Original Article

Combined impact of risk factors on the subsequent development of hypertension

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Objectives: This study aimed to develop a cumulative score composed of seven risk factors: age, resting heart rate, overweight or obesity, dyslipidemia, hyperuricemia, impaired glucose regulation, and impaired estimated glomerular filtration rate (eGFR), to evaluate the risk of new-onset hypertension.

Methods: We retrospectively conducted a cohort study in 23 665 participants free from hypertension at baseline, who attended at least two annual health examinations between 2011 and 2016. We defined hypertension as SBP of 140 mmHg or less and/or DBP of at least 90 mmHg, according to the 2010 Chinese guidelines for the management of hypertension. We computed a composite, individual-level cumulative score incorporating all seven risk factors (no = 0 point; yes = 1 point; total range 0–7 points). Cox regression was used to analyze the association between cumulative score and risk of hypertension.

Results: A total of 2305 participants developed hypertension during a median follow-up period of 3.6 years. Compared with participants with 0 points, the adjusted hazard ratios (95% confidence intervals) for the development of hypertension for those with 2, 3, and at least 4 points were 1.61 (1.29–2.02), 2.05 (1.64–2.57) and 2.77 (2.22–3.46), respectively (P trend < 0.001). This association was present after adjustment for sex and baseline blood pressure.

Conclusion: Age, resting heart rate, overweight or obesity, dyslipidemia, hyperuricemia, impaired glucose regulation, and impaired eGFR were associated with significant risk of new-onset hypertension and when combined there was an accumulation of risk.

Keywords: heart rate, hypertension, hyperuricemia, risk factor

Abbreviations: CIs, confidence intervals; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RHR, resting heart rate

INTRODUCTION

Hypertension is a common problem worldwide and a major risk factor for cardiovascular disease. In 2014, the prevalence of hypertension was 27.8% and there are 292 million hypertensive patients in China, representing an absolute increase of 139 million since 2002. Despite efforts to improve its detection and antihypertensive treatment, just 9.7% of hypertensive patients have adequately controlled blood pressure [1]. Identifying high-risk, nonhypertensive individuals with multiple risk factors at an early stage is critical to preventing the progression of hypertension. It is recognized that age [2,3], resting heart rate (RHR) [4,5], overweight or obesity [6,7], dyslipidemia [8,9], hyperuricemia [10,11], impaired glucose regulation [12,13], and estimated glomerular filtration rate (eGFR) [14] are all independent risk factors for the development of hypertension. However, it is not clear whether these risk factors are additive with respect to the risk of new-onset hypertension. Therefore, we aimed to develop a cumulative score composed of these seven risk factors (age, RHR, overweight or obesity, dyslipidemia, hyperuricemia, impaired glucose regulation, and impaired eGFR) and to evaluate the relationship between the clustering of risk factors and the risk of hypertension.

MATERIALS AND METHODS

Study population

A total of 28 923 participants (15 570 men and 13 353 women) aged at least 18 years, who underwent routine annual health examinations between October 2011 and August 2016 at Nanfang Hospital Health Management Center in Guangzhou, Guangdong Province, China, were recruited. The participants came from all social backgrounds, including teachers, professional technical personnel, civil servants, and administrative staff. We excluded 1100 individuals with incomplete data and 3028 individuals with SBP of at least 140 mmHg and/or a DBP of at least 90 mmHg or with antihypertensive medicine. We also excluded 1130

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individuals who only participated in 2011 and only included individuals that were examined more than once. Consequently, the study population for analysis consisted of 23 665 participants. The institutional review boards at the participating institutions (Nanfang Hospital, Southern Medical University) approved the study protocol. Written informed consent was obtained from all participants.

Measurements and definitions

The annual heath examination included a physical examination, anthropometric measurements, electrocardiography, blood pressure measurement and blood biochemical measurements. BMI was calculated as mass in kilograms divided by the square of height in meters. Participants were asked to rest in a quiet room at least 10 min and not allowed to smoke, drink coffee, alcohol, or tea, or to exercise within 30 min of the RHR and blood pressure measurements. A 12-lead electrocardiogram was used to measure RHR. Right brachial artery blood pressure was measured twice at a 2 min interval by a fully automatic sphygmomanometer (Omron, HEM-7200; China). The mean of two blood pressure measurements was used for data analysis. Blood samples were collected from the elbow vein by trained nurses on the morning after an overnight fast of at least 8 h. Serum creatinine, uric acid, fasting plasma glucose (FPG), high-density lipoprotein cholesterol (HDL-C), total cholesterol, and triglyceride were measured using an automated biochemical analyzer. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation [15]. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [16].

