# A *MUC5B* Gene Polymorphism, rs35705950-T Confers Protective Effects Against COVID-19 Hospitalization but not Severe Disease or Mortality

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Some of the results of these studies have been previously reported in the form of a preprint (medRxiv, [29 September 2021] https://doi.org/10.1101/2021.09.28.21263911).

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## At a Glance Commentary

### Scientific knowledge on the subject

Parenchymal fibrosis, a late feature of severe COVID-19 disease, shares characteristics with idiopathic pulmonary fibrosis (IPF). The impact of rs35705950-T, a functional polymorphism upstream of the MUC5B gene and an established risk factor for IPF, on COVID-19 outcomes in an ancestrally diverse population is unclear.

### What this study adds to the field

Rs35705950-T was associated with fewer COVID-19 hospitalizations in a trans-ancestry meta-analysis conducted in the Million Veteran Program (MVP, ntotal=511,965; OR=0.89 [0.82-0.97]) and in joint meta-analysis with the Host Genetics Initiative (ntotal=506,174; OR=0.90 [0.86-0.95]). In subgroup analyses of MVP participants of European ancestry, rs35705950-T was associated with fewer post-COVID-19 pneumonia events, with evidence supportive of a protective dose-response relationship for each copy of the rs35705950-T allele. These results support a potentially protective effect of rs35705950-T against COVID-19 hospitalizations and post-infection pneumonia events.

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## Abstract

**Rationale**: A common *MUC5B* gene polymorphism, rs35705950-T, is associated with idiopathic pulmonary fibrosis (IPF), but its role in SARS-CoV-2 infection and disease severity is unclear.

**Objectives**: To assess whether rs35705950-T confers differential risk for clinical outcomes associated with COVID-19 infection among participants in the Million Veteran Program (MVP).

**Methods**: The *MUC5B* rs35705950-T allele was directly genotyped among MVP participants; clinical events and comorbidities were extracted from the electronic health records. Associations between the incidence or severity of COVID-19 and rs35705950-T were analyzed within each ancestry group in the MVP followed by trans-ancestry meta-analysis. Replication and joint meta-analysis were conducted using summary statistics from the COVID-19 Host Genetics Initiative (HGI). Sensitivity analyses with adjustment for additional covariates (BMI, Charlson comorbidity index, smoking, asbestosis, rheumatoid arthritis with interstitial lung disease and IPF) and associations with post-COVID-19 pneumonia were performed in MVP subjects.

**Measurements and Main Results:** The rs35705950-T allele was associated with fewer COVID-19 hospitalizations ($N_{cases}$=4,325/, $N_{controls}$=507,640; OR=0.89 [0.82-0.97], p=6.86 x $10^{-03}$) in trans-ancestry meta-analysis within MVP and joint meta-analyses with the HGI ($N_{cases}$=13,320, $N_{controls}$=1,508,841; OR=0.90 [0.86-0.95], p =8.99 x $10^{-05}$). The rs35705950-T allele was not associated reduced COVID-19 positivity in trans- ancestry meta-analysis within MVP ($N_{cases}$=19,168/$N_{controls}$=492,854; OR=0.98 [0.95-1.01], p=0.06) but was nominally significant (p


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< 0.05) in the joint meta-analysis with HGI ($N_{cases}$=44,820/$N_{controls}$=1,775,827; OR=0.97 [0.95-1]; p=0.03). We did not observe associations with severe outcomes or mortality. Among MVP individuals of European ancestry, rs35705950-T was associated with fewer post-COVID-19 pneumonia events (OR=0.82 [0.72-0.93], p=0.001).

**Conclusions**: The *MUC5B* variant rs35705950-T may confer protection in COVID-19 hospitalizations.

**Keywords**: coronavirus disease 2019; severe acute respiratory syndrome coronavirus 2; idiopathic pulmonary fibrosis; electronic health records; genetic association

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## Introduction

A respiratory disease caused by a novel coronavirus, now known as SARS-CoV-2, was first reported towards the end of 2019. Despite massive public health measures and vaccination initiatives, the coronavirus disease-2019 (COVID-19) pandemic remains a major global health threat. By February 2022, the COVID-19 pandemic had caused more than 424 million confirmed infections resulting in more than 5.8 million deaths worldwide(1).

Parenchymal fibrosis is a late complication of severe respiratory infections due to COVID-19(2–4). Among chronic lung diseases, idiopathic pulmonary fibrosis (IPF)(5), a disorder characterized by progressive pulmonary scarring which is associated with a median survival of 2-3 years in the absence of lung transplantation(6), shares several risk factors with those for severe COVID-19 disease, including advanced age(7), cardiovascular disease, diabetes, and a history of smoking(5). Thus, common pathological processes may be shared between the fibrotic response towards COVID-19 infection and those underlying IPF.

IPF likely develops from a multifaceted interaction between genetic and environmental factors, age-related mechanisms, and epigenetic profibrotic reprogramming(8, 9). One of the most robust genetic risk factors identified for IPF susceptibility is rs35705950-T, a common G to T transversion located approximately 3 kb upstream of the mucin 5B, oligomeric mucus/gel-forming (*MUC5B)* gene(10, 11). Laboratory evidence supports that rs35705950-T is: 1) a functional variant located within an enhancer subject to epigenetic programming and 2) contributes to pathologic mis-expression in IPF(12). Notably, while rs3705950-T has been robustly associated with increased susceptibility, the same allele has also been associated with

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decreased mortality in IPF (13), though whether this paradoxical effect is attributable to pleiotropy or index event bias remains controversial(14).

Given the high minor allele frequency (MAF) of rs35705950-T (~11% among individuals of European ancestry) and possible shared pathophysiological pathways between IPF and severe COVID-19 disease, we examined the association between rs35705950-T and the clinical outcomes of COVID-19 infection in the Million Veteran Program (MVP), a multi- ancestry cohort of over 650,000 U.S. Veterans with detailed electronic health record (EHR) and genotyping data(15). Following our primary analysis in the MVP, we validated our results with a comparable analysis conducted in the Host Genetics Initiative (HGI), a global collaboration of over 160 genetic studies assembled to facilitate rapid discovery and dissemination of COVID-19 related science(16).

## Methods

### Data Sources

Data from the MVP, a multi- ancestry genetic biobank sponsored by the United States Veterans Affairs (VA), were analyzed(15). All protocols were approved by the VA Central Institutional Review Board and all participants provided written informed consent. Genotyping was performed using a custom Thermo Fisher Axiom genotyping platform (MVP 1.0) which included direct genotyping of rs35705950-T. Ancestry was defined using harmonized ancestry, race, and ethnicity (HARE) derived from self-report and genetic ancestry data(17). Individuals from three major ancestry groups: European (EUR), African (AFR), Hispanic (HIS) were included.

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Demographic and pre-existing comorbidity data were collected from questionnaires and the VA EHR; "pre-COVID" data was from the time of enrollment into the MVP to September 30, 2019. The cohort demographics and a description of the clinical conditions for all genotyped MVP participants and COVID-19 positive MVP participants(18) that were evaluated in this study are shown in **Table 1**.

*COVID-19 outcome definitions*

COVID-19 infection status from 02/2020 - 04/2021 was assessed by either self-report (if testing was performed outside the VA) or by a positive polymerase chain reaction (PCR)-based test(19, 20) performed within the VA health system. The *index date* was defined as a COVID-19 diagnosis date, i.e., specimen date; and for a hospitalized patient, the admission date up to 15 days prior to the COVID-19 diagnosis date.

Our primary analyses used harmonized definitions with the COVID-19 HGI to maximize sample sizes, examine consistent endpoints, and facilitate meta-analyses. In accordance with the HGI phenotype definitions, the following three analyses were performed: (1) COVID-19 Susceptibility: individuals who tested positive for COVID-19; (2) COVID-19 Hospitalization: individuals who were hospitalized due to symptoms of COVID-19; (3) COVID-19 Severe: individuals who were hospitalized and required respiratory support beyond nasal cannula oxygen or died. For each phenotype, population controls were selected i.e., all the MVP participants who were not defined as a case were assigned as control. Controls also include individuals with unknown COVID-19 infection exposure. Additionally for the study of COVID-19 hospitalization, a fourth analysis comprised COVID-19 positive individuals that were

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hospitalized were compared with COVID-19 positive individuals that were not hospitalized.

