Phenome-wide association study to explore the long-term symptoms after infection with novel coronavirus in the UK Biobank

Running title: Phenome-wide association study for infection with novel coronavirus

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Abstract

Background

Observational research studies have shown that even after the acute phase, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can affect patients, and increase the risk of cardiovascular, mental, metabolic, and other disorders. However, the spectrum of diseases for individuals with a genetic predisposition to COVID-19 remains unclear.

Methods

We leveraged individual-level data from UK Biobank to implement a phenome-wide association study to explore the relationships between COVID-19 and 1061 diseases. Then, the inverse-variance weighted (IVW) method was adopted with summary-level data from global consortiums as sensitivity analyses combined with other MR methods with different model assumptions to identify robust associations.

Findings

The PheWAS found severe respiratory, hospitalized, and susceptibility COVID-19 had detrimental effects on 36, 37, and 51 kinds of diseases, separately. The IVW test found severe respiratory COVID-19 had detrimental effects on breast cancer [OR 95% CI: 1.065 (1.000-1.133)], pan-cancer [OR 95% CI: 1.002 (1.000-1.004)], and Alzheimer's disease [OR 95% CI: 1.042 (1.005-1.081)], etc. Hospitalized COVID-19 had detrimental effects on ischemic stroke (IS) [OR 95%CI: 1.049 (1.001-1.100)], breast cancer [OR 95%CI: 1.139 (1.011-1.283)], and pan-cancer [OR 95%CI: 1.003 (1.000-1.006)], etc. Susceptibility COVID-19 had detrimental effects on deep vein thrombosis (DVT) of lower extremities [OR 95%CI: 2.392 (1.167-4.902)], venous thromboembolism [OR 95%CI: 1.962 (1.115-3.453)], pulmonary heart disease/diseases of pulmonary circulation [OR 95%CI: 1.767 (1.142-2.733)], IS (large artery atherosclerosis) [OR 95%CI: 1.405 (1.025-1.927)], myocardial infarction [OR 95%CI: 1.235 (1.012-1.509)], heart failure [OR 95%CI: 1.140 (1.009-1.287)], etc.

Interpretation

This study describes the extensive link between genetically determined COVID-19 and a broad range

of diseases, especially those of the circulatory system, neuropsychiatric system, neoplasms, immune system, and digestive systems. Early detection and management of post-COVID-19 conditions could be tremendously beneficial to public health.

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1. Introduction

The coronavirus disease 2019 (COVID-19) has spread across the world. As of 31 December 2022, more than 657 million confirmed cases of COVID-19 have been recorded worldwide, and more than 6.68 million deaths have been reported by the World Health Organization (WHO). Much research shows that even after the acute phase, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can affect patients and impair their quality of life. Recently, International organizations and Institutes have drawn attention to an increasing number of people experiencing health consequences following the acute phase of SARS-CoV-2 infection and are calling for research into the risk factors, clinical features, diagnosis, management, and outcomes [1–5]. Indeed, even the terminology of the condition is debated with variable terms and definitions for the post-COVID-19 condition including long COVID, long-haul COVID, long COVID-19 condition, post-acute sequelae of SARS-CoV-2 infection (PASC), or post-COVID-19 condition (the term used by WHO) [6–8].

Long-term health consequences of COVID-19 remain unknown, but most study report that the spectrum of long-lasting symptoms is wide and varies from mild discomfort to severe adverse effects on physical, cognitive, and psychosocial health, with important wider implications on functioning, including employment and school attendance [9]. Multiple studies from different countries found that many individuals experienced persistent symptoms 6 months after COVID-19, with fatigue or muscle weakness, sleep difficulties, and anxiety or depression among the most common sequelae [10–12]. A recent study suggests that although most COVID-19 survivors recover both physically and functionally a year after acute infection, some still experience problems with mobility, pain or discomfort, and anxiety or depression compared with non-COVID-19 controls [13]. The data emerging from the controlled studies are in agreement with the earlier reports. A recent analysis of the data from over 87 million electronic health records demonstrated that more than one in three individuals had one or more features of post-COVID-19 condition recorded between 3 and 6 months after a diagnosis of COVID-19, which was significantly higher when compared with individuals with influenza [14–18]. Disease severity, female sex, and age were associated with a higher risk of post-COVID-19 condition development.

However, observational evidence is less likely to account for unknown confounding factors and

reverse causation bias [19]. It is also important to note that most data regarding post-COVID-19 conditions have been generated before the condition definition announcement. Thus, earlier studies may not fit the proposed definition criteria. In addition, these studies have often focused on a single type of disease. The wide range of diseases associated with COVID-19 requires an urgent systematic assessment.

A phenome-wide association study (PheWAS) [20] combined with a two-sample Mendelian randomization (MR) approach was suitable for use in examining genetic evidence between the COVID-19 phenotypes and diseases, providing a more comprehensive assessment of post-COVID-19 condition associated human complex diseases. The PheWAS paradigm was introduced in 2010 as an approach that scans across a range of phenotypes, similar to what was accomplished in genome-wide association studies (GWAS) [20]. Studies that adopted PheWAS analysis have been used to understand the beneficial or detrimental effects of body mass index (BMI), serum urate, age at menarche, smoking intensity, ABO blood groups, and C-reactive protein (CRP) on human complex phenotypes [21–26].

This study leveraged both PheWAS approaches and MR to identify the spectrum of human diseases associated with genetically predisposed COVID-19. In addition, several complementary two-sample MR approaches were used to identify robust associations.

2. Materials and methods

2.1 Study Population

UK Biobank contains in-depth genetic and health information on over 500,000 participants.[27] This prospective study collected data including blood, urine, and saliva laboratory tests and questionnaires, physical measurements, and genome-wide genotyping information.[27] This information is linked to national primary care and inpatient records, cancer diagnosis, and death registration data for longitudinal follow-up.[27] Participants who withdrew from the study or were lost to follow-up, those lacking genotype information, self-reported sex data that did not match genetic records, sex chromosome aneuploidy, >10 putative third-degree relatives in the kinship table, excessive heterozygosity (top 1%), non-Caucasian ancestry, and missing key covariates (age, sex, BMI, smoke,

and drink status) were excluded from the analysis. Genetic quality control was performed centrally by the UK Biobank.[28] Detailed information about this cohort can be found on the Biobank website (https://www.ukbiobank.ac.uk/). For PheWAS, 455,509 participants with genotypes in the UK Biobank were included.

2.2 GWAS summary-level data for COVID-19

We evaluated three COVID-19 phenotypes: severe respiratory, hospitalized, and susceptibility to COVID-19. These data were derived from Release 7 of the GWAS meta-analysis conducted by the COVID-19 Host Genetics Initiative (HGI). (https://www.covid19hg.org/results/r7/) This is an international genetics collaboration that aims to uncover the genetic determinants of COVID-19 susceptibility, severity, and outcomes.[29] For the evaluated COVID-19 outcomes, controls were genetically ancestry-matched individuals without SARS-CoV-2 infection.[29] In our analyses, we used GWAS summary statistics from the comparison between cases and control groups of each exposure. The severe respiratory COVID-19 outcome resulted from the comparison between patients with very severe respiratory failure secondary to COVID-19 (n = 18,152) vs controls (n = 1,145,546). The hospitalized COVID-19 data were generated from the comparison of patients with a laboratory-confirmed SARS-CoV-2 infection that was hospitalized due to COVID-19 symptoms (n = 44,986) vs controls (n = 2,356,386). Finally, the susceptibility COVID-19 analysis was conducted by comparing 159,840 individuals reporting SARS-CoV-2 infection with 2,782,977 controls. Information regarding SARS-CoV-2 infection was derived from a laboratory test, electronic health record, clinically confirmed COVID-19, and self-reported COVID-19 (e.g. by questionnaire).[29] Single nucleotide polymorphisms (SNPs) were filtered according to the following criteria: 1) a genome-wide threshold of significance ($P<5\times10^{-8}$) and 2) linkage disequilibrium (LD) defined as $r^2 < 0.01$ and clump window > 10,000 kb.[30] **(Supplementary Table S1**)

2.3 Phenome Construction

Phenotypes were constructed using the PheCODE system, which was developed to combine one or more relevant International Classification of Diseases (ICD) codes into different disease groups, allowing unbiased interrogation of multiple phenotypes in an EMR-based cohort.[31] To construct the phenotypes, a map designed for large biobanks was used to match ICD-9/10 codes to the

"phecode."[32] The PheCODE system also provided a scheme to automatically exclude patients with similar or related diseases from the controls.[22] Primary and secondary ICD-9/10 codes in the UK Biobank were pooled from hospital records, cancer registry, and death registry data, and mapped into phecodes using the R package, "PheWAS".[33] The phecode-mapping rules, as well as the excluding standards for each code, are available at https://phewascatalog.org/phecodes_icd10. Phecodes with more than 200 cases were included in the final analysis. A total of 1061 phenotypes were utilized in the PheWAS and divided into 17 categories: circulatory, congenital, dermatologic, digestive, endocrine/metabolic, genitourinary, hematopoietic, infectious disease, injuries and poisonings, mental disorders, musculoskeletal, neoplasms, neurological, pregnancy complications, respiratory, sense organ, and symptom disorders. **(Supplementary Table S2**)

2.4 Statistical Analyses

2.4.1 Phenome-wide association study

The PRS was determined using the equation below.

$$\beta_i = In(OR_i) \quad (1)$$

$$PRS = \beta_1 \times SNP_1 + \beta_2 \times SNP_2 + \cdots + \beta_i \times SNP_i \cdots + \beta_n \times SNP_n \quad (2)$$

This PRS calculation method assumes an additive genotype model that an individual may have 0, 1, or 2 risk-increasing alleles. The sum of the risk alleles is calculated using the effect size from the variant-exposure association, defined as β, which is obtained from the discovery of GWAS [34], and n is defined as the total number of SNP included in the model. Z-transformation was performed on GRS to ensure that the final result corresponded to the disease risk of 1-SD PRS increments. All models assumed a multivariable logistic model and adjusted for age, sex, BMI, smoking status, and drinking status. The "PheWAS" package was applied to test associations between genetically determined COVID-19 and hundreds of phenotypes in the UK Biobank cohort. The signals that passed the Bonferroni correction in the PheWAS analysis were used for further two-sample MR analyses.

2.4.2 Two-Sample Mendelian Randomization

For the candidate phenotypes detected using PheWAS, two-sample MR analyses were performed in

parallel to assess the robustness of causal findings. Summary-level datasets for these diseases were acquired from global consortiums and excluded the UK Biobank-related data sources to avoid potential bias from sample overlap. A total of 207 disease phenotypes in the finding phase have available GWAS datasets. These summary-level statistics was shown in **Supplementary Table S3**. The *F*-statistic of >10 could be considered a strong IV.

The IVW approach was used as the primary analysis with the assumption of no invalid IVs.[35] When the number of IVs was less than or equal to three, we applied the fixed-effects model to estimate the causal effect between exposure and outcome, otherwise, the random-effects model was used. Furthermore, the simple median (SME) and weighted-median estimator (WME) allow more powerful genetic variants to contribute more. It could be obtained by weighting the contribution of each genetic variant according to the inverse variance associated with the result. Even if up to 50% of the IVs are invalid, the estimator is consistent. [36] MR-Egger evaluates whether the pleiotropic effect of genetic variants on the result is different from zero on average [37]. MR-Egger is similar to IVW, but the former adjusts IVW analysis by allowing non-zero intercepts, namely, allowing horizontal pleiotropic effects. Even if all of the genetic variants violate IV assumptions 2, MR-Egger also returns an unbiased estimate of causal effects. [37] In MR-Egger regression, the estimate of intercept can be interpreted as an estimate of the average pleiotropy of all genetic variants, and the slope coefficient provides an estimate of the bias of the causal effect. [37] For binary variables, the MR estimates were reported as odds ratios (ORs) which can be interpreted as the risk increase of outcome per unit increase in log odds of exposure.

Phenotypes that passed the sensitivity analysis were defined as robust associations. All analyses were two-tailed and performed using R software (Version 3.6.3) with the 'phewas' and 'TwoSampleMR' packages.

3. Results

Figure 1A and Figure 1B showed the results of the PheWAS analysis between severe respiratory COVID-19 and 1061 binary phenotypes in the UK Biobank. **Figure 1A** showed that severe respiratory COVID-19 had detrimental effects on 36 diseases. These diseases were categorized as neoplasms (n=6), congenital anomalies (n=5), circulatory system (n=3), dermatologic (n=3),

digestive (n=3), infectious diseases (n=3), endocrine/metabolic (n=2), injuries & poisonings (n=2), musculoskeletal (n=2), and one kind of mental disorders, neurological, respiratory, sense organs, symptoms, respectively. No associations were evident between severe respiratory COVID-19 and hematopoietic disorders and pregnancy complications.

The odds ratios are shown in **Figure 2**. For circulatory system diseases, the odds ratio for the association between severe respiratory COVID-19 and atherosclerosis of aorta, other specified cardiac dysrhythmias, varicose veins of lower extremity, varicose veins were 1.160 (95% Confidence interval, 95% CI,1.028−1.293), 1.033 (95% CI,1.001−1.065), 1.022 (95% CI,1.004−1.040), and 1.020 (95% CI,1.002−1.037), respectively. For congenital anomalies, the odds ratios for the association between severe respiratory COVID-19 and congenital anomalies of intestine, lower gastrointestinal congenital anomalies, congenital deformities of feet, digestive congenital anomalies, upper gastrointestinal congenital anomalies were 1.199 (95% CI, 1.082−1.317), 1.151 (95% CI, 1.057−1.245), 1.137 (95% CI, 1.016−1.259), 1.127 (95% CI, 1.061−1.194), and 1.101 (95% CI, 1.007−1.195), respectively. For neoplasms, the odds ratios for the association between severe respiratory COVID-19 and other benign neoplasm of connective and other soft tissue, cancer of esophagus, benign neoplasm of brain and other parts of nervous system, cancer of stomach, benign neoplasm of brain/cranial nerves/meninges, breast cancer, encephalitis were 1.124 (95% CI, 1.048−1.199), 1.092 (95% CI, 1.031−1.153), 1.078 (95% CI, 1.020−1.135), 1.075 (95% CI, 1.007−1.144), 1.066 (95% CI, 1.006−1.126), 1.021 (95% CI, 1.001−1.041), and 1.104 (95% CI, 1.006−1.202), respectively.

