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COVID-19

Identifying factors contributing to increased susceptibility to COVID-19 risk: a systematic review of Mendelian randomization studies

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Abstract

Background: To summarize modifiable factors for coronavirus disease 2019 (COVID-19) suggested by Mendelian randomization studies.

Methods: In this systematic review, we searched PubMed, EMBASE and MEDLINE, from inception to 15 November 2021, for Mendelian randomization studies in English. We selected studies that assessed associations of genetically predicted exposures with COVID-19-related outcomes (severity, hospitalization and susceptibility). Risk of bias of the included studies was evaluated based on the consideration of the three main assumptions for instrumental variable analyses.

Results: We identified 700 studies through systematic search, of which 50 Mendelian randomization studies were included. Included studies have explored a wide range of socio-demographic factors, lifestyle attributes, anthropometrics and biomarkers, predisposition to diseases and druggable targets in COVID-19 risk. Mendelian randomization studies suggested that increases in smoking, obesity and inflammatory factors were associated with higher risk of COVID-19. Predisposition to ischaemic stroke, combined bipolar disorder and schizophrenia, attention-deficit and hyperactivity disorder, chronic kidney disease and idiopathic pulmonary fibrosis was potentially associated with higher COVID-19 risk. Druggable targets, such as higher protein expression of histo-blood group ABO system transferase (ABO), interleukin (IL)-6 and lower protein expression of 2′-5′ oligoadenylate synthetase 1 (OAS1) were associated with higher risk of COVID-19. There was no strong genetic evidence supporting the role of vitamin D, glycaemic traits and predisposition to cardiometabolic diseases in COVID-19 risk.

Conclusion: This review summarizes modifiable factors for intervention (e.g. smoking, obesity and inflammatory factors) and proteomic signatures (e.g. OAS1 and IL-6) that could help identify drugs for treating COVID-19.

Key Messages

- This systematic review provides an up-to-date summary of the evidence on modifiable factors that contribute to COVID-19 outcomes (severity, hospitalization, susceptibility) from Mendelian randomization studies.
- This systematic review highlights modifiable factors for intervention, such as smoking, which are in favour of the recent call from the World Health Organization regarding the importance of tobacco cessation in reducing severe COVID-19.
- Identified druggable targets shall facilitate prioritization of drug targets for assessment of efficacy in COVID-19 treatment in clinical trial settings.
- Mendelian randomization studies in other ethnic populations would be valuable in assessing external validity from existing studies that were predominantly in European populations.

Background

The coronavirus disease 2019 (COVID-19) pandemic is a major global health threat. As of 1 December 2021, the number of cases exceeded 261 million and led to 5.2 million deaths.[1] COVID-19-related research has increased exponentially, although concerns over quality exist,[2] including retraction of studies using questionable data sources.[3] Paradoxical protective effects, such as smoking reducing the risk of COVID-19-related deaths,[4] could arise from selection bias in an observational setting.[5] Given the uncertainty of findings from a single study, in particular observational studies, systematic reviews are increasingly used to consolidate the evidence base for prevention and treatment of COVID-19.[6,7]

Identifying causes of increased susceptibility, hospitalization and severity to COVID-19 based on less biased epidemiologic designs is important to inform prevention and treatment strategies. Mendelian randomization, a study design less susceptible to confounding than conventional observational studies, can help identify causes and possible therapeutic targets.[8] For example, a Mendelian randomization study showed genetic inhibition of the interleukin (IL)-6 receptor may protect against severe COVID-19,[9] consistently with subsequent randomized–controlled trials (RCTs).[6] However, to date, there is no systematic review of Mendelian randomization studies concerning COVID-19 and hence possible targets of intervention/drug reposition opportunities have not been systematically evaluated. This is particularly important as herd immunity is challenging to achieve in view of newly emerging variants,[10] vaccine hesitancy[11] and vaccine inequity.[12] We conducted this systematic review to evaluate possible factors (e.g. socio-demographic factors, lifestyle attributes, anthropometrics, biomarkers, predisposition to diseases and druggable targets) contributing to the risk of COVID-19 from Mendelian randomization studies.

Methods

We conducted this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[13] The protocol of the systematic review was registered at the International Prospective Register of Systematic Reviews (PROSPERO) on 30 April 2021 (CRD42021252079).

Sources of information and study selection

We included Mendelian randomization studies that assessed the associations of genetically predicted exposures with COVID-19-related outcomes. COVID-19 outcomes included the severity, hospitalization and susceptibility of COVID-19. Two reviewers (Y.L. and T.H.T.W.) independently searched published studies in PubMed, EMBASE and MEDLINE from inception to 15 November 2021. We used a pre-defined search strategy, with key search terms ('Mendelian randomization' OR 'Mendelian randomisation') AND ('COVID19' OR 'coronavirus disease 2019') AND ('genome-wide association study' OR 'GWAS'). We restricted the language to English and human studies using PubMed filters. We also manually searched the reference lists of the retrieved studies to identify additional studies. Detailed search term combinations for each database can be found in the Supplementary material (available as Supplementary data at *IJE* online).

Eligibility criteria

We excluded studies that (i) were duplicated across databases; (ii) were without sufficient original data (e.g. reviews, commentaries, corrections and abstracts); (iii) were not Mendelian randomization studies, including studies that only reported variant–outcome associations [i.e. a reduced form of instrumental variable (IV) analysis]; or (iv) did not include COVID-19 phenotypes as the outcomes. Two reviewers (Y.L. and T.H.T.W.) independently screened the titles, abstracts and full text if necessary of all retrieved studies, and compared and resolved any possible discrepancies. A third reviewer (S.L.) was consulted if the discrepancies were not resolved. The study selection process was summarized in a PRISMA flowchart.

