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Shared Genetic Risk Factors for MS/Psoriasis suggest involvement of IL17 and JAK-STAT signaling

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Objective: Psoriasis and multiple sclerosis (MS) are complex immune diseases that are mediated by T-cells and share multiple comorbidities. Previous studies have suggested psoriatic patients are at higher risk of MS; however, causal relationships between the two conditions remain unclear. Through epidemiology and genetics, we provide a comprehensive understanding of the relationship and shared molecular factors between psoriasis and MS.

Methods: We used logistic regression, trans-disease meta-analysis (TDMA) and Mendelian randomization (MR). Medical claims data was included from 30 million patients, including 141,544 with MS and 742,919 with psoriasis. We used GWAS summary statistics from 11,024 psoriatic, 14,802 MS cases and 43,039 controls for TDMA, with additional summary statistics from 5 million individuals for MR.

Results: Psoriatic patients have significantly higher risk of MS (4,637 patients with both diseases; $OR=1.07$, $p=1.2\times10^{-5}$), after controlling for potential confounders. Using inverse variance and equally weighted TDMA, we revealed more than 20 shared and opposing (direction of effect) genetic loci outside the MHC which show significant genetic colocalization (in COLOC and COLOC-SuSiE v5.1.0). Co-expression analysis of genes from these loci further identified distinct clusters which were enriched among pathways for IL-17/TNFα ($p<1.6\times10^{-3}$, $OR>39$) and JAK-STAT ($p=1.1\times10^{-5}$, $OR=35$), including genes such as *TNFAIP3*, *TYK2* and *TNFRSF1A*. MR found psoriasis as an exposure has a significant causal effect on MS ($OR=1.04$, $p=5.8\times10^{-3}$), independent of T1D ($p=4.3\times10^{-7}$, $OR=1.05$), T2D ($p=2.3\times10^{-3}$, $OR=1.08$), IBD ($p=1.6\times10^{-11}$, $OR=1.11$) and vitamin D level ($p=9.4\times10^{-3}$, $OR=0.75$).

Interpretation: By investigating the shared genetics of psoriasis and MS, along with their modifiable risk factors, our findings will advance innovations in treatment for patients suffering from comorbidities.

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Summary for Social Media If Published

What is the current knowledge on the topic?
Both psoriasis and multiple sclerosis (MS) are complex genetic diseases, and previous studies have illustrated that psoriatic patients are at higher risk of MS.

What question did this study address?
By using a multi-omic approach, we aimed to reveal shared genetic and genomic components for psoriasis and MS.

What does this study add to our knowledge?
Our trans-disease meta-analysis (TDMA) revealed multiple genetic loci shared between psoriasis and MS, highlighting the involvement of IL17 and JAK-STAT signaling.

How might this potentially impact on the practice of neurology?
A better understanding of the shared mechanisms between psoriasis and MS can advance our management for patients that suffer from one or both conditions.

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INTRODUCTION

Multiple sclerosis (MS), a chronic central nervous system disease that damages central nervous system myelin or white matter through immune dysregulation[1], is associated with multiple comorbidities and risk factors that can increase susceptibility and/or accelerate neurodegeneration[2,3], such as smoking, cardiovascular disease and low vitamin D. While receiving less attention, psoriasis, a complex chronic skin disease[4] associated with systemic inflammation[5], has been found to impose a higher (1.29 odds ratio[6]) risk of MS. Notably, the risk of MS increases with psoriasis severity[7]. Certain cytokines have been implicated in the pathogenesis of both psoriasis and MS, including IL-17[8,9], IFNγ[10,11] and TNF[12,13]. Clinical responses were observed in both diseases for IL-17 regulating drugs dimethyl fumarate[14,15] and secukinumab[16,17], as well as α4-integrin antagonist, natalizumab[18]; however, even though TNF inhibitors work well for psoriasis, they have been found to exacerbate MS[12]. Similarly, IFNβ is a common treatment for MS but can trigger psoriasis[19]. Until now, there has been limited study to discern the effects of shared genetic and modifiable risk factors on the psoriasis/MS comorbidity and how they are associated with the aforementioned cytokine signaling pathways. However, this is essential for understanding the mechanisms and identifying effective treatments for many patients suffering from both conditions.

Psoriasis and MS each have a substantial genetic component (~70% heritability for psoriasis[20] and 50-64% for MS[21,22]), with genetic signals from both diseases enriched among regulatory regions for $CD4^+$ and $CD8^+$ T-cells[1,4]. Infiltration of activated $CD4^+$/$CD8^+$ T-cells in the skin increases proliferation of keratinocytes to produce psoriatic plaques[23], while in MS, T-cells are involved in an inflammatory process that damages myelin nerve insulation[24]. Myelin-specific $CD4^+$ T-cells are over four times more abundant in MS patients than controls[25], and there is a 10-fold increase of dermal T-cells in psoriasis lesions compared to healthy skin[26]. Psoriasis and MS are both characterized by T_H1 and T_H17 cells[23,27], with T_H17 demonstrating greater ability to cross the choroid plexus (in MS) than other $CD4^+$ subsets[28], whereas in psoriasis, neutrophil extracellular traps (NETs) help enhance T_H17 induction[29]. Both diseases are associated with class I HLA alleles (e.g. *B*44* is protective for MS[30-32] and *C*06:02* increases the risk for psoriasis[33]), although the primary association for MS in the MHC is with class II HLA alleles (including DRB1*15:01)[34]. However, outside the major histocompatibility complex (MHC), little is known about the genetic components they share.

Psoriasis and MS have also been associated with overlapping modifiable risk factors. For instance, both are more prevalent in northern latitudes[35,36] and are connected with vitamin D deficiency[37,38]. There is evidence that vitamin D may be involved in modulating immune responses, including the activation of $CD4^+$/$CD8^+$ T-cells[39,40] and it has also been found to suppress IL-17 induction[41]. However, much remains to be known regarding its precise role in inflammatory diseases, such as psoriasis and MS[42]. In psoriasis, vitamin D analogs are regularly used as topical treatments[38], while there have been multiple inconclusive trials for its use as an oral supplement in MS[43,44]. Ultraviolet radiation is an effective treatment for psoriasis[45], and early trials suggest it may be beneficial for MS[46]. Obesity is another key risk factor for immune-mediated diseases in general[47], and previous Mendelian randomization studies have suggested it can causally affect both psoriasis[48] and MS[49]. Metabolic dysfunction resulting from obesity impacts the immune system[50], for example through the effect of adipokines on TNF[51]. Further modifiable risk factors reported by the literature include smoking[52,53], triggering events[54,55], infections[56,57] and the microbiome[58,59]. These risk factors should be taken into consideration when assessing the causal relationship between psoriasis and MS.

Understanding the pathophysiology of comorbidities is essential for precision medicine and optimal disease management, as it can provide clues to their underlying molecular mechanisms and common etiology. In this study, we conduct epidemiological analysis on a large medical claims dataset to reveal risk factors common to both diseases, and then we apply trans-disease meta-analysis to identify more than

20 shared genetic loci. Finally, we apply Mendelian randomization using genetic variants as instruments to establish a causal relationship between psoriasis and MS independent of their comorbidities and modifiable risk factors.

