



# HPFS NEWS

UPDATES FROM THE HEALTH PROFESSIONALS FOLLOW-UP STUDY

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## DEAR COLLEAGUES,

Despite the difficulties that COVID has caused, we have been busy conducting new medical research and publishing our findings from the Health Professionals Follow-Up Study (HPFS). We are excited to share some of our latest findings. In this year's newsletter, our feature article focuses on our research on Parkinson's disease. We also highlight several other publications on different health outcomes, as well as our interview with HPFS participant, Dr. Perry Dworkin. Lastly, we invite you to visit our website at: [www.hsph.harvard.edu/hpfs](http://www.hsph.harvard.edu/hpfs) where you can find our most recent updates, announcements, and a list of all published articles using HPFS data. Thank you for continuing your tireless support and dedication to HPFS over the past 37 years.

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## Parkinson's Disease

Parkinson's disease is one of the most common neurodegenerative diseases, second only to Alzheimer's disease, with an estimated one million people in North America living with Parkinson's disease. In the 2009 HPFS Newsletter, we reported our results on the potential protective effects of blood urate. These results led to a randomized placebo-controlled trial of inosine, a urate precursor. This trial demonstrated that urate levels could be elevated to the desired range but failed to demonstrate a benefit on disease progression. Many experts believe that the failure of urate elevation and other therapeutic trials in Parkinson's disease is due to the fact that by the time someone is diagnosed with the disease, over 50% of dopaminergic neurons in critical areas of the brain have already been lost, and it is too late to stop the process.

An important breakthrough has been the discovery that the disease process starts at least 10 years before the onset of the characteristic motor symptoms (prodromal phase). Therefore, novel approaches and biomarkers may enable the identification of individuals who are in this long prodromal phase. Such identification would allow starting therapeutic interventions before the occurrence of substantial, and probably irreversible, neuronal loss.



(left to right) Xiaojing Peng, Allison Gordon, Dr. Marianna Cortese, Dr. Kjetil Bjornevik, Dr. Alberto Ascherio, Dr. Helena Sandoval-Insausti, Dr. Mario Flores-Torres

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The Health Professionals Follow-Up Study (HPFS) is at the forefront of this research. The neuroepidemiology research group at Harvard Chan School of Public Health, led by Dr. Alberto Ascherio, is leading diverse projects. We have been funded first by the U.S. Department of Defense (2014 – 2018) and then by the National Institute of Neurological Diseases and Stroke (2022 – 2026) to conduct a large prospective investigation on prodromal PD and includes virtually all HPFS participants. Many of you were invited to complete an olfactory test and a color vision test in 2014-2015 and again in 2017-2018, in addition to a questionnaire addressing features that are commonly observed in prodromal PD. As part of this project, some of you also participated in a cognitive assessment conducted over the phone in 2016-2017. In 2016, we drove a mobile clinic through several states in the Northeast to conduct neurological examinations of a few HPFS participants and to validate the information collected in these tests and questionnaires.

The data collected have contributed to several publications, one describing the non-motor features of prodromal PD (Hughes et al. 2018), another describing objective and perceived cognitive changes as potential markers of prodromal PD (Flores-Torres et al. 2021), and two focusing on specific factors that appear to reduce risk of developing prodromal features, including physical activity (Hughes et al. 2019) and a Mediterranean style diet (Molsberry et al. 2020).

Recently, we obtained funding from the Michael J. Fox Foundation, a foundation supporting the most promising research on Parkinson's disease, to investigate novel biomarkers in sebum, an oily substance found on skin. It has been reported that sebum collected from individuals with Parkinson's disease contains compounds that are not found in



Sebum Collection Kit

individuals without Parkinson's. The collection of sebum samples in HPFS is ongoing. Some of you may have received or will receive a kit containing gauze and swabs to be rubbed on the upper back for this purpose (please see photo above). The objective of our study is to determine whether such compounds are present before the clinical onset of PD, in which case they could contribute to an early disease diagnosis with a simple skin swab.

