Health Professionals Follow-Up Study
NEWSLETTER

HARVARD T.H.CHAN SCHOOL OF PUBLIC HEALTH WINTER 2021

Dear Colleagues,

Thanks to your invaluable contributions, HPFS remains the largest and most detailed long-term study of men's health. In this year's newsletter, our feature article focuses on how healthy lifestyle habits prolong living free of chronic diseases. Also, we highlight our participation in COVID-19 research, along with our discussion with HPFS participant, Dr. Clifford Scott. Lastly, we invite you to visit our website at https://sites.sph.harvard.edu/hpfs/ where you can find our most recent updates and announcements, as well as a list of all published articles using HPFS data. Thank you for your tireless support over the past 35 years!

Walter C. Willett, M.D., Dr. P.H. and Lorelei A. Mucci, MPH, ScD, Principal Investigators

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Five healthy lifestyle habits prolong life free of chronic diseases

- Investigators have studied the effect of five healthy habits on longevity: eating a healthy diet, exercising regularly, keeping a healthy body weight, not drinking too much alcohol, and not smoking
- Men who practiced all five habits gained about seven years of life free of chronic diseases, women who practiced all five habits gained about ten years.

With the improvement of living standards, diets, smoking prevention, and medical treatments, Americans' life expectancy at birth has risen over time, from 39.4 years in 1880, to 62.9 years in 1940, and to nearly 78.9 years in 2019. Still, Americans have a shorter life expectancy compared with other high-income countries, including Japan, Canada, and Norway, and life expectancy has actually declined in three of the last four years. Based on data from the Health Professionals Follow-Up Study (HPFS) and the companion Nurses' Health Study (NHS), we found that Americans could greatly improve total life expectancy by engaging in healthier lifestyle (Circulation 2018: 345).

Another important feature of longevity is living free of disabilities or chronic diseases. The aging of our population has led to a high prevalence of chronic diseases such as diabetes, cardiovascular disease, and cancer, and people with these chronic diseases have a shorter life expectancy than those without these conditions. Previous studies based on HPFS and NHS

indicated that up to 90% of diabetes (N Engl J Med 2001:790), 80% of coronary heart disease (N Engl J Med 2000:16), 70% of cardiovascular mortality, and 50% of cancer mortality (Circulation 2018: 345) could be avoided by adoption of healthy diets and lifestyles.

Using data from up to 28 years of follow-up in HPFS and 34 years of follow-up in NHS, we analyzed the combined effect of healthy lifestyle factors on life expectancy free of cancer, cardiovascular disease, and type 2 diabetes and survival expectancy after diagnosis of diseases. Specifically, the five healthy lifestyle behaviors were not smoking, eating a healthy diet (diet score in the top 40 percent of each cohort), regularly exercising (30+ minutes a day of moderate to vigorous activity), keeping a healthy body weight (18.5-24.9 kg/m), and moderate alcohol consumption (5-15 g/day for women, 5-30 g/day for men).

We found that a healthier lifestyle was associated with a greater total life expectancy and life expectancy free of cancer, cardiovascular disease, and diabetes. Adherence to five healthy lifestyle factors was associated with approximately 7.6 additional years of life without major disease in men and 10 additional years of life without major disease in women compared with participants with no healthy lifestyle factors.

Other findings included:

- Life expectancies free of cancer, cardiovascular disease, or diabetes separately: among men, compared to those with no healthy lifestyle factors, participants with four to five healthy lifestyle factors gained 6.0 more years without cancer, 8.6 more years without cardiovascular disease, or 10.3 more years without diabetes.

- Survival expectancies after diagnosis of chronic diseases: After diagnosis, half of patients with cancer who adopted four or five healthy lifestyle factors survived up to 22.9 years, whereas half of patients with cancer who adopted zero healthy lifestyle factors survived only up to 11.0 years; with similar differential survival probability for people with cardiovascular disease and diabetes.

- Life expectancies associated with individual lifestyle factors: the lowest proportions of years of life expectancy free of cancer, cardiovascular disease, or diabetes as a percentage of total life expectancies were observed among men who smoked heavily (≥15 cigarettes/day) and obese men and women (BMI≥30)

- Importantly, adopting healthy lifestyles did not increase the years of life burdened with chronic disease, but instead added years of life free of chronic disease.

