



BMJ Open Prevalence of isolated diastolic hypertension and the risk of cardiovascular mortality among adults aged 40 years and older in northeast China: a prospective cohort study

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ABSTRACT

Objectives Little is known about the prevalence and impact of isolated diastolic hypertension (IDH) in northeast China. We aimed to investigate the current epidemiology of IDH and to illustrate whether IDH accounted for cardiovascular disease (CVD) mortality.

Design A prospective cohort study.

Setting A population-based study carried out in northeast China.

Participants We built a community-based study of 18 796 residents aged ≥40 years who were living in northeast China with blood pressure measurements between September 2017 and March 2019.

Outcome measures Information on CVD death was obtained from baseline until 31 July 2021. IDH was defined as a diastolic blood pressure ≥90 mm Hg together with systolic blood pressure <140 mm Hg among hypertensive population.

Results The overall prevalence of IDH was 3.9%, which decreased significantly with advancing age ($p<0.001$) and ranged from 7.2% (95% CI: 6.3% to 8.2%) among participants 40–49 years to 1.5% (95% CI: 1.1% to 2.0%) among participants ≥70 years. Moreover, the IDH prevalence was higher in men than in women (5.2% vs 3.1%, $p<0.001$). The awareness and treatment rates of IDH were 25.7% and 17.7%, respectively, which were significantly lower than those of patients with non-IDH (50.1% and 21.7%, $p=0.009$, respectively). During a median follow-up of 3.2 years, 314 subjects died due to CVD (rate 4.84/1000 person-years). IDH and non-IDH were both significantly associated with an increased risk of CVD death (HR: 2.55, 95% CI: 1.35 to 4.82; HR: 2.48, 95% CI: 1.81 to 3.38) when compared with participants with non-hypertension.

Conclusions IDH was mainly prevalent among young and middle-aged populations, and the awareness and treatment rates in IDH were lower than those in non-IDH hypertension. Additionally, IDH and non-IDH were significantly related to an increased risk of CVD mortality. Early management of IDH is urgently required in northeast China.

INTRODUCTION

Hypertension remains a major modifiable risk factor for cardiovascular death that

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ We provided an opportunity to comprehensively evaluate the current isolated diastolic hypertension (IDH) epidemic in a large representative population.
- ⇒ Our study allows accurate assessment of cardiovascular disease risk in the IDH population in northeast China.
- ⇒ The generalisability of our results in other regions and races might be limited, as it was undertaken in northeastern regions of China.

currently affects over 1 billion people globally.¹ Diastolic blood pressure (DBP) reflects peripheral resistance and has long been considered an important cardiovascular risk indicator.² Previous studies indicated that DBP was strongly and directly related to cardiovascular disease (CVD) risk. Each difference of every 10 mm Hg usual DBP was associated with a more than twofold increased risk of stroke mortality,³ and lowering DBP could significantly reduce the risk of cardiovascular events.⁴

Hypertension can be divided into isolated systolic, isolated diastolic and mixed hypertension using proposed thresholds according to recent guidelines.^{1,5} Isolated diastolic hypertension (IDH), characterised by an increase in DBP without an increase in systolic blood pressure (SBP), is a major subtype of hypertension.⁵ However, it has been neglected for a long time in the era of ‘systolic hypertension’, as systolic hypertension is the predominant risk predictor in older people.² A recent study indicated that IDH was significantly related to increased cardiovascular risk, especially among young residents. The relative risks for IDH were 1.4 (95% CI: 1.0 to 2.1) in men aged 45–54 years and 1.8 (95% CI:

1.3 to 2.5) in men aged 55–68 years when compared with normotension according to the meta-analysis.⁶ However, results from other authors have not found this association.² There is still considerable controversy surrounding IDH and cardiovascular risks.

With rapid economic progress and lifestyle changes, the prevalence of hypertension has increased steeply in younger adults, particularly in developing countries.^{7,8} The prevalence of hypertension has reached 56.8% in northeast China according to our previous study.⁸ However, current data on IDH and its relationship with CVD mortality are still lacking in northeast China.⁹ Reliable epidemiologic data of IDH are crucially important in formulating region-specific strategies in terms of reducing CVD burden. Therefore, in the present study, we aimed to profile the up-to-date characteristics of IDH and to further illustrate whether IDH accounted for CVD mortality in northeast China.

