ステップ運動と歩行運動を含めた総身体活動量は介入前の約3倍に増加した。以上の結果から，本プログラムは高齢者の日常の身体活動量の増加に有効であると考えられた.

本研究で認められた効果は，本プログラムが1）実施しやすい在宅個別運動を取り入れ，2）在宅個別運動のモチベーションの維持に週1回の集団運動教室が貢献できたからではないかと考えられる．特に，本研究で行動目標の一つとして採用したステップ運動は，室内でできるため天候に左右されない，強度設定が容易であり無理なく個人に合った強度で実施できる，運動実施時に利用する音楽が運動に付随する不快感と苦痛を和らげ定期的参加を促す[20]，などの利点を有する．これらの利点が良好なステップ運動実施率と身体活動量の大幅な増加に貢献した可能性が大きいと考えられた．また，身体活動の増加には，週一回の集団での運動教室の影響も少なくないと考えられる．集団での教室形式はこれまでの運動介入でも頻繁に採用されており[10, 11]，高齢者が比較的好む形態のひとつとされている[12]．集団での教室の利点は，同じ目標を持った対象者同士の相互作用や，支援者からの励まし，新しい知識の提供による動機づけ効果などである．本研究の介入終了率が90.6%と高いものであったことからも，本プログラムが参加者にとって比較的受入れやすいものであったと考えられた．以上のような取組みのすべてにより，身体活動量の増加と良好なプログラム終了率が得られたものと推察された．しかしながら，本研究では対照群において歩数などの身体活動量を評価できていないため，運動介入により歩数などの身体活動量が増加したのかを断定することができない.

脳血管疾患の危険因子では，介入群の体重，BMI，SBP，およびDBPへの介入効果が対照群より良好であり，本プログラムが脳血管疾患の危険因子を軽減させうると考えられた．特にSBPの平均値は152.3mmHgから132.8mmHgへ，DBPは86.9mmHgから78.3mmHgへと有意に低下し，日本高血圧学会[21]の治療ガイドラインの目標値よりも低い値となった．運動介入を受けない対照群では変化が認められなかったことから，本プログラムは脳血管疾患危険因子を単に低下させただけでなく，医学的に望ましい範囲まで達した可能性がある．

本プログラムが脳血管疾患の危険因子を軽減できた理由は，身体活動量が28.0METs・時/週に増し，厚生労働省が2006年に生活習慣病予防の目標とした23METs・時/週[22]を超えたことの影響が考えられる．しかし，本研究では食行動を測定できていないため，季節変動に伴う食行動の変化や集団健康教室による意図しない食行動の改善が脳血管疾患の危険因子に影響を及ぼした可能性は否定できない．今後，食行動を適切に評価し，本介入効果が運動効果といえるのかを検証すべきである。

本研究では，体力指標6項目に有意な改善がみられ，本プログラムは歩行能力，バランス能力，脚筋力，敏捷性，全身持久力を向上させることに成功した可能性が大きいと考えられた．以上の体力指標の改善効果についても，ステップ運動と歩数の増加による影響が大きいと考えている．その理由は，ステップ運動と歩行の促進により，Nevitt[23]が高齢者における転倒の危険因子として挙げているバランス能力の低下，歩行速度の遅延，身体パフォーマンス（椅子からの立ち上がり，階段の昇り降りなど）の低下，脚筋力低下，敏捷性を今回実際に改善させることができた点である．また，転

倒予防に対する介入効果を運動の種類別に検討したFICSIT研究でも，ストレッチングや有酸素運動の単独実施ではほとんど効果が認められないが，バランス訓練で25%，複合的な運動で13%の転倒減少を示しており，「バランス訓練，筋力増強運動，歩行指導などを含む複合的な運動内容が効果的である」と報告されており[8]，具体的には1）立位で行い，自重のかかる運動であること，2）水平方向への移動動作を含んでいること，3）垂直方向への振幅の大きい動作であること，の3点を転倒予防に有効な運動の特徴としている[24]．特に，水平方向への移動動作は前後左右方向への移動動作であり，もっとも転倒の多い前方向，および重篤な障害をきたしやすい側方や後方へのとっさの一歩を踏み出す訓練となる．さらに垂直方向への運動は，立位姿勢の保持に関わる抗重力筋群の支持力を高める．本研究で用いたステップ運動は立位での自重のかかる運動であり，前後および垂直方向への移動動作を含んでいる．介入期間中に高い頻度で継続してステップ運動を行ったことが，バランス能力を向上させたものと考えられる．以上の理由から，本プログラムは高齢者の転倒の危険因子を軽減できると考えられた．

歩行能力は生活機能の関連要因であり，その加齢に伴う低下は著しく自立度の悪化をもたらす[25]．よって，歩行能力の低下防止は，転倒予防だけでなく，QOLやADLを高い状態で維持させるのに有効である．歩行能力の維持には歩数の増加に加えて，下肢筋力の維持が必要である．しかし，歩行だけで下肢筋力を維持することは難しい[26]．そこで本研究では，歩行とステップ運動による介入を同時に行うことで歩行と脚筋力を増加させ，歩行能力を向上させることを目指した．その結果，転倒と密接に関

連する歩行能力指標[27]である10m歩行テストやTUGの有意な改善がみられたものと考えられる.

以上のことをまとめると，本プログラムの実施は肥満指標，血圧，糖・脂質代謝指標を明らかに改善させ，転倒に関連する体力指標の改善にも貢献しうる可能性が高いことから，脳血管疾患や転倒の予防に有効である可能性が示された．これは，在宅運動に加え集団での運動教室を併用したことにより，良好なステップ実施率が得られ，かつ歩数などの日常の身体活動量も有意に増加させたことの影響と推測された．今後の研究では食行動を適切に評価し，脳血管疾患の危険因子への効果が運動単体のものか，それとも食行動の季節変動の影響が影響しているのかを明らかにすべきでると考えられた.

