

HPFS NEWS

UPDATES FROM THE HEALTH PROFESSIONALS FOLLOW-UP STUDY
WINTER 2025 • HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

HPFS Celebrates 40 years!

February 2026 will mark 40 years of the Health Professionals Follow-Up Study! To celebrate the HPFS 40th Anniversary and your valuable continued participation, we are planning to host an online event (zoom) and also exploring the idea of in-person celebration in Boston and perhaps Florida and California. We would appreciate your opinions and interests about attending an in person event (most likely in the spring 2026) as well as its scope. Unfortunately, due to limited funding, we cannot cover any expenses for participants to attend an in-person event. Some of you may have already received an email inquiry into this 40th Anniversary event. Please feel free to write, call, or email us your thoughts/suggestions (at hpfs@hsph.harvard.edu or 617-998-1067).

An Ultra Brief History of HPFS 40 Years and Going Strong

The Health Professionals Follow-Up Study (HPFS) was founded by Walter Willett and colleagues in 1986, ten years after the Nurses' Health Study (NHS) was begun. NHS, a women's only study, was and remains a rousing success. We then recognized a dearth of epidemiology cohort studies among men, so, we recruited male dentists, veterinarians, optometrists, pharmacists, osteopath physicians, and podiatrists. After a pilot study demonstrated feasibility, we secured funding from the National Heart, Lung, and Blood Institute and enrolled 51,529 men, then aged 40-75, from across the United States (U.S.). We targeted health professionals who would understand the importance of the research effort and to ensure high quality information. We included "follow-up" in the study's name, to identify long term follow-up as a key goal, to enhance the validity of the results. Participants have clearly committed tremendous energy and loyalty to the study, completing questionnaires every two years. Indeed, even as we approach year 40, the follow-up rate exceeds 90%. We are most grateful! HPFS remains one



Dr. Walter Willett and Dr. Meir Stampfer, circa 1987

of the few studies focused solely on health in men. Many important advances have emerged from HPFS, with over 1,300 scientific publications. This article can only skim a few of the highlights.

The initial focus was on cardiovascular diseases, the leading cause of death in the U.S. and worldwide, and especially the role of dietary factors. Skeptical

Continued on page 2

critics appropriately questioned whether valid dietary data could be derived from questionnaires. From detailed studies in HPFS and NHS, we compared the questionnaire data with multiple seven-day diet records and blood levels of nutrients and showed that indeed, the questionnaire derived data were valid and accurate. Research on diet and cardiovascular diseases in the cohorts led to a series of remarkable advances that affected policy recommendations and improved health. When HPFS began, the leading dietary dogma was “fat is bad”. We showed that this advice was overly simplistic, and that while certain kinds of fats are harmful, others promote health. In particular, we discovered that trans-fat, produced by industrial partial hydrogenation of polyunsaturated vegetable oil, was especially harmful. Trans fats were widely used to improve “mouth feel” and extend product shelf life, but they decrease human life. We estimated that trans-fat was causing tens of thousands of premature deaths in the U.S. each year. Based on that work, trans fat was banned in the U.S., but not until 2018. We also showed the harmful effects of saturated fat and the benefits of unsaturated fats, especially from plant sources that were not partially hydrogenated. These healthy fats include olive, soybean, and canola oils. Other plant foods relatively high in fat, such as avocado and nuts, are beneficial compared with the usual American diet.

Analogous to the more nuanced understanding of fat, we showed that different forms of carbohydrates have opposing health effects: refined carbs, like sugar and starch are harmful, whereas whole grain and fiber-rich foods are beneficial. A higher intake of fruits and nonstarchy vegetables also are protective for cardiovascular



HPFS Group, 2024

disease. We showed that diets consisting primarily of healthy plant foods promote lower risk of cardiovascular as well as a range of other diseases. Some individual dietary items were also related to lower risk, including alcohol in moderation (not exceeding two drinks per day for men), yogurt, coffee, and dark chocolate. The detailed and updated diet data have enabled a focus on individual nutrients, foods, and overall dietary patterns.

