Uncovering Shared Genetic Architecture of Cardio-Renal-Metabolic Multimorbidity Using GenomicSEM

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Abstract

Multimorbidity, defined as the coexistence of two or more chronic conditions, represents an escalating public health challenge, particularly among older populations. In Australia, approximately 38% of individuals live with multiple long-term conditions, with prevalence increasing markedly in older age groups. Cardio-Renal-Metabolic (CRM) multimorbidity [comprising type 2 diabetes (T2D), cardiovascular disease (CVD), and chronic kidney disease (CKD)] is central to this burden, collectively affecting nearly 600M individuals globally. These conditions are highly interconnected through shared biological mechanisms, common risk factors, and overlapping genetic pathways. Despite this interrelationship, a critical research gap persists in identifying pleiotropic genetic variants and common genes contributing to CVD, T2D, and CKD.

Genomic Structural Equation Modelling (GenomicSEM), a multivariate framework, was employed to uncover shared genetic architectures of CRM multimorbidity separately in European (EUR) [N_{eff} = 353,130] and African (AFR) [N_{eff} = 75,436] ancestries. We utilized univariate GWAS summary statistics for CVD (including ischemic heart disease, heart failure, and hypertension), CKD, and T2D, sourced from four major biobank cohorts: UK Biobank, FinnGen, All of Us, and the Million Veteran Program.

We observed moderate to strong genetic correlations among CVD traits (0.6-0.7) in both EUR and AFR ancestries. T2D showed moderate correlations with CVD (0.4-0.5) across ancestries. For CKD, correlations varied: CKD-CVD ranged from moderate to strong (0.3-0.6), while CKD-T2D was strong in EUR (0.6) but weak in AFR (0.3). The latent CRM multimorbidity factor explained the largest variance in CVD (EUR: 72%, AFR: 85%), followed by T2D (EUR: 56%, AFR: 28%) and CKD (EUR: 55%, AFR: 36%). We identified 155 COJO SNPs in EUR and 16 in AFR, of which 60 in EUR and 13 in AFR were novel based on the GWAS Catalog.

CVD, T2D, and CKD exhibit significant genetic correlations and share common genetic determinants contributing to CRM multimorbidity. Key loci such as *FTO*, *TCF7L2*, *LINC02742*, and *XKR6* were implicated in both EUR and AFR ancestries. Additionally, ancestry-specific latent genetic factors underlying multimorbidity were identified, highlighting distinct genetic architectures across populations.