به نام خدا

Combined effects of blood pressure and glucose status on the risk of chronic kidney disease

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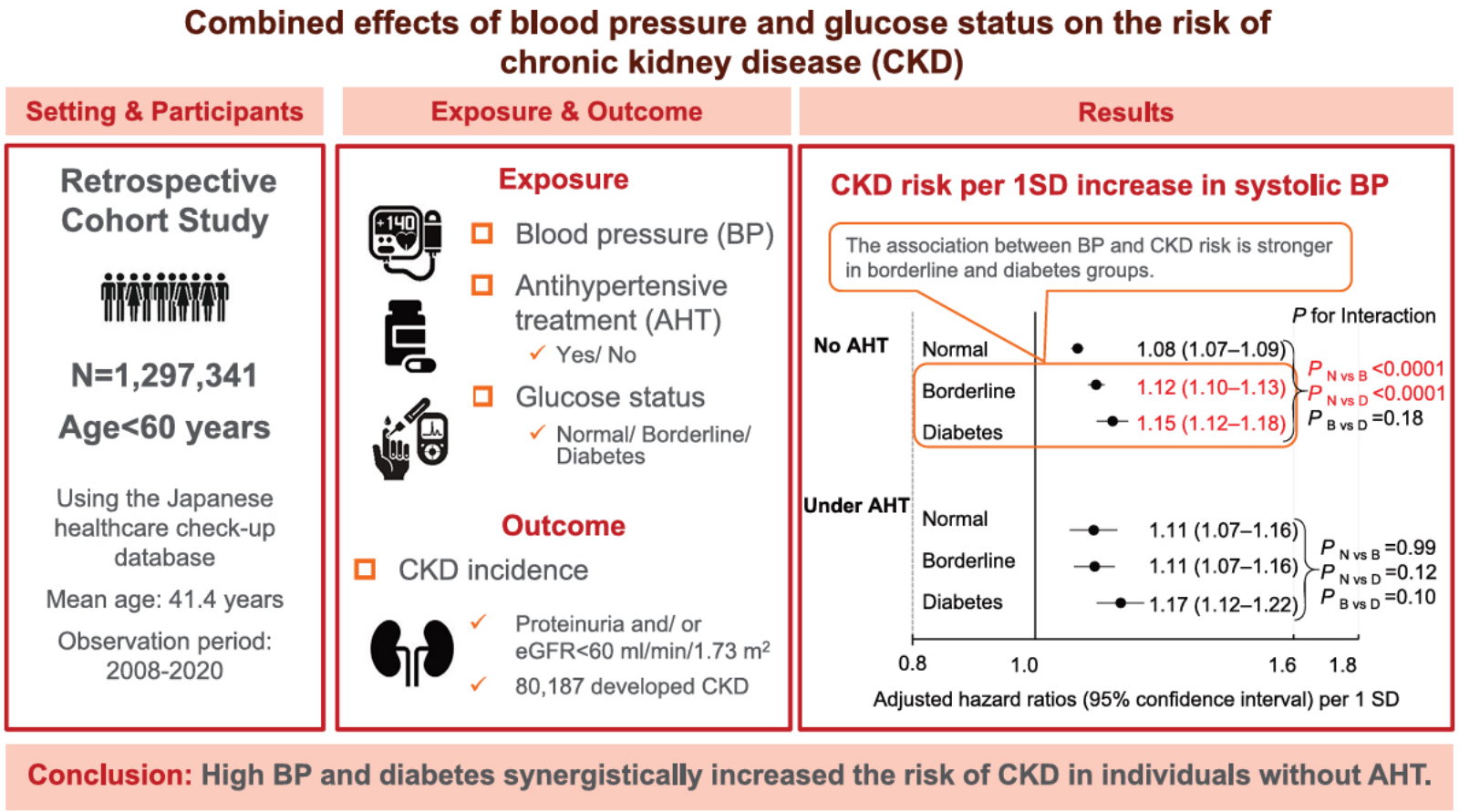
Abstract

- This study aimed to assess the combined effects of blood pressure (BP) and glucose status on chronic kidney disease (CKD) incidence in young and middle-aged adults. We examined data from 1,297,341 Japanese individuals aged <60 years (60.1% men; mean age 41.4±9.3 years) with no history of CKD at baseline. The interval-censored Cox proportional hazards model with covariates was used. During a median follow-up period of 2.1 years, new onset CKD (estimated glomerular filtration rate <60ml/min/1.73 m2 and/or proteinuria) occurred in 80,187 participants. In participants without antihypertensive treatment (AHT), the adjusted hazard ratios (95% confidence interval) per 1-standard deviation, that is, 15 mmHg increase in systolic BP for CKD incidence, were 1.08 (1.07–1.09), 1.12 (1.10–1.13), and 1.15 (1.12–1.18) in normoglycemia, borderline glycemia, and diabetes groups, respectively.

