

Supplementary Table 1. Effect of rheumatoid arthritis (RA) and MUC5B on risk of interstitial lung disease (ILD), accounting for competing risks (non-ILD related death).

	Population	MUC5B	RA	RA and MUC5B
Risk of ILD in men				
Lifetime risk, %	1.5 %	4.8 %	8.5 %	19.5 %
HR (95% CI)	Reference	3.20 (2.84-3.62)	6.00 (4.66-7.73)	11.7 (8.52-16.1)
p-value	-	4.13×10^{-79}	7.21×10^{-44}	1.79×10^{-51}
Risk of ILD in women				
Lifetime risk, %	1.1 %	2.9 %	4.6 %	14.1 %
HR (95% CI)	Reference	2.64 (2.25-3.09)	4.54 (3.57-5.77)	12.6 (9.49-16.7)
p-value	-	1.64×10^{-33}	2.68×10^{-35}	8.91×10^{-70}

Supplementary Table 2. Characteristics of the epidemiological and disease-based cohorts, and hospital biobanks (marked with an asterisk) in the FinnGen dataset used in the study.

	Interstitial lung disease			Rheumatoid arthritis			Mean age at recruitment	Mean age at the end of follow-up or death
	Number of controls	Number of cases	Prevalence	Number of controls	Number of cases	Prevalence		
AURIA BIOBANK*	31371	208	0.66 %	30433	1146	3.63 %	62.8	64.0
BIOBANK OF CENTRAL FINLAND*	7957	54	0.67 %	7547	464	5.79 %	58.6	59.6
BIOBANK OF EASTERN FINLAND*	9798	62	0.63 %	9456	404	4.10 %	62.2	63.1
BLOOD SERVICE BIOBANK	34330	14	0.04 %	34315	29	0.08 %	43.6	44.7
BOREALIS BIOBANK*	8657	96	1.10 %	8372	381	4.35 %	62.6	63.8
HELSINKI BIOBANK*	60819	502	0.82 %	59440	1881	3.07 %	56.9	58.3
TAMPERE BIOBANK*	20147	218	1.07 %	19725	640	3.14 %	56.7	58.1
TERVEYSTALO BIOBANK	6644	11	0.17 %	6498	157	2.36 %	51.0	50.7
THL BIOBANK ATBC	8446	102	1.19 %	8472	76	0.89 %	62.9	77.0
THL BIOBANK BOTNIA	11441	40	0.35 %	11348	133	1.16 %	51.5	68.3
THL BIOBANK COROGENE	4377	69	1.55 %	4346	100	2.25 %	65.8	75.6
THL BIOBANK FINHEALTH 2017	5719	15	0.26 %	5648	86	1.50 %	54.6	57.4
THL BIOBANK FINRISK 1992	4760	32	0.67 %	4685	107	2.23 %	44.2	69.7
THL BIOBANK FINRISK 1997	6799	48	0.70 %	6712	135	1.97 %	48.3	68.9
THL BIOBANK FINRISK 2002	6689	34	0.51 %	6605	118	1.76 %	47.9	64.8
THL BIOBANK FINRISK 2007	4969	27	0.54 %	4896	100	2.00 %	51.2	63.6
THL BIOBANK FINRISK 2012	5093	12	0.24 %	5021	84	1.65 %	51.1	58.8
THL BIOBANK HEALTH 2000	6293	19	0.30 %	6190	122	1.93 %	55.7	72.0
THL BIOBANK HHS	3253	39	1.18 %	3266	26	0.79 %	47.5	79.0
THL BIOBANK MIGRAINE	7700	28	0.36 %	7610	118	1.53 %	44.8	58.6
THL BIOBANK SUPER	8249	16	0.19 %	8222	43	0.52 %	46.9	49.3
THL BIOBANK T1D	9891	28	0.28 %	9701	218	2.20 %	32.7	52.0
THL BIOBANK TWINS	11003	98	0.88 %	10892	209	1.88 %	48.5	68.9
Other	7602	193	2.48 %	7703	92	1.18 %	54.8	58.8

Supplementary Table 3. Diseases excluded from the study. We excluded from all analyses 11,808 individuals without rheumatoid arthritis who had at least one record for any of these diseases.

