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Healthy lifestyle and the risk of Alzheimer dementia

Findings from 2 longitudinal studies

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Abstract

Objective

To quantify the impact of a healthy lifestyle on the risk of Alzheimer dementia.

Methods

Using data from the Chicago Health and Aging Project (CHAP; n = 1,845) and the Rush Memory and Aging Project (MAP; n = 920), we defined a healthy lifestyle score on the basis of nonsmoking, ≥150 min/wk moderate/vigorous-intensity physical activity, light to moderate alcohol consumption, high-quality Mediterranean-DASH Diet Intervention for Neurodegenerative Delay diet (upper 40%), and engagement in late-life cognitive activities (upper 40%), giving an overall score ranging from 0 to 5. Cox proportional hazard models were used for each cohort to estimate the hazard ratio (HR) and 95% confidence interval (CI) of the lifestyle score with Alzheimer dementia, and a random-effect meta-analysis was used to pool the results.

Results

During a median follow-up of 5.8 years in CHAP and 6.0 years in MAP, 379 and 229 participants, respectively, had incident Alzheimer dementia. In multivariable-adjusted models, the pooled HR (95% CI) of Alzheimer dementia across 2 cohorts was 0.73 (95% CI 0.66–0.80) per each additional healthy lifestyle factor. Compared to participants with 0 to 1 healthy lifestyle factor, the risk of Alzheimer dementia was 37% lower (pooled HR 0.63, 95% CI 0.47–0.84) in those with 2 to 3 healthy lifestyle factors and 60% lower (pooled HR 0.40, 95% CI 0.28–0.56) in those with 4 to 5 healthy lifestyle factors.

Conclusion

A healthy lifestyle as a composite score is associated with a substantially lower risk of Alzheimer's dementia.

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Glossary

BMI = body mass index; **CESD** = Center for Epidemiologic Studies Depression; **CHAP** = Chicago Health and Aging Project; **CI** = confidence interval; **FINGER** = Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; **HR** = hazard ratio; **MAP** = Memory and Aging Project; **MIND** = Mediterranean-DASH Diet Intervention for Neurodegenerative Delay.

In 2018, >50 million people worldwide—5.7 million Americans—were living with Alzheimer dementia, posing a significant burden on health and social care.[1] As the population ages, it is projected that the prevalence of Alzheimer dementia will triple in the next 30 years, urging the need for prevention and treatment strategies. Up to now, clinical trials investigating various therapies in patients with dementia have failed to modify the course of the disease.[2] In contrast, data from epidemiologic studies and clinical trials suggest that primary prevention can delay the onset of the disease.[3–5] Therefore, directing the focus toward prevention strategies has become a public health priority.

A number of preventive factors, including lifestyle behaviors and cardiovascular conditions, have been identified that individually contribute to a lower risk of cognitive decline and Alzheimer dementia.[4,5] Many of these factors (e.g., diet and exercise) are likely to have synergistic effects on dementia risk, yet few studies have examined the overall effect of multiple modifiable risk factors in combination.[6–9] Those that do have focused on cardiovascular risk factors, some of which may not be modifiable solely by the individual.[10–14] In the current study of 2 prospective longitudinal studies, we assessed risk of incident Alzheimer dementia according to a composite score of healthy lifestyle behaviors for dementia prevention, including diet,[15] exercise,[16] abstention from smoking,[17] light to moderate alcohol consumption,[18] and participation in cognitive activities.[19]

Methods

Study populations

The Chicago Health and Aging Project (CHAP) is a population-based cohort study that examined risk factors for Alzheimer dementia.[20] The study began in 1993 with the enrollment of individuals ≥65 years of age from a geographically defined community of blacks and non-Hispanic whites in the Southside of Chicago. From 1993 to 2012, 10,802 participants (78.7% of eligible residents) had been enrolled in the CHAP study. Of the 10,802 participants, 2,137 individuals without dementia were selected randomly for a detailed clinical assessment of incident Alzheimer dementia over the 18-year follow-up.[21] The Rush Memory and Aging Project (MAP) is an ongoing community-based cohort study of aging and risk factors for cognitive decline.[22] Since 1997, MAP has enrolled 2,022 adults from retirement facilities, subsidized housings, and individual homes across the Chicago metropolitan area. The data collection and clinical outcomes assessment in the CHAP and MAP cohort studies have followed similar methods, including measures of exposure variables and diagnostic assessment of Alzheimer dementia. A primary distinction between the 2 studies was the conduct of clinical evaluations for incident Alzheimer dementia every 3 years in a stratified random sample in CHAP and annually in MAP.

