Using genetics to understand the role of antihypertensive drugs modulating angiotensin-converting enzyme in immune function and inflammation

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Aim: Angiotensin-converting enzyme 2 (ACE 2) is the binding domain for severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2. Some antihypertensive drugs affect ACE2 expression or activity (ACE inhibitors and angiotensin II receptor blockers [ARBs]), suggesting use of other hypertensives might be preferable, such as calcium channel blockers (CCBs). Given the limited evidence, the International Society of Hypertension does not support such a policy.

Methods: We used a Mendelian randomization study to obtain unconfounded associations of antihypertensives, instrumented by published genetic variants in genes regulating target proteins of these drugs, with immune (lymphocyte and neutrophil percentage) and inflammatory (tumour necrosis factor alpha [TNF-α]) markers in the largest available genome-wide association studies.

Results: Genetically predicted effects of ACE inhibitors increased lymphocyte percentage (0.78, 95% confidence interval [CI] 0.35, 1.22), decreased neutrophil percentage (−0.64, 95% CI −1.09, −0.20) and possibly lowered TNF-α (−4.92, 95% CI −8.50, −1.33). CCBs showed a similar pattern for immune function (lymphocyte percentage 0.21, 95% CI 0.05 to 0.36; neutrophil percentage −0.23, 95% CI −0.39 to −0.08) but had no effect on TNF-α, as did potassium-sparing diuretics and aldosterone antagonists, and vasodilator antihypertensives. ARBs and other classes of hypertensives had no effect on immune function or TNF-α.

Conclusion: Varying effects of different classes of antihypertensives on immune and inflammatory markers do not suggest antihypertensive use based on their role in ACE2 expression, but instead suggest investigation of the role of antihypertensives in immune function and inflammation might reveal important information that could optimize their use in SARS-CoV-2.

KEYWORDS
ACE inhibitor, immune function, inflammation

Principal investigator statement: The authors confirm that the PI for this paper is Dr Zhao JV. The study only used summary statistics, without any involvement of individual information from patients.
1 | INTRODUCTION

Angiotensin-converting enzyme 2 (ACE2) is the binding domain of the severe acute respiratory syndrome coronaviruses (SARS-CoV) and SARSCoV-2. A key concern is that ACE inhibitors and angiotensin II receptor blockers (ARBs), commonly used antihypertensives, may increase ACE2 expression or activity, and thereby increase the risk of COVID-19 infection. Correspondingly, calcium channel blockers (CCBs), which do not affect ACE2 expression or activity, have been proposed as an alternative treatment. In contrast, it has also been suggested that upregulation of ACE2 expression might protect against infection if binding of the coronavirus spike protein to ACE2 leads to ACE2 downregulation, but the mechanism has not been assessed. Given the unclear role of ACE inhibitors and ARBs in infection, the International Society of Hypertension has stated “there is no good evidence to change the use of ACE-inhibitors or ARBs for the management of raised blood pressure in the context of avoiding or treating COVID-19 infection.” Consistently, limited evidence from a small observational study suggests patients using ACE inhibitors or ARBs had higher CD3 and CD8 T cell counts. Recent observational studies also show no association of use of ACE inhibitors and ARBs with risk of in-hospital death in patients with COVID-19. A potential benefit was seen with ACE inhibitor use, but this “may be due to residual confounding” and needs to be confirmed in clinical trials, as well as contextualized by mechanistic insight.

In these circumstances when experimental evidence is lacking from drug testing, Mendelian randomization (MR) provides an alternative approach by exploiting genetic variants, randomly allocated at conception, that mimic drug effects. This study design has been successfully applied to assess the efficacy of several medications. Published genetic variants corresponding to the effects of a range of antihypertensives exist. Here, to be comprehensive we used these genetic variants to assess the effects of a comprehensive range of antihypertensives on key markers of immune function and inflammation related to COVID-19, ie, lymphocyte percentage, neutrophil percentage and tumour necrosis factor alpha (TNF-α). Severe COVID-19 is associated with a major immune inflammatory response with abundant lymphocytes, neutrophils and excess inflammation. Lymphocyte percentage is an established predictor of the severity of COVID-19, neutrophils are a modulator of immune response, and TNF-α, an amplifier of inflammation, is important in acute inflammatory reactions; anti-TNF therapy has recently been proposed as a promising COVID-19 treatment strategy.

