Foundation Kidney Disease Outcomes Quality Initiative guidelines [17].

Endpoint definition

Cardiovascular disease was defined as first-ever development of stroke or coronary heart disease. In principle, stroke was defined as an acute onset of nonconvulsive and focal neurological deficit lasting more than 24 h. The clinical diagnosis of stroke was determined on the basis of a detailed history, neurological examination, and ancillary laboratory examinations, including computed tomography and magnetic resonance image. Stroke was classified as either ischaemic or haemorrhagic (intracerebral or subarachnoid haemorrhage).

The criteria for a diagnosis of coronary heart disease included acute myocardial infarction, silent myocardial infarction, sudden cardiac death within 1 h after the onset of acute illness, and coronary artery disease followed by coronary intervention or bypass surgery. Acute myocardial infarction was diagnosed when a participant met at least two of the following criteria: typical symptoms, including prolonged severe anterior chest pain; abnormal cardiac enzymes more than twice the upper limit of the normal range; evolving diagnostic ECG changes; and morphological changes, including local asynergy of cardiac wall motion on echocardiography, persistent perfusion defect on cardiac scintigraphy, or myocardial necrosis or scars greater than 1 cm long accompanied by coronary atherosclerosis at autopsy. Silent myocardial infarction was defined as myocardial scarring without any historical indication of clinical symptoms or abnormal cardiac enzyme changes. Clinical diagnoses were corrected by autopsy findings when necessary.

Statistical analysis

The age and sex-adjusted mean values of risk factors were calculated and tested by the analysis of covariance. Frequencies of risk factors were adjusted for age and sex by the direct method and were compared using the logistic regression analysis. The age and sex-adjusted cumulative incidence of CVD was estimated, and the differences among BP categories were tested using the Cox proportional hazards model. The incidence rate was calculated by the person-year method and adjusted for age and sex by the direct method. Differences in age and sex-adjusted incidences among BP levels were tested by the Cox proportional hazards model. The adjusted hazard ratio and its 95% confidence interval (CI) were also calculated using the Cox proportional hazards model. The heterogeneity in the relationship between subgroups was estimated by adding an interaction term to the Cox model. The PAF of each BP category was calculated using the following equation with the observed multivariate-adjusted hazard ratio of each category and its frequency in event cases (Pe) [18].

$$PAF = Pe(HR - 1)/HR$$

The CI of the PAF was estimated by the method proposed by Greenland [19]. All statistical analyses were performed with the SAS program package version 9.2 (SAS Institute Inc., Cary, North Carolina, USA). P values of less than 0.05 were considered statistically significant.

Ethical considerations

The study protocol was approved by Kyushu University Institutional Review Board for Clinical Research, and the procedures followed were in accordance with national guidelines. The participants provided written informed consent.

RESULTS

The frequencies of normal BP, prehypertension, stage 1 hypertension, and stage 2 hypertension were 24.9, 37.7, 23.8, and 13.6%, respectively. The age and sex-adjusted mean values or frequencies of cardiovascular risk factors are listed according to BP categories in Table 1. Individuals with higher BP levels were older and more likely to be men. The mean values of body mass index and total cholesterol, and frequencies of diabetes, chronic kidney disease, ECG abnormalities, and alcohol intake increased with elevating BP levels, whereas the mean value of HDL cholesterol and frequency of smoking habits decreased. Such trends were not observed for regular exercise.

During the 19-year follow-up, 449 individuals developed CVD events (229 men and 220 women). These CVD cases had 305 first-ever stroke (213 ischaemic and 92 haemorrhagic strokes), and 187 first-ever coronary events. Figure 1 shows the age and sex-adjusted cumulative incidence curves of CVD according to BP categories. The incidence of CVD significantly increased with elevating BP categories; compared with normal BP, the incidence of CVD became significantly higher from the 6th year in lower range of prehypertension, the 6th year in higher range of prehypertension, the 4th year in stage 1 hypertension, and the 5th year in stage 2 hypertension. Table 2 shows the age and sex-adjusted incidence of CVD and its subtypes according to BP categories. The age and sex-adjusted incidence of CVD rose progressively with elevation of BP levels: normal BP 7.5 per 1000 person-years, lower range of prehypertension 12.6, higher range of prehypertension 12.1, stage 1 hypertension 13.7, and stage 2 hypertension 24.6. The incidence rates were significantly higher from the lower range of prehypertension compared to normal BP. Similar associations were observed in both sexes ($P = 0.62$ for heterogeneity). The age and sex-adjusted incidence of stroke increased continuously with elevating BP levels, and the difference in the incidence between normal BP and lower range of prehypertension was significant. A similar tendency was observed for both ischaemic and haemorrhagic strokes. The association between BP levels and the incidence of coronary heart disease was somewhat weak, and the incidence was significantly elevated only in stage 2 hypertension. The associations of BP categories with the risks of CVD, stroke, and coronary heart disease were substantially unchanged even after adjusting for potential confounding factors such as age, sex, body mass index, total and HDL cholesterol, diabetes, chronic kidney disease, ECG abnormalities, smoking, drinking, and regular exercise (Table 3). There was a continuous relationship of BP levels with total CVD, and a significant increase was observed from the

TABLE 1. Age and sex-adjusted mean values or prevalence of risk factors according to blood pressure categories at baseline

Variable	Blood pressure category					
		Prehypertension				
	Normal BP ($n=657$)	Lower range ($n=545$)	Higher range ($n=447$)	Stage 1 HT ($n=626$)	Stage 2 HT ($n=359$)	*P* for trend
Age (years)	55.1±0.4	56.4±0.5	58.8±0.5	61.8±0.5	66.2±0.6	<0.001
Men (%)	32.4	42.9	45.4	47.8	44.0	<0.001
Systolic blood pressure (mmHg)	110.8±0.3	123.5±0.3	133.8±0.4	145.9±0.3	170.3±0.4	<0.001
Diastolic blood pressure (mmHg)	66.7±0.3	73.7±0.3	78.6±0.4	84.2±0.3	91.9±0.4	<0.001
Antihypertensive medication (%)	3.1	7.5	13.2	23.4	32.6	<0.001
Body mass index (kg/m^2)	21.4±0.1	22.6±0.1	23.4±0.1	23.6±0.1	23.9±0.2	<0.001
Total cholesterol (mmol/l)	5.24±0.04	5.31±0.05	5.49±0.05	5.38±0.04	5.34±0.06	0.02
HDL cholesterol (mmol/l)	1.33±0.01	1.29±0.01	1.30±0.01	1.28±0.01	1.28±0.02	0.009
Diabetes (%)	5.1	12.6	14.7	15.1	19.5	<0.001
Chronic kidney disease (%)	7.0	12.1	11.7	16.2	23.5	<0.001
Electrocardiogram abnormalities (%)	10.6	12.8	15.5	18.6	29.3	<0.001
Current drinking (%)	20.9	30.4	30.4	34.5	39.5	<0.001
Current smoking (%)	29.7	24.4	25.2	21.6	22.7	0.004
Regular exercise (%)	9.2	12.0	9.2	9.7	10.7	0.78

BP, blood pressure; HT, hypertension; HDL, high-density lipoprotein. All values are given as means±SE or as percentages. Neither age nor sex was adjusted for covariates.

lower range of prehypertension (hazard ratio 1.58, 95% CI 1.11–2.26). When lower and higher ranges of prehypertension were combined, multivariate-adjusted hazard ratio of total prehypertension (120–139/80–89 mmHg) for the development of CVD was 1.64 (95% CI 1.18–2.26). Similar findings were obtained after excluding those taking antihypertensive agents at baseline from the study participants (Table 4).

As shown in Table 3, the PAFs of prehypertension, stage 1 hypertension, and stage 2 hypertension for development of CVD were 13.2, 13.6, and 16.5%, respectively. Approximately one-third of excess cardiovascular events attributable to elevated BP occurred among participants with prehypertension. PAFs for stroke incidence (16.1, 17.8, and 17.8 for prehypertension, stage 1 hypertension, and stage 2 hypertension, respectively) were larger than those for coronary heart disease (5.8, 8.0, and 12.6%).

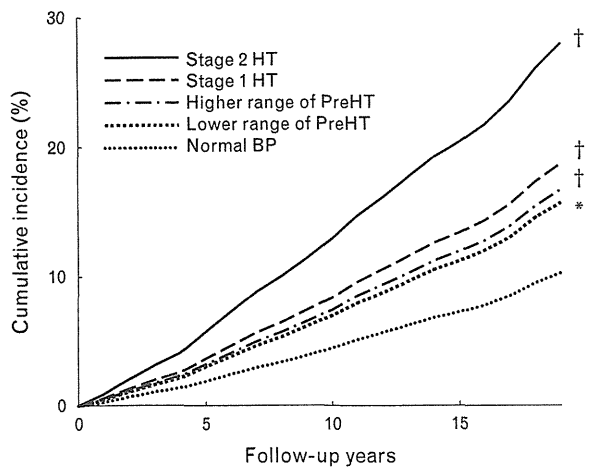


FIGURE 1 Age and sex-adjusted cumulative incidence of cardiovascular disease according to blood pressure categories. Cardiovascular disease was defined as stroke or coronary heart disease. BP, blood pressure; HT, hypertension. *$P<0.05$, †$P<0.01$ vs. normal BP.

