











## RESEARCH ARTICLE

# Baseline Characteristics in the Remote Diet Intervention to REduce long-COVID Symptoms Trial (ReDIRECT) [version 1; peer review: 2 approved, 2 approved with reservations]

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## Abstract

### Background




The persistence of symptoms for  $\geq 12$  weeks after a COVID-19 infection is known as Long COVID (LC), a condition with unclear pathophysiology and no proven treatments to date. Living with obesity is a risk factor for LC and has symptoms which may overlap with and aggravate LC.


### Methods


ReDIRECT is a remotely delivered trial assessing whether weight management can reduce LC symptoms. We recruited people with LC and BMI  $>27\text{kg/m}^2$ . The intervention was delivered remotely by dietitians, with online data collection (medical and dietary history, COVID-19 infection and vaccination, body composition, LC history/symptoms, blood pressure, quality of life, sociodemographic data). Participants self-selected the dominant LC symptoms they most


## Open Peer Review


Approval Status    

	1	2	3	4
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wanted to improve from the intervention.

## Results

Participants (n=234) in England (64%) and Scotland (30%) were mainly women (85%) of white ethnicity (90%), with 13% living in the 20% most deprived areas, a mean age of 46 (SD10) years, and median BMI of 35kg/m<sup>2</sup> (IQR 32-40). Before starting the study, 30% reported more than one COVID-19 infection (82% confirmed with one or more positive tests). LC Diagnosis was mainly by GPs (71%), other healthcare professionals (9%), or self-diagnosed (21%). The median total number of symptoms was 6 (IQR 4–8). Self-selected dominant LC symptoms included fatigue (54%), breathlessness (16%), pain (12%), anxiety/depression (1%) and "other" (17%). At baseline, 82% were taking medication, 57% reported 1+ other medical conditions. Quality of life was poor; 20% were on long-term sick leave or reduced working hours. Most (92%) reported having gained weight since contracting COVID-19 (median weight change +11.5 kg, range -11.5 to +45.3 kg).

## Conclusions

Symptoms linked to LC and overweight are diverse and complex. Remote trial delivery enabled rapid recruitment across the UK yet certain groups (e.g. men and those from ethnic minority groups) were under-represented.

## Trial registration

ISRCTN registry (ISRCTN12595520, 25/11/2021).

## Plain Language summary

Long COVID (LC, symptoms lasting 12 weeks or more after a COVID-19 infection) is a poorly understood condition, with no proven treatments. Living with obesity increases the risk of developing LC; symptoms of obesity overlap and aggravate those of LC.

The ReDIRECT study tests, in people living with both LC and overweight, whether weight management can reduce LC symptoms. The study involves total diet replacement (with porridge, soups and shakes) for 12 weeks and is delivered remotely, with dietitian support via internet and/or phone. Researchers collected all data via online forms (medical and diet history, COVID-19 infection and vaccination, weight, height, LC history and symptoms, blood pressure, quality of life, and other demographic data). Each participant selected the LC symptom they most wanted to see improve.

Participants (n=234) lived across the UK, were mainly women (85%) of white ethnicity (90%), with 13% living in the 20% most deprived areas. Their average age was 46 years old with an average body mass index (BMI) of 35kg/m<sup>2</sup>.

Diagnosis of LC was mainly by GPs (71%), other healthcare professionals (9%), or self-diagnosed (21%). Participants reported on average 6 symptoms each, identifying fatigue (54%), breathlessness (16%), pain (12%), anxiety/depression (1%) and "other" (17%) as the symptom they would most like to see improve.

At the start of the study, most (82%) were taking medication, half (57%) reported 1+ other medical conditions. Quality of life was poor, and 20% were on long-term sick leave or reduced working hours. Most (92%) reported gaining weight since contracting COVID-19, on average +11.5 kg.

The baseline characteristics of ReDIRECT study participants show that symptoms linked to LC and overweight are diverse and complex. The study being "remote" means that recruitment was rapid and across the UK, yet certain groups (e.g. men and those from ethnic minority groups) were under-represented.

### Keywords

Long COVID, Weight management, Diet, Remote delivery, Personalisation, Post COVID-19 Syndrome, Fatigue, Pain, Breathlessness

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**Competing interests:** NB is an employee and shareholder of Counterweight Ltd., subcontracted to the University of Glasgow to deliver the ReDIRECT intervention. AM is a member of Clinical Steering Committee for ARC Medical Inc. NS has received institutional grant support from AstraZeneca, Boehringer Ingelheim, Novartis, Roche Diagnostics and honoraria from Abbott Laboratories, Afimmune, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceuticals, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Sanofi. ML has consulted for Novo Nordisk, Nestle, Oviva, Merck, and Sanofi and is an unpaid medical advisor to Counterweight Ltd. No other competing interests were disclosed.

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## Introduction

The term 'Long COVID' (LC) refers to prolonged symptoms following infection with SARS-CoV-2, the viral cause of COVID-19, that are not explained by an alternative diagnosis (Greenhalgh *et al.*, 2022). Other names include 'post-COVID-19 syndrome' (National Institute for Health and Care Excellence, 2021), 'post COVID-19 condition' (Soriano *et al.*, 2022), 'post-covid conditions' (Centers for Disease Control and Prevention, 2023), and post-acute sequelae of SARS CoV-2 infection (PASC) (Horberg *et al.*, 2022). LC is a multi-system condition that affects approximately 10% of people following COVID-19 infection. However, estimates vary and may be lower following vaccination and with more recent COVID-19 variants (Ballering *et al.*, 2022) (Office for National Statistics, 2022).

LC is characterised by a constellation of symptoms, with some studies phenotyping the condition based on symptom clusters (Evans *et al.*, 2022). For people living with LC, symptoms can vary in duration, severity, and impact on daily functioning. LC can follow an unpredictable, relapsing and remitting course, with 'flare-ups' following particular triggers (e.g. physical exertion) (Brown & O'Brien, 2021; Hastie *et al.*, 2023). Among the most common symptoms are fatigue, breathlessness, pains, cognitive dysfunction, loss of taste/smell, and anxiety/depression (Davis *et al.*, 2021; Sudre *et al.*, 2021), though over 50 symptoms have been identified (Lopez-Leon *et al.*, 2021). The long-term impact of LC symptoms on the well-being and quality of life of people affected by this condition is unknown, nor is the economic impact.

The underlying pathophysiology of LC is not well understood, with several – likely interacting – proposed mechanisms. These include viral factors (e.g., viral persistence, reactivation); host factors (e.g., chronic inflammation, metabolic and endocrine dysregulation, autoimmunity); and downstream impacts (e.g., tissue damage from the initial infection, tissue hypoxia, and autonomic nervous system dysfunction) (Castanares-Zapatero *et al.*, 2022; Davis *et al.*, 2023).

Comorbidities, such as cardiovascular disease, diabetes, obesity, and respiratory conditions, have been identified as risk factors for COVID-19. However, their influence on LC symptoms is not well understood. Moreover, there are also substantially higher odds of LC based on sex (female), higher deprivation and occupation (especially education or health-related occupations) (Shabnam *et al.*, 2023).

Lifestyle factors, such as physical activity levels and dietary patterns, may influence LC symptoms, yet their association remains understudied. At the time of writing (02/11/2023), 501 trials investigating LC treatments were registered on clinicaltrials.gov and ISRCTN since 2020 (search terms included Long COVID and synonyms named above). Around 2/3 of the studies were interventional, focusing mainly on rehabilitation and alleviating individual symptoms. With only 26 studies investigating dietary approaches, mostly dietary supplements, dietary strategies to manage LC lack a solid evidence base. Results are awaited for most of these trials.

Weight increase was widely reported across populations following the first COVID-19 lockdown period (March–May 2020) (Bakaloudi *et al.*, 2022), compounding an existing high prevalence of overweight and obesity in the general population – in the UK, 64% of all adults were reported to have a BMI greater than 25kg/m<sup>2</sup> in 2021 (Organisation for Economic Co-operation and Development, 2021). Generally, body composition and weight changes post-COVID have not been thoroughly described in people living with LC. However, the EPILOC study highlighted a consistent association between increasing BMI and post-COVID fatigue, neurocognitive impairment, and chest symptoms, with the greatest recovery rate in those with BMI between 21 and 22 kg/m<sup>2</sup> (Peter *et al.*, 2023).

