Persistence, prevalence, and polymorphism of sequelae after COVID-19 in unvaccinated, young adults of the Swiss Armed Forces: a longitudinal, cohort study (LoCoMo)

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Summary

Background Persistent COVID-19 sequelae could have global, public health ramifications. We therefore aimed to describe sequelae presenting more than 180 days after COVID-19—focussing on several organ systems, general health, and laboratory parameters—in non-hospitalised, unvaccinated, young adults.

Methods We did a longitudinal cohort study of all army bases in Switzerland. Eligible participants were personnel of the Swiss Armed Forces (SAF) who were aged 18–30 years with a positive or negative RT-PCR test for SARS-CoV-2 during their service between March 1, 2020, and Dec 31, 2020. Exclusion criteria were unwillingness to participate in testing. Females or men with a known reproductive anomaly were excluded from the optional component of male fertility testing. COVID-19 was defined as a positive diagnostic RT-PCR test result for SARS-CoV-2 with concurrent symptoms compatible with COVID-19. Participants were subdivided into four groups: control group (ie, serologically negative), asymptomatic infection group (ie, serologically positive but with no symptoms), non-recent COVID-19 group (>180 days since positive PCR test), and recent COVID-19 group (≤180 days since positive PCR test). Outcomes of interest were part of a comprehensive, intensive test battery that was administered during a single day. The test battery quantified the effect of SARS-CoV-2 infection on cardiovascular, pulmonary, neurological, renal, ophthalmological, male reproductive, psychological, general health, and laboratory parameters. This study was registered with ClinicalTrials.gov, number NCT04942249.

Findings Between May 20, 2021, and Nov 26, 2021, we enrolled 501 participants. 29 (6%) of 501 were female and 464 (93%) were male, and the median age was 21 years (IQR 21–23). Eight (2%) of 501 had incomplete data and were not included into the study groups. 177 participants had previous COVID-19 that was more than 180 days (mean 340 days) since diagnosis (ie, the non-recent COVID-19 group) compared with 251 serologically negative individuals (ie, the control group). We included 19 participants in the recent COVID-19 group and 46 in the asymptomatic infection group. We found a significant trend towards metabolic disorders in participants of the non-recent COVID-19 group compared with those in the control group: higher BMI (median 24·0 kg/m² [IQR 22·0–25·8] *vs* 23·2 kg/m² [27·1–25·0]; p=0·035), lower aerobic threshold (39% [36–43] *vs* 41% [37–46]; p=0·012), and higher blood cholesterol (4·2 µM [3·7–4·7] *vs* 3·9 µM [3·5–4·5]; p<0·0001) and LDL concentrations (2·4 µM [1·9–2·9] *vs* 2·2 µM [1·7–2·7]; p=0·001). The only significant psychosocial difference was found in the results of the Chalder Fatigue scale with the non-recent COVID-19 group reporting higher fatigue scores than the control group (median 12 points [IQR 11–15] *vs* 11 [9–14]; p=0·027). No significant differences in other psychosocial questionnaire scores, ophthalmological outcomes, and sperm quality or motility were reported between the control group and non-recent COVID-19 group.

Interpretation Young, previously healthy, individuals largely recover from SARS-CoV-2 infection. However, the constellation of higher BMI, dyslipidaemia, and lower physical endurance 180 days after COVID-19 is suggestive of a higher risk of developing metabolic disorders and possible cardiovascular complications. These findings will guide future investigations and follow-up management.

Funding Swiss Armed Forces.

Introduction

For the **latest global confirmed cases of COVID-19** see https://covid19.who.int

The COVID-19 pandemic, caused by SARS-CoV-2, is marked by intense global transmission with more than 535 million confirmed cases as of June 15, 2022. Mounting evidence suggests that SARS-CoV-2 is a multisystem infection. Data for how long symptoms persist and the sequelae of the infection need to be researched. Available original research tends to focus on patients who have been admitted to hospital[1,2] or restricts evaluations to a single organ system.[2] Studies to date show that persisting sequelae of COVID-19 are common in people with the following risk factors: older adults (≥50 years), smokers, and those with underlying comorbidities such as hypertension, obesity, diabetes,

Research in context

Evidence before this study

The intermediate-term and long-term sequelae of SARS-CoV-2 infections have scarcely been researched in young, unvaccinated individuals. Available original research tends to focus on patients who have been admitted to hospital or restricts evaluations to a single organ system. Few, if any, of these studies have a control group of non-exposed individuals. To evaluate possible sequelae of SARS-CoV-2 infection in young Swiss military personnel, we designed a test battery based on the results of our systematic review of COVID-19 sequelae in previously healthy adults. No language restrictions were used in the systematic literature search of Embase, WHO, Scopus, PubMed, Litcovid, bioRxiv, and medRxiv, which was done to mid-September, 2020 (PROSPERO CRD42020208725). The search terms included "COVID 19", "coronavirus disease 2019", "SARS-CoV-2", "sequelae", and "consequence". Studies of adults older than 50 years and children younger than 18 years were excluded. Bias assessment was done using a modified Newcastle-Ottawa Scale. The results of that systematic review indicated that SARS-CoV-2 is a multisystem infection that might lead to sequelae in many body systems. We updated our literature search on May 6, 2022 (Embase, Medline, Web of Science) and found nine new studies that looked at sequelae of COVID-19 in young individuals (<40 years). One of the studies followed-up on patients admitted to hospital for COVID-19. These studies had a follow-up timeframe ranging from 2 weeks to 12 months and were mainly phone surveys or online questionnaires. They found a wide range of persisting symptoms including reduced physical activity, exercise intolerance, hyposmia, ageusia, fatigue, and memory impairment. Female sex was found to be a predictor for persisting sequelae.