Data extraction

For each included Mendelian randomization study, one reviewer (Y.L.) extracted key information using a tailored template based on the PRISMA checklist[13] and the guidelines for strengthening the reporting of observational studies in epidemiology using Mendelian randomization (STROBE-MR).[14] These included the name of the first author, the year of publication, the type of Mendelian randomization study (one-sample or two-sample), the number of genetic variants, the data source(s) and ancestry for the genetic variants and outcomes, the sample size of the outcome, the effect estimate for exposure on outcome and the corresponding 95% CI. For a one-sample Mendelian randomization study, both one-sample methods (e.g. two-stage least square and a genetic risk score) and two-sample methods (e.g. a meta-analysis of Wald estimates, i.e. inverse variance weighted) were considered as the main analysis.[15] For a two-sample Mendelian randomization study, inverse variance weighted was normally considered as the main analysis.[15] By default, we extracted the effect estimates with 95% CI from the main analysis reported in the main text. In addition, for associations reaching statistical significance (nominal P-value < 0.05, or P-value after correcting for multiple testing, if mentioned in the original studies), we additionally extracted the results from the sensitivity analyses (e.g. different sets of genetic variants or statistical methods). The extracted data were verified by another reviewer (S.L.).

Risk of biases in each study

There is no quality assessment tool available for systematic reviews of Mendelian randomization studies. Mendelian randomization studies rely on three main IV assumptions for a valid causal inference.[16] Specifically, the genetic variant is strongly associated with the exposure (IV1: relevance), independent of the (measured and unmeasured) confounding factors of the exposure–outcome association (IV2: independence) and has no effect on the outcome except via the exposure (IV3: exclusion-restriction).[16] Reviewers (S.L., Y.L. and S.L.A.Y.) independently evaluated whether the included Mendelian randomization studies assessed the validity of each IV assumption adequately. Any inconsistencies were resolved by discussion until a consensus was reached.

IV1: Relevance

For the relevance assumption, we checked the strength of the instruments such as P-values of the variant–exposure association (usually genome-wide significant, P-value $< 5 \times 10^{-8}$), instrument strength (F-statistic > 10 indicates that weak instrument bias is less likely) and the variance of exposure explained by the variants (R^2).[17] We rated IV1 as 'high' if the selection of variants used genome-wide significance (P-value $< 5 \times 10^{-8}$) and an F-statistic > 10; as 'moderate' if the selection of variants used a more lenient significance threshold (P-value range from 0.05 to 5×10^{-8}) and an F-statistic > 10; and 'poor' if none of above was assessed, reported or met.

IV2: Independence

It is assumed that the variant is largely independent of potential confounders because of the random allocation of genetic variants at conception.[18] For the independence assumption, we evaluated whether IV2 was assessed in each study, such as exploring the variant–confounder(s) association using individual-level data or curated databases (e.g. PhenoScanner),[19] controlling for population stratification or use of ethnically homogenous populations, or assessing the possibility of confounding by linkage disequilibrium (LD) using Bayesian colocalization analysis (for *cis*-Mendelian randomization studies only).[20] The posterior probability of Hypothesis 4 (two traits share a common variant) > 0.80 from colocalization analysis supports causality, i.e. the putative association by the *cis*-Mendelian randomization study is less likely confounded by variants in LD.[20] We rated IV2 as 'high' if this assumption was properly assessed using the above-mentioned approaches, 'moderate' if this assumption was only described and 'poor' if the assumption was not described.

IV3: Exclusion-restriction

Although the exclusion-restriction assumption cannot be fully verified, this can be partly checked via assessment of horizontal pleiotropy,[21] e.g. searching for genetic pleiotropic effects via curated databases or the use of statistical methods that rely on different and alternative IV assumptions, such as

weighted median (majority valid), weighted mode (plurality valid) and Mendelian randomization-Egger (instrument strength independent of direct effect).[22–24] We rated IV3 as 'high' if this assumption was properly assessed using above-mentioned approaches, 'moderate' if this assumption was only described and 'poor' if the assumption was not described.

Searching preprint servers

Preprints are now increasingly used in the dissemination of COVID-19 research.[25] Two reviewers (T.H.T.W. and Y.L.) also searched unpublished studies from preprint servers (medRxiv and bioRxiv) using the same search strategy, which may help anticipate upcoming research findings. Two reviewers (T.H.T.W. and S.L.) identified eligible studies with the same selection criteria. We did not include preprints that were published in peer-reviewed journals as they would have been included in our main search. As these preprints have not been peer-reviewed, we only briefly summarized the findings given the concerns over validity.[26]

Meta-analysis

Based on a preliminary search, we found that the majority of the Mendelian randomization studies used the COVID-19 Host Genetics Initiative (HGI)[27] to obtain genetic

associations with COVID-19, although the version and hence the sample size used varied across studies. As such, we did not conduct a meta-analysis to pool estimates from Mendelian randomization studies of the same topic.

Results

The search returned 700 studies, of which 318 remained after removing 382 duplicates. A further 198 studies were excluded on title and/or abstract as not meeting the eligibility criteria, leaving 120 studies. A further 75 studies were excluded after full text review because they were not Mendelian randomization studies or did not assess COVID-19 outcomes. Five additional studies were identified via the reference list. In total, 50 eligible Mendelian randomization studies were included in this review (Figure 1). The included studies were published between May 2020 and November 2021.

