Variables Associated with Cognitive Function in Elderly California Seventh-day Adventists

Gary E. Fraser, Pramil N. Singh, and Hannelore Bennett

From a cohort of white, non-Hispanic California Seventh-day Adventists, 99 subjects over age 75 years in 1991 were randomly selected. Dietary habits and educational status had been measured in 1976. Subjects completed the Mini-Mental State Examination (MMSE) in 1991, and at that time, they or caregivers also gave information on current medical problems and drug therapy. Those who ate more calories in 1976 had lower MMSE scores in 1991 (p = 0.03), an association strengthened by excluding those with previous stroke or Parkinson’s disease by 1991. This raises the possibility that higher consumption of calories in middle age may accelerate the decline in cognitive function seen with aging, as apparently occurs in some animals. Less-educated subjects had lower MMSE scores, especially among the very elderly. The statistical model predicts that the negative association between use of psychotropic drugs and MMSE score (p = 0.004) is particularly potent in those cognitively impaired for other reasons. If causal, this suggests that physicians should use these agents very cautiously in such subjects.

In different cross-sectional studies, the reported prevalence of dementia ranges from 10 to 50 percent in elderly subjects over age 85 years (1). The increasing number of elderly in both the United States and developing nations over the last 2 decades will undoubtedly further increase the social burden of dementia in the future. While age and family history of a dementing illness are the only unequivocally identified risk factors, the wide international variation in the rates of dementia suggests a possible etiologic role for environmental factors as well (1, 2). Previous studies of Alzheimer’s disease and other dementias have identified associations with education, smoking, alcohol use, head trauma, meat consumption, aluminum, comorbid psychiatric disorders, hypertension, diabetes mellitus, and hypothyroidism (2-7). However, these factors need further confirmation as etiologic agents. A higher prevalence of vascular dementia has been observed in populations with a high prevalence of risk factors for vascular disease (8-11). The identification of modifiable risk factors may allow not only the reduction of excess morbidity due to the dementia itself but also the reduction of other problems associated with dementia such as decreased functional capacity (12, 13) and adverse drug effects (14).

The Mini-Mental State Examination (MMSE) is a screening test for dementia that has been successfully used in a number of different cultural and ethnic subgroups (15-20). Since its development in 1975, the MMSE has also been validated against more comprehensive measures of cognitive assessment (21, 22) and several physiologic measures (23-25). As a research instrument, the MMSE has also been used to evaluate...
cognitive impairment in many population-based epidemiologic studies (16, 20, 26, 27). In this study, we administered the MMSE to an elderly Seventh-day Adventist population to investigate the possible effects of education, past dietary exposure, medical history, and certain other lifestyle variables on cognitive function.

MATERIALS AND METHODS

The population studied was a random sample of surviving participants from a cohort study of California Seventh-day Adventists who, in 1991, were over age 74 years and lived within 30 miles of Loma Linda. The Adventist Health Study is a cohort investigation of 34,198 non-Hispanic white California Seventh-day Adventists. The details of the study design have been described elsewhere (28). However, briefly, between 1974 and 1976, an attempt was made to identify all California Seventh-day Adventists over age 25 years. All subjects completed two extensive mailed questionnaires containing demographic, dietary, exercise, psychosocial, socioeconomic, and medical history information. Dietary assessment was by a semiquantitative food frequency questionnaire that included 55 foods or food groups. Most dietary questions had eight frequency categories ranging from "never consume" to "more than once each day."

Exercise was categorized as low, moderate, or high. This represents a cross-classification of two questions regarding occupational and leisure activities. "High" exercise reflects high occupational and/or high leisure activity status, indicating at least 15 minutes of named vigorous activities at least three times each week. "Low" exercise refers to subjects with both low leisure and occupational activities. "Moderate" exercise includes the remainder.

