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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.

Methods We built a community-based study of 18796 residents aged ≥ 40 years who were living in northeast China with blood pressure (BP) measurements between September 2017 and March 2019. Information on CVD death was obtained from baseline until July 31, 2021.

Results The overall prevalence of IDH was 3.9%, which decreased significantly with age (P<0.001) and ranged from 7.2% (95% CI: 6.3-8.2) among participants 40-49 years to 1.5% (95% CI: 1.1-2.0) 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 non-IDH patients (50.1% and 39.5%, P<0.001, respectively). During a median follow-up of 3.3 years, 314 subjects died due to CVD (rate 5.14/1,000 person-years). IDH and non-IDH were both significantly associated with an increased risk of CVD death (HR: 2.40, 95% CI 1.28-4.52; HR: 2.32, 95% CI 1.70-3.18, respectively) when compared to non-hypertension participants.

Conclusion 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.

Key Words: Isolated Diastolic Hypertension; Prevalence; Cardiovascular mortality

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 (CVD) risk in the IDH population in northeast China.
- The prevalence of IDH was 3.9% among participants ≥ 40 years in northeast China, higher in men than in women. The burden of IDH in northeast China was substantial, with low awareness and treatment rates as well as high cardiovascular mortality risk.
- The limitation of the study was that we only collected CVD deaths in the follow-up, and the impact of IDH on CVD incidence should be investigated in future studies.

INTRODUCTION

Hypertension remains a major modifiable risk factor for cardiovascular death that 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 mmHg 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), characterized 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: 1.0-2.1) in men aged 45-54 years and 1.8 (95% CI: 1.3-2.5) in men aged 55-68 years when compared to normotension.[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 counties.[7, 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 3.3 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 July 31, 2021 for the status of survivor and specific cause of death (**Figure 1**). The study was approved by the Ethics Commission of the CPC Central Committee of the China Cardiovascular Disease Center (Beijing). All participants obtained written informed consent.

Baseline data collection

At baseline, detailed information on demographic characteristics, lifestyle and

diseases history were collected by face-to-face questionnaires, physical examinations, and laboratory tests. All investigators underwent uniform training before starting the survey.

Blood pressure was measured three times at 2-min intervals after at least 5 min of rest in the sitting position using a standardized automatic electronic sphygmomanometer (J30; Omron, Kyoto, Japan). Participants were instructed to avoid coffee or tea drinking, alcohol consumption, smoking and perform excise 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 mmHg and/or mean DBP ≥ 90 mmHg, or use of antihypertensive medication in the past 2 weeks, otherwise was non-hypertensive. In hypertensive population, IDH was defined as a DBP ≥ 90 mmHg together with SBP <140 mmHg,[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 dyslipidemia in our study has been described previously.[13]

Outcome measures

Information on CVD death was obtained from baseline until July 31, 2021. Mortality data was 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 July 31, 2021.The cause of death was determined by reviewing the death certificates and classified according to the death code (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 24.0 software. The continuous variables with normal distribution are reported as means and standard deviations (SD), numerical data were expressed as rates, and a chi-square test ($\chi 2$) was used to evaluate differences between groups. Age standardization 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, stroke and heart disease, level of triglyceride, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol and total cholesterol, treatment for hypertension, current smoking, current drinking, education, income, physical activity. 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 mmHg and 85.4±11.6 mmHg, respectively. Additionally, there were significant differences between region and gender for all characteristics (P <0.001).

Prevalence of isolated diastolic hypertension

The overall prevalence of IDH was 3.9% (95% CI: 3.6-4.2) at baseline. There was no significant difference in the prevalence of IDH between urban and rural residents (3.8% vs. 4.1%, 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: 6.3-8.2) among participants 40-49 years to 1.5% (95% CI: 1.1-2.0) among participants ≥70 years. The age-standardized prevalence of IDH was 5.0% (urban 5.2% and rural 4.5%, men 6.9% and women 4.0%) (**Table 2**).

Table 1. Baseline characteristics of study participants

Characteristics	Region		Sex		Total	*P* for region	*P* for sex
	Urban	Rural	Men	Women			
Participant, n (%)	13372(28.9)	5424(71.1)	7336(39.0)	11460(61.0)	18796(100.0)		
Followed time, years	3.02±0.39	3.35±0.53	3.23±0.56	3.27±0.48	3.25±0.51		
Mean age, years	60.86±9.47	60.15±10.11	61.32±10.15	59.73±9.74	60.35±9.93	<0.001	<0.001
40-49	662(12.2)	2233(16.7)	1046(14.3)	1849(16.1)	2895(15.4)	<0.001	<0.001
50-59	1717(31.7)	4047(30.3)	2018(27.5)	3756(32.7)	5764(30.7)		
60-69	2113(39.0)	4650(34.8)	2742(37.4)	4021(35.1)	6763(36.0)		
≥70	932(17.2)	2442(18.3)	1530(20.9)	1844(16.1)	3374(18.0)		
Education, n (%)							
Primary school or lower	1362(25.1)	7927(59.3)	3103(42.3)	6186(54.0)	9289(49.4)	<0.001	<0.001
Middle school	2876(53.0)	4329(32.4)	3126(42.6)	4079(35.6)	7205(38.3)		
High school or above	1186(21.9)	1116(8.3)	1107(15.1)	1195(10.4)	2302(12.2)		

Annual household income (yuan), n (%)							
<5000	435(8.0)	5901(44.1)	2283(31.1)	4053(35.4)	6336(33.7)	<0.001	<0.001
5000-9999	348(6.4)	2955(22.1)	1324(18.0)	1979(17.3)	3303(17.6)		
10000-19999	897(16.5)	2360(17.6)	1192(16.2)	2065(18.0)	3257(17.3)		
≥20000	3744(69.0)	2156(16.1)	2537(34.6)	3363(29.3)	5900(31.4)		
Mean BMI, kg/m²	24.90±3.41	24.64±3.75	24.37±3.56	24.94±3.70	24.72±3.65	<0.001	<0.001
Mean SBP, mmHg	137.6±19.9	145.1±23.3	143.7±21.5	142.4±23.3	142.9±22.6	<0.001	<0.001
Mean DBP, mmHg	83.4±10.6	86.2±11.9	87.1±11.5	84.3±11.5	85.4±11.6	<0.001	<0.001
Current Smocking, %	1029(19.0)	3607(27.0)	3882(52.9)	754(6.6)	4636(24.7)	<0.001	<0.001
Current Drinking, %	1106(20.4)	3858(28.9)	3918(53.4)	1046(9.1)	4964(26.4)	<0.001	<0.001
Diabetes, %	1096(20.2)	2104(15.8)	1210(16.5)	1990(17.4)	3200(17.1)	<0.001	0.113
Dyslipidemia, %	2681(49.5)	4031(30.2)	2414(33.0)	4298(37.6)	6712(35.8)	<0.001	<0.001
Lack of exercise, %	485(8.9)	2015(15.1)	881(12.0)	1619(14.1)	2500(13.3)	<0.001	<0.001

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

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 standardized rates by China census population 2010.

