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Genetic and Epidemiological Evidence Linking Respiratory and Musculoskeletal Diseases: Shared Risk Factors and Intervention Windows

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Abstract

Background

We previously identified genetic correlation between pairs of musculoskeletal (MSK) and respiratory conditions. Strategies to prevent or delay their onset remain underexplored in the context of multimorbidity. This study investigated whether MSK–respiratory disease pairs show evidence of potential causal relationships, identified modifiable risk factors, and quantified intervention windows to prevent progression to multimorbidity.

Methods and Findings

We examined combinations of one respiratory condition (asthma, COPD) and one MSK condition [rheumatoid arthritis (RA), osteoarthritis (OA), polymyalgia rheumatica (PMR), psoriasis]. Two-sample Mendelian randomisation (MR) evaluated potential causal relationships in both directions. Linked electronic health records from CPRD (N = 11,042,985; age ≥40 years) were used to assess longitudinal disease trajectories, prognostic consequences, and mediation by potentially modifiable or treatable factors.

We found evidence for bidirectional relationships between COPD and RA/OA (ORs 1.10–1.19) and between asthma and RA/OA (ORs 1.03–1.14). COPD genetic liability also increased PMR risk (OR 1.14, 95% CI 1.03–1.25). Psoriasis liability increased risk of COPD (OR 1.04, 95% CI 1.02–1.07) and asthma (OR 1.05, 95% CI 1.03–1.08).

Across disease pairs, the median interval between first and second diagnoses was 5–13 years, indicating a substantial window for intervention. Obesity, smoking, hypertension, and thyroid conditions were risk factors common across all studied conditions. Mediation analyses suggested reduced physical activity and lipid changes partially contributed to the onset of respiratory disease following MSK conditions. Colocalisation identified genetic variants causal for specific condition pairs (implicating genes *IFIH1*, *APOE*, and *CXCR5*), highlighting inflammatory and lipid pathways.

Conclusions

MSK and respiratory conditions commonly develop sequentially over many years. Targeted strategies promoting physical function, optimising lipid and cardiovascular risk management may help delay or prevent multimorbidity progression.

Introduction

Musculoskeletal (MSK) conditions are common worldwide: at least 7.6 million people have rheumatoid arthritis (RA) [1] and 595 million people have osteoarthritis (OA) [2]. Respiratory diseases are also widespread with an estimated 262 million people affected by asthma [3] and 174 million by chronic obstructive pulmonary disease (COPD) [4]. COPD is responsible for approximately 3.5 million deaths annually [5].

We previously identified genetic overlap between pairs of MSK and respiratory conditions, indicating potential shared mechanisms (e.g., genetic correlation between RA and COPD is 35%, (95% CI 27–43) [6]. People with RA were also 80%, (95% CI 75–84) more likely to have COPD compared to those without RA after adjusting for age and sex. The co-occurrence of multiple long-term conditions, multimorbidity, is associated with higher mortality rates [7] and reduced quality of life [8]. Some combinations of respiratory and MSK conditions could lead to

worsening prognosis. Understanding the causality of the condition relationships and clarifying these prognostic differences could help prioritise cases for screening and intervention.

Multimorbidity studies have largely examined broad patterns of disease without informing specific interventions [9]. In turn, studies that do investigate risk factors either focus on single disease impact [10] or multimorbidity counts that are agnostic to specific combinations of diseases [11]. Disease onset can lead to barriers to maintaining a healthy lifestyle, for example, pain in OA [12] and RA [13] and breathlessness in COPD [14] can reduce the ability to exercise. Reviews on interventions for multimorbidity call for targeting patient-centred outcomes such as physical activity (PA) and disease-specific interventions relevant to multimorbidity [15]. Distinct clinical windows for intervention opportunities may exist: 1) before first disease onset, 2) between onset of a first and a second disease, and 3) after multimorbidity is established, each potentially requiring unique intervention strategies. Here, we focus on identifying potential interventions to prevent, delay or treat multiple long-term conditions. We use Mendelian randomization to identify which genetically linked disease pairs and risk factors are most likely to be causal, and therefore promising targets for intervention and mediation analyses in observational data.

To explore intervention opportunities, we prespecified the following causal questions: (1) Do causal relationships exist between musculoskeletal (MSK) and respiratory conditions? (2) Are there identifiable windows for intervention? (3) Which combinations of conditions lead to the worst prognosis? (4) Which modifiable risk factors can be targeted to prevent future disease, including those that may mediate the onset of a second condition after the first? and (5) Are there shared biological pathways that could inform drug repurposing for multimorbidity? We used two-sample Mendelian randomization (MR), which under specific assumptions estimates causal effects of genetically proxied exposures on outcomes, to test causal relationships between diseases and risk factors, and population-representative electronic health record data to examine temporal relationships and prognosis.

Methods

Data sources

We investigated pairs of diseases that included respiratory and MSK associated conditions that we have previously found to be genetically correlated (**Supporting information Table S1**). Respiratory conditions included COPD and asthma, and MSK associated conditions include polymyalgia rheumatica (PMR), OA, RA, and psoriasis, which can be associated with psoriatic arthritis. Code lists for diseases are available at Murrin *et al*.[1].

Genetic associations with disease outcomes were identified from our meta-analyses of 72 long-term conditions in the GEMINI research collaborative using two large cohort studies: UK Biobank (N = 502,000) [16], FinnGen (release 9; N = 377,000) [17] and condition-specific consortium data when available [6]. These summary statistics are available from (https://doi.org/10.5281/zenodo.14284046).

We also used summary statistics of recently published GWAS from leading consortia for ten potential risk factors: BMI [18], waist-hip ratio [19], cholesterol (LDL, HDL, triglycerides) [20], educational attainment [21], smoking status (ever smoked, and separately smoking intensity in smokers) [22], alcohol consumption [22], and PA [23].

Observational data were analysed from the UK Clinical Practice Research Datalink Aurum (CPRD) [24]. We replicated the observed near causal time-to-event analyses (described below) in the Spanish Information System for Research in Primary Care (SIDIAP) [25]. Data included N = 11,046,182 CPRD (2010–2020) and N = 2,625,989 SIDIAP (2013–2020) registered patients over 40 years of age. Clinical records in CPRD codes are a mixture of Read v2 Codes, EMIS and SNOMED while in SIDIAP they are recorded using the International Classification of Disease, version 10 (ICD-10).

We ascertained 26 variables to be tested as potential covariates in observational pairwise analyses. These variables include diseases, lifestyle and demographic variables, health biometric data and biomarkers. Potentially relevant disease comorbidities were ascertained using the GEMINI code lists (**Supporting information Table S2**). Deprivation was measured using CPRD-linked data (Townsend Index of Multiple Deprivation 2019) [26]. Biometric and biomarker covariates were ascertained using code lists and data cleaning protocols adapted from the "EHRBiomarkr" package (https://github.com/Exeter-Diabetes/EHRBiomarkr) [27]. Biometric variables such as blood pressure are frequently missing not-at-random in routine electronic health records [28]. Continuous variables were categorised according to clinically relevant cut-offs (**S2**) and analysed as nominal categorical variables, with missing values retained as an explicit category ("unknown") to preserve sample size and reflect potential informativeness of missingness.

Ethics

This study was approved by the relevant ethics committees:

UK Biobank: North West MREC (11/NW/0382), Application 14631. CPRD ISAC: 23_003109. SIDIAP Scientific and Ethical Committees: 19/518-P (18/12/2019). All analyses used anonymised data.

Mendelian Randomisation:

We used two-sample Mendelian randomisation (MR) methods to estimate the bidirectional causal effect between each respiratory and MSK condition, and to estimate the causal effect of potential risk factors on respiratory and MSK conditions (**S2**). Mendelian randomization (MR) analysis can estimate the causal effect between an exposure and an outcome by using genetic variants as instrumental variables, thereby minimizing bias from confounding and reverse causation present in conventional observational studies. Selected genetic instruments were 1) strongly associated with the exposure ($p < 5\times10^{-8}$), 2) common (minor allele frequency [MAF] > 0.1%), and 3) independent ($r^2 < 0.01$). Due to GWAS data availability analyses included participants genetically similar to the 1000 Genomes project European (EUR) subset [29].

Analyses were performed using the TwoSampleMR R package v0.6.15 [30]. Multiple sensitivity analyses were performed after a primary analysis using inverse variance weighted (IVW) regression, including the weighted median and weighted mode estimators, and MR-Egger. We assessed instrument heterogeneity using Cochran's Q statistic and applied Radial MR to identify pleiotropic outliers [31, 32] and Steiger filtering to remove variants with greater effect on the outcome than on the exposure [33]. Detailed MR rationale is available from Voller et al., [34].

