RHEUMATOLOGY

Rheumatology 2022;00:1–14
https://doi.org/10.1093/rheumatology/keac403
Advance access publication 21 July 2022

Original article

Association between psoriatic disease and lifestyle factors and comorbidities: cross-sectional analysis and Mendelian randomization

Sizheng Steven Zhao [1,*], Eftychia Bellou[2,3,*], Suzanne M.M. Verstappen[1,4], Michael J. Cook [1], Jamie C. Sergeant [1,5], Richard B. Warren[6], Anne Barton [2,4] and John Bowes [2,4]

Abstract

Objectives. To examine associations between PsA and psoriasis *vs* lifestyle factors and comorbidities by triangulating observational and genetic evidence.

Methods. We analysed cross-sectional data from the UK Biobank (1836 PsA, 8995 psoriasis, 36 000 controls) to describe the association between psoriatic disease and lifestyle factors (including BMI and smoking) and 15 comorbidities [including diabetes and coronary artery disease (CAD)] using logistic models adjusted for age, sex and lifestyle factors. We applied bidirectional Mendelian randomization (MR) to genome-wide association data (3609 PsA and 7804 psoriasis cases, up to 1.2 million individuals for lifestyle factors and 757 601 for comorbidities) to examine causal direction, using the inverse-variance weighted method.

Results. BMI was cross-sectionally associated with risk of PsA (OR 1.31 per 5 kg/m^2 increase; 95% CI 1.26, 1.37) and psoriasis (OR 1.23; 1.20, 1.26), with consistent MR estimates (PsA OR 1.38; 1.14, 1.67; psoriasis OR 1.36; 1.18, 1.58). In both designs, smoking was more strongly associated with psoriasis than PsA. PsA and psoriasis were cross-sectionally associated with diabetes (OR 1.35 and 1.39, respectively) and CAD (OR 1.56 and 1.38, respective). Genetically predicted glycated haemoglobin (surrogate for diabetes) increased PsA risk (OR 1.18 per 6.7 mmol/mol increase; 1.02, 1.36) but not psoriasis. Genetic liability to PsA (OR 1.05; 1.003, 1.09) and psoriasis (OR 1.03; 1.001, 1.06) were associated with increased risk of CAD.

Conclusion. Observational and genetic evidence converge to suggest that BMI and glycaemic control are associated with increased psoriatic disease risk, while psoriatic disease is associated with increased CAD risk. Further research is needed to understand the mechanism of these associations.

Key words: PsA, psoriasis, lifestyle factors, BMI, smoking, alcohol, education, socioeconomic position

Rheumatology key messages

- Smoking is more strongly associated with risk of psoriasis than PsA.
- Higher genetically predicted glycated haemoglobin is associated with increases risk of PsA but not psoriasis.
- Genetic liability to PsA and psoriasis are each associated with increased risk of coronary artery disease.

Introduction

Psoriatic disease, comprising psoriasis and psoriatic arthritis, is among the commonest immune-mediated inflammatory diseases worldwide (prevalence up to 2%

[1]Centre for Epidemiology Versus Arthritis, [2]Centre for Genetics and Genomics Versus Arthritis, Division of Musculoskeletal and Dermatological Sciences, School of Biological Sciences, Faculty of Biology Medicine and Health, The University of Manchester, Manchester Academic Health Science Centre, Manchester, [3]UK Dementia Research Institute, Cardiff University, Cardiff, [4]NIHR Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, [5]Centre for Biostatistics, Faculty of Biology Medicine and Health, The University of Manchester, Manchester Academic Health Science Centre and [6]Dermatology Centre, Salford Royal NHS Foundation Trust, Manchester NIHR Biomedical Research Centre, University of Manchester, Manchester, UK

Submitted 9 March 2022; accepted 3 July 2022

Correspondence to: John Bowes, Centre for Genetics and Genomics Versus Arthritis, Division of Musculoskeletal & Dermatological Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Oxford Road, Manchester M13 9PT, UK. E-mail: j.bowes@manchester.ac.uk

*Sizheng Steven Zhao and Eftychia Bellou contributed equally to this study.

© The Author(s) 2022. Published by Oxford University Press on behalf of the British Society for Rheumatology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac403/6647933 by University of Cardiff - Journal of Biochemistiy Trial user on 12 October 2022

BASIC SCIENCE

and 0.3%, respectively [1, 2]). Both cutaneous and musculoskeletal manifestations can significantly impact quality of life, physical function and mortality, resulting in substantial psychological, social and economic burden [1]. Psoriatic disease is not limited to the skin and joints, but also reported to be associated with psychological, metabolic and cardiovascular comorbidities [3].

The pathoaetiology of psoriatic disease is not fully understood. It has a strong genetic component [4] but also non-genetic factors that likely converge to trigger onset [5]. Examples of lifestyle factors linked to psoriasis include cigarette smoking and obesity [6, 7]. Evidence for PsA-related risk factors is more scarce and conflicting; for example, smoking is associated with increased risk of PsA in the general population, but is associated with decreased risk of PsA in patients with psoriasis [8]. Establishing cause in observational studies is limited by confounding and reverse causation; the latter makes it challenging to untangle whether various traits are causes or consequences of psoriatic disease.

Combining different study designs with complementary strengths to answer the same underlying question—or 'triangulation'—can improve causal inference [9]. Mendelian randomization (MR) uses genetically predicted levels of, or liability to, an exposure to estimate its effect on an outcome [10]. Instrumental variable assumptions that underpin MR differ from those invoked in traditional observational analyses. When these assumptions are met, MR is more robust to confounding and allows interrogation of causal direction, e.g. whether psoriatic disease causes comorbidities, or vice versa. We aimed to examine the associations between psoriatic disease and lifestyle factors and comorbidities, using cross-sectional analysis complemented by bidirectional MR.

Methods

Observational analysis of the UK Biobank

The UK Biobank study recruited over half a million participants between 2006 and 2010 from assessment centres across the UK. The study received ethical approval and is described in detail elsewhere [11]. Cross-sectional data from the baseline assessment were used for the current observational analysis. The current analysis was approved under application number 72723. Use of other publicly available summary statistics data did not require additional ethics approval.

Psoriatic disease definition in the cross-sectional analysis

PsA and psoriasis were defined using ICD-10 codes (Table 1) derived from linked hospital inpatient data (available for >99% of participants from 1992 to 2020) and/or self-report obtained through verbal interview by a trained nurse (at baseline assessments). PsA was not excluded from the psoriasis population in the primary analysis. These populations were compared against a randomly sampled common control group without PsA or psoriasis. We selected a subgroup of controls approximately four times the number of cases to reduce case-control imbalance that would arise from using the entire UK Biobank population.

Lifestyle factors and comorbidities in the cross-sectional analysis

Full definitions for each variable in the observational analysis are summarised in Table 1. BMI (per 5 kg/m^2), pack years of smoking (per 10 pack years) and educational attainment (per 5 years) were scaled to facilitate interpretation and/or comparison with MR estimates. We used educational attainment, defined as age at completion of full-time education, as a proxy for individual-level socioeconomic position.

We considered the following comorbidities informed by a prior systematic review [3] based on their prevalence or clinical relevance: hypertension, coronary artery disease, heart failure, stroke, COPD, asthma, type 2 diabetes mellitus, non-alcoholic fatty liver disease (NAFLD), gastro-oesophageal reflux disease (GORD), chronic kidney disease (CKD), any cancer, depression, chronic widespread pain (pain all over the body >3 months), uveitis and inflammatory bowel disease (IBD). As with psoriatic disease, comorbidities were assumed to be absent if not reported or there were no ICD codes. Definitions for each comorbidity using ICD codes and/or self-report are shown in Table 1.

Two-sample Mendelian randomization

MR is an observational study design that estimates the effect of an exposure on an outcome, using genetic variants that are associated with exposure variation at a population level (an overview can be found in [10, 12]). Because variants are randomly allocated at conception, MR can be conceptualized as a quasi-randomised natural experiment; for example, comparing PsA risk according to levels of genetically predicted BMI. A genetic variant can be considered as a valid instrumental variable for an exposure if it satisfies the instrumental variable assumptions: it is associated with the exposure in a specific way that does not affect the outcome except via the exposure, and it is not associated with the outcome due to confounding [10,12] (Fig. 1). Exposure-outcome estimates for each variant are then pooled.