METHODS

Study population and design

This is a community-based prospective cohort study with a median follow-up period of 3.2 years. The design of the study has been described previously.^{10,11} In brief, from September 2017 to March 2019, a multistage, random cluster sampling method was employed to select a representative sample aged ≥ 40 years in rural and urban areas of Liaoning Province, in northeast China. All permanent residents aged ≥ 40 years in each village and community ($n=22\,009$) were eligible to participate, a total of 18 796 (85.4%) participants finally completed the study. All study participants were follow-up until 31 July 2021 for the status of survivor and specific cause of death (figure 1).

Baseline data collection

At baseline, detailed information on demographic characteristics, lifestyle and diseases history was collected by face-to-face questionnaires, physical examinations and laboratory tests. All investigators underwent uniform training before starting the survey.

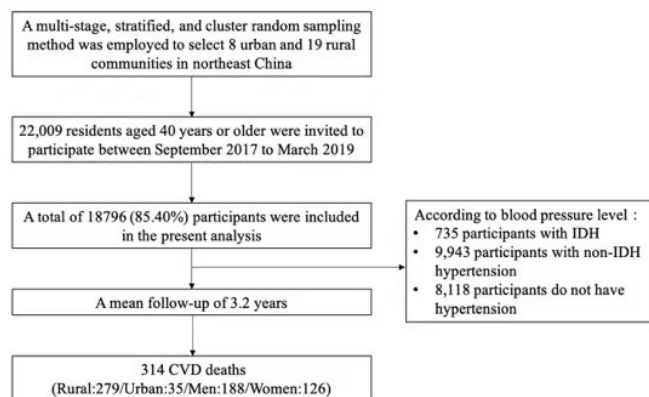


Figure 1 Flowchart of population selection. CVD, cardiovascular disease; IDH, isolated diastolic hypertension.

Blood pressure (BP) was measured three times at 2 min intervals after at least 5 min of rest in the sitting position using a standardised automatic electronic sphygmomanometer (J30; Omron, Kyoto, Japan). Participants were instructed to avoid coffee or tea drinking, alcohol consumption, smoking and perform exercise for at least 30 min before BP measurements. The average of the three BP values was used for subsequent analysis.

According to the recommendations from China Hypertension Guidelines 2018, hypertension was diagnosed if the individual met either of the following criteria: mean SBP ≥ 140 mm Hg and/or mean DBP ≥ 90 mm Hg, or use of antihypertensive medication in the past 2 weeks, otherwise was non-hypertensive. In hypertensive population, IDH was defined as a DBP ≥ 90 mm Hg together with SBP < 140 mm Hg,¹² others were non-IDH.

Awareness was defined as hypertensive patients self-reported that they were previously diagnosed with hypertension by professional doctor, treatment was defined as the use of anti-hypertensive medicine within 2 weeks at the time of the interview.

Definitions such as diabetes and dyslipidaemia in our study have been described previously.¹³ Physical measurements including height, weight and waist circumference were noted to the nearest 0.1 kg and 0.1 cm with participants wearing lightweight clothes without shoes. Body mass index (BMI) was calculated as weight divided by the square of height (kg/m^2). All data were obtained according to standardised protocols.

Fasting blood samples were collected in the morning after an overnight fast of ≥ 8 hours. The samples were obtained from an antecubital vein into BD Vacutainer tubes containing ethylenediaminetetraacetic acid (Becton, Dickinson and Co, Franklin Lakes, New Jersey, USA). Serum samples were isolated from whole blood and frozen at -20°C for storage. The biochemical parameters, including fasting blood glucose (FBG), glycosylated haemoglobin (HbA1c), total cholesterol (TC), triglyceride (TG), serum high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), were measured using an Abbott Diagnostics C800i auto-analyzer (Abbott Laboratories, Abbott Park, Illinois, USA) with commercial kits. To ensure the testing was accurate, 10% of the specimens were randomly selected from each laboratory for centralised retesting by the Ministry of Health's National Center for Clinical Laboratory of China.