The characteristics of the included Mendelian randomization studies are presented in Table 1. Of the 50 studies, 46 used a two-sample study design. Forty-one studies used COVID-19 HGI to obtain the genetic associations of outcomes, whilst several studies used the GWAS conducted in the UK Biobank,[28] cohorts from Italy and Spain,[29] the US Million Veteran Program[30] and China Wuhan Union Hospital. Thirty-seven studies focused on the role of socio-demographic factors, lifestyle attributes, anthropometrics, biomarkers and predisposition to disease;[27,31–66] and 13
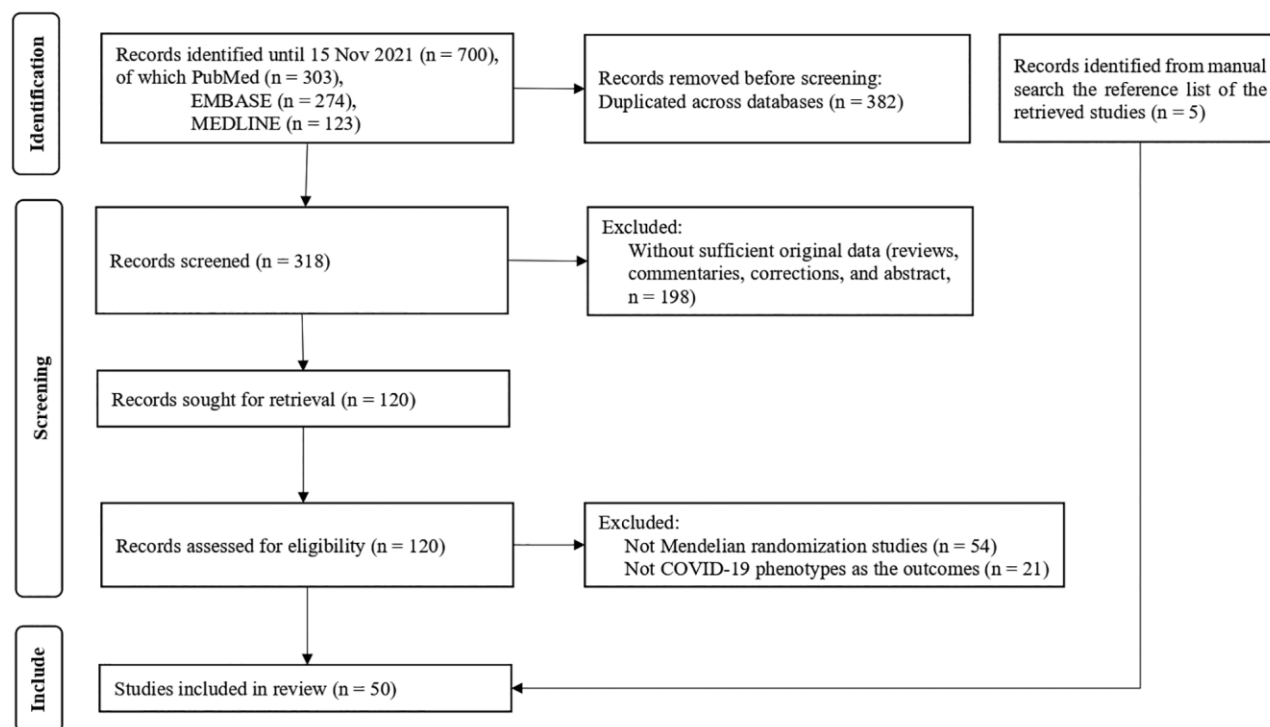

Figure 1 Flow diagram of the study search and selection process

Table 1 The characteristics of the included Mendelian randomization studies of factors on COVID-19 outcomes [(A) severity, (B) hospitalization, (C) susceptibility]

Study (author, year)	Study design	Category	Exposure (unit)	Outcomes (log odds) [(A) severity, (B) hospitalization, (C) susceptibility]	Source of outcome	Ethnicity of exposure	Ethnicity of outcome
Anisul M 2021	Two-sample	Druggable targets	pQTL (SD)	A, B, C	COVID-19 HGI R4	European	European
Au Yeung SL 2021	Two-sample	Biomarkers, predisposition to diseases	2-h glucose (mmol/L), fasting glucose (mmol/L), HbA$_{1c}$ (%), type 2 diabetes (log odds)	A, B, C	COVID-19 HGI R4	European	Mixed*
Aung N 2020	One-sample and two-sample	Biomarkers	BMI (4.7 kg/m^2), BMI-adjusted waist circumference (13.4 cm), SBP (per 20.5 mmHg), fasting glucose (1.2 mmol/L), HbA$_{1c}$ (6.3 mmol/mol), LDL cholesterol (0.87 mmol/L), HDL cholesterol (0.38 mmol/L), triglycerides (1 mmol/L)	C	UKB and COVID-19 HGI R2	European	European (UKB), mixed* (COVID-19 HGI)
Bovijn J 2020	Two-sample	Biomarkers	IL-6 receptor inhibitor (0.1 SD lower CRP)	A, B, C	COVID-19 HGI R3	European	Mixed*
Bovijn J 2021—Reply	Two-sample	Biomarkers	IL-6 receptor inhibitor (0.1 SD lower CRP)	A, B, C	COVID-19 HGI R3 and 4	European	Mixed*
Butler-Laporte G 2021	Two-sample	Druggable targets	Angiotensin-converting enzyme (SD decrease)	A, B, C	COVID-19 HGI R3	Mixed*	European
Butler-Laporte G 2021	Two-sample	Biomarkers	25OHD (log nmol/L)	A, B, C	COVID-19 HGI R4	European	European
Cai G 2021	Two-sample	Druggable targets	Protein expression (SD)	A, C	UKB, Ellinghaus *et al.* GWAS	European	European
Clift AK 2021	One-sample	Lifestyle attributes	Smoking initiation, smoking heaviness (SD)	A, B, C	UKB	European	European
Cui Z 2021	Two-sample	Biomarkers	25OHD (log nmol/L)	A, B, C	COVID-19 HGI R5	European	European
Fadista J 2021	Two-sample	Predisposition to disease	Idiopathic pulmonary fibrosis (log odds)	A, B, C	COVID-19 HGI R4	European	Mixed*
Fan X 2021	One-sample	Lifestyle attributes	Being a frequent drinker (log odds), weekly alcohol consumption	A, B, C	UKB	Mixed*	Mixed*
Freuer D 2021	Two-sample	Biomarkers	BMI (SD), waist circumference (SD), trunk fat ratio (SD)	B, C	COVID-19 HGI R3	European	Mixed*
Gaziano L 2021	Two-sample	Druggable targets	eQTL (SD), pQTL (SD)	B	COVID-19 HGI R4 and MVP	Mixed	Mixed
Gordon DE 2020	Two-sample	Druggable targets	Soluble interleukin 17 receptor A (SD)	B, C	COVID-19 HGI R3	Mixed*	Mixed*
Hernández Cordero AI 2021	Two-sample	Druggable targets	eQTL in lung and blood (SD), pQTL in blood (SD)	A, C	COVID-19 HGI R4	Mixed* (eQTL), European (pQTL)	Mixed*
Hilser JR 2021	One-sample and two-sample	Biomarkers	HDL-cholesterol (mmol/L)	A, B, C	UKB and Ellinghaus *et al.* GWAS	European	Mixed*

