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Raynaud's phenomenon is associated with an increased risk of cardiovascular disease and venous thromboembolism

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ABSTRACT

Objectives: Raynaud's phenomenon (RP) is common affecting 3–5 % of the population; however, there are little data concerning vascular outcomes. We aimed to estimate risk of cardiovascular disease (CVD) and venous thromboembolism (VTE) in individuals with RP without underlying relevant systemic autoimmune rheumatic diseases (SARDs).

Methods: A cohort study using data from North American electronic healthcare organization records. RP was defined using ≥2 ICD codes (I73.0), excluding those with SARDs. Comparators had ≥2 irritable bowel syndrome (IBS) ICD codes (K58); selected as a condition with similar demographics but not typically associated with adverse CVD outcomes. Cohorts were stratified by age (<45 and ≥45 years). Co-primary outcomes were 1) major adverse cardiovascular events (MACE), and 2) VTE. Secondary outcomes included: myocardial infarction, stroke, any CVD. Risk of each outcome was compared using 1:1 propensity score matched Cox proportional hazard models.

Results: Among 30,088 matched pairs aged <45, hazard ratios (HR [95 % CI]) of MACE (HR 1.23 [1.07, 1.42]) and VTE (HR 1.32 [1.20, 1.46]) were higher in RP (excluding SARD) than IBS. Similarly, in 60,145 matched pairs ages ≥45, MACE (HR 1.17 [1.13, 1.22]) and VTE (HR 1.20 [1.14, 1.26]) were higher in RP. Risk of secondary outcomes was higher in RP, although estimates for DVT in both analyses and myocardial infarction in patients under 45 lacked precision.

Conclusions: RP was associated with an increased risk of CVD and VTE, independent of age and traditional cardiovascular risk factors. Future research is warranted to confirm, explore pathobiological mechanisms, and develop therapeutic strategies.

Introduction

Raynaud's phenomenon (RP) is a common vasospastic condition characterised by stereotypical reversible digital ischaemia provoked by environmental and/or emotional stressors [1]. Although estimates vary, in general, around 3–5 % of the population experience RP [2]. The majority of individuals have primary ('idiopathic') RP (PRP), which tends to affect younger females, often with a family history of the

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condition [2,3]. However, in approximately 10–20 % of individuals, there is an underlying secondary cause. A broad range of aetiopathogenic drivers are associated with secondary RP (SRP) including systemic autoimmune rheumatic diseases (SARDs), which represent a significant proportion of SRP. In particular, RP is almost universally (>95 %) observed in patients with systemic sclerosis (SSc), and often occurs years (and potentially decades) before the clinical onset of disease [4]. Irrespective of the underlying aetiopathogenic drivers, RP can significantly impact all the activities of daily living, including the need for self-vigilance and adaption [5,6].

The pathogenesis of RP is complex but mechanistically can be conceptualised as a fundamental imbalance between prevalent *vasoconstrictor* and *vasodilatory* factors [1]. Recent work has provided major insights into the genetic basis of RP (i.e., contribution of *ADRA2A* and *IRX1* genes), including confirmation of the central role of alpha-2 adrenergic control in mediating cold-induced vasoconstriction [7]. In patients with SRP, other factors may also be implicated including (but not limited to) intravascular (e.g., platelet) and structural (e.g., microvascular remodelling in SSc) abnormalities [3,4].

Historically, RP has not typically been linked to any long-term negative health effects, unless when associated with a relevant secondary cause (e.g., malignancy-related). However, this dogma has been challenged in recent times, particularly concerning adverse cardiovascular disease (CVD) outcomes. A study which included 20+ years of follow-up from 830 individuals (none with SARDs) from the Charleston Heart Study cohort observed that RP was associated with an increased risk of cardiovascular-related death (HR: 1.55, 95 % CI: 1.10–2.20) in white (but not black) individuals. In their study, the authors used a broad definition of RP which included both blanching (pallor) and cyanotic colour changes, and a narrower definition which only included blanching [8]. To our knowledge, no studies to date have evaluated the association between RP and venous thromboembolism (VTE).

Therefore, against this background, the aim of our study was to examine whether CVD and VTE were more common in individuals with RP, compared to those without, in the absence of any underlying SARD. The rationale for excluding SARDs was that we wanted to approximate a patient cohort phenotypically closer to PRP, in order to assess for RP as an independent risk factor concerning CVD and VTE.