A second MR analysis excluding the human leukocyte antigen (HLA) region was performed to reduce the influence of highly pleiotropic variants, considering that many pairs of conditions included one or both with

autoimmune components. MR results for disease relationships are reported as odds ratios, denoting the change in risk of the outcome based on a doubling of genetic liability to the exposure disease [35]. Multivariable MR (MVMR), including a Q-minimisation estimate, which is more robust against conditionally weak instruments [36], assessed whether the effects of genetic liability to each disease were robust when accounting for correlated risk factors [37] (**see supplemental material-MR Method overview).**

This study complied with the STROBE-MR guidelines for reporting MR [38].

Observational Analyses

Observational Near-Causal Inference Models

We estimated "near-causal" effects, defined as associations that approximate causal effects. We worked under the assumption that conditions of exchangeability (or 'no confounding') were met by matching and weighting exposure groups on important confounders, while acknowledging that residual bias may remain [39].

Longitudinal analyses assessed the effect of disease A on the subsequent incidence of disease B. For everyone with disease A (the exposed group), the index date was defined as the earliest date of (1) reaching age 40 years, (2) GP registration date, or (3) the date of diagnosis with disease A.

A control group free from both diseases at the index date was matched 1:1 on age and sex (**Supporting Information Tables S3–S4**).

Propensity scores (*p*) were estimated using logistic regression models including covariates significantly associated with outcome disease B [40]. Overlapping weights [41] derived from these scores were applied to balance differences in baseline characteristics between exposed and control groups:

$$w_i = (1 - p_i) + (1 - A_i)\, p_i, \text{ Where } A_i = 1 \quad (has\ disease\ A)$$

We used overlap-weighted Cox proportional hazards models to estimate the association minimally confounded by measured covariates between prior disease A and incident disease B in the overlap population.

Prognostic Consequences

We compared mortality rates between those with disease A, disease B, and both (A&B), using people without either disease as the reference group. The index date for exposed individuals was the earliest of reaching age 40 years, CPRD registration, or diagnosis with the target condition(s), with the date of the second diagnosis used for those with both conditions (A&B group). The multimorbid group was matched 1:1 to single disease groups on age, sex, and calendar year of index date. A single control individual without either disease was then matched on age and sex and shared across the three exposed groups. This strategy allows us to directly compare hazard ratios (HRs) between multimorbid and single condition groups [42]. Each control was assigned the index date of their matched multimorbid case (**Supporting Information Table S5**). During the analyses we separated the A&B group by order of disease diagnosis (i.e., A before B and B before A).

Mortality was defined as the earliest date from the Office for National Statistics (ONS) death registration and CPRD AURUM data using an algorithm prioritising ONS death dates with a higher match rank [43]. Cox proportional hazards models estimated the risk of 10-year incident all-cause mortality. LASSO-penalised Cox

regression with cross-validation with 10 folds selected covariates from 26 potential variables (**S2**) based on non-zero coefficients at the optimal *lambda* [44].

The number of hospitalisations (1 year of follow-up) for all admissions and unplanned admissions were extracted from the CPRD-linked hospital episode statistics admitted patient care. Negative binomial models compared counts across groups. These models were adjusted for relevant covariates identified using 'glmnet' LASSO regression variable selection [44].

Disease sequences and the window for intervention

We examined temporal trajectories to characterise the diagnostic sequence between respiratory and MSK conditions. For each disease pair, we estimated the proportion of individuals diagnosed with A then B and vice-versa, the mean age at diagnosis, and the mean and median times between diagnoses. The mean and median time between conditions were considered as a potential window for intervention. The standard deviation (SD) and interquartile ranges (IQR) were reported.

Risk factor prioritisation

We prioritised risk factors that were precipitated by or exacerbated by the first condition and that could be targeted within the intervention window. A time-to-event mediation analysis estimated the proportion of the observed relationship (e.g., A leading to B) that is explained by a risk factor. Candidate mediators were selected based on: 1) MR evidence that condition A influences the mediator (**Supporting information Tables S6**), and 2) a Z test comparing the adjusted and unadjusted observed odds ratio of the disease pair relationship (**Supporting information Tables S7**) [45].

This time-to-event mediation analysis is an extension of the near causal inference analyses in CPRD described above and shown in Table 1 [41],[46]. The candidate mediator is excluded from the propensity score. Mediator values were defined using the first recorded measurement after the index date; individuals with missing mediator data were excluded.

Table 1

causal relationships and consequences of asthma- MSK multimorbidity pairs: In causality analyses, "→" denotes the direction of the causal effect tested; in consequence analyses, it indicates the sequence of diagnoses ("then"). Mendelian randomisation (MR) results are expressed on the exp(b × $\log_2$) scale, representing the risk associated with a doubling of genetic liability to the exposure disease. Observational near-causal estimates indicate risk of disease onset within 10 years of follow-up. For consequences, mortality estimates reflect 10-year mortality risk. Incidence rate ratios (IRRs) compare hospitalisation rates per person-year between groups during the first year of follow-up. All hazard ratio (HR) and IRR estimates are relative to individuals with neither condition. MR results are shown with and without HLA (chr6:25–34 Mb); attenuation after HLA exclusion suggests auto-immune related pleiotropy and causal estimates should be treated with caution.

		Causality Estimates				**Consequences**		
Pair	**Variable**	**IVW MR (OR)**	**IVW MR (no HLA) (OR)**	**CPRD (HR)**	**SIDIAP (HR)**	**Mortality CPRD (HR)**	**All Hosp (IRR)**	**Unplanned Hosp (IRR)**
Asthma OA	Only OA	-	-	-	-	0.95 (0.94–0.97)***	1.27 (1.25–1.29)***	1.13 (1.1–1.15)***
	Only asthma	-	-	-	-	1.38 (1.36–1.4)***	1.25 (1.24–1.27)***	1.49 (1.47–1.52)***
	asthma → OA	1.03 (1.02–1.05)***	1.03 (1.01–1.05)***	1.36 (1.34–1.37)***	1.21 (1.18–1.25)***	1.12 (1.10–1.14)***	1.51 (1.49–1.54)***	1.55 (1.52–1.58)***
	OA → asthma	1.14 (1.09–1.19)***	1.14 (1.08–1.19)***	1.54 (1.49–1.58)***	1.29 (1.25–1.33)***	1.11 (1.09–1.14)***	1.45 (1.42–1.48)***	1.55 (1.51–1.59)***
Asthma PMR	Only PMR	-	-	-	-	1.09 (1.04–1.14)***	1.23 (1.18–1.28)***	1.26 (1.19–1.33)***
	Only asthma	-	-	-	-	1.31 (1.26–1.36)***	1.21 (1.16–1.26)***	1.45 (1.38–1.53)***
	asthma → PMR	1.01 (0.95–1.08)	1.03 (0.96–1.1)	1.38 (1.33–1.43)***	1.21 (1.1–1.33)***	1.33 (1.27–1.39)***	1.42 (1.36–1.48)***	1.73 (1.64–1.83)***
	PMR → asthma	1.02 (0.98–1.07)	$	1.36 (1.26–1.47)***	1.05 (0.87–1.27)	1.36 (1.28–1.45)***	1.25 (1.16–1.34)***	1.61 (1.48–1.76)***
Asthma RA	Only RA	-	-	-	-	1.61 (1.53–1.7)***	1.64 (1.56–1.71)***	1.53 (1.44–1.63)***
	Only asthma	-	-	-	-	1.30 (1.23–1.37)***	1.24 (1.18–1.30)***	1.53 (1.43–1.62)***

*p < 0.05, ** p < 0.01, ***p < 0.001, $ Analysis excluding HLA region not possible due to insufficient genetic instruments