For the present study, we selected participants whose baseline data were available on diet, lifestyle factors, genetics (i.e., *APOE* ε4), and clinical assessment for Alzheimer dementia. In CHAP, of 2,137 participants with detailed clinical assessment of incident Alzheimer dementia 1,930 completed the food frequency questionnaire. In MAP, the food frequency questionnaire was introduced in March 2004 when there were 1,306 active participants, of whom 1,068 completed the dietary questionnaires. We excluded participants with no information on lifestyle factors (n_{CHAP} = 22; n_{MAP} = 14), as well as those for whom data were missing on *APOE* ε4 status (n_{CHAP} = 63; n_{MAP} = 8). In MAP, because the baseline was the date of the initial diet assessment, we excluded 126 participants with dementia at the start of follow-up. After exclusions, 1,845 participants in CHAP and 920 in MAP were included for analysis in this study.

Assessment of lifestyle factors and other covariates

Dietary intake was assessed by the same 144-item food frequency questionnaire in both studies that was validated for use in older Chicago residents.[23] Participants were asked how often, on average, they consumed specific foods and beverages with prespecified portion sizes over the past year. To assess the overall diet quality, we calculated the Mediterranean-DASH Diet Intervention for Neurodegenerative Delay (MIND) diet score, which summarizes information on 10 brain healthy food groups (green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, seafood, poultry, olive oil, and wine) and 5 unhealthy food groups (red meats, butter and stick margarine, cheese, pastries and sweets, and fried/fast food).[24] Participants reported their average frequency of intake of wine and other alcoholic beverages through the food frequency questionnaires.[23] Because we evaluated the alcohol intake separately, we did not include wine in the MIND diet score calculation. Physical activity in both cohorts was assessed by the same validated questionnaire from the 1985 US Health Interview Survey that was adapted for use in older adults.[25] Participants reported the time spent in any of 5 moderate or vigorous activities (i.e., walking for exercise, gardening or yard work, calisthenics or general exercise, bicycle riding, and swimming) within the past 2 weeks. Information on smoking status was obtained through the interview at baseline, in which participants specified whether they were current, former, or never smokers.[17] Participation in

Table 1 Definition of healthy lifestyle factors

Lifestyle factor	Low-risk category	High-risk category
MIND diet	Upper 2/5ths (highest 40%) of the score distribution	Bottom 3/5ths (lower 60%) of the score distribution
Physical activity	≥150 min/wk in moderated or vigorous activities	<150 min/wk or sedentary
Cognitive activity	Upper 2/5ths (highest 40%) of the distribution	Bottom 3/5ths (lower 60%) of the distribution
Smoking	Never or former smoker	Current
Alcohol intake	Women ≥1–<15 g/d, men ≥1–<30 g/d	Nondrinkers or women ≥15 and men ≥30 g/d

Abbreviation: MIND = Mediterranean-DASH Diet Intervention for Neurodegenerative Delay diet score.
Lifestyle factors were selected a priori on the basis of guidelines or evidence for health benefits in the prevention of chronic diseases and mortality. From these guidelines and other evidence, we defined the healthy category groups. For each healthy factor, the participants received a score of 1 or otherwise 0. The sum of these 5 scores gave a final score within the range of 0 to 5, with higher scores indicating a healthier lifestyle.

cognitively stimulating activities was assessed with a structured questionnaire of usual time spent in the past year on 7 activities, including reading, writing letters, visiting a library, and playing games such as chess or checkers. Each of these 7 activities was scored on a 5-point scale ranging from 1 for once a year or less to 5 for every day or about every day and then averaged to yield a composite measure of the frequency of participation in cognitively stimulating activities.[26] *APOE* genotype was determined for each participant by the Broad Institute for Population Genetics using the hME Sequenom MassARRAY platform in CHAP and by Polymorphic DNA Technologies in MAP. Participants were classified as *APOE* ε4 carrier (≥1 ε4 allele) or noncarrier. Race/ethnicity was defined with questions from the 1990 US Census. Education was measured as the number of years of formal schooling completed. Body mass index (BMI; weight in kilograms divided by height in meters squared) was computed from measured weight and height. Information on statins and antihypertensive medication was obtained during the interview when the research assistant had a direct visual inspection of all prescriptions that the participant was receiving. History of heart disease and stroke was determined by self-report questions from the Established Populations for the Epidemiologic Study of the Elderly. Depressive symptoms were assessed with a modified 10-item version of the Center for Epidemiologic Studies Depression (CESD) scale.[27]

Classification of healthy lifestyle categories

Based on evidence,[15–19] guidelines,[28,29] and expert knowledge, for health benefits of lifestyle factors in the prevention of dementia, we considered a priori 5 healthy lifestyle behaviors: (1) MIND diet score (without alcohol) in the top 40% of the cohort distribution, (2) cognitive activities in the top 40% of the cohort distribution, (3) not current smoking, (4) moderate or vigorous exercise activities for at least 150 min/wk, and (5) light to moderate alcohol consumption (1–15 g/d in women and 1–30 g/d in men, i.e., up to ≈1 drink a day for women and 2 drinks for men) (table 1).

