A multi-centre, cross-sectional study of the clinical and demographic factors that influence the severity of palmoplantar pustulosis

Subtitle: Findings from the APRICOT, PLUM and ERASPEN consortia

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Key points

Question: What are the clinical and demographic factors underlying the severity of palmoplantar pustulosis (PPP)?

Findings: In a multi-centre cross-sectional study of 203 UK cases, we observed that the palmoplantar pustulosis area and severity index was significantly higher in females compared to males (9.6 vs 4.0) and in current smokers vs former and never-smokers (10.7 vs 7 vs 2.2). Both trends were replicated in an independently ascertained, Northern European cohort (n=159).

Meaning: These findings suggest that smoking cessation interventions may be beneficial in PPP, so that their impact should be investigated in clinical studies.

Abstract

Importance: While palmoplantar pustulosis (PPP) can have a profound impact on quality of life, the factors underlying disease severity have not been studied.

Objective: To define the factors associated with PPP severity.

Design: We undertook an observational, cross-sectional study of two cohorts. A UK dataset was recruited through the APRICOT clinical trial (2016-2019) and its sister research study PLUM (2016-2020). A Northern European cohort was independently ascertained by the European Rare And Severe Psoriasis Expert Network (2013-2017).

Settings: Patients were recruited in secondary or tertiary dermatology referral centres.

Participants: The UK and Northern European cohort included 203 and 193 cases, respectively. All were or European descent. PPP was diagnosed by dermatologists, based on clinical examination and/or published consensus criteria.

Main outcomes and measures: Demographics, comorbidities, smoking status, Palmoplantar Pustulosis Area Severity Index (PPPASI) or Physician Global Assessment (PGA).

Results: Among the 203 UK patients (43 males, 160 females; median age of onset [IQR] 48 [38-59] years), the PPPASI was inversely correlated with age of onset (r=-0.18, *P*=0.014). Similarly, in the 159 Northern European cases that were eligible for inclusion in this analysis (25 males, 134 females ; median age of onset [IQR] 45 [34-53.3] years), the median [IQR] age of onset was lower in individuals with moderate-to-severe PGA compared to those with mild-to-clear PGA 41 [30.5-52] vs 46.5 [35-55], *P*=0.043).

In the UK sample, the median [IQR] PPPASI was higher in females than males (9.6 [3.0-16.2] vs 4.0 [1.0-11.7], *P*=0.0096). Likewise, moderate-to-severe PPP was more prevalent among Northern European females compared to males 57 of 134 [43%] vs 5 of 25 [20%], *P*=0.026).

In the UK cohort, the median PPPASI [IQR] was elevated in current smokers compared to ex- and non-smokers (10.7 [4.2-17.5] vs 7 [2.0-14.4] vs 2.2 [1-6], *P*=0.003). Comparable differences were observed in the Northern European dataset, as the prevalence of moderate-to-severe PPP was higher in former/current smokers compared to non-smokers (51 of 130 [39%] vs 6 of 24 [25%], *P*=0.14).

Conclusions and relevance: PPP severity is associated with early-onset disease, female sex and smoking status. Thus, smoking cessation intervention might be beneficial.

INTRODUCTION

Palmoplantar pustulosis (PPP) is an uncommon pustular eruption affecting the palms and/or the soles. It is observed in approximately 1:2,000 individuals of European descent and 1:800 East Asians[1]. The disease typically manifests in adulthood, with a median age of onset >45 reported in most studies[2]. PPP shows a very marked sex bias, as females account for 60-90% of affected individuals[2,3]. It is also characterised by a very strong association with cigarette smoking, with up to 90% of patients self-identifying as smokers at the time of diagnosis[2,4-6]. The disease manifests with the eruption of sterile, neutrophil-filled pustules on the palms and soles. The lesions, which can occur on a background of normal or inflamed skin, are persistent (>3 months), painful and disabling. They can be accompanied by fissures, pruritus and a burning sensation[7]. Co-morbidities are also common, as affected individuals are at increased risk of psoriasis vulgaris (PsV), psoriatic arthritis and autoimmune thyroid disease[8].

While PPP can have a profound impact on quality of life, the factors underlying variable disease severity have not been investigated. In fact, the rarity of the condition has hindered the ascertainment and characterisation of adequately powered datasets. In this context, the objective of our study was two-fold: i) to evaluate the features of PPP in two independent patient cohorts; ii) to determine whether PPP severity is influenced by sex and smoking status, the two most well-established risk factors for the disease. Given that symptoms typically manifest in adulthood, we also sought to establish whether the presentation of PPP is more severe in early-onset cases.

METHODS

Patients

This study was carried out in accordance with the principles of the declaration of Helsinki and with the approval of the participating institutions' ethics committees. All patients granted their informed consent in writing.

