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The Incidence of Dementia and Intake of Animal Products: Preliminary Findings from the Adventist Health Study

Key Words
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Abstract
We investigated the relationship between animal product consumption and evidence of dementia in two cohort substudies. The first enrolled 272 California residents matched for age, sex, and zip code (1 vegan, 1 lacto-ovo-vegetarian, and 2 'heavy' meat eaters in each of 68 quartets). This design ensured a wide range of dietary exposure. The second included 2,984 unmatched subjects who resided within the Loma Linda, California area. All subjects were enrolled in the Adventist Health Study. The matched subjects who ate meat (including poultry and fish) were more than twice as likely to become demented as their vegetarian counterparts (relative risk 2.18, $p = 0.065$) and the discrepancy was further widened (relative risk 2.99, $p = 0.048$) when past meat consumption was taken into account. There was no significant difference in the incidence of dementia in the vegetarian versus meat-eating unmatched subjects. There was no obvious explanation for the difference between the two substudies, although the power of the unmatched substudy to detect an effect of 'heavy' meat consumption was unexpectedly limited. There was a trend towards delayed onset of dementia in vegetarians in both substudies.

Significance

Dementia is now recognized to be a major medical, epidemiologic, sociologic and economic problem, particularly in developed nations in which those over 65 years now frequently comprise approximately 10% of the total population [1]. Some estimates of the prevalence rate are 5–7% for moderate or severe dementia in the over 65 population

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and 10–50% for mild, early, or borderline demented states [2, 3]. The economic burden of senile dementia is estimated to be approximately $20 billion for the care of these persons in the US [1]. It has been estimated [4] that 30% of those not dying of other causes by the age of 85 will develop the most common type of dementia: senile dementia of the Alzheimer type (SDAT). As the age of the population increases, one may anticipate an increase in the prevalence and seriousness of the problem. There are hypothetical reasons for believing that diet might have some influence on the development of the most common forms of dementia. First, multi-infarct dementia (MID) may be related to the consumption of cholesterol and the kinds of fatty acids in the diet. Second, SDAT is felt by many to be identical to Alzheimer's disease (AD) except for the age group and rapidity of progression. AD bears a certain resemblance to the spongioform encephalopathies [5, 6], which are all transmissible. One of these diseases, kuru, is usually contracted by eating infected material. There is evidence for this mode of transmission in nonhuman primates [7], and anecdotal evidence [8–11] and evidence from two case-control studies [12, 13] for this mode of transmission in Creutzfeldt-Jacob disease, but there is conflicting evidence in the literature [14]. It seems possible that AD and SDAT might be spread by a similar infectious mechanism. More recent research [15, 16] has provided suggestive evidence that AD also may have an infectious component, and that an infective agent may be present in human blood [16]. These considerations led us to attempt a pilot study to provide preliminary insight into the possible effect of animal product consumption on the risk of dementia. A similar hypothesis has been independently proposed by others [17, 18].

Methods

The relationship between animal product intake and the risk of senile dementia, with major components SDAT and MID, has not been specifically described in the literature. Seventh-day Adventists (SDAs) present an excellent population in which to examine the relationship between dietary intake of meat, other animal products (such as dairy products and eggs), and dementia. The SDA church proscribes the consumption of alcohol, tobacco, and 'unclean' meats such as pork and shellfish, and encourages members to avoid other foods such as meat, poultry, fish, coffee, tea, and other caffeine-containing beverages. Subjects for the study of this report were selected from a larger study of SDAs (The Adventist Health Study, AHS) described in detail elsewhere [19].

In 1976, a lifestyle questionnaire was mailed to all SDAs in California who had responded to an earlier demographic questionnaire. Of the adult white non-Hispanic SDAs or household members 34,198 responded, for a response rate of 75% (this was estimated to include 50–60% of all adult non-Hispanic white California SDAs). Of these subjects, 55% were lacto-ovo-vegetarian, and approximately 5% pure vegetarians or vegans. For our study pure vegetarians were defined as those not reporting consumption of any animal products since age 40 if they were age 65–69, or since age 50 if they were 70 or above. Lacto-ovo-vegetarians were defined as those reporting no consumption of meat products during the same time period, but who did eat eggs and/or dairy products. Meat eaters were defined as those reporting meat consumption, including beef, pork, poultry, fish, and shellfish. Baseline data were collected in 1976 by mailed lifestyle questionnaire, which included questions on demographic variables, information on current and past dietary habits, exercise patterns, use of prescription drugs, use of alcohol and tobacco, occupational histories, anthropometric data, and education.