Awareness and treatment of patients with isolated diastolic hypertension

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 (**Table 3**).

Table 3. Awareness and treatment among IDH patients aged 40 years or older in northeastern China

Age group	Region		Sex		Total	*P* for region	*P* for sex
	Urban	Rural	Men	Women			
Awareness among participants with IDH							
40-49	5(15.2)	36(20.5)	15(15.2)	26(23.6)	41(19.6)	0.481	0.123
50-59	29(34.1)	47(23.4)	30(20.7)	46(32.6)	76(26.6)	0.060	0.022
60-69	26(32.5)	28(25.9)	29(28.7)	25(28.7)	54(28.7)	0.325	0.997
≥70	8(34.8)	10(34.5)	11(33.3)	7(36.8)	18(34.6)	0.982	0.798
Overall	68(30.8)	121(23.5)	85(22.5)	104(29.1)	189(25.7)	0.040	0.039
Treatment among participants with IDH							
40-49	2(6.1)	22(12.5)	6(6.1)	18(16.4)	24(11.5)	0.287	0.020
50-59	20(23.5)	26(12.9)	16(11.0)	30(21.3)	46(16.1)	0.026	0.018
60-69	24(30.0)	18(16.7)	21(20.8)	21(24.1)	42(22.3)	0.030	0.583
≥70	8(34.8)	10(34.5)	11(33.3)	7(36.8)	18(34.6)	0.982	0.798
Overall	54(24.4)	76(14.8)	54(14.3)	76(21.3)	130(17.7)	0.002	0.013
Treatment among participants who aware IDH							
40-49	2(40.0)	22(61.1)	6(40.0)	18(69.2)	24(58.5)	0.369	0.067
50-59	20(69.0)	26(55.3)	16(53.3)	30(65.2)	46(60.5)	0.237	0.300
60-69	24(92.3)	18(64.3)	21(72.4)	21(84.0)	42(77.8)	0.013	0.307
≥70	8(100.0)	10(100.0)	11(100.0	7(100.0)	18(100.0)	-	-
Overall	54(79.4)	76(62.8)	54(63.5)	76(73.1)	130(68.8)	0.018	0.159

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 non-IDH patients, the treatment rate was 39.5%, higher than that in IDH patients ($P<0.001$). 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 IDH patients ($P=0.001$) (**Figure 2**).

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

During the median follow-up of 3.3 years, 314 (1.7%) participants died due to CVD. Among subjects with IDH, the risk of CVD death was 4.84/1,000 person-years (PY), which was 2.47 times higher than that in the non-hypertension group ($P=0.005$). IDH patients had a 2.38 (95% CI, 1.26-4.48) 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=2.40, 95% CI: 1.28-4.52). Among non-IDH patients, the risk of CVD death was 7.78/1,000 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=2.44, 95% CI: 1.80-3.30) and Model 3 (HR=2.32, 95% CI: 1.70-3.18) (**Table 4, Figure 3**).

Table 4. Hazard ratios with 95% CI of CVD death among participants with different blood pressure types

Characteristics	Number of events	Follow-up (person-years)	Rate (per 1,000	Model 1	Model 2	Model 3
Non-hypertension	51	26420	1.93	ref.	ref.	ref.
IDH	12	2478	4.84	2.47(1.32-4.64)	2.38(1.26-4.48)	2.40(1.28-4.52)
Non-IDH	251	32242	7.78	4.03(2.98-5.44)	2.44(1.80-3.30)	2.32(1.70-3.18)

ref., reference; HR, hazard ratio. Model 1 was unadjusted. Model 2 was adjusted for age and sex. Model 3 was further adjusted for BMI, history of atrial fibrillation, stroke and heart disease, level of triglyceride, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol and total cholesterol, treatment for hypertension, current smoking, current drinking, education, income, physical activity.

DISCUSSION

The prevalence of IDH was 3.9% in adults aged ≥ 40 years old in northeast China, which was higher than the national level of 3.2% reported in 2014-2018;[14] however, it was lower than the China Health and Nutrition Survey (CHNS) 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 progress and urbanization in recent years.[13] Consistent with most previous studies,[17, 18] 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. Additionally, a sedentary lifestyle and the increasing prevalence of metabolic disorders might contribute to the high prevalence of IDH in young adults.[19, 20] Therefore, health education, screening and treatment of IDH in young men should be highlighted.

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

awareness and treatment rates were still 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,[21] 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.[22] Notably, the proportion of awareness in IDH subjects was even worse. Even in participants who were aware of their hypertensive condition, the treatment rate was only 78.7% in the non-IDH hypertensive population; however, in subjects with IDH, the rate was only 68.8%. Compared with other subtypes of hypertension, IDH patients tended to be younger, and silent symptoms in IDH patients might also be responsible for the low awareness and treatment rates.[20] 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, 1.04-1.29)[23, 24], and our study further confirmed this finding. In the unadjusted model, the risk of CVD mortality was significantly higher in non-IDH patients 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.[25] 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: firstly, McEvoy's study included persons using antihypertensive medications while subjects were not receiving in our study, 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 IDH patients 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 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 generalizability 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 to 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 emphasized in terms of improving prognosis in northeast China.

Abbreviations

SBP: systolic blood pressure; DBP: diastolic blood pressure

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Author' Contributions

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.

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Availability of data and materials

The datasets generated for and analyzed in the study are not publicly available due to China Medical University's privacy policy, but are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

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.

Consent for publication

Not applicable.

Competing interests

None.

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Figure Legends

Figure 1. Flowchart of population selection.

Figure 2. Awareness and treatment among participants with hypertension according to hypertension subtypes in northeast China by region and sex. (A) Awareness among hypertension patients, (B) Treatment among hypertension patients, (C) Treatment among patients who already aware of hypertension.

Figure 3. 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.

