The effect of inflammation, SARS-CoV-2 infection, age and mental health on serotonin, kynurenine and catecholamine pathway activity

Manuscript

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2023-06-07

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Running title: Activity of the kynurenine, serotonin and dopamine metabolic pathways and COVID-19

# Abstract

**Background:** COVID-19 patients frequently develop symptoms of depression, anxiety and mental stress. The serotonin, kynurenine and catecholamine metabolic pathways determine systemic levels of serotonin and dopamine, whose insufficiency was linked to mental health disorders. We investigated factors that affect their activity in SARS-CoV-2 infection and recovery.

**Methods:** The cross-sectional SIMMUN (n = 165) and longitudinal INCOV cohort (n = 167, Su et al. 2022) were analyzed. Demographic and clinical characteristic, inflammatory markers, SARS-CoV-2 infection, signs of depression and anxiety (HADS), and mental stress (PSS-4) served as explanatory variables. Plasma markers of the serotonin and kynurenine (serotonin, kynurenine/tryptophan ratio), and catecholamine pathway activity (dopamine 3-O-sulfate, phenylalanine/tyrosine ratio) were modeled by multi-parameter linear regression.

**Results:** In the SIMMUN cohort, the inflammatory marker neopterin ( = 0.47 [95% CI: 0.34-0.61]), SARS-CoV-2-positivity (0.42 [0.16-0.68]), mental stress (0.18 [0.055-0.31]) and age were positively associated with elevated kynurenine/tryptophan ratio. Phenylalanine/tyrosine ratio was lower in SARS-CoV-2-positive participants (-0.38 [-0.68–0.08]). In the INCOV cohort, inflammation markers were associated with decreased serotonin (IL6: -0.22 [-0.38–0.053]) and dopamine 3-O-sulfate (interferon-gamma: -0.15 [-0.26–0.036]). Serotonin (0.76 [0.34-1.2]) and dopamine 3-O-sulfate levels (0.63 [0.28-0.99]) were higher during recovery than in acute SARS-CoV-2 infection.

**Conclusion:** SARS-CoV-2 infection, inflammation, mental stress and age are the key independent predictors of high kynurenine pathway activity, which decreases systemic serotonin levels by depleting its precursor tryptophan. These factors are also associated with suppressed catecholamine pathway activity. This lowered serotonin and dopamine availability may contribute to mental health problems in COVID-19 patients.

# Keywords

serotonin and dopamine availability, COVID-19, kynurenine, tryptophan, inflammation, mental health

# Introduction

The immune system and the brain interact at multiple levels (Dantzer et al., 2008). Physical conditions such as infections, cardiovascular disease, frailty, autoimmune illness or malignancy are often accompanied by symptoms of depression, anxiety, mental stress and other psychiatric disorders (Dickens and Creed, 2001; Hüfner et al., 2022; Hüfner et al., 2015; Mayerl et al., 2020; Mitchell et al., 2011; Rajan et al., 2020; Renault et al., 1987). Inflammation interferes with key metabolic processes controlling serotonin and dopamine availability, the serotonin, kynurenine and catecholamine pathways, and was proposed as an important link between mental and physical health (Bonaccorso et al., 2002; Brown et al., 2021; Dantzer et al., 2008; Gostner et al., 2020; Hüfner et al., 2015; Valdiglesias et al., 2018).

Serotonin is synthesized from the essential aminoacid tryptophan (TRP) via serotonin pathway reactions catalyzed by tryptophan hydroxylase (TPH) and aromatic L-amino acid decarboxylase. Most systemic TRP is catabolized by the kynurenine pathway, which limits serotonin pathway activity (Lukić et al., 2022). Its first rate-limiting step, the TRP - kynurenine (KYN) breakdown catalyzed by tryptophan 2,3-dioxygenase (TDO) or indoleamine 2,3-dioxygenases (IDO1, IDO2), controls TRP levels available for serotonin synthesis (Badawy, 2017; Lukić et al., 2022). Importantly, IDO1 is stimulated by inflammatory signals (Badawy, 2017; Robinson et al., 2003) and TDO activity is increased by glucocorticoids released upon depression and mental stress (Knox, 1951; Maes et al., 1990). Kynurenine pathway metabolites such as KYN or quinolinic acid [QUIN] can additionally pass the blood-brain barrier, interfere e.g. glutamatergic signaling and exert neurotoxicity (Brown et al., 2021; Schwarcz et al., 2012). Hence, the kynurenine pathway, whose activity can be assessed by the ratio of blood KYN to TRP (KYN/TRP), poses a connex of inflammatory and hypothalamic–pituitary–adrenal axis signals, systemic serotonin availability and neural signal transmission (Badawy, 2017; Brown et al., 2021; Schwarcz et al., 2012). Consequently, elevated levels of circulating kynurenine pathway metabolites, high KYN/TRP, decreased TRP or lowered serotonin were reported for numerous physical conditions and associated with symptoms of mental disorders (Capuron et al., 2011; Cervenka et al., 2017; Fellendorf et al., 2022; Hüfner et al., 2021, 2019; Hüfner et al., 2015; Hunt et al., 2020; Marx et al., 2020).

Dopamine synthesis via the catecholamine pathway involves the conversion of phenylalanine (PHE) to tyrosine (TYR) catalyzed by phenylalanine hydroxylase (PAH) followed by hydroxylation of TYR by tyrosine 5-hydroxylase (TH). PAH, TH and the serotonin pathway enzyme TPH rely on tetrahydrobiopterin (BH4) as an essential cofactor (Meiser et al., 2013; Neurauter et al., 2008). During inflammation, BH4 is oxidized to its inactive derivative and consumed in a competitor reaction of nitric oxide formation (Neurauter et al., 2008; Rahimian et al., 2022). As a result of such functional BH4 deficiency, reflected e.g. by an elevated blood PHE to TYR ratio, biosynthesis of dopamine and serotonin is suppressed (Capuron et al., 2011; Geisler et al., 2013; Vancassel et al., 2018). Accordingly, changes in PHE and TYR levels have been reported in different physical disorders such as cancer, infections and inflammatory conditions and associated with depression and anxiety (Capuron et al., 2011; Geisler et al., 2013; Hüfner et al., 2015; Vancassel et al., 2018).

SARS-CoV-2 virus is the causal pathogen of coronavirus disease 2019 (COVID-19). Apart from sustained physical disability, psychiatric disorders in millions of patients amount to the persistent burden of the COVID-19 pandemic (Al-Aly et al., 2021; Huang et al., 2021; Hüfner et al., 2022; Sahanic et al., 2023; Staudt et al., 2022). Increased kynurenine pathway activity suggestive of lowered systemic serotonin availability has recently been identified in acute COVID-19 and during COVID-19 recovery and associated with infection severity (Bizjak et al., 2022; Dewulf et al., 2022; Lionetto et al., 2021; Santiago-Mujika et al., 2022). Theoretical considerations (Bower et al., 2022) and preliminary experimental data suggest that highly active kynurenine pathway along with suppression of serotonin and catecholamine biosynthesis may contribute to symptoms of mental stress, anxiety and depression in COVID-19 patients (Kucukkarapinar et al., 2022; Matits et al., 2023).

Still, clinical and experimental evidence for interaction of inflammation, mental health and systemic availability of serotonin and dopamine in COVID-19 is scarce. To address this question, we explored effects of demographic, clinical, psychometric (anxiety, depression, mental stress), inflammation- and SARS-CoV-2-related factors on markers of systemic activity of the serotonin, kynurenine and catecholamine pathways in two cross-sectional cohorts of SARS-CoV-2 patients: the SIMMUN cohort and the published longitudinal INCOV study (Su et al., 2022).

# Materials and Methods

Details on study cohorts, procedures and analysis are provided in **Supplementary Methods**.

## Ethics statement

The SIMMUN study was conducted in accordance with the Declaration of Helsinki and European Data Policy. All participants gave written informed consent prior to enrollment. Participants’ data were stored and analyzed in anonymized form. This study was approved by the ethics committee of the Medical University Innsbruck (Austria, approval number: 1132/2020). No approval by the ethics committee was required for the published INCOV dataset (Su et al., 2022).