The findings suggest that promotion of a healthy lifestyle would help to reduce the healthcare burdens through lowering the risk of developing multiple chronic diseases, including cancer, cardiovascular disease, and diabetes, and extending disease-free life expectancy. Public policies for improving food and the physical environment conducive to adopting a healthy diet and lifestyle, as well as relevant regulations (e.g., smoking ban in public places or trans-fat restrictions), are critical to improving life expectancy, especially life expectancy free of major chronic diseases.

The United States is one of the wealthiest nations worldwide and has invested more money on health than any other countries in the world. However, the life expectancy at birth of the US population only ranked 31st in the world in 2015, which was shorter than people in most other high-income countries and around four years shorter than the Japanese who had the longest life expectancy in 2015. Our findings highlight the importance of prevention of chronic disease morbidity and mortality by adopting healthy lifestyles. Prevention, through diet and lifestyle modifications, has enormous benefits in terms of reducing occurrence of chronic diseases, improving total and healthy life expectancy, and reducing healthcare cost.

Li, Y., J. Schoufour, D. D. Wang, K. Dhana, A. Pan, X. Liu, M. Song, G. Liu, et al. (2020). Healthy lifestyle and life expectancy free of cancer, cardiovascular disease, and type 2 diabetes: prospective cohort study. BMJ 368: l6669

Discussing the 2021 newsletter, pandemic edition.
Clockwise from top-left corner: Liza Gazeeva, Betsy Frost-Hawes, Walter Willett, Lorelei Mucci

Interview with Dr. Walter Willett

This year marks a 35th anniversary of the HPFS. We talked with Dr. Walter Willett, the study's founder and Co-Principal Investigator, about his career, research, and the history of the study.

How did you begin your medical career and interest in nutrition?

Food was always central to our family as the Willetts had been dairy farmers in Michigan for generations, and my father did research on improving milk production in dairy cattle. While growing up, I won many blue ribbons in 4-H club for outstanding vegetables and helped pay my tuition at Michigan State by growing sweetcorn and tomatoes commercially. I studied physics and food science; this increased my interest in the health effects of foods, so I went to medical school and then specialized in internal medicine at Harvard. Caring for patients made me realize that it would be far better to prevent the conditions I was seeing, such as heart disease, diabetes, and cancer, so I obtained a masters degree in public health and then a doctoral degree in epidemiology. This provided tools that I needed to begin to connect what we eat with the long-term consequences of our choices.

How did you start the HPFS and in what year? What motivated you to start this study?

While I was a doctoral student working on a study of oral contraceptive use and breast cancer, the Nurses' Health Study, I realized that we had the potential to expand the questionnaires to include information on diet and physical activity. After extensive pilot testing, we began collecting dietary data in 1980. As that study included only women, my colleagues and I began developing plans for a parallel study to look at diet and major health outcomes in men, and with the help of the American Dental Association and other professional organizations, we launched the Health Professionals Follow-Up Study in 1986.

What keeps you motivated with your continued research with this study?

We have learned a great deal from the HPFS, but there is still much more to learn. Only now after more than 30 years are we able to have a good look at risk factors for some cancers and later-life conditions like dementia or Parkinson's disease. Also, new molecular tools are becoming available to understand more deeply how we can best stay well as we get older, and we can apply these to the blood and tissue samples we have collected over the years.

Are there findings from the study that have changed your lifestyle?

I grew up with the traditional Midwestern diet; lots of mashed potatoes, beef, and gravy. My diet has changed enormously, now emphasizing healthy fats like olive oil and what we call a plant-forward way of eating. I also make it a point to be physically active almost every day.

Have there been findings that have surprised you?

When we started our work, most people thought that diet was somehow related to risk of heart disease, but I have been surprised that the risk of almost every disease that we study is influenced by diet. Also, when we started, our general belief was that saturated fat was the main contributor to risk of heart disease, but we learned that trans fat was even worse, and unsaturated fats could reduce our risk of heart disease. Saturated fat is about equal to refined carbohydrate with respect to risk of heart disease.

With the increasing age of the current cohort, where do you hope to see your research going in the future?

This is giving us the opportunity to study healthy aging, how we can increase our chances of adding healthy years to our lives, and to look at the effects of our lifestyle in our 40's and 50's on health outcomes many decades later.