The UK resource included 203 unrelated and prospectively ascertained patients. Forty-two were recruited between 2016 and 2019 through the APRICOT clinical trial (Anakinra in Pustular psoriasis, Response In a Controlled Trial; EudraCT n. 2015-003600-23). The remaining 161 were enrolled between 2016 and 2020, through the sister research study PLUM (Pustular psoriasis, eLucidating Underlying Mechanisms). A total of 23 Dermatology centres located across the UK were involved in the recruitment.

The Northern-Europe resource included 193 unrelated patients. Affected individuals were mostly ascertained between 2013 and 2017, through three centres affiliated to the European Rare And Severe Psoriasis Expert Network (ERASPEN). These were the Dermatology Departments of the Medical University of Vienna, Austria (n=100), Tartu University, Estonia (n=57) and University Medical Centre Schleswig-Holstein, Campus Kiel, Germany (n=31). The remaining 5 patients were recruited outside the main reference centres, by clinicians who provided individual cases to the ERASPEN Consortium.

Pustular psoriasis was always diagnosed by a dermatologist, based on clinical examination and/or the ERASPEN consensus criteria[7]. The observation of sterile, macroscopically visible pustules on palms or soles was the main inclusion criterion. Conversely, the presence of pustules restricted to the edges of psoriatic plaques represented an exclusion criterion. Individuals with concomitant generalised pustular psoriasis or concomitant acrodermatitis

continua of Hallopeau were also excluded from the study, given that lesions affecting nails or non-acral skin are deemed incompatible with a diagnosis of PPP[9].

Clinical information and key demographics were collated using a standardised case report form, shared by all centres. In the UK cohort, disease severity was measured using the Palmoplantar Pustulosis Area Severity Index (PPPASI)[10] and the Dermatology Life Quality Index (DLQI) (eFigure 1 in the Supplement). In the Northern European cohort, patients were assessed with the Physician Global Assessment (PGA), which has been shown to correlate with the PPPASI[11]. The individuals who recorded clinical data and measured disease severity (reporting dermatologists or trained research nurses) were blinded to the study objectives.

Statistical analysis

Given that different scoring systems were used in the UK and Northern European cohort, the two datasets were analysed separately.

The quantitative PPPASI and DLQI measures obtained in the UK cohort were analysed using the Mann-Whitney test (for binary variables such as sex) or the Kruskal-Wallis test (for categorical variables such as smoking status). The correlation between PPPASI (or DLQI) and age of onset was assessed using Spearman's Rank correlation coefficient. To account for the confounding effects of therapeutic intervention, statistical significance was also confirmed by regression analysis. PPPASI and DLQI values were normalised (square root transformation) and analysed vs sex, age of onset or smoking status, using treatment as a co-variate

To maximise statistical power, the categorical PGA scores recorded in the Northern European dataset were dichotomised into clear-to-mild (including PGA-0 [clear], PGA-1 [almost clear], PGA-2 [mild]) and moderate-to-severe (including PGA-3 [moderate], PGA-4

[severe]). The two groups were then compared using Fisher's exact test. Given that the purpose of the PGA analysis was to replicate results showing statistical significance in the UK cohort, P-values were computed based on a one-tailed distribution. As the number of individuals receiving systemic treatment was relatively small (n=25 from the Medical University of Vienna and 9 from Tartu University) the confounding effect of therapeutic intervention was addressed by simply excluding these cases from downstream analyses. Individuals for whom information on smoking status or age-of-onset was missing (see Table 1 for details) were excluded from the relevant analyses. All statistical tests were implemented in R (version 3.6.1). P-values<0.05 were considered statistically significant.

RESULTS

Features of patient cohorts

The features of the UK and Northern European cohorts are summarised in Table 1. All patients were of European descent. The percentage of females (>75%), median age of onset (≥45 years) and prevalence of current/former smokers (>80%) were comparable in the two datasets. Prominent nail involvement was observed in both study populations, with >30% of patients presenting with at least one of the following: pustules involving the nail apparatus, subungual hyperkeratosis, permanent nail loss, non-pustular nail dystrophy.

Concurrent PsV was observed in substantial numbers of study participants (66/203 [33%] British patients and 22/193 [11%] Northern European cases), while psoriatic arthritis was reported in ~10% of patients from both cohorts (20/203 British cases and 17/193 Northern European individuals).

Auto-immune thyroid disease was reported in several affected individuals from both datasets (14/203 [7%] of UK cases and 25/193 (13%) of Northern-European patients).

Interestingly, the prevalence of obesity (60/150 [40%] in the UK dataset and 51/193 (26%) in the Northern European sample) was comparable to that observed among British (36%)[12], German (25%)[13] and Estonian (21%)[13] adults. In keeping with this observation, there was no correlation between the body mass index of PPP patients and their PPPASI (data not shown).