		Causality Estimates				Consequences		
Pair	**Variable**	**IVW MR (OR)**	**IVW MR (no HLA) (OR)**	**CPRD (HR)**	**SIDIAP (HR)**	**Mortality CPRD (HR)**	**All Hosp (IRR)**	**Unplanned Hosp (IRR)**
	asthma → RA	1.19 (1.13–1.24)***	1.12 (1.07–1.18)***	1.48 (1.43–1.54)***	1.25 (1.08–1.45)**	1.87 (1.77–1.98)***	1.97 (1.87–2.07)***	2.14 (2.00-2.29)***
	RA → asthma	1.07 (1.05–1.1)***	1.07 (1.04–1.1)***	1.4 (1.31–1.49)***	1.35 (1.18–1.55)***	1.95 (1.82–2.08)***	2.09 (1.97–2.22)***	2.22 (2.05–2.41)***
Asthma psoriasis	Only asthma	-	-	-	-	1.29 (1.24–1.34)***	1.28 (1.24–1.32)***	1.54 (1.47–1.61)***
	Only psoriasis	-	-	-	-	1.17 (1.12–1.22)***	1.12 (1.09–1.16)***	1.12 (1.07–1.17)***
	asthma → psoriasis	1.05 (1.01–1.1)*	1.03 (0.99–1.08)	1.27 (1.24–1.31)***	1.11 (1.02–1.2)*	1.4 (1.34–1.47)***	1.42 (1.37–1.47)***	1.7 (1.62–1.79)***
	psoriasis → asthma	1.02 (1-1.04)*	1.05 (1.03–1.08)***	1.27 (1.23–1.32)***	1.12 (1.02–1.22)*	1.38 (1.32–1.45)***	1.37 (1.32–1.43)***	1.63 (1.54–1.72)***

*p < 0.05, ** p < 0.01, ***p < 0.001, $ Analysis excluding HLA region not possible due to insufficient genetic instruments

This approach separates the total effect of Disease A on Disease B into indirect and direct effects while accounting for censored time-to-event data [47]. The model reports the proportion of the effect explained by the mediator. P values were corrected for multiple testing using the Benjamini-Hochberg method for each disease pair [48]. Mediation analyses were performed using the R “mediation” package [49]. We do not report results where the direct and indirect effects have opposite directions as there is no clinically valid interpretation of the findings.

This study complied with the RECORD (Reporting of Studies Conducted using Observational routinely collected Data) statement [50].

Identifying shared genetic mechanisms

Colocalisation

For each combination of respiratory and MSK conditions, we identified the genome-wide significant variants ($p < 5\times10^{-8}$) shared by the disease pair. Starting with the variant with the smallest p-value, we defined regions of ± 250 kb around each variant, until all variants were assigned to a region. To investigate whether the disease pairs shared causal variants, we then performed statistical colocalisation using the “coloc.abf” function from the “coloc” R package (version 5.2.3) [51].

Coloc is a Bayesian method that computes posterior probabilities for five hypotheses (H0–H4) per genomic region; we focus on PPH4 (a single shared causal variant). For regions with strong evidence of a shared causal variant, coloc can identify possible variants and estimate the probabilities of each being the specific shared variant (referred to as SNP PPH4). We used the default prior probabilities: $p_1 = 1 \times 10^{-4}$, $p_2 = 1 \times 10^{-4}$, $p_{12} = 1 \times 10^{-5}$, where p_1 and p_2 are the probabilities that a random SNP in the region is causally associated with trait 1 or trait 2 respectively, and p_{12} is the probability that a variant is causal for both traits. These methods are described in further detail in Voller et al., [34].

Follow-up of shared signals

To assess whether circulating proteins play a role in the shared genetic architecture between disease pairs, we used proteomic data for 2,923 plasma proteins produced by the Olink platform in the UK Biobank pharma proteomic project (N = 48,195 European individuals) to identify whether colocalising variants were protein quantitative trait loci (pQTLs) ($p < 5x10^{-5}$) [52]. Variants within 1 MB of the encoded gene's transcription start site were classified as *cis*-pQTLs, all others as *trans*-pQTLs.

Where colocalisation supported a causal role of a protein in a trait-pair, we assessed the druggability of the protein (the likelihood that a protein can be targeted by an existing or developable drug), using DrugBank [53], and the Drug-Gene Interaction Database [54]. We highlighted cases where druggable proteins were targeted by existing or investigational therapies.

Results

We analysed data from individuals aged ≥ 40 years in CPRD (N = 11,042,985). At study entry, mean age was 55.9 years (SD 14.9) and 50.2% were women; deprivation was broadly distributed (IMD1 21.4%, IMD5 18.1%). We built age and sex matched cohorts for our time-to-event analyses.-In the near-causal time-to-event analyses, the mean age at index ranged from 52.6 years (asthma, excluding prior OA) to 77.3 years (PMR, excluding prior asthma) (**S3–S4**). The female proportion ranged from 23% (COPD, excluding prior OA) to 76% (RA, excluding prior COPD).

For participants in the prognostic consequences analysis, the mean age at index ranged from 55.3 years (asthma then psoriasis) to 78.1 years (PMR then COPD) (**S5**). Patients with asthma or COPD who later developed an MSK condition were more likely to be in the most deprived IMD quintile (IMD5)—up to 28.5%—whereas MSK patients without a lung condition generally showed similar deprivation to their matched controls; the lowest IMD5 proportion was among those with PMR but without COPD (9.2%).

For each long-term condition (LTC) pair—stratified by order of onset and by respiratory index disease e.g. asthma preceding MSK conditions—we report: (1) causal estimates from two-sample MR (Table 1–2; Supplementary Material – Comprehensive MR results, S8 Table), expressed as odds ratios (OR) per doubling of genetic liability (OR = exp(β × log 2)) The near causal observational estimates are reported in Tables 1:2; (2) disease trajectories and time between diagnoses derived from longitudinal EHRs (Figs. 1–2; S9 **Table**).

Table 2

causal relationships and consequences of COPD - MSK multimorbidity pairs: In causality analyses, "→" denotes the direction of the causal effect tested; in consequence analyses, it indicates the sequence of diagnoses ("then"). MR results are expressed on the exp(b × $\log_2$) scale, representing the risk associated with a doubling of genetic liability to the exposure disease. Observational near-causal estimates indicate risk of disease onset within 10 years of follow-up, while mortality estimates reflect 10-year mortality risk. Incidence rate ratios (IRRs) compare hospitalisation rates per person-year between groups during the first year of follow-up. All hazard ratio (HR) and IRR estimates are relative to individuals with neither condition. MR shown with and without HLA (chr6:25–34 Mb); attenuation after HLA exclusion suggests autoimmune related pleiotropy and causal estimates should be treated with caution.

		Causality Estimates				**Consequences**		
Pair	**Variable**	**IVW MR (OR)**	**IVW MR (no HLA) (OR)**	**CPRD (HR)**	**SIDIAP (HR)**	**Mortality CPRD (HR)**	**All Hosp (IRR)**	**Unplanned Hosp (IRR)**
COPD OA	Only COPD	-	-	-	-	2.22 (2.18–2.25)***	1.47 (1.44–1.49)***	1.92 (1.88–1.96)***
	Only OA	-	-	-	-	1.00 (0.98–1.01)	1.2 (1.19–1.22)***	1.11 (1.09–1.14)***
	COPD → OA †	1.1 (1.06–1.13)***	1.1 (1.06–1.13)***	1.11 (1.08–1.15)***	1.05 (1.02–1.08)**	1.79 (1.75–1.82)***	1.66 (1.63–1.7)***	1.99 (1.93–2.04)***
	OA → COPD	1.18 (1.13–1.24)***	1.19 (1.13–1.25)***	1.19 (1.16–1.21)***	1.05 (1.03–1.08)***	1.79 (1.76–1.82)***	1.63 (1.6–1.66)***	1.93 (1.89–1.98)***
COPD PMR	Only COPD	-	-	-	-	2.03 (1.94–2.13)***	1.31 (1.25–1.38)***	1.68 (1.25–1.38)***
	Only PMR	-	-	-	-	1.08 (1.03–1.13)**	1.11 (1.06–1.17)***	1.15 (1.06–1.17)***
	COPD → PMR	1.14 (1.03–1.25)**	1.14 (1.03–1.25)**	1.1 (1.02–1.19)*	1.03 (0.94–1.13)	2.08 (1.97–2.2)***	1.55 (1.46–1.64)***	2.14 (1.46–1.64)***
	PMR → COPD †	1.05 (1.02–1.08)**	$	1.2 (1.14–1.26)***	0.96 (0.84–1.11)	1.95 (1.85–2.06)***	1.56 (1.47–1.66)***	1.92 (1.47–1.66)***
COPD RA	Only COPD	-	-	-	-	2.22 (2.11–2.33)***	1.43 (1.36–1.51)***	1.95 (1.82–2.08)***
	Only RA	-	-	-	-	1.55 (1.47–1.64)***	1.38 (1.32–1.46)***	1.43 (1.34–1.53)***

*p < 0.05, ** p < 0.01, *** p < 0.001 † Estimate at least partially explained by another variable in MVMR (see supplementary MR document). PMR → COPD is completely attenuated by adjustment for asthma. COPD → OA attenuated by both asthma and BMI. OA ->COPD partially attenuated by BMI. COPD → RA partially attenuated by asthma. $ non-HLA analysis not possible because of insufficient number of instruments. COPD had no HLA instruments.