Beyond diet, the HPFS cohort has provided important evidence regarding how obesity affects health. This had been controversial in part because smokers tend to have less obesity, and many illnesses cause weight loss before death; these associations tend to artifactually link normal weight to higher risk. We found that after careful adjustment for those factors, having a body mass index (BMI) of 25 kg/m² or less was associated with lower mortality risk. In addition, we have provided strong evidence that a healthy body weight is associated with a lower risk of cardiovascular disease and many types of cancer. Physical activity – importantly including both aerobic and resistance training – are also highly beneficial. We project that adherence to five healthy behaviors – not smoking, good diet, moderate alcohol, weight maintenance and physical activity – could prevent the vast majority of diabetes and cardiovascular

INTERVIEW WITH

Dr. William Freitag



TO CELEBRATE NEARLY FORTY YEARS OF THE HPFS, we recently had the privilege of interviewing Dr. William Freitag, a retired veterinarian, who has been an active HPFS participant since 1986. Ever since Dr. Freitag was in high school, he knew he wanted to be a veterinarian. Dr. Freitag graduated from Michigan State

University in 1964. Then, on a NIH fellowship, he attended the University of Wisconsin to pursue cancer research. Dr. Freitag decided academia was not for him and joined a fellow Michigan State graduate in a mixed veterinary practice in Fond du Lac, Wisconsin. While working at this practice, Dr. Freitag developed a fondness for cats and decided he wanted to start a feline-only practice. In 1970, he moved to Seattle, Washington and joined the Cat Clinic of Seattle. He was told by an author and veterinarian of feline medicine that, at the time, this was the second only cat practice in the world. He grew this practice from one veterinarian to 3.5 veterinarians and a staff of 20.

Dr. Freitag sold the practice to his associate and retired at age 58. Dr. Freitag's wife, Janet Freitag, had been diagnosed with Multiple Sclerosis and was failing. They had done a fair amount of international travel and now wanted to see the southern half of the U.S. They bought a motorhome and hit the road in the wintertime and did extensive boating in the summer (on his boat named the "Cats Meow!"). In 2010, they moved into a Continuing Care Retirement Community to provide care for his wife.

Mrs. Freitag died in 2013. Dr. Freitag still travels in his motor home with his 19-year-old cat. Since retiring, he has been involved with Rotary International, many nonprofits, social clubs, and professional organizations, while taking on many leadership positions within these organizations.

We asked Dr. Freitag why he originally participated in the HPFS study nearly 40 years ago. Having attended the University of Wisconsin on a NIH fellowship and conducting cancer research, he realized the importance of research and published research. He joined because he thought that the HPFS had the opportunity, supported by Harvard School of Public Health, for long-term valuable research and publications.

We realize that participating in the HPFS study for nearly 40 years requires dedication and persistence. When we asked Dr. Freitag what motivates his continued participation, he said hopefully his involvement will be helpful for the lives of generations to come. He appreciates the diversity and completeness of the questionnaires, including the questions on diet, medication, exercise, mental acuity and lifestyle. When it came to our question about whether his participation has changed his lifestyle in any way, Dr. Freitag feels that he has always adopted a healthy lifestyle and has incorporated the Mediterranean style diet. However, he continues to learn from the Study, since "we are never too old to learn"!

Lastly, we asked Dr. Freitag if there is anything we can do to improve the HPFS. He mentioned that the online survey could increasingly become more valuable. Currently, nearly 40% of participants answer the survey online. He also had an excellent suggestion of sending a pamphlet describing the study to participants to share with family members and/or contacts. These family members/contacts would then have our information and could notify us in the event that the participant could no longer participate.

As a message to all fellow HPFS participants: "Please stay with the program, it is very valuable".

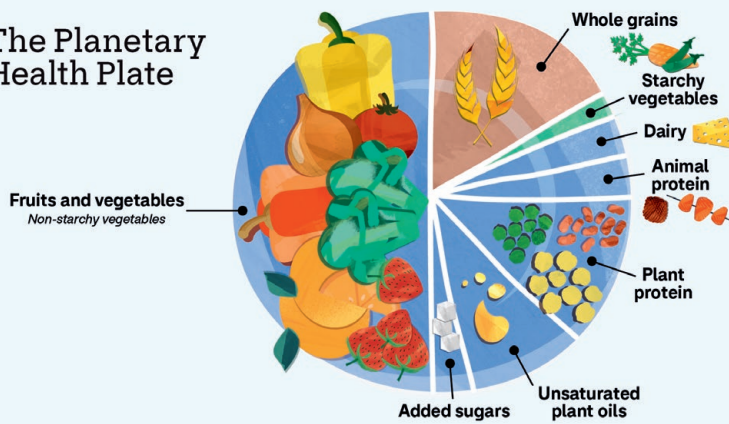
In advance of 40 years, we are so grateful for Dr. Freitag and all our dedicated HPFS participants. We could never have reached this milestone without your engagement or commitment these past 39 years. Thank you!