Psoriatic disease definition in MR

Genome-wide association studies (GWAS) for all traits are summarised in Table 1; additional details of demographics, genotyping and phenotype definitions for each study are available in each original publication referenced. For PsA as the outcome, we used existing summary data from a GWAS comprising 3609 cases and 9192 controls; the majority of cases satisfied the CASPAR classification criteria, but some were recruited prior to its publication [13]. PsA data were independent of the above observational analyses.

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac403/6647833 by University of Cardiff - Journal of Biochemisty Trial user on 12 October 2022

from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac403/6647833 by University of Cardiff - Journal of Biochemisty Trial user on 12 C

Table 1 Summary of exposure and outcome definitions and data sources

	Cross-sectional analysis of UK Biobank		Mendelian randomization analysis	
	ICD coded (field 41270)	Self-report code (field 20002/20001)	Genetic association data as exposure	Genetic association data as outcome
Psoriatic arthritis	M07.0, M07.1, M07.2, M07.3, L40.5	1477	Trait: Psoriatic arthritis (physician diagnosis) [13] N: 3609/9192 No SNPs: 14 F: 335	
Psoriasis	L40*	1453	Trait: Psoriasis [14] N: 10 588/22 806 No SNPs: 57 F: n/a (EAF not reported)	Trait: Psoriasis (ICD and/or self-report from UK Biobank) N: 7804/36 000
Body mass index	Scaled to represent change in outcome per 5 kg/m^2 increase in BMI. Field 21001.		Trait: BMI [32] Unit: 1SD = 4.8 kg/m^2 N: 681 275 No SNPs: 507 F: 74	
Smoking status	Current, previous, never. Field 20116.		Trait: Ever *vs* Never [33] N: 1 232 091 No SNPs: 378 F: 191	
Cumulative smoking exposure	Pack years, scaled to show change in outcome per 10 pack years. Field 20161.		Trait: Smoking index, takes into account status (current/former/never), and exposure (duration/heaviness/cessation) among ever smokers [34]. Unit: 1SD is equivalent to, e.g., an individual smoking 20 cigarettes a day for 15 years and stopping 17 years ago. N: 462 690 No SNPs: 126 F: 15	
Alcohol intake	Daily or almost daily, 3–4 times a week, 1–2 times a week, 1–3 times a month (merged with 'Special occasions only'), Never. Field 1558.		Trait: Number of alcoholic drinks per week [33] Unit: 1SD = 9 drinks/week N: 335 394 No SNPs: 98 F: 65	
Educational attainment	Age completed full-time education (field 845). Where missing, assumed to be 16 if reported to have GCSEs and 18 if A-levels (field 6138). Scaled to represent change in outcome per 5-year increase in age.		Trait: Educational attainment (years of schooling) [35] Unit: 1SD = 4.2 years N: 766 345 No SNPs: 1271 F: 48	

(continued)

Table 1 Continued

	Cross-sectional analysis of UK Biobank		Mendelian randomization analysis	
	ICD coded (field 41270)	Self-report code (field 20002/20001)	Genetic association data as exposure	Genetic association data as outcome
Hypertension	I10*, I11*, I12*, I13*, I16*, O10*, I67.4	1065, 1072; Blood pressure medication (field 6153)	Trait: Systolic blood pressure [36] Unit: mmHg N: 757 601 No SNPs: 188 F: 20	Trait: Hypertension (defined by ICD10 code I10) [33] N: 54 358/408 652
Coronary artery disease	I20*, I21*, I22*, I23*, I24*, I25*; not I25.3, I25.4	1074, 1075; with age diagnosed ≥30 (field 3627)	Trait: Coronary artery disease (Clinically confirmed ACD, e.g. myocardial infarction, acute coronary syndrome, chronic stable angina or coronary stenosis of >50%) [37] N: 42 096/99 121 No SNPs: 42 F: 448	
Heart failure	I50*	1076	Trait: Heart failure (Clinical diagnosis of any aetiology with no inclusion criteria based on left ventricular ejection fraction) [38] N: 47 309/930 014 No SNPs: 12 F: 1330	
Stroke	I61*, I63*, I66*, I67.2, I67.8, I67.9, I69.1, I69.3, I69.8, I69.9	1081, 1082; with age diagnosed ≥30 (field 4056)	Trait: Stroke (World Health Organization definition) [39] N: 40 585/406 111 No SNPs: 17 F: 647	
COPD	J40*, J41*, J42*, J43*, J44*	1112, 1113; with age diagnosed ≥30 (field 3992). Emphysema/chronic bronchitis diagnosed by a doctor (field 6152)	Trait: COPD (spirometry) [40] N: 35 735/222 076 No SNPs: 18 F: 955	Trait: COPD (ICD10 J44, phecode 496.21) [41] N: 13 530/454 945 EUR; 4017/162 653 East Asian
Asthma	J45*	1111; Asthma diagnosed by a doctor (field 6152)	Trait: Asthma (self-reported, physician diagnosed, ICD10 J45, J46) [42] N: 64 538/329 321 No SNPs: 145 F: 650	Trait: Asthma (ICD10 J45, phecode 495) [41] N: 38 369/411 131 EUR; 13 015/162 933 East Asian
Type 2 diabetes mellitus	E11*, E13*	1220, 1223; with age diagnosed ≥18 (field 2976)	Trait: Glycated haemoglobin (HbA1c) [43] Unit: 1SD = 6.7 mmol/mol	Trait: Type 2 diabetes [44] N: 61 714/596 424

(continued)

from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac403/6647833 by University of Cardiff - Journal of Biochemisty Trial user on 12 C

from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac403/6647833 by University of Cardiff - Journal of Biochemisty Trial user on 12 C

Table 1 Continued

	Cross-sectional analysis of UK Biobank		Mendelian randomization analysis	
	ICD coded (field 41270)	Self-report code (field 20002/20001)	Genetic association data as exposure	Genetic association data as outcome
			N: 344 182 No SNPs: 320 F: 146	
Non-alcoholic fatty liver disease	K760	n/a	Trait: NAFLD (elevated ALT without other liver disease) [45] N: 90 408/128 187 No SNPs: 18 F: 809	Trait: NAFLD (ICD 10 code K760) [46] N: 894/217 898
Gastro-oesophageal reflux disease	K22.7, K21*	1159, 1160	Trait: GORD (self-report, ICD code, main operative procedures code, medication) [47] N: 80 265/305 011 No SNPs: 25 F: n/a (EAF not reported)	
Chronic kidney disease	N18*	1192, 1193	Trait: CKD (estimated glomerular filtration rate <60 mL/min/1.73m^2) [48] N: 41 395/439 303 No SNPs: 23 F: 1719 (eGFR GWAS yielded insufficiently strong instruments)	
Cancer	C*	20001	Trait: Any cancer (ICD 10 code C and D0-4) [46] N: 38 036/180 756 No SNPs: 11 F: 382	
Depression	F32*, F33*, F31.3, F31.4, F31.5, F31.6	1286; Depression ever diagnosed by a professional (field 20544)	Trait: Major depression (self-reported and clinically diagnosed) [49] N: 246 363/561 190 No SNPs: 102 F: 151 (depressive symptoms GWAS yielded insufficiently strong instruments)	Trait: Major depression (self -reported and clinically diagnosed) [49] N: 170 756/329 443
Chronic widespread pain	M79.7	1542 (fibromyalgia); general pain for >3 months (field 2956)	Trait: Multisite chronic pain (number of chronic pain sites across the body ranging from 0 to 7) [49] $n = 387\,649$ Unit = per additional site of pain No SNPs: 39 F: 37	Trait: Chronic widespread pain (general pain for >3 months) [49] $n = 387\,649$

(continued)

Table 1 Continued

	Cross-sectional analysis of UK Biobank		Mendelian randomization analysis	
	ICD coded (field 41270)	Self-report code (field 20002/20001)	Genetic association data as exposure	Genetic association data as outcome
Uveitis	H20*	1530	Trait: Uveitis (ICD10 H20, phecode 371.1) [41] N: 2616/478 126 EUR; 110/175 543 East Asian No SNPs: 6 F: 76170	
Inflammatory bowel disease	M50*, M51*, K52.3	1461, 1462, 1463	Trait: IBD (endoscopic, histopathological or radiological criteria) [50] N: 12 882/21 770 No SNPs: 132 F: 441	

COPD: chronic obstructive pulmonary disease; F: F-statistic (>10 suggestive of adequate instrument strength), note that this is an approximation; ICD: International Classification of Diseases; MR: Mendelian randomization; N: sample size total or case/control (all of European ancestry unless otherwise stated); SD: standard deviation; SNP, single nucleotide polymorphism.