Figure 1C showed that hospitalized COVID-19 had detrimental effects on 37 diseases. These diseases were categorized as neoplasms (n=7), congenital anomalies (n=4), genitourinary(n=4), circulatory system (n=3), dermatologic (n=3), digestive (n=3), endocrine/metabolic (n=3), injuries & poisonings (n=2), musculoskeletal (n=2), neurological (n=2), mental disorders (n=1), respiratory (n=1), and sense organs (n=1). The odds ratios are shown in **Figure 3**. For circulatory system diseases, the odds ratio for the association between hospitalized COVID-19 and cancer of esophagus, other benign neoplasm of connective and other soft tissue, breast cancer, breast cancer [female], lipoma of skin and subcutaneous tissue, cancer of prostate, malignant neoplasm of female breast were 1.104 (95% CI, 1.043−1.165), 1.087 (95% CI, 1.010−1.163), 1.032 (95% CI, 1.012−1.051), 1.030 (95% CI,

1.010−1.049), 1.029 (95% CI, 1.001−1.057), 1.025 (95% CI, 1.005−1.046), and 1.023 (95% CI, 1.001−1.044), respectively. For circulatory system, the odds ratio for the association between hospitalized COVID-19 and atherosclerosis of aorta, varicose veins of lower extremity, varicose veins were 1.197 (95% CI, 1.064−1.329), 1.021 (95% CI, 1.004−1.039), and 1.019 (95% CI, 1.001−1.036), respectively.

Figure 2E showed that susceptibility to COVID-19 had detrimental effects on 51 diseases. These diseases were categorized as endocrine/metabolic (n=10), circulatory system (n=9), neoplasms (n=7), dermatologic (n=6), digestive (n=4), musculoskeletal (n=3), respiratory (n=3), genitourinary (n=2), sense organs (n=2), symptoms (n=2), injuries & poisonings (n=1), neurological (n=1), and congenital anomalies (n=1). The odds ratios are shown in **Figure 4**. For endocrine/metabolic system diseases, the odds ratio for the association between COVID-19 infection and mineral deficiency, crystal arthropathies, type 2 diabetes with ophthalmic manifestations, vitamin D deficiency, vitamin deficiency, vitamin B−complex deficiencies, electrolyte imbalance, disorders of fluid/electrolyte/ and acid−base balance, diabetes mellitus, type 2 diabetes were 1.118 (95% CI, 1.016−1.221), 1.097 (95% CI,1.007−1.186), 1.096 (95% CI, 1.041−1.151), 1.078 (95% CI, 1.013−1.143), 1.067 (95% CI, 1.023−1.111), 1.063 (95% CI, 1.003−1.122), 1.034 (95% CI, 1.009−1.060), 1.025 (95% CI, 1.005−1.046), 1.020 (95% CI, 1.006−1.034), and 1.019 (95% CI, 1.005−1.033), respectively. For circulatory system, the odds ratio for the association between COVID-19 infection and atherosclerosis of aorta, other venous embolism and thrombosis, phlebitis and thrombophlebitis of lower extremities, phlebitis and thrombophlebitis, cardiac arrest and ventricular fibrillation, circulatory disease, other disorders of circulatory system, precordial pain, cardiac dysrhythmias, other specified congenital anomalies of kidney were 1.164 (95% CI, 1.031−1.296), 1.153 (95% CI, 1.034−1.271), 1.117 (95% CI, 1.057−1.177), 1.085 (95% CI, 1.034−1.136), 1.068 (95% CI, 1.007−1.129), 1.034 (95% CI, 1.019−1.048), 1.032 (95% CI, 1.018−1.046), 1.032 (95% CI, 1.002−1.061), 1.016 (95% CI, 1.004−1.028), and 1.121 (95% CI, 1.025−1.216), respectively.

As shown in **Figure 5**, IVW test found a statistically significant association between critical COVID-19 and 26 diseases, including circulatory system (n=3): ischemic stroke (small−vessel) (OR, 95% CI: 0.941, 0.887-0.998), conduction disorders (OR, 95% CI: 0.935, 0.880 -0.992), atrioventricular (AV)-block (OR, 95% CI: 0.900, 0.830-0.976); digestive system (n=5):

gastroesophageal reflux disease (OR, 95% CI: 1.022, 1.004-1.040), hernia (OR, 95% CI: 0.942, 0.914-0.970), inguinal hernia (OR, 95% CI: 0.932, 0.898-0.968), ulcerative colitis (OR, 95% CI: 0.924, 0.860-0.992), and Crohn's disease (OR, 95% CI: 0.327, 0.211-0.505); neoplasms (n=7): malignant neoplasm of breast (HER-positive) (OR, 95% CI: 1.065, 1.000-1.133), malignant neoplasm of breast (HER2−negative, all cancers excluded) (OR, 95% CI: 1.064, 1.012-1.118), malignant neoplasm of breast (HER2−negative) (OR, 95% CI: 1.061, 1.011-1.114), malignant neoplasm of breast (all cancers excluded) (OR, 95% CI: 1.057, 1.007- 1.110), pan cancer (OR, 95% CI: 1.002, 1.000-1.004), ovarian cancer (OR, 95% CI: 1.001, 1.000-1.002), oesophageal cancer (OR, 95% CI: 1.000, 1.000 -1.001); neuropsychiatric system (n=8): Alzheimer's disease or family history of Alzheimer's disease (OR, 95% CI: 1.042, 1.005-1.081), father's history of Alzheimer's disease (OR, 95% CI: 1.041, 1.005 -1.077), paternal history of Alzheimer's disease (OR, 95% CI: 1.003, 1.000-1.006), family history of Alzheimer's disease (OR, 95% CI: 0.923, 0.860-0.990), major depressive disorder (OR, 95% CI: 0.839, 0.730-0.965), hyperkinetic disorders (more controls excluded) (OR, 95% CI: 0.744, 0.615-0.901), mixed disorders of conduct and emotions (OR, 95% CI: 0.731, 0.584-0.916), mixed disorders of conduct and emotions (OR, 95% CI: 0.664, 0.455-0.970); in addition, there were 2 endocrine system disorders and 1 immune disorder: nontoxic diffuse goitre (OR, 95% CI: 1.270, 1.051-1.536), thyrotoxicosis with diffuse goitre (OR, 95% CI: 1.121, 1.017-1.235), and systemic lupus erythematosus (OR, 95% CI: 0.789, 0.643-0.968). SME, WME, and MR-Egger provided reasonably consistent associations (**Supplementary Table S5**).

As shown in **Figure 6**, IVW test found a statistically significant association between hospitalized COVID-19 and 24 diseases, including circulatory system (n=3): ischemic stroke (cardioembolic) [OR 95%CI: 1.092 (1.004−1.186)], ischemic stroke [OR 95%CI: 1.049 (1.001−1.100)], AV−block [OR 95%CI: 0.871 (0.775−0.979)]; digestive system (n=5): gastroesophageal reflux disease [OR 95%CI: 1.035 (1.011−1.061)], hernia [OR 95%CI: 0.930 (0.891−0.971)], inguinal hernia [OR 95%CI: 0.915 (0.869−0.965)], ulcerative colitis [OR 95%CI: 0.694 (0.588−0.819)] , Crohn's disease [OR 95%CI: 0.140 (0.065−0.303)]; neoplasms (n=8): breast cancer [OR 95%CI: 1.139 (1.011−1.283)] , malignant neoplasm of breast (HER−positive, all cancers excluded) [OR 95%CI: 1.124 (1.028−1.229)], malignant neoplasm of breast (HER−positive) [OR 95%CI: 1.121 (1.027−1.224)], malignant neoplasm of breast (HER2−negative, all cancers excluded) [OR 95%CI: 1.104 (1.028−1.185)],

malignant neoplasm of breast (HER2−negative) [OR 95%CI: 1.100 (1.026−1.179)], malignant neoplasm of breast (all cancers excluded) [OR 95%CI: 1.097 (1.026−1.174)] , pan cancer [OR 95%CI: 1.003 (1.000−1.006)] , oesophageal cancer [OR 95%CI: 1.001 (1.000−1.001)].

As shown in **Figure 7**, the IVW test found a statistically significant association between susceptibility to COVID-19 and 24 diseases, including circulatory system (n=12): deep vein thrombosis (DVT) of lower extremities [OR 95%CI: 2.392 (1.167−4.902)], DVT of lower extremities and pulmonary embolism [OR 95%CI: 2.052 (1.181−3.564)], venous thromboembolism [OR 95%CI: 1.962 (1.115−3.453)], pulmonary embolism [OR 95%CI: 1.867 (1.161−3.002)], pulmonary heart disease, diseases of pulmonary circulation [OR 95%CI: 1.767 (1.142−2.733)], ischemic stroke (large artery atherosclerosis) [OR 95%CI: 1.405 (1.025−1.927)], coronary heart disease [OR 95%CI: 1.350 (1.006−1.812)], myocardial infarction [OR 95%CI: 1.235 (1.012−1.509)], varicose veins [OR 95%CI: 1.215 (1.001−1.474)], all−cause heart failure [OR 95%CI: 1.140 (1.009−1.287)], conduction disorders [OR 95%CI: 0.780 (0.609−0.997)], AV−block [OR 95%CI: 0.651 (0.467−0.908)]. For full results of the two-sample MR see **Supplementary Table S5**.

4. Discussion

Hypothesis-free PheWAS combined with two-sample MR analysis indicated that genetically determined COVID-19 has a detrimental effect on a broad range of diseases, in particular those impacting the circulatory system, neuropsychiatric system, neoplasms, endocrine/metabolic, and immune system. Results also highlighted the potential impact of COVID-19 on dermatologic, genitourinary, infectious, respiratory, and musculoskeletal disorders. Early detection and management of long COVID-19 could be tremendously beneficial to public health.

COVID-19 as an emerging infectious disease has caused a global pandemic and is spreading at a very rapid rate resulting in an extremely high proportion of people being infected. Clinical symptoms of COVID-19 range from asymptomatic infection to fatal disease [38]. The known potential mechanism is that SAS-CoV-2 enters cells via the angiotensin-converting enzyme 2 (ACE2) receptor [39]. Once inside the body, the virus undergoes replication and maturation, triggering an inflammatory response in which various cytokines are activated and infiltrate a large number of immune cells [40]. ACE2 receptors are present in multiple cell types in the body, including oral and

nasal mucosa, lung, heart, gastrointestinal tract, liver, kidney, spleen, brain, and arterial vein endothelial cells, partially explaining the damage caused by SARS-CoV-2 to multiple systems in the body [41]. To date, the generation of long COVID-19 has had numerous effects on the human body [3].

COVID-19-related cardiovascular diseases (CVDs) such as ischemic stroke, coronary heart disease, myocardial infarction, varicose veins, heart failure, and venous thromboembolism occur not only in the early stages of infection but also months later. [42] A study from the UK including 4,182 community patients showed that 13.3% developed at least one persistent symptom 4 weeks after infection, half of which were thought to be of cardiac origin. [16] A recent cohort study by Yan Xie and colleagues based on the national healthcare databases from the US Department of Veterans Affairs found that COVID-19 patients had an increased risk of CVDs compared with controls even among patients who were not hospitalized during the acute phase of infection. [43] In addition, an increased risk of CVDs was observed in the presence or absence of cardiovascular risk factors or preexisting CVDs [43]. These studies suggest that COVID-19 increases the risk of CVDs after acute infection, even in individuals with a low risk of CVDs before COVID-19 infection. Our results suggest that both hospitalized and confirmed neo-coronaries may increase the risk of stroke, and therefore more attention should be paid to patients with neo-coronaries, especially hospitalized neo-coronaries, in terms of stroke prevention. For patients with COVID-19, routine screening for stroke is recommended, including clinical presentation, laboratory tests such as coagulation tests, imaging such as brain imaging, and cerebral angiography. For patients with hospitalized COVID-19, aggressive secondary prevention of stroke should be performed, and anticoagulation therapy is recommended to prevent stroke once laboratory results show a hypercoagulable state.

Significant associations were found between COVID-19 and the neuropsychiatric system using the PheWAS in the UK Biobank. The MR results showed that there was a strong causal effect of COVID-19 on Alzheimer's disease. Previous studies have suggested that COVID-19 may trigger clinical manifestations of neurodegenerative diseases. [44,45] Recent studies have shown that patients infected with SARS-CoV-2 exhibit reduced brain size, cognitive decline, and damage to brain regions associated with odor. [46] Previous studies have shown that SARS-CoV-2 infection activates TGF-β signaling and oxidative overload and that neuropathological pathways normally associated

with AD that lead to tau hyperphosphorylation are activated in COVID-19 patients. [47] However, since most neurodegenerative diseases are late-onset and slowly progressive, current epidemiological studies may not detect such effects to an observable extent. In addition, our MR study found that COVID-19 may increase the risk of neoplasms development. However, no cancer has been reported due to the short observation period of each study. Neoplasms are a serious burden on human health care, thus, it is critical to developing active prevention and treatment solutions for at-risk populations. In addition, the impact of COVID-19 on other systems deserves further evaluation and analysis.