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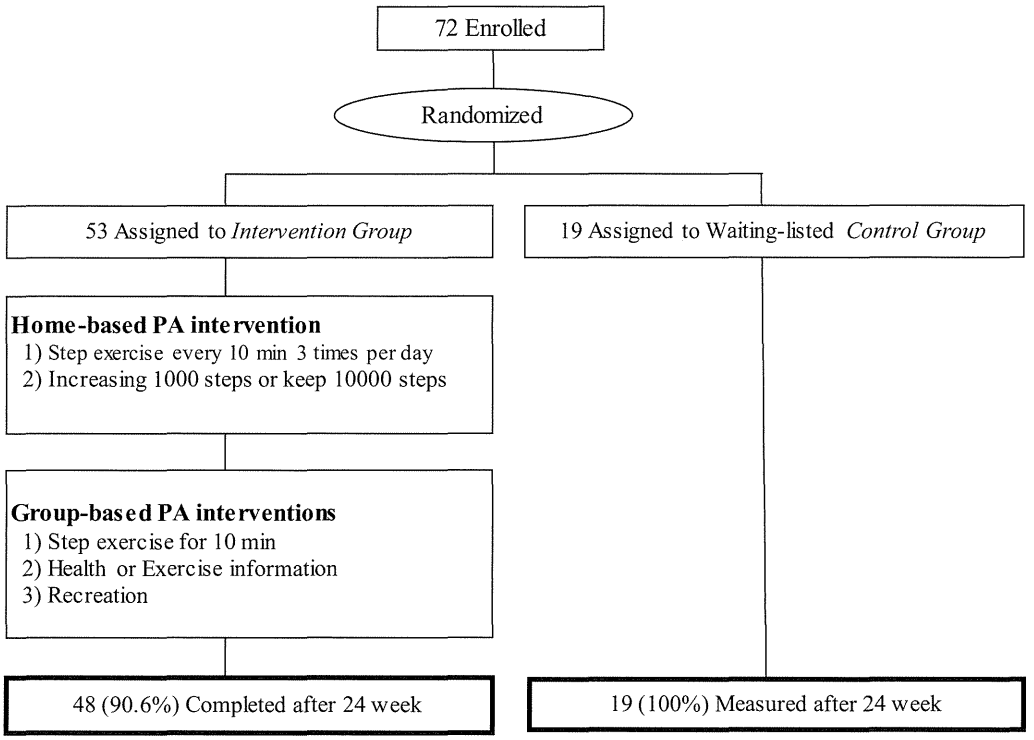

Fig. 1 Participant flow

Table 1. Cerebrovascular risk factors in Intervention and Control Groups

	Intervention Group			*Control Group*			ANOVA	
	Baseline	12 week	24 week	Baseline	12 week	24 week	P^c	P^d
Weight (kg)	56.7±8.1		55.1±8.4 [a]	54.6±7.9		53.7±7.8 [a]	<0.001	0.027
BMI (kg/m^2)	24.2±2.9		23.5±2.9 [a]	23.5±2.8		23.2±2.6 [a]	<0.001	0.032
SBP (mmHg)	152.3±21.8	133.8±22.1 [a]	132.8±19.2 [a]	131.8±13.2	140.2±18.8	135.3±22.7	0.005	<0.001
DBP (mmHg)	86.9±13.0	77.4±11.4 [a]	78.3±10.3 [a]	75.4±8.3	78.3±10.7	75.8±9.6	0.003	<0.001
T-C (mg/dl)	224.2±32.5	212.6±32.5 [a]	212.6±28.5 [a]	231.5±34.0	223.6±35.0	229.4±38.8	0.006	0.292
HDL-C (mg/dl)	67.4±11.6	67.5±12.5	67.3±12.0	71.1±15.3	71.8±14.8	73.9±15.5	0.481	0.404
LDL-C (mg/dl)	126.1±26.1	110.9±26.6 [a]	122.1±24.8 [b]	131.6±28.1	125.2±26.5	127.0±28.1	0.000	0.102
TG (mg/dl)	93.8±42.1	76.0±29.1 [a]	83.9±31.1	87.2±26.3	84.6±24.7	84.3±20.1	0.040	0.169
BS (mg/dl)	90.6±10.0	93.5±12.1	91.1±11.1	93.5±16.5	94.8±14.7	97.9±17.9	0.100	0.077
HbA1c (%)	5.80±0.37	5.73±0.35 [a]	5.63±0.39 [a,b]	5.75±0.42	5.63±0.41 [a]	5.65±0.46	<0.001	0.267
T-C/HDL-C	3.4±0.8	3.3±0.8 [a]	3.2±0.7	3.4±0.7	3.2±0.6	3.2±0.7	0.002	0.986
LDL-C/HDL-C	1.9±0.6	1.7±0.6 [a]	1.9±0.6 [b]	1.9±0.6	1.8±0.5	1.8±0.5	<0.001	0.093

a: vs Baseline (P<0.05), *b*: vs 12 week (P<0.05), *c*: Time main effect P value, *d*: Time×Group interacation P value mean±SD

Table 2. Fall-related physical fitness in intervention group

	Baseline	12 week	24 week
10 m maximum gait (sec)	4.7±0.6	4.3±0.6 a	4.2±0.7 a
Timed Up and Go (sec)	6.0±1.0	5.7±0.7 a	5.3±0.7 a,b
Reaction Time (msec)	453.0±62.2	368.5±47.8 a	366.1±64.3 a
30-second Chair-Stand Test (times)	24.6±6.2	27.8±5.8 a	29.1±6.3 a,b
Functional Reach Test (cm)	35.2±6.2	36.6±4.5	36.7±5.0
Single-leg balance with eyes open (sec)	66.5±46.0	79.3±41.2 a	84.4±40.5 a,b
Aerobic fittness by step test (METs)	5.2±0.6	5.9±0.9 a	6.3±0.9 a,b

a: vs Baseline ($P<0.05$), *b*: vs 12 week ($P<0.05$) mean±SD

Dietary patterns and risk of dementia in an elderly Japanese population: the Hisayama Study[1–3]

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ABSTRACT

Background: To our knowledge, there are no previous reports that assessed the association between dietary patterns and risk of dementia in Asian populations.

Objective: We investigated dietary patterns and their potential association with risk of incident dementia in a general Japanese population.

Design: A total of 1006 community-dwelling Japanese subjects without dementia, aged 60–79 y, were followed up for a median of 15 y. The reduced rank regression procedure was used to efficiently determine their dietary patterns. Estimated risk conferred by a particular dietary pattern on the development of dementia was computed by using a Cox proportional hazards model.