Has the pandemic affected the research in any way?

Fortunately, much of our research had already shifted to being online, and the pandemic has accelerated those changes. In collaboration with others, we have added a COVID component to the HPFS to study consequences of the pandemic. The importance of having adequate PPE for health care providers was an early finding, and we expect to learn more.

Any interesting anecdotes you may have regarding

this study and/or from participant responses?

Our favorite participant response was from someone who, after repeated mailings, had not returned a questionnaire. We had sent him a certified letter to be sure we were reaching him. Upset by the inconvenience of having to go to the post office to pick up the certified letter, he sent us back a brick with our self-return postage paid stamp. We sent him a note conveying the appreciation of our Dean for his contribution to our new building fund. Taking this in good humor, he has been among our best respondents since that time!

On a personal level, what does a typical day look like for you for meals and activity?

Before the pandemic, I would usually start the day with a few exercises, have some steel-cut oats with yogurt, nuts, and fruit, and ride my bike to work. Lunch would usually be a large salad with tofu and nuts, and I would ride home to dinner with fish, chicken or some plant protein source and lots of vegetables. After dinner usually means catching up with emails. Of course, the pandemic has turned our lives upside down, but I am fortunate to be able to work from our lakeside cottage in New Hampshire, where I can hike and ride my bike in the hills and mountains.

Would you like to add any words of wisdom to the HPFS participants?

First, I would like to convey my enormous gratitude to the HPFS participants, who have shared their personal experiences so we can all learn from them. People everywhere around the world have learned so much from this. I would encourage all our participants to take advantage of what we have learned about healthy eating and active living, and enjoy every day that we have been given.

Research Highlights

Consuming More Olive Oil is Associated with Less Heart Disease in Americans

Olive oil has been traditionally used as the main culinary fat and cooking oil in Mediterranean regions, and, recently, has become popular worldwide.

Compared with men in the HPFS who consumed no olive oil, those who consumed at least one-and-a-half teaspoons of olive oil per day had a 14% lower risk for cardiovascular disease, and an 18% lower risk for coronary heart disease. Olive oil was better in reducing cardiovascular disease than most animal fats and margarine, although other vegetable oils appeared to have similar benefits in this study population. Findings support current recommendations to replace saturated and animal fats with unsaturated plant oils, such as olive oil, for the prevention of cardiovascular disease.

Photo credit: Fabio Balbi/Shutterstock.com

Guasch-Ferré M, et al. Olive Oil Consumption and Cardiovascular Risk in U.S. Adults. J Am Coll Cardiol. 2020 Apr 21;75(15):1729-1739.

Red Meat Intake and Risk of Coronary Heart Disease Among US Men

In controlled-feeding studies, red meat consumption increases low density lipoprotein (LDL, i.e. bad cholesterol) compared with healthy plant protein sources. In several epidemiologic studies, high consumption of red meat, especially processed red meat, was associated with higher risk of mortality and major chronic diseases. Men are at higher risk of coronary heart disease. As such, we sought to examine red meat consumption and coronary heart disease within the HPFS cohort. During 30 years of follow-up of HPFS participants who were initially free of cardiovascular disease, 4,456 newly diagnosed cases of coronary heart disease were documented. Compared to men with low intake of red meat, men with a higher intake of red meat were at 11-15% higher risk of developing coronary heart disease. Substituting plant protein sources, such as nuts, legumes, and soy, for red meat was associated with 14-17% lower risk of CHD. These findings support a health benefit for men to limit red meat consumption and to replace red meat with plant-based protein sources.

Al-Shaar L., et al. Red meat intake and risk of coronary heart disease among US men: prospective cohort study BMJ 2020; 371 :m4141

Mediterranean Diet and Cardiometabolic Disease Risk

The human microbiome is the collection of bacteria, viruses, and other organisms that reside in and on our bodies. In the past decade, the study of the human microbiome has been revolutionized by advancements in sequencing-based technologies. From 2011 to 2013, 307 HPFS participants donated up to four stool samples for studies of the gut microbiome. Using new gene-sequencing technologies to identify specific species of bacteria, the beneficial metabolic effects of the Mediterranean diet were particularly strong in a subgroup of participants defined by the depletion of specific bacteria in the stool samples. This initial finding supports the premise that dietary interventions or recommendations for cardiometabolic disease prevention might be tailored to an individual's microbial profile, and encourages further research in the area.

