

Sugar-Sweetened Beverages



CONSUMPTION OF SUGAR-SWEETENED BEVERAGES has increased dramatically over the past three to four decades, in the U.S. and around the globe, paralleling trends in obesity. Research from the Health Professionals Follow-Up study (HPFS) and Nurses' Health Studies (NHS and NHS II) has provided scientific evidence on the adverse effects these beverages have on body weight and related chronic diseases. This evidence has helped shape recommendations and policies surrounding consumption of these beverages.

What are Sugar-Sweetened Beverages?

Sugar-sweetened beverages (SSBs) are defined as soft drinks (carbonated or not) and fruit drinks or energy drinks that contain added sugars (such as sucrose [table sugar], high fructose corn

syrup, or fruit juice concentrates). Collectively, they are the largest source of added sugar in the U.S. diet, with average intake levels even exceeding the American Heart Association's recommendation for all added sugar—a maximum of 100-150 calories per day. On average, a 12-ounce serving (a typical can of soda) contains 140-150 calories and approximately 35 grams of sugar—equivalent to around 10 teaspoons.

Weight Gain

One of the most direct effects of SSBs on the body is weight gain. Sugar-sweetened beverages can add weight because the liquid calories are not filling, and people do not reduce their food intake at subsequent meals.

Recently, we examined the relationship between diet and lifestyle changes and long-term weight gain at four-year intervals in healthy, lean men and women (Mozaffarian et al. *N Engl J Med.* 2011;364(25):2392-404). During each interval, participants gained an average of 3.35 pounds. Overall, this gain was strongly associated with SSBs; each additional daily serving added 1 pound over four years. Although these results

appear modest, weight gain attributable to SSBs can accumulate over time and have serious implications for more severe health conditions.

To further explore the relationship between these sugar-sweetened beverages and body weight, we examined whether SSB consumption can modify genetic risk of obesity (Qi et al. *N Engl J Med.* 2012;367(15):1387-96). This study, which was conducted among initially healthy men and women from the HPFS and NHS (and replicated in another large group), showed that greater consumption of SSBs was associated with increased genetic susceptibility to an elevated body mass index (BMI) and increased obesity risk. Individuals who consumed at least one serving of SSBs per day had genetic effects on BMI and obesity risk that were approximately twice as large as those who consumed less than one serving per month. These data provide further evidence of a causal link between SSBs and weight gain.

Continued on page 5

THANK YOU to all the participants who have completed the 2012 questionnaire!

This was the first year we offered the questionnaire online, and more than 5,000 of you took advantage of this opportunity. If you have not yet filled out your questionnaire and would like to do so online, please visit www.hpfstudy.org.

What's Inside

Benefits of Coffee.....	2	Lifestyle Validation Study.....	6
Physical Activity.....	3	Eating Patterns.....	7
Flavonoids.....	4	Focus on our Research Team.....	8
Healthy Aging.....	6		



Benefits of Coffee

HUMANS HAVE BEEN DRINKING COFFEE for at least 500 years. It is now one of the most widely consumed beverages in the U.S. and worldwide. Traditionally, high consumption of coffee has been considered to have negative health consequences, often attributed to the stimulant effects of caffeine. However, coffee is also one of the largest sources of antioxidants in the diet and contains various compounds with potential beneficial effects on glucose metabolism, inflammation and blood vessel function. Because smokers tend to drink more coffee than non-smokers, some of the negative consequences attributed to coffee in previous studies may have been due to smoking.

In the HPFS, we have extensively studied the health consequences of coffee, and have generally not found negative consequences. In fact, we have found several potential health benefits of coffee. The clearest benefits include less inflammation, lowered insulin resistance, and decreased diabetes risk. In the HPFS, men who drank four to five cups per day had a 29 percent lower risk of diabetes; those consuming six or more cups had a 54 percent lower risk. This lower risk was observed for decaffeinated coffee as well as caffeinated coffee (Bhupathiraju et al. *Am J Clin Nutr*. 2012 Nov 14 [Epub ahead of print]).

We also found no evidence of harm for coronary heart disease. As with diabetes, we even saw potential benefits with higher consumption in relation to cardiovascular mortality. For overall mortality, compared to very light coffee drinkers (those who consumed less than one cup per day), participants who drank four to five cups per day had a 7 percent lower risk of death from any cause. Those who drank six or more cups per day had even less risk—a 20 percent reduction. This apparent benefit was mainly due to

a reduced risk for cardiovascular mortality. Decaffeinated coffee consumption was associated with a small reduction in overall and cardiovascular mortality (Zhang et al. *Diabetes Care*. 2009 Jun;32(6):1043-5. Lopez-Garcia et al. *Ann Intern Med*. 2008 Jun 17;148(12):904-14).