For psoriasis as the outcome, we performed a GWAS of psoriasis in the UK Biobank using the same case definition as the above cross-sectional analysis (i.e. ICD-10 code and/or self-report). Genetic associations were derived from 7804 unrelated cases of white British ancestry and 36 000 controls. Full details of the GWAS are provided in the supplementary materials available at *Rheumatology* online. PsA was not excluded from the psoriasis population in the primary analysis.

We additionally estimated the 'reverse' effects of psoriatic disease (as the 'exposure') on lifestyle factors or comorbidities. To instrument PsA or psoriasis, we used independent GWAS-significant variants reported in Soomro *et al.* [13] and Tsoi *et al.* [14], respectively (Supplementary Table S1, available at *Rheumatology* online). The Tsoi psoriasis GWAS differed from our UK Biobank GWAS in having a larger sample size (it could not be used above as the outcome because summary statistics were not available).

Validation of psoriatic disease definition using genetic correlation

Psoriasis and PsA in the UK Biobank were defined using ICD code and/or self-report, which may be susceptible to misclassification. To examine the accuracy of the UK Biobank psoriasis case definition (used in both cross-sectional and MR analyses), we estimated genetic correlation with data from a GWAS of physician-diagnosed psoriasis, using cross-trait linkage disequilibrium score regression [15]. Genetic correlation coefficient was 0.96 ($P = 1.00 \times 10^{-11}$) between the two phenotypes; the correlation coefficient would be low if a significant proportion of the UK Biobank psoriasis cases were misclassified. Repeating the approach for PsA was not possible due to the small number of cases in the UK Biobank.

Lifestyle factors and comorbidities in MR

To instrument each lifestyle factor and comorbidity, we used independent GWAS-significant variants reported by the original study where possible (references in Table 1); otherwise, we selected variants that were independent (linkage disequilibrium threshold $r^2 < 0.001$ using PLINK and phase 3 version 5 of the 1000 genomes project as the reference panel) and reaching genome-wide significance ($P < 5 \times 10^{-8}$). We used continuous traits to proxy comorbidities where possible, as using binary exposures can have methodological limitations [16].

Statistical analysis

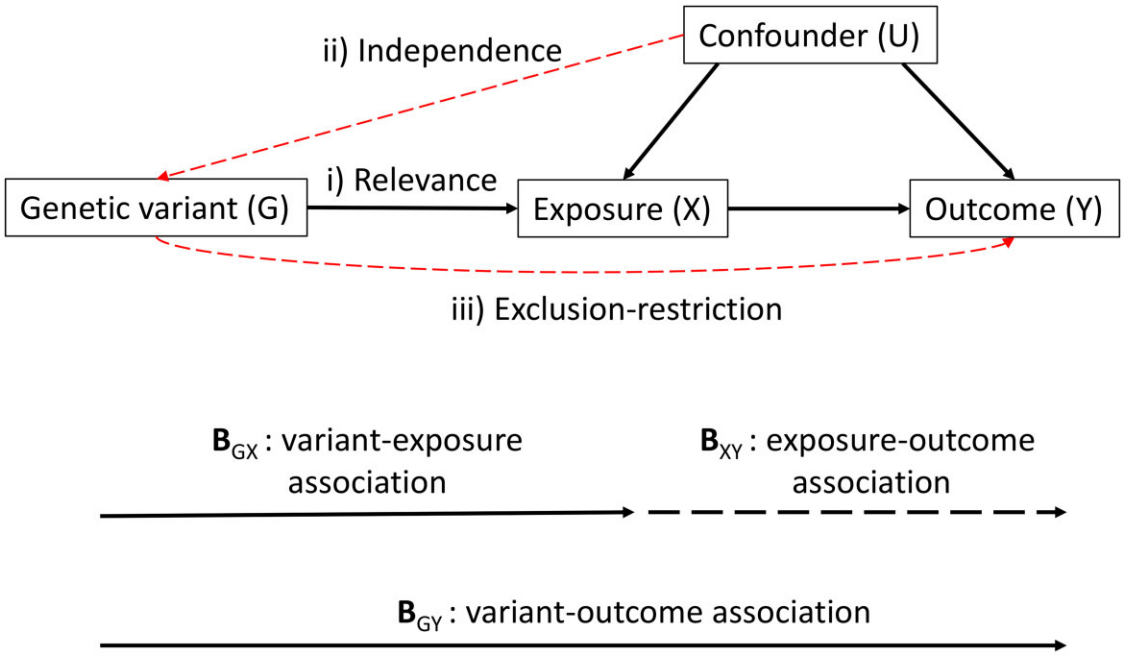
Cross-sectional analysis

Participant characteristics, lifestyle factors and comorbidities were summarised using descriptive statistics. We examined the association between lifestyle factors and each psoriatic disease using univariable logistic models with the case-control status as the dependent variable and each lifestyle factor and comorbidity in turn as the independent variable. Each model was then

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac403/6647833 by University of Cardiff - Journal of Biochemisty Trial user on 12 October 2022

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac403/6647833 by University of Cardiff - Journal of Biochemisty Trial user on 12 October 2022

FIG. 1 Illustration of instrumental variable assumptions and the Wald ratio method



$$\text{Exposure-outcome association } (\mathbf{B}_{XY}) = \frac{\text{Variant–outcome association } (\mathbf{B}_{GY})}{\text{Variant–exposure association } (\mathbf{B}_{GX})}$$

The first assumption, relevance, requires that the variant is associated with the exposure. This is the only verifiable assumption. The second assumption, independence, requires the absence of unmeasured confounders of the associations between genetic variants and outcome. Assumption three, exclusion restriction, requires the genetic variants to affect the outcome only through their effect on the exposure of interest. B_{GX} can be obtained from genome-wide association study (GWAS) of the exposure, and B_{GY} from GWAS of the outcome. If instrumental variable assumptions are met, then $B_{GY}=B_{GX} * B_{XY}$, and it follows that the exposure-outcome association can be derived as B_{GY}/B_{GX}.

adjusted for age, sex and all lifestyle factors to examine associations independent of these potential confounders; for example, association between smoking and PsA was adjusted for age, sex, BMI, alcohol status and educational attainment, while association between hypertension and PsA was adjusted for age, sex and all lifestyle factors. Missing data were not imputed (given the known completeness of most variables used in this analysis).

ICD codes were available after the baseline assessment. It is possible that diseases (psoriatic disease or comorbidities) had not developed at the time of baseline assessment. As a sensitivity analysis, we restricted codes to those before or within 6 months after each individual's baseline assessment, such that analyses pertain to only prevalent cases at baseline.

Mendelian randomization

All effect alleles were checked to be on the forward strand; ambiguous palindromes were not excluded. Where possible, SNPs absent in one of the exposure-outcome sets were proxied using variants in linkage disequilibrium ($r^2>0.8$). Variance explained (r^2) was calculated using $2EAF(1-EAF)\beta^2$, where EAF is the effect allele frequency and β the association estimate. F statistic was derived using $(r^2/K)/[(1-r^2)(N-K-1)]$, where K is the number of SNPs and N the sample size. F statistics >10 is considered suggestive of adequate instrument strength [17].

We used the inverse-variance weighted method to combine estimates from each SNP (derived using the Wald ratio method in Fig. 1) using random-effect meta-analysis [18]. Estimates are interpreted as per unit increase for continuous exposures (defined in Table 1). We used the weighted median [19], weighed mode [20] and MR Egger [21] methods to test the robustness of univariable IVW estimates to horizontal pleiotropy ('exclusion restriction' assumption in Fig. 1). Each method relaxes certain MR assumptions such that a consistent estimate provides evidence against bias from horizonal pleiotropy.