(Continued)

Table 1 Continued

Study (author, year)	Study design	Category	Exposure (unit)	Outcomes (log odds) [(A) severity, (B) hospitalization, (C) susceptibility]	Source of outcome	Ethnicity of exposure	Ethnicity of outcome
Hui LL 2021	Two-sample	Biomarkers	Vitamin C	A, B, C	COVID-19 HGI R5	European	European
Larsson SC 2021	Two-sample	Druggable targets	IL-6 receptor inhibitor (0.1 SD lower CRP)	A, B, C	COVID-19 HGI R4 and Ellinghaus *et al.* GWAS	European	Mixed*
Larsson SC 2021	Two-sample	Predisposition to diseases	Allergic disease (log odds)	B, C	COVID-19 HGI R4	European	European
Leong A 2021	Two-sample	Biomarkers, predisposition to diseases	BMI (kg/m^2), CRP, DBP (mmHg), SBP (mmHg), waist–hip ratio—BMI-adjusted, fasting glucose—BMI-adjusted (mg/dl), fasting insulin—BMI-adjusted (natural log), creatinine-based eGFR (mL/min/1.73 m^2), HbA$_{1c}$ (%), HDL cholesterol (mmol/L), LDL cholesterol (mmol/L), triglycerides (mmol/L) Coronary artery disease, any stroke, type 1 diabetes, type 2 diabetes, chronic kidney disease (log odds)	A, C	COVID-19 HGI R4	European or mixed*	European
Li GHY 2021	Two-sample	Socio-demographic factors	Education attainment (year), intelligence (SD)	A, B, C	COVID-19 HGI R5	European	European
Li M 2021	Two-sample	Biomarkers	Cytokines (SD)	C	COVID-19 HGI R5	European	European
Li S 2021	Two-sample	Biomarkers, lifestyle attributes	BMI (SD); lifetime smoking index (SD), accelerometer-measured physical activity (SD), alcohol consumption per week (SD)	A, B	COVID-19 HGI R4	European	Mixed*
Li X 2021	Two-sample	Biomarkers	25OHD (SD)	C	UKB	European	European
Liu D 2021	Two-sample	Druggable targets	eQTL in blood and lung (SD)	A, B, C	COVID-19 HGI R3	Mixed*	Mixed*
Liu D 2021	Two-sample	Biomarkers	25OHD (log nmol/L)	A, B, C	COVID-19 HGI R3 and Ellinghaus *et al.* GWAS	European	Mixed*
Liu N 2021	Two-sample	Predisposition to disease	ADHD, bipolar disorder, depressive disorder, schizophrenia (log odds)	A, B	COVID-19 HGI R5	European	European
Lorincz-Comi N 2021	Two-sample	Biomarkers, predisposition to disease	BMI (kg/m^2), DBP (mmHg), SBP (mmHg), PP (mmHg) type 2 diabetes (log odds)	B	COVID-19 HGI R3 and 4	European	European and mixed*

Table 1 Continued

Study (author, year)	Study design	Category	Exposure (unit)	Outcomes (log odds) [(A) severity, (B) hospitalization, (C) susceptibility]	Source of outcome	Ethnicity of exposure	Ethnicity of outcome
Luykx JJ 2021	Two-sample	Predisposition to disease	Alzheimer's dementia, bipolar disorder, major depressive disorder, schizophrenia, combined bipolar disorder and schizophrenia (log odds)	A, B, C	COVID-19 HGI R4 and 5	European	Mixed*
Ong JS 2021	Two-sample	Predisposition to diseases	Gastro-esophageal reflux disease (log odds)	A, B, C	COVID-19 HGI R5	European	European
Pairo-Castineira E 2021	Two-sample	Druggable targets	eQTL of *IFNAR2, IFNAR1, IL6R, JAK1, CTSL, IFNGR2, CSF3* (SD)	A	GenOMICC, COVID-19 HGI R2, 23andMe, UKB	European	European
Patchen BK 2021	Two-sample	Biomarkers	25OHD (SD of log), vitamin D deficiency (log odds), vitamin D insufficiency (log odds)	A, B, C	COVID-19 HGI R4	European	Mixed*
Ponsford MJ 2020	Two-sample	Biomarkers, lifestyle attributes, predisposition to diseases	BMI (SD), SBP (SD), LDL cholesterol (mmol/L); lifetime smoking index (SD); type 2 diabetes (log odds)	B, C	Ellinghaus *et al.* GWAS and COVID-19 HGI R3	European	European and mixed*
Qiu S 2021	Two-sample	Predisposition to diseases	Alzheimer's disease (log odds)	C	COVID-19 HGI R5	European	European
Qiu S 2021	Two-sample	Biomarkers	Blood metabolites	C	COVID-19 HGI R4	European	European
Rao S 2021	Two-sample	Lifestyle attributes	Smoking (cigarettes per day, cigarette pack-years, age of smoking initiation, ever regular vs never smokers, smoker vs non-smokers, ever vs never smokers) Drinking (drinks per week, drinks per day)	A, B, C	COVID-19 HGI R5	European	European
Richardson TG 2021	Two-sample	Biomarkers, lifestyle attributes, druggable targets	BMI, waist–hip ratio adjusted for BMI, childhood adiposity age 10, SBP, DBP, HDL cholesterol, LDL cholesterol, triglycerides, ApoA1, ApoB; liability to lifetime smoking; pQTL (SD)	A	Ellinghaus *et al.* GWAS	European	European
Rosoff DB 2021	Two-sample	Lifestyle attributes	Lifetime smoking index (SD), cannabis use, cannabis use disorder (log odds), drinks per week, alcohol use disorder (log odds)	A, B, C	COVID-19 HGI R5	European	European

(Continued)