Added value of this study

The Long COVID in Military Organisations (LoCoMo) study is novel in that it quantitatively evaluated multi-organ function using a sensitive, minimally invasive, test battery in a homogenous group of people several months after COVID-19. A valuable facet of the study is the control group, serologically confirmed to have had no SARS-CoV-2 exposure. Unlike other studies that looked at one body system, LoCoMo evaluates cardiovascular, pulmonary, neurological, ophthalmological, male fertility, psychological, and general systems using an innovative test battery in a clinic setting rather than online or using phone surveys or database analyses. The LoCoMo study adds to the evidence base on the spectrum and persistence of COVID-19 sequelae in the context of young, previously healthy adults. Our findings show overall recovery from mild COVID-19 (defined as symptomatic but no admission to hospital) more than 180 days after illness. We did find some persisting sequelae: increased BMI, dyslipidaemia, and decreased physical endurance lasting many months after infection with lower aerobic threshold. The study also provided evidence that recent infections (≤180 days before testing) were associated with significant hyposmia and with poorer motile sperm counts but that these findings were no longer significant for non-recent infections (>180 days previously). Anxiety and depression scales showed higher psychological burdens in the recent COVID-19 group compared with the non-recent COVID-19 group. Overall, the results of these quantitative analyses show recovery from mild COVID-19 and resolution of most sequelae more than 10 months after infection but persistence of some metabolic sequelae.

Implications of all the available evidence

Young, previously healthy, non-hospitalised individuals largely recover from mild infection and the multi-system effect of COVID-19 is less than that seen in older or hospitalised patients. These results might be extrapolated to other young, male, workforce adults and augur well for recovery in many body systems. The LoCoMo study, however, provides new evidence that even mild infections in young adults can lead to sequelae that persist several months after infection. The most important implication for post-pandemic long COVID management were symptoms suggestive of an increased risk of developing metabolic disorders and possible cardiopulmonary complications.

cardiovascular disease, chronic lung disease, chronic kidney disease, chronic liver disease, cerebrovascular disease, cancer, and immunodeficiency. Sequelae of infection have however also been observed following milder SARS-CoV-2 infections[3–5] in population-based studies that followed-up on prescription data or in electronic health databases[6] or on patients presenting to clinics after COVID-19.[4]

In a telephone survey[7] in adults who tested positive for SARS-CoV-2, 95 (35%) of 274 symptomatic respondents, including 22 (26%) of 85 amongst those aged 18–34 years, reported not having returned to their usual state of health 2 weeks or more after testing. The Pan American Health Organization has issued an epidemiological alert on the need for information about COVID-19 sequelae.[8] WHO has added "post COVID-19 condition" to the International Classification of Diseases codes to describe a condition that occurs following probable or confirmed SARS-CoV-2 infection with symptoms that last for at least 2 months and that cannot be explained by an alternative diagnosis.[9] In late 2020, a Long COVID Forum brought together stakeholders and policy makers to identify research gaps and a recommendation was to expand research beyond patients who were admitted to hospital.[10] Systematic evaluation of multiorgan function with quantitative outcomes and negative controls are needed for discrete population groups. Such data are particularly important in the context of young adults who constitute a large proportion of any country's workforce.

We therefore aimed to design a minimally invasive test battery to follow-up on long-term sequelae of COVID-19 with a focus on pulmonary, cardiovascular, neurological, renal, ophthalmological, male reproductive, psychological, and general health in addition to serological and laboratory parameters.

Methods

Study design and participants

We did a longitudinal cohort study (ie, the Long COVID in Military Organisations [LoCoMo] study), which focused on the assessment of COVID-19 sequelae in young, mainly male, recruits in all army bases in Switzerland. The Swiss Armed Forces (SAF) has a conscription system with a 10-year duration of mandatory service. Soldiers who are recruited as young adults return annually for repetition courses. Potential participants were aged 18–30 years and received an invitation by post to voluntarily enrol in the LoCoMo study using an online booking tool. After the target sample size was reached, the online booking tool was closed.

Participants were recruited prospectively before the outcome of interest (ie, the presence or absence of COVID-19 sequelae) was known. Participants could be included in the study if they had a positive or negative RT-PCR test for SARS-CoV-2 during their army service between March 1, 2020, and Dec 31, 2020. Exclusion criteria were being unwilling or unavailable to participate in the study testing day in Zürich, Switzerland. Regarding the optional component of sperm count and male fertility testing, the additional exclusion criteria were female sex or men with a known reproductive anomaly.

See Online for appendix

We obtained written informed consent from all participants before testing was initiated. No financial incentives were offered to participate but volunteers could travel to the test centre free of charge (ie, travel payments were reimbursed or the participants could travel to the test centre for free as Swiss army personnel) and received meals and refreshments. The LoCoMo cohort study was approved by the Swiss Cantonal Ethics Committee of Zürich (BASEC-number 2021-00256).

Procedures

COVID-19 was defined as a positive diagnostic RT-PCR test result for SARS-CoV-2 from a commercial provider and concurrent symptoms compatible with COVID-19 as per the definition of the Federal Office of Public Health in Switzerland (ie, fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhoea, and loss of taste or smell). Pragmatically, the day of the PCR test was considered as the first day of COVID-19. Participants were subdivided into the recent COVID-19 group (≤180 days since positive PCR test) and the non-recent COVID-19 group (>180 days). A positive antigen test alone or symptoms alone did not satisfy the definition of COVID-19. Asymptomatic infection was assumed in individuals not matching the aforementioned definition of COVID-19 but who had a positive serological test for anti-nucleocapsid (Roche Elecsys Anti-SARS-CoV-2; Roche Diagnostics [Schweiz] AG, Rotkreuz, Switzerland). These participants were classified into the asymptomatic infection group. Only participants with a negative anti-nucleocapsid serology and who did not match the COVID-19 case definition were classified into the control group.

