In the ever-evolving saga about body weight and dementia, the plot just thickened. In fact, it put on some serious poundage. According to the largest study ever conducted on the subject, obese people in the United Kingdom carried a third lower risk of developing dementia than healthy-weight peers, while their underweight compatriots padded their risk by the same amount. The study stands against a backdrop of conflicting evidence—some previous studies linked mid-life obesity to dementia; others did not. The findings underscore the complex relationships between dementia and lifestyle factors, such as body weight. Researchers led by Stuart Pocock at the London School of Hygiene and Tropical Medicine reported their findings in the April 10 Lancet Diabetes and Endocrinology.

Before you inhale that entire tub of ice cream, know that the other health risks of obesity still outweigh the benefits of potentially dodging Alzheimer’s and similar diseases. “Even if obesity protects you from developing dementia, you may not live long enough to get the benefit,” cautioned first author Nawab Qizilbash of OXON Epidemiology, a contract research organization in Madrid. Shorter life expectancy did not explain why people with high body-mass index were spared from dementia, however, because Qizilbash and colleagues corrected for a host of potentially confounding factors including mortality.

Research conducted in the last decade paints a murky picture of the body weight/dementia dynamic. Epidemiological data from several countries indicates that obesity in middle age increases the risk of dementia later in life. Typifying the “obesity paradox,” other findings suggested that while middle-age obesity raises the later risk of dementia, obesity in old age actually protects people. Others found that being underweight can precipitate dementia, while being overweight protects. Some studies found that the girth of the midsection, but not body mass index, elevated dementia risk. Overall, a meta-analysis on AlzRisk indicated that being over or underweight may be a risk factor for dementia at some point in life, but that more studies with longer follow-up times were needed.
Obesity cont’d…..

Qizilbash and colleagues drew from the United Kingdom Clinical Practice Research Datalink. CPRD is a massive database containing health information about anyone in the country who has visited a general practitioner. They looked at the earliest available BMI measurement for nearly 2 million people who were 40 years old or older between 1992 and 2007, and retrospectively tracked the cohort for dementia diagnoses until 2013. They then compared dementia rates with those one-time baseline BMI measurements.

During an average of more than nine years of follow-up, a dementia diagnosis was made in 45,507 people, or 2.4 percent of the cohort. Compared to people who had a healthy BMI of 20-24.9, those whose BMI was lower had a 34 percent higher incidence of dementia. In contrast, dementia incidence went down as BMI rose above 25, with very obese people with a BMI over 40 having a 29 percent lower risk of developing dementia than healthy-weight people. These associations held up when the researchers adjusted the data for age, smoking, alcohol use, diabetes, previous heart attack, and the use of statins or anti-hypertensive drugs.

The correlations held up regardless of how long people were tracked after their baseline BMI measurement. In other words, underweight people had the highest risk of dementia of all BMI groups at one year or 15 years after their BMI measurement. Obese people in the study were younger, on average, at baseline than those who were underweight, but that did not explain why they were protected—the relationships between BMI and dementia held steady even when the researchers considered only people whose initial BMI measurement was taken by age 55.

To address the obvious question of whether obese people escaped dementia by dying earlier, the researchers adjusted for mortality. They found that while body weight associated with mortality (both obese and underweight people had higher death rates than healthy-weight people), adjusting for that did not dramatically alter the association with dementia. Even when taking each person who died and counting him or her as a survivor who was twice as likely to develop dementia because of some ongoing co-morbidity, obese people still had a 20 percent lower risk of developing dementia than healthy-weight people.

Deborah Barnes of the University of California San Francisco, was impressed by the study’s size and extensive controls. “This is a really interesting study that calls into question the belief that obesity in mid-life is associated with an increased risk of developing dementia later in life,” she wrote. “It still is not clear whether this is a causal relationship or whether BMI is a marker of something else—perhaps socio-economic status or access to enough food.”

Continued on next page...
Researchers were hesitant to speculate why obesity would protect against dementia. Costantino Iadecola of Weill Cornell Medical College in New York offered that increases in adipocyte hormones such as leptin might be involved because they are thought to be neuroprotective. However, he noted that the protective effect of being overweight flattened out as BMI increased in the study, suggesting that a simple linear relationship between leptin and reduced dementia risk was unlikely.