Overweight and obesity were defined by BMIs of 24–27.9 kg/m^2 and at least 28 kg/m^2, respectively, according to Chinese criteria [17]. Impaired glucose regulation was defined by the presence of impaired fasting glucose (5.6 mmol/l $\leq$FPG $<$ 7.0 mmol/l) and/or diabetes mellitus (FPG $\geq$7.0 mmol/l), in accordance with the American Diabetes Association criteria [18]. Hyperuricemia was defined as uric acid greater than 420 μmol/l in men and 360 μmol/l in women. Dyslipidemia was defined as total cholesterol at least 5.2 mmol/l and/or triglyceride at least 1.7 mmol/l and/or LDL at least 3.4 mmol/l and/or HDL less than 1.0 mmol/l. On the basis of the 2010 Chinese guidelines for the management of hypertension [19], incident hypertension was recorded at the first follow-up health check at which a participant had an SBP at least 140 mmHg and/or a DBP at least 90 mmHg.

Statistical analysis

The study participants were divided into two groups according to whether hypertension developed or not, and their baseline characteristics are presented as means and standard deviations (SDs) or percentages. Differences in values or percentages between the two groups were compared using the unpaired Student's *t*-test or the χ^2 test. The seven nominated risk factors [age, RHR, overweight or obesity, dyslipidemia, hyperuricemia, impaired glucose regulation, and impaired eGFR ($<$90 ml/min per 1.73 m^2)] were included in Cox regression analysis to analyze their independent influences on the development of hypertension, and were adjusted for sex and baseline SBP, and DBP. Given that the average age and resting heart rate of those who became hypertensive were 45 years and 80 bpm, respectively, we used these as cut-off values in the Cox regression model. We used a binary score for each factor and participants were assigned one point for the presence of each risk factor at baseline, then we added the points to yield a cumulative score of 0–7 points. According to the cumulative score, participants were placed into five categories: those with 0, 1, 2, 3, or at least 4 points. The number of person-years of follow-up was determined from the date of enrolment to the date hypertension was first recorded or the date of the last complete follow-up examination. Further Cox regression analysis was used to compute hazard ratios and 95% confidence intervals (CIs) for the incidence of hypertension in the five groups after adjusting for confounding factors (sex and baseline SBP and DBP). Statistical analyses were performed using SPSS 23.0 (IBM Corp., Armonk, New York, USA). All reported *P* values were two-tailed and *P* less than 0.05 was considered to represent statistically significance.

RESULTS

After a mean of follow-up period of 3.6 years 2502 participants (1903 men and 599 women) had developed hypertension. One thousand, three hundred and seventy-eight participants (993 men and 385 women) and 550 participants (437 men and 113 women), developed high SBP or DBP alone, respectively, whereas 574 participants (473 men and 101 women) developed high SBP and DBP.

The baseline characteristics of participants who were or not diagnosed with new-onset hypertension during the follow-up period are presented in Table 1. Participants who developed hypertension during the follow-up period were more likely to be men, to be older, to have higher BMI and baseline SBP and DBP, and to have lower eGFR and

TABLE 1. Baseline characteristics of study population with and without hypertension during follow-up

	Without new-onset hypertension (n = 21 163)	With new-onset hypertension (n = 2502)
Age (year)	34.8 ± 9.8	44.9 ± 13.5*
Sex [male (%)]	10857 (51.3)	1903 (76.1)
BMI (kg/m^2)	22.5 ± 3.1	24.9 ± 3.2*
SBP (mmHg)	114.3 ± 11.6	126.8 ± 8.9*
DBP (mmHg)	69.8 ± 7.9	77.8 ± 7.4*
Resting heart rate (beats/min)	78.9 ± 11.4	79.7 ± 11.6#
Serum creatinine (μmol/l)	66.7 ± 16.1	72.3 ± 16.9*
eGFR (ml/min per 1.73 m^2)	112.8 ± 14.3	103.7 ± 15.4*
Urid acid (μmol/l)	346.9 ± 93.7	392.4 ± 97.5*
Fasting plasma glucose (mmol/l)	4.7 ± 0.7	5.0 ± 1.1*
LDL-C (mmol/l)	2.9 ± 0.7	3.1 ± 0.8*
HDL-C (mmol/l)	1.5 ± 0.4	1.4 ± 0.4*
TC (mmol/l)	5.0 ± 1.0	5.3 ± 1.1*
TG (mmol/l)	1.3 ± 1.2	1.9 ± 1.8*
Follow-up period [median (IQR)], years	2.4 (2.2)	3.1 (1.2)

Values are the mean ± SD or the number of participants eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, SBP; TC, total cholesterol; TG, triglyceride.
*P < 0.001 vs. 'without new-onset hypertension' group.
#P < 0.01 vs. 'without new-onset hypertension' group.