After check-in and a saliva SARS-CoV-2 rapid antigen test (COVID-19 Antigen Detection Kit [Colloidal Gold]; Zhuhai Lituo Biotechnology, Zhuhai, China) to exclude concurrent SARS-CoV-2 infection, participants answered baseline questions (age, sex, body height, bodyweight, test status, comorbidities, smoker status, educational level, and vaccination status). All consent forms, questionnaires, and flyers were available in German, French, and Italian.

Based on our previous systematic review of COVID-19 sequelae[11] and a scrutiny of the literature to identify the best test methods to quantify sequelae, we designed an intensive but minimally invasive test battery. Participants took part in a day of intensive testing at the University of Zürich and associated clinics at the University Hospital of Zürich (figure 1). All procedures were done by specially trained scientists, study nurses, and physicians. Several standardised questionnaires were self-administered on iPads that were available to the participants throughout the day. Assistants were available to bring participants to their allotted appointments in the ophthalmology and andrology clinics.

All baseline characteristics of participants including co-medication, vaccination status, allergies, and sport frequency were recorded, and vitals were measured (appendix pp 3–4). Fatigue was assessed using the validated Chalder Fatigue Scale and using the Profile of Moods States 2. Kidney function was assessed using the estimated glomerular filtration rate (eGFR) and serum creatinine and cystatin C concentrations. Venous blood sampling allowed for measurement of routine laboratory parameters including white cell counts (counts and full differential) and C-reactive protein concentration. All chemical analyses were done in the routine clinical chemistry laboratory of the University Hospital of Zürich. We evaluated lung function using spirometry,[12] and carbon monoxide diffusion capacity testing was done to provide an index of possible damage to microcirculation or interstitial damage and to estimate the total lung capacity (Power Cube Diffusion +; Schiller Reomed AG, Obfelden, Switzerland). Fractional exhaled nitric oxide (FeNO) was assessed to provide an indication of inflammatory processes within the lungs (NIOX Vera; Stallergenes, Dietlikon, Switzerland). We measured serum troponin T concentration as a marker for myocarditis. A cardiopulmonary exercise test (CPET) was done on a treadmill to evaluate fitness, heart rate, blood pressure, inspiratory and expiratory CO_2 concentration and O_2 concentration, as well as gas flow (Metalyser; Reavita, Zurich, Switzerland).[13]

We evaluated olfactory function using the Sniffin' Sticks extended test[14] (Veteresen, Germany). Gustatory performance was measured using Taste Strips[15] (Veteresen, Germany), investigating the ability to taste and perceive four primary tastes (sweet, salty, sour, and bitter). All participants underwent a complete ophthalmic examination including optical coherence tomography (OCT) and OCT angiography (OCTA) and fundus photography (Optovue Solix; Optovue Inc Freemont, CA, USA), ultrawide field fundus colour and autofluorescence imaging (Optos California; Optos Inc, Marlborough, MA, USA).[16] To evaluate psychological and emotional health sequelae, the following questionnaires were self-administered: Quality of Life-EQ-5D-5L, COVID-19 post-traumatic stress disorder, Zung Self-rating Depression Scale, Beck Depression Inventory (13 items), State-Trait Anxiety Inventory form-Y, and Profile of Mood States 2. To evaluate male fertility, a standard WHO sperm count was done measuring semen volume, sperm concentration, motility, and morphology.[17] Sex hormones (testosterone, follicle stimulating hormone [FSH], and luteinising Hormone [LH]) were measured. Neutralising antibody titres were measured in participants of all four groups.[18]

At the end of the testing day, participants did a check-out to ensure that all test components and questionnaires had been completed. All questionnaire answers and data about the study participants were stored in the REDCap secure database (version 12.2.10) with an auto-archiver. Completed files were stored in a secure file repository.

Outcomes

Outcomes of interest were BMI, clinical chemistry parameters (cholesterol, HDL, C-reactive protein, eGFR, creatinine, cystatin C, and troponin T), male fertility (ejaculate pH, ejaculate volume, FSH, LH, normal sperm morphology, progressive motility, and testosterone), olfactory (the composite Threshold-Discrimination-Identification [TDI] score, which indicates normosmia [TDI ≥31], hyposmia [TDI <31], or functional anosmia [TDI ≤16]), lung function (functional vital capacity and FeNO), CPET parameters (VO_2 max and aerobic threshold [ie, percentage of VO_2 max]), gustatory scores (scores <9 suggested hypogeusia), ophthalmological parameters (OCT and OCTA measurements), and standardised scores from the psychological and emotional health questionnaires (appendix p 2).

Statistical analysis

We did not define a primary outcome, because we did not know a priori which organ systems would be affected from long-COVID in young adults. Outcome measures were changes in cardiovascular, pulmonary, neurological, renal, ophthalmological, male reproductive, psychological, general health, and laboratory parameters measured with the test battery. The target sample size of 500 participants was determined based upon an a priori power calculation, in which 21% of the 2500 potential participants were mailed and took part in the study. Assuming a normal distribution of the test variable, we would be able to detect differences of 30% of the standard deviation at a significance level of 0·05 with a power of 80%.