Separate sensitivity analyses were conducted within the MVP cohort to evaluate the effect of possible confounding variables that were not evaluated in the HGI. To ensure complete capture of relevant clinical information, we included only individuals who were tested for COVID-19 at one of the VA sites; individuals who did not have COVID testing within the VA were excluded. The four phenotypes evaluated included COVID-19 testing positive rate, COVID-19 hospitalization, severe COVID-19 infection or death, and COVID-19 death (Modified from the WHO Working Group criteria(21) (**Supplemental Methods**)). All models were adjusted for additional possible confounders, including body mass index (BMI), Charlson comorbidity index (CCI), smoking history, asbestosis(22), rheumatoid arthritis with interstitial lung disease (RA-ILD)(23) and idiopathic pulmonary fibrosis (IPF)diagnosis(24). These variables were derived from the data within two years prior to the index date of diagnosis (**Table E1)**.

*Post-index pneumonia definition*

Post-index pneumonia was defined from ICD codes within 60 days after the index date. Association with COVID-19 pneumonia events (pneumonia60d) were performed among patients who received COVID-19 PCR testing at VA sites (**Table E2**). The ICD codes used to define pneumonia events within 60 days COVID-19 infection (pneumonia60d) are presented in **Table E3**.

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**Statistical analysis**

*Meta-analysis with HGI*

The analysis recommendations from the COVID-19 HGI were utilized to test for associations between the rs35705950-T allele and COVID-19 outcomes. First, we conducted analyses within MVP by each ancestry group using plink2a. Inverse-variance weighted meta-analyses were then performed with summary statistics from Release 5 (01/18/2021) of the HGI using GWAMA (18) (**Additional details in supplemental methods**).

*Sensitivity analysis*

Firth logistic regression as implemented in the R (v3.6.1) package "brglm2" (version 0.7.1) was used in the sensitivity analyses as it provides a bias-reduced estimate in the setting of small sample sizes and is most powerful for analyses of genetic mutations. This was relevant since adjustment for multiple variables can lead to small sample sizes within covariate categories. Associations between COVID-19 outcomes and rs35705950-T were performed separately by ancestry, with adjustment for age, age$^2$, sex, BMI, CCI, smoking history, asbestosis, RA-ILD and IPF (**Table E1**), and first 20 principal components. The meta-analyses were performed using random-effects models in "metafor" (version 2.4-0).

*Post-index pneumonia*

Interactions between COVID-19 infection status and rs35705950-T on the outcome of COVID-19 pneumonia within 60 days (pneumonia60d) were assessed using a multiplicative interaction term followed by stratified analyses by COVID-19 infection status. The Firth logistic model for

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interaction included the independent variables of interest: COVID-19 infection status, rs35705950-T, and their multiplicative interaction term, adjusted for pre-index pneumonia (yes/no, within 2 years pre-index), age, age$^2$, sex, BMI, CCI, smoking history, asbestosis, RA-ILD and IPF diagnosis, and first 20 ancestry-specific principal components (PC1-20). The SNP rs35705950-T was modeled as a continuous variable (additive genetic model with values 0,1,2) so that the interaction odds ratio (OR) is equal for heterozygous vs homozygous WT and homozygous mutation vs heterozygous. The additive interaction of COVID-19 and rs35705950-T (for every increase in one allele, i.e., 0 to 1, or 1 to 2 copies) was also assessed with the estimate of excess risk due to interaction (RERI) and the 95% confidence interval estimated with the Delta Method.

*Phenome-wide and Laboratory-wide association studies (PheWAS and LabWAS)*

Associations between rs35705950-T and pre-existing comorbid conditions and laboratory values were examined using clinical data prior to the COVID-19 pandemic (Sept 2019). Individuals with ≥2 Phecodes(25) were defined as cases. Phecodes with <200 cases within each ancestry group were excluded, resulting in 1618 (EUR, 1289 (AFR), 994 (HIS) Phecodes. LabWAS was conducted for 69 clinical tests; for individuals with repeated measures, the median of the individuals' EHR record was used. Logistic/Firth regression and linear regression were used for Phecodes and laboratory measurements, respectively. A Bonferroni-adjusted p-value threshold of $1.2 \times 10^{-05}$ (0.05/3901) accounted for all the models tested across three ancestries for significance. Analyses were performed using PLINK2(26) (Additional details in **Supplemental Methods**).

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## Results

*Association between rs35705950-T with COVID-19 positivity and outcome severity*

Our study included 19,168 COVID-19 positive patients from three major ancestry groups (EUR, AFR, HIS). The minor allele frequency for rs35705950-T was 9% among the entire MVP and 8% among COVID-19 positive individuals (**Table 1**); among these 14.4% (n=2,758) and 0.7% (n=138) were carriers of 1-copy and 2-copies of *MUC5B* rs35705950-T, respectively (**Table 1, Figure E1)**. Associations between rs35705950-T and clinical outcomes by ancestry group within MVP, trans-ancestry meta-analysis within MVP (MVP-ALL), and joint meta-analysis with HGI (META) are shown in **Figure 1 and Table 2**. In the joint meta-analysis, the most significant association was between rs35705950-T and fewer hospitalization events compared with population controls (OR = 0.90 [0.86-0.93], $p=8.99 \times 10^{-5}$, **Figure 1 and Table 2**). The MUC5B rs35705950-T allele was not associated with reduced COVID-19 positivity in trans- ancestry meta-analysis within MVP (OR=0.98 [0.95-1.01], p=0.06) but was nominally significant ($p<0.05$) in the joint meta-analysis with HGI (OR=0.97 [0.95-1]; p=0.02). The *MUC5B* rs35705950-T allele was not associated with severe COVID-19 disease (critically ill).

To further evaluate the robustness of our findings from the primary analyses, we performed sensitivity analyses among MVP participants from 3 ancestry groups (EUR, AFR, HIS) who had COVID-19 testing performed within the VA (n=136,164). Associations between rs35705950-T and COVID-19 positivity and outcomes with adjustment for additional covariates, including BMI, smoking status, CCI, asbestosis, RA-ILD and IPF diagnosis, which were not available in HGI, were performed in MVP participants. We observed similar effect sizes as the

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primary analyses (**Table E4**), with the association between rs35705950-T allele and reduced risk of hospitalization, compared with non-hospitalization, due to COVID-19 remaining robust (OR= 0.86 [0.77, 0.95], P=0.004, **Table E4**). The OR and 95% CI were very similar to the primary analyses (OR=0.88 [0.81, 0.96]. Notably, rs35705950-T was associated with a reduced risk of testing positive for COVID-19 (OR=0.95 [0.90, 0.99], P=0.03) in this MVP sub-population. The *MUC5B* rs35705950-T allele was not associated with severe outcomes plus mortality (OR = 0,89 [0.67-1.20], p= 0.45) or mortality alone (OR = 0.93 [ 0.74-1.17], p=0.56; **Table E4**).

*Association between rs35705950-T and pneumonia events within 60 days of COVID-19 infection*

Among MVP participants of European ancestry who tested positive for COVID-19 (n=8541), the adjusted odds ratio for post-index pneumonia was 18% less with each additional *MUC5B* rs35705950-T allele (OR = 0.82 [0.72, 0.93], p=0.001). Among COVID-19 negative MVP participants, the adjusted odds for post-index pneumonia non-significantly increased with each additional *MUC5B* rs35705950-T allele (OR=1.06 [0.98, 1.15], p=0.13). Increasing copy numbers of the *MUC5B* rs35705950-T allele were associated with progressive reduction of the post-index pneumonia risk, with adjusted ORs of 10.9 [10.2, 11.7], 8.41 [7.36, 9.61], and 6.47 [4.93, 8.48] in patients with 0, 1, and 2 copies of MUC5B rs35705950-T respectively among COVID-19 positive relative to negative subjects ($p < 0.0001$, **Table 3**). This differential effect of an additional *MUC5B* rs35705950-T allele on post-index pneumonia in COVID-19 positive vs. COVID-19 negative patients was statistically significant (multiplicative scale interaction OR = 0.77 [0.66, 0.89], p=0.0004) in EUR (**Table 3**). There was also evidence of a negative additive interaction, with the relative excess risk due to interaction (RERI) corresponding to an increase

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of one copy of rs35705950-T allele estimated as -2.07 (95% CI -3.24, -0.9). This suggests that the relative risk for pneumonia in COVID-19 positive patients is -2.07 less for each increase in one copy of MUC5B rs35705950-T allele than if there were no interaction between COVID-19 and *MUC5B* rs35705950-T. The number of post-COVID-19 pneumonia events in HIS or AFR was too low to permit further analysis.

*Exploring shared pathobiology with the MUC5B rs35705950-T through PheWAS and LabWAS*

To explore clinical conditions and biomarkers associated with the *MUC5B* rs35705950-T allele which may impact the susceptibility and severity of COVID-19, PheWAS and LabWAS using pre-COVID-era data (through Sept 2019) were performed. The sample sizes for MVP participants included in PheWAS and COVID-19 association studies are shown in **Table 1** (**Figure E1**). The results of the PheWAS are shown in **Figure 2** with full summary statistics presented in **Table E5**.

