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ORIGINAL COMMUNICATION

Joint impact of seven risk factors on incident dementia in elderly Japanese: the Ohsaki Cohort 2006 Study

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Abstract

Background This cohort study estimated the population attributable fraction (PAF) of seven combined major risk factors for incident dementia.

Methods We conducted a cohort study of 8563 community-dwelling individuals aged ≥ 65 years. In a baseline survey (2006), we collected data on major seven risk factors: diabetes mellitus, hypertension, obesity, physical inactivity, severe psychological distress, smoking, and low educational attainment. The total number of risk factors was applied as an exposure variable. Subjects were categorized into four groups according to the total number of risk factors they possessed (0, 1, 2, ≥ 3 risk factors). Data on incident dementia were retrieved from the public Long-term Care Insurance database. Hazard ratios (HRs) and 95% confidence interval (95% CI) were estimated using the Cox proportional regression model. We also calculated the PAF using HRs and the prevalences in our cohort data.

Results The number of cases of incident dementia was 577 (6.7%). A dose–response relationship between the total number of risk factors and incident dementia was observed; in comparison with no risk factors (reference), the age- and sex-adjusted HRs (95% CIs) were 1.25 (0.92–1.70) for one risk factor, 1.59 (1.18–2.15) for two, and 2.21 (1.62–3.01) for three or more (P trend < 0.001). If subjects had adhered to none of the risk factors, the PAF would have been 32.2%. If subjects had improved toward one better category, the PAF would have been 23.0%.

Conclusion Our findings suggest that reducing the combined number of risk factors would contribute significantly to reducing the incidence of dementia.

Keywords Dementia · Joint effect · Cohort · Attributable fraction · Risk factors

Background

Along with the rapid aging of the world's population, the number of dementia cases worldwide is estimated to increase from 46.8 million in 2015 to 131.5 million by 2050 [1]. However, current medical treatments for dementia have only limited efficacy [2] and, therefore, it is necessary to plan strategies aimed at primary prevention. To do so, it is important to clarify major risk factors that have a considerable impact (i.e., the population attributable fraction: PAF) on incident dementia.

Seven major risk factors for dementia have been highlighted: diabetes mellitus, hypertension, obesity, physical inactivity, depression, smoking, and low educational attainment [3, 4]. Based on systematic reviews of multiple modifiable risk factors for dementia, several previous studies have estimated the preventive fraction of dementia; the preventable fraction of combined major risk factors for dementia is 28.2–48.4% [3–5]. However, because those studies were based on systematic reviews, there was a limitation in that the results might have insufficiently accounted for overlapping of the risk factors [3]. To our knowledge, no cohort study has estimated the joint impact of major risk factors on dementia. To clarify the joint impact of these major risk factors on incident dementia, further cohort study is necessary.

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A few cohort studies have examined the relationships between multiple risk factors and dementia [6–8]. Those studies commonly set smoking, obesity, and physical activity as exposure variables, but did not calculate the PAF of combined risk factors for dementia and, therefore, the joint impact of major risk factors on incident dementia is still uncertain. Accordingly, it is still necessary to verify the degree to which combined major risk factors affect incident dementia with a cohort study.

The purpose of the present cohort study was to clarify the joint impact of seven risk factors on incident dementia based on estimates of PAF.

Methods

Study cohort

The data used for this study were from the Ohsaki Cohort 2006 Study, whose design has been described in detail elsewhere [9]. Briefly, in the baseline survey, the source population comprised all citizens (aged 65 years and older) resident in Ohsaki City, northeastern Japan, on 1 December 2006: 31,694 men and women.

The baseline survey was conducted between 1 December and 15 December 2006, and the subsequent follow-up survey between April 1, 2007 and November 30, 2012. Data on risk factors were collected at the baseline using a self-reported questionnaire. A questionnaire was distributed by the heads of individual administrative districts, and then collected by mail.

