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Gut microbiota and pulmonary hypertension: a Mendelian randomization study

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Article

Figures & Data

Info & Metrics

Abstract

Misbalanced bacterial ecosystem is likely involved in the pathogenesis of pulmonary hypertension (PH). Recent studies showed changes in the gut microbiota composition were associated with PH. To investigate whether the risk of PH causally resulted from gut microbiota alteration, we conducted a two-sample Mendelian randomization study.

We identified quantitative trait locus as instrumental variables from genome-wide association study summary data. Microbial taxa affected by host genetic variation was proxied by 40 single nucleotide polymorphisms (SNPs) from 1812 European individuals, while microbial function was proxied by 16 SNPs from 984 European individuals. We derived SNPs-PH effect estimates from 463010 individuals in the UK Biobank.

This study showed changes in microbial taxa and function units associated with host-microbe intersection (MetaCyc pathways and Gene Ontology terms with at least 2000 genes (GO2000 terms)) had no causal effect to develop PH, except decreased function units (Table 1). Further subgroup analysis indicated a decreased risk of secondary PH resulted causally from microbial function units per Z-score decrease (OR 0.999, 95% CI: 0.9998-0.99999, $P=1.88\times 10^{-2}$).

Our study supported a causal role of declining gut microbiota function in the etiology of PH. Suggestive evidence showed that host-microbe intersection, notably MetaCyc pathway components and GO2000 terms were associated with secondary PH.

Table1. MR estimates of the causality between Gut microbiota and PH

Exposure	Gut microbiota					
	Bacterial taxa				Functional units	
	NR Z-score decrease	NR Z-score increase	Unit decrease	Unit increase	NR Z-score decrease	NR Z-score increase
Outcome	diagnoses-secondaryICD10;127.0 primary pulmonary hypertension id:UKB-b:439					
Number of SNPs	3	3	31	3	8	8
MR Egger	OR	-	1.00002	0.99998	0.9997	0.99991
	95%CI	-	0.99937-1.00066	0.99990-1.00006	0.99883-1.00057	0.99967-1.00014
	P value	-	0.958	0.69	0.627	0.480
Weighted median	OR	-	0.99999	0.99995	0.99984	0.99999
	95%CI	-	0.99998-1.00001	0.99989-1.00002	0.99959-1.00008	0.99998-1.00000
	P value	-	0.741	0.224	0.201	0.198
Inverse variance weighted	OR	1.00000	0.99999	0.99996	0.99983	0.99999
	95%CI	0.99998-1.00003	0.99997-1.00000	0.99991-1.00000	0.99963-1.00004	0.99998-1.00001
	P value	0.623	0.46	0.096	0.129	0.019
Weighted mode	OR	-	1.000000	0.99995	0.99981	0.99999
	95%CI	-	0.99998-1.00002	0.99986-1.00004	0.99954-1.00008	0.99998-1.00000
	P value	-	0.881	0.341	0.316	0.98
Egger regression	interpret	-0.0039	-0.0011	-1.1E-06	0.000041	0.00062
	P value	0.343	0.632	0.958	0.81	0.393

MR, Mendelian randomization; PH, pulmonary hypertension; SNP, single-nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence intervals

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Genomics Microbiome/Microbiota

Footnotes

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[^ Back to top](#)

Vol 56 Issue suppl 64 [Table of Contents](#)

- [Table of Contents](#)
- [Index by author](#)

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