In PheWAS analyses between rs35705950-T and PheCodes with > 200 cases, significant associations were identified exclusively with pulmonary processes. Increased risk for "other alveolar and parietoalveolar pneumonopathy" (Phecode 504, OR = 2.64 [2.50 - 2.78], P = 7.07 x $10^{-289}$) and "post-inflammatory pulmonary fibrosis" (Phecode 502, OR = 2.85 [2.65 - 3.05], P = 8.90 x $10^{-186}$) were significantly associated ($P_{bonferroni} < 1.2 \times 10^{-5}$) with rs35705950-T in all three ancestry groups (EUR, AFR, HIS). Among the EUR and AFR groups, rs35705950-T was also associated with increased risk for idiopathic fibrosing alveolitis (Phecode 504.1). Notably, there were no significant associations identified between rs35705950-T and influenza infection (Phecode 481) or bacterial pneumonia (Phecode 480.1) in any of the ancestry groups. The power to detect a difference with these conditions was >95% as there were 4,728 cases of

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influenza and 10,579 cases of bacterial pneumonia in EUR cohort. There were also no significant associations between rs35705950-T and non-pulmonary conditions potentially relevant to COVID-19 outcomes, including pulmonary embolism/deep vein, systemic inflammatory syndrome / sepsis, or acute renal failure (**Figure E2** and **Table E5)**.

The LabWAS of *MUC5B* rs35705950-T with median values of pre-COVID clinical laboratory tests is shown in **Table E6** and **Figure E3**. Among EUR participants, 10 laboratory tests were significant after Bonferroni adjustment, with the majority belonging to white blood cell counts or fractions, with an increase in monocyte count also significant in the HIS subgroup. There were no significant associations among the AFR subgroup.

**Discussion**

Our study supports that the "T" allele of rs35705950 in *MUC5B*, which has been associated with an *increased* risk for the development of IPF, confers a *decreased* risk for COVID-related hospitalization among MVP participants; among participants of European descent, a decreased incidence of pneumonia following COVID-19 infection was also observed. The protective effect of the rs35705950-T may appear to contradict previous work demonstrating an increased risk for acute respiratory distress syndrome (ARDS) in the pre-COVID era(27) as well as the increased risk of severe COVID-19 disease observed for other well-established causal variants of IPF located in the *TERC*, *DEPTOR,* and *FAM13A(28)* genes. However, our findings are consistent with previous studies conducted in European cohorts(29) and in the HGI(28) which support that pathophysiological changes due to rs35705950-T may result in distinct interactions with SARS-CoV-2 which confer the differential risks observed.

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The rs35705950 polymorphism is located within an enhancer region of the *MUC5B* gene, the protein product of which is a major gel-forming mucin in the lung that plays a key role in mucociliary clearance and host defense(30–33). Consistent with this, mouse knockout models for *Muc5b* demonstrate increased susceptibility towards bacterial infections of the respiratory tract and persistent inflammation. In contrast to the loss-of-function of knockout models, the "T" allele of rs35705950 results in a gain-of-function and is associated with enhanced expression of the *MUC5B* transcript in lung tissue from human subjects (24)without clinical IPF. Notably, while excess MUC5B protein is observed in the epithelial cells of respiratory bronchioles and honeycomb cysts (31, 32, 34) of individuals with IPF, differential expression in lung tissue by rs35705950 genotype has not been consistently observed in patients with advanced disease and may be attributable to the universally elevated MUC5B protein levels in IPF patients regardless of their rs35 705950 allelic configuration(24, 32, 34).

The functional impact of increased *MUC5B* expression on clinical outcomes in populations both with and without IPF remains incompletely understood. In a study which antedated the COVID-19 pandemic, a modestly increased risk for the development of ARDS, a major feature of severe SARS-CoV-2 infection, was observed among homozygotes for rs35705950-T who were >50 years old, none of whom had clinical or radiographic evidence of IPF on post-hoc chart review(27). It should be noted, however, that the underlying etiologies for ARDS in the population examined were heterogeneous, with over half of cases attributed to either trauma or non-pneumonia-related sepsis. In contrast to the increased risk for pre-COVID-era ARDS, the rs35705950-T allele was associated with decreased risk for acute respiratory exacerbation events among non-Hispanic white ever-smokers with interstitial lung

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abnormalities (ILA), defined as non-dependent parenchymal infiltrates which are frequently considered subclinical precursors to clinically-apparent interstitial lung disease (ILD), in the COPDGene study(35). Whether increased mucin production confers protection against viral infections(36), which are believed to contribute to a substantial proportion of acute respiratory exacerbation events in chronic lung disease(37), should be explored in future studies.

Our analyses suggest that the decreasing risk of post-index pneumonia associated with rs35705950-T may be specific to COVID-19. First, to our knowledge, there have been no previously published reports of differential susceptibility or clinical outcomes in non-COVID-19 respiratory viral or bacterial infections by rs35705950-T genotype. Within our own MVP data, there were no associations between pre-pandemic influenza infection or bacterial pneumonia and rs35705950-T allele**.** Second, although rs35705950-T carrier status or number of allele copies did not impact testing rates for COVID-19 (which were 22.2%, 22.3%, and 22.4% for individuals of European descent with 0, 1, and 2 copies of rs35705950-T, respectively), individuals with the "T" allele demonstrated a trend towards decreasing rates of testing positive in MVP, supporting that rs35705950-T may modulate an individual's susceptibility to infection by SARS-CoV-2. Third, in addition to attenuating the risk for post-index pneumonia exclusively among COVID-19 positive individuals, differential risk by rs35705950-T copy number was observed, supporting a dose-response relationship for this outcome.

We did not observe associations between rs35705950 and severe COVID-19 illness or mortality. This may be due to the low incidence and/or multifactorial causes of these severe outcomes which may include non-respiratory disorders, such as shock and multi-system organ

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failure. This is supported by the PheWAS analysis, which found nearly exclusive associations between rs35705950-T with pulmonary processes, with no evidence of association (with >80% power to detect differential effects) with other processes potentially relevant to severe COVID-19 disease, including thromboembolic disease, septic shock, and acute renal failure.

The COVID-19 pandemic amplified healthcare disparities due to socioeconomic factors and likely contributed to differences in outcomes(40). However, heterogeneity in the magnitude of disparities between healthcare systems exists, with numerous studies demonstrating *reduced* levels of disparities and relatively equitable access to care among VA healthcare users (relative to non-VA healthcare users)(41–43); thus, differences in outcomes attributable to socioeconomic factors within the VA may be less than those in the general population. Consistent with this, a study by Trivedi et al(44), reported minimal changes in 30-day mortality rates for heart failure and pneumonia hospitalizations following adjustment for a comprehensive panel of socioeconomic factors, including poverty, housing, education, and rurality. Within our cohort, access to care was uniformly high, with >98% of individuals having $\geq$ 1 primary care visit within the preceding 18 months and comparable numbers of patients with $\geq$ 1 clinical encounter or admission in the preceding year. However, due to the complexities of socioeconomic factors and their potential impact on and interactions with rs35705950-T, we acknowledge that future studies in this area are needed.

**Strengths & Limitations**

The strengths of our study include a large, ethnically- and geographically- diverse cohort with harmonized prospective outcomes data, directly genotyped rs35705950 data, and the use of

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robust statistical approaches. In addition to interrogating the relationships between rs35705950-T and clinical outcomes, the availability of rich clinical phenotyping data permitted exploration of the underlying pathobiological mechanisms through PheWAS and LabWAS and support that the differential risks observed by rs35705950-T are likely mediated by pulmonary-specific processes. Despite these strengths, we acknowledge the following limitations. First, although the MVP is one of the largest and most diverse genomic medicine databases established to date, participants are predominantly male and of European ancestry; this, and the lower minor allele frequency of rs35705950-T among non-European populations may have impacted our power to detect associations between rs35705950-T genotype and clinical outcomes among females and racial/ethnic minorities. Second, due to the timing of the data freeze for our analysis, only short-term outcomes were captured. F uture studies with extended follow-up to explore the potential relationship between rs35705950-T and post-COVID syndromes, including lung fibrosis, are needed. Third, although our analyses were adjusted for critical variables, residual confounding and bias may still exist. Given the association between rs35705950-T and an increased incidence of subclinical ILA and respiratory symptoms(45), individuals harboring the *MUC5B* variant may exhibit behavior modifications (increased testing or more stringent self-isolation ) which could have introduced biases not be captured or adjusted for in our analyses(28). Fourth, viral subtypes, vaccination status and treatment approaches evolved with time which may have impacted severity outcomes. Fifth, we acknowledge that the effect estimates associated with rs35705950-T in our study are modest and may limit its application in clinical or predictive algorithms. However, despite these limitations, we assert our results, which identify a potentially protective role of rs35705950-T in

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COVID-19 outcomes, support that this functional polymorphism confers pleiotropic effects which may be modulated by epistasis and environmental interactions; longer term follow-up and future analyses into these complex relationships are warranted.