We continue our efforts to identify factors that could help prevent or delay the occurrence of Parkinson's disease. We will soon publish findings from a recent investigation using HPFS data suggesting that a higher intake of vitamin B12 may be beneficial against the development of Parkinson's disease, although more research is needed to confirm these results.

Over the next five years, we plan to complete the ongoing studies and expand our investigation to other potential predictors of prodromal disease and Parkinson's disease. The extension of the follow-up of HPFS participants who report a diagnosis of Parkinson's disease will be critical to validate the information collected over the past 10 years. We still count on your collaboration for the timely identification of new Parkinson's disease diagnoses

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## INTERVIEW WITH

# Dr. Perry Dworkin

To celebrate more than 37 years of the Health Professionals Follow-Up Study (HPFS), we recently had the privilege of interviewing Dr. Perry Dworkin who has been a dedicated participant since the study began in 1986. Dr. Dworkin is an Osteopath Physician and is Past President of the Florida Osteopathic Medical Association and the Miami-Dade County Osteopathic Medical Association. He served on the American Osteopathic Association House of Delegates and in several other professional organizations. Among his many achievements, one of his most proud accomplishment has been participating in the Health Professionals Follow-Up Study all these years.

During our conversation as we reminisced on 37 years, we asked him why he decided to initially participate in the HPFS. Dr. Dworkin said “This study was (is) real and important—this had to be supported. A 30-plus-year prospective study with more than 50,000 initial volunteers all holding degrees in medicine or health professional careers was something that HAD to be supported.”

Staying engaged in a long-term study takes dedication, and so we asked Dr. Dworkin what has kept him motivated to be an active participant. He admitted that it was not always easy to complete the questionnaires biannually. Although some years he may have “dreaded” the questionnaire, he never considered stopping, as he deemed the questionnaire and data to be too important to quit! He also mentioned that over the years he noted changes in his lifestyle and life choices, while responding to the questionnaires. This connection between his own health and how it would benefit the study made his involvement even more meaningful. Dr. Dworkin attributes positive changes to his diet and lifestyle from his participation in, as well as the findings and feedback of, the Health Professionals Follow-Up Study.

As a result of the study’s findings, he now focuses on eating a plant-based diet, consuming a moderate level of alcohol, avoiding sugars and saturated fats, and ex-



Dr. Perry and Eileen Dworkin

ercising at least five hours a week. In fact, Dr. Dworkin is a local, state, and two-time national champion power weightlifter. At his 50th high school reunion, the former captain of the football and wrestling teams approached him and said “We were athletes then; you are now!” We asked Dr. Dworkin about suggestions he may have for the study. He acknowledged that with the long-term continued cohort, we have an opportunity to investigate future health outcomes. Although in extremely good health, Dr. Dworkin shared that he has manageable prostate cancer and had an ischemic stroke. He regained his ability to walk and continues to improve steadily. The continued research in various health outcomes and in healthy aging, especially in cognitive function, is of utmost importance to him.

As a message to all fellow HPFS participants, Dr. Dworkin says “We are not done investigating aging, please continue your involvement. We might live to one hundred, but living must be worthwhile. One thing that I tell youngsters: ‘You are going to make mistakes, learn from them. You will learn more from errors than successes.’”

We are so grateful for Dr. Perry Dworkin and all our dedicated HPFS participants for their continued engagement and commitment to the Health Professionals Follow-Up Study for the past 37 years! Thank you!