Results: Seven dietary patterns were extracted; of these, dietary pattern 1 was correlated with high intakes of soybeans and soybean products, vegetables, algae, and milk and dairy products and a low intake of rice. During the follow-up, 271 subjects developed all-cause dementia. Of these individuals, 144 subjects had Alzheimer disease (AD), and 88 subjects had vascular dementia (VaD). After adjustment for potential confounders, risks of development of all-cause dementia, AD, and VaD were reduced by 0.66 (95% CI: 0.46, 0.95), 0.65 (95% CI: 0.40, 1.06), and 0.45 (95% CI: 0.22, 0.91), respectively, in subjects in the highest quartile of score for dietary pattern 1 compared with subjects in the lowest quartile.

Conclusion: Our findings suggest that a higher adherence to a dietary pattern characterized by a high intake of soybeans and soybean products, vegetables, algae, and milk and dairy products and a low intake of rice is associated with reduced risk of dementia in the general Japanese population. *Am J Clin Nutr* 2013;97:1076–82.

INTRODUCTION

The number of patients with dementia is growing rapidly in conjunction with the aging of the world population (1). However, the cause of most types of dementia has not been fully clarified. Consequently, those factors that are known to affect dementia and can be modified, such as dietary factors, have been widely discussed in terms of their potential to prevent the development of the disease (2). Some epidemiologic studies have reported that the intake of certain types of foods, such as fish and vegetables, may protect against all-cause dementia and Alzheimer disease (AD)[4], but these results are still inconsistent (3, 4). In any case, we do not consume foods or nutrients in isolation but, rather, combined as meals. Therefore, a key part of the solution may be to identify the dietary patterns that make the greatest contribution to dementia prevention. In Western countries, there have been several epidemiologic reports that suggested that a Mediterranean dietary pattern is protective against dementia (5–7). However, a Mediterranean diet is very different from a traditional Asian diet, and it is possible that there is another dietary pattern that would be equally or more effective for Asian people. Thus, it is important to determine whether there is a dietary pattern specific to Asian customs that would help to reduce risk of dementia. To clarify this issue, we performed a prospective cohort study to evaluate dietary factors associated with the development of dementia in a general Japanese elderly population. The ultimate goal of this study was to identify a dietary pattern that could contribute to risk of dementia and its subtypes in elderly Japanese.

SUBJECTS AND METHODS

Study populations

The Hisayama Study is a population-based prospective cohort study ongoing in the town of Hisayama, which is located in

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[4] Abbreviations used: AD, Alzheimer disease; DP1, dietary pattern 1; RRR, reduced rank regression; VaD, vascular dementia.

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a suburb of the Fukuoka metropolitan area on Kyushu Island, Japan (8). The study began in 1961 to elucidate the actual conditions of cerebrocardiovascular diseases and their risk factors in Japanese. Data from the national census and nutrition survey has shown that the age and occupational distributions and nutrient intake of the population of Hisayama have been mostly the same as those of Japan as a whole for each year from 1961 until now (9). Comprehensive surveys of cognitive impairment and dementia in the elderly, including neuropsychological tests, have been conducted since 1985 (8). In 1988, a screening examination, including a dietary survey, was performed in 1073 residents aged 60–79 y (participation rate: 89.6%) for the current study. After the exclusion of 15 subjects who already suffered from dementia, one subject with no blood sample, and 51 subjects who did not complete dietary questionnaires at baseline, the remaining 1006 subjects (433 men and 573 women) were enrolled in this study.

Follow-up survey

Subjects were followed up from December 1988 to November 2005. The median follow-up time was 15 y. During this time, health examinations were performed every 1–2 y (10). For subjects who did not have examinations or who had moved out of town, the postal service or telephone was used to collect their health information (11). We also established a daily monitoring system in the study team and local physicians or members of the Health and Welfare Office of the town to identify new events, including stroke, cognitive impairment, and dementia. Follow-up screening surveys of cognitive function, including neuropsychological tests, the Hasegawa Dementia Scale (12), the Hasegawa Dementia Scale-Revised (13), or the Mini-Mental State Examination (14), were conducted in 1992, 1998, and 2005. When a subject was suspected to have new neurologic symptoms, including cognitive impairment, the subject was carefully evaluated by the study physician and psychiatrist, who conducted comprehensive investigations including interviews of the family or attending physician, physical and neurologic examinations, and a review of the clinical records. Furthermore, when a subject died, we reviewed all available clinical information, interviewed the attending physician and the family of the deceased subject, and tried to obtain permission for an autopsy from the family. During follow-up, 446 subjects died; of those, 326 (73.1%) underwent a brain examination at autopsy. No subjects were lost to follow-up.

Diagnosis of dementia

The guidelines of the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition, were used for defining the diagnosis of dementia (15). The criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association were used to define subjects with AD (16), and the criteria of the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences were used to determine the diagnoses of vascular dementia (VaD) (17). Clinical information, including neuroimaging, was used to diagnose possible and probable dementia subtypes. Definite dementia subtypes were also determined on the basis of clinical and neuropathologic information in dementia subjects who underwent autopsy. The diagnostic procedure for autopsy cases has been reported previously (18). Definite VaD cases were confirmed with a causative stroke or cerebrovascular change and no neuropathologic evidence of other forms of dementia. Each case of dementia was adjudicated by expert stroke physicians and psychiatrists.

During the follow-up period, 271 incident cases of dementia were shown. Of these cases, 128 subjects (47.2%) underwent an autopsy, and 114 subjects were examined by using brain imaging, such as computed tomography and MRI. Therefore, 242 subjects in all (89.3%) underwent some kind of morphologic examination. The remaining 29 subjects were examined by using clinical features. In all dementia cases, 19 AD cases and 15 VaD cases had other subtypes of dementia; of those, 11 cases were a mixed type of AD and VaD. These cases were counted as events in the analyses for each subtype. Finally, 144 subjects experienced AD, 88 subjects experienced VaD, and 50 subjects experienced other subtypes of dementia.

Nutritional survey

At the baseline screening examination in 1988, a dietary survey was conducted by using a 70-item semiquantitative food-frequency questionnaire concerning food intake (19). The validity of this questionnaire has been reported previously (20). The questionnaire was completed by each participant in advance and was checked by a trained dietitian or a nutritionist in the screening examination. The average food intake per day was calculated from the weekly frequency of intake of various foods and the amount (quantity) of each food portion. The nutritional intake was calculated by using the fourth revision of the Standard Tables of Food Composition in Japan (21). Each nutritional element was adjusted for energy intake by using the nutrient density method (22).