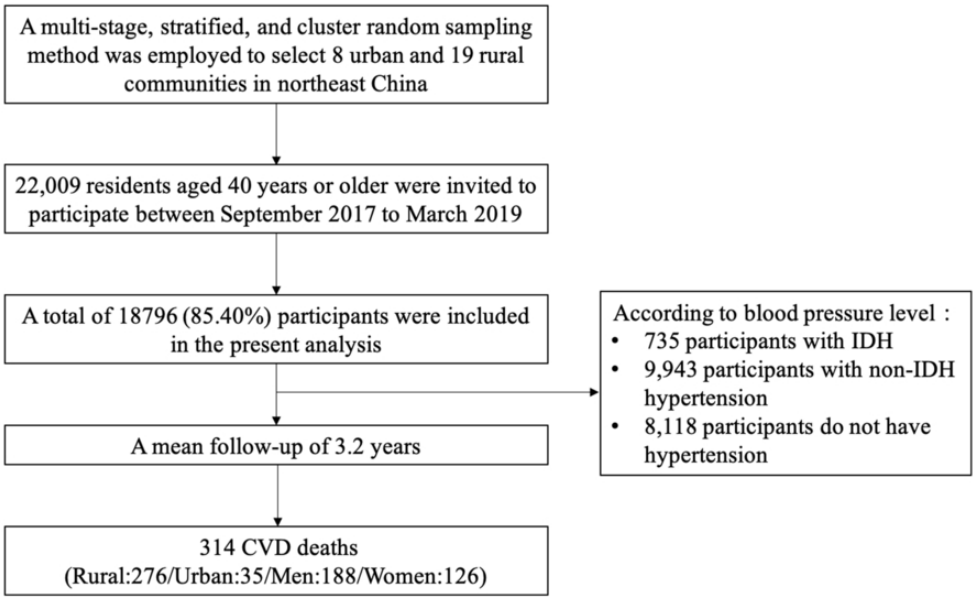

Figure 1. Flowchart of population selection.

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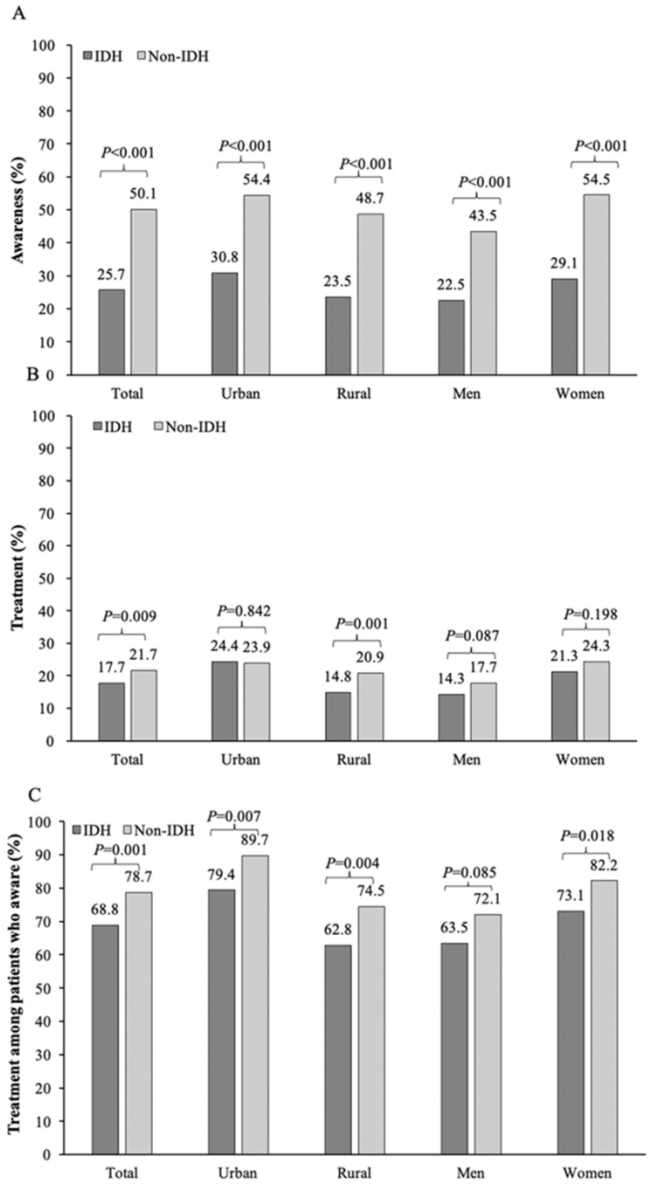

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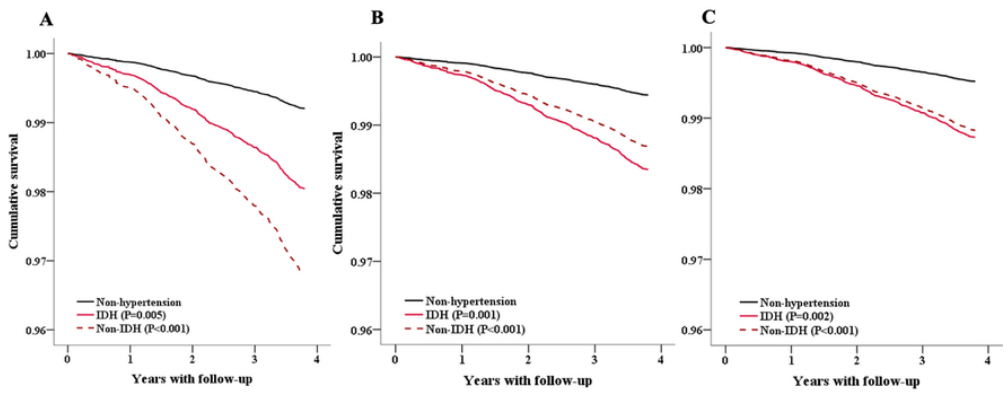

Figure 3. Kaplan-Meier survival curves for CVD death among participants with different blood pressure types. (A) unadjusted model, (B) HRadj1 model, (C) HRadj2 model.

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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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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.

Methods We built a community-based study of 18796 residents aged ≥ 40 years who were living in northeast China with blood pressure (BP) measurements between September 2017 and March 2019. Information on CVD death was obtained from baseline until July 31, 2021. IDH was defined as a DBP ≥ 90 mmHg together with SBP <140 mmHg among hypertensive population.

Results The overall prevalence of IDH was 3.9%, which decreased significantly with age (P<0.001) and ranged from 7.2% (95% CI: 6.3-8.2) among participants 40-49 years to 1.5% (95% CI: 1.1-2.0) 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 non-IDH patients (50.1% and 39.5%, P<0.001, respectively). During a median follow-up of 3.3 years, 314 subjects died due to CVD (rate 5.14/1,000 person-years). IDH and non-IDH were both significantly associated with an increased risk of CVD death (HR:2.55,95% CI 1.35-4.82; HR: 2.48, 95% CI 1.81-3.38) when compared to non-hypertension participants.

Conclusion 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.

Key Words: Isolated Diastolic Hypertension; Prevalence; Cardiovascular mortality

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 (CVD) risk in the IDH population in northeast China.
- The prevalence of IDH was 3.9% among participants ≥ 40 years in northeast China, higher in men than in women. The burden of IDH in northeast China was substantial, with low awareness and treatment rates as well as high cardiovascular mortality risk.
- The limitation of the study was that we only collected CVD deaths in the follow-up, and the impact of IDH on CVD incidence should be investigated in future studies.

