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Pleiotropy of systemic lupus erythematosus risk alleles and cardiometabolic disorders: a phenome-wide association study and inverse-variance weighted meta-analysis

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Abstract

Objectives: To test the hypothesis that genetic predisposition to systemic lupus erythematosus (SLE) increases the risk of cardiometabolic disorders.

Methods: Using 41 single nucleotide polymorphisms (SNPs) associated with SLE, we calculated a weighted genetic risk score (wGRS) for SLE. In a large biobank we tested the association

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between this wGRS and 9 cardiometabolic phenotypes previously associated with SLE: atrial fibrillation, ischemic stroke, coronary artery disease, type 1 and type 2 diabetes, obesity, chronic kidney disease, hypertension, and hypercholesterolemia. Additionally, we performed a phenome-wide association analysis (pheWAS) to discover novel clinical associations with a genetic predisposition to SLE. Findings were replicated in the Electronic Medical Records and Genomics (eMERGE) Network. To further define the association between SLE-related risk alleles and the selected cardiometabolic phenotypes, we performed an inverse variance weighted regression (IVWR) meta-analysis.

Results: The wGRS for SLE was calculated in 74,759 individuals of European ancestry. Among the pre-selected phenotypes, the wGRS was significantly associated with type 1 diabetes (OR [95%CI] =1.11 [1.06, 1.17], P-value=$1.05x10^{-5}$). In the pheWAS, the wGRS was associated with several autoimmune phenotypes, kidney disorders, and skin neoplasm; but only the associations with autoimmune phenotypes were replicated. In the IVWR meta-analysis, SLE-related risk alleles were nominally associated with type 1 diabetes (P=0.048) but the associations were heterogeneous and did not meet the adjusted significance threshold.

Conclusion: A weighted GRS for SLE was associated with an increased risk of several autoimmune-related phenotypes including type 1 diabetes but not with cardiometabolic disorders.

Keywords

systemic lupus erythematosus; genetic risk score; pleiotropy

INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex autoimmune disorder that is associated with several cardiometabolic co-morbidities. SLE has a strong genetic component with more than a hundred risk alleles associated with disease (1). Although some risk alleles are shared with other autoimmune disorders, little is known about their association with the cardiometabolic disorders that are prevalent in SLE.

Cardiometabolic diseases contribute substantially to morbidity and mortality in SLE. For example, we and others have shown that coronary artery disease (CAD) is a prominent feature in SLE(2); also, patients with SLE have increased risk for atrial fibrillation (AF)(3), dyslipidemia (4), type 1 diabetes (T1D) and type 2 diabetes (T2D) (5), hypertension (HTN) (6), chronic kidney disease (CKD) (7), and central obesity (4) compared to the general population. Whether this increased risk for CAD and other cardiometabolic diseases and risk factors in SLE is imparted by the genetic predisposition to SLE is not known.

With the availability of large genome-wide association studies (GWAS) that have identified common single nucleotide polymorphisms (SNPs) associated with many phenotypes including SLE and cardiometabolic disorders, it is possible to study the shared genetic predisposition between various phenotypes. For example, in a previous study that used information from large GWAS, we found that genetic liability for rheumatoid arthritis (RA) was associated with increased risk of T1D and decreased risk of multiple sclerosis (MS) (8).

To define whether a genetic predisposition to SLE increases risk of cardiometabolic disorders we used two approaches: a) we examined whether a weighted genetic risk score (GRS) for SLE identified individuals in a large de-identified electronic health record (EHR) system with increased prevalence of selected prespecified cardiometabolic phenotypes; we also performed an global phenome wide association study (PheWAS) to identify potential novel clinical associations with the SLE GRS; b) we used inverse variance weighted regression (IVWR) meta-analysis to test for a causal association between predisposition to SLE and selected cardiometabolic phenotypes using publicly available genome-wide association data.