In 1974, a substudy conducted on 147 Adventists randomly selected from the local area was used to validate nutrient indices. Five telephone 24-hour recalls were obtained on two random weekends and three random weekdays over a period of 3 months as a reference against which to correlate responses to an extensive food frequency questionnaire. The Extended Table of Nutrient Values database (29) provided nutrient values. Corrected (30, 31) nutrient indices, developed by a stepwise correlation procedure, had validity correlation coefficients as follows: total calories, 0.57; total fat, 0.47; and polyunsaturated, monounsaturated, and saturated fats, 0.39, 0.45, and 0.44, respectively. Similar coefficients for foods or food groups were 0.49, 0.59, 0.46, 0.49, 0.47, and 0.54 for beef, poultry, nuts, fruits, eggs, and cheese, respectively. These are similar in magnitude to those reported by others (32–34).

The MMSE is a test that is widely used in epidemiologic and community studies. It is not intended to provide a diagnosis of any particular nosologic entity but was created to provide scores that were "useful in quantitatively estimating the severity of cognitive impairment" (35, p. 189) and "in serially documenting cognitive change" (35, p. 189). It contains 12 items concerning orientation in time and place, repetition, concentration, memory, language, and praxis.

Although we had no formal contact with this population for 7 years, from a variety of small studies we knew that we could trace at least 90 percent of subjects. Thus, a list of all 1,011 subjects over age 74 years as of January 1, 1991, who lived in one of the local zip code areas and who were not known to be deceased was prepared. A random selection of 186 names from this list was used as a basis for tracing. Potential participants were initially contacted by telephone to determine their willingness to be interviewed. Those residing in rest homes were included. There were no further exclusion criteria, since we wished this to be a population sample of those with the appropriate age and residential status. Of these 186 subjects, 10.3 percent were lost to follow-up, 6.5 percent declined to participate, 17.8 percent had moved from the local area, and 11.9 percent were deceased. Thus, of subjects who could be contacted and still lived locally, the response rate was 89 percent (100/112). One subject was subsequently determined to have a meningioma causing dementia and hence is excluded from further consideration. A further nine subjects were excluded because of missing data for one of the foods required to calculate the calorie index. These last subjects did not differ significantly from those remaining with respect to MMSE score, age, education, use of psychoactive medications, or number of chronic diseases. Thus, the analyses presented below are the results from the 90 eligible living subjects with adequate calorie intake data.

One of us (H. B.) was trained in the interview technique for the MMSE test by staff at the Geriatric Neurobehavior and Alzheimer Center, Rancho Los Amigos Medical Center, Los Angeles, California. All subjects were interviewed early in 1991 at their place of residence. When necessary in residential homes or hospitals, the caregiver was interviewed, and the medical chart was consulted to obtain current medication and medical history information. The following medical conditions were included on the 1991 questionnaire: coronary heart disease, stroke, emphysema, renal failure, arthritis, diabetes, Parkinson's disease, osteoporosis, chronic back pain, depression, nervous breakdown, and high blood pressure. Medications
judged as possibly affecting cognitive function included benzodiazepines, phenothiazines, antidepressants, haloperidol, antiepileptic medications, opiate pain medications, hydroxyzine, and carbidopa-levodopa.

Thus, the 90 elderly subjects in this analysis had extensive dietary and other data collected in 1974–1976 and approximately 16 years later underwent the MMSE/medical history home interview.

Statistical methods

An immediate problem was the usual, pronounced negative skew of the MMSE data, with a number of subjects scoring the maximum value of 30. We found that \(-\log(30.6 - \text{MMSE})\) produced a distribution with acceptable normality (skewness, -0.021; kurtosis, 0.043). Thus, all regression analyses and statistical tests involving MMSE used this transformation:

\[
-\log(30.6 - \text{MMSE})_j = \alpha + \sum_{i=1}^{p} \beta_i X_{ij} + \epsilon_j,
\]

where we used log to the base 10. Plots of residuals from these regressions also demonstrated excellent normality.

Predicted values of MMSE, i.e., \((\text{MMSE})\), were calculated using the inverse transformation, \(\text{MMSE} = 10^{-(\log(30.6 - \text{MMSE}))} + 30.6\). If \([C]\) is the Covariance Matrix of the regression coefficients \(\beta_i\), and \(X^T = (1, X_1, \ldots, X_p)\) are the chosen exposure values at which to evaluate MMSE, then \(\text{Var}[f(\text{MMSE})] = X^T[C]X\), as usual (36).

