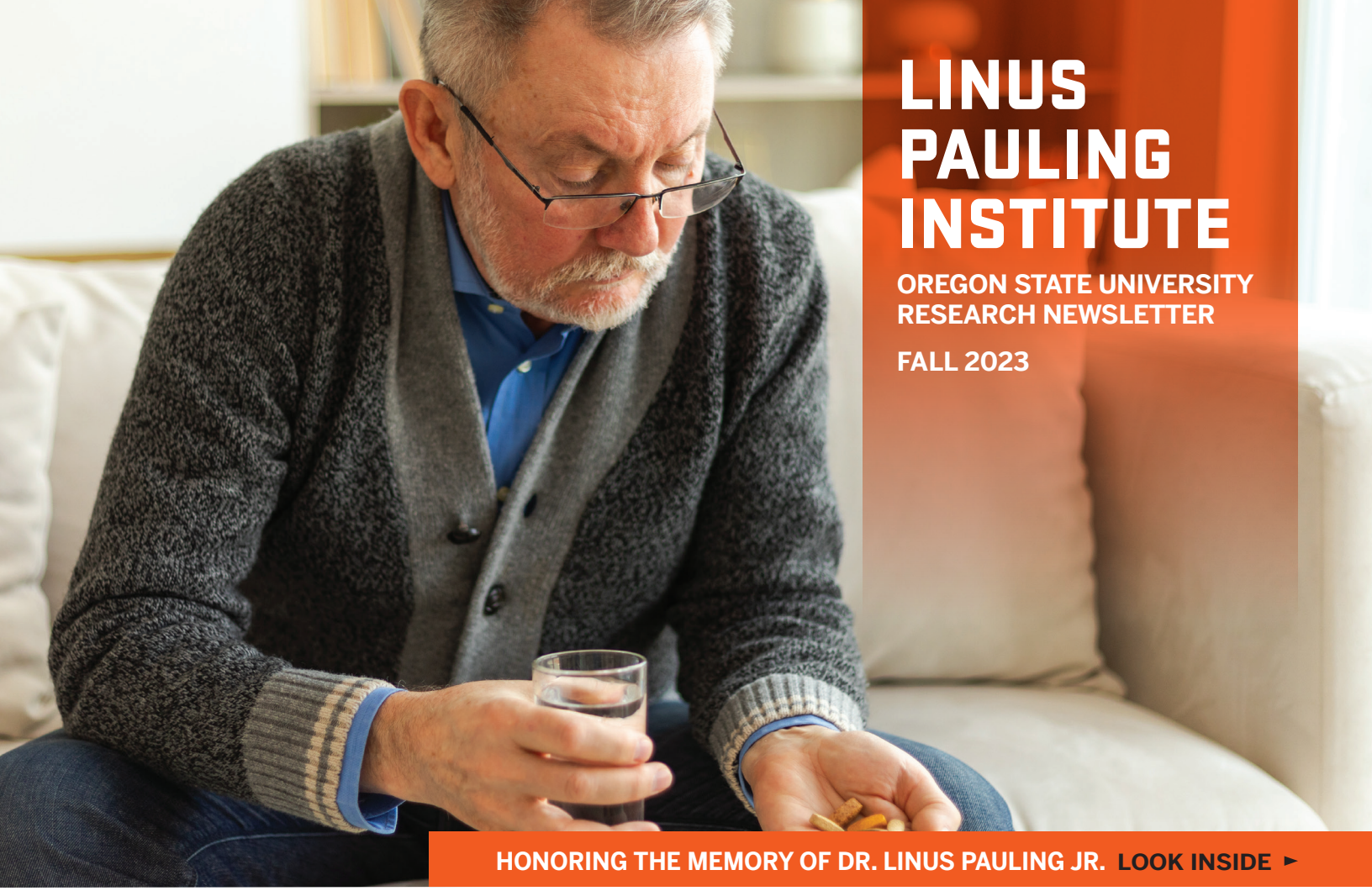


LINUS PAULING INSTITUTE

OREGON STATE UNIVERSITY
RESEARCH NEWSLETTER

FALL 2023

HONORING THE MEMORY OF DR. LINUS PAULING JR. LOOK INSIDE ►

THE BENEFITS OF MULTIVITAMINS

Multivitamin Use Improves Nutritional Status in Older Men

Multivitamins are often recommended to help older adults fill nutritional gaps and improve their vitamin and mineral status, but do they work as intended? The results of a new clinical trial from Dr. Tory Hagen and colleagues at the Linus Pauling Institute show that older men do benefit from taking a daily multivitamin, with gains that go beyond meeting nutritional needs.

