

Metabolic Cardiovascular Syndrome and Risk of Dementia in Japanese-American Elderly Men

The Honolulu-Asia Aging Study

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Abstract—Cardiovascular risk factors often cluster into a metabolic syndrome that may increase the risk of dementia. The objective of the present study was to assess the long-term association between clustered metabolic cardiovascular risk factors measured at middle age and the risk of dementia in old age. This prospective cohort study of cardiovascular disease was started in 1965 and was extended to a study of dementia in 1991. The subjects were Japanese-American men with an average age of 52.7 ± 4.7 (mean \pm SD) years at baseline. Dementia was diagnosed in 215 men, according to international criteria, and was based on a clinical examination, neuropsychological testing, and an informant interview. The z scores were calculated for 7 risk factors (random postload glucose, diastolic and systolic blood pressures, body mass index, subscapular skinfold thickness, random triglycerides, and total cholesterol). The relative risk (RR [95% CI]) of dementia (subtypes) per 1 SD increase in the sum of the z scores was assessed after adjustment for age, education, occupation, alcohol consumption, cigarette smoking, and years of childhood lived in Japan. The z -score sum was higher in demented subjects than in nondemented subjects, indicating a higher risk factor burden (0.74 versus -0.06 , respectively; $P=0.008$). Per SD increase in the z -score sum, the risk of dementia was increased by 5% (RR 1.05, 95% CI 1.02 to 1.09). The z -score sum was specifically associated with vascular dementia (RR 1.11, 95% CI 1.05 to 1.18) but not with Alzheimer's disease (RR 1.00, 95% CI 0.94 to 1.05). Clustering of metabolic cardiovascular risk factors increases the risk of dementia (mainly, dementia of vascular origin). (*Arterioscler Thromb Vasc Biol.* 2000;20:2255-2260.)

Key Words: Alzheimer's disease ■ dementia ■ elderly ■ epidemiology ■ insulin resistance syndrome

Researchers have long noted a clustering of cardiovascular risk factors, termed syndrome X or the metabolic cardiovascular syndrome.¹⁻⁵ Factors commonly included in this syndrome are hypertension, obesity, dyslipidemia, and glucose intolerance.¹⁻⁵ Development of these risk factors is thought to reflect a common underlying pathology. The syndrome leads to an increased risk of diabetes and cardiovascular disease.¹⁻⁵ Both these clinical conditions have been linked to an increased risk of vascular dementia (VaD)^{6,7} and Alzheimer's disease (AD),^{7,8} the 2 most common subtypes of dementia in the elderly. Therefore, the metabolic cardiovascular syndrome may be a subclinical condition that also increases the risk of dementia.

The clinical states of AD and VaD are characterized by hypometabolic features, such as low blood pressure, body mass index (BMI), and glucose levels. Therefore, to investigate the association of these risk factors with dementia, they

should be measured long before the clinical onset of dementia. Most studies investigating the relation of metabolic cardiovascular risk factors to AD have been cross-sectional.⁹⁻¹⁶ Most prospective studies on the association of individual metabolic risk factors with the risk of AD have been based on a relatively short follow-up time.^{17,18} Furthermore, most studies on the risk factors for VaD focus on clinical stroke and hypertension.⁶ To our knowledge, there are no studies on the relationship between the clustering of metabolic risk factors and the risk of dementia with a long follow-up.

The Honolulu-Asia Aging Study (HAAS) gave us the opportunity to examine the long-term association between the metabolic cardiovascular syndrome at middle age and the risk of dementia in late age. The HAAS is based on a cohort of Japanese-American men followed since 1965. Previously, we reported that AD and VaD were associated with high blood pressure¹⁹ and that VaD was associated with diabetes, 1-hour postprandial glucose levels, and coronary heart disease.^{20,21}

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Methods

The cohort was started as the Honolulu Heart Program (1965 to 1971) on cardiovascular disease²² and was followed up as a part of the HAAS (1991 to present) involving the diseases of old age.²³ The original cohort included 8006 Japanese-American men who were born between 1900 and 1919 and were living on the island of Oahu, Hawaii, in 1965. Metabolic cardiovascular risk factors were assessed at baseline when the men were aged 45 to 68 years. Screening for dementia took place in 1991 to 1993, when the men ranged in age from 71 to 93 years. Of the 4678 men who were still alive at that time, 3734 (80%) participated in the dementia case-finding effort. The study was approved by an institutional review committee, and informed consent was obtained from the study participants.