INTRODUCTION

Hypertension remains a major modifiable risk factor for cardiovascular death that 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 mmHg 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), characterized 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: 1.0-2.1) in men aged 45-54 years and 1.8 (95% CI: 1.3-2.5) in men aged 55-68 years when compared to 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 counties.[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 3.3 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 July 31, 2021 for the status of survivor and specific cause of death (**Figure 1**). The study was approved by the Ethics Commission of the CPC Central Committee of the China Cardiovascular Disease Center (Beijing). All participants obtained written informed consent.

Baseline data collection

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

Blood pressure was measured three times at 2-min intervals after at least 5 min of rest in the sitting position using a standardized automatic electronic sphygmomanometer (J30; Omron, Kyoto, Japan). Participants were instructed to avoid coffee or tea drinking, alcohol consumption, smoking and perform excise 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 mmHg and/or mean DBP ≥ 90 mmHg, or use of antihypertensive medication in the past 2 weeks, otherwise was non-hypertensive. In hypertensive population, IDH was defined as a DBP ≥ 90 mmHg together with SBP <140 mmHg,[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 dyslipidemia in our study has been described previously.[13] Physical measurements including height, weight, and waist circumference were noted to the nearest 0.1 kilogram (kg) and 0.1 centimeter (cm)

with participants wearing lightweight clothes without shoes. Body mass index (BMI) was calculated as weight divided by the square of height (kg/m2). All data were obtained according to standardized 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, NJ, USA). Serum samples were isolated from whole blood and frozen at -20°C for storage. The biochemical parameters, including fasting blood glucose (FBG), glycosylated hemoglobin (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, IL, USA) with commercial kits. To ensure the testing was accurate, 10% of the specimens were randomly selected from each laboratory for centralized retesting by the Ministry of Health's National Center for Clinical Laboratory of China.

Dyslipidemia 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 World Health Organization (WHO) criteria: FBG ≥7.0 mmol/L or HbA1c ≥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 July 31, 2021. Mortality data was 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 July 31, 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 24.0 software. The continuous variables with normal distribution are reported as means and standard deviations (SD), numerical data were expressed as rates, and a chi-square test ($\chi 2$) was used to evaluate differences between groups. Age standardization 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, Dyslipidemia, current smoking, current drinking, education, income, physical activity (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 mmHg and 85.4±11.6 mmHg, respectively. Additionally, there were significant differences between region and gender for all characteristics (P <0.001).

Prevalence of isolated diastolic hypertension

The overall prevalence of IDH was 3.9% (95% CI: 3.6-4.2) 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: 6.3-8.2) among participants 40-49 years to 1.5% (95% CI: 1.1-2.0) among participants ≥70 years. The age-standardized prevalence of IDH was 5.0% (urban 4.5% and rural 5.2%, men 6.9% and women 4.0%) (**Table 2**).

Table 1. Baseline characteristics of study participants

Characteristics	Non-hypertension (n=8118)	IDH (n=735)	Non-IDH (n=9943)	Overall	*P*
Participant, n (%)	8118 (43.2)	735 (3.9)	9943 (52.9)	18796 (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)	11460 (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)	
10000-19999	1541 (19.0)	147 (20.0)	1569 (15.8)	3257(17.3)	
≥20000	2952 (36.4)	276 (37.6)	2672 (26.9)	5900(31.4)	

Mean BMI, kg/m²	23.910±3.35	25.36±3.90	25.33±3.74	24.72±3.65	<0.001
Mean SBP, mmHg	124.12 ± 10.35	133.63 ± 5.28	158.90±18.10	142.89 ±22.62	<0.001
Mean DBP, mmHg	77.61 ± 6.96	93.45 ± 3.40	91.14 ± 11.23	85.39 ± 11.59	<0.001
Current Smocking, 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
Dyslipidemia, 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

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

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 standardized rates by China census population 2010.

Awareness and treatment of patients with isolated diastolic hypertension

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 non-IDH patients, the treatment rate was 39.5%, higher than that in IDH patients (*P*<0.001). 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 IDH patients (*P*=0.001) (**Figure 3**).

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

During the median follow-up of 3.3 years, 314 (1.7%) participants died due to CVD. Among subjects with IDH, the risk of CVD death was 4.84/1,000 person-years (PY), which was 2.47 times higher than that in the non-hypertension group (*P*=0.005).

IDH patients had a 2.38 (95% CI, 1.26-4.48) 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=2.40, 95% CI: 1.28-4.52). Among non-IDH patients, the risk of CVD death was 7.78/1,000 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=2.44, 95% CI: 1.80-3.30) and Model 3 (HR=2.32, 95% CI: 1.70-3.18) (**Table 3, Figure 4**).

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

Characteristics	Number of events	Follow-up (person-years)	Rate (per 1,000 person-years)	Model 1	Model 2	Model 3
Non-hypertension	51	26420	1.93	ref.	ref.	ref.
IDH	12	2478	4.84	2.47	2.85 (1.52-5.36)	2.55 (1.35-4.82)
Non-IDH	251	32242	7.78	4.03	2.51 (1.85-3.40)	2.48 (1.81-3.38)

ref., reference; HR, hazard ratio. 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, Dyslipidemia, current smoking, current drinking, education, income, physical activity.

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 2014-2018;[14] however, it was lower than the China Health and Nutrition Survey (CHNS) 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 progress and urbanization 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 systolic blood pressure 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 IDH patients were 25.7% and

17.7% in northeast China. Although they were higher than the national levels, the awareness and treatment rates were still 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, IDH patients tended to be younger, and silent symptoms in IDH patients 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, 1.04-1.29) when compared to participants with normal systolic blood pressure [24, 25], and our study further confirmed this finding. In the unadjusted model, the risk of CVD mortality was significantly higher in non-IDH patients 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.[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: firstly, 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 IDH patients 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 analyze 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 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 generalizability 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 to 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 emphasized in terms of improving prognosis in northeast China.

Abbreviations

SBP: systolic blood pressure; DBP: diastolic blood pressure

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Author' Contributions

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.

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Availability of data and materials

The datasets generated for and analyzed in the study are not publicly available due to China Medical University's privacy policy, but are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

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.

Consent for publication

Not applicable.

Competing interests

None.

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Figure Legends

Figure 1. Flowchart of population selection.

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

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

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.

