

## Original article

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

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## 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<sup>2</sup> 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, respectively). 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.

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## Introduction

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

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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 pathoetiology 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<sup>2</sup>), 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.

**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 <sup>2</sup> increase in BMI. Field 21001.		Trait: BMI [32] Unit: 1SD = 4.8 kg/m <sup>2</sup> 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 $\geq 30$ (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 $\geq 30$ (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 $\geq 30$ (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 $\geq 18$ (field 2976)	Trait: Glycated haemoglobin (HbA1c) [43] Unit: 1SD = 6.7 mmol/mol	Trait: Type 2 diabetes [44] N: 61 714/596 424

(continued)

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
Non-alcoholic fatty liver disease	K760	n/a	N: 344 182 No SNPs: 320 F: 146 Trait: NAFLD (elevated ALT without other liver disease) [45]	Trait: NAFLD (ICD 10 code K760) [46] N: 894/217 898
Gastro-oesophageal reflux disease	K22.7, K21*	1159, 1160	N: 90 408/128 187 No SNPs: 18 F: 809 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 <sup>2</sup> ) [48] N: 41 395/439 303 No SNPs: 23 F: 1719	
Cancer	C*	20001	(eGFR GWAS yielded insufficiently strong instruments) 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	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)	(depressive symptoms GWAS yielded insufficiently strong instruments) 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.

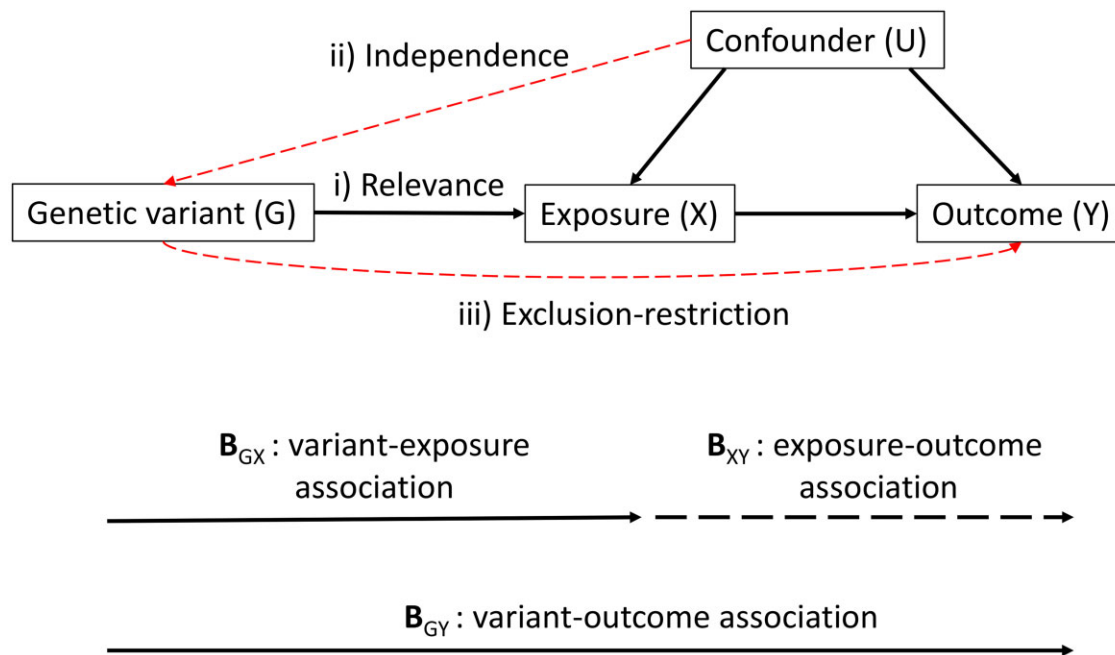
#### Lifestyle factors and comorbidities in MR

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

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

$$\text{Exposure-outcome association } (B_{XY}) = \frac{\text{Variant-outcome association } (B_{GY})}{\text{Variant-exposure association } (B_{GX})}$$

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  $B_{GY}/B_{GX}$ .

turn as the independent variable. Each model was then 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  $\beta$  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 horizontal pleiotropy.