- These ratios were significantly higher in the borderline glycemia and diabetes groups compared with those in the normoglycemia group (interaction $p<0.0001$). The interaction between BP and borderline glycemia was evident when the outcome definition was restricted to proteinuria. In participants under AHT, systolic BP was most strongly associated with CKD risk in the diabetes group, although no significant interaction was observed. High BP and high glucose status may synergistically increase the incidence of CKD. Strict BP management may play an important role in the early prevention of CKD in individuals with worse glucose status within the young and middleaged population.

Graphical Abstract



Point of view

- Clinical relevance : High BP and worse glucose status have a positive synergistic interaction effect on the risk of chronic kidney disease (CKD) in individuals without antihypertensive treatment (AHT). Strict BP management may play an important role in the early prevention of CKD in individuals with worse glucose status within the young and middle-aged population.
- Future direction : To further investigate the combined effects of BP and glucose status on CKD incidence, a nationwide survey taking into account the duration of hypertension and diabetes and information regarding the type of AHT should be conducted.
- Consideration for the Asian population : Given the large number of people with CKD in Asian populations, urgent action may be needed in Asia for the early prevention of CKD through strict management of BP and blood glucose levels.

Introduction

- Chronic kidney disease (CKD) has emerged as a significant global health burden in the past two decades. In 2017, the global prevalence of CKD was 9.1% (about 697.5 million cases), representing a 29.3% increase compared to 1990.
- Globally, hypertension and diabetes are considered the two leading drivers of CKD [5], and various studies suggested that both of them were independent risk factors in the incidence of CKD [6–8]. Hypertension and diabetes often coexist and share similar etiological and pathological mechanisms [9–11]. Thus, exploring the association between the coexistence of hypertension and diabetes and the heightened risk of CKD in the younger population may provide insights for the early prevention of future CKD incidence through effective management and treatment of these two diseases.

- Similarly, another longitudinal study involving 5823 Asians demonstrated a synergistic interaction between hypertension and diabetes in relation to CKD incidence [14]. However, the previous study categorized participants into only four groups based on the presence or absence of hypertension and diabetes, with a limited number of participants (n =309) having both conditions. This limited sample size hindered a detailed assessment of the association between BP and diabetes [14]. Meanwhile, some studies have reported no significant synergistic interaction between hypertension and diabetes concerning kidney function decline [12, 13].

- One possible explanation for these inconsistent findings is that these studies did not consider the use of antihypertensive treatment (AHT) among participants [12–15]. The association between BP and the risk of CKD incidence is reported to change with AHT [16]. Given these issues, our study aimed to evaluate the combined effects of BP and glucose status on CKD incidence in the young and middle-aged population, using data from a large-scale health examination. We further stratified the participants based on their use of AHT to gain insights into the association between BP and diabetes.

Methods

- Study design and populations
- Data collection
- Definitions
- Outcome and follow-up
- Statistical analysis

