

Participation in Novelty-Seeking Leisure Activities and Alzheimer's Disease

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ABSTRACT

The objective was to study the associations between participation in different types of mentally stimulating leisure activities and status as Alzheimer's disease (AD) case or normal control. Research suggests that participation in leisure activities, especially mentally stimulating activities, is associated with a lower risk for AD. However, no study has yet evaluated associations between AD and different types of mental leisure activities, especially those involving "novelty seeking." The authors used a case-control design to compare participation in activities across the life span in persons with AD and normal controls. Cases ($n = 264$) were recruited from clinical settings and from the community. Controls were drawn from 2 populations. Control group A members ($n = 364$) were the friends or neighbors of the cases or members of the same organizations to which the cases belonged. Control group B members ($n = 181$) were randomly drawn from the community. The 2 control groups did not differ in their responses to most activity questions, so they were combined. Factor analysis of activity questions identified 3 activity factors: (1) novelty seeking; (2) exchange of ideas; and (3) social. Logistic regression analysis indicated that, adjusting for control variables, greater participation in novelty-seeking and exchange-of-ideas activities was significantly associated with decreased odds of AD. The odds of AD were lower among those who more often participated in activities involving exchange of ideas and were lower yet for those who more frequently participated in novelty-seeking activities. We conclude that participation in a variety of mental activities across the life span may lower one's chances of developing AD. (*J Geriatr Psychiatry Neurol* 2005;18:134-141)

Keywords: Alzheimer's disease; novelty seeking; leisure time activity; risk factors

Alzheimer's disease (AD) is a chronic debilitating neurological condition causing gradual but inexorable cogni-

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tive and functional decline. It was estimated that in 2000 there were 4.5 million Americans with AD, but by 2050 that number is projected to increase to 13.2 million.¹ The most robust risk factor for AD is advancing age, and during the past decade, researchers have identified other factors, such as female gender,² low educational attainment,³ and jobs with low mental demands,⁴ that may also increase the likelihood for AD. Recent work has emphasized the identification of mutable risk factors, in hopes that lifestyle modifications could decrease the occurrence of AD. In this article, we evaluate whether participation in leisure activities during the life span—especially mental leisure activities involving "novelty seeking"—is associated with lower chances for development of AD in later adulthood.

At least 2 case-control studies have shown that participation in leisure activities is associated with lower odds of AD. In their research, Kondo and colleagues compared 60 cases to 120 age-matched and gender-matched controls on lifestyle variables covering the fifth and sixth decades of life.⁵ The researchers gathered data about involvement in leisure-time activities, as well as data

about diet, substance use (cigarettes and alcohol), medical history, family environment, education, and occupation. Several independent logistic regression analyses were performed to model the risk of AD as a function of the lifestyle variables. The statistical analyses revealed that psychosocial inactivity, physical inactivity, head injury, loss of teeth, and low education were risk factors for AD. A multivariate model, including all 5 significant predictor variables, showed that persons with all 5 risk factors were 934.5 times more likely to have AD than persons with none of the 5 risk factors.

In another case-control study, our research team evaluated the development of AD as a function of participation in 26 nonoccupational activities from ages 20 through 60.⁶ Participants were 193 persons with "probable" or "possible" AD and 358 healthy controls who were friends, neighbors, or members of the same organizations to which the cases belonged. We gathered activity data from a Life History Questionnaire and classified activity patterns as "intellectual," "passive," or "physical," based on rational groupings informed by previous research. We found that the odds ratio (OR) for AD in those performing less than the mean value of all possible activities was 3.85 (95% confidence interval [CI], 2.65-5.58). We also determined that increases in intellectual activities from early adulthood (ages 20 to 39 years) to middle adulthood (ages 40 to 60 years) were associated with decreased chances of being in the AD group.