An approximate 95 percent confidence interval for the expected or predicted MMSE is 30.6 - 10^{(\frac{1}{2} \cdot f(\text{MMSE})^2 + 1.96 \times \text{SE}[f(\text{MMSE})])}. The predicted effect on the MMSE score of changing one of the predictor variables by one unit is of interest. This is used below to evaluate the effect of using psychoactive medications. Specifically, let \(Y\) be the predicted MMSE score without use of psychoactive drugs, \(Y'\) be the score with use of psychoactive drugs, \(\beta_i\) be the regression coefficient for psychoactive drug use, and \(\sum_{i=2}^{p} \beta_i X_{ij}\) be other terms in the model. Then

\[
-\log(30.6 - Y')_j = \alpha + \sum_{i=2}^{p} \beta_i X_{ij},
\]

Thus, \(Y' - Y = (1 - 10^{-\beta}) (30.6 - Y)\) is the predicted change in MMSE score with the use of psychoactive drugs, which evidently depends on the initial score.

RESULTS

The subjects ranged in age from 75 to 93 years at the time of cognitive assessment. Figure 1 shows the distribution of MMSE scores for the 90 subjects. Seventeen subjects scored 23 or less. The study population exhibits health behaviors that are in some respects different from those of the general United States population. On a lifestyle questionnaire administered 15 years prior to cognitive assessment: 1) no subject indicated current smoking; 2) only one subject indicated any use of beer, wine, or liquor; and 3) 44 percent of the subjects indicated no meat consumption (see table 1).

In univariate analyses, a significant negative association was found between age (years) and the normalized MMSE score (\(\beta = -0.035, p < 0.0001\)); years of education was positively but nonsignificantly associated with the normalized MMSE score (\(\beta = 0.016, p = 0.20\)). However, a linear regression model

![Figure 1. Distribution of Mini-Mental State Examination (MMSE) scores in a sample of elderly California Adventists.](https://academic.oup.com/aje/article-abstract/143/12/1181/70877)
TABLE 1. Selected characteristics of the study population of 90 elderly California Adventists (32 males, 58 females)*, 1991

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean (SD†) (years))</td>
<td>81 (5)</td>
<td>80 (4)</td>
<td>81 (5)</td>
</tr>
<tr>
<td>Years of education (mean (SD) (years))</td>
<td>15 (4)</td>
<td>13 (3)</td>
<td>14 (3)</td>
</tr>
<tr>
<td>Body mass index (mean (SD) (kg/m²))</td>
<td>25 (3)</td>
<td>25 (3)</td>
<td>24 (3)</td>
</tr>
<tr>
<td>Total energy intake (mean (SD) (kcal))</td>
<td>1,889 (370)</td>
<td>1,706 (220)</td>
<td>1,771 (280)</td>
</tr>
<tr>
<td>No. of chronic diseases‡</td>
<td>1.3 (1.2)</td>
<td>1.6 (1.2)</td>
<td>1.5 (1.2)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current use</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Past use</td>
<td>37</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Never used</td>
<td>83</td>
<td>95</td>
<td>83</td>
</tr>
<tr>
<td>Meat consumption (per week) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>33</td>
<td>50</td>
<td>44</td>
</tr>
<tr>
<td>&lt;1</td>
<td>30</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>1–4</td>
<td>17</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>&gt;4</td>
<td>20</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Exercise level (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None/low</td>
<td>16</td>
<td>31</td>
<td>26</td>
</tr>
<tr>
<td>Moderate</td>
<td>34</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td>High</td>
<td>50</td>
<td>51</td>
<td>50</td>
</tr>
<tr>
<td>Occupation (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blue collar</td>
<td>37</td>
<td>53</td>
<td>47</td>
</tr>
<tr>
<td>White collar</td>
<td>63</td>
<td>47</td>
<td>53</td>
</tr>
<tr>
<td>Psychoactive medication use (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>6</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>9</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Opiate</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>9</td>
<td>7</td>
</tr>
</tbody>
</table>

* All variables except number of chronic diseases are those reported in 1976 (28).
† SD, standard deviation.
‡ Coronary event (angina pectoris, myocardial infarction), high blood pressure, stroke, diabetes, emphysema or chronic lung disease, kidney failure, Parkinson's disease, osteoporosis or fractures, chronic back pain, and depression.

including the variables age, education, and a two-way interaction term for the product of education and age demonstrated significant associations between the normalized MMSE score and both age ($\beta = -0.034$, $p < 0.0001$), and the two-way interaction term for education and age ($\beta = 0.0062$, $p = 0.02$). Hence, this interaction term was subsequently included in all models containing education.