METHODS

Data Sources

We used BioVU, the Vanderbilt University Medical Center (VUMC) DNA biobank, to study the association between genetic liability for SLE and 9 cardiometabolic outcomes previously associated with SLE: AF, ischemic stroke, CAD, T2D, obesity, HTN, CKD, hypercholesterolemia, and T1D. A full description of BioVU has been published (9). Briefly, BioVU accrues DNA from blood samples obtained during routine clinical care from patients who have consented to have a DNA sample collected. DNA is extracted from blood samples that would otherwise be discarded, de-identified, and linked to a de-identified version of the EHR. Approval for the study was obtained from the Vanderbilt Institutional Review Board. For replication of findings, we use data from the electronic Medical Records and Genomics (eMERGE) Network that has been fully described elsewhere (10). Because BioVU and eMERGE participants were predominantly self-reported white, we restricted our sample to individuals of European ancestry (EA) determined by principal components in conjunction with the HapMap population as described elsewhere (11). The eMERGE network included EA individuals born prior to 1990 (n=31,773, excluding VUMC dataset) while the BioVU dataset included more than 74,000 EA individuals over 18 years old.

We selected the largest genetic meta-analysis with summary-level data available for EA individuals for SLE and the other phenotypes of interest (or proxies when the exact phenotype was not available) (Supplementary Table S1 and S2). We studied the same 9 phenotypes (or proxies) used in the GRS association analyses and 2 additional biomarkers that have been associated with increased risk of cardiometabolic disease for which there are no good phenotype equivalents in the EHR: C-reactive protein (CRP) and interleukin 6 (IL-6) concentrations in the absence of acute inflammation (12).

Genotyping

In the BioVU cohort, genotyping was performed by the Vanderbilt Technologies for Advance Genomics (VANTAGE) according to standard protocols on the Illumina Infinium Multi-Ethnic Genotyping Array (MEGA^{EX}) platform. eMERGE participants were genotyped on multiple platforms and underwent QC analyses and imputation as previously described (13). Quality control (QC) analyses used PLINK version 1.90β3 (14) and included reconciling strand flips, verifying that allele frequencies were concordant among data sets, and identifying duplicate and related individuals (one of each pair of subjects with a pi-

hat>0.05 was excluded). Data sets were standardized using the HRC-1000G-check tool v4.2.5 (http://www.well.ox.ac.uk/~wrayner/tools/) and pre-phased using SHAPEIT (15). BioVU data was imputed using IMPUTE2 (16), in conjunction with the same reference panel from which the SLE risk alleles were derived (1000 Genomes cosmopolitan reference haplotypes). All other genetic data were imputed using the Michigan Imputation Server (HRC v1.1). Imputed data were filtered for a sample missingness rate <2%, a SNP missingness rate <4% and SNP deviation from Hardy-Weinberg $P<5x10^{-6}$. Principal components (PCs) were calculated using the SNPRelate package (17).

Phenotypes

For the 9 prespecified phenotypes, we extracted clinical diagnoses from the EHR using the 9^{th} and 10^{th} International Statistical Classification of Diseases and Related Health Problems (ICD) Clinical Modification (CM) codes that mapped to the phenotype and transformed these ICD9/ICD10 codes into phecodes, which aggregate one or more related ICD codes into distinct diseases or traits (18). For each phenotype, cases were defined as individuals with 2 or more instances of the specific phecode in the EHR. Controls were defined as individuals without the phecode or related phecodes (see map of phecodes at https://phewascatalog.org/phecodes). For the PheWAS analysis, we followed the same procedures and extracted information for 1162 clinical phenotypes with 100 or more cases (to assure statistical power) in the EHR. ICD9/10 codes extraction was performed on December 2019 for BioVU and October 2019 for eMERGE.