- Study design and populations

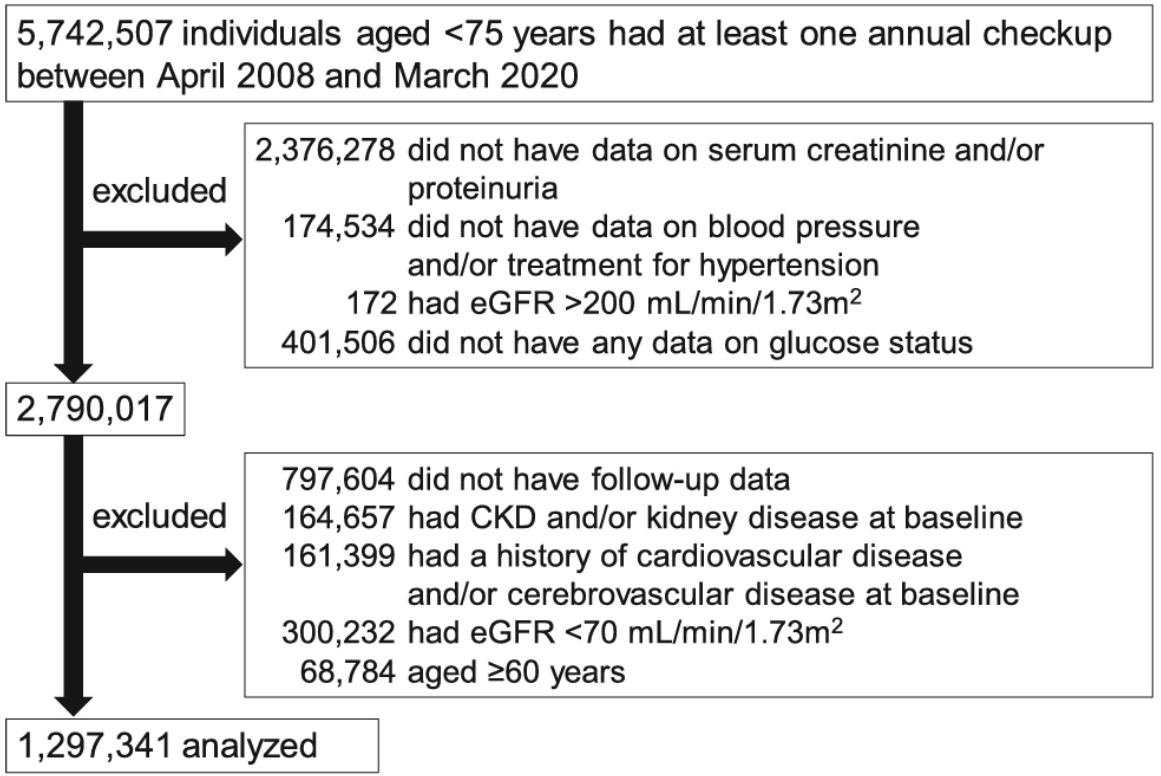


Fig. 1 Flowchart of the participant selection process. CKD chronic kidney disease, eGFR estimated glomerular filtration rate

• Definitions

- First, we divided the participants into two groups: those not taking AHT and those taking AHT. Participants not taking AHT were further classified into five or four categories based on their systolic BP (≤119, 120–129, 130–139, 140–159, ≥160mmHg) or diastolic BP (≤79, 80–89, 90–99, ≥100mmHg) according to the Japanese Hypertension Society (JSH) 2019 guidelines [23]. Participants under AHT were also classified into three categories according to systolic and diastolic BP (≤129, 130–139, ≥140 mmHg and ≤79, 80–89, ≥90mmHg), taking into account target levels of BP control [23] and the number of participants in each group. Additionally, participants were further classified as having diabetes, borderline glycemia, or normoglycemia based on fasting glucose levels, HbA1c levels, and the use of glucose lowering medications

Outcome and follow-up

- For this study, CKD was defined as an estimated glomerular f iltration rate (eGFR) < 60ml/min/1.73m2 and/or the presence of proteinuria, based on previous epidemiological studies [8, 14, 18, 20]. The eGFR was calculated using a modified version of the equation used most commonly in Japan: Japanese Society of Nephrology (JSN) eGFR (ml/min per 1.73m2)=194×(serum creatinine)−1.094×Age−0.287 (×0.739, if female) (hereinafter referred to as eGFR)

• Statistical analysis

- Adjusted hazard ratios were then calculated per 1SD, that is, 15mmHg increase in systolic BP or 11.5 mmHg increase in diastolic BP, in each glucose status for comparability between systolic and diastolic BP. Interactions between BP and borderline glycemia or diabetes vs. normoglycemia were tested using the BP× borderline glycemia category (for calculation of interaction P Nvs. B) and the BP× diabetes category (for calculation of interaction P Nvs.D) in the models. For interactions between BP and borderline glycemia vs. diabetes, the model included the BP×diabetes category (for calculation of interaction P Bvs.D) and the BP× normoglycemia category.

