A long-term study of the elderly has revealed that their average rate of weight loss doubles in the year before symptoms of Alzheimer's-type dementia first become detectable.

The finding may help researchers seeking ways to detect and treat Alzheimer's before it causes irreversible brain damage.

The study is the first to confirm in precise detail a link between weight loss and dementia tentatively identified a decade ago. Researchers report in the September Archives of Neurology that one year before study volunteers were diagnosed with very mild dementia, their rate of weight loss doubled from 0.6 pounds per year to 1.2 pounds per year. The analysis used data from the Memory and Aging Project at the Alzheimer's Disease Research Center (ADRC) at the School of Medicine.

Alzheimer's researchers are working to find biomarkers or indicators that can be used to detect the presence of Alzheimer's before clinical symptoms become obvious. Studies at the ADRC and elsewhere strongly suggest that if Alzheimer's treatments are ever to prevent lasting cognitive damage, they may have to be given to patients before memory loss and other disruptions caused by the disorder are evident.

"A person's weight can vary substantially in a given year, so weight loss alone can't serve as a definite indicator for physicians," said David K. Johnson, Ph.D., research instructor in neurology. "But it's interesting from a biochemical perspective — we don't know why these two phenomena are linked. And weight loss may one day be incorporated into a battery of biomarkers that physicians keep their eyes on for early warning of Alzheimer's-type dementia."

The Memory and Aging Project, which began in 1979, is a long-term study of the links between cognitive health and aging. The project is made possible through the cooperation of hundreds of volunteers age 65 and older who undergo a detailed annual evaluation of their cognitive, neurological and physical health.

In 1991, investigators added patient weight to this annual assessment. Although scientific information on weight loss in the elderly is sparse, studies have suggested that weight generally begins a slow but steady decline of about half a pound per year in the late 50s and early 60s. Gerontologists have speculated that the decline may be attributable to physical shrinkage of the body seen in old age, loss of interest in eating or the wasting effects of cancers and other health factors.

The study analyzed data on 449 participants, most in their 70s and 80s, but some as young as 65. All were cognitively normal at the beginning of the study, but 125 eventually were diagnosed with mild dementia.

"Interestingly, the group of volunteers who developed dementia started the study weighing about eight pounds less on average than the patients who did not develop dementia," Johnson notes. "The two groups lost weight at the same rate for four to five years, and then one year before the detection of even the mildest cognitive symptoms, weight loss increased in the group that would eventually be diagnosed with mild dementia."

It's unclear why the group that developed dementia began the study at a lower average weight. Johnson speculated that a process somehow related to Alzheimer's might have become active earlier in the participants' lives and started to drive their weight down. Alternatively, persons with lower average weight may be more vulnerable to Alzheimer's.

"No matter what we did to control for other health variables, such as diabetes, stroke and hypertension, none of them could account for this effect," Johnson said.

Continued on page 7
Selected Papers from ADRC Investigators

Recently and soon to be published papers by ADRC researchers use data collected from our research participants:


Dr. Mintun and colleagues lead the world in use of a new PET imaging technique to visualize amyloid plaques in the brains of persons with AD. This technique can also be used to see the early formation of plaques in persons without any cognitive symptoms, suggesting that this & like techniques may be beneficial for identifying persons at risk for AD that may benefit from preventative treatment.


Dr. Fagan and colleagues combined their groundbreaking work on biological markers for AD found in cerebrospinal fluid with a new PET imaging technique being tested at Washington University. The results of this combination, when graphed, revealed a potential means to identify persons at high and low risk for AD based on biological and imaging measures.


In this soon to be published article, ADRC investigator, Dr. James Galvin, demonstrates the effectiveness of an 8-item informant (family) questionnaire for detecting dementia. A score of 2 points or higher indicates a high probability that dementia is present. First published in 2005, this tool is attracting a lot of attention for its simplicity and effectiveness.