2 | METHODS

2.1 | Study design

We used an MR study to obtain unconfounded associations of the effects of antihypertensive drug use largely from published sources with lymphocyte percentage, neutrophil percentage and TNF-α. Specifically, we used as instruments published genetic variants predicting the effects of the use of different classes of antihypertensives drugs from genes regulating the drug-target proteins which were related to systolic blood pressure (SBP) in the UK Biobank. For ACE inhibitors, we also replicated our findings using genetic variants related both to ACE concentration and to SBP in the UK Biobank as instrument. As we used several different sets of instruments, for ease of comparison of the MR estimates, we used their genetic associations with SBP from the UK Biobank in 361 194 white British as a proxy for their effects on antihypertensives.

2.2 | Exposure

We obtained genetic instruments predicting the effects of the use of ACE inhibitors, ARBs and CCBs, as well as other classes of antihypertensives, specifically alpha-adrenoceptor blockers, adrenergic neurone blocking drugs, beta-adrenoceptor blockers, centrally acting antihypertensive drugs, loop diuretics, potassium sparing diuretics (PSDs) and aldosterone antagonists, renin inhibitors, thiazides and related diuretics, and vasodilator antihypertensives from published sources. Specifically, these published studies gave the genetic variants regulating the expression of the relevant drug target genes.
and selected the genetic variants related to SBP in different studies (UK Biobank summary statistics released in 2017\textsuperscript{12} or meta-analysis of UK Biobank and the International Consortium of Blood Pressure Genome-wide Association Study [GWAS]\textsuperscript{13}), as summarized in Supporting Information Table S1. We further checked the genetic association of these published single nucleotide polymorphisms (SNPs) with SBP in the latest UK Biobank summary statistics (http://www.nealelab.is/uk-biobank/) in 361 194 white British, adjusted for age, age\textsuperscript{2}, sex, interaction of sex with age, and with age\textsuperscript{2} and 20 principal components, and kept the SNPs related to SBP in the updated summary statistics. Where several different published genetic predictors of the same drug classes existed, we provide estimates for all sets of predictors. The selection process and the resulting genetic predictors are summarized in Supporting Information Tables S1 and S2. We also looked up these SNPs in Phenoscanner (http://www.phenoscanner.medschl.cam.ac.uk/upload/), a platform with comprehensive genotype-phenotype associations, to check whether these SNPs are associated with immune function or inflammation biomarkers. For ACE inhibitors, we also used as instruments serum ACE concentration, based on a published study in 4147 participants of European ancestry from the Outcome Reduction with Initial Glargine I nitervention (ORIGIN) cohort.\textsuperscript{14} Specifically, the study provided 17 SNPs predicting serum ACE. For validity we selected SNPs also related to SBP in the UK Biobank as instrument in the main analysis, and used all these SNPs (if the SNP-outcome association was available) in sensitivity analysis (Supporting Information Table S2).

2.3 | Outcomes

Genetic associations with lymphocyte percentage and neutrophil percentage were obtained from UK Biobank summary statistics provided by Neale Lab (http://www.nealelab.is/uk-biobank/). The UK Biobank is a large, ongoing, prospective cohort study with median follow-up time of 11.1 years.\textsuperscript{18} It recruited 502 713 people (intended to be aged 40-69 years, mean age 56.5 years, 45.6\% men) from 2006 to 2010 in England, Scotland and Wales, 94\% of self-reported European ancestry. Here, the genetic associations are based on 361 194 white British (167 020, 46\% men), adjusted for age, age\textsuperscript{2}, sex, interaction of sex with age, and with age\textsuperscript{2} and 20 principal components. Genetic associations with inverse normal transformed TNF-\textgreek{a} concentration were obtained from a large GWAS (n = 24 925) in people of European ancestry, mean age 44.6 years, 55\% women,\textsuperscript{19} adjusted for age, sex, body mass index and the first ten genetic principal components.