In the absence of a threshold for a healthy diet and cognitive activities, we imposed an upper 40% cutoff based on the cohort distribution, in line with previous publications.[30–32] This cutoff will tend to be achievable for most of the people who plan to modify their lifestyle.

For each healthy lifestyle factor, the participants received a score of 1 if they met the criteria for healthy and 0 if they did not meet the criteria. The sum of these 5 scores yielded a final score within the range of 0 to 5, with higher scores indicating a healthier lifestyle.[30]

BMI was not included in the score because it is not a behavior and because of both cause and effect relations of obesity in older ages and the risk of dementia.[33,34]

Clinical diagnosis of Alzheimer dementia

The clinical diagnosis of Alzheimer dementia was determined at each evaluation as previously described.[20,35] In short, using data from a structured neurologic examination, medical history, and cognitive performance testing and with the assistance of an algorithmically based rating of cognitive impairment, an experienced clinician determined the diagnosis of Alzheimer dementia on the basis of criteria of the joint working group of the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.[36] Data on incident Alzheimer dementia were collected until February 2012 in CHAP and August 2018 in MAP.

Statistical analysis

Baseline characteristics of the study populations are presented as mean and SD, percentages of participants, and medians and quartiles. Participants contributed person-time from the baseline questionnaire until the date of clinical diagnosis for Alzheimer dementia, censored due to mortality/loss to follow-up, or the end of the follow-up period, whichever came first. The maximum follow-up time was 17 years in CHAP and 14 years in MAP. We censored data after 14 years of follow-up in analyses that compared and pooled the studies.

Cox proportional hazards models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) of incident Alzheimer dementia for the categories of healthy lifestyle score.

We grouped study participants into 3 categories of lifestyle factor score (0–1, 2–3, and 4–5 factors) and compared the HRs with the lowest category as the referent. We also evaluated the risk of Alzheimer dementia per 1-point increase in a healthy lifestyle factor. All models were adjusted for age (year), sex (male vs female), race (black vs non-Hispanic white), education (years), *APOE* ε4 carrier (none vs any ε4 allele), and prevalence of cardiovascular disease (including heart disease or stroke, yes vs no) at the baseline. The proportional hazard assumption was assessed through the interaction between time and Schoenfeld residuals.

The analyses were performed separately in each cohort study, and we pooled the HRs to obtain a summarized estimate with the use of an inverse variance–weighted random-effect meta-analysis.[37] We used the Cochrane *Q* statistic and the I^2 statistic to examine the heterogeneity of associations among the cohorts.

In the sensitivity analysis, we applied a series of analyses to test the robustness of our findings. First, we evaluated effect modification of the Alzheimer dementia risk factors in each cohort by conducting 6 stratified analyses, including analysis stratified by sex (women and men), by race (black and non-Hispanic white), by *APOE* ε4 carrier status (noncarrier and carrier), by education (≤12 and 13+ years), by BMI (normal weight and overweight), and by the prevalence of cardiovascular disease (no and yes). Second, to address the potential effect of cardiovascular risk factors on the association between lifestyle and Alzheimer dementia, we also adjusted our multivariable model by BMI, hypertension, dyslipidemia, and diabetes mellitus. Third, to account for the effect of depressive symptoms in our association, we additionally adjusted for the CESD scores. Fourth, to account for possible reverse causation, we conducted an analysis in which we estimated the HRs after excluding Alzheimer dementia events during the first 2.5 years of follow-up (n = 99 in CHAP, n = 60 in MAP). Fifth, to limit the variability of baseline assessment during the follow-up, we limited the follow-up time to 10 years and excluded Alzheimer dementia events after this period. Sixth, to address the concern about the potential adverse effects of light to moderate alcohol intake, we created a healthy lifestyle score that was based on the other 4 healthy factors without alcohol. In this analysis, we adjusted for alcohol intake in the multivariable-adjusted model. Seventh, to address the adverse effect of former smokers, we created a healthy lifestyle score that was based on never smokers as a healthy lifestyle factor. Eighth, given that the role of *APOE* ε4 allele on Alzheimer dementia risk may be different in blacks and non-Hispanic whites, in CHAP, we conducted another analysis among *APOE* ε4 carries to evaluate the association of lifestyle score with Alzheimer dementia stratified by race.

All the analyses were performed with R software, CRAN version 3.6.0 (with the survival,[38] survey,[39] metafor,[40] and fmsb packages; R Foundation for Statistical Computing, Vienna, Austria).

