

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

3 Subtitle: Findings from the APRICOT, PLUM and ERASPEN consortia

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42 Revision date: 18th June 2020; Word count: 2,232

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49 **Key points**

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

52 Findings: In a multi-centre cross-sectional study of 203 UK cases, we observed that the
53 palmoplantar pustulosis area and severity index was significantly higher in females
54 compared to males (9.6 vs 4.0) and in current smokers vs former and never-smokers (10.7 vs
55 7 vs 2.2). Both trends were replicated in an independently ascertained, Northern European
56 cohort (n=159).

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

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60

61 **Abstract**

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

64 Objective: To define the factors associated with PPP severity.

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

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

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

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

75 Results: Among the 203 UK patients (43 males, 160 females; median age of onset [IQR] 48
76 [38-59] years), the PPPASI was inversely correlated with age of onset ($r=-0.18$, $P=0.014$).
77 Similarly, in the 159 Northern European cases that were eligible for inclusion in this analysis
78 (25 males, 134 females ; median age of onset [IQR] 45 [34-53.3] years), the median [IQR]
79 age of onset was lower in individuals with moderate-to-severe PGA compared to those with
80 mild-to-clear PGA 41 [30.5-52] vs 46.5 [35-55], $P=0.043$).

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

84 In the UK cohort, the median PPPASI [IQR] was elevated in current smokers compared to ex-
85 and non-smokers (10.7 [4.2-17.5] vs 7 [2.0-14.4] vs 2.2 [1-6], $P=0.003$). Comparable
86 differences were observed in the Northern European dataset, as the prevalence of
87 moderate-to-severe PPP was higher in former/current smokers compared to non-smokers
88 (51 of 130 [39%] vs 6 of 24 [25%], $P=0.14$).

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

91

92 **INTRODUCTION**

93 Palmoplantar pustulosis (PPP) is an uncommon pustular eruption affecting the palms and/or
94 the soles. It is observed in approximately 1:2,000 individuals of European descent and 1:800
95 East Asians¹. The disease typically manifests in adulthood, with a median age of onset >45
96 reported in most studies². PPP shows a very marked sex bias, as females account for 60-90%
97 of affected individuals^{2,3}. It is also characterised by a very strong association with cigarette
98 smoking, with up to 90% of patients self-identifying as smokers at the time of diagnosis^{2,4-6}.

99 The disease manifests with the eruption of sterile, neutrophil-filled pustules on the palms
100 and soles. The lesions, which can occur on a background of normal or inflamed skin, are
101 persistent (>3 months), painful and disabling. They can be accompanied by fissures, pruritus
102 and a burning sensation⁷. Co-morbidities are also common, as affected individuals are at
103 increased risk of psoriasis vulgaris (PsV), psoriatic arthritis and autoimmune thyroid
104 disease⁸.

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

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115

116 **METHODS**

117 **Patients**

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

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

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

134 Pustular psoriasis was always diagnosed by a dermatologist, based on clinical examination
135 and/or the ERASPEN consensus criteria⁷. The observation of sterile, macroscopically visible
136 pustules on palms or soles was the main inclusion criterion. Conversely, the presence of
137 pustules restricted to the edges of psoriatic plaques represented an exclusion criterion.

138 Individuals with concomitant generalised pustular psoriasis or concomitant acrodermatitis

139 continua of Hallopeau were also excluded from the study, given that lesions affecting nails
140 or non-acral skin are deemed incompatible with a diagnosis of PPP⁹.
141 Clinical information and key demographics were collated using a standardised case report
142 form, shared by all centres. In the UK cohort, disease severity was measured using the
143 Palmoplantar Pustulosis Area Severity Index (PPPASI)¹⁰ and the Dermatology Life Quality
144 Index (DLQI) (eFigure 1 in the Supplement). In the Northern European cohort, patients were
145 assessed with the Physician Global Assessment (PGA), which has been shown to correlate
146 with the PPPASI¹¹. The individuals who recorded clinical data and measured disease severity
147 (reporting dermatologists or trained research nurses) were blinded to the study objectives.

148

149 **Statistical analysis**

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

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

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

163 [severe]). The two groups were then compared using Fisher's exact test. Given that the
164 purpose of the PGA analysis was to replicate results showing statistical significance in the UK
165 cohort, P-values were computed based on a one-tailed distribution. As the number of
166 individuals receiving systemic treatment was relatively small (n=25 from the Medical
167 University of Vienna and 9 from Tartu University) the confounding effect of therapeutic
168 intervention was addressed by simply excluding these cases from downstream analyses.
169 Individuals for whom information on smoking status or age-of-onset was missing (see Table
170 1 for details) were excluded from the relevant analyses. All statistical tests were
171 implemented in R (version 3.6.1). P-values<0.05 were considered statistically significant.