This initial questionnaire was relatively complex and was to be completed by the subject personally. This requirement unintentionally but effectively screened out most demented people from entering the study. From 1977 through 1982, study subjects were requested to report all hospitalizations including convalescent and nursing home stays. The AHS staff examined the hospital records of all but the convalescent hospitals, classified each discharge diagnosis, and sought further documentation on all diagnoses of cancer and heart disease (the primary areas of interest). Neurological and/or psychiatric diagnoses on a hospi-

tal face sheet or discharge summary were noted, as were convalescent hospitalizations.

The present study was performed in two parts. Both substudies were cohort studies. In one substudy, because of the very small number of pure vegetarians in the Loma Linda area (22 over age 65), all the pure vegetarians in the AHS throughout the state of California 65 years old or older were selected. We found 69 such pure vegetarians. We then matched them with 69 lacto-ovo-vegetarians, of the same age (to within 1 year), the same sex, and living in the closest zip code available. We also matched them with 138 'heavy' meat eaters (at least 5 times per week) using the same age, sex, and zip code criteria. Of these subjects, 63 required review of their records for a total of 100 charts.

We also did an unmatched substudy. All subjects who originally resided in the area surrounding Loma Linda, California (ZIP codes 92320, 92324, 92354, 92373, or 92399), and who had adequately completed their lifestyle questionnaires, totalling 2,984 subjects, were selected for the unmatched substudy. Most of these subjects' records were conveniently located at nearby hospitals and convalescent hospitals. There were 302 subjects with hospitalizations resulting in neuropsychiatric diagnoses or convalescent hospitalizations. These subjects had their records reviewed for a total of 445 charts.

Data Collection

Any of the subjects in either substudy who did not have a neuropsychiatric diagnosis or a convalescent hospitalization reported was considered to be not demented. Any subject who had a neuropsychiatric diagnosis or convalescent hospitalization reported had his or her hospital record reviewed by the principal investigator, blinded to the dietary practices of the subjects. These subjects were classified as: no dementia noted, mental status unknown, probable dementia, or severe dementia. The definitions are as follows:

No dementia noted: Fulfilling one of the following sets of criteria: (A) No convalescent hospitalizations, and neuropsychiatric diagnoses all not related to mental status ('neuropsychiatric diagnoses' included sense organ diagnoses such as cataracts and hearing loss, as well as peripheral nervous system diseases such as ulnar neuropathy, which would have been rejected by a more specific screen). (B) No diagnosis of chronic brain syndrome (CBS) or equivalent (e.g. SDAT, senility, organic brain syndrome with chronic history), no reason to suspect so from history and physical, and oriented to time, place, and person (0×3) on either (a) the only time orientation was checked, or (b) on two or more occasions.

Probable dementia: Diagnosis of CBS or equivalent, or consistently abnormal on mental examination (including either not being 0×3 on at least two separate occasions, or failing another specific mental test).

Severe dementia: Oriented to place or time less than 2 times, disoriented to place and time at least once, and never 0×3. This was to correspond with the definition of Åkesson [20].

Mentation unknown: Not falling into any of the above categories. Subclassified as probably demented, probably not demented, or not enough information to decide probability of dementia.

For purposes of assessing mental status certain general statements were discounted because they were used frequently in a manner inconsistent with the rest of the evidence on a chart. Thus, 'alert and oriented' was not considered sufficient evidence of orientation, whereas '0×3' or 'oriented to time, place, and person' was. Also, 'confused' was not considered sufficient evidence of mental dysfunction, but 'disoriented' was.

The use of more complex and accurate definitions of dementia such as DSM III was not feasible, as the charts which were reviewed almost never gave enough information to use such definitions. However, orientation was almost always mentioned.

Demented subjects were further classified as follows: Probable SDAT: Diagnosis by typical clinical picture from physical and neurological examination and compatible laboratory findings including at least the following: Complete blood count, 12-item chemistry panel or equivalent, syphilis serology, serum vitamin B12 and thyroxine levels, and computed tomography of head. There were no autopsy or biopsy data in these subjects which proved definite SDAT. Possible SDAT: Progressive dementia without another cause diagnosed. Probable MID: At least 2 clinical strokes with either nonprogressive or suddenly progressive then nonprogressive course. Dementia due to other causes: Diagnosed other cause of dementia. Dementia, etiology unclear: Demented but not falling into any of the above categories of dementia.