Methods

Data source

We performed a retrospective cohort study using data from electronic health records (EHR) from over 140 million individuals across >100 healthcare organizations (HCOs), mostly secondary and tertiary centres in North America, from March 2005 to March 2025. Details of the data source (from TriNetX, the global federated health research network) have been described [9], and are available from trinetx.com. Additional ethical approval was exempt because this study used only de-identified data and did not involve the collection, use, or transmission of individually identifiable data.

Eligibility

RP cases were required to have at least two ICD-10 codes (I73.0), without any SARDs (systemic connective tissue diseases) (M30–36). We chose irritable bowel syndrome (IBS) as the comparator group for several reasons. First, its epidemiology is similar to RP (i.e., more common among younger and female individuals). Second, it is not currently known to be definitively associated with adverse arterial or venous cardiovascular outcomes. We decided *a priori* not to compare the patients with RP to "healthy" controls because such individuals are unlikely to have EHR data or comparable healthcare contact or utilisation. IBS comparators were similarly required to have two ICD-10 codes (K58).

Outcome

Our co-primary outcomes were 1) major adverse cardiovascular events (MACE), a composite of myocardial infarction (MI), other acute ischaemic heart diseases, coronary revascularization, ischaemic stroke, cerebral revascularization, non-traumatic intracerebral haemorrhage, and 2) VTE comprising pulmonary embolism (PE), phlebitis and thrombophlebitis (including deep vein thrombosis, DVT), portal vein thrombosis, other venous embolism and thrombosis, thrombolysis and thrombectomy. Secondary outcomes included: MI, stroke, any CVD (ischemic heart diseases or cerebrovascular diseases), PE, and DVT. A full list of codes is shown in Supplementary Table S1.

Covariates

We included the following covariates assessed within one year prior to the index date (i.e., date of the first RP or IBS code respectively in each group): demographics, (i.e., age, sex, ethnicity); comorbidities including arterial and venous cardiovascular disease, proxies for smoking (COPD, tobacco use, nicotine dependence), overweight/obesity, hypertension, dyslipidaemia, type 2 diabetes, mood disorders; medications including antihypertensives, lipid lowering drugs, aspirin, anti-depressants; BMI and CRP (mg/L). All codes are provided in Supplementary Table S1.

Statistical analysis

We stratified all analyses *a priori* by age, above or below 45 years, because we wanted to understand whether later-onset RP (in those without any known SARD) could be an independent risk factor for CVD/VTE. This pragmatic cut-off was chosen being mindful that RP is almost always secondary if symptoms develop *after* 40 years of age [4]. We described the unadjusted incidence rate of each outcome and the incidence rate ratio between two comparator groups using Poisson approximation for confidence intervals. To account for potential confounding variables, we compared the risk of each CVD/VTE outcome between two exposure groups using 1:1 propensity score matched Cox proportional hazard models. Standardised mean difference (SMD) of <0.1 was taken as satisfactory matching. Follow-up started from one day after the index date (to reduce reverse causation) until the outcome, date of their last health record entry (e.g., lost to follow-up, emigration, or death), 10 years of follow-up, or end of the data cut (14th March 2025).

Results

In the analysis of individuals under 45 years of age, we identified 30,149 individuals meeting the case definition for RP and 153,002 IBS controls. Analyses included 30,088 matched pairs, followed over a mean of 4.6 ± 3.2 and 4.4 ± 3.2 years respectively. All covariates were adequately matched (SMD<0.1); further post-matching demographic details between groups are presented in Table 1. Baseline characteristics before propensity score matching are presented in Table 2. For RP and IBS groups, respectively, MACE occurred in 424 and 345, and VTE occurred in 881 and 671, over 131,129 and 131,448 patient years of follow-up. The incidence of MACE [IRR 1.23 (1.07, 1.42)] and VTE [IRR 1.32 (1.19, 1.46)] were higher in the RP group than in the IBS group. The hazard of MACE [HR 1.23 (1.07, 1.42)] and VTE [HR 1.32 (1.20, 1.46)] were similarly higher in RP.

