A 32-Year Prospective Study of Change in Body Weight and Incident Dementia

The Honolulu-Asia Aging Study

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Background: The course of weight loss associated with dementia is unclear, particularly prior to and around the onset of the clinical syndrome.

Objective: To compare the natural history of weight change from mid to late life in men with and without dementia in late life.

Design and Setting: The Honolulu-Asia Aging Study, a 32-year, prospective, population-based study of Japanese American men who had been weighed on 6 occasions between 1965 and 1999 and who had been screened for dementia 3 times between 1991 and 1999.

Participants: Of 1890 men (aged 77-98 years), 112 with incident dementia were compared with 1778 without dementia at the sixth examination (1997-1999).

Main Outcome Measure: Weight change up to and including the sixth examination was treated as the dependent variable and estimated using a repeated measures analysis.

Results: Groups with and without dementia did not differ with respect to baseline weight or change in weight from mid to late life (first 26 years’ follow-up). In the late-life examinations (final 6 years), mean age- and education-adjusted weight loss was −0.22 kg/y (95% confidence intervals, −0.26 to −0.18) in participants without dementia. Men with incident dementia at the same examination had an additional yearly weight loss of −0.36 kg (95% confidence interval, −0.53 to −0.19). This was not changed substantially with adjustment for risk factors for vascular disease or functional impairment and was significant for both Alzheimer disease and vascular dementia subtypes.

Conclusions: Dementia-associated weight loss begins before the onset of the clinical syndrome and accelerates by the time of diagnosis. The potential impact on prognosis should be considered in the case of elderly persons at risk for dementia.

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WEIGHT LOSS IN OLD age is common and may be related to subclinical or clinical disease. It has long been observed that weight loss is common in Alzheimer disease (AD), but this has been documented in people who already have dementia. In AD cases, weight loss may be due to a variety of factors, including difficulties with maintaining nutritional intake and increased energy expenditure. However, neurodegenerative processes that begin before a clinical diagnosis is made may also be a primary cause of weight loss. Findings from some studies suggest that weight loss may actually start in the preclinical period of dementia. This weight loss may have important prognostic value.

The Honolulu-Asia Aging Study cohort of men was examined on 6 occasions over a period of up to 34 years. Weight was measured at all examination points, and dementia was ascertained at the 3 most recent examinations. The objective of the analysis presented in this article was to compare the natural history of weight change in men with and without incident dementia at the last study examination.

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METHODS

PARTICIPANTS

The baseline sample consisted of Japanese American men, identified from selective service records, who were born between 1900 and 1919 and were living on the island of Oahu,
Hawaii, in 1965. Participants were examined on 3 occasions between 1965 and 1971 as part of the Honolulu Heart Program. Of 4768 survivors, 3734 (80%) participated in a fourth examination between 1991 and 1993 as a part of the Honolulu-Asia Aging Study. A further 2 examinations were subsequently carried out, with participation rates among survivors of 84% and 90%, respectively (Figure 1). The mean±SD interval between the third and fourth examinations was 19±1 years (range, 16-22 years). The mean±SD interval between the fourth and fifth examinations was 2.9±0.3 years (range, 2-4 years), and that between the fifth and sixth examinations was 3.2±0.4 years (range, 2-4 years). Prevalent dementia was ascertained at examination 4 and incident dementia at examinations 5 and 6. The sample for the analysis presented here consists of participants at examination 6 without dementia at previous examinations (n=1890). All participants gave written, informed consent at each examination. Proxies gave permission for cases of dementia. The protocol was approved by the Kuakini Medical Center institutional review board.

DEMENTIA CASE-FINDING AND DIAGNOSIS

The 3-stage procedure for dementia case-finding has previously been described in detail. In brief, cognitive function was measured in all participants using the 100-point Cognitive Abilities Screening Instrument; scores used to identify a subsample for further diagnostic evaluation. In examination 6, the cutoff was a score of less than 70 on the Cognitive Abilities Screening Instrument. The dementia evaluation in all examinations included neuropsychological investigation, a proxy interview, a neurological examination, and neuroimaging. Consensus diagnoses were made by the study neurologist and at least 2 study physicians. Dementia was diagnosed according to DSM-III-R criteria, probable and possible AD according to National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria, and vascular dementia according to California Alzheimer Disease and Treatment Centers criteria. The remaining subtypes included subdural hematoma, Parkinson disease, cortical Lewy body disease, Pick disease, and cause not determined.

