aging news

NEWSLETTER OF THE INSTITUTE ON AGING (IOA) | UNIVERSITY OF WISCONSIN-MADISON | SUMMER/FALL 2016

Feeling Older May Increase Your Risk of Hospitalization

Hospital Stays Can Lead to Complications

Hospitalization in old age can be a significant life event. Beyond whatever individual health issues patients are facing, hospital stays have been linked to additional risks, including:

- declines in ability to perform activities of daily living (such as dressing & bathing)
- declines in thinking ability (as measured by cognitive testing).

When severe, these declines can trigger nursing home placement & increased risk of death. Researchers therefore are working to identify factors that contribute to risk of hospitalization in order to prevent such adverse results.

Does the Age You Feel Matter?

Data from over 3400 older adults in three national studies were examined:

- Subjective Age: During an initial survey, participants specified, in years, how old they felt. This was compared to their actual age.
- Hospital Stays: In a later survey, participants reported whether they had had an overnight hospital stay in the previous 1-2 years.

Researchers found that those who felt older than their actual age at the initial survey had an increased likelihood of future hospitalization. For every standard deviation increase in tendency to feel older, risk of future hospitalization increased by 10% in the NHATS sample to almost 25% in the MIDUS study.

Why is Feeling Older Associated with Hospitalization?

- Having more chronic illnesses (e.g., high blood pressure, diabetes) and symptoms of depression explained part of this association, especially in the sample with the oldest participants (NHATS).
- *However, even when chronic illness and depression were taken into account, the association between feeling older and hospitalization remained significant in the MIDUS, the HRS, and the three samples combined.*
- Feeling older is associated with higher inflammation (swelling in bodily tissues), as well as being sedentary, both of which could contribute to hospitalization by increasing vulnerability to disease.

Exercise May Help

Individuals who feel older may benefit from physical activity or exercise programs, which:

- could reduce depression & lessen symptoms of chronic illness, thus reducing risk of hospitalization.
- make people feel younger, by improving physical functioning and increasing positive emotions.
- challenge negative stereotypes about aging to promote more youthful self-perceptions.

Going Forward

This study provided new evidence that the age people feel could be a valuable tool in identifying who is at risk for hospitalization. Future research could test whether programs that promote a more active lifestyle could have an impact on how old we feel, reducing risk of hospital stays and their associated complications.

Study Participants:
Data for this research was drawn from three national studies that surveyed older adults over time:

- **MIDUS-** the Midlife in the United States Survey of Americans 24-75 years old
- **HRS-** the Health & Retirement Study of Americans over 50 & their spouses
- **NHATS-** the National Health & Aging Trends Study of Medicare enrollees 65 years & older.

Source:
Stephan, Y., Sutin, A. R., & Terracciano, A. (2016). Feeling older & risk of hospitalization: Evidence from three longitudinal cohorts. Health Psychology. Advance online publication. doi:10.1037/hea0000335

"Think of the cell as a house during spring cleaning"

says Prof. Luigi Puglielli. "You clean out the attic and clean up the basement, and put out the trash on the curb, but the trash truck never arrives and so the heaps of garbage get higher and higher."

His team has been researching ways to help brain cells take out the trash that contributes to Alzheimer's.

Cleaning Up the Brain Plaques Linked to Alzheimer's

The cause of Alzheimer's disease (AD) is not completely understood, but the build-up of amyloid plaques in the brain is believed to play a major role. IOA Affiliate Luigi Puglielli (Prof., Geriatrics & Gerontology, UW-Madison) and his colleagues have been working to find drugs that can enhance the ability of brain cells to remove these toxic plaques.

Compound 9 Cleans Up Plaque in Mice:

Their research shows that inhibiting two cellular proteins, ATase1 and ATase2, helps clean up the gunky amyloid plaques that form in the brains of mice with AD. When a compound they discovered (#9) was incorporated into the regular diet of these mice, it inhibited ATase1 and ATase2 and reduced the buildup of both amyloid and another Alzheimer's-related protein called tau. It also improved the plasticity of the synapses that let brain cells communicate and increased the lifespan of the mice.

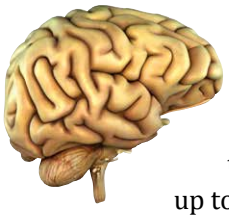
Many Steps Led to this Discovery:

- 2007– Acetylation Creates Plaque: In 2007, Puglielli's team discovered that new proteins can undergo a chemical reaction called acetylation, which occurs within the endoplasmic reticulum, an organelle within the cell that assembles proteins. They found that if the enzyme BACE1 (beta-site APP cleaving enzyme) is acetylated, it can travel through the cell in a series of steps to cleave APP (amyloid precursor protein) and produce amyloid beta peptide (Aβ), the main component of the amyloid plaques that play a major role in Alzheimer's.
- 2009– Two Proteins Control Acetylation: In 2009, they found that two proteins, ATase1 and ATase2, control the acetylation of BACE1.
- 2012– Turning Off the Proteins: After screening 15,000 compounds, they reported in 2012 that two (compound 9 & 19) worked in living cells to shut down ATase1 and ATase2, which in turn resulted in less acetylation of BACE1, and less production of amyloid within cells.
- 2016– Testing in Mice: Compound 9 was shown to reduce amyloid plaque build up in the brains of mice with Alzheimer's.

Will it Work in Humans?

Prof. Puglielli cautions that researchers have a long way to go before testing in humans: "The mice data are strong, but that doesn't mean that compound 9 will succeed in humans...."

"Typically, about 95 percent of compounds that work in vitro fail when you test them in mice. Of those that succeed, about the same percentage fails when you test them in humans."