Figure 1 shows the flowchart for this analysis. Among 23,091 persons who provided valid responses, we excluded 6333 who did not provide written consent for review of their Long-term Care Insurance (LTCI) information, 2102 who had already been certified as having disability by the LTCI before follow-up, 62 who had died or moved out of the district during the period of the baseline survey, 192 whose Doctor's Opinion Paper and cognitive status therein were unavailable, 5826 whose risk factor data were missing, and 13 whose body mass index (BMI) value fell outside the 0.1–99.9% total BMI range. Thus, 8563 persons were analyzed for the purposes of this study.

During the 5.7-year period, the follow-up rate was 98.8%, 102 individuals (1.2%) being lost to follow-up due to emigration from the study area without developing dementia. From the resulting 43,499 person-years, incident dementia was determined in 577 persons (6.7%).

Exposure (total number of seven risk factors)

Based on previous studies [3–5], we selected seven major risk factors: diabetes mellitus, hypertension, obesity, physical inactivity, severe psychological distress, smoking, and low educational attainment. Table 1 defines the seven risk factors. Furthermore, the total number of risk factors in any given individual was applied as the exposure variable. Subjects were categorized into four groups according to the total number of risk factors they possessed (0, 1, 2, ≥ 3 risk factors).

Diabetes mellitus was assessed using a question that asked whether participants had a history about diabetes mellitus. Hypertension was defined as an affirmative response to any of the following: having a history of hypertension, a self-reported systolic blood pressure (SBP) of ≥ 140 mmHg or a diastolic blood pressure (DBP) of ≥ 90 mmHg. Obesity was assessed in terms of BMI, calculated as the self-reported body weight (kg) divided by the square of the self-reported body height (m) [10]. Physical inactivity was evaluated by asking about time spent walking per day (< 30 min, 30–60 min or ≥ 60 min), the validity of which had been confirmed in our previous study [11]. The Kessler 6-Item Psychological Distress Scale (K6) was used as an indicator of severe psychological distress, including depression [12, 13]. Using six questions for which total point scores ranged from 0 to 24, subjects were asked about their mental status over the last month. As the optimal cut-off point for mental illness in the validation study, subjects who had K6 scores of ≥ 13 were classified as having psychological distress [14]. Smoking status was assessed using a question that asked whether a participant had been smoking at the time of the baseline survey (current, former, never). Educational attainment was assessed using the question "How old were you when you left school?" and answered using a positive integer.

Covariates

The baseline survey also included questions about age, sex and cognitive function according to the Kihon Checklist, an instrument developed by the Ministry of Health, Labor, and Welfare of Japan to predict functional decline in community-dwelling elderly. With regard to the cognitive function score for the Kihon Checklist, subjects were assessed for their current cognitive function status using three binary questions yielding a total point score ranging from 0 to 3 [15]. The validity of the cognitive function score in the Kihon Checklist had been previously confirmed using the Clinical Dementia Rating as a gold standard [16].

Follow-up and incident dementia

The primary outcome was incident dementia, which was defined as disabling dementia according to the criteria of the LTCI system used in Japan [17].

The LTCI is a mandatory system of national social insurance to support daily life for disabled older people in Japan

