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Systematic Reviews and Meta- and Pooled Analyses

Prediction of Cardiovascular Disease Mortality by Proteinuria and Reduced Kidney Function: Pooled Analysis of 39,000 Individuals From 7 Cohort Studies in Japan

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There are limited studies addressing whether proteinuria and estimated glomerular filtration rate (eGFR) are independently associated with cardiovascular disease in Asia. Using data from 7 prospective cohorts recruited between 1980 and 1994 in Japan, we assessed the influence of proteinuria (≥1+ on dipstick) and reduced eGFR on the risk of cardiovascular disease mortality in 39,405 participants (40–89 years) without kidney failure. During a 10.1-year follow-up, 1,927 subjects died from cardiovascular disease. Proteinuria was associated with a 1.75-fold (95% confidence interval (CI): 1.44, 2.11) increased risk of cardiovascular disease mortality after adjustment for potential confounding factors. Additionally, the multivariate-adjusted hazard ratio of cardiovascular disease mortality increased linearly with lower eGFR levels ($P_{trend} < 0.001$): Subjects with eGFR of <45 mL/minute/1.73 m^2 had a 2.22-fold (95% CI: 1.60, 3.07) greater risk of cardiovascular disease mortality than those with eGFR of ≥90 mL/minute/1.73 m^2. Subjects with both proteinuria and eGFR of <45 mL/minute/1.73 m^2 had a 4.05-fold (95% CI: 2.55, 6.43) higher risk of cardiovascular disease mortality compared with those with neither of these risk factors. There was no evidence of interaction in the relationship between proteinuria and lower eGFR ($P_{interaction} = 0.77$). The present results suggest that proteinuria and lower eGFR are independent risk factors for cardiovascular disease mortality in the Japanese population.

cardiovascular disease; coronary artery disease; meta-analysis; proteinuria; renal insufficiency

Abbreviations: CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; EPOCH-JAPAN, Evidence for Cardiovascular Prevention from Observational Cohorts in Japan; ICD-9, *International Classification of Diseases, Ninth Revision*; ICD-10, *International Classification of Diseases, Tenth Revision*; IDMS-MDRD, isotope dilution mass spectrometry–traceable 4-variable Modification of Diet in Renal Disease; JSN-CKDI, Japan Society of Nephrology Chronic Kidney Disease Initiative; KDIGO, Kidney Disease: Improving Global Outcomes.

Kidney disease is increasingly being recognized as a leading public health issue. Chronic kidney disease, usually defined by the presence of proteinuria and/or reduced estimated glomerular filtration rate (eGFR), affects 10%–15% of the adult population in developed Western countries (1, 2). On the other hand, chronic kidney disease is expected to be more prevalent in Asian countries (3, 4). We previously reported that the prevalence of chronic kidney disease increased significantly over the last 3 decades in a general Japanese population, indicating that the burden of chronic kidney disease is gradually increasing in Japan (5).

Growing evidence suggests that proteinuria and reduced eGFR are associated with an increased risk of not only progressive kidney failure but also cardiovascular disease (6, 7). A recent meta-analysis using data from community-based cohort studies has suggested that both proteinuria and reduced eGFR were independently associated with cardiovascular disease or death (8). On the basis of this finding,

the Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference has recommended the following: 1) the assessment of both proteinuria and eGFR in general practice and 2) the classification of chronic kidney disease stages by using both kidney parameters, that is, proteinuria and reduced eGFR (9). With regard to Asian populations, a prospective cohort study in Taiwan has demonstrated that the risk for all-cause mortality increased with the amount of proteinuria at any given eGFR level (10). However, few studies have addressed whether the influence of these 2 parameters on the risk of cardiovascular outcomes is mutually independent or synergistic in Asian populations.

In the present study, we discuss the findings of pooled analysis from the Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN), which is an overview of individual participants' data from 13 longitudinal observational studies in Japan. The purpose of this study was to investigate the independent and combined influences of proteinuria and reduced eGFR on cardiovascular disease mortality in the Japanese population.

MATERIALS AND METHODS

Study design and participants

The rationale, study design, and methods of the EPOCH-JAPAN Study have been described elsewhere (11, 12). In brief, cohort studies were eligible for inclusion in this analysis if they met the following criteria: 1) collected health examination measures, 2) had almost 10 years of follow-up, and 3) included >1,000 participants. Both nationwide and regional cohort studies were included. Individual records of 188,141 participants in 13 cohort studies were included in the present analysis. Quality control of the collected cohort data was performed at the EPOCH-JAPAN Study Coordinating Center. Permission to submit data from each cohort to the EPOCH-JAPAN Study Coordinating Center was obtained from the relevant institutional review boards for ethical issues.

Of the 13 cohorts, 3 were excluded from the present analysis because of the absence of cause-of-death information, and 3 were excluded because of the lack of proteinuria or serum creatinine data. From a total of 44,588 participants in the remaining 7 cohorts (13–19), we excluded participants who were <40 years of age ($n = 5,099$) or ≥90 years of age ($n = 59$), as well as those with an eGFR of <15 mL/minute/1.73 m^2 ($n = 25$). A final total of 39,405 participants were included in the analysis, with 92.5% of the participants from 6 community-based cohorts and 7.5% from 1 work site–based cohort.

Risk factors

Proteinuria was tested by the dipstick method and defined as a result of 1+ or over. Because serum creatinine was measured by the Jaffé method in each cohort, the serum creatinine value was corrected by the subtraction of 18.3 μmol/L in order to convert the finding to a value measured by the enzymatic method (20). The value of eGFR was calculated by using the Japanese coefficient–modified Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (21). Other formulas of eGFR, that is, the Japan Society of Nephrology Chronic Kidney Disease Initiative (JSN-CKDI) equation (22) and the modified isotope dilution mass spectrometry–traceable 4-variable Modification of Diet in Renal Disease (IDMS-MDRD) Study equation with a Japanese correction coefficient of 0.808 (13), were used for sensitivity analyses. In accordance with the recommendation from the KDIGO (9), eGFR levels were classified in the following ranges: ≥90, 60–89, 45–59, and <45 mL/minute/1.73 m^2. Blood pressure was measured by a standard sphygmomanometer in all cohorts. The mean value was used in several cohorts that measured 2 or more blood pressure values. Diabetes was defined as a fasting blood glucose level of ≥7.0 mmol/L, a casual blood glucose level of ≥11.1 mmol/L, or current use of insulin or oral medication for diabetes. Body mass index was calculated by using the following equation: weight (kg)/height $(m)^2$. Measurement of serum total cholesterol was standardized in 5 cohorts such that values would be traceable to the Centers for Disease Control and Prevention reference method. Information on current smoking and drinking status was obtained through standard questionnaires and classified as current habitual use or lack thereof.

End points

For each deceased subject, a primary underlying cause of death was coded according to the *International Classification of Diseases* National Vital Statistics System based on criteria proposed by the World Health Organization. Causes of cardiovascular disease mortality were sought in great detail with the sources available in each cohort study, and the findings were classified as follows: coronary heart disease, stroke, and other cardiovascular diseases. In many studies, death certificates were reviewed and/or the National Vital Statistics System was utilized after obtaining permission from the Ministry of Internal Affairs and Communications of Japan. Other sources utilized in some studies included autopsy, medical records, health examination, and questionnaire. Causes of cardiovascular disease mortality were coded by either the *International Classification of Diseases, Ninth Revision* (ICD-9) or *Tenth Revision* (ICD-10), classification. Classification codes used in the study were as follows: death from cardiovascular disease (ICD-9 codes 390–459, ICD-10 codes I00–I99), coronary heart disease (ICD-9 codes 410–414, ICD-10 codes I20–I25), and stroke (ICD-9 codes 430–438, ICD-10 codes I60–I69).

