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Letter to the Editor

Systemic Lupus Erythematosus and B12-deficiency Anemia: MHC Pleiotropy as a Sensitivity-analysis Consideration

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Dear Editors,

We read with interest the bidirectional two-sample Mendelian randomization (MR) study by Guo *et al.*,[1] which reported that genetically predicted systemic lupus erythematosus (SLE) was associated with an increased risk of vitamin B12-deficiency anemia (B12DA; inverse-variance-weighted (IVW) odds ratio (OR) = 1.08, 95% confidence interval (CI) 1.04–1.13, $P = 2.3 \times 10^{-4}$), while genetically predicted B12DA was associated with an increased risk of SLE (IVW OR = 2.22, 95% CI 1.93–2.55, $P = 1.6 \times 10^{-29}$).[1] The purpose of this letter is to examine, direction by direction, whether extended major histocompatibility complex (MHC) pleiotropy can plausibly account for these associations, and to frame this explicitly as an instrument-level sensitivity consideration rather than an established mechanism.

The 8.1 ancestral haplotype (AH8.1; HLA-A*01:01–B*08:01–C4A-null–DRB1*03:01–DQA1*05:01–DQB1*02:01) has long been recognized as a major SLE risk unit characterized by dense linkage disequilibrium (LD) spanning classes I, II, and III.[2,3] It is tempting to invoke AH8.1 pleiotropy to interpret SLE-related MR findings. However, Guo *et al.*[1] selected 20 SLE exposure instruments genome-wide (LD-clumped at $r^2 < 0.001$ over windows > 10,000 kb). One of these, rs9262046, was itself later flagged as a potential outlier by the study's own MR-PRESSO test (Supplementary Table 5)[1]; whether this or other instruments map to the extended MHC has not been independently confirmed from Supplementary Table 3 of Guo *et al.*,[1] and we do not assert a specific count or percentage here. Because the original study did not report a sensitivity MR excluding MHC-region variants, we cannot determine how much the SLE→B12DA estimate depends on them. The forward MR-Egger intercept showed no evidence of directional pleiotropy ($P = 0.832$)[1]; stringent LD clumping was applied, and residual correlation should not be assumed. Establishing whether any MHC-linked variant materially influences the estimate requires a leave-one-out and MHC-excluded sensitivity reanalysis.

The study's MR-PRESSO outlier-exclusion step also warrants careful interpretation.[1] Guo *et al.*'s Supplementary Table 5 lists seven removed variants, including rs9262046 in the SLE→B12DA, with non-significant and partly identical *P* values (0.171–0.501).[1] We did not classify the remaining outliers as MHC variants without a separately validated coordinate audit, and therefore do not claim an MHC-enriched outlier-removal pattern. More broadly, the original Supplementary Table 4 of Guo *et al.*[1] reports an identical mean *F*-statistic of 71.14 for each of the five forward SLE-exposure analyses, despite different instrument counts and *F*-statistic ranges.[1] This apparent discrepancy complicates interpretation of instrument strength and should be clarified by the authors. We do not replace the published values with reconstructed means from a fragmented supplementary table.

The reverse B12DA→SLE analysis relies on a distinct five-variant instrument set selected for B12DA.[1] Because the forward and reverse analyses use different instruments, the specific SLE instruments used in the forward analysis cannot directly explain the reverse estimate; the reverse instrument set requires a separate pleiotropy assessment. Although the reverse IVW estimate is statistically significant (OR = 2.22, 95% CI 1.93–2.55, $P = 1.6 \times 10^{-29}$), statistical significance must not be conflated with evidence for causal direction. The Steiger test supported the forward direction ($R^2_{SLE} = 0.105$ *vs.* $R^2_{B12DA} = 4.4 \times 10^{-5}$) but did not support the reverse direction ($R^2_{B12DA} = 0.00105$ *vs.* $R^2_{SLE} = 0.0101$).[1] With only five instruments, the nonsignificant MR-Egger estimate ($P = 0.058$) and intercept ($P = 0.538$) also have limited power.[1] The reverse result should therefore be regarded as an unvalidated directional hypothesis requiring replication.

Several prior studies illustrate the internal complexity of MHC associations across ancestries. Table 1 summarizes the evidence layers relevant to this SLE–B12DA causal inference.[1-11]

Hanscombe *et al.*[4] reported ancestry-specific differences in SLE-associated MHC linkage disequilibrium structure in European and African American cohorts. Separately, Yu *et al.*[5] reported independent HLA amino-acid and C4 copy-number signals in Korean cohorts. These findings should not be merged into a single ancestry-invariant model, and their transferability to Guo *et al.*'s European-ancestry instruments remains uncertain.