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**Conflict of Interest**

CJO is an employee of Novartis Institute for Biomedical Research. PN reports grant support from Amgen, Apple, AstraZeneca, Boston Scientific, and Novartis, personal fees from Apple, AstraZeneca, Blackstone Life Sciences, Genentech, and Novartis, and spousal employment at Vertex, all unrelated to the present work.

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## Tables and Figures

**Table 1.** Demographics for COVID-19 tested positive and all MVP participants examined in this study.

| Characteristics | Million Veteran Program Number (%) | COVID-19 Positive Number (%) |
|---|---|---|
| Total Patients | 658,582[Ψ] | 19,168 |
| Male | 592,516 (90) | 17,151 (89) |
| **Genetic Ancestry** | | |
| European | 464,961 (70) | 11,778 (61) |
| African | 123,120 (19) | 4,893 (26) |
| Hispanic | 52,183 (8) | 2,497 (13) |
| Asian* | 8,329 (1) | N/A |
| Other* | 9,989 (2) | N/A |
| ***MUC5B* rs35705950-T** | | |
| GG | 547,846(83.2) | 16,272 (84.9) |
| GT | 104,834(15.9) | 2,758 (14) |
| TT | 5,902(0.9) | 138 (0.7) |
| **Comorbidities** | | |
| Obesity (phecode = 278) | 283,197 (43) | 10,844 (56) |
| Hypertension (phecode = 401.1) | 451,998 (69) | 14,036 (73) |
| Type 2 Diabetes (phecode = 250.2) | 227,575 (34) | 8,190 (43) |
| Coronary Artery Disease (phecode = 411.4) | 152,136 (23) | 4,664 (24) |
| Chronic Kidney Disease (phecode = 585.2) | 100,46 (1.5) | 335 (2) |
| **Outcomes** | | |
| Hospitalized | - | 4,234 (22) |
| Severe/ Deceased | - | 947 (5) |

[Ψ] *MVP participants who died before March 2020 were excluded from the analysis described in **Table 2**.*
** Due to small sample size, individuals from Asian and other ancestry group were not included*

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**Table 2**. Association between rs35705950-T in MUC5B with COVID-19 clinical outcomes.

| Analysis | Population | Group | Case \| Controls | Sample Size | EA: EAF | OR 95% CI | P |
|---|---|---|---|---|---|---|---|
| COVID-19 Positive Vs Population Controls | MVP | AFR | 4,893 \| 94,556 | 99,449 | T: 0.021 | 0.96 [0.83-1.11] | 0.572 |
| | | EUR | 11,778 \| 357,198 | 368,975 | T: 0.109 | 0.96 [0.92-1] | 0.076 |
| | | HIS | 2,497 \| 41,100 | 43,597 | T: 0.074 | 0.97 [0.86-1.08] | 0.555 |
| | | META | 19,168 \| 492,854 | 512,021 | T: 0.089 | 0.96 [0.93-1] | 0.060 |
| | HGI | META | 25,652 \| 128,2973 | 1,308,625 | T: 0.111 | 0.98 [0.95-1.01] | 0.134 |
| | MVP + HGI | META | 44,820 \| 1,775,827 | 1,820,646 | T: 0.105 | 0.97 [0.95-1] | **0.019** |
| COVID-19 Hospitalized Vs Population Controls | MVP | AFR | 1,300 \| 98,129 | 99,429 | T: 0.021 | 0.84 [0.63-1.13] | 0.259 |
| | | EUR | 2,417 \| 366,449 | 368,865 | T: 0.109 | 0.89 [0.81-0.98] | 0.015 |
| | | HIS | 517 \| 43,062 | 43,579 | T: 0.074 | 0.93 [0.73-1.19] | 0.562 |
| | | META | 4,234 \| 507,640 | 511,873 | T: 0.089 | 0.89 [0.82-0.97] | **$6.86 \times 10^{-03}$** |
| | HGI | META | 9,086 \| 1,001,201 | 1,010,287 | T: 0.106 | 0.91 [0.85-0.97] | **$4.12 \times 10^{-03}$** |
| | MVP + HGI | META | 13,320 \| 1,508,841 | 1,522,160 | T: 0.1 | 0.9 [0.86-0.95] | **$8.99 \times 10^{-05}$** |
| COVID-19 Hospitalized Vs COVID-19 Not-Hospitalized | MVP | AFR | 1,300 \| 3,573 | 4,873 | T: 0.02 | 0.84 [0.6-1.19] | 0.327 |
| | | EUR | 2,417 \| 9,251 | 11,668 | T: 0.106 | 0.9 [0.81-1.01] | 0.063 |
| | | HIS | 517 \| 1,962 | 2,479 | T: 0.071 | 0.91 [0.68-1.2] | 0.493 |
| | | META | 4,234 \| 14,786 | 19,020 | T: 0.079 | 0.9 [0.81-0.99] | **0.030** |
| | HGI | META | 4,420 \| 11,093 | 15,513 | T: 0.162 | 0.97 [0.88-1.08] | 0.575 |
| | MVP + HGI | META | 8,654 \| 25,879 | 34,533 | T: 0.116 | 0.93 [0.87-1] | **0.049** |
| COVID-19 Severe Vs Population Controls | MVP | AFR | 284 \| 99,165 | 99,449 | T: 0.021 | 0.74 [0.38-1.44] | 0.375 |
| | | EUR | 543 \| 368,432 | 368,975 | T: 0.109 | 0.97 [0.8-1.18] | 0.774 |
| | | HIS | 120 \| 43,477 | 43,597 | T: 0.074 | 0.88 [0.52-1.48] | 0.620 |
| | | META | 947 \| 511,074 | 512,021 | T: 0.089 | 0.94 [0.79-1.12] | 0.509 |
| | HGI | META | 3,757 \| 699,885 | 703,642 | T: 0.108 | 0.81 [0.73-0.9] | **$6.69 \times 10^{-05}$** |
| | MVP + HGI | META | 4,704 \| 1,210,959 | 1,215,663 | T: 0.1 | 0.93 [0.79-1.1] | 0.410 |

Odds ratio (OR) and 95% confidence interval (95% CI) reported for the minor (T) allele. Results are shown for VA Million Veteran Program (MVP) African Americans (AFR), European Americans (EUR), Hispanic/Latino Americans (HIS), and multi- ancestry meta-analysis (ALL), the COVID-19 Host Genetics Initiative (HGI) multi- ancestry round 5 meta-analysis excluding MVP and 23&Me, and the meta-analysis of MVP and HGI (META).

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**Table 3**. Associations between *MUC5B* rs35705950-T allele and pneumonia within 60 days of COVID-19 testing among MVP participants of European ancestry.

| **Odds Ratios (95% Confidence Intervals) for Pneumonia within 60 days of COVID-19 test** | | | |
|---|---|---|---|
| | | **OR 95% CI** | **P** |
| **Effect of rs35705950-T allele by COVID-19 strata** | **COVID-19 Negative** | 1.06 (0.98, 1.15) | 0.13 |
| | **COVID-19 Positive** | 0.82 (0.72, 0.93) | 0.001 |
| **Risk of pneumonia (COVID+ versus COVID-) by rs35705950-T copies** | **Copy number = 0** | 10.9 (10.2, 11.7) | < 0.0001 |
| | **Copy number=1** | 8.42 (7.36, 9.61) | < 0.0001 |
| | **Copy number=2** | 6.47 (4.93, 8.48) | < 0.0001 |
| **Measures of Interaction between COVID-19 and *MUC5B* allele** | | | |
| **Multiplicative Scale OR (95% CI)** | 0.77 (0.66, 0.89) p=0.0004 | | |
| **Additive Scale RERI (95% CI)** | -2.07 (-3.24, -0.9) | | |
| Odds ratios and 95% confidence intervals are estimated from Firth logistic regression adjusting for pre-index pneumonia, age, age$^2$, sex, BMI, CCI, smoking, IPF, asbestosis, RA-ILD, and principal components PC1-20, including a multiplicative interaction between additive MUC5B rs35705950-T allele and COVID-19 infection. An estimate of the relative excess risk due to interaction (RERI) and 95% confidence interval (Delta method) corresponding to an additive interaction effect is estimated from the logistic regression model. | | | |

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**Figure Legends**

**Figure 1. Forest plot association of rs35705950-T in MUC5B** with (i) COVID-19 Positive vs Population Controls, (ii) COVID-19 Positive, Hospitalized vs Population Controls, (iii) COVID-19 Positive, Hospitalized vs COVID-19 Positive, not Hospitalized, and (iv) Hospitalized for COVID-19 with high-flow oxygen or died of COVID-19 vs Population Controls. Odds ratio (OR) and 95% confidence interval (95% CI) is reported for the minor (T) allele, and results are shown for VA Million Veteran Program (MVP) African Americans (AFR), European Americans (EUR), Hispanic/Latino Americans (HIS), and multi- ancestry meta-analysis (ALL), the COVID-19 Host Genetics Initiative (HGI) multi- ancestry round 5 meta-analysis excluding MVP and 23&Me, and the meta-analysis of MVP and HGI (META).