MR analyses were performed first with psoriatic disease as the outcome (i.e. effect of lifestyle factor/comorbidities on psoriatic disease), then repeated with

Table 2 Baseline characteristics of psoriatic arthritis and psoriasis groups compared with controls

		Psoriatic arthritis	Psoriasis	Controls
N		1836	8995	36 000
Age at recruitment, years, mean (S.D.)		56.6 (7.7)	57.1 (8.0)	56.5 (8.1)
Male, *n* (%)		874 (47.6%)	4688 (52.1%)	16 466 (45.7%)
White British ethnicity, *n* (%)		1763 (96.6%)	8645 (96.6%)	33 841 (94.5%)
BMI, mean (S.D.)		29.1 (5.5)	28.6 (5.3)	27.4 (4.8)
Smoking status	Never	848 (46.5%)	3733 (41.7%)	19 736 (55.1%)
	Previous	757 (41.5%)	3788 (42.3%)	12 417 (34.7%)
	Current	218 (12.0%)	1429 (16.0%)	3656 (10.2%)
Pack years, median (IQR)		21.0 (10.9, 33.0)	22.5 (12.3, 35.5)	19.4 (10.0, 32.0)
Alcohol intake	Never	208 (11.4%)	784 (8.7%)	2889 (8.0%)
	One to three times a month	463 (25.3%)	2088 (23.3%)	8131 (22.7%)
	Once or twice a week	458 (25.0%)	2176 (24.3%)	9308 (25.9%)
	Three or four times a week	376 (20.5%)	1958 (21.8%)	8360 (23.3%)
	Daily or almost daily	325 (17.8%)	1962 (21.9%)	7209 (20.1%)
Age completed full time education, median (IQR)		17.0 (2.0)	17.0 (2.1)	17.1 (2.0)
Hypertension		960 (52.3%)	4288 (47.7%)	13 611 (37.8%)
Coronary artery disease		346 (18.8%)	1613 (17.9%)	4176 (11.6%)
Heart failure		111 (6.0%)	518 (5.8%)	1174 (3.3%)
Stroke		110 (6.0%)	612 (6.8%)	1582 (4.4%)
COPD		172 (9.4%)	890 (9.9%)	1865 (5.2%)
Asthma		335 (18.2%)	1529 (17.0%)	5149 (14.3%)
Type 2 diabetes mellitus		280 (15.3%)	1344 (14.9%)	3188 (8.9%)
NAFLD		80 (4.4%)	314 (3.5%)	424 (1.2%)
GORD		313 (17.0%)	1414 (15.7%)	4043 (11.2%)
Chronic kidney disease		154 (8.4%)	632 (7.0%)	1374 (3.8%)
Any cancer		395 (21.5%)	2260 (25.1%)	7612 (21.1%)
Depression		380 (20.7%)	1715 (19.1%)	4995 (13.9%)
Chronic widespread pain		206 (11.2%)	447 (5.0%)	664 (1.8%)
Uveitis		22 (1.2%)	47 (0.5%)	62 (0.2%)
IBD		180 (9.8%)	655 (7.3%)	1507 (4.2%)

Pack years relate to ever-smokers only. COPD: chronic obstructive pulmonary disease; GORD: gastro-oesophageal reflux disease; NAFLD: non-alcoholic fatty liver disease.

psoriatic disease as the exposure (i.e. in the reverse causal direction).

For both cross-sectional and MR analyses with psoriasis as outcome, we repeated all analyses after excluding those with PsA. Analyses were performed in Stata v14, or R v4.0.3 using the TwoSampleMR package [22].

Results

Cross-sectional analysis of UK biobank

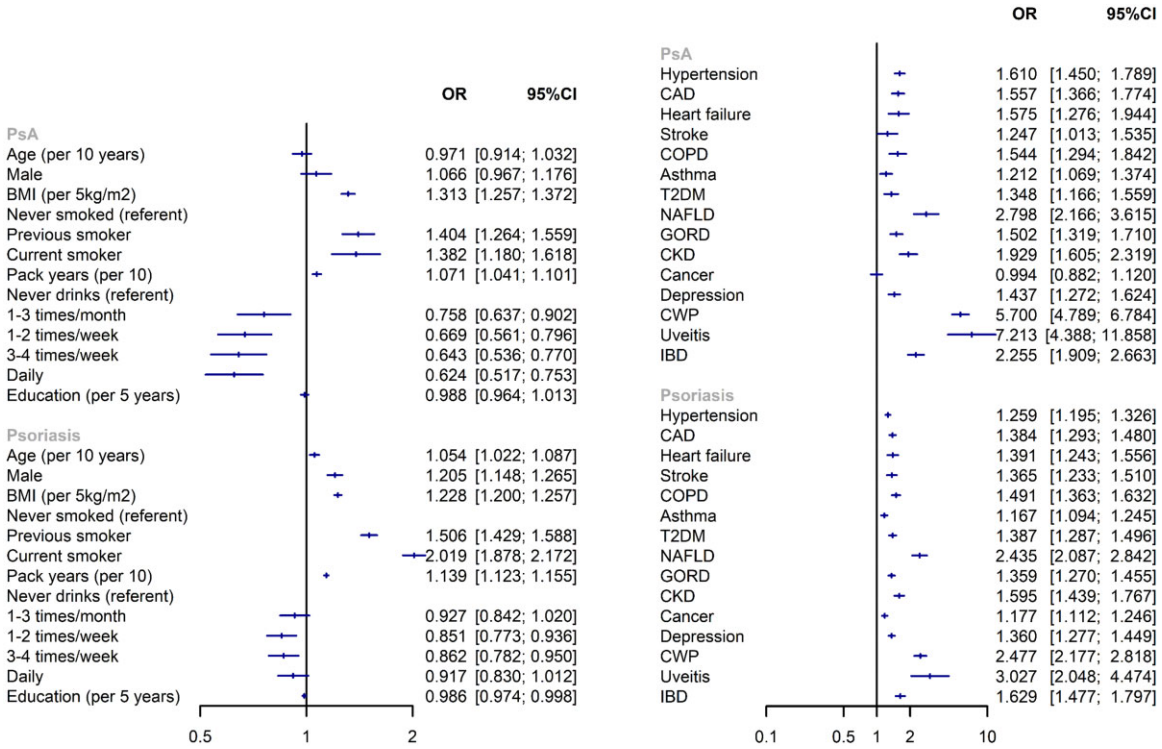
Of the 502 420 participants in the UK Biobank, 1836 (0.37%) had PsA (1424 ICD, 938 self-report) and 8995 (1.8%) had psoriasis (5244 ICD, 5574 self-report). A total of 7373 (82%) had psoriasis without PsA. We randomly selected 36 000 controls without psoriatic disease. Participant characteristics across the three groups were numerically comparable, except for a higher proportion of males and current smokers in the psoriasis group, and higher proportion of never drinkers in the PsA group (Table 2). Missing data did not exceed 2% for any variable (Supplementary Table S2, available at *Rheumatology* online).

Model estimates were similar in unadjusted (shown in supplementary Figure S1 and Table S3, available at *Rheumatology* online) and adjusted models. The following results refer to adjusted estimates (Fig. 2). BMI was associated with PsA (OR 1.31 per 5 kg/m^2 increase in BMI; 95% CI 1.26, 1.37) and psoriasis (OR 1.23; 1.20; 1.26). Previous and current smoking were associated with both PsA and psoriasis (e.g. current smoking was associated with 1.38-fold higher odds of PsA and 2.02-fold higher odds of psoriasis, compared with never). Estimates were also larger with psoriasis than PsA when using cumulative exposure with pack years. Alcohol intake was associated with lower risk of PsA and psoriasis.

Common comorbidities (for PsA, psoriasis, controls, respectively) included hypertension (52%, 48%, 38%), depression (22%, 25%, 21%), chronic widespread pain (21%, 19%, 14%), coronary artery disease (19%, 18%, 12%) and diabetes (18%, 17%, 14%) (Table 2). The proportion of most comorbidities was higher in the psoriatic disease groups, with the exception of depression, which was highest in psoriasis, and uveitis, which was highest in PsA.

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac403/6647833 by University of Cardiff - Journal of Biochemisty Trial user on 12 October 2022

Fig. 2 Cross-sectional associations between psoriatic disease and lifestyle factors and comorbidities



Logistic regression models adjusted for age, sex, BMI, education, smoking and alcohol. Lifestyle factors for each psoriatic disease were all entered into a single model (one for smoking status and another for pack years), whereas each comorbidity was examined in a separate adjusted model. CAD: coronary artery disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary diease; CWP: chronic widespread pain; GORD: gastro-oesophageal reflux disease; NAFLD: non-alcoholic fatty liver diease; T2DM: type 2 diabetes melitus.