Volunteers Needed for ADRC Studies

Two projects of the ADRC are in need of new volunteers this year. The Memory & Aging Project enrolls persons aged 65+ with mild memory problems. The Adult Children Study needs a few additional adult volunteers, age 55 or older, with a family history of Alzheimer’s disease (AD) in at least one parent, as well as adult volunteers 45 and older for whom neither parent had AD.

If you know of a potential volunteer, please ask that person to call the ADRC at 314-286-2683. Thank you!

Would you like to make a gift in support of the ADRC?

You may support our research, education and service goals by joining the Friends of the ADRC. Members of the Friends are entitled to attend periodic Friends Receptions featuring presentations on research findings from Dr. John C. Morris, Director of the ADRC, and other investigators, and also receive free admission to various ADRC-sponsored conferences. Friends are encouraged to make an annual gift in support of the ADRC.

Donations from Friends support both the infrastructure upon which the ADRC depends, as well as specific research and educational projects of the Center. Private donations help to fund promising pilot research projects (i.e., small projects to test out new ideas), educational conferences such as the Leonard Berg Symposium series, the training of medical students and fellows, and other worthwhile projects.

To join, simply call the Friends Coordinator (314-286-2683) e-mail adrcfriends@abraxas.wustl.edu.

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HORIZONS is the newsletter of the Alzheimer’s Disease Research Center (ADRC) — a research program in the Department of Neurology, Washington University School of Medicine, funded by grants from the National Institute on Aging and private donations. The ADRC supports and promotes interdisciplinary research on Alzheimer’s Disease. The Memory & Aging Project (MAP) — the clinical research office of the ADRC — provides expert clinical assessments of cognitive functioning in normal aging and dementia.

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John C. Morris, MD, Director, ADRC, & Director, MAP
Eugene M. Johnson, PhD, Associate Director, ADRC
David M. Holtzman, MD, Associate Director, ADRC
Martha Storandt, PhD, Psychometric Core Leader
Nigel J. Cairns, PhD, MRCPath, Neuropathology Core Leader
Alison Goate, DPhil, Genetics Core Leader
Mark Mintun, MD, & Denise Head, PhD, Neuroimaging Core Leaders
J. Philip Miller, MA, Biostatistics Core Leader
Monique Williams, MD, Interim African American Satellite Leader
Thomas M. Meuser, PhD, Education Core/Rural Satellite Leader

Washington University in St. Louis
School of Medicine
Two decades ago, James watched his mother gradually grow worse with Alzheimer’s disease. When he realized that his mother could no longer care for herself, James organized his mother’s care with his two sisters and their kids.

“We all took care of our mother so that none of us had to do it alone.”

Alzheimer’s disease affects 4.5 million people in the United States today. Advancing age is a primary risk factor, such that those over age 75 are especially vulnerable. With a continually aging population, the number of people diagnosed with Alzheimer’s is expected to increase to 14 million by 2050.

As a social worker for the Memory and Aging Project Satellite (MAPS), an in-home assessment and case management program affiliated with the Alzheimer’s Disease Research Center (ADRC), James understands these statistics. Prior to joining the MAPS team in 1992, James gained social work experience with Alzheimer’s through some of his previous clients. During that time, he saw a gap in work with the elderly population. So, he turned his career in that direction.

“It made sense for me to focus on Alzheimer’s,” James explained, “since Alzheimer’s is predominantly a disease of the elderly. So, I joined one of the few centers studying it at the time.”

At the ADRC, James works to help individuals afflicted with Alzheimer’s secure services necessary to maintain independent living. Possible services include daycare, financial support, and a nurse to assist with personal hygiene. After an initial assessment, James and fellow staff determine for which services the individual qualifies. Since 1992, the MAP team has assessed over 1000 Alzheimer’s patients.

During his early days at MAPS, a chance meeting eventually changed his life. While working on the side as a YMCA trainer, he began conversing with a lovely lady named Jackie. After learning of his work, Jackie questioned James about the symptoms of Alzheimer’s because her father was demonstrating unusual behavior. Though her father was not diagnosed with Alzheimer’s, her mother was. A few years after this initial meeting, James and Jackie were married.

