Hypertension Research
https://doi.org/10.1038/s41440-023-01386-9

COMMENT

# Don't miss the isolated diastolic hypertension

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Received: 26 June 2023 / Accepted: 3 July 2023


**Keywords** Chronic kidney disease · Proteinuria · Isolated diastolic hypertension

Hypertension is not only one of the most prevalent diseases worldwide, but it is also a crucial risk factor for cardiovascular disease (CVD) and renal dysfunction. The 2017 American College of Cardiology/American Heart Association (ACC/AHA) guideline revised the definition/classification of hypertension to systolic/diastolic blood pressure (SBP/DBP) ≥ 130/ 80 mmHg [1], whereas the European Society of Hypertension (ESH) and the Japanese Society of Hypertension (JSH) employs the hypertension threshold of hypertension as BP ≥ 140/90 mmHg [2, 3]. It is not entirely clear whether an isolated high SBP or isolated high DBP is associated with a higher risk of CKD. As for the target BP values, the 2021 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommends a SBP of <120 mmHg for the management of hypertension in CKD, with or without diabetes, nor receiving dialysis [4]. Uncertainty remains regarding the target DBP value to retard CKD progression. In the issue of Hypertens Res, the study by Suenaga et al. demonstrates that isolated high SBP and separately isolated high DBP are associated CKD progression in middle-aged, Japanese, and non-CKD population [5].

This retrospective cohort study evaluated the data of 1,492,291 participants without CKD and without antihypertensive treatment in the JMDC (Japan Medical Data Center) Inc., which includes the annual health check-up data of Japanese employees and their dependents with less than 75 years of age (mean age, 40.9 years old). CKD was defined as eGFR <60 mL/min/1.73 $m^2$ and/or the presence of proteinuria. To assess the CKD risk according to BP classification, these individuals were categorized into seven levels in ranges of 10 mmHg for SBP and 5 mmHg for DBP; during a mean follow-up of 3.2 ± 2.6 years, CKD, proteinuria, and eGFR < 60 mL/min/1.73 $m^2$ occurred in 92,587 (6.2%), 67,021 (4.5%), and 28,858 (1.9%) participants, respectively. In this study, the authors found that SBP ≥ 120 mmHg was significantly associated with elevated risks for CKD, proteinuria, and eGFR < 60 mL/min/1.73 $m^2$ after adjusting for confounding factors when compared with an SBP of 110–119 mmHg. As for DBP and CKD risks, DBP ≥ 80 mmHg was significantly associated with an elevated risk when compared with a DBP of <75 mmHg. The J-curve phenomenon was not observed in this study.

Suenaga et al. also evaluated the CKD risk according to cross-classification by SBP and DBP levels. The analysis clearly showed that both isolated systolic hypertension (ISH) and isolated diastolic hypertension (IDH) were significantly associated with an elevated CKD risk. Among the DBP ≥ 80 mmHg groups, the hazard ratio (HR) for CKD was highest in the SBP/DBP of ≥150/100 mmHg group (HR, 1.89). Especially, the HR for CKD was 1.44–1.89 in the high DBP category (SBP/DBP of 130–139/ ≥ 90 mmHg), compared with 1.23–1.47 in the high SBP category (SBP/DBP of ≥140/80–89 mmHg). A similar result was observed for developing proteinuria and eGFR <60 mL/min/1.73 $m^2$. Increased risk of CKD in IDH was also evident when ACC/AHA threshold was applied (130/80 mmHg). These data indicate that, not only SBP, the stratification by DBP provides potentially useful information to predict the risk of CKD progression particularly in the young and middle-aged Asian population.