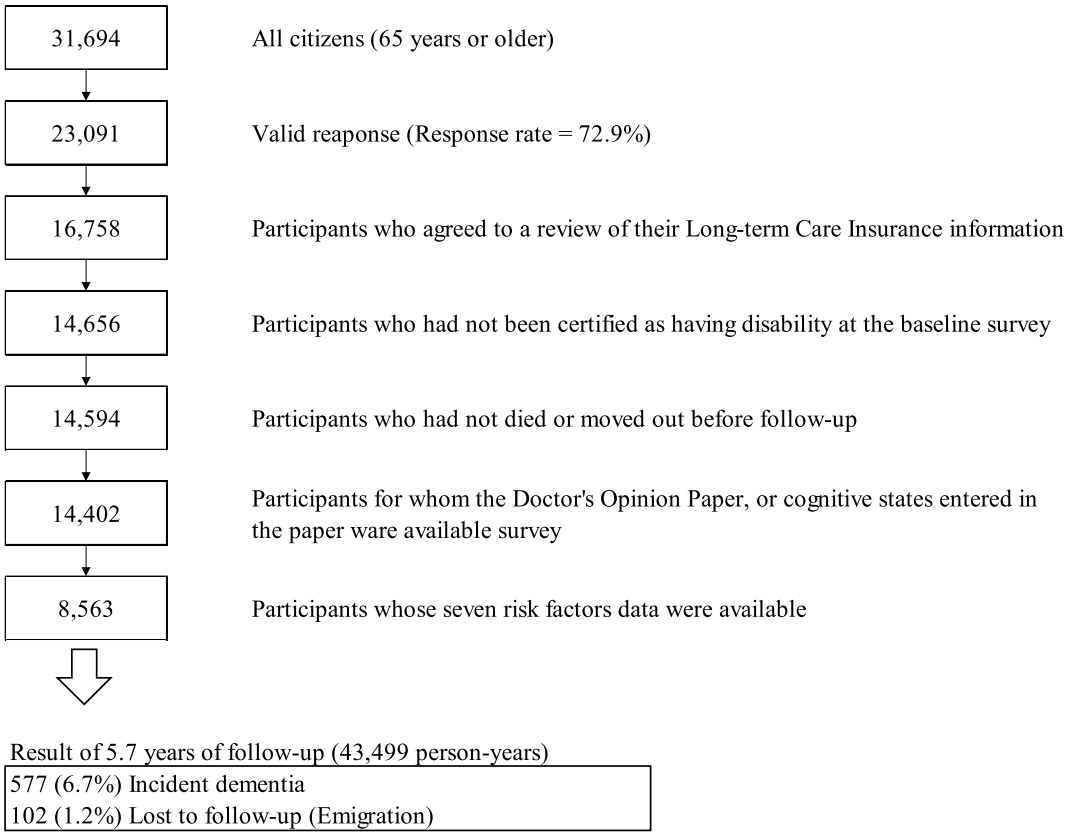

Fig. 1 Flowchart of study participants

[18, 19]. Everyone aged over 40 years pays premiums, and everyone aged over 65 years is eligible for formal caregiving services under a uniform standard of disability certification. The procedure for disability certification consists of two parts: (1) assessment of the degree of functional disability using a questionnaire developed by the Ministry of Health, Labor, and Welfare, and (2) reference to the Doctor's Opinion Paper prepared by the attending physician [20].

Disabling dementia was defined as incident functional disability with dementia according to the LTCI system, and dementia exceeding rank I (rank ≥ II) on the Dementia Scale (Degree of Independence in Daily Living for Elderly with Dementia) along with the Doctor's Opinion Paper. The Dementia Scale is categorized into six ranks (0, I–IV, M. Rank M means that a person has severe dementia-related behavioral disturbance that requires medical intervention). Exceeding rank I is normally used as an outcome measure of incident dementia as individuals who have mild or moderate dementia are classified as rank II [17, 21–23].

The person-years of follow-up for each subject were counted from 1 April 2007 until the date of incident dementia, the date of death, the date of emigration from Ohsaki City, incident functional disability without dementia, or the end of the study period (30 November 2012), whichever occurred first. Also, deaths without LTCI certification were treated as censored in this analysis. We obtained a dataset including information on LTCI certification, death or emigration from Ohsaki City after obtaining an agreement from the subjects. Under an agreement related to Epidemiologic Research and Privacy Protection, all data were transferred from the Ohsaki City Government yearly each December.