Statistical analysis

The hazard ratio and its 95% confidence interval for the outcome were estimated with the Cox proportional hazards regression model stratified by cohort. The heterogeneity across cohorts was examined with the Cochran Q test and the I^2 statistic (23). The interaction effect of both proteinuria and reduced eGFR levels on the outcome was estimated by adding interaction terms between eGFR categories assigned serial numerical codes and the status of proteinuria to the relevant model. All statistical analyses were performed by

Table 1. Baseline Characteristics of EPOCH-JAPAN Participants in 7 Cohorts Recruited Between 1980 and 1994

Cohort, Year (Reference No.)	No. of Participants	Mean Age (SD), Years	Men, %	Baseline SurveyYear	Mean Follow-up Period (SD), Years	Mean eGFR (SD), mg/dL/ 1.73 m^2	Proteinuria[a], %	Mean SBP (SD), mm Hg	Mean DBP (SD), mm Hg	Diabetes, %	Mean BMI (SD)[b]	Mean Total Cholesterol (SD), mmol/L	Current Smoking, %	Current Drinking, %	No. of Events		
															CVD	CHD	Stroke
Osaki, 1994 (13)	15,989	62 (9)	42.5	1994	6.0 (1.4)	92.1 (14.0)	1.7	131 (18)	79 (11)	4.6	23.9 (3.1)	5.3 (0.9)	21.8	41.7	251	67	116
Ohasama[c], 1987 (14)	189	64 (9)	51.3	1987	7.0 (2.1)	76.6 (11.0)	12.2	137 (18)	78 (11)	1.1	23.6 (3.2)	5.0 (0.9)	19.6	24.3	10	3	6
YKK workers, 1990 (15)	2,966	47 (5)	65.4	1990	10.9 (2.4)	90.0 (8.8)	4.1	119 (16)	74 (12)	2.7	22.5 (2.6)	5.3 (0.9)	37.5	59.6	13	1	3
RERF cohort, 1986 (16)	4,553	62 (12)	32.7	1986	14.3 (4.7)	68.7 (11.1)	4.4	135 (23)	82 (12)	13.6	22.7 (3.5)	5.4 (1.0)	22.3	41.8	574	108	235
Hisayama, 1988 (17)	2,711	59 (12)	42.7	1988	11.0 (2.6)	73.8 (11.6)	5.7	134 (21)	78 (11)	9.1	22.8 (3.2)	5.3 (1.1)	25.2	30.8	158	33	66
NIPPON DATA 80, 1980 (18)	7,065	56 (11)	44.0	1980	16.7 (4.5)	78.8 (12.3)	2.8	140 (22)	83 (12)	4.6	22.8 (3.2)	5.0 (0.9)	31.6	41.8	719	136	338
NIPPON DATA 90, 1990 (19)	5,932	57 (11)	42.9	1990	9.5 (1.7)	86.2 (12.6)	3.0	139 (20)	83 (12)	4.8	23.1 (3.2)	5.4 (0.9)	27.5	28.3	202	49	82
Total	39,405	59 (11)	43.5		10.1 (5.0)	84.6 (15.2)	2.9	134 (20)	80 (12)	5.8	23.3 (3.2)	5.3 (1.0)	25.9	40.2	1,927	397	846

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EPOCH-JAPAN, Evidence for Cardiovascular Prevention from Observational Cohorts in Japan; NIPPON DATA 80 or 90, the cohort study of the National Survey on Circulatory Disorders in 1980 or 1990 in Japan; RERF, Radiation Effects Research Foundation; SBP, systolic blood pressure; SD, standard deviation; YKK, Yoshida Kogyo K.K.

[a] Proteinuria was defined as ≥1+ on dipstick.

[b] Body mass index: weight (kg)/height (m)^2.

[c] In the Ohasama cohort, those without serum creatinine data (n = 2,965) or proteinuria data (n = 60) were excluded from a total of 3,174 participants, and the remaining 189 participants were included in the analysis.

Table 2. Adjusted Mortality Rates and Hazard Ratios of Cardiovascular Disease According to Proteinuria Status From EPOCH-JAPAN Participants Recruited Between 1980 and 1994 With an Average 10.1-Year Follow-up

Proteinuria	No. of Participants	No. of Deaths	Person-Years	Mortality Rate/1,000 Person-Years[a]	95% CI	Age and Sex Adjusted		Multivariate Adjusted (Model A)[b]		Multivariate Adjusted (Model B)[c]	
						HR	95% CI	HR	95% CI	HR	95% CI
Cardiovascular Disease											
Absent	38,256	1,776	387,918	4.4	4.2, 4.7	1	Referent	1	Referent	1	Referent
Present	1,149	151	10,979	10.8**	8.7, 12.9	2.03**	1.72, 2.41	1.75**	1.44, 2.11	1.66**	1.37, 2.01
Coronary Heart Disease											
Absent	38,256	359	387,918	0.9	0.8, 1.1	1	Referent	1	Referent	1	Referent
Present	1,149	38	10,979	2.7**	1.7, 3.7	2.53**	1.80, 3.55	1.89*	1.28, 2.78	1.75*	1.18, 2.59
Stroke											
Absent	38,256	792	387,918	2.0	1.8, 2.1	1	Referent	1	Referent	1	Referent
Present	1,149	54	10,979	4.2**	2.9, 5.5	1.61**	1.21, 2.12	1.50*	1.11, 2.04	1.45*	1.07, 1.98

Abbreviations: CI, confidence interval; EPOCH-JAPAN, Evidence for Cardiovascular Prevention from Observational Cohorts in Japan; HR, hazard ratio.

* $P < 0.01$; ** $P < 0.001$.

[a] Mortality rates and their 95% confidence intervals were adjusted for age and sex by using the direct standardized method.

[b] Model A was adjusted for age, sex, systolic blood pressure, diabetes, total cholesterol, body mass index, history of cardiovascular disease, current smoking, and current drinking.

[c] Model B was adjusted for potential confounding factors included in Model A and eGFR levels.

using SAS, release 9.13, software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

The characteristics of the study participants in 7 cohorts are shown in Table 1. Overall, the mean age was 59 years, and the proportion of men was 43.5%. The subjects were followed for an average of 10.1 years. The mean eGFR value was 84.6 mL/minute/1.73 m^2, and the frequency of proteinuria was 2.9%. During the follow-up period, a total of 1,927 experienced cardiovascular disease mortality, of which 397 subjects died from coronary heart disease and 846 from stroke.

Table 2 shows the pooled estimate of adjusted hazard ratios for cardiovascular disease mortality according to the status of proteinuria. Subjects with proteinuria had a 1.75-fold (95% confidence interval (CI): 1.44, 2.11) higher risk of cardiovascular disease mortality than those with negative proteinuria after adjustment for age, sex, systolic blood pressure, diabetes, serum total cholesterol, body mass index, history of cardiovascular disease, current smoking, and current drinking. This relationship was not altered substantially after adjustment for the aforementioned confounding factors and eGFR levels. Comparable results were found for mortalities from coronary heart disease and stroke. Additionally, when we divided proteinuria levels into 3 categories of negative, trace, and ≥1+ proteinuria, subjects with trace proteinuria and ≥1+ proteinuria had 1.44-fold (95% CI: 1.17, 1.77) and 1.80-fold (95% CI: 1.48, 2.17) higher risk of cardiovascular disease mortality than those with negative proteinuria after adjustment for the aforementioned risk factors, respectively (Appendix Table 1).