Weight management programmes in adults with overweight/obesity have been reported to reduce symptoms such as fatigue, breathlessness, and pain, which are also common with LC (pain and QoL (Höchsmann *et al.*, 2022), dyspnoea (Bernhardt & Babb, 2014; Riddle & Stratford, 2013; Stenius-Aarniala *et al.*, 2000). However, the effectiveness of intentional weight loss to reduce symptoms of LC and prevent future cardiometabolic ill-health has not been studied despite that group's specific needs.

The Remote Diet Intervention to Reduce Long-COVID Symptoms Trial (ReDIRECT) tests the impact of an evidence-based dietary weight management programme on LC symptoms in people with overweight or obesity. Here, we describe the baseline characteristics of ReDIRECT participants, focusing on socioeconomic and demographic factors as well as dietary and medical history, including LC diagnosis and symptoms.

## Methods

### Patient and Public Involvement

People living with Long COVID were involved throughout this research. Before submitting the funding application for the research, in March 2021, we conducted an online consultation via the Long Covid Scotland patient group (n=34) to assess interest in the study and to define priorities. Over 75% (n=26) were very interested, with 85% (n=30) prioritising the relief of fatigue and breathlessness as long COVID symptoms they would most like to improve. This informed our decision to use a novel personalised primary outcome measure.

The lay co-investigator (JO) has lived experience of Long COVID since March 2020 and is an active member of the Long Covid Scotland action group. JO and another co-author with lived experience of Long COVID (CW) were part of the study team and members of the monthly trial management team. A designated UoG staff member (TI) coordinated PPI input throughout, including input from a separate COVID-19 PPI group (6 people).

Throughout the study, the group regularly provided advice relating to the intervention, recruitment, data collection and topics for qualitative interviews, and also shaped dissemination activities, contributed to publications and the development of an animation aimed at the general public. Throughout the trial,

the impact of involvement was tracked using the Guidance for Reporting Involvement of Patients and the Public' (GRIPP2) short form, including highlighting where patient perspectives influenced study decision-making.

**Ethical approval.** Ethical approval was obtained from the South-East Scotland Research Ethics Committee 01 (reference number: 21/SS/0077) on 19<sup>th</sup> November 2021. The REC favourable opinion was subject to the following conditions being met prior to the start of the study.

Confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or NHS management permission (in Scotland) should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

At the time of writing, the latest version of the protocol was v1.3, dated June 15<sup>th</sup>, 2022 and the study status is ongoing, with the final participant visit scheduled in March 2024.

This trial was registered on ISRCTN registry (ISRCTN12595520), on the 25<sup>th</sup> of November 2021. Study opened to recruitment on the 20<sup>th</sup> of December 2021.

**Study design and participants.** The full protocol has been previously reported (Haag *et al.*, 2022). In brief, ReDIRECT is a randomised, wait-list controlled, open-label study. The study is conducted entirely remotely, including recruitment, screening, written informed consent, randomisation, intervention, and outcome assessments.

The main inclusion criteria were people living with self-reported LC (symptoms persisting > 3 months before first recruitment contact, BMI > 27 kg/m<sup>2</sup> (BMI > 25 kg/m<sup>2</sup> for South Asians), and age ≥ 18 years. Study exclusion included lengthy hospitalisations (> 10 days) or intensive care unit (ICU) admissions related to COVID-19, people on insulin or anti-obesity drugs, proven myocardial infarction within the last 6 months, severe mental illness (including severe depression and eating disorder), women who are pregnant or considering pregnancy, history of substance abuse, active illness likely to cause a weight change, people who underwent bariatric surgery within the last 3 years or are planning bariatric surgery, advanced kidney problems (eGFR < 50 ml/min/1.73m<sup>2</sup>), gallstones or pancreatitis, participating in another clinical research trial likely to affect diet or weight change, learning disability, and inability to understand English (written or spoken).

A total of 240 participants based in the UK were recruited through a wide range of avenues including social media (Facebook, Twitter), via support from individuals and organisations who disseminated the information within their networks (including Long Covid Scotland, Long Covid Podcast, GP practices, LC

clinics, clinical research networks, councils and occupational health services across the UK, as well as colleagues in NHS Health Boards, Scottish government, and charities, including British Heart Foundation and Chest, Heart and Stroke Northern Ireland, The Wheatley Group, Men's Shed Govan, Glasgow Weight Management Service, newspaper ads (Metro and Daily Mail), and local recruitment activities (e.g., posters and flyers at Glasgow libraries and leisure centres, local pharmacies, GP practices, supermarkets and banks, advert post on the University of Glasgow Yammer platform, community health promotion events at local places of worship, and local football clubs).

Research staff assessed eligibility during a screening telephone call, and participants gave informed consent electronically before enrolment.

After completing a baseline assessment, participants were randomised to either i) treatment: Counterweight-Plus programme (a professionally supported and evidence-based weight loss programme delivered entirely remotely), or ii) control: usual health care. The primary outcome is evaluated at the six-month time point, after which the control group gains delayed entry to the Counterweight-Plus intervention. Participants who did not complete the baseline assessment were withdrawn (n=5), and 235 were randomised. One participant withdrew consent following randomisation. In total, baseline data was available for 234 participants.

The published protocol describes the diet intervention (Haag *et al.*, 2022). In brief, the Counterweight-Plus programme involves a very low-calorie total diet replacement (about 850 kcal/d) and behaviour change. The formula diet is consumed for 12 weeks, followed by food reintroduction and weight management up to the end of one year. Trained dietitians provide personalised support tailored to the needs of the individual via phone or video calls and text chats. Further support is provided through in-app weekly monitoring and nudges, personalised messaging, and group support.

**Outcomes and assessments.** Outcomes were assessed for all participants at baseline prior to randomisation. Data were self-reported via bespoke online questionnaires, verbally over the telephone, email and/or text messages, and collected using a web-based bespoke electronic case report form (eCRF). The questions had pre-defined answer options (yes/no) and free text boxes for additional comments. The questionnaire can be found as *Extended data* to the published protocol (Combet *et al.*, 2022). Participants received digital scales (Model UC-502, A&D Instruments Ltd, Abingdon, UK) and automatic blood pressure monitors (arm type monitor TMB-1970, Kinetik Medical Devices Ltd, Redhill, UK) for measurements of body weight and blood pressure. Self-reported outcomes included COVID-19 and LC-related outcomes, body composition measurements, comorbidities, prescribed medication, wellbeing and health outcomes, work productivity, healthcare use, and food expenditure Table 1.

**Table 1. Primary and secondary outcome measures in the ReDIRECT trial.** (Haag *et al.*, 2022). CFQ: Chalder Fatigue Scale, EQ-5D-5L: EuroQuol 5-dimensional 5-level questionnaire, LC: Long COVID, MRC: Medical Research Council.

	Primary outcome measures	Scales / Tools	References
Self-selected LC symptom	Fatigue	Validated Chalder Fatigue Scale CFQ-11	(Chalder <i>et al.</i> , 1993)
	Breathlessness	Modified MRC Dyspnoea Scale	(Bestall <i>et al.</i> , 1999)
	Pain	P4 Numeric Pain Rating Scale	(Spadoni <i>et al.</i> , 2004)
	Anxiety and depression	Hospital Anxiety and Depression Scale (HADS) questionnaire	(Zigmond & Snaith, 1983)
	Other	Visual Analogue Scale (0-10) for other symptoms with no pre-specified scale	
	Secondary outcome measures	Scales / Tools	References
All non-selected primary LC symptoms	Fatigue, breathlessness, pain, anxiety/depression, other	As above	As above
Body composition and health	Weight	Digital scales (Model UC-502, A&D Instruments Ltd, Abingdon, UK)	
	Height		
	Blood pressure	Arm type monitor (TMB-1970, Kinetik Medical Devices Ltd, Redhill, UK)	
	COVID vaccination		
	Medical history		
	Medication		
Other	Quality of life	EQ-5D 5L	(Buchholz <i>et al.</i> , 2018)
	Work productivity	Work Productivity and Activity Impairment	(Reilly <i>et al.</i> , 1993)
	Healthcare utilisation	Bespoke questionnaire	
	Food expenditure	Bespoke questionnaire	

### LC symptoms

LC symptoms were assessed using validated questionnaires for the four core symptoms of fatigue (Chalder Fatigue Scale, CFS (Chalder *et al.*, 1993)), breathlessness (modified Medical Research Council dyspnoea scale mMRC (Bestall *et al.*, 1999)), pain (P4 pain scale (Spadoni *et al.*, 2004)) and anxiety/depression (Hospital Anxiety and Depression Scale, HADS (Zigmond & Snaith, 1983)). Caseness for the four core symptoms was determined as follows.