## Study cohorts

### SIMMUN study

Individuals tested for SARS-CoV-2 via PCR at the University Hospital of Innsbruck and patients of the University Clinic for Psychiatry I and II (Innsbruck, Austria) undergoing routine SARS-CoV-2 PCR were invited to participate. The study was conducted between June 2020 and May 2021. The inclusion criteria were age of 18 - 70 years, proficiency in German, residence in the study region (Tyrol, Austria), and a SARS-CoV-2 PCR conducted at the study site. The exclusion criteria were active SARS-CoV-2 infection (< 14 days after diagnosis), pregnancy, active malignancy, organ transplantation, surgery in the past 3 months, inflammatory illness and oral corticosteroid treatment. Only individuals with complete explanatory and response variables presented in **Supplementary Table S1** and **Supplementary Figure S1** were analyzed. Significant differences between the analyzed and excluded participants are listed in **Supplementary Table S2**.

### INCOV study

Proteome, metabolome and clinical data are [publicly available](https://data.mendeley.com/datasets/96v329bg7g/1) (Su et al., 2022). Samples with complete explanatory and response variables presented in **Supplementary Figure S1** and **Supplementary Table S3** were analyzed.

## Procedures

### SIMMUN study

The SIMMUN data were collected during a single on-site visit at median 139 days after the SARS-CoV-2 PCR (interquartile range: 119 - 157) or extracted from electronic patient records (**Supplementary Table S1**). Demographic and clinical characteristic included age, sex, body mass index (BMI), mental disorders diagnosed by a physician, self-reported physical disorders, smoking and alcohol consumption, result and date of the SARS-CoV-2 PCR. Inflammatory markers, plasma neopterin concentrations (NEO) measured by ELISA (Werner et al., 1990) and neutrophil/lymphocyte ratio (NLR) were determined by a certified laboratory at the University Hospital of Innsbruck. Plasma TRP, KYN, PHE and TYR were determined by high-performance liquid chromatography (Neurauter et al., 2008; Widner et al., 1997). Immunoglobulin gamma against receptor binding domain S1/S2 protein (anti-RBD IgG) was quantified by ELISA (Deisenhammer et al., 2021). Laboratory measurements beyond the detection limits were substituted with the respective detection limit value. Mental stress was scored with the 4-item perceived stress scale (PSS-4) (Cohen et al., 1983). Clinically relevant symptoms of anxiety and depression were defined as 8 points in the hospital anxiety and depression scale (HADS) (Bjelland et al., 2002; Zigmond and Snaith, 1983).

### INCOV cohort

Plasma proteomes and metabolomes in the INCOV cohort were measured by proximity extension assay (Olink, Sweden) and liquid chromatography/tandem mass spectrometry (Metabolon, USA), respectively, and expressed as age- and sex-adjusted, log2-transformed concentrations (Su et al., 2022, 2020). Markers of the serotonin (serotonin, TRP) (Lukić et al., 2022), kynurenine (KYN, kynurenine/tryptophan ratio [KYN/TRP], QUIN) (Badawy, 2017) and catecholamine pathway activity (PHE, TYR, phenylalanine/tyrosine ratio [PHE/TYR] and dopamine 3-O-sulfate [DA sulfate]) (Goldstein et al., 1999; Meiser et al., 2013; Suominen et al., 2013), cytokine markers of inflammation (interleukin-6 [IL6], interleukin-10 [IL10], tumor necrosis factor-alpha [TNF] and interferon-gamma [IFNG]), age, sex and BMI were analyzed (**Supplementary Table S3**).

Plasma samples were collected in during in acute and sub-acute infection, and recovery at median 10, 14), 64 days after diagnosis of SARS-CoV-2 infection via PCR, respectively (**Supplementary Table S4**).

## Analysis endpoints

The first endpoint was to determine demographic, clinical, psychometric, inflammation- and SARS-CoV-2-related factors influencing plasma markers of kynurenine and catecholamine pathway activity (TRP, KYN, KYN/TRP, PHE, TYR, PHE/TYR) by multi-parameter modeling in the SIMMUN cohort. The second endpoint was to investigate how markers of systemic serotonin and dopamine availability (DA sulfate), are influenced by age, sex, body mass, inflammatory cytokines, timepoint of SARS-CoV-2 infection, neurotransmitter precursor amino acids (TRP, PHE, TYR) and kynurenine pathway metabolites (KYN, QUIN). This endpoint was addressed by multi-parameter robust linear modeling, time course modeling and correlation analysis in the INCOV cohort (**Supplementary Figure S1**).

## Statistical analysis

R version 4.2.3 was used for statistical analysis.

Numeric variables were presented as medians with interquartile ranges and ranges. Categorical variables are presented as percentages and counts. Normality and variance homogeneity was assessed by Shapiro-Wilk and Levene test, respectively. In the SIMMUN cohort, non-normally distributed numeric variables were logarithm- or square root-transformed prior to modeling and parametric tests (**Supplementary Table S1**). Since most of the INCOV study variables were non-normally distributed, robust linear modeling and non-parametric testing were employed. Consistency of psychometric tools was investigated by global McDonald’s (McDonald, 1999). Except for multi-parameter modeling, p values were corrected for multiple testing with the false discovery rate method (Benjamini and Hochberg, 1995) separately for each analysis task. Effects with p < 0.05 were considered significant.

Significance was determined by Mann-Whitney test with r effect size, two-tailed T test with Cohen’s d effect size statistic or test with Cramer’s V effect size statistic. Correlation was assessed by Pearson’s or Spearman’s rank test and visualized as bubble or force-directed network plots (Csardi and Nepusz, 2006).

Responses and explanatory variables were normalized prior to modeling. In the SIMMUN cohort, effects of age, sex, body mass class, physical and psychiatric disorders, BMI, smoking and alcohol consumption, inflammation markers (NEO, NLR), SARS-CoV-2 infection, anti-RBD IgG titer, clinically relevant symptoms of depression and anxiety (HADS), mental stress (PSS-4) on pathway activity markers were assessed by multi-parameter linear regression with backward elimination. In the INCOV cohort, effects of age, sex, BMI, cytokine markers of inflammation (IL6, IL10, TNF, IFNG), SARS-CoV-2 infection timepoint (uninfected, acute, sub-acute, recovery), serotonin and catecholamine pathway metabolites (TRP, PHE, TYR) and kynurenine pathway metabolites (QUIN, KYN) on plasma serotonin and DA sulfate were modeled by multi-parameter robust linear regression (Huber, 2011). Explanatory performance, reproducibility and proper parameterization of the multi-parameter models was investigated by R2 and root mean square error (RMSE) in 10-fold cross-validation. Differences in cytokines and metabolites between SARS-CoV-2 infection timepoints in the INCOV collective were investigated by robust linear modeling with uninfected subset or acute infection serving as baselines.

# Results

## Characteristic of the cohorts

Two cohorts of uninfected and SARS-CoV-2-infected individuals were analyzed (SIMMUN and INCOV). Out of 215 individuals enrolled in the SIMMUN study, 165 participants with complete study variables were analyzed (**Supplementary Figure S1**, **Supplementary Table S1**). The excluded individuals were characterized by more frequent mental disorders and clinically relevant symptoms of depression and anxiety (HADS), higher scores of mental stress (PSS-4) and less frequent SARS-CoV-2 infections than the analyzed participants (**Supplementary Table S2**). In the analyzed SIMMUN cohort, males represented 38% and the median age was 50 years. The SIMMUN study data were recorded at median 139 days after the SARS-CoV-2 PCR. None of the participants had received anti-SARS-CoV-2 vaccination prior to enrollment. SARS-CoV-2-positive individuals accounted for 39% of the analyzed participants. The gender and age structure of the SARS-CoV-2-negative and -positive subsets was comparable. In the entire SIMMUN cohort, 47% of participants were overweight or obese, and 51% reported a physical disorder; these figures were comparable between SARS-CoV-2-negative and -positive individuals. Mental disorders diagnosed by a physician affected 41% of participants and were significantly more common in SARS-CoV-2-negative (50%) than in SARS-CoV-2-positive individuals (28%, p = 0.021, effect size: V = 0.21) (**Table 1**). The psychometric tools for assessment of perceived mental stress (PSS-4), depression and anxiety (HADS) displayed good-to-excellent internal consistency ( = 0.74 - 0.96) (McDonald, 1999) (**Supplementary Figure S2**). Clinically relevant symptoms of anxiety (HADS 8) were more frequent in SARS-CoV-2-negative (43%) than in SARS-CoV-2-positive participants (20%, p = 0.013, effect size: V = 0.23). Clinically relevant symptoms of depression (HADS 8) were more common in SARS-CoV-2-negative (31%) than in SARS-CoV-2-positive participants (16%), yet this effect was no statistically significant. Scores of mental stress were comparable in both SARS-CoV-2 subsets (negative: median 6, positive: median 5 points). As expected, titer of antibodies against the S1/S2 SARS-CoV-2 protein (anti-RBD IgG) was significantly higher in the SARS-CoV-2-positive subset (median: 16 AU) as compared with uninfected individuals (median: 0.31 AU, p < 0.001, effect size: r = 0.84). In 73% of SARS-CoV-2-infected SIMMUN study participants, the infection was mild and treated on an outpatient basis (**Table 1**).