172

173 **RESULTS**

174 **Features of patient cohorts**

175 The features of the UK and Northern European cohorts are summarised in Table 1. All
176 patients were of European descent. The percentage of females (>75%), median age of onset
177 (≥ 45 years) and prevalence of current/former smokers (>80%) were comparable in the two
178 datasets. Prominent nail involvement was observed in both study populations, with >30% of
179 patients presenting with at least one of the following: pustules involving the nail apparatus,
180 subungual hyperkeratosis, permanent nail loss, non-pustular nail dystrophy.

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

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

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

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

196

197 **Factors associated with disease severity**

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

206 In the UK sample, the median PPPASI [IQR] was higher in females compared to males (9.6
207 [3.0-16.2] vs 4.0 [1.0-11.7], $P=0.0096$) (Figure 2A). The same applied to the median DLQI
208 [IQR] (10.5 [4.3-17] vs 4 [1-9], $P=8.2 \times 10^{-5}$) (eFigure 2 in the Supplement). Both associations
209 were confirmed when the effect of systemic treatment was included in a linear regression
210 model ($P=0.03$ for PPPASI, $P=0.0001$ for DLQI) (eTable 1 in the Supplement). In agreement

211 with these observations, the analysis of the Northern European dataset revealed that
212 moderate-to-severe PPP was more prevalent among females compared to males 57 of 134
213 [43%] vs 5 of 25 [20%], $P=0.026$) (Figure 2B). Thus, PPP severity is influenced by the
214 biological sex of the patient, in both the UK and Northern European study populations.
215 Among UK patients, the median PPPASI [IQR] was highest in current smokers, intermediate
216 in former smokers and lowest among non-smokers (10.7 [4.2-17.5] vs 7 [2.0-14.4] vs 2.2 [1-
217 6], $P=0.003$) (Figure 3A). Comparable findings were obtained when the median DLQI [IQR]
218 was analysed (10 [4.8-16.3] vs 9 [3-17] vs 5 [1-10.8], $P=0.042$) (eFigure 3 in the Supplement).
219 Both associations could be replicated when the effects of systemic treatment were
220 incorporated into a linear model ($P=0.005$ for PPPASI, $P=0.043$ for DLQI) (eTable 1 in the
221 Supplement). Of note, the percentage of current smokers (18/43 [42%] males and 72/160
222 [45%] females) and former smokers (19/43 [44%] and 69/160 [43%] females) was
223 comparable in the two sexes. Moreover, multivariable regression modelling found no
224 evidence that the effect of smoking differed by gender (data not shown).
225 While the analysis of the smaller Northern European dataset did not yield statistically
226 significant results, we observed a similar trend towards increased disease severity in
227 smokers. In fact, moderate-to-severe PPP was more frequent among current/former
228 smokers than non-smokers (51 of 130 [39%] vs 6 of 24 [25%], $P=0.14$) (Figure 3B).

229

230 **DISCUSSION**

231 To the best of our knowledge, this is the first systematic study of the factors associated with
232 PPP severity. It builds on previous work from our network, which enabled the definition of
233 consensus diagnostic criteria for PPP⁷ and demonstrated that the disease is genetically
234 different from other forms of pustular psoriasis².

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

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

244 We observed nail involvement in approximately a third of affected individuals. Interestingly,
245 subungual pustulation was reported in a similar fraction of cases in a small UK study¹⁵,
246 suggesting that nail abnormalities are a consistent feature of PPP.

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

250 Obesity was relatively uncommon, affecting only a third of all study participants. This
251 contrasts with findings obtained in PsV, where the association with obesity is well
252 established¹⁷ and up to 42% of individuals with severe disease have a body mass index>30¹⁸.

253 Overall, these findings suggest that PPP is part of the psoriasis spectrum, as the substantial
254 co-morbidity with PsV and psoriatic arthritis points to shared pathogenic pathways. At the
255 same time, the distinctive demographics of PPP suggest the involvement of risk factors that
256 are specific to this particular disease. It is interesting, for instance, that the marked female
257 bias that characterises PPP is not observed in palmoplantar psoriasis¹⁹. Likewise, PsV affects

258 both sexes equally²⁰ and occurred with comparable frequency in the male and female
259 patients examined in this study (data not shown).

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

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

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

272

273 **Limitations**

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

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

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

285

286 **CONCLUSIONS**

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

292

293 **ACKNOWLEDGEMENTS**

294 Access to data and data analysis: Miss Benzian-Olsson and Dr Capon had full access to all the
295 data in the study and take responsibility for the integrity of the data and the accuracy of the
296 data analysis.

297 Conflict of interest disclosures: Prof Barker has received grants and consultancy fees from
298 Boehringer Ingelheim and AnaptysBio. Dr Borroni has received honoraria and grants from
299 Celgene and Abbvie. Prof Burden has received payments for advisory boards, lecturing and
300 research from Abbvie, Boehringer Ingelheim, Novartis, Celgene, Almirall and Janssen. Dr
301 Capon has received grants and consultancy fees from Boehringer Ingelheim and AnaptysBio.
302 Prof Koks is an owner and board member of Prion Ltd. Prof Navarini reports grants and
303 advisory consulting fees from AbbVie, Amgen, Boehringer Ingelheim and Eli Lilly; advisory
304 consulting fees from Almirall, Biomed, Galderma, Leo Pharma, Novartis, Sanofi and UCB;
305 advisory consulting fees and non-financial support from Janssen-Cilag.

