Symptoms, physical measures and cognitive tests after SARS-CoV-2 infection in a large population-based case-control study

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Abstract

Persistent symptoms are common after SARS-CoV-2 infection but the correlation with objective measures is unclear. We utilized the deCODE Health Study to compare multiple symptoms and physical measures between 1,721 Icelanders with prior SARS-CoV-2 infection (cases) and 546 contemporary and 13,842 historical controls. Cases participated in the study five to 17 months after the acute infection. One percent reported still suffering severe symptoms more than a year after the infection. 46 of the 88 symptoms explored associated with prior infection, most significantly disturbed smell and taste, memory disturbance, and dyspnea. On the contrary, only a handful of objective measures associated with prior infection. Cases were more likely to have measured impairment in smell and taste, lower grip strength, and poorer immediate and delayed memory recall than controls. No other objective measure associated with prior infection including heart rate, blood pressure, postural orthostatic tachycardia, oxygen saturation, exercise tolerance, hearing, and traditional inflammatory, cardiac, liver and kidney blood biomarkers. There was no evidence of more anxiety or depression among cases. We estimated the prevalence of long Covid to be 7–8%. Thus, in our large case-control study of mostly non-hospitalized Icelanders, diverse symptoms were common after SARS-CoV-2 infection while objective differences between cases and controls were few and, except for smell and taste, small. Discrepancies between symptoms and objective measures suggest a more complicated biological or biopsychosocial contribution to symptoms related to prior infection than is captured by conventional tests. Traditional clinical assessment would thus not be expected to be particularly informative in relating symptoms to a past SARS-CoV-2 infection.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that causes coronavirus disease 2019 (Covid-19), emerged in December 2019.[1] As of March 2022, the pandemic has resulted in 480 million confirmed cases worldwide[2] while the true number of infected persons is likely much higher.[3]

Covid-19 is an acute respiratory infection with potential for widespread extrapulmonary complications.[4,5] Several studies on the sequelae of severe Covid-19 in hospitalized patients found persistent symptoms and multiorgan abnormalities,[6–8] but good physical and functional recovery has also been reported.[9] Less is known about the longer-term effect of SARS-CoV-2 infection on physical and mental health in those with milder disease, the majority of infected persons. Protracted post-infection symptoms (long Covid),[10] including fatigue, dyspnea and brain fog have been described, with prevalence estimates ranging from 3.0–52%[11–13] in non-hospitalized cohorts. However, comprehensive comparison of post-Covid symptoms and objective measures in non-hospitalized persons is lacking.

To investigate health outcomes after SARS-CoV-2 infection, we invited Icelanders with (cases) and without (contemporary controls) prior infection[14] to participate in a modified deCODE Health Study (dHS),[15] a prospective cohort study including both questionnaires on symptoms and comprehensive physiological, cognitive and blood testing, between September 2020 and September 2021, verifying infections with PCR tests[14] and SARS-CoV-2 antibodies.[16] Cases participated in the study five to 17 months after the acute infection. In addition to contemporary controls, our study includes a large control dataset of persons that participated in the dHS prior to the pandemic (historical controls), facilitating assessment of time effects, importantly the pandemic itself, on measures. Furthermore, a subset of cases participated twice in the dHS, before and after the infection, allowing for assessment of longitudinal measures. Similar longitudinal measures were available for a subset of controls. Our study is mostly of non-hospitalized persons as only 5% of cases required hospitalization during the acute infection.

Results

Study design and study participants

We invited 3,602 Icelanders who had contracted SARS-CoV-2 to participate in the dHS Covid Study and 1,721 (48%) persons participated between September 2020 and September 2021 (Fig. 1). Demographics and comorbidities were similar among those who participated and those who did not (Table S1). The average age of the 1,721 Covid cases was 46 years (range: 18–93) and 51% were women. The most common comorbidities were obesity (33%), hypertension (18%), asthma (11%) and immunocompromised state (10%) (Table 1). We compared cases to 14,388 controls, comprised of 13,842 historic and 546 contemporary study participants. The average age of the controls was 56 years (range: 18–97), 57% were women, and hypertension and immunocompromised state were more common among controls than cases (Table 1).

The study design is shown in Fig. 1, including the definition of contemporary and historical controls and the data used in assessment of longitudinal measures for a subset of cases and controls. Overview of data collection is presented in Fig. 2.

The severity of the acute SARS-CoV-2 infection ranged from no to mild symptoms (40%) to severe illness requiring hospitalization (5%) (Table S2). Persons of older age and women were at higher risk of more severe acute infection as were those with obesity, asthma and several other medical conditions that have previously been associated with severity[17] (Table S1, Supplementary Methods). Levels of antibodies against SARS-CoV-2 measured at the time of study visit correlated with the severity of the acute infection (Figure S1). The duration from the diagnostic qPCR test to study visit ranged from five to 17 months (median = 273, range = 157–539 days) (Figure S2).

To establish association of symptoms and test measures with prior SARS-CoV-2 infection, we compared cases with all available controls and accounted for multiple testing, arriving at $P < 0.05/96 = 5 \times 10^{-4}$ for health and symptom questionnaire data, $P < 0.05/87 = 6 \times 10^{-4}$ for physiological and cognitive test results, and $P < 0.05/63 = 8 \times 10^{-4}$ for blood tests. To take into account possible confounding of time in the effect estimates for SARS-CoV-2 status, e.g., via simultaneous pandemic effects, we required consistent results (same direction and non-heterogeneity in effect estimates) when the analysis was restricted to contemporary controls or same direction in the effect estimates in the comparison of longitudinal measures between cases and controls (Fig. 1).

Self-reported data

At five to six months after infection, 33% of cases reported not having recovered from the acute illness and 5% still had severe symptoms. These fractions decreased to 21% and 1%, respectively, 13 months after infection. One in four of all cases had sought medical attention for residual symptoms.

All 1,721 cases and 546 contemporary controls answered a questionnaire (the C19Q) assessing symptoms during the four weeks prior to study visit. In addition, an online version of the C19Q was sent to a subset of the historic controls, 2,000 persons, age and sex matched to the cases, and 737 responded between September 2020 and September 2021, resulting in a control group of 1283 persons for the C19Q symptom data. Symptoms were more frequent among cases, at 5 to 17 months after the acute infection, with 46 out of 88 symptoms (52%) associating with history of SARS-CoV-2 infection ($P < 5 \times 10^{-4}$, Fig. 3, Table S3).

The symptoms associating most significantly with history of SARS-CoV-2 infection were disturbed smell and taste, memory disturbance, and dyspnea. Cases reported disturbed smell and taste 11 and nine times more frequently than controls, respectively, and memory disturbance and dyspnea 3.5 times more commonly (Fig. 3, Table S3). While disturbed smell and taste were rather rare symptoms in the general population, with a prevalence of 4% and 3% among controls, respectively, memory disturbance and dyspnea were common, with a prevalence among controls of 23% and 22%, respectively (Fig. 3, Table S3). The prevalence of seven symptoms changed with time from the acute infection ($P < 0.05$); smell, taste and fatigue improving but others including malaise after physical exertion worsening (Table S3).

We noted a large cluster of correlated symptoms including dyspnea, fatigue, weakness, malaise after physical exertion, memory disturbance, and lack of concentration (r: 0.38–0.68, Figure S3). Impaired or disturbed smell and taste correlated highly with each other (r = 0.79) and considerably less with other symptoms (r < 0.27), but highest with memory disturbance (r = 0.23 and 0.26, respectively).