MR analyses were performed first with psoriatic disease as the outcome (i.e. effect of lifestyle factor/

**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, <i>n</i> (%)	874 (47.6%)	4688 (52.1%)	16 466 (45.7%)
White British ethnicity, <i>n</i> (%)	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.

comorbidities on psoriatic disease), then repeated with 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

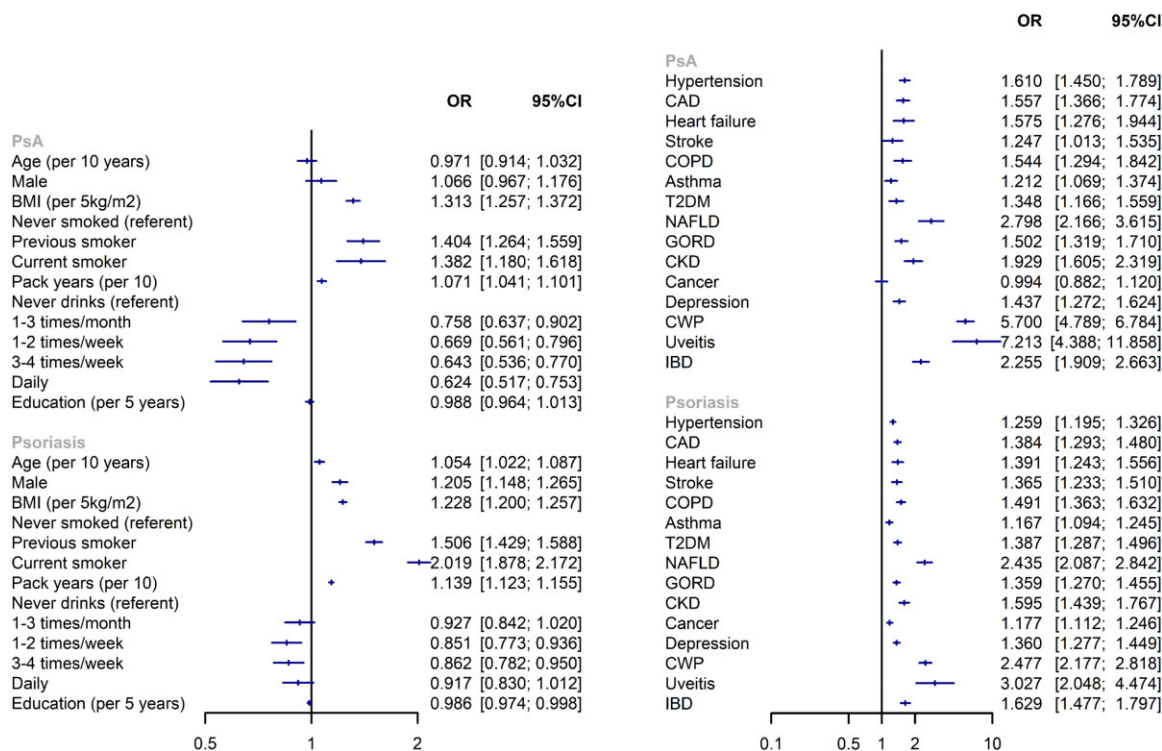
Of the 502 420 participants in the UK Biobank, 1836 (0.37%) had PsA (1424 ICD, 938 self-report) and 8995 (1.8%) had psoriasis (5244 ICD, 5574 self-report). A total of 7373 (82%) had psoriasis without PsA. We randomly selected 36 000 controls without psoriatic disease. Participant characteristics across 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<sup>2</sup> 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



**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 disease; CWP: chronic widespread pain; GORD: gastro-oesophageal reflux disease; NAFLD: non-alcoholic fatty liver disease; T2DM: type 2 diabetes melitus.

was highest in psoriasis, and uveitis, which was highest in PsA.