Next, we estimated the relationship between eGFR levels and the risk of cardiovascular disease outcomes (Table 3). The risk of mortality from cardiovascular disease and stroke increased progressively with declining eGFR levels after adjustment for the aforementioned confounding factors. Likewise, an increasing trend was observed in the risk of mortality from coronary heart disease. Subjects with an eGFR of <45 mL/minute/1.73 m^2 had a 2.22-fold (95% CI: 1.60, 3.07) greater risk of cardiovascular disease mortality than those with an eGFR of ≥90 mL/minute/1.73 m^2. The relationships showed little change after adjustment for the aforementioned confounding factors and proteinuria levels. Furthermore, similar associations of proteinuria or reduced eGFR with the risk of cardiovascular disease mortality were observed in middle-aged (<60 years of age) and elderly (≥60 years of age) populations. Additionally, we compared the influence of proteinuria and eGFR of <60 (vs. ≥60) mL/minute/1.73 m^2 on the risk of cardiovascular disease mortality among study cohorts (Figure 1). We found no evidence of heterogeneity in the effects across study cohorts ($Q = 4.3$, $I^2 = 0\%$, $P = 0.64$ for proteinuria; and $Q = 2.3$, $I^2 = 0\%$, $P = 0.89$ for eGFR of <60 mL/minute/1.73 m^2).

Finally, we investigated the combined influences of proteinuria and reduced eGFR levels on the risk of cardiovascular disease mortality (Figure 2). The influence of proteinuria and that of lower eGFR on the risk of cardiovascular disease mortality were independent of each other ($P_{interaction} = 0.77$). Compared with those subjects lacking proteinuria who had an eGFR level of ≥90 mL/minute/1.73 m^2, those with both proteinuria and an eGFR of <45 mL/minute/1.73 m^2 were at 4.05-fold (95% CI: 2.55, 6.43) higher risk of cardiovascular disease mortality. The sensitivity analysis, in which proteinuria levels were divided into 3 categories of negative, trace,

Table 3. Adjusted Mortality Rates and Hazard Ratios of Cardiovascular Disease According to eGFR Levels From EPOCH-JAPAN Participants Recruited Between 1980 and 1994 With an Average 10.1-Year Follow-up

eGFR, mg/dL/1.73 m^2	No. of Participants	No. of Deaths	Person-Years	Mortality Rate/1,000 Person-Years[a]	95% CI[a]	Age and Sex Adjusted			Multivariate Adjusted (Model A)[b]			Multivariate Adjusted (Model B)[c]		
						HR	95% CI	P_{trend}	HR	95% CI	P_{trend}	HR	95% CI	P_{trend}
Cardiovascular Disease														
≥90	14,720	135	123,511	1.8	0.5, 3.2	1	Referent	<0.001	1	Referent		1	Referent	<0.001
60–89	22,736	1,286	256,444	4.7	4.4, 5.0	1.20	0.98, 1.46		1.19	0.96, 1.48	<0.001	1.19	0.96, 1.48	
45–59	1,593	403	16,267	8.8***	6.9, 10.7	1.78***	1.40, 2.26		1.58***	1.21, 2.05		1.56**	1.20, 2.02	
<45	356	103	2,676	16.9***	11.2, 22.6	2.45***	1.82, 3.28		2.22***	1.60, 3.07		2.06***	1.48, 2.85	
Coronary Heart Disease														
≥90	14,720	46	123,511	0.7	0.4, 0.9	1	Referent	<0.001	1	Referent		1	Referent	0.08
60–89	22,736	256	256,444	1.0	0.8, 1.1	0.79	0.55, 1.14		0.75	0.51, 1.10	0.04	0.75	0.51, 1.10	
45–59	1,593	70	16,267	1.6	1.0, 2.3	1.20	0.74, 1.94		0.96	0.57, 1.62		0.95	0.57, 1.60	
<45	356	25	2,676	4.8*	1.6, 8.0	2.11*	1.18, 3.76		1.71	0.90, 3.23		1.55	0.82, 2.93	
Stroke														
≥90	14,720	54	123,511	0.6	0.0, 1.6	1	Referent	<0.001	1	Referent	0.002	1	Referent	0.003
60–89	22,736	584	256,444	2.1*	1.9, 2.3	1.38*	1.01, 1.88		1.37	0.98, 1.92		1.37	0.98, 1.92	
45–59	1,593	172	16,267	3.2***	2.3, 4.1	1.91***	1.32, 2.76		1.72**	1.15, 2.58		1.70*	1.14, 2.55	
<45	356	36	2,676	5.0***	2.3, 7.6	2.09***	1.30, 3.36		2.06**	1.23, 3.47		1.95*	1.16, 3.29	

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; EPOCH-JAPAN, Evidence for Cardiovascular Prevention from Observational Cohorts in Japan; HR, hazard ratio.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

[a] Mortality rates and their 95% confidence intervals were adjusted for age and sex by using the direct standardized method.

[b] Model A was adjusted for age, sex, systolic blood pressure, diabetes, total cholesterol, body mass index, history of cardiovascular disease, current smoking, and current drinking.

[c] Model B was adjusted for the potential confounding factors included in Model A and proteinuria levels.