While different scoring systems were used in the two cohorts, both included a substantial proportion of individuals with severe PPP, reflecting ascertainment in hospital settings. Specifically, 84 of 203 (41%) British patients had a PPPASI>10 and 73/193 (38%) of their Northern European counterparts had a PGA≥3 (Table 1)

Factors associated with disease severity

Among UK patients, age of onset was inversely correlated with PPPASI (r=-0.18, *P*=0.014) (Figure 1A), although not with DLQI (r=-0.08, *P*=0.21). Of note, the association with PPPASI remained significant when the confounding effect of systemic treatment was taken into account by linear regression (*P*=0.039) (eTable 1 in the Supplement). In keeping with these findings, the analysis of the Northern European cohort revealed that the median [IQR] age of onset was lower in patients with moderate-to-severe PGA compared to those with clear-to-mild PGA (41 [30.5-52] vs 46.5 [35-55], *P*=0.043) (Figure 1B). Thus, severe PPP appears to be associated with early disease onset.

In the UK sample, the median PPPASI [IQR] was higher in females compared to males (9.6 [3.0-16.2] vs 4.0 [1.0-11.7], *P*=0.0096) (Figure 2A). The same applied to the median DLQI [IQR] (10.5 [4.3-17] vs 4 [1-9], $P=8.2 \times 10^{-5}$) (eFigure 2 in the Supplement). Both associations were confirmed when the effect of systemic treatment was included in a linear regression model (*P*=0.03 for PPPASI, *P*=0.0001 for DLQI) (eTable 1 in the Supplement). In agreement

with these observations, the analysis of the Northern European dataset revealed that moderate-to-severe PPP was more prevalent among females compared to males 57 of 134 [43%] vs 5 of 25 [20%], *P*=0.026) (Figure 2B). Thus, PPP severity is influenced by the biological sex of the patient, in both the UK and Northern European study populations.

Among UK patients, the median PPPASI [IQR] was highest in current smokers, intermediate in former smokers and lowest among non-smokers (10.7 [4.2-17.5] vs 7 [2.0-14.4] vs 2.2 [1-6], *P*=0.003) (Figure 3A). Comparable findings were obtained when the median DLQI [IQR] was analysed (10 [4.8-16.3] vs 9 [3-17] vs 5 [1-10.8], *P*=0.042) (eFigure 3 in the Supplement). Both associations could be replicated when the effects of systemic treatment were incorporated into a linear model (*P*=0.005 for PPPASI, *P*=0.043 for DLQI) (eTable 1 in the Supplement). Of note, the percentage of current smokers (18/43 [42%] males and 72/160 [45%] females) and former smokers (19/43 [44%] and 69/160 [43%] females) was comparable in the two sexes. Moreover, multivariable regression modelling found no evidence that the effect of smoking differed by gender (data not shown).

While the analysis of the smaller Northern European dataset did not yield statistically significant results, we observed a similar trend towards increased disease severity in smokers. In fact, moderate-to-severe PPP was more frequent among current/former smokers than non-smokers (51 of 130 [39%] vs 6 of 24 [25%], *P*=0.14) (Figure 3B).

DISCUSSION

To the best of our knowledge, this is the first systematic study of the factors associated with PPP severity. It builds on previous work from our network, which enabled the definition of consensus diagnostic criteria for PPP[7] and demonstrated that the disease is genetically different from other forms of pustular psoriasis[2].

Our investigation confirms key epidemiological features of PPP, such as the late age of onset and marked sex bias (male to female ratios were >1:3.5 in both cohorts). PsV concurrence, which is frequently reported in PPP, was also observed in the two datasets. While the prevalence of PsV in the two cohorts was consistent with published estimates (14-61%)[14], the number of individuals suffering from PPP with PsV was too small for subgroup analyses and the use of different scoring systems prevented us from merging the UK and Northern European datasets.

Conversely, the study of the entire resource highlighted aspects of PPP which had not been systematically investigated before.

We observed nail involvement in approximately a third of affected individuals. Interestingly, subungual pustulation was reported in a similar fraction of cases in a small UK study[15], suggesting that nail abnormalities are a consistent feature of PPP.

We also report substantial co-morbidity with psoriatic arthritis, which was present in both cohorts at a frequency >9%. This markedly exceeds the prevalence of the disease in the general population (0.1-0.3%)[16].

Obesity was relatively uncommon, affecting only a third of all study participants. This contrasts with findings obtained in PsV, where the association with obesity is well established[17] and up to 42% of individuals with severe disease have a body mass index>30[18].

Overall, these findings suggest that PPP is part of the psoriasis spectrum, as the substantial co-morbidity with PsV and psoriatic arthritis points to shared pathogenic pathways. At the same time, the distinctive demographics of PPP suggest the involvement of risk factors that are specific to this particular disease. It is interesting, for instance, that the marked female bias that characterises PPP is not observed in palmoplantar psoriasis[19]. Likewise, PsV affects

both sexes equally[20] and occurred with comparable frequency in the male and female patients examined in this study (data not shown).