Findings from these case-control studies are supported by recent prospective studies showing that the risk for developing AD some time later is increased in less active older adults without dementia. At least 4 prospective studies have demonstrated protective effects of participation in mental activities, with relative risk estimates ranging from 0.54 to 0.93.⁷⁻¹⁰ Conclusions from the prospective and retrospective studies have been used to make recommendations about lifestyle choices, urging persons to increase their mental activity throughout life to decrease the risk for AD.^{11,12}

Both prospective and retrospective studies of activities assessed involvement in mental, physical, and social activities in some fashion.^{6-8,10} However, the operational definitions and instruments used to measure activities have varied. In some studies, activity items are divided into activity classes based on rational classification schemes that have face validity but are nonetheless subjective.^{6-8,10} Furthermore, although the protective effects of participation in mentally stimulating activities have received attention in the research literature, no study has yet examined the impact of *different types* of mental activities. For example, mental activities could emphasize to a greater or lesser degree memory, problem solving, abstract thinking, creativity, etc, but studies have not yet considered how these differences may be related to the development of dementia.

In prospective studies, the reported low activity levels among cases may simply reflect preclinical manifestations of the disease. For example, persons with AD commonly present with apathy, depression, and disengagement.¹³ In prospective studies, these early symptoms could be misidentified as reflecting low activity levels. Studies that examine activity levels earlier in life, before the earliest symptoms of the disease emerge and become clinically manifested, are therefore valuable for circumventing this misidentification.

The selection of an appropriate comparison group is vital in a case-control design. The control group members must be as similar to the cases as possible, differing only in the factor of interest.¹⁴ There are 2 common sources for control group members in case-control studies: (1) the friends, neighbors, relatives, or associates of the cases; and (2) healthy persons living in the community or geographic area from which the cases arose (community controls). These latter control group members are often selected via probability sampling or random digit dialing. Because each of these methods for selecting a control group has limitations,¹⁴ this study presents results based on both types of controls.

Our goal was to examine the association of participation in mentally stimulating activities and AD status, with a special focus on activities that involve "novelty seeking." Novel activities, we hypothesize, may offer extra protection, because performing them requires active mental processing, which could increase cognitive reserve. As in our previous work, we used a case-control design to examine the hypothesized relationships. However, we used an empirical method (factor analysis) to develop activity scales, rather than relying on rational groupings of activity items, as done in many other studies. We collected data on activities performed between the ages of 20 to 60 years. Information about activities performed after 60 years of age was not collected, because it is clear that the disease itself is associated with reduced activities. This reduction could very well occur in the premorbid period before the subject or family is aware of the onset of dementia. We compared cases to 2 control groups, drawn from different populations, which together were thought to produce a suitable control group for our cases. Our plan was to combine the 2 control groups unless important patterns of differences between them could be shown.

METHOD

Subjects

Subjects were participants in the Alzheimer's Disease Case-Control Study at the Case Western Reserve University School of Medicine and University Hospitals of Cleveland in Ohio. This project, initiated in 1991, was approved by the Institutional Review Board of Univer-

sity Hospitals of Cleveland (09-92-210). Subjects with AD ($n = 264$) were recruited from clinical settings and the community and were all enrolled in the Research Registry of the University Memory and Aging Center (UMAC), a federally-funded Alzheimer's Disease Research Center affiliated with University Hospitals of Cleveland and Case Western Reserve University. Cases were evaluated by neuropsychological, functional, laboratory, and neurological examinations, and had magnetic resonance imaging or x-ray computed tomography scans of the brain. Exclusion criteria were a history of alcoholism, drug abuse, major head trauma, cancer, or other illnesses likely to impair cognition. All cases either had the diagnosis of probable AD (76.1%) or possible AD (23.9%) reached by consensus conference using NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Strokes/Alzheimer's Disease and Related Disorders Association) criteria.¹⁵ Two board-certified neurologists, a neuropsychologist, registered nurses with specialization in geriatric assessment, and project staff members attended the consensus conference meetings. Cases were required to have had onset of symptoms within 5 years of evaluation in the UMAC, to minimize the impact of premorbid features on the findings. All cases had surrogates available who had known the case for at least the past 10 years and who had had a close personal relationship with the case. Of the surrogates for the cases, 65.2% were spouses, 25.0% were children, and 9.8% were siblings, other relatives, or friends.

Control group members were drawn from 2 populations. Control group A members ($n = 364$) were the friends or neighbors of the cases or members of the same organizations to which the cases belonged. The control group members were identified by the cases' surrogates. Data from control group A members were gathered from 1991 to 1997.