This study has several key strengths. First, a hypothesis-free PheWAS approach was used to gather evidence for a possible causal association between COVID-19 across the range of disease outcomes. Second, the availability of UK Biobank resources enabled the use of information, including hospital episode statistics and mortality data, from over 500,000 individuals. Third, the SNPs used to construct the PRS score were from the most comprehensive COVID-19 GWAS developed to this point.[34] Fourth, the comprehensive analysis strategy included several two-sample univariate MR approaches that could overcome potential pleiotropic effects and avoid overestimating results.

This study also had some limitations. Due to a lack of more publicly available summary-level data, the two-sample MR method could not be used to repeat all results from the PheWAS analysis. In addition, despite the large sample size, UK Biobank is not representative of the general population; [48] however, estimations of risk factor associations are generalizable.[49] Third, the analyses were restricted to participants of White-British descent, thus the generalisability of results to other ethnic groups should be made with caution.

Conclusions

This study shows a causal effect of genetically determined COVID-19 on a broad range of diseases, in particular those impacting the circulatory system, neuropsychiatric system, neoplasms, immune system, and digestive systems. Early detection and management of long COVID-19 could be a tremendous benefit to public health.

References

1. None TL. Facing up to long COVID. Lancet (London, England) [Internet]. Lancet; 2020 [cited 2023 Feb 1];396. Available from: https://pubmed.ncbi.nlm.nih.gov/33308453/

2. Meeting the challenge of long COVID. Nature medicine [Internet]. Nat Med; 2020 [cited 2023 Feb 1];26. Available from: https://pubmed.ncbi.nlm.nih.gov/33288947/

3. The Lancet null. Understanding long COVID: a modern medical challenge. Lancet. 2021;398:725.

4. NIH experts discuss post-acute COVID-19 [Internet]. National Institutes of Health (NIH). 2021 [cited 2023 Feb 1]. Available from: https://www.nih.gov/news-events/news-releases/nih-experts-discuss-post-acute-covid-19

5. Expanding our understanding of post COVID-19 condition: report of a WHO webinar - 9 February 2021 [Internet]. [cited 2023 Feb 1]. Available from: https://www.who.int/publications/i/item/9789240025035

6. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV, WHO Clinical Case Definition Working Group on Post-COVID-19 Condition. A clinical case definition of post-COVID-19 condition by a Delphi consensus. Lancet Infect Dis. 2022;22:e102–7.

7. Overview | COVID-19 rapid guideline: managing COVID-19 | Guidance | NICE [Internet]. [cited 2023 Feb 1]. Available from: https://www.nice.org.uk/guidance/NG191

8. Datta SD, Talwar A, Lee JT. A Proposed Framework and Timeline of the Spectrum of Disease Due to SARS-CoV-2 Infection: Illness Beyond Acute Infection and Public Health Implications. JAMA. 2020;324:2251–2.

9. Crispo A, Bimonte S, Porciello G, Forte CA, Cuomo G, Montagnese C, et al. Strategies to evaluate outcomes in long-COVID-19 and post-COVID survivors. Infect Agent Cancer. 2021;16:62.

10. C H, L H, Y W, X L, L R, X G, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet (London, England) [Internet]. Lancet; 2021 [cited 2023 Feb 1];397. Available from: https://pubmed.ncbi.nlm.nih.gov/33428867/

11. Munblit D, Bobkova P, Spiridonova E, Shikhaleva A, Gamirova A, Blyuss O, et al. Incidence and risk factors for persistent symptoms in adults previously hospitalized for COVID-19. Clin Exp Allergy. 2021;51:1107–20.

12. Sigfrid L, Drake TM, Pauley E, Jesudason EC, Olliaro P, Lim WS, et al. Long Covid in adults discharged from UK hospitals after Covid-19: A prospective, multicentre cohort study using the ISARIC WHO Clinical Characterisation Protocol. Lancet Reg Health Eur. 2021;8:100186.

13. Huang L, Yao Q, Gu X, Wang Q, Ren L, Wang Y, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. Lancet. 2021;398:747–58.

14. Méndez R, Latorre A, González-Jiménez P, Feced L, Bouzas L, Yépez K, et al. Reduced Diffusion Capacity in COVID-19 Survivors. Ann Am Thorac Soc. 2021;18:1253–5.

15. Townsend L, Dowds J, O'Brien K, Sheill G, Dyer AH, O'Kelly B, et al. Persistent Poor Health after COVID-19 Is Not Associated with Respiratory Complications or Initial Disease Severity. Ann Am Thorac Soc. 2021;18:997–1003.

16. Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, et al. Attributes and predictors of long COVID. Nat Med. 2021;27:626–31.

17. Raman B, Cassar MP, Tunnicliffe EM, Filippini N, Griffanti L, Alfaro-Almagro F, et al. Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. EClinicalMedicine. 2021;31:100683.

18. Taquet M, Dercon Q, Luciano S, Geddes JR, Husain M, Harrison PJ. Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. PLoS Med. 2021;18:e1003773.

19. Smith GD, Ebrahim S. "Mendelian randomization": can genetic epidemiology contribute to understanding environmental determinants of disease? Int J Epidemiol. 2003;32:1–22.

20. Huang JY, Labrecque JA. From GWAS to PheWAS: the search for causality in big data. Lancet Digit Health. 2019;1:e101–3.

21. Hyppönen E, Mulugeta A, Zhou A, Santhanakrishnan VK. A data-driven approach for studying the role of body mass in multiple diseases: a phenome-wide registry-based case-control study in the UK Biobank. Lancet Digit Health. 2019;1:e116–26.

22. Li X, Meng X, He Y, Spiliopoulou A, Timofeeva M, Wei W-Q, et al. Genetically determined serum urate levels and cardiovascular and other diseases in UK Biobank cohort: A phenome-wide mendelian randomization study. PLoS Med. 2019;16:e1002937.

23. Magnus MC, Guyatt AL, Lawn RB, Wyss AB, Trajanoska K, Küpers LK, et al. Identifying potential causal effects of age at menarche: a Mendelian randomization phenome-wide association study. BMC Med. 2020;18:71.

24. King C, Mulugeta A, Nabi F, Walton R, Zhou A, Hyppönen E. Mendelian randomization case-control PheWAS in UK Biobank shows evidence of causality for smoking intensity in 28 distinct clinical conditions. EClinicalMedicine. 2020;26:100488.

25. Li S, Schooling CM. A phenome-wide association study of ABO blood groups. BMC Med. 2020;18:334.

26. Si S, Li J, Tewara MA, Xue F. Genetically Determined Chronic Low-Grade Inflammation and Hundreds of Health Outcomes in the UK Biobank and the FinnGen Population: A Phenome-Wide Mendelian Randomization Study. Front Immunol. 2021;12:720876.

27. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12:e1001779.

28. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, et al. The UK Biobank resource with deep phenotyping and genomic data. Nature. 2018;562:203–9.

29. COVID-19 Host Genetics Initiative. The COVID-19 Host Genetics Initiative, a global initiative to elucidate the role of host genetic factors in susceptibility and severity of the SARS-CoV-2 virus pandemic. Eur J Hum Genet. 2020;28:715–8.

30. Yuan S, Mason AM, Burgess S, Larsson SC. Genetic liability to insomnia in relation to cardiovascular diseases: a Mendelian randomisation study. Eur J Epidemiol. 2021;36:393–400.

31. Denny JC, Bastarache L, Ritchie MD, Carroll RJ, Zink R, Mosley JD, et al. Systematic comparison of phenome-wide association study of electronic medical record data and genome-wide association study data. Nat Biotechnol. 2013;31:1102–10.

32. Li X, Meng X, Spiliopoulou A, Timofeeva M, Wei W-Q, Gifford A, et al. MR-PheWAS: exploring the causal effect of SUA level on multiple disease outcomes by using genetic instruments in UK Biobank. Ann Rheum Dis. 2018;77:1039–47.

33. Carroll RJ, Bastarache L, Denny JC. R PheWAS: data analysis and plotting tools for phenome-wide association studies in the R environment. Bioinformatics. 2014;30:2375–6.

34. Jansen PR, Watanabe K, Stringer S, Skene N, Bryois J, Hammerschlag AR, et al. Genome-wide analysis of insomnia in 1,331,010 individuals identifies new risk loci and functional pathways. Nat Genet. 2019;51:394–403.

35. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. Genet Epidemiol. 2013;37:658–65.

36. J B, G DS, Pc H, S B. Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. Genetic epidemiology [Internet]. Genet Epidemiol; 2016 [cited 2023 Feb 15];40. Available from: https://pubmed.ncbi.nlm.nih.gov/27061298/

37. J B, G DS, S B. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. International journal of epidemiology [Internet]. Int J Epidemiol; 2015 [cited 2023 Feb 15];44. Available from: https://pubmed.ncbi.nlm.nih.gov/26050253/

38. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368:m1091.

39. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020;181:271-280.e8.

40. Hussman JP. Cellular and Molecular Pathways of COVID-19 and Potential Points of Therapeutic Intervention. Front Pharmacol. 2020;11:1169.

41. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203:631–7.

42. Raman B, Bluemke DA, Lüscher TF, Neubauer S. Long COVID: post-acute sequelae of COVID-19 with a cardiovascular focus. Eur Heart J. 2022;43:1157–72.

43. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. Nat Med. 2022;28:583–90.

44. P P, P G, Jp H, T T, Rm D, R G, et al. Neurological manifestations and COVID-19: Experiences from a tertiary care center at the Frontline. Journal of the neurological sciences [Internet]. J Neurol Sci; 2020 [cited 2023 Feb 15];415. Available from: https://pubmed.ncbi.nlm.nih.gov/32570113/

45. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol. 2020;77:683–90.

46. Douaud G, Lee S, Alfaro-Almagro F, Arthofer C, Wang C, McCarthy P, et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. Nature. 2022;604:697–707.

47. Reiken S, Sittenfeld L, Dridi H, Liu Y, Liu X, Marks AR. Alzheimer's-like signaling in brains of COVID-19 patients. Alzheimers Dement. 2022;18:955–65.

48. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, et al. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. Am J Epidemiol. 2017;186:1026–34.

49. Batty GD, Gale CR, Kivimäki M, Deary IJ, Bell S. Comparison of risk factor associations in UK Biobank against representative, general population based studies with conventional response rates: prospective cohort study and individual participant meta-analysis. BMJ. 2020;368:m131.

Declarations

Ethics approval and consent to participate: UK Biobank received approval from the UK Biobank Research Ethics Committee (REC; REC reference 11/NW/0382). The ethical approval of summary-level statistics was not applicable but has been approved in the original research.

Consent for publication: Not applicable.

Availability of data and materials: Details of summary-level data can be found in the supplementary material. Individual-level data that support the findings of this study are available from the UK Biobank (http://www.ukbiobank.ac.uk) (Application ID: 51470).

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: FX and KZ have the conception. FX acquire the UK Biobank dataset. KZ did the statistical analyses and drafted the initial manuscript. All authors participated in the interpretation of the results, edited and reviewed the manuscript.

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Figure Titles and Legends

Figure 1. The results of PheWAS analysis in UK Biobank.

The blue line indicates the false discovery rate (FDR) threshold. The red line indicates the self-defining notable threshold (P_{PheWAS} <0.01) to facilitate ideal visualization. Y-axis is minus log transformed *P*-value of the association between COVID-19 polygenic risk score (PRS) and disease outcomes; the X-axis provides the list of labels of 17 diseases category.

Figure 2. The odds ratios of PheWAS analysis between severe respiratory COVID-19 and diseases.

Some diseases noted with 'other' and 'un-specified' was not shown in this Figure but displayed in the supplement material; OR: odds ratio; CI: Confidence interval.

Figure 3. The odds ratios of PheWAS analysis between hospitalized COVID-19 and diseases.

Some diseases noted with 'other' and 'un-specified' was not shown in this Figure but displayed in the supplement material; OR: odds ratio; CI: Confidence interval.

Figure 4. The odds ratios of PheWAS analysis between susceptibility COVID-19 and diseases.

Some diseases noted with 'other' and 'un-specified' was not shown in this Figure but displayed in the supplement material; OR: odds ratio; CI: Confidence interval.

Figure 5. The odds ratios of IVW analysis between severe respiratory COVID-19 and diseases.

The forest plot shows a summary of statistically significant (P<0.05) results under IVW MR methods; IVW, inverse-variance weighted; OR: odds ratio; CI: Confidence interval;

Figure 6. The odds ratios of IVW analysis between hospitalized COVID-19 and diseases.