Figure 2 shows the association of BP categories with the risk of CVD between two groups defined by the number of other cardiovascular risk factors (diabetes, hypercholesterolaemia, smoking, and chronic kidney disease). The multivariate-adjusted hazard ratio of CVD continuously increased with BP levels both among participants with 0–1 risk factor and those with 2–4 risk factors. However, stronger associations of prehypertension and hypertension with CVD were observed for participants with 2–4 risk factors compared to those with 0–1 risk factor ($P=0.04$ for heterogeneity).

DISCUSSION

In a long-term prospective study of a general Japanese population, we demonstrated that higher BP levels were associated with increased risks of CVD, and significantly higher incidence of CVD was observed from the lower range of prehypertension compared to normal BP. This association remained unchanged even after adjustment for other cardiovascular risk factors such as age, sex, body mass index, total and HDL cholesterol, diabetes, ECG abnormalities, chronic kidney disease, smoking, drinking, and regular exercise. Because the prevalence rate of prehypertension was high, about one-third of the burden of CVD attributable to elevated BP was likely to occur from prehypertension. Furthermore, the effects of BP on the risks of CVD were stronger among 'high-risk' participants with multiple cardiovascular risk factors than among participants with 0–1 risk factor.

A number of large-scale cohort studies have demonstrated that prehypertension, particularly higher-range prehypertension, was associated with increased risks of CVD and death [4,20,21]. However, these studies were mainly conducted in Western populations, and it has been unclear to what extent these findings apply to Japanese populations. The Ohsaki study did not show significant effects of prehypertension on cardiovascular or total deaths in a general Japanese population [7]. The Evidence for

TABLE 2. Age and sex-adjusted incidence of cardiovascular disease according to blood pressure categories, 1988–2007

Endpoint	Blood pressure category					
		Prehypertension				
	Normal BP ($n=657$)	Lower range ($n=545$)	Higher range ($n=447$)	Stage 1 HT ($n=626$)	Stage 2 HT ($n=359$)	*P* for trend
Cardiovascular disease						
Total: no. of events/person-years	53/11148	76/8954	77/7142	127/9075	116/4440	
Age and sex-adjusted incidence	7.5	12.6*	12.1†	13.7‡	24.6‡	<0.001
Male: no. of events/person-years	24/3385	37/3747	47/3074	65/4108	56/1867	
Age-adjusted incidence	9.5	15.8	16.7†	17.8†	32.6‡	<0.001
Female: no. of events/person-years	29/7763	39/5207	30/4068	62/4968	60/2573	
Age-adjusted incidence	6.1	10.4*	8.5	10.9†	19.5‡	<0.001
Stroke						
No. of events/person-years	31/11238	50/9048	53/7262	92/9183	79/4535	
Age and sex-adjusted incidence	4.1	8.2*	8.5†	9.9‡	16.8‡	<0.001
Ischaemic stroke						
No. of events/person-years	25/11238	36/9048	39/7262	66/9183	47/4535	
Age and sex-adjusted incidence	3.4	6.3	6.5*	6.9†	9.4†	<0.001
Haemorrhagic stroke						
No. of events/person-years	6/11238	14/9048	14/7262	26/9183	32/4535	
Age and sex-adjusted incidence	0.7	1.8*	2.0*	2.9†	7.4‡	<0.001
Coronary heart disease						
No. of events/person-years	26/11267	32/9225	29/7381	52/9596	48/4754	
Age and sex-adjusted incidence	3.7	5.1	4.0	5.2	8.7†	0.002

Cardiovascular disease was defined as stroke or coronary heart disease.
BP, blood pressure; HT, hypertension. Incidence, per 1000 person-years.
*$P<0.05$.
†$P<0.01$.
‡$P<0.001$ vs. normal BP.

Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN) has reported a significant increase in all-cause mortality associated with prehypertension only among participants aged 50–69 [22]. The Jichi Medical School Cohort Study has shown a clear association between the higher range of prehypertension and incident CVD, but not for lower range of prehypertension [23]. In contrast, the Japan Atherosclerosis Longitudinal Study (JALS) and the

TABLE 3. Age and sex-adjusted and multivariate-adjusted hazard ratios and population-attributable fractions for cardiovascular disease according to blood pressure categories, 1988–2007

Endpoint	Blood pressure category					
		Prehypertension				
	Normal BP ($n=657$)	Lower range ($n=545$)	Higher range ($n=447$)	Stage 1 HT ($n=626$)	Stage 2 HT ($n=359$)	*P* for trend
Cardiovascular disease						
Age and sex-adjusted HR	1.00	1.58 (1.11–2.25)	1.69 (1.19–2.40)	1.92 (1.39–2.65)	3.04 (2.17–4.25)	<0.001
Multivariate-adjusted HR	1.00	1.58 (1.11–2.26)	1.70 (1.18–2.44)	1.93 (1.37–2.72)	2.78 (1.93–4.01)	<0.001
PAF (%)		6.2 (1.3–10.9)	7.0 (2.1–11.7)	13.6 (6.9–19.8)	16.5 (11.0–21.7)	
Stroke						
Age and sex-adjusted HR	1.00	1.80 (1.15–2.81)	2.05 (1.31–3.19)	2.44 (1.62–3.69)	3.54 (2.31–5.44)	<0.001
Multivariate-adjusted HR	1.00	1.79 (1.14–2.82)	2.05 (1.30–3.24)	2.44 (1.59–3.75)	3.21 (2.03–5.08)	<0.001
PAF (%)		7.2 (1.5–12.6)	8.9 (3.2–14.3)	17.8 (10.0–24.9)	17.8 (11.3–23.9)	
Ischaemic stroke						
Age and sex-adjusted HR	1.00	1.57 (0.94–2.61)	1.76 (1.06–2.92)	1.99 (1.25–3.17)	2.27 (1.37–3.75)	<0.001
Multivariate-adjusted HR	1.00	1.48 (0.88–2.49)	1.63 (0.97–2.73)	1.80 (1.10–2.94)	1.77 (1.02–3.05)	0.03
PAF (%)		5.5 (−1.9 to 12.3)	7.0 (−0.6 to 14.1)	13.8 (2.8–23.5)	9.6 (0.7–17.7)	
Haemorrhagic stroke						
Age and sex-adjusted HR	1.00	2.74 (1.05–7.15)	3.18 (1.22–8.31)	4.38 (1.79–10.74)	10.06 (4.13–24.53)	<0.001
Multivariate-adjusted HR	1.00	2.96 (1.13–7.74)	3.76 (1.42–9.98)	5.26 (2.10–13.18)	11.97 (4.73–30.32)	<0.001
PAF (%)		10.1 (0.8–18.4)	11.2 (2.4–19.1)	22.9 (11.3–32.9)	31.9 (20.6–41.6)	
Coronary heart disease						
Age and sex-adjusted HR	1.00	1.27 (0.76–2.14)	1.17 (0.69–1.99)	1.42 (0.88–2.29)	2.28 (1.40–3.72)	0.002
Multivariate-adjusted HR	1.00	1.23 (0.72–2.10)	1.11 (0.64–1.94)	1.35 (0.81–2.25)	1.97 (1.14–3.41)	0.02
PAF (%)		3.2 (−6.5 to 8.9)	1.6 (−8.8 to 7.5)	7.2 (−5.3 to 18.1)	12.6 (2.8–21.5)	

Cardiovascular disease was defined as stroke or coronary heart disease.
BP, blood pressure; HT, hypertension; HR, hazard ratio; PAF, population-attributable fraction.
Multivariate analyses were adjusted for age, sex, body mass index, total cholesterol, high-density lipoprotein cholesterol, diabetes, chronic kidney disease, electrocardiogram abnormalities, smoking, drinking, and regular exercise.

TABLE 4. Age and sex-adjusted and multivariate-adjusted hazard ratios and population-attributable fractions for cardiovascular disease according to blood pressure categories in participants without antihypertensive medication, 1988–2007