A balanced diet is essential to health for many reasons. For one, it provides the vitamins and minerals that are needed for proper bodily function. However, many people do not meet their vitamin and mineral needs.

Older adults are at greater risk for deficiencies in certain vitamins and minerals. One possible reason is that as we age, we tend to eat less food, leading to lower micronutrient intake. Other factors contribute to poor micronutrient status in older adults, such as changes in dietary habits, food preferences, decreased nutrient absorption, gastrointestinal problems, inflammation, and the influence of certain medications.

"All of this creates a strong case for multivitamins on top of a balanced diet," says Dr. Tory Hagen, one of the principal investigators focused on healthy aging at the Linus Pauling Institute. This is one reason the Institute recommends that all adults, especially older adults, take a daily multivitamin supplement that contains 100% of the daily value (DV) for most vitamins and minerals.

Continued on page 4

IN THIS ISSUE

Oregon State University
Linus Pauling Institute

Photo credit: Karl Maadsam

Emily Ho, PhD
Endowed Chair and Director,
Linus Pauling Institute

FROM THE DIRECTOR

I hope you are having a wonderful fall and are looking forward to an amazing new year! It is exciting to reflect on the successful year that we had at the Institute, and I am eagerly anticipating all of the new events coming in 2024.

We held our 12th biennial *Diet and Optimum Health* conference on September 19th and 20th. The event was filled with fascinating presentations and panel discussions on the topic of precision health.

In this issue, we highlight a presentation from one of our conference's Young Investigator Award winners, Paige Jamieson. More details from the conference will be published in the next issue of the *LPI Digital Digest*, scheduled for early 2024.

Speaking of the *LPI Digital Digest*, our inaugural issue was released in October. If you signed up for a print copy, this has already been sent to you. You can still sign up for print copies of the *LPI Digital Digest* by contacting us by mail or email.

On December 12, I presented *Aging Well & Optimal Health: The Role of Micronutrients* – a webinar reviewing the micronutrients older adults should consider for optimal health. If you're interested in watching the recording, please use the link on the back cover.

Our first event of 2024 will happen on Linus Pauling Day – February 28 (Linus Pauling's birthday) – when we will hold an open house at the Linus Pauling Science Center in Corvallis. You are all invited; please let us know if you plan to attend. I enjoyed connecting with so many of you at last year's event, and we look forward to showcasing our latest discoveries for you again.

This is only the beginning of what we have planned for 2024. Our webinar series will continue, and other in-person events will follow. Please watch this newsletter, the *LPI Digital Digest,* and our emails to know when an event is happening near you.

Here's to a happy and healthy new year!

Jessica Merkner, JD
Senior Development Director,
OSU Foundation

Developments

Dear Friends,

My name is Jessica, and I am the new Senior Development Director for the Linus Pauling Institute. I bring over a decade of experience in higher education fundraising and passion for helping people achieve their philanthropic goals.

I am honored to be a part of this community. Please consider me your resource for learning how to support the Institute.

Your generosity ensures that the Linus Pauling Institute continues to make discoveries and innovations that benefit us all. Your commitment to research excellence and the next generation of scientists inspires OSU faculty, staff, and students to make great strides in advancing science.

If you have any questions about making a gift before the end of the year, please let me know. I would love to hear your story and why you choose to donate to the Institute. You can best reach me at **jessica.merkner@osufoundation.org** or (541) 543-8337.

We are so grateful for all that you do for us. Thank you.

IN MEMORIAM

Dr. Linus Carl Pauling Jr.

Linus Pauling's eldest son, Dr. Linus Carl Pauling Jr. was born in Pasadena, California on March 10, 1925. Although in his early life he felt a certain obligation to follow in his father's footsteps, he soon discovered that research was not his passion and instead pursued a career in medicine.

