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Central obesity and increased risk of dementia more than three decades later

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ABSTRACT

Background: Numerous reports show that a centralized distribution of adiposity is a more dangerous risk factor for cardiovascular disease and diabetes than total body obesity. No studies have evaluated whether the same pattern exists with dementia. The objective was to evaluate the association between midlife central obesity and risk of dementia three decades later.

Methods: A longitudinal analysis was conducted of 6,583 members of Kaiser Permanente of Northern California who had their sagittal abdominal diameter (SAD) measured in 1964 to 1973. Diagnoses of dementia were from medical records an average of 36 years later, January 1, 1994, to June 16, 2006. Cox proportional hazard models adjusted for age, sex, race, education, marital status, diabetes, hypertension, hyperlipidemia, stroke, heart disease, and medical utilization were conducted.

Results: A total of 1,049 participants (15.9%) were diagnosed with dementia. Compared with those in the lowest quintile of SAD, those in the highest had nearly a threefold increased risk of dementia (hazard ratio, 2.72; 95% CI, 2.33–3.33), and this was only mildly attenuated after adding body mass index (BMI) to the model (hazard ratio, 1.92; 95% CI, 1.58–2.35). Those with high SAD (>25 cm) and normal BMI had an increased risk (hazard ratio, 1.89; 95% CI, 0.98–3.81) vs those with low SAD (<25 cm) and normal BMI (18.5–24.9 kg/m^2), whereas those both obese (BMI >30 kg/m^2) and with high SAD had the highest risk of dementia (HR, 3.60; 95% CI, 2.85–4.55).

Conclusions: Central obesity in midlife increases risk of dementia independent of diabetes and cardiovascular comorbidities. Fifty percent of adults have central obesity; therefore, mechanisms linking central obesity to dementia need to be unveiled. ***Neurology***® ▪▪▪

GLOSSARY

AD = Alzheimer disease; **BMI** = body mass index; **KP** = Kaiser Permanente; **MHC** = Multiphasic Health Checkups; **SAD** = sagittal abdominal diameter.

It has been known for some time that a centralized distribution of fat is linked with numerous health risks. The abdominal distribution of body fat, referred to as central obesity, is an independent and more potent risk factor for type 2 diabetes, insulin resistance, coronary heart disease, stroke, and mortality than total body obesity.[1-4] Indeed, individuals with a healthy weight but with a centralized distribution of adipose tissue have a much higher risk of disease and death. This may be attributable in part to the role of intraabdominal fat, also known as visceral adiposity, on metabolic abnormalities, which increases risk of diabetes and cardiovascular disease. Visceral fat is more metabolically active than subcutaneous fat and is thought to have a stronger influence on adipocytokine production and insulin resistance.[5]

Recent population-based research shows that obesity contributes to cognitive impairment.[6,7] Obesity, as measured by body mass index (BMI), particularly in middle age,

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increases the risk of dementia, Alzheimer disease (AD), and neurodegenerative changes.[8-12] However, it remains unknown whether distribution of adiposity plays a similar role in dementia risk as it does with cardiovascular disease and diabetes. Thus far, the potential link between central obesity and risk of dementia has not been reported.

As people age, there is a greater accumulation of fat in the midsection accompanied by loss of bone and muscle mass, a condition referred to as sarcopenia.[13] Therefore, anthropometric measures of centralized fat distribution in late life as predictors of disease are somewhat problematic.[13,14] Effects of midlife body composition on dementia risk are less biased by aging processes and can provide a more informative view of the long-term effects of central adiposity. The goal of the current study was to determine the role of midlife central obesity as measured by sagittal abdominal diameter (SAD) on risk of developing dementia assessed more than three decades later. We also sought to evaluate if the effect of central obesity on dementia risk was independent of total body obesity (as assessed by BMI), varied by weight status, and was different from any risk associated with peripheral obesity (as measured by thigh circumference).