	Blood pressure category					
		Prehypertension				
Endpoint	Normal BP ($n=642$)	Lower range ($n=510$)	Higher range ($n=388$)	Stage 1 HT ($n=474$)	Stage 2 HT ($n=227$)	*P* for trend
Cardiovascular disease						
No. of events	47	67	64	92	70	
Age and sex-adjusted HR	1.00	1.67 (1.15–2.42)	1.83 (1.26–2.67)	2.03 (1.42–2.89)	3.41 (2.33–4.98)	<0.001
Multivariate-adjusted HR	1.00	1.72 (1.17–2.51)	1.85 (1.25–2.74)	2.06 (1.42–3.01)	3.31 (2.19–4.99)	<0.001
PAF (%)		8.2 (2.3–13.8)	8.7 (3.0–14.0)	13.9 (6.9–20.4)	14.4 (9.2–19.3)	
Stroke						
No. of events	29	44	42	65	50	
Age and sex-adjusted HR	1.00	1.78 (1.16–2.85)	1.99 (1.24–3.20)	2.38 (1.53–3.71)	4.02 (2.51–6.43)	<0.001
Multivariate-adjusted HR	1.00	1.81 (1.13–2.91)	2.00 (1.22–3.25)	2.41 (1.52–3.83)	3.82 (2.31–6.32)	<0.001
PAF (%)		8.6 (1.5–15.1)	9.1 (2.4–15.3)	16.5 (8.1–24.2)	16.0 (9.7–22.0)	
Ischaemic stroke						
No. of events	23	31	32	47	25	
Age and sex-adjusted HR	1.00	1.56 (0.91–2.68)	1.83 (1.07–3.14)	2.01 (1.21–3.34)	2.23 (1.25–4.00)	0.003
Multivariate-adjusted HR	1.00	1.54 (0.89–2.65)	1.69 (0.97–2.95)	1.84 (1.07–3.14)	1.84 (0.98–3.45)	0.04
PAF (%)		6.8 (–2.3 to 15.1)	8.3 (–0.8 to 16.5)	13.5 (1.8–23.9)	7.2 (–0.5 to 14.4)	
Haemorrhagic stroke						
No. of events	6	13	10	18	25	
Age and sex-adjusted HR	1.00	2.63 (1.00–6.94)	2.51 (0.91–6.93)	3.75 (1.48–9.55)	12.37 (4.99–30.66)	<0.001
Multivariate-adjusted HR	1.00	2.83 (1.07–7.51)	3.00 (1.07–8.45)	4.60 (1.76–11.99)	15.28 (5.88–39.74)	<0.001
PAF (%)		11.7 (0.3–21.8)	9.3 (–0.4 to 17.9)	19.6 (7.1–30.3)	32.4 (19.9–43.1)	
Coronary heart disease						
No. of events	22	27	27	37	25	
Age and sex-adjusted HR	1.00	1.34 (0.76–2.35)	1.51 (0.86–2.65)	1.55 (0.91–2.63)	2.34 (1.31–4.20)	0.008
Multivariate-adjusted HR	1.00	1.38 (0.77–2.46)	1.46 (0.80–2.65)	1.47 (0.83–2.62)	2.25 (1.19–4.28)	0.03
PAF (%)		5.3 (–4.8 to 14.5)	6.1 (–4.0 to 15.3)	8.6 (–4.4 to 20.0)	10.1 (1.7–17.7)	

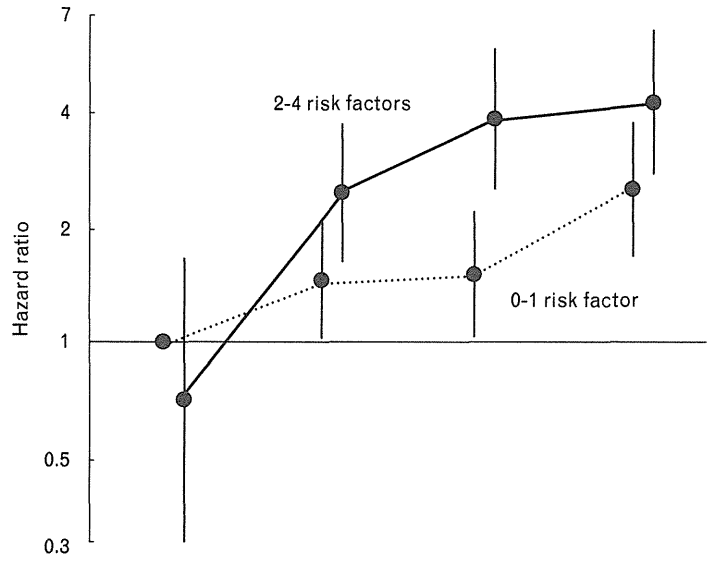
Cardiovascular disease was defined as stroke or coronary heart disease.
BP, blood pressure; HT, hypertension; HR, hazard ratio; PAF, population-attributable fraction.
Multivariate analyses are adjusted for age, sex, body mass index, total cholesterol, high-density lipoprotein cholesterol, diabetes, chronic kidney disease, electrocardiogram abnormalities, smoking, drinking, and regular exercise.

Japan Public Health Center-based Prospective (JPHC) Study have demonstrated clear associations between BP and stroke incidence, with significant increase from the lower range of prehypertension [6,24]. The Suita Study has also reported that both higher and lower ranges of prehypertension were associated with increased risks of stroke and total CVD among Japanese men [25]. The present analysis from the Hisayama Study confirmed the hypothesis generated from previous cohort studies that prehypertension is not innocent even in the lower range of 120–129/80–84 mmHg, and that this level of BP definitely promotes systemic arteriosclerosis, resulting in incident stroke, coronary heart disease, and other manifestations of cardiovascular events. These findings could also be supported by our previous findings that prehypertension increased the risk of renal arteriosclerosis and arteriolar hyalinosis in an autopsy series of Hisayama residents [26].

In the present study, the highest risks of CVD were observed among patients with stage 1 and 2 hypertension. The third highest risk was among patients with higher range of prehypertension, and the fourth highest among those with lower range of prehypertension. These findings are directly in line with the results of large-scale cohort studies [6,24,25]. They confirm that the risks of CVD is slightly higher among patients with higher range of prehypertension than among those with lower range of prehypertension and support the European and Japanese guidelines for management of hypertension [27,28] which distinguish these two groups as high-normal and normal BP.

In the present analysis, the prevalence of prehypertension was as high as 38% of the total population. As a result, the PAF of prehypertension for development of CVD was similar to those of stage 1 and 2 hypertension. This finding is compatible with the results of several other cohort studies [6,25]. These results suggest that approximately one-third of the burden of excess CVD attributable to elevated BP levels comes from prehypertension. Therefore, in order to reduce the enormous burden of CVD, a high-risk strategy to treat patients with hypertension should be complemented with population strategies to lower BP levels which include lifestyle modifications such as weight loss in the overweight, physical activity, moderation of alcohol intake, a diet with increased fresh fruit and vegetables and reduced saturated fat content, reduction of dietary sodium intake, and increased dietary potassium intake [1,27,28].

Another important finding from the present analysis of the Hisayama Study is that the effects of prehypertension on the risks of CVD were larger among 'high-risk' participants with multiple cardiovascular risk factors than among 'lower-risk' participants with only a few risk factors. Furthermore, the risk of CVD among these 'high-risk' participants with prehypertension was equivalent to that among participants with stage 2 hypertension who have only a few risk factors. Therefore, a pharmaceutical



N of events/person-years				
0-1 risk factor	47/9785	107/13 142	81/7315	66/3122
2-4 risk factors	6/1363	46/2954	46/1760	50/1300

FIGURE 2 Multivariate-adjusted hazard ratios for cardiovascular disease according to blood pressure categories and the number of risk factors. Risk factors included diabetes, hypercholesterolaemia, smoking, and chronic kidney disease. Cardiovascular disease was defined as stroke or coronary heart disease. BP, blood pressure; HT, hypertension. Hazard ratios were adjusted for age, sex, body mass index, high-density lipoprotein cholesterol, electrocardiogram abnormalities, drinking, and regular exercise. $P = 0.04$ for heterogeneity in the effects of blood pressure categories between participants groups defined by the number of risk factors.

treatment to lower BP may be necessary for participants with prehypertension who are at high risk of CVD as well as for hypertensive patients. In fact, several randomized controlled trials of BP-lowering have demonstrated that patients with high cardiovascular risk benefit from BP-lowering treatment regardless of whether they were hypertensive or not [29–32]. These findings support the concept of treating patients with high cardiovascular risk who have BP levels of prehypertension, which is recommended by current national and international guidelines [27,28].

The strengths of our study include its longitudinal population-based study design, no true loss to follow-up for a long period, sufficient number of cardiovascular events, and accuracy for diagnosis of CVD subtypes. In contrast, the present study was limited by the fact that BP was only measured at baseline and that BP during the follow-up period was not considered for the analysis. However, this limitation is not likely to invalidate the findings observed in the present study, because a random misclassification of this nature would tend to cause an underestimation of the true relationship. The participants of the present analysis were leaner compared to more westernized populations that exist today. Further studies are required to determine whether the findings obtained from the present study are applicable to more westernized populations.

In conclusion the present study confirmed the strong and continuous associations between BP levels and the incidence of CVD in a general Japanese population. The lowest incidence of CVD was observed among individuals with normal BP, and even a slight increase in BP (e.g. lower range of prehypertension) was associated with significantly higher risks of CVD. Approximately one-third of excess CVD events attributable to elevated BP were likely to occur among individuals without hypertension. These results support the current guidelines for management of hypertension which recommend lifestyle modification with/without BP-lowering agents for moderate to high-risk patients with prehypertension as well as hypertensive patients [1,27,28].

ACKNOWLEDGEMENTS

This study was supported in part by Grants-in-Aid for Scientific Research C (20591063, 21590698 and 22590892) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and a Health and Labour Sciences Research Grant (Comprehensive Research on Aging and Health: H20-Chouju-004) from the Ministry of Health, Labour and Welfare of Japan.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Insulin Resistance and the Development of Cardiovascular Disease in a Japanese Community: the Hisayama Study

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Aims: Although several surrogate measures of insulin resistance have been proposed, their associations with cardiovascular disease (CVD) have not been evaluated sufficiently.
Methods: A total of 2,356 community-dwelling Japanese individuals aged 40 to 79 years who underwent a 75 g oral glucose tolerance test were followed up for 14 years. The status of insulin resistance was estimated by using the Matsuda index or homeostasis model assessment of insulin resistance (HOMA-IR).
Results: During follow-up, 260 subjects developed CVD. The age- and sex-adjusted hazard ratios of CVD significantly decreased with an increasing Matsuda index and rose with increasing HOMA-IR levels (both p for trend <0.05). After adjustment for age, sex, serum total cholesterol, electrocardiogram abnormalities, proteinuria, smoking habits, alcohol intake, and regular exercise, the risk of CVD was significantly lower in the third to fifth quintiles of the Matsuda index and higher in the fifth quintile of HOMA-IR values compared with the first quintile of the corresponding index (Matsuda index Q3: hazard ratio (HR)=0.59 [95% confidence interval 0.40-0.87]; Q4: HR=0.66 [0.45-0.97]; and Q5: HR=0.67 [0.47-0.97]; HOMA-IR Q5: HR=1.55 [1.05-2.29]); however, these associations were attenuated after further adjustment for the metabolic syndrome status. In regard to CVD subtypes, the risks for stroke and coronary heart disease significantly decreased with an increasing Matsuda index, while elevated HOMA-IR levels were a significant risk factor for stroke, but not for coronary heart disease.
Conclusion: Our findings suggest that insulin resistance significantly increases the risk of incident CVD through metabolic syndrome in Japanese.