Their next step is to study the toxicology of compound 9 and to continue screening for more compounds that help enhance the ability of brain cells to clean up toxic garbage. By searching for additional compounds, the investigators hope to have a better chance to find one that succeeds in humans, in hopes of ultimately stopping Alzheimer's disease.

Source: *Peng, Y., Kim, M. J., Hullinger, R., O'Riordan, K. J., Burger, C., Pehar, M., & Puglielli, L. (2016). Improved proteostasis in the secretory pathway rescues Alzheimer's disease in the mouse. Brain, 139, 937-952. doi:10.1093/brain/awv385*

Aging News

IOA Director
Carol D. Ryff, PhD
Prof. of Psychology

IOA Associate Director
Neil Binkley, MD
Prof. of Medicine-Geriatrics

Aging News
Editing & Layout
Theresa Berrie
berrie@wisc.edu

Subscriptions are free, see:
aging.wisc.edu/publications/newsletter.php

Finding Effective Drugs to Slow the Impact of Aging

Rapamycin is an Anti-Aging Drug with Serious Side Effects:

Research suggests that the drug rapamycin can slow the normal aging process as well as slow the progression of aging-related diseases such as Alzheimer's & cancer. However, it has serious sides effects, including:

- changes to glucose tolerance that can lead to high blood sugar and diabetes
- suppression of the immune system that can lead to increased risk of infection.

The FDA-approved drug rapamycin (also known as sirolimus):

- is used to prevent rejection in organ transplants
- and is being tested in human clinical trials to treat cancer.
- However, the drugs' serious side effects may prevent its use as an anti-aging therapy if it needs to be taken daily on a long-term basis.

Can the Side Effects be Reduced?

IOA Affiliate Dudley Lamming (Asst. Prof., School of Medicine & Public Health- Endocrinology, UW-Madison) and his colleagues are hoping to explore ways in which rapamycin can be used for the treatment of age-related diseases in spite of its side effects. They discovered two strategies that yield similar benefits at the molecular level as taking daily doses of rapamycin:

- Using Related Drugs: They tested two FDA-approved drugs similar to rapamycin called everolimus & temsirolimus (which are being studied in cancer treatment) and found that daily doses administered to mice reduced side effects.
- Using Intermittent Instead of Daily Doses: They also tested several rapamycin treatment schedules in mice and discovered that rapamycin taken every five days showed reduced negative side effects on both glucose tolerance and immune suppression.

Intermittent Doses Show Anti-Aging Effects:

Next Prof. Lamming's team tested whether the once every five days rapamycin dosage schedule displayed the drugs' anti-aging benefits. They found that in mice the intermittent dosage continued to significantly extend both average & maximum life span.

Promising Results:

While important questions remain, including the impact of these strategies on other rapamycin-associated side effects, these results demonstrate that the anti-aging potential of rapamycin can be separated from many of its negative side effects. It further suggests that a carefully designed dosing strategy may permit the safer use of rapamycin and its related drugs in humans to impede aging-related diseases.

Sources: *Arriola Apelo, S. I., Neuman, J. C., Baar, E. L., Syed, F. A., Cummings, N. E., Brar, H. K., . . . Lamming, D. W. (2016). Alternative rapamycin treatment regimens mitigate the impact of rapamycin on glucose homeostasis and the immune system. Aging Cell, 15(1), 28-38. doi:10.1111/acel.12405* and *Arriola Apelo, S. I., Pumper, C. P., Baar, E. L., Cummings, N. E., & Lamming, D. W. (2016). Intermittent administration of rapamycin extends the life span of female C57BL/6J mice. Journals of Gerontology Series A: Biological Sciences and Medical Sciences. Advance online publication. doi:10.1093/gerona/glw064*

How Does Rapamycin Work to Reduce the Affects of Aging?

- Rapamycin inhibits a key metabolic protein called mTOR, which plays a role in cellular growth and survival.
- The beneficial anti-aging properties of rapamycin result from inhibition of mTOR complex 1 (mTORC1), which is very sensitive to rapamycin.
- Many of rapamycin's negative side effects are caused by disrupting a second mTOR-containing complex, mTORC2, which is disrupted only after prolonged exposure to rapamycin.
- Prof. Lamming's team therefore looked at rapamycin related drugs or dosage schedules that would more specifically target mTORC1, without disrupting mTORC2.

institute on aging
University of Wisconsin–Madison
2245 Medical Sciences Center
1300 University Ave.
Madison, WI 53706-1532

www.aging.wisc.edu
aging@ssc.wisc.edu
(608) 262-1818

ADDRESS SERVICE REQUESTED

Age is an issue of mind over matter.
If you don't mind, it doesn't matter.

— *Mark Twain*

IOA's 28th Annual
Colloquium on Aging
Tuesday, September 27, 2016

at the Gordon Dining & Event Center on the UW-Madison Campus

SPEAKERS

Keynote- Challenging the Bard: Well-Being and Health into Shakespeare's 7th Age
Elliot Friedman, PhD, Purdue University

A Novel Systems Biology Approach to Sarcopenia: New Molecular Insights Enabled by Cutting-edge Technologies
Ying Ge, PhD, UW-Madison

Maintenance of Balance with Aging: Choose Your Steps Carefully
Darryl G. Thelen, PhD, UW-Madison

Who Cares? The People Who Support Older Adult Health and What They Need
Barbara Bowers, PhD, UW-Madison

MARK YOUR CALENDAR!

For more details see: aging.wisc.edu

HEALTH and RESOURCE FAIR

Showcasing aging-related resources for improving quality of life.

POSTER SESSION

UW-Madison researchers share their recent aging research.

REGISTRATION OPENS AUGUST 1ST
& fills up within a week!

FREE & OPEN to the PUBLIC
but SPACE is LIMITED