Risk-factor measurements

At baseline, each subject completed a self-administered questionnaire that covered medical history, antidiabetic and antihypertensive treatments, educational status, smoking habits, and physical activity. A history of stroke was defined as a preexisting sudden onset of nonconvulsive and focal neurologic deficit that persisted >24 h on the basis of all available clinical data. Educational levels were divided into 3 categories as follows: low (<7 y of education), intermediate (7–12 y of education), and high (≥13 y of education). Smoking habits were categorized as either current use or no current use. Physical activity during leisure time was defined as 4 categories as follows: always sedentary, walking, exercise or sports 1–2 d/wk, and exercise or sports ≥3 d/wk. Blood pressure was measured 3 times by using a standard mercury sphygmomanometer in the sitting position after rest for ≥5 min. The mean of 3 measurements was used for the analysis. Hypertension was defined as blood pressure ≥140/90 mm Hg or current use of antihypertensive drugs. Body height and weight were measured in light clothing without shoes, and BMI (in kg/m^2) was calculated. Diabetes was defined as a fasting plasma glucose concentration ≥7.0 mmol/L, 2-h postload glucose concentrations or postprandial

glucose concentrations ≥11.1 mmol/L, or the current use of insulin or oral medication for diabetes.

Statistical analysis

Dietary patterns associated with risk of dementia were assessed by using a reduced rank regression (RRR) analysis (23). Usually, a dietary pattern analysis is conducted by using either a hypothesis-oriented approach that requires a known ideal dietary pattern (eg, the Mediterranean diet) or a principal components analysis that determines dietary patterns specific to the target population. In contrast with these analyses, RRR does not require any known dietary pattern and can allow for previous information about the pathway from the diet to relevant disease. RRR identifies linear functions of food groups (ie, the dietary pattern) that explain as much of the variation of nutrients selected as risk or preventive factors for the relevant disease as possible. Consequently, the score for dietary pattern computed by this method is likely to be associated with risk of the relevant disease. RRR could be the most appropriate method to estimate the ideal dietary pattern for the prevention of dementia. We selected the following 7 nutrients as risk or preventive factors for dementia: SFA (24, 25), MUFA (25), PUFA (25, 26), vitamin C (27), potassium (28), calcium (28), and magnesium (28). These nutrients were known or suspected to confer risk of or protection against dementia and were variables with $P < 0.2$ in the univariate analyses regarding their intakes and risk of the development for dementia. Dietary patterns related to the intakes of these 7 nutrients were derived on the basis of 19 food groups. Pearson's correlation coefficients in nutrients, food groups, and scores for the extracted dietary pattern were calculated. Scores for the dietary pattern were categorized in quartiles. Trends in mean values or frequencies of risk factors across scores for the dietary pattern were tested by using the general linear model or logistic regression analysis, respectively. The age- and sex-adjusted or multivariate-adjusted HRs and 95% CIs were estimated by using the Cox proportional hazards model. The heterogeneity of HRs in subgroups was tested by adding interaction terms to the relevant Cox model. Two-sided $P < 0.05$ was considered statistically significant in all analyses. The SAS software package (version 9.2; SAS Institute) was used to perform all statistical analyses.

Ethical considerations

This study was conducted with the approval of the Kyushu University Institutional Review Board for Clinical Research. Written informed consent was obtained from participants.

RESULTS

The mean age of the overall study population was 68 y, and the proportion of women was 57%. The prevalence of diabetes and hypertension was 15.0% and 51.7%, respectively. In total subjects, 23.7% of subjects had smoking habits, and 70.5% of subjects were sedentary during leisure time.

In our subjects, 7 dietary patterns were extracted by using RRR. These dietary patterns explained 87.1% of the total variation of intakes of the following 7 nutrients selected as responsible variables: SFA, MUFA, PUFA, vitamin C, potassium, calcium, and magnesium. Scores for dietary pattern 1 (DP1) accounted for 54.3% of the total variation of all responsible variables, and scores for dietary patterns 2–7 explained very few variations (*see* Table 1 under "Supplemental data" in the online issue). Therefore, we selected scores for DP1 as a target dietary pattern in this study. Scores for DP1 were highly correlated with intakes of each nutrient (all Pearson's correlation coefficients >0.50) (**Table 1**).

Factor loadings of the 19 food groups associated with scores for DP1 and correlation coefficients between food groups and 7 response variables are shown in **Table 2**. Factor loadings represent the magnitude and direction of each food group's contribution to scores for DP1. A positive value of a factor loading indicated that a higher score for DP1 was associated with an increased intake for that food group. Food groups with a factor loading ≥0.2 were soybeans and soybean products, green vegetables, other vegetables, algae, and milk and dairy products, whereas the food with a factor loading less than −0.2 was rice.

Clinical characteristics of study subjects according to the quartile of scores for DP1 at baseline are shown in **Table 3**. Subjects with higher scores for DP1 were likely to be women and more likely to have diabetes and smoking habits. Mean values of serum total cholesterol and BMI increased with higher scores for DP1.

We estimated HRs and 95% CIs for the development of dementia and its subtypes according to the quartile of scores for DP1 (**Table 4**). Risk of all-cause dementia decreased by two-thirds in subjects with the highest quartile of scores for DP1 compared with subject with the lowest quartile; the age- and sex-adjusted HR (95% CI) was 0.66 (0.47, 0.94). This relation remained unchanged even after adjustment for education, diabetes, hypertension, total cholesterol, history of stroke, BMI, smoking habits, and the intake of energy. With regard to subtypes of dementia, subjects with the highest quartile of scores for DP1 had a significant lower risk of either AD or VaD after adjustment for the aforementioned confounding factors; the HR (95% CI) was 0.65 (0.40, 1.06) for AD and 0.45 (0.22, 0.91) for VaD (**Table 5**). There was a significant linear relation between scores for DP1 levels and risk of VaD (P-trend = 0.02) but not for AD (P-trend = 0.17). As a reference, there was no evidence of a significant relation between dietary patterns 2–7 and dementia.