Iadecola cautioned against over-interpretation of the results, pointing out that BMI is not a measurement of overall health, and does not explain why a person is over or underweight. “Someone’s body weight is a result of myriad different influences that you cannot just sum up with one number,” he said. Iadecola said that, for example, the location of fat tissue in the body influences its health effects. Also, people who are underweight could have lost fat, muscle, or bone, all of which influence health outcomes differently. He added that food intake should not be interpreted as the only factor influencing weight loss or gain, as metabolic conditions can play a role. Finally, Iadecola noted that different forms of dementia are likely to be influenced by different health and cardiovascular factors, and the study did not distinguish between dementia types.

“This provocative study brings to the forefront our need to gain an understanding of how body weight is regulated in different age groups, and its cognitive impact,” he said. “We have to use this as a starting point.”

Because this study was based on a baseline measure of BMI, Qizilbash said the researchers will next consider how gaining or losing weight affects dementia. For example, dementia risk could be different for a person who has been underweight all of his or her life than another person who rapidly starts shedding pounds due to a health problem. Qizilbash said the most important finding of his study is that being underweight is a strong risk factor for dementia, even many years prior to onset. “This risk factor needs to be addressed,” he said. Regarding the obesity side of the data, Qizilbash said, “The idea that reduction in obesity will lead to a reduction in dementia is probably incorrect.”

In an accompanying commentary, Deborah Gustafson of the University of Gothenberg in Sweden struck a cautious tone. She mentioned several limitations, including the lack of specific dementia diagnoses and the wide distribution of age at which BMI was measured in the cohort. “To understand the association between BMI and late-onset dementia should sober us as to the complexity of identifying risk and protective factors for dementia,” she wrote. “The report by Qizilbash and colleagues is not the final word on this controversial topic.”—Jessica Shugart

This article originally appeared on Alzforum. Reprinted with permission.
The Alzheimer’s Disease Neuroimaging Initiative – Depression Project (ADNI-D)

An exciting new partnership is underway between University of California San Francisco’s Late-Life Depression Program and the Alzheimer’s Disease Neuroimaging Initiative (ADNI), collaborating to help pave the way for new information in the areas of major depression, Alzheimer’s research, and mental health. Due to limitations experienced in past studies, researchers have had inconclusive results in understanding specific causes of cognitive dysfunction in depressed adults older the age of 65. With the development of new imaging technology however, medical researchers now have a tremendous opportunity to clarify and answer the neurobiological questions associated with cognitive impairment and late life depression. ADNI-D aims to use these new techniques to explore the association of amyloid distribution, the impact of low blood flow in the brain, and cerebral atrophy with late life depression, which may help explain the perplexing association between cognitive decline and depressive symptoms in older adults. The study is currently enrolling at two different sites in San Francisco, California and Pittsburgh, Pennsylvania.

For more information please call:
University of California, San Francisco: (415) 476-7046
University of Pittsburgh: (412) 586-9061
To Learn more about the study, visit us online at
http://adcs.org/Studies/ADNI-D.aspx
UTMB Scientists Use Immunotherapy to Reduce Memory Problems with Alzheimer’s Disease

A new study from the University of Texas Medical Branch at Galveston has revealed that a single dose of an immunotherapy reverses memory problems in an animal model of Alzheimer’s disease. The article appears in the March 25 issue of the Journal of Neuroscience.

Researchers have been working for decades to map out how Alzheimer’s disease wields its devastating effects. Although it’s known that two molecules – tau and amyloid beta – are considered responsible for the disease’s progression, the relationship between these two proteins and resulting memory problems has remained unclear.

Brain cells depend on tau protein to form highways for the cell to get nutrients and get rid of waste. In some neurodegenerative diseases such as Alzheimer’s disease, the tau protein changes into a more toxic form referred to as an oligomer. When this happens, molecular nutrients can no longer move to where they are needed and the brain cells eventually die.

Scientists from UTMB have previously shown their anti-tau oligomer immunotherapy reduced levels of tau oligomers and reversed memory deficits in an animal model of Alzheimer’s. In the current study, it came as a surprise that the immunotherapy also reduced amyloid beta oligomer levels, suggesting that the detrimental effects of amyloid beta are dependent on the presence of toxic forms of tau.

“Our findings with this immunotherapy study indicate a link between tau oligomers and amyloid beta,” said lead author and associate professor of neurology, Rakez Kayed. “Because of this relationship, removing tau oligomers with our immunotherapy may also decrease the harmful effects amyloid beta and mitigate memory deficits.”

What sets Kayed's therapy apart from other tau immunotherapy drugs is that his targets only the toxic oligomer form of tau and leaves the normal tau alone and able to carry out its typical functions. These findings provide strong evidence of the benefits of targeting tau oligomers with immunotherapeutic approaches as an Alzheimer’s disease treatment.