Our criteria were chosen before the publication of the NINCDS-ADRDA criteria [21] but approximate them. It was acknowledged that this classification scheme would not correctly classify all subjects either as to presence or kind of dementia. However, it was felt that since many subjects were already deceased at the start of the chart review, substantial bias might have been introduced by combining chart review with personal examination of subjects. On the other hand, more stringent chart criteria would have led to a large increase in unclassifiable subjects. Often recording of disorientation (and occasionally a diagnosis of demen-

Table 1. Consumption of meat, poultry, or fish by type of diagnosis (matched substudy)

	Not demented	Possible SDAT[1]	Probable MID	Other	Unknown type	Total
Pure Veg	63	2	0	0	3	68
LOV	65	1	0	1	1	68
Meat	120	5	5	0	6	136
Total	248	8	5	1	10	272

Pure veg = Pure vegetarian; LOV = lacto-ovo-vegetarian; Meat = 'heavy' (>4 ×/week) meat eater.

[1] No cases satisfied criteria for probable SDAT.

tia) was the only neurological evaluation on the chart. However, for the purpose of a pilot study, we believe that the simple criteria described allow a sufficiently accurate classification of dementia status to allow some analysis of the effect of animal product consumption on the risk of dementia. This preliminary study was conducted as a part of the AHS, and the confidentiality procedures of the AHS were followed.

Exclusions

Subjects with a diagnosis of probable dementia before 1977 were considered prevalent cases and therefore were not part of the incidence population. They were excluded from the study. There were 13 such subjects in this study. Four of these subjects were excluded from the matched substudy. One was a pure vegetarian, and since this subject could not be replaced, the entire matched quartet to which this subject belonged was excluded, leaving 68 matched quartets available for analysis. The other 3 subjects (1 lacto-ovo-vegetarian and 2 'heavy' meat eaters) were replaced by subjects with similar animal product exposure, and the medical records of their replacements were evaluated. One pure vegetarian was also noted to have not filled out the questionnaire completely. However, the partial answers strongly suggested a pure vegetarian diet, and so that subject and its quartet were retained. There were no cases of probable dementia within that quartet and thus exclusion would have made no difference in the statistical results.

Analytical Methods

All exposure data were examined for missing or invalid values, and corrections were made where possible. Variables relating to animal product consumption were initially examined using the Mantel-Haenszel procedure modified for person years [22] and using age and sex as the stratifying variables. Kaplan-Meier survival curves with 95% confidence intervals (BMDP1L [23]) were also calculated to compare the two meat consumption groups. Additional adjustment was made for educational status. The choice of boundaries for all exposure variables was made a priori to analysis. For the matched study, a conditional logistic regression (EGRET [24]) was also used where the stratifying variable was the ID number of the matched (for age and sex) quartet. Because of low numbers, variables in the model included the following variables taken one at a time in addition to meat consumption: history of stroke, history of hypertension, history of diabetes, alcohol intake, smoking status, and body mass index. A likelihood ratio χ^2 test was used to test for confounding of the relationship of animal product consumption to diagnosis of senility by these variables.

Results

The matched substudy indicated no significant difference in the incidence of probable dementia between pure vegetarians and lacto-ovo-vegetarians (table 1), and so for purposes of analysis these two groups were combined. On stratified analysis by matched quartets adjusted for follow-up time there was a difference between the vegetarians and the 'heavy' meat eaters (relative risk 2.18) that was of borderline significance at $p = 0.065$ (table 2). Survival analysis gave identical results (fig. 1). When account was taken (by Mantel-Haenszel analysis adjusted for age and sex) for the

Table 2. Consumption of meat, poultry, or fish by diagnosis (matched substudy)

	Demented subjects	Nondemented subjects	Total
Pure vegetarians and lacto-ovo-vegetarians	8	128 (740)[1]	136
'Heavy' (>4 ×/week) meat eaters	16	120 (678)[1]	136
Total	24	248	272

Mantel-Haenszel relative risk 2.18; χ^2 3.41; p = 0.065 (with 68 strata).
[1] Person-years.