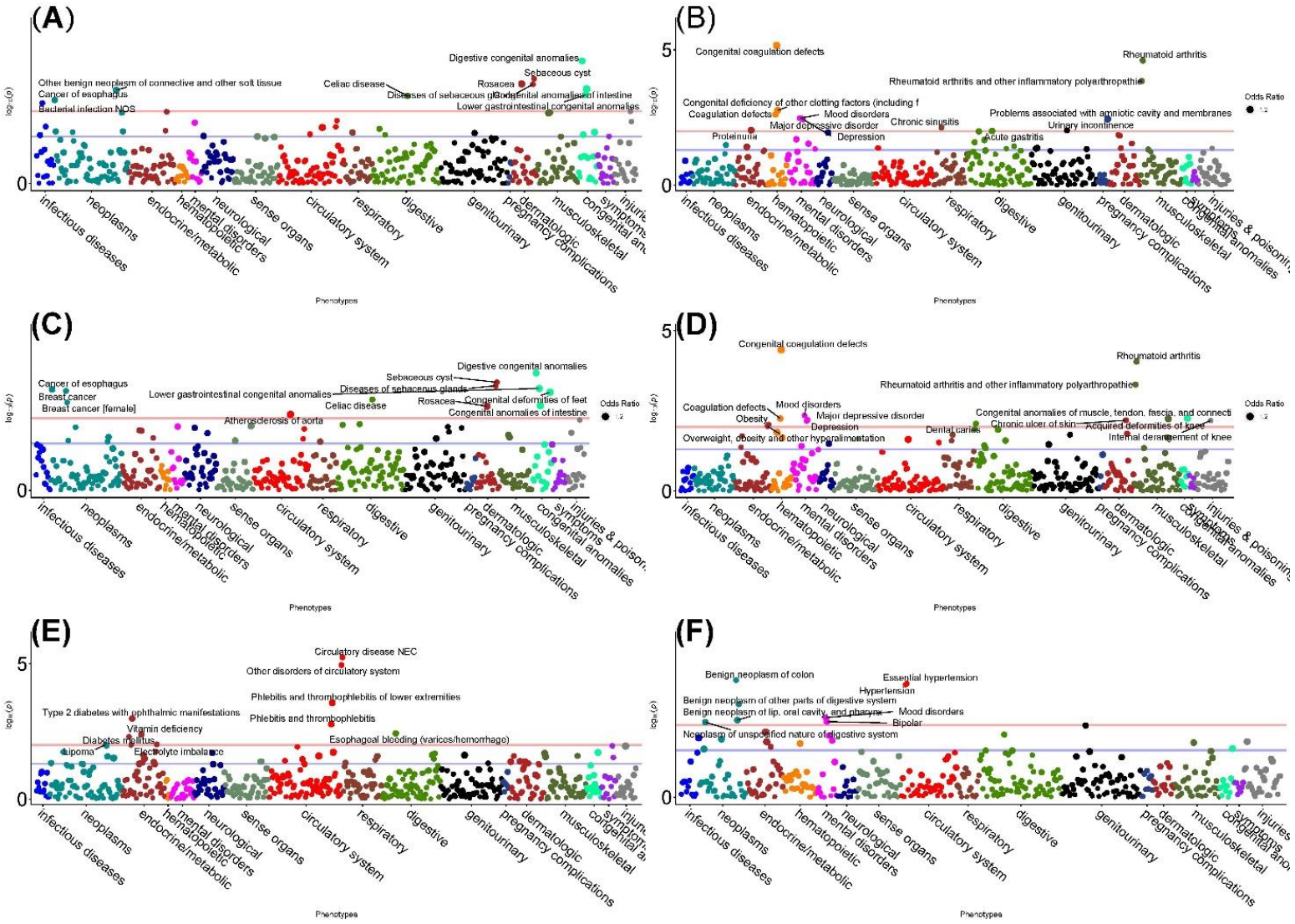
The forest plot shows a summary of statistically significant (P<0.05) results under IVW MR methods; IVW, inverse-variance weighted; OR: odds ratio; CI: Confidence interval;

Figure 7. The odds ratios of IVW analysis between susceptibility COVID-19 and diseases

The forest plot shows a summary of statistically significant (P<0.05) results under IVW MR methods;

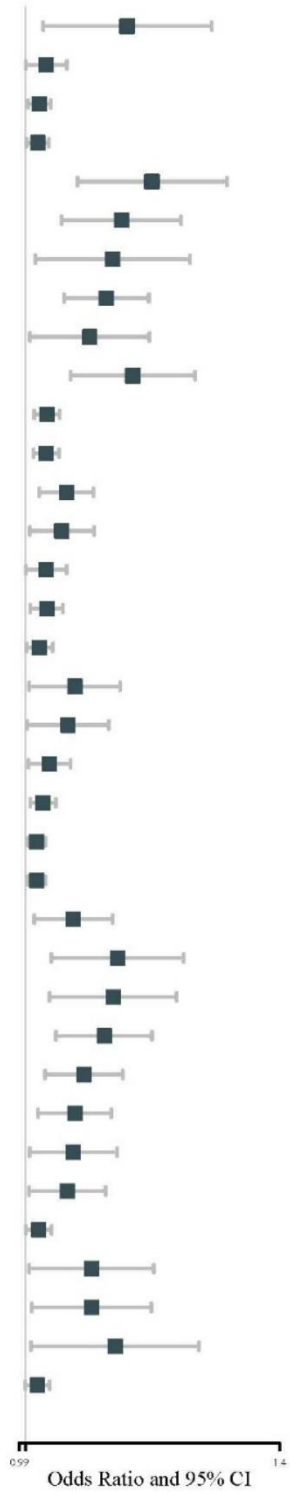
523 IVW, inverse-variance weighted; OR: odds ratio; CI: Confidence interval;

524 **Figure 1. The Manhattan plot of PheWAS analysis in UK Biobank.**



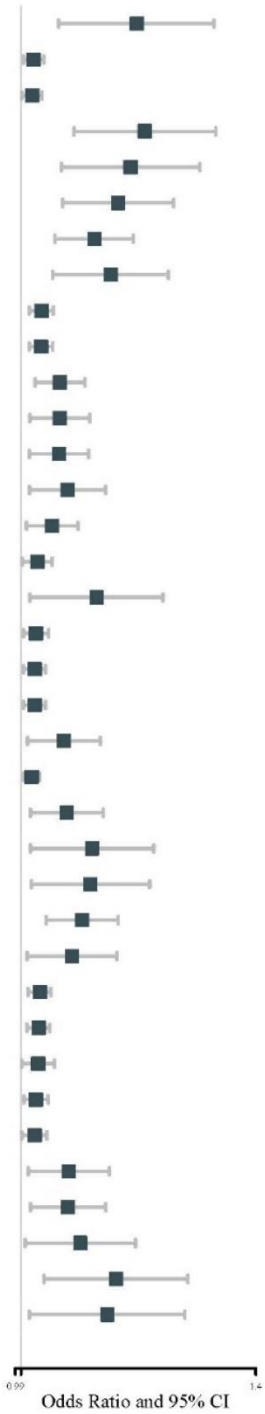
525 **Figure 2. The odds ratios of PheWAS analysis between COVID-19 and diseases.**

Group	Description	Cases	Controls	OR(95%CI)	*P* value
circulatory system	Atherosclerosis of aorta	206	394438	1.160 (1.028−1.293)	0.0281
circulatory system	Other specified cardiac dysrhythmias	3865	371344	1.033 (1.001−1.065)	0.0436
circulatory system	Varicose veins of lower extremity	12432	382323	1.022 (1.004−1.040)	0.0181
circulatory system	Varicose veins	12968	382323	1.020 (1.002−1.037)	0.0269
congenital anomalies	Congenital anomalies of intestine	261	402154	1.199 (1.082−1.317)	0.0024
congenital anomalies	Lower gastrointestinal congenital anomalies	410	402154	1.151 (1.057−1.245)	0.0035
congenital anomalies	Congenital deformities of feet	248	403110	1.137 (1.016−1.259)	0.0382
congenital anomalies	Digestive congenital anomalies	835	402154	1.127 (1.061−1.194)	<0.001
congenital anomalies	Upper gastrointestinal congenital anomalies	421	402154	1.101 (1.007−1.195)	0.0444
dermatologic	Rosacea	379	393610	1.169 (1.071−1.267)	0.0017
dermatologic	Sebaceous cyst	9439	394795	1.034 (1.014−1.054)	0.0012
dermatologic	Diseases of sebaceous glands	9524	394795	1.033 (1.013−1.053)	0.0018
digestive	Celiac disease	2117	345490	1.065 (1.022−1.107)	0.0037
digestive	Diseases and other conditions of the tongue	1472	400209	1.057 (1.007−1.108)	0.0307
digestive	Barrett's esophagus	3765	361201	1.033 (1.001−1.065)	0.0450
endocrine/metabolic	Electrolyte imbalance	6060	394025	1.034 (1.008−1.059)	0.0103
endocrine/metabolic	Disorders of fluid, electrolyte, and acid−base balance	9413	394025	1.022 (1.002−1.043)	0.0346
genitourinary	Other signs and symptoms in breast	733	402418	1.078 (1.006−1.149)	0.0400
infectious diseases	Viral Enteritis	929	399855	1.067 (1.003−1.131)	0.0454
infectious diseases	E. coli	3563	390773	1.038 (1.005−1.071)	0.0265
infectious diseases	Bacterial infection NOS	9931	390773	1.028 (1.008−1.048)	0.0059
injuries & poisonings	Poisoning by antibiotics	21709	372989	1.018 (1.004−1.032)	0.0101
injuries & poisonings	Allergy/adverse effect of penicillin	18829	372989	1.018 (1.003−1.032)	0.0191
mental disorders	Agorophobia, social phobia, and panic disorder	992	381825	1.075 (1.014−1.137)	0.0208
musculoskeletal	Disorders of coccyx	337	396319	1.145 (1.041−1.249)	0.0108
musculoskeletal	Disorders of sacrum	368	396319	1.138 (1.038−1.238)	0.0112
neoplasms	Other benign neoplasm of connective and other soft tissue	642	397055	1.124 (1.048−1.199)	0.0026
neoplasms	Cancer of esophagus	993	385410	1.092 (1.031−1.153)	0.0048
neoplasms	Benign neoplasm of brain and other parts of nervous system	1128	402214	1.078 (1.020−1.135)	0.0109
neoplasms	Cancer of stomach	808	385410	1.075 (1.007−1.144)	0.0362
neoplasms	Benign neoplasm of brain, cranial nerves, meninges	1046	402214	1.066 (1.006−1.126)	0.0361
neoplasms	Breast cancer	10545	378892	1.021 (1.001−1.041)	0.0383
neurological	Encephalitis	387	403311	1.104 (1.006−1.202)	0.0482
respiratory	Throat pain	423	385395	1.104 (1.010−1.198)	0.0386
sense organs	Optic neuritis/neuropathy	211	397781	1.141 (1.009−1.273)	0.0495
symptoms	Syncope and collapse	10856	393660	1.019 (1.000−1.038)	0.0498



526 **Figure 3. The odds ratios of PheWAS analysis between COVID-19 and diseases.**

Group	Description	Cases	Controls	OR(95%CI)	*P* value
circulatory system	Atherosclerosis of aorta	206	394438	1.197 (1.064–1.329)	0.0079
circulatory system	Varicose veins of lower extremity	12432	382323	1.021 (1.004–1.039)	0.0199
circulatory system	Varicose veins	12968	382323	1.019 (1.001–1.036)	0.0376
congenital anomalies	Congenital deformities of feet	248	403110	1.211 (1.090–1.332)	0.0019
congenital anomalies	Congenital anomalies of intestine	261	402154	1.187 (1.069–1.305)	0.0045
congenital anomalies	Lower gastrointestinal congenital anomalies	410	402154	1.165 (1.071–1.260)	0.0015
congenital anomalies	Digestive congenital anomalies	835	402154	1.125 (1.058–1.191)	<0.001
dermatologic	Rosacea	379	393610	1.153 (1.054–1.251)	0.0047
dermatologic	Sebaceous cyst	9439	394795	1.035 (1.014–1.055)	0.0010
dermatologic	Diseases of sebaceous glands	9524	394795	1.034 (1.014–1.054)	0.0013
digestive	Celiac disease	2117	345490	1.066 (1.024–1.109)	0.0030
digestive	Appendiceal conditions	1445	403071	1.066 (1.015–1.117)	0.0146
digestive	Diseases and other conditions of the tongue	1472	400209	1.065 (1.014–1.115)	0.0153
endocrine/metabolic	Vitamin D deficiency	894	400874	1.079 (1.014–1.144)	0.0223
endocrine/metabolic	Vitamin deficiency	1947	400874	1.053 (1.009–1.097)	0.0217
endocrine/metabolic	Electrolyte imbalance	6060	394025	1.028 (1.002–1.053)	0.0355
genitourinary	Inflammatory diseases of uterus, except cervix	287	209025	1.129 (1.015–1.242)	0.0365
genitourinary	Polyp of corpus uteri	8410	205661	1.025 (1.004–1.047)	0.0240
genitourinary	Menopausal and postmenopausal disorders	11235	186879	1.023 (1.004–1.042)	0.0186
genitourinary	Polyp of female genital organs	11440	205661	1.023 (1.004–1.042)	0.0174
injuries & poisonings	Mechanical complication of unspecified genitourinary device, implant, and graft	989	400441	1.073 (1.011–1.135)	0.0254
injuries & poisonings	Poisoning by antibiotics	21709	372989	1.018 (1.004–1.032)	0.0112
mental disorders	Agorophobia, social phobia, and panic disorder	992	381825	1.078 (1.016–1.140)	0.0171
musculoskeletal	Disorders of coccyx	337	396319	1.121 (1.016–1.226)	0.0337
musculoskeletal	Disorders of sacrum	368	396319	1.118 (1.018–1.219)	0.0292
neoplasms	Cancer of esophagus	993	385410	1.104 (1.043–1.165)	0.0016
neoplasms	Other benign neoplasm of connective and other soft tissue	642	397055	1.087 (1.010–1.163)	0.0334
neoplasms	Breast cancer	10545	378892	1.032 (1.012–1.051)	0.0018
neoplasms	Breast cancer [female]	10358	196884	1.030 (1.010–1.049)	0.0037
neoplasms	Lipoma of skin and subcutaneous tissue	4858	397055	1.029 (1.001–1.057)	0.0450
neoplasms	Cancer of prostate	9941	161969	1.025 (1.005–1.046)	0.0178
neoplasms	Malignant neoplasm of female breast	8708	196884	1.023 (1.001–1.044)	0.0415
neurological	Other conditions of brain	800	390558	1.081 (1.012–1.150)	0.0262
neurological	Extrapyramidal disease and abnormal movement disorders	918	390558	1.080 (1.016–1.144)	0.0185
respiratory	Throat pain	423	385395	1.101 (1.007–1.195)	0.0446
sense organs	Tympanosclerosis and middle ear disease related to otitis media	245	400302	1.162 (1.039–1.284)	0.0164
sense organs	Optic neuritis/neuropathy	211	397781	1.147 (1.014–1.279)	0.0424