Standard protocol approvals, registrations, and patient consents

The study was approved by the institutional review board of Rush University Medical Center. Written informed consent was obtained from all study participants.

Data availability

Data of the MAP cohort study are available via the Rush Alzheimer's Disease Center Research Resource Sharing Hub, which can be found at radc.rush.edu. It has descriptions of the studies and available data. Any qualified investigator can create an account and submit requests for deidentified data.

Results

At baseline, the mean age of participants in the CHAP study was 73.2 (SD 5.8) years and in MAP was 81.1 (SD 7.2) years; 62.4% of the CHAP and 75.2% of the MAP participants were women (table 2). A large fraction of the CHAP participants were black (53.2%), whereas the majority of MAP participants were non-Hispanic white (94.5%). Compared to the CHAP, participants of the MAP study reported on average more years of education (12.9 vs 14.9), a higher MIND score (6.85 vs 7.60), and more minutes per week in moderate/vigorous activities (105 vs 150 min/wk). The adherence to healthy lifestyle behaviors was lower in CHAP compared to MAP; 24.4% of CHAP participants and 31.5% of MAP had 4 or 5 healthy lifestyle behaviors. Participants with 2 or 3 healthy behaviors made up the majority of CHAP and MAP population, 58.2% and 55.1%, respectively. Adherence to 0 or 1 healthy behaviors was 17.4% in CHAP and 13.4% in MAP. The contribution of each lifestyle factor on the overall score by cohort is shown in table 1 available from Dryad (doi.org/10.5061/dryad.vmcvdncp8).

During a median follow-up of 5.8 (interquartile range 3.2–9.7) years in CHAP and 6.0 (interquartile range 3.0–9.0) years in MAP, a total of 379 and 229 participants, respectively, developed Alzheimer dementia. The incidence rates decreased with an increasing number of healthy lifestyle behaviors (table 3). Compared with the incidence rate of Alzheimer dementia in those with 0 or 1 healthy behaviors (CHAP 5.22 [95% CI 4.65–5.79], MAP 6.47 [95% CI 4.44–8.49] per 100 person-years), the absolute rate differences per 100 person-years in those with 2 or 3 healthy behaviors were −2.63 (95% CI −3.24 to −2.03) in CHAP and −2.39 (95% CI −4.53 to −0.25) in MAP, and in those with 4 or 5 healthy behaviors, the absolute rate differences were −4.00 (95% CI −4.46 to −3.39) in CHAP and −3.81 (95% CI −5.96 to −1.66) in MAP.

In multivariable models, the HRs for Alzheimer dementia per 1 additional healthy behavior in the score were 0.70 (95% CI 0.59–0.83) in CHAP and 0.74 (95% CI 0.66–0.84) in MAP. Across the 2 cohorts, the risk of incident Alzheimer disease was 27% lower per 1 healthy behavior increase in lifestyle score (pooled HR 0.73, 95% CI 0.66–0.80). Furthermore, compared to participants with 0 or 1 healthy behavior, the HRs of

Table 2 Baseline characteristics of the participants included in the study

	CHAP	MAP
No.	1,845	920
Age, y	73.2 ± 5.8	81.1 ± 7.2
Sex, male, n (%)	639 (37.6)	228 (24.8)
Race, non-Hispanic white, n (%)	864 (46.8)	869 (94.5)
BMI, kg/m^2	27.2 ± 5.4	27.2 ± 5.2
Education, y	12.9 ± 3.4	14.9 ± 2.9
***APOE* ε4, n (%)**	590 (32.0)	199 (21.6)
Hypertension, n (%)	985 (53.4)	642 (69.8)
Dyslipidemia, n (%)	219 (12.5)	351 (38.2)
Diabetes mellitus, n (%)	336 (18.2)	131 (14.2)
Heart disease, n (%)	245 (13.3)	116 (12.6)
Stroke, n (%)	147 (8.0)	97 (10.5)
MIND diet score	6.85 ± 1.58	7.60 ± 1.65
Late-life cognitive activity score	3.25 ± 0.63	3.24 ± 0.65
Moderate/vigorous-intensity exercise, min/wk	105 (0–270)	150 (45–270)
Smoking status, n (%)		
Never smoker	904 (49.0)	533 (57.9)
Former smoker	737 (39.9)	363 (39.5)
Current smoker	204 (11.1)	24 (2.6)
Alcohol intake, g/d	4.4 ± 10.1	4.6 ± 8.9

Abbreviations: BMI = body mass index; CHAP = Chicago Health and Aging Project; MAP = Memory and Aging Project; MIND = Mediterranean-DASH Diet Intervention for Neurodegenerative Delay diet score.
For continuous variables, data are show as mean (SD) or median (interquartile range); for categorical variables, data are given as absolute numbers (proportions).
Table 9 available from Dryad (doi.org/10.5061/dryad.vmcvdncp8) presents baseline characteristics of participants of the CHAP cohort study weighted for the stratified random sampling.