Statistical analysis

The Cox proportional hazards model was used to calculate the hazard ratios (HRs) and 95% confidence intervals (95% CIs) for incident dementia according to each risk factor and four groups. Dummy variables were created for four groups in terms of the number of risk factors (0, 1, 2, ≥ 3 risk factors), and no risk factor was defined as a reference category. Model 1 was adjusted for sex and age categories (65–69, 70–74, 75–79, 80–84, or ≥ 85 years). Assuming the non-independence of risk factors, model 2 was adjusted for model 1 plus history of diabetes mellitus (present, absent), hypertension (history of hypertension

Table 1 Definitions used for seven major risk factors

Diabetes mellitus	History of diabetes mellitus
Hypertension	History of hypertension or systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg
Obesity	Body mass index (BMI) ≥ 30 kg/m^2
Physical inactivity	Time spent walking < 30 min/day
Severe psychological distress	Kessler 6-Item Psychological Distress Scale (K6) score ≥ 13
Smoking	Current smoker
Low educational attainment	Age at least school graduation < 16 years

or systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg), BMI (in kg/m^2; <30 or ≥ 30), time spent walking per day (< 30 or ≥ 30 min), K6 score (< 13 or ≥ 13), smoking status (former/never or current), and education attainment (age at last school graduation; <16 or ≥ 16 years). All statistical tests described here were two sided, and differences at P values of < 0.05 were accepted as significant.

Sensitivity analysis was conducted by excluding subjects who developed incident dementia in the first 2 years during follow-up. Furthermore, considering the possibility of reverse causality, we conducted analysis after excluding subjects who had only normal cognitive function (Cognitive function score in the Kihon Checklist = 0) [24]. All data analyses above were performed using SAS Software Version 9.4.

PAF is the fraction of disease in the population attributable to a specific risk factor. Barnes and Yaffe [4] derived the PAF of major risk factors for Alzheimer's dementia using Levin's formula [25]:

$$\mathrm{PAF}\ (\%) = \{P \times (\mathrm{HR} - 1)\}/\{1 + P \times (\mathrm{HR} - 1)\} \times 100,$$

where P means the population prevalence of each factor in our cohort study and HR means hazard risk. Along with the formula [4], we calculated the PAFs of each single risk factor for incident dementia.

To examine the PAF of seven combined risk factors for incident dementia, we also calculated $\mathrm{PAF}_{\mathrm{Combined}}$ using the below formula [3]:

$$\mathrm{PAF}_{\mathrm{Combined}}(\%) = \{1 - \Pi(1 - \mathrm{PAF})\} \times 100.$$

Furthermore, we estimated two PAFs under the following conditions: (1) $\mathrm{PAF}_{\mathrm{ALL}}$: if all subjects would have adhered to none of risk factor [26]:

$$\mathrm{PAF}_{\mathrm{ALL}}(\%) = \{\sum P_i[\mathrm{HR}_i - \mathrm{HR}_1]\}/\{1 \times \mathrm{HR}_1 + \sum P_i[\mathrm{HR}_i - \mathrm{HR}_1]\} \times 100,$$

and (2) PAF_{+1}: if subjects who had some risk factors would have improved toward one better group [26]:

$$\mathrm{PAF}_{+1}(\%) = \{\sum P_i[\mathrm{HR}_{i+1} - \mathrm{HR}_i]\}/\{1 \times \mathrm{HR}_1 + \sum P_i[\mathrm{HR}_{i+1} - \mathrm{HR}_i]\} \times 100,$$

where P_i means the prevalence of the subjects in each group and HR_i means the age- and sex-adjusted HRs of each group i.

Results

Baseline characteristics

Table 2 shows baseline characteristics according to four categories of the number of dementia risk factors. Among 8563 subjects, the proportion of men was 50.4%, and the mean (SD) age of the subjects overall was 73.1 (5.6) years. Subjects with a higher total number of risk factors for dementia were more likely to be older and to be men.