Dyslipidaemia was determined according to the criteria of National Cholesterol Education Program-Third Adult Treatment Panel (ATP III). High LDL-C was defined as LDL-C ≥ 4.16 mmol/L, low HDL-C was defined as HDL-C < 1.03 mmol/L, high TG was defined as TG ≥ 2.26 mmol/L, high TC was defined as TC ≥ 6.21 mmol/L.

Diabetics was defined according to the WHO criteria: FBG ≥ 7.0 mmol/L or HbA1c $\geq 6.5\%$ and/or self-reported diagnosis of diabetics that was identified by a certified physician previously.

Current smoking (≥ 1 cigarette/day and continued for ≥ 1 year) and current drinking (any dose of alcohol, ≥ 1 time/week) were determined according to the self-report.

Lack of exercise was defined as failing to meet the standards for regular exercise including moderate-intensity exercise (equivalent to walking) for ≥ 30 mins and ≥ 3 times per week.¹³ We classified awareness and treatment of hypertension, current smoking, current drinking and exercise status based on self-report.¹³

Outcome measures

Information on CVD death was obtained from baseline until 31 July 2021. Mortality data were obtained from the National Population Registry of the China National Statistical Office. We accessed the database containing death certificates for CVD deaths that occurred between the cross-sectional study conducted date and 31 July 2021. The cause of death was determined by reviewing the death certificates and classified according to the death code (I60–I64, I21–I22, International Classification of Diseases, 10th Revision).

Statistical analysis

The Epidata3.0 software was used to double input data to ensure their quality, and data processing and analysis were carried out using the SPSS V.24.0 software. The continuous variables with normal distribution are reported as means and SD, numerical data were expressed as rates, and a χ^2 test was used to evaluate differences between groups. Age standardisation was performed according to China census population in 2010. Cox proportional hazard regression models were used in the evaluation of CVD mortality in each group. Model 1 was unadjusted. Model 2 was adjusted for age and sex. Model 3 was further adjusted for BMI, history of atrial fibrillation, history of stroke, history of heart disease, dyslipidaemia, current smoking, current drinking, education, income, physical activity (online supplemental table 1). Kaplan-Meier analysis with log-rank test was used to estimate the cumulative survival of CVD events in each group. A p value of <0.05 was considered as significant.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

RESULT

Characteristics of the study participants

The baseline characteristics of the population are described in table 1. There were 18 796 participants (28.9% urban and 71.1% rural; 39.0% men and 61.0% women) included in our study, with an average age of 60.35 ± 9.93 years; 87.8% of the participants had a middle school education or lower, and 33.7% were low-socioeconomic participants with an annual income less than 5000 yuan. The mean SBP and DBP levels were 142.9 ± 22.6 mm Hg

and 85.4 ± 11.6 mm Hg, respectively. Additionally, there were significant differences between region and gender for all characteristics ($p < 0.001$).

Prevalence of IDH

The overall prevalence of IDH was 3.9% (95% CI: 3.6% to 4.2%) at baseline. There was no significant difference in the prevalence of IDH between urban and rural residents (4.1% vs 3.8%, $p=0.460$); however, the IDH prevalence in men was higher than that in women (5.2% vs 3.1%, $p < 0.001$). Moreover, the prevalence of IDH decreased significantly with advancing age ($p < 0.001$) and ranged from 7.2% (95% CI: 6.3% to 8.2%) among participants 40–49 years to 1.5% (95% CI: 1.1% to 2.0%) among participants ≥ 70 years. The age-standardised prevalence of IDH was 5.0% (urban 4.5% and rural 5.2%, men 6.9% and women 4.0%) (table 2).