Out of 225 individuals initially enrolled in the INCOV study (Su et al., 2022), 167 participants with complete study variables providing 354 metabolome and proteome samples were analyzed (**Supplementary Figure S1**, **Supplementary Tables S3 - S4**). In the analyzed INCOV cohort, the median age was 60 years and 56% of participants were male. SARS-CoV-2-positive individuals comprised 84% of the cohort. SARS-CoV-2-positive individuals (median age: 62 years) were significantly older than uninfected participants (median age: 56 years, p = 0.044, effect size: r = 0.17). Percentages of overweight or obese individuals were higher among SARS-COV-2-positive (74%) than SARS-CoV-2-negative participants (55%), this effect was not statistically significant. Nearly all (97%) of SARS-CoV-2-positive participants of the INCOV study experienced moderate-to-critically severe infections and were hospitalized during COVID-19 (**Table 2**).

As compared with the SIMMUN cohort, the INCOV cohort had a significantly higher percentage of males (p = 0.0014, effect size: V = 0.18), higher age (p < 0.001, effect size: p < 0.001), higher rates of overweight or obese participants (p < 0.001, effect size: V = 0.28), more frequent SARS-CoV-2 infections (p < 0.001, effect size: V = 0.46), and higher hospitalization rates (p < 0.001, effect size: V = 0.72) (**Supplementary Table S5**).

## Inflammation, SARS-CoV-2 infection, age, mental stress and depression influence systemic activity of the kynurenine pathway

In the SIMMUN dataset, we initially searched for predictors of activity of the kynurenine and catecholamine pathways. TRP, KYN and KYN/TRP served as markers of the kynurenine pathway (Badawy, 2017), and PHE, TYR and PHE/TYR were investigated as markers of the catecholamine pathway activity (Meiser et al., 2013). The candidate explanatory variables were age, sex, BMI, the presence of physical and mental disorders, smoking, alcohol consumption, SARS-CoV-2 infection, anti-SARS-CoV-2 antibody titer, NEO and NLR as inflammatory markers, perceived mental stress, and symptoms of depression and anxiety (**Supplementary Table S1**).

Meaningful multi-parameter models optimized by backward elimination could be established for TRP, KYN, KYN/TRP, TYR and PHE/TYR. The PHE model had a negligible explanatory performance, proved non-significant as compared with the intercept-only null model and was hence not further analyzed (**Supplementary Table S6**). The remaining models were characterized by good reproducibility and proper parameterization as indicated by comparable fit errors (RMSE) in the training dataset and cross-validation. The KYN and KYN/TRP ratio models had the best, moderate-to-substantial explanatory performance measured by cross-validated R2 of 0.21 and 0.3, respectively. The cross-validated R2 metric values for the TRP, TYR and PHE/TYR models ranged from 0.1% to 0.15 indicative of weak-to-moderate explanatory value (**Supplementary Figure S3**).

Regarding the kynurenine pathway, the inflammatory marker NEO ( = -0.19 [95% CI: -0.34–0.04]) and clinically relevant depression symptoms (HADS 8, = -0.48 [95% CI: -0.83–0.14]) were independently associated with reduced plasma TRP. KYN and KYN/TRP were significantly associated with SARS-CoV-2 infection (KYN: = 0.48 [95% CI: 0.2-0.76], KYN/TRP: = 0.42 [95% CI: 0.16-0.68]), higher NEO (KYN: = 0.35 [95% CI: 0.2-0.49], KYN/TRP: = 0.47 [95% CI: 0.34-0.61]) and age (KYN: = 0.21 [95% CI: 0.067-0.35], KYN/TRP: = 0.26 [95% CI: 0.12-0.39]). Additionally, high perceived mental stress (PSS-4) was identified as a significant predictor of increased KYN/TRP ( = 0.18 [95% CI: 0.055-0.31]).  
High KYN concentrations were related to low NLR ( = -0.19 [95% CI: -0.32–0.051]) (**Figure 1A**).

Concerning the catecholamine pathway, plasma TYR concentrations were negatively associated with NEO ( = -0.2 [95% CI: -0.35–0.048]) and positively with age ( = 0.37 [95% CI: 0.21-0.52]). SARS-CoV infection ( = -0.38 [95% CI: -0.68–0.08]) and age ( = -0.27 [95% CI: -0.41–0.12]) were significant predictors of lower PHE/TYR (**Figure 1B**).

By analysis of single significant predictors identified by modeling, we could corroborate significant, positive, moderate-to-strong correlations of age and NEO with KYN and KYN/TRP in the SIMMUN cohort. This analysis revealed also a significant positive correlation of age with TYR and a significant negative correlation of age with PHE/TYR (**Supplementary Figure S4 - S5**, **Supplementary Tables S7 - S8**).

## Inflammatory cytokines, SARS-CoV-2 infection course, age and availability of biosynthesis precursors regulate systemic serotonin and dopamine levels

Next, we investigated factors affecting plasma levels of serotonin (Lukić et al., 2022) and a major circulating catabolite of dopamine, DA sulfate (Goldstein et al., 1999; Meiser et al., 2013), as direct markers of the serotonin and catecholamine pathway activity, respectively. This analysis was done in the INCOV cohort (Su et al., 2022) with age, sex, BMI, cytokines markers of inflammation (IL6, IL10, TNF, IFNG), timepoint of SARS-CoV-2 infection, concentrations of serotonin and catecholamine pathway metabolites (TRP, PHE, TYR), and kynurenine pathway metabolite levels (KYN, QUIN) as candidate explanatory variables (**Supplementary Table S3**). Metabolites and cytokines were sampled in SARS-CoV-2-positive participants during acute and sub-acute infection, and recovery, at median 10, 14 and 64 days after infection diagnosis via PCR, respectively (**Supplementary Table S4**).

The multi-parameter robust regression model (Huber, 2011) for plasma serotonin was characterized by moderate explanatory performance (cross-validated R2 = 0.15). The explanatory performance of the DA sulfate model was weak (cross-validated R2 = 0.053). Comparable fit errors (RMSE) in the training dataset and cross-validation indicated good reproducibility and proper parameterization of the models (**Figure 2A**).

In the INCOV collective, five significant predictors of plasma serotonin were identified. Age ( = -0.16 [95% CI: -0.27–0.055]), male sex ( = -0.24 [95% CI: -0.44–0.039]) and the inflammatory cytokine IL6 ( = -0.22 [95% CI: -0.38–0.053]) were associated with significantly lower serotonin levels, whereas TRP ( = 0.17 [95% CI: 0.047-0.29]) and recovery from SARS-CoV-2 infection ( = 0.76 [95% CI: 0.34-1.2] versus uninfected controls) were predictors of higher plasma serotonin. Significantly higher DA sulfate levels were identified for recovery from SARS-CoV-2 infection ( = 0.63 [95% CI: 0.28-0.99] versus uninfected control) and high TNF concentrations ( = 0.18 [95% CI: 0.074-0.28]). In turn, obesity ( = -0.3 [95% CI: -0.52–0.085] versus normal weight) and IFNG ( = -0.15 [95% CI: -0.26–0.036]) were independently associated with significantly decreased DA sulfate levels (**Figure 2B**, **Supplementary Table S9**).