The CFS is an 11-item scale with four answer options: 'less than usual', 'no more than usual', 'more than usual', and 'much more than usual'. A bimodal scoring system for each item (0, 0, 1, 1) was used and summed to a total score ranging from 0 to 11. As established in the validation study (Chalder *et al.*, 1993), a score of at least 4 was used to indicate the

caseness of fatigue. A continuous score (0, 1, 2, 3) can also be used to assess the intensity of symptoms. For both scoring systems, a higher score indicates greater fatigue severity. The CFS can be subdivided into two components to separately measure physical fatigue (items 1 to 7) and mental fatigue (items 8 to 11).

The HADS questionnaire comprises two subscales for anxiety and depression, with seven items, each scored 0 to 3. A total sum of 11 or more for each subscale was used to indicate the caseness of anxiety or depression (Zigmond & Snaith, 1983).

The P4 pain scale consists of four items which assess pain levels on a numeric scale of 0 to 10 in the morning, afternoon, and evening, and with activity with a total score ranging from 0 (no pain) to 40 (pain as bad as it can be). A caseness for pain was considered with a score of 1 or more.

The mMRC is a tool to assess the degree of breathlessness on a scale of 0 (no breathlessness) to 4 (extreme breathlessness). A score of at least 1 ('I get short of breath when hurrying on level ground or walking up a slight hill' or worse) indicated breathlessness.

Participants could add further LC symptoms in free text boxes along with a rating on how troublesome the symptoms were on a 10-point numeric scale. All symptoms entered at baseline were considered active.

### Health status

Health status on the day of the baseline assessment was measured using the EQ-5D-5L questionnaire (Buchholz *et al.*, 2018). This validated tool indicates health status across five dimensions for mobility, self-care, usual activities, pain/discomfort and anxiety/depression with five levels each (no, slight, moderate, severe or extreme problems). The combination of these five domains can be mapped to a health utility score, which ranges from 0 (a state as bad as being dead) to 1 (perfect health) (Hernandez Alava *et al.*, 2023). An additional visual analogue scale asks the participant to rate their health on the day, ranging from 0 ('The worst health you can imagine') to 100 ('The best health you can imagine'). Data were analysed by individually considering each dimension and the VAS and combining the five dimensions to a composite health status.

**Statistical analysis.** Baseline data is presented as n (%) for categorical variables and mean (SD) or median (IQR) for continuous variables. Percentages for recruitment are based on the total number of participants recruited (n=240). All other percentages are based on the available data (n=234).

Free text responses were evaluated and grouped into categories using Microsoft Excel following a defined coding dictionary (see extended data). Free text data and pre-defined answer options were combined where they overlapped to avoid duplication.

Medication entries were analysed as medications (Table 3) if included in the British National Formulary (BNF) catalogue and grouped following the main BNF categories. Entries not considered in the medication analysis (n=15) include Andro-feme, Sterimar nasal spray, several dietary supplements (multivitamins, vitamin C, cod liver oil, flushing niacin, quercetin, co-enzyme Q10, probiotics, blackcurrant seed oil, flaxseed oil, bromelain), and CBD oil. All dietary supplements entered as medications were also included in the nutritional supplement analysis (Figure 6H). CBD oil was included in private healthcare.

Group differences between those who had COVID-19 before and after vaccination were tested using the Mann-Whitney-U test in R for the median number of symptoms and the chi-squared test for the type of symptoms. A p-value of 0.05 was considered statistically significant.

All graphs were created in R using the ggplot2 package and HH package. Plot panels were compiled using Inkscape. BioRender.com was used to partially create one of the figures.

## Results

### Study population

In total, 240 participants from across the UK were enrolled in the ReDIRECT study, of whom 235 (98%) were randomised to either the diet intervention Counterweight-Plus (n=117, treatment group) or usual care (n=118, control group). One participant in the treatment group withdrew consent after randomisation, resulting in n=116 in the treatment group.

The main source of recruitment was social media (n=104, 43%), followed by other online sources, including e-newsletters, websites, and podcasts (n=40, 17%), communication through health care professionals (n=33, 14%), word of mouth (n=31, 13%), LC support groups (n=13, 5%), and newspapers (n=8, 3%). Local recruitment activities (at Glasgow Gurdwaras and football clubs) and GP practice searches conducted in 14 practices in the NHS Greater Glasgow and Clyde health board (32 invitations sent to participants) were least successful with only n=4 (2%) and n=3 (1%) recruited, respectively. One person in the Public Patient Involvement group participated; the recruitment source was unknown for 3 participants. These methods facilitated rapid recruitment of 240 participants in slightly over 6 months.

Baseline demographic characteristics are described in Table 2. Most participants were women (n=198, 85%) of white ethnicity (n=211, 90%) from a range of socioeconomic backgrounds with a mean age of 46 years (SD 10), a median BMI of 35 kg/m<sup>2</sup> (IQR 32 - 40) and at least an undergraduate degree (n=143, 61%). Participants lived in England (n=149, 64%), Scotland (n=71, 30%), Wales (n=11, 5%), and Northern Ireland (n=3, 1%). While participants were from across the spectrum of area deprivation, those living in the most deprived areas were somewhat less represented than those from the least deprived areas (13% vs. 27%). Most participants reported living with others in a household (n=204, 87%). Most lived with a partner/spouse (n=167, 82%) and/or at least one child (n=127, 54%).

### Employment

Participants were asked to choose one of the six categories that best described their employment status before COVID-19 and at baseline (full-time, part-time, retired, student, unemployed, other). Between becoming ill with COVID-19 and entering the study, 85 (36%) participants experienced a change in employment status (Figure 1A). Before the first COVID-19 infection, most participants (n=167, 71%) were in full-time employment, compared to 101 (43%) at the start of the study. Following COVID, changes in full-time employment included switching to part-time (n=28, 12%), being on long-term sick leave (n=28, 12%), reduced working hours (n=6, 3%),

**Table 2. Participant characteristics at baseline.**

Characteristics (n % unless otherwise specified)	
n	234
Women	198 (85%)
Age, years, mean (SD)	46 (10)
Systolic blood pressure, mmHg, mean (SD)	131 (14)
Diastolic blood pressure, mmHg, mean (SD)	80 (9)
Body mass index, kg/m <sup>2</sup> (IQR), n (%)	35 (32 - 40)
Below 27 (South Asian ethnicity)	1 (<1%)
27 to 29.9	32 (14%)
30 to 34.9	80 (34%)
35 to 39.9	58 (25%)
40 or above	63 (27%)
<b>Region</b>	
England	149 (64%)
Scotland	71 (30%)
Wales	11 (5%)
Northern Ireland	3 (1%)
<b>Ethnicity</b>	
White	211 (90%)
South Asian	10 (4%)
Other Asian, Asian British	5 (2%)
Black, African, Caribbean or Black British	2 (1%)
Other or mixed ethnic group	6 (3%)
<b>Education</b>	
School leaver/standard grade/GCSE	28 (12%)
Highers/A levels	14 (6%)
Higher education HND/HNC/NVQs	47 (20%)
Undergraduate degree	87 (37%)
Master's degree/PhD	56 (24%)
Prefer not to say	2 (1%)
<b>Living situation</b>	
Alone	30 (13%)
With partner	167 (71%)
With children under 18	106 (45%)
With children over 18	29 (12%)
With parents	16 (7%)
With siblings	15 (6%)

Characteristics (n % unless otherwise specified)	
With friends	4 (2%)
Other (parents-in-law, grandparents, lodger)	3 (1%)
<b>Index of multiple deprivation</b>	
1 (most deprived)	31 (13%)
2	44 (19%)
3	45 (19%)
4	51 (22%)
5 (least deprived)	63 (27%)

retiring (n=2, 1%), or becoming unemployed (n=9, 4%). Including people who worked part-time, 44 (19%) participants were on long-term sick leave, and 7 (3%) were on reduced hours due to LC at baseline.

Based on the International Standard Classification of Occupations (ISCO-08), occupations ranged across seven major occupational groups (Figure 1B). Healthcare and teaching professionals were the most common occupation groups, with over one-third of participants working in healthcare and over 10% in the educational sector. No participant worked as a skilled agricultural, forestry and fishery worker in elementary occupations or the armed forces.