306 Prof Reynolds has received research funding for clinical trials from AnaptysBio through
307 Newcastle Hospitals NHS Foundation Trust. Prof Smith has received non-financial support
308 from SOBI during the conduct of the APRICOT clinical trial. Dr Wahie has received
309 sponsorship to attend dermatology from Abbvie, Janssen, Almirall and Novartis. Prof
310 Warren has received honoraria and research grants from AbbVie, Almirall, Amgen,
311 Boehringer Ingelheim, Celgene, Janssen, Leo, Lilly, Novartis, Pfizer, Sanofi, Xenoport, and
312 UCB.

313 We acknowledge support from the Department of Health via the National Institute for
314 Health Research (NIHR) BioResource Clinical Research Facility and comprehensive
315 Biomedical Research Centre awards to Guy's and St Thomas' NHS Foundation Trust in
316 partnership with King's College London and King's College Hospital NHS Foundation Trust
317 (guysbrc-2012-1). We also acknowledge support from the Newcastle NIHR Biomedical
318 Research Centre. The APRICOT trial is funded by the Efficacy and Mechanism Evaluation
319 (EME) Programme, an MRC and NIHR partnership (grant EME 13/50/17 to CHS, FC, JNB and
320 CEMG). This work was supported by the European Academy of Dermatology and
321 Venereology (grant PPRC-2018-25 to JNB, FC and AAN; grant PPRC-2012-11 to AAN and
322 JNB). NBO is funded by a NIHR pre-doctoral fellowship (grant NIHR300473). ND is funded by
323 Health Data Research UK (MR/S003126/1). CEMG is funded in part by the NIHR Manchester
324 Biomedical Research Centre and is an NIHR Emeritus Senior Investigator. NJR is a NIHR
325 Senior Investigator. He acknowledges support from the Newcastle MRC/EPSRC Molecular
326 Pathology Node and the Newcastle NIHR Medtech and In vitro diagnostic Co-operative.
327 RBW is supported by the Manchester NIHR Biomedical Research Centre.

328 None of the funders were involved in the study design, the collection, analysis and
329 interpretation of data, the writing of the manuscript or the decision to submit it for

330 publication. The views expressed in this publication are those of the authors and not
331 necessarily those of the MRC, NHS, NIHR or the Department of Health.

332

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338 College London), Suzie Cro (Imperial College London), Giles Dunnill (University Hospitals
339 Bristol), Christopher Griffiths (University of Manchester), John Ingram (University Hospital of
340 Wales), Helen Lachmann (Royal Free Hospital, London), Effie Ladoyanni (Russell's Hall
341 Hospital, Dudley), Nick Levell (Norfolk & Norwich University Hospital), Areti Makrygeorgou
342 (West Glasgow Ambulatory Care Hospital), Helen McAteer (The Psoriasis Association,
343 Northampton), John McKenna (Leicester Royal Infirmary), Freya Meynell (Guy's Hospital,
344 London), Richard Parslew (Royal Liverpool), Prakash Patel (Guy's Hospital, London), Andrew
345 Pink (Guy's Hospital, London), Angela Pushparajah (Guy's Hospital, London), Nick Reynolds
346 (Newcastle Hospitals), Catherine Smith (Guy's Hospital, London), Shyamal Wahie (University
347 Hospital of North Durham and Darlington Memorial Hospital), Richard Warren (Salford Royal
348 Infirmary), Rosemary Wilson (Guy's Hospital, London), Andrew Wright (St Lukes Hospital,
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356 Universitario de Leon), Hannes Trattner (Spezialambulanz für Psoriasis, Vienna).

357

358 REFERENCES

- 359 1. Mahil SK, Barker JN, Capon F. Pustular forms of psoriasis related to
360 autoinflammation. In: Hashkes P, Laxer R, Simon A, eds. *Textbook of*
361 *Autoinflammation*. Switzerland: Springer Nature; 2019:471-484.
- 362 2. Twelves S, Mostafa A, Dand N, et al. Clinical and genetic differences between
363 pustular psoriasis subtypes *The Journal of allergy and clinical immunology*.
364 2019;143:1021-1026.
- 365 3. Wilsmann-Theis D, Jacobi A, Frambach Y, et al. Palmoplantar pustulosis - a cross-
366 sectional analysis in Germany. *Dermatol Online J*. 2017;23(4).
- 367 4. Kharawala S, Golembesky AK, Bohn RL, Esser D. The clinical, humanistic, and
368 economic burden of generalized pustular psoriasis: a structured review. *Expert Rev*
369 *Clin Immunol*. 2020:1-14.
- 370 5. Naldi L, Chatenoud L, Linder D, et al. Cigarette smoking, body mass index, and
371 stressful life events as risk factors for psoriasis: results from an Italian case-control
372 study. *J Invest Dermatol*. 2005;125(1):61-67.
- 373 6. Naldi L, Peli L, Parazzini F. Association of early-stage psoriasis with smoking and male
374 alcohol consumption: evidence from an Italian case-control study. *Archives of*
375 *dermatology*. 1999;135(12):1479-1484.