For each outcome of interest or test result, we used odds ratios (ORs), calculated from the Welch two sample

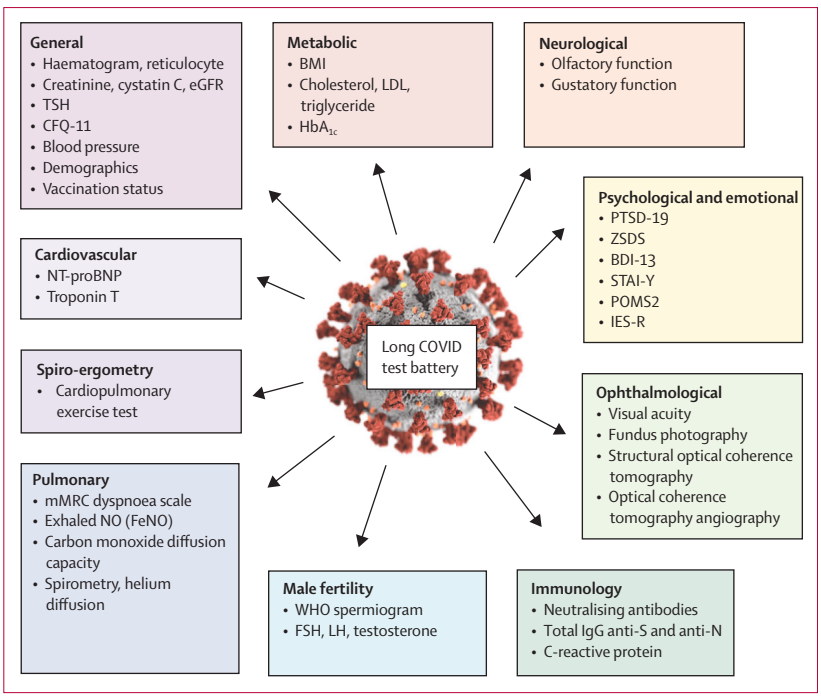

Figure 1: **Test battery used in the Long COVID in Military Organisations study**
The test battery was used to evaluate the long-term sequelae of COVID-19 in young adults. A variety of quantitative tests and standardised questionnaires were used to measure the effect on various organ systems and parameters in participants following COVID-19, asymptomatic SARS-CoV-2 infection, or in individuals who were non-exposed to SARS-CoV-2. Anti-N=anti-SARS-CoV-2 nucleocapsid. Anti-S=anti-SARS-CoV-2 spike. BDI-13=Beck Depression Inventory (13 items). CFQ-11=Chalder Fatigue Scale. eGFR=estimated glomerular filtration rate. FeNO=fractional exhaled nitric oxide. FSH=follicle stimulating hormone. HbA1c=glycated haemoglobin. IES-R=Impact of Event Scale-Revised. LH=luteinising hormone. mMRC=modified Medical Research Council. NT-proBNP=N-terminal pro-B-type natriuretic peptide. POMS2=Profile of Mood States 2. PTSD-19=COVID-19 post-traumatic stress disorder questionnaire. STAI-Y= State-Trait Anxiety Inventory form-Y. TSH=thyroid stimulating hormone. ZSDS=Zung Self-Rating Depression Scale.

	Control group (n=251)	Asymptomatic infection group (n=46)	Non-recent COVID-19 group (n=177)	Recent COVID-19 group (n=19)
Age (years)	21 (21–21)	21 (20–22)	22 (21–24)	21 (21–22)
Sex				
Males	238 (95%)	42 (91%)	166 (94%)	18 (95%)
Females	13 (5%)	4 (9%)	11 (6%)	1 (5%)
Days since COVID-19	NA	NA	317 (272–414)	101 (83–155)
Anti-N (AU)*	0·064 (0·059–0·067)	4·62 (2·06–8·44)	3·61 (1·00–10·0)	14·4 (4·52–39·3)
Vaccinated†	191 (76%)	30 (65%)	118 (67%)	10 (53%)

Data are median (IQR) or n (%). Eight (2%) of 501 had incomplete data and were not included in the baseline characteristics. Anti-N=anti-SARS-CoV-2 nucleocapsid. AU=arbitrary unit. NA=not applicable. *Definite indicator of infection independent of vaccination. †One or more vaccinations.