Our analysis of PPPASI and PGA scores demonstrated that PPP severity is elevated in females. Further experimental studies will be required to dissect the causes of this phenomenon. These may involve genetic modifiers or hormonal imbalances that could be targeted for disease treatment.

Our study also showed an association between cigarette smoking and disease severity. This was statistically significant in the UK cohort ($P<0.01$), where PPPASI values were highest in smokers, intermediate in former smokers and lowest in non-smokers. This observation suggests a clinically relevant dosage effect, which could be validated and refined by analysing pack-year data in further patient resources.

Of note, smoking cessation is sometimes applied to the management of PPP and was found to be beneficial in a pilot study [21,22]. In this context, our findings suggest that the effects of smoking cessation should be systematically investigated in adequately powered trials.

Limitations

Our study was exclusively based in secondary and tertiary referral centres, where the proportion of patients with severe PPP and the burden of co-morbid disease may be higher than in other settings. Thus, the potential for ascertainment bias limits the generalisability of our findings.

Different measures of disease severity were used in the UK (DLQI, PPPASI) and Northern European cohorts (PGA). While all the above scores are widely used in clinical practice, our results show that the categorical nature of PGA affected the statistical power of the Northern European cohort and limited our ability to apply correlation-based methods. Thus,

quantitative measurements such as the PPPASI (or even more sensitive methods such as machine-learning based pustule counts) should be considered the gold-standard for studies of PPP severity.

CONCLUSIONS

Our cross-sectional study underscores the benefits of multi-centre collaborations and standardised data collection in the analysis of rare skin diseases. It also shows that PPP symptoms are particularly severe in patients with early onset disease, females and current smokers. While the latter observation will need to be replicated in further datasets, it suggests that smoking cessation interventions may benefit the treatment of PPP.

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Membership of the PLUM and APRICOT study team

The following members of the PLUM and APRICOT study team contributed to this work: Mahmud Ali (Worthing Hospital), Nisha Arujuna (Kingston Hospital), Suzannah August (Poole Hospital), David Baudry (Guy's Hospital, London), A David Burden (Glasgow Western Infirmary), Hywel Cooper (St Marys Hospital, Portsmouth), Victoria Cornelius (Imperial College London), Suzie Cro (Imperial College London), Giles Dunnill (University Hospitals Bristol), Christopher Griffiths (University of Manchester), John Ingram (University Hospital of Wales), Helen Lachmann (Royal Free Hospital, London), Effie Ladoyanni (Russell's Hall Hospital, Dudley), Nick Levell (Norfolk & Norwich University Hospital), Areti Makrygeorgou (West Glasgow Ambulatory Care Hospital), Helen McAteer (The Psoriasis Association, Northampton), John McKenna (Leicester Royal Infirmary), Freya Meynell (Guy's Hospital, London), Richard Parslew (Royal Liverpool), Prakash Patel (Guy's Hospital, London), Andrew Pink (Guy's Hospital, London), Angela Pushparajah (Guy's Hospital, London), Nick Reynolds (Newcastle Hospitals), Catherine Smith (Guy's Hospital, London), Shyamal Wahie (University Hospital of North Durham and Darlington Memorial Hospital), Richard Warren (Salford Royal Infirmary), Rosemary Wilson (Guy's Hospital, London), Andrew Wright (St Lukes Hospital, Bradford).

Membership of the ERASPEN study team

The following members of the ERASPEN study team contributed to this work:

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REFERENCES

1. Mahil SK, Barker JN, Capon F. Pustular forms of psoriasis related to autoinflammation. In: Hashkes P, Laxer R, Simon A, eds. *Textbook of Autoinflammation.* Switzerland: Springer Nature; 2019:471-484.
2. Twelves S, Mostafa A, Dand N, et al. Clinical and genetic differences between pustular psoriasis subtypes *The Journal of allergy and clinical immunology.* 2019;143:1021-1026.
3. Wilsmann-Theis D, Jacobi A, Frambach Y, et al. Palmoplantar pustulosis - a cross-sectional analysis in Germany. *Dermatol Online J.* 2017;23(4).
4. Kharawala S, Golembesky AK, Bohn RL, Esser D. The clinical, humanistic, and economic burden of generalized pustular psoriasis: a structured review. *Expert Rev Clin Immunol.* 2020:1-14.
5. Naldi L, Chatenoud L, Linder D, et al. Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: results from an Italian case-control study. *J Invest Dermatol.* 2005;125(1):61-67.
6. Naldi L, Peli L, Parazzini F. Association of early-stage psoriasis with smoking and male alcohol consumption: evidence from an Italian case-control study. *Archives of dermatology.* 1999;135(12):1479-1484.

7. Navarini AA, Burden AD, Capon F, et al. European Consensus Statement on Phenotypes of Pustular Psoriasis. *Journal of the European Academy of Dermatology and Venereology : JEADV.* 2017:1792-1799.