Our evaluation of mental health and quality of life with validated questionnaires (Fig. 2) showed less symptoms of stress (PSS[18]) among cases than controls ($P < 5 \times 10^{-4}$) and longitudinal measures demonstrated less symptoms of stress among cases during the pandemic than before it (Table 2, Table S4). We did not find differences between cases and controls for symptoms of anxiety (GAD-7[19]), health anxiety (SHAI[20]), depression (PHQ-7[21]), fatigue (SIQR[22]), satisfaction of life (SWLS[23]) or health-related quality of life (36-SF[24]) in these data (Table S4).

Physiological tests

The physiological test traits that associated with prior SARS-CoV-2 infection, accounting for multiple testing ($P < 6 \times 10^{-4}$), were smell, taste and grip strength (Table 2, Table S5).

Several test measures reflecting disturbed smell and taste were more common among cases than controls, including partial anosmia, hyposmia and partial ageusia (Table 2). Cases performed worse in odor identification and reported lower pleasantness ratings for most odors than controls, with the intensity rating of lemon odor being most different (Table S5). Comparison of longitudinal smell test results for 126 cases showed worse results after infection for many smell measures, confirming the effect of the infection (Table 2, Table S6). Several measures of smell improved with time from the acute infection such as hyposmia which was equally common among cases and controls nine months after infection (Table S5). We did not see temporal improvements of partial anosmia or partial ageusia among cases.

Cases had less grip strength than all controls (-0.74 kg, 95% CI: -1.14 to -0.35, Table 2) with consistent results when cases were compared to the smaller contemporary control group.

No other physiological test measures associated with prior SARS-CoV-2 infection accounting for age, sex and multiple testing, including body mass index (BMI), oxygen saturation, blood pressure, heart rate, heart rate variability, orthostatic hypotension, postural orthostatic tachycardia, exercise capacity, hearing, and spirometry (Table S5, Fig. 2, Supplementary Methods).

Cognitive tests

We compared 12 measures from six cognitive tests (Fig. 2) between cases and controls, using contemporary and historical control data for all tests except the Wechsler Memory Scale (WMS) Logical Memory tests for which only contemporary control data existed (Table S7). Cases performed worse than controls on the WMS Logical Memory tests of both delayed memory recall (-0.25 standard deviations (SD), 95% CI: -0.35 to -0.14)) and immediate memory recall (-0.20 SD, 95% CI: -0.30 to -0.10)) accounting for multiple testing ($P < 6 \times 10^{-4}$, Table 2, Table S7).

We calculated the prevalence of memory impairment, defined as z-score of less than or equal to -1.5, among cases and controls, adjusting for age, gender and educational level.[25] The prevalence of impairment in delayed memory recall was 13.4% for cases and 7.5% for controls (OR = 1.91, 95% CI, 1.54 to 2.29, $P = 3.6 \times 10^{-4}$) and the prevalence of impairment in immediate memory recall was 11.6% for cases and 9.4% for controls, respectively (OR = 1.27, 95% CI, 0.92 to 1.62, $P = 0.17$). Restricting the analysis to cases with symptoms of memory disturbance at least five times per week yielded a prevalence of impairment of 18.1% for delayed recall and 16.0% for immediate recall.

Blood test results

We compared multiple blood tests between cases and controls and none associated with prior infection, including C-reactive protein, white blood cell count, and conventional cardiac, kidney, liver and thyroid function tests, accounting for multiple testing ($P < 8 \times 10^{-4}$, Table S8).

Association of symptoms and test measures with severity of the acute infection

We tested for association of measures with severity of the acute infection and required $P < 0.05$ to establish association for measures that associated here with prior infection. If association with prior infection had not been demonstrated, we required the same multiple testing thresholds as listed above to establish association with severity of the acute infection.

All but one SARS-CoV-2 associating symptom correlated also with severity of the acute infection ($P < 0.05$) with malaise after physical exertion, dyspnea and correlating symptoms associating most significantly (Table S3). Impaired smell and taste associated considerably less significantly with severity of the acute infection. Similarly, more stress (PSS, $P < 0.05$), anxiety (GAD-7), health anxiety (SHAI), depression (PHQ-7), and fatigue (SIQR), as well as less satisfaction of life (SWLS) and poorer health-related quality of life (36-SF) associated with more severe acute illness ($P < 5 \times 10^{-4}$, Table S4).

The three physiological test measures that associated with prior infection, impaired smell and taste, and lower grip strength, associated also with more severe acute illness ($P < 0.05$). Other measures associating with severity were higher fat mass index (FMI), BMI and lean mass index, and lower risk of postural orthostatic tachycardia ($P < 6 \times 10^{-4}$). The WMS Logical Memory tests of immediate and delayed recall did not associate with severity ($P > 0.05$).

Lower HDL-cholesterol and Apolipoprotein A and higher triglyceride levels associated with more severe acute infection ($P < 8 \times 10^{-4}$).

Long Covid symptom cluster

The term long Covid has been used to describe symptoms that develop during or following SARS-CoV-2 infection and last for more than four weeks per the National Institute for Health and Care Excellence guidelines[26] or two months with an impact on daily function according to the World Health Organization (WHO) definition.[27] We assigned long Covid to cases who reported fatigue, lack of concentration, memory disturbance, dyspnea or weakness, five or more days per week, or malaise after physical exertion, chest pain, or tachycardia three or more days per week, in the four weeks prior to study visit, assessed with the C19Q, five to 17 months after infection. For comparison, we assessed how many of the controls fulfilled the same criteria.

30% of cases (29% of non-hospitalized cases) and 15% of controls met our long Covid symptom criteria. Cases were 2.5 (95% CI, 2.1 to 3.1) times more likely to fulfill the criteria than controls. Adjustment for comorbidities increased the odds ratio to 3.2 (95% CI, 2.6 to 4.0). 54% of cases fulfilling the criteria had to reduce their regular hours for work, school, household or other, due to persistent symptoms or complications from their SARS-CoV-2 infection, compared to 23% overall. This translates to a long Covid prevalence of 7–8% according to the WHO case definition.[27] Women were more likely to satisfy the long Covid criteria and other associating factors were more severe acute infection and several medical conditions including heart failure, immunocompromised state and coronary artery disease, but not age or time from the infection (Table 1 and S1).

We explored the effect of the long Covid symptom criteria on physiological, cognitive and blood traits in cases and controls separately (Table S9). We found that among both cases and controls the criteria associated most significantly with lower exercise capacity measured by lower oxygen consumption (VO2) at maximal exertion in a cardiopulmonary exercise test, higher BMI and FMI, and with impaired smell and taste among cases.

Discussion

We performed a detailed assessment of 1,721 persons with history of SARS-CoV-2 five to 17 months after the verified acute infection and compared to 14,388 controls. A wide variety of symptoms associated with prior infection and for objective measures associations were observed for smell, taste, grip strength, and memory recall.

Our case population represents the severity spectrum of the acute SARS-CoV-2 infection, ranging from no symptoms to severe illness with 5% hospitalized in the acute phase.[2,26,28] It follows that our study population consists mainly of persons who did not require hospitalization during the acute illness. The comorbidities that predisposed to severe acute infection in our sample were the same as others have reported[17], suggesting that our sample is representative of those infected with SARS-CoV-2. Based on self-report, one fifth had not recovered and 1% still suffered severe symptoms 13 months after the infection.