The association of serotonin and DA sulfate levels with inflammation was confirmed by time course modeling (**Figure 3**, **Supplementary Tables S10 - S11**). The maximum plasma concentrations of inflammation markers IL6, IL10, TNF and IFNG were observed during acute infection. They were paralleled by changes in metabolites of the serotonin and kynurenine pathways with a significantly decreased TRP ( = -1.9 [95% CI: -2.7–1]), increased KYN ( = 1.5 [95% CI: 0.99-2]) and elevated QUIN ( = 1.8 [95% CI: 1.3-2.4]) during acute infection as compared with uninfected individuals. The inflammatory milieu of acute infection was also associated with significantly increased levels of the catecholamine pathway substrate PHE ( = 1.4 [95% CI: 0.97-1.9] versus uninfected controls). Resolution of systemic inflammation during sub-acute SARS-CoV-2 infection and recovery was reflected by decreasing plasma levels of IL6, IL10, TNF and INFG as compared with acute disease. This was paralleled by decreasing levels of KYN (sub-acute: = -0.31 [95% CI: -0.6–0.022], recovery: = -1.3 [95% CI: -1.6–0.9]) and QUIN (sub-acute: = -0.29 [95% CI: -0.61-0.022], recovery: = -1.4 [95% CI: -1.8–0.97]), and increasing TRP (sub-acute: = 0.75 [95% CI: 0.25-1.3], recovery: = 1.9 [95% CI: 1.2-2.5]) and serotonin levels (sub-acute: 0.22 [95% CI: -0.1-0.54], recovery: = 1.2 [95% CI: 0.81-1.6]) as compared with acute SARS-CoV-2 infection. Similarly, infection recovery was associated with significantly decreasing PHE (sub-acute: = -0.54 [95% CI: -0.81–0.27], recovery: = -1.2 [95% CI: -1.5–0.83]) and elevated DA sulfate (sub-acute: = 0.68 [95% CI: 0.34-1], recovery: = 1.5 [95% CI: 1.1-2]) as compared with acute infection.

In correlation analysis of inflammation-associated cytokines and metabolites (**Figure 4A**, **Supplementary Figure S6**), TRP was negatively associated with all investigated cytokines during acute (: -0.38 - -0.24) and sub-acute infection (: -0.51 - -0.33) with weak-to-moderate and moderate-to-large effect size. Plasma serotonin levels correlated negatively with IL6 concentrations during acute infection ( = -0.23, effect size: weak) and correlated negatively with IL6, IL10, TNF and IFNG in sub-acute infection (: -0.44 - -0.26, effect size: weak-to-moderate). By contrast, KYN (acute, : 0.42 - 0.58; sub-acute. : 0.56 - 0.65) and QUIN (acute, : 0.39 - 0.69; sub-acute, : 0.59 - 0.71) correlated positively with circulating IL6, IL10, TNF and IFNG with a moderate-to-large strength.  
Serotonin levels correlated with TRP during acute ( = 0.2) and sub-acute infection ( = 0.3) with weak and moderate effect size, respectively.

Concerning the catecholamine pathway metabolites (**Figure 4B**, **Supplementary Figure S6**), positive weak-to-moderate correlations of PHE with IL6, IL10 and TNF were observed in acute infection (: 0.24 - 0.39). PHE was weakly positively associated with IL10 in sub-acute SARS-CoV-2 infection ( = 0.29). In turn, TYR plasma concentrations correlated negatively with TNF and IFNG during acute ( = -0.23) and sub-acute infection (: -0.26 - -0.22) with weak effect size. DA sulfate correlated negatively with IFNG and IL6 in acute (IFNG, = -0.22) and sub-acute infection (IL6, = -0.23), respectively, with weak effect size.

# Discussion

## Result summary

In two separate cohorts, we investigated factors affecting the key metabolic pathways determining systemic availability of serotonin and dopamine in SARS-CoV-2 infection. Our analysis underlines the pivotal role of SARS-CoV-2-dependent and -independent inflammation on the serotonin and kynurenine pathway activity. In particular, levels of the kynurenine pathway markers, KYN, KYN/TRP and QUIN, were higher, whereas concentration of the serotonin precursor TRP was lower, in the presence of inflammation reflected by elevated NEO or IL6. This observation and the significant association of serotonin with TRP levels in the INCOV cohort suggest collectively that depletion of TRP via highly active kynurenine pathway can limit systemic serotonin availability during SARS-CoV-2 infection (Badawy, 2017). Age, male sex, mental stress and depression were proposed as infection-independent predictors of high kynurenine pathway activity, lowered TRP and, consequently, reduced serotonin formation. Our data suggest similar inhibitory effects of inflammation on the first step of the catecholamine pathway, PHE - TYR conversion, and a reduced systemic dopamine availability reflected by lowered circulating DA sulfate (Meiser et al., 2013).

Few discrepancies need a more thorough discussion. First, explanatory performance of analyses of the serotonin and kynurenine pathway activity measured by R2 and correlation coefficients were generally higher than explanatory values of the catecholamine pathway analyses. This indicates that the predictors identified by our analysis, inflammation, SARS-CoV-2-positivity and infection timepoint impact the TRP metabolic pathways to a larger degree than catecholamine metabolism, in line with a metabolomic study in COVID-19 individuals (Thomas et al., 2020). Second, effects of inflammation on markers of the kynurenine and catecholamine pathway activity were stronger in the INCOV than in the SIMMUN cohort, which may reflect more severe infection in INCOV study participants. Third, in the SIMMUN cohort, the inflammatory marker NLR could be unexpectedly linked to lower KYN, which may be explained by a sustained low-grade neutropenia reported for up to 1 year after COVID-19 (Lin et al., 2022).

## Effects of inflammation and infection on the serotonin and kynurenine pathways, and systemic levels of serotonin

IDO1, together with TDO and IDO2, catalyzes the first reaction of the kynurenine pathway, the TRP - KYN conversion, which catabolizes >90% of TRP and may limit serotonin availability (Badawy, 2017; Lukić et al., 2022). Expression and activity of IDO1 are induced by inflammatory stimuli such as IL6, TNF and IFNG (Badawy, 2017; Robinson et al., 2003). Consequently, elevated metabolite levels and activity readouts of the kynurenine pathway were reported for multiple inflammatory conditions (Badawy, 2017). In COVID-19, levels of metabolites of the kynurenine pathway in blood and urine were found to correlate positively with inflammatory markers (Dewulf et al., 2022; Santiago-Mujika et al., 2022), disease severity (Ceballos et al., 2022; Dewulf et al., 2022; Lionetto et al., 2021) and was implicated in persistent COVID-19 symptom (Bizjak et al., 2022; Cysique et al., 2022; Matits et al., 2023). These findings were summarized in a recent metaanalysis demonstrating increased KYN/TRP in COVID-19 and particularly in its severe manifestations (Almulla et al., 2022). Using high-throughput metabolomics, tryptophan metabolism via serotonin and kynurenine pathways was identified as the most prominently affected metabolic system in acute COVID-19. In this study, TRP and serotonin were demonstrated to decrease and KYN was shown to increase in an IL6-dependent way (Thomas et al., 2020). Of note, IL6 was also identified by us as a predictor of lower plasma serotonin in the INCOV study. We demonstrated significant, positive associations of serotonin and TRP levels in acute and sub-acute infection in the INCOV cohort. This suggests that kynurenine pathway may especially efficiently compete for TRP with systemic serotonin synthesis in the highly inflammatory milieu of early COVID-19. In turn, increasing TRP and serotonin during infection recovery in the INCOV cohort may reflect decreasing IDO1 activity and re-routing of TRP to the serotonin biosynthesis (Badawy, 2017; Lukić et al., 2022). The multi-parameter modeling in the SIMMUN cohort revealed an additional, inflammation-independent effect of SARS-CoV-2-positivity at median 139 days after infection on KYN and KYN/TRP. While its mechanism remains unclear, an analogical sustained increase in KYN in absence of the inflammatory marker C-reactive protein was described in long-term COVID-19 recovery (Bizjak et al., 2022). Age was identified by us as another predictor of high kynurenine pathway activity and low serotonin availability, which may be a result of a chronic low-grade inflammation observed in elderly (Capuron et al., 2011; Sorgdrager et al., 2019). Furthermore, significantly lower levels of serotonin were observed in male participants of the INCOV study. This may reflect a generally stronger inflammatory response to SARS-CoV-2 in males (Ceballos et al., 2022), which was also evident in our data (INCOV, IL6: = 0.69 [95% CI: 0.073-1.3], male versus female, robust linear modeling).