- 376 7. Navarini AA, Burden AD, Capon F, et al. European Consensus Statement on
377 Phenotypes of Pustular Psoriasis. *Journal of the European Academy of Dermatology*
378 *and Venereology : JEADV*. 2017;1792-1799.
- 379 8. Trattner H, Bluml S, Steiner I, Plut U, Radakovic S, Tanew A. Quality of life and
380 comorbidities in palmoplantar pustulosis - a cross-sectional study on 102 patients.
381 *Journal of the European Academy of Dermatology and Venereology : JEADV*.
382 2017;31(10):1681-1685.
- 383 9. Brunasso AM, Puntoni M, Aberer W, Delfino C, Fancelli L, Massone C. Clinical and
384 epidemiological comparison of patients affected by palmoplantar plaque psoriasis
385 and palmoplantar pustulosis: a case series study. *Br J Dermatol*. 2013;168(6):1243-
386 1251.
- 387 10. Bhushan M, Burden AD, McElhone K, James R, Vanhoutte FP, Griffiths CE. Oral
388 liarozole in the treatment of palmoplantar pustular psoriasis: a randomized, double-
389 blind, placebo-controlled study. *Br J Dermatol*. 2001;145(4):546-553.
- 390 11. Terui T, Kobayashi S, Okubo Y, Murakami M, Hirose K, Kubo H. Efficacy and Safety of
391 Guselkumab, an Anti-interleukin 23 Monoclonal Antibody, for Palmoplantar
392 Pustulosis: A Randomized Clinical Trial. *JAMA Dermatol*. 2018;154(3):309-316.
- 393 12. NHS Digital. Statistics on Obesity, Physical Activity and Diet, England, 2019. In:2019.
- 394 13. WHO Global Health Observatory Data Repository 2013.
- 395 14. Andersen YMF, Augustin M, Petersen J, et al. Characteristics and prevalence of
396 plaque psoriasis in patients with palmoplantar pustulosis. *Br J Dermatol*.
397 2019;181(5):976-982.
- 398 15. Burden AD, Kemmett D. The spectrum of nail involvement in palmoplantar
399 pustulosis. *Br J Dermatol*. 1996;134(6):1079-1082.

- 400 16. Ogdie A, Langan S, Love T, et al. Prevalence and treatment patterns of psoriatic
401 arthritis in the UK. *Rheumatology*. 2013;52(3):568-575.
- 402 17. Coimbra S, Catarino C, Santos-Silva A. The triad psoriasis-obesity-adipokine profile.
403 *Journal of the European Academy of Dermatology and Venereology : JEADV*.
404 2016;30(11):1876-1885.
- 405 18. Iskandar IY, Ashcroft DM, Warren RB, et al. Demographics and disease characteristics
406 of patients with psoriasis enrolled in the British Association of Dermatologists
407 Biologic Interventions Register. *Br J Dermatol*. 2015;173(2):510-518.
- 408 19. Timotijevic ZS, Trajkovic G, Jankovic J, et al. How frequently does palmoplantar
409 psoriasis affect the palms and/or soles? A systematic review and meta-analysis.
410 *Postepy Dermatol Alergol*. 2019;36(5):595-603.
- 411 20. Burden AD, Kirby B. Psoriasis and related disorders. In: Griffiths CEM, Barker JN,
412 Bleiker T, Chalmers RJ, Creamer D, eds. *Rook's Textbook of Dermatology*. Chichester:
413 Wiley-Blackwell; 2016.
- 414 21. Michaelsson G, Gustafsson K, Hagforsen E. The psoriasis variant palmoplantar
415 pustulosis can be improved after cessation of smoking. *J Am Acad Dermatol*.
416 2006;54(4):737-738.
- 417 22. Mrowietz U, van de Kerkhof PC. Management of palmoplantar pustulosis: do we
418 need to change? *Br J Dermatol*. 2011;164(5):942-946.