Definition of Variables

Cardiovascular metabolic risk factors were measured at baseline (1965) and included the following: BMI (in kilograms per square meter), subscapular skinfold thickness (in millimeters), diastolic and systolic blood pressure (in millimeters of mercury), random postload glucose (in milligrams per deciliter), random triglycerides (in milligrams per deciliter), and total cholesterol (in milligrams per deciliter).²⁴ BMI was calculated as weight (in kilograms), measured with subjects in light clothing and without shoes, divided by height (in meters) squared. Subscapular skinfold thickness, an estimate of central obesity, was measured to the nearest millimeter with Lange calipers. Systolic and diastolic blood pressures were measured with a standard sphygmomanometer and a standard cuff on the left arm of a seated subject. The mean of 3 measurements was used in the analysis. Blood was collected with the patient in a nonfasting state 1 hour after a 50-g glucose load and was frozen at -20°C for shipment to the Public Health Service, Heart Disease Control Program Laboratory, San Francisco, Calif. Serum total cholesterol, triglycerides, and serum glucose levels were measured by using Auto-Analyzer methods.²⁵ The nonfasting 1-hour post-50-g load glucose test reflects glucose tolerance status²⁶ and is comparable to levels observed after the now standard 2-hour post-75-g load test.²⁷

Confounding variables that were taken into account included age, years of education, occupation, alcohol consumption, cigarette smoking, years of childhood lived in Japan, and antihypertensive medication. We also examined whether the apolipoprotein $\epsilon 4$ allele and smoking modified the association. ApoE is a marker of genetic susceptibility and may modify the association between atherosclerosis and dementia.⁸ Self-reported alcohol consumption was categorized into <1 drink per week, <1 drink per day, <2 drinks per day, and ≥ 2 drinks per day. Cigarette smoking from examination I to III was coded as never smokers at both exams, former smokers at both exams, quitters at examination III, and those who continued to smoke at both exams. Apolipoprotein ϵ genotyping was performed at the Joseph and Kathleen Bryan Alzheimer's Disease Research Center²⁸ with restriction isotyping by use of a polymerase chain reaction protocol described by Hixson and Vernier.²⁹ Subjects who were either heterozygous or homozygous for the $\epsilon 4$ allele were grouped together; those without an $\epsilon 4$ allele (apoE33, apoE23, and apoE22) served as the reference group. Subjects with apoE24 ($n=32$) were excluded from these analyses, because this is a combination of potentially protective ($\epsilon 2$) and adverse ($\epsilon 4$) alleles.

Variables thought to mediate the association between metabolic cardiovascular risk factors and dementia were stroke, coronary heart disease, subclinical atherosclerosis, and diabetes.⁶⁻⁸ A history of stroke was ascertained by continuous surveillance of hospital discharge records, death certificates, local obituary notices, and Medical Examiner's cases on the island of Oahu.³⁰ A history of coronary heart disease was ascertained on the basis of the surveillance data, as well as ECG and questionnaire data collected at all 4 examinations. The ankle to brachial index measured at the fourth examination was used as a proxy for subclinical atherosclerosis.^{31,32} The brachial blood pressure was measured twice at the right arm, and the ankle blood pressure was measured twice at the right and the left sides with patients in the supine position by use of a Doppler stethoscope attached to a standard sphygmomanometer. The mean of the 2 measurements was taken, and the lowest value of the ankle to brachial index was taken when the right and left side differed. Thereafter, the ankle to brachial index was categorized into quartiles.