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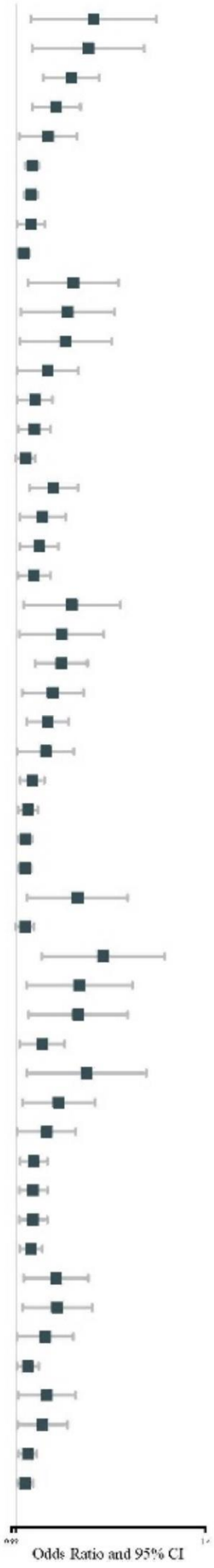
528 **Figure 4. The odds ratios of PheWAS analysis between COVID-19 and diseases.**

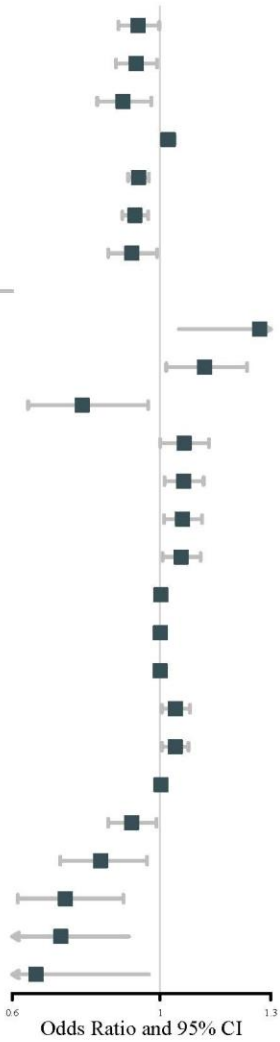
52[illegible]

Group	Description	Cases	Controls	OR(95%CI)	*P* value
circulatory system	Atherosclerosis of aorta	206	394438	1.164 (1.031 1.296)	0.0256
circulatory system	Other venous embolism and thrombosis	262	382323	1.153 (1.034 1.271)	0.0186
circulatory system	Phlebitis and thrombophlebitis of lower extremities	1045	382323	1.117 (1.057 1.177)	<0.001
circulatory system	Phlebitis and thrombophlebitis	1450	382323	1.085 (1.034 1.136)	0.0017
circulatory system	Cardiac arrest and ventricular fibrillation	1023	371344	1.068 (1.007 1.129)	0.0338
circulatory system	Circulatory disease NEC	20281	378015	1.034 (1.019 1.048)	<0.001
circulatory system	Other disorders of circulatory system	20527	378015	1.032 (1.018 1.046)	<0.001
circulatory system	Precordial pain	4435	399636	1.032 (1.002 1.061)	0.0387
circulatory system	Cardiac dysrhythmias	29845	371344	1.016 (1.004 1.028)	0.0117
congenital anomalies	Other specified congenital anomalies of kidney	406	402154	1.121 (1.025 1.216)	0.0191
dermatologic	Rosacea	379	393610	1.109 (1.010 1.208)	0.0405
dermatologic	Pyogenic granuloma	398	401321	1.105 (1.009 1.202)	0.0422
dermatologic	Pruritus and related conditions	907	403609	1.067 (1.003 1.132)	0.0482
dermatologic	Psoriasis	2752	390150	1.040 (1.003 1.077)	0.0397
dermatologic	Disturbance of skin sensation	3318	397627	1.039 (1.005 1.073)	0.0258
dermatologic	Diseases of sebaceous glands	9524	394795	1.021 (1.000–1.041)	0.0497
digestive	Esophageal bleeding (varices/hemorrhage)	1408	361201	1.079 (1.028 1.131)	0.0038
digestive	Other disorders of gallbladder	1695	385016	1.056 (1.009–1.104)	0.0234
digestive	Acute pancreatitis	2336	401185	1.049 (1.008 1.089)	0.0209
digestive	Diseases of pancreas	3331	401185	1.038 (1.004 1.072)	0.0327
endocrine/metabolic	Mineral deficiency NEC	353	400874	1.118 (1.016 1.221)	0.0326
endocrine/metabolic	Crystal arthropathies	466	401373	1.097 (1.007 1.186)	0.0433
endocrine/metabolic	Type 2 diabetes with ophthalmic manifestations	1273	381357	1.096 (1.041–1.151)	0.0011
endocrine/metabolic	Vitamin D deficiency	894	400874	1.078 (1.013 1.143)	0.0236
endocrine/metabolic	Vitamin deficiency	1947	400874	1.067 (1.023–1.111)	0.0041
endocrine/metabolic	Vitamin B complex deficiencies	1072	400874	1.063 (1.003 1.122)	0.0452
endocrine/metabolic	Electrolyte imbalance	6060	394025	1.034 (1.009–1.060)	0.0095
endocrine/metabolic	Disorders of fluid, electrolyte, and acid–base balance	9413	394025	1.025 (1.005–1.046)	0.0179
endocrine/metabolic	Diabetes mellitus	22662	381357	1.020 (1.006–1.034)	0.0050
endocrine/metabolic	Type 2 diabetes	21710	381357	1.019 (1.005–1.033)	0.0100
genitourinary	Fibroadenosis of breast	328	211640	1.130 (1.024 1.236)	0.0238
genitourinary	Polyp of female genital organs	11440	205661	1.019 (1.000–1.038)	0.0477
injuries & poisonings	Allergic reaction to food	213	399988	1.184 (1.054 1.314)	0.0110
musculoskeletal	Osteomyelitis	295	397828	1.134 (1.022–1.246)	0.0273
musculoskeletal	Osteomyelitis, periostitis, and other infections involving bone	338	397828	1.131 (1.027–1.236)	0.0205
musculoskeletal	Joint effusions	1693	399006	1.056 (1.008–1.103)	0.0254
neoplasms	Benign neoplasm of other female genital organs	231	188509	1.149 (1.023–1.275)	0.0305
neoplasms	Other benign neoplasm of connective and other soft tissue	642	397055	1.090 (1.014–1.167)	0.0266
neoplasms	Cancer of esophagus	993	385410	1.065 (1.003–1.126)	0.0467
neoplasms	Lipoma of skin and subcutaneous tissue	4858	397055	1.037 (1.009–1.066)	0.0107
neoplasms	Melanomas of skin, dx or hx	4343	384239	1.036 (1.007–1.066)	0.0184
neoplasms	Melanomas of skin	4343	384239	1.036 (1.007–1.066)	0.0184
neoplasms	Lipoma	6839	397055	1.032 (1.008–1.056)	0.0100
neurological	Other conditions of brain	800	390558	1.085 (1.016–1.153)	0.0197
respiratory	Respiratory abnormalities	695	403821	1.087 (1.014–1.161)	0.0259
respiratory	Chronic pharyngitis and nasopharyngitis	1090	385395	1.062 (1.003–1.121)	0.0458
respiratory	Shortness of breath	7296	394166	1.025 (1.002–1.048)	0.0360
sense organs	Perforation of tympanic membrane	1024	400302	1.065 (1.005–1.126)	0.0413
sense organs	Other disorders of tympanic membrane	1377	400302	1.056 (1.004–1.109)	0.0413
symptoms	Syncope and collapse	10856	393660	1.025 (1.006–1.044)	0.0109
symptoms	Nausea and vomiting	13766	390750	1.019 (1.002–1.036)	0.0290



530 **Figure 5. The odds ratios of IVW analysis between COVID-19 and diseases.**

Group	Description	OR(95%CI)	*P* value
circulatory system	Ischemic stroke (small−vessel)	0.941 (0.887−0.998)	0.0415
circulatory system	Conduction disorders	0.935 (0.880−0.992)	0.0273
circulatory system	AV−block	0.900 (0.830−0.976)	0.0110
digestive system	Gastroesophageal reflux disease	1.022 (1.004−1.040)	0.0143
digestive system	Hernia	0.942 (0.914−0.970)	<0.001
digestive system	Inguinal hernia	0.932 (0.898−0.968)	<0.001
digestive system	Ulcerative colitis	0.924 (0.860−0.992)	0.0289
digestive system	Crohn's disease	0.327 (0.211−0.505)	<0.001
endocrine/metabolic	Nontoxic diffuse goitre	1.270 (1.051−1.536)	0.0136
endocrine/metabolic	Thyrotoxicosis with diffuse goitre	1.121 (1.017−1.235)	0.0210
immune system	Systemic lupus erythematosus	0.789 (0.643−0.968)	0.0228
neoplasms	"Malignant neoplasm of breast, HER−positive" (all cancers excluded)	1.065 (1.000−1.133)	0.0486
neoplasms	"Malignant neoplasm of breast, HER2−negative" (all cancers excluded)	1.064 (1.012−1.118)	0.0153
neoplasms	Malignant neoplasm of breast, HER2−negative	1.061 (1.011−1.114)	0.0165
neoplasms	Malignant neoplasm of breast (all cancers excluded)	1.057 (1.007−1.110)	0.0263
neoplasms	Pan cancer	1.002 (1.000−1.004)	0.0178
neoplasms	Ovarian cancer	1.001 (1.000−1.002)	0.0039
neoplasms	Oesophageal cancer	1.000 (1.000−1.001)	0.0292
neuropsychiatric system	Alzheimer's disease or family history of Alzheimer's disease	1.042 (1.005−1.081)	0.0261
neuropsychiatric system	Paternal history of Alzheimer's disease	1.041 (1.005−1.077)	0.0232
neuropsychiatric system	Family history of Alzheimer's disease	1.003 (1.000−1.006)	0.0348
neuropsychiatric system	Major depressive disorder	0.923 (0.860−0.990)	0.0256
neuropsychiatric system	Hyperkinetic disorders (more controls excluded)	0.839 (0.730−0.965)	0.0137
neuropsychiatric system	Mixed disorders of conduct and emotions (KRA_PSY_CODUCTEMOT)	0.744 (0.615−0.901)	0.0024
neuropsychiatric system	Mixed disorders of conduct and emotions (more controls excluded)	0.731 (0.584−0.916)	0.0065
neuropsychiatric system	frontotemporal dementia (TDP subtype)	0.664 (0.455−0.970)	0.0341



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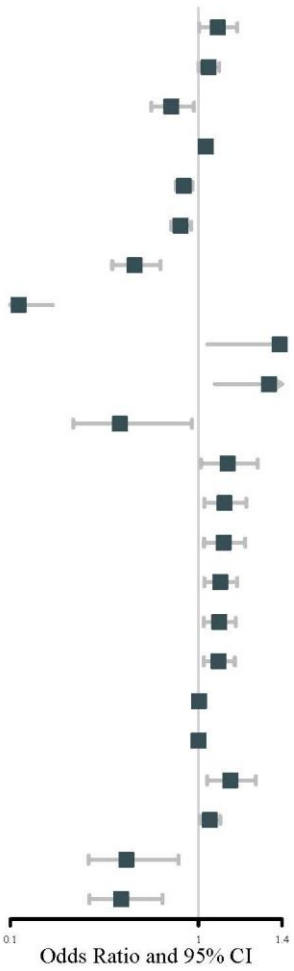
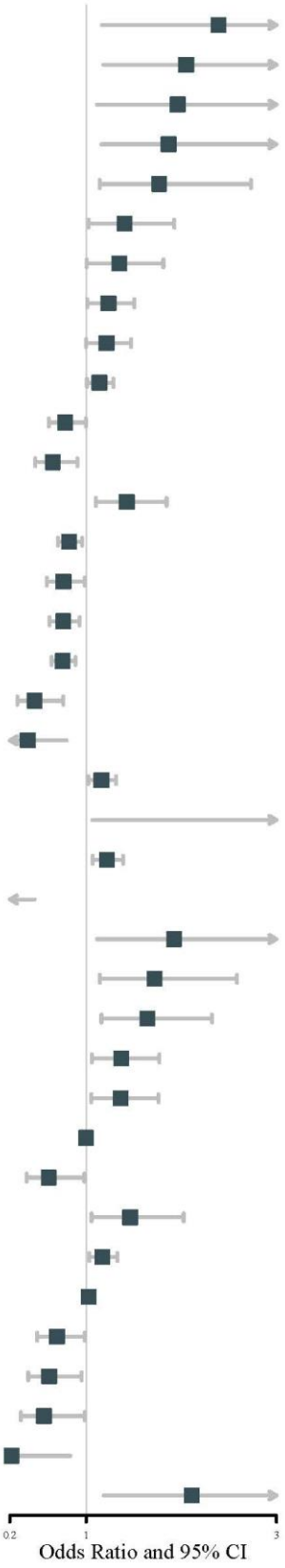
532 **Figure 6. The odds ratios of IVW analysis between COVID-19 and diseases.**