Deficits in smell and taste are common symptoms of the acute SARS-CoV-2 infection[29] and reports suggest full recovery in most at six months.[30,31] We found both subjective and objective measures of smell and taste impairment to be more common among cases than controls in our study, with slow temporal improvement of symptoms. Some tests of smell and taste improved with time, with hyposmia normalizing at nine to 10 months after infection, but partial anosmia and partial ageusia did not improve.

Sensorineural hearing loss is a recognised complication of viral infections and there are multiple reports on hearing loss in persons with history of SARS-CoV-2, with most studies based on self-reported questionnaires or medical reports without conclusive hearing tests.[32] Here, cases noted worsening of hearing from before the pandemic four times more often than controls, with half of them linking the noted change to the infection. However, objective hearing measures did not associate with history of SARS-CoV-2. Thus, we do not have objective evidence of SARS-CoV-2 causing hearing loss among our mostly non-hospitalized patients.

We observed lower grip strength in persons with prior SARS-CoV-2 infection, likely due to deconditioning. Grip strength, a measure of muscle strength, is a strong predictor of cardiovascular disease and mortality,[33] and indeed incident cardiovascular outcomes appear to be more common in survivors of acute Covid-19 than controls.[34] It should be noted that although significant, the difference in grip strength between cases and controls was small. We did not observe association between prior infection and exercise capacity as measured by a cardiopulmonary exercise test.

It has been suggested that chronic myocardial inflammation is a common complication of SARS-CoV-2 infection, irrespective of both pre-existing conditions and severity of the acute infection.[35–37] One case-control study, assessing 443 individuals after SARS-CoV-2 infection, reported a small reduction in left ventricular ejection fraction and higher concentration of hs-TNT and NTproBNP after infection compared to controls.[37] Complicating the interpretation of that

study is the lack of contemporary controls, as the control data were derived from persons assessed prior to the pandemic, precluding exploration of time trends in measures as well as any effect of the pandemic itself. The lack of association of the cardiac biomarkers hs-TNT and NT-proBNP with history of SARS-CoV-2 infection in our study of 1721 cases, argues against a persistent myocardial involvement. Similarly, we found no evidence of persistent systemic inflammation, hematologic abnormalities, kidney or liver dysfunction using conventional blood biomarkers.

We performed extensive cognitive testing and observed that poorer delayed and immediate memory recall associated with history of SARS-CoV-2 infection, but the associating effects were small. We calculated the prevalence of impairment in delayed memory recall as 13.4% for cases and 7.5% for controls providing an objective measure of the memory disturbance commonly reported after infection. The prevalence of memory recall impairment in our study is comparable to the 12% reported by Becker et al[25] for non-hospitalized persons. However, we did not find significant differences between cases and controls in other cognitive tests, unlike Becker and colleagues who reported high prevalence of cognitive impairment of many domains in the smaller study of 740 persons evaluated after Covid-19 in a clinical setting.

The protracted symptoms of fatigue and neurocognitive disturbance after SARS-CoV-2 infection are reminiscent of other post-infective fatigue syndromes and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).[38–40] The subjective cognitive impairments that are some of the more debilitating symptoms of ME/CFS[41] have been captured by objective measures[42] but discrepancies between symptoms and test results are common, possibly due to inability of cognitive tests to capture mild impairment and deficits affecting real-life tasks.[43] The WMS Logical Memory test may be a relatively sensitive measure to detect cognitive deficits following SARS-CoV-2 infection, as it has previously been used to detect subtle changes in memory.[44] Furthermore, the pathogenesis of these symptoms are unclear. A study leveraging longitudinal brain imaging data from the UK Biobank reported changes in brain structure associated with prior infection with SARS-CoV-2 but changes in areas related to memory did not associate with cognitive tests results.[45] It is also notable that while symptoms of neurocognitive disturbance associate with severity of the acute infection in our study, measured deficits in memory recall do not.

Higher BMI, higher triglycerides and lower HDL-C levels associated with severity of the acute infection but not with prior SARS-CoV-2 infection per se. These are all risk factors of more severe acute infection,[46] and thus the observed association can be assumed to reflect the predisposition, rather than being a consequence of more severe infection. The causal relationship between the association of increasing levels of anxiety and depression with more severe infection, seen by us and previously described by others,[37] in light of the lack of association of these phenotypes with prior infection, is less clear.

The high prevalence of symptoms among cases compared to controls contrasts notably with the small difference observed in test measures between the two groups, as well as with discrepancies between some symptoms and related test measures. For example, tachycardia was a prominent symptom after infection but there was no significant difference in measured heart rate between the two groups. Cases more often than controls reported having gained weight since before the pandemic, but there was no difference in BMI between cases and controls or in longitudinal measures for cases. Similar observations for hearing are described above. Measured memory impairment was 1.91-fold more common in cases than controls while self-reported memory disturbance was described 3.5-fold more commonly by the cases. These observations support an element of response bias[47] in self-reported symptoms following SARS-CoV-2 infection and a more complicated biological or biopsychosocial contribution to the persistent symptoms[48] that are not well captured by conventional tests. These are important considerations for both research and clinical assessment of post-Covid conditions. Conventional clinical assessment would thus not be expected to be particularly informative in relating reported symptoms to a past SARS-CoV-2 infection.

Our attempt to estimate the prevalence of long Covid highlights not only how common the symptoms of long Covid are in the general population but also the importance of control data for comparison. The excess of cases meeting our criteria for long Covid was 15% with half of those reporting impact on everyday function, translating to a long Covid prevalence of 7–8%. These estimates do not account for potential biases in self-reported symptoms.

This study has limitations. First, although half of Icelanders diagnosed with SARS-CoV-2 infection before February 2021 participated in the study, participation bias cannot be excluded and it is plausible that cases with more pronounced symptoms were more likely to participate, although demographics and comorbidities were similar among those who participated and those who did not. Second, while the study represents adults of all ages, it does not include children. Third, while the availability of measures before and after the infection with similar longitudinal measures for controls is a particular strength of the study, this sample set was relatively small.

We believe that the inclusion of both historic and contemporary controls is a major strength of our study, allowing for consideration of possible time effects, i.e., general consequences of the pandemic itself (social isolation, reduced mobility) in addition to direct effects of the SARS-CoV-2 infection (viral invasion, resulting illness).

In conclusion, in our comprehensive case-control study of mostly non-hospitalized Icelanders, multiple and diverse symptoms were more common among cases than controls five to 17 months after SARS-CoV-2 infection while objective differences between cases and controls were few. Cases performed worse than controls in tests of smell and taste with improvement in some of these measures over time. Cases also performed worse in tests of grip strength and immediate and delayed memory recall, but differences between cases and controls were small. We show that many symptoms associated with prior SARS-CoV-2 infection are common in the general population and, accounting for that, estimate the prevalence of long Covid to be 7–8%. Discrepancies between symptoms and objective measures suggest an element of response bias in self-reported symptoms and a more complicated biological or biopsychosocial contribution to symptoms related to prior infection than is captured by conventional tests.