Research Updates

Planetary Health Diet Index and Risk of Total and Cause-Specific Mortality in Three Prospective Cohorts

Dr. Willett and his colleagues have broken new ground in developing a novel dietary pattern, the Planetary Health Diet. This is a diet pattern that captures food components that promote both health and sustainable food systems as described in the 2019 EAT-Lancet Commission report. The dietary pattern emphasizes diverse plant foods, those that are minimally processed, and allows for modest consumption of meat and dairy foods: this could include approximately one serving of dairy foods per day and an additional one serving of fish, poultry, eggs, or other meat.

The Planetary Health Plate



In a study published in June 2024, researchers found that participants in the top 10% for adherence to the Planetary Health Diet had 30% lower risk of premature death compared to those in the bottom 10%. These results were consistent for all major causes of death, including cancer and cardiovascular disease, neurodegenerative disease, pulmonary disease, and infectious diseases. Of note, the traditional Mediterranean diet is an example of the Planetary Health Diet.

In a separate study, dietary intakes that were more consistent with the Planetary Health Diet, AHEI,

and healthy plant-based diet was all linked to lower greenhouse gas emissions, fertilizer needs, cropland use, and irrigation water needs. (Bui, Linh P, et al. *The American Journal of Clinical Nutrition*, July 2024)

Healthy Dietary Patterns and Risk of Prostate Cancer in Men at High Genetic Risk

As mentioned earlier, prostate cancer has the highest heritability, or the relative contribution of inherited genetic factors. While one cannot change their genes, we found maintaining a healthy lifestyle may reduce lethal prostate cancer among men with high genetic risk. Whether a healthy dietary pattern could attenuate high prostate cancer genetic risk is unknown. In this study, we prospectively followed 10,269 genotyped men from 1993 to 2019 and investigated five dietary patterns: Healthy Eating Index, Mediterranean, diabetes risk-reducing diet, hyperinsulinemic diet, and inflammatory diet. We found that men with high genetic risk, adhering to a diabetes risk-reducing diet or a low insulinemic diet, was associated with a substantially lower risk of overall and lethal prostate cancer. Other dietary patterns showed weaker but similar associations. Among men at high genetic risk, men with healthy lifestyles based on body weight, physical activity, and low insulinemic diet had a 73% lower rate of lethal prostate cancer compared to men with unhealthy lifestyles, translating to a lifetime risk of 3.4% among men with healthy lifestyles and 9.5% among those with unhealthy lifestyles. Our study indicates that lifestyle modifications that reduce insulin resistance and chronic hyperinsulinemia may be a potential primary prevention strategy of aggressive prostate cancer among men with high genetic predisposition. (Zhang Y, et al. *Int J Cancer*. July 2024.)

Men at Increased Genetic Risk of Prostate Cancer May Benefit from Maintaining a Healthy Lifestyle

Beyond dietary patterns, HPFS colleagues investigated the role of a healthy lifestyle in offsetting genetic susceptibility of prostate cancer. In a study based on 12,000 men enrolled in the HPFS and the Physicians' Health Study, colleagues investigated the role of genetic and lifestyle factors on the risk of developing lethal prostate cancer during a follow-up period of nearly 30 years. The team found that while a genetic risk score was strongly associated with an increased risk, a healthy lifestyle may provide protection. Among men at high genetic risk, adherence to a healthy lifestyle was associated with close to a 50% reduced risk of developing lethal prostate cancer compared with those not adhering to a healthy lifestyle.

The investigators defined a high genetic risk based on genetic risk variants identified from large genome-wide association studies of prostate cancer cases and controls. Currently, over 400 such variants have been identified. A healthy lifestyle was defined based on a previously developed healthy lifestyle score for prostate cancer. This score includes a healthy weight, vigorous physical activity, absence of smoking, and presence of a healthy diet that is rich in cooked tomatoes and fish, and low intake of processed meat.