8. Trattner H, Bluml S, Steiner I, Plut U, Radakovic S, Tanew A. Quality of life and comorbidities in palmoplantar pustulosis - a cross-sectional study on 102 patients. *Journal of the European Academy of Dermatology and Venereology : JEADV.* 2017;31(10):1681-1685.

9. Brunasso AM, Puntoni M, Aberer W, Delfino C, Fancelli L, Massone C. Clinical and epidemiological comparison of patients affected by palmoplantar plaque psoriasis and palmoplantar pustulosis: a case series study. *Br J Dermatol.* 2013;168(6):1243-1251.

10. Bhushan M, Burden AD, McElhone K, James R, Vanhoutte FP, Griffiths CE. Oral liarozole in the treatment of palmoplantar pustular psoriasis: a randomized, double-blind, placebo-controlled study. *Br J Dermatol.* 2001;145(4):546-553.

11. Terui T, Kobayashi S, Okubo Y, Murakami M, Hirose K, Kubo H. Efficacy and Safety of Guselkumab, an Anti-interleukin 23 Monoclonal Antibody, for Palmoplantar Pustulosis: A Randomized Clinical Trial. *JAMA Dermatol.* 2018;154(3):309-316.

12. NHS Digital. Statistics on Obesity, Physical Activity and Diet, England, 2019. In:2019.

13. WHO Global Health Observatory Data Repository 2013.

14. Andersen YMF, Augustin M, Petersen J, et al. Characteristics and prevalence of plaque psoriasis in patients with palmoplantar pustulosis. *Br J Dermatol.* 2019;181(5):976-982.

15. Burden AD, Kemmett D. The spectrum of nail involvement in palmoplantar pustulosis. *Br J Dermatol.* 1996;134(6):1079-1082.

16. Ogdie A, Langan S, Love T, et al. Prevalence and treatment patterns of psoriatic arthritis in the UK. *Rheumatology.* 2013;52(3):568-575.

17. Coimbra S, Catarino C, Santos-Silva A. The triad psoriasis-obesity-adipokine profile. *Journal of the European Academy of Dermatology and Venereology : JEADV.* 2016;30(11):1876-1885.

18. Iskandar IY, Ashcroft DM, Warren RB, et al. Demographics and disease characteristics of patients with psoriasis enrolled in the British Association of Dermatologists Biologic Interventions Register. *Br J Dermatol.* 2015;173(2):510-518.

19. Timotijevic ZS, Trajkovic G, Jankovic J, et al. How frequently does palmoplantar psoriasis affect the palms and/or soles? A systematic review and meta-analysis. *Postepy Dermatol Alergol.* 2019;36(5):595-603.

20. Burden AD, Kirby B. Psoriasis and related disorders. In: Griffiths CEM, Barker JN, Bleiker T, Chalmers RJ, Creamer D, eds. *Rook's Textbook of Dermatology.* Chichester: Wiley-Blackwell; 2016.

21. Michaelsson G, Gustafsson K, Hagforsen E. The psoriasis variant palmoplantar pustulosis can be improved after cessation of smoking. *J Am Acad Dermatol.* 2006;54(4):737-738.

22. Mrowietz U, van de Kerkhof PC. Management of palmoplantar pustulosis: do we need to change? *Br J Dermatol.* 2011;164(5):942-946.

420 **Table 1. Features of study cohorts**

Cohort	**UK**	**Northern European**
Demographics [a]		
Sex, F	160/203 (79%)	161/193 (83%)
Age of onset (years), median (IQR) [b]	48 (38 - 59)	45 (33 - 54)
Family history of PsV	65/203 (32%)	33/193 (17%)
Family history of pustular psoriasis	9/203 (4%) [c]	10/93 (11%) [d]
Smoking status		
Current smokers	90/203 (44%)	124/193 (64%)
Former smokers	88/203 (43%)	36/193 (19%)
Never smokers	23/203 (11%)	28/193 (15%)
Unknown	2/203 (1%)	5/193 (3%)
Clinical presentation		
Disease duration (years), median (IQR) [b]	6 (2 – 14)	16 (10 – 20) [d]
Nail involvement	65/203 (32%)	64/193 (33%)
Concurrent PsV	66/203 (33%)	22/193 (11%)
Concurrent PsA	20/203 (10%)	17/193 (9%)
Severity		
PPPASI, median (IQR)	8.2 (2.2 – 15.6)	-

	DLQI, median (IQR) [e]	10 (3.3 - 16)	-
	On systemic treatment [f]	78/203 (38%)	34/193 (18%)
PGA			
	Clear/Mild (0-2)	-	120/193 (62%)
	Moderate/Severe (3-4)	-	73/193 (38%)
Comorbid disease			
	Asthma	25/203 (12%)	5/93 (5%) [d]
	Depression	31/203 (15%)	28/193 (15%)
	Diabetes	26/203 (13%)	29/193 (15%)
	Hypertension	41/203 (20%)	58/193 (30%)
	Autoimmune thyroid disease	14/203 (7%)	25/193 (13%)
	Obesity [g]	60/150 (40%) [h]	51/193 (26%)