Medical history data collected at the time of cognitive assessment (1991) identified subjects with a history of coronary events (13 percent), high blood pressure (23 percent), stroke (12 percent), diabetes (8 percent), emphysema or chronic lung disease (4 percent), arthritis (46 percent), depression (17 percent), Parkinson’s disease (1 percent), chronic back pain (17 percent), and osteoporosis/fractures (12 percent). There were no cases of kidney failure among the study subjects. The effect of disease history on MMSE score was evaluated by using multiple regression models that included the covariates age, sex, education, education × age, and disease history (yes/no), and taking the medical disorders one at a time in separate models. A history of diabetes mellitus was associated with a lower MMSE score ($\beta = -0.19$, $p = 0.12$), but no other association was close to statistical significance. In particular, the coefficient for depression was 0.022 ($p = 0.84$). Further, no significant association was found between the total number of these chronic diseases for which there was a positive history and the normalized MMSE score.

The effect of various lifestyle variables on the normalized MMSE score was evaluated by using multiple
linear regression models that included the variable of interest, age, sex, years of education, and education × age. The results are presented in table 2. Use of medications with known psychoactive effects was associated with a significant decrease in MMSE score ($\beta = -0.32, p < 0.001$). No associations were found with smoking, body mass index, exercise, or social class (blue collar/white collar). Among women, a borderline significant positive association was found with age at menopause.

Next, associations between dietary intake measured in 1976 and the MMSE score measured in 1991 were evaluated. Higher total energy intake (kcal/24 hours) in 1976 was associated with a significantly lower ($\beta = -0.00032; 95\%$ confidence interval (CI) $-0.00059$ to $-0.00038; p < 0.03$) MMSE score as measured in 1991, independent of age, sex, and education. The effects of specific nutrients and foods were tested by using linear regression models that included age, sex, education (years), education × age, and the selected food or calorie-adjusted nutrient. The results are presented in table 3. Significant negative associations between MMSE score, calorie-adjusted magnesium, calorie-adjusted vegetable fat, and fruit intake were found. However, in models that included calorie-adjusted magnesium and vegetable fat together (a nutrient model), neither were close to statistical significance. Further, whenever the variable total calories was added to the models of table 3, the coefficient for fruits was no longer close to statistical significance.

Table 4 presents a linear regression model that includes all variables of interest simultaneously. These are age, education, education × age, sex, total energy intake, total number of chronic diseases, exercise habits, and use of medication with known psychoactive effects. In this model, age, education, education × age, total energy, and use of psychoactive medications showed significant associations with the normalized MMSE score. The other variables were retained in the model to adjust for potential confounding in the associations with education, total energy, and medication use.

The negative association between total energy intake and MMSE score shown in the model in table 4 was examined further. The strength of this association with calories was not substantially altered by the elimination of the six subjects above the 95th percentile of caloric intake ($\beta = -0.00033, p = 0.08$) or when the 17 subjects with an MMSE score of 23 or less were eliminated ($\beta = -0.00033, p < 0.05$). The results of table 4 predict an average MMSE score of 28.3 (95 percent CI 27.3–28.9) for those eating 1,300 calories per day, reducing in a curvilinear fashion to a predicted score of 23.9 (95 percent CI 17.7–27.1) in those who ate 2,800 calories per day in 1976. This is when covariates in the regression take average values.

We did not have available further diagnostic tests to determine the causes of the reduced cognitive function that were measured in some subjects. However, in an attempt to indicate whether the variables in our model ($n = 89$) may be specifically associated with Alzheimer-type pathology, the 11 subjects with a history of stroke and two subjects with history of Parkinson's disease were excluded from a further analysis.