Hypertension decreases eGFR and increases the risk of developing CKD and end-stage kidney disease [6–9]. In Japan, Kanno et al. reported that SBP was significantly associated with the incidence of CKD [8]. In that study, 2150 participants were categorized into normotension, pre-hypertension, Stage 1 hypertension, and Stage 2 hypertension. During a mean follow-up of 6.5 years, 461 incidences of CKD were recorded. Compared to

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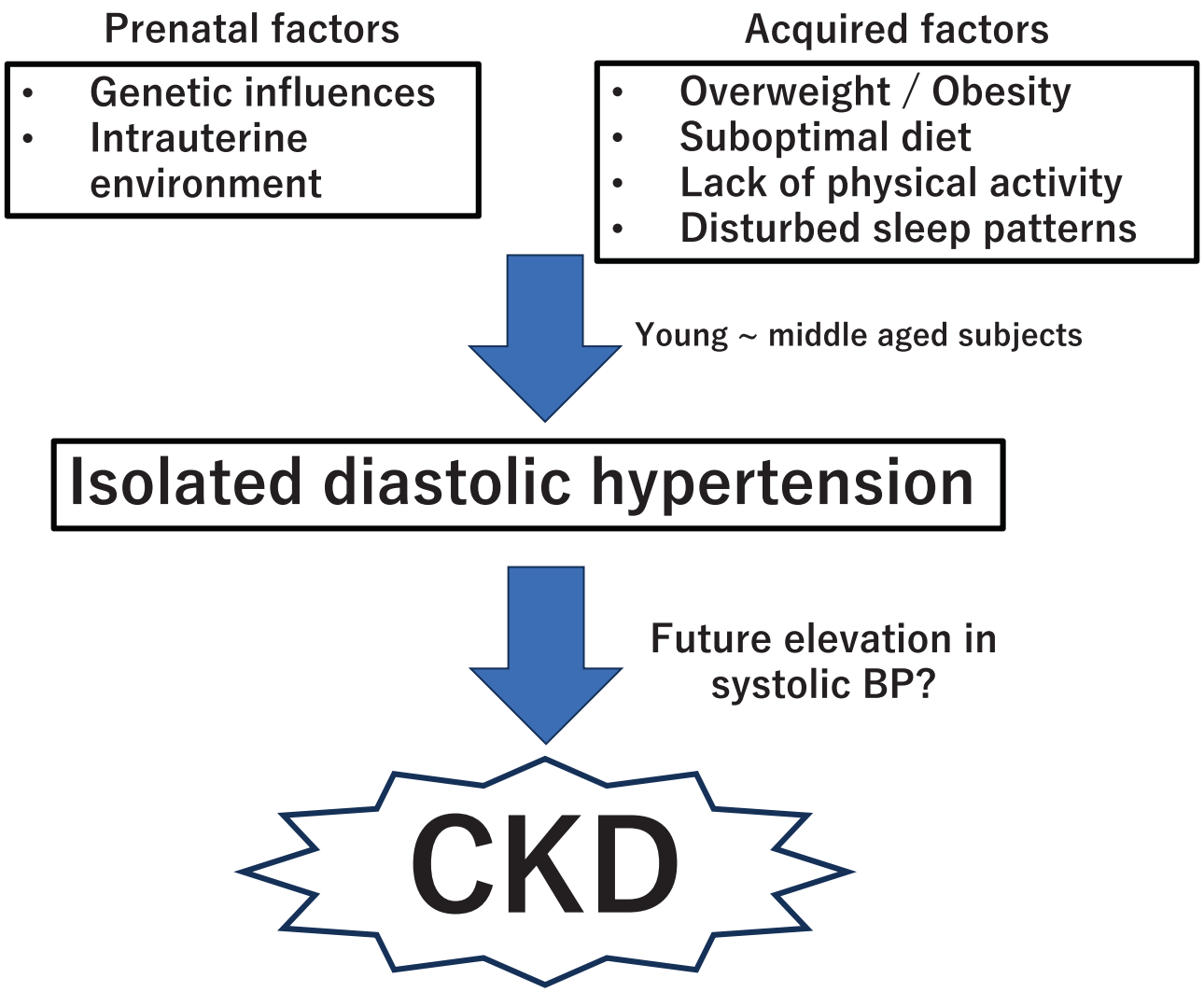
Published online: 01 August 2023

**Graphical Opinion**




normotension, adjusted hazard ratios of CKD were significantly higher for pre-hypertension (120–139/80–89 mmHg) (HR 1.49, $P < 0.003$), Stage 1 (140–159/90–99 mmHg) (HR 1.83, $P < 0.001$) and Stage 2 (>160/100 mmHg) (HR 2.55, $P < 0.001$) hypertension. There are several other studies from Japan that describes the risk of CKD progression in hypertensive patients [7, 9]. However, many reports indicate that SBP is associated with a higher risk than DBP and the description of the several guidelines is less intense regarding IDH [1–3].