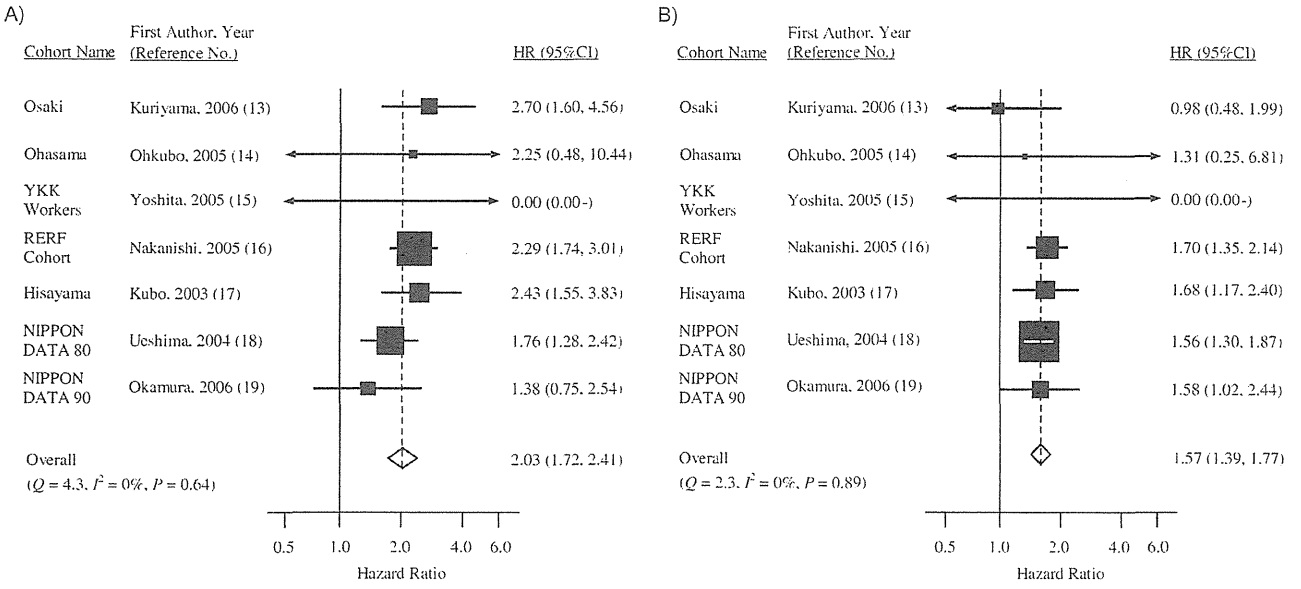

Figure 1. Forest plots of age- and sex-adjusted hazard ratios and 95% confidence intervals of A) proteinuria (vs. absence) or B) eGFR <60 mL/minute/1.73 m^2 (vs. ≥60) on cardiovascular disease mortality from EPOCH-JAPAN participants recruited between 1980 and 1994 with an average 10.1-year follow-up. CI, confidence interval; eGFR, estimated glomerular filtration rate; EPOCH-JAPAN, Evidence for Cardiovascular Prevention from Observational Cohorts in Japan; HR, hazard ratio; NIPPON DATA 80 or 90, the cohort study of the National Survey on Circulatory Disorders in 1980 or 1990 in Japan; RERF, Radiation Effects Research Foundation; YKK, Yoshida Kogyo K.K. (a metal-products factory in Toyama, Japan). Black squares indicate hazard ratios, horizontal lines indicate 95% confidence intervals, and diamonds indicate results of pooled analyses. The area of black squares reflects the weight of each cohort contribution to the meta-analysis. In the study of YKK workers, cardiovascular disease deaths were not observed among subjects with proteinuria or those with an eGFR of <60 mL/minute/1.73 m^2.

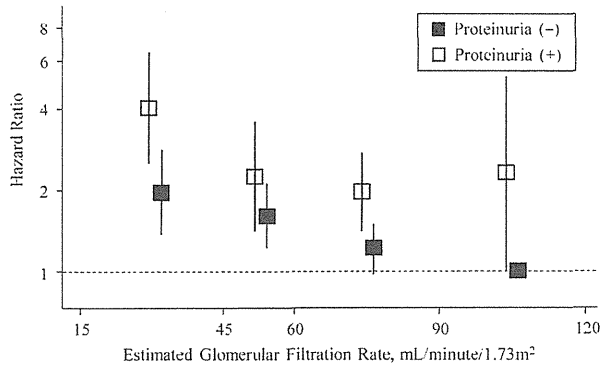

Figure 2. Combined influences of proteinuria and eGFR levels on the risk of cardiovascular disease mortality from EPOCH-JAPAN participants recruited between 1980 and 1994 with an average 10.1-year follow-up. The squares and vertical lines correspond to hazard ratios and 95% confidence intervals, respectively. The estimate was adjusted for age, sex, systolic blood pressure, diabetes, serum total cholesterol, body mass index, history of cardiovascular disease, current smoking, and current drinking. Subjects lacking proteinuria and with an estimated glomerular filtration rate (eGFR) of <60 mL/minute/1.73 m^2 and those with proteinuria in all eGFR levels had statistically significant higher risk of cardiovascular disease mortality compared with those with neither of these risk factors (all P's < 0.05). There was no evidence of heterogeneity in the association of eGFR levels with the risk of cardiovascular disease mortality between proteinuria status ($P_{interaction}$ = 0.77). EPOCH-JAPAN, Evidence for Cardiovascular Prevention from Observational Cohorts in Japan.

and ≥1+, did not make any material difference in the findings (Appendix Table 2).

The sensitivity analyses using other formulas of eGFR, namely, the JSN-CKDI equation (22) and the Japanese coefficient modified IDMS-MDRD Study equation (20), did not reveal any material differences in the respective influences of proteinuria and eGFR levels on cardiovascular disease mortality (Table 4).

DISCUSSION

On the basis of a pooled analysis of individual data from 39,405 Japanese participants, we confirmed a clear association of proteinuria or reduced eGFR with the risk of cardiovascular disease death. Additionally, we demonstrated that both proteinuria and reduced eGFR were associated significantly and independently with the risk of cardiovascular disease mortality. There was no evidence of any interaction between these risk factors, and those subjects with both proteinuria and reduced eGFR were at the highest risk of cardiovascular disease. Therefore, these findings highlight the potential clinical value of the measurement of both proteinuria and eGFR levels for cardiovascular risk assessment in the Japanese population.

The effects of the combined assessment of proteinuria and eGFR on cardiovascular risk have been addressed in several community-based cohort studies (24–26). Additionally, the

Table 4. Multivariate-Adjusted Hazard Ratios and 95% Confidence Intervals of Cardiovascular Disease According to Proteinuria and eGFR Levels, Determined With Different eGFR Formulas From EPOCH-JAPAN Participants Recruited Between 1980 and 1994 With an Average 10.1-Year Follow-up

Proteinuria	eGFR, mL/minute/1.73 m^2								$P_{interaction}$
	≥90		60–89		45–59		<45		
	HR[a]	95% CI	HR[a]	95% CI	HR[a]	95% CI	HR[a]	95% CI	
JSN-CKDI Equation									
Absent	1	Referent	1.02	0.86, 1.20	1.22*	1.00, 1.48	1.69***	1.27, 2.26	0.37
Present	1.57	0.78, 3.18	1.76***	1.28, 2.41	1.70**	1.17, 2.49	3.46***	2.29, 5.22	
IDMS-MDRD Study Equation									
Absent	1	Referent	1.11	0.95, 1.29	1.46***	1.21, 1.76	1.92***	1.44, 2.56	0.41
Present	1.47	0.78, 2.77	1.86***	1.36, 2.53	2.19***	1.51, 3.18	3.76***	2.47, 5.71	

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; EPOCH-JAPAN, Evidence for Cardiovascular Prevention from Observational Cohorts in Japan; HR, hazard ratio; IDMS-MDRD, isotope dilution mass spectrometry–traceable 4-variable Modification of Diet in Renal Disease; JSN-CKDI, Japan Society of Nephrology Chronic Kidney Disease Initiative.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

[a] Adjusted for age, sex, systolic blood pressure, diabetes, total cholesterol, body mass index, history of cardiovascular disease, current smoking status, and current drinking status.

Chronic Kidney Disease Prognosis Consortium has presented results from a collaborative meta-analysis of 21 general population cohorts (8), which included more than 1.2 million participants from 14 countries in North America, Europe, Asia, and Oceania. The meta-analysis demonstrated that an albumin/creatinine ratio of >1.1 mg/mmol and an eGFR of <60 mL/minute/1.73 m^2 were independently associated with cardiovascular disease mortality and traditional cardiovascular risk factors (8). Comparable findings were also observed in the meta-analysis of 10 high-risk population cohorts (27). In the first chronic kidney disease guideline proposed by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative in 2002, chronic kidney disease stage was classified into 5 stages according to eGFR levels, regardless of the albuminuria level. However, on the basis of the most recent findings, the KDIGO Controversies Conference proposed a new chronic kidney disease stage classification, in which chronic kidney disease stages were divided by both albuminuria and eGFR levels. Likewise, the present study clearly showed that proteinuria and reduced eGFR were associated with the risk of cardiovascular disease mortality in a manner independent of each other and were also independently associated with other potential cardiovascular risk factors in a meta-analysis of 7 Japanese cohort studies. These results support the view that assessment of both proteinruia (or albuminuria) and eGFR level is needed in order to improve the identification of individuals at high risk of cardiovascular complications and to establish appropriate preventative measures for the Japanese population.

The mechanism by which the relationship between proteinuria or glomerular filtration rate and cardiovascular and renal outcomes might be mediated is an area of great interest. In the present study, the effects of proteinuria and reduced eGFR on the risk of cardiovascular disease mortality were independent of each other. This suggests that proteinuria and reduced glomerular filtration rate are markers of different pathological processes. It has been acknowledged that proteinuria reflects systemic endothelial dysfunction (28, 29), whereas the reduced glomerular filtration rate is associated with the severity of systemic atherosclerosis (30, 31). The pathophysiology of influence of both risk factors requires further exploration.