“My friends tell me that God sent James to me for my parents,” Jackie said with a smile. “He got them to the right sources to get assessed and to obtain the right medicines.”

Using his knowledge of Alzheimer’s, James efficiently organized care for Jackie’s mother – even contributing himself – until her mother’s death in 2002. Jackie was frequently out of town during that time because of her work and was grateful for James’s timely help.

By being married to James, Jackie became knowledgeable about Alzheimer’s and increasingly aware of the need for Alzheimer’s research. So two years ago, she signed up to regularly participate in research procedures at the ADRC, including MRI and positron emission tomography (PET) brain scans.

“You can’t physically examine the brain while a person is living, but you can do these studies to learn more about what happens in the brain over time,” Jackie stated.

James also uses his knowledge to educate families about the consequences of Alzheimer’s. The disease not only affects a person’s ability to recall recent events, he explained. Eventually, Alzheimer’s hinders a person’s ability to perform everyday routines: personal hygiene, pay bills, clean house, and cook. Because of the need for extensive care, James encourages the entire family to share caregiving responsibilities.

“I have seen families with 13 siblings where only two of them take responsibility to care for their mother,” James laments. “If all contributed, each would only have to see their mother once every two weeks.”

Another reason for watchful attention of Alzheimer’s patients is called ‘sun-downing’. This occurs at night when a person gets confused and begins to wander.

“I knew a person,” James recalls, “who opened the door and went to sit outside on the parking lot all night. It was the coldest night of the year. She died from hypothermia.”

This example underscores the importance of understanding the consequences of Alzheimer’s and of dedicated care to an individual with the disease.

“I just think that knowledge is power,” Jackie said. “If I had known back then what I now know, I would have interacted differently with my mother.”

This knowledge motivates James and Jackie to participate in Alzheimer’s research. As an ADRC staff member, James educates people everyday about the disease. Jackie, as a research participant, encourages others involvement by explaining her experiences.

Both stress the importance of doing research today to find better therapies in the future.

“Why wouldn’t you participate?” Jackie asks. “To me, you’re building for the future prevention of Alzheimer’s disease.”

This article was commissioned by the ADRC for public education and originally appeared in the October 19, 2006 issue of the St. Louis American newspaper.
Dr. Alison Goate is the Samuel and Mae S. Ludwig Professor of Genetics in Psychiatry and Leader of the ADRC Genetics Core.

Alzheimer’s Q & A — Genetics

Is Alzheimer’s disease a genetic disorder, passed on from parent to child?

There are basically 2 types of Alzheimer’s disease: Autosomal dominant and sporadic.

**Autosomal Dominant** Alzheimer’s disease is passed on from generation to generation: each child of a person with disease has a 50% chance of inheriting the disease from their affected parent. This usually results, by chance, in half of the children of an affected parent getting disease. The cause of this is a genetic mutation in a gene on one of 3 different chromosomes: 1, 14, or 21. Just one change in the genetic code can cause this disease in families with these mutations. Inherited Alzheimer’s disease accounts for less than 1% of all Alzheimer’s disease.

**Sporadic** Alzheimer’s disease is the more common type of Alzheimer’s disease, which increases in frequency with increasing age. This type of Alzheimer’s is said to be a complex genetic disorder, meaning that there are probably multiple genetic and environmental factors that contribute to the onset of the disease. No single change in our DNA is either sufficient or necessary to cause this type of Alzheimer’s disease. APOE4 is one of these risk factors. Sporadic AD may show some modest clustering in families because the disease is common among the elderly but the increase in risk to a child of an individual with this type of dementia is modest.

The majority of our research through the ADRC is focused on understanding the factors that increase or decrease risk for sporadic Alzheimer’s disease. We have learned an immense amount about the disease from families with rare mutations, enabling researchers to develop animal models of the disease for the first time. These animal models will allow for the development and testing of new treatments for Alzheimer’s disease.

I’m a participant and have given blood for genetic studies. How are such samples processed and used in the research?