**Figure 2**. **Phenome-Wide Association Study (PheWAS) of *MUC5B* rs35705950-T allele in the Million Veteran Program.** A PheWAS plot shows associations of rs35705950-T and phenotypes derived from the electronic health records data prior to COVID-19 in MVP participants from European ancestry. The phenotypes are shown on the x-axis and organized by disease categories. The p-value (-log10) of each association is shown on the y-axis the direction of the triangle represents the direction of effect of the associations - with the upward triangle as increased risk and the downward triangle as reduced risk. The red line indicates the significance threshold based on the Bonferroni correction. The forest plot of Bonferroni significant associations are shown on the right top corner of the PheWAS plot.

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Figure 1

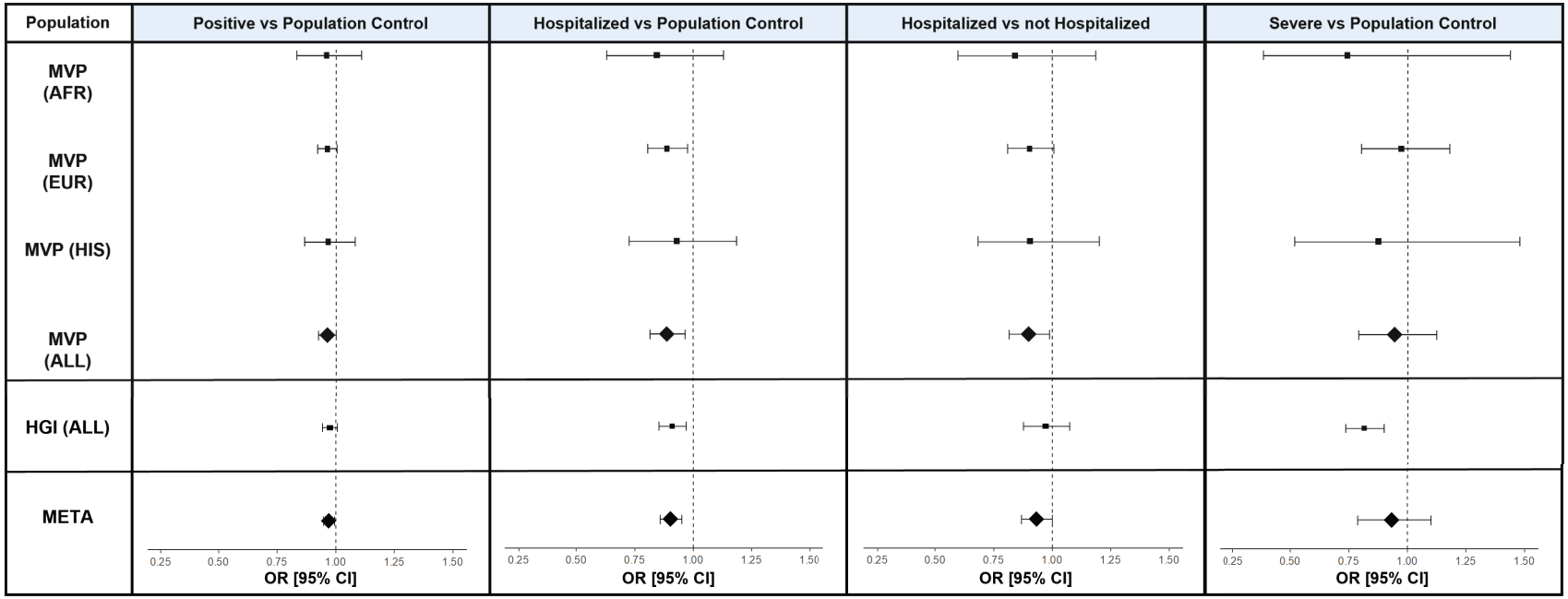


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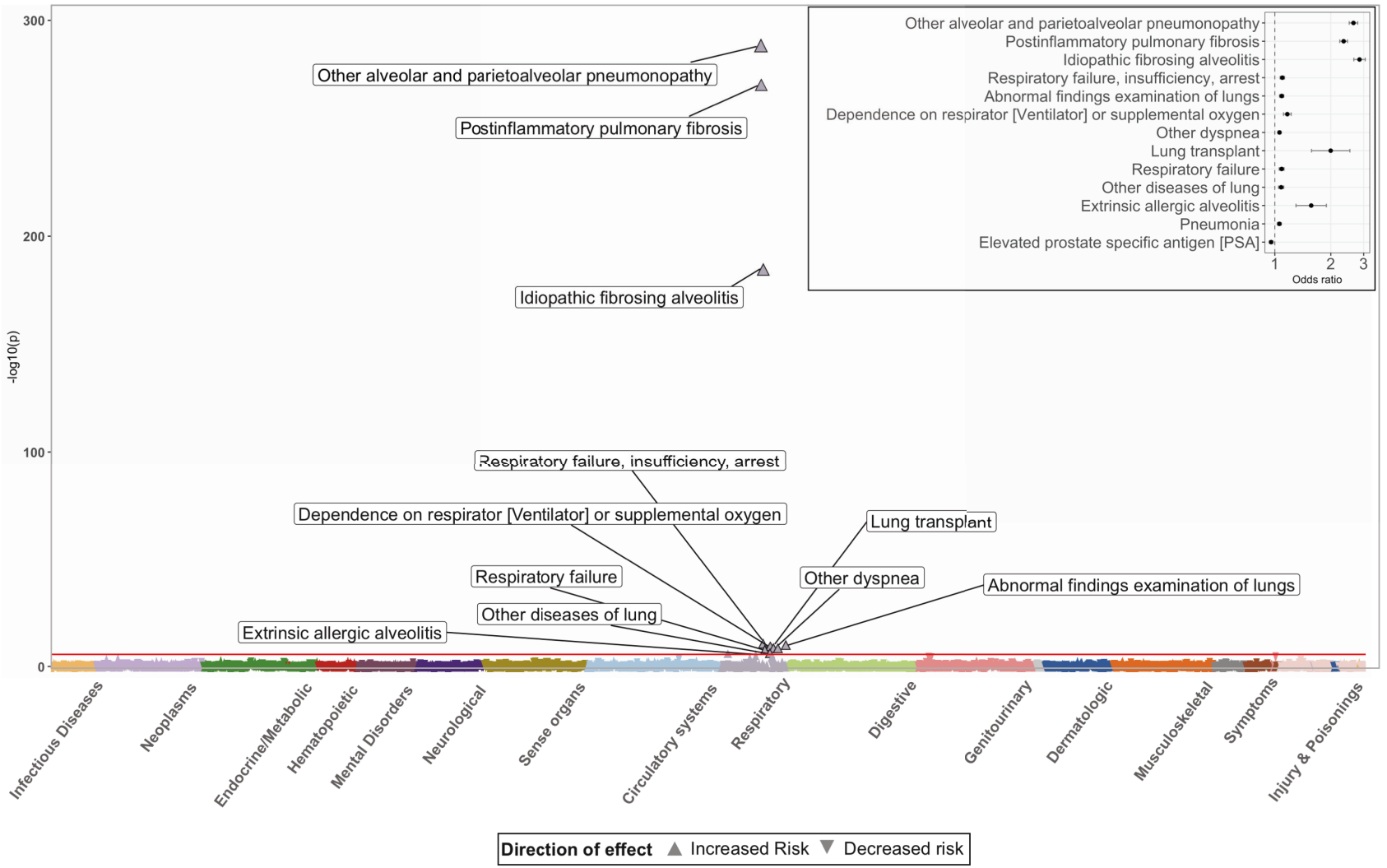
Figure 2

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**Supplemental Materials**

# A *MUC5B* Gene Polymorphism, rs35705950-T Confers Protective Effects Against COVID-19 Hospitalization but not Severe Disease or Mortality

**Supplemental Methods.**

- **Figure E1.** Overview of genetic association of *MUC5B* allele and COVID-19 phenotypes as well as phenome-wide association study.
- **Figure E2. Phenome-Wide Association Study (PheWAS) of *MUC5B* rs35705950-T allele in three Million Veteran Program ancestry groups.** A PheWAS plot shows associations of rs35705950-T and phenotypes derived from the electronic health records data prior to COVID-19 in MVP participants from A) European ancestry B) African ancestry and C) Hispanic ancestry.
- **Figure E3. Laboratory-Wide Association Study (PheWAS) of *MUC5B* rs35705950-T allele in the Million Veteran Program.** A LabWAS plot shows associations of rs35705950-T and median values of laboratory measures extracted from electronic health records data prior to COVID-19 in MVP participants. The bottom panel shows the -log10 (p-value) on the y-axis and laboratory test descriptions on the x-axis. Triangles points up have increasing effects and points down have decreasing effects. The colors represent the different ancestry groups. The top panel shows beta from the regression model for each laboratory measure. The significant results are highlighted in the color corresponding to ancestry groups and other results are plotted in grey.