METHODS

Study population. We studied 6,583 continual members of the Kaiser Permanente (KP) Medical Care Program of Northern California who participated in voluntary periodic Multiphasic Health Checkups (MHC) in San Francisco and Oakland, CA, between 1964 and 1973 when they were ages 40 to 45 years. The MHC examination was performed as part of routine medical care between the years 1964 to 1973 and included standardized anthropometric measurements. To determine the effect of midlife risk factors only, we identified participants who were still alive and members of KP when electronic medical diagnoses of dementia were available in 1994 (N = 8,664). After excluding those who were missing SAD, thigh circumference, or BMI data (2,081), our analytic cohort was comprised of 6,583 elders.

KP of Northern California is a nonprofit, group practice health-integrated delivery system that covers more than one third of the population in the geographic areas served. KP members are representative of the sociodemographics of the local population.[15]

Data collection. ***Determinants of midlife characteristics and comorbidity.*** At the MHC, participants were interviewed and information was collected on demographics, lifestyle, and medical history, including questions on medical conditions, medication use, and health behaviors.[16] Many participants completed the MHC examination more than once; however, we used information from the baseline examination in the current study. Education was categorized as level of schooling, including grade school, high school, trade school, or college. Race categories in the MHC included self-reported white, black, or Asian. Smoking was classified as never or ever smoked.

The MHC also included a comprehensive clinical examination (for more details, see references [16-19]). Fasting blood was drawn for total serum cholesterol analysis and glucose. Cholesterol was determined with an Auto-Analyzer (Technicon Co., White Plains, NY) from 1964 to 1968 with an Autochemist (AGA Corp., Stockholm, Sweden) from 1969 to 1972 and with an Auto-Analyzer (model SMA-12; Technicon, Co.) in 1973.[18,20] Hypertension was defined as self-report of physician-diagnosed hypertension or use of antihypertensive medication or systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg. High cholesterol was defined as total serum cholesterol ≥240 mg/dL. Diabetes was defined by self-report of physician-diagnosed diabetes, use of insulin or oral hypoglycemic agents, a fasting glucose (last food eaten in ≥8 hours) of ≥126 mg/dL, or nonfasting (last food eaten in ≤4 hours) glucose of ≥200 mg/dL.

Central and peripheral obesity. Trained technicians performed all anthropometric measures according to the Nutritional Academy of Anthropometry Standards. The SAD, the distance between the back surface and the top of the abdomen midway between the lower rib margin and the superior anterior iliac crest, was measured after gentle expiration with the patient in a standing position using an anthropometer. High SAD was categorized as ≥25 cm vs those <25 cm based on prior work on clinical cut points for central obesity.[21] Thigh circumference also was measured using an anthropometer evaluating the distance between the middle of the back of the thigh and the middle of the front of the thigh defined as halfway between the patella and the hip joint. Height and weight were measured using a balance beam scale calibrated to the nearest 8 ounces and a tape measure with standard positioning.[17] BMI was calculated as weight in kilograms divided by height in meters squared.

Comorbidities after midlife were collected using the KP electronic records of inpatient and outpatient diagnoses and disease registries. We collected information on the following diagnoses from 1994 through the end of the study: hyperlipidemia, hypertension, ischemic heart disease, stroke, and diabetes. Mortality information was available through the end of 2004 using the California Automated Mortality Linkage System, which has a sensitivity of 0.97 compared with the National Death Index.[22] Mortality information from 2004 to 2006 was achieved through a matching linkage system incorporating social security number, name, and address. We examined frequency of number of medical visits during the dementia ascertainment period. The numbers of medical visits per person per year were divided by person-years to achieve a medical utilization rate.

Dementia. We ascertained dementia status from January 1, 1994, to June 16, 2006 when the participants were 73 to 87 years of age. Dementia diagnoses were obtained from medical records at KP hospitals and clinics in visits to primary care, neurology, and psychiatry departments using Interna-

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tional Classification of Diseases, 9th Revision codes and excluding HIV and alcohol-associated dementia. Dementia diagnoses included the following: dementia, AD, vascular dementia, and dementia not otherwise specified, International Classification of Diseases codes 290.0, 290.1, 290.2, 290.3, 290.4, 331.0.