Results

1. Baseline characteristics

- The number of CKD events and the sex-andage-adjusted incidence rate for CKD per 1000 person-years were highest in the group with the highest BP and diabetes. Similar associations were observed among participants under AHT

Table 1 Baseline characteristics and the number of CKD events in each systolic BP-glucose status among participants without AHT

	SBP ≤ 119 mmHg			SBP 120–129 mmHg			SBP 130–139 mmHg		
	Glucose status			Glucose status			Glucose status		
Characteristics	**Normal**	**Borderline**	**Diabetes**	**Normal**	**Borderline**	**Diabetes**	**Normal**	**Borderline**	**Diabetes**
N	568,368	151,258	11,558	193,833	80,876	10,069	83,407	46,910	7724
Men, %	46.6	57.9	76.8	71.1	74.6	82.1	74.8	77.1	83.6
Age, years	38.5 ± 8.8	44.0 ± 8.1	47.2 ± 7.8	39.7 ± 9.2	44.6 ± 8.1	47.3 ± 7.6	41.4 ± 9.2	45.4 ± 8.2	47.4 ± 7.6
Body mass index, kg/m^2	21.3 ± 2.8	22.5 ± 3.3	24.6 ± 4.1	22.9 ± 3.3	24.2 ± 3.7	26.3 ± 4.4	23.7 ± 3.6	25.0 ± 4.1	27.2 ± 4.8
Current smoker, %	22.2	28.0	41.3	28.7	32.0	40.8	30.3	32.5	39.5
Alcohol consumption, %	16.0	20.5	18.4	24.3	28.1	23.0	28.8	31.6	26.1
Systolic BP, mmHg	106.4 ± 8.4	108.1 ± 8.0	109.9 ± 7.3	124.1 ± 2.9	124.3 ± 2.9	124.5 ± 2.9	133.9 ± 2.8	134.1 ± 2.9	134.3 ± 2.9
Diastolic BP, mmHg	65.6 ± 7.9	67.7 ± 8.1	70.0 ± 7.8	75.8 ± 7.4	77.5 ± 7.1	78.5 ± 6.9	82.0 ± 7.9	83.4 ± 7.5	83.9 ± 7.3
FPG, mg/dl	87.0 ± 6.5	98.1 ± 9.1	143.7 ± 46.9	88.5 ± 6.4	100.6 ± 8.8	144.4 ± 43.4	89.2 ± 6.2	101.8 ± 8.8	146.9 ± 44.6
HbA1c, %	5.3 ± 0.2	5.7 ± 0.3	7.3 ± 1.6	5.3 ± 0.2	5.7 ± 0.3	7.3 ± 1.5	5.3 ± 0.2	5.7 ± 0.3	7.3 ± 1.5
Serum creatinine, mg/dl	0.70 ± 0.13	0.72 ± 0.13	0.72 ± 0.12	0.75 ± 0.13	0.75 ± 0.12	0.73 ± 0.12	0.76 ± 0.12	0.76 ± 0.12	0.73 ± 0.12
eGFR, ml/min/1.73 m^2	88.4 ± 13.2	85.1 ± 11.6	88.3 ± 14.3	87.2 ± 12.5	84.8 ± 11.5	88.5 ± 14.1	86.5 ± 12.1	84.7 ± 11.4	88.4 ± 14.3
Event, *n* (Event rate 1000 person-year[a])	28,821 (16.84)	8582 (18.26)	1038 (29.19)	10,861 (18.35)	5322 (20.97)	1158 (39.09)	5406 (20.32)	3682 (24.57)	1004 (44.05)