**TABLE 2. Multiple linear regression models relating the normalized MMSE* score to selected lifestyle variables in a sample of elderly California Adventists, 1991**

<table>
<thead>
<tr>
<th>Variable in each model</th>
<th>No. of subjects</th>
<th>Regression coefficient†</th>
<th>95% CI*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of chronic diseases‡</td>
<td>90</td>
<td>-0.0083</td>
<td>-0.077 to 0.060</td>
<td>0.81</td>
</tr>
<tr>
<td>Use of medications with known psychoactive effects‡ (0 = no, 1 = yes)</td>
<td>90</td>
<td>-0.32</td>
<td>-0.51 to -0.13</td>
<td>0.001</td>
</tr>
<tr>
<td>Past smoking§ (0 = no, 1 = yes)</td>
<td>90</td>
<td>0.088</td>
<td>-0.14 to 0.32</td>
<td>0.46</td>
</tr>
<tr>
<td>Body mass index§ (kg/m²)</td>
<td>80</td>
<td>0.0015</td>
<td>-0.025 to 0.028</td>
<td>0.91</td>
</tr>
<tr>
<td>Exercise level§ (low/moderate/high)</td>
<td>89</td>
<td>0.036</td>
<td>-0.033 to 0.10</td>
<td>0.30</td>
</tr>
<tr>
<td>Occupation§ (blue collar/white collar)</td>
<td>72</td>
<td>0.0054</td>
<td>-0.21 to 0.22</td>
<td>0.96</td>
</tr>
<tr>
<td>Age at menopause§,‖ (years)</td>
<td>56</td>
<td>0.013</td>
<td>-0.00066 to 0.026</td>
<td>0.06</td>
</tr>
</tbody>
</table>

* MMSE, Mini-Mental State Examination; CI, confidence interval.
† Regression coefficients represent the linear increase in the transformed MMSE score [log (30.6 − MMSE)] (see Materials and Methods) per unit increase of the selected independent variable in a model including additional independent variables age, sex, years of education, and education × age.
‡ Reported in 1990 questionnaire administered at the time of cognitive assessment.
§ Reported in 1976 questionnaire (28).
‖ Females only.
TABLE 3. Multiple linear regression models relating the normalized MMSE* score (1991) to dietary intake of selected nutrients and foods reported in 1976† in a sample of elderly California Adventists, 1991

<table>
<thead>
<tr>
<th>Dietary variable in each model</th>
<th>No. of subjects</th>
<th>Regression coefficient‡</th>
<th>85% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrient models (calorie adjusted)§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total fat</td>
<td>86</td>
<td>-0.082</td>
<td>-0.22 to 0.056</td>
</tr>
<tr>
<td>Total protein</td>
<td>89</td>
<td>-0.13</td>
<td>-0.31 to 0.037</td>
</tr>
<tr>
<td>Monounsaturated fat</td>
<td>88</td>
<td>-0.065</td>
<td>-0.20 to 0.067</td>
</tr>
<tr>
<td>Polyunsaturated fat</td>
<td>81</td>
<td>-0.19</td>
<td>-0.42 to 0.046</td>
</tr>
<tr>
<td>Total fiber</td>
<td>86</td>
<td>-0.11</td>
<td>-0.23 to 0.015</td>
</tr>
<tr>
<td>Saturated fat</td>
<td>76</td>
<td>0.0081</td>
<td>-0.074 to 0.091</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>77</td>
<td>0.023</td>
<td>-0.070 to 0.12</td>
</tr>
<tr>
<td>Calcium</td>
<td>68</td>
<td>-0.0032</td>
<td>-0.092 to 0.086</td>
</tr>
<tr>
<td>Iron</td>
<td>79</td>
<td>0.025</td>
<td>-0.13 to 0.18</td>
</tr>
<tr>
<td>Magnesium</td>
<td>81</td>
<td>-0.24</td>
<td>-0.43 to -0.038</td>
</tr>
<tr>
<td>Animal fat</td>
<td>83</td>
<td>0.018</td>
<td>-0.051 to 0.086</td>
</tr>
<tr>
<td>Vegetable fat</td>
<td>84</td>
<td>-0.32</td>
<td>-0.56 to -0.069</td>
</tr>
<tr>
<td>Animal protein</td>
<td>82</td>
<td>0.0011</td>
<td>-0.081 to 0.083</td>
</tr>
<tr>
<td>Vegetable protein</td>
<td>81</td>
<td>-0.23</td>
<td>-0.47 to 0.01</td>
</tr>
<tr>
<td>Food models</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruit index</td>
<td>83</td>
<td>-0.077</td>
<td>-0.15 to -0.00069</td>
</tr>
<tr>
<td>Beans</td>
<td>84</td>
<td>-0.016</td>
<td>-0.033 to 0.0015</td>
</tr>
<tr>
<td>Green vegetables</td>
<td>85</td>
<td>-0.0055</td>
<td>-0.012 to 0.0010</td>
</tr>
<tr>
<td>Nuts</td>
<td>83</td>
<td>-0.0012</td>
<td>-0.0065 to 0.0041</td>
</tr>
<tr>
<td>Meat index</td>
<td>86</td>
<td>0.023</td>
<td>-0.060 to 0.11</td>
</tr>
</tbody>
</table>