Genetic Risk Score and Statistical Analysis

To construct the GRS, we selected 41 autosomal SNPs that were associated with SLE in the largest meta-analysis performed in EA individuals (1) (Supplementary Table S1), and only included EA individuals in the analyses. Summary statistics for these 41 SNPs were included into a weighted GRS (wGRS) to calculate genetically-predicted risk for SLE using the following equation:

$$\text{Weighted genetic risk score (wGRS)} = \sum_{i=1}^{\#SNPs} (\beta^{i} \text{ x } [\text{SNP genotype}]^{i})$$

where β is the effect size (log odds-ratio) of the risk allele and the genotype is the number of copies of the risk allele coded as 0, 1, or 2. Only SNPs that passed quality control were included in the calculation of the wGRS. A multivariable regression analyses adjusting for the first 5 PCs, median age in the EHR, and sex was performed for the nine pre-specified phenotypes. For these 9 prespecified phenotypes, a Bonferroni-corrected P-value <0.0056 (0.05/9 phenotypes) was considered significant. In addition, we tested whether the wGRS was associated with the selected phenotypes in patients with SLE and with lupus nephropathy. SLE was defined as the presence of two or more SLE-related phecodes and lupus nephropathy as the presence of 2 or more nephropathy-related phecodes in individuals with SLE (19). A Benjamini-Hochberg false discovery rate (FDR) q<0.05 was considered significant for the global PheWAS and the replication in eMERGE. The PheWAS was adjusted by the same covariates included in the regression analysis using the PheWAS R

package (20). As a secondary analysis, we performed a PheWAS that excluded patients with SLE or common autoimmune diseases (see Supplementary Table S3). All PheWAS associations were expressed as odds- ratios (OR) and 95% confidence interval (95%CI), where ORs represent the risk of disease per standard deviation (s.d.) increase in the GRS.

To further test the association between genetic liability for SLE and the selected phenotypes we performed IVWR meta-analyses. The same 41 autosomal SNPs included in the GRS were used to select a linkage disequilibrium (LD)-reduced (r^2<0.05) set of SNPs with a MAF>0.05 as instrumental variables (IVs) for SLE in the IVWR meta-analysis. Heterogeneity p-values are based on the Cochran's Q statistic, and a low p-value indicates that one or more variants in the GRS may be pleiotropic.

As a sensitivity analysis, we performed weighted median regression since this approach, while less well powered than IVWR, provides better estimates of the true effect size when less than 50% of the IVs are not valid (21). In addition, we also tested for unbalanced horizontal pleiotropy using MR-Egger regression, which provides unbiased estimates in the presence of pleiotropy (21). Analyses were performed using the Mendelian Randomization R-package and a Bonferroni-adjusted P-value<0.0045 (0.05/11 outcomes) was considered significant. A P-value<0.05 for the intercept estimate in the Egger regression indicated the presence of horizontal pleiotropy.

RESULTS

Genetic risk score analysis

All 41 autosomal SNPs passed quality control and were included in the calculation of the wGRS. We calculated the wGRS for SLE in all 74,759 individuals of European ancestry in BioVU with genotype information and clinical data available; 41,934 (56%) were women and the median value (IQR) of the average age on the EHR was 52.5 (32.7, 65.14).

Among the pre-selected phenotypes, T1D was significantly associated with the wGRS for SLE (OR [95%CI] =1.11 [1.06, 1.17], P=$1.05x10^{-5}$) and a nominal association was observed for CKD (1.05 [1.01, 1.08], P=0.007) (Table 1).

In addition, none of the selected phenotypes were associated with the wGRS (P>0.05) when only patients with SLE were studied. The average wGRS was higher in patients with lupus nephropathy compared to SLE patients without nephropathy (0.082 vs. 0.080, P=0.001); but the wGRS was not associated with any of the selected cardiometabolic phenotypes in patients with lupus nephropathy (P>0.05, Supplementary Table S4)

The global PheWAS in BioVU showed that the wGRS for SLE was significantly associated with 42 clinical diagnosis including several autoimmune phenotypes (FDR q<0.05) such as SLE, diffuse diseases of the connective tissue, sicca syndrome, rheumatoid arthritis (RA) related phenotypes, systemic sclerosis, celiac disease, autoimmune thyroiditis-related phenotypes, and T1D-related phenotypes among others (Table 2, Figure 1). The wGRS for SLE was also associated with non-autoimmune disorders including renal phenotypes and skin neoplasms. The replication analysis was performed in 31,773 EA individuals (55%

female) from eMERGE and 24 of the 42 associated phenotypes in BioVU were also strongly associated (FDR q<0.05) in the eMERGE population; most of which were autoimmune disorders (Table 2, Supplementary Table S5).