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METHODS

The genetic cohorts involved in both the psoriasis and MS GWAS were IRB approved (details in previous publications). The Optum Clinformatics® data was exempt from IRB approval.

Epidemiology

We investigated the association between psoriasis and MS, in the context of potential confounders, through an epidemiological analysis of 30,445,892 patients from Optum's deidentified Clinformatics® Data Mart[60]. All included individuals had a recorded year of birth, self-reported sex and race; the majority (75%) were White and just over half (55%) were female, with a mean age of 45 (at the most recent encounter) and mean enrollment (follow-up) of 5 years. The status of the following traits among the patients were evaluated by presence/absence of ICD-9/10 codes, as indicated in **Supplementary Table 1**: type 1 diabetes (T1D), type 2 diabetes (T2D), coronary artery disease (CAD), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), asthma, vitamin D deficiency, obesity / morbid obesity, smoking and alcohol use disorder (AUD). In total, our analysis included 141,544 patients with MS, 742,919 patients with psoriasis and 4,637 patients with both diseases.

Logistic regression was applied to medical claims data extracted for the years 2001 to 2018 from 30,445,892 patients in Optum's deidentified Clinformatics® Data Mart[60] (version 7.2). Patients were included that had a recorded year of birth (from which we calculated the age at most recent encounter), sex and race, then we added up the total enrollment periods, to give the total enrollment for each patient. Traits were ascertained by ICD-9/10 codes, as indicated in **Supplementary Table 1**, including obesity, smoking and alcohol use disorder, as no quantitative data on BMI, smoking or alcohol consumption was readily available.

Trans-disease meta-analysis (TDMA)

To compare genetic signals between psoriasis and MS, we performed trans-disease meta-analysis (TDMA) on GWAS summary statistics from psoriasis (11,024 cases, 16,336 controls) [61] and MS (14,802 cases, 26,703 controls) [1] cohorts. Meta-analyses were prepared as per the data collection and processing steps described in their respective GWAS[1,61]. We applied the standard fixed effects inverse variance weighted (IVW) approach[62] to meta-analysis summary statistics, and also implemented TDMA using an equally weighted combination[63] of effect sizes ($\beta_{Psor,CAD} = \frac{\beta_{Psor}+\beta_{CAD}}{2}$) and variances ($V_{Psor,CAD} = \frac{V_{Psor}+V_{CAD}}{4}$). Loci were considered independent if they are separated by >500kb or revealed through approximate conditional analysis (GCTA-COJO[64]), with the largest psoriasis cohort (11,675 cases and controls) being used as the reference dataset for LD computation. We also applied HESS[65] to identify locally correlated regions, using the European 1000 Genomes data provided with the software as reference, and the recommended partitions[66]. Colocalization analysis was performed using COLOC[67] and its SuSiE extension[68] on markers within ±100kb of each lead TDMA marker, with the same reference cohort as COJO.

Mendelian randomization (MR)

We applied MR to investigate potential causal relationships between psoriasis, MS and their comorbidities. We employed six different MR techniques (MR-PRESSO[69], MR-Egger[70], MR-Robust[71], MR-RAPS[72], MR-Median[73] and MR-Mode[74]) to provide confidence in the results, by minimizing the risk of spurious findings due to the weaknesses of any one approach. First, MR-PRESSO[69] was used to correct for horizontal pleiotropy by removing outliers, which addressed distortion for asthma ($p=0.012$), T1D ($p=0.002$) and RA ($p<3.3\times10^{-5}$) on MS. Then, the other techniques were used to test assumptions in different ways: MR-Egger[70] includes the intercept in its model; MR-Robust[71] uses Tukey's loss function for robust regression; MR-RAPS[72] accounts for variance in effect sizes and uses a random effects model;

MR-Median[73] and MR-Mode[74] control for heterogeneity by calculating weighted median- or mode-based estimates, respectively. We extracted genetic data from full GWAS summary statistics for 10 traits (**Supplementary Table 6**), in addition to psoriasis and MS. Genetic instruments were selected from the intersection of markers across traits, through LD clumping ($p \leq 1 \times 10^{-4}$, LD≥0.001, window size=10Mbp), using the European 1000 Genomes data as reference. The six different MR techniques were applied in univariable analysis, to estimate the causal effect of each trait on psoriasis and MS; and then we conducted multivariable analysis using GRAPPLE[75], by pooling the genetic markers from each trait.

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RESULTS

Epidemiology

Unlike psoriasis, MS was more strongly associated with female sex (**Table 1**; $OR=2.36$, $p=1.2\times10^{-4,323}$), and both MS and psoriasis had reduced prevalence in Asian ($OR=0.36$, $p=2.7\times10^{-513}$) and Hispanic ($OR=0.62$, $p=1.7\times10^{-488}$) patients, while psoriasis also had lower prevalence among Black patients ($OR=0.67$, $p=7.2\times10^{-1,693}$). Vitamin D deficiency ($OR=3.02$, $p=1.9\times10^{-368}$) had the strongest association for MS and was also associated with psoriasis ($OR=1.77$, $p=9.2\times10^{-8,302}$). The strongest association for psoriasis was RA ($OR=3.82$, $p=1.2\times10^{-21,815}$), which was also associated with MS ($OR=2.64$, $p=9.1\times10^{-1,792}$). Both MS and psoriasis were associated with AUD, smoking, asthma, T1D, T2D, CAD, IBD and morbid obesity. When including all covariates in a conditional model, the effect of psoriasis on MS was OR=1.07 ($p=1.2\times10^{-5}$), while the effect of MS on psoriasis was OR=1.10 ($p=9.4\times10^{-10}$).

Shared and opposing genetic loci

Table 2 shows the results of TDMA using fixed effects inverse variance weighted (IVW) meta-analysis, while **Supplementary Tables 2-3** shows the results using the equally weighted approach. TDMA signals with shared or opposing direction of effect are presented as circular Manhattan plot tracks (**Figure 1a** and **1b** for IVW, **Supplementary Figure 1a** and **1b** for equally weighted). In total, 22 and 20 genetic loci were identified for IVW and equally weighted approaches respectively (counting the major histocompatibility complex, MHC, as a single locus due to its complex linkage disequilibrium, LD) in which the TDMA lead marker was: *1)* genome-wide significant ($p<5x10^{-8}$) in TDMA; *2)* suggestively significant ($p<1x10^{-4}$) for each trait; and *3)* more significant in TDMA than in both traits. IVW and equally weighted approaches were highly concordant, with only two loci identified by each approach not by the other (two loci appear both shared and opposing in IVW). Indicated in **red** on **Figure 1a** and **1b** are 11 shared and 11 opposing loci, revealed using IVW TDMA, of which **Figure 2** illustrates two shared and two opposing loci using regional association plots. We then performed conditional analysis separately on psoriasis and MS outside the MHC using conditional and joint analysis (GCTA-COJO[64]) and applied the TDMA criteria to each independent signal identified, discovering an additional two shared and one opposing IVW TDMA locus (indicated in **blue** in **Figure 1**), of which one of the shared loci was identified by the equally weighted approach, leading to 27 independent TDMA signals across the three approaches (**Supplementary Figures 2-24**); we also confirmed seven shared and six opposing loci. **Table 2** and **Supplementary Tables 4-5** present the loci identified by TDMA and COJO, respectively.