# Prostate Cancer

Prostate cancer is the most common malignancy in men. It is the second leading cause of cancer death in men, and the first among non-smokers. Prostate cancer is the most heritable common cancer and many genes have been identified that explain the strong family predisposition of prostate cancer. Although the effect of an individual gene is small, some men may inherit many high-risk genes which add up to increase risk substantially. For example, in HPFS, we showed that men who had the top 25% of these high-risk genes were four times more likely to die of prostate cancer in their life than those in the lowest 25%. There has been a great need to identify possible modifiable factors for men at an increased genetic risk of prostate cancer. Our prostate cancer research team led an analysis in HPFS to examine whether a healthy lifestyle defined by healthy weight, vigorous physical activity, not smoking, and a healthy diet could lower risk of prostate cancers that have metastasized (often leading to death), particularly in those with high genetic risk. We found that among men in the highest 25% of genetic risk, adhering to a healthy lifestyle was associated with a substantial decreased rate of metastatic prostate cancer (Plym A, et al . *European Urology* 2022 May 27:S0302-2838(22)02342-9). This effect was dramatic; those with an unhealthy lifestyle experienced a 5.3% lifetime risk of metastatic prostate cancer and those with the healthy lifestyle had a 1.6% lifetime risk. With a healthy lifestyle, the men at high genetic risk brought their high-risk down to about the average risk. These results clearly show that genetic risk is not deterministic; even men who are born with high risk genes can dramatically lower their risk of dying from prostate cancer.

While the benefits of not smoking, maintaining a healthy body weight and being physically active have been well established for prostate cancer prevention,



***We found that among men in the highest 25% of genetic risk, adhering to a healthy lifestyle was associated with a substantial decreased rate of metastatic prostate cancer***



the role of diet has been less clear. Because healthful plant-based diets, including vegetables, fruits, nuts, beans, and whole grains, are associated with numerous health benefits, including reductions in diabetes, cardiovascular disease, and overall mortality, we were interested if these dietary factors are related to prostate cancer risk. In HPFS, we found that overall plant-based consumption was associated with a 20% lower risk of fatal prostate cancer (Loeb S. et al. *American Journal of Clinical Nutrition* 2022;115(3):662-670). The reduced risk may have been due in part to beneficial compounds in the plant foods but also partly due to limiting some animal products, particularly red and processed meat and high-fat dairy products. In a related study from the HPFS, we found that some of the benefits of this dietary pattern may be mediated through a reduction of low-grade chronic inflammation and in keeping insulin levels low (Fu B, et al *European Urology*. 2021 Mar;79(3):405-412). In addition to these being beneficial in all men, we are now also exploring whether specific dietary patterns could influence prostate cancer risk in those at high genetic risk.

# Lower Sodium and Higher Potassium in the Diet are Associated with Lower Risk of Heart Disease and Stroke

The role of sodium or “salt” in the diet for heart disease prevention has long been debated by scientists. A new study conducted by HPFS investigators provides strong evidence that limiting sodium and increasing potassium leads to better cardiovascular health (Ma Y et al. *NEJM* Jan 2022).

## Why did the authors choose to investigate this question?

Sodium and potassium are essential to maintaining electrolyte balance. Studies consistently show that diets high in sodium and low in potassium can raise blood pressure, but their relationship with heart attack and stroke risk is controversial. Thus, HPFS investigators aimed to further understand whether less sodium and more potassium in the diet would lead to better heart disease outcomes.

## What challenges influenced how the authors conducted their study?

Measuring dietary sodium is very difficult because sodium can be hidden in many foods, particularly processed foods and restaurant meals. The Nutrition Facts label on processed foods indicates the sodium

content. Restaurant meals almost always contain added sodium, and many restaurants do not disclose nutrition facts for their menu items. Thus, you may be unaware of the amount of sodium in a meal, and the amount can vary greatly by restaurant.

Potassium was recently added to the Nutrition Facts label, making it easier for you to find out how much potassium is in prepared foods. However, potassium is found naturally in many whole foods that have no nutrition labels, including fruits, vegetables, and seafood. It is important to note that potassium from supplements, not foods, can lead to health problems. Thus, potassium supplements should be avoided unless directed by your doctor.

To overcome these challenges in measuring sodium and potassium in the diet, the authors used 24-hour urine samples from HPFS participants to estimate the amount in their diet. A subgroup of participants provided urine samples collected over at least two full 24-hour periods, enabling an accurate estimate of sodium and potassium in the diet.