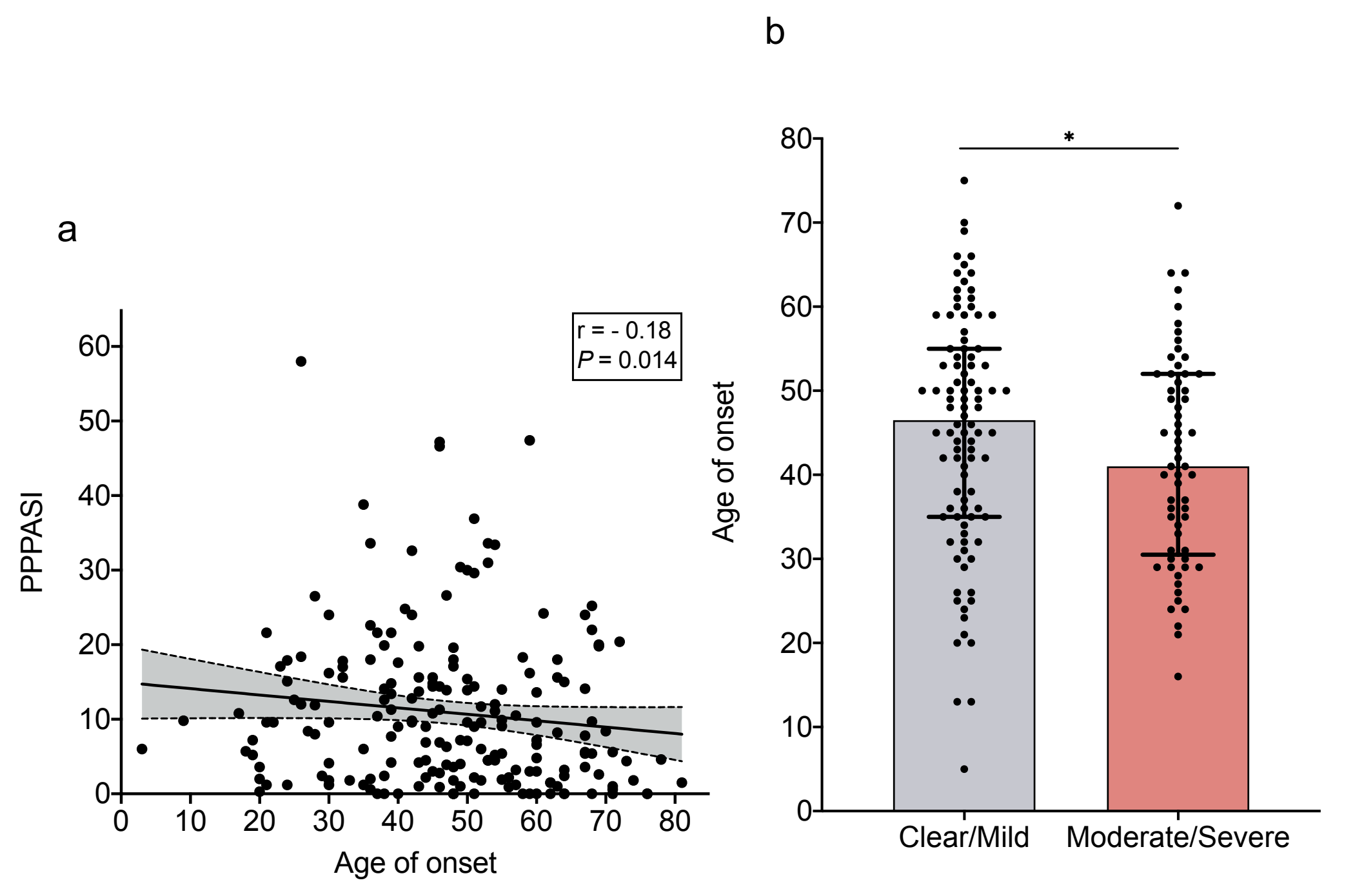
Abbreviations: ACH, Acrodermatitis continua of Hallopeau; DLQI, Dermatology Life Quality Index; F, Female; GPP, Generalised Pustular Psoriasis; PPPASI, Palmo-plantar Pustular Psoriasis Area Severity Index; PsA, Psoriatic Arthritis; PsV, Psoriasis Vulgaris; [a] All study participants were of European descent; [b] Data not available for 11 UK and 1 Northern European cases; [c] one patient had a family history of both PsV and pustular psoriasis; [d] Information not available for the 100 cases recruited in Vienna; [e] Data not available for 8 UK cases; [f] On systemic treatment at the time of recruitment or the preceding four weeks; [g] Body Mass Index > 30; [h] Data not available for 53 UK cases.