We additionally evaluated broader genetic correlations between psoriasis and MS using Heritability Estimation from Summary Statistics (HESS)[65]. Three LD-independent regions[66] had significant correlation between psoriasis and MS (FDR≤5%): a chromosome 5 (157-159Mbp; $p=4.3\times10^{-17}$) and chromosome 10 (81-82Mbp; $p=8.6\times10^{-5}$) region, which encompass loci identified by our previous two approaches, and the adjacent chromosome 5 region (159-160Mbp; $p=1.3\times10^{-6}$), which does not. Marker rs72804018 from this region (**Table 2**) is in low LD (r^2=0.03, D'=0.32) with the shared locus 154kb upstream and meets our three criteria (MS $p=4.6\times10^{-7}$; psoriasis $p=1.8\times10^{-7}$; IVW TDMA $p=5.2\times10^{-13}$; equally weighted TDMA $p=4.6\times10^{-13}$), suggesting it may be a secondary signal.

Colocalization analysis

We investigated whether the shared and opposing loci colocalize to the same causal signals in psoriasis and MS, using COLOC[67] (**Supplementary Table 6**). 16 of the 25 non-MHC loci (identified by the three approaches) showed strong evidence of colocalization, with posterior probabilities ranging from 0.68 (for the opposing locus, centered on rs3843503 in chromosome 5) to 0.99 (for the rs9591325 shared locus in chromosome 13). For the remaining loci, we used the Sum of Single Effects (SuSiE) COLOC extension[68], which applies fine-mapping to provide more accurate inference by assuming the potential presence of multiple causal variants per locus. Significantly, all of the loci identified by the equally weighted TDMA

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approach had evidence (PP=1.0) of colocalization with SuSiE (**Supplementary Table 7**), and interestingly it was the secondary signal (i.e., rs72804018) identified by HESS that colocalized for the chromosome 5 locus. However, none of the additional loci from the GCTA-COJO analysis had evidence of colocalization, suggesting there may be different causal variants in psoriasis and MS.

To evaluate which TDMA loci might be explained by comorbidities, we retrieved full summary statistics from the largest available GWAS of European-ancestry individuals for each comorbidity. **Supplementary Table 8** presents the shared and opposing TDMA loci that had at least suggestively significant association with each trait. Traits with the most associated loci (e.g., RA, with 7 loci, and IBD, with 5 loci) are primarily mediated by immunology rather than modifiable risk factors. T1D (an autoimmune disorder) has 7 associated loci, whereas T2D (a metabolic condition) has none. The risk allele locus associated with the most traits, rs413024, is positively associated with IBD, T1D and RA. All but one of the risk alleles for the shared loci exhibit increased risk of the comorbidities, while for the opposing loci, psoriasis and MS impart increasing/decreasing risk on the same traits. These results suggest no one comorbidity dominates the genetic relationship between psoriasis and MS, with the loci instead pertaining to complex imbalances in systemic inflammation.

Functional analysis

Using H3K27ac marks for active enhancers in 33 different cell types[77], we conducted binomial enrichment tests to identify how the genetic signals can play regulatory roles in the specific cells involved in psoriasis/MS. **Supplementary Table 9** compares enriched cell types for the 23 equally weighted TDMA plus GCTA-COJO loci outside the MHC, against the 62 MS and 20 psoriasis genome-wide significant loci, identified from their respective GWAS outside these regions. Immune cells were the highest enriched among TDMA, psoriasis and MS loci, with stimulated Th17 cells ranking among the most enriched in each (TDMA $p=2.1\times10^{-8}$, MS $p=2.0\times10^{-12}$, psoriasis $p=0.011$). Other $CD4^+/CD8^+$ T-cell subsets were highly enriched in TDMA, including Th0 ($p=1.5\times10^{-8}$), Th1 ($p=1.4\times10^{-7}$) and $CD8^+$ memory T-cells ($p=6.3\times10^{-5}$). However, centroblasts were the most enriched cell type for TDMA ($p=7.7\times10^{-12}$), while they were less enriched in MS ($p=4.6\times10^{-7}$) and psoriasis ($p=0.038$), respectively. **Figure 1c** presents the H3K27ac active enhancer marks for B-cell centroblasts as a density plot, showing that regions of higher density (darker color on the plot) often co-occur with TDMA loci. We compared enrichments in TDMA against the other psoriasis and MS loci using binomial tests and found centroblasts to be the most significant cell type compared to psoriasis ($p=3.4\times10^{-5}$) and MS ($p=9.4\times10^{-4}$). As a sensitivity check, we repeated the enrichment analysis excluding the four TDMA loci identified using the conditional analysis approach (that did not colocalize) and found once again that centroblasts were more enriched in TDMA than the other psoriasis ($p=1.4\times10^{-4}$) and MS ($p=2.3\times10^{-3}$) loci. Interestingly, brain cell types were only significantly enriched (adjusting for FDR) among the TDMA loci, and not the MS- or psoriasis-only loci. Of these, mid-frontal lobe ($p=1.9\times10^{-4}$), hippocampus middle ($p=1.0\times10^{-3}$) and inferior temporal lobe ($p=1.1\times10^{-3}$) had the strongest enrichment.

Gene Co-Expression

Previous studies highlight the value of integrating gene co-expression networks with GWAS results to infer biological functions. Therefore, we utilized the L1000 assay perturbation experiment from NIH's Library of Integrated Network-Based Cellular Signatures (LINCS)[78] to understand the molecular network regulated by the TDMA loci. Links between these loci shown in **Figure 1d** indicate at least one gene from the first locus is co-expressed with a gene from the other. The opacity of each link is proportional to the log-scaled number of experiments in which the genes are co-expressed, such that pairs of loci with stronger evidence of connection are more clearly visible. As might be expected, links between the MHC and other loci are among the strongest; however, there are also connections between many of the non-MHC loci. For example, the 17q21.2 (*STAT3*, *STAT5A/B*) shared locus is highly connected with the 7p14.1 (*ELMO1*) shared locus (co-expressing in 642 experiments), while the 5q31.1 (*CSF2*, *P4HA2*)

opposing locus is highly connected with the 2p16.1 (*REL*, *PUS10*) opposing locus (in 505 experiments).

We inferred distinct groups of loci/genes from the log-weighted LINCS data by applying four different community detection algorithms (leading eigenvector, Louvain, optimal integer programming and spin-glass) in the iGraph software package[79]. Three co-expressing clusters (**Supplementary Table 10**) were consistently identified by all four algorithms and were unaffected by including or excluding the MHC. We applied pathway enrichment analysis (excluding the MHC) using Enrichr[80], which aggregates annotations from multiple sources. In the Kyoto Encyclopedia of Genes and Genomes (KEGG), the most significant pathway for cluster 1 (including *CSF2* and *TNFAIP3*) was IL-17 signaling *($p=1.6\times10^{-3}$, $OR=39.32$*), for cluster 2 (including *IL12B* and *TYK2*) it was JAK-STAT signaling ($p=1.1\times10^{-5}$, $OR=35.85$) and for cluster 3 (including *CAMK2G* and *TNFRSF1A*), it was necroptosis ($p=3.7\times10^{-9}$, $OR=161.01$).