From 1999 to 2001, a second set of controls was recruited, reflecting our concern that the controls in the first group (friends or neighbors and members of organizations to which the cases belonged) would be too similar to the cases with respect to activity and other lifestyle factors, thus biasing results toward the null (failing to reject the hypothesis of a significant difference in risk between the 2 groups for those factors). Those members making up control group B ($n = 181$) were drawn from a list of persons living in northeastern Ohio who were in the Center for Medicare and Medicaid Services database. They were frequency-matched to cases at random by year of birth, gender, ethnicity, and zip code.

Control group members in both groups were examined in the same way as the cases, undergoing neuropsychological, functional, laboratory, and neurological exams. Neuroimaging was available for control group members only in rare instances. As with the cases, control group members were determined to be free of neurological, psychiatric, or medical diseases affecting cognition. Persons

with a history of alcoholism, drug abuse, major head trauma, cancer, or other illnesses likely to impair cognition were not accepted as control group members. Informed consent or assent was obtained from each participant or a caregiver.

Procedures

Study participants completed a Life History Questionnaire that requested medical, occupational, dietary, activity, and smoking histories. Surrogates responded for cases and control group members responded for themselves. We have previously shown that self-reporting of control group members did not introduce systematic biases in responses across a variety of measures.^{16,17}

Measures

Educational attainment. Education was measured in terms of the highest year of schooling completed. Persons with a master's degree or a law degree were coded as having completed 18 years of education, and persons with a PhD or MD were coded as having completed 20 years, regardless of actual years in school. Educational attainment ranged from 4 to 22 years.

Occupational status. Socioeconomic index (SEI) scores¹⁸ were used to measure occupational status. SEI scores measure the perceived prestige of an occupation and reflect a person's general social standing. Respondents first identified the subjects' longest held occupation. Then, 2 research assistants independently coded these occupations, using the 1980 US Census Occupational scheme. In the case of disagreement, discrepancies were resolved by consensus. We used the 1980 scheme because many of our subjects were approaching retirement age during the 1980s, when the longest held occupation could be accurately reported. Next, SEI scores¹⁸ were assigned, based on the census occupation codes. SEI scores can range from 0 to 100, with higher scores indicating more prestigious jobs. In this study, scores ranged from 14.53 socioeconomic index points ("textile sewing machine operators") to 90.45 points ("law teachers"). The mean SEI score was 48.01 (SD, 20.56). Of the subjects, 3% were homemakers. Based on other research that developed an SEI score for homemakers,¹⁹ we assigned "homemakers" SEI scores of 51.00.

Activities. Sixteen questions from our Life History Questionnaire assessed activities. The intent of these questions, authored by members of our research group for this study, was to assess involvement in activities mainly related to novelty-seeking behaviors. Questions regarding other mental activities, as well as social and physical activities, were also included. Respondents were asked to indicate how often the subject looked for opportunities to do each of the 16 activities from age 20 to 60 years (control

group members) and from 20 years of age to 5 years before age at onset of AD (cases). Involvement in each activity was rated on a 3-point scale: 0, never; 1, sometimes; and 2, often.

Analysis Plan

We used 1-way between-subjects analyses of variance (ANOVA) and χ^2 tests for independence, where appropriate, to compare groups (cases, control group A members, and control group B members) on sociodemographic characteristics. We next compared responses to the 16 different activity questions between control group A members and control group B members to examine potential differences in the control groups. Our plan was to combine the groups unless the responses indicated important patterns of differences. The comparisons of responses were accomplished using independent-samples *t* tests. Because we were not trying to detect significant differences in these analyses, we did not make an adjustment to the α level (ie, a Bonferroni correction) for multiple comparisons. Next, the 16 activity questions were submitted to factor analysis (principal components with varimax rotation) to derive activity groupings. Logistic regression analysis was used to calculate the odds of AD as a function of participation in activities, controlling for year of birth, gender, ethnicity, education, and occupational status. Because we have previously analyzed other activity items from our Life History Questionnaire in this same sample of subjects,⁶ results in the present study are expressed as OR, with 97.5% CI to account for multiple comparisons.