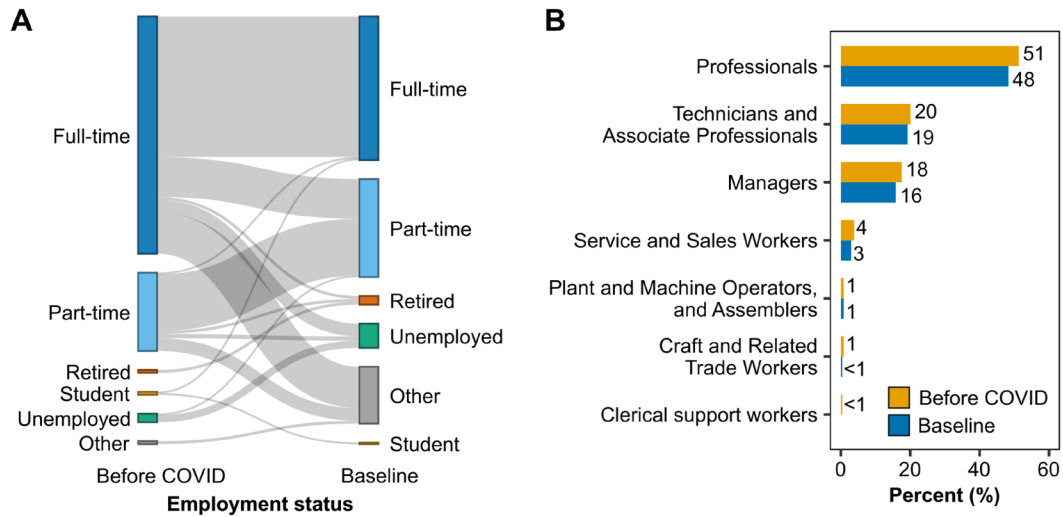
#### Contracting COVID-19

Dates of the first COVID-19 infection ranged from October 2019 to March 2022 (Figure 2A). Most participants (n=178, 76%) had at least one positive COVID-19 test (PCR 64%, LFT 37%, antibody test 19%, unsure which test 2%). Those who did not have a positive COVID-19 test predominantly became ill in the first five months of the outbreak (up to May 2020). Following the first infection, 30 (13%) were admitted to the hospital (mean length of stay 6 days (SD 5)).

A third of participants (n=71, 30%) contracted COVID-19 at least a second time before the start of the study, which mostly occurred in the winter wave in 2021/2022 (Figure 2A). Nearly all (n=70, 99%) had at least one positive test (PCR 68%, LFT 77%, antibody test 7%). Hospital admission rates following the second infection were slightly lower than the first (n=5, 7%), and the mean stay was 3 days (SD 3).

At the start of the study, most participants (n=228, 97%) had been vaccinated at least once, with 2 (1%) having received one vaccination, 19 (8%) two vaccinations, and 207 (91%) three vaccinations. Most participants contracted COVID-19 for the first time before their first vaccination (n=169, 72%). Of the 65 participants who contracted COVID-19 after the first vaccination, 8 (3%) became ill before the second vaccination, 28 (12%) became ill after the second but before the third vaccination, and 26 (11%) became ill after the third vaccination.





**Figure 1. Employment status and occupation groups before COVID and at baseline.** (A) Participants were asked to choose one of the six categories in the figure which best described their employment status before COVID-19 and at baseline. Pre-covid, ‘other’ includes homemaker and full-time carer/part-time student. At baseline, ‘other’ includes long-term sick leave, homemaker, disabled, part-time student, and agency worker. (B) Occupations were classified based on the International Standard Classification of Occupations (ISCO-08) and ranged across seven of the ten major occupational groups both before COVID-19 and at study baseline.

Data on any further infections prior to the study start were not collected.

**Long COVID**

LC was mainly diagnosed by a GP (n=166, 71%), other healthcare professionals such as hospital consultants (n=20, 9%) or self-diagnosed (n=48, 21%) (Figure 2B). At baseline, most participants had lived with LC for at least one year (n=142, 61%). A small proportion reported having had LC over two years (n=17, 7%).

**Symptoms.** The dominant LC symptom was fatigue (n=128, 55%), followed by breathlessness (n=37, 16%), pain (n=32, 14%), and cognitive impairment (n=12, 5%) (Figure 2C). Outside of these four symptoms, 25 participants (11%) named symptoms such as anxiety/depression, loss of taste and smell, tremors, and tinnitus as their main symptom.

Fatigue was prevalent in all but one participant (n=233, 99.6%) (assessed using the bimodal scoring system) (Figure 2E). The continuous scores ranged from 0 to 33, with a high median score of 28 (IQR 24 – 31). The median physical fatigue score was 18 (IQR 15 – 20, max 21), while the median mental fatigue score was 10 (IQR 8 – 12, max 12).

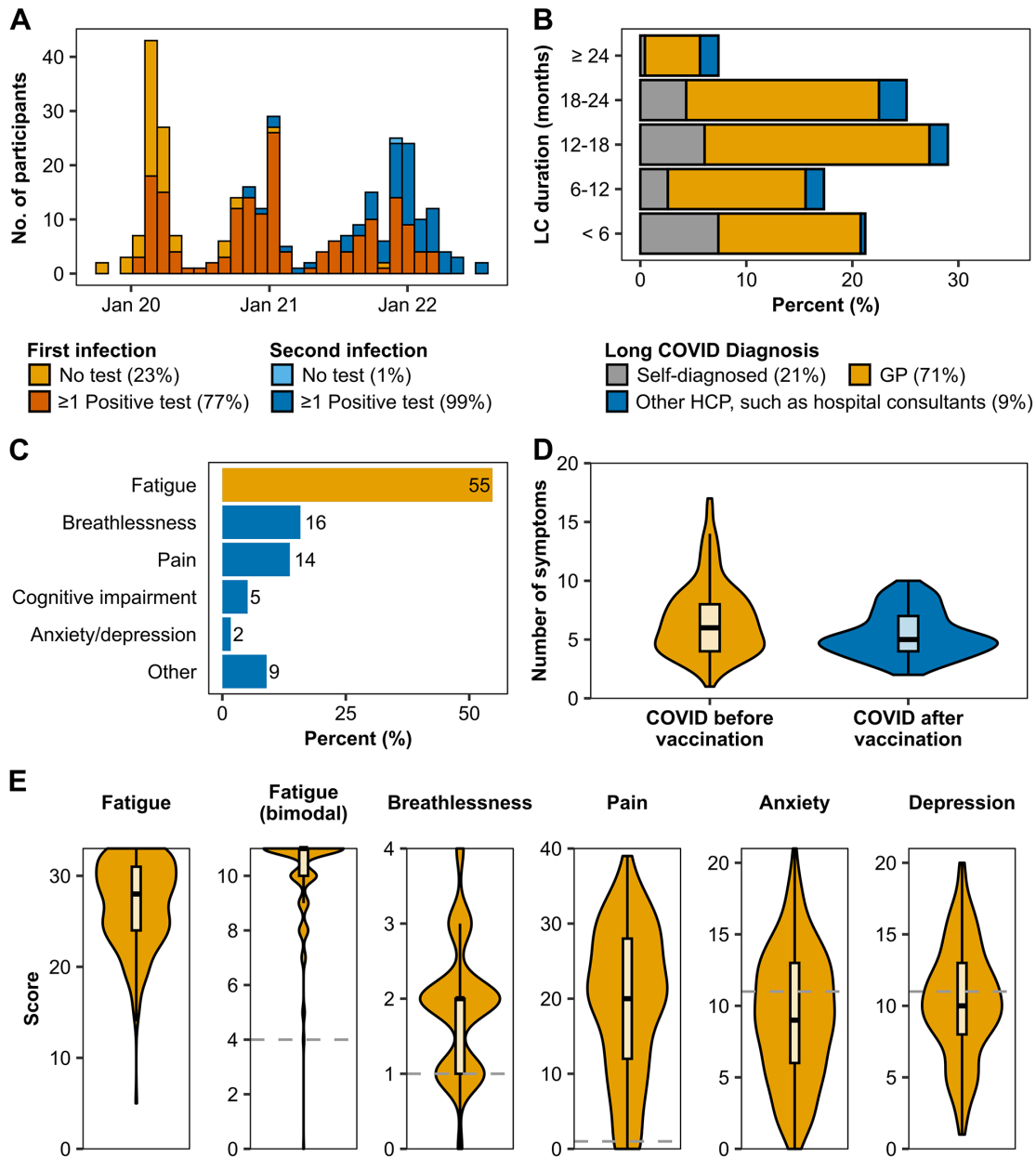
Similarly, both breathlessness (n=228, 97%) and pain (n=219, 94%) were highly prevalent among participants (Figure 2E). The median for breathlessness was 2 (IQR 1 – 2) of a maximum of 4, i.e. most participants had moderate breathing difficulties (‘On level ground, I walk slower than people of the same age because of breathlessness or have to stop for breath when walking at my own pace’).