Cluster 1 was also significantly enriched for TNFα signaling pathways in the National Center for Advancing Translational Sciences (NCATS) BioPlanet ($p=1.4\times10^{-6}$, $OR=67.37$) and the Molecular Signatures Database (MSigDB) ($p=2.7\times10^{-4}$, $OR=30.14$), while cluster 2 and 3 were both significant for IL-6/JAK/STAT3 signaling in MSigDB ($p=6.2\times10^{-5}$, $OR=47.38$ and $p=6.6\times10^{-6}$, $OR=118.49$, respectively). Cluster 2 was also significantly enriched for IL-12 signaling in BioPlanet ($p=3.0\times10^{-7}$, $OR=93.31$). Overall, there appear to be two main mechanisms in which the TDMA loci are involved: IL-17/TNFα signaling (cluster 1) and JAK-STAT signaling (clusters 2 and 3). We annotated **Supplementary Table 10** to indicate which loci have genes involved in each pathway.

Mendelian randomization (MR)

Figure 3 provides estimates of causal effects on MS for each MR technique we applied, while **Supplementary Figure 25** presents the same for psoriasis. Psoriasis was estimated to have a significant (FDR<0.05) effect on MS by four of the six techniques, while it was nominally significant for the remaining two (MR-Egger and MR-Robust). By contrast, none of the techniques indicated a significant effect for MS on psoriasis, and only one (MR-RAPS) was nominally significant. Consistent with the (covariate adjusted) epidemiological analysis, estimates of the effect of psoriasis on MS ranged from $p=7.1\times10^{-3}$, $OR=1.05$ for MR-PRESSO to $p=7.9\times10^{-3}$, $OR=1.07$ for MR-Mode. We confirmed the causal effect of psoriasis on MS with a significant Steiger test result ($p=6.6\times10^{-298}$), indicating higher correlation between the genetic instruments with psoriasis ($r^2=0.144$) than MS ($r^2=0.011$).

Selecting the six comorbidities/traits (T1D, T2D, IBD, vitamin D, BMI and drinks/week) estimated to have a significant causal effect by at least one technique, we conducted a multivariable analysis using MR-GRAPPLE[75]. The causal effect of psoriasis on MS remained significant ($p=5.8\times10^{-3}$, $OR=1.04$), after conditioning on effects of T1D ($p=4.3\times10^{-7}$, $OR=1.05$), T2D ($p=2.3\times10^{-3}$, $OR=1.08$), IBD ($p=1.6\times10^{-11}$, $OR=1.11$) and vitamin D levels ($p=9.4\times10^{-3}$, $OR=0.75$); however, BMI and drinks/per week were no longer even nominally significant. While by univariable analysis BMI was the only trait (apart from psoriasis) estimated to have at least a nominally significant effect on MS by all six techniques, it is known to have a causal effect on other traits, so it is possible that it affects MS indirectly.

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DISCUSSION

By combining large-scale epidemiological analysis with genetics, we confirmed a significant and causal association between psoriasis and MS that is independent of different confounding factors. A fully adjusted odds ratio of 1.07 *($p=1.2\times10^{-5}$)* was estimated using medical claims data from ~900 thousand patients with psoriasis and/or MS and ~30 million controls. Mendelian randomization (MR) techniques gave comparable effect sizes (OR=1.05-1.07), with OR=1.04 ($p=5.8\times10^{-3}$) when conditioning on T1D, T2D, IBD, vitamin D, BMI and drinks/per week (traits significant in univariable analysis), while no significant causal effect was observed for MS on psoriasis. In total, more than 20 non-MHC genome-wide significant shared or opposing genetic loci were identified between psoriasis and MS that were at least suggestively significant ($p<1\times10^{-4}$) for each trait and more significant in TDMA than both traits. In an independent replication study for MS, two of the suggestively significant loci (rs6672420 and rs5756405) were genotyped, and both were confirmed to be genome-wide significant ($p=1.5\times10^{-9}$, OR=1.06; $p=5.4\times10^{-11}$, OR=1.07)[1]. No significant heterogeneity was identified for these markers between the main MS and replication cohorts, nor between the individual psoriasis cohorts. When combining the MS and psoriasis cohorts together (rather than applying TDMA), rs6672420 has nominally significant (p=0.01) heterogeneity, while for rs5756405 it is not significant (p=0.98). The mixture of shared and opposing loci is interesting, as it suggests a complex genetic relationship between psoriasis and MS. This could help explain why certain treatments (e.g., TNFα inhibitors and IFNβ) are beneficial in only one of the two diseases. Our analysis of the co-expression of genes at these loci suggests IL-17/TNFα and JAK-STAT signaling to be particularly important mechanisms for the psoriasis/MS comorbidity.

We evaluated multiple different approaches for TDMA: inverse weighted (IVW) meta-analysis[62], typically used for single trait GWAS, can favor loci that are dominated by one or the other trait, while equally weighted TDMA avoids this bias, however it does not fully take advantage of the greater accuracy provided by larger studies; we also applied approximate conditional analysis (GCTA-COJO). It is reassuring that most of the loci were found by all three approaches; however, the loci from our equally weighted TDMA all had evidence of colocalization (through COLOC and SuSiE), whereas not all of the additional loci from the other approaches did. This does not rule out these loci from affecting the same genes and pathways in psoriasis and MS, but it suggests they may have different causal variants that could affect these pathways in different ways (i.e., pleiotropy). We addressed potential pleiotropy in MR by removing any outliers detected by MR-PRESSO and using five other techniques that test the assumptions of MR. Furthermore, by applying multivariable analysis in addition to the traditional univariable approach, we controlled for the effect of confounding factors.

The TDMA loci we identified are enriched in H3K27ac active enhancer marks for B-cell centroblasts, both compared to the rest of the genome and to the psoriasis/MS-specific loci. While the role of B-cells has been elucidated in MS[1], they have been less well studied in psoriasis, potentially because they are detected in smaller numbers than T-cells in lesional skin[81]. Nevertheless, regulatory B-cell involvement in responses to the phosphodiesterase 4 inhibitor apremilast has recently been reported[82], and they are able to suppress IL-23-mediated inflammation[83]. Previous research showed tonsils from psoriasis patients had lower germinal center to marginal zone area ratio[84], and germinal center affinity maturation plays an important role in MS[85]. B-cell activation is believed to be enhanced by neutrophil extracellular traps (NETs) in MS[86] as well as in lupus[87]. While NETs have been found to promote psoriatic inflammation, particularly through Th17[29,88], it has yet to be investigated whether they assist B-cell maturation in a similar way to other diseases. Biological effects of genetic signals are challenging to identify, and require mechanistic study, for example through multiomic analysis. In **Table 2**, we indicate which genes have eQTL support in two large datasets (eQTLGen[89] and GTEx[90]), finding the lead marker of 80% of the loci to be an eQTL, however further work is required to pinpoint and validate specific gene targets.