WEIGHT AND OTHER INDEPENDENT VARIABLES

Participants were weighed at all 6 examination points in light clothing according to a standard protocol. At examination 1, participants were also asked about their weight at the time of military service (early adulthood). For descriptive analyses, body mass index (weight in kilograms divided by height in meters squared) was calculated for each examination using the mean height for examinations 1 and 3 as the denominator. Because the association between weight change and dementia might be confounded by socioeconomic factors or comorbidity, we adjusted our analyses for several factors, most of which were ascertained up to examination 4. These included age (at entry to the study), years of formal education, history of stroke obtained through surveillance of hospital records, hypertension (previous treatment, systolic blood pressure >160 mm Hg or diastolic blood pressure >95 mm Hg), diabetes (detailed according to World Health Organization criteria), and smoking (never, previous, or current). Impaired physical function at examination 4 was defined as an inability to rise from a chair or a walking speed of 0.4 m/s or slower. Midlife height and weight were defined as the mean values for measurements at examinations 1-3. Depressive symptoms at examination 4 were ascertained using an 11-item version of the Centers for Epidemiologic Studies Depression Scale, which was categorized by quartiles for inclusion in multivariate models with missing values included as a dummy category. Apolipoprotein E (APOE) genotype (presence or absence of the ε4 allele) was considered as a potential modifying factor for the association between weight change and dementia.

ANALYTICAL SAMPLE

The analytical sample consisted of 1890 men, including 112 with incident dementia at examination 6, of whom 74 had AD and 15 had vascular dementia. Weight loss was associated with attrition up to the sixth examination. Among the 3734 examination 4 participants, those who did not participate in examination 6 had a mean±SD weight loss of −3.4±6.8 kg between examinations 3 and 4 while those who participated had a mean±SD weight loss of −1.3±5.9 kg between examinations 3 and 4.

STATISTICAL ANALYSIS

Independent variables associated with weight change were investigated initially by analyzing as dependent variables mean changes in weight from mid to late life (examinations 3-4) and in late life (examinations 4-6). These were adjusted for age at examination 4 using linear regression models. Individual weight changes across the 6 examinations were analyzed as follows. To account for between-subject heterogeneity and unequal time intervals between visits, we used a random-effects model to estimate trajectories of weight change from examination 1 to examination 6. Random effects in this context can be interpreted as the difference in the slope of weight change between an individual and the mean slope based on the total sample. Weight was entered as the dependent variable with dementia, time, and a dementia × time interaction entered as independent variables. The coefficient for the binary dementia variable represented the difference in the intercept (ie, baseline
weight) associated with dementia; the coefficient for the time variables represented the weight change over time in participants without dementia; and the coefficient for the dementia × time interaction represented the additional rate of weight change associated with dementia. Time intervals were calculated individually from examination dates. To accommodate the nonlinear trajectory of weight change from mid to late life (Figure 2), 2 straight lines were fitted with different slopes for the time variable, connected at examination 4. This allowed 2 slopes for weight change to be estimated. The first time coefficient estimated the rate of weight change from mid to late life (examinations 1-4), and the second time coefficient estimated the difference in the rate of weight change between examinations 1-4 and examinations 4-6. Hence, the sum of the 2 time coefficients measured the rate of change over the late-life examinations (examinations 4-6). Individual interaction terms between dementia and the 2 time variables were similarly summed to estimate the additional rate of weight change associated with dementia across the late-life examinations, and standard errors were calculated from the covariance matrix. Other independent variables were entered into the model to investigate confounding or mediating effects. The fully adjusted model was then repeated for dementia subtypes and was stratified for baseline age and presence/absence of the APOE ε4 allele to check for effect modification.

RESULTS

The age range for the cohort at the first examination was 46 to 68 years, and at the sixth examination it was 77 to 98 years. The mean ± SD midlife body mass index for examination 6 participants was 23.9 ± 2.7 kg/m². Compared with those without dementia, incident patients at examination 6 were older, were more likely to have previously impaired physical function, and had a higher APOE ε4 allele frequency but were similar in other respects (Table 1).