Pauling Jr. graduated from Harvard Medical School in 1952. He enjoyed a long and successful career in psychiatry with more than 35 years in private practice and as an administrator of psychiatric services at The Queen's Medical Center in Honolulu, Hawaii. He retired from practice in 1990.

Pauling Jr. also served on the Board of Trustees of the Linus Pauling Institute of Science and Medicine (LPISM) from its inception. In the early 90s, Pauling Jr. took on an increasingly active role and served as LPISM president and the chair of the Board of Trustees.

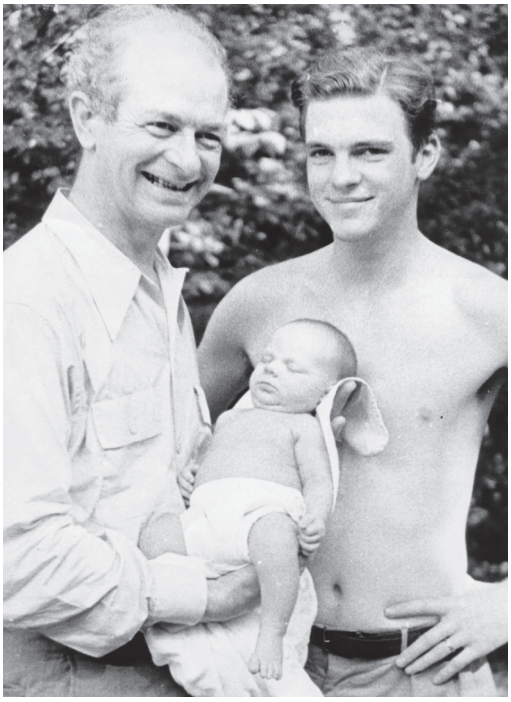
Unfortunately, this was during a time of financial instability for the Institute. Because of this, the Board of Trustees decided that the legacy of Linus Pauling and the Institute would be best sustained and enhanced by associating with a university.

After the elder Pauling died in 1994, Pauling Jr. and Stephen Lawson, then Chief Executive Officer of LPISM, made the choice to move to Oregon State University (OSU). Rebranded as the Linus Pauling Institute, it has operated as one of OSU's research centers since 1996.

Linus Pauling Jr. died in Honolulu in June 2023 at the age of 98.

Everyone at the Institute is deeply indebted to him for his selfless work on behalf of his father and his legacy. We would not be here today without him.

Pauling Jr. visited the Institute in 2011 for the dedication of the Linus Pauling Science Center, where he gave the keynote address entitled, "Out of the Ashes, the Phoenix Rose." He expressed great pleasure that his father's legacy in orthomolecular medicine would continue in such a fine, modern research building.



Left photo: Three generations together in 1949: with Linus Carl Pauling (left), Linus Carl Pauling Jr. (right), and baby Linus Jr.'s eldest son, Linus Fowler Pauling. Right photo: Linus Pauling Jr. at an event with his father in 1971.

Continued from Cover

However, only a few studies have examined how multivitamin use improves vitamin and mineral status in older adults. Ideally, this status would be assessed by an objective measure of the effect of multivitamins on the body, such as a blood or cellular biomarker. For multivitamins to be deemed effective, they would need to improve micronutrient status over time.

To tackle the question of the effectiveness of multivitamins in older adults, Dr. Hagen assembled a team of Linus Pauling Institute researchers to conduct a randomized controlled trial in men 67 years of age and above. The study was recently published in the journal *Nutrients*.

Room for Improvement

To enroll in the study, men had to be generally healthy for their age, although some were taking prescription medications to treat chronic health conditions. Many used supplements regularly; participants needed to cease the use of any supplements containing vitamins and minerals prior to and during the trial. An exception was made for vitamin D because it is often recommended by physicians.

At the beginning of the study, each participant gave blood samples to assess their baseline vitamin status. For each vitamin measured, the researchers used literature reports to classify participants as "optimal" (i.e., blood vitamin levels that were considered ideal) or "suboptimal" (i.e., lower than "optimal"; for more detail, see below).