A diagnosis of diabetes was based on a subject's report of a physician's diagnosis of diabetes, the use of oral diabetic medication or insulin, or, at examination IV, on the basis of a glucose tolerance test.

Dementia Assessment

Case finding for dementia followed a 3-stage procedure, described in detail elsewhere.²³ Briefly, all men were administered the 100-point Cognitive Abilities Screening Instrument (CASI) at phase I.³³ Those with a CASI score <74 (sensitivity for dementia according to the *Diagnostic and Statistical Manual of Mental Disorders*, edition 3, revised [DSM-III-R] was 80%, and the specificity was 91%), and all men aged ≥ 85 years were invited back for phase II. In addition, a random subsample of respondents was selected for phase II by using cell-sampling fractions proportional to the probability of dementia. The phase II examination included a second CASI, a neurological examination, and tests of hearing and vision. An informant was given the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) to assess changes in cognition, autonomy, and behavior over the past 10 years.³⁴ All individuals with consistently low CASI scores, those with an IQCODE score of >3.6 , and a stratified random sample of the remaining phase II participants were invited back for phase III, in which dementia was diagnosed by a neurologist according to DSM-III-R criteria.³⁵ Probable and possible AD was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria,³⁶ and VaD was diagnosed according to criteria proposed by the California Alzheimer's Disease and Treatment Centers.³⁷ Approximately 86% of all cases had CT imaging to carefully exclude vascular lesions contributing to the dementia in AD cases. Of the 507 subjects selected for the full 3-step procedure, 426 (84%) completed it. Two hundred twenty-six persons received a diagnosis of dementia.

For these analyses, subtypes of dementia were classified as follows: AD designated as the sole or principal cause and no contributing cerebrovascular disease; AD with contributing cerebrovascular disease (CVD); VaD as the sole or principal cause without any apparent AD component; and other dementias attributed to Parkinson's disease, progressive supranuclear palsy, subdural hematoma, trauma, and vitamin B₁₂ deficiency.

Statistical Analysis

Complete information on dementia and risk factors was available for 3555 men, including 82 cases of AD, 73 cases of VaD, 32 cases of AD with CVD, and 28 cases of other dementia. Baseline characteristics between demented and nondemented subjects were compared with the Kruskal-Wallis test for nonnormally distributed variables. Differences between participants and nonparticipants at follow-up were compared by adjusting for age by ANCOVA.

Because we were interested in examining the effect of risk factor clusters, we converted all risk factors into the same unit, ie, a z score. The z score ranks individuals according to their place in a normal distribution of values. The z scores ranged from ≈ -4 SDs to 4 SDs, with a mean of 0. A subject with a z score of 0.5 has a blood pressure that is 0.5 SDs higher than the mean of a normalized distribution. To normalize the distributions, serum triglycerides and glucose levels were logarithmically transformed before the z score was calculated. For each individual, the sum of the z scores of all 7 factors (ie, random postload glucose, systolic and diastolic blood pressures, BMI, subscapular skinfold thickness, total cholesterol, and triglycerides) was calculated as a summary measure of metabolic risk factor burden.³⁸ This z -score sum gives equal weights to all factors. The z -score sum was shown to yield a measure of the insulin resistance syndrome similar to one derived with a principal components analysis.³⁸ Principal components analysis generates a component, ie, a new linear variable, that explains as much of the variance of all the measured risk factors as possible. By use of the continuous z -score sum, the dementia risk across the complete range of risk factor levels can be examined. The method assumes a linear relation of the risk factors to the outcome. We checked for a nonlinear relationship between any of the risk factors and dementia by categorizing them into quintiles and also by adding the risk factor as a quadratic term

TABLE 1. Adjusted RR for Dementia According to 1-SD Increase in Metabolic Cardiovascular Risk Factors: The HAAS

	SD	RR	95% CI
BMI	2.9 kg/m ²	1.21	1.05–1.40
Subscapular skinfold thickness	6.5 mm	1.21	1.06–1.40
Diastolic blood pressure	11.0 mm Hg	1.05	0.91–1.21
Systolic blood pressure	18.5 mm Hg	1.07	0.94–1.22
Serum triglycerides*	181.2 mg/dL	1.26	1.09–1.45
Serum total cholesterol	35.5 mg/dL	1.10	0.95–1.26
Serum postload glucose*	48.2 mg/dL	1.07	0.93–1.23

RR was adjusted for age and education.