419

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		
PPASI, 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%)

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

428

429

430 **Figure legends**

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

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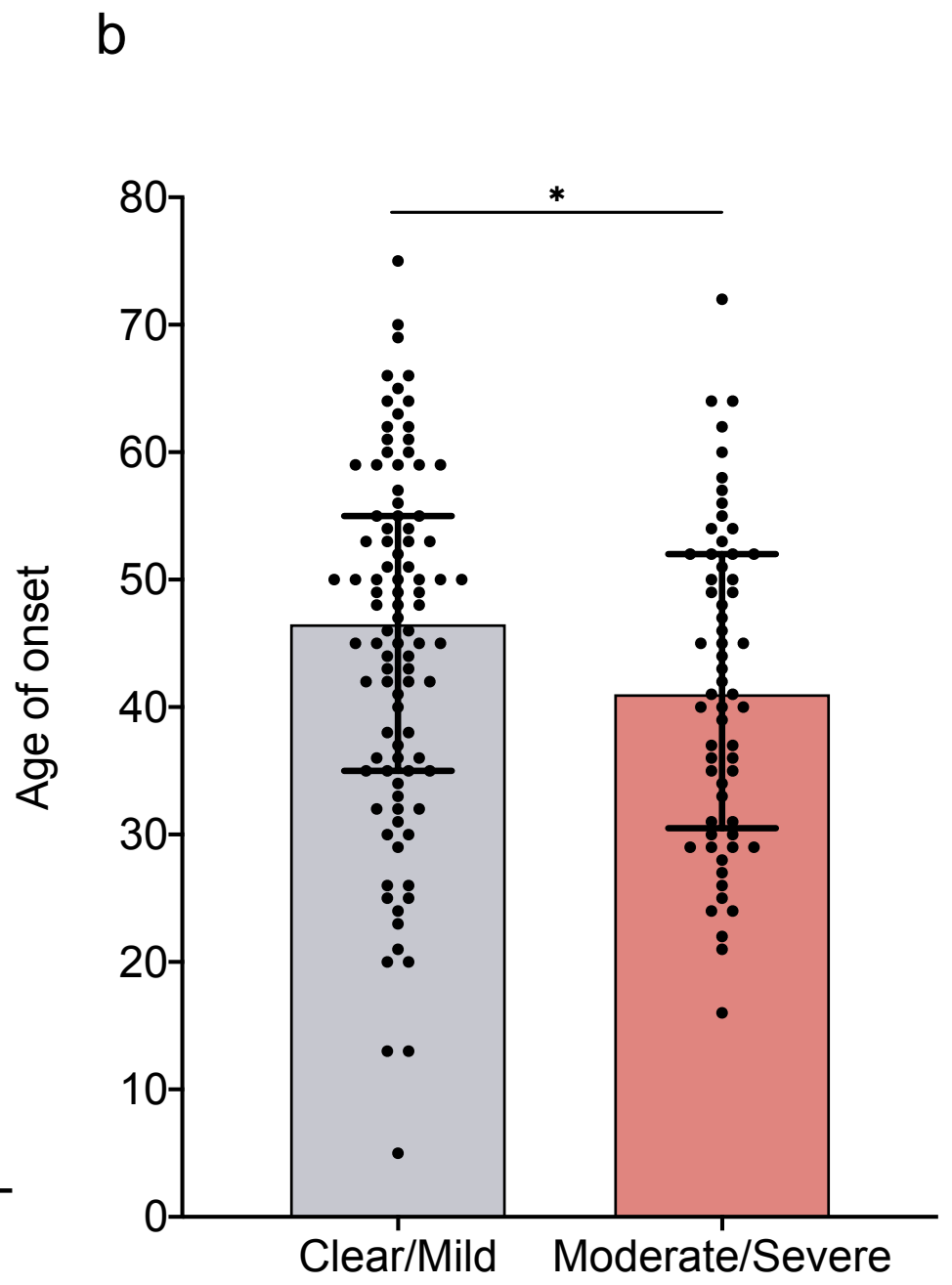