The combined findings suggest that having a high genetic risk for prostate cancer may not be deterministic for a poor cancer outcome. Early detection and treatment combined with lifestyle modifications may offer a way to offset a high genetic risk. (Plym A, et al. Increased Genetic Risk for Prostate Cancer *European urology* April 2023; Plym A, et al. Early Prostate Cancer Deaths Among Men With Higher vs Lower Genetic Risk. *JAMA network open* 2024)

Consumption of Olive Oil and Diet Quality and Risk of Dementia-Related Death

Olive oil, rich in monounsaturated fats and antioxidant compounds, may protect the brain. It is a key component of the Mediterranean diet, which appears to have a beneficial effect in preventing cognitive decline. While higher olive oil intake was previously associated with a lower risk of cardiovascular disease and mortality, its association with dementia mortality was largely unknown.

Our analysis within HPFS and NHS revealed that individuals consuming more than 0.5 tablespoons of olive oil daily had a 28% reduced risk of dying from dementia compared to those who rarely or never consumed it. Moreover, this association was linear, indicating that as olive oil consumption was higher, the risk of dementia-related mortality was lower. Interestingly, this protective association was independent of the overall diet quality, which is typically better among those who include olive oil in their diet.

Additionally, replacing just one teaspoon of margarine or mayonnaise with an equivalent amount of olive oil was associated with an 8-14% lower risk of dying from dementia. We observed no similar benefits when substituting olive oil with other vegetable oils. This finding reinforces current dietary guidelines that recommend choosing olive oil and other vegetable oils, such as canola oil, for cooking, baking, and dressing foods. Regularly incorporating olive oil into your diet could significantly lower your risk of dementia-related death.

Your participation in this study has been crucial in advancing our understanding of how diet is associated with cognitive health. This research not only underscores the significant role of dietary choices on individual health but also highlights the broader public health implications of these findings. This is all thanks to your involvement. (Tessier A. et al. *JAMA Netw Open*. 2024)

Future Substudies

Grief and Bereavement Substudy

Although older adults experience a greater burden of bereavement than any other age group, there remain considerable gaps in our knowledge of its impact on their health. We are launching the Grief and Bereavement Substudy to learn more about grief after the death of a loved one, aiming to identify risk and protective factors that can play a role in supporting healthy outcomes for grieving adults.

We will be inviting members of the Health Professionals Follow-Up Study and Nurses' Health Studies, who indicated on the latest questionnaire that they had experienced the death of a loved one, to participate in this research. Participants will be asked to complete a questionnaire on their experience of grief following the death of a loved one. A small subset of participants who complete the questionnaire may be invited to participate in a brief telephone interview. However, participation in the substudy does not require completing the telephone interview. As this research is funded by the National Institutes of Mental Health, which has required that de-identified data to be shared, participants will be asked to complete a signed consent that includes data sharing.

This research is funded by National Institutes of Mental Health, which requires de-identified data to be shared. Participants in this substudy will be asked to complete a signed consent (if they choose to participate) which includes the data sharing information.

Participation in this research will provide greater insight into well-being after bereavement. As always, thank you in advance for taking time to be part of this invaluable research effort.

We are launching the Grief and Bereavement Substudy to identify risk and protective factors that can play a role in supporting healthy outcomes for grieving adults.

New Collection of Blood Samples

Approximately 30 years ago, 18,000 HPFS participants provided us with a blood sample. These samples have greatly contributed to our understanding of disease and important strategies to maintain good health.

In the coming months, we will be reaching out to all participants who donated a blood sample in the past to invite them to provide a second blood sample. Collecting a second blood sample will be an unprecedented opportunity to understand how men age and how to maintain good health and function as we age. This effort is supported by a major grant we received from the National Institute on Aging at the National Institutes of Health.

If you are interested in participating, please wait until we contact you. We will provide all the necessary materials to complete the blood draw and return the samples. You will need to find a healthcare worker trained in phlebotomy who can draw the blood

disease cases. Moreover, the benefits are additive to medical treatment of high blood pressure and high cholesterol.

The longitudinal design, with repeated questionnaire assessments, permitted the study of many health outcomes apart from cardiovascular disease. Also, the impressive support from participants enabled the collection of blood samples from 18,000 participants, sets of toenail samples from 32,000 participants (mainly for trace metal analyses), and thousands of tumor tissue samples from individuals diagnosed with cancers. The scope of HPFS expanded to focus on cancer and received support from the National Cancer Institute through their cancer epidemiology cohort program. The return on that research investment was rapidly realized through a plethora of major findings, particularly in HPFS for colorectal cancer and prostate cancer.