Group	Description	OR(95%CI)	*P*value
circulatory system	Ischemic stroke (cardioembolic)	1.092 (1.004−1.186)	0.0392
circulatory system	Ischemic stroke	1.049 (1.001−1.100)	0.0448
circulatory system	AV−block	0.871 (0.775−0.979)	0.0204
digestive system	Gastroesophageal reflux disease	1.035 (1.011−1.061)	0.0044
digestive system	Hernia	0.930 (0.891−0.971)	<0.001
digestive system	Inguinal hernia	0.915 (0.869−0.965)	<0.001
digestive system	Ulcerative colitis	0.694 (0.588−0.819)	<0.001
digestive system	Crohn's disease	0.140 (0.065−0.303)	<0.001
endocrine/metabolic	Nontoxic diffuse goitre	1.388 (1.043−1.846)	0.0244
immune system	Rheumatoid arthritis	1.337 (1.078−1.657)	0.0081
immune system	Systemic lupus erythematosus	0.624 (0.401−0.969)	0.0358
neoplasms	Breast cancer (iCOGS)	1.139 (1.011−1.283)	0.0321
neoplasms	"Malignant neoplasm of breast, HER−positive" (all cancers excluded)	1.124 (1.028−1.229)	0.0102
neoplasms	Malignant neoplasm of breast, HER−positive	1.121 (1.027−1.224)	0.0106
neoplasms	"Malignant neoplasm of breast, HER2−negative" (all cancers excluded)	1.104 (1.028−1.185)	0.0068
neoplasms	Malignant neoplasm of breast, HER2−negative	1.100 (1.026−1.179)	0.0073
neoplasms	Malignant neoplasm of breast (all cancers excluded)	1.097 (1.026−1.174)	0.0070
neoplasms	Pan cancer	1.003 (1.000−1.006)	0.0452
neoplasms	Oesophageal cancer	1.001 (1.000−1.001)	0.0084
neuropsychiatric system	Locus of control over disease	1.152 (1.041−1.275)	0.0060
neuropsychiatric system	Alzheimer's disease or family history of Alzheimer's disease	1.054 (1.006−1.104)	0.0266
neuropsychiatric system	Mixed disorders of conduct and emotions (more controls excluded)	0.655 (0.474−0.905)	0.0102
neuropsychiatric system	Mixed disorders of conduct and emotions (KRA_PSY_CODUCTEMOT)	0.630 (0.479−0.828)	<0.001



533 **Figure 7. The odds ratios of IVW analysis between COVID-19 and diseases.**

Group	Description	OR(95%CI)	P value
circulatory system	DVT of lower extremities	2.392 (1.167−4.902)	0.0172
circulatory system	DVT of lower extremities and pulmonary embolism	2.052 (1.181−3.564)	0.0107
circulatory system	Venous thromboembolism	1.962 (1.115−3.453)	0.0194
circulatory system	Pulmonary embolism	1.867 (1.161−3.002)	0.0100
circulatory system	Pulmonary heart disease, diseases of pulmonary circulation	1.767 (1.142−2.733)	0.0105
circulatory system	Ischemic stroke (large artery atherosclerosis)	1.405 (1.025−1.927)	0.0347
circulatory system	Coronary heart disease	1.350 (1.006−1.812)	0.0457
circulatory system	Myocardial infarction	1.235 (1.012−1.509)	0.0383
circulatory system	Varicose veins	1.215 (1.001−1.474)	0.0493
circulatory system	All−cause Heart Failure	1.140 (1.009−1.287)	0.0347
circulatory system	Conduction disorders	0.780 (0.609−0.997)	0.0473
circulatory system	AV−block	0.651 (0.467−0.908)	0.0115
digestive system	Personality disorders (more controls excluded)	1.428 (1.104−1.846)	0.0066
digestive system	Hernia	0.822 (0.706−0.957)	0.0117
digestive system	Gastroduodenal ulcer	0.762 (0.589−0.986)	0.0386
digestive system	Diverticular disease of intestine	0.758 (0.617−0.932)	0.0085
digestive system	Inguinal hernia	0.753 (0.638−0.888)	<0.001
digestive system	Duodenal ulcer	0.459 (0.278−0.760)	0.0025
digestive system	Oesophageal obstruction	0.387 (0.189−0.796)	0.0098
endocrine/metabolic	Hypothyroidism, strict autoimmune	1.161 (1.024−1.316)	0.0200
immune system	Type 1 diabetes	3.530 (1.067−11.674)	0.0388
immune system	Glaucoma (multi−trait analysis)	1.219 (1.070−1.389)	0.0029
immune system	Paget's disease	0.180 (0.070−0.461)	<0.001
neoplasms	Low malignant potential mucinous ovarian cancer	1.925 (1.116−3.320)	0.0185
neoplasms	ER+ Breast cancer (iCOGS)	1.721 (1.145−2.586)	0.0091
neoplasms	Breast cancer (iCOGS)	1.642 (1.161−2.323)	0.0050
neoplasms	"Malignant neoplasm of breast, HER−positive" (all cancers excluded)	1.371 (1.062−1.770)	0.0155
neoplasms	Malignant neoplasm of breast, HER−positive	1.364 (1.056−1.761)	0.0173
neoplasms	Oral and oropharyngeal cancer	0.999 (0.998−1.000)	0.0260
neoplasms	Malignant neoplasm of endocrine gland	0.607 (0.375−0.982)	0.0421
neuropsychiatric system	Emotionally unstable personality disorder	1.463 (1.057−2.025)	0.0217
neuropsychiatric system	Paternal history of Alzheimer's disease	1.172 (1.033−1.330)	0.0139
neuropsychiatric system	childhood absence epilepsy	1.026 (1.004−1.048)	0.0190
neuropsychiatric system	Internalizing problems	0.694 (0.487−0.988)	0.0428
neuropsychiatric system	Major depressive disorder	0.612 (0.392−0.954)	0.0301
neuropsychiatric system	Hyperkinetic disorders (more controls excluded)	0.558 (0.315−0.986)	0.0447
neuropsychiatric system	frontotemporal dementia (TDP subtype)	0.216 (0.056−0.835)	0.0263
respiratory	Percent emphysema	2.110 (1.186−3.755)	0.0111



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(A)

Digestive congenital anomalies
Sebaceous cyst
Other benign neoplasm of connective and other soft tissue
Celiac disease
Rosacea
Cancer of esophagus
Diseases of sebaceous glands
Congenital anomalies of intestine
Bacterial infection NOS
Lower gastrointestinal congenital anomalies
$-\log_{10}(p)$
0
infectious diseases
neoplasms
endocrine/metabolic
hematopoietic
mental disorders
neurological
sense organs
circulatory system
respiratory
digestive
genitourinary
pregnancy complications
dermatologic
musculoskeletal
congenital anu
symptoms
injurie
Phenotypes

(B)

5
Congenital coagulation defects
Rheumatoid arthritis
Rheumatoid arthritis and other inflammatory polyarthropathie
Congenital deficiency of other clotting factors (including f
Coagulation defects
Mood disorders
Problems associated with amniotic cavity and membranes
Major depressive disorder
Chronic sinusitis
Urinary incontinence
Depression
Proteinuria
Acute gastritis
$-\log_{10}(p)$
0
Odds Ratio
1.2
infectious diseases
neoplasms
endocrine/metabolic
hematopoietic
mental disorders
neurological
sense organs
circulatory system
respiratory
digestive
genitourinary
pregnancy complications
dermatologic
musculoskeletal
congenital anomalies
injuries & poisonin
Phenotypes

(C)

Digestive congenital anomalies
Sebaceous cyst
Cancer of esophagus
Diseases of sebaceous glands
Breast cancer
Lower gastrointestinal congenital anomalies
Celiac disease
Rosacea
Congenital deformities of feet
Breast cancer [female]
Congenital anomalies of intestine
Atherosclerosis of aorta
$-\log_{10}(p)$
0
Odds Ratio
1.2
infectious diseases
neoplasms
endocrine/metabolic
hematopoietic
mental disorders
neurological
sense organs
circulatory system
respiratory
digestive
genitourinary
pregnancy complications
dermatologic
musculoskeletal
congenital anomalies
injuries & poisonin
Phenotypes

(D)

5
Congenital coagulation defects
Rheumatoid arthritis
Rheumatoid arthritis and other inflammatory polyarthropathie
Coagulation defects
Mood disorders
Obesity
Major depressive disorder
Congenital anomalies of muscle, tendon, fascia, and connecti
Chronic ulcer of skin
Acquired deformities of knee
Depression
Dental caries
Overweight, obesity and other hyperalimentation
Internal derangement of knee
$-\log_{10}(p)$
0
Odds Ratio
1.2
infectious diseases
neoplasms
endocrine/metabolic
hematopoietic
mental disorders
neurological
sense organs
circulatory system
respiratory
digestive
genitourinary
pregnancy complications
dermatologic
musculoskeletal
congenital anomalies
injuries & poisonings
Phenotypes

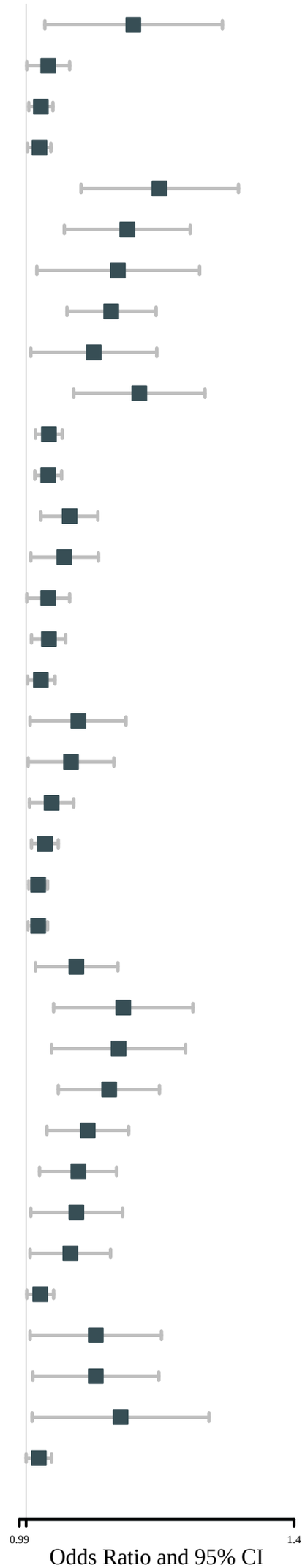
(E)

5
Circulatory disease NEC
Other disorders of circulatory system
Phlebitis and thrombophlebitis of lower extremities
Type 2 diabetes with ophthalmic manifestations
Phlebitis and thrombophlebitis
Vitamin deficiency
Esophageal bleeding (varices/hemorrhage)
Diabetes mellitus
Lipoma
Electrolyte imbalance
$-\log_{10}(p)$
0
infectious diseases
neoplasms
endocrine/metabolic
hematopoietic
mental disorders
neurological
sense organs
circulatory system
respiratory
digestive
genitourinary
pregnancy complications
dermatologic
musculoskeletal
congenital a
symptom
injurie
Phenotypes

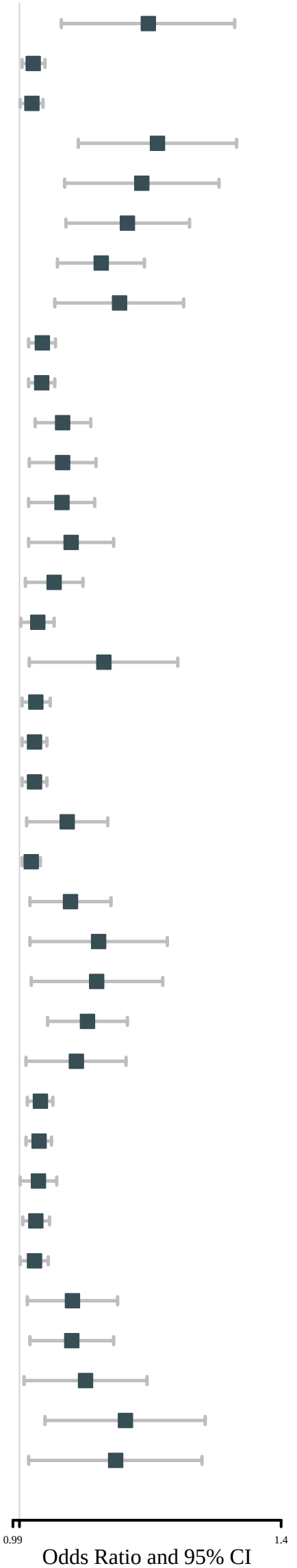
(F)

5
Benign neoplasm of colon
Essential hypertension
Hypertension
Benign neoplasm of other parts of digestive system
Benign neoplasm of lip, oral cavity, and pharynx
Mood disorders
Bipolar
Neoplasm of unspecified nature of digestive system
$-\log_{10}(p)$
0
infectious diseases
neoplasms
endocrine/metabolic
hematopoietic
mental disorders
neurological
sense organs
circulatory system
respiratory
digestive
genitourinary
pregnancy complications
dermatologic
musculoskeletal
congenital anom
injuries
Phenotypes