Table 1 Continued

Study (author, year)	Study design	Category	Exposure (unit)	Outcomes (log odds) [(A) severity, (B) hospitalization, (C) susceptibility]	Source of outcome	Ethnicity of exposure	Ethnicity of outcome
Sun Y 2021	Two-sample	Biomarkers	Basophil, basophil % of white cells, eosinophil, eosinophil % of white cells, lymphocyte, lymphocyte % of white cells, monocyte, monocyte % of white cells, myeloid white cell count, neutrophil, neutrophil % of white cells, WBC	A, B, C	COVID-19 HGI R4 and R5	European	European
The COVID-19 HGI 2021	Two-sample	Biomarkers, lifestyle attributes, predisposition to diseases	25OHD, BMI, height, CRP, DBP, SBP, PP, eGFR, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, platelet count, RBC, WBC Smoking initiation (log odds), cigarettes (per day), sleep duration (h) ADHD, Alzheimer's disease, amyotrophic lateral sclerosis, asthma, autism spectrum disorder, bipolar disorder, chronic kidney disease, depression, diabetes, heart failure, idiopathic pulmonary fibrosis, insomnia symptoms, ischaemic stroke, lupus, multiple sclerosis, Parkinson's disease, rheumatoid arthritis, risk tolerance, schizophrenia (log odds)	A, B, C	COVID-19 HGI R5	European	European
Wang K 2021	Two-sample	Biomarkers	Haematological traits (basophil, eosinophil, hematocrit, haemoglobin, lymphocyte, MCHC, MCH, MCV, monocyte, neutrophil, platelet, RBC, RCDW, WBC), liver function markers (ALT, ALP, AST, GGT, albumin, total bilirubin, direct bilirubin, total protein), renal function marker (serum creatinine), SD	B	COVID-19 HGI R4	European	European
Wang Q 2021	One-sample	Biomarkers	Leukocyte telomere length, SD shorter	C	UKB	European	European
Yoshikawa M 2021	Two-sample	Societal factors	Educational attainment (SD, 4.2-year)	A	COVID-19 HGI R5	European	European

(Continued)

Table 1 Continued

Study (author, year)	Study design	Category	Exposure (unit)	Outcomes (log odds) [(A) severity, (B) hospitalization, (C) susceptibility]	Source of outcome	Ethnicity of exposure	Ethnicity of outcome
Zhang K 2021	Two-sample	Biomarkers, predisposition to diseases	ApoA1, ApoB, HDL-cholesterol, LDL cholesterol, total cholesterol, triglyceride (SD) Dyslipidemia (log odds)	A, C	COVID-19 HGI R4, UKB, Ellinghaus *et al.* GWAS	European and mixed*	European
Zhang X 2020	One-sample	Lifestyle attributes	Self-reported moderate-to-vigorous physical activity, acceleration vector magnitude physical activity	C	UKB	European	European
Zhou S 2021	Two-sample	Druggable targets	pQTL (SD)	A, B, C	COVID-19 HGI R4	European or mixed*	European
Zhou Y 2021	Two-sample	Biomarkers	Coagulation factors (SD)	A, C	COVID-19 HGI R5, and Ellinghaus *et al.* GWAS	European	Mixed* European
Zhu H 2021	One-sample and two-sample	Biomarkers	Laboratory assessment	A	China Wuhan Union Hospital	East Asian	East Asian
Zuber V 2021	Two-sample	Predisposition to diseases	Stroke subtypes (ischaemic, cardioembolic, large artery, small artery, log odds)	A	COVID-19 HGI R5	European	European

ADHD, attention-deficit hyperactivity disorder; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; AST, aspartate aminotransferase; Baso, basophil count; CRP, C-reactive protein; DBil, direct bilirubin; DBP, diastolic blood pressure; Eosino, eosinophil count; eQTL, gene expression; GGT, γ-glutamyl transferase; Hb, haemoglobin; HbA$_{1c}$, glycated haemoglobin; Ht, hematocrit; Lym, lymphocyte count; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; mixed*, mixed (majority of European ancestry); Mono, monocyte count; MVP, Million Veteran Program; Neutro, neutrophil count; Plt, platelet count; PP, pulse pressure; pQTL, protein expression; RBC, red blood cell count; RDW, red cell distribution width; SBP, systolic blood pressure; sCr, serum creatinine; TBil, total bilirubin; The COVID-19 HGI, The COVID-19 Host Genetics Initiative; TP, total protein; UKB, UK Biobank; WBC, white blood cell count.

The unit of the exposure is per unit increases, unless specified.

studies focused on druggable targets,[9,67–78] amongst which one study also explored the effects of cardiometabolic exposures.[77] The findings from these Mendelian randomization studies are summarized in Supplementary Table S1 (available as Supplementary data at *IJE* online). Eleven of these studies reported the assessment of all three IV assumptions. Most studies were rated as having high validity for IV1 relevance (41/50) and IV3 exclusion-restriction (44/50). Only 13 studies were rated as having high validity for IV2 independence given that these studies conducted analyses to assess the plausibility of IV2 (Supplementary Table S2, available as Supplementary data at *IJE* online).

Socio-demographic factors

Two Mendelian randomization studies assessed the role of educational attainment in COVID-19, which showed that higher educational attainment was associated with reduced risk of COVID-19 severity and hospitalization but not COVID-19 susceptibility.[43,61] One of these studies also showed that higher intelligence was associated with reduced risk of COVID-19 hospitalization (Supplementary Table S1, available as Supplementary data at *IJE* online).[43]