Alzheimer dementia in those with 2 or 3 behaviors were 0.58 (95% CI 0.37–0.93) in CHAP and 0.66 (95% CI 0.46–0.94) in MAP, and in those with 4 or 5 healthy behaviors, the HRs were 0.33 (95% CI 0.18–0.61) in CHAP and 0.43 (95% CI 0.28–0.66) in MAP. Across the 2 cohorts, the risk of incident Alzheimer dementia was 37% lower in those with 2 or 3 healthy behaviors (pooled HR 0.63, 95% CI 0.47–0.84) and 60% lower in those with 4 or 5 healthy behaviors (pooled HR 0.40, 95% CI 0.28–0.56) compared to participants with 0 or 1 healthy behaviors (figure).

Stratified analysis by sex, race, and *APOE* ε4, education, BMI, and prevalence of cardiovascular disease yielded results principally similar to those of the overall analysis (table 4). No heterogeneity was observed between cohorts (p for heterogeneity >0.2 for all comparisons). The pooled HRs of Alzheimer dementia per 1 healthy behavior increase in the lifestyle score were 0.74 (95% CI 0.66–0.84) in women and 0.70 (95% CI 0.60–0.82) in men. Among non-Hispanic white participants of CHAP and MAP, the pooled HR was 0.74 (95% CI 0.67–0.83) and in blacks (only CHAP participants included) was 0.72 (95% CI 0.59–0.87). In the stratified analyses by the presence of the *APOE* ε4 allele, the pooled HR among noncarriers was 0.68 (95% CI 0.58–0.80) and in carriers was 0.80 (95% CI 0.68–0.94). In the CHAP cohort, notably, a strong HR was observed among non–*APOE* ε4 allele carriers (HR 0.62, 95% CI 0.49–0.77) compared to *APOE* ε4 allele carriers (HR 0.82, 95% CI 0.64–1.05). In the analysis stratified by education levels, the pooled HRs were 0.69 (95% CI 0.60–0.80) in those with ≤12 years of education and 0.75 (95% CI 0.66–0.87) in those with >12 years. In participants without cardiovascular disease at the baseline, the pooled HRs were 0.72 (95% CI 0.64–0.80); among patients with cardiovascular disease, the HR was 0.70 (95% CI 0.57–0.85). In the stratified analysis by BMI, the pooled HRs were 0.66 (95% CI 0.56–0.77) in normal-weight participants (BMI <25 kg/m^2) and 0.77 (95% CI 0.68–0.88) in overweight individuals (table 4).

The associations between lifestyle and incident Alzheimer dementia were not different when we also adjusted for BMI, hypertension, dyslipidemia, and diabetes mellitus; also adjusted for the CESD scores; excluded Alzheimer dementia events during the first 2.5 years of follow-up to account for reverse causality; or limited the follow-up to 10 years. When we used a healthy score without light to moderate alcohol intake, the HRs of Alzheimer dementia per 1 healthy factor increase in the lifestyle score were 0.71 (95% CI 0.59–0.86) in CHAP and 0.70 (0.61–0.81) in MAP, similar to the primary analysis. Similar results were found when we used never smoking as a healthy lifestyle factor. Focusing the analysis on *APOE* ε4 allele carriers and stratifying by race in CHAP showed broadly similar associations in blacks (HR 0.81, 95% CI 0.63–1.04) and non-Hispanic whites (HR 0.84, 95% CI 0.49–1.43). Results of the sensitivity analyses are available from Dryad, tables 2–8 (doi.org/10.5061/dryad.vmcvdncp8).

Discussion

In 2 prospective cohort studies of older adults, an increased number of healthy lifestyle behaviors was associated with a lower risk of Alzheimer dementia. Older adults who adhere simultaneously to 4 or 5 healthy behaviors (i.e., high-quality diet, engagement in cognitive activities, regular physical activity, light to moderate alcohol intake, and not smoking) had 60% lower risk of developing incident Alzheimer dementia than individuals with 0 or 1 healthy behaviors. These associations were independent of other established risk factors of Alzheimer dementia and persisted among white participants who were carriers of the *APOE* ε4 allele. From these findings and the fact that the lifestyle factors we studied are modifiable and in direct control of the individual, it is imperative to promote them concurrently among older adults as a strategy to delay or prevent Alzheimer dementia.

