It has been well documented that eating a diet with consistently fewer calories can dramatically slow the aging process and improve health in older age. But exactly how a reduced diet acts at the molecular level to blunt the age-related decline of tissues and cells has mostly remained a mystery before now. IOA Affiliates Shinichi Someya (Assist. Scientist, Genetics, UW-Madison) and Tomas Prolla (Prof., Genetics, UW-Madison) were part of a recent study that provided the first direct proof for a mechanism underlying the anti-aging effects that are observed with caloric restriction.

The study focused on an enzyme known as Sirt3, which acts on mitochondria, structures inside cells that produce energy and are the source of the free radicals that cause oxidative damage. Sirt3 belongs to a class of proteins called sirtuins that are known to have anti-aging effects in lower organisms including yeast and flies. Now there is clear evidence that the effect extends to mammals. The recent study involved a mouse model that exhibited age-related hearing loss, which is the most common sensory disorder among older humans. Hearing loss is associated with free radical damage to the cochlea, a structure in the inner ear that converts sound vibrations into nerve impulses.

In normal mice, lowering calorie intake to 75% of a regular diet was shown to delay the onset of age-related hearing loss, but in Sirt3-deficient mice, dietary restriction had no such effect. Further, after caloric restriction, middle-aged mice lacking Sirt3 lost more of the cellular structures vital for hearing than did normal, age-matched mice on a similarly restricted diet. Closer examination revealed that Sirt3 regulates a mitochondria-based defense mechanism called the glutathione antioxidant system, via which caloric restriction works to help maintain the appropriate chemical balance needed to keep safely absorbing free radicals as they appear.

Effects seen in the ear were also observed in brain and liver tissue, suggesting that Sirt3 might have a role well beyond age-related hearing loss, and may be of potential benefit for cardiovascular and neurological diseases. Knowing the molecular basis of how the sirtuin enzymes work may ultimately lead to the development of drugs that slow down the damaging effects of the aging process and contribute to better health in older age.


Life would be infinitely happier if we could only be born at the age of eighty and gradually approach eighteen.
— Mark Twain
Hearing Loss May Not Be Inevitable

IOA Affiliates Karen Cruickshanks, Ronald Klein, and Barbara Klein (Professors, Ophthalmology & Visual Sciences), along with other researchers at the UW-Madison EpiSense Research Program, have been studying human populations to explore whether a healthier lifestyle can delay the onset of hearing loss. The Beaver Dam Offspring Study collected data on 3285 adults, aged 21-84 years, to analyze age related sensory disorders.

Participants were considered hearing impaired if at least one ear had trouble hearing quiet sounds within the range of human speech. It was not surprising that hearing impairment increased with age, but the rate of increase was considerable, from 6% in those aged 35-44, to 11% in those aged 45-54, to 25% in participants aged 55-64, to 43% in the oldest participants aged 65-84.

Factors that contributed to hearing loss included having a parent with hearing impairment, a noisy job, or a history of ear surgery. Lower socioeconomic status, measured by education and occupation, was also associated with worse hearing, as well as several traditional risk factors for cardiovascular disease, including pack-years of smoking, use of statins (usually prescribed for high cholesterol), and self-reported history of myocardial events (such as heart attacks).

“Hearing loss may not be an inevitable part of aging, and our findings point to the possibility that if we live healthier lifestyles, lifestyles that can reduce our chance of cardiovascular disease for example, we may be able to prevent or delay hearing loss,” said lead researcher Scott D. Nash.

The NIH has funded a five year follow-up study for the Beaver Dam Offspring population, which began in 2010. It should shed more light on whether taking care of one’s overall health may help preserve hearing as our population ages.


Universally Understandable Computer Interfaces

The ability to use computers is rapidly becoming essential for effective participation in our society. More and more of the information we need is only available online, from public library catalogs to job applications. This creates a problem for people who can’t use computers due to age, literacy, or disability related barriers, especially for those with limited financial resources. As high speed internet makes the web more accessible to everyone, including those in remote areas, it is important to ensure that all people can actually use and benefit from all that the web has to offer.

IOA Affiliate Gregg Vanderheiden (Prof., Industrial & Systems Engineering and Biomedical Engineering, UW-Madison) founded and is leading Raising The Floor, an international organization that has launched the Global Public Inclusive Infrastructure (GPII) initiative, that seeks to make the web accessible to everyone.