- **Table E1**. The demographics and clinical conditions were documented within two years prior to the index dates for MVP subjects used for association studies with severe outcomes of COVID-19 infection and post-index pneumonia events (pneumonia60d) in this study. **See Excel Document**
- **Table E2.** Sample sizes and rates of pneumonia within 60 days post index date for MVP subjects

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of European ancestry with no missing data for pre- or post- index pneumonia events after sensitivity analysis.

- **Table E3.** The ICD codes used for data pull of post-index pneumonia diagnosis (pneumonia60d) in this study. **See Excel Document**
- **Table E4.** Association of rs35705950-T allele with COVID-19 outcomes: 1) Testing positive, 2) hospitalization, 3) Severe COVID-19 + Death and 4) COVID-19 related Death in MVP participants after sensitivity analysis.
- **Table E5**. Full summary statistics of PheWAS associations with *MUC5B* rs35705950-T allele. **See Excel Document**
- **Table E6.** LabWAS reveals laboratory measurements associated with the presence of a *MUC5B* rs35705950-T allele. **See Excel Document**

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## Supplemental Methods

### Data Sources

In this COVID-19 study, we used data from MVP, a large multi-ethnic genetic biobank at Veterans Affairs. MVP began enrolling veterans in 2011 and has now enrolled over 850,000 veterans and genotyped over 650,000. The Veterans' EHR data included diagnosis codes (ICD-9 and ICD-10), current procedural terminology codes (CPT), clinical laboratory measures, and demographic, lifestyle, and radiology reports (1). Pre-COVID EHR data were collected from participants from the time of enrollment to September 30, 2019.

The MVP cohort SNP data was generated using a custom Thermo Fisher Axiom genotyping platform named MVP 1.0. The MVP cohort quality control and genotyping imputation steps were previously reported(2). Ancestry of participants was defined using Harmonized ancestry, race, and ethnicity (HARE), a variable derived from self-reported survey data and genetically derived ancestry(3). Directly genotyped rs35705950-T information was extracted and utilized for association testing. Relatedness was estimated from Identity-by-descent probabilities and one individual from each related pair with kinship coefficient > 0.125 were dropped. We prioritize retained individuals for cases in post COVID-19 pneumonia, Muc5B rs35705950-T allele, covid death, severe covid outcome, covid hospitalization, and covid testing positive, in this order.

A VA-wide collective effort lead by the VA Informatics and Computing Infrastructure (VINCI) created a shared COVID-19 Shared Data Resource (SDR) during the April-August 2020 period, providing a new data domain related to COVID-19 for the VA. All metadata on documentation regarding conditions, laboratory measures, medications, and procedures pertaining to the COVID-19 pandemic and dissemination of information regarding SDR were provided by the VA Phenomics Library, Centralized

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Interactive Phenomics Resource (CIPHER), to users across the VA healthcare systems. The VA COVID-19 SDR group including the VA National Surveillance Team provided researchers with curated data extracted from electronic health records (EHR) of Veterans, after stripping off identifiable elements, and ensuring data security by requiring restricted access to the data(4). This activity was undertaken centrally by an experienced VA research team in order to ensure consistent applications of dates across the EHR tables, as well as uniform definitions of events preceding and subsequent to COVID-19, in an effort to characterize the trajectory of COVID-19 and other diseases and conditions. VA-wide efforts describing these data are already in public domain(5). Structured data obtained via CPT and ICD9 or ICD10 codes, deposited in the VA Corporate Data Warehouse (CDW),was further enriched with rule-based unstructured events recorded in patient notes via natural language processing (NLP), as was done previously for other projects(6). The purpose of NLP-boosting was to fill gaps in knowledge about the severity of the disease, as well as extract specific dates when procedures (e.g. intubation and extubation) were performed. These curated data were then provisioned in the Million Veteran Program (MVP) study mart for COVID-19 in VINCI ensuring data security behind the VA firewall.

*COVID-19 outcome definitions*

The primary analysis *MUC5B* SNP rs35705950-T with COVID-19 infection and hospitalization included all the patients who were tested from Feb 2020 through April 2021 using RT-PCR based method(7, 8) or self-reported during primary care visit. These patients may have received their COVID-19 PCR testing inside as well as outside of the VA. However, for analysis of the outcome severity of COVID-19 infection such as ICU stay or death (more details below), we only included patients tested within VA. The *index date* was defined as a COVID-19 diagnosis date, i.e., specimen date, or a self-reported date of diagnosis; and for a hospitalized patient, the admission date up to 15 days prior to the COVID-19 case date. "*Pre-index*" and "*post-index*" are hereafter used to denote events and outcomes before and after this *index*

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*date*. To define the COVID-19 related severity and death, we use a modified version of COVID-19 Severity Scale variable from WHO COVID-19 Disease Progression Scale(9). The current version of VA's adaptation of COVID-19 Severity Index classifies severity into mild, moderate, severe and death. The severity rating of COVID-19 infection for the MVP cohort was modified from the WHO criteria to classify into four groups: mild (testing positive for SARS-CoV-2 by PCR); moderate (SARS-CoV-2 positivity and hospitalization within 30 days of index dates); severe (SARS-CoV-2 positivity, hospitalized and having indication of treatment by noninvasive mechanical ventilation (NIV), high flow oxygen support, extracorporeal membrane oxygenation (ECMO), intubation, vasopressor support, and dialysis; and death within 30 days of index dates for COVID-19 infection (10)). All data and variables were provided by the MVP data core.

We applied two approaches to define COVID-19 outcomes. First, for the meta-analysis with HGI summary statistics, we synchronized the phenotype definitions as used by the consortium. The following binary COVID-19 outcomes were examined: (1) COVID Susceptibility: individuals who tested positive for COVID-19 (2) COVID Hospitalization: individuals who were hospitalized due to symptoms of COVID-19 (3) COVID-19 Critically ill: individuals who were hospitalized and required respiratory support.

Secondly, we conducted sensitivity analysis within VA cohort on further refined four binary outcomes using patients who received COVID-19 PCR testing at VA sites: 1) COVID-19 testing: individuals who tested positive vs individuals with negative results, 2) COVID-19 hospitalization: individuals who tested positive and required hospitalization due to COVID-19 vs individuals who tested positive but did not need hospitalization, 3) COVID-19 severity: individuals who tested positive and required respiratory support or died due to complication from COVID-19 vs individuals who were hospitalized due to COVID-19 but didn't require respiratory support 4) and COVID-19 mortality: death within 30 days of COVID-19 infection vs. all other COVID-19 test positives.

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*Phenotyping of pre- and post-index conditions for COVID-19*

To determine pre-index conditions, we used NLP-boosted unstructured notes, ICD and CPT codes, and medications taken 2 years prior. ICD and CPT codes and medications 60 days after the index date were used to derive post-index conditions. Pre- and post-index conditions were obtained from the Shared Data Resource's pre- and post-index tables (SDR). The study's post-index conditions' ICD codes are in the supplemental materials. Post-index pneumonia (Pneumonia60d) was studied 60 days after COVID-19 index dates (**Table E2**).

For the 60-day post-index analysis, the SDR post-index tables were used. We included only patients whose PCR testing was done at the VA. Additionally patients that were initially tested negative in the Patient table but then turned positive in the post-index table were excluded from the post index analysis. Participants who lost follow up in the post-index table were also excluded.

**Meta-analysis with HGI**

Results from the COVID-19 Host Genetics Initiative (HGI)(11) were utilized for replication and meta-analysis with our results. Since MVP contributed to HGI, we used the "leave one out" results that were available only to contributing cohorts. These are currently available only for Release 5 (available January 18, 2021), not the more recent Release 6 (June 15, 2021), and also excluded 23&Me, per their agreement with HGI. Results for rs35705950-T were extracted for both the European-only and trans-ethnic meta-analysis across all phenotype definitions.