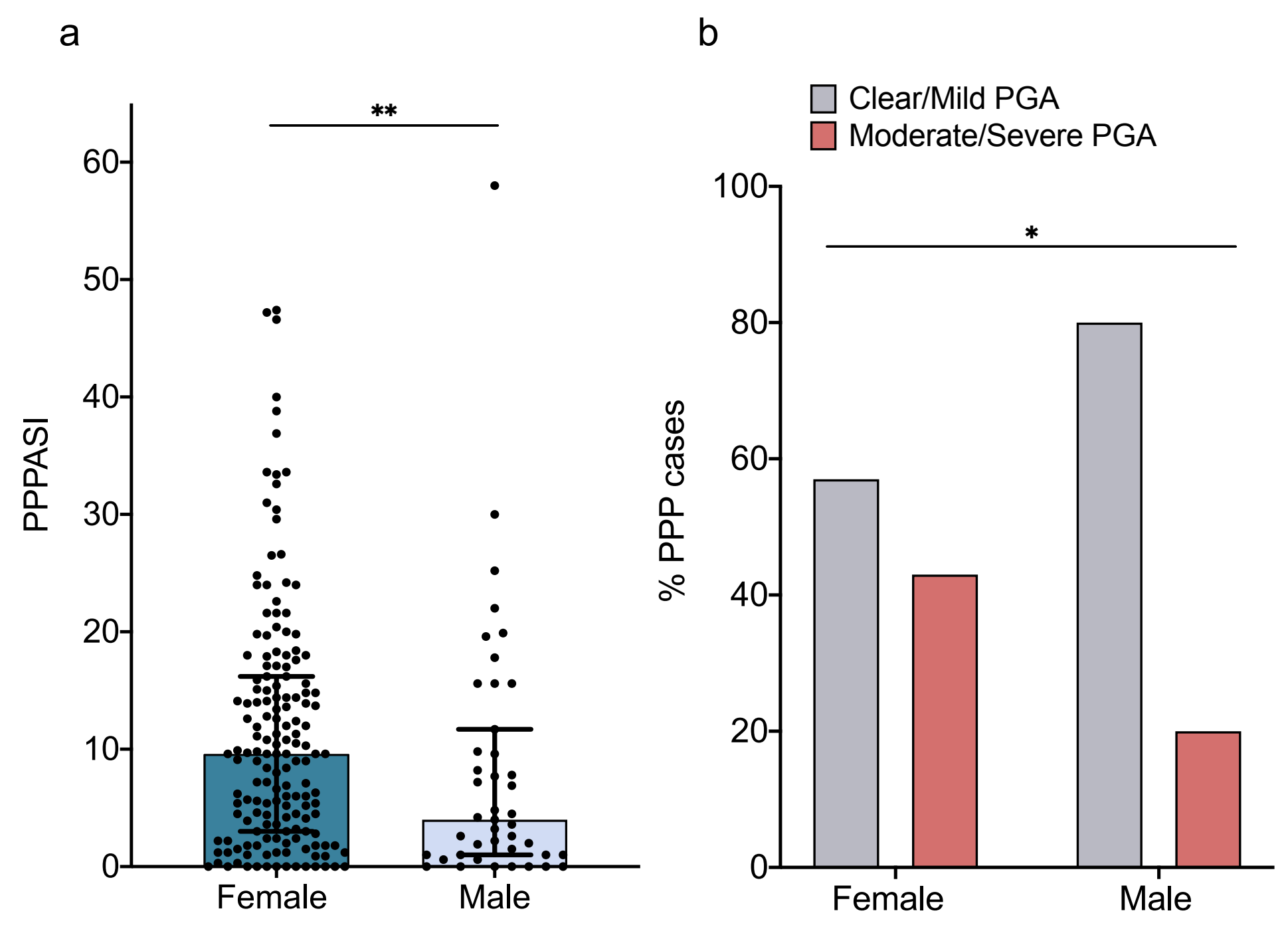
Figure legends

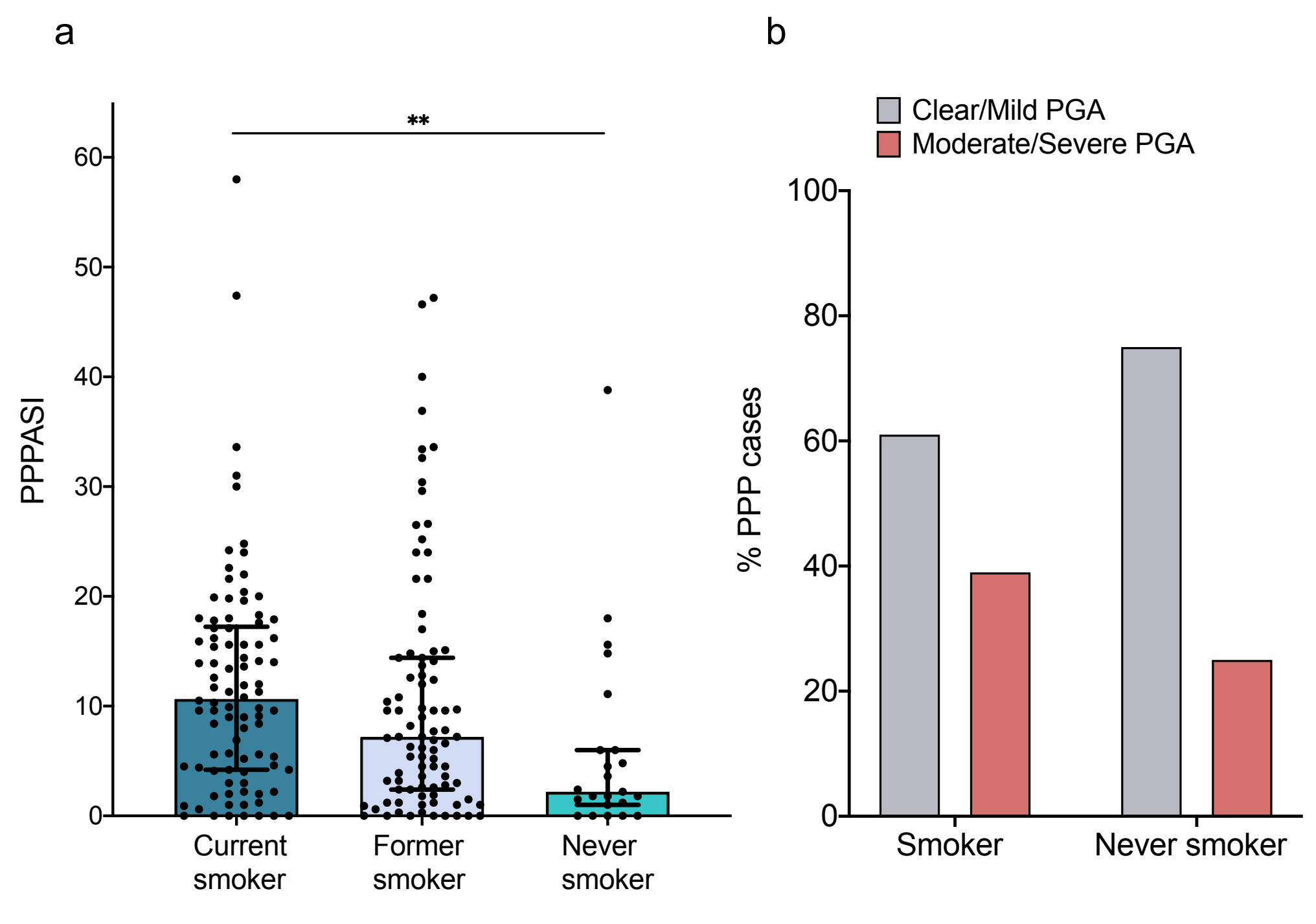
Figure 1. Relationship between disease severity and age of onset. **a:** In the UK cohort, the PPPASI is inversely correlated with age of onset. Regression lines are plotted with their 95% confidence intervals (grey areas). **b:** In the Northern European sample, age of onset is significantly lower among patients with moderate-to-severe disease. Data are presented as median +/- IQR. **P*<0.05 (Mann-Whitney test).

Figure 2. Disease severity scores in females and males. **a:** In the UK cohort, PPPPASI scores are significantly higher in females than males. Data are presented as median +/- IQR. ***P*<0.01 (Mann-Whitney test). **b:** In the Northern European sample, the proportion of individuals with moderate-to-severe disease is significantly elevated in females compared to males. **P*<0.05 (Fisher's Exact test).

Figure 3. Disease severity scores in current, former and never-smokers **a:** In the UK cohort, PPPPASI scores are highest in current smokers, intermediate in former smokers and lowest in never smokers. Data are presented as median +/- IQR. ***P*<0.01 (Kruskal-Wallis test). **b:** In the Northern European sample, the proportion of individuals with moderate-to-severe disease is elevated in current/former smokers compared to never smokers.


a
r = - 0.18
P = 0.014
PPPASI
Age of onset
0
10
20
30
40
50
60
70
80
b
Age of onset
*
Clear/Mild
Moderate/Severe


a
**
PPPASI
60
50
40
30
20
10
0
Female
Male
b
Clear/Mild PGA
Moderate/Severe PGA
% PPP cases
100
80
60
40
20
0
*
Female
Male


a
**
PPPASI
60
50
40
30
20
10
0
Current smoker
Former smoker
Never smoker
b
Clear/Mild PGA
Moderate/Severe PGA
% PPP cases
100
80
60
40
20
0
Smoker
Never smoker