Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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SARS-CoV-2 receptor *ACE2* gene expression and RAAS inhibitors

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) uses membrane-bound angiotensin-converting enzyme 2 (ACE2) to gain cell entry, leading to coronavirus disease 2019 (COVID-19). ACE2 counterbalances the effects of AT1 activation by angiotensin II as part of the renin–angiotensin–aldosterone system (RAAS). Lei Fang and colleagues[1] hypothesised that cardiometabolic diseases (eg, hypertension, diabetes, and cardiac diseases) and RAAS inhibitors (eg, ACE inhibitors (ACEIs) and angiotensin II receptor blockers [ARBs]) might increase the risk of COVID-19 by upregulating ACE2. However, this provocative hypothesis and subsequent debate have occurred in the absence of any empirical evidence that cardiometabolic diseases or RAAS inhibitors affect ACE2 expression in human lungs.

To address this issue, we analysed the gene expression of *ACE2* and two host cell proteases, *TMPRSS2* and *ADAM17*, used as cofactors for virus entry in 1051 lung tissue samples from the Human Lung Tissue Expression

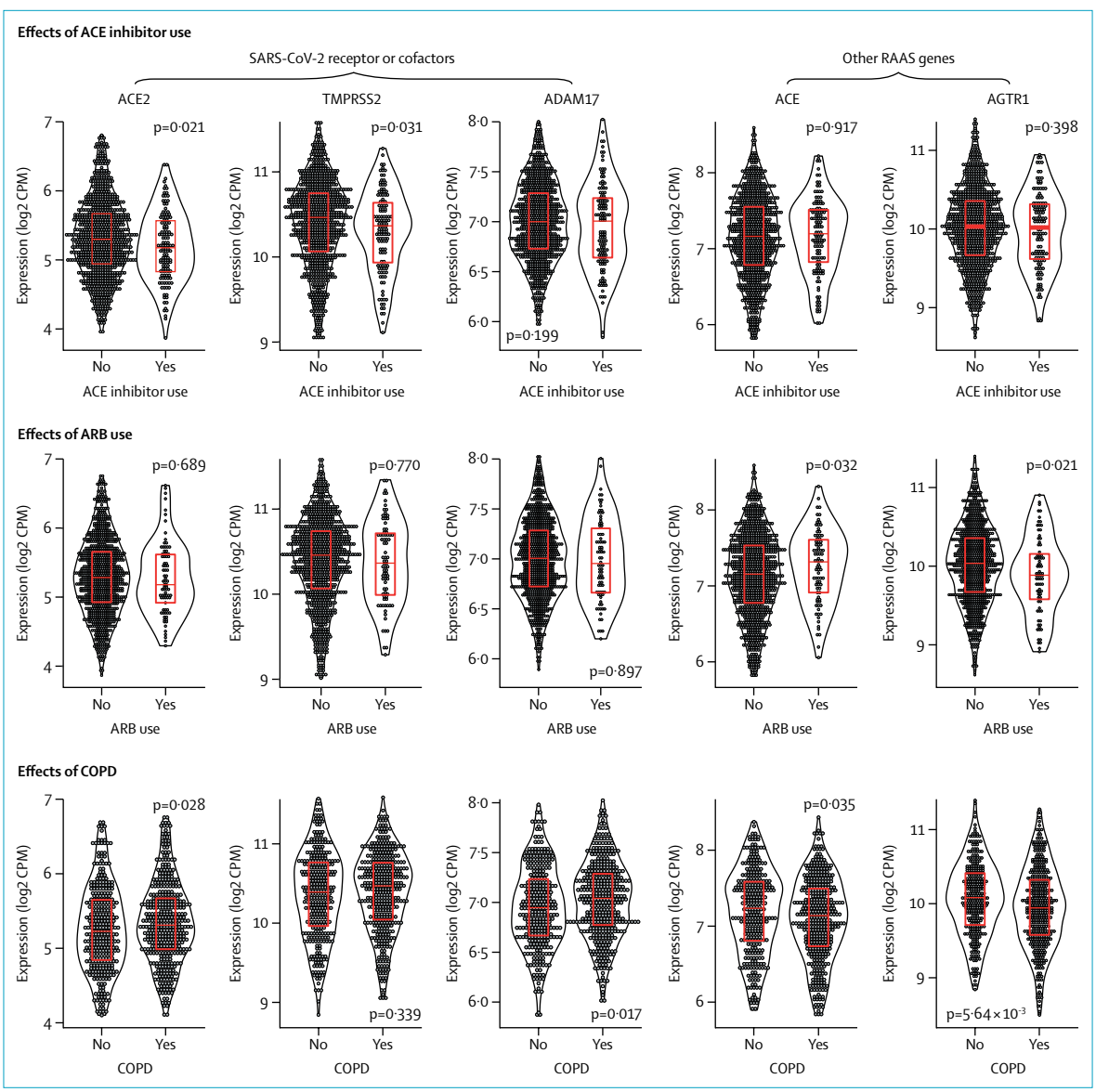

***Figure*: Expression of SARS-CoV-2 receptor or cofactors and RAAS-related genes in human lung tissue**
Lung tissue gene expression and phenotype data from 1051 participants in the Lung eQTL Study.[2] Violin plots show the distribution of gene expression levels in log2 CPM (outliers have been removed). Superimposed box plots show median (IQR). p values are from robust linear models, adjusted for current smoking status. ARB=angiotensin II receptor blocker. COPD=chronic obstructive pulmonary disease. CPM=counts per million. eQTL=expression quantitative trait loci. RAAS=renin–angiotensin–aldosterone system. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Quantitative Trait Loci Study (Lung eQTL Study).[2] Additionally, we analysed the expression of two other important RAAS genes: *ACE* (the protein product of which converts angiotensin I to angiotensin II) and *AGTR1* (encodes for AT1). We related gene expression to each comorbidity or medication using a robust linear model. To determine relevant covariates and replicate our findings, we analysed two additional datasets: St Paul's Hospital cohort[3] and the Lung Tissue Research Consortium (GEO #GSE47460) (appendix p 2).

See Online for appendix

ACEI use was associated with significantly lower *ACE2* and *TMPRSS2* expression, but was not associated with *ADAM17* expression. Neither cardiometabolic diseases (individually or in composite) nor ARBs were associated with altered expression of these genes (figure; appendix pp 3–5), suggesting any increased risk of COVID-19 in these subpopulations is not related to upregulation of the SARS-CoV-2 receptor or cofactors in the lung; although, their expression in the rest of the respiratory tract still needs to be studied. In contrast to studies in other tissue types,[4] we found that ACEIs reduce *ACE2* expression in lung. It is possible that long-term ACEI use downregulates lung *ACE2* expression by reducing substrate (ie, angiotensin II) availability, which might also explain why no effect of ARBs was seen. In theory, *ACE2* downregulation might reduce the risk of SARS-CoV-2 infection because of reduced virus receptor availability. However, animal models suggest that ACE2 deficiency could exaggerate acute lung injury because of an imbalance in angiotensin II or AT1 signalling.[5] The clinical significance of our finding is therefore unknown.