"Overall, we certainly found room for improvement," Hagen points out.

The blood tests revealed that almost all of the participants started the study with "suboptimal" vitamin concentrations. More than half of the participants were falling short in three or more vitamins.

In particular, vitamin B_{12}, vitamin C, and vitamin D were at less-than-ideal levels for this group of older men. Vitamin E and vitamin K concentrations were also low in some individuals.

Although several minerals were measured in the blood samples, the analysis did not reveal anything notable. This was not surprising because mineral levels in the blood stay relatively steady and are generally not considered good biomarkers of adequacy except in the case of severe deficiency. No severe mineral deficiencies were detected in these participants.

The Impact of Multivitamins

To test the effects of supplementation, half of the 35 men participating in this study took Centrum Silver Men (a daily multivitamin supplement containing vitamins, minerals, and other dietary factors) for approximately eight months. The other half took an identical placebo pill. Neither group knew what they were taking, nor did the investigators.

At the end of the study, participants in the multivitamin group had statistically significant increases in blood concentrations of several vitamins compared to the placebo group. This was notable for vitamin B_6, vitamin D, and vitamin E, as well as ß-carotene, a carotenoid compound that contributes to vitamin A status.

What is "optimal" vitamin status?

One of the challenges for this trial, and for precision nutrition in general, is defining "optimal" status. Many researchers around the globe neither agree on an appropriate biomarker for status, such as blood vitamin concentration, nor what these biomarkers may indicate for health.

"Suboptimal" vitamin status is slightly easier to define. This may range from overt deficiency with noticeable negative health outcomes to more subtle effects like increased risk for disease over a lifetime.

For this study, the research team relied on literature reports that related the blood concentrations of a given vitamin to an increased risk for disease or death. Concentrations above this amount were considered "optimal" status.

For some vitamins, the response to the multivitamin supplement was mixed. No improvement was noted in men who began the study with higher-than-average blood concentrations of folate, vitamin B_{12}, vitamin C, and vitamin K, which was not surprising. Yet, a *dramatic* improvement was observed in those participants who started off with the lowest baseline levels.

Ultimately, participants taking the multivitamin improved their vitamin status. Many participants in this group moved from "suboptimal" vitamin status to blood levels that were considered optimal.

By contrast, the blood vitamin status of many participants in the placebo group declined. In fact, several participants who had "optimal" vitamin status at the start of the trial fell into "suboptimal" status after taking a placebo for eight months.

To connect these findings to a measurable impact on bodily function, Hagen analyzed oxygen consumption in the participants' white blood cells. This is because many vitamins are used by the body's cells to produce the energy that maintains metabolism, and cells consume oxygen in that process.

Interestingly, in the placebo group, a noticeable decrease in cellular oxygen consumption was observed between the beginning and the end of the study. By contrast, cellular oxygen consumption was sustained in participants supplemented with multivitamins – and the difference between groups was significant.

Hagen believes that these data reinforce the connections between micronutrients and metabolism.

"We know that multiple nutrients present in the multivitamin supplement are important to the mitochondria and will help sustain metabolic function in older adults," he explained. "Now we would like to know which are the most important. It might help explain why oxygen consumption dropped so dramatically in the placebo group."

The Bottom Line

Results of this study show that taking a daily multivitamin has notable nutritional benefits for healthy older men. In some cases, a multivitamin can improve blood vitamin levels, and in other cases, it can prevent the declines associated with a less-than-perfect diet.

The findings also indicate that multivitamins could influence metabolic health in older adults. This could be one way that multivitamin use influences the risk for chronic disease.

Future studies in older women will determine if these results are influenced by sex.

Additionally, it would be helpful to study the effects of multivitamins in younger adults, to determine the dependency on life stage.

Centrum Silver formulas are specifically formulated for older adults and differ in nutrient content for men and women. The researchers chose to initially focus on men.