In the analysis of individuals over 45 years of age, we identified 60,288 RP cases and 243,000 IBS controls. Analyses included 60,145 matched pairs, followed over a mean of 4.8 ± 3.2 and 4.9 ± 3.2 years respectively. Baseline characteristics before after and before matching are shown in Tables 1 and 2, respectively. All covariates were adequately matched (SMD<0.1) (Table 1). For RP and IBS groups, respectively, MACE occurred in 5353 and 4649, and VTE occurred in 3894 and 3302, over 131,129 and 131,448 patient years of follow up. The incidence of MACE [IRR 1.16 (1.12, 1.21)] and VTE [IRR 1.19 (1.14,

Table 1
Baseline characteristics after propensity score matching. Data are shown as mean (SD) or n (%). BMI: body weight index: COPD: chronic obstructive pulmonary disease; CRP: c-reactive peptide; IBS: Irritable bowel syndrome; RP: Raynaud's phenomenon; SMD: standardised mean difference.

	<45 years			≥45 years		
Characteristic	RP	IBS	SMD	RP	IBS	SMD
N	30,088	30,088		60,145	60,145	
Age	32.4 ± 7.9	32.4 ± 7.8	0.002	61.5 ± 10.6	61.6 ± 10.7	0.009
White	23,159 (77.0 %)	23,166 (77.0 %)	0.001	47,137 (78.4 %)	46,998 (78.1 %)	0.006
Female	23,884 (79.4 %)	24,064 (80.0 %)	0.015	41,393 (68.8 %)	41,611 (69.2 %)	0.008
Ischemic heart diseases	262 (0.9 %)	247 (0.8 %)	0.005	5808 (9.7 %)	5749 (9.6 %)	0.003
Cerebrovascular diseases	257 (0.9 %)	271 (0.9 %)	0.005	3143 (5.2 %)	3112 (5.2 %)	0.002
COPD	138 (0.5 %)	139 (0.5 %)	<0.001	3128 (5.2 %)	3139 (5.2 %)	0.001
Overweight and obesity	1868 (6.2 %)	1834 (6.1 %)	0.005	4909 (8.2 %)	4830 (8.0 %)	0.005
Type 2 diabetes mellitus	510 (1.7 %)	490 (1.6 %)	0.005	4455 (7.4 %)	4460 (7.4 %)	<0.001
Dyslipidaemia	1788 (5.9 %)	1694 (5.6 %)	0.013	18,224 (30.3 %)	18,303 (30.4 %)	0.003
Tobacco use	457 (1.5 %)	424 (1.4 %)	0.009	1298 (2.2 %)	1245 (2.1 %)	0.006
Anxiety and related disorders	6252 (20.8 %)	6200 (20.6 %)	0.004	9846 (16.4 %)	9894 (16.5 %)	0.002
Mood disorders	4392 (14.6 %)	4410 (14.7 %)	0.002	8067 (13.4 %)	7979 (13.3 %)	0.004
Nicotine dependence	1442 (4.8 %)	1377 (4.6 %)	0.01	3982 (6.6 %)	3810 (6.3 %)	0.012
Hypertension	2119 (7.0 %)	1991 (6.6 %)	0.017	18,766 (31.2 %)	18,513 (30.8 %)	0.009
Venous embolism/thrombosis	265 (0.9 %)	240 (0.8 %)	0.009	1060 (1.8 %)	1053 (1.8 %)	0.001
Pulmonary embolism	125 (0.4 %)	108 (0.4 %)	0.009	515 (0.9 %)	508 (0.8 %)	0.001
Lipid modifying agents	848 (2.8 %)	802 (2.7 %)	0.009	12,386 (20.6 %)	12,295 (20.4 %)	0.004
Antihypertensives	934 (3.1 %)	868 (2.9 %)	0.013	3146 (5.2 %)	3046 (5.1 %)	0.008
Aspirin	1073 (3.6 %)	1047 (3.5 %)	0.005	7698 (12.8 %)	7527 (12.5 %)	0.009
Renin-angiotensin agents	1008 (3.4 %)	965 (3.2 %)	0.008	10,434 (17.3 %)	10,166 (16.9 %)	0.012
Calcium channel blockers	1541 (5.1 %)	1477 (4.9 %)	0.01	8004 (13.3 %)	7855 (13.1 %)	0.007
Diuretics	1637 (5.4 %)	1579 (5.2 %)	0.009	9172 (15.2 %)	8849 (14.7 %)	0.015
Beta blocking agents	2322 (7.7 %)	2253 (7.5 %)	0.009	10,772 (17.9 %)	10,564 (17.6 %)	0.009
Antidepressants	6268 (20.8 %)	6239 (20.7 %)	0.002	12,289 (20.4 %)	12,065 (20.1 %)	0.009
CRP (mg/L)	8.9 ± 24.1	8.7 ± 23.3	0.009	15.3 ± 37.4	14.9 ± 37.2	0.011
BMI (kg/m^2)	25.5 ± 6.4	26.0 ± 6.8	0.072	26.2 ± 6.1	26.6 ± 6.3	0.063

Table 2
Pre-matching table. BMI: body mass index; COPD: chronic obstructive pulmonary disease; CRP: C-reactive peptide; IBS: irritable bowel syndrome; RP: Raynaud's phenomenon; SMD: standardised mean difference.