The other authors of this paper include UTMB’s Diana Castillo-Carranza, Marcos Guerrero-Munoz, Urmii Sengupta, Caterina Hernandez, Alan Barrett and Kelly Dineley. This paper was supported by the Cullen Trust, the Alzheimer’s Drug Discovery Foundation, the UTMB Mitchell Center for Neurodegenerative Disease, the UTMB Sealy Center for Vaccine Development and these studies were completed as part of an interdisciplinary research team funded by The Moody Project for Translational Traumatic Brain Injury.

Reprinted with permission from UTMB Galveston
The Mediterranean-DASH Intervention for Neurodegenerative Delay – The MIND Diet and AD

By Neelum T. Aggarwal, MD
Rush Alzheimer’s Disease Center
Rush Institute for Aging
Chicago, IL

Information on the role of diet and physical activity to cardiovascular health has been reported in the literature for many years. Recently, the focus has shifted to brain health; what is the role of nutrition to brain health? Are there certain foods that would prevent cognitive decline or Alzheimer’s disease (AD) or enhance cognition? A recent paper by Morris et al. sought to examine the relationship between diet and developing AD, from a well established longitudinal study of persons in Chicago participating in the Memory and Aging Project (MAP).

The Memory and Aging Project is a cohort study of people aged 65 years and older living in retirement communities and senior public housing units in the Chicago area. The cohort study began in 1997 and includes annual cognitive testing and clinical neurological examinations. From 2004 - February 2013, the MAP study participants were invited to complete food frequency questionnaires. Over the course of the diet study, 1,545 older adults enrolled in the MAP study and 1,068 completed the dietary questionnaires. A total of 923 had at least two neuropsychological assessments and were clinically determined not to have AD at baseline. All data derived was based on this group of people. The food questionnaire asked participants to report usual frequency of intake over the previous 12 months of 144 food items. Nutrient levels and total energy for each food item were based either on portion sizes (e.g. slice of bread) or according to age and sex-specific portion sizes from national dietary surveys.

Continued on next page...
The Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet score has 15 dietary components including 10 brain healthy food groups (green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, fish, poultry, olive oil and wine) and five unhealthy food groups (red meats, butter and stick margarine, cheese, pastries and sweets, and fried/fast food) (1). The total MIND diet score was determined by summing up all 15 of the component scores. The DASH diet scoring, was based on seven food groups and three dietary components (total fat, saturated fat and sodium). (2) The Mediterranean Diet Score includes 11 dietary components, and was computed based on scoring as established scoring scales (3). Over the course of 4.5 years, a total of 144 people developed AD. The MIND diet score was linearly associated with a lower risk of developing AD - people with the top MIND diet scores had a 53% reduction in the rate of developing AD compared with participants with the lowest. Even those participants in the middle range of the MIND diet scores had a statistically significant 35% reduction in AD rate compared with those with the highest scores. Consider how this compares to results from two other diets, the Mediterranean and DASH. Only the highest levels of the Mediterranean and DASH diet scores were significantly associated with reduction of incident AD. (54% reduction in AD for Mediterranean diet and 39% reduction for the DASH diet).

Interestingly, the MIND diet and relationship to developing AD was not modified by age, sex, education, physical activity, obesity, low BMI, or histories of stroke, diabetes, or hypertension. Thus this diet appears to be a more “realistic” type of diet that many adults can apply and derive benefits. Future studies in larger community based populations and populations that are racially / ethnically diverse are needed to examine whether this diet offers the same beneficial effects.

Want to read more? Here are three articles you can review to learn about the diet, nutrition and Alzheimer’s Disease.


Tiny brain bleeds in Alzheimer’s patients put them at a higher risk of stroke and cardiovascular disease. Which one develops depends on where those microbleeds occur, according to the latest findings from the MISTRAL Study. Scientists led by Wiesje van der Flier, VU University Medical Center, Amsterdam, report that AD microbleeds in deep non-lobar regions of the brain, such as the basal ganglia, associate with cardiovascular problems and related mortality. In contrast, those in the outer lobar regions of the brain foretell stroke and stroke-related death. The findings, reported in the March 23 JAMA Neurology, could have implications for understanding subtypes of the disease and conducting Aβ immunotherapy trials.

“The findings are really very striking,” said Costantino Iadecola, Weill Cornell Medical College, New York. “[The study] separates two different groups of patients based on the location of these microscopic abnormalities. This is the first time such a regional specification has been so clear-cut.”