2.4 | Statistical analysis

MR estimates were based on the SNP-specific Wald estimates (genetic association with outcome divided by genetic association with the exposure), meta-analysed using inverse variance weighting with multiplicative random effects, as necessary.

In sensitivity analysis, we used different methods with different assumptions about potential bias from horizontal pleiotropy, including Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO), a mode-based method, and contamination mixture method. MR-PRESSO is able to identify outliers with potential horizontal pleiotropy amongst multiple genetic variants and provide a corrected estimate after removing these outliers.\textsuperscript{20} The mode-based method assumes the true causal effect is the value taken by the largest number of genetic variants,\textsuperscript{21} so it is robust to outliers,\textsuperscript{22} but the estimates are generally conservative.\textsuperscript{21} The contamination mixture method is similar but less conservative than the mode-based method.\textsuperscript{21,23}

All statistical analyses were conducted using R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria), and the R package "MendelianRandomization".

2.5 | Ethical approval

All the estimates of genetic associations were taken from publicly available summary statistics, obtained from studies previously collected with informed consent, without any personal information in the study.

3 | RESULTS

3.1 | Genetic instruments

We used one SNP (rs4968783 in AC\textgreek{E}) for ACE inhibitors, one SNP for ARBs (rs118123032 in AG\textgreek{T}R\textgreek{I}) and 12 SNPs for CCBs scaled to SBP (effect sizes) using UK Biobank summary statistics.\textsuperscript{12} We also used one SNP (rs4291 in AC\textgreek{E}) for ACE inhibitors and 24 SNPs for CCBs derived based on a GWAS meta-analysis of the UK Biobank and the International Consortium of Blood Pressure.\textsuperscript{13} For the 17 SNPs predicting ACE concentration, two SNPs (and also their proxies) were not available in the UK Biobank, leaving 15 SNPs. Of these only three SNPs were also related to SBP in the UK Biobank and retained. In sensitivity analysis, we used all the 15 SNPs as instruments (Supporting Information Table S2).

For the other classes of antihypertensives, we used eight SNPs in ADRA2A, TH, ADRA1D, ADRA1B and ADRA1A for alpha-adrenoceptor blockers; three SNPs in ADRA2A and KCNJ1 for adrenergic neurone blocking drugs; 10 SNPs in ADRB1, ADR\textgreek{A}1D, ADRB2, ADR\textgreek{A}1B, KCNH2, ADRA1A and ADR\textgreek{B}3 for beta-adrenoceptor blockers; six SNPs in ADRA2A, GAB\textgreek{A}5, NISCH, GAB\textgreek{A}2 and GAB\textgreek{A}6 for centrally acting antihypertensive drugs; three SNPs in SLC12A1, SLC12A2 and SLC12A5 for loop diuretics; three SNPs in SCN\textgreek{N}1D, SCN\textgreek{N}1B and NR\textgreek{C}32 for PSDs and aldosterone antagonists; one SNP in REN for renin inhibitors, seven SNPs in GAB\textgreek{R}B3, GAB\textgreek{R}G3, SLC12A1, GAB\textgreek{R}G1, GAB\textgreek{R}B2, GAB\textgreek{R}A6 and CA1 for thiazides and related diuretics; and nine SNPs in NPR\textgreek{I}, KCNJ1, PTGIR, PDE5A, EDNRA and CA1 for vasodilator antihypertensives (Supporting Information Table S2). None of
The genetic variants are directly related to immune function in Phenoscanner.

3.2 Effects on immune and inflammatory markers

The genetically predicted effects of the use of ACE inhibitors and CCBs both increased lymphocyte percentage and decreased neutrophil percentage, with a larger effect size for ACE inhibitors (Table 1). The estimates for ACE inhibitors were robust to using genetic variants predicting ACE concentration (Table 2). The genetically predicted effects of ARBs did not affect lymphocyte percentage or neutrophil percentage (Table 1). The estimates for ACE inhibitors and CCBs were consistent using published genetic variants derived based on the UK Biobank or on the meta-analysis of the UK Biobank and the International Consortium of Blood Pressure (Table 1). Two other classes of antihypertensives, including ARBs, which also increase ACE2 expression, had different effects from ACE inhibitors. CCBs, PSDs and aldosterone antagonists (such as spironolactone) as well as vasodilator antihypertensives (such as ambrisentan), also showed similar effects to ACE inhibitors and CCBs on immune markers, ie, they increased lymphocyte percentage and decreased neutrophil percentage (Table 3).