	SBP 140–159 mmHg			SBP ≥ 160 mmHg		
	Glucose status			Glucose status		
Characteristics	**Normal**	**Borderline**	**Diabetes**	**Normal**	**Borderline**	**Diabetes**
N	33,759	26,237	5427	4686	4649	1304
Men, %	73.4	76.6	82.3	63.3	68.4	75.5
Age, years	44.0 ± 8.7	46.6 ± 7.9	47.8 ± 7.4	46.2 ± 7.8	47.9 ± 7.1	48.0 ± 7.1
Body mass index, kg/m^2	24.4 ± 4.0	25.7 ± 4.5	27.8 ± 5.1	24.9 ± 4.6	26.4 ± 5.0	28.6 ± 5.7
Current smoker, %	31.5	32.1	37.4	31.7	30.5	35.6
Alcohol consumption, %	35.0	35.5	28.4	35.7	36.6	30.4
Systolic BP, mmHg	146.4 ± 5.3	146.8 ± 5.4	147.2 ± 5.5	168.8 ± 9.5	169.5 ± 10.1	171.3 ± 12.3
Diastolic BP, mmHg	90.9 ± 8.8	91.6 ± 8.5	91.3 ± 8.3	102.9 ± 10.7	102.9 ± 10.9	103.5 ± 11.2
FPG, mg/dl	90.0 ± 6.1	103.0 ± 8.8	148.7 ± 45.4	90.4 ± 6.0	104.5 ± 8.9	157.5 ± 50.7
HbA1c, %	5.3 ± 0.2	5.7 ± 0.3	7.3 ± 1.5	5.3 ± 0.2	5.7 ± 0.3	7.5 ± 1.7
Serum creatinine, mg/dl	0.75 ± 0.12	0.75 ± 0.12	0.73 ± 0.12	0.72 ± 0.13	0.73 ± 0.13	0.71 ± 0.13
eGFR, ml/min/1.73 m^2	85.6 ± 11.9	84.7 ± 11.6	88.9 ± 15.1	85.0 ± 11.5	84.7 ± 11.9	89.7 ± 16.1
Event, *n* (Event rate 1000 person-year[a])	2660 (25.42)	2374 (30.58)	793 (53.31)	437 (33.00)	503 (44.19)	217 (64.08)

Data are shown as mean ± SD for continuous variables

AHT antihypertensive treatment, *BP* blood pressure, *FPG* fasting plasma glucose, *eGFR* estimated glomerular filtration rate

[a]CKD incidence rates were standardized by direct method for age (<40, 40–49, and ≥50)

2. CKD risks according to BP and glucose status

- During a median follow-up of 2.1 years (interquartile range 1.2–4.0 years), 80,187 participants developed CKD with 25,357 experiencing eGFR <60ml/min/1.73m2, 57,887 experiencing proteinuria, and 3057 participants experiencing both eGFR <60ml/min/1.73m2 and proteinuria. Table 2 presents the adjusted hazard ratios according to BP and glucose status. In participants without AHT, the group with systolic BP≥160mmHg and diabetes had the highest hazard ratio for CKD incidence, with a value of 3.08 compared to the group with systolic BP<120mmHg and normoglycemia. The risks for CKD incidence increased stepwise with higher systolic BP categories within all glucose status groups and with higher glucose status within all systolic BP category groups. In the participants under AHT, the risks for CKD were also elevated with increased systolic BP and glucose status. Similar results were obtained when all analyses were repeated using diastolic BP instead of systolic BP

Table 2 Adjusted hazard ratios (95% confidence intervals) for CKD incidence according to BP-glucose status

		Glucose status		
		Normal	Borderline	Diabetes
	Systolic BP, mmHg			
No AHT	≤119	1.00 (ref)	1.02 (1.00–1.05)	1.63 (1.53–1.73)
	120–129	1.01 (0.99–1.04)	1.10 (1.07–1.14)	1.96 (1.85–2.08)
	130–139	1.09 (1.06–1.12)	1.25 (1.20–1.29)	2.14 (2.01–2.28)
	140–159	1.35 (1.30–1.41)	1.49 (1.42–1.55)	2.48 (2.31–2.67)
	≥160	1.76 (1.60–1.93)	1.93 (1.76–2.11)	3.08 (2.69–3.53)
Under AHT	≤129	1.00 (ref)	1.11 (1.02–1.20)	1.44 (1.31–1.59)
	130–139	1.05 (0.95–1.16)	1.12 (1.02–1.23)	1.76 (1.58–1.95)
	≥140	1.27 (1.15–1.41)	1.41 (1.29–1.54)	2.08 (1.88–2.30)
	Diastolic BP, mmHg			
No AHT	≤79	1.00 (ref)	1.03 (1.01–1.06)	1.70 (1.62–1.79)
	80–89	1.08 (1.05–1.11)	1.23 (1.19–1.27)	2.20 (2.09–2.32)
	90–99	1.42 (1.36–1.48)	1.55 (1.48–1.62)	2.62 (2.42–2.83)
	≥100	1.69 (1.57–1.81)	1.94 (1.81–2.08)	2.92 (2.59–3.29)
Under AHT	≤79	1.00 (ref)	1.09 (0.99–1.21)	1.55 (1.38–1.73)
	80–89	1.07 (0.97–1.18)	1.16 (1.05–1.27)	1.66 (1.50–1.85)
	≥90	1.21 (1.09–1.35)	1.37 (1.24–1.51)	2.01 (1.79–2.25)