Finally, we conducted sensitivity analyses stratified by diabetic status because subjects with diabetes were likely to modify their

TABLE 1
Pearson's correlation coefficients between nutrients (response variables) and extracted dietary patterns[1]

	Dietary patterns						
Nutrients	1	2	3	4	5	6	7
SFA	0.50[2]	0.49[2]	0.51[2]	0.02	0.06	0.11[2]	0.04
MUFA	0.57[2]	0.58[2]	0.08[2]	0.34[2]	−0.06	−0.13[2]	−0.07
PUFA	0.59[2]	0.45[2]	−0.50[2]	0.16[2]	0.08	0.07	0.05
Vitamin C	0.51[2]	−0.70[2]	0.1	0.35[2]	−0.02	−0.06	0.1
Potassium	0.84[2]	−0.44[2]	−0.04	0.07	−0.1	0.14[2]	−0.09
Calcium	0.84[2]	0.16[2]	−0.05	−0.42[2]	−0.15[2]	−0.06	0.06
Magnesium	0.84[2]	−0.30[2]	0.03	−0.21[2]	0.21[2]	−0.07	−0.05

[1] Dietary patterns were derived by reduced rank regression analysis.
[2] $P < 0.001$.

TABLE 2
Factor loadings of food groups associated with dietary pattern 1 and correlation coefficients between food groups and nutrients (response variable)[1]

Food groups	Factor loadings (dietary pattern 1)	Correlations between food groups and 7 response variables						
		SFA	MUFA	PUFA	Vitamin C	Potassium	Calcium	Magnesium
Rice	−0.45	−0.48[2]	−0.49[2]	−0.53[2]	−0.07	−0.37[2]	−0.57[2]	−0.40[2]
Breads	0.10	0.29[2]	0.12	0.13[2]	−0.04	0.01	0.16[2]	0.06
Noodles and other cereals	0.01	−0.03	−0.03	0.02	−0.03	−0.001	0.02	0.09
Potatoes	0.16	0.01	0.1	0.05	0.22[2]	0.33[2]	0.08	0.23[2]
Soybeans and soybean products	0.37	0.07	0.28[2]	0.72[2]	0.02	0.34[2]	0.46[2]	0.42
Miso	0.01	−0.006	0.09	0.02	0.03	0.03	−0.02	−0.21
Pickles	0.04	−0.08	−0.09	−0.11	0.30[2]	0.31[2]	−0.02	−0.07
Green vegetables	0.40	−0.004	0.06	0.1	0.72[2]	0.70[2]	0.28[2]	0.63[2]
Other vegetables	0.36	−0.009	0.03	0.04	0.74[2]	0.67[2]	0.22[2]	0.57[2]
Fruits and fruit juices	0.19	−0.007	−0.01	−0.03	0.56[2]	0.32[2]	0.07	0.30[2]
Algae	0.24	0.04	0.17[2]	0.21[2]	0.22[2]	0.37[2]	0.22[2]	0.28[2]
Fish	0.17	−0.07	0.16[2]	0.21[2]	−0.05	0.12[2]	0.46[2]	0.13[2]
Meat	0	0.34[2]	0.1	−0.14[2]	0.02	−0.01	−0.11	−0.05
Egg	0.15	0.29[2]	0.36[2]	0.07	0.03	0.1	0.14	0.08
Milk and dairy products	0.37	0.63[2]	0.27[2]	0.06	−0.03	0.26[2]	0.64[2]	0.50[2]
Fats and oils	0.12	0.41[2]	0.61[2]	0.23[2]	0.07	−0.04	−0.07	−0.1
Sugar and confectioneries	−0.1	0.01	−0.06	−0.12[2]	−0.006	−0.11	−0.12	−0.19[2]
Alcoholic drinks	−0.17	−0.14[2]	−0.23[2]	−0.17[2]	−0.19[2]	−0.19[2]	−0.09	−0.14[2]
Salt	−0.008	−0.05	−0.008	−0.13[2]	0.24[2]	0.15[2]	−0.08	−0.14[2]

[1] Factor loadings represent the magnitude and direction of the contribution of each food group to a dietary pattern 1 score. A positive value of factor loading indicated an increased intake of the food group. A negative value of loading indicated less intake of the food group. Patterns were derived by using a reduced rank regression with 7 nutrients (ie, SFA, MUFA, PUFA, vitamin C, potassium, calcium, and magnesium) as response variables and 19 foods and food groups as independent variables.

[2] $P < 0.001$.

dietary customs because of the medical treatment. As a consequence, multivariable-adjusted HRs of all-cause dementia and its subtypes increased linearly with higher scores for DP1 in subjects without diabetes (all P-trend < 0.01) but not in subjects with diabetes.

DISCUSSION

The current study identified a dietary pattern that was associated with lower risk of dementia in a general Japanese elderly population. This dietary pattern was characterized by high intakes of soybeans and soybean products, green vegetables, other vegetables, algae, and milk and dairy products and a low intake of rice, which roughly correspondent to a customary Japanese diet. The findings from this study are expected to provide valuable information for the establishment of preventive strategies against dementia through lifestyle modification in the general Japanese population.

Several studies have assessed the relation between a dietary pattern and risk of dementia (29). Most studies addressed effects of the Mediterranean dietary pattern on risk of dementia and showed that higher intakes of vegetables, fruits, and fish were linked to lower risk of dementia. However, it would not be desirable to apply a Mediterranean dietary pattern to Asian populations because it is not a common dietary pattern for Asian people. For a similar reason, Gu et al (30) have assessed the relation between the dietary pattern and risk of dementia by using RRR in a US population. Gu et al (30) used 7 nutrients as response variables: SFA, MUFA, ω-3 PUFA, ω-6 PUFA, vitamin E, vitamin B-12, and folate. As a consequence, the extracted dietary pattern was positively correlated with the high intake of salad dressing, nuts, tomatoes, poultry, cruciferous vegetables, fruits, and dark-green leafy vegetables and highly negatively correlated with high-fat dairy, red meat, organ meat, and butter, and subjects with a greater adherence to this dietary pattern had lower risk of dementia. Similar findings were also observed in our analysis. This consistency was observed despite the clear difference in dietary customs between the 2 study populations, which underscores the reliability of our results.