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<sup>2</sup> 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

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

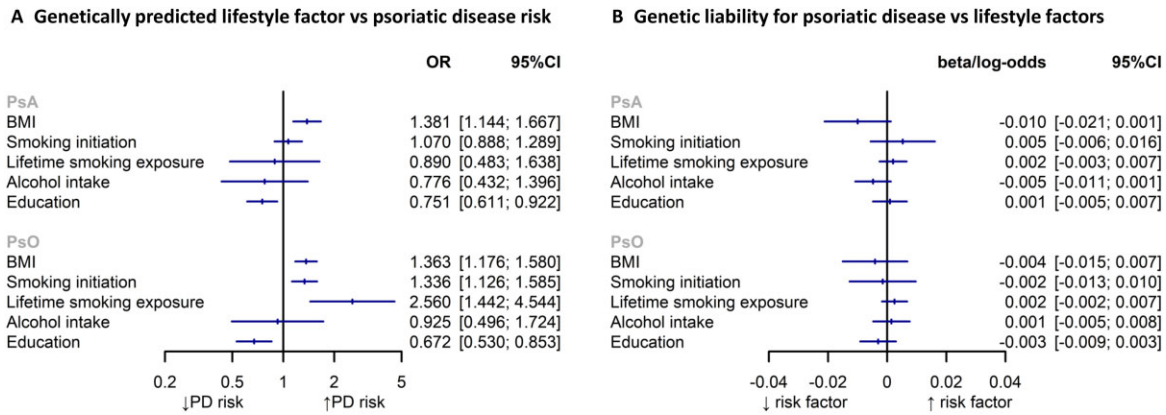
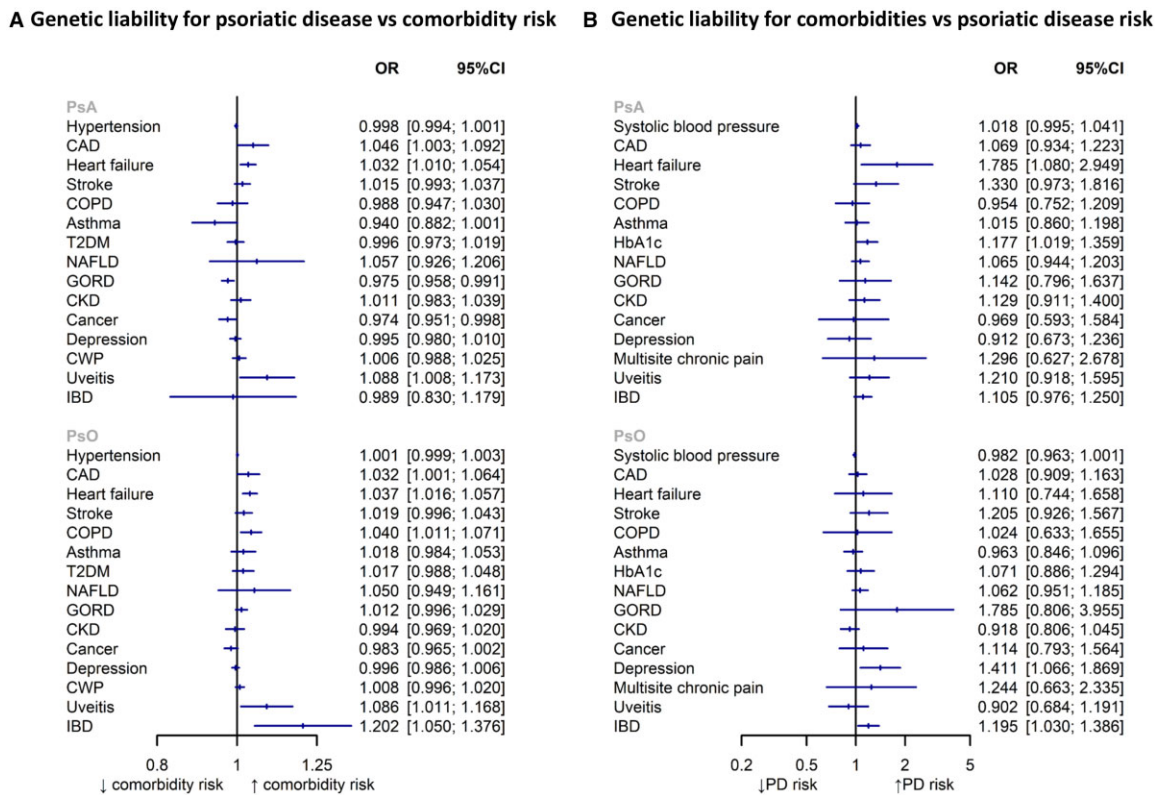


Fig. 4 Mendelian randomization estimates of the effect of psoriatic disease on comorbidities and vice versa



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

estimates with the IVW results, with the exception of associations between and psoriatic disease and heart 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.

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 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.

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

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## 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](http://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.

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