Genetically predicted ACE inhibitors may lower TNF-α (Tables 4 and 5), especially when using genetic variants predicting ACE concentration (Table 5). The estimates were robust to using all the genetic variants predicting ACE concentration and different analysis methods (Supporting Information Tables S3 and S4). CCBs did not clearly affect TNF-α, and nor did other hypertensives (Table 6). The estimates were robust to different analysis methods (Supporting Information Tables S5 and S6).

4 DISCUSSION

Using genetic proxies for drug effects, we found ACE inhibitors, which increase ACE2 expression, increased lymphocyte percentage, decreased neutrophil percentage and may also lower TNF-α. CCBs, PSDs and aldosterone antagonists, and vasodilator antihypertensives similarly increased lymphocyte percentage and decreased neutrophil percentage, but were unrelated to TNF-α. However, other antihypertensives, including ARBs, which also increase ACE2 expression, had no effect on immune markers or inflammation. As such, consistent with the statement from the International Society of Hypertension and previous observational studies, our findings do not suggest use of antihypertensive drugs based on their role in ACE2 expression, but do not exclude the possibility of their use based on effects on the immune system.

Lower lymphocyte percentage is predictive of higher severity of COVID-19 infection. Anti-TNF drugs have been hypothesized as a potential treatment for COVID-19 infection. As such, the associations of ACE inhibitors with lower lymphocyte, lower neutrophil and possibly lower TNF-α are not consistent with the hypothesis that ACE inhibitors impair immune function and increase the risk of infection.

Given the complex immune response to COVID-19 infection, these associations should not be interpreted as a protective role of ACE inhibitors on infection. In vivo experiments suggest ACE inhibitors, such as captopril, do not reduce SARS-CoV-2 infection. Effects via modulating the immune reaction have not been assessed. A beneficial association of the use of ACE inhibitors with COVID mortality has been observed in a systematic review and meta-analysis of observational studies. ACE inhibitors might affect immune function and inflammation via expression of ACE2. However, ARBs, which also affect ACE2 expression, had different effects from ACE inhibitors. The target domain of COVID-19, ACE2, has high expression in the testes. Sex hormones modulate immune response and inflammation in animals. Testosterone is generally immunosuppressive, while oestrogen tends to be immune-promoting. Genetically predicted testosterone was associated with lower lymphocyte percentage in a recent MR study. Statins, which lower testosterone, have been hypothesized to be protective for COVID-19 by modulation of NF-κB, mediated by TNF-α. Further investigation of these mechanistic pathways might help find a unifying explanation for differences in patterns of COVID-19 by sex and setting, similar to differences in other hormone-modulated conditions by setting.

Despite consistency across genetic instruments, this study has several limitations. First, MR relies on three assumptions, ie, the genetic instruments are related to the exposure, are not related to potential confounders and the effect of the genetic instrument on the outcome is exclusively through the exposure. To satisfy these

| Class | Source | ΔSNPs | Lymphocyte | Neutrophil |
|-------|--------|-------|-------------|------------|
|       |        |       | Beta 95% CI  | P          | Beta 95% CI  | P          |
| ACEI  | Walker et al 12 | 1 | 0.78 0.35, 1.22 5 × 10^-4 | -0.64 -1.09, -0.20 0.004 |
|       | Gill et al 13   | 1 | 0.87 0.40, 1.35 3 × 10^-4 | -0.73 -1.21, -0.25 0.003 |
| ARBs  | Walker et al 12 | 1 | -0.61 -1.38, 0.17 0.12 | 0.69 -0.09, 1.47 0.09 |
| CCBs  | Walker et al 12 | 12 | 0.21 0.05, 0.36 0.01 | -0.23 -0.39, -0.08 0.004 |
|       | Gill et al 13   | 24 | 0.24 0.16, 0.31 2.7 × 10^-9 | -0.21 -0.29, -0.13 1.9 × 10^-7 |

