3 (NHS3); the assessment of environmental exposures; data collection using smartphones and wearable devices; and collection of biological samples in 5,000 participants. The overarching goal is to better understand how environmental factors and reproductive life events influence heart and lung health over the life course and across generations. Dr. Manson, Professor of Medicine and Epidemiology at Harvard Medical School (HMS) and the Harvard T.H. Chan School of Public Health (HSPH) and Chief of the Division of Preventive Medicine at Brigham and Women's Hospital, started conducting research in the Nurses' Health Study more than 30 years ago and has led the NHS cardiovascular grant for the past 20 years. Dr. Chavarro, Associate Professor of Nutrition, Epidemiology and Medicine at HSPH and HMS, started his work with NHS II as a doctoral student in 2006, evaluating the role of diet on fertility. He currently leads NHS3 and collaborates on NHS II and

GUTS, evaluating how diet and lifestyle factors impact fertility, pregnancy and other reproductive life events. This new research infrastructure grant will support the documentation of cardiovascular, lung and pregnancy-related disorders in these three cohorts, the assessment of environmental exposures, data collection using smartphones and wearable devices, and collection of biological samples in 5,000 participants. The overarching goal is to better understand how environmental factors and reproductive life events influence heart and lung health over the life course and across generations.

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Findings from our cohorts have also implicated SSBs in the development of several weight-related health conditions. We found that women in NHS II who consumed at least one SSB per day had an 83% higher risk of diabetes compared to infrequent consumers. The data also suggested that half of this increase in diabetes from SSBs could be attributed to weight gain. Again, similar associations were observed in the NHS and HPFS, thus reinforcing our finding.

We also examined the relationship between SSBs and risk of coronary heart disease. Among NHS women followed for 24 years, those who consumed two or more SSBs per day had a 35% higher risk of CHD compared to infrequent consumers. These results are supported by our studies linking SSB intake to cardiovascular risk

factors, hypertension and gout. SSBs can increase diabetes and CHD risk not only through weight gain but also independently through the metabolic effects of their sugars.

The research linking SSBs to adverse health from NHS, NHS II and HPFS provides strong evidence supporting dietary recommendations to limit intake of SSBs, and to drink healthy alternatives such as water, coffee and tea. This work also has broad implications for developing new public health policies targeting SSBs and supports those already in place including SSB taxation, warning labels, regulation of SSB marketing to children and de-incentivizing sales in public spaces and in federal programs.

Friends of the Nurses' Health Study

Thanks to your continued participation, together we are discovering new ways to address major issues in women's health. From heart disease to cancer to healthy aging, we have an unprecedented opportunity to better prevent, diagnose, and treat medical conditions affecting so many around the globe. These advancements would not be possible without your faithful participation and support.

At a time when industry and federal funding have been drastically reduced, philanthropy is more important than ever. We are deeply grateful to many dedicated participants who made donations or who chose to honor their Nurses' Health Study legacy in their estate plans. As one example, last year we received a thoughtful gift from the estate of Helen Levitan. A public health nurse who served in World War II, Helen was a strong advocate of the Study and research. Her estate gift will help in our goal to sustain our research.

Make a Tax-Deductible Donation Today:

To make a gift online: Visit nurseshealthstudy.org/donations

To donate by mail: Make your check payable to Friends of the Nurses' Health Study and mail it to us using the enclosed reply envelope.

If you need assistance or would like to speak to someone about different options to financially support our work, please contact Danielle Hernon at 617-424-4334 or dhernon@bwh.harvard.edu

There are many ways that you can support the Nurses' Health Study:

- Donate cash or appreciated securities
- Make an IRA charitable rollover gift from a qualified retirement plan
- Name the Nurses' Health Study as a beneficiary of your will, trust, retirement plan, or life insurance policy
- Create a gift that provides you and/or a loved one with lifetime income

Let's Be Social!

Want to stay in touch? Like our Facebook page at facebook.com/nhs3.org

We post news on the latest NHS results a couple times a month and feature updates on recruitment for Nurses' Health Study 3 and other topics of interest. Come join us online!

Staying in touch

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



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