Hazard ratios were adjusted for age, sex, body mass index, current smoking, current drinking, dyslipidemia, and eGFR at baseline

AHT antihypertensive treatment, *BP* blood pressure, *CKD* chronic kidney disease

3. Interaction between BP levels and glucose status on CKD risks

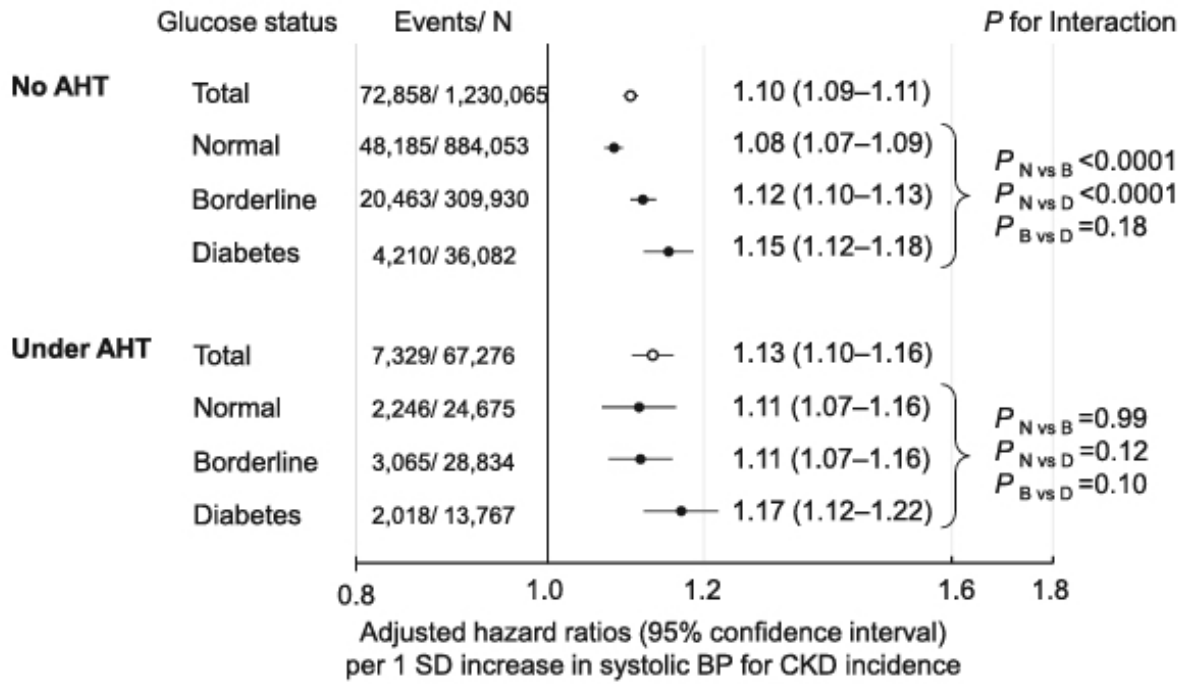


Fig. 2 Adjusted hazard ratios (95% confidence intervals) per 1 SD increase in systolic BP for CKD incidence. Hazard ratios were adjusted for age, sex, body mass index, current smoking, current drinking, dyslipidemia, and eGFR at baseline. One SD of systolic BP is 15.0 mmHg. AHT antihypertensive treatment, BP blood pressure, CKD chronic kidney disease, SD standard deviation

Discussion

- Our results showed that in the general Japanese population, the CKD risk gradually increases with higher BP and glucose status, regardless of AHT. The groups with the highest BP and diabetes were at the greatest risk of CKD. Additionally, the association between BP and CKD incidence was observed even in the normoglycemia group, whereas the association was significantly stronger in the borderline glycemia or diabetes groups compared to the normoglycemia group, especially in patients without AHT. The present study revealed that hypertension and diabetes synergistically increased the risk of CKD in individuals without AHT. It was generally considered that hypertension and diabetes were in dependent risk factors for CKD [6–8]