		Causality Estimates				Consequences		
Pair	**Variable**	**IVW MR (OR)**	**IVW MR (no HLA) (OR)**	**CPRD (HR)**	**SIDIAP (HR)**	**Mortality CPRD (HR)**	**All Hosp (IRR)**	**Unplanned Hosp (IRR)**
	COPD → RA †	1.2 (1.12–1.28)***	1.19 (1.11–1.27)***	1.87 (1.75-2)***	1.4 (1.2–1.64)***	2.7 (2.54–2.88)***	1.87 (1.74-2)***	2.61 (2.4–2.83)***
	RA → COPD	1.06 (1.04–1.09)***	1.1 (1.07–1.12)***	1.68 (1.6–1.76)***	1.45 (1.31–1.6)***	2.91 (2.75–3.07)***	1.95 (1.84–2.06)***	2.54 (2.37–2.73)***
COPD psoriasis	Only COPD	-	-	-	-	2.22 (2.14–2.31)***	1.57 (1.51–1.63)***	2.06 (1.96–2.16)***
	Only psoriasis	-	-	-	-	1.19 (1.15–1.24)***	1.08 (1.04–1.13)***	1.12 (1.07–1.18)***
	COPD → psoriasis	1.08 (1.01–1.15)*	1.08 (1.01–1.15)*	1.45 (1.34–1.57)***	1.26 (1.16–1.37)***	2.4 (2.28–2.52)***	1.54 (1.46–1.63)***	2.19 (2.05–2.34)***
	psoriasis → COPD	1.01 (0.99–1.03)	1.04 (1.01–1.07)**	1.37 (1.33–1.41)***	1.1 (1.04–1.17)**	2.21 (2.12–2.3)***	1.52 (1.45–1.58)***	2.04 (1.93–2.15)***

*p < 0.05, ** p < 0.01, *** p < 0.001 † Estimate at least partially explained by another variable in MVMR (see supplementary MR document). PMR → COPD is completely attenuated by adjustment for asthma. COPD → OA attenuated by both asthma and BMI. OA ->COPD partially attenuated by BMI. COPD → RA partially attenuated by asthma. $ non-HLA analysis not possible because of insufficient number of instruments. COPD had no HLA instruments.

We then report (3) the prognostic consequences of multimorbidity (Tables 1–2); (4) the risk factors implicated by MR for individual diseases (Table 3; S10 **Table**) and factors that become more relevant after a first condition and may mediate onset of a second condition (Fig. 3; S11 **Table**). Finally, we report (5) shared genetic architecture across disease pairs from colocalisation and proteomic analyses (**S12–S13 Tables**).

Table **3** **Risk factor causal effects on single diseases.** Odds ratios (Standard Error) for risk factors affecting the single-disease outcome (inverse-variance–weighted MR). Estimates are OR = exp(β) reported as per 1-SD increase for continuous exposures and per 1-unit increase in genetic liability for binary liabilities (diseases). Detailed results are in Supplementary Table 11. Red denotes OR>1 and blue OR<1. $p < 0.05$; * $p < 0.01$; ** $p < 0.001$.

Risk Factor	COPD	Asthma	RA	OA	PMR	Psoriasis
AF	1.03 (0.01)*	1.03 (0.01)***	1.01 (0.01)	1.00 (0.01)	1.03 (0.03)	1.02 (0.01)
Alcohol	0.99 (0.15)	1.13 (0.08)	1.12 (0.14)	0.99 (0.08)	1.09 (0.18)	1.18 (0.12)
BMI	1.51 (0.03)***	1.29 (0.02)***	1.34 (0.04)***	1.49 (0.02)***	1.21 (0.05)***	1.32 (0.03)***
Education	0.42 (0.03)***	0.78 (0.03)***	0.54 (0.05)***	0.75 (0.02)***	0.76 (0.07)***	0.71 (0.04)***
HF	1.09 (0.07)	1.14 (0.04)**	1.19 (0.05)***	1.00 (0.03)	1.07 (0.09)	1.06 (0.07)
Lipids-HDL	0.96 (0.02)	0.94 (0.02)***	0.94 (0.03)*	0.99 (0.01)	1.00 (0.05)	0.92 (0.03)**
Lipids-LDL	0.96 (0.02)	0.98 (0.02)	1.01 (0.03)	0.96 (0.01)**	1.07 (0.04)	1.05 (0.03)*
Lipids-Trig	1.03 (0.03)	1.01 (0.02)	1.01 (0.03)	1.00 (0.02)	1.03 (0.05)	1.09 (0.03)**
Phys. Activity	0.60 (0.09)***	0.81 (0.11)	0.57 (0.14)***	0.97 (0.09)	0.73 (0.24)	0.86 (0.13)
SBP	1.01 (0.00)***	1.00 (0.00)*	1.01 (0.00)**	1.00 (0.00)*	1.01 (0.00)*	1.00 (0.00)
Smoking-Ever	5.38 (0.13)***	1.63 (0.11)***	1.63 (0.15)**	1.37 (0.08)***	1.61 (0.24)	1.80 (0.14)***
Smoking-Num	2.95 (0.17)***	1.20 (0.07)*	1.17 (0.12)	1.06 (0.06)	1.14 (0.17)	1.07 (0.08)
WHR	1.44 (0.04)***	1.23 (0.03)***	1.29 (0.06)***	1.21 (0.02)***	1.24 (0.07)**	1.37 (0.05)***
Allergic rhinitis	1.32 (0.05)***	2.26 (0.06)***	1.08 (0.06)	0.99 (0.02)	1.04 (0.09)	0.93 (0.05)
Asthma	1.46 (0.02)***		1.30 (0.03)***	1.04 (0.01)***	1.10 (0.05)	1.13 (0.03)***
Coronary heart	1.05 (0.02)*	1.00 (0.01)	1.02 (0.02)	0.99 (0.01)	1.14 (0.04)***	1.09 (0.02)***
Type 2 Diabetes	1.05 (0.01)***	1.04 (0.01)***	1.03 (0.01)	1.02 (0.01)**	1.04 (0.02)	1.08 (0.01)***
Hypertension	1.17 (0.01)***	1.09 (0.01)***	1.09 (0.02)***	1.05 (0.01)***	1.10 (0.03)**	1.08 (0.02)***
Hyperthyroid	1.04 (0.01)***	1.14 (0.01)***	1.12 (0.02)***	1.03 (0.00)***	1.13 (0.03)***	0.89 (0.02)***
Hypothyroid	1.06 (0.01)***	1.05 (0.01)***	1.32 (0.02)***	1.02 (0.01)**	1.22 (0.03)***	1.08 (0.02)***
Obesity	1.32 (0.03)***	1.20 (0.02)***	1.17 (0.03)***	1.26 (0.01)***	1.16 (0.05)**	1.20 (0.03)***

Asthma preceding a MSK condition

Using genetics, we found evidence that asthma could lead to RA. Genetic liability to asthma was associated with increased risk of RA (OR per doubling of genetic liability = 1.19; 95% CI: 1.13–1.24; $p = 1.02\times10^{-12}$). This evidence remained robust in sensitivity analyses including radial MR and Steiger (**Supplementary Table 8)**, which removed variants in *IL33*, *IL1RL1*, *TSLP*, *IL6R*, *HLA-DQA1* (**Supplementary Material – Summary of instrument filtering).** This evidence remained robust after excluding all HLA instruments, although with a weaker effect size: OR = 1.12; 95% CI 1.07–1.18; $p = 1.981\times10^{-6}$.The genetic evidence after excluding HLA instruments was less strong for other MSK conditions. Genetic liability to asthma was modestly associated with OA (OR = 1.03; 95% CI 1.01–1.05; $p = 4.41\times10^{-4}$), whereas there was no clear evidence for an effect on psoriasis (OR = 1.03; 95% CI 0.99–1.08; p = 0.103) or on PMR (OR = 1.03; 95% CI 0.96–1.10; p = 0.390). Observational near-causal analyses with age- and sex-matched, propensity-weighted controls were directionally consistent (Table 1).

In observational data, asthma (median onset age 44 years, CPRD), preceded RA in 71.5% of pairs, OA in 74.6%, and psoriasis in 64.4%; (Fig. 1, S9). The median diagnostic interval is the time it took 50% of individuals to receive the second diagnosis. The median interval from asthma diagnosis to subsequent MSK diagnosis was 12.7 years for OA (IQR 6.0–21.8), 13.2 years for PMR (IQR 6.6–21.6), 12.7 years for RA (IQR 5.8–21.3), and 12.1 years for psoriasis (IQR 5.3–21.2).