## Effects of inflammation and infection on the serotonin and kynurenine pathways, and systemic levels of serotonin

BH4 poses, another junction between neurotransmitter metabolism and inflammation. Activity of GTP cyclohydrolase I, the enzyme catalyzing the rate-limiting step of BH4 synthesis, is strongly stimulated by IFNG and other inflammatory stimuli. However, during inflammation, BH4 availability for catecholamine and serotonin pathway enzymes is limited due to oxidation and depletion by nitric oxide synthesis (Geisler et al., 2013; Meiser et al., 2013; Neurauter et al., 2008). As previously reported (Luporini et al., 2021), we could demonstrate an increased plasma PHE during acute and sub-acute infection in the INCOV cohort. We could also correlate readouts of suppressed catecholamine pathway activity such as increased PHE and PHE/TYR, and low TYR and DA sulfate levels with inflammatory markers NEO, IL6, TNF and IFNG. Collectively, these observations are consistent with the inflammatory BH4 deficiency leading to suppressed PHE - TYR conversion, hyperphenylalaninemia and impaired catecholamine biosynthesis during acute and sub-acute SARS-CoV-2 infection. By contrast, the increased DA sulfate during infection recovery in the INCOV cohort and the significantly lower PHE/TYR at median 139 days after SARS-CoV-2 infection in the SIMMUN cohort may indicate a restored BH4 homeostasis and efficient dopamine synthesis (Geisler et al., 2013; Goldstein et al., 1999; Meiser et al., 2013; Neurauter et al., 2008). Contrary to the reported suppression of catecholamine synthesis with age (Peters, 2006), we observed higher blood levels of TYR and lower PHE/TYR in older participants of the SIMMUN study. However, since we could not corroborate this effect in the INCOV cohort, its reproducibility remains questionable. Analogically, although low DA sulfate levels were associated with obesity in the INCOV cohort, we could no observe any significant effects of obesity on markers of the catecholamine pathway activity in the SIMMUN cohort.

## Interaction of mental health with activity of the serotonin, kynurenine and catecholamine pathways, and systemic serotonin and dopamine availability

Peripheral and central nervous system inflammation was put forward as a neuroimmune mechanism contributing to mental health disorder symptoms such as depression, anxiety and mental stress (Brown et al., 2021; Schwarcz et al., 2012; Vancassel et al., 2018). Sickness behavior accompanying e.g. infections and inflammatory conditions comprises symptoms of depression and anxiety, social disconnection, fatigue, cognitive disturbance, and psychomotor slowing. Mechanistically, sickness behavior was postulated to involve kynurenine pathway along with suppression of serotonin and catecholamine metabolism mediated by acute or protracted low grade inflammation (Dantzer et al., 2008; Maes et al., 2012; Vancassel et al., 2018). Additionally, kynurenine pathway metabolites were ascribed standalone activity in neuronal signaling, e.g. by interfering with glutamatergic receptors (Brown et al., 2021; Schwarcz et al., 2012). Accordingly, markers of the kynurenine pathway activity and suppressed serotonin pathway such as serotonin, TRP, KYN or KYN/TRP were associated with symptoms of depression in recent metaanalyses (Fellendorf et al., 2022; Hunt et al., 2020; Marx et al., 2020). Inflammatory markers were also associated with elevated PHE/TYR indicative of reduced dopamine availability and proposed to contribute to depression in cancer (Hüfner et al., 2015) and trauma (Hüfner et al., 2019). The potential role of protracted inflammation and TRP depletion in persistent symptoms and mental disorders in COVID-19 convalescents was proposed in recent hypothesis papers (Bower et al., 2022; Eroğlu et al., 2021). There is also clinical evidence for concomitantly elevated markers of inflammation, kynurenine pathway activity and lowered TRP availability in COVID-19 patients suffering from persistent symptoms (Bizjak et al., 2022), cognitive impairment (Cysique et al., 2022), or symptoms of anxiety, depression and mental stress (Kucukkarapinar et al., 2022; Matits et al., 2023). In the SIMMUN cohort, clinically relevant depression symptoms (HADS) and mental stress (PSS-4) along with the inflammatory marker NEO could be linked to decreased TRP and higher KYN/TRP, respectively. In the INCOV collective, inflammation was also identified as a major diver of alterations in circulating serotonin, TRP, as well as the kynurenine pathway metabolites KYN and QUIN. Hence, the additive effects of inflammation, infection, mental stress and age may disrupt the homeostasis of the serotonin, kynurenine and catecholamine pathways and predispose to depressive or anxious disorders in COVID-19 patients (Bower et al., 2022; Dantzer et al., 2008).

Still, most evidence for relevance of the peripheral neurotransmitter levels in mental disorders is delivered by observational studies, whereas in vivo experimental reports are scarce (Brown et al., 2021). In the periphery, liver, mesenteric organs and vasculature are the main sites of tryptophan, serotonin and dopamine metabolism (Badawy, 2017; Goldstein et al., 1999; Lukić et al., 2022; Meiser et al., 2013). Although the neurotransmitter precursors TRP and TYR, and kynurenin pathway metabolites were postulated to pass the blood-brain barrier (Brown et al., 2021; Schwarcz et al., 2012; Vancassel et al., 2018), psychiatric disorders are not consistently paralleled by alterations in dopamine, serotonin, and kynurenine pathway metabolites in the central nervous system (Brown et al., 2021; Clark et al., 2016; Miller et al., 2008). Of note, clinical evidence for the serotonin theory of depression was also questioned in a recent systematic review (Moncrieff et al., 2022). Whether inflammatory and infection-related factors impact on peripheral and brain availability of serotonin and dopamine availability and, hence, contribute to psychiatric disorders frequently observed in COVID-19 patients (Al-Aly et al., 2021; Huang et al., 2021; Hüfner et al., 2022; Sahanic et al., 2023), needs validation in a robust experimental and prospective setting.

## Limitations

Our study has limitations. First, incompatibility of study designs and variable sets of the SIMMUN and INCOV studies precluded direct comparison and validation of our findings in the classical training - test cohort analysis setting. In particular, we were not able to validate effects of early infection on the metabolic pathways of interest in the SIMMUN cohort. Conversely, we could not validate the effects of stress, depression and anxiety in the INCOV cohort due to unavailability of psychometric data. Second, relevance of the systemic serotonin, kynurenine and catecholamine pathway activity for the central nervous system and mental health is controversial, as discussed above. Third, the SIMMUN cohort had a limited sample size and a highly variable diagnosis - sampling interval, which likely diminished effect sizes of the SARS-CoV-2 infection. Fourth, the SIMMUN cohort suffered from a selection bias due to enrichment in psychiatric patients with a high rate of physical and mental disorders. Analogically, hospitalized COVID-19 patients constituted the majority of the INCOV cohort. Hence, none of the cohorts is representative for the entire population. Fifth, both cohorts were recruited during initial phases of the pandemic and do not include vaccinated patients. Similarly, the analyzed cohorts were exposed to wild-type-like SARS-CoV-2 variants and do not allow to assess effects of infection with highly transmissible but less virulent omicron pathogens. For these reasons, studies with recent, post-pandemic collectives are urgently needed to validate our findings. Finally, the cross-sectional SIMMUN and INCOV cohorts encompassed uninfected controls and SARS-CoV-2 infections ranging from asymptomatic to critical disease.

## Conclusions

SARS-CoV-2-dependent and -independent inflammation alters activity of the serotonin, kynurenine and catecholamine pathway which may limit systemic availability of serotonin and dopamine. Those effects can be further amplified by advanced age, mental stress and depression. Further research is needed to explore the mechanistic interplay of SARS-CoV-2 infection, inflammation and mental health parameters. It remains to be investigated, if and how this mechanism contributes to psychiatric disorders following SARS-CoV-2 infection.

# Acknowledgements

We thank all participants and patients for the participation in the study.

# Funding

The study was supported by the Science Fund of the Land Tirol (grant number GZ71134 to Katharina Hüfner).

# Conflict of interest

Katharina Hüfner has received research grants from Austria Wirtchaftsservice (AWS) and the State of Tyrol as well as lecturer’s honoraria from Forum Medizinische Fortbildung (FOMF), the Anton Proksch Institute and the Hospital of Schwaz. Piotr Tymoszuk owns a data science company, Data Analytics as a Service Tirol, and receives payments from statistical data analysis, bioinformatic and scientific writing services. Other authors declare that no conflict of interest exists.

# Data and code availability

Anonymized patient data will be made available upon request to the corresponding author. The INCOV cohort data are publicly available at <https://data.mendeley.com/datasets/96v329bg7g/1>. The analysis pipeline code is available at <https://github.com/PiotrTymoszuk/simmun>.