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**BOX 1:** Common sources of sodium and potassium in the diet. Data are derived from the U.S. Department of Agriculture FoodData Central database.

| SODIUM   |              |         | POTASSIUM   |              |       |
|--|--------------|---------|---|--------------|-------|
| <b>Top sources:</b> processed foods, restaurant meals, baked goods, and cheese   |              |         | <b>Top sources:</b> fruit, vegetables, dairy, and seafood         |              |       |
| <b>Recommended Daily Value (DV):</b> less than 2,300 mg per 2,000 daily calories |              |         | <b>Recommended DV:</b> at least 4,700 mg per 2,000 daily calories |              |       |
| FOOD ITEM  | SERVING SIZE | % DV    | FOOD ITEM   | SERVING SIZE | % DV  |
| Pizza  | 1 slice      | ~15-40% | Banana  | 1 medium     | 8%    |
| Cheese   | 1 oz         | ~10-25% | Cantaloupe  | 1 cup        | 9%    |
| Fast food hamburger  | 1 patty      | ~30-45% | Dried apricots  | 1/2 cup      | 16%   |
| Turkey and cheese  | 1 sandwich   | ~40-65% | Orange juice  | 1 cup        | 11%   |
| Soup   | 1 cup        | ~25-50% | Squash, winter  | 1 cup        | 5-12% |
| Processed meats  | 3 oz         | ~40-80% | Spinach   | 2 cups, raw  | 7%    |
| Marinated chicken  | 1 breast     | ~10-35% | Avocado   | 1 half       | 7%    |
| Bread/baked goods  | 1 slice      | ~10-35% | Sweet potato  | 1 medium     | 12%   |
| Condiments   | 1 tbsp       | ~10-60% | Black beans   | 1/2 cup      | 7%    |
| Savory snacks  | 1 cup        | ~10-20% | Low-fat milk  | 1 cup        | 8%    |
| Table salt   | 1 tsp        | 101%    | Low-fat yogurt  | 1 cup        | 12%   |
|  |              |         | Salmon  | 3 oz         | 9%    |

*Sodium and Potassium in the Diet continued from page 5*

**What did the authors find?**

The authors combined data from over 1,000 HPFS participants with four other studies to investigate greater than 10,000 healthy adults from the U.S. and Europe. They compared individuals with high and low levels of sodium and potassium and found that participants with the highest levels of sodium in the urine were 60% more likely to have a heart attack, stroke or coronary artery procedure than those with the lowest sodium levels. Those with the highest levels of potassium had a 31% lower risk of cardiovascular events than those with lowest levels.

**How can I change my lifestyle based on the study findings?**

In general, reducing your use of the salt shaker, intake of store-bought packaged foods and frequency of eating out will help decrease sodium, while increasing intake of fruits, leafy greens, starchy vegetables, beans, low-fat dairy, and seafood will help boost potassium in your diet. Please refer to **Box 1** (page 5) to see whether your diet includes common sources of sodium and potassium – maybe you’ll even get some new ideas about how you can change your diet to reduce your heart disease risk.



## Obtaining Health Care Billing Claims Information

We are planning to obtain billing claims information for participants on costs, diagnostic tests, and treatments to expand the kinds of research we can do. This new information will help to identify optimal prevention strategies for chronic diseases, and potentially ways to reduce healthcare costs.

We will request claims data derived from the Centers for Medicare and Medicaid Services (CMS) or healthcare insurance providers for participants in HPFS. These data will include billing claims from hospitals, skilled nursing facilities, physicians (inpatient and outpatient), and drug prescriptions, along with information on the date of services, billing codes for type of services, codes for diagnosis and diagnostic test performed, and number of payments made by Medicare. These data are derived directly from the CMS Data Center or your healthcare insurance provider and thus, we will not be requesting any information from you, your doctors, or hospitals. We will not receive any of your medical records from Medicare or your insurance provider; the available data only pertain to billing/claims.