When patients with SLE were excluded from the PheWAS analysis in BioVU, most of the autoimmune phenotypes (e.g.: rheumatoid arthritis-related phenotypes, sicca syndrome, celiac disease, systemic sclerosis, autoimmune thyroiditis-related phenotypes, and T1D related phenotypes among others), renal failure, and skin neoplasms remained significantly associated with the wGRS (all FDR q<0.05, Supplementary Table S6); but when we additionally excluded patients with other common autoimmune diseases from the analysis none of the phenotypes were associated with the wGRS for SLE (FDR>0.05). (Supplementary Table S7)

Inverse variance weighted regression meta-analyses

Genetic predisposition to SLE was not significantly associated with any of the pre-selected outcomes (all P>0.0045, Table 3) using the IVWR method. Nominal associations were observed for T1D and LDL cholesterol, with a positive association for T1D (estimate= 0.249, P=0.048), and a negative association for LDL cholesterol (estimate = −0.015, P=0.018). Although the MR-Egger analysis did not show evidence of horizontal pleiotropy (Egger intercept p-value >0.05) for both phenotypes (Supplementary Table S8), we observed that rs2476601 was the SLE-associated SNP with the strongest association with T1D (effect size= 0.636, P-value=$1.10x10^{-122}$), and that exclusion of this SNP from the IVWR attenuated the association with T1D (P=0.093).

DISCUSSION

The main finding of this study was that a genetic predisposition to SLE based on common SNPs is not associated with an increased risk of cardiometabolic phenotypes but is associated with increased risk of other autoimmune disorders. In a similar study in RA, we found that genetic predisposition to RA was not associated with an increased risk of cardiometabolic phenotypes but was associated with increased risk for T1D (8).

The finding that genetic susceptibility to SLE is associated with increased risk of other autoimmune diseases in the PheWAS is not surprising, since autoimmune diseases share clinical and immunological characteristics as well as risk susceptibility loci (22). For example, a cross phenotype meta-analysis found that 44% of risk alleles were shared across seven common autoimmune diseases (SLE, T1D, RA, multiple sclerosis, psoriasis, Crohn's and coeliac disease) although not across all autoimmune disorders (23). The same study found that risk variants that are common to a subset of autoimmune diseases aggregate in discrete pathways such as the tumor necrosis factor (TNF) pathway for shared SNPs in RA and SLE (23). Another study reported only a modest genetic overlap between SLE and 17 common autoimmune diseases with no apparent association between several individual SLE risk loci with these autoimmune diseases (24). In our study, we estimated the aggregated the effect of individual SNPs using a wGRS and found that the GRS is associated with modest increases in risk for several autoimmune diseases.

Because SLE is a heterogenous disease, we also performed a PheWAS that excluded patients with SLE to determine if the associations with autoimmune disorders were independent SLE and found that most of the autoimmune phenotypes remained significantly associated with the wGRS for SLE, supporting the hypothesis of shared immunogenetic mechanisms among autoimmune diseases.

Although several established SLE risk loci have been associated with susceptibility for our pre-selected cardiometabolic phenotypes (e.g. cardiac arrythmias with *BANK1* (25); CAD with *FCGR2A* (26), *TNFSF4* (27), *IL10* (28), *WDFY4* (29), and *SH2B3* (30); HTN with *TNFSF4* (31), *NCF2* (32), and *SH2B3* (33); obesity with *IL10* (34); T2D with *JAZF1* (35); and T1D with *TYK2* (36), *IFIH1* (37), *IRF7* (38), SOCS1(39), *IKZF1* (40), *TNFAIP3* (41), and *SH2B3* (39)), to our knowledge this is the first study that examined the genetic sharing between SLE and cardiometabolic comorbidities that are prevalent among individuals with SLE. Consistent with our findings in the PheWAS analysis, the IVWR analysis did not show significant associations between genetic liability for SLE with the selected cardiometabolic phenotypes, which suggests that genetic liability for SLE is not associated with these disorders. However, we did not examine subpopulations of SLE, and we only studied EA individuals (42).