Pain severity was spread across the entire range from no pain at all (score 0) to pain as bad as it could be (score 40) (Figure 2E). The median for pain was 20 (IQR 12 – 28).

Anxiety (n=95, 41%) and depression (n=110, 47%) were both prevalent in less than half of participants (Figure 2E). The median score for anxiety was 9 (IQR 6-13), and the median for depression was 10 (IQR 8-13) out of a maximum of 21 points for both symptoms.

Aside from the core symptoms (fatigue, breathlessness, pain, anxiety/depression), 179 (76%) participants reported other symptoms, grouped into 27 symptom groups. Symptom groups experienced ranged from 0 to 13 (median 2 (IQR 0 – 4), related to cognitive impairment (n=82, 35%), neurological symptoms such as tremors and feelings of pins and needles (n=66, 28%), cardiovascular symptoms such as palpitations and arrhythmias (n=52, 22%), and digestive disorders including acid reflux, nausea and diarrhoea (n=51, 22%). Figure 3 shows an overview of reported LC symptoms.

The median total number of symptoms was 6 (IQR 4 – 8). The number of symptoms experienced by people who fell ill with COVID-19 before their first vaccination (n=163) and those who got COVID-19 after vaccination (n=65) are displayed in Figure 2D. People who contracted COVID-19 before vaccination had a median of 6 symptoms in comparison to 5 (p=0.003), with more frequent reports of neurological symptoms (34% vs 14%, p=0.004), cutaneous signs (18% vs 3%, p=0.005), hearing loss or tinnitus (20% vs 6%, 0.021), and digestive disorders (25% vs 12%, p=0.045) (Supplementary Figure 2, which can be found as *Extended data* (Haag et al., 2023b)).



**Figure 2. Covid-19 infection and Long COVID symptoms.** (A) COVID-19 infection dates: First COVID infection dates ranged from October 2019 to March 2022, and second infection dates ranged from November 2020 to July 2022. Most infections were confirmed by at least one positive COVID test (PCR, rapid antigen lateral flow test, or antibody test), shown in orange and dark blue. Yellow and light blue bars show the number of infections which were not confirmed by a COVID test. (B) Long COVID duration: Figure shows the length of time in months participants were living with Long COVID at the start of the study. Long COVID was diagnosed either by a GP (yellow), a different healthcare professional (blue), or self-diagnosed (grey). GP: general practitioner, HCP: healthcare professional, LC: Long COVID. (C) Percentage of the Long COVID symptom each participant selected as the one they would most like to see improve. The most selected symptom (fatigue) is highlighted in yellow. (D) Number of Long COVID symptoms (core symptoms and symptom groups) in people who had COVID before (yellow) and after (blue) vaccination. Difference between the groups was significant ( $p=0.003$ ). (E) Core Long COVID symptoms: Fatigue, breathlessness, pain, anxiety, and depression were assessed using validated questionnaires (Chalder Fatigue Scale, modified MRC Dyspnoea Scale, P4 pain scale, Hospital Anxiety and Depression Scale). Fatigue is represented as total fatigue score and bimodal scoring. The y-axes show complete range of possible scores for each scale (0 to 33, 11, 4, 40, 21, 21 for fatigue total, fatigue bimodal, breathlessness, pain, anxiety, and depression, respectively), with higher scores indicating greater severity. The grey dashed line shows the cutoffs used for caseness of the symptoms. No cutoff for total fatigue score was used to determine caseness.

**Support.** Most participants received support from the NHS to manage LC (n=206, 88%). Most participants visited their GPs (n=190, 81%), and half visited specialist LC clinics (n=117, 50%). Hospital specialist services were used by n=113 (48%), and a third (n=74, 32%) received physiotherapy. Only a small proportion received dietary support (n=19, 8%) or mental health support (n=11, 5%). A minority said they received no support (n=29, 12%). In addition to NHS resources, 56 (24%) paid for private healthcare, and 16 (7%) used complementary and alternative medicine. Private healthcare included medical specialists (n=24, 10%), Nuffield Health (n=15, 6%), hyperbaric oxygen treatment (n=8, 3%), physiotherapy (n=7, 3%), nutritionist (n=4, 2%), mental health support (n=3, 1%), private GP (n=2, 1%), medication and testing (n=1, <1%), and LC rehab (n=1, <1%).

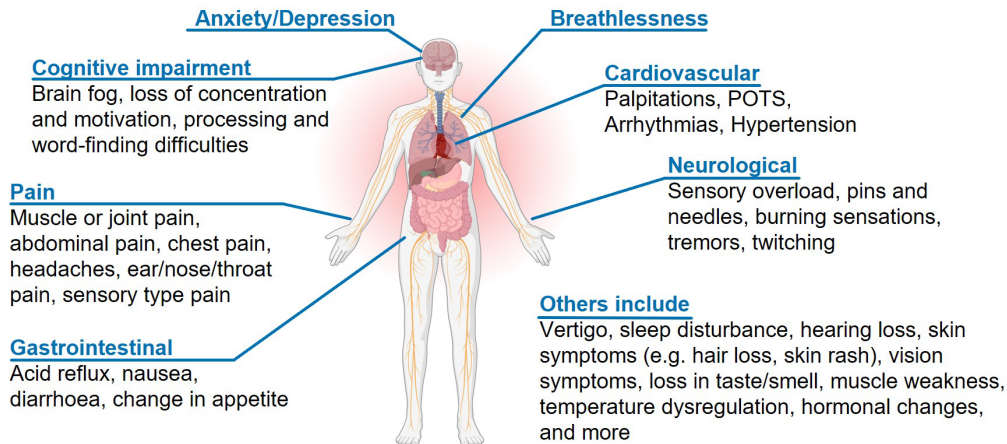
**Comorbidities, medications, health status**

At baseline, the median weight was 98 kg (IQR 86 – 114), and the median BMI was 35.2 kg/m<sup>2</sup> (IQR 32 – 40). Mean blood pressure was 131 (SD 14) / 80 (SD 9) mmHg. Over half of

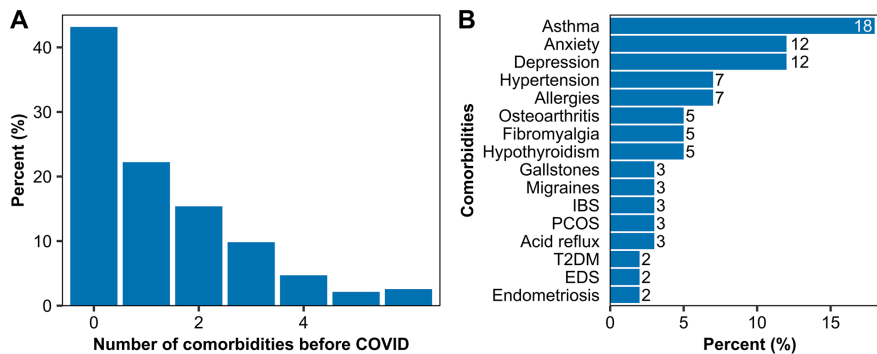
the participants (n=133, 57%) reported at least one other medical condition diagnosed before contracting COVID-19 (Figure 4 and Supplementary Table 6, which can be found as *Extended data* (Haag *et al.*, 2023b)).

The median number of comorbidities was 1 (IQR 0-2), and the total ranged from 0 to 12, not counting overweight and obesity. The most prevalent comorbidity was asthma (n=42, 18%), followed by anxiety (n=29, 12%), depression (n=28, 12%), and hypertension (n=17, 7%). Prior to COVID-19, 12 participants (5%) reported fibromyalgia, 5 (2%) type 2 diabetes mellitus, and 4 (2%) ME/CFS. A full list of comorbidities prior to COVID-19 and their frequency can be found in Supplementary Table 7 as *Extended data* (Haag *et al.*, 2023b).

At baseline, most participants (n=191, 82%) were taking medication, with the total number of medications per participant ranging from 1 to 16 (median (IQR) 4 (2 – 6)). Over half of the participants had been prescribed at least one medication to treat symptoms of LC (n = 124, 53%), while 28 (12%) took



**Figure 3. Overview of Long COVID symptoms reported in the ReDIRECT study.** Participants reported Long COVID symptoms outside of fatigue, breathlessness, pain, and anxiety/depression using free text boxes. Partially created with Biorender.com.