Awareness and treatment of patients with IDH

Among those participants with IDH, 25.7% were aware of their diagnosis, and 17.7% were taking antihypertensive medication. The awareness and treatment rates of IDH in urban areas were higher than those in rural areas (30.8% vs 23.5%, $p=0.040$ and 24.4% vs 14.8%, $p=0.002$, respectively). In addition, women had higher awareness and treatment rates than men (29.1% vs 22.5%, $p=0.039$ and 21.3% vs 14.3%, $p=0.013$, respectively). Among participants who were aware of their diagnosis of IDH, 68.8% of patients were taking antihypertensive medications, and the rate was higher in urban areas than in rural areas (79.4% vs 62.8%, $p=0.018$); however, no significant difference was found between men and women (figure 2).

Differences in awareness and treatment rates between patients with IDH and non-IDH

Among the hypertensive population, the awareness rate in the IDH group was lower than that in the non-IDH group (25.7% vs 50.1%, $p < 0.001$), including all regions and genders ($p < 0.001$). Among the patients with non-IDH, the treatment rate was 21.7%, higher than that in patients with IDH ($p=0.009$). Among those who were aware of their hypertensive condition, 78.7% of non-IDH participants received anti-hypertensive treatment, which was higher than that of patients with IDH ($p=0.001$) (figure 3).

The risk of CVD death in participants with different blood pressure types

During the median follow-up of 3.2 years, 314 (1.7%) participants died due to CVD. Among subjects with IDH, the risk of CVD death was 4.84/1000 person-years (PY), which was 2.47 times higher than that in the non-hypertension group ($p=0.005$). Patients with IDH had a 2.85 (95% CI: 1.52 to 5.36) times higher risk of CVD mortality than the non-hypertension group after adjusting for age and sex. Additional adjustment for multiple variables in Model 3 only slightly attenuated this relationship (HR=2.55, 95% CI: 1.35 to 4.82). Among patients with non-IDH, the risk of CVD death

Table 1 Baseline characteristics of study participants

Characteristics	Non-hypertension (n=8118)	IDH (n=735)	Non-IDH (n=9943)	Overall	P value
Participant, n (%)	8118 (43.2)	735 (3.9)	9943 (52.9)	18 796 (100.0)	
Followed time, years	3.25±0.49	3.37±0.49	3.24±0.53	3.25±0.51	<0.001
Mean age, years	57.55±9.56	55.53±9.24	63.00±9.51	60.35±9.93	<0.001
40–49	1828 (22.5)	209 (28.4)	858 (8.6)	2895 (15.4)	<0.001
50–59	2883 (35.5)	286 (38.9)	2595 (26.1)	5764 (30.7)	
60–69	2535 (31.2)	188 (25.6)	4040 (40.6)	6763 (36.0)	
≥70	872 (10.7)	52 (7.1)	2450 (24.6)	3374 (18.0)	
Sex, n (%)					
Men	3026 (37.3)	378 (51.4)	3932 (39.5)	7336 (39.0)	<0.001
Women	5092 (62.7)	357 (48.6)	6011 (60.5)	11 460 (61.0)	
Education, n (%)					
Primary school or lower	3417 (42.1)	297 (40.4)	5575 (56.1)	9289 (49.4)	<0.001
Middle school	3538 (43.6)	318 (43.3)	3349 (33.7)	7205 (38.3)	
High school or above	1163 (14.3)	120 (16.3)	1019 (10.2)	2302 (12.2)	
Annual household income (yuan), n (%)					
<5000	2224 (27.4)	166 (22.6)	3946 (39.7)	6336 (33.7)	<0.001
5000–9999	1401 (17.3)	146 (19.9)	1756 (17.7)	3303 (17.6)	
10 000–19 999	1541 (19.0)	147 (20.0)	1569 (15.8)	3257 (17.3)	
≥20 000	2952 (36.4)	276 (37.6)	2672 (26.9)	5900 (31.4)	
Mean BMI, kg/m ²	23.910±3.35	25.36±3.90	25.33±3.74	24.72±3.65	<0.001
Mean SBP, mm Hg	124.12±10.35	133.63±5.28	158.90±18.10	142.89±22.62	<0.001
Mean DBP, mm Hg	77.61±6.96	93.45±3.40	91.14±11.23	85.39±11.59	<0.001
Current smoking, n (%)	2135 (26.3)	202 (27.5)	2299 (23.1)	4636 (24.7)	<0.001
Current drinking, n (%)	2138 (26.3)	284 (38.6)	2542 (25.6)	4964 (26.4)	<0.001
History of AF, n (%)	72 (0.9)	22 (3.0)	121 (1.2)	215 (1.1)	<0.001
History of stroke, n (%)	191 (2.4)	42 (5.7)	932 (9.4)	1165 (6.2)	<0.001
History of heart disease, n (%)	295 (3.6)	40 (5.4)	779 (7.8)	1114 (5.9)	<0.001
Diabetes, n (%)	905 (11.2)	99 (13.5)	2196 (22.1)	3200 (17.1)	<0.001
Dyslipidaemia, n (%)	2445 (30.2)	289 (39.4)	3978 (40.1)	6712 (35.8)	<0.001
Lack of exercise, n (%)	831 (10.2)	284 (11.4)	1585 (15.9)	2500 (13.3)	<0.001