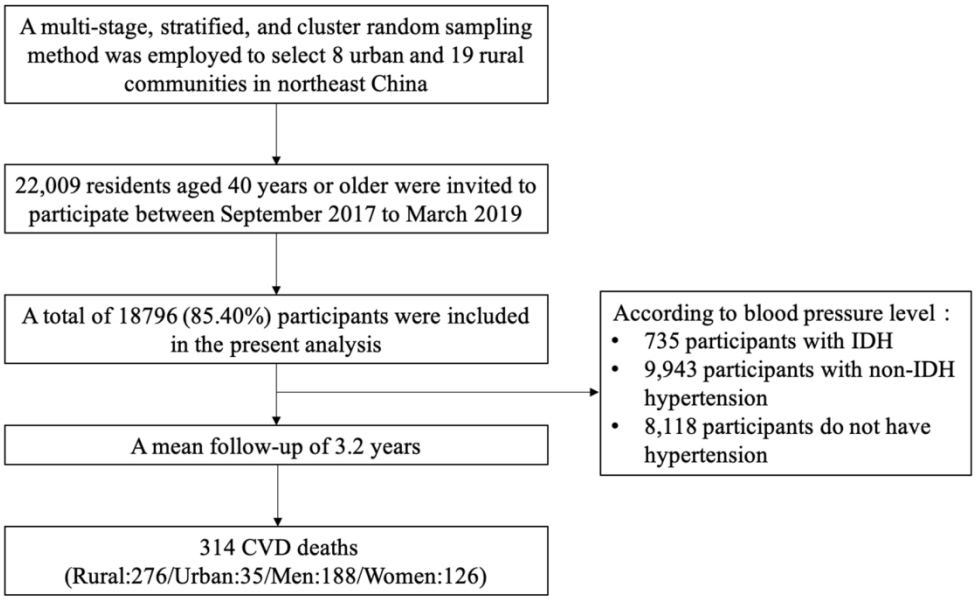

Figure 1. Flowchart of population selection.

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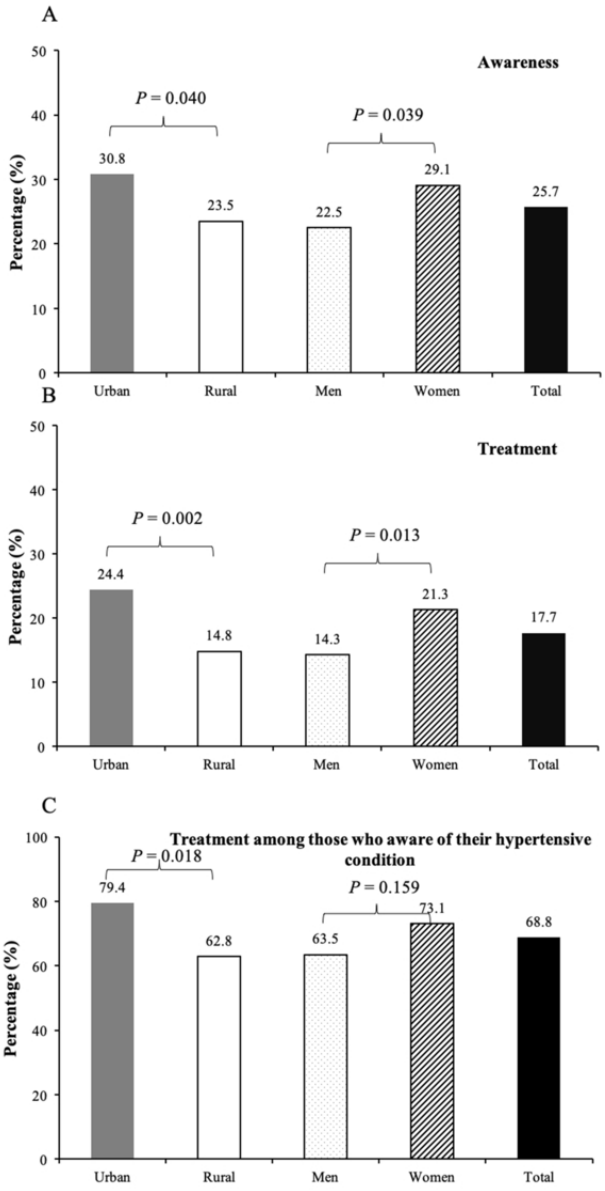
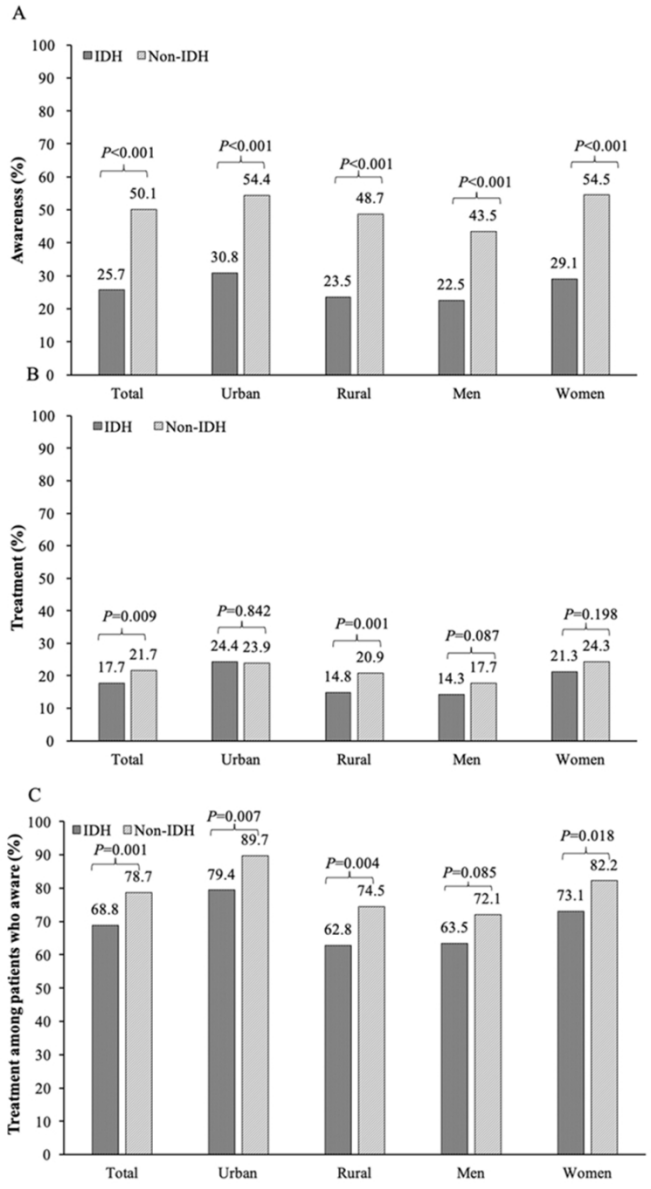


Figure 2. Awareness (A) and treatment (B, C) among IDH patients in aged 40 years or older in northeastern China.