Treatment of Missing Data

Missing data were imputed using "hot deck" procedures.²⁰ "Hot deck" imputation sorts subjects with missing data into groups according to a chosen set of sorting variables. Missing values are replaced with values selected randomly from matching respondents who have data. The technique is an improvement over simple mean substitution and regression-based procedures because it introduces more variability in imputed scores and, as a nonparametric approach, is not subject to strong distributional assumptions. In the current study, the sorting variables were as follows: (1) year of birth; (2) gender; and (3) years of education. The percentages of missing data across the 16 activity variables before imputation ranged from 2.1% to 7.8%. The mean percentage missing across all activity variables was 4.6% (SD, 1.7%). Imputation for such small percentages of missing data (less than 10%) would not be expected to influence results in any systematic way.

RESULTS

Sociodemographic Comparisons

The sociodemographic features of cases and members of control groups A and B are shown in Table 1. The groups differed in terms of year of birth ($F = 4.55$; $P < .05$), gen-

Table 1. Sociodemographic and Clinical Features of Cases and Members of Control Groups A and B

| Variable | Cases (n = 264) | Control Group A (n = 364) | Control Group B (n = 181) |
|-------------------------------------|--------------------|------------------------------|------------------------------|
| Mean year of birth (SD) | 1921 (8.6) | 1923 (6.1) | 1922 (6.3) |
| Percentage female (n) | 55.7 (147) | 60.4 (220) | 48.6 (88) |
| Percentage white (n) | 90.5 (239) | 97.3 (354) | 95.6 (173) |
| Mean education, y (SD) | 13.0 (3.0) | 15.3 (2.7) | 14.4 (2.8) |
| Mean occupational status score (SD) | 40.4 (19.5) | 52.7 (19.4) | 49.6 (21.3) |
| Mean MMSE score (SD) | 17.8 (6.2) | 28.8 (1.0) | 28.5 (1.5) |
| Mean illness duration, y (SD) | 3.13 (1.62) | — | — |

Note: MMSE, Mini-Mental State Examination.

der distribution ($\chi^2 = 6.91$; $P < .05$), ethnicity ($\chi^2 = 14.11$; $P = .001$), education ($F = 48.79$; $P < .001$), occupational status ($F = 30.03$; $P < .001$), and Mini-Mental State Examination (MMSE) scores ($F = 759.70$; $P < .001$). Follow-up tests, adjusted for multiple comparisons, indicated that cases had earlier year of birth than control group A members ($P < .01$), but cases and control group B members did not differ in year of birth ($P > .05$). Control group A members and control group B members also did not differ in year of birth ($P > .05$). Cases had less education than control group B and control group A members (P s $< .001$), and control group B members had less education than control group A members ($P < .01$). Cases had lower occupational status than members of both control groups (P s $< .001$). As expected, cases had lower MMSE scores than members of both control groups (P s $< .001$). There were more females among cases and control group A members than among control group B members, and a greater percentage of minority subjects in the case group than in either control group. Other differences between the groups were not statistically significant (P s $> .05$).

These results indicate that efforts to match cases to controls did not succeed completely. However, in our main analysis (a logistic regression predicting AD status), we included the matching factors (year of birth, gender, ethnicity) to adjust for group differences.

Control Group Comparisons

Responses to the 16 activity questions by control group A and B members were compared with independent-samples *t* tests. Control group A members more frequently look for opportunities to discuss ideas and politics, put in extra hours at work or keeping house, and spend time with friends than did control group B members (P s $< .05$). For the remaining 12 activity items, however, differences were not statistically significant. Because control groups A and B had large sample sizes, which provided high power to detect very small effects (across the 16 items, the mean differences ranged from 0.018 to 0.271), and because most of the activity items did not differ between the control groups, we concluded that it was appropriate to combine the 2 control groups for analysis.