AF, atrial fibrillation; BMI, body mass index; DBP, diastolic blood pressure; IDH, isolated diastolic hypertension; SBP, systolic blood pressure.

was 7.78/1000 PY, which was 4.03 times higher than that of the reference group. Non-IDH also significantly increased the risk of developing CVD death compared

with the reference group in Model 2 (HR=2.51, 95% CI: 1.85 to 3.40) and Model 3 (HR=2.48, 95% CI: 1.81 to 3.38) (table 3, figure 4).

Table 2 The prevalence of isolated diastolic hypertension in northeastern China

Age group	Region		Sex		Total	P for region	P for sex
	Urban	Rural	Men	Women			
40–49	5.0 (3.3–6.6)	7.9 (6.8–9.0)	9.5 (7.7–11.2)	5.9 (4.9–7.0)	7.2 (6.3–8.2)	0.011	<0.001
50–59	5.0 (3.9–6.0)	5.0 (4.3–5.6)	7.2 (6.1–8.3)	3.8 (3.2–4.4)	5.0 (4.4–5.5)	0.979	<0.001
60–69	3.8 (3.0–4.6)	2.3 (1.9–2.8)	3.7 (3.0–4.4)	2.2 (1.7–2.6)	2.8 (2.4–3.2)	0.001	<0.001
≥70	2.5 (1.5–3.5)	1.2 (0.8–1.6)	2.2 (1.4–2.9)	1.0 (0.6–1.5)	1.5 (1.1–2.0)	0.007	0.008
Overall	4.1 (3.5–4.6)	3.8 (3.5–4.2)	5.2 (4.6–5.7)	3.1 (2.8–3.4)	3.9 (3.6–4.2)	0.460	<0.001
ASR	4.5 (3.9–5.1)	5.2 (4.8–5.6)	6.9 (6.3–7.5)	4.0 (3.6–4.4)	5.0 (4.7–5.3)		

ASR, age standardised rates by China census population 2010.