49x95mm (300 x 300 DPI)



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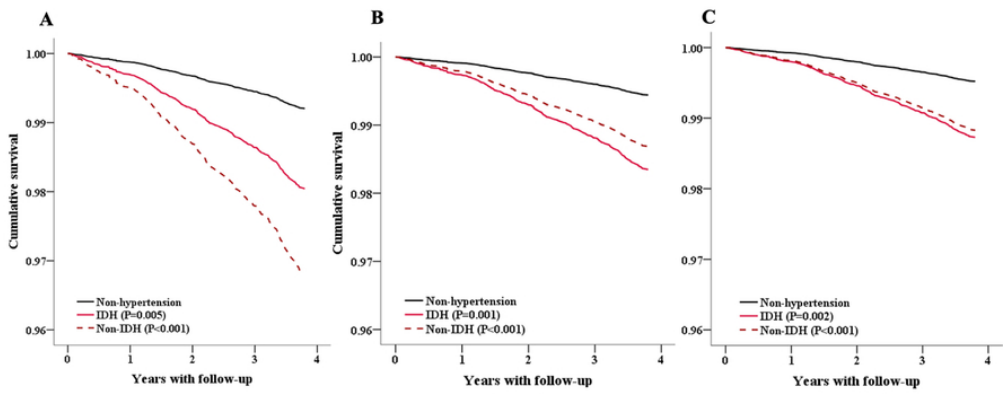

Figure 4. Kaplan-Meier survival curves for CVD death among participants with different blood pressure types. (A) unadjusted model, (B) HRadj1 model, (C) HRadj2 model.

75x29mm (300 x 300 DPI)

Supplemental Table 1. The univariate Cox regression analyses for the hazard ratio of CVD death.

Variables	Number of events	HR (95%CI)	*P*
Age group			
40-49	8	ref.	-
50-59	27	1.74 (0.79-3.83)	0.17
60-69	83	4.56 (2.21-9.42)	<0.001
≥70	196	22.34 (11.02-45.3)	<0.001
Sex			
Men	188	ref.	-
Women	126	2.36 (1.88-2.96)	<0.001
Education			
Primary school or lower	242	ref.	-
Middle school	57	0.31 (0.23-0.41)	<0.001
High school or above	15	0.26 (0.15-0.43)	<0.001
Annual household income (yuan)			
<5000	185	ref.	-
5000-9999	52	0.52 (0.38-0.71)	<0.001
10000-19999	30	0.31 (0.21-0.46)	<0.001
≥20000	47	0.28 (0.20-0.39)	<0.001
BMI, kg/m^2	-	0.87 (0.84-0.90)	<0.001
Current Smocking (yes vs. no)	106 *vs.* 208	1.55 (1.22-1.95)	<0.001
Current Drinking (yes vs. no)	75 *vs.* 239	0.87 (0.67-1.13)	0.31
History of AF (yes vs. no)	26 *vs.* 288	8.14 (5.45-12.16)	<0.001
History of stroke (yes vs. no)	75 *vs.* 239	4.87 (3.76-6.32)	<0.001
History of heart disease (yes vs. no)	43 *vs.*271	2.62 (1.90-3.61)	<0.001
Diabetes (yes vs. no)	64 *vs.* 248	1.30 (0.98-1.70)	0.07
Dyslipidemia (yes vs. no)	80 *vs.* 232	0.65 (0.51-0.84)	0.001
Lack of exercise (yes vs. no)	142 *vs.* 172	5.21 (4.17-6.51)	<0.001

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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 18796 residents aged ≥ 40 years who were living in northeast China with blood pressure (BP) measurements between September 2017 and March 2019.

Outcome measures Information on CVD death was obtained from baseline until July 31, 2021. IDH was defined as a DBP ≥ 90 mmHg together with SBP <140 mmHg 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: 6.3-8.2) among participants 40-49 years to 1.5% (95% CI: 1.1-2.0) 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 non-IDH patients (50.1% and 21.7%, P=0.009, respectively). During a median follow-up of 3.3 years, 314 subjects died due to CVD (rate 4.84/1,000 person-years). IDH and non-IDH were both significantly associated with an increased risk of CVD death (HR:2.55,95% CI 1.35-4.82; HR: 2.48, 95% CI

1.81-3.38) when compared to non-hypertension participants.

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.

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 (CVD) risk in the IDH population in northeast China.
- The generalizability of our results in other regions and races might be limited, as it was undertaken in northeastern regions of China.

INTRODUCTION

Hypertension remains a major modifiable risk factor for cardiovascular death that 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 mmHg 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), characterized 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: 1.0-2.1) in men aged 45-54 years and 1.8 (95% CI: 1.3-2.5) in men aged 55-68 years when compared to 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 counties.[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 3.3 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 July 31, 2021 for the status of survivor and specific cause of death (**Figure 1**). The study was approved by the Ethics Commission of the CPC Central Committee of the China Cardiovascular Disease Center (Beijing). All participants obtained written informed consent.

Baseline data collection

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

Blood pressure was measured three times at 2-min intervals after at least 5 min of rest in the sitting position using a standardized automatic electronic sphygmomanometer (J30; Omron, Kyoto, Japan). Participants were instructed to avoid coffee or tea drinking, alcohol consumption, smoking and perform excise 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 mmHg and/or mean DBP ≥ 90 mmHg, or use of antihypertensive medication in the past 2 weeks, otherwise was non-hypertensive. In hypertensive population, IDH was defined as a DBP ≥ 90 mmHg together with SBP <140 mmHg,[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 dyslipidemia in our study has been described previously.[13] Physical measurements including height, weight, and waist circumference were noted to the nearest 0.1 kilogram (kg) and 0.1 centimeter (cm)

with participants wearing lightweight clothes without shoes. Body mass index (BMI) was calculated as weight divided by the square of height (kg/m2). All data were obtained according to standardized 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, NJ, USA). Serum samples were isolated from whole blood and frozen at -20°C for storage. The biochemical parameters, including fasting blood glucose (FBG), glycosylated hemoglobin (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, IL, USA) with commercial kits. To ensure the testing was accurate, 10% of the specimens were randomly selected from each laboratory for centralized retesting by the Ministry of Health's National Center for Clinical Laboratory of China.

Dyslipidemia 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 World Health Organization (WHO) criteria: FBG ≥7.0 mmol/L or HbA1c ≥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 July 31, 2021. Mortality data was 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 July 31, 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 24.0 software. The continuous variables with normal distribution are reported as means and standard deviations (SD), numerical data were expressed as rates, and a chi-square test ($\chi 2$) was used to evaluate differences between groups. Age standardization 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, Dyslipidemia, current smoking, current drinking, education, income, physical activity (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 mmHg and 85.4±11.6 mmHg, respectively. Additionally, there were significant differences between region and gender for all characteristics (P <0.001).

Prevalence of isolated diastolic hypertension

The overall prevalence of IDH was 3.9% (95% CI: 3.6-4.2) 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: 6.3-8.2) among participants 40-49 years to 1.5% (95% CI: 1.1-2.0) among participants ≥70 years. The age-standardized prevalence of IDH was 5.0% (urban 4.5% and rural 5.2%, men 6.9% and women 4.0%) (**Table 2**).