TABLE 2. Assignment for each risk factor and its prevalence

Risk factors	Assigned point	Number and prevalence in study		
		Male	Female	Overall
Age at least 45 years	1	2808 (22.0%)*	1733 (15.9%)	4541 (19.2%)
Resting heart rate at least 80 bpm	1	4676 (36.6%)*	5964 (54.7%)	10 615 (45.0%)
Overweight or obesity	1	6037 (47.3%)*	1864 (17.1%)	7901 (33.4%)
Dyslipidemia	1	7660 (60.0%)*	4076 (37.4%)	11 736 (49.6%)
Hyperuricemia	1	4965 (38.9%)*	1403 (12.9%)	6368 (26.9%)
Impaired glucose regulation	1	970 (7.6%)*	480 (4.4%)	1450 (6.1%)
eGFR less than 90 ml/min/1.73 m^2	1	1551 (12.2%)*	383 (3.5%)	1934 (8.2%)

*$P < 0.001$ vs. female.

HDL-C. In addition, the mean values of RHR, serum creatinine, uric acid, FPG, LDL-C, total cholesterol, and triglyceride in the participants diagnosed with new-onset hypertension were significantly higher than those who did not develop hypertension.

In this study 10 615 (45%) and 4541 (19.2%) participants had an RHR of greater than 80 bpm and were older than 45 years, respectively (Table 2). Of the participants, 7901 (33.4%) were overweight or obese. Serum lipid, uric acid, and FPG concentrations were not within the recommended range in 50, 27, and 7% of participants, respectively. At baseline, less than 9% of participants had an eGFR of less than 90 ml/min per 1.73 m^2. The prevalence of all the risk factors were higher in men than women ($P < 0.001$).

Table 3 lists the hazard ratios for incident hypertension associated with the presence of specific baseline risk factors. Participants with an RHR greater than 80 bpm or who were over 45 years old had a risk of hypertension that was 72 and 12% greater, respectively. There was a 14% increase in risk for participants who were overweight or obese. Dyslipidemia, hyperuricemia, and impaired glucose regulation were also risk factors for new-onset hypertension. In this analysis, an eGFR less than 90 ml/min per 1.73 m^2 was also a significant risk factor (hazard ratio: 1.35, 95% CI 1.21–1.51, $P < 0.001$), after adjustment for sex and baseline SBP and DBP.

The incidence of hypertension increased with the cumulative score (Table 4). It was substantially higher in participants with at least 4 points (101.51 in 1000 person-years) than in those with 0 points (10.96 in 1000 person-years). The relationship between higher incidence and high cumulative score was also present in participants when they were analyzed according to sex. There was a strong, graded relationship between incident hypertension and cumulative score. After adjustment for sex and baseline SBP and DBP, the hazard ratios (CIs) for incident hypertension for participants with 2, 3, and at least 4 points were 1.61 (1.29–2.02), 2.05 (1.64–2.57), and 2.77 (2.22–3.46), respectively (P trend <0.001) compared with those with 0 points. Each additional point was associated with a 31% higher risk of hypertension. This dose–response relationship was observed in men and women separately after adjustment.

DISCUSSION

In this retrospective study of participants from southern China, the main finding was that a cumulative score