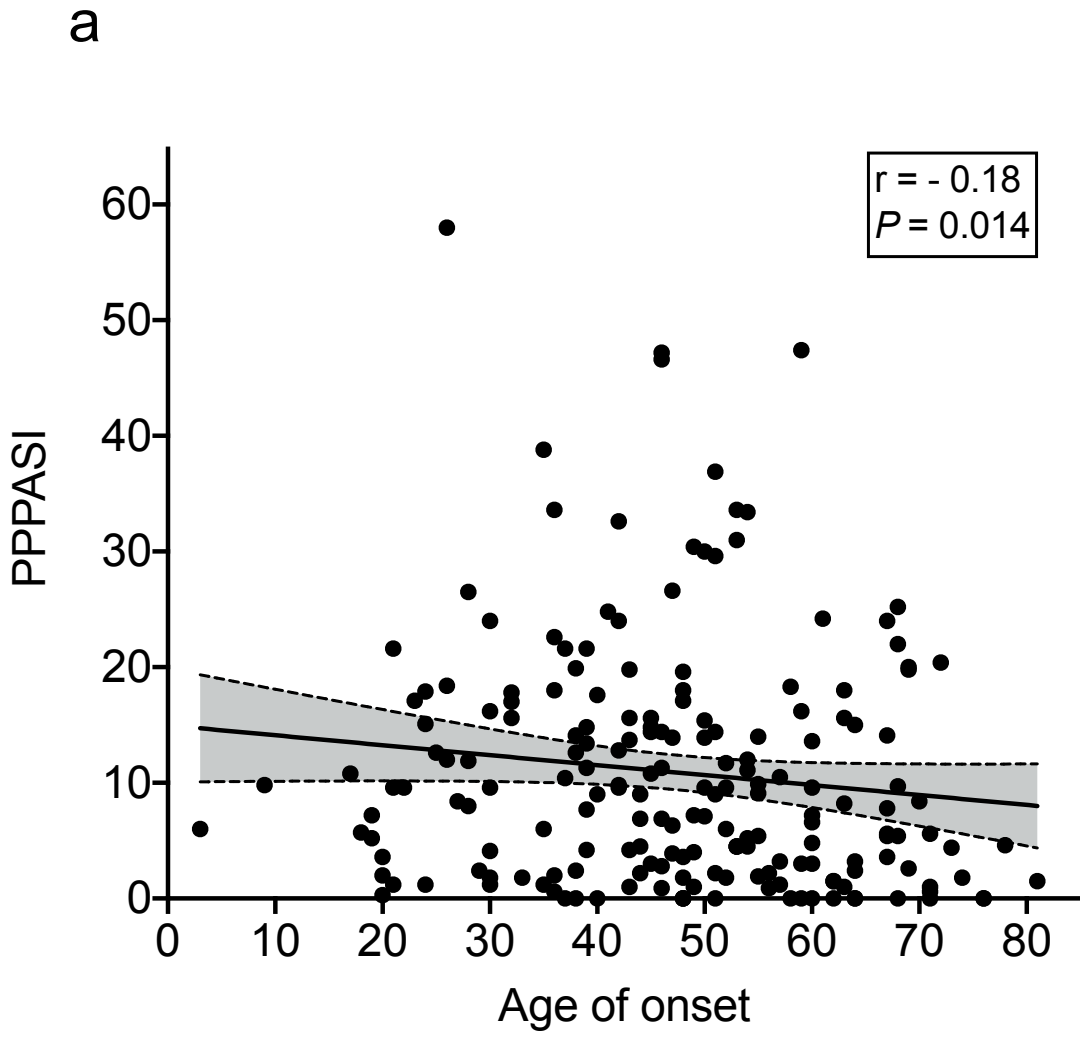
437 **Figure 2.** Disease severity scores in females and males. **a:** In the UK cohort, PPPASI scores
438 are significantly higher in females than males. Data are presented as median +/- IQR.
439 ** $P < 0.01$ (Mann-Whitney test). **b:** In the Northern European sample, the proportion of
440 individuals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