The strengths of this study include the large sample size that allowed for precise estimations of the independent influences of proteinuria and the glomerular filtration rate level on the risk of cardiovascular disease mortality. The limitations of this study should also be noted. First, it has been recognized that the eGFR determined by using the modified CKD-EPI equation may not be sufficiently accurate (21) and might lead to some misclassifications. Such misclassifications would weaken the association found in this study, biasing the results toward the null hypothesis. Furthermore, the sensitivity analyses using other formulas of eGFR, namely, the JSN-CKDI equation (22) and the modified IDMS-MDRD Study equation (20), did not lead to any material differences in the findings. Second, measurements of serum creatinine and proteinuria were conducted locally rather than at a central laboratory and without calibration among laboratories, which may have produced substantial variability in the measured values, likely weakening the association found in the present study. Third, because the YKK workers cohort, one of our study cohorts, was a work site–based cohort, the estimates from this cohort might be biased by a healthy-worker effect to some extent. However, the findings did not change with exclusion of the YKK workers cohort. Fourth, we could not use finer categories of proteinuria (e.g., negative, trace, 1+, and ≥2+) and eGFR levels (e.g., ≥90, 60–89, 45–59, 30–44, and 15–29 mL/minute/1.73 m^2) because the number of subjects with proteinuria of ≥2+ (273 subjects, 0.7%) and that with an eGFR of 15–29 mL/minute/1.73 m^2 (119 subjects, 0.3%) were too small to assess the findings reliably. Finally, in the present study, the absence of data on the albumin/creatinine ratio rendered it impossible to assess the influences of low levels

of albuminuria on the risk of cardiovascular disease outcomes.

In conclusion, the present findings clarified that proteinuria and reduced eGFR were significantly and independently associated with cardiovascular disease outcomes. Measurement of both proteinuria and eGFR is likely to improve the protocol for cardiovascular risk assessment in the Japanese population.

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(Appendix follows)

Appendix Table 1. Adjusted Mortality Rates and Hazard Ratios of Cardiovascular Disease According to Proteinuria Levels From EPOCH-JAPAN Participants Recruited Between 1980 and 1994 With an Average 10.1-Year Follow-up

Proteinuria	No. of Participants	No. of Deaths	Person-Years	Mortality Rate/1,000 Person-Years[a]	95% CI[a]	Age and Sex Adjusted			Multivariate Adjusted (Model A)[b]			Multivariate Adjusted (Model B)[c]		
						HR	95% CI	P_{trend}	HR	95% CI	P_{trend}	HR	95% CI	P_{trend}
Cardiovascular Disease														
Negative	36,692	1,670	387,918	4.4	4.1, 4.6	1	Referent		1	Referent		1	Referent	
Trace	1,564	106	8,597	6.6***	5.1, 8.1	1.54***	1.26, 1.89	<0.001	1.44***	1.17, 1.77	<0.001	1.41**	1.15, 1.74	<0.001
≥1+	1,149	151	2,383	10.8***	8.7, 12.9	2.08***	1.76, 2.47		1.80***	1.48, 2.17		1.71***	1.41, 2.08	
Coronary Heart Disease														
Negative	36,692	340	387,918	0.9	0.8, 1.1	1	Referent		1	Referent		1	Referent	
Trace	1,564	19	8,597	1.2	0.6, 1.9	1.34	0.83, 2.16	<0.001	1.19	0.73, 1.94	0.001	1.17	0.72, 1.92	0.003
≥1+	1,149	38	2,383	2.7***	1.7, 3.7	2.56***	1.82, 3.61		1.91**	1.30, 2.82		1.85**	1.25, 2.73	
Stroke														
Negative	36,692	744	387,918	1.9	1.7, 2.1	1	Referent		1	Referent		1	Referent	
Trace	1,564	48	8,597	2.9**	1.9, 3.9	1.55**	1.14, 2.09	<0.001	1.45*	1.09, 2.01	<0.001	1.46*	1.07, 1.98	0.002
≥1+	1,149	54	2,383	4.2***	2.9, 5.5	1.64***	1.24, 2.18		1.55**	1.14, 2.11		1.49*	1.09, 2.03	

Abbreviations: CI, confidence interval; EPOCH-JAPAN, Evidence for Cardiovascular Prevention from Observational Cohorts in Japan; HR, hazard ratio.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

[a] Mortality rates and their 95% confidence intervals were adjusted for age and sex by using the direct standardized method.

[b] Model A was adjusted for age, sex, systolic blood pressure, diabetes, total cholesterol, body mass index, history of cardiovascular disease, current smoking, and current drinking.

[c] Model B was adjusted for the potential confounding factors included in model A and estimated glomerular filtration rate levels.

Appendix Table 2. The Combined Influence of Proteinuria and Reduced eGFR Levels on the Risk of Cardiovascular Disease Mortality From EPOCH-JAPAN Participants Recruited Between 1980 and 1994 With an Average 10.1-Year Follow-up

Proteinuria	eGFR, mL/minute/1.73 m^2							
	≥90		60–89		45–59		<45	
	HR[a]	95% CI	HR[a]	95% CI	HR[a]	95% CI	HR[a]	95% CI
Negative	1	Referent	1.22	0.98, 1.53	1.59**	1.20, 2.09	1.83**	1.25, 2.68
Trace	1.63	0.72, 3.71	1.58**	1.13, 2.21	2.46***	1.53, 3.95	3.66***	1.87, 7.16
≥1+	2.37*	1.04, 5.41	2.02***	1.45, 2.81	2.31***	1.45, 3.69	4.18***	2.62, 6.65

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; EPOCH-JAPAN, Evidence for Cardiovascular Prevention from Observational Cohorts in Japan; HR, hazard ratio.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

[a] Adjusted for age, sex, systolic blood pressure, diabetes, total cholesterol, body mass index, history of cardiovascular disease, current smoking status, and current drinking status.

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Young Investigator Award Winner's Special Article

Meta-analyses Using Individual Participant Data From Cardiovascular Cohort Studies in Japan: Current Status and Future Directions

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ABSTRACT

Meta-analysis of individual participant data (IPD meta-analysis) has several advantages over meta-analysis using aggregated published data, including the possibility of using statistical methods such as a fine stratification analysis, interaction analysis between 2 risk factors, and absolute risk estimation. The Evidence for Cardiovascular Prevention from Observational Cohorts in Japan Study (EPOCH-JAPAN), which was initiated in 2005, is a collaborative research project for IPD meta-analysis and includes 13 participating cohort studies in Japan. We generated 2 pooled databases with data on all-cause mortality ($n = 199\,047$) and cardiovascular outcomes ($n = 90\,528$) and applied a stratified Cox model to account for the different baseline hazards between cohorts. The results of our analyses show the age- and sex-specific associations between all-cause and cardiovascular disease mortality and established cardiovascular risk factors (blood pressure, smoking, total cholesterol, proteinuria, and kidney function). During the 9 years of its existence, the results generated by EPOCH-JAPAN have had important implications for clinical medicine and public health policy in Japan. The project is expected to draw upon new analytical methods such as interaction analysis and absolute risk evaluation in the near future. We believe that, over the next decade, this project will continue to provide new insights that can be applied to research on other Asian populations.