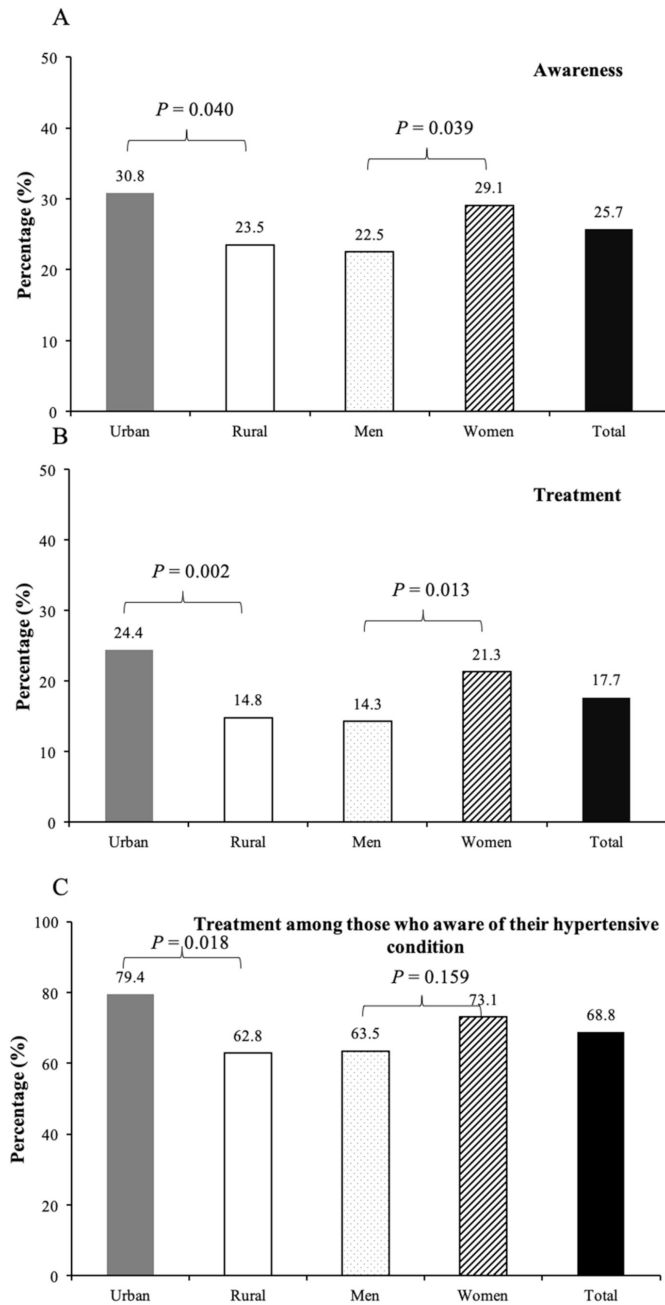


Figure 2 Awareness (A) and treatment (B, C) among patients with IDH in aged 40 years or older in northeastern China. IDH, isolated diastolic hypertension.

DISCUSSION

The prevalence of IDH was 3.9% in adults aged ≥ 40 years old in northeast China, which was slightly higher than the national level of 3.2% reported in 2014–2018¹⁴; however, it was lower than the China Health and Nutrition Survey reported 4.44% in 2011.¹⁵ Compared with other middle-income countries (4.5% in India and 3.95% in Saudi Arabia), the prevalence of IDH was relatively low in northeast China.^{16 17} However, China possesses one-fifth of the world's population; therefore, the IDH population remains substantial. Furthermore, there were no significant differences in the prevalence of IDH between urban and rural subjects, possibly due to rapid economic