Table 1. Baseline characteristics of study participants

Characteristics	Non-hypertension (n=8118)	IDH (n=735)	Non-IDH (n=9943)	Overall	*P*
Participant, n (%)	8118 (43.2)	735 (3.9)	9943 (52.9)	18796 (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)	11460 (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)	
10000-19999	1541 (19.0)	147 (20.0)	1569 (15.8)	3257(17.3)	
≥20000	2952 (36.4)	276 (37.6)	2672 (26.9)	5900(31.4)	

Mean BMI, kg/m²	23.910±3.35	25.36±3.90	25.33±3.74	24.72±3.65	<0.001
Mean SBP, mmHg	124.12 ± 10.35	133.63 ± 5.28	158.90±18.10	142.89 ±22.62	<0.001
Mean DBP, mmHg	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
Dyslipidemia, 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

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

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 standardized rates by China census population 2010.

Awareness and treatment of patients with isolated diastolic hypertension

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 non-IDH patients, the treatment rate was 21.7%, higher than that in IDH patients (*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 IDH patients (*P*=0.001) (**Figure 3**).

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

During the median follow-up of 3.3 years, 314 (1.7%) participants died due to CVD. Among subjects with IDH, the risk of CVD death was 4.84/1,000 person-years (PY), which was 2.47 times higher than that in the non-hypertension group (*P*=0.005).

IDH patients had a 2.85(95% CI, 1.52-5.36) 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: 1.35-4.82). Among non-IDH patients, the risk of CVD death was 7.78/1,000 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: 1.85-3.40) and Model 3 (HR=2.48, 95% CI: 1.81-3.38) (**Table 3, Figure 4**).

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

Characteristics	Number of events	Follow-up (person-years)	Rate (per 1,000 person-years)	Model 1	Model 2	Model 3
Non-hypertension	51	26420	1.93	ref.	ref.	ref.
IDH	12	2478	4.84	2.47	2.85 (1.52-5.36)	2.55 (1.35-4.82)
Non-IDH	251	32242	7.78	4.03	2.51 (1.85-3.40)	2.48 (1.81-3.38)

ref., reference; HR, hazard ratio. 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, Dyslipidemia, current smoking, current drinking, education, income, physical activity.

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 2014-2018;[14] however, it was lower than the China Health and Nutrition Survey (CHNS) 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 progress and urbanization 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 systolic blood pressure 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 IDH patients were 25.7% and

17.7% in northeast China. Although they were higher than the national levels, the awareness and treatment rates were still 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, IDH patients tended to be younger, and silent symptoms in IDH patients 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, 1.04-1.29) when compared to participants with normal systolic blood pressure [24, 25], and our study further confirmed this finding. In the unadjusted model, the risk of CVD mortality was significantly higher in non-IDH patients 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 to 64 years and 1.09 (1.07-1.11)

in the age group of 65 to 89 years ($p < 0.001$ for interaction versus 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: firstly, 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 IDH patients 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 analyze 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 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 generalizability 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 to 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 emphasized in terms of improving prognosis in northeast China.

Abbreviations

SBP: systolic blood pressure; DBP: diastolic blood pressure

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Author' Contributions

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.

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Availability of data and materials

The datasets generated for and analyzed in the study are not publicly available due to China Medical University's privacy policy, but are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

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.

Consent for publication

Not applicable.

Competing interests

None.

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Figure Legends

Figure 1. Flowchart of population selection.

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

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

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.

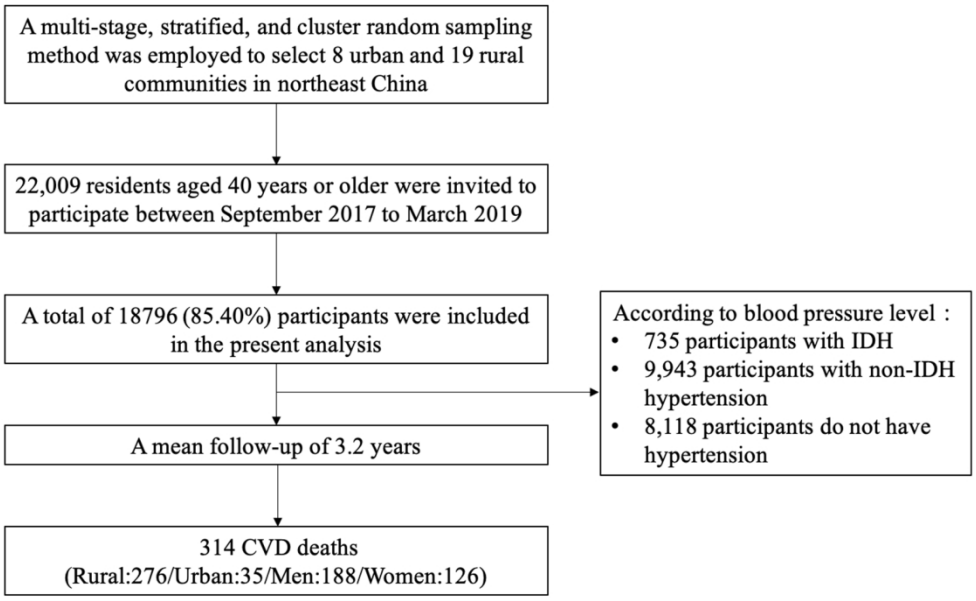


Figure 1. Flowchart of population selection.

77x46mm (600 x 600 DPI)

