ORIGINAL ARTICLE
PULMONARY VASCULAR DISEASE

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Mendelian randomisation analysis of red cell distribution width in pulmonary arterial hypertension

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ABSTRACT Pulmonary arterial hypertension (PAH) is a rare disease that leads to premature death from right heart failure. It is strongly associated with elevated red cell distribution width (RDW), a correlate of several iron status biomarkers. High RDW values can signal early-stage iron deficiency or iron deficiency anaemia. This study investigated whether elevated RDW is causally associated with PAH.

A two-sample Mendelian randomisation (MR) approach was applied to investigate whether genetic predisposition to higher levels of RDW increases the odds of developing PAH. Primary and secondary MR

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analyses were performed using all available genome-wide significant RDW variants (n=179) and five genome-wide significant RDW variants that act *via* systemic iron status, respectively.

We confirmed the observed association between RDW and PAH (OR 1.90, 95% CI 1.80–2.01) in a multicentre case–control study (cases n=642, disease controls n=15 889). The primary MR analysis was adequately powered to detect a causal effect (odds ratio) between 1.25 and 1.52 or greater based on estimates reported in the RDW genome-wide association study or from our own data. There was no evidence for a causal association between RDW and PAH in either the primary (OR_{causal} 1.07, 95% CI 0.92–1.24) or the secondary (OR_{causal} 1.09, 95% CI 0.77–1.54) MR analysis.

The results suggest that at least some of the observed association of RDW with PAH is secondary to disease progression. Results of iron therapeutic trials in PAH should be interpreted with caution, as any improvements observed may not be mechanistically linked to the development of PAH.