	<45 years of age			≥45 years of age		
Characteristic	RP	IBS	SMD	RP	IBS	SMD
N	30,149	153,002		60,288	243,000	
Age	32.5 ± 7.9	31.5 ± 7.6	0.122	61.5 ± 10.6	61.2 ± 10.5	0.029
White	23,218 (77.0 %)	104,655 (68.4 %)	0.194	47,271 (78.4 %)	169,178 (69.6 %)	0.201
Female	23,938 (79.4 %)	111,806 (73.1 %)	0.149	41,462 (68.8 %)	175,135 (72.1 %)	0.072
Ischemic heart diseases	269 (0.9 %)	819 (0.5 %)	0.042	5887 (9.8 %)	18,021 (7.4 %)	0.084
Cerebrovascular diseases	266 (0.9 %)	718 (0.5 %)	0.05	3190 (5.3 %)	9172 (3.8 %)	0.073
COPD	140 (0.5 %)	572 (0.4 %)	0.014	3166 (5.3 %)	10,801 (4.4 %)	0.038
Overweight and obesity	1872 (6.2 %)	13,052 (8.5 %)	0.089	4916 (8.2 %)	26,481 (10.9 %)	0.094
Type 2 diabetes mellitus	512 (1.7 %)	3378 (2.2 %)	0.037	4460 (7.4 %)	26,552 (10.9 %)	0.123
Dyslipidaemia	1801 (6.0 %)	8916 (5.8 %)	0.006	18,318 (30.4 %)	68,173 (28.1 %)	0.051
Tobacco use	460 (1.5 %)	1914 (1.3 %)	0.023	1326 (2.2 %)	4126 (1.7 %)	0.036
Anxiety and related disorders	6276 (20.8 %)	31,998 (20.9 %)	0.002	9872 (16.4 %)	44,987 (18.5 %)	0.056
Mood disorders	4409 (14.6 %)	22,766 (14.9 %)	0.007	8090 (13.4 %)	36,269 (14.9 %)	0.043
Nicotine dependence	1452 (4.8 %)	7231 (4.7 %)	0.004	4035 (6.7 %)	12,259 (5.0 %)	0.07
Hypertension	2150 (7.1 %)	8991 (5.9 %)	0.051	18,877 (31.3 %)	70,162 (28.9 %)	0.053
Venous embolism/thrombosis	274 (0.9 %)	582 (0.4 %)	0.066	1097 (1.8 %)	2644 (1.1 %)	0.061
Pulmonary embolism	128 (0.4 %)	384 (0.3 %)	0.03	530 (0.9 %)	1548 (0.6 %)	0.028
Lipid modifying agents	857 (2.8 %)	4375 (2.9 %)	0.001	12,468 (20.7 %)	47,171 (19.4 %)	0.032
Antihypertensives	952 (3.2 %)	3928 (2.6 %)	0.035	3184 (5.3 %)	11,247 (4.6 %)	0.03
Aspirin	1102 (3.7 %)	3494 (2.3 %)	0.081	7789 (12.9 %)	23,719 (9.8 %)	0.1
Renin-angiotensin agents	1023 (3.4 %)	3922 (2.6 %)	0.049	10,511 (17.4 %)	37,729 (15.5 %)	0.051
Calcium channel blockers	1597 (5.3 %)	3368 (2.2 %)	0.164	8107 (13.4 %)	22,986 (9.5 %)	0.125
Diuretics	1660 (5.5 %)	6406 (4.2 %)	0.061	9260 (15.4 %)	32,448 (13.4 %)	0.057
Beta blocking agents	2356 (7.8 %)	8877 (5.8 %)	0.08	10,873 (18.0 %)	36,899 (15.2 %)	0.077
Antidepressants	6286 (20.8 %)	31,831 (20.8 %)	0.001	12,331 (20.5 %)	53,449 (22.0 %)	0.038
CRP (mg/L)	9.1 ± 24.8	9.8 ± 25.6	0.031	15.3 ± 37.3	15.0 ± 38.3	0.009
BMI (kg/m^2)	25.5 ± 6.4	28.3 ± 7.8	0.396	26.2 ± 6.1	29.1 ± 7.1	0.427

1.25)] were higher in the RP group than the IBS group. The hazard of MACE [HR 1.17 (1.13, 1.20)] and VTE [HR 1.20 (1.14, 1.26)] were similarly higher in those with RP.