J Atheroscler Thromb, 2012; 19:977-985.

Key words; Epidemiology, Cardiovascular disease, Insulin resistance, Cohort study, General populations

Introduction

Insulin resistance and compensatory hyperinsulinemia are closely related to obesity and are considered to be the underlying features of elevated blood pressure[1,2] and metabolic disorder, including impaired glucose tolerance[3,4] and dyslipidemia[5,6], which are collectively identified as metabolic syndrome (MetS)[7]. Prospective population-based studies have shown that subjects with MetS had a significantly higher risk of incident cardiovascular disease (CVD)[8-10], but the association between CVD and insulin resistance itself is less clear. Several surrogate indices have been proposed to evaluate insulin resistance[11-13], because the glucose clamp method, the gold standard for the measurement of insulin resistance, is impractical for use in clinical and epidemiological studies. Homeostasis model assessment of insulin resistance (HOMA-IR), derived from fasting glucose and insulin values, has a strong correlation with insulin sensitivity directly measured by the euglycemic hyperinsulinemic clamp

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Received: March 4, 2012
Accepted for publication: May 10, 2012

method[11, 14] and has been commonly used as a surrogate index of insulin resistance; however, it is uncertain whether insulin resistance estimated by HOMA-IR values is significantly associated with incident CVD[15-22]. Matsuda *et al.* proposed an index of insulin sensitivity calculated by measuring glucose and insulin levels before and after oral glucose loading[12, 13]. Although the Matsuda index also correlates well with directly measured insulin resistance[12, 23], to our knowledge, no prior prospective study has evaluated the association between the Matsuda index and incident CVD.

The purpose of this study was to investigate the associations of the Matsuda index and HOMA-IR levels with the development of CVD in a cohort study of a Japanese population, taking into account various comprehensive risk factors, including the MetS status.

Methods

Study Population

The Hisayama Study is a long-term prospective population-based cohort survey of CVD and its risk factors. It was begun in 1961 in Hisayama, a town of approximately 8,000 people located in a suburb of the Fukuoka metropolitan area on Kyushu Island, Japan[24]. In 1988, a screening survey for the present study was performed in the town. A detailed description of this study has been published previously[25]. In brief, 2,587 residents aged 40 to 79 years (80.2% of the total population of this age range) consented to participate in the examination. After exclusion of 82 subjects who had already had breakfast, 10 who were receiving insulin therapy for diabetes, and 15 who refused a 75-g oral glucose tolerance test (OGTT) due to complaints of nausea or general fatigue during the ingestion of glucose, 2,480 subjects completed the OGTT. Among these, 2 subjects who had died before the start of follow-up, 60 with a past history of stroke or coronary heart disease, 3 for whom either fasting or 2-hour postload insulin levels were not obtained, and 59 who were taking oral hypoglycemic agents were excluded, and the remaining 2,356 subjects (1,006 men and 1,350 women) were included in this study.

Follow-Up Survey

The baseline subjects were followed up prospectively for 14 years from December 1988 through November 2002 by repeated health examinations. The health status was checked yearly by mail or telephone for subjects who did not undergo a regular examination or who had moved out of town. We also established a daily monitoring system among the study team, local physicians, and members of the town's Health and Welfare Office. Using this system, we gathered information on new events of CVD, including suspected cases. When stroke or coronary heart disease occurred or was suspected, physicians in the study team examined the subject and evaluated his/her detailed clinical information. When a subject died, an autopsy was performed in the Department of Pathology of Kyushu University. During the follow-up period, one subject was lost to follow-up and 393 subjects died, of whom 292 subjects (74.3%) underwent autopsy examination.

Definition of Cardiovascular Events

In the present study, incident CVD was defined as the development of stroke or coronary heart disease. Stroke was defined as the sudden onset of nonconvulsive and focal neurological deficit persisting for >24 hours. The diagnosis of stroke was based on the clinical history, neurological examination, all available clinical data, including brain computed tomography and magnetic resonance imaging, and autopsy findings. Coronary heart disease included acute myocardial infarction, silent myocardial infarction, sudden cardiac death within 1 hour after the onset of acute illness, and coronary artery disease treated by coronary artery angioplasty or bypass grafting. Acute myocardial infarction was diagnosed when a subject met at least 2 of the following criteria: 1) typical symptoms, including prolonged severe anterior chest pain; 2) cardiac enzyme levels more than twice the upper limit of the normal range; 3) evolving diagnostic electrocardiographic changes; and 4) morphological changes, including local asynergy of cardiac wall motion on echocardiography, perfusion defect on cardiac scintigraphy, or myocardial necrosis or scars ≥1 cm long accompanied by coronary atherosclerosis at autopsy. Silent myocardial infarction was defined as myocardial scarring without any historical indication of clinical symptoms and/or abnormal cardiac enzyme changes. During the 14-year follow-up, 260 subjects experienced a first-ever CVD event (139 men and 121 women). Of these, 183 had stroke events (83 men and 100 women) and 98 developed coronary heart disease (68 men and 30 women).

Risk Factors

At the baseline examination, after an overnight fast of at least 12 hours, the OGTT was performed with blood samples taken at 0 and 120 min. Plasma glucose levels were determined by the glucose-oxidase method. Serum insulin levels were determined by a commercial double-antibody solid-phase radioimmu-

noassay (Phadeseph Insulin; Pharmacia Diagnostics AB, Uppsala, Sweden). Insulin sensitivity was evaluated by the Matsuda index, calculated as 10,000 per square root of [fasting glucose (mg/dL) × fasting insulin (μU/mL) × postload glucose (mg/dL) × postload insulin (μU/mL)] according to the previously reported method[13]. Insulin resistance was estimated by HOMA-IR values, calculated as [fasting plasma glucose (mg/dL) × fasting serum insulin (μU/mL)] / 405[11]. Diabetes was defined as fasting plasma glucose concentrations of ≥7.0 mmol/L (126 mg/dL), 2-hour postload glucose concentrations of ≥11.1 mmol/L (200mg/dL), and/or the use of antidiabetic medication. Serum total and high-density lipoprotein (HDL) cholesterols and triglyceride concentrations were determined enzymatically. Freshly voided urine samples were collected at the screening, and proteinuria was defined as a value of 1+ or more using a reagent strip.

Waist circumference was measured by a trained staff member at the umbilical level with the subject standing. Blood pressure was measured 3 times using a standard mercury sphygmomanometer in the sitting position after at least 5 minutes of rest. The mean of the 3 measurements was used in the analysis. Hypertension was defined as blood pressure ≥140/90 mmHg and/or current treatment with antihypertensive agents.

Electrocardiogram (ECG) abnormalities were defined as left ventricular hypertrophy (Minnesota Code, 3-1), ST depression (4-1, 2, 3), and/or atrial fibrillation (8-3).

Information on alcohol consumption, smoking habits, and physical activity during leisure time was obtained by the use of a self-administered questionnaire. We also asked whether subjects were taking antihypertensive agents, oral hypoglycemic agents and/or insulin. Alcohol consumption and smoking status were classified as either current use or not. Subjects engaging in sports at least 3 times per week during their leisure time were defined as a regular exercise group.

Subjects were diagnosed as having MetS if 3 or more of the following components were present at baseline: 1) waist circumference ≥90 cm in men and ≥80 cm in women; 2) fasting triglyceride concentrations ≥150 mg/dL (1.7 mmol/L); 3) HDL cholesterol concentrations <40 mg/dL (1.0 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women; 4) blood pressure ≥130/85 mmHg or use of antihypertensive drugs; and 5) fasting plasma glucose ≥100 mg/dL (5.6 mmol/L) or use of antidiabetic medications[26].

Statistical Analysis

The SAS software package version 9.2 (SAS Institute Inc., Cary, NC) was used to perform all statistical analyses. The Matsuda index, HOMA-IR values, fasting plasma insulin, 2-hour postload insulin, and serum triglyceride levels were transformed into logarithms to improve the skewed distribution. The frequencies of possible risk factors at baseline were adjusted for age and sex by a direct method and compared by logistic regression analysis. The age- and sex-adjusted mean values of risk factors at baseline were estimated and compared by analysis of covariance. To analyze the Matsuda index and HOMA-IR values as categorical variables, these levels were divided into sex-specific quintiles: Matsuda index: men, Q1, 0.88 to 4.03; Q2, 4.04 to 6.21; Q3, 6.22 to 8.77; Q4, 8.78 to 13.73; and Q5, 13.74 to 59.72; women, Q1, 0.47 to 4.06; Q2, 4.07 to 5.74; Q3, 5.75 to 7.82; Q4, 7.83 to 10.99; and Q5, 11.00 to 49.21; HOMA-IR: men, Q1, 0.53 to 0.78; Q2, 0.79 to 1.17; Q3, 1.18 to 1.58; Q4, 1.59 to 2.22; and Q5, 2.23 to 16.79; women, Q1, 0.55 to 0.90; Q2, 0.91 to 1.25; Q3, 1.26 to 1.61; Q4, 1.62 to 2.20; and Q5, 2.21 to 15.24. The incidence rates of CVD were calculated by the person-year method and were adjusted for age and sex by the direct method using 10-year age groupings of the overall study population. The age- and sex-adjusted or multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated with the use of the Cox proportional hazards model. The linear trends of HRs across the Matsuda index and HOMA-IR levels were also tested using the Cox proportional hazards model. $P<0.05$ was considered significant in all analyses.