Individual risk factors and incident dementia

Table 3 shows the associations between individual risk factors and incident dementia, along with the HRs, 95% CIs and PAFs. Some risk factors were significantly related to a higher risk of incident dementia, although hypertension, obesity and low educational attainment were not. Even after adjustment for each risk factor, the results did not change substantially (model 2). Physical inactivity had the largest fraction attributable to incident dementia (PAF: 7.3%), while obesity had the smallest (PAF: 1.1%).

We also estimated the PAF of all seven risk factors for incident dementia combined: $\mathrm{PAF}_{\mathrm{Combined}}$ (Table 3). Assuming that the risk factors were each independent, $\mathrm{PAF}_{\mathrm{Combined}}$ would have been 35.0% after adjustment for age and sex (model 1). Assuming that each risk factor was non-independent, $\mathrm{PAF}_{\mathrm{Combined}}$ would have been 29.6% after adjustment for each of the risk factors (model 2).

Total number of risk factors and incident dementia

Having a higher total number of risk factors was significantly associated with the risk of incident dementia (Table 4). Compared with subjects who had none of the risk factors (reference), the age- and sex-adjusted HRs (95% CIs) were 1.25 (0.92–1.70) for subjects who

had one risk factor, 1.59 (1.18–2.15) for subjects who have two and 2.21 (1.62–3.01) for subjects who had three or more (P for trend < 0.001). Even when we stratified for sex and age, the results did not change (data not shown).

To examine whether there was possibility of reverse causality, we conducted sensitivity analysis (Supplementary Table 1). Even after excluding 139 subjects who developed incident dementia in the first 2 years during follow-up, the results remained substantially unchanged (P for trend < 0.001). Additionally, we considered the possibility that lower cognitive function at the baseline might have affected the dose–response relationships. Even after selecting 5655 subjects who had better cognitive function at the baseline (Kihon Checklist cognitive function score = 0), the results remained consistent with the main linear relationship (P for trend < 0.039).

Additionally, two PAFs corresponding to assumptions of change in the number of risk factors are shown in Table 4. If subjects who had some risk factors had adhered their all risk factors to 0, PAF_{ALL} of 32.2% would have been reduced risk of incident dementia, and if subjects with some risk factors had improved to one better category, PAF_{+1} would have been 23.0%.

Discussion

In this cohort study, we examined the joint impact of seven major risk factors on incident dementia. We found that having a higher number of risk factors was significantly associated with the risk of incident dementia. Furthermore, two PAFs for the preventable fraction of incident dementia were estimated: (1) PAF_{ALL} would have been 32.2%, if subjects with some risk factors adhered to none of the risk factors, (2) PAF_{+1} would have been 23.0%, if subjects who had some risk factors showed an improvement to one better category.

Three previous studies have reported the joint impact of combined risk factors on incident dementia [6–8]. The first cohort study including 2235 British men examined the joint impact of five health factors: smoking, BMI, fruit and vegetable intake, physical activity, alcohol intake [6]. The second nested case–control study was conducted on 3468 Japanese–American men, and included physical activity, healthy diet, smoking, and BMI as exposures [7]. The third cohort study including 6626 elderly people examined the relationship of cardiovascular-related factors (Life's Simple 7): smoking, BMI, physical activity, fish/fruit/vegetable intake, cholesterol level, fasting glucose and blood pressure [8]. Although our results indicated trends similar to those in these previous studies, our study was the only one to estimate the joint impact (e.g., PAF).

We observed the impact of combined risk factors when subjects who had some risk factors improved their situation to one better category (PAF_{+1} = 23.0%). Assuming that each risk factor is significantly related to incident dementia, reduction of dementia risk by around one quarter would be expected to have a notable impact on incident dementia. We estimated the PAFs using a population-based cohort study, whereas previous studies were based on systematic reviews [3, 4]. Thus, our estimate could have been considered to reflect overlapping of individual risk factors. In terms of public health, reducing the number of individual risk factors would contribute considerably to lowering the incidence of dementia.