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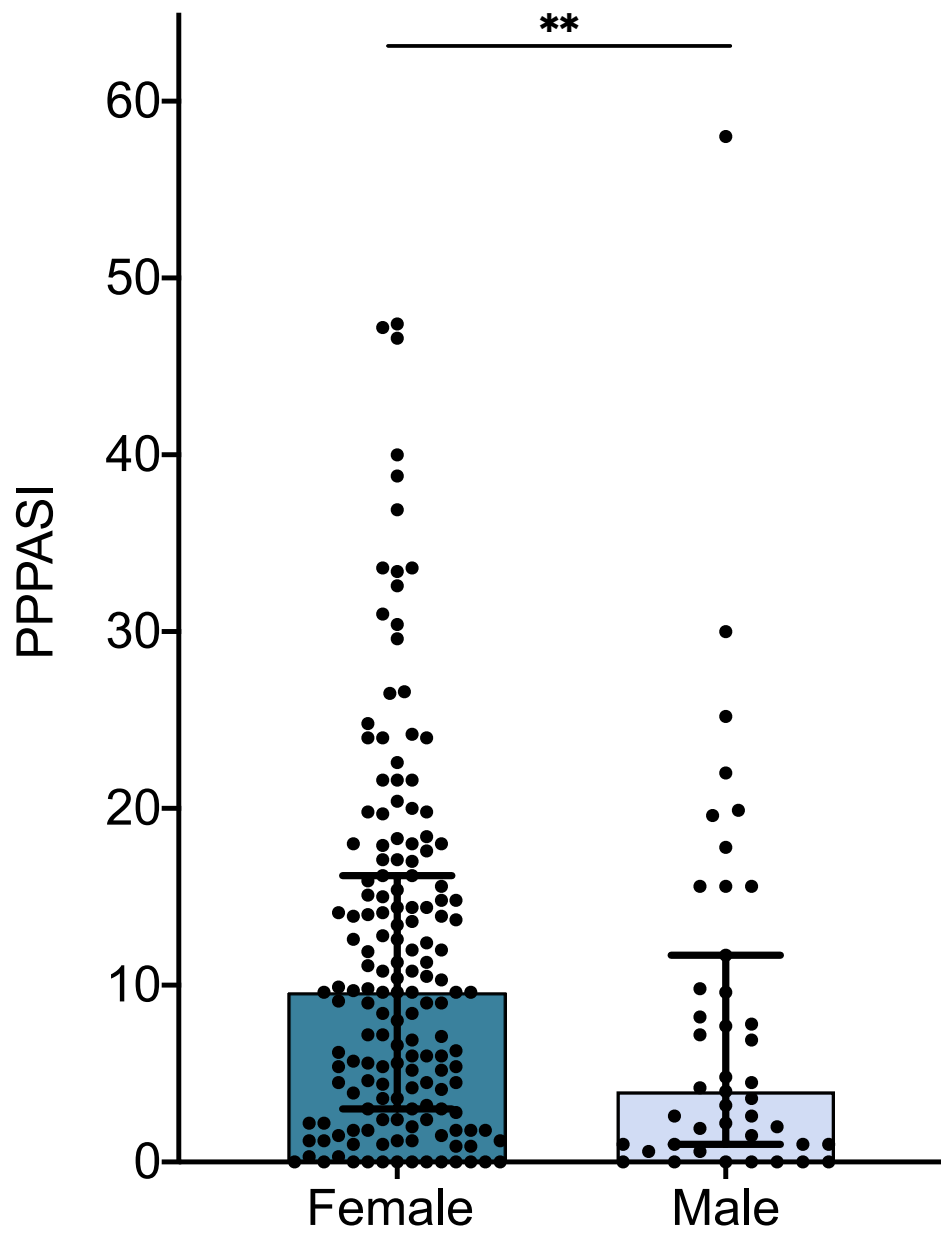
443 **Figure 3.** Disease severity scores in current, former and never-smokers **a:** In the UK cohort,
444 PPPASI scores are highest in current smokers, intermediate in former smokers and lowest
445 in never smokers. Data are presented as median +/- IQR. ** $P < 0.01$ (Kruskal-Wallis test). **b:**
446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