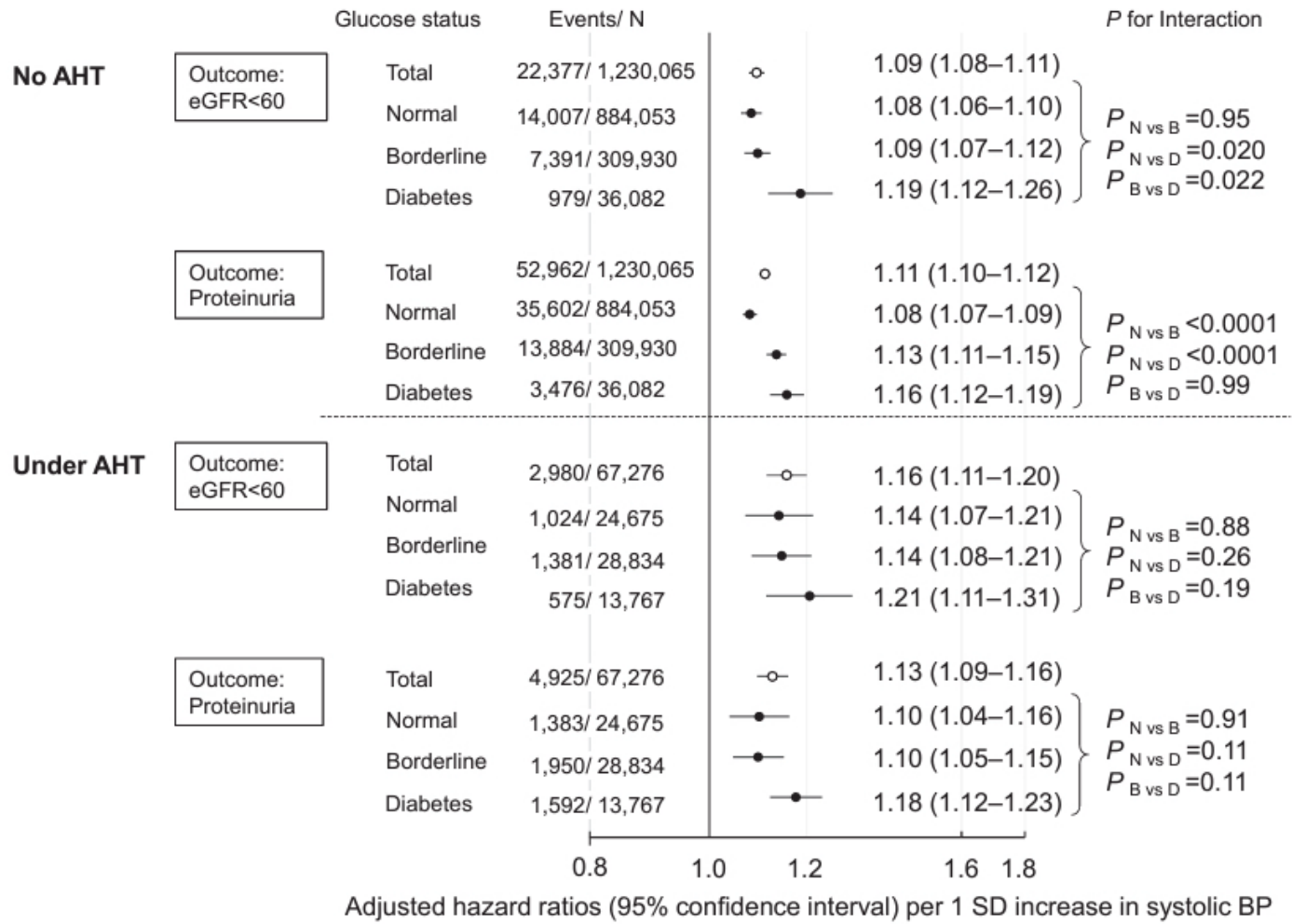


Fig. 3 Adjusted hazard ratios (95% confidence intervals) per 1 SD increase in systolic BP for the incidence of eGFR < 60 ml/min/1.73 m^2 and proteinuria. Hazard ratios were adjusted for age, sex, body mass index, current smoking, current drinking, dyslipidemia, and eGFR at baseline. One SD of systolic BP is 15.0 mmHg. AHT antihypertensive treatment, BP blood pressure, CKD chronic kidney disease, eGFR estimated glomerular filtration rate, SD standard deviation

Conclusion

- Our findings showed that high BP and diabetes synergistically increased the risk of CKD in individuals without AHT. These results suggested that strict management of BP may play an important role in preventing the development of CKD in individuals with worse glucose status in the young and middle-aged population.

Any Question ?