The goal is to make computer interfaces automatically change to a form that people can use. For example, one option would be to have the interface change into one that is so simple and obvious that it could be successfully used by someone who has never used a computer before. Other options would be accessible to people with hearing or vision problems, or those with dementia or other cognitive challenges who may not remember today what they learned about how to use their computer yesterday. With the GPII each person would find that any computer they approached would automatically change into a form right for them, one they can easily understand and use.

GPII would not create new accessibility software, but would instead build the infrastructure needed to make software development and delivery easier, less expensive, and universal. Prof. Vanderheiden will be sharing more information about this project at the IOA Colloquium (see opposite page). For more details, also see: RaisingTheFloor.org and GPII.org, or view the video short on Youtube at: http://tinyurl.com/gpivideo
The prevention of Alzheimer's disease is among the most urgent public health challenges of the 21st century. Dr. Bennett will review the demographic changes taking place regarding the aging population and provide information regarding trends in numbers of persons with Alzheimer's. He will then describe the neurobiology of the disease and discuss how genetic factors appear to lead to the changes in the brain that cause Alzheimer's dementia. By contrast, he will show that a wide range of experiential and psychological factors appear to prevent the disease through the development of brain reserve that reduces the likelihood that the Alzheimer's changes in the brain result in memory loss.

We are rapidly reaching a point where we all need to access information and communication technologies in our daily lives, yet they are increasingly complicated or sometimes beyond our abilities. Even the interfaces on our ovens and thermostats look like computer control panels. What if every device, every thermostat, even computers, were to automatically change into a form that each person is familiar with and can use, whether they prefer a complicated or simple interface? This is the goal of the Global Public Inclusive Infrastructure and the Raising the Floor program. Learn more about how we are working to create a computer that is as easy to use as our TVs used to be.

This presentation will review the growing research literature regarding the benefits of activity in later life. Physical, social, and intellectual activities have all been shown to enhance health and emotional well being, even in the oldest old. The effects of activity on longevity will also be discussed.

Acute respiratory infection (ARI), including colds and influenza, is extremely common, often debilitating, and among the most costly of human illnesses. Other than hand washing, general health measures, contact avoidance, and flu shots, there are no proven preventive measures. With funding from the National Center for Complementary and Alternative Medicine, we conducted a randomized controlled trial to assess potential effects of mindfulness meditation or sustained moderate intensity exercise on the incidence, duration, or severity of ARI. Participants were 50+ years old, and were randomly assigned to 8-weeks of training in meditation or exercise, or to a control group. Findings are very encouraging.
New Risk Factor for Cataracts

Researchers from the Beaver Dam Eye Study have identified a potential new risk factor for age-related cataracts, a disease that clouds the lenses of the eye and can cause reduced vision or blindness. IOA Affiliates Barbara Klein, Karen Cruickshanks, and Ronald Klein (Professors, Ophthalmology & Visual Sciences, UW-Madison) were among the co-authors of a recent article that examined the incidence of one of the three common age-related cataracts with use of sun-sensitizing medications. These widely prescribed medications have the potential side-effect of sensitizing the user’s skin to sunlight, and can cause itching or rashes on skin that is exposed to the sun. Researchers analyzed the relationship between cortical cataracts, exposure to sunlight and ultraviolet rays (which has previously been related to this type of cataract), and the use of sun-sensitizing medications.

A total of 2998 participants from Beaver Dam, Wisconsin were part of the 15 year study. Average annual exposure to UV light (specifically UV-B, or medium wave, ultraviolet light) was based on where participants had lived. Use of sun-sensitizing medications was reported during medical interviews.

Results showed that the use of sun-sensitizing medications increased from 24% at the initial exam to 45% at the 15 year examination. Those with either more UV-B exposure or more use of sun-sensitizing medications had a higher cumulative incidence of cortical cataracts, but the differences were not statistically significant. However, when the interaction between UV-B exposure and the use of sun-sensitizing medications was analyzed, results suggested that those with both higher sun exposure and higher use of sun-sensitizing medications had a greater risk for cortical cataracts. Controlling for diabetes, heavy drinking, or use of a hat or sunglasses to reduce sun exposure to the eyes, did not alter the relationship. If this finding is confirmed through further studies, it may have important implications for future medication use.