Both PsA and psoriasis were associated with most of the 15 comorbidities when compared with controls (Fig. 2), most notably for uveitis (PsA OR 7.21; 95% CI 4.39, 11.9; psoriasis OR 3.03; 2.05, 4.47), chronic widespread pain (PsA OR 5.70; 4.79, 6.78; psoriasis OR 2.48; 2.18, 2.82) and NAFLD (PsA OR 2.80; 2.17, 3.62; psoriasis OR 2.44; 2.09, 2.84).

Sensitivity analyses using ICD codes from before or within 6 months of the baseline assessment showed similar results (Supplementary Figure S2, available at *Rheumatology* online).

MR estimates of lifestyle factors and comorbidities *vs* psoriatic disease

Genetically predicted BMI was associated with increased risk of PsA (OR 1.38 per 4.8 kg/m^2 increase in BMI; 95% CI 1.14, 1.67) and psoriasis (OR 1.36; 95% CI 1.18, 1.58) (Fig. 3A). Genetically predicted educational attainment was protective of PsA (OR 0.75 per additional 4.2 years of schooling; 95% CI 0.61, 0.92) and psoriasis (OR 0.67; 0.53, 0.85). Smoking—whether examined as genetically predicted smoking initiation or lifetime exposure—was associated with psoriasis, but not PsA. Genetically predicted alcohol intake was not associated with PsA or psoriasis. Sensitivity analyses using pleiotropy robust MR methods showed concordant estimates with the primary analysis, except for education *vs* PsA (Supplementary Tables S4–5, available at *Rheumatology* online) suggesting presence of bias.

MR estimates of psoriatic disease *vs* lifestyle factors and comorbidities

In reverse MR, genetically liability to PsA or psoriasis did not demonstrate evidence of reverse causation on any lifestyle factors (Fig. 3B).

Where possible, we used continuous traits to represent exposure comorbidities, namely systolic blood pressure for hypertension, glycated haemoglobin (HbA1c) for diabetes, number of chronic pain sites for chronic widespread pain. GWA studies of depressive symptoms and estimated glomerular filtration rate did not yield sufficiently strong instruments.

Genetic liability to PsA and psoriasis were each associated with increased risk of CAD (PsA OR 1.05; 1.003, 1.09; psoriasis OR 1.03; 1.001, 1.06) and uveitis (PsA OR 1.09; 1.01, 1.17; psoriasis OR 1.09, 1.01, 1.17). Genetic liability to psoriasis increased risk of IBD (OR 1.20; 1.05, 1.38) (Fig. 4A). Sensitivity analyses showed concordant estimates with the IVW results, with the exception of associations between and psoriatic disease and heart

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac403/6647833 by University of Cardiff - Journal of Biochemisty Trial user on 12 October 2022

FIG. 3 Mendelian randomization estimates of the effect of lifestyle factors on psoriatic disease and vice versa

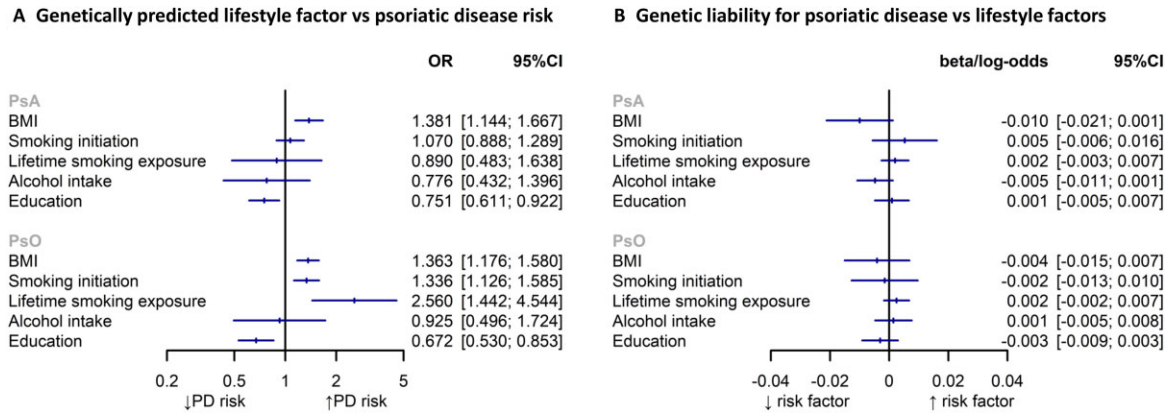
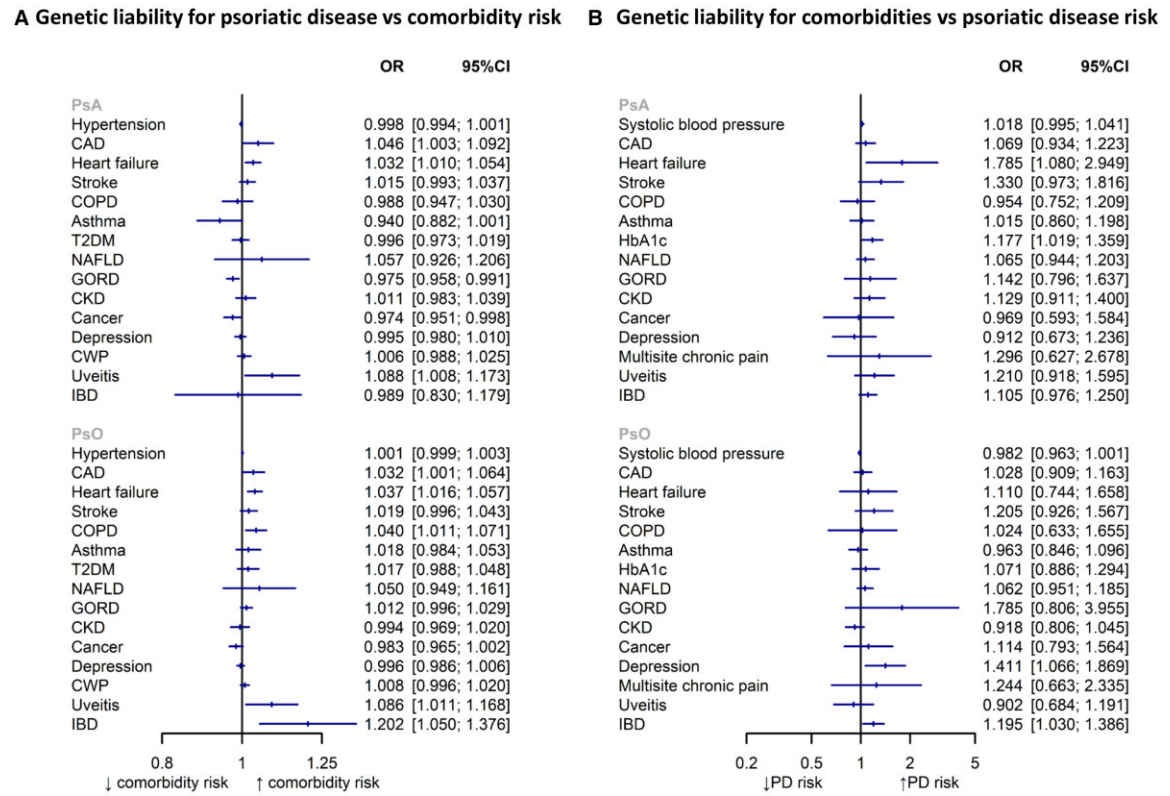


FIG. 4 Mendelian randomization estimates of the effect of psoriatic disease on comorbidities and vice versa



CAD: coronary artery disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary diease; CWP: chronic widespread pain; GORD: gastro-oesophageal reflux disease; IBD: inflammatory bowel disease; NAFLD: non-alcoholic fatty liver diease; T2DM: type 2 diabetes melitus.

failure suggestive of bias (Supplementary Tables S6–7, available at *Rheumatology* online).

Using each comorbidity as the exposure in reverse MR, genetically liability to depression (OR 1.59; 1.24, 2.04) and IBD (OR 1.17; 1.07, 1.28) were associated with increased risk of psoriasis but not PsA (Fig. 4B). Genetically predicted HbA1c was associated with increased risk of PsA (OR 1.18 per 6.7 mmol/mol increase in HbA1c; 95% CI 1.02, 1.36) but not psoriasis. Genetic liability to heart failure was associated with increased risk of both PsA and psoriasis; however, discordant estimates across pleiotropy robust MR methods suggest these results are likely biased.

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac403/6647833 by University of Cardiff - Journal of Biochemisty Trial user on 12 October 2022

Lastly, results were similar in cross-sectional and MR analyses for psoriasis after excluding PsA (Supplementary Table S8, Figs S3 and S4, available at *Rheumatology* online).