# Tables

Table 1: Characteristic of the SIMMUN cohort. Numeric variables are presented as medians with interquartile ranges. Categorical variables are presented as percentages and counts within complete observation sets.

| **Variablea** | **Uninfected** | **SARS-CoV-2 infection** | **Test** | **Significanceb** | **Effect size** |
| --- | --- | --- | --- | --- | --- |
| Participants, n | 101 | 64 |  |  |  |
| Sex | female: 64% (65) male: 36% (36) | female: 58% (37) male: 42% (27) | χ² | ns (p = 0.54) | V = 0.066 |
| Age, years | 50 [IQR: 35 - 58] range: 18 - 69 | 50 [IQR: 32 - 56] range: 20 - 68 | Mann-Whitney | ns (p = 0.45) | r = 0.069 |
| Body mass indexc | normal: 53% (54) overweight: 32% (32) obesity: 15% (15) | normal: 53% (34) overweight: 27% (17) obesity: 20% (13) | χ² | ns (p = 0.6) | V = 0.079 |
| Physical disorder | 54% (55) | 45% (29) | χ² | ns (p = 0.43) | V = 0.089 |
| Mental disorder | 50% (50) | 28% (18) | χ² | p = 0.021 | V = 0.21 |
| HADS anxiety score | < 8: 57% (58) ≥ 8: 43% (43) | < 8: 80% (51) ≥ 8: 20% (13) | χ² | p = 0.013 | V = 0.23 |
| HADS depression score | < 8: 69% (70) ≥ 8: 31% (31) | < 8: 84% (54) ≥ 8: 16% (10) | χ² | ns (p = 0.078) | V = 0.17 |
| Clinically relevant signs of depression or anxiety, HADS ≥ 8 | 45% (45) | 20% (13) | χ² | p = 0.0078 | V = 0.25 |
| PSS-4 mental stress score | 6 [IQR: 3 - 9] range: 0 - 14 | 5 [IQR: 3 - 8] range: 1 - 13 | Mann-Whitney | ns (p = 0.33) | r = 0.095 |
| anti-RBD SARS-CoV-2, IgG, AU | 0.31 [IQR: 0.28 - 0.34] range: 0.21 - 0.99 | 16 [IQR: 14 - 17] range: 0.42 - 20 | Mann-Whitney | p < 0.001 | r = 0.84 |
| COVID-19 severity |  | ambulatory: 73% (47) hospitalized: 27% (17) |  |  |  |
| aHADS: hospital anxiety and depression scale; PSS-4: perceived stress scale, 4 item; RBD: receptor binding domain; IgG: immunoglobulin gamma; AU: arbitrary urnits. | | | | | |
| bCorrected for multiple testing with the false discovery rate method. | | | | | |
| coverweight: body mass index (BMI) 25 - 30 kg/m²; obesity: BMI > 30 kg/m² | | | | | |

Table 2: Characteristic of the INCOV cohort. Numeric variables are presented as medians with interquartile ranges. Categorical variables are presented as percentages and counts within complete observation sets.

| **Variable** | **Uninfected** | **SARS-CoV-2 infection** | **Test** | **Significancea** | **Effect size** |
| --- | --- | --- | --- | --- | --- |
| Participants, n | 27 | 140 |  |  |  |
| Sex | female: 56% (15) male: 44% (12) | female: 41% (58) male: 59% (82) | χ² | ns (p = 0.25) | V = 0.1 |
| Age, years | 56 [IQR: 49 - 60] range: 32 - 70 | 62 [IQR: 48 - 73] range: 26 - 89 | Mann-Whitney | p = 0.044 | r = 0.17 |
| Body mass indexb | normal: 44% (12) overweight: 22% (6) obesity: 33% (9) | normal: 26% (36) overweight: 36% (51) obesity: 38% (53) | χ² | ns (p = 0.17) | V = 0.16 |
| Ethnics | Asian: 0% (0) Black or African-American: 12% (3) White: 88% (21) Other: 0% (0) | Asian: 16% (22) Black or African-American: 9.3% (13) White: 46% (65) Other: 29% (40) | χ² | p = 0.0013 | V = 0.33 |
| COVID-19 severityc |  | mild: 2.9% (4) moderate: 59% (83) severe: 25% (35) critical: 13% (18) |  |  |  |
| aCorrected for multiple testing with the false discovery rate method. | | | | | |
| boverweight: body mass index (BMI) 25 - 30 kg/mm², obesity: BMI > 30 kg/mm² | | | | | |
| cWHO ordinal scale for clinical improvement; mild: 1 - 2, moderate: 3 - 4, severe: 5 - 6, critical: 7; moderate, severe and critical infection patients were hospitalized during COVID-19. | | | | | |

# Figures

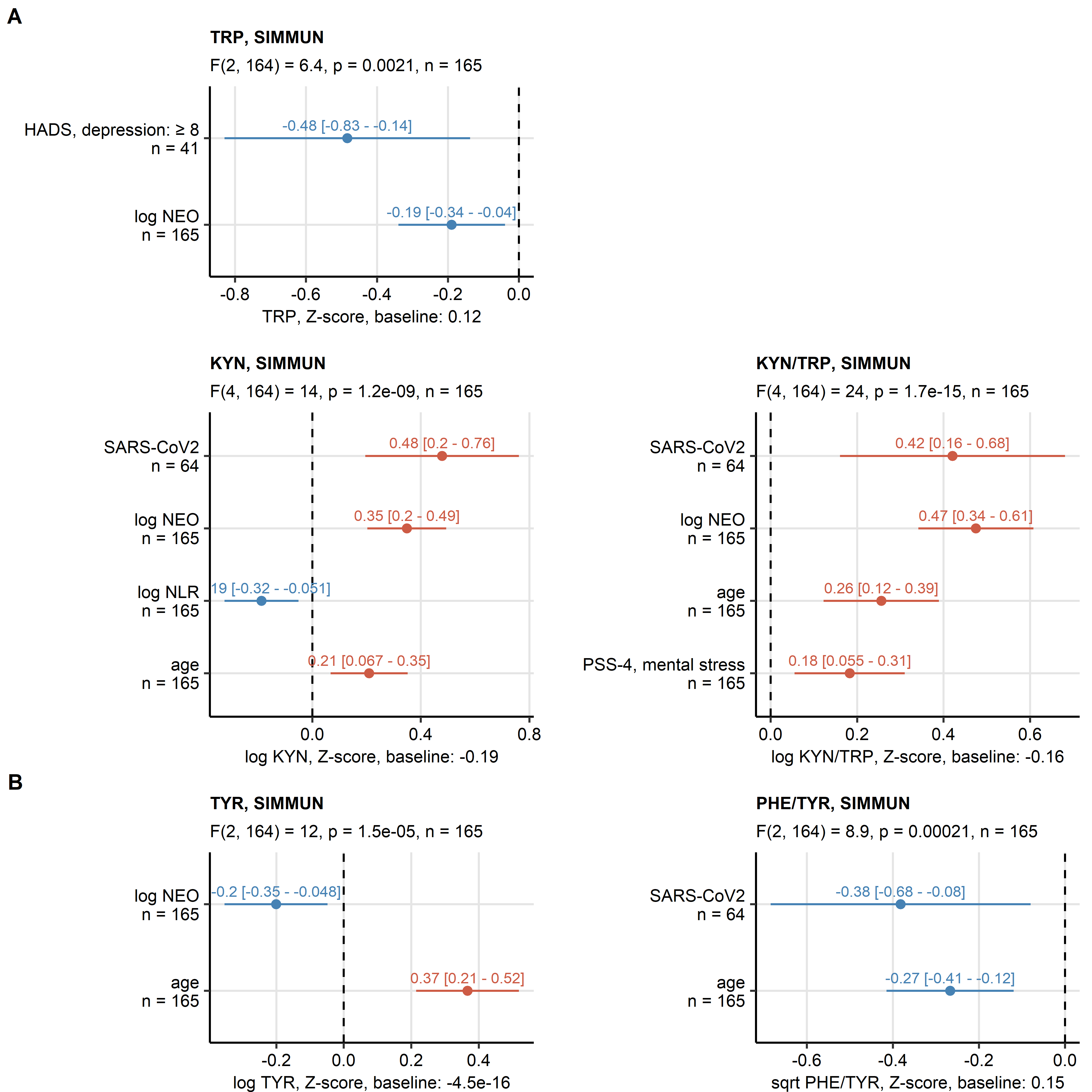


Figure 1: Results of multi-parameter linear modeling of tryptophan, kynurenine, kynurenine/tryptophan ratio, tyrosine and phenylalanine/tyrosine ratio in the SIMMUN cohort.