Blood samples are processed first to obtain plasma and serum for biomarker studies. These are frozen (at -80°C!) long term and utilized by researchers approved by the ADRC Executive Committee for projects that could lead to tests for Alzheimer’s disease, as well as other studies investigating the biology of the disease.

DNA is then extracted from the white blood cells in the blood or from the buccal cells (cheek cells) in the mouth (from a saliva sample). The DNA is processed to look at the genetic code for various proteins which might be different in people with the disease (cases) from people without the disease (controls).

We evaluate participants over years and years (longitudinally) because age is a factor in disease development. We are especially interested in following people to death with an autopsy because verified disease status is especially valuable in this type of research. Some participants do not show any signs of disease in life, but changes might be seen at autopsy. This helps us to more clearly understand the genetic side of the story because we have more complete information about the participant.

Did you know that we can even obtain DNA from brain tissue? For those participants who were unable to give a DNA sample in life, we can still learn about them after they have died!
Why is the analysis of cerebrospinal fluid important for advancing research on Alzheimer’s?

Alzheimer’s disease (AD) is a disease of the brain. Since the brain is bathed by and in direct contact with the cerebrospinal fluid (CSF), analysis of CSF gives researchers a picture of what may be happening in the brain. Currently, depending on the study, our research center uses CSF samples to: 1) measure the presence of different types of substances in the CSF, 2) to search for a possible “marker” of AD that will allow us to develop a simple diagnostic test for AD, and 3) to see if and how the CSF changes in response to specific research treatments.

Lumbar puncture (LP), also known as a spinal tap, is a simple and low-risk method for obtaining samples of CSF and is routinely performed in an outpatient office setting. Researchers are able to measure different substances found in CSF, comparing the levels in individuals with AD with those who don’t have AD, in hopes of discovering “biomarkers” of the disease. Identification of AD biomarkers in CSF will hopefully allow doctors to tell if a person has AD and will help researchers develop and test new treatments. Since the changes taking place in the brain in AD are known to develop 10-20 years before any symptoms can be detected (a stage known as “preclinical AD”), our ultimate goal is to be able to identify people in this “preclinical” stage, before the brain is irreversibly damaged. In this way, treatments will have the best chance to preserve normal brain function. Analysis of CSF will also allow researchers to test whether new treatments are having the right effect on the brain. The quicker we are able to develop and test new treatments, the quicker we will be able to get an effective treatment into the hands of the people who need it.

I’ve been asked to consider having a Lumbar Puncture (LP) to collect cerebral spinal fluid (CSF), but I am worried about side effects. Are there risks involved in this procedure?

Any time the skin is pierced, even by a splinter, there is a risk of infection. The risk of infection from a lumbar puncture (LP), however, is very, very low and is comparable to the very low risk of infection when blood is taken from the arm for laboratory tests. We are extremely cautious about cleaning the skin and maintaining a sterile area during the LP procedure. As a result, there have been no instances of infections related to LP in our program.

Other potential risks associated with LP include minor pain, bruising, and/ or swelling, similar to that obtained when giving a sample of blood. Some people can become dizzy or faint during the procedure. These people are typically those who also feel faint during a routine collection of blood. Another possible side effect of a LP is headache. These headaches are usually mild and last up to two days. Approximately 5 out of every 100 individuals getting a routine LP for our research project experience a more severe headache. Rarely, some individuals may also feel nauseous and dizzy related to the headache itself.

When a severe headache occurs, it usually goes away as long as the person lays flat. Although these headaches will eventually resolve in time and are not a threat to health, a “blood patch” can be performed 24-72 hours after the LP. We recommend a blood patch when a severe headache occurs. A blood patch involves taking a sample of blood from one’s arm and injecting it into the site of the lumbar puncture, sealing it. The blood patch usually provides immediate relief from the headache.