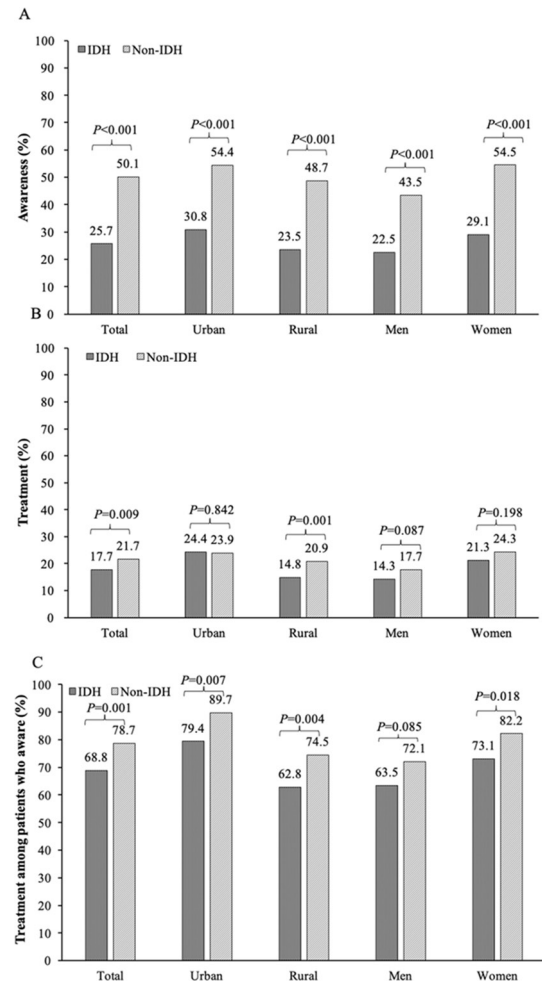


Figure 3 Awareness and treatment among participants with hypertension according to hypertension subtypes in northeast China by region and sex. (A) Awareness among patients with hypertension, (B) treatment among patients with hypertension, (C) treatment among patients who already aware of hypertension. IDH, isolated diastolic hypertension.

progress and urbanisation in recent years.¹⁸ Consistent with most previous studies,^{17 19} the IDH prevalence was higher in men than in women across all age groups, and the high prevalence of smoking and alcohol consumption in men was possibly responsible for this sex-related difference. Similar to previous studies, we found that the IDH prevalence decreased with advancing age, the highest prevalence of IDH in people aged 40–49 years was 7.2%, and the lowest IDH prevalence was found in subjects aged ≥ 70 years (1.5%), possibly due to increased vascular stiffness, or changed to non-IDH type as SBP increased significantly with age. Additionally, a sedentary lifestyle and the increasing prevalence of metabolic disorders might contribute to the high prevalence of IDH in young adults.^{20 21} Therefore, health education, screening and treatment of IDH in young men should be highlighted.

The awareness and treatment rates of hypertension in patients with IDH were 25.7% and 17.7% in northeast China. Although they were higher than the national levels, the awareness and treatment rates were still

Table 3 The HRs and corresponding 95% CI of CVD death among participants with different blood pressure types

Characteristics	Number of events	Follow-up (person-years)	Rate (per 1000 person-years)	Model 1	Model 2	Model 3
Non-hypertension	51	26 420	1.93	Ref.	Ref.	Ref.
IDH	12	2478	4.84	2.47 (1.32–4.64)	2.85 (1.52–5.36)	2.55 (1.35–4.82)
Non-IDH	251	32 242	7.78	4.03 (2.98–5.44)	2.51 (1.85–3.40)	2.48 (1.81–3.38)

Model 1 was unadjusted. Model 2 was adjusted for age and sex. Model 3 was further adjusted for BMI, history of atrial fibrillation, history of stroke, history of heart disease, dyslipidaemia, current smoking, current drinking, education, income, physical activity. BMI, body mass index; CVD, cardiovascular disease; IDH, isolated diastolic hypertension; Ref., reference.

frustratingly low. Moreover, the awareness and treatment rates were significantly higher in urban areas than in rural areas, and higher economic income and education levels in urban residents might contribute to the difference. Consistent with previous reports,²² we found that men were more likely to have increased DBP but lower awareness and treatment rates than women.

Additionally, the awareness rate in non-IDH subjects was 50.1%, which was far below the 84% reported in developed countries.²³ Notably, the proportion of awareness in IDH subjects was even worse. Compared with other subtypes of hypertension, patients with IDH tended to be younger, and silent symptoms in patients with IDH might also be responsible for the low awareness and treatment rates.²¹ Therefore, the poor awareness and treatment of IDH in the northeast remained worrisome, particularly in rural residents and men.

According to UK Biobank research, IDH was significantly associated with an increased risk of CVD events (HR, 1.15; 95% CI, 1.04 to 1.29) when compared with participants with normal SBP,^{24 25} and our study further confirmed this finding. In the unadjusted model, the risk of CVD mortality was significantly higher in patients with non-IDH than in the IDH group. However, after adjusting for age, sex and other factors, we found that IDH drove CVD risk in younger individuals, roughly concordant with Lee's previous study, which showed that HR for CVD events associated with IDH were 1.19 (1.17–1.20) in the age group of 40–64 years and 1.09 (1.07–1.11) in the age

group of 65–89 years ($p < 0.001$ for interaction vs 40–64 years).²⁶ However, McEvoy suggested that IDH was neither associated with increases in subclinical nor clinical CVD, which is contrary to our study.² There are two possible reasons: first, McEvoy's study included persons using antihypertensive medications while our study included subjects not receiving antihypertensive treatment, and the presence or absence of medication may make a difference to the outcome. Second, our study is the first report in China to discuss the association between IDH and the risk of CVD mortality, there may be differences between different ethnic groups.

