At 50, Each Body Mass Index Unit Increase Hastens Alzheimer's 6.7 Months

Cynthia Fox, Science Writer

A new *Molecular Psychiatry* [1] study has found a robust relationship between obesity at age 50—as measured by body mass index (BMI)—and both earlier age, and severity, of Alzheimer's disease (AD).

In particular, a National Institutes of Aging (NIA) team found that each unit increase in midlife BMI predicts earlier onset of AD by 6.7 months.

"This paper reports analysis of a very well-characterized cohort to identify how midlife obesity influences risk of late-life dementia," Kaarin Anstey, Ph.D., F.A.S.S.A., told *Bioscience Technology*. Anstey is director of the Australian National University Dementia Collaborative Research Centre.

"Importantly, the authors showed that high BMI in midlife predicted age of onset of dementia. This is a novel finding. Before this article, we knew that high BMI increased the overall risk of dementia, but we did not know that it also meant that people would develop the disease at a younger age. Another important finding was that the effect of BMI was independent of genetics." Anstey was uninvolved in the new study.

"This article touches on an extremely important health topic, the effects of the epidemic obesity of western populations, in particular the U.S.," University of Gothenburg psychologist Linda Hassing, Ph.D., told *Bioscience Technology*. "I believe the findings of this study reflect a real scenario. Overweight and obesity are significantly contributing cases to dementia, both AD and vascular dementia, [and] overweight and obesity will bring on an earlier onset of dementia." Hassing was also uninvolved with the study.

"Our research specifically shows that midlife obesity lowers the age at onset of AD [and] accelerates AD development," said senior author Madhav Thambisetty, M.D., Ph.D., chief of the NIA's Unit of Clinical and Translational Neuroscience. Novel, he said, was "the amount of brain pathology" his team found associated with mid-life BMI, and the fact "that midlife BMI may have long lasting effect on the age at onset of AD."

BMI's predictive power

The NIA team looked at Baltimore Longitudinal Study on Aging (BLSA) data on 1,394 cognitively healthy people who underwent neuropsychological assessments on average every two years for some 14 years. Thambisetty's team analyzed the link between BMI at age 50, and AD onset.

Out of this pool, 142 people developed AD. In these people, a higher midlife BMI was associated with earlier AD onset. Also, among 191 autopsy results, higher BMI at midlife was linked to more severe AD-related neurofibrillary amyloid.

The study did not explore mechanisms. Needed are larger studies, looking at the link at a variety of ages, the team reported, to get even more precise.

"Understanding how risk factors in midlife may accelerate the onset of AD in later life is important in our efforts to develop interventions/treatments that may delay the onset of AD," Thambisetty told *Bioscience Technology*. "Although being overweight or obese in midlife is known to increase the risk of AD, we do not yet understand how it may affect the age when the disease first begins. Another important question is whether midlife obesity affects the amount of brain pathology due to AD."

Both questions were answered by the study to a certain degree. One unit of BMI was found to advance AD by 6.7 months, and considerable BMI affects severity of AD's physical ravages on the brain.

"We would like to confirm these findings in larger studies with a wider range of BMI values, and in younger individuals," Thambisetty said. "This will be important to conclusively determine whether there are certain BMI values and/or ages when the relationships with age-at-onset, and brain pathology, are especially strong."

Anstey agrees more studies are needed. "The results again provide support for the idea that modifying BMI in middle-aged adults may modify dementia risk," she told *Bioscience Technology*. "The work does need to be replicated in other studies, and further research is required to find out if high BMI in early adulthood, and even in childhood, may affect dementia risk."

Minor reservation

Hassing introduced a "minor" reservation. Although the BLSA source of the data lends credibility to the work given its "scientific reliability in terms of research design and data collection, use of a community-dwelling sample, extensive follow-up time, and accuracy of the methods such as the dementia diagnoses, for this particular article they did not actually measure BMI at age 50," she said. "They used statistical methods to derive a measure that estimates BMI at age 50."

On the other hand, she said, "a perfect study design that examines the association between BMI and dementia would need to follow a big-sized population-based sample from midlife up to old age, a very time consuming and expensive project that, to my knowledge, has not yet been enforced."

Regarding the accuracy of statistical measurements, Thambisetty called the comment on statistical measurement accuracy "a very good question…. In our sample of 1,394 participants in the BLSA, we had 8061 actual BMI measurements, recorded every year or every two years, during the course of follow up. Thus, each participant had, on average, almost six measurements of BMI throughout their participation in the study. The value of BMI at age 50 is then derived from *all* available actual, repeated BMI measurements using well-established statistical methods. This method also allows us to assess and account for the reliability of BMI estimates for each participant at age 50 years."

Otherwise, he agreed, "in order to conclusively establish whether there is a `threshold' of BMI value above which the associations with onset age and brain pathology are especially strong, and whether there is a specific age above which the associations with AD onset and brain pathology become important, it would be essential to follow a much larger sample representing a wider range of BMI values and ages."

April *Lancet* study

A June *Lancet* study [2] came to a surprisingly different conclusion. *Underweight* people in mid-life seemed more at risk for dementia.

Thambisetty told *Bioscience Technology* it is key to compare characteristics of participants across studies "when assessing results that seem contradictory. Our sample in the BLSA is a predominantly healthy, highly educated sample. All participants are cognitively normal at enrollment, and are assessed by detailed neuropsychological evaluations with diagnoses of AD made according to standardized criteria.

"*The Lancet* study, on the other hand, is comprised of clinical records from patients who went in to see their primary physician for medical reason(s). This database is called the Clinical Practice Research Datalink (CPRD). It represents a very heterogeneous group with a variety of co-morbid illnesses that made them go in to see their doctor. We are currently working with collaborators in the UK to analyze the CPRD data from which the *Lancet* results were obtained. We believe that a careful re-analysis of this data, accounting for the effects of obesity on risk of mortality, will be important before drawing conclusions about obesity and AD risk in this sample. This work is currently in progress."

An online BMI calculator is here [3]

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