Online Methods

Ethical consideration

Written informed consent was obtained from all participants, in accordance with the Declaration of Helsinki, and the study was approved by the National Bioethics Committee (VSNb2015120006/03.01 with amendments). Personal identifiers were encrypted by a third-party system overseen by the Icelandic Data Protection Authority.[49]

Study design and participants

The dHS[15] is an ongoing prospective cohort study in Iceland with extensive phenotypic and genotypic information produced and collected from the participants. More than 16,000 individuals participated in the study between its initiation in June 2016 to September 2021, aged between 18 and 97 years at recruitment. Participation in the study includes questionnaires about health and lifestyle, multiple physiological, cognitive and blood tests, and authorization to access health-related information from registries and medical records. The dHS was paused in March 2020 due to the pandemic. To study the health consequences of SARS-CoV-2 infection, a modified dHS, termed the dHS Covid Study, was launched in September 2020. Added measures in the dHS Covid Study included the C19Q questionnaire on symptoms during the previous four weeks, designed by us. We also added these questionnaires to assess symptoms of anxiety, depression, stress, health anxiety, and fatigue: General Anxiety Disorder-7 (GAD-7[19]), Patient Health Questionnaire-9 (PHQ-9[21]), Perceived Stress Scale (PSS[18]), Short Health Anxiety Inventory (SHAI[20]), and Symptom Impact Questionnaire (SIQR[22]), respectively, as well as the the Satisfaction With Life Scale (SWLS[23]) and 36-Item Short Form Survey (36-SF[24]) to assess health-related quality of life. We added tests of taste and orthostatic intolerance and made other changes described in Supplementary Methods.

We invited 3,602 persons over 18 years of age with history of SARS-CoV-2 infection to participate in the dHS Covid Study. These were Icelanders who in September 2020 or February 2021 were known to have been infected at least five months prior. History of infection was confirmed with the presence of antibodies.[16] 1,721 of the 3,602 persons, hereafter termed cases, participated in the study between September 2020 and September 2021 (Fig. 1). Of the 1,721 cases, 129 persons had also participated in the dHS before the pandemic, allowing for comparison of within-individual measures from before and after the infection (longitudinal measures). The majority of those infected (96%) had either been identified through targeted qPCR testing aimed at those at high risk for infection (mainly those who were symptomatic, had recently traveled to high-risk countries, or had contact with infected persons), or through population screening.[14] Others (4%) were identified later through antibody testing.[16] The study control group is comprised of 14,388 persons, 13,842 who participated in the dHS before the pandemic, between June 2016 and March 2020 (historic controls) and 546 persons without history of SARS-CoV-2 infection who participated in the dHS Covid Study between September 2020 and September 2021 (contemporary controls). Included in both numbers are 280 controls that participated twice in the dHS, before and during the pandemic.

In addition to being administered to all participants in the dHS Covid Study (1,721 cases and 546 contemporary controls), an online version of the C19Q, assessing symptoms in the previous four weeks, was sent to a subset of the historic controls, 2,000 persons, age and sex matched to the cases, and 737 have responded, resulting in a C19Q control group of 1283 persons.

For the GAD-7, PHQ-9, PSS, SWLS and 36-SF questionnaires, we obtained additional data from the Icelandic iStopMM study[50] for up to 239 cases and 20,142 contemporary controls for longitudinal assessment and for up to 34,561 other controls. In comparison of cases vs. all available controls for questionnaire scales, the data was restricted to individuals over 45 in accordance with the age distribution in the iStopMM data.

In this study we report the relationship between history of SARS-CoV-2 infection and results from the following measures and tests: a) health and symptom questionnaires including C19Q, GAD-7, PHQ-9, PSS, SHAI, SIQR, SWLS and 36-SF; b) physiological measurements of height, weight, body mass index (BMI), blood pressure, heart rate, oxygen saturation, body composition by whole-body dual-energy X-ray absorptiometry (DXA) scan, grip strength, smell test, taste test, hearing test, spirometry, cardiopulmonary exercise test, ambulatory sleep test; c) cognitive tests: Digit Coding,[51] Letter and Category fluency[52], Logical Memory,[52,53] Spatial Working Memory,[52,54] Trail Making Tests,[52,55] and Wechsler Abbreviated Scale of Intelligence,[56,57] and d) blood tests. The test procedures are described in Supplementary Methods.

Severity of the acute SARS-CoV-2 infection

All persons diagnosed with SARS-CoV-2 infection by qPCR in Iceland were monitored by the telehealth monitoring service (TMS)[58] of the Covid-19 outpatient clinic at Landspitali – the National University Hospital (LUH) in Reykjavik, Iceland. We assigned the cases to four categories by the severity of the acute infection. We based our severity classification on intensity of treatment at the LUH, severity classification by the TMS, and self-assessment of symptoms in our study (Table S2, Supplementary Methods).

Long Covid symptom cluster

The term long Covid has been used to describe symptoms that develop during or following SARS-CoV-2 infection and last for more than four weeks per the National Institute for Health and Care Excellence guidelines[26] or two months with an impact on daily function according to the World Health Organization (WHO) definition.[27] We assigned long Covid to cases who reported at least one of the following symptoms for five or more days per week: fatigue, lack of concentration, memory disturbance, dyspnea or weakness, or at least one of the following for three or more days per week: malaise after physical exertion, chest pain, tachycardia in the four weeks prior to study visit, assessed with the C19Q, five to 17 months after infection. For comparison, we assessed how many of the controls fulfilled the same criteria.

Statistical analysis

We tested all measures for association with SARS-CoV-2 infection adjusting for age and sex. Adjustment for comorbidities (BMI, hypertension, asthma, type 2 diabetes, cancer and coronary artery disease) had minimal effect on associations and thus we report unadjusted results but show both in Supplementary tables. We applied two complimentary study designs, allowing for mindful consideration of the trade-off between statistical power vs. screening for

confounding effects when testing for association of SARS-CoV-2 and the numerous health-related traits. A) We compared outcome measures of cases and all available control data. To account for time effects in (A), we tested for difference in measures between i) cases and contemporary controls (restricting data to measures during the pandemic) and between ii) contemporary and historic controls where divergence from a null finding could indicate a time effect in A). We further plotted the data on physiological and blood traits against time of measure to explore for batch effects. We observed batch effects for the hearing test, oxygen saturation, grip strength and blood tests and for those traits measured data for controls was restricted to using more recent measures for historical controls (measures after 2017 for grip strength and after 2019 for hearing) or using only contemporary controls (oxygen saturation and blood tests, Figure S4, Supplementary Methods). B) We exploited a subset of the data that allows for a controlled before-and-after study, i.e., longitudinal measures for the same individuals collected before and during the pandemic (before and after infection for cases, with similar time duration between repeat measures for controls) providing the added benefit of accounting simultaneously for time effect and time-invariant individual heterogeneity, while acknowledging reduced power.

To establish association with SARS-CoV-2 infection, we required 1) association when comparing cases with all available controls using the following thresholds accounting for multiple testing: $P = 0.05/96 = 5 \times 10^{-4}$ for health and symptom questionnaire data, $P = 0.05/87 = 6 \times 10^{-4}$ for physiological measures and cognitive tests, and $P = 0.05/63 = 8 \times 10^{-4}$ for blood tests, AND 2) at least one of the following, as statistical power varies across measures: i) consistent association results (same direction and non-heterogeneity in the effect estimates) with 1) when comparing cases with contemporary controls, ii) consistent association results with 1) when comparing the subset of cases to the subset of controls with longitudinal measures. For symptoms and objective measures that associated with prior SARS-CoV-2 infection we required a $P < 0.05$ to establish a correlation with time from infection and severity of the infection. For measures that did not associate with prior SARS-CoV-2 infection per se, we required the same multiple testing thresholds as listed above to establish association with severity of the infection. We used multiple linear or logistic regression for association testing. Analyses were performed in R, version 3.6.0.