MSK condition preceding Asthma

Genetic analyses indicated that MSK conditions increase asthma risk. All MR estimates excluded HLA-region variants, except for PMR where insufficient non-HLA instruments were available. Genetic liability to OA was associated with an increased risk of asthma (OR = 1.14; 95% CI 1.08–1.19; $p = 4.48\times10^{-8}$). RA showed a comparable association with asthma (OR = 1.07; 95% CI 1.04–1.10; $p = 1.86\times10^{-6}$), and psoriasis demonstrated a

weaker, directionally consistent effect (OR = 1.05; 95% CI 1.02–1.09; $p = 6.99\times10^{-6}$). There was no evidence of a causal effect of PMR on asthma. Observational cohorts showed consistent associations, with prior diagnoses of RA, OA, psoriasis, and PMR each increasing risk of incident asthma (HRs ~ 1.3–1.5). The median time from MSK diagnosis to subsequent asthma diagnosis was 5.1 years after PMR (IQR 2.2–9.3), 6.0 years after OA (IQR 2.6–11.5), 7.9 years after RA (IQR 3.2–15.5), and 9.1 years after psoriasis (IQR 3.7–18.3).

COPD preceding MSK condition

Genetic liability to COPD was associated with an increased risk of RA (OR = 1.19; 95% CI 1.11–1.27; $p = 3.93\times10^{-7}$) and PMR (OR = 1.14; 95% CI 1.03–1.25; $p = 9.89\times10^{-3}$). Genetic liability to COPD also increased risk of OA (OR = 1.10; 95% CI 1.06–1.13; $p = 4.00\times10^{-8}$) and showed a smaller association with psoriasis (OR = 1.08; 95% CI 1.01–1.16; $p = 3.51\times10^{-2}$). MVMR showed partial attenuation from asthma for the risk of COPD on RA and OA (**Supplementary Material** – **Additional Sensitivity analyses**). Observational analyses were directionally consistent (Table 2).

The median time from COPD diagnosis to subsequent MSK diagnosis was 4.7 years for OA (IQR 1.9–9.0), 5.5 years for PMR (IQR 2.4–10.3), 4.6 years for RA (IQR 1.7–9.2), and 4.6 years for psoriasis (IQR 1.8–8.7). (Fig. 2, S8).

MSK condition preceding COPD

Genetic liability to RA was associated with an increased risk of COPD (OR = 1.10; 95% CI 1.07–1.12; $p = 1.48\times10^{-14}$). Liability to OA was also associated with higher COPD risk (OR = 1.19; 95% CI 1.13–1.25; $p = 1.86\times10^{-11}$); multivariable MR suggested partial attenuation of this effect after adjustment for BMI (Supplementary Material—additional sensitivity analyses). A weaker association was observed for psoriasis (OR = 1.04; 95% CI 1.02–1.07; $p = 2.23\times10^{-3}$) which was only significant after excluding the HLA region. The risk of PMR on COPD could not be estimated without HLA instruments and the risk was attenuated by asthma in MVMR (**see Supplementary Material**). Observational analyses were directionally consistent (Table 2). The median time from MSK diagnosis to subsequent COPD onset was 7.9 years after OA (IQR 3.6–13.9), 5.4 years after PMR (IQR 2.3–10.3), 11.4 years after psoriasis (IQR 4.9–22.6), and 9.1 years after RA (IQR 3.8–17.0)

Prognosis of MSK and Respiratory multimorbidity

Across six of the eight respiratory–musculoskeletal combinations, individuals with two conditions had higher 10-year risks of mortality and more hospitalisation in one year compared with those with the corresponding respiratory disease alone (all $p < 0.001$). The exception was pairs involving OA (Tables 1–2).

For COPD multimorbidity, the greatest excess risk was observed for RA with subsequent COPD. Mortality was higher in the multimorbid group (HR 2.91; 95% CI 2.75–3.07; $p < 0.001$) than in those with COPD alone (HR 2.22; 95% CI 2.11–2.33; $p < 0.001$), and unplanned hospitalisations were also higher (IRR 2.54; 95% CI 2.37–2.73; $p < 0.001$ vs IRR 1.95; 95% CI 1.84–2.06; $p < 0.001$) (Table 1).

For asthma multimorbidity, the strongest effects were seen for RA with subsequent asthma. Mortality was greater in those with both conditions (HR 1.95; 95% CI 1.82–2.08; $p < 0.001$) than in those with asthma alone (HR 1.30; 95% CI 1.23–1.37; $p < 0.001$), and unplanned hospitalisations were also higher (IRR 2.22; 95% CI 2.05–2.41; $p < 0.001$ vs IRR 1.53; 95% CI 1.43–1.62; $p < 0.001$) (Table 2).

The order of diagnoses within the multimorbid groups generally made little difference to these prognostic estimates; where differences were observed, they were modest in size (HR/IRR differences ~ 0.1–0.2) and did not alter the overall pattern.

Risk factors and mediators: candidate targets for intervention

Risk factors for MSK Disease

Risk factor results are reported as ORs per 1 SD increase for continuous exposures and per 1-unit increase in genetic liability for disease.

Genetic liability to adiposity and smoking was consistently associated with higher MSK risk (BMI OR range 1.21–1.49, WHR 1.21–1.37, ever-smoking 1.37–1.80; all $p \leq 0.01$). The largest single effect was ever-smoking for psoriasis (OR 1.80; 95% CI 1.37–2.36; $p = 2.47\times10^{-5}$) (Table 3, S10). Higher educational attainment was protective across all four MSK outcomes (OR range 0.54–0.76; all $p < 0.001$). The strongest protective association was educational attainment for RA (OR 0.54; 95% CI 0.49–0.60; $p = 5.41\times10^{-35}$). Increasing HDL cholesterol was also protective for psoriasis (OR 0.92; 95% CI 0.86–0.98; $p = 9.52\times10^{-3}$), and higher PA was protective for RA (OR 0.57; 95% CI 0.44–0.74; $p = 3.90\times10^{-5}$).

Mediation analysis highlighted risk factors that become more relevant due to pre-existing disease and may speed up onset of a second associated disease (Fig. 3, S11). Mediation analyses show that reduced PA explains a proportion of the relationships between lung conditions leading to MSK conditions. Reduced PA in people with asthma partially explained the increased risk of OA (0.8%, $p < 0.001$), PMR (0.8%, $p = 0.048$) and psoriasis (0.7%, $p = 0.012$). Hypertension in people with asthma also mediated the development of PMR (3.2%, $p < 0.001$), while hypertension in people with COPD mediated a proportion of the risk of RA onset (0.1%, $p = 0.004$).

Risk factors for Asthma

Statistically significant risk factors spanned adiposity, smoking, allergy, and cardiometabolic traits (significant OR range 1.05–2.26; e.g., BMI 1.29; WHR 1.23; ever-smoking 1.63; hypertension 1.09; hyperthyroidism 1.14) (Table 3, S10). The largest single effect was allergic rhinitis (OR 2.26; 95% CI 2.01–2.54; $p = 1.69\times10^{-39}$). Higher HDL levels (OR 0.94; 95% CI 0.91–0.98; $p = 4.20\times10^{-4}$) and education (OR 0.78; 95% CI 0.74–0.82; $p = 3.27\times10^{-21}$) were protective of onset of asthma.

Obesity and cholesterol became more important in the context of multimorbidity (Fig. 3, S11). Obesity and cholesterol mediated the observed effect of MSK conditions on the onset of asthma. LDL level (Low LDL, 0.1%, $p < 0.001$) and weight gain (obesity 2.7%, $p < 0.001$) in participants with OA partially mediated the risk of asthma onset. Similar effects were identified for psoriasis (obesity 1.4%, $p = 0.004$) and RA (high LDL, 1.1%, $p = 0.032$) for asthma onset. Lastly, allergic rhinitis in participants with OA explain 3.5% ($p = 0.004$) of the onset of asthma.

Risk factors for COPD

Statistically significant risk factors included smoking, adiposity, and cardiometabolic traits (e.g., ever-smoking 5.38, cigarettes/week 2.95, BMI 1.51, WHR 1.44, hypertension 1.17; all $p \leq 0.001$) (Table 3, S10). The largest single effect was ever smoking (OR 5.38; 95% CI 4.17–6.93; $p = 1.18\times10^{-38}$). Protective factors included education and PA (OR range 0.42–0.60). The strongest protective factor was education (OR 0.42; 95% CI 0.39–0.45; $p = 8.11\times10^{-145}$).