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Table 1. Evidence layers relevant to SLE–B12DA causal inference

Evidence layer	Key finding	Status and relevance
Guo *et al.*'s forward instruments	20 LD-clumped SLE instruments; rs9262046 is documented in the SLE→B12DA outlier table[1]	Instrument-level MHC membership should be confirmed from the complete Supplementary Table 3 list
MHC/AH8.1 biology	AH8.1 is a high-LD SLE-associated haplotype spanning MHC classes I–III[2,3]	Established background biology; not proof that AH8.1 drives this MR estimate
Ancestry-specific MHC mapping	European/African American LD architecture differs from Korean HLA/C4 fine-mapping findings[4,5]	Established independent findings; transferability requires testing
Cross-disease MHC loci	*SKIV2L* and *NOTCH4* have been implicated in shared autoimmune architecture[6,7]	Plausible pleiotropy; relevance to the retained instruments remains untested
Outcome-side genetics	Pernicious-anemia genome-wide association study signal maps to the DR15 haplotype; DR3/DR4 associations are context-specific[8,9,11]	Does not establish a shared SLE–B12DA DR3/DR4 pathway
Cellular observation	$GZMK^+GZMH^+HLA\text{-}DR^+$ effector-memory $CD8^+$ T-cell expansion reported in active SLE[10]	Preliminary abstract-level observation; no demonstrated AH8.1 link
Summary-statistic quality control	Supplementary Table 4 reports the same mean *F*-statistic (71.14) for five distinct forward analyses[1]	Requires clarification before using these values for comparative power claims

The table distinguishes results reported by Guo *et al.*,[1] established independent MHC biology, preliminary evidence, and hypotheses requiring instrument-level verification. AH8.1, 8.1 ancestral haplotype; B12DA, vitamin B12-deficiency anemia; C4, complement component 4; CD8, cluster of differentiation 8; DR3, HLA-DR3; DR4, HLA-DR4; DR15, HLA-DR15; GZMH, granzyme H; GZMK, granzyme K; HLA, human leukocyte antigen; LD, linkage disequilibrium; MHC, major histocompatibility complex; MR, Mendelian randomization; SLE, systemic lupus erythematosus.

The specific bridge to B12DA requires outcome-side qualification. Autoimmune gastritis and pernicious anemia are possible autoimmune causes of B12 deficiency, but B12DA is not synonymous with pernicious anemia.[8,9] Earlier literature has reported DR3/DR4 associations in selected autoimmune contexts,[8,9] whereas the pernicious-anemia genome-wide association study by Laisk *et al.*[11] identified its strongest MHC signal at the DR15 haplotype (HLA-DRB1*15:01–DQA1*01:02–DQB1*06:02). These observations do not establish shared DR3/DR4 horizontal pleiotropy between SLE and B12DA.

A conference abstract reported an expanded $GZMK^+GZMH^+HLA\text{-}DR^+$ effector-memory $CD8^+$ T-cell population in active SLE.[10] Because the report did not genotype HLA alleles and is not a full-length peer-reviewed article, it does not establish that AH8.1 or HLA-DRB1*03:01 drives this cellular state; it only motivates future genotype-resolved studies.

Future analyses would benefit from the following: (1) a validated audit of the 20 SLE instruments, including chromosomal coordinates and HLA proxies, followed by leave-one-out and MHC-excluded MR analyses; (2) clarification of the identical mean F-statistics(71.14) reported for all five forward analyses despite different numbers of SNPs and R^2 values; (3) replication of the reverse B12DA→SLE direction with expanded instruments and robust directionality assessment; and (4) prospective evaluation of autoimmune and non-autoimmune causes of B12 deficiency in patients with SLE. These are research priorities, not recommendations for routine autoimmune-gastritis screening.

In conclusion, Guo *et al.*[1] provide useful hypothesis-generating evidence, but the two MR directions involve distinct instrument architectures and require different interpretations. One SLE→B12DA instrument (rs9262046) is documented via the study's own outlier table, whereas the complete retained-instrument composition should be confirmed from Guo *et al.*'s Supplementary Table 3 before broader MHC conclusions are drawn. Treating MHC pleiotropy as a sensitivity-analysis consideration, rather than an assumed explanation, will improve causal inference in future autoimmune MR studies.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Conceptualization (HR), writing – original draft (HR) revision in response to peer review (HR), and writing – review & editing (NB, HB, SI). All authors have approved the final version and publication of the manuscript.

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