Patient and public involvement

No patients or members of the public were involved in the conceptualization or design of this study nor in the interpretation of the results.

Declarations

Contributions

H.H., E.V.I., Th.O., P.S., U.Th., D.F.G. and K.S. conceived and designed the study and take responsibility for the integrity of the data and the accuracy of the data analysis. D.L., H.S., G.Th., M.A., I.H., Th.G., Thorsteinn.G., K.S., S.S., T.H.K., E.S., K.E.S., E.E.G, R.Th., M.O.U., R.G. and B.E. participated in planning and designing individual parts of the study. A.K., A.A., G.N., Kristbjorg.B., K.G. and S.G. performed antibody experiments. Br.Th., J.S., Kolbrun.B. and S.K. contributed to sample handling and blood measurements. I.O., E.L.S., D.O.A. and Thorarinn.G. collected data on comorbidities. Bj.Th., E.A.T. and G.M. contributed to data preparation and handling. Thorunn.O., G.B., A.H., V.S., I.J., G.S., J.G., S.S.J. and V.T. prepared and refined phenotypic data. E.V.I., Thorhildur.O., K.N., G.J., U.U., E.E., G.E. and B.J. performed the analysis. M.K., M.G., E.E., D.H., H.L.R., M.I.S., R.F.I. and R.P. collected phenotype information on the acute infection. S.Y.K and Th.J.L. contributed phenotypic data from the iStopMM study. H.H., E.V.I. and Th.O. drafted the manuscript. All authors had full access to all of the data in the study. All authors critically revised the manuscript for important intellectual content and accept responsibility for the version submitted for publication. H.H., E.V.I., Th.O. and D.G. verified the underlying data.

Declaration of interests

A.H., A.K., A.A., B.J., B.E., Bj.Th., Br.Th., D.F.G., D.O.A., E.E.G., E.A.T., E.V.I, G.E., G.S., G.M., G.N., G.T., G.J., G.B., H.H., H.S., I.J., J.S., J.G., K.S., Kolbrun.B., Kristbjorg.B., K.G., K.E.S., K.S., K.N., M.O.U., M.A., P.S., R.G., R.T., S.S.J., S.G., S.K., S.S., T.H.K., Thorhildur.O., Thorsteinn.G., Thorunn.O., Th.R., U.Th., U.U., V.S. and V.T.are employees of deCODE genetics / Amgen Inc. There are no other conflicts of interest.

Role of the funding source

deCODE genetics / Amgen Inc. funded the study. Employees of deCODE genetics / Amgen Inc. conducted the study.

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Data sharing

Individual participant data from the deCODE Health Study will not be made available to others. The study protocol and statistical analysis plan are described in this paper and more detailed information is available on request.

Transparency declaration

The lead authors, Kari Stefansson and Hilma Holm, affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

References

1. Huang, C. *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet Lond. Engl.* **395**, 497–506 (2020).
2. *Coronavirus disease (COVID-19) pandemic. Geneva: World Health Organization* (https://www.who.int/emergencies/diseases/novel-coronavirus-2019).
3. Estimated COVID-19 Burden. https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/burden.html.
4. Gupta, A. *et al.* Extrapulmonary manifestations of COVID-19. *Nat. Med.* **26**, 1017–1032 (2020).
5. Ellul, M. A. *et al.* Neurological associations of COVID-19. *Lancet Neurol.* **19**, 767–783 (2020).
6. Zhao, Y.-M. *et al.* Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. *EClinicalMedicine* **25**, 100463 (2020).
7. Huang, C. *et al.* 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet Lond. Engl.* **397**, 220–232 (2021).
8. Xiong, Q. *et al.* Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study. *Clin. Microbiol. Infect. Off. Publ. Eur. Soc. Clin. Microbiol. Infect. Dis.* **27**, 89–95 (2021).
9. Huang, L. *et al.* 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. *Lancet Lond. Engl.* **398**, 747–758 (2021).
10. Post-COVID Conditions (https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html).
11. Technical article: Updated estimates of the prevalence of post-acute symptoms among people with coronavirus (COVID-19) in the UK: 26 April 2020 to 1 August 2021. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/articles/technicalarticleupdatedestimatesofthepre .
12. Logue, J. K. *et al.* Sequelae in Adults at 6 Months After COVID-19 Infection. *JAMA Netw. Open* **4**, e210830 (2021).
13. Blomberg, B. *et al.* Long COVID in a prospective cohort of home-isolated patients. *Nat. Med.* **27**, 1607–1613 (2021).
14. Gudbjartsson, D. F. *et al.* Spread of SARS-CoV-2 in the Icelandic Population. *N. Engl. J. Med.* **382**, 2302–2315 (2020).
15. Ivarsdottir, E. V. *et al.* Sequence variation at ANAPC1 accounts for 24% of the variability in corneal endothelial cell density. *Nat. Commun.* **10**, 1284 (2019).
16. Gudbjartsson, D. F. *et al.* Humoral Immune Response to SARS-CoV-2 in Iceland. *N. Engl. J. Med.* **383**, 1724–1734 (2020).
17. *https*://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fneed-extra-precautions%2Fgroups-at-higher-risk.html.
18. Cohen, S., Kamarck, T. & Mermelstein, R. A global measure of perceived stress. *J. Health Soc. Behav.* **24**, 385–396 (1983).
19. Spitzer, R. L., Kroenke, K., Williams, J. B. W. & Löwe, B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch. Intern. Med.* **166**, 1092–1097 (2006).
20. Salkovskis, P. M., Rimes, K. A., Warwick, H. M. C. & Clark, D. M. The Health Anxiety Inventory: development and validation of scales for the measurement of health anxiety and hypochondriasis. *Psychol. Med.* **32**, 843–853 (2002).
21. Kroenke, K., Spitzer, R. L. & Williams, J. B. The PHQ-9: validity of a brief depression severity measure. *J. Gen. Intern. Med.* **16**, 606–613 (2001).
22. Bennett, R. M. *et al.* The Revised Fibromyalgia Impact Questionnaire (FIQR): validation and psychometric properties. *Arthritis Res. Ther.* **11**, R120 (2009).
23. Diener, E., Emmons, R. A., Larsen, R. J. & Griffin, S. The Satisfaction With Life Scale. *J. Pers. Assess.* **49**, 71–75 (1985).
24. Ware, J. E. & Sherbourne, C. D. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med. Care* **30**, 473–483 (1992).
25. Becker, J. H. *et al.* Assessment of Cognitive Function in Patients After COVID-19 Infection. *JAMA Netw. Open* **4**, e2130645 (2021).
26. *COVID-19 rapid guideline: managing the long-term effects of COVID-19. NICE guideline.* (https://www.nice.org.uk/guidance/ng188).
27. Post COVID-19 condition (Long COVID). https://www.who.int/srilanka/news/detail/16-10-2021-post-covid-19-condition.
28. Eythorsson, E. *et al.* Clinical spectrum of coronavirus disease 2019 in Iceland: population based cohort study. *BMJ* **371**, m4529 (2020).
29. von Bartheld, C. S., Hagen, M. M. & Butowt, R. Prevalence of Chemosensory Dysfunction in COVID-19 Patients: A Systematic Review and Meta-analysis Reveals Significant Ethnic Differences. *ACS Chem. Neurosci.* **11**, 2944–2961 (2020).
30. Lechien, J. R. *et al.* Prevalence and 6-month recovery of olfactory dysfunction: a multicentre study of 1363 COVID-19 patients. *J. Intern. Med.* (2021) doi:10.1111/joim.13209.
31. Jafar, A., Lasso, A., Shorr, R., Hutton, B. & Kilty, S. Olfactory recovery following infection with COVID-19: A systematic review. *PloS One* **16**, e0259321 (2021).
32. Almufarrij, I. & Munro, K. J. One year on: an updated systematic review of SARS-CoV-2, COVID-19 and audio-vestibular symptoms. *Int. J. Audiol.* 1–11 (2021) doi:10.1080/14992027.2021.1896793.
33. Leong, D. P. *et al.* Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. *Lancet Lond. Engl.* **386**, 266–273 (2015).
34. Xie, Y., Xu, E., Bowe, B. & Al-Aly, Z. Long-term cardiovascular outcomes of COVID-19. *Nat. Med.* **28**, 583–590 (2022).
35. Rajpal, S. *et al.* Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From COVID-19 Infection. *JAMA Cardiol.* **6**, 116–118 (2021).
36. Puntmann, V. O. *et al.* Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol.* **5**, 1265–1273 (2020).
37. Petersen, E. L. *et al.* Multi-organ assessment in mainly non-hospitalized individuals after SARS-CoV-2 infection: The Hamburg City Health Study COVID programme. *Eur. Heart J.* (2022) doi:10.1093/eurheartj/ehab914.