Lifestyle attributes

Six Mendelian randomization studies consistently demonstrated strong associations of smoking traits, including smoking initiation, smoking heaviness and lifetime smoking index (which combined smoking initiation, duration, heaviness and cessation), in the risk of COVID-19 severity, hospitalization and mortality.[27,34,45,53,56,57] Four Mendelian randomization studies explored the role of alcohol drinking in COVID-19 risk,[37,45,56,57] of which two studies found null association.[45,56] However, a study in UK Biobank provided suggestive evidence that alcohol drinking traits (being a frequent drinker and weekly alcohol consumption) were associated with higher risk of COVID-19 severity and mortality amongst participants who were obese.[37] In addition, a study found that alcohol use disorder and cannabis use were nominally associated with higher risk of COVID-19 susceptibility.[57] The role of physical activity in the risk of COVID-19 was inconsistent. Higher accelerometer-measured physical activity was associated with lower risk of COVID-19 severity in COVID-19 HGI.[45] However, null associations of self-reported moderate-to-vigorous physical activity and acceleration vector magnitude physical activity in COVID-19 susceptibility were reported using UK Biobank.[63] There was no evidence supporting the role of sleep duration in COVID-19 risk (Supplementary Table S1, available as Supplementary data at *IJE* online).[27]

Anthropometrics and biomarkers

Mendelian randomization studies have explored the role of a wide range of anthropometrics and biomarkers in COVID-19 risk, including anthropometrics, blood pressure, coagulation factors, cytokines, inflammatory markers, glycaemic traits, haematological traits, lipids, liver functions, renal functions and vitamins.[27,31–33,35,38–40,42,44–47,49,52,53,55,58–60,62,64,65] Consistent evidence suggested that obesity [higher body mass index (BMI) and trunk fat ratio] was associated with higher COVID-19 risk[27,32,38,42,45,53] and one study also showed that increase in height was associated with higher risk of COVID-19 susceptibility.[27] Consistent evidence showed systolic and diastolic blood pressure to have no role in COVID-19 risk,[27,32,42,49,53] although one study found that higher pulse pressure was associated with higher risk of COVID-19 hospitalization in people of mixed ancestry but not of European ancestry.[49] Coagulation factors [higher von Willebrand factor (VWF) and lower disintegrin and metalloprotease with a thrombospondin type 1 motif member 13 (ADAMTS13)][64] and lower cytokine [macrophage inflammatory protein 1b (MIP1b)][44] were associated with higher risk of COVID-19. The inflammatory marker C-reactive protein (CRP) was nominally associated with higher risk of COVID-19 hospitalization and susceptibility in one study[42] but not another study.[27] There is suggestive evidence showed that haematological traits (higher basophil count, basophil percentage of white cells, lymphocyte count, myeloid white cell count, neutrophil count, red blood cell count, white blood cell count and lower mean corpuscular haemoglobin) were associated with reduced risk of COVID-19 severity and hospitalization.[27,58,59] Evidence was inconsistent for lipids with risk of COVID-19,[27,32,39,42,53,55,62,65] where some suggested that higher low-density lipoprotein (LDL)-cholesterol,[32,42] small very LDL cholesterol (VLDL) particles,[55] apolipoprotein B,[62] total cholesterol and total cholesterol in medium VLDL[55,62] and triglycerides[27,62] were associated with higher risk of COVID-19 whereas others suggested null association.[27,32,39,42,53,62,65] Suggestive evidence showed that lower albumin and higher direct bilirubin were associated with higher risk of COVID-19 hospitalization[59] but null associations for other liver function markers [alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), γ-glutamyl transferase (GGT), indirect bilirubin, total bilirubin and total protein].[59,65] No evidence was found for the role of leukocyte telomere length (a determinant of longevity) in COVID-19.[60] Consistent evidence showed that glycaemic traits (HbA$_{1c}$, fasting insulin, fasting glucose and 2-h glucose),[31,32,42] high density lipoprotein (HDL) cholesterol and apolipoprotein A,[27,32,39,42,62,65] renal traits [creatinine-based estimated glomerular filtration

rate (eGFR) and serum creatinine][27,42,59] and vitamins C and D[27,33,35,40,46,47,52] were not associated with risk of COVID-19 (Supplementary Table S1, available as Supplementary data at *IJE* online).

Predisposition to disease

Thirteen Mendelian randomization studies explored whether predisposition to diseases (including diseases of the circulatory, digestive, nervous, respiratory, genitourinary, musculoskeletal systems and connective tissue, metabolic diseases and mental disorders) increased COVID-19 risk.[27,31,36,41,42,48–51,53,54,62,66] Positive association of predisposition to ischaemic stroke in COVID-19 risk was found in one study[27] but not in another study.[66] There was no evidence supporting the role of other circulatory diseases (coronary artery disease, heart failure, any stroke, cardioembolic stroke, large artery stroke and small vessel stroke) in COVID-10 risk.[27,42,66] One study found that predisposition to combined bipolar disorder and schizophrenia was associated with higher risk of COVID-19 (based on self-reported symptoms),[50] although other studies suggested null association of predisposition to bipolar disorder and predisposition to schizophrenia and COVID-19 risk.[27,48] One study suggested a positive association between predisposition to attention-deficit and hyperactivity disorder (ADHD),[48] chronic kidney disease[42] and idiopathic pulmonary fibrosis[36] with COVID-19 risk but this was not confirmed in another study.[27] There was suggestive evidence that predisposition to gastro-esophageal reflux disease was associated with higher risk of COVID-19 hospitalization[51] and an inverse association of predisposition to allergic disease with COVID-19 susceptibility.[41] There was no strong evidence supporting predisposition to metabolic diseases (diabetes, type 1 diabetes, type 2 diabetes),[27,31,42,49,53] mental disorders (autism spectrum disorder, depression, insomnia symptoms),[27,48] lupus, rheumatoid arthritis, asthma, risk tolerance and diseases of the nervous system (Alzheimer's disease, amyotrophic lateral sclerosis, multiple sclerosis, and Parkinson's disease)[27,54] in COVID-19 risk (Supplementary Table S1, available as Supplementary data at *IJE* online).