Key words: meta-analysis; individual participant data; premature death; cardiovascular disease; population attributable fraction

INTRODUCTION

The proliferation of information technology during the past 2 decades has given researchers unprecedented access to a wider range of scientific literature. This has created new opportunities to conduct meta-analyses, ie, systematic overviews of the literature using quantitative methods that allow researchers to enhance the accuracy of their findings by combining information from multiple studies.[1] Individual participant data (IPD) meta-analysis (sometimes referred to as individual participant data meta-analysis or pooled analysis) has several advantages over meta-analysis using aggregated published data.[2,3] One advantage of IPD meta-analyses using individual-based datasets is that they can make use of statistical techniques such as a fine stratification analysis, interaction analysis between 2 risk factors, and absolute risk estimation. None of these methods can be applied to a single-site cohort study because sample size is usually insufficient. Figure 1 shows the relationship between blood pressure (BP) category and cardiovascular disease (CVD) mortality in 3 different sampling sets generated by random sampling from the pooled database. We found that the confidence intervals for the relationship between systolic BP and CVD mortality narrowed as the sample size increased. Moreover, these results show that an apparent trend with narrow confidence intervals can only be achieved when the sample size is sufficient.

The Evidence for Cardiovascular Prevention from Observational Cohorts in Japan Study (EPOCH-JAPAN), which was initiated in 2005, is a collaborative research project for IPD meta-analyses of CVD in Japan. This article will outline the design, methods, and main results of the EPOCH-JAPAN study. Finally, I will offer my perspective on the future of the project and its implications for future research.

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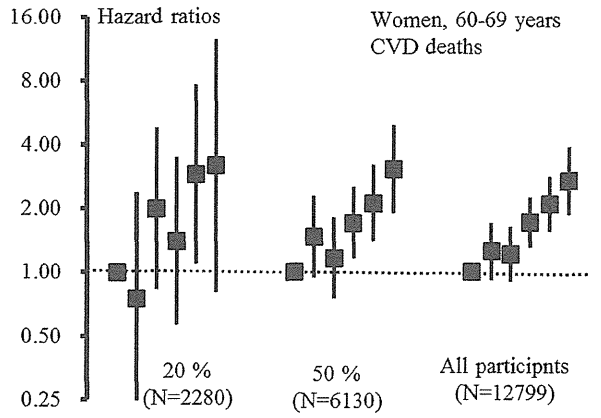


Figure 1. Relationship between blood pressure and cardiovascular disease deaths among different sampling sets: women aged 60–69 years, EPOCH-JAPAN. Three different sampling sets were generated and analyzed separately. The samples were set as follows: 20% sampling (2280 participants), 50% sampling (6130 participants), and all participants (12799). Blood pressure measurements (unit: mm Hg; SBP, systolic blood pressure; DBP, diastolic blood pressure) were grouped into 6 categories (SBP < 120 and DBP < 80 (reference), 120 ≤ SBP < 130 or 80 ≤ DBP < 85, 130 ≤ SBP < 140 or 85 ≤ DBP < 90, 140 ≤ SBP < 160 or 90 ≤ DBP < 100, 160 ≤ SBP < 180 or 100 ≤ DBP < 110, and 180 ≤ SBP or 110 ≤ DBP). The error bars show 95% CIs.

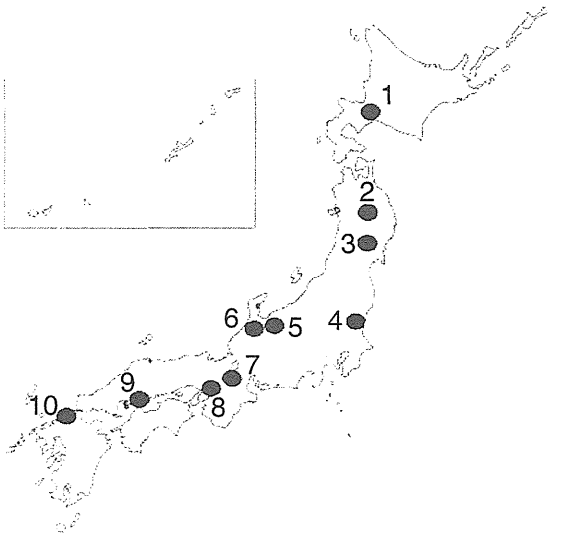


Figure 2. The EPOCH-JAPAN cohort study sites. Each point on the map represents a study site where an EPOCH-JAPAN cohorts were located. The names of the studies are as follows: 1: Tanno-Sobetsu, 2: Ohasama, 3: Osaki, 4: Ibaraki prefecture, 5: YKK workers, 6: Oyabe, 7: Shiga Health Insurance, 8: Suita, 9: Radiation Effects Research Foundation, 10: Hisayama. Three nationwide cohort studies (JACC study, NIPPON DATA80, and NIPPON DATA90) were also included in EPOCH-JAPAN.

BRIEF INTRODUCTION OF EPOCH-JAPAN —

The collection of cohort studies

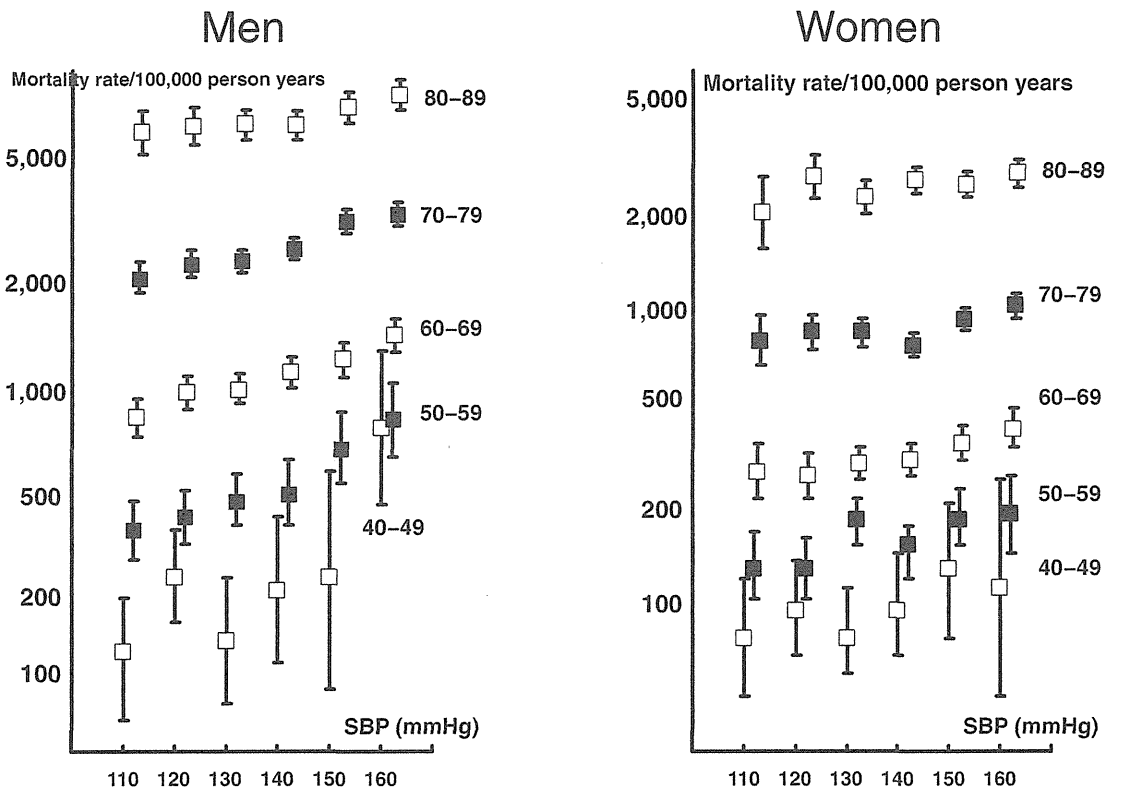
EPOCH-JAPAN comprises 13 cohort studies of the relationships between health measures (including laboratory measures and survey items on lifestyle and behavioral factors) and disease outcomes (total and disease-specific mortality) in the Japanese population. Figure 2 shows the locations of these cohorts, which include 10 single-site and 3 nationwide cohort studies distributed throughout Japan. Only those cohorts that collected results from health examinations, had a mean follow-up period of approximately 10 years, and included more than 1000 participants were eligible for inclusion in EPOCH-JAPAN.