Neither cardiometabolic diseases nor ACEI use were associated with *ACE* or *AGTR1* expression, whereas use of ARBs was associated with increased *ACE* and decreased *AGTR1* expression. The effect of these opposing changes on overall angiotensin II–AT1 signalling and risk of severe COVID-19 is uncertain. The amount of circulating angiotensin II protein might further modify the risk of lung injury, but was not measured in our cohort.

Chronic obstructive pulmonary disease (COPD) is also a proposed risk factor for severe COVID-19,[6] which prompted us to examine its effects on the expression of these genes in the lung. COPD was associated with increased *ACE2* expression in the Lung eQTL Study, a finding that was replicated in the Lung Tissue Research Consortium and St Paul's Hospital cohort. The association between COPD and *ADAM17* and *TMPRSS2* expression was inconsistent across the datasets (figure; appendix pp 3–5). Whether this increased expression translates to increased risk of SARS-CoV-2 infection is unknown because there is no in-vivo evidence that increased receptor availability increases viral entry. Additionally, COPD was associated with decreased expression of *ACE* and *AGTR1* in the Lung eQTL Study, and its association with decreased *AGTR1* expression was replicated in the Lung Tissue Research Consortium dataset (figure; appendix pp 3–5). The combination of increased *ACE2* but decreased *ACE* or *AGTR1* expression might be protective against acute lung injury,[7] which could explain why there is no clear excess of patients with COPD among severe COVID-19 cases.[6]

We also examined the effects of smoking status on lung gene expression. Current smoking was associated with increased expression of *ACE2*, *TMPRSS2*, *ADAM17*, and *ACE* (appendix pp 3–6), which might represent a so-called perfect storm of excess viral receptor or cofactor availability and excess angiotensin II or AT1 activity, leading to severe COVID-19. The strong association between air pollution exposure and COVID-19 mortality[8] suggests that inhaled noxious particles influence COVID-19 outcomes. Whether current cigarette smoking is an independent risk factor for severe COVID-19 is not yet clear.[9]

The limitations of our study are that we analysed gene rather than protein expression, although our recent work shows that the two are positively correlated,[3] and that details such as duration of cardiometabolic diseases and RAAS inhibitor dose are not available.

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*Stephen Milne, Chen Xi Yang, Wim Timens, Yohan Bossé, Don D Sin
stephen.milne@hli.ubc.ca

Centre for Heart Lung Innovation, University of British Colombia at St Paul's Hospital, Vancouver V6Z 1Y6, BC, Canada (SM, CXY, DDS); Division of Respiratory Medicine, University of British Columbia, Vancouver, BC, Canada (SM, CXY, DDS); Department of Pathology and Medical Biology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands (WT); and Institut universitaire de cardiologie et de pneumologie de Québec, Department of Molecular Medicine, Laval University, Quebec City, QC, Canada (YB)

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