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Polygenic scores for hypertension and low-density lipoprotein cholesterol and risk of incident chronic kidney disease

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Objectives : A higher polygenic risk score (PRS) for kidney function is associated with the development of chronic kidney disease (CKD). However, the association of PRSs for risk factors with risk of CKD is unknown. This study examined whether PRSs for hypertension and low-density lipoprotein cholesterol (LDL-C) can collectively predict the future development of CKD.
Methods : We included 344,096 participants enrolled in the UK Biobank between 2006 and 2010 who were followed up until 2022. PRS hypertension and PRS LDL-C were used as the primary exposures. The primary outcome was the onset of incident CKD, which was defined based on ICD-10 or OPCS-4 codes. We examined the individual and combined association of the PRS hypertension and PRS LDL-C with the risk of incident CKD using cause-specific competing risk models.
Results : The mean age of the participants was 56.1 years and 46.8% were men. During a follow-up of 13.6 years (interquartile range 12.8–14.2), 13,379 individuals experienced CKD. A 1-SD increase in PRS hypertension was associated with a 5% higher risk of incident CKD (hazard ratio [HR], 1.05; 95% confidence interval [CI] 1.03–1.07). However, PRS LDL-C was not associated with incident CKD. When both participants were divided into two groups based on the median values of PRSs for hypertension and LDL-C, the HRs (95% CIs) for individuals with both above the median, those with higher PRS hypertension and lower PRS LDL-C, and those with lower PRS hypertension and higher PRS LDL-C were 1.09 (1.03, 1.14), 1.06 (1.01, 1.12), and 1.03 (0.98, 1.08), respectively, compared with those with both below the median.
Conclusions : This study showed a significant association between PRS hypertension and a higher risk of CKD, while PRS LDL-C showed no such association. These two genetic predisposing factors appear to synergistically contribute to a higher risk of CKD when both PRS values are elevated.

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Table 1. LDL-C and HTN polygenic risk score and incident CKD events

		LDL-C PRS	HTN PRS
	Model	HR per SD increase in PRS (95% CI)	HR per SD increase in PRS (95% CI)
Risk of Incident CKD			
	I	1.00 (0.99 ,1.02)	1.16 (1.14 ,1.19)
	II	1.01 (0.99 ,1.03)	1.18 (1.15 ,1.20)
	III	1.00 (0.99 ,1.02)	1.05 (1.03 ,1.07)

Model I: unadjusted, Model II: adjusted for age and sex, Model III: for LDL-C PRS: Model II + additional adjustment for BMI, DM, deprivation index, smoking, alcohol use, eGFR, hsCRP, triglycerides, HDL, SBP, and lipid-lowering medication ; for HTN PRS: Model II + additional adjustment for BMI, DM, deprivation index, smoking, alcohol use, eGFR, hsCRP, triglycerides, HDL, LDL-C, and antihypertensive medication.
HR hazard ratio, SD standard deviation, CI confidence interval, HTN hypertension, LDL-C low density lipoprotein cholesterol, PRS polygenic risk scores

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Table 2. Hazard ratios for incident CKD according to PRS groups

	HTN/LDL-C PRS categories			
	Both PRS < median	**LDL-C PRS ≥ median, HTN PRS < median**	**LDL-C PRS < median, HTN PRS ≥ median**	**Both PRS ≥ median**
Model	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Risk of Incident CKD				
I	Reference	1.02 (0.97, 1.07)	1.25 (1.2, 1.32)	1.26 (1.2, 1.32)
II	Reference	1.03 (0.98, 1.08)	1.27 (1.21, 1.34)	1.29 (1.23, 1.35)
III	Reference	1.03 (0.98, 1.08)	1.06 (1.01, 1.12)	1.09 (1.03, 1.14)

Model I: unadjusted, Model II: adjusted for age and sex, Model III: Model II + additionally adjusted for BMI, DM, deprivation index, smoking, alcohol use, eGFR, hsCRP, triglycerides, HDL, lipid-lowering medication, antihypertensive medication.
HR hazard ratio, CI confidence interval, HTN hypertension, LDL-C low density lipoprotein cholesterol, PRS polygenic risk scores