Ethical Considerations

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

Results

The baseline characteristics of subjects stratified by the presence or absence of incident CVD are shown in **Table 1**. The mean values of age, HOMA-IR, fasting and 2-hour postload glucose, fasting plasma insulin, and systolic and diastolic blood pressures, and the frequencies of men, MetS, diabetes, hypertension, ECG abnormalities, proteinuria, and smoking were higher in subjects who developed CVD than in those who did not. In addition, subjects with incident CVD had lower Matsuda index values and a lower frequency of regular exercise. No differences were observed between subjects with and without

Table 1. Age- and sex-adjusted baseline clinical characteristics of subjects with or without incident cardiovascular disease, 1988

	Incident CVD $n=260$	No incident CVD $n=2,096$	p
Age, years	64 (0.6)	56 (0.2)	<0.001
Men, %	56.3	41.3	<0.001
Fasting plasma glucose, mmol/L	6.0 (0.07)	5.7 (0.03)	<0.001
Two-hour postload glucose, mmol/L	8.1 (0.19)	7.1 (0.07)	<0.001
Fasting plasma insulin, pmol/L	43.6 (41.1-46.3)	40.3 (39.4-41.2)	0.01
Two-hour postload insulin, pmol/L	223.4 (204.1-244.5)	208.9 (202.1-216.0)	0.18
Matsuda index	6.2 (5.7-6.7)	7.0 (6.8-7.3)	0.003
HOMA-IR	1.6 (1.5-1.7)	1.4 (1.38-1.45)	0.002
Diabetes mellitus, %	20.0	9.1	0.001
Waist circumference, cm	82.5 (0.6)	81.3 (0.2)	0.05
Systolic blood pressure, mmHg	141.0 (1.2)	131.9 (0.4)	<0.001
Diastolic blood pressure, mmHg	80.6 (0.7)	77.3 (0.3)	<0.001
Hypertension, %	55.0	36.0	<0.001
Total cholesterol, mmol/L	5.35 (0.07)	5.31 (0.02)	0.57
HDL-cholesterol, mmol/L	1.27 (0.02)	1.30 (0.01)	0.17
Triglycerides, mmol/L	1.25 (1.17-1.33)	1.18 (1.15-1.21)	0.14
Metabolic syndrome, %	49.8	32.6	<0.001
ECG abnormalities, %	23.3	15.5	0.03
Proteinuria, %	8.0	5.2	0.02
Current smoking, %	31.4	24.4	0.02
Current drinking, %	36.9	31.6	0.35
Regular exercise, %	5.3	10.5	0.02

CVD: cardiovascular disease; HOMA-IR: homeostasis model assessment of insulin resistance; HDL: high-density lipoprotein; ECG: electrocardiogram. Values are given as the means (standard error) or as a percentage. Matsuda index, HOMA-IR, fasting plasma insulin, 2-hour postload insulin, and triglycerides are shown as the geometric means and 95% confidence intervals due to the skewed distribution. Hypertension: blood pressures of ≥ 140/90 mmHg and/or current use of antihypertensive medicine. Diabetes: fasting ≥ 7.0 mmol/L, 75 g postload or postprandial glucose levels ≥ 11.1 mmol/L, and/or use of hypoglycemic agents. ECG abnormalities: left ventricular hypertrophy (Minnesota Code 3-1), ST depression (4-1, 2, or 3), and/or atrial fibrillation (8-3).

CVD in the mean values of 2-hour postload insulin, waist circumference, total cholesterol and HDL cholesterols, and triglycerides and the frequency of alcohol intake.

Compared with those within the first quintile of the Matsuda index, the age- and sex-adjusted HR for the development of CVD significantly decreased in subjects in the third to fifth quintiles (model 1 of **Table 2**). As shown in model 2 for the Matsuda index, this association remained unchanged even after adjustment for age, sex, serum total cholesterol, ECG abnormalities, proteinuria, smoking, alcohol intake, and regular exercise (Q3: multivariable-adjusted HR 0.59, 95% CI 0.40 to 0.87, $p=0.008$; Q4: HR 0.66, 95% CI 0.45 to 0.97, $p=0.03$; Q5: HR 0.67, 95% CI 0.47 to 0.97, $p=0.04$). On the other hand, the age- and sex-adjusted HR for CVD was significantly higher in subjects in the fifth quintile of HOMA-IR than in those in the first quintile. This association also remained robust even after adjustment for the aforementioned confounding factors (Q5: HR 1.55, 95% CI 1.05 to 2.29; $p=0.03$). However, these associations between the Matsuda index or HOMA-IR and CVD outcomes were attenuated and became non-significant after further adjustment for the MetS status (model 3). By contrast, MetS was a significant risk factor for CVD events in the model 3 for both indices (for the Matsuda index: HR, 1.53, 95% CI 1.15 to 2.04; $p=0.003$; for HOMA-IR: HR, 1.57, 95% CI 1.19-2.08; $p=0.002$). Similar findings were also observed for a 1 SD increment in the Matsuda index and HOMA-IR values as continuous variables.

In **Table 3**, when CVD was divided into stroke and coronary heart disease, the age- and sex-adjusted incidences and HRs for stroke and coronary heart disease significantly decreased with increasing Matsuda index (p for trend <0.05). By contrast, elevated HOMA-IR levels were a risk factor for stroke, but not

Table 2. Age- and sex-adjusted incidences and adjusted hazard ratios and their 95% confidence intervals of cardiovascular disease according to quintiles of the Matsuda index and HOMA-IR levels, 1988-2002

	Quintile level of insulin resistance					*p* for trend (across categories)	Continuous log scale*	*p* for trend (continuous)
	Q1	Q2	Q3	Q4	Q5			
Matsuda index								
No. of events	73	56	39	43	49			
Population at risk	471	471	473	470	471			
Incidence per 1,000 person-years	13.0	10.6	7.6	8.2	8.9			
Model 1 HR (95% CI)	1.00 (reference)	0.78 (0.55 to 1.10)	0.53 (0.36 to 0.78)	0.60 (0.41 to 0.88)	0.65 (0.45 to 0.93)	0.006	0.75 (0.63 to 0.89)	0.001
Model 2 HR (95% CI)†	1.00 (reference)	0.86 (0.61 to 1.22)	0.59 (0.40 to 0.87)	0.66 (0.45 to 0.97)	0.67 (0.47 to 0.97)	0.01	0.76 (0.64 to 0.91)	0.003
Model 3 HR (95% CI)‡	1.00 (reference)	0.96 (0.67 to 1.37)	0.68 (0.45 to 1.02)	0.82 (0.55 to 1.23)	0.87 (0.58 to 1.31)	0.33	0.86 (0.71 to 1.05)	0.14
HOMA-IR								
No. of events	45	52	48	52	63			
Population at risk	467	479	468	474	468			
Incidence per 1,000 person-years	8.1	9.4	9.6	9.7	11.6			
Model 1 HR (95% CI)	1.00 (reference)	1.14 (0.76 to 1.69)	1.13 (0.76 to 1.70)	1.18 (0.79 to 1.76)	1.63 (1.11 to 2.39)	0.02	1.45 (1.17 to 1.78)	0.02
Model 2 HR (95% CI)†	1.00 (reference)	1.19 (0.80 to 1.78)	1.20 (0.80 to 1.81)	1.28 (0.85 to 1.94)	1.55 (1.05 to 2.29)	0.03	1.41 (1.14 to 1.74)	0.001
Model 3 HR (95% CI)‡	1.00 (reference)	1.15 (0.77 to 1.72)	1.09 (0.72 to 1.65)	1.11 (0.73 to 1.68)	1.19 (0.77 to 1.81)	0.55	1.23 (0.98 to 1.56)	0.08

HR: hazard ratio; CI: confidence interval; HOMA-IR: homeostasis model assessment of insulin resistance.
*HR for 1 standard deviation increase of the log Matsuda index or log HOMA-IR.
Model 1: adjustment was made for age and sex.
Model 2: adjustment was made for age, sex, total cholesterol, electrocardiogram abnormalities, proteinuria, smoking habits, alcohol intake, and regular exercise.
Model 3: adjustment was made for the variables used in Model 2 and metabolic syndrome.

for coronary heart disease.

Discussion

Using data from a 14-year follow-up study of a general Japanese population, we found that surrogate indices of insulin resistance, the Matsuda index and HOMA-IR levels were clearly involved in the development of CVD after adjustment for confounding factors. In regard to CVD subtypes, the Matsuda index was a risk factor for the development of both stroke and coronary heart disease, while HOMA-IR levels were associated only with stroke incidence; however, these associations were attenuated after further adjustment for MetS status.