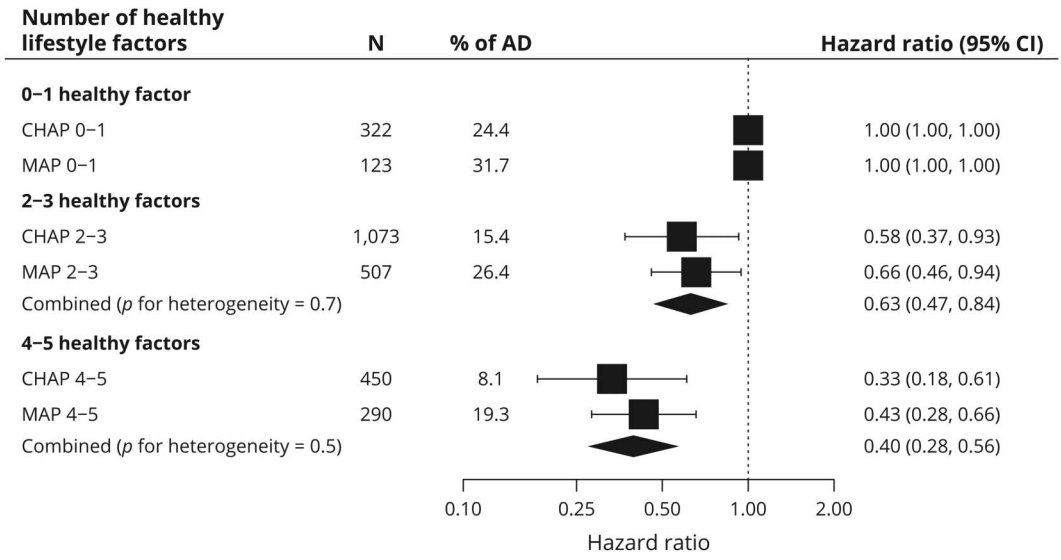
Table 3 Incidence rates of Alzheimer dementia according to number of healthy lifestyle factors in the prospective cohort studies

		No. of healthy lifestyle factors		
	Overall population	0–1	2–3	4–5
CHAP				
Incidence rate per 100 person-y (95% CI)	2.61 (2.46–2.76)	5.22 (4.65–5.79)	2.59 (2.39–2.78)	1.22 (1.02–1.43)
Absolute rate difference (95% CI)		1 (Reference)	−2.63 (−3.24 to −2.03)	−4.00 (−4.46 to −3.39)
MAP				
Incidence rate per 100 person-y (95% CI)	3.82 (3.32–4.31)	6.47 (4.44–8.49)	4.08 (3.39–4.77)	2.66 (1.96–3.35)
Absolute rate difference (95% CI)		1 (Reference)	−2.39 (−4.53 to −0.25)	−3.81 (−5.96 to −1.66)

Abbreviations: CHAP = Chicago Health and Aging Project; CI = confidence interval; MAP = Memory and Aging Project.

Previous epidemiologic studies of lifestyle and dementia have evaluated risk factors individually, including diet,[15] regular physical exercise,[16] and engagement in cognitive activities.[19] For example, using the data from the MAP cohort study, we reported that the risk of incident Alzheimer dementia is substantially lower in older adults who adhere to a high-quality MIND diet.[15] Similar findings of prevention were reported for engagement in mentally stimulating activities.[19] An early meta-analysis of prospective cohort studies summarized that adults who routinely engaged in physical activities have a significantly lower risk of dementia.[16] However, given that these lifestyle factors are often interrelated, evaluating them in combination accounts for a cluster effect within individuals.[30] Indeed, studies assessing the impact of lifestyle factors on cardiovascular disease[30,41] underscored the significance of promoting these lifestyle factors concurrently to optimize preventive effects in the population. Despite the fact that cardiovascular disease and dementia share similar risk factors,[42] only a few studies have investigated the effect of lifestyle factors on the risk of dementia,[6–9] and most of them have focused on cardiovascular risk factors defined by the American Heart Association[43] (i.e., smoking, BMI, physical activity, diet, blood pressure, cholesterol, and glucose) to promote optimal cardiovascular health.[10–14] Overall, these studies showed that better cardiovascular health is associated with lower cognitive decline and incident dementia in the Framingham Heart Study,[10] Northern Manhattan Study,[11] and the Atherosclerosis Risk in Communities Study[12] and with a lower risk of dementia in the Three-City study in France[13] and Chicago Heart Association Detection Project in

Figure HRs of AD according to the combination of healthy lifestyle factors in the prospective cohort studies



Model adjusted for age, sex, race, education, *APOE* ε4, and prevalence of cardiovascular disease (including heart disease or stroke). A random-effects meta-analysis was used to combine cohort-specific results. AD = Alzheimer dementia; CHAP = Chicago Health and Aging Project; CI = confidence interval; HR = hazard ratio; MAP = Rush Memory and Aging Project; N = number of participants in each group.