**Figure 1. Results of multi-parameter linear modeling of tryptophan, kynurenine, kynurenine/tryptophan ratio, tyrosine and phenylalanine/tyrosine ratio in the SIMMUN cohort.**

*Effects of markers of systemic inflammation (neopterin [NEO], neutrophil/lymphocyte ratio [NLR]), SARS-CoV-2 infection status, titre of immunoglobulin gamma against the receptor binding domain of the S1/S2 SARS-CoV-2 protein (anti-RBD IgG), clinically relevant symptoms of anxiety and depression (hospital depression and anxiety scale [HADS] 8 points), intensity of mental stress (perceived stress scale, 4 item [PSS-4]), age and sex on readouts of the kynurenine pathway (A, tryptophan [TRP], kynurenine [KYN], kynurenine/tryptophan ratio [KYN/TRP]) and the catecholamine pathway activity (B, phenylalanine [PHE], tyrosine [TYR], phenylalanine/tyrosine ratio [PHE/TYR]) were investigated by multi-parameter linear regression with backward elimination of non-significant terms. Numeric variables were normalized prior to modeling. Overall model validity was assessed by likelihood-ratio test (LRT) as compared with the respective null models. Coefficient estimates () with 95% confidence intervals are presented in Forest plots. LRT results (F values, degrees of freedom and p values) and total numbers of complete observations are indicated in the plot captions. Model intercepts (baseline) are indicated in the X axis titles.*

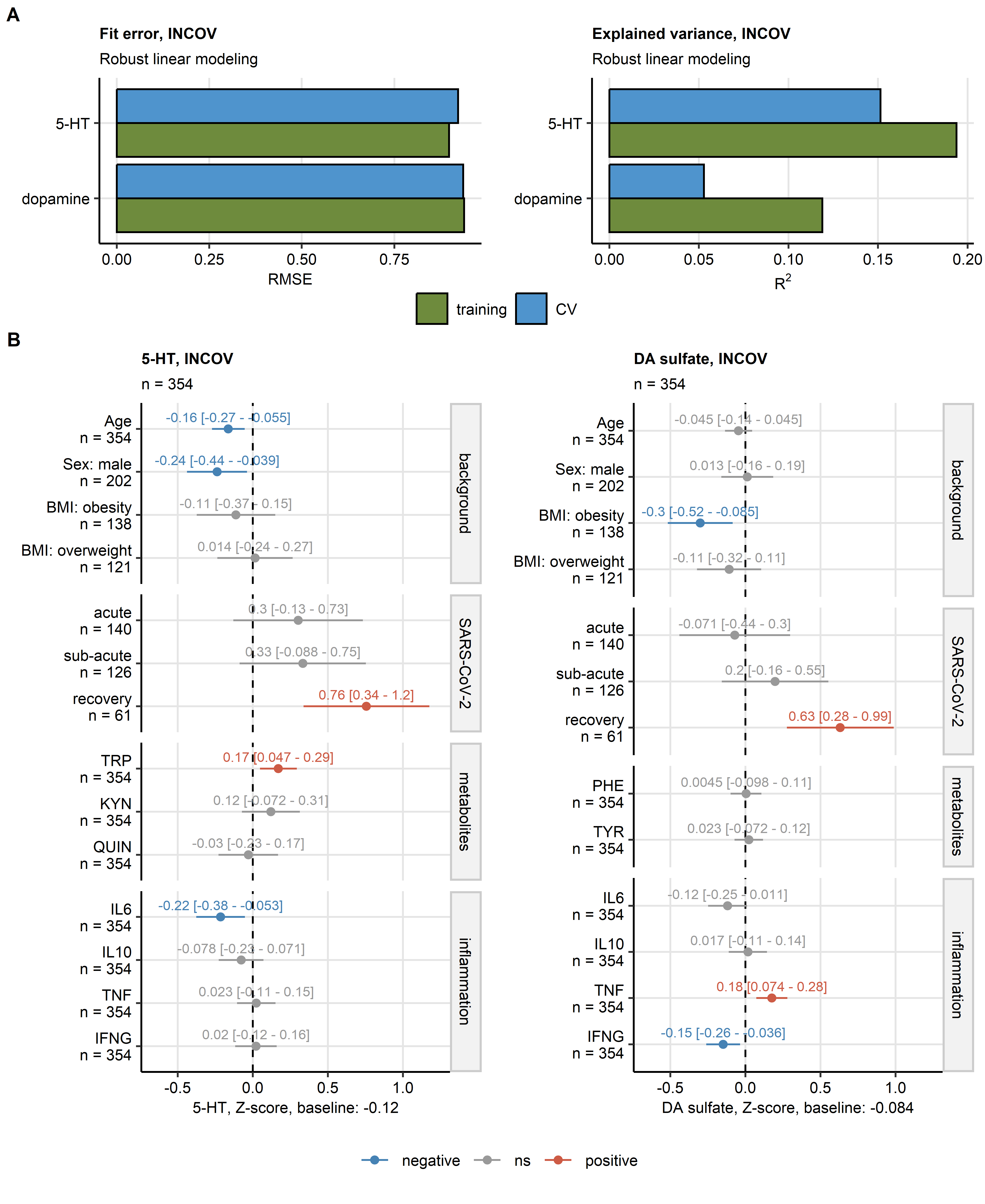


Figure 2: Results of multi-parameter robust linear modeling of plasma levels of serotonin and dopamine 3-O-sulfate in the INCOV cohort.

**Figure 2. Results of multi-parameter robust linear modeling of plasma levels of serotonin and dopamine 3-O-sulfate in the INCOV cohort.**

*Effects of age, timepoint of SARS-CoV-2 infection (acute: median 10 days, sub-acute: median 14 days, recovery: median 64 days after SARS-CoV-2 infection diagnosis via PCR), plasma levels of metabolites of the serotonin and kynurenine pathways (tryptophan [TRP], kynurenine [KYN], quinolinic acid [QUIN]), plasma levels of metabolites of the catecholamine pathway (phenylalanine [PHE], tyrosine [TYR]), and plasma concentrations of cytokine markers of inflammation (interleukin-6 [IL6], interleukin-10 [IL10], tumor necrosis factor-alpha [TNF] and interferon-gamma [IFNG]) on plasma concentrations of serotonin (5-hydroxy tryptamine [5-HT]) and dopamine 3-O-sulfate (DA sulfate) were modeled by multi-parameter robust linear regression.*

*(A) Model fit error (root mean square error [RMSE]) and fraction of explained variance (R2) of the robust linear models assessed in the training dataset and infection timepoint-stratified 10-fold cross-validation (CV).*

*(B) Estimates of model coefficients () with 95% confidence intervals presented in Forest plots. Numbers of complete observations are indicated in the plot captions. Model intercepts (baseline) are indicated in the X axis titles.*