The incidence and hazards of all secondary outcomes were higher in RP, although estimates for DVT in both analyses, and MI in those under 45 lacked precision (Table 3).

Discussion

The key finding of our study is that RP was associated with an increased risk of CVD and VTE in individuals without any underlying SARD. Furthermore, this was independent of age and traditional cardiovascular risk factors. A key strength of our study was the large sample

Table 3
Incidence rates in matched populations. CVD: cardiovascular disease; DVT: deep vein thrombosis; IBS: irritable bowel syndrome; MACE: major adverse cardiovascular event; MI: myocardial infarction; PE: pulmonary embolism; RP: Raynaud's phenomenon; VTE: venous thromboembolism.

		RP			IBS			IRR (95 % CI)	HR (95 % CI)
	Outcome	Events	PYs	IR/1000PY (95 % CI)	Events	PYs	IR/1000PY (95 % CI)		
≥45 years of age	MACE	5353	289,499	18.5 (17.8, 19.2)	4649	292,558	15.9 (15.3, 16.5)	1.16 (1.12, 1.21)	1.17 (1.13, 1.22)
	MI	3008	289,499	10.4 (9.9, 11.0)	2458	292,558	8.4 (8.0, 8.9)	1.24 (1.17, 1.30)	1.24 (1.18, 1.31)
	Stroke	2867	289,499	9.9 (9.4, 10.4)	2603	292,558	8.9 (8.4, 9.4)	1.11 (1.06, 1.17)	1.12 (1.06, 1.18)
	Any CVD	16,468	289,499	56.9 (55.6, 58.2)	15,160	292,558	51.8 (50.7, 53.0)	1.10 (1.07, 1.12)	1.12 (1.09, 1.14)
	VTE	3894	289,499	13.5 (12.8, 14.1)	3302	292,558	11.3 (10.8, 11.8)	1.19 (1.14, 1.25)	1.20 (1.14, 1.26)
	PE	1388	289,499	4.8 (4.4, 5.2)	1202	292,558	4.1 (3.8, 4.4)	1.17 (1.08, 1.26)	1.17 (1.08, 1.26)
	DVT	133	289,499	0.5 (0.4, 0.6)	108	292,558	0.4 (0.3, 0.5)	1.24 (0.97, 1.60)	1.24 (0.97, 1.60)
<45 years of age	MACE	424	131,129	3.2 (2.8, 3.7)	345	131,448	2.6 (2.3, 3.0)	1.23 (1.07, 1.42)	1.23 (1.07, 1.42)
	MI	162	131,129	1.2 (1.0, 1.6)	137	131,448	1.0 (0.8, 1.3)	1.19 (0.94, 1.49)	1.19 (0.95, 1.49)
	Stroke	295	131,129	2.2 (1.9, 2.7)	222	131,448	1.7 (1.4, 2.0)	1.33 (1.12, 1.59)	1.33 (1.12, 1.59)
	Any CVD	1170	131,129	8.9 (8.2, 9.7)	1006	131,448	7.7 (7.0, 8.3)	1.17 (1.07, 1.27)	1.17 (1.08, 1.27)
	VTE	881	131,129	6.7 (6.1, 7.4)	671	131,448	5.1 (4.6, 5.6)	1.32 (1.19, 1.46)	1.32 (1.20, 1.46)
	PE	272	131,129	2.1 (1.7, 2.5)	217	131,448	1.7 (1.4, 2.0)	1.26 (1.05, 1.50)	1.26 (1.05, 1.51)
	DVT	26	131,129	0.2 (0.1, 0.4)	14	131,448	0.1 (0.1, 0.2)	1.86 (0.97, 3.57)	1.86 (0.97, 3.56)

size and well-matched comparator cohort. By excluding patients with RP and known SARDs, this allowed us to approximate a cohort of individuals phenotypically closer to PRP, than has been previously reported.