The use of medical claims data can have limitations, as they are primarily collected for billing purposes rather than research. We also did not have access to quantitative data on obesity, smoking and alcohol use and so used ICD-9/10 codes for these covariates instead. It is conceivable that this information would only be recorded if the physician considers these details to be relevant to the patient's health – for example, ICD codes reflect alcohol use disorder, rather than the number of drinks consumed, and only 16% of patients were indicated as obese, whereas other studies suggest the proportion may be almost twice as high in the USA[91]. The overall consistency with genetic and MR results was reassuring. However, psoriatic arthritis (PsA) occurs in up to 30% of psoriasis patients[92] and can sometimes be misdiagnosed as rheumatoid arthritis (RA). This could explain the strong effect sizes observed for RA in epidemiology, and lack of significance in MR, in which patients were assessed by rheumatologists. A recent survey[93] found the ICD-9/10 codes for MS have up to 92.4% sensitivity and 92.6% specificity, while for psoriasis, 81% of patients who have an ICD-10 code had a confirmed diagnosis[94], with 88% sensitivity for ICD-9 codes[95]. However, ICD codes can still be inaccurate, especially for diseases such as MS that have variable symptoms, and future work will focus on developing and applying more rigorous case definitions, for example based on prescriptions for disease-modifying therapies, or multiple visits to relevant specialists (as is recorded in Optum's deidentified Clinformatics® Data Mart[60]).

These limitations notwithstanding, our study provides genetic and epidemiological evidence for similarity and causal relationship between MS and psoriasis immunomes, while identifying important differences between these two complex diseases that should help guide future research.

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Author Contributions

MTP and LCT contributed to the conception and design of the study; MTP, RPN, JEG, LTE and LCT contributed to the acquisition and analysis of data; MTP contributed to drafting the text or preparing the figures.

Potential Conflicts of Interests

LCT has received support from Galderma, Janssen, and Novartis. J. E. Gudjonsson has served as a consultant to Almirall, BMS, Sanofi, AbbVie, Novartis, Eli Lilly, Pfizer, and Galderma; and has received research support from Almirall, Janssen, Novartis, Pfizer, BMS/Celgene, Timberpharma, and Galderma. S. Ständer has served as a consultant to Almirall, Bayer, Beiersdorf, Bellus, Bionorice, Cara Therapeutics, Celgene, Clexio, DS Biopharma, Galderma, Menlo Therapeutics, Novartis, Perrigo, Trevi Therapeutics, Dermasence, Galderma, Kiniksa, Sanofi, and Vanda Therapeutics.

Data Availability

The medical claims data is available by applying for access to Optum's deidentified Clinformatics® Data Mart. Access to the GWAS summary statistics is detailed in the manuscript for each study. Pathway and LINCS L1000 gene sets are available through the Enrichr website (https://maayanlab.cloud/Enrichr/).

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Figure 1: IVW trans-disease meta-analysis (TDMA). Circular diagram including the following: a) Manhattan plot of shared (same direction of effect) psoriasis/MS TDMA signals, showing markers more significant in TDMA than for either trait. b) Manhattan plot of opposing (opposite direction of effect) psoriasis/MS trans-disease meta-analysis (TDMA) signals, showing markers more significant in TDMA than for either trait. **Red** dashed lines indicate the genome-wide significance ($p<5x10^{-8}$) threshold for shared and opposing signals, respectively. Loci which meet this threshold and are suggestively significant ($p<1\times10^{-4}$) for both traits are highlighted in **red** (if identified through our original TDMA approach) or **blue** (for additional loci identified using GCTA-COJO). c) Density of H3K27ac active enhancer marks for B-cell centroblasts (the most enriched cell type among the TDMA loci, compared to other established loci for psoriasis and MS). The darker the color, the higher the proportion of regulatory marks overlapping each 2Mbp region. Genes reported by previous psoriasis and MS GWAS[1,4,96-99] are labeled for each locus. d) Links between genes, according to co-expression in L1000 assay perturbation experiments from NIH's Library of Integrated Network-Based Cellular Signatures (LINCS). Each link has a random color, with transparency (alpha) values set proportional to the log-scaled number of experiments in which at least one gene from a locus is co-expressed with at least one gene from another locus, such that more opaque links represent pairs of loci with genes co-expressed in more experiments.

Figure 2: Regional association plots for four loci identified by IVW TDMA. For each of the following loci, the lead TDMA marker is indicated in **purple** and the other markers are colored according to their LD with the lead marker: a) 6q25.3 opposing locus, with rs2451279 lead marker; b) 7p14.1 shared locus, with rs17259252 lead marker; c) 10q22.3 opposing locus, with rs1108618 lead marker; d) 13q14.2 shared locus, with rs9591325 lead marker.

Figure 3: Mendelian randomization (MR) results for the effects of psoriasis and other comorbidities on multiple sclerosis. Forest plots generated from the results of six MR techniques (a-f). Abbreviations are as follows: T1D, type 1 diabetes; T2D, type 2 diabetes; CAD, coronary artery disease; RA, rheumatoid arthritis; IBD, inflammatory bowel disease; VitD, vitamin D (25OHD); BMI, body mass index; Smoke, cigarettes per day; Drink, drinks per week; p, p-value; OR, odds ratio.

Table 1: Epidemiological Analysis. The top portion of the table shows the effects of different demographic variables on MS/psoriasis; the bottom portion of the table illustrates the effects of other traits/diseases on MS/psoriasis, after adjusting for the demographic variables.

Table 2: Loci Identified by Trans-Disease Meta-Analysis (TDMA). Susie # indicates the number of pairs of fine-mapped signals with evidence of colocalization (PP>0.7).