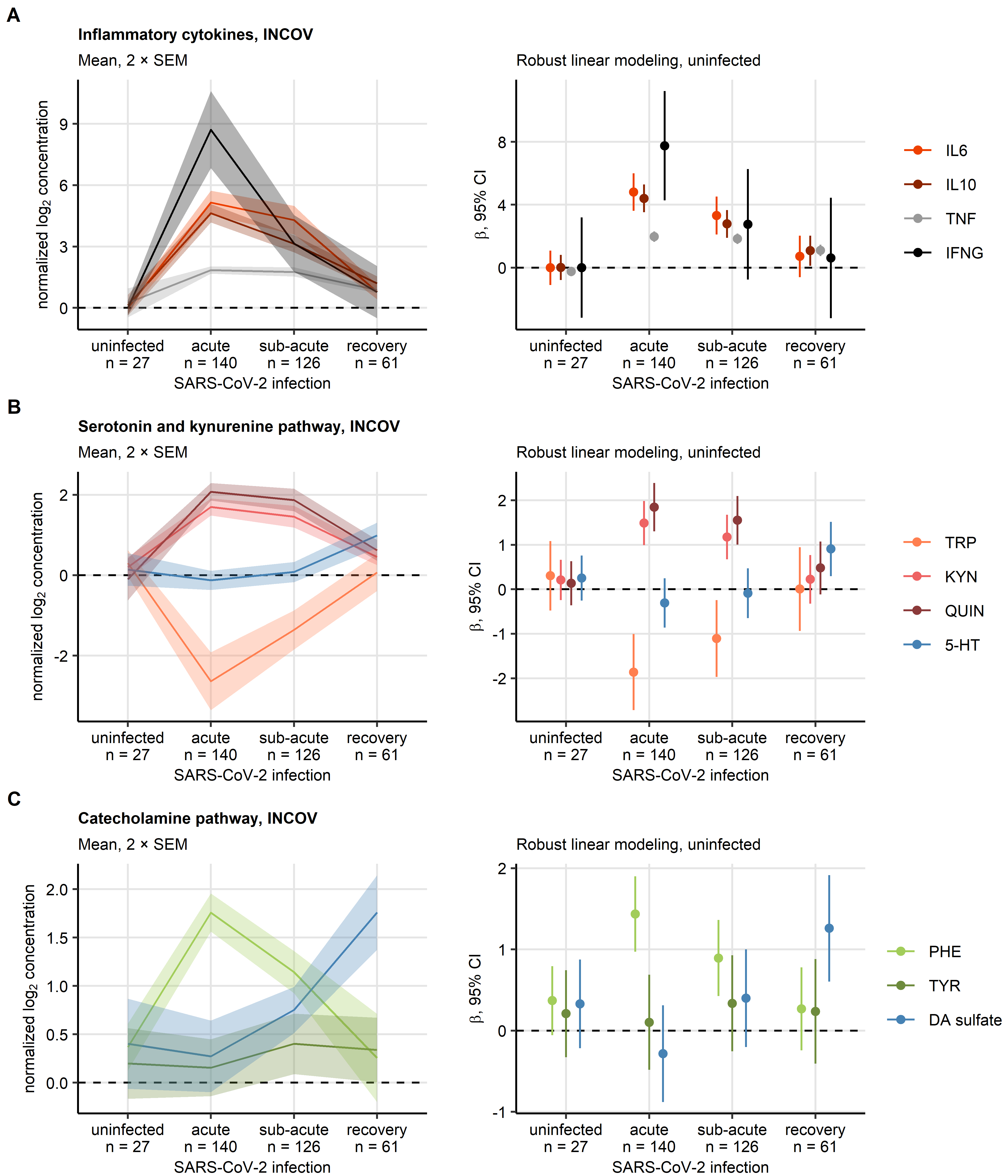


Figure 3: TTime course of cytokine markers of inflammation, and metabolites of the serotonin, kynurenine and catecholamine pathways during SARS-CoV-2 infection and recovery in the INCOV cohort.

**Figure 3. Time course of cytokine markers of inflammation, and metabolites of the serotonin, kynurenine and catecholamine pathways during SARS-CoV-2 infection and recovery in the INCOV cohort.**

*Time courses of normalized log2-transformed plasma concentrations of cytokine makers of inflammation (A, interleukin-6 [IL6], interleukin-10 [IL-10], tumor necrosis factor-alpha [TNF], interferon gamma [INFG]), metabolites of the serotonin and kynurenine pathways (B, tryptophan [TRP], kynurenine [KYN], quinolinic acid [QUIN], serotonin/5-hydroxy tryptamine [5-HT]), and metabolites of the catecholamine pathway (C, phenylalanine [PHE], tyrosine [TYR], dopamine 3-O-sulfate [DA sulfate]). Differences between uninfected controls and acute, sub-acute SARS-CoV-2 infection and recovery (median 10, 14 and 64 days after SARS-CoV-2 infection diagnosis via PCR, respectively) were modeled by robust linear regression with the uninfected controls as baseline. Mean normalized concentrations with 2 standard errors of the mean (2 SEM) are depicted as solid lines with tinted ribbons (plots on the left). Robust linear model coefficient estimates () with 95% confidence intervals are visualized in Forest plots (right). Numbers of complete observations per timepoint are indicated in the X axes.*

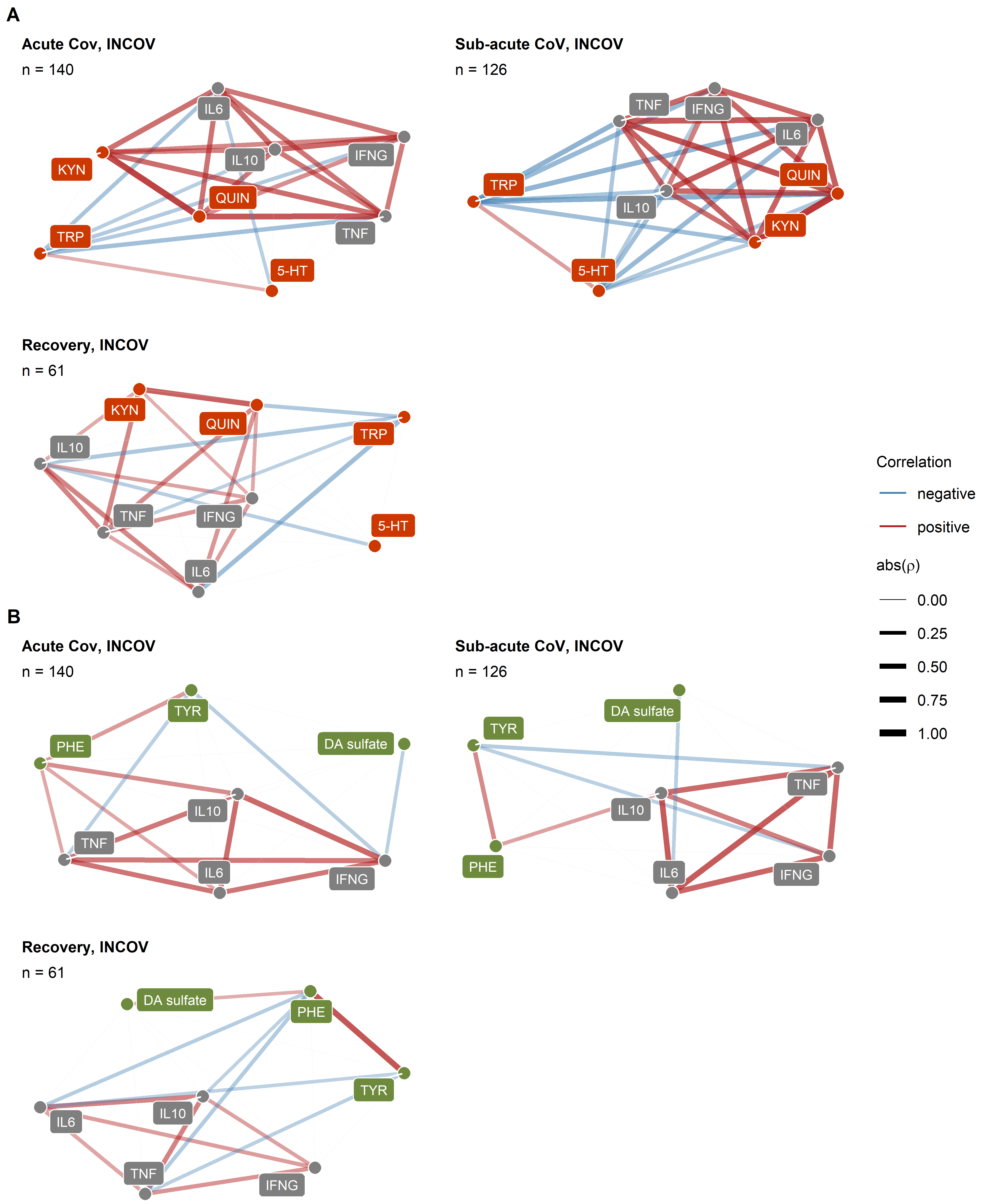


Figure 4: Correlation of plasma levels of cytokine markers of inflammation, and metabolites of the serotonin, kynurenine and catecholamine pathways during SARS-CoV-2 infection in the INCOV cohort.

**Figure 4. Correlation of plasma levels of cytokine markers of inflammation, and metabolites of the serotonin, kynurenine and catecholamine pathways during SARS-CoV-2 infection and recovery in the INCOV cohort.**

*Plasma levels of metabolites of the kynurenine and serotonin pathways (tryptophan [TRP], serotonin [5-hydroxy tryptamine, 5-HT], kynurenine [KYN], quinolinic acid [QUIN]) and metabolites of the catecholamine pathway (phenylalanine [PHE], tyrosine [TYR], dopamine 3-O-sulfate [DA sulfate]) and cytokine markers of inflammation (interleukin-6 [IL6], interleukin-10 [IL10], tumor necrosis factor-alpha [TNF], interferon-gamma [INFG]) were subjected to pairwise correlation analysis in SARS-CoV-2-infected individuals (acute: median 10 days, sub-acute: median 14 days, recovery: median 64 days after SARS-CoV-2 infection diagnosis via PCR). Correlation coefficient matrices for correlation coefficients > 0.2 were visualized as force-directed network plots. Node color codes for the variable type (gray: inflammatory markers, orange: serotonin and kynurenine pathway, green: catecholamine pathway), edge width and color codes for the value and sign of the correlation coefficient.*

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