Wang D, et al. The gut microbiome modulates the protective association between a Mediterranean diet and cardiometabolic disease risk. Nature Medicine. 2021 Feb 11.

Vitamin D-related Biomarkers Linked with Reduced Mortality Among Patients with Colorectal Cancer

Members of our research group earlier reported that, among patients with colorectal cancer, higher vitamin D levels in blood were associated with lower overall mortality. Building upon this finding, we investigated the relationship between vitamin D binding protein – which attaches to vitamin D and helps transport metabolites of the vitamin – and survival among patients with colorectal cancer using blood samples provided by participants in the HPFS and NHS collected in the 1990s. Men and women with higher levels of vitamin D binding protein had a significant decrease in overall mortality and mortality relating to colorectal cancer, compared with those with lower levels of the protein. These findings provide further insight on the potential benefit of vitamin D in treating colorectal cancer.

Yuan C, et al. Prediagnostic Circulating Concentrations of Vitamin D Binding Protein and Survival among Patients with Colorectal Cancer. Cancer Epidemiol Biomarkers Prev. 2020 Nov;29

Photo credit: Foxys Forest Manufacture/Shutterstock.com

Reproducibility and Validity of a Semi-quantitative Food Frequency Questionnaire in Men Assessed by Multiple Methods

Since the beginning of the HPFS cohort in 1986, participants have been completing the Semiquantitative Food Frequency Questionnaire (SFFQ) to estimate their food consumption over the past year and updating it every four years. In 1986, we documented strong validity of this questionnaire, but over these years, new food items have been added, and we have modified the questionnaire to capture the changes in food supply and eating patterns. Therefore, we evaluated the performance of this updated questionnaire in estimating food intake in a new study including a random sample of HPFS participants. The 626 participants were also asked to complete seven-day dietary records twice, completed 24-hour recalls of food intake four times, and provided two fasting blood samples and four 24-hour urine samples to measure important biomarkers of diet. The updated SFFQ, whether complete on paper or online was found to have strong validity for estimating the long-term intake of a wide range of nutrients when compared to the biomarkers of intake or the other more expensive and time-consuming methods. This SFFQ will continue to be used for assessing diet in Harvard cohorts.

Al-Shaar L, et al. Reproducibility and Validity of a Semi-quantitative Food Frequency Questionnaire in Men Assessed by Multiple Methods. Am J Epidemiol. 2020

Interview with HPFS Participant

To celebrate thirty-five years of the Health Professionals Follow-Up Study (HPFS), we recently had the privilege of talking with one of our long-standing participants, Dr. Clifford Scott, who has been a dedicated participant since 1986 when the study began.

Dr. Scott is a highly experienced optometrist with a Master's in Public Health from Harvard T.H. Chan School of Public Health. His career combined private, clinical, teaching, and administrative positions culminating as President of the New England College of Optometry. While leading this institution, his public health perspective helped him modify the academic and clinical curriculum from its oculo-centric focus towards a more comprehensive approach.

As we reflected back on these 35 years, we discussed his decision to participate in the HPFS. Dr. Scott was fascinated by the thesis of this study in following a large group of participants longitudinally. Being from the Boston area, he was familiar with the Framingham Heart Study and knew "all the good that came out of the years they had been monitoring their participants and identifying profiles that improve people's health."

Dr. Scott has been an active and reliable participant, completing each questionnaire on paper or online, as well as participating in many sub-studies, such as the Men's Lifestyle Validation Study (MLVS). Additionally, he has provided multiple biological samples. We were impressed with his dedication while participating in one aspect of the MLVS study which required documenting his entire food intake over one week. While out to eat one evening at a local Thai restaurant, he convinced the chef to write out all the ingredients of his signature Pad Thai dish only after agreeing he would not share the recipe!

We asked Dr. Scott what keeps him motivated to be such an active participant. He looks forward to the feedback in the newsletters and the research from the publications as personal motivational factors. "The feedback I get is excellent. I respect the results knowing how comprehensive and professional the surveys are." He also added "I'm trying to live to be 100, which means making choices every day about what to eat, what to do, and the lifestyle and mental health adjustments required to cope with COVID and other stresses of life." Due in part to Dr. Scott's association with the HPFS, he has maintained a healthy and active lifestyle, including running marathons for many years which, as he has aged into his mid-seventies, has shifted to rowing and handball.