* MMSE, Mini-Mental State Examination; CI, confidence interval.
† Reported in 1976 questionnaire (28).
‡ Regression coefficients represent the linear increase in the transformed MMSE score \([-\log (30.6 - \text{MMSE})]\) per unit increase of the selected independent variable in a model including additional independent variables age, sex, years of education, and education x age.
§ Residual values from calorie adjustment by regression analysis (62).
II Food variables represent frequency of consumption ranging from "never used" to "more than once per day" in eight categories, scored one to eight.

The rationale was that this should at least lead to a sample somewhat enriched with Alzheimer-type pathology. Among the remaining 76 subjects (after these exclusions), 14 scored 23 or less on the MMSE. The results of the analysis of these 76 subjects showed a yet stronger and more significant association of normalized MMSE score with energy intake \((\beta = -0.00043, p < 0.005)\) when compared with the analysis in table 4, in which the above cases were not excluded.

The positive association between MMSE and education and the interaction between age and education shown in the model of table 4 were also examined further. Predicted MMSE scores for 8–18 years of education were calculated across three age strata from models using the mean study population values for all other variables. The results are presented in figure 2. The curves for the different age strata indicate that the lower MMSE scores associated with less education were most pronounced for subjects over age 85 years.

The negative association with psychoactive medication use shown in the model of table 4 predicts that the effect of psychoactive medication use will vary according to the initial MMSE score (see Materials and Methods), which is determined by other factors. This would be such that those with an initial MMSE score of 29 would experience a drop of 1.6 MMSE units when psychoactive medications were added, whereas those with an initial MMSE score of 23 would experience a drop of 7.6 units with medication if a causal association is accepted. Subjects with a lower MMSE score due to other factors have a greater predicted decrease in MMSE score under the influence of psychoactive medications.

DISCUSSION

Our study is unique in that it includes extensive information about the health status and habits of elderly subjects (with no upper age limit) from 15 years before in conjunction with a recent assessment of cognitive status. Most studies of cognitive status have been cross-sectional or retrospective and thereby have great difficulties in establishing previous exposure status in subjects with diminished mental capacity. The design of our study overcomes this difficulty.

The main findings are that 1) those older subjects with relatively higher calorie consumption had lower
cognitive function 15 years later; 2) education was an important predictor of MMSE score, especially among the very elderly, and 3) the use of psychoactive medications was associated with a lower cognitive score. The model predicts a stronger effect with initially lower scores.

This study group is not typical of the elderly US population in that they were Seventh-day Adventists. Nevertheless, we have found that associations between risk factors and several other diseases are not distorted in this population (37, 38).

It is important to note that we did not study dementia. Dementia cannot be diagnosed clinically on the basis of the MMSE alone (39). However, in studies of groups, there is a strong correlation between the MMSE score and probability of dementia (16, 20, 27). Real decreases in cognitive performance must result in subjects coming closer to the clinical dementia threshold and in some cases dropping below it.