Our data substantiates several previous reports of an increased risk of CVD in individuals with RP, and provides further supporting evidence of a similar risk of VTE. Our patient cohort was younger than previously reported in the Charleston Heart Study cohort (by approximately 15 years on average). In a study of 2958 consecutive patients with newly diagnosed RP and no prior SARD, survival over a mean follow-up of 9.3 years was significantly poorer compared to a matched standard population (log-rank $P < 0.0001$) [10]. In patients with RP, mortality was higher in men (Cox proportional hazards model, $P \leq 0.0001$), and in women, the presence of abnormal nailfold capillaries, ANA, and anti–Scl-70 antibodies were associated with an increase in all-cause mortality [10].

Taken together our findings lend further support to suggest that RP (in the absence of any secondary SARD) could be a manifestation of *subclinical* CVD [3]. Of course, this requires further confirmation including prospective studies. Furthermore, the primary MACE composite was driven by both MI and stroke, with larger effect size for the former. Primary VTE composite was driven by both PE and DVT, although the latter lacked precision due to the smaller number of events. A key point is that all patients with RP should undergo a thorough clinical evaluation, including autoantibody testing and nailfold capillaroscopy, both of which independently predict progression to SSc [11].

Important conceptual insights into our findings may be gained from patients with SSc, in which RP is almost universal, and where vascular alterations are *systemic*. In particular, peripheral vascular investigations for RP may provide broader insights into SSc disease outcomes. Specifically, microvascular abnormalities (as assessed by nailfold capillaroscopy) are known to associate with a more severe disease course (including cardiopulmonary complications) in SSc [12]. Furthermore, thermographic abnormality (which assesses large vessel thermoregulatory function) has been reported to be associated with future digital (finger) ulcers and death in patients with SSc [13]. In addition, some studies have reported an increased risk of macrovascular (including coronary and peripheral artery) disease in patients with SSc [14]. However, this remains a subject of ongoing international debate among experts, as does the association between SSc and VTE [15,16]. Furthermore, a 'unified endovascular phenotype' can be conceptualised in SSc [4,17], in which shared disease effector mechanisms likely exist across anatomically distant vascular beds. For example, structural abnormalities of the digital arteries - as measured by the MRI-based Digital Artery Volume Index (DAVIX) - negatively correlate with the FVC:DLCO ratio in patients with SSc, likely reflecting the presence of pulmonary vascular disease [18]. Patient-reported experiences may also provide novel insights; for example, the apparent over-representation of cyanotic colour changes in SSc-RP compared to PRP [19]. Notably, SSc-RP patients with persistent colour changes between RP attacks are reported to have an increased risk of pulmonary arterial hypertension [20].

A main strength of our study was the large sample size and use of a well-matched and appropriate comparator cohort. However, several important limitations remain, many stemming from the analysis of large population-level assembled data. We specifically chose IBS as our comparator cohort, as the known epidemiology is comparable to phenotypically PRP (e.g., more commonly affects younger to middle-aged females), and without definitive known increased CVD/VTE risk. We required at least 2 ICD codes for RP and IBS which should reduce misclassification although this approach has not been validated, and misclassification bias remains possible. Including non-cases of cases or controls is likely to reduce precision and theoretically bias our results towards the null. RP was not subject to further confirmatory expert chart review including for the detection of other (e.g., medical and drug) causes of SRP. Furthermore, data concerning the RP characteristics of these individuals are not available, such as the history of digital ischaemic (e.g., ulcer) episodes, which would not occur in those with phenotypical PRP. Similarly, we also did not have the opportunity to explore the age of onset of RP, or the family history, factors which warrant further investigation in future studies. Additionally, many of the oral drug treatments for RP are vasodilators also used for systemic hypertension, making it difficult to determine the primary indication in our cohort, but an important consideration in future research.

In conclusion, in our large cohort study, RP was associated with increased risk of CVD and VTE, even in younger patients. Future well-designed prospective studies are needed to confirm these findings and to elucidate the biological mechanisms underlying this newly recognized independent risk factor for adverse cardiovascular outcomes.

Availability of data

The data that support the findings of this study are available from TriNetX, LLC but third-party restrictions apply to the availability of these data. The data were used under license for this study with restrictions that do not allow for the data to be redistributed or made publicly available. However, for accredited researchers, the TriNetX data is available for licensing at TriNetX, LLC. To gain access to the data in the TriNetX research network, a request can be made to TriNetX (https://live.trinetx.com), but costs may be incurred, a data sharing agreement would be necessary, and no patient identifiable information can be obtained. No data from Liverpool University Hospitals NHS Foundation Trust was utilized in this analysis.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2025.152799.

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