Statistical analysis. All analyses were performed using SAS version 8.0 (SAS Institute, Cary, NC). χ^2 analyses were conducted to determine if there were any significant differences between those with SAD and thigh circumference data vs those without these measurements. Because SAD and thigh circumference differed significantly by sex ($p < 0.01$), we calculated sex-specific quintiles. We compared clinical and demographic characteristics by midlife central obesity status (high vs low SAD) using χ^2 and log rank tests. We estimated age-adjusted incidence rates of dementia by quintiles of SAD and thigh circumference to examine incidence of dementia using the entire cohort as the standard population. Cox proportional hazard models were used to identify independent predictors of risk of dementia using age as a time scale model. Age was calculated as age at the time of MHC examination (age in midlife) to age at the time of dementia ascertainment or the earliest of the following events: age at time of death, age at end of KP membership (as defined by a gap in membership of 3 months or greater), or age at the end of the study (June 16, 2006).

Three quintile models were generated: 1) a model adjusted for age only, as time scale; 2) a model adjusted for age (as time scale), education, race, sex, marital status, medical utilization, and time-dependent comorbidities (hyperlipidemia, diabetes, hypertension, ischemic heart disease, and stroke); and 3) a model additionally adjusted for BMI using standard World Health Organization categories of obesity ($\geq$30 kg/m^2), overweight (25–29.9 kg/m^2), underweight ($<$18.5 kg/m^2), and normal (18.5–24.9 kg/m^2) to assess the effects of central adiposity independent of overall level of fatness. The midlife and late-life diabetes, hypertension, and hyperlipidemia variables were combined to create time-dependent covariates so that adjustment for length of time of having the disease could be controlled for in the models.

To understand if the effect of SAG on dementia was consistent across weight, we constructed models designed to ascertain if the effect of SAD on risk of dementia was consistent in each World Health Organization BMI stratum. For these models, those with both a normal BMI (18.5–24.9 kg/m^2) and with a healthy SAD (SAD $<$25 cm) were the reference group. These models were fully adjusted for age (as time scale), education, race, sex, martial status, and comorbidities (hyperlipidemia, diabetes, hypertension, ischemic heart disease, and stroke).

RESULTS Comparisons of midlife demographics (age, education, and race) and comorbidities (diabetes, hypertension, and hyperlipidemia), between those with (n = 6,583) and without (n = 2,081) SAD or thigh circumference data, revealed no significant differences ($p > 0.05$). Characteristics of the study population by midlife central obesity are presented in table 1. Those with central obesity were more likely to be nonwhite; to have less than a high school level of education; to smoke cigarettes; to have hyperlipidemia, hypertension, or diabetes; and to be either overweight or obese as determined from World Health Organization BMI categories. Those with central obesity were also more likely to have late-life heart disease and dementia.

As shown in table 2, from January 1, 1994, through June 16, 2006, 1,049 participants were diagnosed with dementia (table 2). Age-adjusted incidence rates of dementia by quintiles of SAD showed an increase in risk of dementia across quintiles with a steep increase in incidence among those in the fifth quintile (324 events per 10,000 person-years vs 214 events for those in the first quintile). There was no significant increase in dementia incidence by quintile of thigh circumference.

In fully adjusted multivariate models shown in table 2, SAD increased risk of dementia in a dose-dependent fashion. Those in the second quintile were 20% more likely to have dementia, those in the third quintile were 49% more likely to have dementia, those in the fourth quintile were 67% more likely to have dementia, whereas those in the fifth quintile were 2.72 times more likely to develop dementia vs those in the first quintile of SAD. Additional inclusion of BMI to the model modestly attenuated the effect of the fourth and fifth quintile to a hazard ratio of 1.35 and 1.98, respectively.

The effect of SAD remained significant after addition of BMI to the final model (figure). After additional adjustment for BMI, those in the fifth quintile of SAD had an almost twofold increased risk of dementia (hazard ratio, 1.92; 95% CI, 1.58–2.35). Because the effect of high SAD ($\geq$25 cm) on dementia risk significantly varied across BMI categories (p value for BMI x SAD interaction term $p < 0.0008$), models were conducted calculating the risk of dementia by high ($\geq$25 cm) and low ($<$25 cm) SAD status across BMI categories. As shown in table 3, compared with those with a normal BMI and a low SAD, those with a normal BMI and high SAD were 89% more likely to have dementia, those overweight and with low SAD were 82% more likely, those overweight and with high SAD were 2.34 times more likely, those obese and with low SAD were 81% more likely, and those both obese and with high SAD had a 3.60-fold increased risk of dementia.