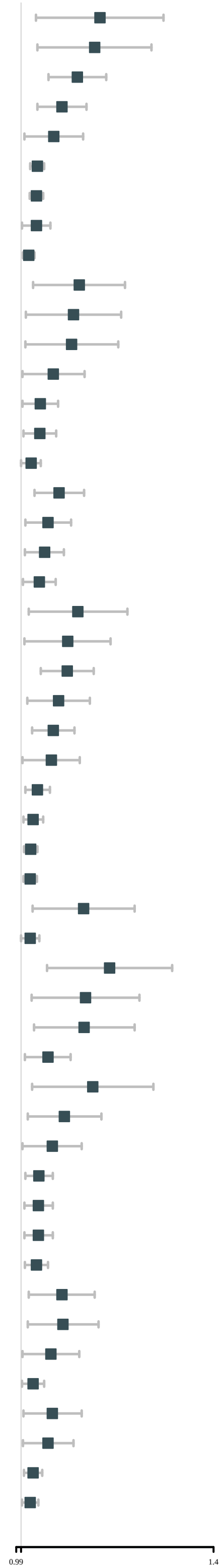
Group	Description	Cases	Controls	OR(95%CI)	*P* value
circulatory system	Atherosclerosis of aorta	206	394438	1.160 (1.028−1.293)	0.0281
circulatory system	Other specified cardiac dysrhythmias	3865	371344	1.033 (1.001−1.065)	0.0436
circulatory system	Varicose veins of lower extremity	12432	382323	1.022 (1.004−1.040)	0.0181
circulatory system	Varicose veins	12968	382323	1.020 (1.002−1.037)	0.0269
congenital anomalies	Congenital anomalies of intestine	261	402154	1.199 (1.082−1.317)	0.0024
congenital anomalies	Lower gastrointestinal congenital anomalies	410	402154	1.151 (1.057−1.245)	0.0035
congenital anomalies	Congenital deformities of feet	248	403110	1.137 (1.016−1.259)	0.0382
congenital anomalies	Digestive congenital anomalies	835	402154	1.127 (1.061−1.194)	<0.001
congenital anomalies	Upper gastrointestinal congenital anomalies	421	402154	1.101 (1.007−1.195)	0.0444
dermatologic	Rosacea	379	393610	1.169 (1.071−1.267)	0.0017
dermatologic	Sebaceous cyst	9439	394795	1.034 (1.014−1.054)	0.0012
dermatologic	Diseases of sebaceous glands	9524	394795	1.033 (1.013−1.053)	0.0018
digestive	Celiac disease	2117	345490	1.065 (1.022−1.107)	0.0037
digestive	Diseases and other conditions of the tongue	1472	400209	1.057 (1.007−1.108)	0.0307
digestive	Barrett's esophagus	3765	361201	1.033 (1.001−1.065)	0.0450
endocrine/metabolic	Electrolyte imbalance	6060	394025	1.034 (1.008−1.059)	0.0103
endocrine/metabolic	Disorders of fluid, electrolyte, and acid−base balance	9413	394025	1.022 (1.002−1.043)	0.0346
genitourinary	Other signs and symptoms in breast	733	402418	1.078 (1.006−1.149)	0.0400
infectious diseases	Viral Enteritis	929	399855	1.067 (1.003−1.131)	0.0454
infectious diseases	E. coli	3563	390773	1.038 (1.005−1.071)	0.0265
infectious diseases	Bacterial infection NOS	9931	390773	1.028 (1.008−1.048)	0.0059
injuries & poisonings	Poisoning by antibiotics	21709	372989	1.018 (1.004−1.032)	0.0101
injuries & poisonings	Allergy/adverse effect of penicillin	18829	372989	1.018 (1.003−1.032)	0.0191
mental disorders	Agorophobia, social phobia, and panic disorder	992	381825	1.075 (1.014−1.137)	0.0208
musculoskeletal	Disorders of coccyx	337	396319	1.145 (1.041−1.249)	0.0108
musculoskeletal	Disorders of sacrum	368	396319	1.138 (1.038−1.238)	0.0112
neoplasms	Other benign neoplasm of connective and other soft tissue	642	397055	1.124 (1.048−1.199)	0.0026
neoplasms	Cancer of esophagus	993	385410	1.092 (1.031−1.153)	0.0048
neoplasms	Benign neoplasm of brain and other parts of nervous system	1128	402214	1.078 (1.020−1.135)	0.0109
neoplasms	Cancer of stomach	808	385410	1.075 (1.007−1.144)	0.0362
neoplasms	Benign neoplasm of brain, cranial nerves, meninges	1046	402214	1.066 (1.006−1.126)	0.0361
neoplasms	Breast cancer	10545	378892	1.021 (1.001−1.041)	0.0383
neurological	Encephalitis	387	403311	1.104 (1.006−1.202)	0.0482
respiratory	Throat pain	423	385395	1.104 (1.010−1.198)	0.0386
sense organs	Optic neuritis/neuropathy	211	397781	1.141 (1.009−1.273)	0.0495
symptoms	Syncope and collapse	10856	393660	1.019 (1.000−1.038)	0.0498



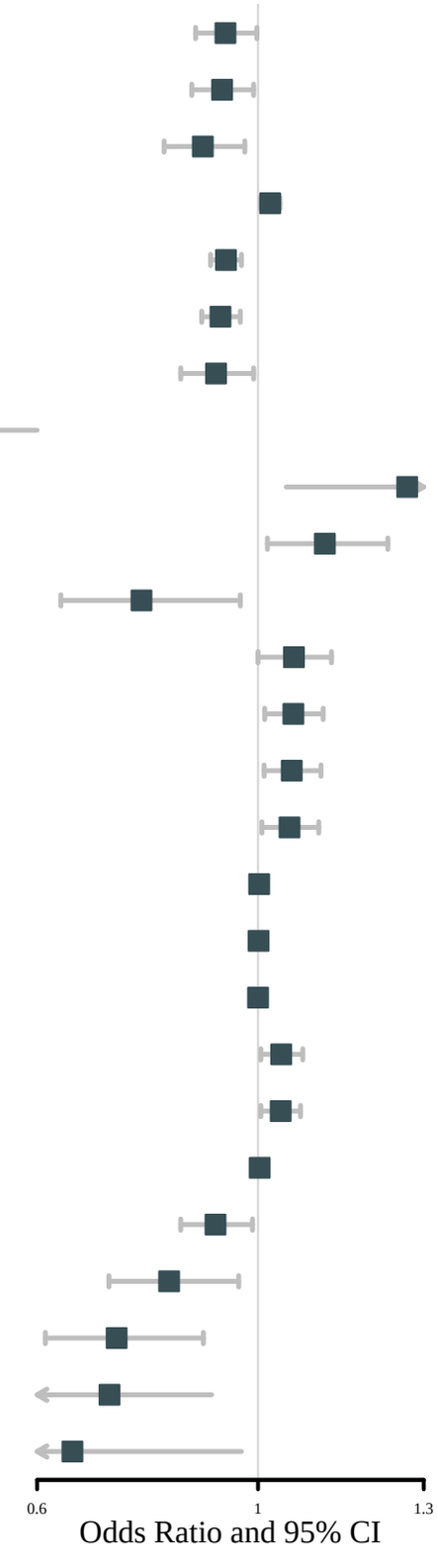
Group	Description	Cases	Controls	OR(95%CI)	*P* value
circulatory system	Atherosclerosis of aorta	206	394438	1.197 (1.064−1.329)	0.0079
circulatory system	Varicose veins of lower extremity	12432	382323	1.021 (1.004−1.039)	0.0199
circulatory system	Varicose veins	12968	382323	1.019 (1.001−1.036)	0.0376
congenital anomalies	Congenital deformities of feet	248	403110	1.211 (1.090−1.332)	0.0019
congenital anomalies	Congenital anomalies of intestine	261	402154	1.187 (1.069−1.305)	0.0045
congenital anomalies	Lower gastrointestinal congenital anomalies	410	402154	1.165 (1.071−1.260)	0.0015
congenital anomalies	Digestive congenital anomalies	835	402154	1.125 (1.058−1.191)	<0.001
dermatologic	Rosacea	379	393610	1.153 (1.054−1.251)	0.0047
dermatologic	Sebaceous cyst	9439	394795	1.035 (1.014−1.055)	0.0010
dermatologic	Diseases of sebaceous glands	9524	394795	1.034 (1.014−1.054)	0.0013
digestive	Celiac disease	2117	345490	1.066 (1.024−1.109)	0.0030
digestive	Appendiceal conditions	1445	403071	1.066 (1.015−1.117)	0.0146
digestive	Diseases and other conditions of the tongue	1472	400209	1.065 (1.014−1.115)	0.0153
endocrine/metabolic	Vitamin D deficiency	894	400874	1.079 (1.014−1.144)	0.0223
endocrine/metabolic	Vitamin deficiency	1947	400874	1.053 (1.009−1.097)	0.0217
endocrine/metabolic	Electrolyte imbalance	6060	394025	1.028 (1.002−1.053)	0.0355
genitourinary	Inflammatory diseases of uterus, except cervix	287	209025	1.129 (1.015−1.242)	0.0365
genitourinary	Polyp of corpus uteri	8410	205661	1.025 (1.004−1.047)	0.0240
genitourinary	Menopausal and postmenopausal disorders	11235	186879	1.023 (1.004−1.042)	0.0186
genitourinary	Polyp of female genital organs	11440	205661	1.023 (1.004−1.042)	0.0174
injuries & poisonings	Mechanical complication of unspecified genitourinary device, implant, and graft	989	400441	1.073 (1.011−1.135)	0.0254
injuries & poisonings	Poisoning by antibiotics	21709	372989	1.018 (1.004−1.032)	0.0112
mental disorders	Agorophobia, social phobia, and panic disorder	992	381825	1.078 (1.016−1.140)	0.0171
musculoskeletal	Disorders of coccyx	337	396319	1.121 (1.016−1.226)	0.0337
musculoskeletal	Disorders of sacrum	368	396319	1.118 (1.018−1.219)	0.0292
neoplasms	Cancer of esophagus	993	385410	1.104 (1.043−1.165)	0.0016
neoplasms	Other benign neoplasm of connective and other soft tissue	642	397055	1.087 (1.010−1.163)	0.0334
neoplasms	Breast cancer	10545	378892	1.032 (1.012−1.051)	0.0018
neoplasms	Breast cancer [female]	10358	196884	1.030 (1.010−1.049)	0.0037
neoplasms	Lipoma of skin and subcutaneous tissue	4858	397055	1.029 (1.001−1.057)	0.0450
neoplasms	Cancer of prostate	9941	161969	1.025 (1.005−1.046)	0.0178
neoplasms	Malignant neoplasm of female breast	8708	196884	1.023 (1.001−1.044)	0.0415
neurological	Other conditions of brain	800	390558	1.081 (1.012−1.150)	0.0262
neurological	Extrapyramidal disease and abnormal movement disorders	918	390558	1.080 (1.016−1.144)	0.0185
respiratory	Throat pain	423	385395	1.101 (1.007−1.195)	0.0446
sense organs	Tympanosclerosis and middle ear disease related to otitis media	245	400302	1.162 (1.039−1.284)	0.0164
sense organs	Optic neuritis/neuropathy	211	397781	1.147 (1.014−1.279)	0.0424