Aging Theory Update

IOA Affiliate Craig S. Atwood, PhD, (Assoc. Prof., Geriatrics, UW-Madison) together with collaborator Richard L. Bowen, MD, recently published an update on the Reproductive-Cell Cycle Theory of Aging. Rather than seeing aging as a loss of functionality as we get older, this theory defines aging as any change in an organism over time, as evidenced by the fact that if all chemical reactions in the body were stopped, no change, and thus no aging, would occur. Since the most important change in an organism through time is the chemical reactions that result in a single cell developing into a multicellular organism, whatever controls these chemical reactions that regulate cell growth, development, and death, is believed to control aging. The authors argue that these cellular changes are directed by reproductive hor-
mones of the hypothalamic-pituitary-gonadal axis (HPG axis). Receptors for reproductive hormones (such as estrogens, progestagens, androgens, and gonadotropins) have been found to be present in all tissues of the body. Thus, HPG axis hormones normally promote growth and development of the organism early in life in order to achieve reproduction. Hormone levels then begin to change in men around age 30 and more abruptly in women when they reach menopause, around age 50. When the HPG axis becomes unbalanced, cellular growth and development is dysregulated, and cell death and dysfunction can occur, both of which can initiate senescence, the accumulated damage to cells, tissues, and organs that occurs with the passage of time and that is associated with functional loss during aging.

The article provides an overview of recent new evidence supporting this theory. Disease studies show that women who reach menopause later have less heart disease and stroke, less dementia, and less osteoporosis, supporting the theory that the longer the HPG axis is in balance, the less likely one is to develop age-related diseases. Also supporting this, early surgical menopause has been demonstrated to increase the incidence of these diseases. However, the most compelling supportive evidence is from studies of Hormone Replacement Therapy (HRT). Research with women and men undertaking HRT has shown that taking sex hormones that are biologically identical to human hormones delays the onset, decreases the incidence of, and can reverse the course of age related illnesses such as heart disease, Alzheimer’s disease, osteoporosis, and some types of cancer. However, it should be noted that only biological hormones appear to have these effects. The use of non-human or synthetic hormones has been shown to increase the risk of certain of these diseases. Compellingly, 18 studies have demonstrated an increase in longevity for women taking HRT.

Further studies in support of the theory have shown that suppressing the HPG axis, such as when organisms experience either caloric restriction, cold, or exercise stress, increases lifespan. This is thought to be an evolutionary conserved mechanism that allows organisms to suppress HPG axis signaling and reproduction, thereby conserving reproductive resources (germ cells) for a later time when the environment is better suited to raising offspring. By having the same hormones regulate both reproduction and aging, an animal is able to adjust its fertility and its rate of aging based on environmental conditions.

The authors argue that because of the accumulating evidence supporting this theory of aging, scientific efforts would be well spent on exploring methods to restore balance to the HPG axis as we get older.


new research grants

IOA Affiliate Corinne Engelman (Assist. Prof., Dept. of Population Health Sciences, UW-Madison), was awarded a New Investigator Research Grant from the Alzheimer’s Association entitled, Genetic Architecture of Alzheimer’s-Related Functional and Structural Brain Aging. This study will follow-up the top genetic variants from published genome-wide association studies of late-onset Alzheimer’s disease and brain volume decline in the almost 1300 participants who are part of the Wisconsin Registry for Alzheimer’s Prevention.

IOA Affiliate Nancy Sweitzer (Assoc. Prof., Dept. of Medicine, UW-Madison) was recently awarded a Demonstration Project Grant from the Wisconsin Genomics Initiative, a state initiative designed to improve collaboration between the Marshfield Clinical Research Foundation and other researchers in Wisconsin. The award, titled Investigation of Genomic Associations between Heart Failure and Diabetes Mellitus, is a one-year grant investigating genetic links between heart failure and diabetes. Work will explore the hypothesis that patients with heart failure and particular genes are more likely to develop diabetes, and, similarly, that patients with diabetes and a different set of genes, are more likely to have changes affecting the heart muscle that may predispose them to later development of heart failure.