Table: **Baseline characteristics**

For the **REDCap secure database** see https://projectredcap.org

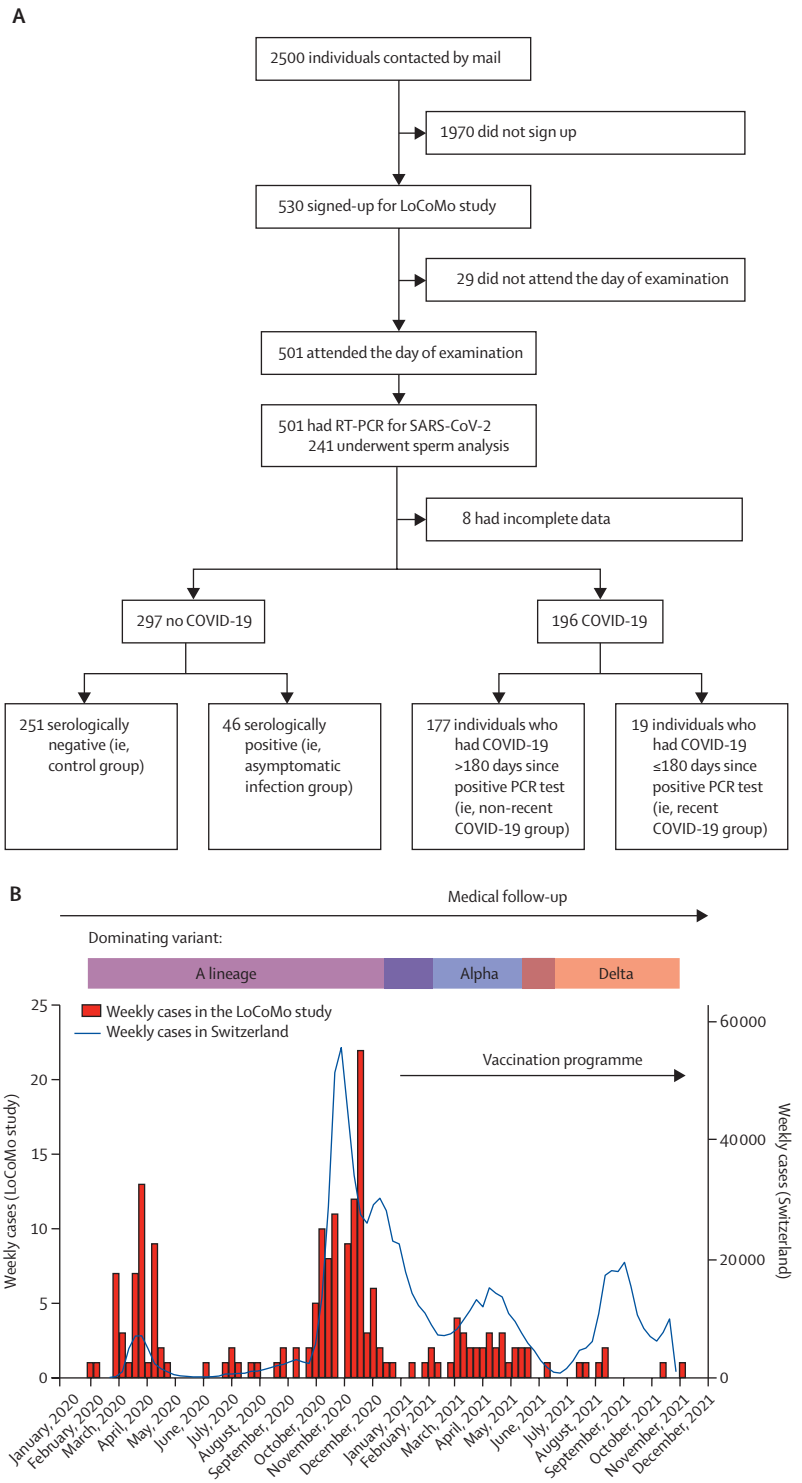

Figure 2: **Flow chart of the LoCoMo study (A) and background epidemiological data for COVID-19 in Switzerland (B)**

Background epidemiological data in Switzerland show the waves of infection, the dominant variants, and the timing of vaccination programmes for young adults in relation to infection levels and testing of the cohort. LoCoMo=Long COVID in Military Organisations.

t-test or Wilcox test using the R package oddsratio (version 1.0.2), to compare post-COVID-19 individuals with SARS-CoV-2-negative individuals by fitting a generalised linear model. Graphics were generated by ggplot2. Exploratory subgroup analyses were done to evaluate differences based on duration elapsed since infection (≤180 days *vs* >180 days) and the severity of infections (asymptomatic *vs* symptomatic). Exploratory multivariate analyses for confounding effects were done by generalised linear modelling of the target variable with pathophysiologically possible confounding effects.

We did all data analyses using the R statistical program (version 4.1.2). This study was registered with ClinicalTrials.gov, number NCT04942249.

Role of the funding source

The initial study protocol was evaluated by the Army Research Committee for input regarding study duration, costs, and outcome measures. The funder of the study had no role in data collection, data analysis, data interpretation, or writing of this report.

Results

Between May 20, 2021, and Nov 26, 2021, we enrolled a total of 501 participants with a median age of 21 years (IQR 21–23). The baseline characteristics of participants are shown in the table and the extended baseline characteristics in the appendix (pp 3–4). 29 (6%) of 501 were female and 464 (92%) were male. Eight (2%) of 501 had incomplete data and were not included into the study groups. 177 participants had previous COVID-19 that was more than 180 days (mean 340 days) since diagnosis (ie, the non-recent COVID-19 group; appendix p 12) compared with 251 serologically negative individuals (ie, the control group; figure 2). The analyses also included 19 participants with recent COVID-19 that was within 180 days or less (ie, the recent COVID-19 group) and 46 asymptomatically infected individuals, with serological evidence of infection but without confirmed COVID-19 (ie, the asymptomatic infection group; figure 2). The baseline characteristics (age and sex) of the participants are well matched between the groups (table; appendix pp 3–4); however, vaccination levels differ between the control group and the-recent COVID-19 group (191 [76%] of 251 *vs* ten [53%] of 19). All participants in the non-recent COVID-19 group tested positive before they were vaccinated (since the vaccination was not available at the time of infection) and vaccination recommendations at the time prioritised non-infected individuals over previously infected individuals.

We found a significant trend towards a constellation of metabolic disorders in participants in the non-recent group compared with those in the control group, with higher BMI (median 24·0 kg/m² [IQR 22·0–25·8] *vs* 23·2 kg/m² [27·1–25·0]; p=0·035), lower aerobic threshold (39% [36–43] *vs* 41% [37–46]; p=0·012), and higher blood cholesterol (4·2 µM [3·7–4·7] *vs* 3·9 µM

[3·5–4·5]; p=0·0010) and LDL concentrations (2·4 µM [1·9–2·9] *vs* 2·2 µM [1·7–2·7]; p=0·0017; figures 3, 4). Participants in the non-recent COVID-19 group reported more fatigue on the Profile of Mood States 2 scale than those in the asymptomatic infection group (median 12 points [IQR 10–16] *vs* 10 points [8·25–13·75]; p=0·0067). The only significant psychosocial difference was found in the results of the Chalder Fatigue scale with the non-recent COVID-19 group reporting higher fatigue scores than the control group (median 12 points [IQR 11–15] *vs* 11 [9–14]; p=0·027). No other significant differences in psychosocial questionnaire scores, ophthalmological outcomes, and sperm quality or motility were reported between participants in the control group and those in non-recent COVID-19 group (appendix pp 5–9).