**Figure 4. Existing comorbidities prior to the first COVID infection.** (A) The number of comorbidities per participant and (B) the 16 most prevalent comorbidities which were present before the first COVID infection.

at least one medication for which they reported not knowing whether they were taking it for LC symptoms or a different condition.

In total, 818 different medications were reported (Table 3), of which 42% were taken to treat LC and 51% were prescribed for other health conditions. The treated condition was unknown to the participant for 6% of medications.

Common medications included drugs for the central nervous system (n= 125, 53% of participants), respiratory system (n=89, 38% of participants), gastro-intestinal system (n=79, 34% of participants), cardiovascular system (73, 31%

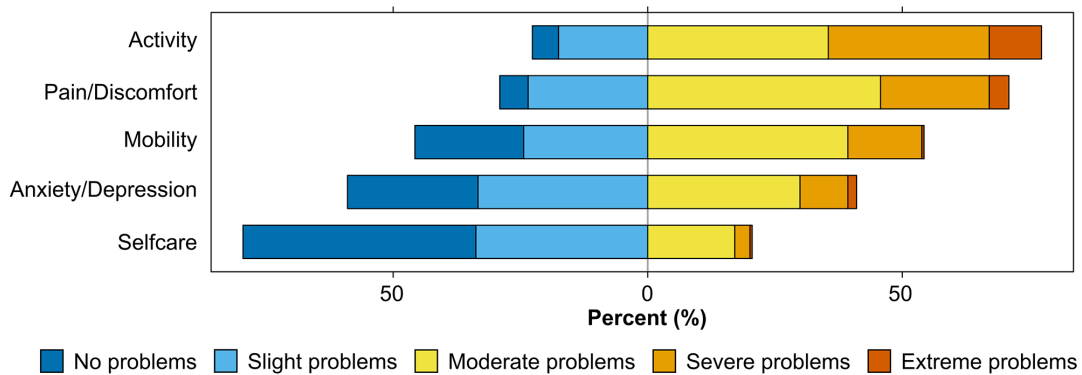
of participants) and obstetrics, gynaecology, and urinary tract disorders (n=41, 18% of participants).

A full list of medications can be found in the supplementary data as *Extended data* (Haag *et al.*, 2023b).

Health status was measured using the EQ-5D-5L questionnaire (Figure 5). At baseline, most participants reported moderate or worse problems with activity (n=181, 77%), pain/discomfort (n=166, 71%), and mobility (n=127, 54%). Slightly less than half reported moderate or worse problems with anxiety/depression (n=96, 41%). Participants had the least problems with self-care (washing or dressing themselves) (moderate or worse problems:

**Table 3. Medications.** Frequency and type of medications taken at baseline.

Drug group	n (%) of n=818 medications	n (%) of n=234 participants
Central Nervous System	235 (29%)	125 (53%)
Respiratory System	163 (20%)	89 (38%)
Gastro-Intestinal System	95 (12%)	79 (34%)
Cardiovascular System	118 (14%)	73 (31%)
Obstetrics, Gynaecology and Urinary-Tract Disorders	51 (6%)	41 (18%)
Endocrine System	42 (5%)	33 (14%)
Nutrition and Blood	51 (6%)	32 (14%)
Musculoskeletal and Joint Diseases	32 (4%)	29 (12%)
Ear, Nose and Oropharynx	10 (1%)	10 (4%)
Infections	7 (1%)	6 (3%)
Malignant Disease and Immunosuppression	4 (<1%)	3 (1%)
Skin	3 (<1%)	3 (1%)
Eye	1 (<1%)	1 (<1%)



**Figure 5. Health status at baseline.** Health status was assessed using the EQ-5D-5L questionnaire across five dimensions (activity, pain/discomfort, mobility, anxiety/depression, selfcare) and five levels each (no, slight, moderate, severe, or extreme problems). All participants (n=234) responded to the questionnaire.

n=48, 20%). The overall health utility score (combining all five domains) was mean (SD) 0.48 (0.243). The mean EQ-5D VAS was 46 (SD 17) (Supplementary Table 9 (Haag *et al.*, 2023b)).

### Support networks

LC support networks, such as online communities, were used by 139 (59%) participants (Supplementary Table 11 (Haag *et al.*, 2023b)). The most common networks included Facebook groups (n=98, 42%) and LC support charities (n=58, 25%; includes Long Covid Support, Long Covid Scotland, Long Covid England, Long Covid Wales, Long Covid SOS). Further support was accessed through local support groups (n=18, 8%), online forums and communities such as Twitter and Reddit (n=12, 5%), and WhatsApp groups (n=5, 2%).

### Weight management and diet

Most participants (n=184, 79%) provided pre-COVID-19 weight data: median weight before COVID-19 was 84.4 kg (IQR 73.5 – 97.2) and 98.0 kg (IQR 86.3 – 114.0) at baseline.

Following COVID, high weight gain was prevalent across all areas of deprivation (Figure 6A). Over 90% of participants reported weight gain (n=215, 92%). A few participants reported not changing in weight (n=10, 4%), losing weight (n=6, 3%), or did not know how their weight changed in comparison to before COVID-19 (n=3, 1%). The highest reported weight gain was 45.3 kg, and the highest weight loss was 11.5 kg. In total, the median (IQR) change in weight from before COVID-19 to the study baseline was 11.5 kg (6.9 – 16.7).

Weight status NICE weight classes (<https://cks.nice.org.uk/topics/obesity/diagnosis/identification-classification/>) changed for 65 (28%) participants. In most cases (n=47, 20%), weight status changed from overweight to obesity classes. Of the 18 participants who were of normal weight before COVID-19, their weight status changed to overweight (n=13, 6%) or obesity (n=5, 2%) (Figure 6E).

We found that median weight gain was highest for people with a pre-COVID BMI below 25 (n=18, 17.1 kg (OQR 13-23)) and lowest for people with a pre-COVID BMI of 35-40 (n=22, 8.8kg (IQR 6-15)) (Figure 6B, Supplementary Table 13 (Haag *et al.*, 2023b)). Weight gain was similar across IMD quintiles (Figure 6A).

Before starting the study, most participants already had experience with weight management (n=194, 83%), of which 80% had successfully lost weight in the past (Figure 6C). Commercial weight loss programmes were the most used method (n=159, 68%) and the most successful for weight loss (n=115, 72% of those who used commercial weight management). Other methods included increased physical activity, self-directed weight loss programmes (e.g., the 5:2 diet), diet change and other methods (bariatric surgery and practising meditation). Pre-COVID-19 BMI and BMI at baseline were higher in those with prior weight management experience (median pre-COVID BMI: 29.2 vs 25.6 kg/m<sup>2</sup>, median BMI at

baseline: 35.6 vs 32.6 kg/m<sup>2</sup>). The median change in weight after COVID-19 was similar regardless of prior weight management experience (8.4 vs 8.2 kg).

Lifestyle changes were common after COVID. Notably, physical activity was reduced for 9 out of 10 participants (n=212, 91%) (Figure 6D). On average, median physical activity levels reduced from exercising occasionally (< 3 times per week) to walking only. The number of people who did not exercise at all rose from n=1 (<1%) before COVID-19 to n=54 (23%) at baseline.

Over half of the participants (n=132, 56%) modified their diet after developing LC, with calorie restriction (n=85, 36%) and low-carb diets (n=56, 24%) being the most common, followed by no dairy (n=49, 21%), low histamine (n=33, 14%), anti-inflammatory (n=32, 14%), vegan (n=21, 9%), and other (such as gluten-free and low FODMAP) (n=9, 4%) (Figure 6F). A third tried more than one type of diet (n=76, 32%). At baseline, most participants were following an omnivorous diet (n=160, 68%) and n=143 (61%) were taking supplements (Figures 6G and 6H). The most common three supplements were Vitamin D (n=93, 40%), multivitamins (n=61, 26%), and plant supplements and bioactives (n=32, 14%).

Further lifestyle changes included stopping drinking alcohol (n=41, 21%) and stopping smoking (n=7, 9%).