DISCUSSION As is the case for diabetes and cardiovascular disease, central obesity is also a risk factor for dementia. In this population-based diverse cohort of middle-aged adults followed for an average of 36 years, central obesity was associ-

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Table 1 Demographic and clinical characteristics of the participants by midlife central obesity status

Characteristic*	Central obesity, sagittal abdominal diameter ≥25 cm (N = 830)	Column percent or SD	No central obesity, sagittal abdominal diameter <25 cm (N = 5,753)	Column percent or SD	*p* Value
Age at midlife (years)	42.59	± 1.7	42.48	± 1.7	0.09
Female	369	44.5%	3,260	56.7%	<0.0001
Nonwhite	300	36.1%	1,383	24.0%	<0.0001
<High school education	494	59.5%	2,826	49.1%	<0.0001
Married at midlife	726	87.5%	4,862	84.5%	<0.01
Smokes at midlife	510	61.5%	3,307	57.5%	0.07
Midlife BMI kg/m^2	30.7	± 4.5	24.2	± 3.0	<0.0001
Midlife underweight	1	0.12%	86	1.5%	<0.0001
Midlife normal weight	43	5.18%	3,558	61.9%	<0.0001
Midlife overweight	382	46.0%	1,915	33.3%	<0.0001
Midlife obese	404	48.7%	194	3.4%	<.0001
Hyperlipidemia†	499	60.1%	3,255	56.6%	0.05
Hypertension†	704	84.8%	4,038	70.2%	<0.0001
Diabetes†	492	59.3%	2,208	38.4%	<0.0001
Ischemic heart disease in late life‡	439	52.9%	2,185	37.9%	<0.0001
Stroke in late life‡	184	22.2%	1,181	20.5%	0.27
Dementia in late life‡	171	20.6%	878	15.3%	<0.0001

*Mean ± SD for continuous variables and N and column percents for categorical variables, χ^2 *p* values unless otherwise noted.
†Comorbidity status from midlife and late life incidence.
‡Log rank *p* value.
BMI = body mass index.

ated with an increased risk of dementia independent of demographics, diabetes, cardiovascular comorbidities, and BMI. For those with normal, overweight, or obese BMI, central obesity increased the risk of dementia. Those overweight or obese but *without* central obesity had an 80% increase in dementia risk; those both overweight or obese and with central obesity had 2.34-fold and 3.60-fold increase in dementia risk, respectively. Even among those with a normal BMI, high central obesity was associated with an increased risk of dementia, although this bordered significance as a result of small numbers. The presence of central obesity in someone of a healthy body weight could be indicative of early insulin resistance or metabolic syndrome. Those with existence of both conditions had a risk that was triple that of those conditions. Peripheral obesity was not associated with dementia. To our knowledge, this is the first study to report an independent association of midlife central obesity with an increased risk of dementia.

Prior work has shown that central obesity is a risk factor for stroke and diabetes, independent of total body obesity, as measured by BMI.[3,4,23] Central obesity is not a problem limited to those who are overweight or obese; indeed, reports have found that among those not overweight, a centralized distribution of adiposity is associated with an increased risk of insulin resistance, diabetes, and coronary artery disease.[4,13] These results are consistent with prior work comparing the effects of BMI and central obesity on risk of diabetes and cardiovascular disease. A prior study found that women with both central obesity and in the highest quintile of BMI had a 29 times greater risk of diabetes vs those in the lowest quintile of BMI and central obesity. Our findings suggest the same pattern for dementia risk. Our observation that thigh adiposity did not increase the risk of dementia is consistent with other research showing that peripheral adiposity is not associated with an increased risk of disease and may possibly protect against diabetes.[24,25] We did not find a protective effect of peripheral adiposity on dementia risk, but this may be because thigh circumference is not the most sensitive marker of peripheral adiposity.