The strength of our study is that we provided an opportunity to comprehensively evaluate the current IDH epidemic in a large representative population including urban and rural residents, which allows accurate assessment of CVD risk in the IDH population in northeast China. However, the present study still had several limitations. First, we only collected CVD deaths in the follow-up, and the impact of IDH on CVD incidence should be investigated in future studies. Second, the study cohort included a relatively small sample size of patients with IDH and a short follow-up period; however, the associations between IDH and the risk of CVD mortality were statistically significant. Third, the study cohort was designed to analyse the risk of CVD mortality, people aged 40 years and older who were at high risk of CVD were included. Therefore, the prevalence of IDH may be underestimated and future increases in the 20–39 years old population

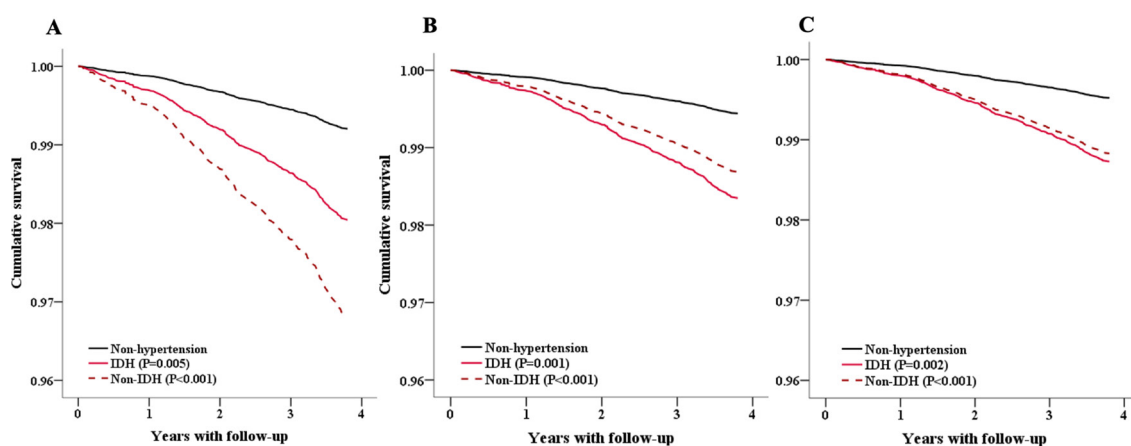


Figure 4 Kaplan-Meier survival curves for CVD death among participants with different blood pressure types. (A) Unadjusted model, (B) HR_{adj1} model, (C) HR_{adj2} model. CVD, cardiovascular disease; IDH, isolated diastolic hypertension.

are needed. But this study focused on elucidating the associations between IDH and the risk of CVD mortality, the association were statistically significant. Last, the study was undertaken in northeastern regions of China, and the generalisability of our results in other regions and races might be limited; therefore, more research from other populations in different regions or races is still needed to replicate the findings.

Conclusions

The prevalence of IDH among adults aged 40–59 years in northeastern China was relatively high, while the awareness and treatment rates remained low, especially in rural areas and men. Moreover, IDH was significantly associated with a high risk of CVD mortality. Therefore, strategies for long-term screening, prevention and management of IDH should be emphasised in terms of improving prognosis in northeast China.

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Contributors SL and LX were responsible for the study designing, conducted the data and writing the manuscript. LY and HC participated in the study design and conducted the study. QS, LS, JS and GL were involved in data collection. All authors contributed to the protocol and approved the final manuscript. SL and LX were the guarantors of our article.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The study was granted approval by the Central Ethics Committee at the China National Center for Cardiovascular Disease (Clinical Research No. [2015]024. Beijing, China). All methods were performed in accordance with the relevant guidelines and regulations. Written informed consent was obtained from all participants. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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