**Prevalence of comorbidity amongst people with palmoplantar pustulosis: a systematic review and meta-analysis.**

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All data was obtained from published studies available in the literature. The data that support the findings of this study and further supplementary materials are openly available in figshare: https://figshare.com/account/articles/28351418?file=52149425

Author Contribution Statement:

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Dear Editor,

Palmoplantar pustulosis (PPP) is closely associated with smoking, but the wider comorbidity burden is poorly described.1 Reviewing this burden is timely; Janus kinase (JAK) inhibitors have emerged as a promising immunomodulatory treatment for PPP. However a possible increased risk of major adverse cardiovascular events (MACE; myocardial infarction/stroke/transient ischaemic attack), venous thrombo-embolic events (VTE) and malignancy has led to regulatory bodies cautioning JAK inhibitor use in at-risk populations (age >65 years; current/long-term ex-smokers; those with cardiovascular or malignancy risk factors).23 We undertook a systematic review and meta-analysis to quantify the prevalence of comorbidities, including cardiovascular risk factors and malignancy, in individuals with PPP.

A systematic search of six databases (Embase, Ovid, Pubmed, Web of Science, Cochrane, Cinahl) was conducted on 29th July 2024 for studies reporting prevalence of relevant comorbidities in adults with PPP (PROSPERO ref CRD42024508151).4 Conference abstracts, review articles, and case reports were excluded. Study quality was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist.5 A consensus decision was made whether to include studies with low quality scores (<5) in the meta-analysis.6

Following quality assessment, studies of dermatologist-confirmed PPP conducted in a specialist setting were included in the meta-analysis. Population studies based on coding and claims databases were excluded.7 Prevalence estimates for comorbidities were pooled using a random-effects model and presented with 95% confidence intervals (95%CI). Heterogeneity between studies was assessed using the *I2* statistic. Egger’s test was used to explore publication bias.

Of 23,727 references identified, 86 studies were included in the systematic review, comprising 233,969 people with PPP (mean age 48.1 years; 67% female; Figure 1). Detailed search results are available on the associated figshare online repository (xxx). Studies reported on populations from Europe (n=44), Asia (n=27), North America (n=16), pan-continental (n=3), and South America (n=1). Study quality was variable; only fourteen studies (16.3%) met all relevant criteria of the JBI Critical Appraisal Checklist. Following quality assessment, 57 studies were included in the meta-analysis. Low heterogeneity was observed between studies for MACE (*I2*=0%) and diabetes mellitus (*I2*=33.2%, *p*=0.08; Table 1). Substantial heterogeneity (*I2*>50%) was observed between studies for all other comorbidities. No significant publication bias was identified.

Psoriasis vulgaris (prevalence 24.4% [95%CI 18.1-30.6%]) and psoriatic arthritis (19.7% [15.5-24.0%]) were common. The most prevalent cardiovascular risk factors were smoking (78.2% [73.6-82.6%]), hypertension (28.6% [24.4-32.8%]), hyperlipidaemia (28.3% [22.3-34.3%]), and obesity (25.2% [17.7-32.7%]). The prevalence of MACE and malignancy was 6.9% (3.8-9.9%) and 6.9% (2.6-11.2%), respectively. No studies were identified that reported the prevalence of VTE.

Sensitivity analyses excluding studies at higher risk of selection bias (case series, trials), studies relating to SAPHO and PAO, and studies not meeting two or more JBI quality criteria all identified only marginal differences in the prevalence estimates for most comorbidities. Analysis including population-based studies also identified only marginal differences in estimates.

Pooled smoking prevalence estimates were highest in studies published in the 2000’s (94.2% [89.6-98.8%]) and 1980’s (91.0% [85.9-94.4%]). Globally, adult smoking prevalence in 2020 was 32.6% and 6.5% among men and women respectively.8 The high prevalence of smoking identified in this study (78.2%) supports the recently described causal role for smoking in PPP pathogenesis.1

Our results were not age- or ethnicity-matched, preventing direct comparisons to the general population. In line with high heterogeneity observed in meta-analyses of disease prevalence studies, our calculated estimates have wide confidence intervals and should be interpreted with caution.9

This systematic review and meta-analysis of 233,969 people with PPP highlights a high prevalence of smoking and cardiovascular risk factors. These findings should inform clinical screening efforts and treatment decision-making for people with PPP with novel therapeutic agents such as JAK inhibitors.

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**Figure 1**. PRISMA flowchart showing the study selection process.



**Table 1.** Prevalence estimates for each comorbidity.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **No. studies** | **No. participants** | **Meta-analysis prevalence estimate, % (95% CI)** | **Heterogeneity assessment** | **Publication bias (Egger’s test)** |
| ***I2 statistic (%)*** | ***p-value*** |
| **Psoriatic Disease:** |  |  |  |  |  |  |
| Psoriatic arthritis | 24 | 2,561 | 19.7 (15.5-24.0) | 88.0 | <0.01\* | 0.06 |
| Psoriasis vulgaris | 29 | 3,742 | 24.4 (18.1-30.6) | 97.5 | <0.01\* | 0.12 |
| **Cardiovascular Risk Factors:** |  |  |  |  |  |  |
| Diabetes mellitus | 18 | 2,716 | 12.6 (10.9-14.3) | 33.2 | 0.08 | 0.18 |
| Hyperlipidaemia | 13 | 1,348 | 28.3 (22.3-34.3) | 83.8 | <0.01\* | 0.67 |
| Hypertension | 20 | 2,742 | 28.6 (24.4-32.8) | 81.9 | <0.01\* | 0.50 |
| Obesity | 9 | 1,637 | 25.2 (17.7-32.7) | 92.6 | <0.01\* | 0.36 |
| Smoking | 43 | 5,361 | 78.2 (73.6-82.6) | 96.0 | <0.01\* | 0.57 |
| **Specific Outcomes:** |  |  |  |  |  |  |
| Ischaemic heart disease | 9 | 941 | 8.9 (5.7-12.2) | 64.3 | <0.01\* | 0.51 |
| MACE | 2 | 261 | 6.9 (3.8-9.9) | 0.00 | - | - |
| Malignancy (exNMSC)  | 3 | 320 | 6.9 (2.6-11.2) | 55.7 | 0.11 | 0.08 |
| VTE | 0 | 0 | - | - | - | - |
| MACE, major adverse cardiovascular events; exNMSC, excluding non-melanomatous skin cancer; VTE, venous thrombo-embolic events; \* p<0.05. |