Previous studies have focused on the identification of risk alleles that may increase the risk of sub-phenotypes of SLE, mainly cardiovascular (CVD) and renal disease (43, 44). The largest study for CVD performed in SLE patients of EA (2088 SLE patients) found that variants at two loci, *IL19* and *SRP54-AS*, were associated with increased risk of stroke and myocardial infarction in patients with SLE (45). Interestingly, none of these loci have been associated with SLE susceptibility or CVD risk in the general population, suggesting a different mechanism for CVD in SLE (45). Likewise, a cross-phenotype meta-analysis of 6 common autoimmune diseases (including SLE) found no association between CVD risk and any SLE risk loci. However, the same study identified 8 genetic clusters strongly associated with CVD in SLE, two of which were enriched for genes in the TNFα and INFγ response, suggesting that genetic variations in these immune pathways could contributed to the increased risk of CVD in SLE (46).

Genetic studies of kidney disorders in SLE have focused on defining the genetic basis lupus nephritis (LN) and have shown that some, but not all, established SLE risk loci are also associated with LN (44). More recent studies have identified genes that are specifically associated with LN (but not with SLE susceptibility), which suggests that genetic liability for LN is a combination of general SLE risk genes and disease specific genes (44). In our study, lupus patients with nephropathy had a higher wGRS than those without nephropathy and the wGRS for SLE was associated with renal phenotypes only when patients with SLE were included in the PheWAS analysis, suggesting that renal disorders were common complications in SLE patients and associated with the wGRS for SLE, which has been previously described (47, 48). Concordant with that interpretation, a genetic predisposition to SLE was not associated with CKD in the IVWR analysis.

The observed association between the wGRS for SLE and T1D-related phenotypes in BioVU and eMERGE, along with the nominal association in the IVWR, suggest shared

genetic risk between these phenotypes. Genetic studies have not only shown that SLE and T1D share risk loci (*IRF7* (38), *SOCS1* (39), *IKZF1* (40), *TNFAIP3* (41), *IL10* (24), *TCF7* (49), and *BANK1*(50)), but they also have common risk alleles (e.g.: rs2476601 in *PTPN22*, rs2304256 in *TYK2* (36), rs2111485 in *IFIH1*(51), and rs1801274 in *FCGR2A* (52)) or risk alleles in close LD (e.g. rs10774625 with rs3184504 in *SH2B3* (39), rs11889341 with rs7574865 in *STAT4* (41), rs12785878 with rs3794060 in *DHRC7* (53)). Also, a study using hierarchical clustering of 47 pleiotropic SNPs across different autoimmune diseases (including SLE and T1D) found that both phenotypes shared cluster patterns that represent distinct molecular mechanisms affected by these variants (23).

Our study has limitations. First, the findings may not generalize to all patients but rather to those of European ancestry seeking care at a tertiary care hospital. Second, because billing codes were aggregated to assemble clinical phenotypes into phecodes and the quality of case-control discrimination varies across phenotypes, there is potential misclassification bias, which can bias the results towards the null, resulting in false negative associations. Third, many unmeasured factors (e.g., diet, smoking, exercise, medications, and other interventions) may modulate the risk for some of the phenotypes examined in the PheWAS and thus obscure a genotype-phenotype relationship. However, the consistency of the findings between the BioVU and the eMERGE populations support the validity of the findings.

