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# Genetic polymorphisms affecting nitric oxide and β-cytokine pathways may contribute to increased COVID-19 mortality in schizophrenia

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## 1. Introduction

Patients with schizophrenia (SCZ) demonstrate higher severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and excessive mortality (4-fold) (Nadalin et al., 2021). Stigma and discrimination limit health care access, overrepresentation of cardiovascular disease (CVD), metabolic syndrome (MetS), obesogenic antipsychotic medications, smoking, poorer lifestyle and activity patterns, contribute to dismal physical health outcomes in SCZ and predispose to severe coronavirus disease 2019 (COVID-19) (Nadalin et al., 2021). SCZ's high heritability implies additional genetic contribution to its pathogenesis with deranged blood and brain levels of nitric oxide (NO) and proinflammatory cytokines, setting the stage for a fatal illness (Kraal et al., 2019; Nadalin et al., 2021; Nasyrova et al., 2020).

## 2. Nitric oxide (NO) and NO synthases (NOS) in SCZ

Nitric oxide (NO) is a short lived, gaseous, lipophilic, and freely diffusible small molecule, generated in an NOS-catalyzed conversion of L-arginine (Fig. 1) involving three NOS variants: neuronal (nNOS), endothelial (eNOS) and inducible (iNOS) (Nasyrova et al., 2020). NO exerts autocrine and paracrine effects on numerous physiological processes involving the brain and its vasculature including physiological neurotransmission (Nasyrova et al., 2020). In the cardiovascular system and kidneys, eNOS-mediated NO-generation induces physiological vasodilation and influences blood pressure control (Nasyrova et al., 2020). While over 90% of the NO in the brain is produced via nNOS, eNOS could mediate a neurovascular coupling with effects of cerebral vascular perfusion on brain tissue (Nasyrova et al., 2020). NOS polymorphisms significantly modify NO effects throughout the human body and have been implicated in CVD, cognitive decline in SCZ associated MetS, and psychoneurological disorders (Kraal et al., 2019; Nadalin et al., 2021; Nasyrova et al., 2020). Underproduction of NO might be critically involved in the development of SCZ as NO metabolites are reduced in the plasma and CSF of patients with SCZ and inversely correlate with negative symptom severity (Nasyrova et al., 2020). Widespread smoking and/or drinking more easily suppresses mutant eNOS genotypes, along with reduced activity patterns further aggravate the effects of NO underproduction in SCZ (Fig. 1) (Nadalin et al., 2021). Renin angiotensin aldosterone system (RAAS) polymorphisms, such as the angiotensin converting enzyme (ACE) D-allele, have been implicated in the pathogenesis of SCZ (Fig. 1) and associated with greater disease severity, continuous progression, worse outcomes, and adverse antipsychotic medication results (Nadalin et al., 2021). ACE polymorphisms are also implicated in increased disease severity and mortality in COVID-19 and engender an adverse predisposition in SCZ (Papadopoulos et al., 2021). Co-inherited eNOS and RAAS polymorphisms synergistically potentiate CVD, nicotine dependence, and modulate pharmacological interventions including the effects of pharmacological RAAS inhibition, with known angiotensin II type 1 receptor blocker (ARB)-induced eNOS upregulation especially of the mutant alleles (Fig. 1) (Cotta Filho et al., 2020; Nadalin et al., 2021). The ARB telmisartan, used as an adjunctive antipsychotic therapy in SCZ, shows significant reductions of Positive and Negative Syndrome Scale scores and pro-inflammatory interleukin (IL)-6 levels (Oh and Fan, 2019). Conversely, clozapine-induced eNOS depression, more pronounced in eNOS loss-of-function SNPs, can deplete endothelial NO levels, enhance oxidative stress, and predispose to SARS-CoV-2 infection/complications through subsequent vascular events (Oh and Fan, 2019). Considering RAAS and eNOS pharmacogenetic influences on atypical antipsychotic

*Abbreviations:* ACE, angiotensin converting enzyme; AGT, angiotensinogen; AGTR1, angiotensin II, type 1 receptor gene; Ang 1/II, angiotensin I/II; AT1R, angiotensin II type 1 receptor; ARB, angiotensin II receptor blocker; RAAS, renin angiotensin aldosterone system; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; CSF2RB, β-common receptor gene; βcR, β-common receptor; IL-3, Interleukin-3; IL-3Rα, IL3 Receptor α; IL-6, Interleukin-6; SNP, single nucleotide polymorphism; EPO, erythropoietin; EPOR, EPO receptor; TPR, tissue protective receptor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019.