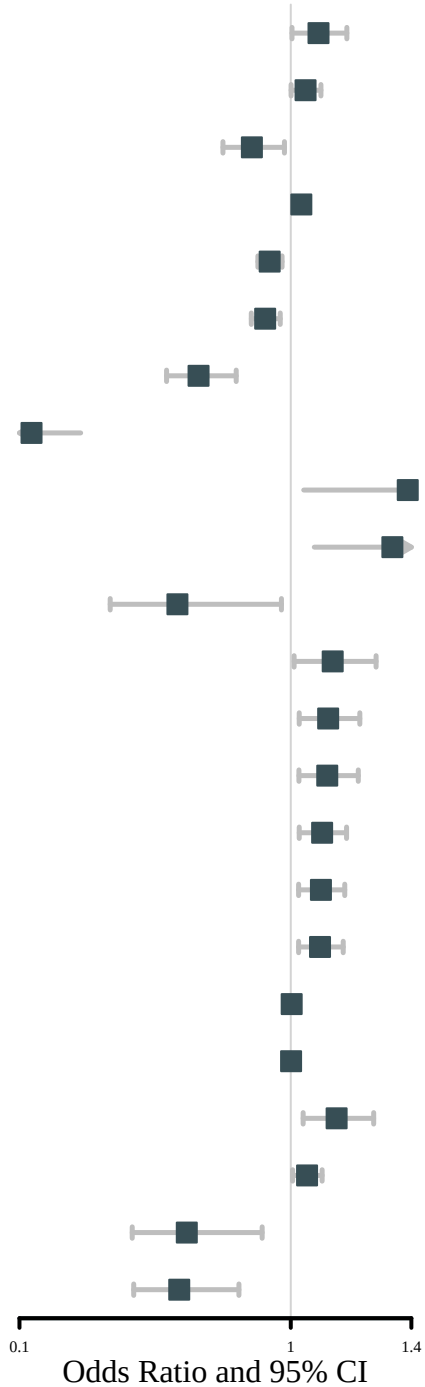
Group	Description	Cases	Controls	OR(95%CI)	*P* value
circulatory system	Atherosclerosis of aorta	206	394438	1.164 (1.031−1.296)	0.0256
circulatory system	Other venous embolism and thrombosis	262	382323	1.153 (1.034−1.271)	0.0186
circulatory system	Phlebitis and thrombophlebitis of lower extremities	1045	382323	1.117 (1.057−1.177)	<0.001
circulatory system	Phlebitis and thrombophlebitis	1450	382323	1.085 (1.034−1.136)	0.0017
circulatory system	Cardiac arrest and ventricular fibrillation	1023	371344	1.068 (1.007−1.129)	0.0338
circulatory system	Circulatory disease NEC	20281	378015	1.034 (1.019−1.048)	<0.001
circulatory system	Other disorders of circulatory system	20527	378015	1.032 (1.018−1.046)	<0.001
circulatory system	Precordial pain	4435	399636	1.032 (1.002−1.061)	0.0387
circulatory system	Cardiac dysrhythmias	29845	371344	1.016 (1.004−1.028)	0.0117
congenital anomalies	Other specified congenital anomalies of kidney	406	402154	1.121 (1.025−1.216)	0.0191
dermatologic	Rosacea	379	393610	1.109 (1.010−1.208)	0.0405
dermatologic	Pyogenic granuloma	398	401321	1.105 (1.009−1.202)	0.0422
dermatologic	Pruritus and related conditions	907	403609	1.067 (1.003−1.132)	0.0482
dermatologic	Psoriasis	2752	390150	1.040 (1.003−1.077)	0.0397
dermatologic	Disturbance of skin sensation	3318	397627	1.039 (1.005−1.073)	0.0258
dermatologic	Diseases of sebaceous glands	9524	394795	1.021 (1.000−1.041)	0.0497
digestive	Esophageal bleeding (varices/hemorrhage)	1408	361201	1.079 (1.028−1.131)	0.0038
digestive	Other disorders of gallbladder	1695	385016	1.056 (1.009−1.104)	0.0234
digestive	Acute pancreatitis	2336	401185	1.049 (1.008−1.089)	0.0209
digestive	Diseases of pancreas	3331	401185	1.038 (1.004−1.072)	0.0327
endocrine/metabolic	Mineral deficiency NEC	353	400874	1.118 (1.016−1.221)	0.0326
endocrine/metabolic	Crystal arthropathies	466	401373	1.097 (1.007−1.186)	0.0433
endocrine/metabolic	Type 2 diabetes with ophthalmic manifestations	1273	381357	1.096 (1.041−1.151)	0.0011
endocrine/metabolic	Vitamin D deficiency	894	400874	1.078 (1.013−1.143)	0.0236
endocrine/metabolic	Vitamin deficiency	1947	400874	1.067 (1.023−1.111)	0.0041
endocrine/metabolic	Vitamin B−complex deficiencies	1072	400874	1.063 (1.003−1.122)	0.0452
endocrine/metabolic	Electrolyte imbalance	6060	394025	1.034 (1.009−1.060)	0.0095
endocrine/metabolic	Disorders of fluid, electrolyte, and acid−base balance	9413	394025	1.025 (1.005−1.046)	0.0179
endocrine/metabolic	Diabetes mellitus	22662	381357	1.020 (1.006−1.034)	0.0050
endocrine/metabolic	Type 2 diabetes	21710	381357	1.019 (1.005−1.033)	0.0100
genitourinary	Fibroadenosis of breast	328	211640	1.130 (1.024−1.236)	0.0238
genitourinary	Polyp of female genital organs	11440	205661	1.019 (1.000−1.038)	0.0477
injuries & poisonings	Allergic reaction to food	213	399988	1.184 (1.054−1.314)	0.0110
musculoskeletal	Osteomyelitis	295	397828	1.134 (1.022−1.246)	0.0273
musculoskeletal	Osteomyelitis, periostitis, and other infections involving bone	338	397828	1.131 (1.027−1.236)	0.0205
musculoskeletal	Joint effusions	1693	399006	1.056 (1.008−1.103)	0.0254
neoplasms	Benign neoplasm of other female genital organs	231	188509	1.149 (1.023−1.275)	0.0305
neoplasms	Other benign neoplasm of connective and other soft tissue	642	397055	1.090 (1.014−1.167)	0.0266
neoplasms	Cancer of esophagus	993	385410	1.065 (1.003−1.126)	0.0467
neoplasms	Lipoma of skin and subcutaneous tissue	4858	397055	1.037 (1.009−1.066)	0.0107
neoplasms	Melanomas of skin, dx or hx	4343	384239	1.036 (1.007−1.066)	0.0184
neoplasms	Melanomas of skin	4343	384239	1.036 (1.007−1.066)	0.0184
neoplasms	Lipoma	6839	397055	1.032 (1.008−1.056)	0.0100
neurological	Other conditions of brain	800	390558	1.085 (1.016−1.153)	0.0197
respiratory	Respiratory abnormalities	695	403821	1.087 (1.014−1.161)	0.0259
respiratory	Chronic pharyngitis and nasopharyngitis	1090	385395	1.062 (1.003−1.121)	0.0458
respiratory	Shortness of breath	7296	394166	1.025 (1.002−1.048)	0.0360
sense organs	Perforation of tympanic membrane	1024	400302	1.065 (1.005−1.126)	0.0413
sense organs	Other disorders of tympanic membrane	1377	400302	1.056 (1.004−1.109)	0.0413
symptoms	Syncope and collapse	10856	393660	1.025 (1.006−1.044)	0.0109
symptoms	Nausea and vomiting	13766	390750	1.019 (1.002−1.036)	0.0290



Group	Description	OR(95%CI)	*P* value
circulatory system	Ischemic stroke (small−vessel)	0.941 (0.887−0.998)	0.0415
circulatory system	Conduction disorders	0.935 (0.880−0.992)	0.0273
circulatory system	AV−block	0.900 (0.830−0.976)	0.0110
digestive system	Gastroesophageal reflux disease	1.022 (1.004−1.040)	0.0143
digestive system	Hernia	0.942 (0.914−0.970)	<0.001
digestive system	Inguinal hernia	0.932 (0.898−0.968)	<0.001
digestive system	Ulcerative colitis	0.924 (0.860−0.992)	0.0289
digestive system	Crohn's disease	0.327 (0.211−0.505)	<0.001
endocrine/metabolic	Nontoxic diffuse goitre	1.270 (1.051−1.536)	0.0136
endocrine/metabolic	Thyrotoxicosis with diffuse goitre	1.121 (1.017−1.235)	0.0210
immune system	Systemic lupus erythematosus	0.789 (0.643−0.968)	0.0228
neoplasms	"Malignant neoplasm of breast, HER−positive" (all cancers excluded)	1.065 (1.000−1.133)	0.0486
neoplasms	"Malignant neoplasm of breast, HER2−negative" (all cancers excluded)	1.064 (1.012−1.118)	0.0153
neoplasms	Malignant neoplasm of breast, HER2−negative	1.061 (1.011−1.114)	0.0165
neoplasms	Malignant neoplasm of breast (all cancers excluded)	1.057 (1.007−1.110)	0.0263
neoplasms	Pan cancer	1.002 (1.000−1.004)	0.0178
neoplasms	Ovarian cancer	1.001 (1.000−1.002)	0.0039
neoplasms	Oesophageal cancer	1.000 (1.000−1.001)	0.0292
neuropsychiatric system	Alzheimer's disease or family history of Alzheimer's disease	1.042 (1.005−1.081)	0.0261
neuropsychiatric system	Paternal history of Alzheimer's disease	1.041 (1.005−1.077)	0.0232
neuropsychiatric system	Family history of Alzheimer's disease	1.003 (1.000−1.006)	0.0348
neuropsychiatric system	Major depressive disorder	0.923 (0.860−0.990)	0.0256
neuropsychiatric system	Hyperkinetic disorders (more controls excluded)	0.839 (0.730−0.965)	0.0137
neuropsychiatric system	Mixed disorders of conduct and emotions (KRA_PSY_CODUCTEMOT)	0.744 (0.615−0.901)	0.0024
neuropsychiatric system	Mixed disorders of conduct and emotions (more controls excluded)	0.731 (0.584−0.916)	0.0065
neuropsychiatric system	frontotemporal dementia (TDP subtype)	0.664 (0.455−0.970)	0.0341



Group	Description	OR(95%CI)	*P* value
circulatory system	Ischemic stroke (cardioembolic)	1.092 (1.004−1.186)	0.0392
circulatory system	Ischemic stroke	1.049 (1.001−1.100)	0.0448
circulatory system	AV−block	0.871 (0.775−0.979)	0.0204
digestive system	Gastroesophageal reflux disease	1.035 (1.011−1.061)	0.0044
digestive system	Hernia	0.930 (0.891−0.971)	<0.001
digestive system	Inguinal hernia	0.915 (0.869−0.965)	<0.001
digestive system	Ulcerative colitis	0.694 (0.588−0.819)	<0.001
digestive system	Crohn's disease	0.140 (0.065−0.303)	<0.001
endocrine/metabolic	Nontoxic diffuse goitre	1.388 (1.043−1.846)	0.0244
immune system	Rheumatoid arthritis	1.337 (1.078−1.657)	0.0081
immune system	Systemic lupus erythematosus	0.624 (0.401−0.969)	0.0358
neoplasms	Breast cancer (iCOGS)	1.139 (1.011−1.283)	0.0321
neoplasms	"Malignant neoplasm of breast, HER−positive" (all cancers excluded)	1.124 (1.028−1.229)	0.0102
neoplasms	Malignant neoplasm of breast, HER−positive	1.121 (1.027−1.224)	0.0106
neoplasms	"Malignant neoplasm of breast, HER2−negative" (all cancers excluded)	1.104 (1.028−1.185)	0.0068
neoplasms	Malignant neoplasm of breast, HER2−negative	1.100 (1.026−1.179)	0.0073
neoplasms	Malignant neoplasm of breast (all cancers excluded)	1.097 (1.026−1.174)	0.0070
neoplasms	Pan cancer	1.003 (1.000−1.006)	0.0452
neoplasms	Oesophageal cancer	1.001 (1.000−1.001)	0.0084
neuropsychiatric system	Locus of control over disease	1.152 (1.041−1.275)	0.0060
neuropsychiatric system	Alzheimer's disease or family history of Alzheimer's disease	1.054 (1.006−1.104)	0.0266
neuropsychiatric system	Mixed disorders of conduct and emotions (more controls excluded)	0.655 (0.474−0.905)	0.0102
neuropsychiatric system	Mixed disorders of conduct and emotions (KRA_PSY_CODUCTEMOT)	0.630 (0.479−0.828)	<0.001



Group	Description	OR(95%CI)	*P* value
circulatory system	DVT of lower extremities	2.392 (1.167−4.902)	0.0172
circulatory system	DVT of lower extremities and pulmonary embolism	2.052 (1.181−3.564)	0.0107
circulatory system	Venous thromboembolism	1.962 (1.115−3.453)	0.0194
circulatory system	Pulmonary embolism	1.867 (1.161−3.002)	0.0100
circulatory system	Pulmonary heart disease, diseases of pulmonary circulation	1.767 (1.142−2.733)	0.0105
circulatory system	Ischemic stroke (large artery atherosclerosis)	1.405 (1.025−1.927)	0.0347
circulatory system	Coronary heart disease	1.350 (1.006−1.812)	0.0457
circulatory system	Myocardial infarction	1.235 (1.012−1.509)	0.0383
circulatory system	Varicose veins	1.215 (1.001−1.474)	0.0493
circulatory system	All−cause Heart Failure	1.140 (1.009−1.287)	0.0347
circulatory system	Conduction disorders	0.780 (0.609−0.997)	0.0473
circulatory system	AV−block	0.651 (0.467−0.908)	0.0115
digestive system	Personality disorders (more controls excluded)	1.428 (1.104−1.846)	0.0066
digestive system	Hernia	0.822 (0.706−0.957)	0.0117
digestive system	Gastroduodenal ulcer	0.762 (0.589−0.986)	0.0386
digestive system	Diverticular disease of intestine	0.758 (0.617−0.932)	0.0085
digestive system	Inguinal hernia	0.753 (0.638−0.888)	<0.001
digestive system	Duodenal ulcer	0.459 (0.278−0.760)	0.0025
digestive system	Oesophageal obstruction	0.387 (0.189−0.796)	0.0098
endocrine/metabolic	Hypothyroidism, strict autoimmune	1.161 (1.024−1.316)	0.0200
immune system	Type 1 diabetes	3.530 (1.067−11.674)	0.0388
immune system	Glaucoma (multi−trait analysis)	1.219 (1.070−1.389)	0.0029
immune system	Paget's disease	0.180 (0.070−0.461)	<0.001
neoplasms	Low malignant potential mucinous ovarian cancer	1.925 (1.116−3.320)	0.0185
neoplasms	ER+ Breast cancer (iCOGS)	1.721 (1.145−2.586)	0.0091
neoplasms	Breast cancer (iCOGS)	1.642 (1.161−2.323)	0.0050
neoplasms	"Malignant neoplasm of breast, HER−positive" (all cancers excluded)	1.371 (1.062−1.770)	0.0155
neoplasms	Malignant neoplasm of breast, HER−positive	1.364 (1.056−1.761)	0.0173
neoplasms	Oral and oropharyngeal cancer	0.999 (0.998−1.000)	0.0260
neoplasms	Malignant neoplasm of endocrine gland	0.607 (0.375−0.982)	0.0421
neuropsychiatric system	Emotionally unstable personality disorder	1.463 (1.057−2.025)	0.0217
neuropsychiatric system	Paternal history of Alzheimer's disease	1.172 (1.033−1.330)	0.0139
neuropsychiatric system	childhood absence epilepsy	1.026 (1.004−1.048)	0.0190
neuropsychiatric system	Internalizing problems	0.694 (0.487−0.988)	0.0428
neuropsychiatric system	Major depressive disorder	0.612 (0.392−0.954)	0.0301
neuropsychiatric system	Hyperkinetic disorders (more controls excluded)	0.558 (0.315−0.986)	0.0447
neuropsychiatric system	frontotemporal dementia (TDP subtype)	0.216 (0.056−0.835)	0.0263
respiratory	Percent emphysema	2.110 (1.186−3.755)	0.0111