The most interesting interpretation of the first of these results would be that higher calorie consumption causes diminished cognitive functions in aged subjects. However, other interpretations must be considered. It is possible that in 1976 there was already an association between calorie intake and cognitive status among respondents to the questionnaire, whom we considered to be nondemented by virtue of their ability to successfully complete a complex questionnaire. If during the next 16 years relative rankings of MMSE score were generally maintained despite the age-related decline, our present findings would be expected but would be based on an initial cross-sectional association of uncertain causal direction.

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Nevertheless, such a persistent hypothetical cross-sectional association would also need explanation. Possible explanations include the interesting causal pathway mentioned above, but it is possible that education, exercise habits, or clinical depression may confound this situation. Interestingly, our cross-sectional data suggest that the better educated in our cohort consume more calories, even when values are adjusted for exercise. Second, among the 1991 elderly sample, exercise habits in 1976 were strongly associated with calorie intake, as expected, but there was no association between exercise in 1976 and MMSE score in 1991. Including education and exercise in the model does not change the association between calories and MMSE, suggesting that they may not be intervening variables. Seventeen percent of these subjects reported some history of depression, but only 6 percent of these were taking antidepressant medication at the time of MMSE evaluation. However, since there was no hint of an association between history of depression and MMSE score in this data set, confounding of the calorie-MMSE association by depression is unlikely to be a problem. Thus, the possibility of a causal link between calorie consumption and MMSE score remains but cannot be proven by the present data.

In our data, the only independent dietary association with MMSE was that with total calories. Interestingly, several studies have suggested that lifelong calorie-restricted rodents (40-46) perform better in simple tests of learning and memory, with the effect being to retard the onset of age-related deterioration in these functions. Such animals show differences in brain chemistry and morphology (47-49). Since the majority of cognitive impairment in most human populations is due to one or both of Alzheimer's or multi-infarct pathology, any possible effect of higher calorie consumption will almost certainly involve one or both of these as well. It is of interest that the association was strengthened when subjects with previous stroke were excluded, perhaps favoring an effect on Alzheimer's pathology.

Many studies have reported that better-educated subjects score higher on cognitive tests (26, 50, 51). This is unlikely to be explained only by their superior test-taking abilities (52-58). Our results also confirm such an association with education, although in our data this was especially marked in very elderly subjects. Expressed differently, the very elderly who were well-educated had substantially higher cognitive scores than did those educated at a grade school level only, a difference less evident at younger ages in our study group. Such an age interaction has also been reported by Teng et al. (51). Possibly, well-educated subjects experience less cerebral pathology with aging or have greater functional reserve to cope with such changes. These interpretations of our findings are compatible with the longitudinal observations of others (55, 57, 58).

The third finding was the statistically significant association between use of psychoactive medications and MMSE score. Similar findings have been reported by others (14, 59). An obvious hypothesis is that such drugs may reduce cognitive abilities in some persons. Our multiplicative model (checked by residual plots) suggests that those who have lower predicted MMSE scores are at special risk of further deterioration with use of psychoactive drugs, as also speculated by others (14, 60). If confirmed, this would underscore the need for careful prescribing to prevent further cognitive, and probably functional (13), impairment.

It must also be considered that such drugs may on occasion be prescribed as a response to preexisting conditions that can reduce cognitive abilities, such as depression or stroke. In our data, only one subject was taking antidepressant medications and of those subjects taking psychoactive agents, only two had a history of stroke. In addition, those who were cognitively impaired had medical history and medication data given by the caregiver (usually a nurse), who consulted the medical chart and medication order forms. It is possible that these data are systematically different from that obtained face-to-face in other subjects, although this seems unlikely.

The marginally significant association in table 2 suggesting that women who experienced menopause later may have better cognitive function in later years may be consistent with findings from the parent Adventist Health Study showing that those who had a later menopause also survived longer (61). Snowdon et al. (61) speculated that later menopause indicating delayed ovarian senescence, may also be a marker for a reduced rate of aging in other organs.

In conclusion, our data are broadly compatible with the findings from several other studies, but add an association between MMSE scores and total calorie intake, the especially strong association of MMSE scores with education in the very elderly, and the possibility that psychotropic drugs have particularly potent effects in subjects who are already cognitively impaired.

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