Table 4 HRs of Alzheimer dementia per additional healthy lifestyle factor increase stratified by sex, race, *APOE* ε4, education, cardiovascular disease, and BMI in the prospective cohort studies

			Model[a]	
Stratified analysis	**No.**	**% of AD**	**HR (95% CI)**	***p* Value**
Sex				
Women				
CHAP	1,152	15.3	0.67 (0.52–0.87)	0.002
MAP	692	25.6	0.77 (0.67–0.88)	<0.001
Pooled[b]			0.74 (0.66–0.84)	<0.001
***p* for heterogeneity**				0.371
Men				
CHAP	693	14.6	0.73 (0.60–0.89)	0.002
MAP	228	22.8	0.67 (0.52–0.85)	0.001
Pooled			0.70 (0.60–0.82)	<0.001
***p* for heterogeneity**				0.577
Race				
Blacks				
CHAP	981	17.9	0.72 (0.59–0.87)	0.001
MAP	NA	NA	NA	NA
Non-Hispanic whites				
CHAP	864	11.3	0.67 (0.48–0.93)	0.018
MAP	869	25.7	0.76 (0.67–0.85)	<0.001
Pooled[b]			0.74 (0.67–0.83)	<0.001
***p* for heterogeneity**				0.511
***APOE* ε4 carrier status**				
No *APOE* ε4				
CHAP	1,255	13.6	0.62 (0.49–0.77)	<0.001
MAP	721	22.6	0.72 (0.62–0.84)	<0.001
Pooled[b]			0.68 (0.58–0.80)	<0.001
***p* for heterogeneity**				0.224
Any *APOE* ε4				
CHAP	590	18.0	0.82 (0.64–1.05)	0.114
MAP	199	33.2	0.79 (0.64–0.97)	0.023
Pooled[b]			0.80 (0.68–0.94)	0.001
***p* for heterogeneity**				0.802
Education				
≤12 y				
CHAP	969	20.8	0.67 (0.56–0.79)	<0.001
MAP	721	27.8	0.74 (0.58–0.95)	0.018
Pooled[b]			0.69 (0.60–0.80)	<0.001

Continued

Table 4 HRs of Alzheimer dementia per additional healthy lifestyle factor increase stratified by sex, race, *APOE* ε4, education, cardiovascular disease, and BMI in the prospective cohort studies *(continued)*

			Model[a]	
Stratified analysis	**No.**	**% of AD**	**HR (95% CI)**	***p* Value**
***p* for heterogeneity**				0.541
>12 y				
CHAP	876	9.4	0.76 (0.53–1.09)	0.134
MAP	199	23.8	0.75 (0.65–0.86)	<0.001
Pooled[b]			0.75 (0.66–0.87)	<0.001
***p* for heterogeneity**				0.882
Cardiovascular disease[c]				
No				
CHAP	1,491	14.9	0.69 (0.57–0.85)	<0.001
MAP	739	23.8	0.73 (0.64–0.83)	<0.001
Pooled[b]			0.72 (0.64–0.80)	<0.001
***p* for heterogeneity**				0.667
Yes				
CHAP	354	15.8	0.67 (0.51–0.90)	0.007
MAP	181	29.3	0.72 (0.55–0.94)	0.016
Pooled[b]			0.70 (0.57–0.85)	0.001
***p* for heterogeneity**				0.764
BMI				
Normal weight (BMI <25 kg/m^2)				
CHAP	679	15.6	0.64 (0.48–0.86)	0.003
MAP	334	27.8	0.67 (0.56–0.80)	<0.001
Pooled[b]			0.66 (0.56–0.77)	<0.001
***p* for heterogeneity**				0.774
Overweight (BMI ≥25 kg/m^2)				
CHAP	1,166	14.7	0.72 (0.58–0.89)	0.002
MAP	586	23.2	0.80 (0.69–0.94)	0.007
Pooled[b]			0.77 (0.68–0.88)	0.001
***p* for heterogeneity**				0.411

Abbreviations: AD = Alzheimer dementia; BMI = body mass index; CHAP = Chicago Health and Aging Project; CI = confidence interval; HR = hazard ratio; MAP = Memory and Aging Project; NA = not applicable.
[a] Model adjusted for age, sex, race, education, *APOE* ε4, and prevalence of cardiovascular disease. We removed the variable (i.e., sex) from the model when we stratified for it (i.e., sex).
[b] A random-effects meta-analysis was used to combine cohort-specific results.
[c] Cardiovascular disease includes heart disease and stroke.