In the current study, intakes of potassium, calcium, and magnesium were included in the RRR analysis as preventive factors for dementia on the basis of our previous findings (28). These minerals are abundantly present in milk and dairy products. As a consequence, a greater milk and dairy intake was positively correlated with higher scores for DP1, which linked to lower risk of dementia. Some cross-sectional studies have shown that the lower intake of dairy products was related to poor cognitive function (31, 32). These findings may support our results. We also showed that scores for DP1 were positively correlated with the intake of SFA. Even though the favorable effects of ω-3 PUFA on dementia have been well established in several epidemiologic studies (33, 26), effects of SFA remain inconclusive (34). The Chicago Health and Aging Project showed a positive association between SFA intake and risk of AD (24), whereas the Rotterdam study indicated no association between saturated fat and risk of dementia (35). Despite this fact, DP1, which suggested a protective effect on dementia, showed a positive correlation with SFA. Our findings could be attributable to the abundance of SFA in milk and dairy products, which also contain a lot of favorable minerals such as calcium and magnesium.

We showed a negative correlation between rice intake and DP1. Rice constitutes a large part of the Japanese daily diet. This association may arise from an imbalance in food intake (ie, a high

TABLE 3
Clinical characteristics of the study population by quartiles of score for dietary pattern 1[1]

Variables	Score for dietary pattern 1				
	Quartile 1 (n = 251), less than −0.82	Quartile 2 (n = 252), −0.82 to −0.05	Quartile 3 (n = 252), −0.06 to 0.83	Quartile 4 (n = 251), ≥0.83	P-trend
Scores for dietary pattern 1[2]	−1.5	−0.4	0.4	1.6	<0.001
Age (y)	68 ± 5.5[3]	69 ± 5.6	68 ± 5.4	69 ± 5.6	0.63
Women (%)	42.7	53.2	57.1	74.9	<0.001
Education (%)					
<7 y	11.9	11.9	12.3	7.6	0.15
7–12 y	82.9	80.6	78.6	80.9	0.47
≥13 y	5.2	7.5	9.1	11.5	0.01
Systolic blood pressure (mm Hg)	140 ± 24	136 ± 22	138 ± 23	138 ± 20	0.36
Diastolic blood pressure (mm Hg)	77 ± 11	75 ± 10	76 ± 10	76 ± 11	0.47
Hypertension (%)	55.0	50.0	51.6	50.6	0.46
Diabetes (%)	10.0	13.1	13.5	23.5	<0.001
Serum total cholesterol (mg/dL)	199 ± 43	207 ± 46	214 ± 42	217 ± 40	<0.001
BMI (kg/m^2)	22 ± 3	22.3 ± 3	22.5 ± 3	22.8 ± 3	0.01
History of stroke (%)	4.4	4.8	4.0	4.4	0.89
Smoking habits (%)	33.5	24.6	25.8	10.8	<0.001
Physical activity (%)					
Always sedentary	75.3	71.0	69.9	65.7	0.02
Walking	6.0	9.5	8.7	12.0	0.04
Exercise or sport 1–2 d/wk	5.2	6.0	7.1	5.6	0.72
Exercise or sport ≥3 d/wk	13.5	13.5	14.3	16.7	0.30
Energy intake (kcal/d)	1721 ± 469	1605 ± 392	1620 ± 374	1649 ± 358	0.08

[1] General linear model was used to test trends in mean values of risk factors across scores for the dietary pattern. Logistic regression analysis was used to test trends in frequencies of risk factors across scores for the dietary pattern.
[2] All values are medians.
[3] Mean ± SD (all such values).

intake of rice may result in lower intake of foods favorable for the prevention of dementia) rather than any harmful effects of rice itself. Therefore, these findings cannot be taken to mean that ta cessation of rice consumption per se will have any benefit against dementia; rather, they findings may simply underscore that a well-balanced meal with many nutritional foods is recommended for a reduction in risk of dementia.

In the current study, diabetes was associated with a greater adherence to DP1. This may be because subjects with diabetes tend to adopt a more favorable pattern of diet in response to diet therapy. Because diabetes has been considered a risk factor for dementia (36), this reclassification of the dietary pattern is likely to weaken the relation between the dietary pattern and risk of dementia, especially AD, in subjects with diabetes. In support of this idea, the analysis stratified by diabetic status revealed significant linear relationships between the dietary pattern and risk of all-cause dementia and its subtypes in subjects without diabetes. In contrast, there was no significant relation between DP1 and dementia in

TABLE 4
HRs (95% CIs) of incident dementia associated with the score for dietary pattern 1[1]

	Score for dietary pattern 1				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-trend
All-cause dementia					
Events/population at risk (n)	69/251	72/252	63/252	67/251	—
Age and sex adjusted	1	0.84 (0.60, 1.18)	0.70 (0.50, 0.99)	0.66 (0.47, 0.94)	0.01
Multivariate adjusted[2]	1	0.85 (0.61, 1.19)	0.72 (0.50, 1.02)	0.66 (0.46, 0.95)	0.02
Alzheimer disease					
Events/population at risk (n)	36/251	31/252	37/252	40/251	—
Age and sex adjusted	1	0.64 (0.39, 1.03)	0.70 (0.44, 1.11)	0.62 (0.39, 0.99)	0.096
Multivariate adjusted[2]	1	0.64 (0.39, 1.04)	0.74 (0.46, 1.18)	0.65 (0.40, 1.06)	0.17
Vascular dementia					
Events/population at risk (n)	26/251	27/252	21/252	14/251	—
Age and sex adjusted	1	0.93 (0.54, 1.60)	0.72 (0.40, 1.29)	0.48 (0.24, 0.93)	0.02
Multivariate adjusted[2]	1	0.97 (0.56, 1.68)	0.74 (0.41, 1.34)	0.45 (0.22, 0.91)	0.02

[1] Cox proportional hazards model was used to estimate the age- and sex-adjusted or multivariate-adjusted HRs (95% CIs).
[2] Adjusted for age, sex, education, diabetes, hypertension, total cholesterol, history of stroke, BMI, smoking habits, exercise, and energy intake.