The fluid that is removed with the LP procedure is called cerebrospinal fluid (CSF). The CSF surrounds and is within the brain. The CSF fully replenishes itself 3 times each day, so any amount obtained with the LP is quickly restored naturally by the body.
Older adults in rural Missouri face a host of obstacles to receiving comprehensive Alzheimer’s disease (AD) screening and specialized care. The challenges of living in a rural area also extend to caregivers, who are frequently unable to utilize in-home services and other forms of support their counterparts in more populated places access routinely.

Shannon Kitchen, Southeast Missouri Outreach Coordinator for the Alzheimer’s Association, addresses the special needs of older adults in rural Missouri. He recognizes common hurdles to receiving Alzheimer’s care, and his goal is to raise awareness about Alzheimer’s Association resources. According to Kitchen, the most common obstacles to receiving AD screening, diagnosis, and treatment in rural Missouri include:

- Lack of specialist physicians, such as neurologists, geriatric psychiatrists, and geriatricians.
- Transportation limitations: it can be difficult for older adults to travel long distances for medical care.
- Lack of support programs and services, both for the person with AD and for his or her caregiver.

Where are the Specialist Physicians?

While primary care physicians are commonly found in rural Missouri, specialists are not. Neurologists and geriatric psychiatrists, who may specialize in diagnosing and treating AD, more often practice in densely populated areas like St. Louis or Kansas City and surrounding suburbs.

With his colleague Lisa Hicks, Shannon Kitchen provides rural physicians and healthcare centers with AD-related resources. “Part of our job,” says Kitchen, “is to reach out to and educate physicians and other professionals about Alzheimer’s Association resources.” These healthcare providers may frequently see patients with dementia, so it’s important that we help them stay up-to-date.”

Susan Luedde, MetroWest Outreach and Support Group Coordinator for the Alzheimer’s Association, recommends that rural physicians, nurse practitioners, and physician assistants educate themselves about current best practices for AD screening and care. Luedde specifically suggests that rural clinicians who regularly see older patients attend continuing medical education (CME) programs, such as the ADRC’s Rural Clinician Partners Program (CPP). The CPP is designed as a 3-day mini-residency in dementia diagnosis, treatment, and care. Funded by the ADRC’s federal grant, the CPP is free of charge and covers all trainee expenses in visiting St. Louis, including up to 20 hours of CME credit. “I wish,” Luedde says, “that more doctors in rural Missouri would take advantage of all CPP has to offer.”

Traveling Long Distances for Medical Care

When treatment is required beyond the scope of the primary care setting, rural Missourians may have to travel as far away as St. Louis, Kansas City, or even Memphis, Tennessee for medical care. Transportation to these urban areas, however, can be difficult for the rural older adult and his or her family to organize. “Some older adults,” says Kitchen, “do not or cannot drive. In addition, the rural elderly may not have nearby children or other family members to provide transportation to a big city for specialized Alzheimer’s care.” Further complicating matters, the financial burden of transportation – due to the cost of gas or fare for a bus or train – may prevent rural elderly from keeping appointments with specialists in urban areas. This is especially problematic for patients with Alzheimer’s, where follow-up visits are frequently required to monitor the course and treatment of the disease.

Securing nursing home placement is also stressful in the rural environment because the closest nursing home may be 30 to 40 miles away from family members’ homes. Traveling such distances to visit a loved one can be difficult, and, in effect, may reduce contact between the person with AD and his or her family. Susan Luedde also finds that families “often misunderstand what different levels of care entail.” Families may not choose the nursing home or long-term care facility that best fits their loved one’s needs, but opt instead for the most conveniently located facility.

In Need of Support and Services

Caregivers in rural Missouri may at times feel stressed or overwhelmed by the day-to-day work of taking care of a loved one with AD. Unfortunately, many in-home services offered in urban and suburban areas are not available or accessible in rural Missouri. But help does exist for the rural caregiver. The Alzheimer’s Association provides funds for respite care and has a 24-hour Helpline that puts caregivers, family members, and people with AD in touch with helpful resources and informative materials (see resources on page 7).