The strong associations between insulin resistance and cardiovascular risk factors, including metabolic abnormalities, are well known; however, studies on the influence of directly measured insulin sensitivity on the risk of CVD are limited: only a prospective cohort study in Sweden has revealed a significant inverse association between insulin sensitivity measured by an euglycemic insulin clamp and CVD risk[27, 28]. The methods used to directly measure insulin sensitivity are invasive, complex, and generally too expensive for clinical practice. Thus, some surrogate indices have been developed using insulin and/or glucose levels in the fasted state alone or in combination with insulin and glucose levels on the OGTT. Among these, HOMA-IR levels based on fasting measurements have been most commonly used as a surrogate marker of insulin resistance in epidemiological studies, but findings on the association between HOMA-IR and incident CVD have been inconsistent[15-22]. On the other hand, the Matsuda index derived from OGTT samples has been reported to show the strongest correla-

Table 3. Age- and sex-adjusted incidences and hazard ratios and their 95% confidence intervals of stroke and coronary heart disease according to quintiles of the Matsuda index and HOMA-IR levels, 1988-2002

	Quintile level of insulin resistance					*p* for trend (across categories)	Continuous log scale*	*p* for trend (continuous)
	Q1	Q2	Q3	Q4	Q5			
Stroke								
Matsuda index								
No. of events	55	33	29	31	35			
Incidence per 1,000 person-years	9.8	6.2	5.7	5.7	6.1			
Age- and sex-adjusted HR (95% CI)	1.00 (reference)	0.62 (0.40 to 0.95)	0.53 (0.34 to 0.84)	0.59 (0.38 to 0.91)	0.63 (0.41 to 0.96)	0.03	0.76 (0.61 to 0.94)	0.01
HOMA-IR								
No. of events	33	34	33	36	47			
Incidence per 1,000 person-years	5.9	5.9	6.4	6.6	8.6			
Age- and sex-adjusted HR (95% CI)	1.00 (reference)	1.00 (0.62 to 1.62)	1.05 (0.65 to 1.70)	1.11 (0.69 to 1.79)	1.62 (1.03 to 2.52)	0.03	1.47 (1.14 to 1.88)	0.003
Coronary heart disease								
Matsuda index								
No. of events	25	26	14	17	16			
Incidence per 1,000 person-years	4.0	4.7	2.5	3.3	3.0			
Age- and sex-adjusted HR (95% CI)	1.00 (reference)	1.01 (0.58 to 1.75)	0.52 (0.27 to 1.00)	0.69 (0.37 to 1.28)	0.59 (0.31 to 1.10)	0.04	0.71 (0.53 to 0.94)	0.02
HOMA-IR								
No. of events	18	21	19	17	23			
Incidence per 1,000 person-years	3.1	3.9	3.7	3.1	3.8			
Age- and sex-adjusted HR (95% CI)	1.00 (reference)	1.16 (0.62 to 2.17)	1.16 (0.62 to 2.17)	0.98 (0.50 to 1.89)	1.59 (0.86 to 2.96)	0.28	1.38 (0.98 to 1.95)	0.07

HR: hazard ratio; CI: confidence interval; HOMA-IR: homeostasis model assessment of insulin resistance.
*HR for 1 standard deviation increase of the log Matsuda index or log HOMA-IR.

tions with directly measured insulin sensitivity among surrogate indices[12, 13, 23]; however, it is not known if the Matsuda index is associated with the development of incident CVD. To our knowledge, this is the first population-based prospective study reporting the association of the Matsuda index with incident CVD. Our results showed that the elevated Matsuda index levels were significantly and inversely associated with the risk of stroke and coronary heart disease, while HOMA-IR levels were a risk factor for the development of stroke, but not for coronary heart disease. These findings imply that the measurement of Matsuda index levels might be more valuable for identifying individuals at high risk of CVD than the measurement of HOMA-IR levels.

Although the precise reasons are not clear, one possible explanation for the finding that the Matsuda index was more strongly associated with the risk of coronary heart disease than with HOMA-IR levels is as follows. HOMA-IR values are derived from fasting plasma glucose and insulin concentrations[11]. Since hepatic glucose production is the primary determinant of fasting plasma glucose concentrations[29], and fasting plasma insulin concentrations are the primary regulator of hepatic glucose production[30], the parameters of fasting plasma glucose and serum insulin, such as HOMA-IR, may reflect mainly hepatic insulin resistance. This hypothesis has been confirmed in a study of subjects who received tritiated glucose to measure hepatic glucose production[31]. On the other hand, the Matsuda index calculated from the OGTT is likely to represent insulin resistance of the whole body, which consists mainly of a combination of hepatic and muscle insulin resistance[12]. Thus, a stronger association of

the Matsuda index with coronary heart disease might be observed, since the Matsuda index more accurately reflects insulin resistance than HOMA-IR levels[32].

In our study, both surrogate indices of insulin resistance, the Matsuda index and HOMA-IR levels, were significantly involved in the development of CVD, but these associations were attenuated after further adjustment for MetS status. MetS has also been used as a surrogate measure of the insulin resistance phenotype and as a practical tool for identifying individuals at high risk of CVD. To date, prospective studies in several different communities have examined the associations between MetS and the risk of CVD, but there has been controversy over whether MetS captures all CVD risks associated with insulin resistance. In some epidemiological studies of Western populations, CVD risk significantly increased along with the elevations in surrogate indices of insulin resistance, even after adjusting for MetS and other cardiovascular risk factors[17-22]. On the other hand, in a Chinese population, insulin resistance indices including HOMA-IR levels were also associated with CVD risk, but these associations disappeared after adjustment for MetS[15]. These findings were in accordance with ours. Although the reason for this difference among the studies is unclear, the diversity of insulin resistance levels among races might explain it. Insulin resistance results in a spectrum of metabolic disturbances that includes inflammation[33], endothelial dysfunction[34], and hypercoagulability[35] in addition to the MetS status. For example, Asians have been shown to have much lower levels of systemic inflammation than other ethnic groups[36]. Thus, pathways other than MetS in the insulin resistance state might play more important roles in the development of CVD in Western populations.

The strengths of our study include its longitudinal population-based study design, long duration of follow-up, complete follow-up of subjects, sufficient number of cardiovascular events, and accuracy of the diagnosis of CVD, including stroke and coronary heart disease. However, two limitations of our study should be discussed. The primary limitation is that our findings were based on a single measurement of plasma glucose and insulin concentration, as was the case in other epidemiological studies. During follow-up, risk factor levels could have changed due to modifications of lifestyle or medication, and thus misclassification of insulin resistance was possible. However, this source of variability could not account for the associations observed in the present study, because a random misclassification of this nature would tend to cause an underestimation of study findings and bias the results toward the null hypothesis. Thus, the true association could be stronger than that observed in our study. Another limitation is that the values of the Matsuda index were not derived from 5 times of sampling, as reported in the initial publication of the index, but rather were calculated using samples from only 0 and 120 min; however, DeFronzo *et al.* reported that the Matsuda index calculated using 2-point samples, 0 and 120 min, had a strong correlation with the values determined by the original method[13]. If the calculation using 2-point samples were inferior to that of full-point samples, this would also weaken the association found in this study. Thus, we believe that such a bias does not invalidate the present findings.

In conclusion, the present analysis clearly showed that elevated insulin resistance indices estimated by the Matsuda index and HOMA-IR levels were significant risk factors for the incidence of CVD in a Japanese community. The measurement of these indices may help to identify individuals at high risk of CVD. Further studies are needed to investigate the associations between these indices and CVD.

Acknowledgements

We thank the residents of Hisayama for their participation in the survey and the Division of Health and Welfare of Hisayama for their cooperation with our study.

Sources of Funding

This study was supported in part by Grants-in-Aid for Scientific Research (Nos. 22590892, 21590698, and 20591063) from the Ministry of Education, Culture, Sports, Science and Technology of Japan and Health and Labour Sciences Research Grants of the Ministry of Health, Labour and Welfare of Japan (Comprehensive Research on Aging and Health: H20-Chouju-004; Comprehensive Research on Life-Style Related Diseases including Cardiovascular Diseases and Diabetes Mellitus: H22-Junkankitou [Seishuu]-Ippan-005 and H23-Junkankitou [Seishuu]-Ippan-005).

Disclosures

The authors report no conflicts of interest.