TABLE 5
HRs (95% CIs) of incident dementia associated with the score for dietary pattern 1 by diabetes status[1]

	Score for dietary pattern 1				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P*-trend
All-cause dementia					
Without diabetes					
Events/population at risk (*n*)	64/226	62/219	55/218	42/192	—
Age and sex adjusted	1.0	0.81 (0.57, 1.16)	0.69 (0.48, 0.99)	0.52 (0.35, 0.78)	<0.001
With diabetes					
Events/population at risk (*n*)	5/25	10/33	8/34	25/59	—
Age and sex adjusted	1.0	0.94 (0.32, 2.81)	0.58 (0.18, 1.86)	0.87 (0.31, 2.50)	0.87
Alzheimer disease					
Without diabetes					
Events/population at risk (*n*)	35/226	28/219	31/218	27/192	—
Age and sex adjusted	1.0	0.60 (0.36, 0.99)	0.62 (0.38, 1.01)	0.49 (0.29, 0.82)	0.01
With diabetes					
Events/population at risk (*n*)	1/25	3/33	6/34	13/59	—
Age and sex adjusted	1.0	1.36 (0.14, 13.36)	2.17 (0.25, 19.02)	2.37 (0.29, 19.64)	0.31
Vascular dementia					
Without diabetes					
Events/population at risk (*n*)	23/226	23/219	20/218	7/192	—
Age and sex adjusted	1.0	0.94 (0.53, 1.69)	0.82 (0.45, 1.50)	0.32 (0.13, 0.76)	0.01
With diabetes					
Events/population at risk (*n*)	3/25	4/33	1/34	7/59	—
Age and sex adjusted	1.0	0.63 (0.14, 2.93)	0.12 (0.01, 1.30)	0.42 (0.09, 2.04)	0.30

[1] Cox proportional hazards model was used to estimate the age- and sex-adjusted HRs (95% CIs).

subjects with diabetes, probably because of the limited sample size and existence of confounders caused by diet therapy. Additional investigations will be needed to elucidate this issue.

Some potential limitations of this study should be noted. Information regarding the intake of dietary nutrients derived from a semiquantitative food-frequency questionnaire may not be fully valid. In addition, the dietary assessment was performed only once at baseline. These limitations were likely to lead to some extent of misclassification of food intake. Such misclassifications would have weakened the association shown in the current study and biased the results toward the null hypothesis. In addition, there is a possibility of reverse causation (ie, our subjects might have already changed their dietary custom because of underlining dementia and other diseases in older age). However, after the sensitivity analysis in which cases who were diagnosed with dementia in the first 3 y after the baseline survey were excluded did not make any material differences in the findings. Finally, we may not have been able to completely exclude the influence of residual confounding on the relation between the identified dietary pattern and dementia risk.

In conclusion, to our knowledge, this is the first report to suggest a dietary pattern that protects against dementia in a general Japanese population. Subjects with this dietary pattern had an inverse relation with risk of all-cause dementia, AD, and VaD. These results could help to motivate changes in the dietary behavior of the general population in Japan and, thereby, lower risk of the development of dementia.

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Secular Trends in Cardiovascular Disease and Its Risk Factors in Japanese: Half-Century Data From the Hisayama Study (1961 –2009)

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Secular Trends in Cardiovascular Disease and Its Risk Factors in Japanese

Half-Century Data From the Hisayama Study (1961–2009)

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Background—Changes in lifestyle and advances in medical technology during the past half century are likely to have affected the incidence and mortality of cardiovascular disease and the prevalence of its risk factors in Japan.

Methods and Results—We established 5 cohorts consisting of residents aged ≥40 years in a Japanese community, in 1961 (n=1618), 1974 (n=2038), 1983 (n=2459), 1993 (n=1983), and 2002 (n=3108), and followed up each cohort for 7 years. The age-adjusted incidence of stroke decreased greatly, by 51% in men and by 43% in women, from the 1960s to the 1970s, but this decreasing trend slowed from the 1970s to the 2000s. Among the stroke subtypes, ischemic stroke in both sexes and intracerebral hemorrhage in men showed a similar pattern. Stroke mortality decreased as a result of the decline in incidence and a significant improvement in survival rate. Although the incidence of acute myocardial infarction did not change in either sex, disease mortality declined slightly in women. From the 1960s to the 2000s, blood pressure control among hypertensive individuals improved significantly and the smoking rate decreased, but the prevalence of glucose intolerance, hypercholesterolemia, and obesity increased steeply.

Conclusions—Our findings suggest that in Japanese, the decreasing trends in the incidence of ischemic stroke have recently slowed down, and there has been no clear change in the incidence of acute myocardial infarction, probably because the benefits of hypertension control and smoking cessation have been negated by increasing metabolic risk factors. **(*Circulation*. 2013;128:1198-1205.)**

Key Words: coronary disease ■ incidence ■ mortality ■ stroke ■ trends

Cardiovascular disease (CVD), including stroke and coronary heart disease (CHD), is one of the leading causes of death worldwide.[1] Changes in lifestyle and advances in medical technology during the past half century have likely affected the prevalence of cardiovascular risk factors and thereby the incidence and mortality of CVD. According to vital statistics, Japanese populations were characterized by higher stroke mortality and lower CHD mortality than Western populations in the 1960s, and then stroke mortality in Japan began to decline in the 1970s.[1–3] However, the vital statistics based on death certificates cannot determine whether the secular change in mortality reflected a change in CVD incidence or the prevalence of its risk factors or an improvement in case fatality. In addition, diagnosis on death certificates is not always accurate[4] and is not based on standardized criteria. Therefore, population-based studies with standardized diagnostic criteria are needed to examine accurate trends in the incidence, mortality, and survival rate of CVD, as well as the prevalence of its risk factors.

Clinical Perspective on p 1205

Several population-based observational studies have examined the secular trends in CVD in Western[5–7] and Japanese populations[8–13]; however, there have been very few studies on CVD in Japan that have covered a period of multiple decades from the 1960s to the 2000s.[8] In our previous report from the Hisayama Study,[9] a long-term population-based prospective study in Japan, the incidence and mortality of stroke decreased significantly, but those of CHD did not show a clear secular change in either sex during the 40-year period from 1961 to 2000. For the present

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study, we extended the study period to 2009 and examined 5 cohorts, which were established in different years and were used to represent each decade from the 1960s to the 2000s. The aims of the present study were thus to provide an overview of the secular trends in the incidence, mortality, and survival rates of stroke and CHD along with the prevalence of risk factors during the past half century and to confirm whether or not the previously reported secular changes in CVD had continued into the most recent decade.