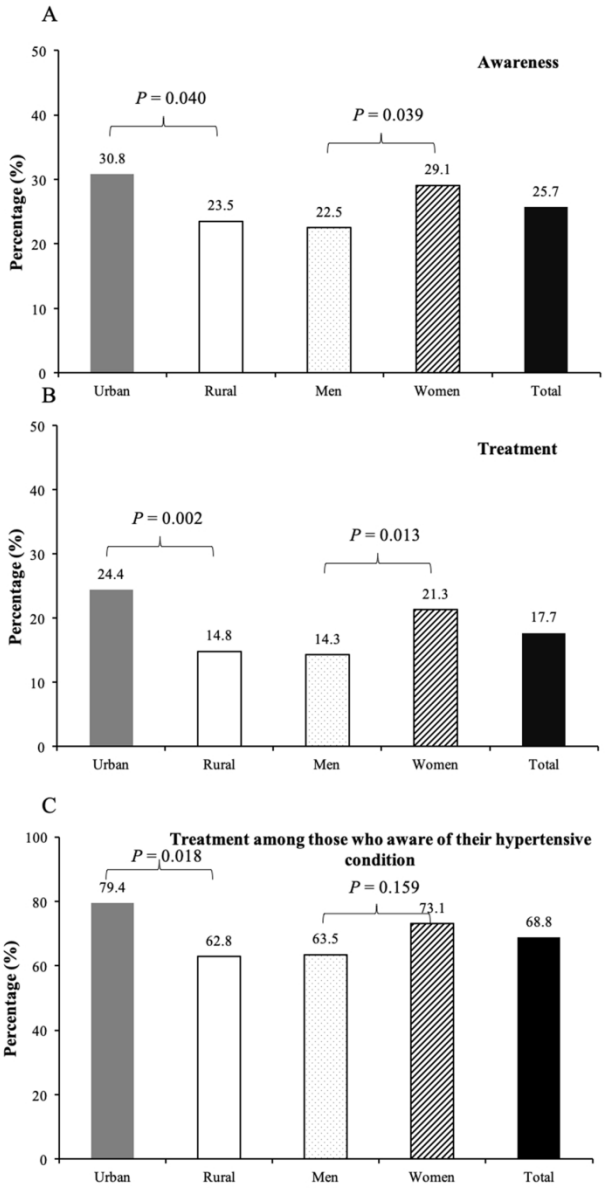
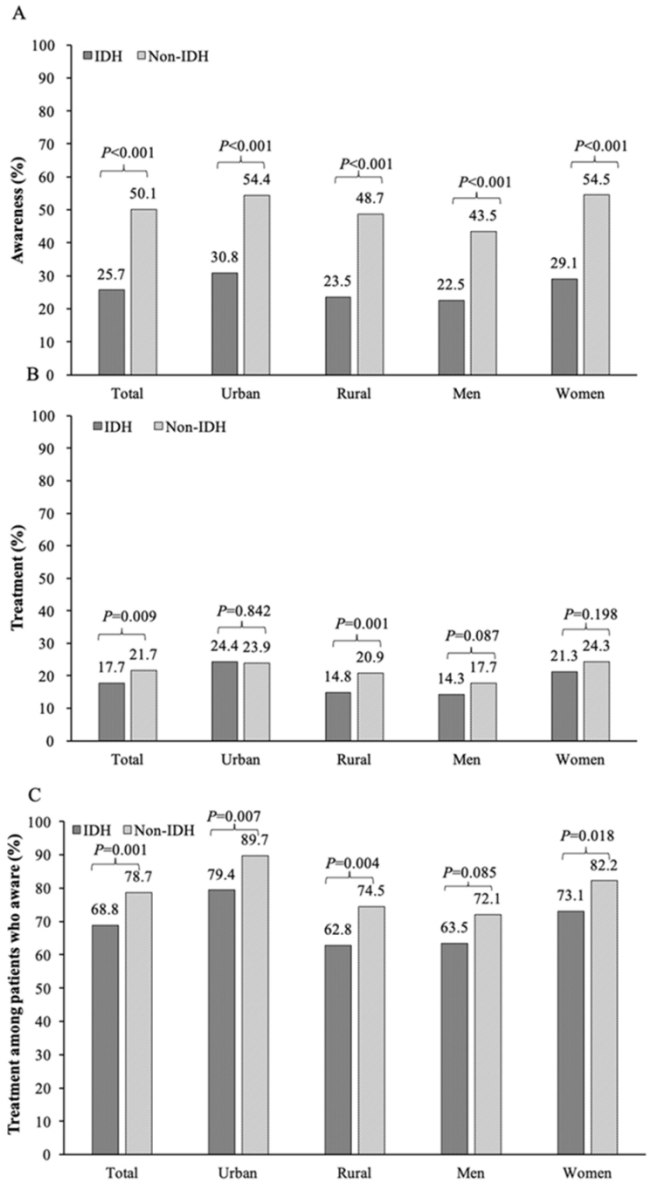


Figure 2. Awareness (A) and treatment (B, C) among IDH patients in aged 40 years or older in northeastern China.

49x95mm (600 x 600 DPI)



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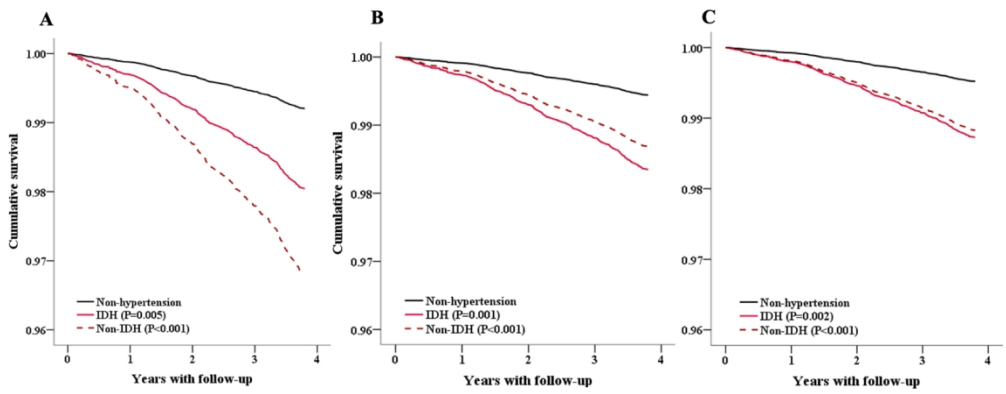

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Supplemental Table 1. The univariate Cox regression analyses for the hazard ratio of CVD death.

Variables	Number of events	HR (95%CI)	*P*
Age group			
40-49	8	ref.	-
50-59	27	1.74 (0.79-3.83)	0.17
60-69	83	4.56 (2.21-9.42)	<0.001
≥70	196	22.34 (11.02-45.3)	<0.001
Sex			
Men	188	ref.	-
Women	126	2.36 (1.88-2.96)	<0.001
Education			
Primary school or lower	242	ref.	-
Middle school	57	0.31 (0.23-0.41)	<0.001
High school or above	15	0.26 (0.15-0.43)	<0.001
Annual household income (yuan)			
<5000	185	ref.	-
5000-9999	52	0.52 (0.38-0.71)	<0.001
10000-19999	30	0.31 (0.21-0.46)	<0.001
≥20000	47	0.28 (0.20-0.39)	<0.001
BMI, kg/m^2	-	0.87 (0.84-0.90)	<0.001
Current Smoking (yes vs. no)	106 *vs.* 208	1.55 (1.22-1.95)	<0.001
Current Drinking (yes vs. no)	75 *vs.* 239	0.87 (0.67-1.13)	0.31
History of AF (yes vs. no)	26 *vs.* 288	8.14 (5.45-12.16)	<0.001
History of stroke (yes vs. no)	75 *vs.* 239	4.87 (3.76-6.32)	<0.001
History of heart disease (yes vs. no)	43 *vs.*271	2.62 (1.90-3.61)	<0.001
Diabetes (yes vs. no)	64 *vs.* 248	1.30 (0.98-1.70)	0.07
Dyslipidemia (yes vs. no)	80 *vs.* 232	0.65 (0.51-0.84)	0.001
Lack of exercise (yes vs. no)	142 *vs.* 172	5.21 (4.17-6.51)	<0.001