*Logarithmically transformed before conversion to z scores.

to the model; this revealed that the associations between the risk factors and dementia were linear.

The age- and education-adjusted z-score sum across dementia subtypes was estimated by ANCOVA. We used multiple logistic regression to estimate the odds ratios and 95% CIs for the relation of the individual z scores and the overall z-score sum to dementia (subtypes). Under the rare disease assumption, the odds ratio can be considered an estimation of the relative risk (RR). Adjustments were made for confounders. In addition, mediating variables were included in the models. Finally, we stratified the analyses according to the apoE genotype, smoking (ever versus never), and diabetes mellitus type 2. Analyses were conducted with the Statistical Analysis System (version 6.09).³⁹

Results

Not included in our analyses were subjects who participated at baseline in 1965 but who had died before 1991 (n=3328), subjects who refused participation in 1991 (n=937), or subjects who had missing data for the present analyses (n=186). Compared with those included in the analysis, those excluded were older at baseline (55.8 versus 52.7 years, *P*<0.001), and after adjustment for age, they had higher systolic and diastolic blood pressures (*P*<0.001), higher glucose levels (*P*<0.001), and higher triglyceride levels (*P*<0.001) at baseline.

The mean±SD age of the participants was 52.7±4.7 years at baseline and 77.8±4.6 years at follow-up. At follow-up, 11% had a history of stroke. Thirty-five percent of the men had diabetes at 1 of the 4 exams. Forty-two percent of the population had no elevated risk factors (>1 SD higher than average), 29% had 1 elevated risk factor, and 30% had ≥2 elevated risk factors. Men who were demented at follow-up

were older at baseline (57.4 versus 52.4 years, *P*<0.001), had fewer years of education (9.1 versus 10.6 years, *P*<0.001), had a higher systolic blood pressure (*P*=0.002), and had a higher postload glucose level (*P*=0.05).

After adjustment for age and education, an increase of 1 SD of the following risk factors increased the risk of dementia 25 years later: BMI, skinfold thickness, and triglyceride levels (Table 1). None of these individual risk factors was associated with AD (results not shown). All of the metabolic cardiovascular risk factors, except cholesterol and triglyceride levels, were positively and significantly associated with VaD. Compared with men with no risk factors, men with 1 elevated risk factor had no increased risk of dementia (RR 0.91, 95% CI 0.62 to 1.32), whereas men with ≥2 elevated risk factors had a 56% increased risk of dementia (95% CI 1.12 to 2.18). The risk of VaD in this group was even stronger (RR 2.97, 95% CI 1.70 to 5.18).

The z-score sum of all 7 risk factors, as a measure of metabolic risk factor burden, ranged from -12.8 to 13.4 (higher levels indicate a higher burden). There were 4.4% of the men with a z-score sum >7, which means that all their risk factors were, on average, 1 SD higher than the sample mean. The proportion of men with a z-score sum >7 was higher in demented men than in nondemented men (8.8% versus 4.1%, *P*=0.001). The age- and education-adjusted z-score sum was -0.06 (95% CI -0.20 to 0.08) for nondemented subjects and 0.74 (95% CI 0.17 to 1.30) for subjects with dementia (*P*=0.008, Table 2). Men with VaD had the highest z-score sum (1.68, 95% CI 0.73 to 2.63; *P*<0.001 versus nondemented men).