Discussion

Through triangulation of evidence from both cross-sectional and MR analyses, this study confirmed that elevated BMI is associated with both PsA and psoriasis risk. Smoking appeared, in both designs, to have a stronger association with psoriasis than PsA. Our study also revealed novel insights into comorbidities in psoriatic disease; genetically predicted HbA1c increased risk of PsA, while genetic liability to PsA or psoriasis were associated with increased risk of coronary artery disease.

Excess adiposity, proxied using BMI, increases systemic inflammatory burden and immune dysregulation, but also generates excess mechanical stress that may contribute to pathology of spondyloarthritis [23]. Our finding that higher BMI increases risk of PsA and psoriasis is consistent with existing evidence [7]. One mechanism through which BMI may exert its effect, on PsA at least, may be through glycaemic control. A plethora of evidence supports increased risk of insulin resistance and diabetes among people with psoriatic disease [24], but the influence of genetically predicted HbA1c on PsA risk has not been reported to our knowledge. This finding may represent a novel risk factor for PsA that warrants further study, although it should be interpreted in the context of multiple comparisons. These results support holistic management of psoriatic disease, including optimizing metabolic comorbidities.

A striking observation is the strong associations between psoriatic disease and almost all comorbidities in the cross-sectional analysis. Higher burden of comorbidities compared with controls is well-recognised and supports the importance of holistically addressing comorbidities in patient-centred care. A much smaller proportion of associations were replicated in MR. This may be due to presence of residual confounding in the cross-sectional analysis or limitations of MR (lower power and use of binary exposures). Another limitation of MR is that genetic liability to psoriatic disease risk does not capture heterogeneity in clinical features or levels of inflammatory burden after disease onset.

Psoriatic disease is recognised to increase risk of coronary artery disease [3, 25], which was replicated in the current analyses. Although this may in part be due to common risk factors such as obesity and smoking, genetic evidence from MR supports a direct influence of psoriatic disease on CAD, which may represent shared genetic risk factors. Overall, these results lend support to the importance of screening for and optimizing cardiovascular comorbidities when managing psoriatic disease. The associations between psoriatic disease and heart failure may be due to general increased cardiovascular risk, rather than any direct causal effect (i.e. results not robustly replicated in MR).

Spondyloarthritis, psoriasis, uveitis and inflammatory bowel disease share common pathological mechanisms [23]. Individuals with each index disease can often have overt or subclinical manifestations of the others. Cross-sectional analyses confirmed the strong association with uveitis and IBD, in PsA more so than psoriasis. Bidirectional MR associations likely reflect the shared underlying genetics. These extra-articular manifestations are well-recognised in axial spondyloarthritis, but our results also highlight their importance in psoriatic disease [26].

The seemingly protective associations between alcohol use and PsA in cross-sectional analyses were not replicated in MR. The most plausible explanation is reverse causation (i.e. chronic disease diagnoses and/or use of methotrexate leading to reduced alcohol intake [27]), but reverse MR estimate of PsA *vs* alcohol included the null. Alcohol is unlikely to be protective since it is a recognised trigger of psoriasis.

This study's strength lies in the integration of two methodological approaches. Cross-sectional analyses benefit from the large sample size and statistical power, but do not allow the causal direction to be examined. MR helps to examine reverse causation and is more robust to confounding; for example, a genetic risk score derived from the same BMI variants as in this study was not meaningfully associated with age, sex, smoking, alcohol or education in a prior study [28].

The current analysis also had limitations. Because psoriasis and PsA are overlapping diseases, it was not always possible to interrogate associations specific to each phenotype alone. Excluding PsA from the psoriasis population did not change the results. However, some PsA may not have developed or been diagnosed. It was not feasible to study the minority (12%) of PsA without psoriasis. There is also risk of misclassification of psoriatic disease for analyses using UK Biobank ICD and/or self-reported data. However, we showed strong genetic correlation between this phenotype definition and physician diagnosed psoriasis, which suggests that misclassification is likely small. It was not possible to perform the equivalent test for PsA; significant outcome misclassification is likely to bias estimates towards the null.

We did not compare PsA *vs* psoriasis directly, due to concerns for collider bias. This occurs when a risk factor for disease onset (derived from comparison of disease *vs* healthy controls) is then interrogated within the disease population for prognosis [29]. Cigarette smoking is a well-recognised example in PsA [8]. We showed consistent observational and genetic evidence that smoking is causally associated with risk of psoriasis, whereas observational estimates for smoking *vs* PsA were smaller in comparison. If smoking is a stronger risk factor for psoriasis than PsA when each disease is compared with controls, then smoking would appear protective of PsA when PsA is compared directly against psoriasis. Therefore, smoking can be detrimental for psoriatic disease overall (and need not biologically protect against PsA among people with psoriasis) for this paradoxical association to be observed. A similar paradoxical example in PsA is HLA-Cw*06—the primary genetic

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac403/6647833 by University of Cardiff - Journal of Biochemisty Trial user on 12 October 2022

susceptibility allele for psoriasis—which is associated with 6.9-fold higher odds of psoriasis *vs* healthy controls, and 3.6-fold increased risk for PsA *vs* healthy controls. The relative effect of this risk factor appears protective when directly comparing PsA against psoriasis (OR 0.52), which is likely explained by underlying bias [30].

The UK Biobank participants were predominantly white and relatively healthy, which may limit generalizability of our results particularly to other ethnic groups. This limitation similarly applies to GWAS participants that were of European ancestry. The main source of potential bias in MR studies is horizontal pleiotropy; that is, when variants influence the exposure and outcome via separate biological pathways. For example, a prior study showed genetic overlap between educational attainment, BMI and smoking [31]; thus the protective effect of education on psoriatic disease is likely mediated through other risk factors. Lastly, MR assumptions can be violated when a continuous exposure is dichotomized (e.g. blood pressure dichotomized into hypertension). We avoided this where possible, but were limited by availability of GWAS data; genetic variants can influence the outcome via the continuous risk factor even if the binary exposure does not change [16].

In conclusion, we used both observational and genetic epidemiologic designs to show BMI, smoking and glycaemic control are likely risk factors that, if modified, may reduce risk of psoriatic disease. The influence of each risk factor may differ between psoriasis and subsequent development of PsA, which at least partly explains paradoxical protective effects observed in prior studies. Genetic evidence supports a causal role of psoriatic disease on coronary artery disease. Lifestyle factors and comorbidities are important clinical considerations for the management of psoriatic disease.

Acknowledgement

S.S.Z. and E.B. analysed the data and wrote the manuscript with significant input from all co-authors.

Funding: This work was supported by Versus Arthritis (grant number 21173, grant number 21754 and grant number 21755) and by the NIHR Manchester Biomedical Research Centre. S.S.Z. was funded by a National Institute for Health Research (NIHR) Academic Clinical Lectureship. M.J.C. is funded by a National Institute for Health Research Doctoral Research Fellowship. R.B.W. is supported by the Manchester NIHR Biomedical Research Centre.

Disclosure statement: The authors have declared no conflicts of interest.

Data availability statement

The UK Biobank dataset used in this paper is available via application directly to the UK Biobank. Applications are assessed for meeting the required criteria for access, including legal and ethics standards. More information regarding data access can be found at www.ukbiobank.ac.uk. Summary statistics are available from each consortia (references in Table 1) or via the MR-Base platform (https://gwas.mrcieu.ac.uk).

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Parisi R, Iskandar IYK, Kontopantelis E *et al.* National, regional, and worldwide epidemiology of psoriasis: systematic analysis and modelling study. BMJ 2020;369:m1590.

2 Ogdie A, Weiss P. The epidemiology psoriatic arthritis. Rheum Dis Clin North Am 2015;41:545–68.

3 Gupta S, Syrimi Z, Hughes DM, Zhao SS. Comorbidities in psoriatic arthritis: a systematic review and meta-analysis. Rheumatol Int 2021;41:275–84.

4 López-Estebaranz JL, Sánchez-Carazo JL, Sulleiro S. Effect of a family history of psoriasis and age on comorbidities and quality of life in patients with moderate to severe psoriasis: results from the ARIZONA study. J Dermatol 2016;43:395–401.