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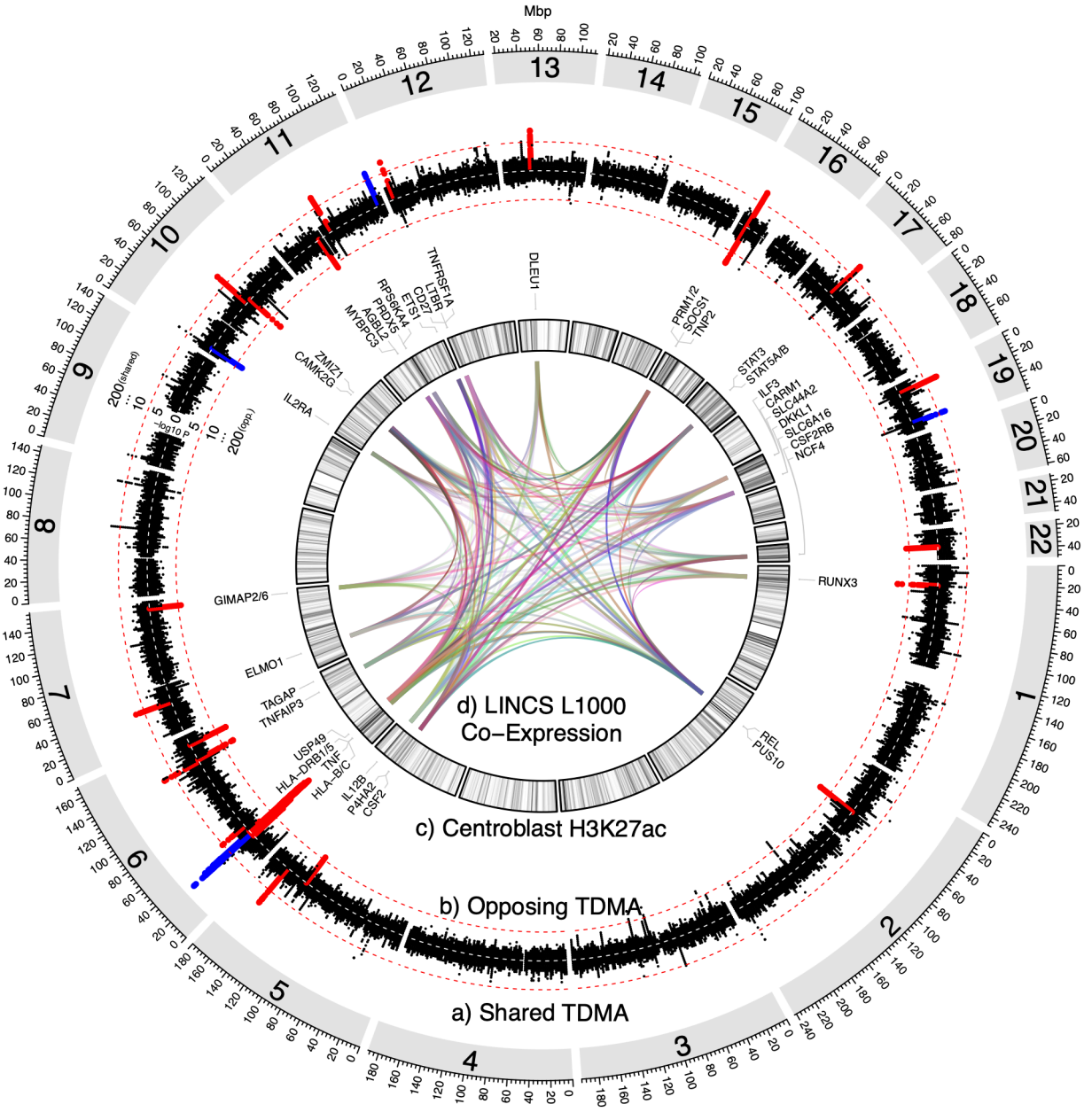

Figure1.tiff

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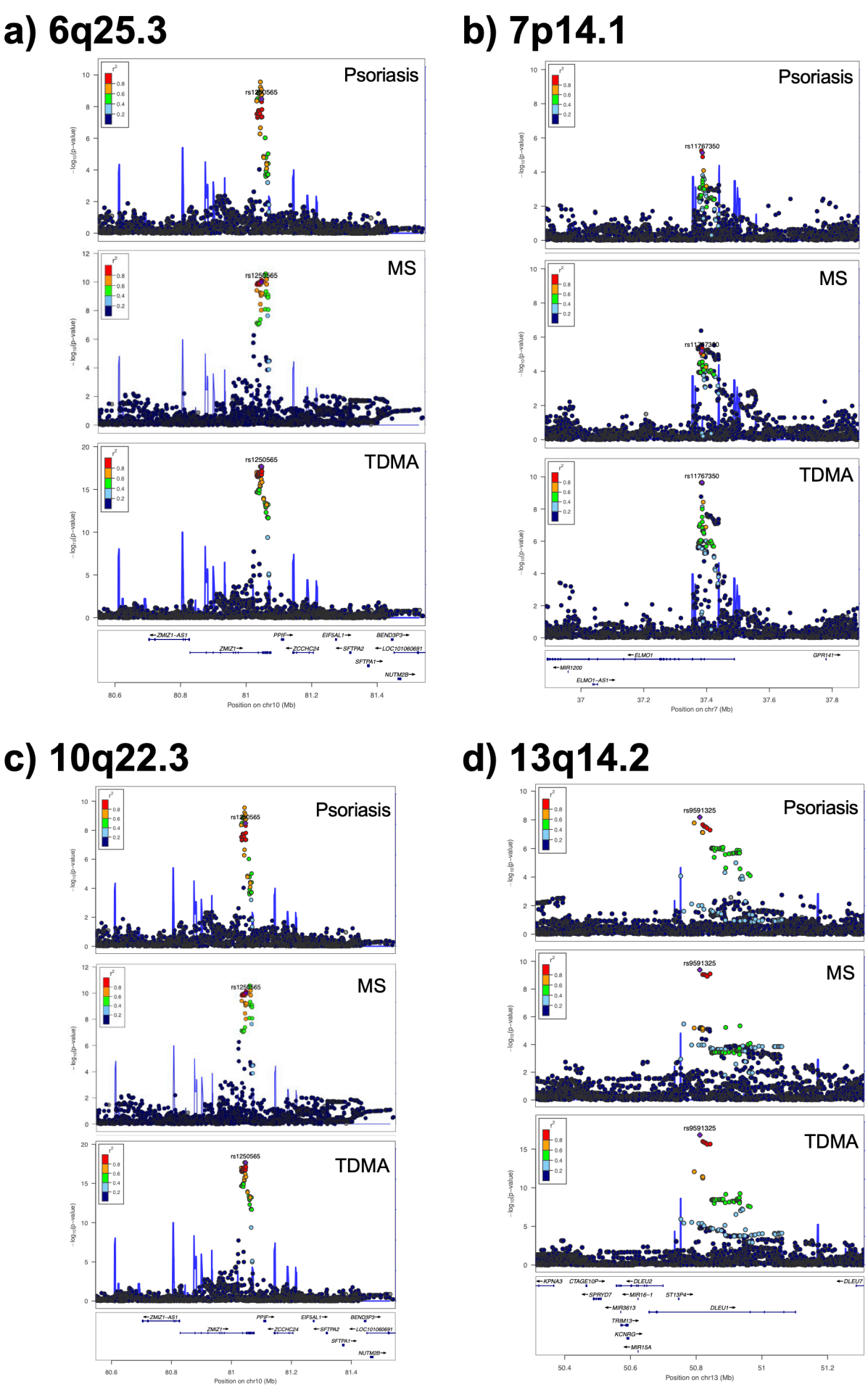