In regards to overall cancer, coffee consumption was neutral—no perceived benefit or harm. However, coffee may have some benefits against specific types of cancer. For example, last year we reported that coffee was associated with a lower risk of developing an advanced or potentially lethal prostate cancer (Wilson et al. *J Natl Cancer Inst*. Epub 2011 May 17). One to three cups per day was associated with a 29 percent lower risk, and risk was further reduced with higher intakes. Men with at least six cups per day had a 60 percent lower risk. The findings were similar for caffeinated and decaffeinated coffee. Please note that these findings are novel and researchers in our group are now examining this hypothesis in other studies.

In addition to prostate cancer, we have found that consumption of five or more cups of coffee and tea daily was associated with a 40 percent lower risk of brain cancer (glioma), compared with no consumption (Holick et al. *Cancer Epidemiol Biomarkers Prev*. 2010 Jan;19(1):39-47). The lower risk appeared to be attributed largely to caffeine. Higher caffeine intake was also associated with a 13 percent lower risk of basal cell skin cancer, the most common type of skin cancer.

Our past research highlights other benefits of coffee. Among men, after adjustment for age and smoking, the risk of Parkinson's disease was 58 percent lower for those with high caffeine intake (the top one-fifth of men) compared to those with low caffeine intake (the bottom one-fifth). This inverse association—the more caffeine consumed, the lower the risk of Parkinson's disease—was observed with consumption of coffee, caffeine from non-coffee sources, and tea, but not decaffeinated coffee. These results suggest that caffeine is the beneficial component.

Additionally, we have found that men who consistently drank two to three cups of regular coffee per day were at 40 percent lower risk for developing symptomatic gallstone disease. Drinking at least four cups was associated with almost half the risk. As in Parkinson's disease, decaffeinated coffee was not associated with a decreased risk.

In the past several decades, the HPFS has been at the forefront of research regarding the health consequences of coffee and caffeine. The findings on diabetes, cardiovascular disease, total mortality, Parkinson's disease and gallstones have been largely confirmed by other studies. The novel findings on prostate and brain cancer require further study.

Physical Activity

THE IMPORTANCE OF PHYSICAL ACTIVITY in disease prevention has been widely studied and is generally well accepted. Regular exercise has been shown to lower the risk of diabetes, coronary heart disease, stroke, some types of cancer, and overall mortality. Using our data from the HPFS, we continue to identify additional benefits of living an active lifestyle.

Several studies in the HPFS and NHS have provided evidence that physical activity helps maintain a healthy body weight. In a recent study, we examined the effect of changes in diet and lifestyle factors, including physical activity, on long-term weight gain. We found that men and women with greater increases in physical activity gained 1.76 fewer pounds within each four-year period, compared to those with decreased activity (Mozaffarian et al. *NEJM*. 2011; 364(25): 2392-404). In another study, we looked at the interaction between a genetic predisposition to obesity and physical activity. Among more active participants, we found that obesity genes were less influential on body mass index (BMI) than among those who were inactive (Qi et al. *Circulation*. 2012; 126(15): 1821-7).

Greater physical activity provides greater health benefit but the benefits of vigorous-intensity exercise need to be investigated further—especially if too much exercise causes harm, as has been a recent concern among marathon runners and other endurance athletes. To examine this, we recently assessed the relationship between vigorous physical activity and risk of major chronic disease. We found that men who engaged in approximately three hours per week of vigorous exercise had a 14 percent lower risk of developing major chronic diseases compared to men who reported no vigorous activity. When examined individually, running, tennis, and brisk walking provided the greatest benefit for cardiovascular disease. Importantly, we also found no evidence of increased cardiovascular risk for the highest amounts of vigorous exercise, even among men in the top 1-2 percent of reported activity (corresponding to at least 10 hours per week) (Chomistek et al. *Med Sci Sports Exerc*. 2012; 44(10): 1898-905).

In addition to preventing disease, physical activity is also associated with survival benefits following a cancer diagnosis. We have found that among men with prostate cancer, those who were most active (approximately seven to eight hours per week of vigorous activity, or 12-16 hours per week of moderate activity) had a significantly lower risk of dying of any cause, as well as a lower risk of cancer death (Kenfield et al. *J Clinical Oncology*. 2011; 29(6):726-32). Moreover, participating in moderate activities like brisk walking, as well as vigorous activities such as running, was associated with lower overall mortality and improved prostate cancer survival.