We also asked Dr. Scott about some recommendations and suggestions he may have for improving the study. He feels that the addition of the online survey has made it more user friendly. He did suggest that the newsletter be published more frequently than every two years. "I think the older you get, the more important the feedback becomes. Some of it is, 'Okay, I am still here, that's good. So why am I still here?' And then you compare your modifiable behaviors and those of the other people still in the study." He also suggested that we make our website and publications using the HPFS research more available and accessible to the study participants.

As a message to fellow HPFS participants, Dr. Scott says "Congratulations for participating and staying so long! I think the data that you are providing are incredibly valuable!"

We are so grateful to Dr. Clifford Scott and all of our dedicated HPFS participants for their continued engagement and commitment to the Health Professionals Follow-Up Study for the past thirty-five years and counting!

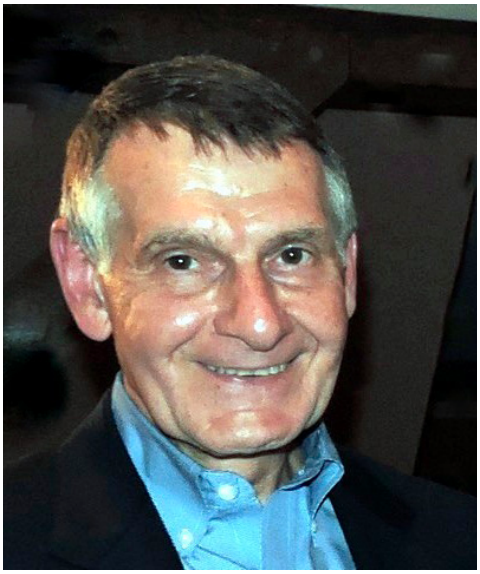

Photo courtesy of Dr. Clifford Scott

COVID-19

While the COVID-19 coronavirus pandemic continues to grip the US, many HPFS participants have participated in studies related to understanding the short and longer-term health effects of the pandemic. Almost 4,500 men in HPFS have completed an online questionnaire on COVID-19, examining its effect on overall health, mental and physical health, eating habits, physical activity, and other health factors. We have just sent out a follow-up online questionnaire.

Over 1,200 men in HPFS have joined our COVID Symptom Study which uses a free app to log experiences related to the COVID-19 pandemic. This study is now following 4.5 million people from across the U.S., the United Kingdom, and Sweden. The app is providing critical real-time information on COVID-19 symptoms, baseline health factors, infection status, and clinical outcomes to researchers every day. Information about those who remain symptom-free also supports better understanding of COVID-19. The U.S. research is being led by HPFS investigator Andrew T. Chan, MD, MPH, a physician at Massachusetts General Hospital and Professor in the Department of Immunology and Infectious Diseases at Harvard T.H. Chan School of Public Health.

If you have not joined the study, we invite you to do so now. Anyone can take part by downloading the free COVID Symptom Study app on iOS from the Apple App store or Android from the Google Play store. As HPFS participants, we ask that you use the same e-mail address that you use to connect with us. The ability to link data from this app to information that you have already contributed through the HPFS will be invaluable to improving our understanding of risk factors for COVID-19 and outcomes from the disease.

This study has already resulted in many important research papers which have helped scientists, as well as the public health community, understand more about COVID-19. These are a few of our most important papers that have been published:

Chan, A.T., et al. The COronavirus Pandemic Epidemiology (COPE) Consortium: A Call to Action. Cancer Epidemiol Biomarkers Prev. 2020 Jul; (29) (7): 1283-1289

Drew, D. A., et al. Rapid implementation of mobile technology for real-time epidemiology of COVID-19. Science. 2020 Jun 19; 368 (6497): 1362-1367

Nguyen, L.H., et al. Risk of COVID-19 among front-line health-care workers and the general community: a prospective cohort study. Lancet Public Health. 2020 Sep 1; 5 (9): E475-E483

Menni, C., et al. Real-time tracking of self-reported symptoms to predict potential COVID-19. Nature Medicine. 2020 May 11; 26: 1037–1040

