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COMMENT

# Clinical implementation of polygenic risk scores based on GWAS in the management of hypertension among Asian populations

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Commentary to *"Integration of polygenic risk score with measured blood pressure reveals hidden risks of cardiovascular disease mortality: a Japanese prospective cohort study" by Okumiya and Fujii* et al.

Genome-wide association studies (GWAS) have demonstrated multiple genetic factors related to occurrence of cardiovascular diseases [1, 2]. A polygenic risk scores (PRS) aggregates the small effect sizes of many single-nucleotide polymorphisms. A PRS represents an individual's genetically determined susceptibility to a given phenotype, quantified as a single continuous variable derived from GWAS summary statistics. Prior studies have accumulated evidence on the associations between PRS and increased risks of hypertension and cardiovascular diseases [3–8].

In the study by Okumiya and Fujii et al., the blood pressure (BP) PRS was constructed using effect sizes from GWAS summary statistics for systolic and diastolic BP in Biobank Japan, and this BP PRS was applied to the dataset of a nationwide cohort involving more than 100,000 participants from 14 institutions, the Japan Multi-Institutional Collaborative Cohort (J-MICC) Study. They assessed the association of the combination of the BP PRS and BP levels with cardiovascular mortality. The key findings may be summarized as follows. In the analysis of 6 strata combining tertiles of the BP PRS with 2 office BP categories, SBP < 140 mm Hg or ≥140 mm Hg (or DBP < 90 mm Hg or ≥90 mm Hg), compared with participants in the first tertile of BP PRS who had normal BP, those in the third tertile of BP PRS with normal (well-controlled) BP and those in the third tertile of BP PRS with high (uncontrolled) BP had an increased risk of cardiovascular death [9]. This result suggests that individuals with a high BP PRS are at increased risk of cardiovascular mortality even when their office BP remains within the normal range. While the study did not report hazard ratios for the BP PRS as a continuous variable, mortality rates were presented across deciles of the BP PRS, and this gradient showed a trend of linear increase. This pattern indicates a linear association between higher BP PRS and increased cardiovascular mortality. Based on these findings, Okumiya and Fujii et al. stated that even individuals with normal or well-controlled BP may have a residual cardiovascular risk when their genetic predisposition is high.

Prior studies have reported that GWAS have identified Asian-specific genetic variants for the development of hypertension [2, 3, 10]. In addition, several genes related to salt sensitivity of BP exhibit higher risk-allele frequencies among Asian populations compared with those in Europe and North America [2, 11, 12]. Japan, in particular, has been reported to have lower rates of adequate BP control among adults with hypertension than Western countries [13]. These genetic predispositions may partly explain the greater burden of hypertension and the lower control rates observed in East Asian populations [14]. Integrating genetic susceptibility with BP assessments may therefore improve risk stratification and support individualized preventive strategies for cardiovascular disease.

Okumiya and Fujii et al. described the BP PRS as a hidden risk [9]. In the diagnosis and management of hypertension, hypertensive phenotypes such as masked hypertension, nocturnal hypertension, and elevated BP variability may be considered unrecognized (undetected) or subclinical risk, as they are not detectable by office BP alone [15, 16]. Subclinical organ damage, residential

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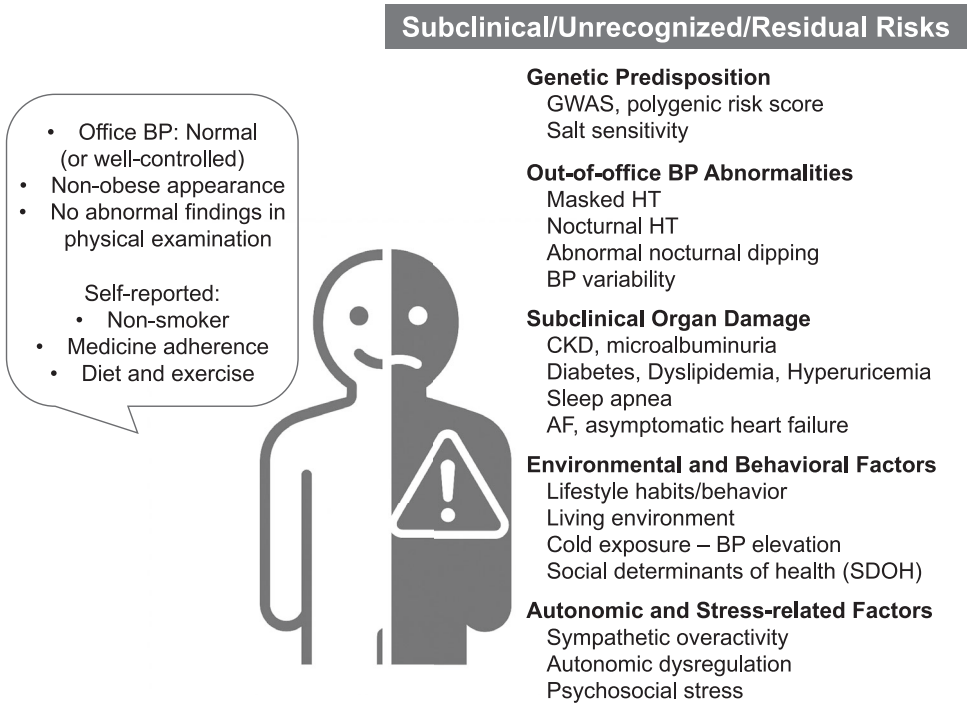


**Fig. 1** Subclinical, unrecognized (undetected), or residual risk factors for cardiovascular disease. This figure presents examples of cardiovascular risk factors that are difficult to identify through office-based assessment alone. GWAS-derived polygenic risk scores are included among these latent risk factors. These factors often coexist and may interact with one another. Detecting one latent risk factor may help predict the presence of additional unrecognized risks. AF atrial fibrillation, BP blood pressure, CKD chronic kidney disease, GWAS genome-wide association study, HT hypertension

environment, social determinants of health, psychosocial stress, and autonomic dysregulation can also be included within these categories of subclinical, unrecognized (undetected), or residual risks (Fig. 1). Among individuals with elevated cardiovascular risk, multiple subclinical risks often coexist, and the identification of one subclinical risk may facilitate the detection of others [17–20]. Asian individuals, in particular, are more likely to exhibit masked hypertension and nocturnal hypertension compared with other racial/ethnic groups [21, 22]. The findings by Okumiya and Fujii et al. demonstrated that participants with the high BP PRS had increased cardiovascular mortality even if their office BP remained within the normal range [9]. Those individuals might carry unrecognized hypertension phenotypes such as masked hypertension or nocturnal hypertension. Although the evidence is limited, genetic susceptibility may have potential to help predict the presence of masked hypertension and other subclinical risks for cardiovascular disease. Assessment of genetic risk using GWAS-derived risk equations provides additional information on cardiovascular disease risk and may help identify other subclinical risk factors.

## Compliance with ethical standards

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

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