In conclusion, we found that a weighted GRS for SLE was associated with an increased risk of several autoimmune-related phenotypes but not with cardiometabolic disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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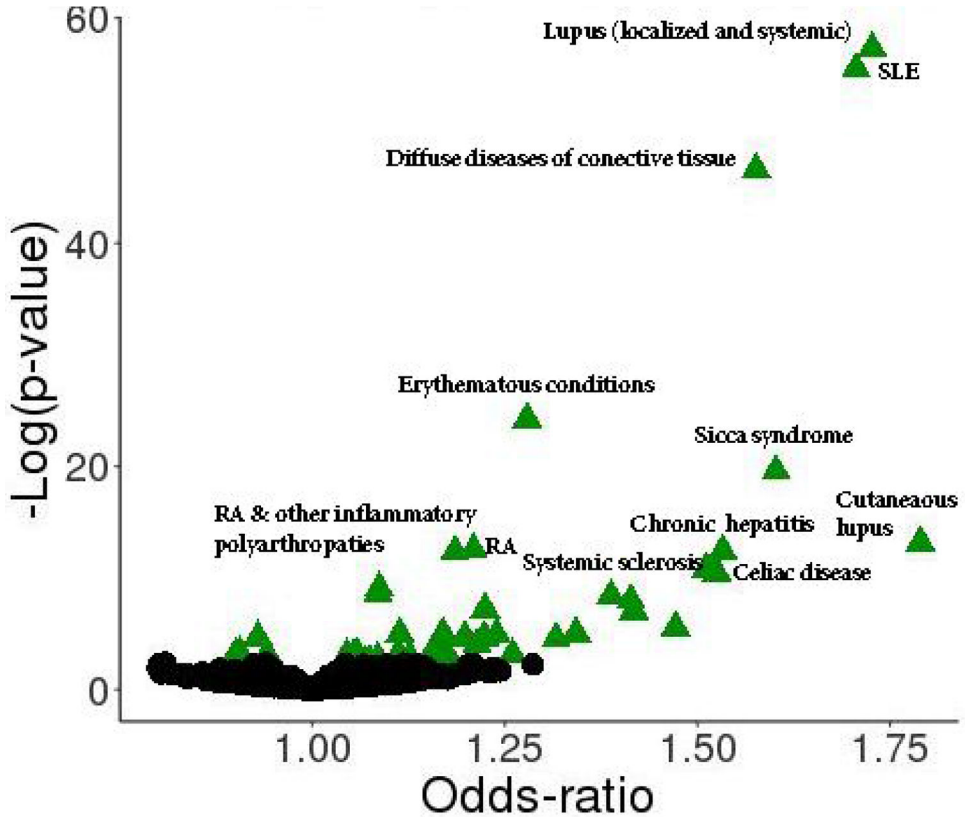

Figure 1:

Clinical diagnoses associated with a weighted genetic risk score (wGRS) for SLE in individuals of European ancestry in BioVU. Green triangles represent significant associations at FDR q<0.05. Black dots represent non-significant associations. Table 2 shows the complete list of significant associations arranged by FDR

Table 1:

Association of the weighted genetic risk score for systemic lupus erythematosus and selected cardiometabolic phenotypes

Phenotype	Phecode	# cases	# controls	OR (95%CI)	P-value
Atrial fibrillation	427.21	6601	32787	0.99 [0.96, 1.02]	0.320
Ischemic stroke	433.21	1830	47571	1.04 [0.99, 1.09]	0.935
Coronary atherosclerosis	411.4	10357	38740	1.01 [0.99, 1.04]	0.370
Type 2 diabetes	250.2	9741	38763	1.01 [0.98, 1.03]	0.279
Essential hypertension	401.1	25911	26027	0.99 [0.97, 1.01]	0.260
Chronic renal failure	585.3	4742	42181	1.05 [1.01, 1.08]	0.007
Obesity	278.1	6424	42347	1.01 [0.99, 1.04]	0.355
Type 1 diabetes	250.1	1881	38647	1.11 [1.06,1.17]	$1.05x10^{-5}$
Hyperlipidemia	272.13	9448	33414	0.99 [0.97, 1.02]	0.607

Table 2:

Clinical diagnoses associated with a weighted genetic risk score for systemic lupus erythematosus