Table 2. Factor Loadings Derived From Factor Analysis of Activity Questions (n = 809)

| | Factor I | Factor II | Factor III | Factor IV |
|---|-------------|-------------|-------------|-------------|
| Learn a new skill | .788 | .137 | -.017 | .092 |
| Learn about a new subject | .708 | .056 | .285 | .063 |
| Do things that are challenging mentally | .671 | .149 | .303 | .144 |
| Solve a problem | .640 | -.001 | .318 | .068 |
| Get a new experience | .620 | .264 | .266 | .057 |
| Take up a new hobby | .604 | .233 | -.109 | -.105 |
| Do something that is challenging physically | .463 | .207 | .156 | -.060 |
| Visit a place you had been before | .082 | .794 | .010 | .029 |
| Visit a new place | .269 | .723 | .079 | .128 |
| Spend time with friends | .133 | .623 | .238 | .013 |
| Put in extra hours at work or keeping house | .288 | .314 | .041 | -.262 |
| Discuss politics | .086 | .087 | .838 | .006 |
| Discuss ideas | .352 | .140 | .710 | .030 |
| Take a risk | .336 | .289 | .370 | .081 |
| Rest or take a nap | .031 | .023 | -.057 | .799 |
| Spend time alone | .098 | .088 | .130 | .714 |
| % variance explained | 30.28 | 8.07 | 7.82 | 6.70 |

Note: Factor I, novelty-seeking activities; Factor II, social activities; Factor III, exchange-of-ideas activities; Factor IV, passive activities. Values in boldface type represent items that factored together.

Development of Activity Scales

The activity data from cases and the 2 control groups were subjected to a principal components analysis with varimax rotation. Four factors that emerged with eigenvalues greater than 1 were retained in the factor solution. Activity items with factor loadings less than 0.5 were excluded from consideration as items in the factors. The cumulative variance attributable to the 4 factors was 52.87%. The factor loadings derived from the analysis are shown in Table 2.

We assigned the following labels to the 4 factors: "novelty-seeking activities," "social activities," "exchange-of-ideas activities," and "passive activities." The internal consistency reliability coefficients (Cronbach α) for the first 3 factors were, respectively: .82, .65, and .64. The "passive activities" factor had poor internal consistency reliability ($\alpha = .41$) and was therefore excluded from subsequent analyses.

Next, we created novelty-seeking, exchange-of-ideas, and social scales by summing the activity items making up each respective factor and dividing by the number of items in each factor. Thus, higher scores on each scale indicated a greater tendency to seek that type of activity. The respective mean scores for novelty-seeking, social, and exchange-of-ideas activities among cases were 1.11 (SD, 0.43), 1.39 (SD, 0.45), 1.12 (SD, 0.56), and the respective mean scores among controls were 1.41 (SD, 0.36), 1.54 (SD, 0.38), 1.40 (SD, 0.50). Independent-samples *t* tests indicated that these case-control differences were significant, with *P* less than .001.

Relationships With AD Status

Logistic regression analysis was used to calculate the odds of AD as a function of the activity variables and control variables (year of birth, gender, ethnicity, education, and occupational status). We used simultaneous entry of variables

to study the independent effects of each variable while controlling for all others. As seen in Table 3, greater participation in novelty-seeking activities was associated with reduced odds of AD (OR, 0.248; 97.5% CI, 0.139-0.443). Greater participation in activities involving exchange of ideas was also associated with a reduced odds of AD (OR, 0.695; 97.5% CI, 0.467-1.034). Participation in social activities did not increase or decrease the odds of being in the AD group (OR, 1.057; 97.5% CI, 0.636-1.756). However, earlier year of birth (older age), male gender, lower educational attainment, and lower occupational status were significantly associated with AD status in this model.

In secondary analyses, we generated regression-based scores for each factor. When the 3 regression-based factor scores were included as independent variables in the logistic regression model in place of the 3 activity scale scores, the patterns of results were similar. Finally, in an analysis that included Hachinski Ischemia Scores²¹ in the model to control for vascular risk, we found that the results were essentially unchanged, although the exchange-of-ideas variable was only marginally significant (OR, 0.729; 97.5% CI, 0.486-1.093; *P* = .080).