Microbleeds, especially in the lobar region, are more common in AD than in the general population (Cordonnier et al., 2006). Van der Flier and colleagues previously reported that these ruptures of teeny blood vessels predicted mortality in AD (Hennemen et al., 2009). However, it was unclear what was driving this mortality.

To find out, first author Marije Benedictus and colleagues conceived of the MISTRAL study, short for “do Mircrobleeds predict STRoke in ALzheimer’s” disease. They recruited participants from a memory clinic in Amsterdam who had been diagnosed with AD between 2002 and 2009. They gave each a physical and neurologic examination, and a brain MRI. Out of 5,229 volunteers, 111 people, with an average age of 71, showed evidence of microbleeds in the brain. Benedictus followed up on those patients using data from the Dutch Municipal Population Register, and from the national register, Statistics Netherlands, to see who had died, and how, between 2012 to 2014. She correlated microbleeds with stroke-related deaths and cardiovascular mortality. To see how microhemorrhages related to morbidities and other factors, the researchers sent questionnaires to patients’ physicians asking about incidence of stroke, cardiovascular events, nursing-home placement, and use of antithrombotics—anticoagulant or antiplatelet drugs that reduce the formation of blood clots. For comparison, the researchers selected another 222 age- and sex-matched AD patients with no microbleeds for follow-up as well.

Continued on next page...
Microbleeds cont’d……

While only 38 percent of people in the group without microbleeds died, 56 percent (62 people) from the group with microbleeds passed away. Within the latter group, those who had lobar microbleeds at baseline were likelier to die of stroke or to have experienced a stroke. Though the number of these events was too small to calculate which stroke subtype was responsible, intracerebral hemorrhage seemed to occur more frequently in people with lobar microbleeds, as compared to ischemic stroke. This implied that a higher risk for bleeding could explain the more frequent strokes. On the other hand, patients with non-lobar microbleeds were likelier to die of a cardiovascular-related illness or to suffer a cardiovascular event such as myocardial infarction, heart failure, cardiac arrhythmia, or aortic aneurysm. People with lobar and non-lobar microbleeds had even greater chances of incident stroke and cardiovascular events if they were taking antithrombotic medication. Antithrombotics previously had been found to increase the risk of cerebral microbleeds in elderly people.

All in all, the study confirms the group’s previous finding that microbleeds predict mortality in AD. It further establishes that microbleeds from lobar regions predict stroke, while those in deeper, non-lobar regions predict cardiovascular-related problems in AD patients. A previous study in the general population linked lobar microbleeds with amyloid deposition and cerebral amyloid angiopathy (CAA)—the buildup of Aβ in blood vessels.

That microbleeds predispose for stroke could have implications for trials of Aβ immunotherapy, Iadecola said. A worrisome side effect seen in immunotherapy trials for AD are amyloid-related imaging abnormalities (ARIA) that indicate leakiness or bleeding in the brain’s blood vessels. “If these vessels are already damaged, as indicated by the presence of microbleeds, immunotherapy may further increase the vascular risk,” said Iadecola. He suggested paying special attention to these patients during trials to see if and how they differ, and whether they require special doses or treatments. “Amyloid around blood vessels has become a major issue,” agreed Alex Roher, Arizona Alzheimer’s Consortium, Phoenix, saying that the paper supports an association between CAA and microbleeds. “We should investigate the effects of immunotherapy on blood vessels that are loaded with amyloid.” Benedictus noted that they are unsure whether the spontaneously occurring microbleeds are the kind that result from clearing amyloid, but echoed that these trial participants deserve special consideration.

In terms of the risk from antithrombotics, Benedictus was careful not to over-interpret those results. They could suggest that physicians need to balance the lowered risk of ischemic stroke and cerebrovascular disease that comes with these medications, with the possible heightened risk of bleeding, she said.

—Gwyneth Dickey Zakaib

This article originally appeared on Alzforum. Reprinted with permission.
ADCS Clinical Trials Enrolling...

For information on the following studies please visit:

http://www.adcs.org/Studies/c|linalResearchStudy.aspx

A4 – Anti Amyloid in Asymptomatic Alzheimer’s Disease

NOBLE A Study for People with Mild to Moderate Alzheimer’s Disease

The CONNECT Study for people with Mild-Stage Alzheimer’s Disease.
On a temporary enrollment hold until further notice:

SNIFF – the Study of Nasal Insulin to Fight Forgetfulness

More studies coming later in 2015....