We then generated 2 pooled databases for different outcome measures. While the first contained data from 199 047 participants showing all-cause deaths only, the second included data on cardiovascular outcomes from 90 528 participants. In some analyses, we included follow-up data only from participants aged 40 to 90 years. This was considered appropriate because the end-point of follow-up varied across cohorts. A full list of the members of the EPOCH-JAPAN Study Research Group is shown in the Appendix.[4]

Statistical analyses

The stratified Cox proportional hazards model, which can account for differences in baseline hazards between strata, was the default method used for most analyses in EPOCH-JAPAN. Because the baseline hazard (absolute mortality rate) of each cohort was likely to be different, the stratified Cox model was considered one of the best models to satisfy this assumption. This method can be easily applied using standard statistical software such as SAS, STATA, and SPSS and has been widely used in other IPD meta-analyses.[3] In addition, we used Poisson regression to estimate absolute risk (ie, mortality rate). In our Poisson regression analyses, we modeled a separate indicator (dummy) variable for each cohort to adjust for differences in baseline mortality rates between cohorts.

The age- and sex-specific results generated have given us key insights into various exposure–disease relationships in different groups within the Japanese population. For the purposes of analysis, participants in the all-cause mortality database were stratified into 10-year age groups, from 40 to 80 years, which were analyzed using separate models. Population attributable fraction (PAF), which shows the impact of an exposure across the population as a whole, was also an important outcome measure in EPOCH-JAPAN. Most articles published from EPOCH-JAPAN have used this measure to represent the potential impact of specific risk factors on the Japanese population.



(Murakami Y et al. Hypertension 2008;51:1483-1491.)

Figure 3. Relationship between systolic blood pressure and adjusted mortality rate by age group. Each square represents a multivariate estimate of mortality rates after adjusting for smoking status, alcohol use, and body mass index; the error bars show 95% CIs. The number of events in each age category are as follows: men aged 40–49 years: 137; age 50–59 years: 566; age 60–69 years: 1900; age 70–79 years: 3782; age 80–89 years: 2183; women aged 40–49 years: 128; age 50–59 years: 518; age 60–69 years: 1392; age 70–79 years: 2708; age 80–89 years: 2258.

In our IPD meta-analyses, correction for regression dilution bias was sometimes done using the MacMahon and Peto method. This bias correction was applied in our investigation of the relationship between BP and all-cause mortality.[4] All statistical analyses were performed using SAS 9.13 (SAS Institute Inc).

RESULTS

Several reports have already been published from EPOCH-JAPAN.[4–9] Brief summaries of each study are shown below.

BP and all-cause mortality[4]

Hypertension is a leading cause of premature death, and cardiovascular disease is a major contributor to total mortality. To examine possible ways to reduce avoidable deaths from hypertension, we examined 13 cohorts from EPOCH-JAPAN to assess the impact of hypertension on total mortality in Japan. The results of our multivariate model (Figure 3) show the relationship between BP and mortality rate by age group. While adjusted mortality rates rose as BP increased, this effect was most pronounced in younger men and women. The PAF for hypertension was approximately 20% when only participants with normal BP were included in the reference group and 10% when we included those with prehypertension in the reference group. These results indicate that high BP increased the risk of total mortality and that this effect was strongest among younger Japanese.

Smoking and all-cause mortality[5]

To determine age- and sex-specific PAFs and the number of premature deaths attributable to smoking in an Asian population, we examined hazard ratios and corresponding PAFs using EPOCH-JAPAN. Figure 4 shows the age-specific hazard ratios according to smoking status and the PAFs from EPOCH-JAPAN. The overall proportion of deaths attributable to smoking was 24.6% in men and 6.0% in women. The age-specific PAF was highest in men aged 60 to 69 years (47.7%) and in women aged 50 to 59 years (12.2%). Among those aged 70 to 79 years and 80 to 89 years, the PAFs were 15.4% and 8.0%, respectively, in men and 3.5% and 1.5% in women. Our results show that age-specific PAFs

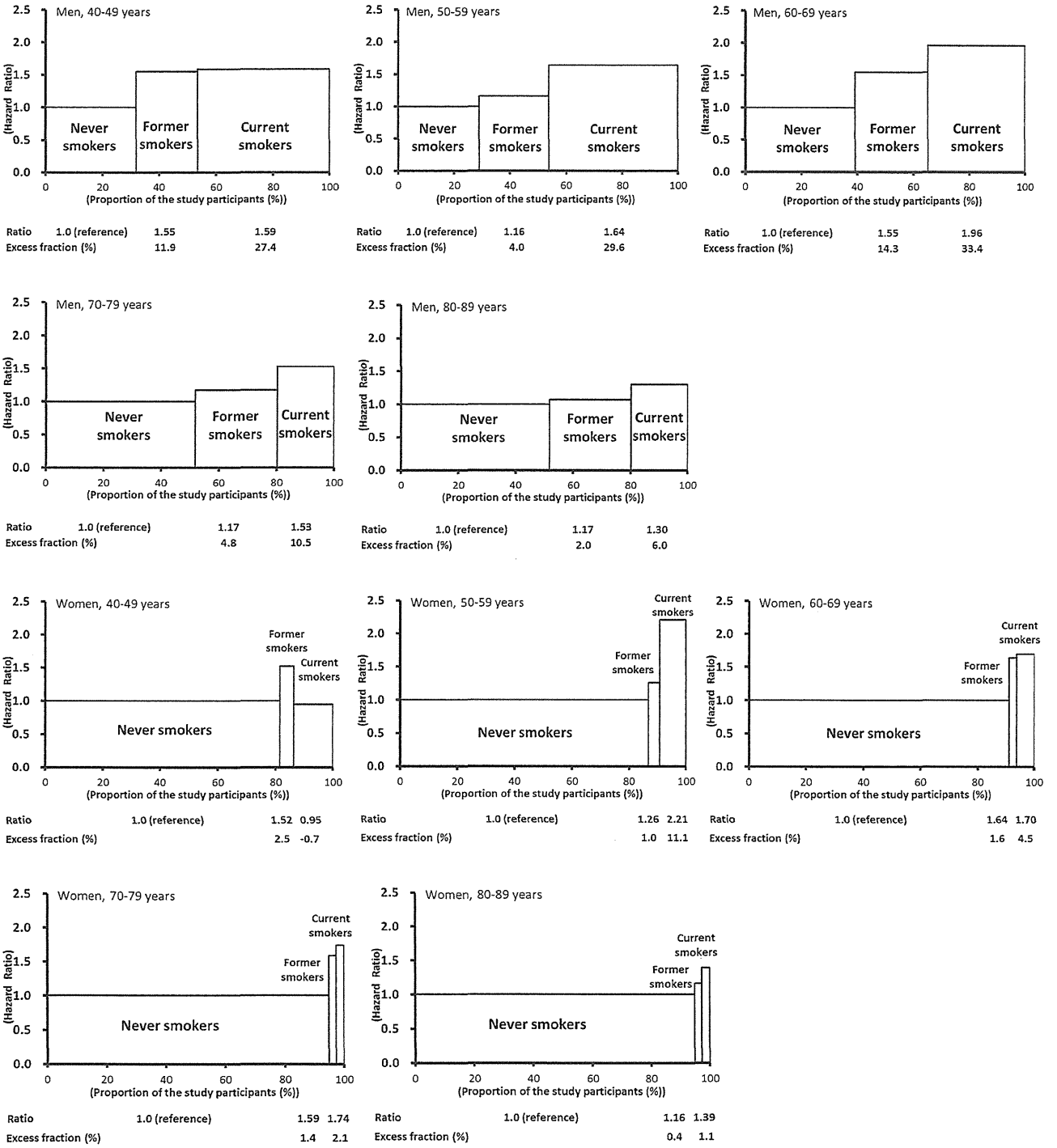


Figure 4. Age- and sex-specific hazard ratios and their population attributable fractions in EPOCH-JAPAN. In each graph, the X-axis represents the proportion of the study population in each smoking status category (never smoker, former smoker, and current smoker). The Y-axis shows the hazard ratios for each category of smoking status. The excess fraction shows the proportion of excess deaths in each smoking status category as compared with the reference group (never smokers).