There are several potential biologic mechanisms whereby central obesity could increase risk of dementia. The most obvious is through increased risk of stroke, diabetes, and cardiovascu-

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Table 2 Age-adjusted incidence rates of dementia by quintile of sagittal abdominal diameter and thigh circumference, and Cox proportional hazard model of quintiles of sagittal abdominal diameter, thigh circumference, and risk of dementia

		Dementia cases				HR (95% CI)	
Quintile of sagittal abdominal diameter		N	Person-years	Incidence rate per 10,000	Lower, upper limits	Fully adjusted model*	Fully adjusted model plus BMI
1		194	13,274.9	214.6	(171.7, 257.7)	1.0	1.0
Men	10–19.4 cm						
Women	10–17.5 cm						
2		205	13,142.9	256.4	(209.1, 303.7)	1.20 (0.98–1.46)	1.11 (0.95–1.22)
Men	19.5–21.2 cm						
Women	17.6–19.1 cm						
3		188	11,624.0	280.4	(220.8, 340.1) 0	1.49 (1.22–1.83)	1.26 (0.92– 1.49)
Men	21.3–22.7 cm						
Women	19.2–20.8 cm						
4		219	12,399.4	301.0	(243.7, 358.4)	1.67 (1.37–2.05)	1.35 (1.07–1.77)
Men	22.8–24.4 cm						
Women	20.9–23.1 cm						
5		243	11,006.3	324.3	(259.5, 389.2)	2.72 (2.23– 3.33)	1.98 (1.33– 2.32)
Men	24.5–40.0 cm						
Women	23.2–40.0 cm						
Quintile of thigh circumference							
1		212	12,525.0	266.2	(215.2, 317.2)	1.0	1.0
Men	7–14.0 cm						
Women	7–13.4 cm						
2		218	13,395.9	261.2	(208.6, 313.8)	1.01 (0.83– 1.22)	0.89 (0.79–1.46)
Men	14.1–15.3 cm						
Women	13.5–14.9 cm						
3		193	11,585.8	278.4	(224.0, 332.7)	1.01 (0.83–1.23)	0.94 (0.77– 1.43)
Men	15.4–16.4 cm						
Women	15.0–16.1 cm						
4		218	12,780.7	273.7	(220.2, 327.2)	1.01 (0.83–1.24)	1.02 (0.79– 1.52)
Men	16.5–17.6 cm						
Women	16.2–17.9 cm						
5		220	11,716.4	286.4	(230.9, 341.9)	0.99 (0.79–1.23)	1.01 (0.81– 1.31)
Men	17.7–69.1 cm						
Women	18.0–66.6 cm						

*Cox proportional hazards model adjusted for age (as time scale), education, race, sex, marital status, medical utilization, diabetes, hypertension, hyperlipidemia, ischemic heart disease, and stroke.
BMI = body mass index; HR = hazard ratio.

lar disease because these conditions increase the risk of dementia and are associated with obesity.[26-29] Nonetheless, adjustment for both mid- and late-life exposure to these conditions did not attenuate the effect of central adiposity on dementia risk. It is possible that insulin resistance could be a confounder in the association between midlife central obesity and dementia; studies have shown it to be a consequence of central obesity and to be associated with cognitive decline and dementia. We did not have a measure of insulin resistance and could not adjust for this marker. However, those with insulin resistance in midlife would be highly likely to develop type 2 diabetes, which we could account for.

There may be something intrinsic to the condition of central adiposity that increases risk of dementia. The central adiposity measurement was obtained in midlife and may reflect a lifetime exposure to an altered metabolic and inflammatory state

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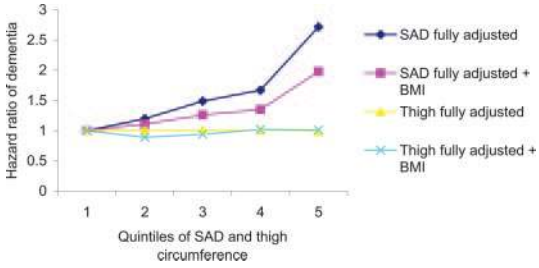
Figure **Quintiles of sagittal abdominal diameter and thigh circumference and risk of dementia from a Cox proportional hazards model adjusted for age (as time scale), sex, race, education, marital status, medical utilization, diabetes, hyperlipidemia, hypertension, ischemic heart disease and stroke; quintile 1 is the reference group**