Figure2.tiff

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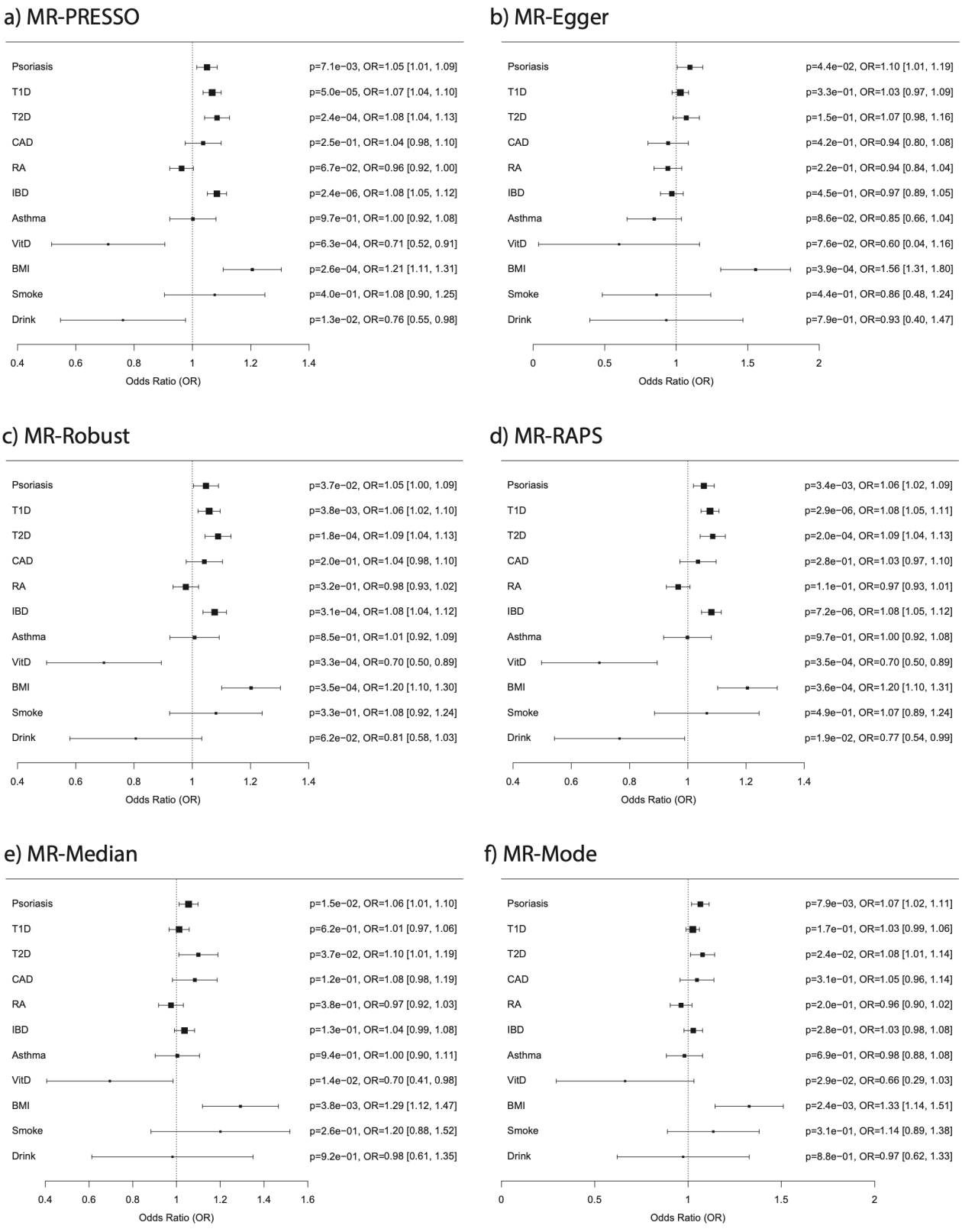

Figure3.tiff

Covariate	Demographics				Effect on MS		Effect on Psoriasis	
	All	*MS*	*Psor*	*Both*	*OR (95% CI)*	*P-value*	*OR (95% CI)*	*P-value*
Age in Years	45	54	53	56	1.47	$1.2x10^{-4,442}$	1.49	$1.2x10^{-24,027}$
Mean (SD)	(23)	(15)	(18)	(14)	(1.46-1.48)		(1.48-1.49)	
Sex – Male	13,645,873	36,302	355,342	1,294	*Reference group*			
Sample Size (%)	(44.82)	(0.27)	(2.60)	(0.01)				
– Female	16,800,019	105,242	387,577	3,343	2.36	$1.2x10^{-4,323}$	0.88	$8.8x10^{-608}$
Sample Size (%)	(55.18)	(0.63)	(2.31)	(0.02)	(2.34-2.39)		(0.88-0.89)	
Race – White	22,779,120	113,748	591,317	3,886	*Reference group*			
Sample Size (%)	(74.82)	(0.50)	(2.60)	(0.02)				
– Asian	1,259,402	2,245	28,175	68	0.36	$2.7x10^{-513}$	0.86	$8.9x10^{-135}$
Sample Size (%)	(4.14)	(0.18)	(2.24)	(0.01)	(0.34-0.37)		(0.85-0.87)	
– Black	3,015,614	15,050	52,679	366	1.00	0.92	0.67	$7.2x10^{-1,693}$
Sample Size (%)	(9.90)	(0.50)	(1.75)	(0.01)	(0.98-1.02)		(0.66-0.67)	
– Hispanic	3,391,756	10,461	70,748	317	0.62	$1.7x10^{-488}$	0.80	$4.5x10^{-676}$
Sample Size (%)	(11.14)	(0.31)	(2.09)	(0.01)	(0.60-0.63)		(0.79-0.81)	

Trait	Sample Size (%)				Effect on MS		Effect on Psoriasis	
	All	*MS*	*Psor*	*Both*	*OR (95% CI)*	*P-value*	*OR (95% CI)*	*P-value*
Psoriasis	742,919 (2.44)	-	-	4,637 (0.02)	1.22 (1.20-1.24)	$5.3x10^{-41}$	-	-
MS	141,544 (0.46)	-	-	4,637 (0.02)	-	-	1.24 (1.22-1.26)	$8.0x10^{-47}$
Type 1 Diabetes	923,543 (3.03)	7,158 (0.78)	33,256 (3.60)	331 (0.04)	1.34 (1.33-1.36)	$3.9x10^{-126}$	1.14 (1.13-1.15)	$4.7x10^{-115}$
Type 2 Diabetes	4,767,871 (15.66)	32,595 (0.68)	172,729 (3.62)	1,405 (0.03)	1.24 (1.23-1.25)	$1.5x10^{-211}$	1.19 (1.19-1.20)	$4.8x10^{-747}$
Coronary Artery Disease	3,170,317 (10.41)	21,996 (0.69)	119,635 (3.77)	991 (0.03)	1.13 (1.12-1.14)	$1.1x10^{-53}$	1.03 (1.02-1.03)	$8.5x10^{-15}$
Rheumatoid Arthritis	813,738 (2.67)	9,495 (1.17)	66,613 (8.19)	813 (0.10)	1.85 (1.83-1.87)	$1.0x10^{-699}$	3.11 (3.09-3.12)	$6.8x10^{-14,924}$
Inflammatory Bowel Disease	403,112 (1.32)	3,935 (0.98)	18,686 (4.64)	206 (0.05)	1.76 (1.73-1.79)	$6.5x10^{-265}$	1.65 (1.64-1.67)	$2.8x10^{-948}$
Asthma	4,026,381 (13.22)	25,643 (0.64)	116,560 (2.89)	1,128 (0.03)	1.36 (1.35-1.37)	$3.9x10^{-433}$	1.24 (1.24-1.24)	$1.0x10^{-949}$
Vitamin D Deficiency	3,937,160 (12.93)	43,555 (1.11)	152,644 (3.88)	1,846 (0.05)	2.30 (2.29-2.32)	$1.5x10^{-3,974}$	1.42 (1.42-1.43)	$1.1x10^{-2,867}$
Obesity – Obese	3,256,617 (10.70)	19,918 (0.61)	115,156 (3.54)	806 (0.02)	1.22 (1.21-1.23)	$2.4x10^{-148}$	1.43 (1.42-1.43)	$1.8x10^{-2,475}$
– Morbidly Obese	1,686,290 (5.54)	13,077 (0.78)	67,983 (4.03)	646 (0.04)	1.47 (1.46-1.48)	$1.1x10^{-370}$	1.68 (1.67-1.69)	$4.5x10^{-3,350}$
Smoking	4,605,396 (15.13)	38,163 (0.83)	174,563 (3.79)	1,587 (0.03)	1.78 (1.77-1.79)	$3.5x10^{-1,857}$	1.38 (1.38-1.39)	$2.6x10^{-2,738}$
Alcohol Use Disorder	836,527 (2.75)	5,491 (0.66)	31,853 (3.81)	238 (0.03)	1.53 (1.51-1.55)	$1.8x10^{-204}$	1.43 (1.42-1.44)	$4.7x10^{-803}$