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Hypertension
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Effects of Parental Hypertension on Longitudinal Trends in Blood Pressure and Plasma Metabolic Profile : Mixed-Effects Model Analysis

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Hypertension. published online September 24, 2012;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563

Original Article

Effects of Parental Hypertension on Longitudinal Trends in Blood Pressure and Plasma Metabolic Profile

Mixed-Effects Model Analysis

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Abstract—The mechanism underlying the association of parental hypertension with cardiovascular events in offspring remains unclear. In this study, the effects of parental hypertension on longitudinal trends of blood pressure and metabolic parameters were examined by mixed-effects model analysis. From 1977 to 2006, 5198 subjects participated in the Tanno-Sobetsu Study, and we selected 2607 subjects (1095 men and 1512 women) for whom data on parental history of hypertension were available. In both men and women with and without parental hypertension, systolic blood pressure and fasting blood glucose levels consistently increased from the third to eighth decades of life, whereas diastolic blood pressure and serum triglyceride levels followed biphasic (inverted U shape) time courses during that period. However, the relationships between the parameters and age were significantly shifted upward (by ≈5.3 mm Hg in systolic blood pressure, 2.8 mm Hg in diastolic blood pressure, 0.30 mmol/L in blood glucose, and 0.09 mmol/L in triglyceride) in the group with parental hypertension compared with those in the group without parental hypertension. Both paternal and maternal histories of hypertension were determinants of systolic blood pressure and diastolic blood pressure, and there was no significant interaction between the sides of parental history. There were no significant effects of parental hypertension on age-dependent or body mass index-dependent changes in serum low-density lipoprotein cholesterol or high-density lipoprotein cholesterol level. The present results indicate that parental hypertension has an age-independent impact on elevation of blood pressure, plasma glucose, and triglyceride levels, which may underlie the reported increase in cardiovascular events by family history of hypertension. (***Hypertension.* 2012;60:00-00.) • Online Data Supplement**

Key Words: parental hypertension ■ blood pressure ■ risk factor ■ epidemiology

Previous studies have shown that cardiovascular disease clusters within families,[1,2] and a family history of atherosclerotic disease is an established risk factor for cardiovascular events. There have been several studies on the impact of a family history of hypertension on cardiovascular events in offspring, and associations of parental hypertension with blood pressure (BP) elevation and insulin resistance in offspring have been indicated by cross-sectional studies.[3–6] However, because BP level and some metabolic parameters (eg, plasma glucose and insulin level) are age dependent, the results of cross-sectional analyses may have been biased depending on the age distribution of the study subjects. In addition, the effect of parental hypertension on the time course of BP during aging cannot be assessed by cross-sectional analysis. Although there have been a few longitudinal studies in which children or adolescents (ie, university students) were recruited,[7–11] the number of subjects in those studies was relatively small or the subjects were restricted to white men. More importantly, the relationship between effects of parental history of hypertension on longitudinal changes in metabolic risk factors and effects on longitudinal BP changes has not been clarified.

In the present study, we examined the effects of parental hypertension on time courses of both BP and metabolic risk factors during the third to eighth decades of life. We retrieved data from the Tanno-Sobetsu Study and used a mixed-effects model for analyses of longitudinal changes in parameters. The results of the present study indicated that parental hypertension has additive effects not only on age-dependent elevation of BP but also on fasting blood glucose (fasting blood sugar [FBS]) and triglyceride (TG) levels in both men and women. These effects of parental hypertension on the risk factors may contribute to the increase in atherosclerotic cardiovascular events in subjects with a family history of hypertension.

Methods

The protocol of this study was approved by the ethics committee of Sapporo Medical University. Detailed methods are described in the online-only Data Supplement.

Received June 27, 2012; first decision July 13, 2012; revision accepted August 16, 2012.

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The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.112.201129/-/DC1

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Hypertension **is available at http://hyper.ahajournals.org** **DOI: 10.1161/HYPERTENSIONAHA.112.201129**

Study Subjects

We retrieved data obtained in the Tanno-Sobetsu Study,[12] a study with a population-based prospective cohort design that recruited residents in 2 rural towns, Tanno and Sobetsu, in Japan. Citizens at the age of ≥20 years in the towns were eligible for this cohort study. Eligible subjects who agreed to join the study received medical examinations biennially from 1977 to 1993 and annually from 1994 to 2006. At each annual or biannual examination, participants were asked to complete a questionnaire, in which parental hypertension was included as an item. Parental hypertension was defined as hypertension in parents who were examined by a local physician or nurse, and diagnostic criteria of hypertension defined by the Japanese Society of Hypertension have been used by healthcare professionals in the Tanno-Sobetsu areas as in other parts of Japan. Of 5198 subjects in the cohort who underwent medical examinations at least once between 1977 and 2006, we selected subjects born during the period from 1921 to 1960 (n=3678), and data on parental history of hypertension were available in 2607 subjects (1095 men and 1512 women). These subjects were divided into a parental hypertension-positive group (PH^+ group) and a parental hypertension-negative group (PH^- group) according to the presence or absence of a history of hypertension in one or both parents, and the grouping by parental history of hypertension was done for each subject at the initial examination. Items for paternal hypertension and maternal hypertension were separately included in questionnaires used in 1977 and 1978, and data on the items were available in 1750 subjects (780 men and 970 women). The effects of paternal and maternal histories of hypertension were separately analyzed by use of data from this subgroup.

Measurements

Medical examinations were performed early in the morning after an overnight fast. Participants in the medical examination were asked about their medical history, medications, smoking status, habitual drinking, and whether their parents had hypertension.

Statistical Analysis

In the present study, we used a mixed-effects model, an appropriate statistical method for repeated measurements with a lack of uniformity in measurement intervals. This analysis accounts for correlations among measurements within an individual and variations across subjects.[13,14]

Results

Study Subject Characteristics

Sample sizes by age were similar in sex-parental hypertension categories as shown in Figure S1 in the online-only Data Supplement. Because the number of study participants <30 years of age was very small, the data set was truncated at the age of 30 years in the present study. A total of 20 126 data points during follow-up from 1977 to 2006 were used for the following analyses. The characteristics of the subjects at their initial medical examination are presented in Table 1: 42.0% of the subjects were men, 35.5% were born in 1941–1960, and 35.2% had a parental history of hypertension. There was no significant difference between the 2607 study subjects (ie, with known parental history) and the excluded subjects with unknown parental history (n=1071) in demographic parameters except for age, percentage of men, systolic BP (SBP), and TG being slightly higher in the excluded group (Table S1 in the online-only Data Supplement).

Effects of Parental Hypertension on Longitudinal Trend of BP

The mixed-effects regression modeling indicated that age, body mass index, and parental hypertension were significant predictors of longitudinal changes in SBP and diastolic BP (DBP) in both men and women. (Table 2 for main results and Tables S2 through S7 for full results). There was no significant interaction of parental history with body mass index or birth-year category in modeling for SBP and DBP. Longitudinal changes in SBP and DBP are shown in Figure 1. The relationship between SBP and age in the PH^+ group was shifted upward to the relationship in the PH^- group by ≈5 mm Hg in both men and women (Figure 1A). Parental hypertension was significant as a main term for predicting SBP in both men and women (Table 2). The interaction between parental hypertension and age was not significant, indicating that parental hypertension does not have an impact on age-dependent elevation of SBP. A similar impact of parental hypertension was observed on the longitudinal trend of DBP. DBP increased from the 30s, peaked in the 60s, and then decreased (Figure 1B). Parental hypertension was significant as a main term for DBP in both men and women, and interaction between DBP and age was insignificant. As shown in Figure 1B, there was an upward shift in the DBP–age relationship by ≈3 mm Hg in the PH^+ group compared with that in the PH^+ group in both sexes.

Effects of Parental Hypertension on Longitudinal Trend of Metabolic Profiles

The impact of parental hypertension on longitudinal changes in metabolic parameters differed depending on the parameter. As shown in Figure 2A, FBS increased with advancing age

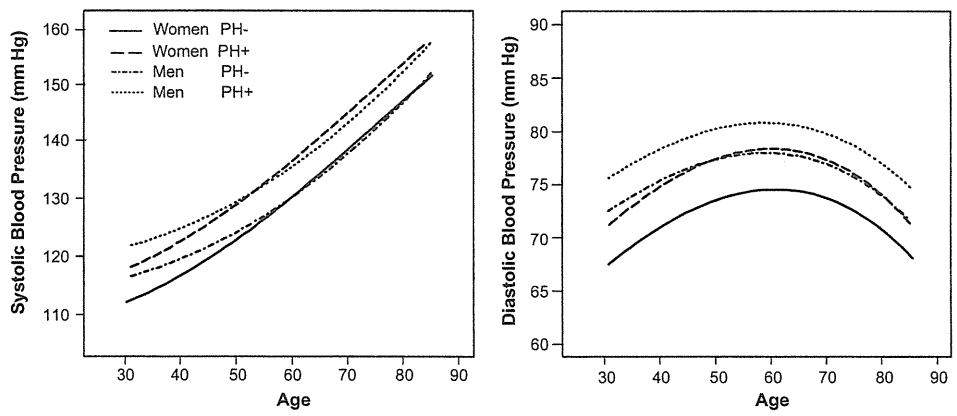

Figure 1. Longitudinal blood pressure (BP) changes and parental history of hypertension. **Left panel**, systolic BP; **right panel**, diastolic (BP). Prediction is shown for subjects with body mass index of 22, no drinking or smoking habit, and birth-year category of 1941–1960. PH^+ indicates the group with parental hypertension; PH^-, group without parental hypertension.