In a subgroup analysis, relative hyposmia was observed in participants in the recent COVID-19 group (ie, ≤180 days since diagnosis) compared with those in the non-recent COVID-19 group (ie, >180 days since diagnosis; median TDI score 30 [IQR 26·8–34·8] *vs* 32·5 [30·0–35·5]; p=0·025; appendix p 15). The andrology results showed poorer progressive motile sperm count in participants in the recent COVID-19 group compared with those in the control group (median $36·39\times10^6$ motile sperm per ejaculate [IQR $3·5\times10^6$ to $50·84\times10^6$] *vs* $43·0\times10^6$ [$15·85\times10^6$ to $85·27\times10^6$]; p=0·041), although no significant difference was observed between those in the control group and non-recent COVID-19 group (ie, >180 days after COVID-19; appendix p 16). State-Trait Anxiety Inventory State (STAI-S) scores of anxiety levels were significantly higher in participants of the recent COVID-19 group than in those of the control group (median score 47 [IQR 45–48] *vs* 45 [42–48]; p=0·020; appendix p 17). Participants of the recent COVID-19 group showed higher psychological burdens than those of the non-recent COVID-19 group for the COVID-19

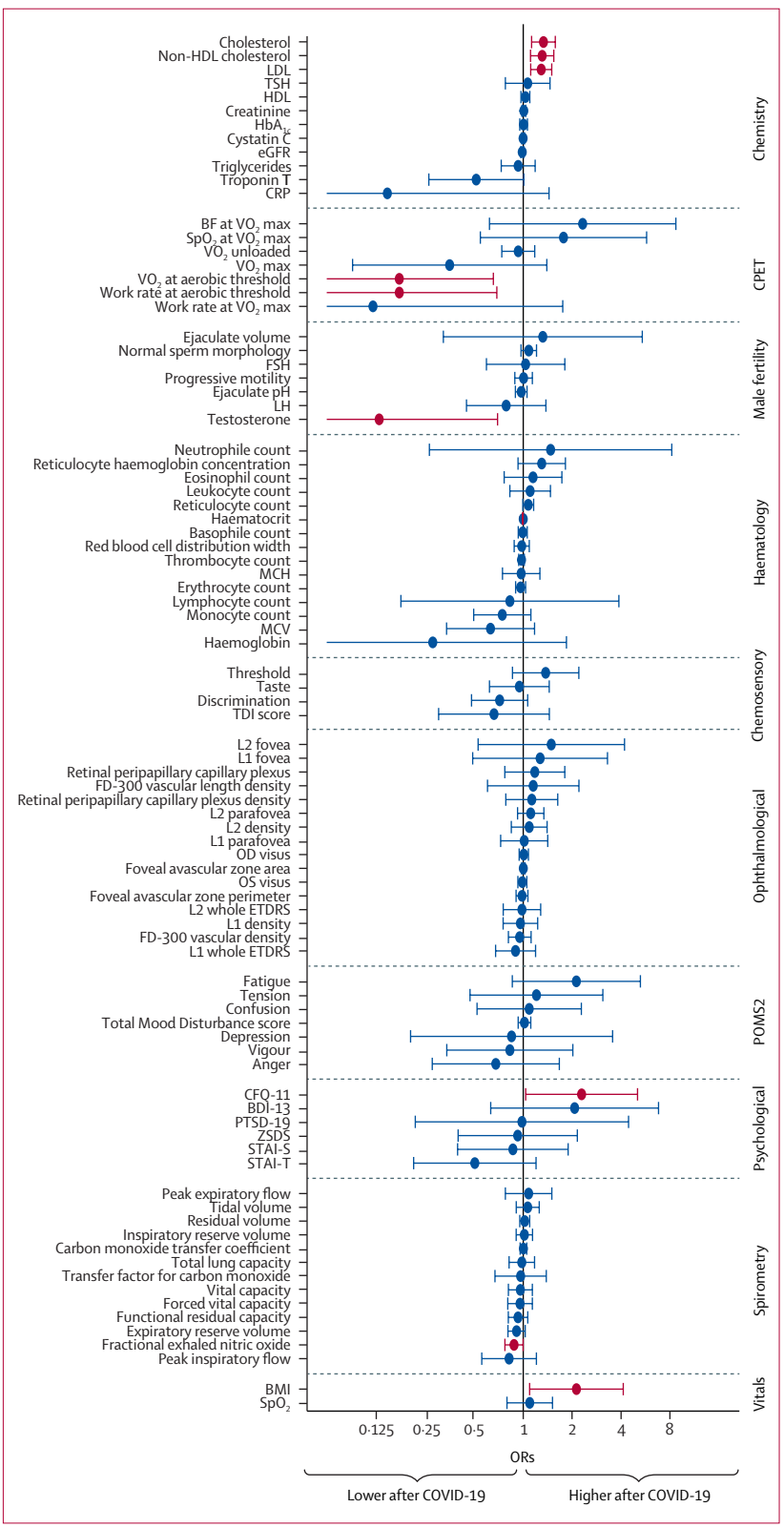

Figure 3: **Multi-system sequelae after COVID-19**
Participants more than 180 days after confirmed COVID-19 (ie, non-recent COVID-19 group) were compared with non-infected individuals (ie, control group). ORs for various parameters were calculated. Error bars are 95% CIs. BDI-13=Beck Depression Inventory (13 items). BF=Breathing frequency. CFQ-11=Chalder Fatigue Scale. CPET=cardiopulmonary exercise test. CRP=C-reactive protein. eGFR=estimated glomerular filtration rate. FSH=follicle stimulating hormone. L1 density=overall superficial capillary plexus density. L1 fovea=superficial capillary plexus density at the fovea. L1 parafovea=superficial capillary plexus density parafoveal. L1 whole ETDRS=superficial capillary plexus Early Treatment Diabetic Retinopathy Study score. L2 density=overall deep capillary plexus density. L2 fovea=deep capillary plexus density at the fovea. L2 parafovea=deep capillary plexus density parafoveal. L2 whole ETDRS=deep capillary plexus Early Treatment Diabetic Retinopathy Study score. LH=luteinising hormone. MCH=mean corpuscular haemoglobin. MCV=mean corpuscular volume. OD visus=visus (with best correction) of the right eye. OR=odds ratio. OS visus=visus (with best correction) of the left eye. POMS2=Profile of Mood States 2. PTSD-19=COVID-19 post-traumatic stress disorder questionnaire. RPC=radial peripapillary capillary. STAI-S=State-Trait Anxiety Inventory State. STAI-T=State-Trait Anxiety Inventory Trait. TDI=Threshold-Discrimination-Identification. TSH=thyroid stimulating hormone. ZSDS=Zung Self-Rating Depression Scale.