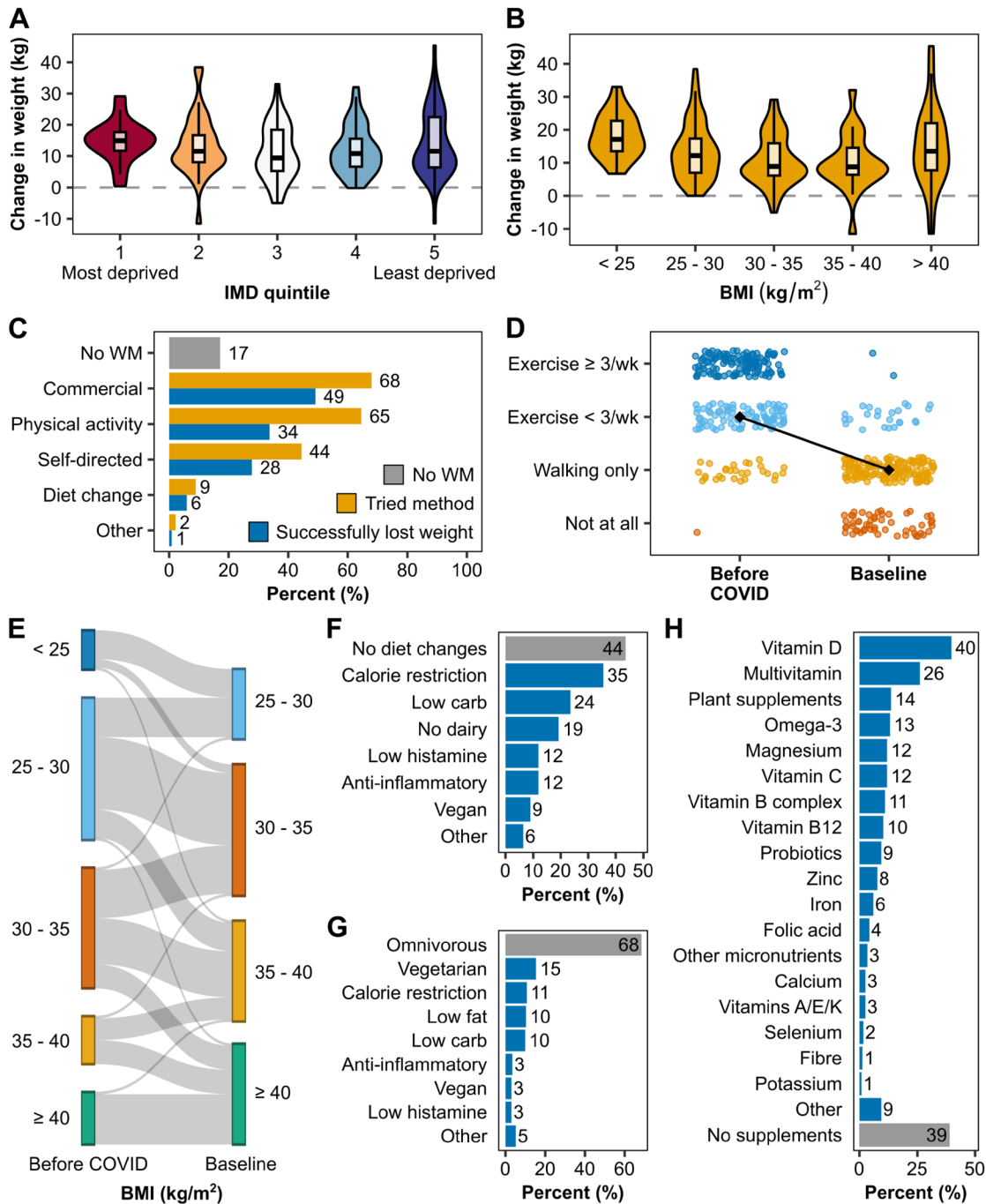
## Discussion

### Summary of key findings

The baseline characteristics of participants in the Remote Diet Intervention to Reduce Long-COVID Symptoms Trial (ReDIRECT) describe a diverse group of adults across the UK who are predominantly middle-aged women of white ethnicity.

The remote nature of the study allowed for rapid recruitment, with a broad geographic spread of participants across the UK. While participants were from a range of socioeconomic backgrounds, those living in the most deprived areas were underrepresented compared to those from the least deprived areas (13% vs. 27%). Two-thirds of participants had at least an undergraduate degree, with a third working in healthcare. Representation of healthcare professionals reflects some of our recruitment strategies, including dissemination through NHS Health Boards in Scotland and electronic bulletins aimed at healthcare professionals, and the fact that front-line staff were markedly more exposed to COVID-19 in the earlier parts of the pandemic (Nguyen *et al.*, 2020).

A critical methodological feature of the ReDIRECT study is the personalised primary outcome, with participants nominating at baseline the LC symptom that they would most like to see improve (Haag *et al.*, 2022). The LC symptom nominated by most participants was fatigue, followed by breathlessness, pain, and cognitive impairment. A small proportion of participants named other symptoms (such as anxiety/depression, loss of taste and smell, tremors, and tinnitus) as their main



**Figure 6. Weight management, diet and lifestyle changes from before COVID to baseline.** Pre-COVID weight data was provided by 184 (79%) participants. The change in weight from before the first COVID infection to the baseline assessment is shown per IMD quintile (A) and BMI category prior to COVID (B). BMI (kg/m<sup>2</sup>) was categorised as follows: < 25 = normal weight, 25 - 30 = overweight, 30 - 35 = obesity class I, 35 - 40 = obesity class II, > 40 = obesity class III. The number of participants per BMI category before COVID and how their weight status had changed at baseline is illustrated in (E). (C) Most participants had prior experience with weight management using different methods (yellow) with varying degrees of success in losing weight (blue). A minority did not attempt to lose weight prior to joining the study (grey). (D) Physical activity levels before COVID and at baseline were reported in four levels: regular exercise (≥ 3 times per week), occasional exercise (< 3 times per week), walking only, or no physical activity at all. The black diamond and line show the change in median activity levels before and after COVID. (F) Dietary changes following the development of Long COVID were common. Other diets not explicitly listed include reduction in lactose, gluten, FODMAPs, sugar, as well as vegetarian, pescetarian, anti-obesity medication, and general healthy eating. (G) shows the diet consumed at baseline. Other includes reduction in gluten, dairy, lactose, sugar, FODMAPs and increase in healthy eating. Supplements taken at baseline are listed in (H). For the full list of supplements, see Supplementary Table 16, which can be found as *Extended data* (Haag et al., 2023b). BMI: body mass index, IMD: index of multiple deprivation, WM: weight management.

symptom. These symptoms have also commonly been reported in other LC studies (Davis *et al.*, 2021; Kim *et al.*, 2023; Lopez-Leon *et al.*, 2021; Marjenberg *et al.*, 2023; Sudre *et al.*, 2021; Whitaker *et al.*, 2022; ).

Fatigue was reported by nearly all participants, with a high median score on the Chalder Fatigue Scale. Similarly, both breathlessness and pain were highly prevalent, affecting close to all participants. Anxiety and depression were present in approximately half of the participants, reflecting a high level of illness burden and distress across the study population, with corresponding impacts on quality of life. There is a well-established relationship between obesity and health-related quality of life. However, the EQ-5D VAS mean score of 46 (SD 17) in the ReDIRECT study population is markedly lower than would be expected from raised BMI alone (74 and 69, for people living with overweight and obesity, respectively (Sach *et al.*, 2007)). The major impact on health-related quality of life is further highlighted by the health utility score, half that of the UK general population (0.48 vs 0.86) (Ara & Brazier, 2011), and the high proportion of participants unable to carry out usual activities (10%), compared to 1% in the general population aged 35-64 in Europe including the UK (Janssen *et al.*, 2021).

Most participants had not been vaccinated before becoming ill with COVID-19, with the number of affected organ systems (based on core symptoms and symptom group counts) lower by one in people infected after vaccination, in line with evidence linking vaccination with reduced LC severity (Byambasuren *et al.*, 2023; Tran *et al.*, 2023).

Nearly all participants received healthcare support for LC through the NHS, mainly through GPs, Long COVID clinics, hospital specialist services and physiotherapy. A quarter of participants had turned to private healthcare, anecdotally because of difficulties accessing support through the NHS. Our qualitative analysis will further explore the reasons for accessing private healthcare and the additional burden on participants and their families.

Non-healthcare-related support was sought by every 3 of 5 participants, mostly through online LC communities or local support groups. Online LC communities evolved early in the pandemic, with patients sharing experiences of the after-effects of COVID-19 on social media and collectively coining the term “Long Covid” (Callard & Perego, 2021). At a time of social distancing and with evidence about LC first emerging through these patient groups, online communities were an important source of support for LC patients, providing a safe space to speak about symptoms and concerns, filling a gap in care, and helping patients find validation in others sharing similar experiences (Day, 2022; Russell *et al.*, 2022).