Dr. Sweitzer also received an R21 award from the NHLBI Institute at the NIH, entitled Reduced Contractile Reserve: A Therapeutic Target in Heart Failure with Normal Ejection Fraction. This type of heart failure particularly affects the elderly, and disproportionately affects women as well. Researchers are trying to identify the precise abnormalities in heart function that occur in this disease, and are investigating drug therapies targeted at these abnormalities.
**Does Weight Discrimination Contribute to Diabetes?**

The development of type 2 diabetes as people age has been strongly associated with obesity (as measured by Body Mass Index or BMI) and central adiposity (having a larger waist-to-hip ratio and larger waist circumference). However, although most people with type 2 diabetes are obese, most obese people never develop diabetes. Researchers have therefore looked for other influences that affect the progression of the disease, such as psychological vulnerabilities. This MIDUS study went one step further and explored whether there is an interaction between the biological health risks and one possible psychosocial factor, that of perceived weight discrimination.

938 MIDUS participants who did not have diabetes were involved in this study. Nine questions assessed whether participants perceived that they had been discriminated against on a day-to-day basis due to their weight, such as how often they were treated with less courtesy and respect than others, how often they were insulted or called names, how often others acted as if they were not as good as them, or how often they received poorer service at restaurants or stores. Weight, height, waist, and hip measurements were also obtained. Glycosylated hemoglobin (HbA$_1c$) levels, higher quantities of which are used to diagnose diabetes, were taken as a measurement of participant’s prior few month’s blood sugar levels.

Results showed that perceived weight discrimination did not interact with BMI or waist circumference to affect HbA$_1c$ levels. However, there was a significant interaction with waist-to-hip ratios. The highest levels of HbA$_1c$ were found among people with high waist-to-hip ratios who also reported weight discrimination. Thus, the physical burden of carrying excessive weight was considerably exacerbated by perceptions of weight discrimination, and may be one of the factors that leads to the development of diabetes.

Understanding how biological and psychosocial factors interact in those who do not yet have diabetes to increase their vulnerability to develop the disease could have important implications in disease prevention. Research has shown that the prevalence of perceived weight discrimination has increased by 66% over the last decade. Effective prevention may need to address sources of weight discrimination, rather than focusing solely on changing health behaviors in overweight people.


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**Social Contact & Mental Function as We Age**

Studies have shown that higher levels of social engagement can decrease the risk for mental or cognitive decline in older age. This MIDUS study researched whether this association is also present at younger ages, and whether different types of social interactions can affect cognition differently.

More than 3000 participants, aged 35 to 84 years, were included in the research. At both MIDUS I and II (approximately 10 years apart), participants reported on three aspects of social engagement, including the frequency of social contacts with their family and friends, and the level of social support and social strain involved in these contacts. Social support was measured by responses to questions about how much one’s family or friends understood you and cared about you, how much they could be relied upon, and how much you could open up to them. Social strain was similarly measured by how much friends and family made demands on you, criticized you, let you down, or got on your nerves.

Mental functioning was tested at MIDUS II through a brief telephone interview. Episodic or verbal memory was assessed through the ability to recall a list of 15 words (i.e., flower, truck, school). Executive functioning, the ability to organize and coordinate ongoing mental tasks, was measured through several similar tasks, was measured through several similar
Over the course of approximately 10 years between data collection for MIDUS I and II, 132 adults in the study experienced the death of a spouse. 52 had lost their spouse within 3 years prior to MIDUS II and were included in this research. Frequency of negative interactions in the marriage was reported through responses to questions about one’s husband or wife, such as, “How often does he or she get on your nerves,” or “How often does he or she argue with you?” Participants also reported the amount of time in the past 30 days that they experienced positive emotions (such as being cheerful, or calm and peaceful) and negative emotions indicating depression (such as being sad or nervous). Sense of resilience was measured in response to agreement with such questions as, “Even when everything seems to be going wrong, I can usually find a bright side to the situation.”

Not surprisingly, results showed that widowed respondents reported significantly greater depression and lower positive emotions at MIDUS II, when compared with the still married control group. However, higher levels of resilience during MIDUS I appeared to buffer the effects of loss on feelings of happiness. Those with high levels of resilience before the loss of their spouse reported similar levels of positive emotions at both MIDUS I & II, whereas lower levels of resilience at MIDUS I were associated with reduced levels of positive emotions at MIDUS II, over and above levels of postloss depression.