DISCUSSION

Results from this study suggest that participation in mental leisure activities, especially those involving novelty seeking, is negatively associated with AD. However, an inverse relationship was also seen for activities involving exchange of ideas. These results are consistent with findings reported in other studies, showing that participation in mentally stimulating activities lowers one's chances of developing AD or other dementia.⁵⁻¹⁰ Our results extend these findings by showing that the *magnitude* of the associations between mentally stimulating activities and AD depends on the type of mental activity performed: the

Table 3. Logistic Regression Analysis Where Alzheimer's Disease Status Is a Function of Activity and Control Variables

| Predictor | OR | 97.5% CI | P |
|------------------------------|-------|-------------|-------|
| Year of birth | 0.976 | 0.951-1.003 | .043 |
| Gender | 1.557 | 1.046-2.318 | .013 |
| Ethnicity | 1.721 | 0.776-3.817 | .127 |
| Education | 0.871 | 0.798-0.950 | <.001 |
| Occupational status | 0.988 | 0.976-1.001 | .033 |
| Novelty-seeking activities | 0.248 | 0.139-0.443 | <.001 |
| Exchange-of-ideas activities | 0.695 | 0.467-1.034 | .040 |
| Social activities | 1.057 | 0.636-1.756 | .807 |

Note: For gender, females were coded as 0 and males as 1; for ethnicity, whites were coded as 0 and minority subjects (mostly African Americans) were coded as 1. OR, odds ratio; CI, confidence interval.

odds of AD were relatively lower for novelty-seeking activities than for activities involving exchange of ideas.

The associations we report in this study can be interpreted in several ways. First, the observed effects may be a reflection of the early symptoms of AD. Among persons who develop AD, apathy, depression, and disengagement are common and early symptoms.¹³ Thus, the lower participation in novelty-seeking activities and activities involving exchange of ideas among our cases may be a direct result of disease processes manifesting themselves earlier in life. Evidence is accumulating to suggest that AD has a long preclinical period, predating frank clinical symptoms by decades.²² However, we minimized the impact of this long preclinical course on our interpretations of the data by collecting activity data covering age 20 years to 5 years before symptom onset for cases and age 20 years to present for control group members.

The finding that persons with AD were less novelty seeking could be related to a depletion of neurotransmitters associated with AD neuropathology, such as dopamine. Although the cholinergic system shows the most consistent deficits in AD,²³ the dopamine system also is compromised in AD.²⁴ A depletion of dopamine has been implicated in the risk-averse style and tendency toward lower novelty seeking sometimes seen in Parkinson's disease patients.²⁵

Alternatively, a tendency to seek situations in which one can exchange ideas with others, and the need for novelty seeking could reflect underlying dimensions of *personality*. Such personality traits could have their own relation to dementia risk. Consistent with this idea are results from a recent prospective study that showed that higher scores on the neuroticism subscale of the NEO-PI personality inventory, assessed at baseline, predicted the development of AD over 5 years.²⁶ Although this study was undertaken to evaluate the potential link between stress and AD, it also implies, as does our study, that further investigations of the relationships between premorbid personality and dementia are needed.

It is possible that participation in activities involving novelty seeking and exchange of ideas had an effect on bio-

logical processes associated with aging that directly reduced the odds of being in the AD group, which would be consistent with the well-known "use it or lose it" scenario.^{27,28}

Thus, frequent participation in novel activities and activities involving exchange of ideas may result in increased neural activation. This increased neural activation is believed to maintain and build up a neuronal reserve that can help persons to resist the challenges of AD.²⁷ Thus, people who frequently seek novel experiences may build cognitive reserve through their continual, relatively high effort devoted to encoding and storage processes. Persons who often exchange ideas with others may also build up reserve through this type of mental work. Indirect support for this biological-cognitive interpretation comes from studies of cerebral flow. In analyses controlling for age and disease severity, engagement in various activities in AD patients was negatively associated with cerebral blood flow.²⁹ The association was still present when controlling for education and premorbid IQ. These findings were taken as evidence that participation in activities may increase cognitive reserve, thereby increasing one's ability to resist clinical manifestations of AD.