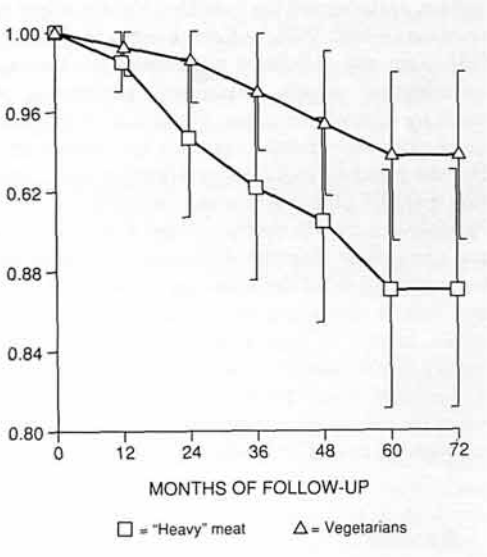

Fig. 1. Proportion free of dementia (with 95% confidence intervals: matched substudy).

fact that some of the subjects had eaten meat within 30 years and others had not filled out the part of the questionnaire regarding past meat consumption, the trend for increasing probable dementia with increasing meat consumption was significant at p = 0.048, with 'heavy' meat eaters having a relative risk of 2.99 compared with those not eating meat for at least 30 years (table 3). Due to the substudy design, no subjects were included with 'occasional' (≤4×/week) meat consumption. (Much of the difference between the vegetarians and the meat eaters was seen in probable MID cases but some difference was also noted in possible SDAT cases). The trend for severe dementia was similar but not statistically significant at least partly because of small numbers [data not shown].

On the other hand, for the unmatched substudy there was no significant difference between the different dietary groups, and in fact the trend, although far from statistical significance, was in favor of the meat eaters (table 4). (There was a relatively low number of cases of probable MID in the meat eaters in this substudy). The number of 'heavy' meat eaters in the unmatched substudy was unexpectedly low, resulting in only 3 cases of probable dementia and thus a wide confidence interval for the relative risk in this group (table 4).

Controlling for educational status made negligible difference in either substudy. Other possible confounding factors were evaluated in the matched substudy using conditional logistic regression. There was no noticeable influence of previous stroke, hypertension, diabetes, alcohol intake, or smoking (small numbers of cases were involved). The initial obesity of the subjects (measured as the weight divided by the height squared) had a small and

Table 3. Age- and sex-adjusted incidence of probable dementia (matched substudy)

Dietary group	Person-years	Observed cases	Expected cases	Relative risk	95% confidence limit	
					lower limit	upper limit
No meat in 30 years	488	4	7.84	1.00	–	–
No meat now, possible in past	254	4	5.25	1.35	0.34	5.38
>4 ×/week currently	678	16	10.91	2.99	1.00	9.00

Mantel-Haenszel χ^2 for trend 3.90; p = 0.048.

Table 4. Age- and sex-adjusted incidence of probable dementia (unmatched substudy)

Dietary group	Person-years	Observed cases	Expected cases	Relative risk	95% confidence limit	
					lower limit	upper limit
No meat in 30 years	3,604	23	20.76	1.00	–	–
No meat now, unknown past	716	23	21.23	0.95	0.53	1.71
No meat now, some in past	2,466	12	10.22	1.04	0.52	2.11
Less than 1 ×/week currently	4,258	17	21.64	0.70	0.38	1.32
1–4 ×/week currently	3,558	9	10.36	0.80	0.37	1.76
>4 ×/week currently	1,106	3	3.20	0.86	0.25	2.94

There were also 552 unknown person-years and 4 cases (with 3.7 expected cases) which were not included in the analysis.

not statistically significant interaction with dietary meat intake [data not shown].

A vegetarian diet appeared to influence the age of onset of probable dementia similarly in both substudies. In the unmatched substudy only one person who had not eaten meat within 30 years developed probable dementia before the age of 75 (that subject had probable MID), whereas 9 subjects with one of the other meat exposures developed probable dementia before the age of 75 (table 5). There were 2 cases of possible SDAT, 1 of possible AD (age <65), 1 of an unknown type of probable dementia, 2 of probable MID, and 3 of probable dementia of other causes. There was a similar trend for the matched substudy (table 6). Thus for both substudies there was a tendency for probable dementia to present earlier in the subjects who ate meat.