5 Greb JE, Goldminz AM, Elder JT *et al.* Psoriasis. Nat Rev Dis Primers 2016;2:16082.

6 Armstrong AW, Harskamp CT, Dhillon JS, Armstrong EJ. Psoriasis and smoking: a systematic review and meta-analysis. Br J Dermatol 2014;170:304–14.

7 Blake T, Gullick NJ, Hutchinson CE, Barber TM. Psoriatic disease and body composition: a systematic review and narrative synthesis. PLoS ONE 2020;15:e0237598.

8 Nguyen UDT, Zhang Y, Lu N *et al.* Smoking paradox in the development of psoriatic arthritis among patients with psoriasis: a population-based study. Ann Rheum Dis 2018;77:119–23.

9 Lawlor DA, Tilling K, Smith GD. Triangulation in aetiological epidemiology. Int J Epidemiol 2016;45:1866–86.

10 Davies NM, Holmes MV, Smith GD. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. BMJ 2018;362:k601.

11 Sudlow C, Gallacher J, Allen N *et al.* UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015;12:e1001779.

12 Zhao SS, Mackie SL, Zheng J. Why clinicians should know about Mendelian randomization. Rheumatology 2021;60:1577–9.

13 Soomro M, Stadler M, Dand N *et al.* Comparative genetic analysis of psoriatic arthritis and psoriasis for the discovery of genetic risk factors and risk prediction modelling. Arthritis Rheumatol 2022;doi:10.1002/art.42154.

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac403/6647833 by University of Cardiff - Journal of Biochemisty Trial user on 12 October 2022

14 Tsoi LC, Stuart PE, Tian C *et al.* Large scale meta-analysis characterizes genetic architecture for common psoriasis associated variants. Nat Commun 2017;8:15382.

15 Bulik-Sullivan B, Finucane HK, Anttila V *et al.* An atlas of genetic correlations across human diseases and traits. Nat Genet 2015;47:1236–41.

16 Burgess S, Labrecque JA. Mendelian randomization with a binary exposure variable: interpretation and presentation of causal estimates. Eur J Epidemiol 2018;33:947–52.

17 Burgess S, Thompson SG, CRP CHD Genetics Collaboration. Avoiding bias from weak instruments in Mendelian randomization studies. Int J Epidemiol 2011; 40:755–64.

18 Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. Genet Epidemiol 2013;37:658–65.

19 Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. Genet Epidemiol 2016;40:304–14.

20 Hartwig FP, Davey Smith G, Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. Int J Epidemiol 2017;46: 1985–98.

21 Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol 2015;44:512–25.

22 Walker VM, Davies NM, Hemani G *et al.* Using the MR-Base platform to investigate risk factors and drug targets for thousands of phenotypes. Wellcome Open Res 2019; 4:113.

23 McGonagle D, Aydin SZ, Gül A, Mahr A, Direskeneli H. 'MHC-I-opathy'-unified concept for spondyloarthritis and Behçet disease. Nat Rev Rheumatol 2015;11: 731–40.

24 Coto-Segura P, Eiris-Salvado N, González-Lara L *et al.* Psoriasis, psoriatic arthritis and type 2 diabetes mellitus: a systematic review and meta-analysis. Br J Dermatol 2013;169:783–93.

25 Prodanovich S, Kirsner RS, Kravetz JD *et al.* Association of psoriasis with coronary artery, cerebrovascular, and peripheral vascular diseases and mortality. Arch Dermatol 2009;145:700–3.

26 Pittam B, Gupta S, Harrison NL *et al.* Prevalence of extra-articular manifestations in psoriatic arthritis: a systematic review and meta-analysis. Rheumatology 2020; 59:2199–206.

27 Baker JF, England BR, Mikuls TR *et al.* Changes in alcohol use and associations with disease activity, health status, and mortality in rheumatoid arthritis. Arthritis Care Res 2020;72:301–8.

28 Budu-Aggrey A, Brumpton B, Tyrrell J *et al.* Evidence of a causal relationship between body mass index and psoriasis: a Mendelian randomization study. PLoS Med 2019;16:e1002739.

29 Choi HK, Nguyen US, Niu J, Danaei G, Zhang Y. Selection bias in rheumatic disease research. Nat Rev Rheumatol 2014;10:403–12.

30 Ho PYPC, Barton A, Worthington J *et al.* Investigating the role of the HLA-Cw06 and HLA-DRB1 genes in susceptibility to psoriatic arthritis: comparison with psoriasis and undifferentiated inflammatory arthritis. Ann Rheum Dis 2007;67:677–82.

31 Zhao SS, Holmes MV, Zheng J, Sanderson E, Carter AR. The impact of education inequality on rheumatoid arthritis risk is mediated by smoking and body mass index: Mendelian randomization study. Rheumatology 2021;61:2167–75.

32 Yengo L, Sidorenko J, Kemper KE *et al.* Meta-analysis of genome-wide association studies for height and body mass index in ~700000 individuals of European ancestry. Hum Mol Genet 2018;27:3641–9.

33 Liu M, Jiang Y, Wedow R *et al.* Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. Nat Genet 2019;51:237–44.

34 Wootton RE, Richmond RC, Stuijfzand BG *et al.* Evidence for causal effects of lifetime smoking on risk for depression and schizophrenia: a Mendelian randomisation study. Psychol Med 2020;50: 2435–43.

35 Lee JJ, Wedow R, Okbay A *et al.* Gene discovery and polygenic prediction from a 1.1-million-person GWAS of educational attainment. Nat Genet 2018;50: 1112–21.

36 Evangelou E, Warren HR, Mosen-Ansorena D *et al.* Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. Nat Genet 2018;50:1412–25.

37 Nikpay M, Goel A, Won HH *et al.* A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. Nat Genet 2015;47: 1121–30.

38 Shah S, Henry A, Roselli C *et al.* Genome-wide association and Mendelian randomisation analysis provide insights into the pathogenesis of heart failure. Nat Commun 2020;11:163.

39 Malik R, Chauhan G, Traylor M *et al.* Multiancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes. Nat Genet 2018;50:524–37.

40 Sakornsakolpat P, Prokopenko D, Lamontagne M *et al.* Genetic landscape of chronic obstructive pulmonary disease identifies heterogeneous cell-type and phenotype associations. Nat Genet 2019;51:494–505.

41 Sakaue S, Kanai M, Tanigawa Y *et al.* A cross-population atlas of genetic associations for 220 human phenotypes. Nat Genet 2021;53:1415–24.

42 Han Y, Jia Q, Jahani PS *et al.* Genome-wide analysis highlights contribution of immune system pathways to the genetic architecture of asthma. Nat Commun 2020; 11:1776.

43 NealeLab. Rapid GWAS of thousands of phenotypes for 337,000 samples in the UK Biobank. 2020. http://www.nealelab.is/uk-biobank (16 June 2020, date last accessed).

44 Xue A, Wu Y, Zhu Z *et al.* Genome-wide association analyses identify 143 risk variants and putative regulatory

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac403/6647833 by University of Cardiff - Journal of Biochemisty Trial user on 12 October 2022

mechanisms for type 2 diabetes. Nat Commun 2018;9:2941.

45 Vujkovic M, Ramdas S, Lorenz KM, Schneider CV, Park J, Lee KM *et al.* A genome-wide association study for nonalcoholic fatty liver disease identifies novel genetic loci and trait-relevant candidate genes in the Million Veteran Program. 2021. https://www.medrxiv.org/content/10.1101/2020.12.26.20248491v1 (20 November 2021, date last accessed).

46 FinnGen research project is an expedition to the frontier of genomics and medicine. FinnGen https://www.finngen.fi/en/finngen_research_project_is_an_expedition_to_the_frontier_of_genomics_and_medicine (15 January 2022, date last accessed).

47 An J, Gharahkhani P, Law MH *et al.* Gastroesophageal reflux GWAS identifies risk loci that also associate with subsequent severe esophageal diseases. Nat Commun 2019;10:4219.

48 Wuttke M, Li Y, Li M *et al.* A catalog of genetic loci associated with kidney function from analyses of a million individuals. Nat Genet 2019;51:957–72.

49 Howard DM, Adams MJ, Clarke TK *et al.* Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. Nat Neurosci 2019;22:343–52.

50 de Lange KM, Moutsianas L, Lee JC *et al.* Genome-wide association study implicates immune activation of multiple integrin genes in inflammatory bowel disease. Nat Genet 2017;49:256–61.