	Hospital discharge registry			Hospital discharge registry codes to exclude	Cause of death registry			Cause of death registry codes to exclude	Kela* reimbursement codes
	ICD-10	ICD-9	ICD-8	ICD-9	ICD-10	ICD-9	ICD-8	ICD-9	
Systemic lupus erythematosus	M32	7100	7431		M32	7100	7431		
Inflammatory bowel disease									
Crohn disease	K50	555	5630		K50	555	5630		
Ulcerative colitis	K51	556	5631 or 569	5564A	K51	556	5631 or 569	5564A	
IBD patients in Kela*-register									208 or 209
Systemic sclerosis	M34	7101	7340		M34	7101	7340		
Ankylosing spondylitis	M45	7200	7124		M45	7200	7124		
Dermatopolymyositis	M33				M33				
Juvenile dermatomyositis	M330	7103A			M330	7103A			
Other dermatomyositis	M331	7103B	7160		M331	7103B	7160		
Polymyositis	M332	7104	7161		M332	7104	7161		
Dermatopolymyositis, unspecified	M339				M339				
Myositis	M60	7280	732		M60	7280	732		

*KELA = the Social insurance Institute of Finland

Supplementary Methods

Diseases

FinnGen is a collection of prospective epidemiological and disease-based cohorts and hospital biobank samples, aiming for a collection of 500,000 genotype samples from Finnish individuals by 2023. The study uses FinnGen data freeze 7. Further information about the subcohorts included in FinnGen can be found in **Supplementary Table 2**.

Age at RA onset was defined through the first registered diagnosis in the registries (age ≥ 16 at diagnosis accepted as case). Age at ILD diagnosis was defined through the first registered diagnosis in the registries (at death, if death was the only event; age ≥ 16 at diagnosis accepted as case, with 8 individuals excluded due to diagnosis under age 16). 630 individuals were excluded due to no further healthcare contacts with ILD within 5 years after the initial diagnosis (individuals with ILD death as first event considered as cases). Competing risks were defined as any non-ILD related cause of death identified from the registry on causes of death. We excluded from all analyses a further 11,808 individuals without RA who had at least one record for any of the following diseases: systemic lupus erythematosus, inflammatory bowel disease, systemic sclerosis, ankylosing spondylitis, dermatomyositis, or myositis (**Supplementary Table 3**). The full FinnGen Data Freeze 7 consists of 306,418 adults (age ≥ 18), and with the exclusions listed above, the final sample size was 293,972.

Genotyping and imputation

The samples are genotyped with Illumina and Affymetrix arrays (Illumina Inc., San Diego, and Thermo Fisher Scientific, Santa Clara, CA, USA). Individuals with ambiguous gender, high genotype missingness ($>5\%$), excess heterozygosity ($\pm 4SD$) and non-Finnish ancestry were excluded, as well as all variants with high missingness ($>2\%$), low Hardy–Weinberg equilibrium p-value ($<1e-6$) and minor allele count ($MAC < 3$). Array data pre-phasing was carried out with Eagle 2.3.527 with the number of conditioning haplotypes set to 20,000. The genotypes have been imputed with using the SISu v3 population-specific reference panel developed from high-quality data for 3,775 high-coverage (25–30x) whole-genome sequencing in Finns. The detailed genotype imputation workflow can be found at <https://dx.doi.org/10.17504/protocols.io.xbgfijw>. The dataset uses genome build 38 (hg38). Variant extraction from VCF files with PLINK v2.00a2.3LM.45 using `--export A`. The HWE p-value for rs35705950 was 0.18.

Replication in UK Biobank

UK Biobank is a prospective cohort study comprising approximately 500,000 individuals from across the United Kingdom, aged between 40 and 69 at recruitment. The cohort contains deep phenotyping, including biological measurements, lifestyle factors, and blood biomarkers. The dataset has been imputed using the merged UK10K and 1000 Genomes (phase 3) reference panels.¹ Details on the cohort, as well as data generation and imputation have been previously described.² RA was defined as at least two contacts with ICD-10 codes beginning with M05 (seropositive RA) or M06 (seronegative RA) in the inpatient hospital data (data field 41270; age for earliest visit from data field 41280). The sample size in the UK Biobank analysis was 343,676 (White British individuals unrelated based on KING kinship coefficient <0.0442). We identified 1,911 RA cases (1,368 women), with their mean age at RA onset at 58.5 years (s.d. 8.9 years). This analysis was conducted with the UK Biobank Resource under Application Number 22627.

Statistical analysis

With age as time scale, all regression models were stratified by sex, adjusting for ten principal components of ancestry, as well as genotyping array (FinnGen and UK Biobank), cohort (FinnGen), and batch (UK Biobank). The proportional hazards assumption was evaluated by Schoenfeld residuals and log–log inspection. Meta-analysis was performed by inverse-variance weighting. Competing risk models were performed by fitting the Fine and Gray proportional subdistribution hazards regression model using the R package *cmprsk*. Function *crr()* was used for obtaining sex-specific effect sizes with 95% confidence intervals (CIs) with the covariates inputted as a numerical covariate matrix. The lifetime risks were estimated with *cuminc()*, which estimates the cumulative incidence functions from the output generated by *crr()*. All tests were two-tailed.

Supplementary References

1. Huang, J., *et al.* Improved imputation of low-frequency and rare variants using the UK10K haplotype reference panel. *Nat Commun* **6**, 8111 (2015).
2. Bycroft, C., *et al.* The UK Biobank resource with deep phenotyping and genomic data. *Nature* **562**, 203-209 (2018).

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