Results from our studies have implications for individuals at all levels of physical activity. Individuals who are currently inactive can feel encouraged that even modest amounts of moderate activity—like brisk walking—can help maintain a healthy weight, lower the risk of disease, and extend life for cancer survivors. Active individuals may even see added benefits by including more vigorous exercise as part of their daily activity.

Flavonoids

FLAVONOIDS ARE BIOACTIVE COMPOUNDS that naturally occur in a wide variety of plant-based foods, such as fruit, vegetables, herbs, tea, and wine. Previous experimental studies have suggested that some subclasses of flavonoids might alleviate cellular damage, and thus could protect against risk of several major chronic illnesses such as cardiovascular disease, diabetes, and neurodegenerative diseases.

However, such protective effects of flavonoids have not been comprehensively examined before in large population-based studies, because early food composition databases included such a limited number of flavonoid subclasses, or types—not even 10 percent of the total flavonoids. But not long ago, the U.S. Department of Agriculture updated and expanded the flavonoid content of their food composition database. With this updated database plus

additional information from European databases, we were able to conduct more extensive research on the effects of flavonoids.

We recently conducted a series of studies to examine whether participants with greater intake of flavonoids (both total and by individual subclasses) and flavonoid-rich foods had lower risk of developing Parkinson's disease, hypertension, and diabetes in the HPFS and NHS I and II. Interestingly, anthocyanins, a subclass of flavonoids, have indeed been found to be associated with a lower risk of Parkinson's disease, diabetes, and hypertension (Gao et al. *Neurology*. 2012; 78; 1138-1145. Wedick et al. *Am J Clin Nutr*. 2012;95;925-33. Cassidy et al. *Am J Clin Nutr*. 2011;93;338-47).

Anthocyanins are water-soluble pigments that determine the red, blue, or purple color of many fruit and vegetables. Among the HPFS and NHS participants in this study, more than half of the consumed anthocyanins were from berry fruits. We found that participants with one or more cups of berry fruits each week were approximately 10-25 percent less likely to develop these chronic diseases, relative to those who ate berry fruits less than once per month. In a similar study based on the NHS only, a greater intake of anthocyanins (from berry

fruits) was also associated with slower rates of cognitive decline (Devore et al. *Ann Neurol*. 2012;72;135-43).

We also looked at other subclasses of flavonoids, including flavonols, flavan-3-ols and polymers—all found in apples. We found that men in the HPFS who ate at least five medium-size apples per month had approximately a 45 percent reduced risk of developing Parkinson's disease and 21 percent reduced risk of developing diabetes, relative to those who ate less than one apple per month.

Finally, we looked at the subclass flavonones. Citrus fruits are rich in flavonones and we know from animal and laboratory experiments that these bioactive compounds can exert anti-inflammatory effects and improve blood vessel function. In the NHS, we found that women who ate the most citrus fruits had a 10 percent reduction in risk of developing ischemic stroke (the most common type of stroke, caused by one or more blocked arteries leading to the brain).

We are just beginning to understand all of the benefits that flavonoids have to offer. With continued research, we will learn more about the effects these powerful bioactive substances have on major chronic diseases.

GOOD SOURCES OF FLAVONOIDS

Berries

Apples

Citrus fruits

Tea

Red wine

Dark chocolate

Red onions

Chronic Diseases

In addition to weight gain, SSBs are implicated in several weight-related health conditions. We examined the association between SSBs and risk of **type 2 diabetes** in healthy men followed for over 20 years in the HPFS (de Koning et al. *Am J Clin Nutr.* 2011;93:1321-7). Men who consumed about one SSB per day had a 24 percent increased risk of diabetes compared to men who consumed none, after taking into account other dietary and lifestyle factors.

These data and similar results from the NHS I and II were included in a meta-analysis of eight studies that evaluated SSBs and diabetes risk (Malik et al. *Diabetes Care.* 2010 Nov;33(11):2477-83). This meta-analysis found that individuals who consumed one or two servings of SSBs per day had a 26 percent increased risk of developing diabetes compared to infrequent consumers, thus reinforcing the HPFS findings on the harmful effects of SSBs on diabetes.

Because of our observed associations regarding weight gain and diabetes, we also examined the association between SSB consumption and development of **coronary heart disease (CHD)** (de Koning et al. *Circulation.* 2012;125(14):1735-41). In this study we found that men in the top quartile of SSB intake (who consumed about 6.5 servings per week) had a 20 percent increased risk of CHD compared to those in the bottom quartile (who consumed no SSBs).

Sugar-sweetened beverages can increase diabetes and CHD risk by contributing to obesity, in part because fructose (found in table sugar and high fructose corn syrup in relatively equal amounts) may specifically promote

abdominal obesity—a condition which is closely linked to diabetes and CHD risk. But SSBs can also increase diabetes and CHD risk through consuming large amounts of rapidly absorbable sugars, which raise blood sugar levels and can lead to inflammation and insulin resistance.