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac403/6647833 by University of Cardiff - Journal of Biochemisty Trial user on 12 October 2022

Jyseleca® filgotinib

A 2nd generation, JAK1 preferential inhibitor for moderate to severe RA[1-6]

While 1st generation JAK inhibitors are relatively non-selective,[2-6] JYSELECA has over 5x greater potency for JAK1 over JAK2/3 and TYK2[1]*

Balancing sustained efficacy[7-11] with acceptable tolerability[1,12]

Indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti-rheumatic drugs.[1] May be used as monotherapy or in combination with methotrexate.[1]

*From biochemical assays, the clinical relevance of which is uncertain.
JAK, Janus kinase; RA, rheumatoid arthritis; TYK, tyrosine kinase.

Learn more at strengthofbalance.co.uk

Refer to Summary of Product Characteristics (SmPC) before prescribing, and for full prescribing information.

JYSELECA® ▽ filgotinib 100 mg or 200 mg film-coated tablets. **Indication:** Jyseleca is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs). Jyseleca may be used as monotherapy or in combination with methotrexate (MTX). **Dosage:** Adults: 200 mg once daily. Taken orally with/without food. It is recommended that tablets are swallowed whole. Laboratory Monitoring: Refer to the SmPC for information regarding laboratory monitoring and dose initiation or interruption. Elderly: A starting dose of 100 mg once daily is recommended for patients aged 75 years and older as clinical experience is limited. Renal impairment: No dose adjustment required in patients with estimated creatinine clearance (CrCl) ≥ 60 mL/min. A dose of 100 mg of filgotinib once daily is recommended for patients with moderate or severe renal impairment (CrCl 15 to < 60 mL/min). Not recommended in patients with CrCl < 15 mL/min. Hepatic impairment: Mild/moderate hepatic impairment: no dose adjustment required. Severe hepatic impairment: not recommended. Children (< 18years): Safety and efficacy not yet established. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Active tuberculosis (TB) or active serious infections. Pregnancy. **Warnings/Precautions:** See SmPC for full information. Immunosuppression: Combination use, with immunosuppressants e.g., ciclosporin, tacrolimus, biologics or other Janus kinase (JAK) inhibitors is not recommended as a risk of additive immunosuppression cannot be excluded. Infections: Infections, including serious infections such as pneumonia and opportunistic infections e.g. tuberculosis (TB), oesophageal candidiasis, and cryptococcosis have been reported. Risk benefit should be assessed prior to initiating in patients with risk factors for infections (see SmPC). Patients should be closely monitored for the development of signs and symptoms of infections during and after filgotinib treatment. Treatment should be interrupted if the patient is not responding to antimicrobial therapy, until infection is controlled. There is a higher incidence of serious infections in the elderly aged 75 years and older, caution should be used when treating this population. Tuberculosis: Patients should be screened for TB before initiating filgotinib, and filgotinib should not be administered to patients with active TB. Viral reactivation: Cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical studies (see SmPC). If a patient develops herpes zoster, filgotinib treatment should be temporarily interrupted until the episode resolves. Screening for viral hepatitis and monitoring for reactivation should be performed. Malignancy: Immunomodulatory medicinal products may increase the risk of malignancies. Malignancies were observed in clinical studies (see SmPC). Fertility: In animal studies, decreased fertility, impaired spermatogenesis, and histopathological effects on male reproductive organs were observed (see SmPC). The potential effect of filgotinib on sperm production and male fertility in humans is currently unknown. Haematological abnormalities: Do not start therapy, or temporarily stop, if Absolute Neutrophil Count (ANC) <1 × 10^9 cells/L, ALC <0.5 × 10^9 cells/L or haemoglobin <8 g/dL. Temporarily stop therapy if these values are observed during routine patient management. Vaccinations: Use of live vaccines during, or immediately prior to, filgotinib treatment is not recommended. Lipids: Treatment with filgotinib was associated with dose dependent increases in lipid parameters, including total cholesterol, and high-density lipoprotein (HDL) levels, while low density lipoprotein (LDL) levels were slightly increased (see SmPC). Cardiovascular risk: Rheumatoid arthritis patients have an increased risk for cardiovascular disorders. Patients should have risk factors (e.g., hypertension, hyperlipidaemia) managed as part of usual standard of care. Venous thromboembolism: Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving JAK inhibitors including filgotinib. Caution should be used in patients with risk factors for DVT/PE, such as older age, obesity, a medical history of DVT/PE, or patients undergoing surgery, and prolonged immobilisation. Lactose content: Contains lactose; patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take filgotinib. **Pregnancy/Lactation:** Filgotinib is contraindicated in pregnancy. Filgotinib should not be used during breast-feeding. Women of childbearing potential must use effective contraception during and for at least 1 week after cessation of treatment. **Driving/Using machinery:** No or negligible influence, however dizziness has been reported. **Side effects:** See SmPC for full information. Common (≥1/100 to <1/10): nausea, upper respiratory tract infection, urinary tract infection and dizziness. Uncommon (≥1/1000 to <1/100): herpes zoster, pneumonia, neutropenia, hypercholesterolaemia and blood creatine phosphokinase increase. Serious side effects: See SmPC for full information **Legal category:** POM **Pack:** 30 film-coated tablets/bottle **Price:** UK Basic NHS cost: £863.10 **Marketing authorisation number(s):** Great Britain Jyseleca 100mg film-coated tablets PLGB 42147/0001 Jyseleca 200mg film-coated tablets PLGB 42147/0002 Northern Ireland Jyseleca 100mg film-coated tablets EU/1/20/1480/001 EU/1/20/1480/002 Jyseleca 200mg film-coated tablets EU/1/20/1480/003 EU/1/20/1480/004 **Further information:** Galapagos UK, Belmont House, 148 Belmont Road, Uxbridge UB8 1QS, United Kingdom 00800 7878 1345 medicalinfo@glpg.com Jyseleca® is a trademark. **Date of Preparation:** January 2022 UK-RA-FIL-202201-00019

▽ Additional monitoring required

Adverse events should be reported.
For Great Britain and Northern Ireland, reporting forms and information can be found at yellowcard.mhra.gov.uk or via the Yellow Card app (download from the Apple App Store or Google Play Store).
Adverse events should also be reported to Galapagos via email to DrugSafety.UK.Ireland@glpg.com or 00800 7878 1345

References: 1. JYSELECA SPC. Available at: www.medicines.org.uk. Last accessed: June 2022. **2.** Angelini J, *et al.* Biomolecules 2020;10(7):E1002. **3.** Banerjee S, *et al.* Drugs 2017;77:521–546. **4.** O'Shea JJ, *et al.* Nat Rev Rheumatol 2013;9(3):173–182. **5.** Traves PG, *et al.* Ann Rheum Dis 2021;0:1–11. **6.** McInnes IB, *et al.* Arthr Res Ther 2019;21:183. **7.** Combe B, *et al.* Ann Rheum Dis 2021;doi:10.1136/annrheumdis-2020-219214. **8.** Genovese MC, *et al.* JAMA 2019;322 (4):315–325. **9.** Westhovens R, *et al.* Ann Rheum Dis 2021;doi:10.1136/annrheumdis-2020-219213. **10.** Combe B, *et al.* Arthritis Rheumatol 2021;73(suppl 10). https://acrabstracts.org/abstract/clinical-outcomes-up-to-week-48-of-filgotinib-treatment-in-an-ongoing-long-term-extension-trial-of-ra-patients-with-inadequate-response-to-mtx-initially-treated-with-filgotinib-or-adalimumab-during-th/. Last accessed: June 2022. **11.** Buch MH, *et al.* Arthritis Rheumatol 2021;73 (suppl 10). https://acrabstracts.org/abstract/clinical-outcomes-up-to-week-48-of-ongoing-filgotinib-ra-long-term-extension-trial-of-biologic-dmard-inadequate-responders-initially-on-filgotinib-or-placebo-in-a-phase-3-trial/. Last accessed: June 2022. **12.** Winthrop K, *et al.* Arthritis Rheumatol 2021;73(suppl 10). Available at: https://acrabstracts.org/abstract/integrated-safety-analysis-update-for-filgotinib-in-patients-with-moderately-to-severely-active-rheumatoid-arthritis-receiving-treatment-over-a-median-of-2-2-years/. Last accessed: June 2022.

Galápagos

June 2022 GB-RA-JY-202205-00033

JYSELECA, GALAPAGOS and the JYSELECA and GALAPAGOS logos are registered trademarks of Galapagos NV.
© 2022 Galapagos NV. All rights reserved.