for Japanese men were much larger than those reported in studies of other Asian countries. The corresponding total number of premature deaths annually due to smoking in Japan, as calculated from our PAFs, was 121 854 (109 998 men; 11 856 women).

Cardiovascular disease mortality and its established risk factors

Blood pressure[6]

The risk of CVD according to BP category and age group has not been thoroughly investigated in an Asian population.

To investigate the risk of CVD mortality according to BP category and age group, we examined individual data from 10 cohorts, including 67 309 individuals aged 40 to 89 years who had not received a diagnosis of CVD at baseline. We observed an elevated risk of CVD in very old participants (age, 75–89 years) with a systolic/diastolic blood pressure (SBP/DBP) of 130/85 mm Hg or higher and a significant increase among members of other age groups (65–74 years and 75–89 years) with an SBP/DBP of 120/80 mm Hg or higher. The PAFs for CVD mortality ranged from 23.4% to 60.3% among very old and middle-aged participants, respectively, with an SBP/DBP lower than 120/80 mm Hg. These PAFs suggest that maintaining a low BP is an important strategy for primary CVD prevention, even in elderly populations.

Smoking[7]

To inform effective smoking prevention strategies that safeguard the nation's health, large-scale analyses using pooled data are needed in order to provide reliable information on the adverse effects of smoking and its impact on mortality, particularly among individuals with hypertension or high serum cholesterol. In our multivariate model, adjusted hazard ratios in male and female current smokers with hypertension were 2.57 (95% CI: 1.51–4.38) and 6.14 (95% CI: 3.49–10.79) for coronary heart disease, respectively, and 3.28 (95% CI: 1.89–5.71) and 1.61 (95% CI: 0.81–3.18) for cerebral infarction, as compared with participants with neither risk factor. The percentages of deaths attributable to coexistence of current smoking and hypertension in men and women were 24.6% and 9.6%, respectively, for coronary heart disease and 28.1% and 2.0% for cerebral infarction. Smokers with high serum cholesterol were broadly comparable to hypertensive smokers only with respect to coronary mortality risk: the hazard ratios were 4.19 (95% CI: 2.33–7.53) for men and 3.90 (95% CI: 1.57–9.67) for women when compared with participants with neither risk factor. Particular attention should be given to smokers with hypertension or high serum cholesterol, due to their high risk of mortality from cardiovascular disease.

Total cholesterol[8]

We examined a total of 65 594 participants aged 40 to 89 years without a history of cardiovascular disease, which we divided into 2 age groups: middle-aged (40–69 years; mean age, 55 years) and elderly (70–89 years; mean age, 75 years). In our multivariate model, the adjusted hazard ratios for coronary heart disease among men in the highest total cholesterol (TC) category (≥6.21 mmol/L) as compared with the lowest category (<4.14 mmol/L) were 2.52 (95% CI: 1.15–5.07) for middle-aged participants and 2.77 (95% CI: 1.09–7.03) for elderly participants. In women, the hazard ratios for the highest TC category (≥6.72 mmol/L) as compared with the lowest category (<4.66 mmol/L) were 3.20 (95% CI: 1.44–7.09) for middle-aged participants and 1.02 (95% CI: 0.42–2.49) for elderly participants. Although high serum TC levels were associated with coronary heart disease in middle-aged Japanese men and women, evidence of an association in elderly Japanese individuals remains limited.

Proteinuria and reduced kidney function[9]

Few studies have examined whether proteinuria and estimated glomerular filtration rate (eGFR) are independently associated with cardiovascular disease in an Asian population. Using data from 7 prospective cohorts in EPOCH-JAPAN, we investigated the influence of proteinuria (≥1+ on dipstick) and reduced eGFR on the risk of cardiovascular disease mortality in 39 405 participants (40–89 years) without kidney failure. Proteinuria was associated with 1.75-fold (95% CI: 1.44–2.11) increased risk of cardiovascular disease mortality, after adjustment for potential confounding factors. Additionally, in our multivariate model, we found a negative linear association between cardiovascular disease mortality and low eGFR ($P_{trend} < 0.001$). The hazard ratio for subjects with an eGFR of less than 45 mL/minute/1.73 m^2 was 2.22 (95% CI: 1.60–3.07), when compared with those with an eGFR of 90 mL/minute/1.73 m^2 or greater. The hazard ratio for participants with both proteinuria and an eGFR of less than 45 mL/minute/1.73 m^2 was 4.05 (95% CI: 2.55–6.43) when compared with subjects with neither of these risk factors. These results suggest that proteinuria and a low eGFR are independent risk factors for cardiovascular disease mortality in the Japanese population.

DISCUSSION AND FUTURE DIRECTIONS

We have described our data-pooling project for cardiovascular epidemiology in Japan, EPOCH-JAPAN, and have presented some of the results it has generated to date. This project is ongoing and is being constantly updated and expanded by recruiting other cohort studies. The study collaborators are constantly encouraged to conduct new analyses, and, in particular, to undertake interaction analyses[10,11] and evaluations of absolute risk.[4] In these analyses, we tested for interaction, or the effect when 2 risk factors co-occur, using a likelihood ratio test to compare goodness-of-fit of the main model against that of the alternative model including the interaction terms. In most cases, this type of interaction analysis requires a large sample size because the inclusion of interaction terms increases the number of model parameters. This approach is only possible when a large database of participants is available. The most significant advantage of this approach for interaction analyses is that it allows us to draw comprehensive conclusions regarding the presence of interaction effects.[10,11]

When we classified our study population according to level of exposure, the number of cases in the exposed group would often be too small to yield reliable estimates of disease risk. For example, because of the difficulty in recruiting a sufficient sample of people with a rare cardiovascular risk factor such as isolated systolic hypertension, its impact on mortality could not be investigated using a single-site cohort study. While

there had previously been much uncertainty regarding the association between isolated diastolic hypertension and cardiovascular disease, an IPD meta-analysis from the Asia-Pacific region produced new insights by examining this issue using large datasets.[12] While small exposure groups and low numbers of cases have been limiting factors in a number of epidemiologic studies, particularly those of rare diseases, we have shown that IPD meta-analyses can provide an effective approach for studying a range of epidemiologic topics.

Nearly a decade has passed since we initiated this IPD meta-analysis project. During this period, several of its research outputs have been used to provide important evidence for drafting clinical guidelines and informing government health policy in Japan. As rapid economic growth in Asia accelerates lifestyle changes in many populations, the burden of chronic disease is likely to increase in a number of countries during the next decade. Over the coming years, we believe that our research will continue to provide further insights that can be applied to research on other Asian populations as they undergo epidemiologic transition.

ONLINE ONLY MATERIALS

Abstract in Japanese.

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