Table 1. Characteristics of Study Subjects at the First Medical Examination

	All (n=2607)		Men (n=1095)		Women (n=1512)	
Variables	Mean	SD	Mean	SD	Mean	SD
Age, y	48.8	9.2	49.3	9.5	48.5	9.0
Sex, % men	42.0	–	–	–	–	–
No. of visit, n	7.6	4.0	7.5	4.0	7.7	4.0
Follow-up (y)	15.5	9.0	15.5	9.2	15.5	9.0
Birth-year categories, % born in 1941–1960	29.2	–	24.7	–	32.5	–
Parental hypertension, %	35.2	–	37.2	–	33.8	–
Antihypertensive drugs use, %	19.6	–	19.3	–	20.0	–
Lipid-lowering drugs use, %	2.2	–	2.8	–	1.9	–
Antidiabetic drugs use, %	3.1	–	4.6	–	2.1	–
Smoker, %	26.2	–	51.0	–	16.5	–
Habitual drinking, %	48.8	–	56.2	–	26.0	–
BMI, kg/m^2	23.6	3.0	23.5	2.8	23.7	3.2
SBP, mm Hg	128.7	19.1	128.2	18.0	129.1	19.8
DBP, mm Hg	78.6	11.0	79.6	10.9	77.9	11.0
FBS, mmol/L	5.14	1.11	5.18	1.22	5.12	1.02
LDL-C, mmol/L	2.88	0.83	2.71	0.84	3.00	0.80
HDL-C, mmol/L	1.34	0.34	1.27	0.33	1.39	0.31
TG, mmol/L	1.34	0.93	1.60	1.17	1.16	0.67

BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

in both men and women, and the FBS–age relationship was shifted upward by ≈0.4 mmol/L in the PH$^+$ group compared with that in the PH$^-$ group in both sexes. TG increased from the 30s, peaked in the 50s in men and 60s in women, and then decreased. The longitudinal changes in TG were similar in the groups with and without parental hypertension, but TG level was consistently higher by ≈0.09 mmol/L in the PH$^+$ group than in the PH$^-$ group in both men and women (Figure 2B). In contrast to FBS and TG, parental hypertension was not included in optimal models for low-density lipoprotein cholesterol and for high-density lipoprotein cholesterol, both of which have age and body mass index terms, in either men or women (Tables S6 and S7).

Subgroup Analyses of Subjects on No Medication

Of the total 20 126 data points used for the present analysis, 38.7%, 6.6%, and 4.8% were data points under medication for hypertension, diabetes mellitus, and dyslipidemia, respectively. To exclude the effects of the medication, we conducted modeling for BP, FBS, and TG by use of only data at time points without relevant medical therapy. The effect of parental hypertension on the response variables in both men and women was slightly weakened by the exclusion of data on medication (Table S8), but the results were similar to those obtained by using the full data set.

Subgroup Analyses on the Effects of Paternal Versus Maternal Hypertension

Possibly different effects of paternal hypertension and maternal hypertension on BP and metabolic profiles were examined in subjects who were asked about parental and maternal histories of hypertension at the baseline examination (n=1750). In both men and women, paternal hypertension and maternal hypertension were significant predictors of longitudinal changes in SBP and DBP, and there was no significant interaction between the two (Tables S9 and S10). As shown in Figures 3 and 4, there were parallel shifts in time courses of SBP and DBP either by paternal hypertension or by maternal hypertension, and the presence of hypertension in both parents afforded additive effects on BP levels.

Significant effects of paternal hypertension and maternal hypertension on FBS were also found. However, there was a significant interaction between the two in women (Table S11), and the presence of both paternal hypertension and maternal hypertension was not additive in terms of their effects on FBS (Figure S2).

As for longitudinal changes in TG, paternal hypertension, but not maternal hypertension, was a significant determinant in both men and women (Table S12). History of paternal hypertension was associated with a parallel and upward shift of the age–TG relationship as shown in Figure S3.

Discussion

Several lines of evidence indicate that both genetic and environmental factors are involved in the association of parental hypertension with elevation of BP in offspring. Determination of BP in related and unrelated individuals in a community (Techmesh, Michigan) and calculation of heritability have suggested that genetic components and shared household environment contribute to familial aggregation of BP elevation.[15] SBP and DBP were correlated between spouse pairs (r=0.102 for SBP and 0.114 for DBP, both P<0.05, respectively).[16] BP correlation between parents and biological offspring (r=0.32 for SBP and r=0.37 for DBP) was significantly closer than that between parents and adopted offspring (r=0.09 for SBP and r=0.10 for DBP).[17] Furthermore, linkage studies have revealed chromosomal regions that potentially contribute to elevation of BP.[18] The present study does not provide a strong insight into the mechanism by which parental hypertension increases BP in an age-independent manner. However, the parallel shift of the age–BP relationship by parental hypertension (Figures 1 and 2) suggests that a set point of BP is elevated by parental hypertension-associated genetic factors and environmental factors before the third decade of life.

Effects of parental hypertension on longitudinal changes in BP have been examined in 4 earlier studies.[7–11] However, there are notable differences regarding statistical methods adopted and characteristics of subjects in the earlier studies and the present study. In a study by Lie et al[9] in which third-grade school children were recruited, the effect of parental history of hypertension was not consistent over the ages they examined. In a study by Burke et al,[7] an effect of parental

Table 2. Main Results of Mixed-Effects Regression Model Analysis

	Men				Women			
Parameter	Predictors	β	SE	*P* Value*	Predictors	β	SE	*P* Value*
SBP	cAGE^3	54.67	4.31	<0.01	cAGE^3×BMI	−4.23	0.74	<0.01
	cAGE^3×log (cAGE)	−47.34	18.82	<0.01	cAGE^3×log (cAGE) × BMI	−25.57	4.34	<0.01
	BMI	1.64	0.11	<0.01	PH	6.46	0.83	<0.01
	PH	5.25	0.97	<0.01				
DBP	cAGE	44.09	5.30	<0.01	cAGE×BMI	2.69	1.30	<0.01
	cAGE^3×BMI	−1.22	0.43	<0.01	cAGE^3×BMI	−3.22	1.29	0.04
	PH	2.82	0.55	<0.01	PH	3.81	0.45	<0.01
log FBS	cAGE^3×cBMI	3.02	0.58	<0.01	cAGE^3×cBMI	1.10	0.39	<0.01
	PH	0.06	0.01	<0.01	PH	0.04	0.01	<0.01
log TG	cAGE	0.99	0.23	<0.01	cAGE^3×cBMI	−7.38	1.73	<0.01
	cAGE^3×cBMI	−7.30	1.70	<0.01	cAGE^3×log (cAGE)×cBMI	−37.78	10.08	<0.01
	PH	0.08	0.02	<0.01	PH	0.06	0.02	<0.01

SBP indicates systolic blood pressure; BMI, body mass index; PH, parental hypertension; DBP, diastolic blood pressure; FBS, fasting blood glucose; TG, triglycerides. In PH, 1=having parent with hypertension and 0=not having parent with hypertension. cAGE = AGE/100, cBMI=BMI/100.

All models were adjusted for smoking, alcohol use, and birth-year category. Main results are shown in this table and full results are presented in tables in the online-only Data Supplement.

*P value was based on the likelihood ratio test for a model including the term against a reduced model excluding the terms.

history of hypertension on BP was not detected at the age of 9 years, and a parallel shift of the BP–age relationship by parental history of hypertension was not detected in the age range that they examined (9–18 years old). van den Elzen et al[10] examined the relationship between natural history of BP in children aged 5 to 19 years and level of BP in their parents. They found that SBP was consistently higher by 2.7 mm Hg from the age of 5 years to the age of 40 years in subjects with parents in the highest tertile of SBP, whereas such a parallel shift of BP was not observed for DBP. Wang et al[11] recruited university students, but they used only data from white men in their analysis. Similar to our results, the BP–age relationship within the age range of 20 to 80 years was shifted upward by ≈2 mm Hg in subjects with a parental history of hypertension compared with that in subjects without a parental history.

Our study has examined for the first time the effects of parental hypertension on the longitudinal BP changes in both men and women and showed that parental history of hypertension is associated with age-independent elevation of BP in Asian men and women (Figure 1). Furthermore, the effects of paternal hypertension and maternal hypertension appear to be additive on the longitudinal change in BP in a subgroup analysis (Figures 3 and 4). Taken together, the results in the present and earlier studies indicate that parental history of hypertension induces elevation of BP from as early as the second to third decades of life until the eighth decade of life, although it remains unclear at which age such an effect of parental history on BP emerges.

The present study showed that parental history of hypertension had impact on longitudinal changes in FBS and TG

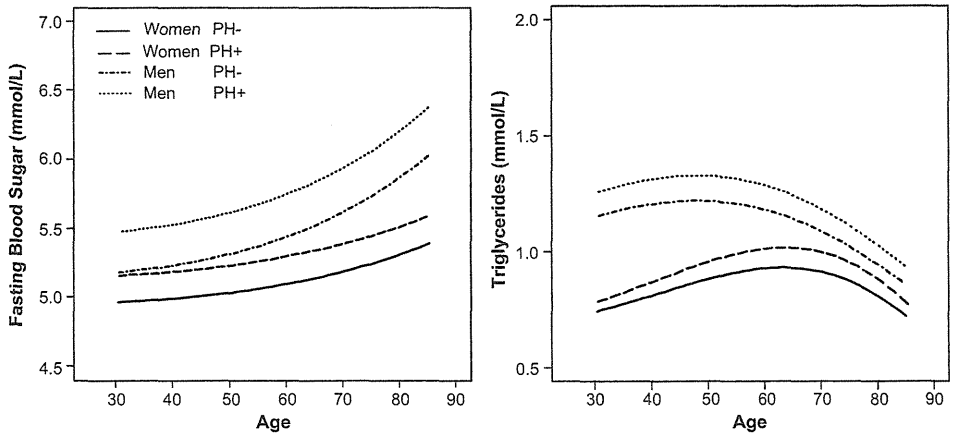

Figure 2. Longitudinal fasting blood sugar (FBS) and triglycerides (TG) changes and parental hypertension. **Left panel**, FBS; **right panel**, TG. Prediction is shown for subjects with body mass index of 22, no drinking or smoking habit, and birth-year category of 1941–1960. PH$^+$ indicates the group with parental hypertension; PH$^-$, group without parental hypertension.