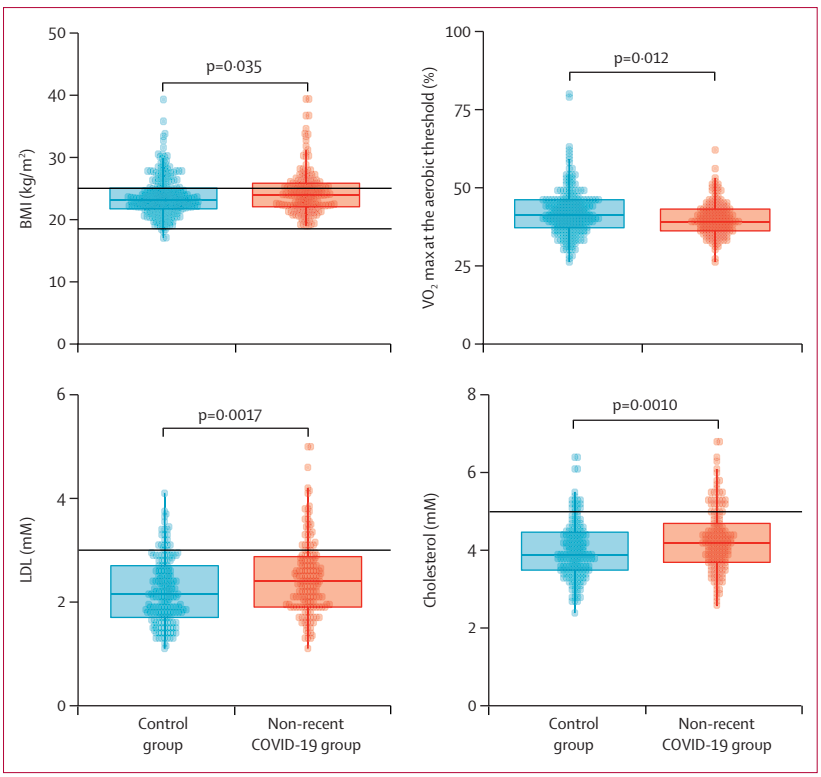

Figure 4: **Signs of metabolic disorders after COVID-19**
Limits of normal values (25 kg/m² for BMI, 5 μM for total cholesterol, and 3 μM for LDL) are indicated as horizontal lines.

post-traumatic stress disorder scores (p=0·018) and Beck Depression Inventory scale (p=0·028; appendix pp 18–19).

We did exploratory multivariate analyses to estimate the influence of vaccination status and other parameters on our main findings (ie, changes in LDL, BMI, and aerobic threshold) and found no confounding effect of gender, other diseases, medication, smoking status, or vaccination status on LDL concentrations; however, BMI correlated significantly with LDL concentrations. Additionally, we found no confounding effect of gender, medication, vaccination status, or smoking status on BMI but other diseases correlated with BMI levels. No effect was found for other diseases, medication, and vaccination status on VO_2 max; however, gender, smoking status, and physical activity levels correlated with VO_2 max (appendix pp 10–11).

Discussion

This comprehensive test battery, evaluating cardiovascular, pulmonary, neurological, ophthalmological, male fertility, psychological, and general systems, administered more than 180 days after COVID-19 showed significant sequelae of increased BMI, dyslipidaemia, and decreased physical endurance. Such a constellation suggests that previously healthy young adults might have an increased risk of developing metabolic disorders and possible cardiovascular complications. Otherwise, the results of these quantitative analyses show overall recovery from mild COVID-19 (defined as symptomatic but not requiring hospital admission) and resolution of most sequelae at a mean of more than 340 days after infection. To date, LoCoMo is the most comprehensive, controlled study, with the longest follow-up of sequelae in young, previously healthy, mainly male adults. The multisystem effect of mild COVID-19 in this cohort with a mean age of 21 years, appears to be far less than that seen in older, multimorbid or hospitalised patients. Overall, these findings are a positive perspective for young adult populations globally who have been infected with SARS-CoV-2.

Regarding male fertility, one study has postulated that SARS-CoV-2 infection might have a potentially detrimental effect.[19] In our subgroup analyses, we found evidence that recent infections (≤180 days before testing) were associated with poorer motile sperm counts but that this finding was no longer significant for non-recent infections (ie, >180 days). Our findings are corroborated by other studies. Donders and colleagues[20] found sperm quality to be suboptimal after COVID-19 with an estimated recovery time of 3 months. In addition, we found significant hyposomia (TDI score <31) in those infected in the previous 180 days. Observational studies of individuals with SARS-CoV-2 also report high levels of hyposmia.[21] In another army study, we recently followed-up on army personnel using an App to self-report symptoms and found that individuals that had tested positive for SARS-CoV-2 with a mean follow-up time of 54 days had a significantly reduced sense of smell compared with non-infected individuals (OR 18·24 [95% CI 4·23–78·69]; p<0·0001) and that the hyposmia persisted for a mean duration of 6·4 weeks after testing positive.[22] In addition, we found STAI S scores of anxiety levels to be significantly higher in recent COVID-19 participants. In an earlier study, Mazza and colleagues[23] used questionnaires to screen for psychiatric symptoms in 402 adults 1 month after COVID-19. A significant proportion of the participants self-rated in the psychopathological range for post-traumatic stress disorder (28%), depression (31%), anxiety (42%), and insomnia (40%). In our study, no significant differences were observed in the psychosocial questionnaire results between the control group and the non-recent COVID-19 group; however, a significant difference in the Chalder Fatigue scale was observed, with the non-recent COVID-19 group reporting higher fatigue scores than the control group. We consider these sequelae persisting beyond 180 days to be particularly important especially the excess burden of metabolic disorders, including the elevated LDL and total cholesterol concentrations. Our study could not differentiate whether COVID-19 in young adults predisposes for metabolic disorders or whether this predisposition existed previously and was accentuated by the infection. An earlier evaluation of the US Department of Veteran Affairs National Healthcare