Obesity became more relevant for COPD prevention in the context of pre-existing conditions (Fig. 3, S11). Obesity and cholesterol also mediated the causal effect of MSK conditions (except PMR) on onset of COPD [OA leading to COPD: low HDL 0.3%, $p < 0.0001$; RA leading to COPD: both low LDL (0.7%, $p = 0.004$) and high LDL (2.7%, $p = 0.048$); psoriasis leading to COPD: high triglycerides (0.6%, $p = 0.024$)]. Some cardiovascular diseases in participants with OA partially mediated the risk of COPD [coronary heart disease (3.7%, $p < 0.0001$); hypertension (0.4%, $p < 0.0001$)]. Limited PA in people with OA (3.5%, $p = 0.004$) and psoriasis (1.7%, $p = 0.012$) also mediated risk of COPD onset.

Colocalisation and shared biology

Colocalisation analysis identified shared variants for three multimorbidity pairs (**Supporting information S12 Table**).

For asthma–psoriasis, a variant on chromosome 2 (rs2111485) between the *FAP* and *IFIH1* genes had strong evidence of colocalising for both conditions (region PPH4 = 0.98, SNP PPH4 = 0.97). The effect allele (rs2111485 A) had opposite directions of effect for risk of asthma ($\beta = 0.031$) and psoriasis ($\beta = -0.066$), compared to the G allele. The variant is not a known cis-pQTL but is a trans-QTL for BST2 (Bone marrow stromal antigen 2), linked to IFN-induced antiviral host response. rs2111485 has appeared in many previous GWAS of autoimmune and inflammatory conditions, in addition to strong haematology (white blood cell) count associations (GWAS cataolog www.ebi.ac.uk/gwas Nov 2025). This variant is in strong LD ($R^2 = 0.95$) with rs1990760, a common *IFIH1* missense variant with a well-established link to type-1 diabetes [55]. Another region near the gene *IL7R* (region PPH4 = 0.99) showed weaker evidence for a specific variant (rs4594881, SNP PPH4 = 0.27) but with concordant directions.

For asthma–RA, the strongest signal was a variant (rs4938573) near the ~ 12kbp upstream of gene CXCR5 (region PPH4 = 0.94, SNP PPH4 = 1). rs4938573 is not a known pQTL but is a known eQTL for gene PHLDB1 (https://www.gtexportal.org/home/snp/rs4938573). UK Biobank participants carrying predicted loss-of-function variants in PHLDB1 had significantly reduced lung function (FEV1) and increased kidney diseases [56]. rs4938573 itself has appeared in a study in the GWAS catalog associated with neoplasm of mature B-cells [57]. There was weaker support evidence for variants in regions near ACOXL-AS1 on chromosome 2 (region PPH4 = 0.97, SNP PPH4 = 0.57 for rs77004761) and RUNX1 on chromosome 21 (region PPH4 = 0.97, SNP PPH4 = 0.53 for rs8129030).

For COPD–OA, rs429358 (in the *APOE* gene) had strong evidence of colocalisation (region PPH4 = 1.00, SNP PPH4 = 1 for rs429358), alongside weaker evidence near *BLK* on chromosome 8 (region PPH4 = 0.92, PPH4 = 0.12 for rs2409799). The *APOE* variant was found to be a cis-pQTL for APOE itself, and a *trans*-pQTL for 24 proteins including LEP (leptin), FBP1, and NCAN. Existing drugs targeting these proteins include lovastatin, gemfibrozil, and carvedilol (lipid and cardiovascular modulation), cyclosporine and tacrolimus (immunosuppressants), and valproic acid (neuroinflammation) (**Supporting information S13 Table).**

Discussion

We used large genetic and EHR datasets to elucidate causal relationships between respiratory and musculoskeletal conditions, highlighting shared risk factors and diagnostic sequences. These findings provide insights into disease trajectories and suggest opportunities for preventive interventions to delay the onset of subsequent conditions.

MR suggested that some conditions share bidirectional relationships. Our findings support asthma as a causal factor for RA, consistent with higher rates of RA in individuals with childhood asthma [58]. The literature is sparse on evidence of RA causing asthma; however RA treatment may drive asthma exacerbations [59]. There is previous work showing COPD increases risk of RA [60]; sero-positive RA in particular is related to COPD [61]. MVMR suggests that OA and COPD appear to be related via shared associations with BMI and asthma [62].

Other associations appeared unidirectional. We identified a potentially novel causal link between COPD and the onset of PMR. A possible mechanism is through susceptibility to infections, as PMR has been observed to have a seasonal pattern [63]. Although there was initial evidence for PMR causing COPD, further analysis with MVMR suggested this was mediated by overlap with asthma [64]. There was weak evidence for psoriasis being implicated in both lung conditions; psoriasis is known to associate with multiple conditions through pleiotropy [65].

Having both MSK and respiratory conditions is associated with higher mortality and hospitalisation rates, particularly for individuals with COPD and RA [66]. Preventing the onset of the second disease in an LTC pair provides opportunities for more targeted approaches that may extend survival and quality of life [66].

The median time between first and second diagnosis (the time by which 50% of the group had been diagnosed with the second disease) ranged from 5.5 years (COPD leading to PMR) to 13.2 years (asthma leading to PMR). Asthma often precedes the studied MSK conditions by over 10 years. Similarly, COPD often occurs an average of eight or more years after MSK conditions. These intervals reveal prolonged intervention windows to prevent progression to multimorbidity.

Shared risk factors across respiratory and MSK conditions included smoking status [67], obesity (e.g. BMI and waist-hip ratio) [68, 69], education level [70], and prior diagnosis of hypertension [71], hyperthyroidism and hypothyroidism. Thyroid dysfunction, including hyperthyroidism and hypothyroidism is known to be associated with respiratory impairment and MSK disorders [72, 73].

Mediation analyses showed that some risk factors emerged or gained importance in individuals diagnosed with the first disease of the pair, contributing to the onset of subsequent conditions. However, the estimated proportions mediated were small, indicating that most of the association likely operates through other pathways and these findings should be interpreted cautiously. PA is an example. For pairs with asthma as the first condition, low PA, possibly due to avoidance of respiratory symptoms [74], explains part of its causal relationship with the incidence of PMR and psoriasis. Including PA as part of treatment plans for asthma should improve asthma symptoms [75] and reduce the risk of some comorbidities [76]. People with asthma who regularly exercised developed OA faster, which may result from an interaction with a negative effect of corticosteroids on bone health and consequent wear and tear during activity [77]. Hypertension was a relatively strong mediator between asthma and PMR. Asthma has been found to increase the risk of primary hypertension; the replacement of long acting beta agonists with biologics has been suggested for individuals for whom asthma medications may have contributed to the onset of hypertension [78].

Among those with MSK conditions, some risk factors increased susceptibility to later respiratory disease LDL cholesterol emerged as a context-dependent mediator, with both low and high LDL contributing to respiratory multimorbidity. Low LDL in those with RA —consistent with the 'RA lipid paradox' [79] - mediated the onset of COPD. In RA, low LDL (often during active phases of the disease) reflects heightened systemic inflammation

rather than favourable lipid status. Low LDL had been previously identified as a potential risk factor for COPD exacerbations [80]. A potential mechanism is reduced delivery of lipid-soluble antioxidants to airway tissues, promoting oxidative stress [81]. At the same time, high LDL also mediated COPD onset after RA, indicating that traditional cardiometabolic pathways may additionally contribute to respiratory risk in some individuals with RA. Obesity was an important factor in developing respiratory conditions after a MSK condition. Reduced mobility, chronic pain, and medications can lead to weight gain [82], which in turn can affect lung mechanics and general inflammation, triggering the onset of asthma and COPD [83].

We found genetic overlap between asthma and psoriasis, asthma and RA, and COPD and OA. We identified a shared causal variant between asthma–psoriasis near to gene *IFIH1* (rs2111485), where the A allele reduced risk for psoriasis yet increased risk of asthma [84]. *IFIH1* encodes protein MDA5 (melanoma differentiation-associated protein 5), involved in immune activation following virus detection. Our apparently discordant results may therefore reflect the antiviral role of MDA5, where variants that dampen interferon signalling can protect against autoimmune activation while increasing vulnerability to viral-triggered asthma [85]. The variant is co-inherited with a common MDA5 amino-acid-modifying variant (rs1990760) with a well-established link to type-1 diabetes [55] For COPD and OA the known *APOE* e4 genetic variant (rs429358) had a high probability of being causal for both conditions. The variant is highly pleiotropic, affecting risk for Alzheimer's disease, lipid levels, and cardiovascular traits. There are limited studies on many of the drugs associated with the shared protein pathways. In vitro evidence has shown valproic acid (normally an anti-epileptic) to reduce smoking-induced inflammation [86] and to repair damage in an inflammatory environment modelled on OA [87]. Future studies are needed to confirm the causal pathways, associated protein targets, and disease risk. There are also significant issues with valproate and teratogenicity, and use is highly restricted in those aged less than 55 years, which would limit its use clinically [88]. There was also some evidence for a colocalised variant in *BLK* (rs2409797). The variant is known to affect other proteins that are targets of existing drugs, such as fostamatinib. Fostamatinib is currently used to treat chronic immune thrombocytopenia, and some evidence shows success for treating OA in model organisms [89]. However, this drug is associated with numerous side effects [90].