With regard to the non-independence of risk factors, combination of all seven risk factors accounted for 29.6% of incident dementia ($PAF_{combined}$). Additionally, around one-third of incident dementia was attributed to seven major risk factors, adjusting for each risk factor (PAF_{ALL} = 32.2%). These results were consistent with

Table 2 Baseline characteristics by number of dementia risk factors (n = 8563)

Characteristics	All participants	Number of dementia risk factors			
		0	1	2	≥ 3
Number of participants	8563	1395	3079	2656	1433
Mean age years ± SD	73.1 ± 5.6	71.6 ± 5.1	72.5 ± 5.3	73.8 ± 5.7	74.5 ± 5.9
Sex (males, %)	50.4	38.6	47.2	55.1	60.2
Diabetes mellitus (%)	12.6	0	5.1	14.8	36.8
Hypertension (%)	59.5	0	54.2	79.7	91.6
Obesity (%)	2.8	0	0.4	2.8	10.6
Physical inactivity (%)	33.4	0	18.3	47.1	73.3
Severe psychological distress (%)	4.0	0	1.3	3.4	14.8
Smoking (%)	13.0	0	5.8	16.7	34.3
Low educational attainment (%)	26.8	0	15.0	35.5	62.1

Obtained using chi-square test for variables of proportion

SD standard deviation

Table 3 Population attributable fraction between dementia and risk factors ($n = 8563$)

	Prevalence (%)	Crude HR	(95% CI)	PAF (%)	Model 1[a]	(95% CI)	PAF (%)	Model 2[b]	(95% CI)	PAF[c] (%)
Diabetes mellitus	12.6	1.49	(1.20–1.85)	5.8	1.55	(1.25–1.93)	6.5	1.57	(1.26–1.95)	6.6
Hypertension	59.5	1.34	(1.13–1.59)	16.8	1.13	(0.95–1.34)	7.0	1.06	(0.89–1.26)	3.2
Obesity	2.8	1.29	(0.82–2.04)	0.8	1.50	(0.95–2.38)	1.4	1.41	(0.89–2.24)	1.1
Physical inactivity	33.4	1.63	(1.38–1.92)	17.3	1.31	(1.11–1.55)	9.3	1.23	(1.04–1.46)	7.3
Severe psychological distress	4.0	2.71	(2.04–3.61)	6.4	2.68	(2.01–3.56)	6.3	2.54	(1.90–3.38)	5.8
Smoking	13.0	1.06	(0.84–1.35)	0.8	1.49	(1.16–1.92)	6.0	1.47	(1.14–1.89)	5.8
Low educational attainment	26.8	1.77	(1.49–2.09)	17.1	1.20	(1.01–1.43)	5.2	1.17	(0.99–1.39)	4.4
$PAF_{Combined}$[d]				50.5			35.0			29.6

PAF population attributable fraction, *HR* hazard ratios, *95% CI* 95% confidence interval, *ref.* referent values

[a]Model 1 was adjusted for age (65–69, 70–74, 75–79, 80–84, or ≥ 85 years) and sex

[b]Model 2 was adjusted for model 1 plus history of diabetes mellitus (present or absent), hypertension (history of hypertension or systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg), body mass index (in kg/m^2; < 30 or ≥ 30), time spent walking per day (< 30 or ≥ 30 min), Kessler 6-Item Psychological Distress Scale (K6) score (< 13 or ≥ 13), smoking status (former/never or current), educational level (age at last school graduation; < 16 or ≥ 16 years)

[c]PAF is the fraction of disease in the population attributable to a specific risk factor