Druggable targets

There were 13 *cis*-Mendelian randomization studies that explored potential druggable targets on COVID-19 risk,[9,67–78] of which 4 studies performed Bayesian colocalization analysis to assess whether the putative association was confounded by LD.[67,71,73,78] Both *cis*-Mendelian randomization studies and colocalization analyses (PPH4 > 0.80) suggested that higher circulating protein

histo-blood group ABO system transferase (ABO)[67,73,78] and lower circulating 2′-5′ oligoadenylate synthetase 1 (OAS1)[73,78] were associated with higher risk of COVID-19, regardless of severity. Inhibition of IL6 receptor (proxied by lower CRP)[9,67,68,74] and its common signal-transducing receptor subunit, glycoprotein 130 (gp130),[77] higher IL10 receptor beta subunit (IL10RB)[78] and higher IL17 receptor A (IL17RA)[72] were associated with lower risk of COVID-19. There was no evidence supporting the role of protein angiotensin-converting enzyme (ACE), ACE2 and liver/lymph node-specific intercellular adhesion molecule-3-grabbing non-integrin (L-SIGN) in COVID-19 risk,[69,70] although positive association of dendritic cell (DC)-SIGN (also known as cluster of differentiation, CD209) in COVID-19 susceptibility and severity was found.[67,70] Higher protein expression of family with sequence similarity 3, member D (FAM3D), intercellular adhesion molecule 1 (ICAM1) and sulfhydryl oxidase 2 (QSOX2) and lower protein expression of e-selectin (SELE) were associated with higher COVID-19 risk.[67] Extensive tissue-specific gene expression of druggable targets has also been explored[71,73,75,76,78] in which gene expression of OAS1,[78] ACE2,[71] IL10RB[71] and interferon (IFN) alpha receptor 2 (IFNAR2)[71,73,75,76] across several tissues was related to COVID-19 risk (Supplementary Table S1, available as Supplementary data at *IJE* online).

Works to come

There were 24 studies identified from the preprint servers that explored a wide range of socio-demographic factors, lifestyle attributes, anthropometrics, biomarkers, predisposition to diseases and druggable targets[79–102] (Supplementary Table S3, available as Supplementary data at *IJE* online). Some studies corroborated previous findings, such as the detrimental role of smoking and obesity.[79,100] There is one Mendelian randomization study in an East Asian population that also showed a detrimental effect of obesity in severe COVID-19.[88] Others identified new determinants including increased testosterone,[96] and reduced carnitine and acetyl-carnitine[84] was associated with higher risk of COVID-19 severity and hospitalization, respectively. The updated GWAS of COVID-19 HGI included assessment of a wide range of exposures in COVID-19 risk and highlighted increased liability of type 2 diabetes associated with higher risk of COVID-19 susceptibility and hospitalization, although the association was abolished after adjusting for BMI.[82] Another study that was published in a peer-reviewed journal showed accelerated ageing was associated with higher COVID-19 risk, although the publication was not indexed in PubMed.[102] However, there were methodological concerns in some studies, such as interpreting liability as the

effect of disease diagnosis,[87] the lack of comprehensive assessment of IV assumptions[96] and insufficient details for replication.[100]

Discussion

To the best of our knowledge, this is the first systematic review focusing on evidence concerning factors contributing to COVID-19 from Mendelian randomization studies. This systematic review summarizes modifiable risk factors for intervention (e.g. obesity and smoking), as well as proteomic signatures (e.g. OAS1 and IL6) that could help identify relevant drugs for treatment of COVID-19.

Possible factors contributing to increased risk of COVID-19

Socio-demographic factors and lifestyle attributes

Our review found two Mendelian randomization investigations of the role of socio-demographic factors (education attainment and intelligence) in COVID-19. This is consistent with previous observational studies[103] and highlights the issue of inequalities in the COVID-19 pandemic. Possible pathways may include unhealthy lifestyles associated with lower socio-economic position such as smoking, and possibly physical inactivity and alcohol drinking, where our review suggested a possible link with increasing risk of COVID-19 severity and hospitalization,[27,34,37,45,53,56,57] and are consistent with conventional observational studies.[104,105] A popular mechanism related to increased risk of COVID-19 concerning smoking was an increased expression of ACE2, a receptor for SARS-CoV-2 in the airway epithelium.[106] This is also consistent with the *cis*-Mendelian randomization study that showed high gene expression of ACE2 at the Brodmann area 9 (BA9) at the brain frontal cortex was associated with higher risk of COVID-19 hospitalization.[71] This evidence supports the recent call from the World Health Organization (WHO) regarding the importance of tobacco cessation in reducing severe COVID-19.[107] Whilst obesity and hence subsequent pro-inflammatory response may explain why people who were physically inactive have higher risk of COVID-19,[108] whether alcohol use is relevant to COVID-19 remains unclear where only a possible positive association amongst participants who were obese was observed.[37]

Anthropometrics and biomarkers

Our review highlights that CRP, MIP1b, VWF, ADAMTS13, height, obesity and some haematological traits have a role in COVID-19 risk. Age is a key host factor determining disease severity and progression,[109] and

age-related immunosenescence and age-related decrease in physiological reserve can contribute to vulnerability to COVID-19 in older adults.[110] Furthermore, ageing may induce a more pro-inflammatory environment (i.e. inflammaging);[111] the same phenomenon may also explain the potential harmful effects of obesity in COVID-19 risk,[112] alongside downstream factors such as reduced ADAMTS13 activity and increased VWF.[113] The finding that basophil count was inversely associated with the hospitalization and severity of COVID-19[58] is consistent with a small immune-monitoring study that observed a positive correlation between basophil count and the level of IgG antibody against SARS-CoV-2.[114] This may then enhance the adaptive immune response to SARS-CoV-2 infection.[115]

Predisposition to diseases

Our review highlights the role of genetic predisposition to ischaemic stroke, idiopathic pulmonary fibrosis, ADHD and combined bipolar disorder and schizophrenia in COVID-19 risk. These findings are consistent with some but not all studies.[116] Possible biological mechanisms included differing profile of individuals with bipolar disorders and schizophrenia[117] and their genetic variability across human leukocyte antigens that could contribute to differences in immune responses to SARS-CoV-2 infections.[118] Alternatively, relevant societal factors may include socio-economic deprivation, social isolation[119] and barriers to accessing healthcare services for COVID-19 in individuals with mental health disorders and neurodevelopmental disorders.[120] Possible mechanisms for the link of ischaemic stroke and COVID-19 risk may again be due to the pro-inflammatory environment and increased coagulation factors.[121] Although genetic predisposition to chronic kidney disease was related to higher risk of hospitalized COVID-19, renal traits (creatinine-based eGFR and creatinine) were not related to COVID-19 and the underlying mechanisms linking kidney function and COVID-19 have yet to be established.[122] One limitation with Mendelian randomization studies using binary disease exposures is the interpretation, as the effect may represent the consequence of liability to disease instead of having the disease.[123]