Clinical diagnoses	BioVU				eMERGE			
	# Cases	# Controls	OR (95%CI)	FDR (q)	# Cases	# Controls	OR (95%CI)	FDR (q)
Lupus (localized and systemic)	867	47037	1.73 [1.62, 1.85]	6.64E-55	418	18304	1.82 [1.66, 2.00]	6.62E-35
Systemic lupus erythematosus	880	47037	1.71 [1.60, 1.82]	2.26E-53	393	18305	1.86 [1.69, 2.04]	6.62E-35
Diffuse diseases of connective tissue	1034	47690	1.58 [1.48, 1.68]	1.55E-44	797	17923	1.28 [1.19, 1.37]	1.07E-10
Erythematous conditions	1916	48513	1.28 [1.22, 1.34]	1.72E-22	3029	18445	1.08 [1.04, 1.13]	1.55E-04
Sicca syndrome	388	47650	1.60 [1.45, 1.77]	6.63E-18	318	17740	1.29 [1.16, 1.44]	2.29E-05
Cutaneous lupus erythematosus	161	47160	1.79 [1.54, 2.08]	1.31E-11	120	18302	2.02 [1.71, 2.40]	5.12E-15
Rheumatoid arthritis (RA)	1623	48410	1.21 [1.15, 1.27]	5.07E-11	1262	21595	1.20 [1.13, 1.26]	4.73E-09
Chronic hepatitis	285	46822	1.53 [1.37, 1.72]	5.41E-11	140	18968	1.11 [0.94, 1.31]	0.251
RA and other inflammatory polyarthropathies	2024	48385	1.19 [1.13, 1.24]	5.84E-11	1531	21594	1.18 [1.12, 1.25]	1.33 E-09
Systemic sclerosis	269	47798	1.51 [1.34, 1.70]	1.81E-09	313	17908	1.35 [1,20, 1.50]	9.72E-07
Celiac disease	242	37413	1.53 [1.35, 1.73]	3.69E-09	179	13860	1.31 [1.13, 1.51]	5.29E-04
Hypothyroidism NOS	7095	44977	1.09 [1.06, 1.12]	8.63E-08	5489	19992	1.07 [1.04, 1.10]	5.73E-05
Hypothyroidism	6807	44975	1.09 [1.06, 1.12]	2.43E-07	5229	20012	1.07 [1.04, 1.10]	7.40E-05
Nephritis and nephropathy classified elsewhere	327	42085	1.39 [1.24, 1.55]	3.62E-07	554	18075	1.17 [1.07, 1.27]	6.46E-04
Type 1 diabetes with renal manifestations	276	38522	1.41 [1.26, 1.59]	8.16E-07	165	17977	1.38 [1.19, 1.60]	7.28E-05
Other immunological findings	768	51528	1.22 [1.14, 1.31]	4.43E-06	437	26572	1.10 [1.01, 1.21]	0.062
Other specified diffuse diseases of connective tissue	241	47543	1.42 [1.25, 1.61]	6.28E-06	72	17792	1.21 [0.97, 1.53]	0.131
Unspecified diffuse connective tissue disease	149	46663	1.47 [1.25, 1.73]	1.84E-04	267	17937	1.30 [1.16, 1.47]	5.59E-05
Primary biliary cirrhosis	230	42393	1.34 [1.18, 1.53]	5.85E-04	73	20749	1.14 [0.90, 1.43]	0.293
Type 1 diabetes	1881	38647	1.11 [1.06, 1.17]	6.43E-04	1156	18035	1.11 [1.05, 1.18]	9.55E-04
Nephritis; nephrosis; renal sclerosis	836	42105	1.17 [1.09, 1.26]	6.66E-04	1263	18185	1.13 [1.06, 1.19]	1.10E-04
Raynaud's syndrome	438	46322	1.24 [1.13, 1.36]	6.72E-04	687	17499	1.17 [1.09, 1.27]	1.10E-04
Renal failure NOS	834	42085	1.17 [1.09, 1.25]	8.92E-04	824	18003	1.06 [0.99, 1.13]	0.156
Nephritis & nephropathy without glomerulonephritis	471	42066	1.22 [1.12, 1.34]	9.73E-04	851	18186	1.12 [1.04, 1.20]	0.003
Chronic lymphocytic thyroiditis	592	44562	1.20 [1.10, 1.30]	9.73E-04	437	20049	1.09 [0.99, 1.29]	0.128
Skin cancer	4321	46382	0.93 [0.90, 0.96]	9.73E-04	4570	20651	0.98[0.94, 1.01]	0.188