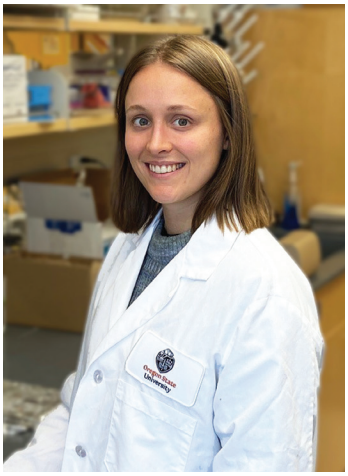
References:

Michels et al. *Nutrients* **15 (2023);** doi: 10.3390/nu15122691

Wallace et al. *J Nutr Gerontol Geriatr* **38 (2019);** doi: 10.1080/21551197.2019.1656135

Blumberg et al. *Nutrients* **9 (2017);** doi: 10.3390/nu9080849

Mitochondria consume oxygen in the production of energy for the cell. Thus, the cellular oxygen consumption rate can be used as a proxy for energy metabolism.



Paige's graduate studies have been supported by the Marion T. Tsefalas Graduate Fellowship, the Caron and Donald Reed Fellowship, and the Simone and Balz Frei Graduate Fellowship.

CHANGING THE GUT MICROBIOME:
Understanding Enterotypes

By Paige Jamieson

Paige Jamieson, a PhD student in the Nutrition program at Oregon State University, works in the laboratory of Dr. Fred Stevens, a principal investigator at the Institute. At our recent Diet and Optimum Health Conference, Paige presented her work examining gut microbiome data from a clinical trial of xanthohumol supplementation. She found that the response to xanthohumol appeared to be tied to enterotype – a classification of bacterial communities in the human gut. She shares more about that work below.

I became interested in the gut microbiome during my work with the Xanthohumol Microbiome and Signature study (also known as the XMaS trial) led by my PhD mentor, Dr. Fred Stevens. This was a randomized, placebo-controlled trial in healthy adults investigating the safety of a dietary supplement called xanthohumol, a compound from the hops plant.

One of the trial's objectives was to learn about the impact of xanthohumol on the human gut microbiome, which is connected to work we conduct in animals (see page 7, sidebar). This investigation also led to observations about "enterotypes," which are related to the gut microbiome and may be key to understanding xanthohumol's role in gut health.

What is an Enterotype?

The gut microbiome refers to the diverse community of microorganisms, primarily bacteria and fungi, that inhabit our gastrointestinal tract. This complex ecosystem consists of trillions of microorganisms that play crucial roles in various bodily functions, such as digestion, metabolism, and even regulation of immune function.

The term enterotype is a classification of gut microbial communities found in healthy people. Since our guts have many different types of organisms present, and describing them all would be difficult, an enterotype is a way of grouping based on the dominant types of bacteria present.

Importantly, these classifications are a part of healthy variation in gut microbiomes. The classifications are stable but can change over time since they are influenced by factors like diet, lifestyle, and the environment.

What Enterotype Do You Have?

Scientists have identified two primary enterotypes that are commonly found in the human gut. It is only possible to know which type you have through testing. Although we still have a lot to learn about these enterotypes, each is associated with different long-term dietary patterns.

The first is the *Prevotella* enterotype, associated with diets low in protein and rich in carbohydrates and simple sugars. Individuals with a *Prevotella*-dominant gut microbiome often consume plant-based diets.

The second is the *Bacteroides* enterotype, associated with diets high in protein and animal fat. Individuals who consume a Western diet tend to have enriched *Bacteroides* populations in their microbiome.

Other enterotypes may exist in the human gut, but they are currently not well defined. So for the purposes of my work, I only considered the role of these two classifications.

How Does This Inform Xanthohumol Research?

The XMaS trial was focused on xanthohumol metabolism and its effects on the gut microbiome. Previous research in laboratory animals suggests that some of the health benefits of xanthohumol might be connected to specific actions on the gut microbiome. In these studies, xanthohumol was both a prebiotic, enhancing beneficial bacteria, and an antibiotic towards other bacteria.

In humans, we found that the response to xanthohumol was quite different from person to person within the trial. Some people's gut microbiome appeared to change with xanthohumol supplementation, while others did not.

To look for the reason for this variation, we examined each participant's gut microbiome enterotype. We observed that xanthohumol supplementation only influenced the gut bacterial population of people with the *Prevotella* enterotype. Those with the *Bacteroides* enterotype did not show any change.