38. Komaroff, A. L. & Lipkin, W. I. Insights from myalgic encephalomyelitis/chronic fatigue syndrome may help unravel the pathogenesis of postacute COVID-19 syndrome. *Trends Mol. Med.* **27**, 895–906 (2021).
39. Mackay, A. A Paradigm for Post-Covid-19 Fatigue Syndrome Analogous to ME/CFS. *Front. Neurol.* **12**, 701419 (2021).
40. Hickie, I. *et al.* Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. *BMJ* **333**, 575 (2006).
41. Ocon, A. J. Caught in the thickness of brain fog: exploring the cognitive symptoms of Chronic Fatigue Syndrome. *Front. Physiol.* **4**, 63 (2013).
42. Cockshell, S. J. & Mathias, J. L. Cognitive functioning in chronic fatigue syndrome: a meta-analysis. *Psychol. Med.* **40**, 1253–1267 (2010).
43. Cvejic, E., Birch, R. C. & Vollmer-Conna, U. Cognitive Dysfunction in Chronic Fatigue Syndrome: a Review of Recent Evidence. *Curr. Rheumatol. Rep.* **18**, 24 (2016).
44. Ahn, Y. D. *et al.* Normative Data for the Logical Memory Subtest of the Wechsler Memory Scale-IV in Middle-Aged and Elderly Korean People. *Psychiatry Investig.* **17**, 1247 (2020).
45. Douaud, G. *et al.* SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *Nature* (2022) doi:10.1038/s41586-022-04569-5.
46. Scalsky, R. J. *et al.* Baseline cardiometabolic profiles and SARS-CoV-2 infection in the UK Biobank. *PloS One* **16**, e0248602 (2021).
47. Althubaiti, A. Information bias in health research: definition, pitfalls, and adjustment methods. *J. Multidiscip. Healthc.* **9**, 211–217 (2016).
48. Henningsen, P. *et al.* Persistent Physical Symptoms as Perceptual Dysregulation: A Neuropsychobehavioral Model and Its Clinical Implications. *Psychosom. Med.* **80**, 422–431 (2018).
49. Gulcher, J. R., Kristjánsson, K., Gudbjartsson, H. & Stefánsson, K. Protection of privacy by third-party encryption in genetic research in Iceland. *Eur. J. Hum. Genet. EJHG* **8**, 739–742 (2000).
50. Rögnvaldsson, S. *et al.* Iceland screens, treats, or prevents multiple myeloma (iStopMM): a population-based screening study for monoclonal gammopathy of undetermined significance and randomized controlled trial of follow-up strategies. *Blood Cancer J.* **11**, 94 (2021).
51. Ebaid, D., Crewther, S. G., MacCalman, K., Brown, A. & Crewther, D. P. Cognitive Processing Speed across the Lifespan: Beyond the Influence of Motor Speed. *Front. Aging Neurosci.* **9**, 62 (2017).
52. Stefansson, H. *et al.* CNVs conferring risk of autism or schizophrenia affect cognition in controls. *Nature* **505**, 361–366 (2014).
53. Morris, J. C. *et al.* The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology* **39**, 1159–1165 (1989).
54. Owen, A. M., Downes, J. J., Sahakian, B. J., Polkey, C. E. & Robbins, T. W. Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia* **28**, 1021–1034 (1990).
55. Reitan, R. M. Validity of the trail making test as an indicator of organic brain damage. 271–276 (1958).
56. Wechsler. *Wechsler Abbreviated Scale of Intelligence (WASI) Manual. Psychological Corporation.* (1999).
57. Gudmundsson, E. Mat á greind fullorðinna: WASI-IS [The Assessment of Intelligence in Adults: WASI-IS]. *Menntamalastofnun* (2015).
58. Helgason, D. *et al.* Beating the odds with systematic individualized care: Nationwide prospective follow-up of all patients with COVID-19 in Iceland. *J. Intern. Med.* **289**, 255–258 (2021).

Tables

Table 1. Comparing sex, age and comorbidities between cases, controls, and cases with long Covid. Shown are associations of history of SARS-CoV-2 infection with sex, age, and comorbidities using three different control groups; all controls, contemporary controls and controls answering the C19Q symptom questionnaire. Sex, age, time since diagnosis of SARS-CoV-2 and comorbidities were also compared between cases with long Covid and other SARS-CoV-2 cases. Association testing for sex was performed with logistic regression. For age and time since diagnosis the association testing was performed with linear regression. Association testing for comorbidities was performed with logistic regression, adjusting for age and sex. Effects for sex and comorbidities are given in odds ratios and 95% confidence intervals (CI) are given for all effects. Associations marked with * have P-value < 0.05 and associations marked with ** have P-value < 0.001.

