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Albuminuria and Cardiovascular Diseases

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Objectives : Albuminuria is well-known risk factor for cardiovascular diseases (CVDs) in patients, but whether this relationship is causal remains unclear. We aimed to investigate the bidirectional causal relationship between albuminuria and major cardiovascular diseases and to explore potential mediating mechanisms.

Methods : We conducted an observational cohort analysis and a bidirectional two-sample Mendelian randomization (MR) study. The observational analysis included 170,518 participants from the UK Biobank. MR analyses were performed using summary statistics from CKDGen, UK Biobank, and FinnGen, predominantly involving individuals of European ancestry. The exposures were urinary albumin-to-creatinine ratio (uACR) and albuminuria (uACR $\geq$ 30 mg/g). Outcomes included incident coronary artery disease (CAD), stroke, heart failure (HF), and atrial fibrillation (AF). Observational associations were assessed using bidirectional Cox proportional hazards models. MR analyses employed inverse variance-weighted, weighted median, and MR-Egger approaches. Two-step MR and mediation analyses incorporating clinical risk factors and plasma protein quantitative trait loci were conducted to identify potential mediators.

Results : In observational analyses, baseline albuminuria was independently associated with increased risks of CAD, stroke, HF, and AF. MR analyses demonstrated that genetically predicted higher uACR was causally associated with greater risks of CAD and AF but not stroke or HF. Reverse MR analyses provided no evidence that CVDs causally influence albuminuria. Mediation analyses showed that hypertension partially mediated the causal effects of albuminuria on CAD (41.2%) and AF (30.7%). Additionally, plasma FURIN levels mediated 18.9% of the causal effect of albuminuria on AF.

Conclusions : Albuminuria appears to exert a unidirectional causal effect on the development of CAD and AF rather than serving solely as a marker of vascular risk. Hypertension and FURIN partially mediate these relationships, highlighting potential mechanistic pathways and reinforcing albuminuria as an active contributor to cardiovascular disease pathogenesis.

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Table. Two-sample MR analysis from uACR to CVDs

Exposure/Outcome	IVW		Weighted median		MR-Egger		MR-Egger Pleiotropy test	Cochran's Q Heterogeneity	MR- PRESSO Global test
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	P-value	P-value	P-value
uACR/CAD									
CKDGen/FinnGen	1.38 (1.08 - 1.77)	0.011	1.30 (0.93 - 1.83)	0.127	1.83 (0.70 - 4.78)	0.217	0.552	0.276	0.255
UKBB/FinnGen	2.03 (1.36 - 3.02)	<0.001	1.83 (1.11 - 3.00)	0.017	0.88 (0.20 - 3.82)	0.865	0.247	0.112	0.080
uACR/STR									
CKDGen/FinnGen	1.73 (0.74 - 4.04)	0.207	0.95 (0.28 - 3.23)	0.934	1.40 (0.15 - 13.28)	0.770	0.843	0.928	0.940
UKBB/FinnGen	1.03 (0.73 - 1.45)	0.885	0.55 (0.09 - 3.56)	0.531	0.56 (0.02 - 13.50)	0.718	0.587	0.267	0.256
uACR/HF									
CKDGen/FinnGen	1.00 (0.81 - 1.23)	0.973	0.90 (0.66 - 1.24)	0.524	0.69 (0.40 - 1.19)	0.178	0.148	0.518	0.506
UKBB/FinnGen	0.90 (0.66 - 1.23)	0.514	1.00 (0.65 - 1.54)	0.994	0.84 (0.41 - 1.71)	0.626	0.819	0.665	0.670
uACR/AF									
CKDGen/FinnGen	1.54 (1.20 - 1.98)	0.001	1.41 (0.99 - 2.01)	0.055	1.67 (0.86 - 3.25)	0.129	0.797	0.163	0.135
UKBB/FinnGen	1.72 (1.22 - 2.43)	0.002	1.61 (1.00 - 2.60)	0.053	1.43 (0.64 - 3.22)	0.382	0.623	0.369	0.327

Abbreviation: 95% CI, 95% confidence interval; AF, atrial fibrillation; CAD, coronary artery disease; CVDs, cardiovascular diseases; HF, heart failure; IVW, inverse variance weighted; MR, mendelian randomization; MR-PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier; OR, odds ratio; uACR, urine albumin-to-creatinine ratio.

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Table. Two-sample MR analysis from CVDs to uACR

Exposure/Outcome	IVW		Weighted median		MR-Egger		MR- Egger Pleiotropy test	Cochran's Q Heterogeneity	MR- PRESSO Global test
	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value	P-value	P-value	P-value
CAD/uACR									
FinnGen/CKDGen	-0.003 (-0.017 to 0.010)	0.605	-0.013 (-0.032 to 0.007)	0.199	-0.026 (-0.069 to 0.016)	0.219	0.262	0.643	0.663
FinnGen/UKBB	0.002 (-0.009 to 0.012)	0.768	-0.006 (-0.021 to 0.009)	0.452	-0.014 (-0.048 to 0.020)	0.421	0.347	0.420	0.417
STR/uACR									
FinnGen/CKDGen	0.000 (-0.006 to 0.006)	0.986	-0.002 (-0.010 to 0.006)	0.606	-0.004 (-0.017 to 0.009)	0.515	0.464	0.927	0.938
FinnGen/UKBB	0.000 (-0.005 to 0.005)	0.922	0.001 (-0.005 to 0.008)	0.716	0.003 (-0.008 to 0.013)	0.632	0.622	0.938	0.936
HF/uACR									
FinnGen/CKDGen	0.041 (-0.002 to 0.084)	0.064	0.049 (0.009 to 0.090)	0.017	-0.089 (-0.290 to 0.112)	0.384	0.195	0.101	0.173
FinnGen/UKBB	0.028 (-0.015 to 0.070)	0.199	0.048 (0.005 to 0.092)	0.029	0.065 (-1.146 to 1.276)	0.916	0.951	0.076	0.119
AF/uACR									
FinnGen/CKDGen	0.008 (0.001 to 0.016)	0.033	0.012 (0.000 to 0.023)	0.041	0.013 (-0.008 to 0.034)	0.214	0.612	0.928	0.936
FinnGen/UKBB	0.005 (-0.001 to 0.012)	0.122	0.005 (-0.005 to 0.015)	0.318	0.002 (-0.017 to 0.022)	0.819	0.759	0.633	0.615

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