Per increase of 1 unit in the z-score sum, the risk of dementia was increased by 5% (95% CI 1.02 to 1.09, Table 3). Per increase of 1 SD in the z-score sum, the risk was highest for VaD (RR 1.11, 95% CI 1.05 to 1.18) and intermediate for mixed and other dementias; there was no increased risk for AD (RR 1.00, 95% CI 0.94 to 1.05). If, for example, all 7 risk factors would increase at least 1 SD, the risk of dementia would be increased by 42% (RR 1.42, 95% CI 1.11 to 1.82), and the risk of VaD would be increased by >2-fold (RR 2.10, 95% CI 1.40 to 3.16). Additional adjustment for occupation, alcohol consumption, cigarette smoking, blood pressure medication, and years of childhood lived in Japan did not appreciably alter the estimates. Investigating quartiles of the z-score sum showed a gradual and significant increase in the risk of dementia (RRs were 1.24, 1.28, and

TABLE 2. Adjusted z-Score Sum of Metabolic Cardiovascular Risk Factors According to Dementia (Subtypes) at Follow-Up: The HAAS

	Dementia					
	None	All	Vascular	AD With CVD	AD	Other
n	3340	215	73	32	82	28
Adjusted mean*	-0.06	0.74	1.68	0.67	-0.15	0.63
95% CIs	-0.20–0.08	0.17–1.30	0.73–2.63	-0.75–2.10	-1.04–0.75	-0.88–2.14
P†		0.008	<0.001	0.32	0.83	0.38

Sum of z-scores included BMI, subscapular skinfold thickness, diastolic blood pressure, systolic blood pressure, serum triglycerides, cholesterol, and postload glucose.

*Adjusted for age and years of education.

†*P* for difference with nondemented group.

TABLE 3. RR (95% CI) for Dementia. (Subtypes) According to 1-Unit Increase in z-Score Sum of Metabolic Cardiovascular Syndrome: The HAAS

	Dementia					
	None	All (n=215)	Vascular (n=73)	AD With CVD (n=32)	AD (n=82)	Other (n=28)
Adjustments*	1.0	1.06 (1.02–1.10)	1.11 (1.04–1.18)	1.06 (0.97–1.15)	1.00 (0.94–1.06)	1.06 (0.95–1.17)
Plus adjustment for intermediates						
History of stroke	1.0	1.04 (1.00–1.08)	1.09 (1.01–1.15)	1.04 (0.96–1.14)	1.00 (0.94–1.05)	1.04 (0.95–1.13)
History of CHD	1.0	1.05 (1.01–1.09)	1.10 (1.04–1.17)	1.03 (0.94–1.13)	1.00 (0.95–1.06)	1.04 (0.95–1.14)
ABI	1.0	1.03 (0.99–1.07)	1.08 (1.01–1.15)	1.03 (0.94–1.13)	0.99 (0.94–1.06)	1.00 (0.90–1.11)

Metabolic Cardiovascular Syndrome includes BMI, subscapular skinfold thickness, diastolic blood pressure, systolic blood pressure, serum triglycerides, cholesterol, and postload glucose. CHD indicates coronary heart disease; ABI, ankle-brachial index.

*Adjusted for age and years of education.

1.60 for quartiles 2, 3, and 4 versus quartile 1, respectively; P for trend=0.03). Smoking history or the presence of the apolipoprotein $\epsilon 4$ allele did not modify the reported associations. Among subjects without type 2 diabetes, the association between the syndrome and VaD, but not all dementias, appeared to be stronger than among those with diabetes (for nondiabetics, RR 1.16, 95% CI 1.07 to 1.26; for diabetics, RR 1.06, 95% CI 0.97 to 1.15; P for interaction=0.10).

Discussion

The cardiovascular metabolic syndrome (syndrome X) has long been recognized as a clustering of risk factors that leads to an increased risk of diabetes and cardiovascular disease.^{1–5} In this prospective population-based study among Japanese-American men, we found that a higher cardiovascular metabolic risk factor burden in middle age increased the risk of dementia 25 years later. The metabolic cardiovascular syndrome particularly increased the risk of VaD, not AD. Associations were independent of age, education, occupation, smoking, and alcohol consumption.