Methods

Study Cohorts

The town of Hisayama is located in a suburb of the Fukuoka metropolitan area in Kyushu, Japan. According to the national census, the population of the town was approximately 6500 in 1960 and 8400 in 2010, and the age and occupational distributions in the town have been very similar to those in the country of Japan as a whole (Figures I and II in the online-only Data Supplement). Since 1961, annual health examinations for residents of Hisayama aged ≥40 years have been repeated by the town government and Kyushu University to determine their health status. We attempted to examine >80% of the residents in this age group in health examinations every 2 to 5 years to establish new cohorts. In the present study, the examinations in 1961, 1974, 1983, 1993, and 2002 were used to establish 5 different cohorts. In 1961, 1658 residents aged ≥40 years participated in the examination (90% of the total population in this age group). Similarly, the number of participants was 2135 (participation rate, 81%) in 1974, 2551 (81%) in 1983, 2111 (53%) in 1993, and 3328 (78%) in 2002. After excluding those with a history of stroke or CHD, we established 5 cohorts consisting of 1618 participants in 1961, 2038 in 1974, 2459 in 1983, 1983 in 1993, and 3108 in 2002, and each cohort was followed up for 7 years (Figure III in the online-only Data Supplement). Consequently, these 5 cohorts roughly covered the decades of the 1960s, 1970s, 1980s, 1990s, and 2000s, respectively. The study was approved by the Kyushu University Institutional Review Board for Clinical Research.

Follow-Up Survey

Each cohort was followed up for 7 years by the annual health examinations or by mail or telephone for any participants who did not undergo the examination or who moved out of the town. The development of CVD was also checked by a daily monitoring system organized by the study team, local physicians, and the town government. All available information about potential CVD events and deaths among the study participants was collected and reviewed by physician members of the study to determine the occurrence of CVD events or cause of death under the standardized diagnostic criteria throughout the study period. When a participant died, autopsy was performed at the Department of Pathology of Kyushu University, if consent for autopsy was obtained. Our cohorts were characterized by extraordinarily high autopsy rates. During the 7-year follow-up period of each cohort, autopsy examination was performed for 181 (78%) of 232 deceased participants in the 1960s cohort, 165 (84%) of 196 in the 1970s cohort, 185 (84%) of 221 in the 1980s cohort, 156 (82%) of 190 in the 1990s cohort, and 170 (64%) of 267 in the 2000s cohort (Figure III in the online-only Data Supplement). The autopsy findings were used to adjudicate the underlying cause of death and confirm the existence of CVD (stroke lesions, myocardial necrosis, and atherosclerotic lesions in coronary, carotid, cerebral, and other major arteries) and to classify subtypes of stroke. Twenty-four participants (1%) in the 1990s cohort were lost to follow-up, and no participants in the other cohorts were lost to follow-up during the follow-up periods (Figure III in the online-only Data Supplement).

Risk Factors

Information on medical history, treatment of hypertension and diabetes mellitus, smoking habits, and alcohol intake was obtained by use of a standardized questionnaire. Smoking habits and alcohol intake were categorized as current use or not. Current smoking was defined as being when the participant smoked at least 1 cigarette per day. Current drinking was defined as when the participant drank at least 1 alcohol beverage per month. Blood pressure was measured in a supine position in 1961 and in a seated position in 1974, 1983, 1993, and 2002. Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg (average of 3 measurements) or the use of antihypertensive agents. Glucose intolerance was defined by an oral glucose tolerance test in participants with glycosuria in 1961, by fasting or postprandial plasma glucose concentrations in 1974 and 1983, and by a 75-g oral glucose tolerance test in 1993 and 2002, in addition to a medical history of or treatment for diabetes mellitus (online-only Data Supplement).[9,14–16] Serum total cholesterol concentrations were measured by the modified Zak-Henly method in 1961, by the Zurkowski method in 1974, and by the enzymatic method in 1983, 1993, and 2002.[9,14,17] Hypercholesterolemia was defined as serum total cholesterol levels ≥5.7 mmol/L (220 mg/dL). Body height and weight were measured in light clothing without shoes, and obesity was defined as body mass index ≥25 kg/m^2.

Diagnostic Criteria for CVD

Stroke was defined as a sudden onset of nonconvulsive and focal neurological deficit persisting for >24 hours and was classified as ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, or undetermined type. The diagnosis of CHD included acute myocardial infarction, silent myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, and sudden cardiac death within 1 hour after the onset of acute illness. Acute myocardial infarction was diagnosed when a participant met at least 2 of the following 4 criteria: (1) Typical symptoms, including prolonged severe anterior chest pain; (2) evolving diagnostic ECG changes; (3) cardiac enzyme levels more than twice the upper limit of the normal range; and (4) morphological changes (local asynergy of cardiac wall motion on echocardiography, persistent perfusion defect on cardiac scintigraphy, or myocardial necrosis or scars ≥1 cm long accompanied by coronary atherosclerosis at autopsy). Silent myocardial infarction was diagnosed for participants without any historical indication of clinical symptoms or abnormal cardiac enzyme changes by either of the following 2 criteria: (1) New onset of abnormal Q waves on ECG plus morphological myocardium changes (local asynergy on echocardiography or persistent perfusion defect on scintigraphy), or (2) myocardial necrosis or scars ≥1 cm long accompanied by coronary atherosclerosis at autopsy. For participants who died, the underlying causes of death were classified as stroke, CHD, or others, using all available information such as autopsy examination, medical records, and death certificates. Deaths attributed to stroke and CHD were further classified as to their subtypes.

During the follow-up periods of the 5 cohorts, a total of 487 participants had first-ever stroke (344 ischemic stroke, 93 intracerebral hemorrhage, 45 subarachnoid hemorrhage, and 5 undetermined type) and a total of 208 participants had first-ever CHD. Among the 1106 deceased participants in total, 144 died of stroke (67 ischemic stroke, 48 intracerebral hemorrhage, 25 subarachnoid hemorrhage, and 4 undetermined type) and 61 died of CHD (Figure III in the online-only Data Supplement). Only 4 participants had no information for cause of death and were diagnosed as death of unknown cause.

Statistical Analysis

The prevalence of each risk factor was adjusted for age by the direct method and compared among the cohorts by logistic regression analysis. The World Health Organization standard population was used as a standard population for the age adjustment. The age-adjusted mean values of risk factors as continuous variables were calculated and compared by the linear regression model. Because the cohorts contained overlapping individuals, the logistic and linear regression analyses were fit by generalized estimating equations to account for individuals contributing to >1 examination. The incidence and mortality rates of CVD were calculated by the person-year method with adjustment for age by the direct method and compared by Poisson regression. Because individuals who developed CVD could not contribute to future cohorts, generalized estimating equations were not necessary in the analyses for incidence and mortality.[18] Participants who developed stroke or acute myocardial infarction were also followed up for the subsequent 5 years or to the end of the follow-up