Discussion

The reason for the conflicting results of the two studies is not immediately apparent. It could be due to chance, in which case we are left with the question of which substudy is the more reliable. The matched substudy is smaller overall, but has many more subjects at the extremes of the dietary spectrum, particularly 'heavy' meat eaters. On the other hand, the two populations may be different. The dif-

Table 5. Meat consumption versus diagnosis of probable dementia (unmatched substudy)

Age years	None in 30 years		None now, unknown past		None now, some in past		<1×/week		1–4×/week		>4×/week		Unknown	
<55	0 1,626	0.0	0 269	0.0	0 1,553	0.0	0 2,353	0.0	1 2,164	0.5	0 681	0.0	0 264	0.0
55–59	0 273	0.0	0 91	0.0	0 209	0.0	0 336	0.0	0 300	0.0	0 88	0.0	0 37	0.0
60–64	1 279	3.6	0 89	0.0	1 175	5.7	0 270	0.0	0 254	0.0	0 93	0.0	0 61	0.0
65–69	0 321	0.0	0 116	0.0	1 123	8.1	1 308	3.2	0 304	0.0	0 70	0.0	0 40	0.0
70–74	0 317	0.0	1 151	6.6	0 117	0.0	0 320	0.0	3 251	12.0	1 76	13.2	0 33	0.0
75–79	3 267	11.2	3 205	14.6	2 91	22.0	4 282	14.1	0 130	0.0	1 54	18.5	1 41	24.4
80+	19 380	50.0	19 450	42.2	8 196	40.8	12 382	31.4	5 154	32.4	1 44	22.7	3 75	40.0

Each cell is configured as follows: $\frac{\text{cases}}{\text{person-years}}$ cases/1,000 person-years.

Table 6. Meat consumption versus diagnosis of probable dementia (matched substudy)

Age years	None in 30 years		None now, unknown past		None now, some in past		>4×/week		Unknown	
60–64	0 0	–	0 0	–	0 0	–	0 1	0.0	0 0	–
65–69	0 60	0.0	0 11	0.0	0 20	0.0	0 103	0.0	0 4	0.0
70–74	0 162	0.0	0 27	0.0	0 31	0.0	0 209	0.0	0 2	0.0
75–79	0 113	0.0	0 26	0.0	0 21	0.0	5 141	35.5	0 0	–
80+	4 153	26.1	2 76	26.3	2 37	54.1	11 223	49.3	0 0	–

Each cell is configured as follows: $\frac{\text{cases}}{\text{person-years}}$ cases/1,000 person-years.

ference between the incidence of probable MID in the two substudies might suggest this. For example, it is possible that there is minimal or no difference in the incidence of probable dementia between 'occasional' ($\leq 4\times$/week) meat eaters and vegetarians, whereas there is a difference in incidence between 'heavy' meat eaters and vegetarians. The unmatched substudy had only 3 cases of probable dementia in the 'heavy' meat group, and the matched substudy, by design, had no 'occasional' meat eaters. It might be noted that the 95% confidence limits for the relative risk for probable dementia for the 'heavy' meat eaters in the unmatched substudy (see table 4) is wide and includes the value (2.18) in the matched substudy. Other possible explanations of the difference between the two substudies are more speculative. It is possible, though unlikely, that the selective factors operating in determining the study population may have tended to overrepresent vegetarians who were at lower risk for dementia for other reasons. We have no evidence to suggest this. The risk factor associations for other chronic diseases such as breast cancer [25] and coronary artery disease [26] are well preserved in this population. Conceivably, 'unhealthy' vegetarians might tend to move to the Loma Linda area and 'unhealthy' meat eaters to move out. However, this seems improbable, as our selection of subjects was based on the initial zip code, and there was a healthy volunteer effect in both substudies (the incidence of probable dementia for the first year was about half that for subsequent years), suggesting that demented persons of all types were initially underrepresented in our study.

It is possible that vegetarians in outlying areas have more close-knit families which care for them at home longer, or perhaps they are otherwise healthier and do not come to medical attention as often when they are demented.

Our results strongly suggest that not all dementia is caused by eating animal products. However, it is possible that eating animal products is one of the causes of dementia, along with others whose relative importance becomes greater with increasing age. Perhaps vegetarians in the Loma Linda area are more likely to have some other risk factors, thus nullifying the apparent advantage that their fellow vegetarians in the rest of California may have.

It is also possible that meat eating may serve in some cases as a marker for some other variable, such as perhaps decreased fruit, vegetable, or legume intake which may be primarily related to the incidence of dementia. We have no evidence of such an association, and our small numbers make it impractical to test such hypotheses.

The authors are especially aware of the possibility for misclassification. In particular, it is probable that substantial underreporting of cognitive decline has occurred (we have no data to suggest that this underreporting was influenced by diet). However, major investigator bias seems unlikely, as blinding was successful in all but 8 subjects, and in 2 of these the suspected dietary group turned out to be incorrect.

This study is a preliminary study to see whether the hypothesis that meat intake influences the incidence of dementia warrants further research. We believe that our data increase the credibility of this hypothesis. Particular attention might be paid to that relationship in the age range of 60–80 years.

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