Age-adjusted weight change was associated with several of the independent variables measured in late life (examination 4). However, the direction of change differed according to the period analyzed (Table 2). Higher education and increased disability were associated with weight loss up to examination 4 but were not significantly associated with weight change after that point. Diabetes was associated with weight loss over both periods. Hypertension, previous smoking, and increased body mass index ascertained at examination 4 were associated with previous weight gain and subsequent weight loss. Current smoking at examination 4 was only associated with subsequent weight loss.
There were no significant differences in weight in early adulthood between men who did and did not develop dementia at examination 6 ($P = .28$). Neither did these 2 groups differ in weight over the course of the 3 midlife examinations (Table 1). The estimated changes in weight for the men without dementia at examination 6, in a fully adjusted model (Table 3), were +0.01 kg/y (95% confidence interval, −0.01 to +0.02) from examinations 1-4 and −0.22 kg/y (95% confidence interval, −0.26 to −0.18) from examinations 4 to 6. However, there was an increasing difference in body mass index between participants with and without dementia over the 6 years prior to the diagnosis (Figure 2), with an additional weight loss of −0.35 kg/y in those with dementia at the end of this period compared with those without dementia (95% confidence interval, −0.52 to −0.18). In a comparison of those with and without dementia, there were some differences in the pattern of weight change by dementia subtype. Men with AD lost significantly more weight over the 6 years between examinations 4 and 6 compared with those without dementia. Men with vascular dementia had significant weight gain from mid to late life but then tended to lose more weight between examinations 4 and 6 than men with AD. There were no significant interactions with age or APOE genotype. The rate of weight change was, if anything, weaker in AD cases with APOE ε4 (age- and education-adjusted coefficients, −0.10 kg/y for APOE ε4 and −0.36 kg/y for non–APOE ε4).

The differences in weight loss between men with and without dementia were particularly marked with respect to more extreme weight loss. For example, weight loss of 5 kg or more between midlife (mean values for examinations 1 and 3) and examination 6 was present in 57% of participants with incident dementia compared with 35% of those without dementia at examination 6. Weight loss of 5 kg or more between examinations 5 and 6 was present in 30% of participants with incident dementia compared with 12% of those without.

**COMMENT**

Incident dementia was associated with significant previous weight loss, which was independent of a large number of potential confounding factors. A high proportion of men with dementia at examination 6 had lost at least 5 kg, which approaches 10% of average body weight for this cohort. This weight loss occurred in many cases over

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**Table 2. Associations of Late-Life Characteristics With Previous and Subsequent Weight Change**

<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>Associated Mean Weight Change, kg/5 y (95% Confidence Interval)†</th>
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<tbody>
<tr>
<td></td>
<td>Examinations 3-4: Mid to Late Life</td>
</tr>
<tr>
<td>Education, per year increase</td>
<td>−0.04 (−0.06 to −0.02)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>+0.11 (−0.35 to +0.58)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>+0.22 (−0.08 to +0.35)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>−0.15 (−0.29 to 0)</td>
</tr>
<tr>
<td>Smoking: past vs never</td>
<td>+0.22 (−0.07 to +0.36)</td>
</tr>
<tr>
<td>Smoking: current vs never</td>
<td>−0.13 (−0.41 to +0.15)</td>
</tr>
<tr>
<td>Impaired physical function‡</td>
<td>−0.56 (−1.08 to −0.05)</td>
</tr>
<tr>
<td>Body mass index, kg/m², per unit increase</td>
<td>+0.22 (−0.20 to +0.24)</td>
</tr>
<tr>
<td>Incident dementia at examination 6</td>
<td>−0.22 (−0.51 to +0.07)</td>
</tr>
</tbody>
</table>

*Measured at examination 4 unless otherwise indicated. †Analyses are restricted to those participants who survived to examination 6 with or without incident dementia at that interview (n=1890). All associations are adjusted for age at examination 4. ‡Inability to rise from a chair or a walking speed of 0.4 m/s or slower.