Clinical diagnoses	BioVU				eMERGE			
	# Cases	# Controls	OR (95%CI)	FDR (q)	# Cases	# Controls	OR (95%CI)	FDR (q)
Type 1 diabetes with ophthalmic manifestations	240	38262	1.32 [1.16, 1.50]	1.18E-03	230	18024	1.34 [1.18, 1.52]	2.85E-05
Graves' disease	425	44697	1.21 [1.10, 1.34]	4.42E-03	293	19949	1.26 [1.12, 1.41]	2.02E-04
Thyroiditis	710	44885	1.16 [1.08, 1.25]	5.57E-03	483	20027	1.07 [0.98, 1.18]	0.160
Melanomas of skin, diagnosed or personal history	1463	46873	0.91 [0.86, 0.96]	0.020	783	21163	1.01 [0.94, 1.09]	0.790
Vitamin deficiency	4596	41765	1.06 [1.02, 1.09]	0.024	3359	20746	1.02 [1.99, 1.06]	0.268
Melanomas of skin	1226	47151	0.90 [0.85, 0.96]	0.025	666	21175	1.03 [0.95, 1.11]	0.469
Other non-epithelial cancer of skin	3968	44957	0.94 [0.91, 0.97]	0.025	4428	20232	0.96 [0.93, 1.00]	0.064
Anemia in chronic kidney disease	1136	36565	1.11 [1.05, 1.18]	0.025	915	16227	1.07 [1.00, 1.15]	0.067
Glomerulonephritis	222	41878	1.26 [1.10, 1.44]	0.025	510	18124	1.17 [1.07, 1.28]	8.03E-04
Osteoarthrosis	8248	41162	1.04 [1.02, 1.07]	0.029	11092	13738	0.99 [0.97, 1.02]	0.668
Chronic airway obstruction	4931	44980	1.05 [1.02,1.09]	0.034	3843	17874	1.03 [0.99, 1.06]	0.188
Primary hypercoagulable state	426	43779	1.18 [1.07, 1.30]	0.036	466	21377	1.14 [1.04, 1.25]	0.010
Diabetic retinopathy	790	51138	1.13 [1.05, 1.21]	0.039	913	20135	1.11 [1.04, 1.18]	0.006
Type 1 diabetes with neurological manifestations	475	38597	1.16 [1.06, 1.28]	0.044	218	17911	1.13 [0.99, 1.29]	0.114
Other retinal disorders	1727	51681	1.08 [1.03, 1.14]	0.045	3987	19275	1.04 [1.00, 1.08]	0.059
Chronic thyroiditis	411	44294	1.17 [1.06, 1.30]	0.050	369	19996	1.08 [0.97, 1.20]	0.188

OR (95%CI): Odds ratio (95% confidence interval); FDR: False discovery rate (significant associations FDR q<0.05)

Table 3:

Association between genetic predictors for SLE and genetic predictors of selected cardiometabolic phenotypes in the IVWR

Cardiometabolic phenotypes	#SNPs	Estimate	[95%CI]	P-value
Atrial fibrillation	30	0.006	[−0.007, 0.019]	0.381
Ischemic stroke	30	0.009	[−0.010, 0.029]	0.342
Coronary atherosclerosis	30	0.021	[−0.004, 0.046]	0.096 *
Type 2 diabetes	30	0.027	[−0.002, 0.056]	0.070 *
Systolic blood pressure	30	0.034	[−0.101, 0.170]	0.620 *
Chronic renal failure	30	0.014	[−0.006, 0.035]	0.171 *
Waist circumference	27	0.003	[−0.007, 0.013]	0.598 *
Type 1 diabetes	18	0.249	[0.002, 0.496]	0.048 *
LDL cholesterol	26	−0.015	[−0.027, −0.003]	0.018 *
C-reactive protein	30	0.004	[−0.007, 0.014]	0.467 *
Interleukin 6	30	0.023	[−0.002, 0.049]	0.111

estimates represent change in risk for the outcome per unit of change in the exposure

* heterogeneity P-value <0.05