There was also a significant interaction between widowhood and quality of marital interactions. Widows who reported more positive interactions with their spouse prior to the spouse’s death had greater declines in positive emotion after their death. In contrast, those who reported more negative interactions with their spouse prior to their death had significantly higher positive emotions at MIDUS II, showing that relief from a chronically stressful condition can result in improvements in emotional health.

Historically, positive emotions following a loss were believed to be an unhealthy response brought on by denial. Now it is believed that positive emotions after a loss are relatively common and indicate genuine adjustment. However, this study showed that the ability to sustain positive emotions after a loss is linked to important preloss factors.

Positive Emotions

After the Death of a Spouse

Most research on emotional reactions to the death of a spouse has been conducted after the loss has occurred, making it difficult to determine if post-loss emotions were a result of the loss or were present beforehand. Through the use of longitudinal data, this MIDUS study researched the question of whether reactions to the loss of a spouse varied according to the surviving partner’s pre-loss sense of resilience or the quality of the marital relationship that was reported before the spouse’s death.

This study further showed the importance of taking into account both the positive and negative aspects of social engagement when trying to promote better mental functioning as we age. Source: Seeman, T. E., Miller-Martinez, D. M., Stein Merkin, S., Lachman, M. E., Tun, P. A., & Karlanbargi, A. S. (2010). Histories of social engagement and adult cognition: Midlife in the U.S. Study. *Journals of Gerontology: Series B, Psychological Sciences and Social Sciences*. Advance online publication. http://dx.doi.org/10.1093/geronb/gbq091

Tests, including reaction time when switching between different instructions (i.e., Say “Go” when the interviewer says “Green,” changed to say “Go” when the interviewer says “Red.”)

Results revealed that higher levels of social contact and support were associated with both better executive functioning and better episodic memory, at all ages. Reports of greater social strain, however, were associated with poorer executive function, but not with episodic memory. Findings also showed that those who reported a decrease in social contacts during the decade between MIDUS I and II experienced a decrease in both types of mental functioning.

This was the first study to show social influences on mental functioning are evident across the life course, not just for those over 65. Greater social interaction may contribute to better mental functioning in part due to the mental demands associated with such interactions. This study further showed the importance of taking into account both the positive and negative aspects of social engagement when trying to promote better mental functioning as we age.


Higher levels of social contact were associated with better mental functioning at all ages.

Over the death of a spouse varied according to the surviving partner’s pre-loss sense of resilience or the quality of the marital relationship that was reported before the spouse’s death.
Despite increasingly low pay lines at the National Institute on Aging, 2011 has been a banner year for the UW-Madison Institute on Aging. Our proposal to continue the MIDUS Study (Midlife in the U.S.) was approved. Indeed, we received a perfect score in review! MIDUS has become a leading public-use dataset for studying the aging process as the interplay between biological, psychological, and social factors. Over 335 publications have been generated to date, across a wide array of scientific fields.

The new 5-year grant will support expansion of the sample by recruiting over 2500 new participants from across the U.S. Data collection will cover the same comprehensive assessments of psychosocial factors, daily stress, cognitive abilities, biological risk factors, and neuroscience as were obtained on the original sample. In addition, the third wave of longitudinal data collection from the original 1995 sample will be launched, thereby covering a 20-year period of change in health and well-being. A thematic focus for the new research will be to evaluate the impact of the economic recession (e.g., financial worries, work/family stress, unemployment, home foreclosures) on the mental and physical health of mid- and later-life adults.

Another MIDUS grant was funded to standardize and improve documentation of the medication data already collected from MIDUS respondents. These data show high use of multiple types of medications and supplements (e.g., prescription and over the counter meds, vitamins and herbs). Standardizing the collected data will make it more readily available for use in future research.

Also approved for 5 years of additional funding is the parallel study in Japan, known as MIDJA (Midlife in Japan). In the prior grant, survey data comparable in content to MIDUS were collected from a probability sample of over 1,000 adults from Tokyo. Biological assessments were then collected on approximately 400 of these individuals. Findings have focused on differences in social and emotional experiences between the two cultures, as well as differences in health risk profiles. The new funds will be used to collect another wave of longitudinal data from the Tokyo sample, as well as increase biological assessment participation.

The MIDUS grant renewal received a perfect score!

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The trick is growing up without growing old.
— Casey Stengel