Implications for Health and Wellness

Understanding your gut microbiome enterotype can offer insights into how your body responds to different dietary components and supplements. And this knowledge will help inform a personalized approach to nutrition.

Further research in this area holds promise for the development of targeted dietary and therapeutic interventions for various health conditions related to the gut microbiome.

The next step for our research with xanthohumol is to investigate its use as a therapy for inflammatory bowel diseases. Since these diseases can involve a dysfunctional gut microbiome, we think xanthohumol might help ameliorate those pathologies.

Considering our work on enterotypes, we now believe that xanthohumol may only be effective in individuals with a *Prevotella* enterotype.

Image Credit: Alteza Films

Two students from the Stevens laboratory, Roza Thavrin (center) and Paige Jamieson (right), received a Young Investigator Award from Director Emily Ho (left) for outstanding oral presentations at the 2023 Diet and Optimum Health Conference.

Exploring the Effects of Tetrahydroxanthohumol

Tetrahydroxanthohumol (TXN) is a synthetic xanthohumol derivative that – in laboratory animals – can counteract some of the negative effects of eating a high-fat diet.

With collaborators at Oregon State University, Dr. Adrian "Fritz" Gombart and Dr. Fred Stevens used a new computational method called a "Transkingdom Network Analysis" to explore connections between TXN, the gut microbiome, and genes associated with the development of disease in animals. One of the key findings in their latest publication is that TXN supplementation modulates the growth of bacteria species in the gut associated with negative health outcomes.

For example, animals eating a high-fat diet had higher-than-normal amounts of *Oscillibacter* species in the gut and increased inflammatory signals from immune cells in the animal's adipose (fat) tissue. However, animals eating a high-fat diet supplemented with TXN had reduced gut levels of *Oscillibacter*, reduced inflammation, improved glucose metabolism, and less weight gain.

This connection with specific gut bacteria provides a solid foundation for future investigations with TXN and the potential to develop innovative therapies for metabolic disorders.

References:

Newman et al. *Microbiome* **11 (2023);** doi: 10.1186/s40168-023-01637-4

Miranda et al. *Sci Rep* **8 (2018);** doi: 10.1038/s41598-017-18992-6

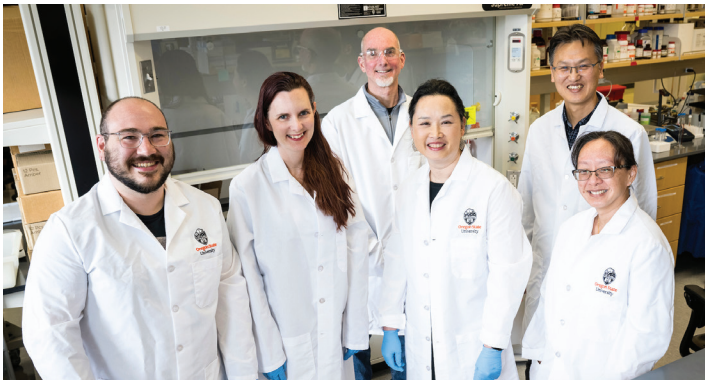
Oregon State University
Linus Pauling Institute

LINUS PAULING INSTITUTE RESEARCH NEWSLETTER

Alexander Michels, Newsletter Editor
Victoria J. Drake, Associate Editor
Sandra Uesugi, Assistant Editor

Oregon State University
307 Linus Pauling Science Center
2900 SW Campus Way
Corvallis, Oregon 97331

phone: 541-737-5075
fax: 541-737-5077
email: lpi@oregonstate.edu
website: lpi.oregonstate.edu



GIVE TO THE INSTITUTE TODAY!

We believe that no matter where you are in life, you can achieve your best health. Supporting the Linus Pauling Institute helps us advance research you care about. Together, we will find the ways to live longer, better.

2023 LINUS PAULING INSTITUTE WEBINAR SERIES

AGING WELL & OPTIMAL HEALTH

THE ROLE OF MICRONUTRIENTS

Recording available online at:
lpi.pub/Ho2023

Emily Ho, PhD
Director, Linus Pauling Institute