[d]$PAF_{combined}$ is the fraction of incident dementia attributable to all seven risk factors combined using below formula; $1 - \Pi (1 - PAF)$

previous studies [3, 5]. Norton et al. examined the PAFs of seven major risk factors for Alzheimer's disease [3]. Accounting for the non-independence of each risk factor, their PAFs were estimated to be 28.2% worldwide, 30.6% in the USA, 31.4% in the Europe, and 30.0% in UK. Furthermore, Ashby-Mitchell made similar estimations in Australia using the same formula [3], and concluded that 48.4% of dementia was attributable to the seven major risk factors after adjustment for each one [5]. Thus, our PAFs for combined risk factors were similar to those in previous studies. However, each PAF in our study might have been underestimated because of differences in the prevalence of some factors, especially obesity. Compared with the prevalence of obesity in this study (2.8%), that in the USA is reported to be 41.0% among older adults age 60 years and over [27]. Because such differences in prevalence may exist among different areas, PAFs need to be directly compared between areas. Focusing on relative risk factors, PAF for physical inactivity had the largest fraction attributed to incident dementia in our cohort study. This result also supports previous studies [3, 5] and suggests that giving priority to improving the level of physical activity might play a key role in prevention of dementia.

Our study had several strengths. First, it had a prospective design based on a relatively large population ($n = 8563$). Second, PAFs were directly calculated by accounting for non-independence of risk factors. Third, considering overlapping of risk factors individually, the joint impact of combined risk factors on incident dementia was estimated.

However, some limitations of this study should also be pointed out. First, because we did not obtain clinical diagnosis data on dementia, we did not evaluate the types of dementia, such as Alzheimer's disease or vascular dementia. Additionally, some misclassification of incident dementia in the present study participants might have occurred. If so, then our results might have been underestimated [28]. However, a previous study has reported that the Dementia Scale had a sensitivity (95% CI) of 73% (65–80%) and a specificity of 96% (94–97%) against clinical diagnosis by neuropsychiatrists (using a clinical interview defined by the International Psychogeriatric Association) [29]. Furthermore, it has been shown that the Dementia Scale is well correlated with the Mini Mental State Examination score (Spearman's rank correlation coefficient = − 0.736) [30]. Second, each risk factor was assessed only at the baseline. Therefore, the total number of risk factors might have changed during follow-up. Third, our results might have included a degree of selection bias. Among 8563 subjects included in the present analysis, the number of deaths was 914 (10.7%). On the other hand, among 5839 subjects on the basis of the criteria mentioned earlier, the number of deaths was 875 (15.0%). Thus, if our results had been biased towards healthier people in the community, underestimation might have occurred [28, 31].

Table 4 Association between number of risk factors and incident dementia ($n = 8563$)

	Number of dementia risk factors				*P* for trend	PAF_{ALL}[b](%)	PAF_{+1}[c] (%)
	0	1	2	≥3			
Number of participants	1395	3079	2656	1433			
Incident dementia (%)	3.94	5.36	7.57	10.89			
Crude HR (95% CI)	1.00 (ref.)	1.41 (1.04–1.92)	2.11 (1.57–2.84)	3.29 (2.42–4.48)	< 0.001	46.7	36.0
Adjusted[a] HR (95% CI)	1.00 (ref.)	1.25 (0.92–1.70)	1.59 (1.18–2.15)	2.21 (1.62–3.01)	< 0.001	32.2	23.0

ref. referent values, *PAF* population attributable fraction, *HR* hazard ratios, *95% CI* 95% confidence interval

[a]Adjusted for age (65–69, 70–74, 75–79, 80–84, or ≥ 85 years) and sex

[b]PAF_{ALL} is the preventable fraction of incident dementia if all subjects would have adhered to none of risk factor

[c]PAF_{+1} is the preventable fraction of incident dementia if subjects would have improved toward one better group

In conclusion, the present study has suggested that reducing the number of combined risk factors would contribute considerably to lowering the incidence of dementia in the elderly population.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standards The study protocol was reviewed and approved by the Ethics Committee of Tohoku University Graduate School of Medicine (Sendai, Japan) (Approval number: 2006-206, 2013-1-289). The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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