TABLE 3. Correlation of risk factors at baseline and incidence of hypertension

	Case	Person-year	Incidence rate*	Unadjusted hazard ratio (95% CI)	Adjusted[a] hazard ratio (95% CI)
Age at least 45 years					
No	1299	45 839.14	28.34	1	1
Yes	1203	13 025.50	92.36	2.91 (2.69–3.15)	1.72 (1.58–1.87)
Resting heart rate at least 80 bpm					
No	1342	32 833.14	40.87	1	1
Yes	1160	26 031.50	44.56	1.22 (1.13–1.32)	1.12 (1.03–1.22)
Overweight/obesity					
No	989	37 693.98	26.24	1	1
Yes	1513	21 170.66	71.47	2.35 (2.17–2.55)	1.14 (1.05–1.24)
Dyslipidemia					
No	758	28 798.64	26.32	1	1
Yes	1744	30 066.00	58.01	2.13 (1.95–2.32)	1.12 (1.03–1.23)
Hyperuricemia					
No	1492	43 358.52	34.41	1	1
Yes	1010	15 506.12	65.14	1.73 (1.60–1.88)	1.15 (1.06–1.25)
Impaired glucose regulation					
No	2090	54 831.22	38.12	1	1
Yes	412	4033.42	102.15	2.45 (2.21–2.73)	1.17 (1.05–1.31)
eGFR less than 90 ml/min per 1.73 m^2					
No	2067	54 101.60	37.70	1	1
Yes	435	4763.04	91.33	2.54 (2.29–2.81)	1.35 (1.21–1.51)

[a]Adjusted for sex and baseline SBP and DBP. eGFR, estimated glomerular filtration rate.

TABLE 4. Risk for hypertension according to the accumulative scores

Accumulative scores	Cases	Incidence rate[a]	Unadjusted hazard ratio (95% CI)	*P*	Adjusted[b] hazard ratio (95% CI)	*P*
All participants						
0	91	10.96	1.00	—	1.00	—
1	294	17.38	1.66 (1.31–2.10)	<0.001	1.16 (0.92–1.47)	0.206
2	528	35.68	3.29 (2.63–4.11)	<0.001	1.61 (1.29–2.02)	<0.001
3	666	63.48	5.42 (4.35–6.74)	<0.001	2.05 (1.64–2.57)	<0.001
≥4	923	110.51	9.22 (7.43–11.44)	<0.001	2.77 (2.22–3.46)	<0.001
P trend			<0.001		<0.001	
Per one point increase			1.74 (1.68–1.80)		1.32 (1.27–1.36)	
Males						
0	59	17.92	1.00	—	1.00	—
1	205	28.30	1.66 (1.24–2.22)	0.001	1.21 (0.91–1.62)	0.193
2	402	46.19	2.71 (2.06–3.56)	<0.001	1.59 (1.21–2.10)	0.001
3	513	67.32	3.84 (2.94–5.03)	<0.001	1.88 (1.43–2.47)	<0.001
≥4	724	109.68	6.29 (4.82–8.20)	<0.001	2.58 (1.97–3.39)	<0.001
P trend			<0.001		<0.001	
Per one point increase			1.55 (1.49–1.62)		1.28 (1.22–1.33)	
Females						
0	32	6.39	1.00	—	1.00	—
1	89	9.20	1.53 (1.02–2.29)	0.040	1.05 (0.70–1.58)	0.813
2	126	20.68	3.47 (2.36–5.12)	<0.001	1.54 (1.04–2.29)	0.032
3	153	53.29	8.19 (5.59–11.00)	<0.001	2.51 (1.69–3.72)	<0.001
≥4	199	113.61	16.17 (11.12–23.51)	<0.001	3.16 (2.12–4.69)	<0.001
P trend			<0.001		<0.001	
Per one point increase			2.14 (2.00–2.28)		1.41 (1.31–1.52)	

[a]Incidence rate per 1000 person-years.
[b]Adjusted for sex (except where sex-stratified), baseline SBP and DBP.

indicative of the presence or absence of seven risk factors (age, RHR, overweight or obesity, dyslipidemia, hyperuricemia, impaired glucose regulation, and eGFR <90 ml/min per 1.73 m^2) at baseline was associated with the risk of new-onset hypertension. There was a strong, graded relationship between higher cumulative score and a greater risk of developing hypertension. In addition, higher scores in men and women were individually associated with progressively higher incidences of hypertension. This score may be of clinical value for the identification of nonhypertensive individuals who are at high risk of developing hypertension, in order to prevent its development, and suggests that the clustering of multiple risk factors plays an important role in the pathogenesis of hypertension.

Previous cross-sectional studies have demonstrated that hypertension occurs in combination with other risk factors. In a study of 3227 Han and Mongolian participants, a dose–response relationship was identified between the number of risk factors present and hypertension. Specifically, the odd ratios (ORs) for hypertension increased as the number of risk factors increased [20]. In another study of 176 740 men and women, Li and colleagues showed that clustering of risk factors was associated with higher BP [21]. However, the cross-sectional design of these studies does not allow exploration of the causal relationships between risk factor clustering and the development of hypertension.