(continued on next page)
"There is a higher risk of cognitive impairment... and of Alzheimer’s disease among ethnic minorities in the United States... among African Americans and among Hispanic elders."

“There is a bias in our instruments and how accurate we are at detecting subtle... memory deficits that occur in early Alzheimer’s disease.”

“I do not believe that race itself is what we need to be paying attention to when we look at these cognitive effects. Race is a proxy for other, more meaningful variables. Race is a proxy for your cultural experience, and there are huge differences within us on our cultural... and our educational experience.”

“We know that African Americans have higher rates of hypertension and diabetes. The ethnic discrepancies in rates of Alzheimer’s disease persist, even after controlling for these higher rates (of disease)."

“We need longitudinal studies of a large number of African Americans age 50 and older... We need to answer this question: How accurate are we in making our diagnosis of Alzheimer’s disease?”

Weight-loss rate doubles

"Sometime between the last evaluation when they were healthy," Johnson continued, “and this first evaluation when they had mild dementia, a metabolic process kicked in, or kicked into higher gear, and made their Alzheimer's detectable. And increased weight loss went hand-in-hand with that change.”

Johnson and co-authors Consuelo Wilkins, M.D., assistant professor of medicine, and John Morris, M.D., the Harvey A. and Dorismae Hacker Friedman Distinguished Professor of Neurology and director of the ADRC, said they hope to learn more about the links between weight loss and dementia through the Adult Children of Alzheimer’s Project, a new long-term study of volunteers whose parents were diagnosed with Alzheimer’s.

This article originally appeared in the Washington University Record on Thursday, October 5, 2006.
Notables

**David Holtzman**, MD, presented the prestigious Soriano Lecture at the American Neurological Association annual meeting in Chicago on October 8th.

**Alison Goate**, DPhil, and **John Morris**, MD, were invited speakers at the Alzheimer Centenary Meeting, "Alzheimer: 100 years and beyond", which was held in Tubingen, Germany, November 4-5th (see http://www.alz100.de/idea.html).

**John Morris**, MD, received the Mensch Award from the Alzheimer’s Research Forum at the Society for Neuroscience meeting in early November.

**James Galvin**, MD, was recently named to the Editorial Board for Acta Neuropathologica and to the International Scientific Advisory Council for the Lewy Body Dementia Association.

**Anne Fagan Niven**, PhD, was awarded the "Alzheimer's Disease Neuroimaging Award" from the Alzheimer's Association at the 2006 International Conference on AD in Madrid, Spain. The award was in recognition of recent work published in the Annals of Neurology.

**Consuelo Wilkins**, MD, was awarded the NMA/MCMF “Distinguished Leadership and Service Award” at the Mound City Medical Forum Scholarship Dinner on November 4th.

**Lei Wang**, PhD, and colleagues Erik Herzog and Michael Neff, both in the Department of Biology, raised over $12,000 for the MS Society on the Missouri Bike Tour this past summer.

**Guojun Bu**, PhD, notes the launch of a new journal, *Molecular Neurodegeneration*. Dr. Bu is the inaugural Editor-in-Chief. For more information, please visit the website at www.molecularneurodegeneration.com.

**ADRC Anniversaries**

Congratulations to three members of the ADRC family who are celebrating important anniversaries:

- **Mary Coats** — 20 Years at ADRC
- **Betsy Grant** — 20 Years
- **Virginia Buckles** — 15 Years

Congratulations are also in order for the staff and participants who give their time to the ADRC, year after year. Ten years have now passed since the ADRC moved to its current location at 4488 Forest Park! How time flies!

3 ADRC Investigators Named to Prestigious “2006 Scientific American 50”

The magazine's board of editors chose David Holtzman, M.D., the Andrew B. and Gretchen P. Jones Professor and head of the Department of Neurology; Randall Bateman, M.D., assistant professor of neurology; and John Cirrito, Ph.D., a postdoctoral research associate in neurology and psychiatry, for the list based on their outstanding contributions to understanding how Alzheimer's disease originates in and affects the brain. Congratulations to all three!