Limitations of the present study must be taken into account when interpreting these findings. At the time of the diagnosis of dementia, the men were relatively old. Therefore, selective participation, most of which was due to death, may have influenced our findings. Men who did not participate at the fourth examination were older and less healthy at baseline in 1965 than those who did participate. Possibly, subjects with a clustering of metabolic risk factors and susceptibility to dementia were more likely to die or to refuse to participate. In this case, the observed association may underestimate the real association. Furthermore, risk factors ascertained at the baseline examination may have changed during the 25 years of follow-up, which could ultimately modify the risk of dementia. Furthermore, insulin resistance is viewed as an underlying cause for the clustering of risk factors.^{1–5} However, fasting insulin, a surrogate measure of insulin resistance, was not measured at baseline. When we included fasting insulin levels measured at the fourth examination in the z-score sum, the results did not change appreciably.

The present study has a number of strengths. It had a long duration of follow-up (25 years). Therefore, it is not likely that risk factor levels were affected by subclinical dementia.

In addition, it is a large study, which enabled us to examine the relationship of subtypes of dementia and to investigate whether diabetes, smoking, or the apolipoprotein $\epsilon 4$ allele modified the associations of interest. Furthermore, a very high percentage of cases had neuroimaging, which allowed us to separate out cases with AD and concomitant contributing CVD.

The calculation of a z score allowed us to combine data with different units. The analyses of the individual risk factors suggested that some, such as body weight, body fat distribution, and triglycerides, were more strongly related to the risk for all dementia than were other factors. However, because these risk factors are interrelated and are thought to exert a synergistic effect on the risk of cardiovascular disease and diabetes, we were interested in the relationship between the clustering of these risk factors and dementia. Most previous studies of the risk factors for VaD focus on stroke and hypertension.⁶ Recent studies have identified other risk factors, including diabetes mellitus,⁷ atrial fibrillation,⁴⁰ triglyceride levels,¹³ a high saturated fat intake,⁴¹ and LDL cholesterol levels.⁴² From the present study, we see that the clustering of traditional metabolic cardiovascular risk factors contributes to the risk of VaD. There was no association of the metabolic syndrome with AD, and there was a moderately increased risk in cases of AD with CVD. The results of other studies on the association of cardiovascular risk factors with AD have been inconsistent, with some showing a positive association,^{9–12,18,19} some showing no association,^{14,15,21} and some showing an inverse association.^{13,16,17} Discrepancies may depend on the duration of follow-up or the proportion of mixed AD with CVD cases included in the AD group. It is also possible that genetic or other environmental factors not taken into account in these studies can account for differences. Furthermore, the HAAS does not include women, whose risk patterns for AD may differ from those of men.⁴³

Additional studies are needed to determine whether the results can be extrapolated to other ethnic groups or to women. Social, environmental, and genetic factors may be different in this population of Japanese-American men. Although the prevalence of AD in this cohort was similar to the prevalence in US and European studies, the prevalence of VaD was substantially higher, as is the case in

other Japanese populations.²³ However, the clustering of these risk factors among ethnic groups shows striking similarities, despite the difference in prevalence of the individual risk factors.³ In addition, a relationship between the cardiovascular metabolic syndrome and cardiovascular disease has been observed in western populations as well as in this population.

Cardiovascular disease and subclinical atherosclerosis did not strongly mediate the association between the metabolic cardiovascular syndrome and (vascular) dementia. Perhaps these are not good measures of atherosclerosis in the brain. Alternatively, the cardiovascular metabolic syndrome may influence dementia by mechanisms other than atherosclerosis. In subjects with diabetes type 2, the association between the syndrome and VaD was lower than in those without diabetes, suggesting that part of the influence of the syndrome on VaD is mediated through diabetes.

In conclusion, we found that the clustering of metabolic risk factors at middle age increased the risk of late-age dementia and, in particular, of VaD. Modification of metabolic risk factors at middle age may reduce not only the risk of cardiovascular disease but also the most prevalent neurodegenerative disease of old age, dementia.

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