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Shared (same direction of effect) loci:

Cyt. Band	rsID	Position (hg19)	RA/ NR	*MS*		*Psoriasis*		*TDMA*		*Heterogeneity*		*Colocalization*		*Nearby Genes*
				OR	P	OR	P	OR	P	Q	P	COLOC PP	SuSiE #	
5q33.3	rs2546890	158759900	A/G	1.12	1.0×10^{-12}	1.33	6.4×10^{-51}	1.21	7.1×10^{-58}	1.4×10^{-2}	0.91	4.4×10^{-7}	0	*IL12B*
6p21.1	rs59024520	42238973	C/T	1.16	6.3×10^{-5}	1.19	8.2×10^{-5}	1.17	2.3×10^{-8}	4.4×10^{-4}	0.98	0.83	0	*USP49*
6q23.3	rs9321623	137958265	C/T	1.08	4.5×10^{-6}	1.10	4.5×10^{-7}	1.09	9.5×10^{-12}	1.7×10^{-4}	0.99	1.5×10^{-3}	1	*TNFAIP3*
7p14.1	rs11767350	37385365	A/G	1.07	6.5×10^{-6}	1.09	7.4×10^{-6}	1.08	2.2×10^{-10}	6.4×10^{-5}	0.99	0.80	3	*ELMO1**
10q22.2	rs2459446	75601596	C/T	1.07	7.9×10^{-5}	1.13	1.5×10^{-10}	1.09	8.9×10^{-14}	1.8×10^{-3}	0.97	0.87	3	*CAMK2G**
11q13.1	rs479777	64107477	T/C	1.08	3.5×10^{-5}	1.13	2.1×10^{-9}	1.10	6.0×10^{-13}	9.1×10^{-4}	0.98	0.87	0	*PRDX5**, *RPS6KA4**
12p13.31	rs4149576	6449115	T/C	1.11	3.5×10^{-9}	0.07	8.8×10^{-5}	1.09	6.8×10^{-12}	3.4×10^{-4}	0.99	0.07	6	*CD27, TNFRSF1A**
13q14.2	rs9591325	50811220	T/C	1.24	4.2×10^{-10}	1.24	6.6×10^{-9}	1.24	2.0×10^{-17}	1.7×10^{-5}	1.00	0.99	2	*DLEU1**
16p13.13	rs243324	11354970	A/G	1.12	5.9×10^{-12}	1.08	6.6×10^{-5}	1.10	5.5×10^{-15}	6.6×10^{-4}	0.98	3.1×10^{-4}	0	*SOCS1, RMI2**
17q21.2	rs957970	40519890	A/G	1.14	1.1×10^{-13}	1.11	7.3×10^{-8}	1.13	6.4×10^{-20}	2.2×10^{-4}	0.99	0.97	7	*STAT3**, *STAT5A**/*B*
19p13.2	rs55677033	11166293	T/C	1.09	2.6×10^{-6}	1.08	9.0×10^{-5}	1.09	9.5×10^{-10}	1.0×10^{-5}	1.00	0.17	2	*ILF3, CARM1*

Opposing (opposite direction of effect) loci:

Cyt. Band	rsID	Position (hg19)	RA/ NR	*MS*		*Psoriasis*		*TDMA*		*Heterogeneity*		*Colocalization Prob.*		*Nearby Genes*
				OR	P	OR	P	OR	P	Q	P	COLOC PP	SuSiE #	
1p36.11	rs6672420	25291010	A/T	1.07	2.2×10^{-5}	0.86	8.8×10^{-15}	1.11	6.3×10^{-18}	2.9×10^{-3}	0.96	0.93	3	*RUNX3*
2p16.1	rs1177213	61079090	A/G	0.93	4.6×10^{-6}	1.16	2.1×10^{-15}	1.11	5.2×10^{-18}	3.0×10^{-3}	0.96	0.73	6	*REL**, *PUS10**
5q31.1	rs3843503	131466629	T/A	1.08	1.9×10^{-5}	0.92	2.1×10^{-5}	1.08	1.6×10^{-9}	1.5×10^{-6}	1.00	0.68	3	*CSF2, P4HA2**
6p22.1	rs1611653	29841702	G/C	1.31	3.9×10^{-50}	0.73	1.5×10^{-61}	1.34	6.4×10^{-109}	1.5×10^{-3}	0.97	-	-	*HLA-B**/*C, TNF*
6q23.3	rs7746779	138154501	A/G	0.90	8.8×10^{-7}	1.15	1.1×10^{-9}	1.13	1.1×10^{-14}	7.8×10^{-4}	0.98	3.2×10^{-3}	0	*TNFAIP3, WAKMAR2*
6q25.3	rs2451279	159515077	G/A	1.10	6.4×10^{-8}	0.91	3.6×10^{-6}	1.10	1.8×10^{-12}	4.3×10^{-6}	1.00	2.6×10^{-3}	2	*TAGAP**
7q36.1	rs10243355	150356318	G/A	1.09	3.4×10^{-5}	0.89	1.8×10^{-5}	1.10	3.4×10^{-9}	6.2×10^{-4}	0.98	0.81	1	*GIMAP2**/6*
10q22.3	rs1250565	81047015	A/G	1.12	1.0×10^{-10}	0.89	3.3×10^{-9}	1.12	2.1×10^{-18}	2.4×10^{-5}	1.00	0.83	2	*ZMIZ1**
11p11.2	rs12574410	47169228	C/G	1.11	3.9×10^{-6}	0.90	9.3×10^{-5}	1.11	1.5×10^{-9}	1.3×10^{-5}	1.00	0.88	0	*MYBPC3**, *AGBL2**
16p13.13	rs3862471	11113463	G/T	1.17	3.2×10^{-23}	0.92	6.4×10^{-6}	1.14	1.3×10^{-25}	3.0×10^{-3}	0.96	0.85	0	*CLEC16A**
22q12.3	rs5756405	37310954	A/G	1.07	2.4×10^{-5}	0.93	4.3×10^{-5}	1.07	4.3×10^{-9}	4.7×10^{-5}	0.99	0.76	3	*CSF2RB**, *NCF4*

*eQTL evidence in eQTLGen or GTEx v8

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