	SARS-CoV-2 cases participating in study	Long SARS-CoV-2	All controls	Contemporary controls	C19Qcontrols	SARS-CoV-2 cases (1) vs all controls (0)	SARS-CoV-2 cases (1) vs contemporary controls (0)	SARS-CoV-2 cases (1) vs C19Qcontrols (0)	SARS-CoV-2 cases with long Covid (1) vs other SARS-CoV-2 cases (0)
						Effect (95% CI)	Effect (95% CI)	Effect (95% CI)	Effect (95% CI)
N all	1721	503	14388	546	1283				
Sex, N women	879 (51%)	336 (67%)	8102 (57%)	269 (49%)	706 (55%)	0.80 (0.73 to 0.89)**	1.07 (0.89 to 1.3)	0.85 (0.74 to 0.99)*	2.48 (1.99 to 3.08)**
Age, mean (range)	45.6 (18-93)	46.6 (18-88)	55.5 (18-97)	47.6 (19-89)	47.5 (18-88)	-10.0 (-10.7 to -9.2)**	-2.0 (-3.4 to -0.6)*	-2.0 (-3.0 to -0.9)**	1.3 (-0.3 to 2.9)
Time since diagnosis, mean (range)	273 (157-539)	268 (165-530)							-6.7 (-13.7 to 0.2)
Comorbidities									
Obesity	561 (33%)	217 (43%)	4886 (34%)	170 (31%)	427 (33%)	1.08 (0.96 to 1.20)	1.14 (0.92 to 1.4)	1.03 (0.88 to 1.21)	1.83 (1.46 to 2.30)**
Hypertension	293 (18%)	101 (21%)	5188 (36%)	118 (23%)	292 (23%)	0.68 (0.59 to 0.79)**	0.77 (0.59 to 1.01)	0.72 (0.58 to 0.88)*	1.31 (0.96 to 1.78)
Asthma	179 (11%)	81 (17%)	1986 (14%)	75 (14%)	182 (14%)	0.83 (0.71 to 0.98)*	0.74 (0.55 to 0.99)*	0.76 (0.61 to 0.95)*	2.03 (1.47 to 2.81)**
Immunocompromised state	99 (10%)	55 (17%)	2433 (17%)	46 (12%)	159 (14%)	0.69 (0.56 to 0.86)**	0.79 (0.54 to 1.15)	0.67 (0.51 to 0.87)*	3.01 (1.93 to 4.68)**
Cancer	75 (4%)	32 (6%)	1340 (9%)	24 (4%)	65 (5%)	0.81 (0.63 to 1.04)	1.07 (0.66 to 1.75)	0.87 (0.61 to 1.24)	1.68 (1.02 to 2.78)*
Type 2 diabetes	80 (5%)	31 (6%)	1092 (8%)	26 (5%)	68 (5%)	0.83 (0.66 to 1.06)	1.02 (0.64 to 1.61)	0.92 (0.66 to 1.29)	1.40 (0.87 to 2.27)
Coronary artery disease	69 (4%)	30 (6%)	1460 (10%)	20 (4%)	56 (4%)	0.76 (0.58 to 0.99)*	1.18 (0.68 to 2.04)	0.89 (0.60 to 1.31)	2.37 (1.34 to 4.20)*

Table 2. Test measures that associate with prior SARS-CoV-2 infection. The association testing was performed using logistic regression for binary traits (B) and linear regression for quantitative traits (Q), adjusting for sex and age, and also for education when testing for association with memory recall. Effects for binary traits are given in odds ratios (OR) in columns 1 and 2a but as betas in column 2b. Shown are all associations that are significant when comparing cases with all available controls, accounting for multiple testing (1). Consistent association results with (1) when comparing cases with contemporary controls (same direction and non-heterogeneity in the effect estimates) are marked with * in (2a) and significant effects (same direction) of Covid status on the difference between longitudinal measures for cases and controls (2b), are marked with * in (2b).

		(1) Covid cases vs all controls		(2a) Covid cases vs contemporary controls		(2b) The effect of Covid status on the difference between pandemic and pre-pandemic measurements	
Test, trait (unit)		Cases/ctrls	Effect (95% CI)	Cases/ctrls	Effect (95% CI)	Cases/ctrls	Effect (95% CI)
Perceived Stress Scale (score)	Q	882/34368	-1.95 (-2.35 to -1.54)	1498/557	-0.09 (-0.73 to 0.56)	238/19885	-1.70 (-2.36 to -1.03)*
Smell, partial anosmia	B	1685/14024	3.91 (3.65 to 4.17)	1685/413	4.56 (3.65 to 5.47)*	126/280	0.06 (0.02 to 0.11)*
Smell, hyposmia	B	1685/14024	1.90 (1.74 to 2.06)	1685/413	2.75 (2.29 to 3.20)*	126/280	0.12 (0.04 to 0.20)*
Taste, partial aguesia	B	1697/552	2.88 (2.31 to 3.45)	1697/552	2.88 (2.31 to 3.45)	NA[2]	NA[2]
Grip strength (kg)	Q	1695/8100	-0.73 (-1.12 to -0.33)	1695/546	-0.39 (-1.19 to -0.41)*	61/130	0.55 (-1.31 to 2.41)
Delayed memory recall[1] (SD)	Q	1613/534	-0.25 (-0.35 to -0.14)	1613/534	-0.25 (-0.35 to -0.14)	NA[2]	NA[2]
Immediate memory recall[1] (SD)	Q	1612/534	-0.20 (-0.30 to -0.10)	1612/534	-0.20 (-0.30 to -0.10)	NA[2]	NA[2]

CI = 95% confidence interval. CPET = Cardiopulmonary exercise test. [1]Wechsler Memory Scale Logical Memory recall. [2]Taste and delayed memory recall were not tested prior to the pandemic. SD = standard deviations.