Database[6] found a substantial burden of health loss including diagnoses, medication use, and laboratory abnormalities in patients with COVID-19 who survived at least for 30 days after diagnosis. The sequelae risk gradient increased according to the severity of the acute COVID-19 disease. Previous studies have shown that even slightly higher LDL and cholesterol concentrations in young adults are associated with increased risk of cardiovascular disease later in life.[24,25] In line with this result, lowering concentrations of LDL in such a population is effective in decreasing the risk for cardiovascular disease.[26] Although post-viral symptoms are not new and have been described after influenza and other pandemics in the past,[27] metabolic disturbances after a viral infection as described here have, to the best of our knowledge, not been described after influenza infections and might be specific to COVID-19. Our findings also highlight lower physical endurance persisting many months after infection, with significantly lower aerobic threshold. An earlier study of aerobic capacity in young Swiss army recruits (median age 21 years),[28] compared the results of physical endurance tests before infection with the same tests done 45 days after infection and found a significant decline in predicted maximal aerobic capacity in SARS-CoV-2 convalescent recruits. Our results suggest that this reduction in physical endurance can persist for longer than 180 days and we advocate further follow-up to define the duration of this sequela. Even mild infections with SARS-CoV-2 should not be underestimated.[6,22,28] With the circulation of highly transmissible variants such as omicron (B.1.1.529), a reduction in public health mitigation measures, and a resumption of social activities,[29] young adults will have increased contact with SARS-CoV-2 and must live with the potential consequences of these sequalae. Our study highlighted a positive sequela of COVID-19 showing that vaccinated, recovered individuals exhibited a high titre of neutralising antibody, regardless of the severity of the previous infection course. This finding further underpins the need to vaccinate individuals who have recovered from COVID-19 regardless of the severity of their infection. The economic costs of even mild, long-term COVID-19 sequelae and associated loss of productivity and possible need for disability allowances have still to be elucidated.

Our study has several strengths. We used a unique cohort of young, Swiss, mainly male, army recruits. In contrast to other studies, we had a control group, unequivocal evidence of SARS-CoV-2 infection, and our test battery yielded objective and quantitative scores for analyses. Another strength of our study is the specifically designed, comprehensive test battery to quantify possible multi-organ sequelae based on the results of a systematic review.[11]

However, an important limitation of the LoCoMo study was the small proportion of female participants, which precluded meaningful sex-based evaluation of sequelae in young women. This limitation could not be avoided in the military context, but future studies should ensure strong female participation. Another possible limitation is that the intensive nature of the testing day and associated logistics might have selected more enthusiastic participants. The testing for sequelae was done before the emergence of the omicron variant of concern but future follow-up of this cohort can evaluate possible sequelae of omicron and other variants of concern.

The test battery developed for this study can be applied and even expanded for use in other population groups especially young women. We plan further follow-up of this LoCoMo cohort, feasible within the military structure of recurring service and the initiation of other longitudinal studies to understand the trajectory of sequelae persistence beyond 1 year and focused research to clarify the pathophysiology and triggers of the identified sequelae and possibly the increased risk of cardiovascular disease. A clearer definition of long-COVID or post-acute sequelae of COVID-19 is also urgently needed[30] and we suggest that this definition should be nuanced for different population groups.

We conclude that young, previously healthy, non-hospitalised individuals largely recover from mild infection and that the multi-system effect of COVID-19 is less than that seen in older, multi-morbid, or hospitalised patients. These results might be extrapolated to other young, male adults and augur well for recovery in many body systems. However, findings from this study and others suggest that even mild infections in young adults can lead to sequelae that persist up to 180 days such as fatigue, hyposmia, poor psychological scores, and a short-term, negative impact on male fertility. Moreover, this controlled, cohort study with a long follow-up provided evidence of a persisting constellation of higher BMI, dyslipidaemia, and lower physical endurance even 10 months after COVID-19. These results have societal and public health effects and can guide strategies for broad interdisciplinary evaluation of COVID-19 sequelae, their management, curative treatments, and support in young adult populations.

Contributors

PS and JWD designed the study and have access to all the data, verified the underlying data, and take responsibility for the integrity of the data. PS, EL, TL, SZ, MIM, RZ, and JWD contributed to data collation. NG and AS were instrumental in initiating the study, in financing, and in liaising at the army or university interface. PS supervised the study. JWD did the data analysis. PS drafted the paper and revisions. JWD and PS accessed and verified the underlying data. All authors contributed to the revisions of the paper. All authors have read and approved the final version of the manuscript. All authors had access to the data and responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Because of data protection regulation, individual data cannot be shared directly by the authors. We can share details of the test battery, questionnaires used, and some deidentified pooled data. Requests for data sharing should be sent to the Principal Investigator and

corresponding author (patricia.schlagenhauf@uzh.ch) after publication of the paper and submission of a request for data sharing.

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