To the best of our knowledge, only a few studies have shown an association between the clustering of risk factors and incident hypertension. However, a retrospective study constituting 4857 normotensive individuals showed that clustering of risk factors significantly predicted the development of hypertension. Participants with four or more risk factors, including a family history of hypertension, obesity, diabetes, hypercholesterolemia, and hypertriglyceridemia, had a 4.86-fold higher risk of developing hypertension [22]. In addition, a longitudinal study of 3784 male Japanese office workers documented that compared with the presence of no risk factors (obesity, hypercholesterolemia, low HDL-C, hypertriglyceridemia, high FPG, hyperuricemia, and high white blood cell count), the relative risk of hypertension was 1.41, 1.64, 1.93, 2.01, and 3.34 for participants with 1, 2, 3, 4 and at least 5 risk factors, respectively [23]. However, these studies did not include eGFR and RHR in their analyses. We have extended these previous findings by adding these additional risk factors for hypertension to our analysis.

Renal mechanisms, such as greater norepinephrine secretion and salt sensitivity have been demonstrated to cause or accelerate hypertension [24,25]. In the REACTION Study, individuals with impaired eGFR (<90 ml/min per 1.73 m^2) had a higher risk of hypertension compared with those who had normal eGFR (≥90 ml/min per 1.73 m^2) [26]. Takase *et al.* [14] showed that baseline eGFR independently predicted the onset of hypertension: a reduction in eGFR of 10 ml/min per 1.73 m^2 was associated with an 11% increase in the risk of developing hypertension. Our study also demonstrated that a baseline eGFR of less than 90 ml/min per 1.73 m^2 is a predictor of incident hypertension after adjustment.

RHR is simply measured on an electrocardiogram, an essential component of a health check. Epidemiologic studies of either the general or hypertensive population have found significantly greater all-cause and cardiovascular mortality risk is associated with an RHR of 76–84 bpm or more [27–31]. Some studies have also evaluated the association between RHR and the risk of progression to hypertension. The Kailuan cohort study conducted in China indicated that an increase in RHR of 10 bpm was associated

with an 8% increase in new-onset hypertension [32]. Prospective studies in other locations have also shown that RHR is an independent risk factor for incident hypertension [33–36]. The statement from European Society of Hypertension defined RHR to be high when it is greater than 80–85 bpm and recommended that RHR be measured as part of the overall assessment of the hypertensive patient [37]. Our results are consistent with this statement and show that RHR plays an important role in predicting the risk of hypertension.

As baseline blood pressure is the strongest predictor of incident hypertension [38,39], the impact of the clustering of risk factors on the development of hypertension may be masked by high baseline blood pressure. However, in our study, the association between higher cumulative score and higher risk of developing hypertension persisted even after accounting for baseline blood pressure. This indicates that the presence of a number of risk factors increases the risk of the patient subsequently developing hypertension irrespective of baseline blood pressure classification, and that appropriate risk stratification and risk factor control are required to prevent hypertension, even in currently normotensive patients.

Compared with previous studies, a strength of the present study is that the cohort population was relatively large. Another strength is that all the participants were examined in the same location and all the blood samples were analyzed using the same devices and reagents each year. However, our study has some potential limitations. First, because of its retrospective design, we cannot rule out the possibility that other known risk factors for hypertension may affect our results, such as plasma insulin level, family history of hypertension, smoking, heavy drinking, and socioeconomic status. Thus, further prospective studies taking account of these factors are necessary to confirm our findings. Thirdly, the study data might be skewed because the participants likely represent the healthier portion of the general southern Chinese population who participate in regular health checks, and may therefore, not be representative of all Chinese people. In addition, masked hypertension may not be detected as incident hypertension was defined by a single measurement of blood pressure, which was repeated at follow-up. It should be assessed using either self-monitoring of blood pressure by the patients at home or ambulatory BP monitoring in future study.

In conclusion, our findings demonstrate that a higher cumulative score created from the presence or absence of seven risk factors (age $\geq$45 years, RHR $\geq$80 bpm, overweight or obesity, dyslipidemia, hyperuricemia, impaired FPG, and eGFR less than 90 ml/min per 1.73 m^2) is associated with a higher risk of incident hypertension. Early identification of high-risk individuals with multiple risk factors may be crucial for the prevention of future hypertension, irrespective of their baseline blood pressure.

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Conflicts of interest

There are no conflicts of interest.

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