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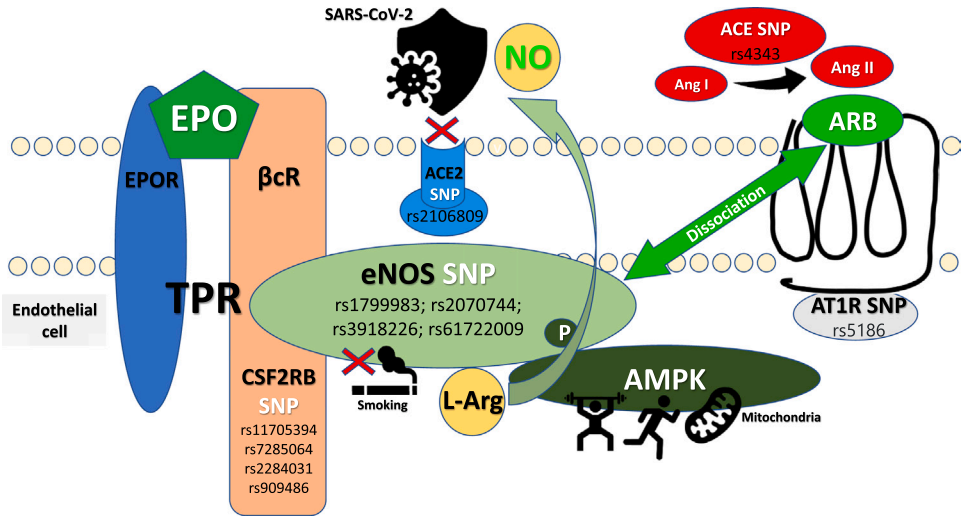


**Fig. 1.** Schematic molecular mechanisms of NO production in endothelial cells. SNPs affecting βcR/CSF2RB, eNOS, ACE, ACE2, and AT1R may lead to NO-generation and bioavailability impairments, independently, indirectly, or synergistically. ARBs will dissociate AT1R from eNOS and induce NO-increase. Increases in NO-bioavailability may inhibit SARS-CoV-2 replication and mitigate its cell entry. Smoking downregulates while exercise upregulates eNOS. SNP: single nucleotide polymorphism; EPO: erythropoietin; EPOR: EPO receptor; βcR: β-common receptor; CSF2RB: βcR coding gene; TPR: tissue protective receptor; eNOS: endothelial nitric oxide synthase; NO: nitric oxide; ACE: angiotensin converting enzyme (2); Ang 1/II: angiotensin I/II; AT1R: angiotensin II type 1 receptor; ARB: angiotensin II receptor blocker; P: phosphorylation; L-Arg: arginine; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

use in SCZ could unravel additional COVID-19 mortality associations (Cotta Filho et al., 2020).

## 3. Nitric oxide (NO) in SARS-CoV-2

Increased NO-generation and bioavailability through eNOS activation may counteract SARS-CoV-2 spike (S) protein-induced endotheliitis and inhibit SARS-CoV-1/2 infection at an early stage, as shown to inhibit i) fusion of the SARS-CoV (S) protein to ACE2 by decreasing its palmitoylation, and ii) early production of viral RNA, processes critical in controlling membrane fusion and virion infectivity (Fig. 1) (Papadopoulos et al., 2021). Downregulated eNOS have been reported in adults with severe COVID-19 and related acute respiratory distress syndrome (ARDS) (Vassiliou et al., 2021). Chronically impaired NO-bioavailability along with genetic eNOS perturbations in SCZ may be early predisposing factors for more severe SARS-CoV-2 infection.

## 4. β-common (βc) cytokines in SCZ and SARS-CoV-2

Genetic polymorphisms in all three components of the IL-3 signaling pathway, CSF2RB (coding for the βc Receptor (βcR)), IL-3, and IL- 3 Receptor α (IL-3Rα) genes, are potentially able to directly change gene expressions and have been reported in SCZ (Chen et al., 2008; Chen et al., 2007). IL-3 activity may be lower in SCZ patients while impaired IL-3 function is associated with increased disease severity as well as increased viral load and mortality in SARS-CoV-2 infected patients (Benard et al., 2021; Chen et al., 2008).

An extra level of complexity in NO regulation is added as CSF2RB polymorphisms in SCZ potentially impact βcR function. Apart from canonical βc-cytokine effects, βcR demonstrates non-canonical interactions with erythropoietin (EPO) by forming its effector, the tissue protective receptor (TPR), a heterodimer between βcR and EPO receptor (EPOR) (Papadopoulos et al., 2021). βcR is essential in the formation of a βcR-EPOR-eNOS complex, integral in mediating EPO's non-erythropoietic, neuro-, cardio-, reno-, and potentially SARS-CoV-2 protective effects. CSF2RB polymorphisms could thus lead to decreased EPO-mediated NO-generation by inhibiting βcR-dependent EPO-induced eNOS activation, hence abolishing EPO-engendered SARS-Cov-2 protection (Fig. 1) (Chen et al., 2008; Papadopoulos et al., 2021).

Taken together, the above-described genetic polymorphisms connect several disparate lines of evidence that may significantly contribute to increased COVID-19 mortality in this vulnerable patient group. eNOS, RAAS, and CSF2RB genotype combinations, may additionally compromise an already impaired endothelial and brain NO-bioavailability in SCZ and abolish NO-engendered immediate and delayed anti-SARS-CoV-2 protection. IL-3 signaling pathway polymorphisms mediating IL-3-cytokine disruptions could induce more severe COVID-19 disease. Further studies considering the above genetic polymorphisms are needed in COVID-19 infected SCZ patients.

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## Author contributions

Papadopoulos KI had the original idea on the review concept and composed the manuscript; Sutheesophon W and Aw TC assisted in literature search, and all have made substantial, direct, and intellectual contributions to the review; all authors critically assessed the manuscript and approved it for publication.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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