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CI, confidence interval; SNP, single nucleotide polymorphism.
assumptions, we used SNPs related to the expression of genes regulating the drug target proteins. We also checked that these SNPs are not directly related to immune function, although we cannot exclude the possibility that unidentified pleiotropic association may exist, which is a common limitation of MR studies. However, we compared the estimates using different SNP selections, which gave consistent findings. Given the possibility of unidentified pleiotropy, we used several different analytic methods that are based on different assumptions. The consistent directions of associations across these methods add confidence to the findings. These methods may differ in precision, for example the estimates from mode-based methods are generally more conservative than the contamination mixture method $^{21}$ so they are used as sensitivity analysis supplementary to the main analysis.

Second, measurement error might exist in the single time-point assay of lymphocyte percentage, neutrophil percentage and TNF-$\alpha$. However, any measurement error should be nondifferential, thus bias towards the null, rather than give positive associations with lymphocyte percentage and inverse associations with neutrophil percentage.

Third, the genetic associations with TNF-$\alpha$ were obtained from a relatively small GWAS, which might explain the wide confidence intervals in the association of ACE inhibitors with TNF-$\alpha$. The associations were also adjusted for body mass index, which can cause a bias in some situations $^{39}$ but is unlikely to do so here $^{40}$. The study was also limited by the few large GWAS of immunity, thus replication in other large GWAS when they are available will be worthwhile.

Fourth, genetic assumptions, we used SNPs related to the expression of genes regulating the drug target proteins. We also checked that these SNPs are not directly related to immune function, although we cannot exclude the possibility that unidentified pleiotropic association may exist, which is a common limitation of MR studies. However, we compared

### TABLE 2  
Associations of ACE inhibitors with lymphocyte and neutrophil percentage using ACE SNPs as instrument

| Class                          | Source                  | #SNPs | Beta  | 95% CI          | P   |
|--------------------------------|-------------------------|-------|-------|-----------------|-----|
| ACEI                           | Genetic predictors of ACE $^{14}$ | 3     | 0.52  | 0.14, 0.90      | 0.01|
| Neutrophil                     |                          |       | −0.61 | −0.99, −0.22    | 0.002|

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; CI, confidence interval; SNP, single nucleotide polymorphism.

### TABLE 3  
Associations of other antihypertensive drugs with lymphocyte and neutrophil percentage using published genetic variants

| Class                                | Source                  | #SNPs | Beta  | 95% CI          | P   |
|--------------------------------------|-------------------------|-------|-------|-----------------|-----|
| Alpha-adrenoceptor blockers          | Walker et al $^{12}$    | 8     | −0.08 | −0.28, 0.11     | 0.41|
| Adrenergic neurone blockers          | Walker et al $^{12}$    | 3     | 0.46  | 0.05, 0.87      | 0.03|
| Beta-adrenoceptor blockers           | Walker et al $^{12}$    | 10    | 0.01  | −0.17, 0.19     | 0.93|
| Central acting antihypertensives     | Walker et al $^{12}$    | 6     | 0.14  | −0.08, 0.37     | 0.21|
| Loop diuretics                      | Walker et al $^{12}$    | 6     | 0.10  | −0.39, 0.59     | 0.68|
| PDEs and aldosterone antagonists     | Walker et al $^{12}$    | 3     | 0.20  | −0.22, 0.63     | 0.34|
| Renin inhibitors                     | Walker et al $^{12}$    | 3     | 0.77  | 0.35, 1.18      | 0.34|
| Thiazides and related diuretics      | Walker et al $^{12}$    | 7     | 0.22  | −0.08, 0.52     | 0.15|
| Vasodilator antihypertensives        | Walker et al $^{12}$    | 9     | 0.50  | 0.04, 0.97      | 0.03|

Abbreviations: CI, confidence interval; SNP, single nucleotide polymorphism.