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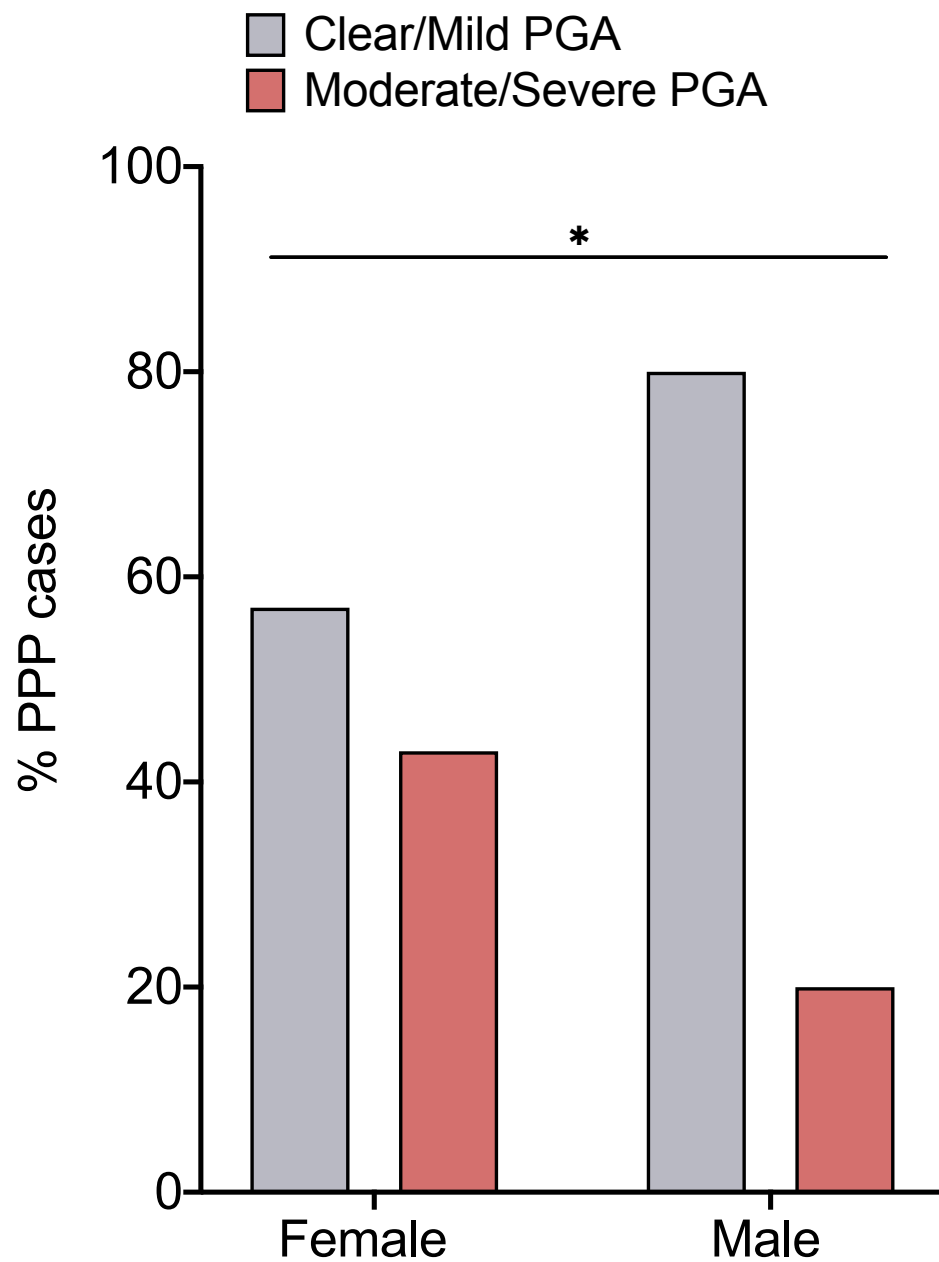
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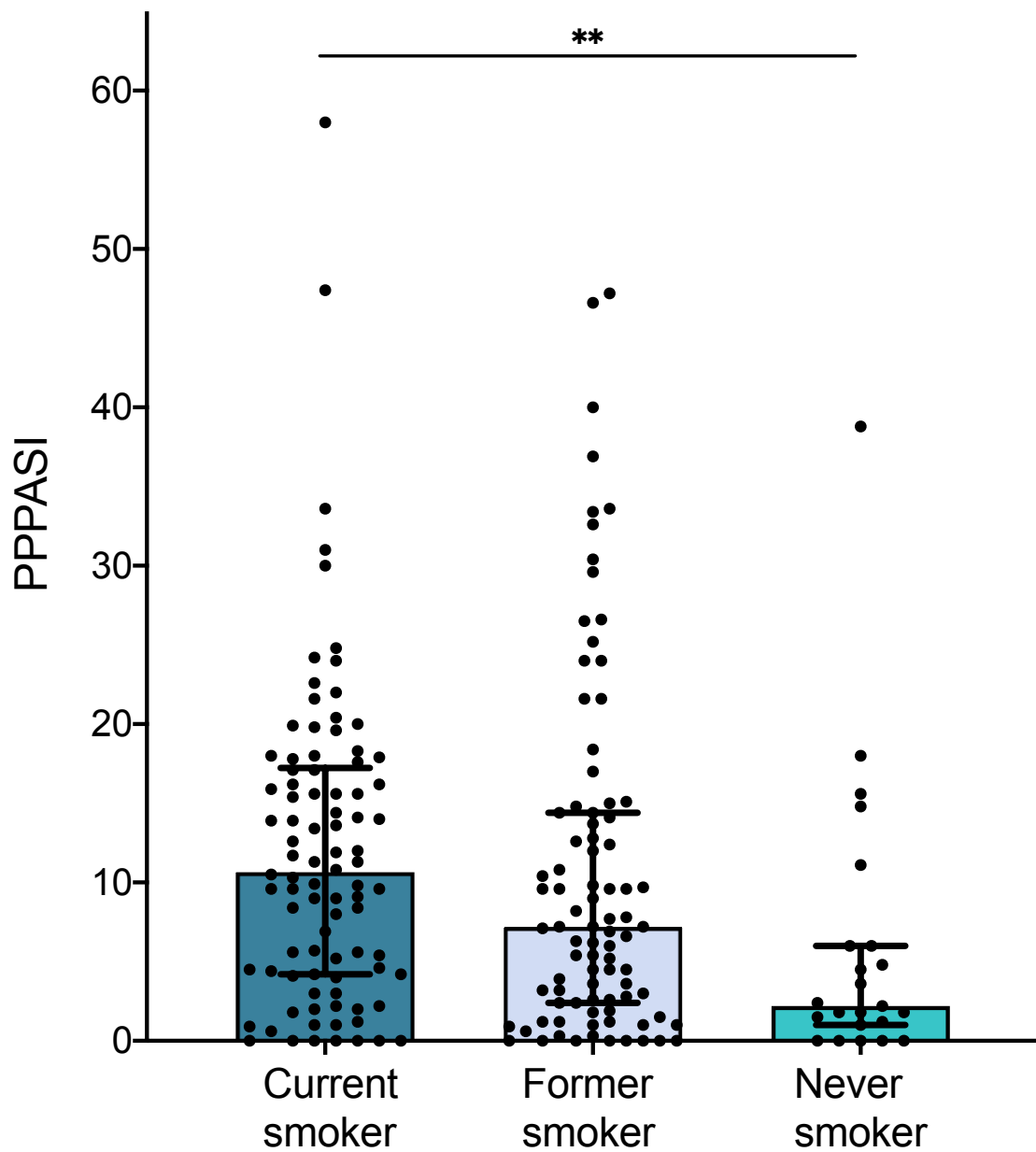
a



b



a



b