This study has limitations related to data availability. The genetic analyses are limited to common genetic variants in participants of European genetic ancestry. Future work including other genetic ancestries and population representative data is required to get the full picture. Mendelian randomisation studies using instruments from the HLA region should be treated with caution given the extensive correlation between variants and with multiple conditions. The observed diagnosis trajectories may not accurately reflect patient experience of disease onset; there may be greater delays in diagnosis and accessing health care for MSK conditions compared to respiratory conditions. Due to limited data collection on risk factors in CPRD, the percentage mediated by risk factors is likely underestimated. The lack of granularity in smoking data means that the relationship between diagnosis with a disease and smoking behaviour often showed inconsistent mediation. In these cases, a mediation effect cannot be estimated even if present. There is likely to be residual confounding in observational analyses from unmeasured confounders.

Intervention, focusing on preventing or delaying a second potentially genetically and thus innately driven chronic condition likely requires a multidisciplinary strategy [91, 92]. Optimised pharmacological management, including appropriate use of inhaled therapies for respiratory disease and analgesics, or disease-modifying agents for musculoskeletal disorders, is equally critical [93, 94]. The risk factors identified have highlighted gaps in current understanding of how strategies for cardiovascular prevention, such as statins, impact patients with RA [79] and

how blood pressure medications impact those with asthma [78]. We showed that physical activity has a strong association with onset of multimorbidity, suggesting that in individuals with respiratory or MSK conditions structured activity programmes, particularly supervised exercise training, could mitigate risk of a future additional long-term comorbidity [95].

Overall, our findings indicate individuals diagnosed with a respiratory or MSK condition have increased genetic risk of a subsequent condition and represent a key target for intervention to delay multimorbidity. Further research is required to directly evaluate the effectiveness of specific preventive strategies during key intervention windows — both prior to and between the onset of diseases. Future research could also test therapeutic targets along the pathways connecting shared risk factors such as smoking, BMI, and inflammation to cellular damage and ageing to determine whether they can prevent downstream disease [96].

Declarations

Ethics Approval and Consent to Participate

This study used anonymised, routinely collected health data from CPRD, SIDIAP and UK Biobank, accessed under institutional agreements (see ethics section of methods for more details and protocol numbers).
Consent to Participate: Not applicable. Consent for Publication: Not applicable.

Consent for Publication

Not Applicable

Data Availability

The UK routine clinical data used in this study are available from CPRD. Access to CPRD data requires approval from the Medicines and Healthcare products Regulatory Agency's Independent Scientific Advisory Committee (ISAC). The data are not publicly available due to licensing restrictions, but researchers may apply directly to CPRD at the following link:
https://cprd.com/research-applications

The UK Biobank data used in this research were accessed under Application 14631. Researchers may apply for access to UK Biobank at:
https://www.ukbiobank.ac.uk/enable-your-research

The SIDIAP data used in this study are not publicly available. Access may be requested directly from SIDIAP at:
https://www.sidiap.org/index.php/en/solicituds-en

The GWAS summary statistics generated and/or used in this study, together with the diagnostic code lists used to define phenotypes, are openly available in our Zenodo repository:
https://zenodo.org/records/14284047

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Declaration of interests

SK's group has received funding support from Amgen BioPharma outside of this work. JB is a part time employee of Novo Nordisk Research Centre Oxford, limited, unrelated to this work. TF has consulted for several pharmaceutical companies. All other authors have no disclosures to declare.

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Figures

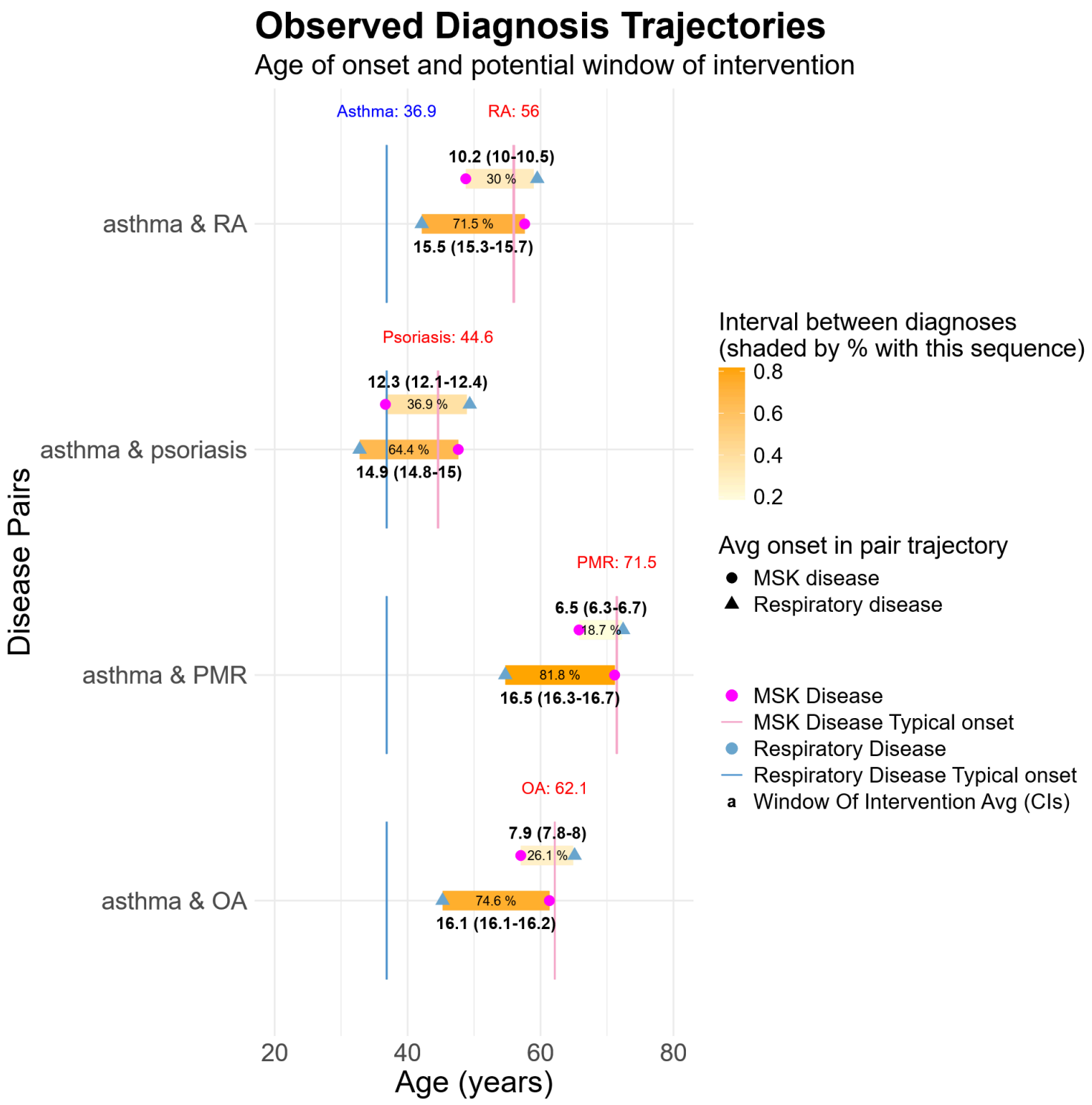

Figure 1

Observed asthma and MSK disease trajectories. Vertical lines show the overall mean age at onset in CPRD for each disease (i.e., across all patients with that disease, not limited to multimorbid pairs). Circles (MSK) and triangles (respiratory) mark the mean age at onset within the specific disease-pair trajectory (i.e., among patients who developed disease A then disease B). The horizontal segment spans the mean interval between the two diagnoses, with the number above or below the segment giving that mean interval. For visual clarity we plot means with confidence intervals; median ages and IQRs are reported in the main text and Supplementary Table S9.