We also examined the association between SSB consumption and risk of developing **hypertension** in the HPFS and NHS I and II (Cohen et al. *J Gen Intern Med.* 2012;27(9):1127-34). We observed modest associations in men and stronger associations in women. Overall, those who consumed at least one SSB per day had a 13 percent increased risk for developing hypertension compared to those who did not consume SSBs.

Gout is a form of inflammatory arthritis that also occurs when uric acid builds up in blood (and fructose increases the production of uric acid). We examined the association between SSB consumption and development of gout and found that men who consumed two or more SSBs per day had an 85 percent greater risk of developing gout compared to infrequent consumers (Choi et al. *BMJ.* 2008;336(7639):309-12).

Conclusion

Taken together, this body of research provides strong evidence that intake of sugar-sweetened beverages should be limited. Replacing these beverages with water, tea, or coffee will promote health and weight control and reduce risk of related chronic diseases. Our findings have broad implications for developing new public health strategies and policies targeting SSBs and support those already underway.

Tissue Block Collection

Over the past several years, we have started collecting the tissue specimens from men in the HPFS who have been diagnosed with cancers of the prostate, bladder, colon, pancreas, and brain, as well as colon polyps. To date, we have collected specimens for almost 5,000 men, making it the largest tumor tissue biorepository within a male cohort study in the world.

We work with molecular pathologists to evaluate tissue biomarkers on these specimens and classify each cancer based on molecular subtypes. We then link this information with lifestyle, medical, and outcome information from HPFS participants. Combining this information will help us to identify factors that cause or prevent cancer and to determine the best treatment for each person with cancer.



Healthy Aging

Medical research has been very successful at identifying ways to extend the lifespan. However, as our population ages, we must also understand how to extend the “healthspan”—i.e., the maintenance of health, vigor, and quality of life with aging. In the NHS, we have been focusing our efforts to investigate healthy aging. We have found that lifestyle modification, such as increased physical activity (including walking), moderate alcohol intake, and consumption of flavonoids (especially anthocyanins, common plant pigments found in berries—see page 4) may help to maintain memory in aging, while some chronic conditions, such as type 2 diabetes, can make memory worse with aging. In additional research, we have found that those with lower body mass index (BMI) or greater levels of physical activity seem more likely to survive to older ages with exceptional health and well-being (often defined by a combination of intact memory, good physical function and physical health—i.e., no major chronic diseases—and good mental health). Thus, we are beginning to unravel the mysteries of successful aging with our research efforts.

We hope to expand this type of research to the HPFS participants by evaluating lifestyle and biologic factors which could help prolong health through old age. For example, we may be contacting some HPFS participants to try computer-based assessments of memory; this is a new method of research which allows participants to take several memory assessments using just their home computers. We will also be asking more questions about aging on the upcoming HPFS questionnaires. Together, these new projects will expand the contributions of the HPFS cohort, and enable critical new discoveries to help all of us age more healthfully!

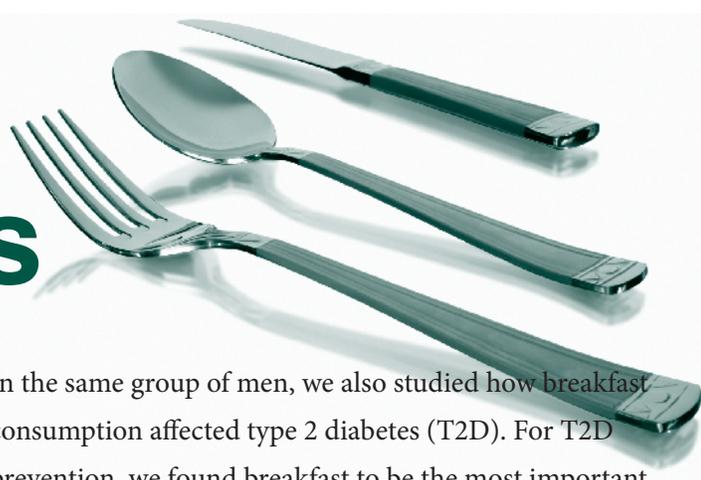
Lifestyle Validation Study

The Men’s Lifestyle Validation Study (MLVS), conducted by the Harvard School of Public Health in collaboration with the National Cancer Institute (NCI), collects information on lifestyle factors among a subset of HPFS participants and the Harvard Pilgrim Health Care Insurance Company (HPHC) clients. We have 693 participants currently enrolled; 499 from the HPFS and 194 from the HPHC. These participants, ages 46-82, regularly provide detailed information on their diet and physical activity throughout the year. Participants are completing Web and paper questionnaires, collecting meal-by-meal diet recordings, and using physical activity monitor over periods of seven days. In addition, these participants provide multiple blood, urine, and saliva samples. Data collection for the MLVS is expected to be completed by the end of September 2013.