Finally, other variables that are correlated with AD, novelty-seeking activities, and activities involving exchange of ideas but for which we did not control, could explain the activity level-AD relationship. If this were the case, the association between activity level and AD would be spurious. However, we made efforts to control for variables that are likely risk factors for AD (year of birth, gender, ethnicity, education, occupational status) and that may correlate with activity level so that the links between activities and AD we observed are independent of those other risk factors. We did not control for apolipoprotein (APOE) genotype, because the sample that provided DNA was too small to achieve adequate power in our analyses. However, unless APOE genotype is correlated with participation in activities, it would have no biasing effects on our results.

There are several factors that increase confidence in our results. Cases and control groups were members of our Alzheimer's Disease Research Center research registry, and their cognitive status was well characterized through medical and neurological examination, laboratory testing, neuroimaging, neuropsychological testing, and functional evaluation, ascertained through interviews with knowledgeable family members. Respondents were asked to provide data covering the course of subjects' lives—their 20s through 60s, thus minimizing the impact of early symptomatology on study results and conclusions. We gathered data from 2 very different control groups, finding that responses from members of these 2 groups were, for the most part, similar. This finding increased confidence that the case-control differences we observed were valid. We note, however, that our control groups were not drawn from clinical settings, a sampling strategy that can sometimes compensate for the selection biases associated with the sampling of cases from clinical settings.

Our study used an asymmetrical design. Thus, proxies reported for cases, and control group members reported for themselves. A more common practice is to use the same source of information (proxy or self) for all participants. In studies that require proxy report for cases, the practice of using surrogate respondents for healthy controls is motivated by a desire to achieve comparable mechanisms of generating nonrandom errors for cases and control group members. Previously, we reported the results of 2 studies comparing responses from our first 50 control group members with responses from their surrogates on a variety of measures.^{16,17} Generally, we found no systematic underreporting or overreporting by the surrogates for the control group members across a wide array of variables. Hence, we conclude that if there are biases in the responses of the surrogates for the AD cases in our study, they are not likely to be canceled out by using surrogates for control group members. As a result, we believe that self-report by control group members in our study results in unbiased report on exposures for control group members and higher power to detect meaningful differences between cases and control group members. It is possible, however, that the type and intensity of activities engaged in long ago are more reliably represented by self-reporting control group members than by surrogate respondents.

Reports of activity levels also may have been biased if informants gave extra weight to more recent activities. This bias would be especially relevant when proxies report about cases' engagement, because the proxy respondents may have better knowledge of the cases' current activities than their earlier activities. If extra weight is given to cases' activity patterns closer in time to AD diagnosis, this activity pattern may have been influenced by preclinical AD.

The assessment of activity levels in this study was dependent on retrospective accounts that could be inaccurate. Methodologists have devoted considerable attention to studying the validity of retrospective reports of health-related information, such as diet,³⁰ and chronic illness and medication use.³¹ Relatively few studies have examined whether long-term recall of activity patterns are accurate. However, in a recent report,³² Swedish women, ages 70 to 92 years, were asked to recall their leisure-time physical activities from 32 years ago. These contemporary estimates of their earlier activity levels were compared with activity ratings made by the same subjects in 1968. Results indicated that approximately 44% of subjects classified themselves consistently at both evaluations; approximately 49% overestimated their activity levels; and approximately 7% underestimated their previous activity levels. Thus, these data suggest that systematic errors occur in the recall of physical activity patterns. However, in the present study, a bias to overestimate activity levels is less important than a bias in reporting by control group members and proxies for cases. As indicated earlier, we do not find such a bias in our sample.

In our study, participation in leisure activities was associated with reduced odds of having AD. The odds of being in the AD group were lower among those who more often participated in activities involving exchange of ideas and were lower yet for those who more frequently participated in novelty-seeking activities. Our study could mean that persons who participate in a variety of mental activities have reduced chances of developing AD compared with those who limit their mental activities to 1 type. Our study may have lower external validity than some prospective studies because it used a case-control design. However, given recent evidence from both retrospective and prospective studies suggesting that mental activity may protect against cognitive decline and clinical manifestations of dementia in aging, increased emphasis should be placed on providing programs that offer opportunities to read, think, discuss, and learn new things to people across the life span.

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