Protein targets for potential drug reposition

The *cis*-Mendelian randomization studies integrated with colocalization analyses provided strong genetic evidence for several druggable targets, which can help prioritize possible targets to be tested in an RCT.[124] For example, some *cis*-Mendelian randomization studies suggested that IL6-related pathways (e.g. IL6 receptor and soluble gp130) are related to the risk of COVID-19.[9,77] These are generally consistent with suggestive evidence from RCTs that

evaluated the efficacy of IL-6 antagonists (tocilizumab, sarilumab and siltuximab) for COVID-19 severity.[125] Whether relevant medications such as soluble gp130Fc (Olamkicept) can be repurposed to reduce the severity of COVID-19 should be explored.[126,127] Strong genetic evidence suggested a positive association of protein ABO with the risk of COVID-19.[73,78] Nevertheless, ABO is highly pleiotropic and has been linked to various phenotypes,[78] suggesting that these *cis*-Mendelian randomization studies may still suffer from horizontal pleiotropy and should be interpreted with caution. OAS1 variants (rs10735079, rs6489867 and rs4767027, in high LD $r^2 > 0.80$) were associated with susceptibility to SARS-CoV-1 and SARS-CoV-2 in populations of different ancestries.[76,128,129] The protective effects of protein OAS1 in COVID-19 risk may be due to increased levels of p46 isoform,[73,78] which was later verified in a human genetic analysis.[130] ACE2 is a functional receptor for SARS-CoV-1 and SARS-CoV-2.[131,132] Human recombinant soluble ACE2 (hrsACE2) reduced SARS-CoV-2 viral load in infected Vero-E6 cells[133] and its role as a therapeutic target for COVID-19 is currently being explored in a phase II clinical trial (NCT04335136).[134] DC-SIGN was considered as a potential receptor for SARS-CoV-2.[135] However, the testing of hydroxychloroquine (a modulator of the dendritic cell)[136] has been halted due to increased mortality risk reported in RCTs.[137]

Strengths and limitations

This is the first systematic review on COVID-19-related Mendelian randomization studies to have summarized potentially more credible evidence concerning causes of COVID-19 risk. Nevertheless, there are some limitations in this review. First, Mendelian randomization studies rely on IV assumptions (e.g. relevance, independence and exclusion-restriction),[16] although most studies have addressed/acknowledged these assumptions when conducting respective Mendelian randomization studies (Supplementary Table S2, available as Supplementary data at *IJE* online). It is not generally acknowledged that Mendelian randomization studies, like all observational studies, are open to selection bias from inevitably only including survivors of the genetic predictors of the exposure and competing risk of COVID-19.[138] As a result, Mendelian randomization studies may not fully identify effects of harmful exposures on COVID-19 because people who have died from a harmful exposure or from a competing risk of COVID-19 are not available for recruitment. Second, Mendelian randomization studies based on an earlier release of COVID-19 HGI databases (with small number of cases) and the *cis*-Mendelian randomization studies (with single genetic variant) have relatively lower statistical power and hence null findings from these studies should be interpreted with caution. Third, most (82%) studies used COVID-19 HGI to obtain the variant–outcome associations, given it is the largest available GWAS available, implying that meta-analysis of studies addressing the same question was technically impossible to increase statistical power. Fourth, most studies pertained to populations of predominantly European ancestry and might not be generalizable to other populations, although causes are usually consistent but not always relevant. Genetic data from diverse ancestral populations can better evaluate whether determinants of COVID-19 risk and its severity vary across ethnicities or possibly identify causes of COVID-19 not evident in European populations.[139] Fifth, we only included published studies in this review, given the varying quality of preprints, although such issues also applied to published studies (Supplementary Table S2, available as Supplementary data at *IJE* online). However, given that preprints may foreshadow upcoming publications, we summarized the findings from the preprints briefly although interpretation of these findings should be with caution (Supplementary Table S3, available as Supplementary data at *IJE* online). Sixth, the factors chosen for investigation may represent those that are best understood rather than those most relevant to equitably protecting the population against the effects of COVID-19. For example, the greater vulnerability of disadvantaged populations and of men to COVID-19 has not yet been investigated using Mendelian randomization. Lastly, whether these factors contribute to milder forms of COVID-19, which comprises most cases, requires additional investigation in larger studies. This is of particular relevance given a recent prospective study indicated that young, home-isolated adults with mild to moderate COVID-19 suffer from long-term complications from COVID-19.[140]

This systematic review highlighted increases in smoking, obesity and inflammatory factors as causes of increased risk of COVID-19, whilst other factors that were thought to be relevant to COVID-19, such as vitamin D, were unlikely causal in increased susceptibility to COVID-19. Our study also summarized possible druggable targets that are related to COVID-19 risk, thus providing additional insights regarding the prioritization and repositioning of medications to mitigate the risk of COVID-19. This systematic review reveals factors contributing to COVID-19 risk that would guide subsequent policy interventions to mitigate the global COVID-19 pandemic.

Ethics approval

Not applicable. All the work was developed using published data.

Data availability

The data underlying this article are available in the article and in its online Supplementary material.

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

S.L.A.Y. and S.L. contributed to the study conception and design. Y.L., T.H.T.W. and S.L. contributed to the literature search, study selection and data extraction. S.L., Y.L. and S.L.A.Y. evaluated the quality assessment of the included studies. S.L. and S.L.A.Y. drafted the manuscript with critical feedback and revisions from C.M.S., Y.L. and T.H.T.W. All authors approved the final version of the manuscript. S.L. is the guarantor. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Conflict of interest

None declared.

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