Figures

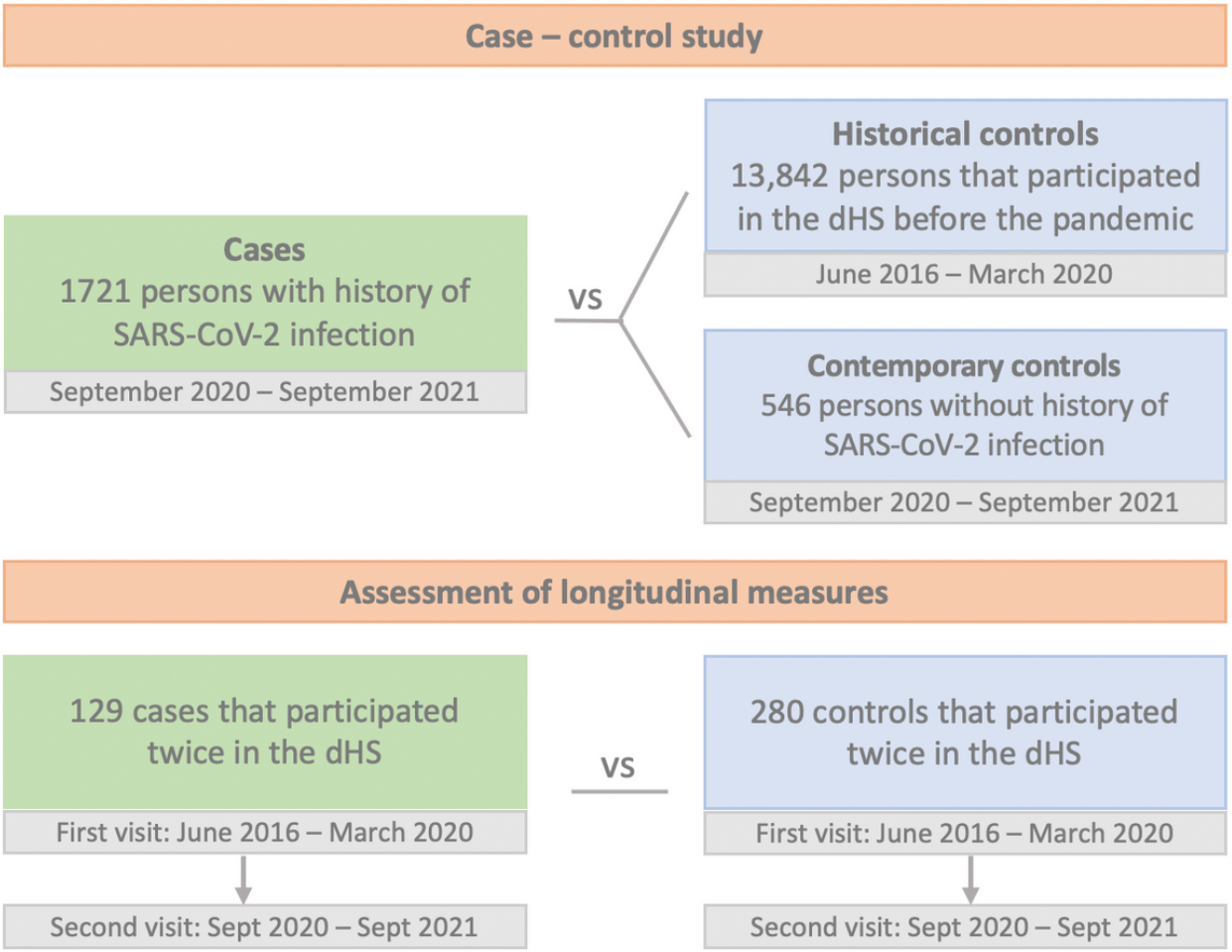

Figure 1

The dHS Covid Study design. Cases and contemporary controls participated in the dHS Covid Study between September 2020 and September 2021. Historical dHS controls participated in the study between June 2016 and March 2020. To establish association with prior SARS-CoV-2 infection, we required association when comparing cases with all available controls, accounting for multiple testing, and consistent results when comparing cases with contemporary controls or when comparing the subset of cases to the subset of controls with longitudinal measures.

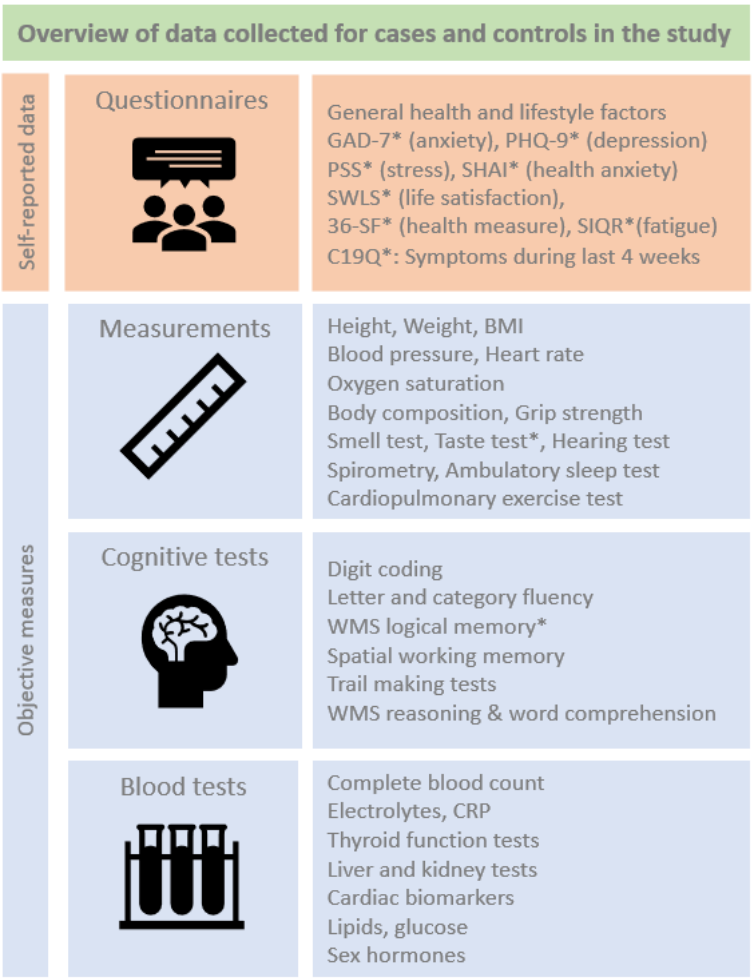

Figure 2

Overview of data collected in the study. Traits marked with * were added to the dHS Study in September 2020 for the dHS Covid Study and thus historical dHS control data was not available for those. Historical data was available from the iStopMM study for the GAD-7, PHQ-9, PSS, SWLS, and 36-SF questionnaires. A subset of the dHS historical controls answered the C19Q between September 2020 and September 2021 enriching the contemporary control data for C19Q.

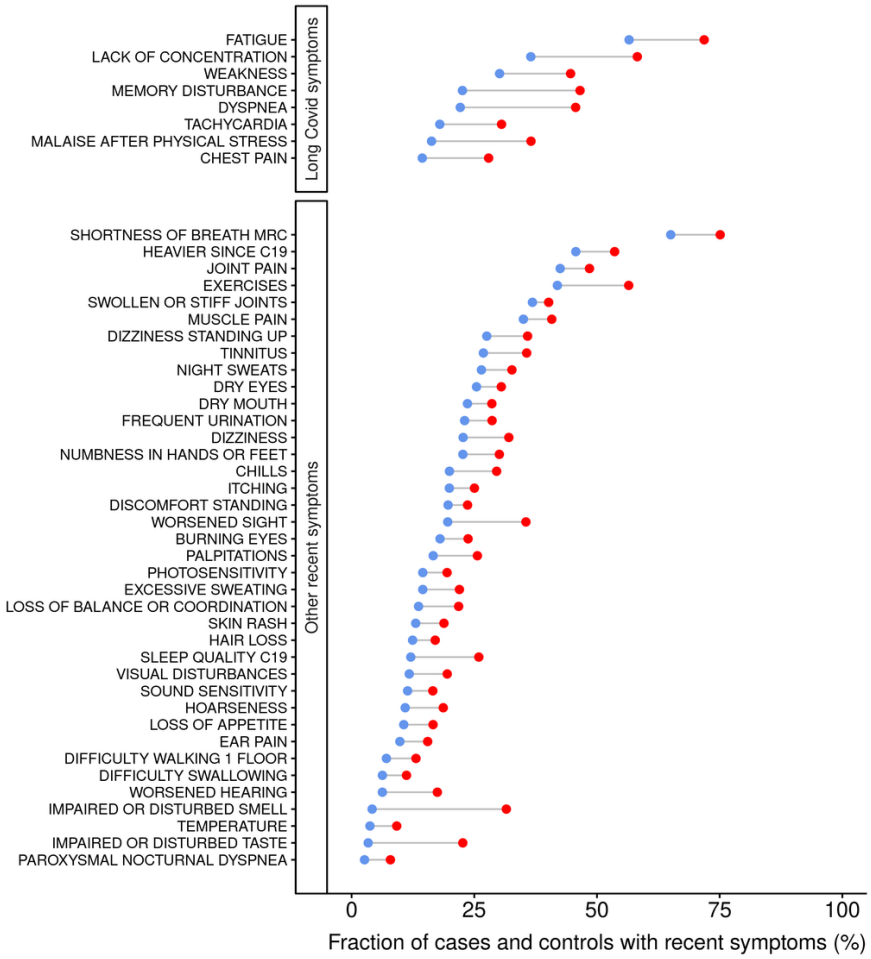

Figure 3

The fraction of cases and controls reporting the 46 recent symptoms that associated with history of SARS-CoV-2 infection. All 1721 cases and 1283 controls answered the C19Q on symptoms during the four weeks prior to answering. Red dots denote cases and blue dots denote controls and results are sorted by fraction of controls reporting symptoms, in descending order within panels. The symptoms included in the long Covid definition are displayed in the upper panel.

Supplementary Files

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