Logistic regression was performed to determine the association of rs35705950-T with each of these outcomes within each of three HARE AFR, HIS, and EUR ancestry) within plink2a(12) adjusting for age, sex, sex$^2$, and the first 15 ethnicity-specific principal components. Inverse-variance weighted meta-analysis was performed in GWAMA(13) to combine MVP with HGI.

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**Phenome-wide association study (PheWAS)**

For the PheWAS analysis on the *MUC5B* rs35705950-T allele, we used Phecodes (14) and laboratory measures from the clinical data available prior to the onset of COVID-19 infection (Sept 2019). Individuals with two or more Phecodes were defined as cases, while those without were defined as controls. In our previous study, we found that cases under 200 provide >80% statistical power and low type I error therefore we excluded phecodes with fewer than 200 cases within each ancestry group. It yielded 1618 (EUR), 1289 (AFR), 994 (HIS) Phecodes. We also performed a laboratory-wide association study using 69 clinical labs extracted from the EHR of MVP participants. We used the median of each person's entire lab history. We used logistic regression for Phecodes and linear regression for laboratory measurements in PLINK2(15). When the logistic regression model failed to converge for binary outcomes, firth regression was used. Regression models were adjusted for sex, age (at the time of data freeze), quadratic term of age, and the first 20 principal components. We applied Bonferroni correction to each ancestry specific analysis to adjust for multiple hypothesis testing, and following threshold were use select significant associations: EUR = $3.09 \times 10^{-05}$ (0.05/1618), AFR = $3.8 \times 10^{-05}$ (0.05/1289), EUR = $5.03 \times 10^{-05}$(0.05/994).

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**Supplemental Tables**

**Table E1**. The demographics and clinical conditions documented within two years prior to the index dates for MVP subjects used for association studies with severe outcomes of COVID-19 infection and post-index pneumonia events (pneumonia60d) in this study. **See Excel Document**

**Table E2.** Sample sizes and rates of pneumonia within 60 days post index date for MVP subjects of European ancestry with no missing data for pre- or post- index pneumonia events after sensitivity analysis.

| | **rs35705950-T _0 copy** | | **rs35705950-T _1 copy** | | **rs35705950-T _2 copies** | |
|---|---|---|---|---|---|---|
| *HARE* | Pneumonia_no | Pneumonia_yes | Pneumonia_no | Pneumonia_yes | Pneumonia_no | Pneumonia_yes |
| **COVID-19 Tested Positive** | | | | | | |
| *EUR* | 4994 | 1854 | 1228 | 372 | 76 | 17 |
| **COVID-19 Tested Negative** | | | | | | |
| *EUR* | 62076 | 2593 | 15267 | 689 | 941 | 47 |

**Table E3.** The ICD codes used for data pull of post-index pneumonia diagnosis (pneumonia60d) in this study. **See Excel Document**

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**Table E4.** Association of rs35705950-T allele with COVID-19 outcomes: 1) Testing positive, 2) hospitalization, 3) Severe COVID-19 + Death and 4) COVID-19 related Death in MVP participants after sensitivity analysis

| MVP Cohort Ancestry | Copy number_0 | | Copy number_1 | | Copy number_2 | | OR [95% CI] | P_value |
|---|---|---|---|---|---|---|---|---|
| COVID-19 Testing | COVID-19 Negative | COVID-19 Positive | COVID-19 Negative | COVID-19 Positive | COVID-19 Negative | COVID-19 Positive | | |
| African | 25992 | 3701 | 1126 | 151 | 18 | 2 | 0.98 [0.83, 1.16] | 0.83 |
| European | 64759 | 6860 | 15981 | 1604 | 989 | 93 | 0.95 [0.90, 1.00] | 0.05 |
| Hispanic | 9450 | 1654 | 1568 | 248 | 64 | 9 | 0.94 [0.82, 1.07] | 0.34 |
| Random Effect Meta-analysis | | | | | | | 0.95 [0.90, 0.99] | **0.03** |
| COVID-19 Hospitalization | COVID-19 Not-hospitalized | COVID-19 Hospitalized | COVID-19 Not-Hospitalized | COVID-19 Hospitalized | COVID-19 Not-Hospitalized | COVID-19 Hospitalized | | |
| African | 2322 | 1379 | 104 | 47 | 1 | 1 | 0.79 [0.55, 1.13) | 0.21 |
| European | 4607 | 2241 | 1143 | 457 | 65 | 28 | 0.86 [0.77, 0.97] | **0.015** |
| Hispanic | 1189 | 459 | 179 | 69 | 9 | 0 | 0.88 [0.65, 1.20] | 0.49 |
| Random Effect Meta-analysis | | | | | | | 0.86 [0.78, 0.95] | **0.004** |
| COVID-19 Severe + Death | COVID-19 Not-Severe | COVID-19 Severe + Death | COVID-19 Not-Severe | COVID-19 Severe + Death | COVID-19 Not-Severe | COVID-19 Severe + Death | | |
| African | 3314 | 387 | 138 | 13 | 2 | 0 | 0.82 [0.46, 1.45] | 0.46 |
| European | 6257 | 591 | 1463 | 137 | 87 | 6 | 1.01 [0.85, 1.21] | 0.71 |
| Hispanic | 1502 | 146 | 232 | 16 | 9 | 0 | 0.69 [0.41, 1.17] | 0.13 |
| Random Effect Meta-analysis | | | | | | | 0.92 [0.72, 1.16] | 0.48 |
| COVID-19 Related Death | COVID-19 Survivors | COVID-19 Deaths | COVID-19 Survivors | COVID-19 Deaths | COVID-19 Survivors | COVID-19 Deaths | | |
| African | 3547 | 154 | 143 | 8 | 2 | 0 | 1.41 [0.69, 2.89] | 0.42 |
| European | 6530 | 318 | 1535 | 65 | 90 | 3 | 0.91 [0.71, 1.17] | 0.59 |
| Hispanic | 1579 | 69 | 241 | 7 | 9 | 0 | 0.67 [0.32, 1.40] | 0.30 |
| Random Effect Meta-analysis | | | | | | | 0.92 [0.74, 1.16) | 0.50 |

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**Table E5**. Full summary statistics of PheWAS associations with *MUC5B* rs35705950-T allele. **See Excel Document**

**Table E6.** LabWAS reveals disease conditions associated with the presence of a *MUC5B* rs35705950-T allele. **See Excel Document**

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- VA COVID-19 Shared Data Resource – Scott L. DuVall, Ph.D.; Kristine E. Lynch, Ph.D.; Elise Gatsby, M.P.H.

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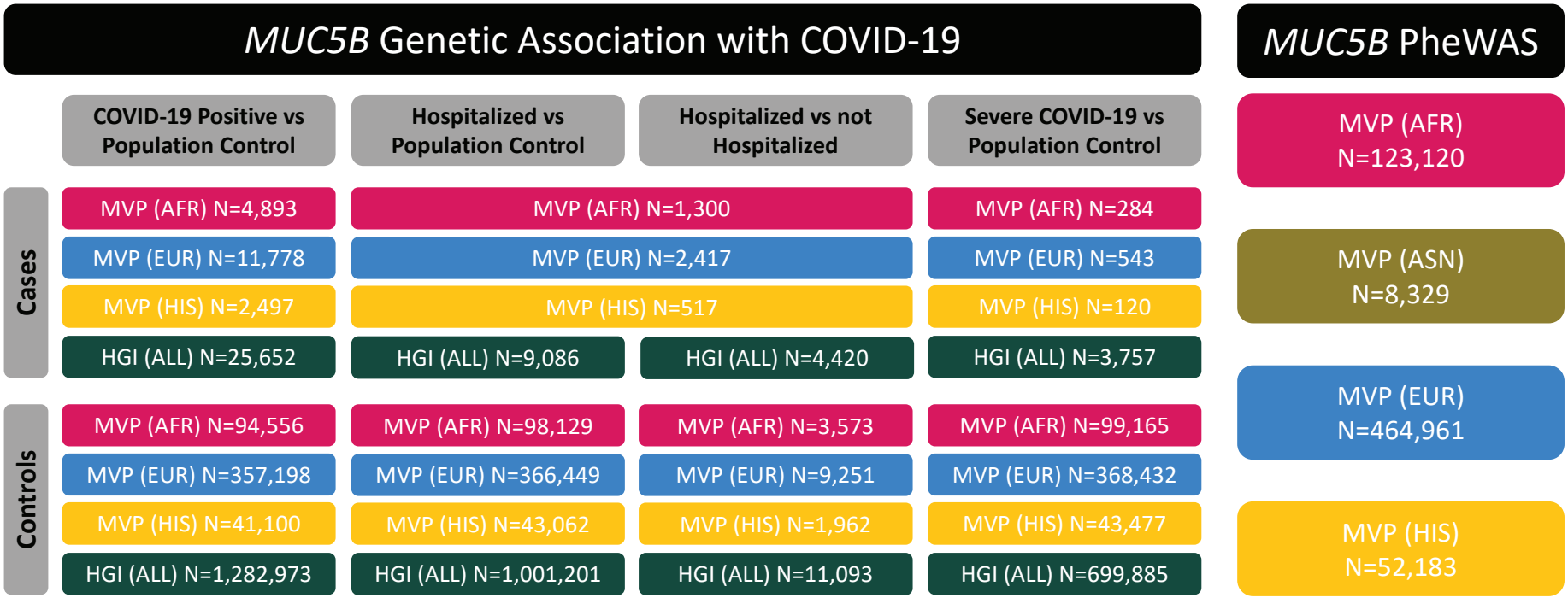
# Figure E1