For colorectal cancer, we identified and refined evidence for many potential risk and preventive factors. Red meat, especially processed meat, smoking, being overweight, and excessive alcohol were associated with higher risk, whereas dietary calcium, fiber/whole grains, folate (from fruits and vegetables and multivitamin supplements), physical activity and regular aspirin use were all associated with lower risk. Taken together, adherence to these life factors was associated by a risk reduction of two-thirds or more. HPFS has also made major contributions to assessment of the considerable additional benefits of colonoscopy, which reduces risk of colorectal cancer mortality both through early detection as well as prevention, by enabling removal of precancerous polyps.

With its focus on men's health, HPFS has been at the forefront of prostate cancer research. In 2025, more than 300,000 new cases of prostate cancer will be diagnosed in the U.S. While prostate cancer is the second leading cause of cancer mortality among U.S. men, many patients have a slower growing form of the disease and can live a long and healthy life after diagnosis. HPFS has been on

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the forefront in identifying the factors that cause prostate cancer, how to prevent it, particularly prevention of potentially lethal forms of prostate cancer. Data from the HPFS have been essential in showing the benefits of regular physical activity to lower risk of lethal prostate cancer. In addition, more plant-forward dietary patterns also lower lethal prostate cancer. The blood samples in HPFS have been essential in defining the role of inherited genetic factors in prostate cancer. Many of our participants diagnosed with prostate cancer have contributed to our substudies on prostate cancer survivorship, and we are very grateful!

For both prostate and colorectal cancer research, the HPFS has been a leader in identifying “molecular subtypes”, or specific subgroups of patients’ tumors based on biological markers. This information has led to important discoveries of new etiologic factors and also has been used to define biomarkers associated with prognosis after a cancer diagnosis.

While cancer and cardiovascular disease remain important focuses of HPFS investigators, we are expanding into new areas, including healthy aging. The information in HPFS is shedding new light on how people can maintain cognitive and physical health into old age. Already we have made important contributions in this area, showing the importance of a healthy diet and physical activity. Moreover, we have shown it is never too late to start living a healthy lifestyle. With continued active engagement from participants, we look forward to a bright future as we move into the fifth decade of this study!

Valuable Data from Cancer Registries

When a member of the Health Professionals Follow-Up Study reports a new cancer diagnosis, we generally contact the participant to request permission to review his medical records relating to this diagnosis. In addition, we may request data from the Virtual Pool Registry- Cancer Linkage System (VPR-CLS), which is funded by the National Cancer Institute. This system links data from state cancer registries on diagnosis date and tumor characteristics such as type of tumor, stage and grade of disease, and cancer treatment. This detailed diagnostic information from the registry, combined with the extensive lifestyle, health and biologic data that the HPFS has collected across decades, is vital to understanding the causes of cancer and allows us to learn more about improving survival for a variety of cancers. Most U.S. states participate in the Virtual Pool Registry.

To accurately locate the correct information, we securely send the patient's name, date of birth, address and social security number to the Virtual Pool Registry to look for a match. If you do not wish to have your data linked with the Virtual Pool Registry data, in the event you are diagnosed with cancer, please send an email to hpfs@hsph.harvard.edu or write us at HPFS Cancer Registry, 665 Huntington Ave, Boston, MA 02115.

If you have any questions, please call Siobhan Saint Surin at (617) 998-1067. If you would like to speak to someone who is not involved in this research regarding your rights as a research subject or with any concerns you may have about the research, please contact the Office of Regulatory Affairs and Research Compliance (ORARC) toll free at 1-866-606-0573.

Data Security and Data Sharing

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

HPFS data that could be linked to individual participants are never shared with employers' insurance companies or government agencies.

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

Health Professionals Follow-Up Study

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To report name or address changes, please email the project coordinator at hpfs@hsph.harvard.edu or visit www.hsph.harvard.edu/hpfs. Letters and feedback are welcome.

Donations and bequests to the Friends of the Health Professionals Follow-Up Study Fund help to sustain our continued work. Donations may be sent to the Harvard T.H. Chan School of Public Health. For information on how to give or to make a secure gift online, please visit www.hsph.harvard.edu/give and indicate that the gift is in support of the Friends of the Health Professionals Follow-Up Study Fund.