Industry study in the United States.[14] However, cardiovascular health addressed by these studies includes metabolic factors and conditions (blood cholesterol, blood glucose, blood pressure, and obesity) in addition to health behaviors.[43] While these factors are modifiable, they often require medical treatment and are not always under control of the individual. Therefore, from a public health perspective, promoting healthy lifestyle behaviors is a feasible strategy that is likely to have a significant impact on dementia prevention and cardiovascular-related conditions.[44]

The mechanisms underlining the protective effects of healthy lifestyles in Alzheimer dementia are not entirely understood.

A number of studies indicate that healthier diets rich in nutrients and vitamins, physical exercise, and smoking abstinence could initiate a chain of metabolic and molecular alterations that presumably inhibit inflammation and oxidative stress and may reduce amyloid accumulation, neuritic plaques, and neurofibrillary tangles in the brain,[45–47] but insights into the specific pathways involved are limited.

We did not consider the inclusion of BMI in our healthy lifestyle score because of the complex relation of weight as both a risk factor and a cause of dementia. A cohort study in which nearly 2 million people were followed up for 2 decades showed an inverse association between obesity and the risk of dementia, opposing the hypothesis that obesity increases the risk of dementia in old age.[33] However, we did adjust for the BMI in the sensitivity analysis, and results were consistent with the primary analysis.

We observed some degree of heterogeneity between the CHAP and MAP cohort studies when we focused our investigation on participants with the *APOE* ε4 allele. We found a lower risk of Alzheimer dementia with each additional healthy lifestyle behavior in MAP, whereas in CHAP, the presence of the *APOE* ε4 allele diminished the effect of lifestyle. Consistent with our MAP findings, the 2-year Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial in Finland[48] and a large-scale observational study (UK Biobank) in the United Kingdom[8] concluded that healthy lifestyle changes may prevent cognitive decline in individuals with the *APOE* ε4 allele. In contrast, these protective effects of healthy lifestyle among individuals at high genetic risk were not demonstrated in population-based study in the Netherlands.[9] The heterogeneity in our findings between cohorts (CHAP vs MAP) could be explained in part by the characteristics of each cohort. A high proportion of the CHAP population is black with lower education and a poor lifestyle profile compared to MAP cohort. The MAP cohort is made up of 94% non-Hispanic whites and is much older. In fact, it was expected that the contribution of *APOE* ε4 would have been limited in the CHAP cohort given a weaker contribution of genetic risk to dementia among blacks.[49] However, in a recent study involving CHAP participants, we showed that the association of the *APOE* genotypes with cognitive decline was not different between blacks and non-Hispanic whites.[50] We also confirmed these findings in our study when we investigated the association of lifestyle factors with Alzheimer dementia within carriers of the *APOE* ε4 allele stratified by race in CHAP and found similar HRs (nonsignificant) in both blacks and non-Hispanic whites. Although our small sample size in the stratified analysis does not allow us to draw conclusions, we hypothesize that the heterogeneity observed between cohorts among carriers of the *APOE* ε4 allele could be attributed to the differences in the lifestyle profile and education.

The assessments of diet and physical activity in these studies were self-reported and thus could be prone to measurement error, although these questionnaires were validated.[23,25] Lifestyle factors were assessed at baseline, and changes over time were not considered in this study. Although the effect size of each lifestyle factor to Alzheimer dementia is different, we did not weight them in the analysis because of our limited sample size, and our central hypothesis was to evaluate an overall healthy lifestyle as a cluster of factors within an individual. Despite the exclusion of events occurring in the first 2.5 years of follow-up, reverse causality remains a limitation of our study because of the long prodromal phase of Alzheimer dementia. A significant strength of this study is the generalizability of the findings across age and race. Although our 2 cohorts have different mean ages and proportions of blacks, the adherence to a healthy lifestyle had similar effects on incident Alzheimer dementia. Another strength is the accurate diagnosis of Alzheimer dementia through frequent neuropsychological testing and structured clinical neurologic evaluations by clinicians blinded to the lifestyle factors profile.

Our study suggests that a healthy lifestyle as a composite score is associated with a substantially lower risk of Alzheimer dementia.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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Klodian Dhana, MD, PhD	Rush University Medical Center, Chicago, IL	Study concept and design; data acquisition; statistical analyses; interpretation; drafting and revision of the manuscript
Denis A. Evans, MD	Rush University Medical Center, Chicago, IL	Study concept and design; acquisition of data; critical revision of manuscript for intellectual content
Kumar B. Rajan, PhD	University of California at Davis	Study concept and design; acquisition of data; critical revision of manuscript for intellectual content

Appendix *(continued)*

Name	Location	Contributions
David A. Bennett, MD	Rush University Medical Center, Chicago, IL	Study concept and design; acquisition of data; critical revision of manuscript for intellectual content
Martha C. Morris, ScD	Rush University Medical Center, Chicago, IL	Study concept and design; acquisition of data; interpretation; critical revision of manuscript for intellectual content and study supervision

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