**Table 3. Differences in the Rate of Weight Change Between Participants With and Without Incident Dementia at Examination 6: A Comparison Between 2 Life Stages**

<table>
<thead>
<tr>
<th>Dementia Subtype</th>
<th>Dementia-Associated Weight Change, kg/y (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Examinations 1-4: Mid to Late Life</td>
</tr>
<tr>
<td>All dementia</td>
<td>Model1*</td>
</tr>
<tr>
<td></td>
<td>Model2†</td>
</tr>
<tr>
<td>Alzheimer disease</td>
<td>Model1*</td>
</tr>
<tr>
<td></td>
<td>Model2†</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>Model1*</td>
</tr>
<tr>
<td></td>
<td>Model2†</td>
</tr>
</tbody>
</table>

*Adjusted for age and education. †Adjusted for age, education, vascular factors, impaired physical function, and depression.
the 2 to 4 years prior to reaching the clinical threshold of dementia. The association was similar in AD and vascular dementia. The association between dementia and late-life weight loss (examinations 4-6) was considerably stronger than associations with the other independent variables we examined.

The time course of dementia-associated weight loss has received little research attention, particularly in mild cases detected in community-based studies. Findings from several studies suggest that weight loss occurs not only in severe cases of dementia but also in more mild cases. Results from one study suggested that this may start before the onset of the clinical syndrome, although weight data were only available for 3 time points and dementia only ascertained at the third. In another study, low reported body mass index predicted the onset of dementia within 5 years of follow-up but did not predict dementia over a longer follow-up period. The Honolulu-Asia Aging Study presented a valuable opportunity to investigate the natural history of weight loss prior to the onset of dementia. Particular advantages were the large sample size, 6 examination points, and formal screening and diagnostic procedures for dementia on 3 occasions.

Bias due to attrition is an important consideration in longitudinal studies. Weight loss is associated with increased mortality in older populations and was positively associated with attrition in this cohort. Cognitive impairment has also been found to be associated with increased mortality and nonresponse. Selective attrition is therefore more likely to have obscured than exaggerated the association between weight loss and dementia in the cohort. A limitation is that weight change is composed of a constellation of processes. For example, it is not known whether the weight loss reflected loss of fat, loss of skeletal muscle, or both. Midlife obesity was uncommon in this population, and therefore most weight loss occurred from levels within the normal range for height.

Processes underlying unexplained weight loss and frailty in older people remain poorly understood. Dementia is an important cause of weight loss, and our findings confirm that weight loss began before the emergence of the clinical syndrome. Early neurodegenerative changes may have a role. Reduced serotonin levels in the lateral hypothalamus associated with AD have been found, and hypothalamic Alzheimer pathologic features have been described, although cell loss in this region associated with aging and AD is uneven. These neuropathological findings may not necessarily be generalized to preclinical stages of the illness, and little research has investigated underlying mechanisms in vivo. One magnetic resonance imaging study found an association between reduced volume of the mesial temporal cortex and low body mass index in community-dwelling people with AD. Two studies have found that weight loss in AD is greater in APOE ε4 carriers. Impaired olfaction associated with mild AD and modified by APOE genotype has been suggested as a possible factor underlying this association. This would predict a stronger association between weight loss and early dementia in the presence of APOE ε4. In our study, the association between AD and weight loss was, if anything, weaker in the presence of APOE ε4. However, only men were included in this cohort, and previous research has found that the APOE ε4 association with weight loss was only present in women. The same consideration may apply regarding the absent association between midlife body weight (or body mass index) and dementia, since the largest prospective study of obesity and dementia to date found a positive association only in women. On the other hand, in a subgroup of participants without dementia in the Framingham Study, obesity was only associated with lower cognitive function in men. Our results do not suggest a prospective association between obesity and dementia in men although, as previously mentioned, it should be borne in mind that levels of obesity were low in this cohort.

An important consideration arising from research in this area is the extent to which weight loss may be prevented or minimized in dementia. Poor nutrition and frailty frequently complicate later stages of dementia, causing falls, poor wound healing, and increased physical dependence. Cachexia was found to account for the increased mortality associated with people with AD compared with people without dementia in one community study. Forgetting to eat meals and behavioral disturbances have been identified as potentially remediable causes of weight loss in established disease. As far as we are aware, no interventions to reduce weight loss in people with dementia have been formally evaluated to date, although one program is in progress. It is not unreasonable to assume that prompt and preventative interventions are likely to have the greatest impact. The results presented here suggest that weight change and nutritional state in people with dementia should be taken seriously at least from the time of diagnosis if not at earlier stages of more mild cognitive impairment.

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