Previous studies, in other cohorts, have regularly used billing claims data to study trends in treatment,

costs and healthcare utilization. Adding this type of information to the HPFS will enhance the utility and value of the many years of questionnaire data that you have graciously provided since the start of the study.

We will never receive your true Medicare beneficiary ID or health insurance provider ID. All the claims data we receive will be maintained by HPFS in the same secure and confidential manner as the data you have provided to us directly. We will not share any information about you with Medicare, your health insurance provider or anyone else.

If you have any questions about these billing claims studies, or wish to be excluded from such studies, now or any time in the future, please send an email to [hpfs@hsph.harvard.edu](mailto:hpfs@hsph.harvard.edu) or write us at HPFS/Medicare Studies, Department of Nutrition, 677 Huntington Avenue, Boston, MA 02115.

If you prefer not to participate in this health claims-based research, your decision will not affect your standing as a valued member of the Health Professionals Follow-Up Study.

*Parkinson's Disease continued from page 2*

and for permission to review the relevant medical records. These records are being reviewed by our collaborators, Dr. Michael Schwarzschild and Dr. Albert Hung at Massachusetts General Hospital, to make sure that the Parkinson's disease diagnoses meet rigorous research criteria. Further, we are conducting pilot studies in a movement disorder clinic to determine whether saliva, nasal swab, or blood samples can be used to identify the presence of abnormal aggregates of a protein called alpha-synuclein, which has been identified as the underlying pathological mechanism in a large proportion of individuals with Parkinson's disease. Preliminary results suggest that the presence of alpha-synuclein aggregates in body fluids is a specific marker of Parkinson's disease. We will therefore explore whether it could be leveraged as another method to identify prodromal PD.

Overall, this is a very exciting time for Parkinson's disease research. Moving the timepoint of diagnosis 5-10 years earlier could be critical to finding a way to prevent and cure Parkinson's disease. The initiation of trials in the prodromal phase is thus likely to be a major turning point in Parkinson's disease research. Contributions from participants in the HPFS have been invaluable to these research breakthroughs. The photos in this Parkinson's article include several members of the Parkinson's disease research team at the Harvard Chan School and Massachusetts General Hospital.

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***Moving the timepoint of diagnosis 5-10 years earlier could be critical to find a way to prevent and cure Parkinson's disease.***

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Dr. Albert Hung and Dr. Michael Schwarzschild

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# Flavonoids to Prevent Cognitive Decline

Have you heard the advice to “eat the rainbow”? Eating a variety of fruits and vegetables in different colors can help increase flavonoids in your diet. Flavonoids are a diverse group of plant chemicals that give plants their vibrant colors and are found in many plant foods, including fruits, vegetables, grains, roots, flowers, tea, and wine.

HPFS investigators recently sought to understand whether increasing consumption of foods high in flavonoids can help prevent the onset of cognitive decline, or dementia. The anti-inflammatory and anti-oxidative properties of flavonoids have been proposed to prevent the development of several chronic diseases, including neurological disorders.



Researchers used dietary questionnaires collected from study participants over 20 years to estimate flavonoids in their diets (Yeh TS et al. *Neurology* Sep 2021). Participants who consumed the most flavonoids had better cognitive function later in life compared to those who consumed the least flavonoids.

So, how can you add more flavonoids into your diet? Berries, citrus fruits, or 100% orange juice (up to 1 glass per day), kale, and onions will give you large doses of flavonoids. To ensure you get a wide range of flavonoids, aim for at least five servings of fruits and vegetables daily.

## Privacy

Large studies will be key to the success of efforts to understand the role of genetic factors in the development of different diseases. This highlights the importance of collaboration and careful data sharing with appropriate safeguards on participant confidentiality. Indeed, the National Institutes of Health (NIH) have 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 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 effective 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](mailto:hpfs@hsph.harvard.edu) or write to us at HPFS, 677 Huntington Avenue, Boston, MA 02115.

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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](http://www.hsph.harvard.edu/give) and indicate that the gift is in support of the Friends of the Health Professionals Follow-Up Study Fund.