induced by high visceral adiposity. There are several toxic effects of visceral adipose, which is a metabolically active endocrine tissue secreting several inflammatory cytokines and hormones.[30-32] There are documented differences in endocrine secretion of adiponectin, interleukin-6, and leptin between abdominal visceral fat and subcutaneous fat. Some of these adipocytokines such as leptin and interleukin-6 are associated with greater cognitive decline.[33] Work also suggests that leptin crosses the blood–brain barrier and may play a role in neurodegeneration.[34,35] Leptin is also thought to be involved in deposition of amyloid beta 42, the main ingredient in AD-associated plaques in the brain.[36]

Pathologic studies suggest that AD-associated changes in the brain may start in young to middle adulthood,[37] and a recent study found that obese middle-aged adults have decreased brain volume compared with those of normal weight,[38] whereas another study found that high central obesity in elderly adults was associated with decreased hippocampal brain volume and greater brain atrophy.[39] These findings imply that the harmful effects of central obesity on the brain may start long before clinical signs of dementia appear and are not limited only to those whom are overweight.

Strengths of the study include a well-characterized, ethnically diverse cohort with central, peripheral, and total obesity measures; equal access to medical care; and a long follow-up period. Because the population is all continual members of the same health plan, lifetime exposure to common comorbidities and medical utilization was well evaluated. Moreover, because the cohort was between 40 and 45 years old at the time of risk factor assessment, subclinical dementia at baseline is highly unlikely.

This study also has limitations. No information on dieting, nutrition, or cognitive function was collected, although obese persons have different nutritional and exercise habits than nonobese persons.[40] Many studies suggest that several different nutritional factors are associated with dementia[41-43] and that physical activity in old age lowers the risk of dementia. As a result of body composition imaging technology (CT or MRI) not being available in the 1960s, we were not able to directly distinguish the effects of visceral vs subcutaneous adiposity, but several studies have shown that SAD is more highly correlated with visceral fat than with subcutaneous fat and is a stronger predictor of mortality, diabetes, and insulin resistance than BMI or waist circumference, particularly when evaluating a middle-aged population.[44-47] The MHC examination did not specify a Latino category; therefore, we do not know whom among the race categories is Latino, although this group has a high prevalence of central adiposity. Finally, our study only included those who were still alive in 1994, the onset of dementia ascertainment; therefore, we only could examine the association between central obesity and dementia among those who made it to old age (mean age of 69 years in 1994).

In summary, these results contribute to a recent but growing body of evidence that a centralized distribution of adiposity is particularly dangerous, even for those who are not overweight, and that the brain may also be a target organ to the harmful effects of central obesity. If

Table 3 **Risk of dementia by both weight and central obesity status from a fully adjusted Cox proportional hazards model***

	Dementia (N = 1,049) (N, row %)	Hazards ratio	95% CI
Normal and low SAD‡	524 (14.7)	1.0	Reference group
Normal and high SAD†	8 (18.6)	1.89	0.94–3.81
Overweight and low SAD	320 (16.7)	1.82	1.57–2.12
Obese and low SAD	23 (11.9)	1.81	1.19–2.76
Overweight and high SAD	73 (19.1)	2.34	1.82–3.02
Obese and high SAD	90 (22.3)	3.60	2.85–4.55

*No one in the underweight category had a SAD of ≥25; risk could not be calculated for effects of high SAD in this category. Standard World Health Organization categories of obesity (≥30 kg/m^2), overweight (25–29.9 kg/m^2), underweight (<18.5 kg/m^2), and normal (18.5–24.9 kg/m^2).
†High SAD is ≥25 cm, low SAD is <25 cm.
‡Reference group are those with a normal BMI (18.5–24.9 kg/m^2) *and* with a SAD <25 cm. Model adjusted for age (as time scale), education, race, sex, marital status, medical utilization, diabetes, hypertension, hyperlipidemia, ischemic heart disease, and stroke.
SAD, sagittal abdominal diameter; BMI, body mass index.

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these results are replicated, our findings imply that central obesity may contribute to a degree of cognitive aging.

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