Assessing diet and physical activity data in large epidemiologic studies is difficult, and the various methods used to assess these data can lead to measurement errors. Through the use of multiple types of measurements, the MLVS will evaluate and correct these errors, making it easier to interpret the published literature on diet and health. The NCI has invested considerable resources in this research because the outcomes will provide critical information to help evaluate and improve methods that scientists use to assess diet and physical activity. This in turn will impact future diet and physical activity recommendations for prevention of diseases in men worldwide. A parallel validation/calibration study among 760 women from the NHS (the Women’s Lifestyle Validation Study, or WLVS) has recently been completed.

Please accept our deep gratitude to all of you for graciously committing your time and efforts to make this very important study a success!

Eating Patterns



MOST STUDIES CONDUCTED ON EATING

FREQUENCY—i.e., the total number of meals and snacks consumed per day—and colorectal cancer have suggested that the greater the eating frequency, the higher the colorectal cancer risk. These studies were mostly case-control studies subject to recall bias; hence, no firm conclusion could be made.

Contrary to those findings, in the HPFS we found that over a 14-year period, men who ate frequently (five to eight times per day) did not have a higher risk of colorectal cancer when compared to men who ate less frequently (three times per day). In fact, frequently eating healthier foods (high intakes of fruits, vegetables, legumes and nuts; moderate intakes of low-fat dairy products; low intakes of animal protein and sweets, as well as reduced sodium intake) appeared to even lower colorectal cancer risk, especially for men with higher insulin sensitivity. It is possible that frequently eating healthier foods may keep the insulin concentration at a low, flat level rather than at the high spikes resulting from consumption of fewer unhealthy meals (Mekary et al. *Am J Epidemiol.* 2012 Apr 1;175(7):664-72).

In the same group of men, we also studied how breakfast consumption affected type 2 diabetes (T2D). For T2D prevention, we found breakfast to be the most important meal of the day. Eating breakfast appeared to have independent metabolic effects over and above the role of dietary quality and its protective association with weight control. More precisely, we found that over a 16-year period, there was a 21 percent increased risk of T2D in men who skipped breakfast compared to those who ate breakfast, regardless of their body mass index (BMI) and their diet quality.

In addition to skipping meals, eating too frequently may be risky as well. We found that both decreased eating frequency (one to two times per day) as well as increased eating frequency (four times per day) or snack consumption were associated with increased T2D risk, but these associations appeared to be mediated by higher BMI (Mekary et al. *Am J Clin Nutr.* 2012 May;95(5):1182-9). We are now assessing the association between regular breakfast consumption and type 2 diabetes in the Nurses' Health Study.

Your Privacy

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 contribute to the large international effort to identify the genetic variants underlying the inherited predisposition to cancer, heart disease, diabetes, and other diseases. However, we recognize that DNA sequence data are potentially 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 hpfs@hsph.harvard.edu or write to us at HPFS, 677 Huntington Avenue, Boston, MA 02115.

FOCUS ON OUR

ResearchTeam

A team of research assistants—who hail from as far as Ireland, Greece, and Russia, and as close as New England—are responsible for following up with participants’ reported diseases and deaths. Once a specific condition or disease is reported on the main HPFS questionnaire, each staff member receives notification regarding his or her assigned disease(s). They work diligently to track down medical records, enter questionnaire responses into the database, answer questions, and prepare records for coding and data entry.

Each research assistant works closely with research investigators to ensure data integrity and accuracy. Whether they have worked here for three years or 14, they’re all committed to keeping the HPFS a landmark study!



*Back row: Lauren McLaughlin, Siobhan Saint Surin, Adam Summerfield
Middle row: Cheryl Jones, Eleni Konstantis, Allison Gordon
Front row: Elizaveta Gazeeva, Ann Fisher*

We appreciate your valuable participation!

We are truly grateful for all you have provided.

To report an address change, make a comment, or provide feedback, please email the project coordinator at hpfs@hsph.harvard.edu or contact us at the address or phone number below:

Walter C. Willett, MD, DrPH
The Health Professionals Follow-Up Study
677 Huntington Ave.
Boston, MA 02115
(617) 998-1067

VISIT US ONLINE AT

www.hsph.harvard.edu/hpfs