Varsavsky, T., et al. Detecting COVID-19 infection hotspots in England using large-scale self-reported data from a mobile application: a prospective observational study. Lancet Public Health. 2021 Jan 1; 6 (1): E21-E29

Zazzara, M.B., et al. Probable delirium is a presenting symptom of COVID-19 in frail, older adults: a cohort study of 322 hospitalized and 535 community-based older adults. Age and Aging. 2021 Jan; 50 (1): 40–48

Lee, K.A., et al. Cancer and Risk of COVID-19 Through a General Community Survey. The Oncologist. 2021 Jan; 26 (1)

Ni Lochlainn, M., et al. Key predictors of attending hospital with COVID19: An association study from the COVID Symptom Tracker App in 2,618,948 individuals. Medrxiv.

Sudre, C.H., et al. Attributes and predictors of Long-COVID: analysis of COVID cases and their symptoms collected by the Covid Symptoms Study App. Medrxiv.

Sudre, C.H., et al. Symptom clusters in Covid19: A potential clinical prediction tool from the COVID Symptom study app. Medrxiv.

Bowyer, R.C.E., et al. Geo-social gradients in predicted COVID-19 prevalence and severity in Great Britain: results from 2,266,235 users of the COVID-19 Symptoms Tracker app. Medrxiv.

Molteni, E., et al. SARS-CoV-2 (COVID-19) infection in pregnant women: characterization of symptoms and syndromes predictive of disease and severity through real-time, remote participatory epidemiology. Medrxiv.

Research Highlights *(continued)*

Sugar-sweetened Beverages and Health

Research from the HPFS has provided strong evidence linking intake of sugar-sweetened beverages (SSB) with long-term weight gain and risk of type 2 diabetes, coronary heart disease, hypertension, cardiovascular disease risk factors and other cardiometabolic conditions such as gout. In a recent analysis among over 138,000 participants in the HPFS and NHS, greater consumption of SSBs was associated with higher risk of death from any cause in a dose-response manner. Compared with drinking SSBs less than once per month, drinking two or more per day was associated with a 21% higher risk of overall mortality and a 31% higher risk of death from cardiovascular disease. Replacing SSBs with artificially sweetened beverages was associated with a moderately lower risk of death, suggesting that ASBs may be a useful replacement for SSBs among heavy SSB consumers with the ultimate goal of switching to water.

Malik, V, et al. Long-term consumption of sugar-sweetened and artificially sweetened beverages and risk of mortality in US adults. 2019. Circulation 139(18): 2113-2125

Germline Genetic Factors and Prostate Cancer Risk

Prostate cancer has one of the strongest inherited genetic components of any cancer. Epidemiologic data including from the HPFS has shown that men with a family history of prostate cancer in fathers or brothers are at increased risk of prostate cancer, including aggressive forms of disease. HPFS investigators have participated in international consortia to identify the specific genetic variants associated with prostate cancer. In the latest study, HPFS participants were part of a multiethnic study among 107,000 prostate cancer patients and 127,000 men without prostate cancer. This analysis identified 86 new inherited genetic variants, bringing the total of validated genetic markers associated with prostate cancer to 269. Combining all of the variants together into a genetic score, men in the top 10% of the score had a five-times greater risk of prostate cancer compared to men of average genetic risk. The results of this study may help to identify the biologic causes of prostate cancer and to use the genetic risk score for personalized early cancer detection.

Conti DV, et al. Trans-ancestry genome-wide association meta-analysis of prostate cancer identifies new susceptibility loci and informs genetic risk prediction. Nat Genet. 2021 Jan 20

Privacy

Large studies will be the key to the success of these efforts to understand the role of genes. 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 studies of DNA and disease risk be deposited in a controlled-access database. Any data sent to this database will not contain any personal identifiers (e.g., 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. The goal is to develop more effect prevention and treatment strategies. However, we recognize that DNA sequence data are potentially sensitive. If you have any question about these studies (called GWAS or sequence 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.

Contact Health Professionals Follow-Up Study

677 Huntington Avenue

Boston, MA 02115

(617) 998-1067 (phone)

(617) 384-5400 (fax)

To report name or address changes, please email the project coordinator at hpfs@hsph.harvard.edu or visit https://sites.sph.harvard.edu/hpfs/.

Letters and feedback are welcome.