### TABLE 4  
Associations of antihypertensive drugs with TNF-$\alpha$ using published genetic variants for ACE inhibitors, ARBs and CCBs

| Class                          | Source                  | #SNPs | Beta  | 95% CI          | P   |
|--------------------------------|-------------------------|-------|-------|-----------------|-----|
| ACEI                           | Walker et al $^{12}$    | 1     | −3.95 | −8.40, 0.50     | 0.08|
| ARBs                           | Gill et al $^{13}$      | 1     | −4.11 | −8.94, 0.73     | 0.10|
| CCBs                           | Walker et al $^{12}$    | 2     | −2.58 | −12.3, 7.11     | 0.60|
| Gill et al $^{13}$             | 11                      | 0.39  | −1.92, 2.70    | 0.74|
| Gill et al $^{13}$             | 24                      | 0.83  | 0.02, 1.64      | 0.05|

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CI, confidence interval; SNP, single nucleotide polymorphism; TNF-$\alpha$, tumour necrosis factor alpha.

### TABLE 5  
Associations of ACE inhibitors with TNF-$\alpha$ using ACE SNPs as instrument

| Class                          | Source                  | #SNPs | Beta  | 95% CI          | P   |
|--------------------------------|-------------------------|-------|-------|-----------------|-----|
| ACEI                           | Genetic predictors of ACE $^{14}$ | 3     | −4.92 | −8.50, −1.33    | 0.007|

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; CI, confidence interval; SNP, single nucleotide polymorphism; TNF-$\alpha$, tumour necrosis factor alpha.
associations with neutrophil and lymphocyte percentages were taken from the participants of UK Biobank, who are healthier than the general population, so the estimates might be underestimated and the MR estimates may not be applicable to patients with infections. However, the direction of associations should be consistent, which adds to the limited evidence of these antihypertensives in immune function and inflammation. Fifth, the associations in Europeans may not apply to other populations, such as Asians. However, causal effects should be consistent across settings. Sixth, genetic effects might be diluted by compensatory processes or feedback mechanisms. The compensation would be expected to mitigate the genetic effects, thus biasing toward the null, which may explain some null associations such as CCBs and testosterone. The effect sizes of the associations are relatively small, which may not be clinically significant, but a small effect size may still matter for population health, especially for antihypertensive drugs which are commonly used. In addition, MR study is more useful in determining the direction of causation than the magnitude of an effect size, so the effect on immune function and inflammation might not be comparable to the short-term effect of taking antihypertensive drugs.

From the perspective of clinical practice, our findings do not support the replacement of ACE inhibitors with CCBs because they have similar effects on key markers of immune function, although different effects on inflammation. Our findings suggest a role of ACE inhibitors in immune function and inflammation, but this may not be due to, or at least not totally due, to ACE2 expression because ARBs which also affect ACE2 expression did not affect lymphocyte percentage, neutrophil percentage or TNF-α. Exploring the underlying pathways, especially the pathways that differ between these antihypertensives, would be worthwhile.

5 CONCLUSION

The effect of ACE inhibitors and the null effect of ARBs on key markers of immune function and inflammation support the current International Society of Hypertension statement that there is no evidence to indicate the use of antihypertensive drugs based on their role in ACE2 expression. However, concern about the effects of ACE inhibitors on immune function has revealed a complex pattern of effects of different classes of antihypertensive drugs whose elucidation might be relevant to both infectious diseases and optimization of the use of antihypertensives which should be further explored.

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

J.V.Z. generated the idea, conducted the analysis and reported the work described in this article. C.M.S. and G.M.L. reviewed the first draft and suggested important additions to the design and content. All authors reviewed and approved the final version.

DATA AVAILABILITY STATEMENT

The data is publicly available. The GWAS summary statistics can be obtained from http://www.nealelab.is/uk-biobank/ and http://www.computationalmedicine.fi/data#NMR_GWAS.

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**SUPPORTING INFORMATION**
Additional supporting information may be found online in the Supporting Information section at the end of this article.

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