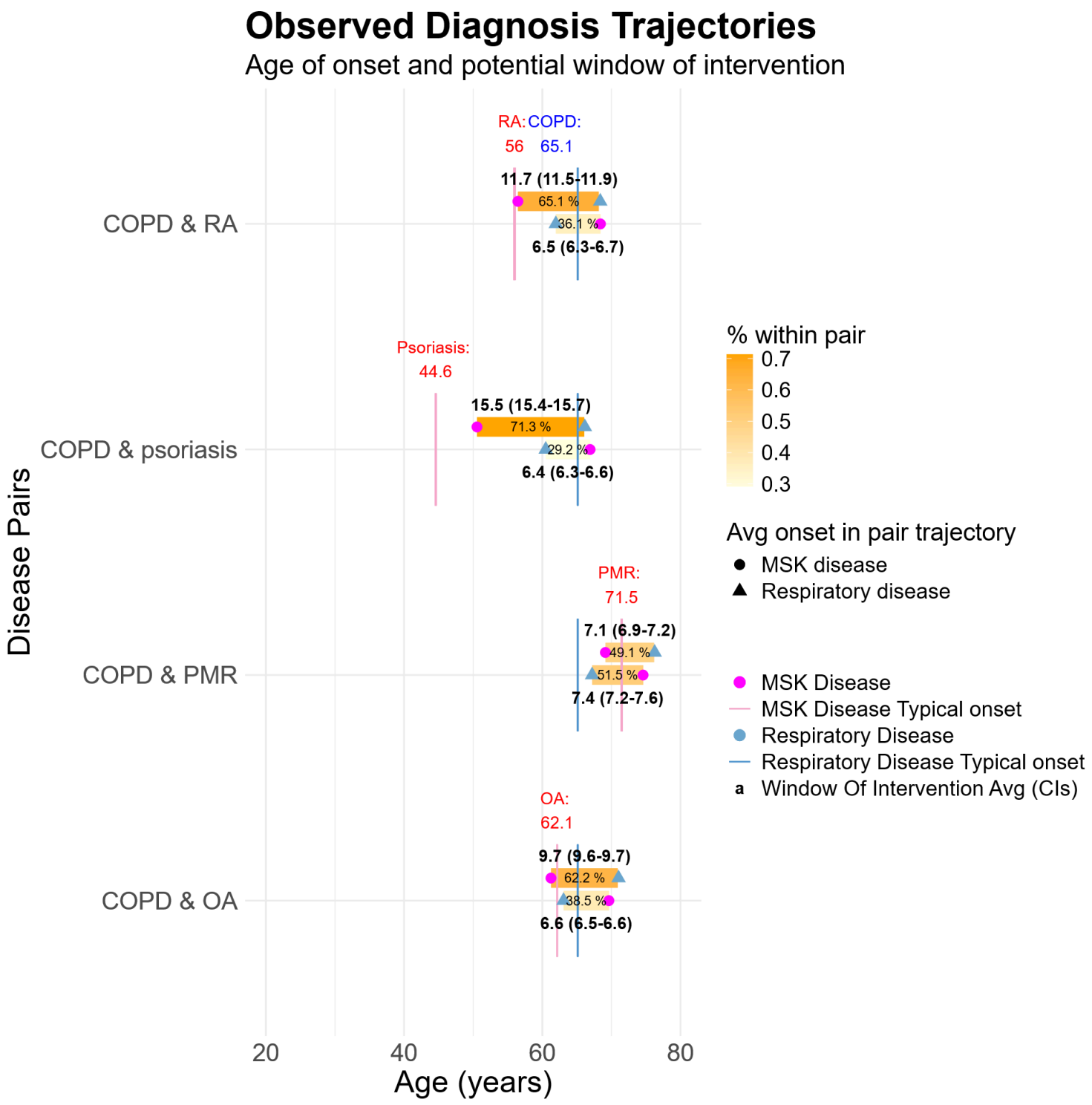

Figure 2

Observed COPD and MSK disease trajectories.
Vertical lines show the overall mean age at onset in CPRD for each disease (i.e., across all patients with that disease, not limited to multimorbid pairs). Circles (MSK) and triangles (respiratory) mark the mean age at onset within the specific disease-pair trajectory (i.e., among patients who developed disease A then disease B). The horizontal segment spans the mean interval between the two diagnoses, with the number above or below the segment giving that mean interval. For visual clarity we plot means with confidence intervals; median ages and IQRs are reported in the main text and Supplementary Table S9.

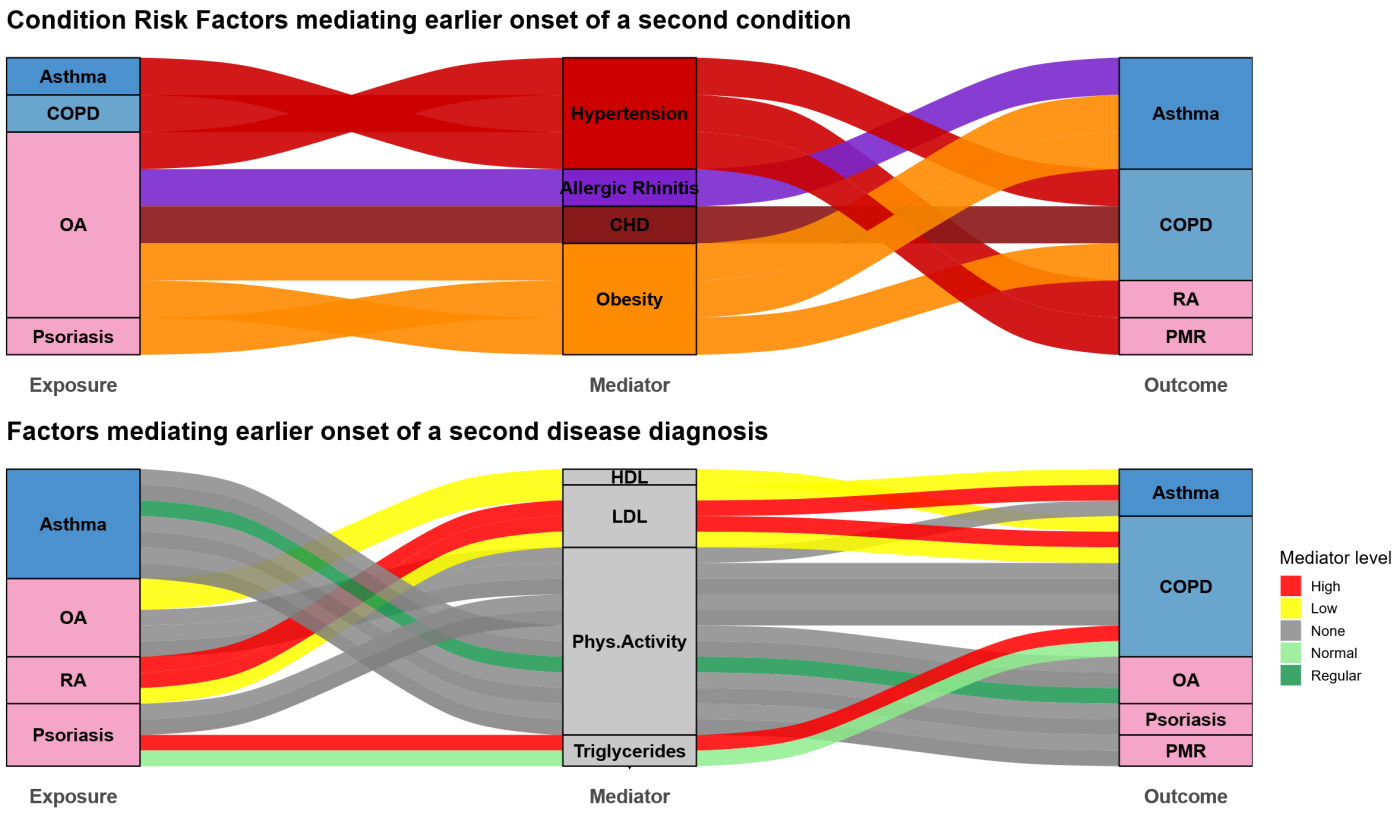

Figure 3

Summary of mediators that accelerate the onset of a subsequent condition. A single line denotes a statistically significant ($p < 0.05$) proportion mediated after correcting for multiple testing (percentage mediated is reported below and in S11.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementarymultimorbidityinterventions.xlsx
- BMCCOPDsupplementaryinfo.docx
- COPDstrobeMR.pdf
- RECORDObservationalChecklistCOPD.pdf