It is worth mentioning that the most participants in the study by Suenaga et al. was middle-aged (1,492,291 participants, mean values were 40.9 ± 10.3 years of age). A majority of previous studies included elder people, which can mask the potential risk of elevated DBP on cardiovascular disorder and CKD, given that DBP tends to decrease in elderly people despite the increase in SBP [10]. However, there are several studies that addressed the risks of IDH in young patients. Bae et al. reported that the multivariable-adjusted HR for CKD in participants aged 20–39 years were 1.24 (95% CI, 1.08–1.42) in stage 1 IDH and 1.84 (95% CI, 1.54–2.19) in stage 2 IDH, respectively, the latter being higher than HR in stage 1 ISH (1.39, 95% CI, 1.28–1.51) [11]. On the other hand, McEvoy et al. analyzed the risk of incident CKD in the ARIC Study (8,703 participants, mean values were 56.0 ± 5.6 years for age) [12]. In that study, the authors found no significant association of IDH with incident CKD (HR 0.98, 95% CI, 0.65–1.11). The reason for the different results may be that participants' ages were older in the latter study. In another study, Lee et al. analyzed the cardiovascular risk for IDH between ages 20 to 39 years. They analyzed 6,424,090 participants, who did not take any medicines against hypertension [13]. The primary endpoint was composite cardiovascular events (myocardial infarction, stroke, heart failure, and cardiovascular disease-related death). During the mean 13.2 years of follow-up, 44,070

events occurred. Multivariable-adjusted hazard ratios of stage 1 IDH (<130/80–89 mmHg) were 1.32 (95% CIs, 1.28–1.36), compared with normal BP(<120/80 mmHg). The result is similar (HRs 1.36) with stage 1 ISH (130–139/<80 mmHg) hazard ratios (95% CI, 1.29–1.43). In Japan, Kanegae et al. analyzed the influence of SBP and DBP on the incidence of developing hypertension under 50-years-old participants (mean age 41.1 years) [14]. In that study, 93,303 participants were enrolled and were followed up for 4.9 years. The primary outcome was newly development of hypertension or started taking antihypertensive drugs. During the follow-up, 14,590 events occurred. The hazard ratios for developing hypertension was 17.5 for isolated diastolic high-normal and 10.5 for isolated systolic high-normal, compared with optimal BP.

Although the causes of early-onset hypertension are not entirely clear, it is likely a multifactorial condition [15], including but not limited to: genetic influences on sodium handling and hormonal factors [16, 17], intrauterine environment resulting in low birth weight [18], environmental factors such as overweight [19, 20], high sodium diet [21], processed foods [22], and low physical activity [23]. Recently, Morita et al. reported that non-ideal cardiovascular health (CVH) metrics was associated with an increased risk for the development of stage 1 and stage 2 hypertension in 66,876 subjects aged 20–39 years in the JMDC Claims Database [24]. Non-ideal body mass index was most strongly associated with a risk for hypertension.

In summary, the study by Suenaga et al. provides clinical evidence that isolated elevation of DBP can increase the risk of CKD progression in middle-aged Japanese participants. More attention needs to be paid to DBP, besides SBP, particularly in this population. The risks of elevated systolic and diastolic BP in developing cardiovascular and kidney diseases in younger subjects (e.g., adolescents and young adults) meris further investigation.

## Compliance with ethical standards

**Conflict of interest** The authors declare no competing interests.

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