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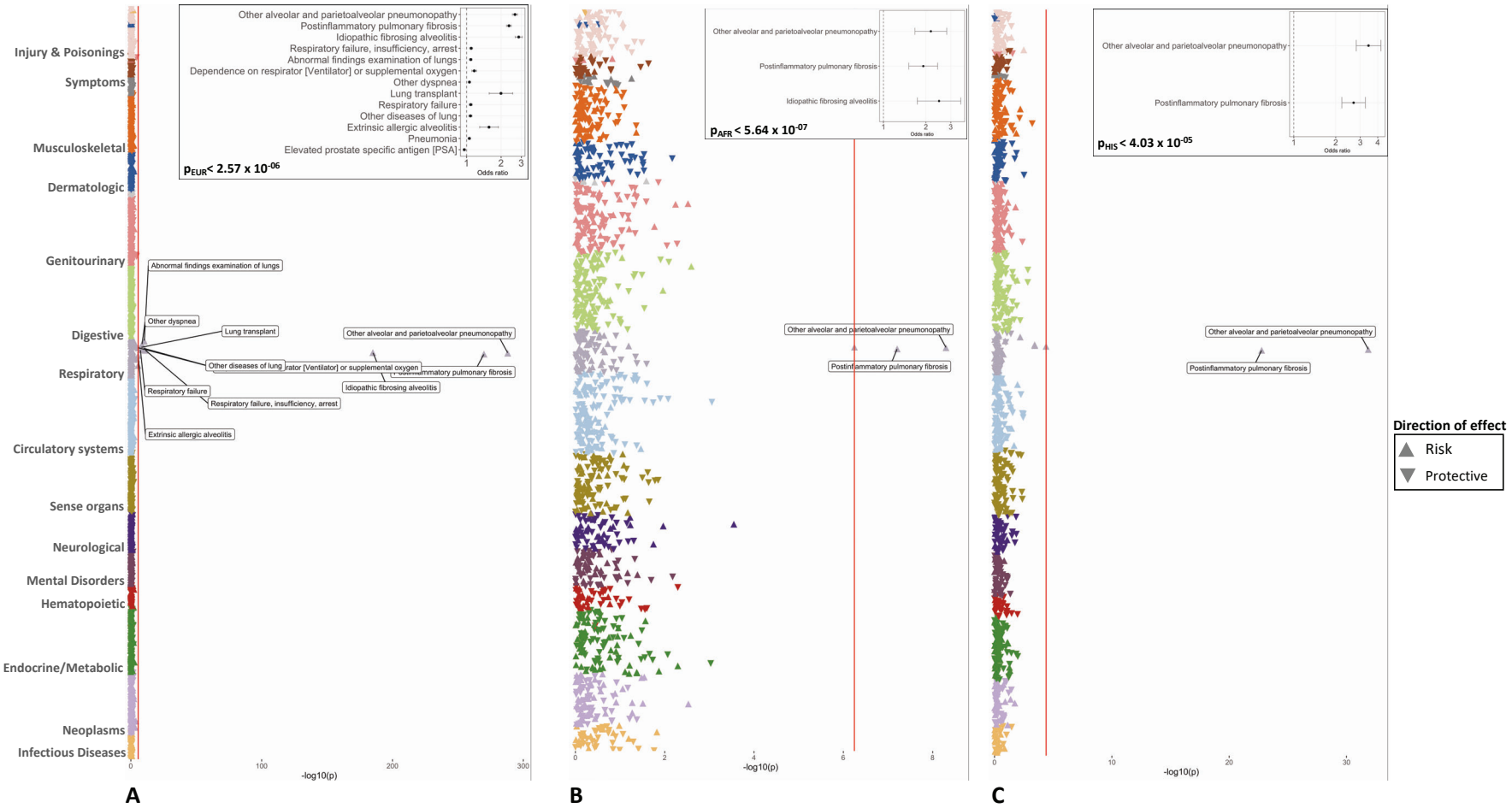
# Figure E2

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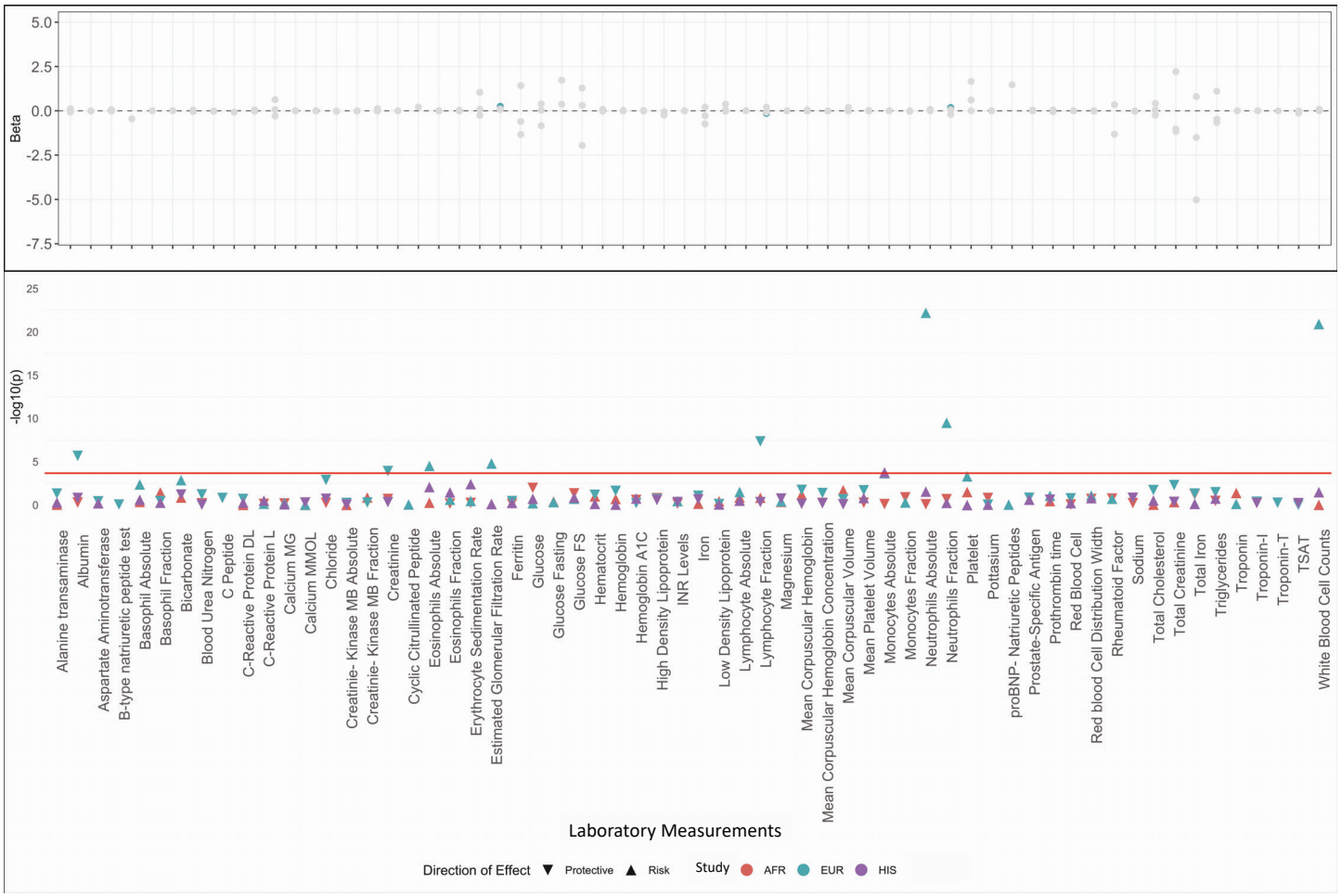
# Figure E3

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