In the ReDIRECT study, the number of pre-existing comorbidities and the prevalence of overweight and obesity before LC corresponded to the average in the UK population (Office for National Statistics UK Health Indicators, 2022; Organisation for Economic Co-operation and Development). Pre-existing

asthma, hypertension and depression have been associated with increased risk for LC (Loosen *et al.*, 2022; Sudre *et al.*, 2021; Tsampasian *et al.*, 2023), which may explain that the proportion of people with asthma in our study was greater than the age-standardised rate in the UK (18% vs 10% for men and 12% for women). While pre-COVID-19 weight data was available for only 79% of our participants, at least 71% were living with overweight or obesity prior to becoming ill with COVID-19. Interestingly, the proportion of pre-existing conditions generally associated with overweight and obesity, such as hypertension, dyslipidaemia, and type 2 diabetes, was about 5% (diabetes) to 10% (hypertension and dyslipidaemia) lower compared to the general population (Office for National Statistics UK Health Indicators, 2022). Whether this is due to the lower mean age (46), the largely female population or other factors is unclear.

Previous studies have highlighted the impacts of the COVID-19 pandemic on health behaviours that influence weight (including eating habits, physical activity, stress, and sleep), with most reporting weight gain across populations (Alah *et al.*, 2021; Almandoz *et al.*, 2022; Flanagan *et al.*, 2021; Khubchandani *et al.*, 2020; Khubchandani *et al.*, 2022; Mason *et al.*, 2022). The ReDIRECT study provides novel insight into body composition and weight management in this participant group living with both LC and overweight. Whilst a significant proportion of participants already lived with overweight or obesity prior to contracting COVID-19 (over two-thirds), a majority (68%) reported having gained a substantial amount of weight (5kg or more) following infection. The reasons for this weight gain may be multiple, including behavioural changes during confinement periods, compounded by fatigue and mobility issues, both common symptoms reported in this study. There is currently limited evidence exploring this in LC, and this aspect will be further explored in the ReDIRECT trial qualitative analysis.

Most participants were already familiar with weight management before enrolling in ReDIRECT, with 4 of 5 participants having previously tried losing weight and 3 of 5 having successfully lost weight at some point in their lifetime. Commercial weight loss programmes were the most popular and effective for losing weight, followed by increased physical activity and self-directed diet regimes. BMI was higher pre-COVID and at baseline for those who had previously attempted weight loss than those who had not. However, the weight gained post-COVID was not different between the two groups.

Behaviour changes were common after contracting COVID-19 infection. Notably, physical activity levels reduced from exercising occasionally (< 3 times per week) to walking only, with nearly a quarter of participants not exercising at all, at baseline. Attempts at dietary modifications were common, with over half modifying their diet after developing LC, commonly using approaches including calorie restriction and low carbohydrate diets as well as other diet modifications including anti-inflammatory, vegetarian/vegan, dairy-free, gluten-free, low sugar, low FODMAP, and low histamine diets, despite

the lack of evidence base in this space. Similarly, dietary supplementation was common and varied. Changes and supplementation were often self-led, short-term, and without professional support. By baseline, most participants had returned to an omnivorous diet.

One of the proposed mechanisms underpinning LC is immune dysregulation and long-term systemic inflammation with elevated levels of inflammatory markers, such as interleukin (IL)-1 $\beta$ , IL-6, and TNF- $\alpha$  (Peluso *et al.*, 2021; Schultheiss *et al.*, 2022; Schultheiss *et al.*, 2023; Zhang *et al.*, 2023). Anti-inflammatory therapies in LC patients are potential treatment strategies currently being studied in several clinical trials (Bonilla *et al.*, 2023). Weight loss has been shown to reduce pro-inflammatory markers present in the chronic low-grade inflammatory state associated with obesity, including CRP, IL-6 and TNF- $\alpha$  (Christiansen *et al.*, 2010; Marfella *et al.*, 2004; Moeller *et al.*, 2016) and may thereby help manage LC symptoms. Weight loss may also benefit people living with both LC and overweight/obesity beyond the effect on inflammation. The symptoms commonly reported in LC, including fatigue, shortness of breath, pain, and mood disorders, are also experienced by people living with obesity. Weight management trials conducted in study populations without LC observed that weight loss improved breathlessness (Bernhardt & Babb, 2014; Stenius-Aarniala *et al.*, 2000), relieved joint pain (Messier *et al.*, 2018; Riddle & Stratford, 2013), had a positive impact on cardiometabolic health and improved quality of life (Avenell *et al.*, 2004).

### Strengths and limitations

A key strength of the ReDIRECT study is its design, which relies on remote data collection and intervention delivery. This is particularly important in the context of the population studied since people living with LC face a high fatigue and mobility burden, sometimes compounded by careful avoidance of higher-risk situations where COVID-19 exposure may be likely. Remote delivery allowed for a flexible approach to recruitment across the UK, increased sample diversity and potentially facilitated greater inclusion by removing the burden on participants linked to attending study centres or clinics to take part. The intervention was a repurposing of the evidence-based weight loss intervention used in the DiRECT study (Lean *et al.*, 2018), known to be safe and effective in people with Type 2 diabetes and overweight/obesity. Using a pragmatic trial design, with professional support, also recognises that dietary choices and adherence are complex and need to be evaluated individually in real-life settings.

The ReDIRECT study relied, from its conception through to its execution, on in-depth co-production with patient representatives. This co-production is fully reflected in the breadth and depth of tools to support data capture and the trial's design to reflect the requirement for personalisation and adjusting how the intervention was delivered. As such, a unique feature of the study is the selection of a personalised primary outcome, whereby participants nominate the LC symptom they

would most like to improve. To our knowledge, no other trial has used such an approach.

There is currently no proven treatment or rehabilitation for LC and limited research on dietary interventions. To our knowledge, this is the first study to investigate a dietary management approach to improve LC symptoms.

The study also has limitations. While the remote nature of data collection eased the burden of not attending study visits in person, it also increased the need for computer literacy and the burden linked to engaging with data capture forms for participants, linked to anecdotal study fatigue. ReDIRECT relies on self-measurement of weight and blood pressure and self-reports. Flexibility was built into questionnaire completion timelines to minimise missing data and alleviate participant burden with assistance via email, text messages and phone calls if required. Questionnaires were also carefully checked for missing answers, and entry mistakes were followed up with participants.

In total, five participants in our study reported their first COVID-19 infection before or around the time of the first COVID-19 confirmed case in the UK (January 26, 2020) (The-nCoV Outbreak Joint Field Epidemiology Investigation Team & Li, 2020) in October and November 2019, and in January 2020. At that time, there was no testing available to confirm these infections. In all five cases, however, participants reported awareness of LC symptoms within 7 to 14 months of infection with LC diagnosed by healthcare professionals and also had a second (confirmed) infection in 2020-2022 before joining the study.

Despite focused efforts to reach out to a broad segment of the population, men are under-represented in this study, as are people from more socioeconomically disadvantaged backgrounds and minority ethnic groups. Recruitment through general practices was challenging, possibly linked to the limited use of clinical codes and challenges in identifying patients with LC (Jeffrey *et al.*, 2023; Walker *et al.*, 2021). Several factors may also have contributed to our study's high proportion of women. Being a woman is associated with 50% higher odds of developing LC (Su *et al.*, 2022; Subramanian *et al.*, 2022; Thompson *et al.*, 2022; Tsampasian *et al.*, 2023; Whitaker *et al.*, 2022). The PHOSP study also found that women were less likely to have recovered from COVID-19 after one year (OR 0.68) (Evans *et al.*, 2022). Finally, past studies have shown that structured weight loss programmes, such as the Counterweight-Plus programme, are largely used by women (Robertson *et al.*, 2014; Stubbs *et al.*, 2015; Tudor *et al.*, 2021).

### Conclusions

The baseline characteristics of the ReDIRECT study participants outline a complex presentation of symptoms attributable to LC but also to having excess weight, which increased substantially during the pandemic. With excess weight being a risk factor for LC and a large proportion of the participants



having attempted dietary changes, often without support, in the context of their infection and subsequent LC, there is an urgent need to develop evidence supporting dietary strategies for people living with both LC and overweight, recognising that such approach will need a high level of personalisation to meet the needs of the individuals.

## Data availability

### Underlying data

As per our study protocol, access to the raw data is restricted to the primary research team whilst the research is being conducted (until the end of the project, May 2024) and publication of the primary research papers. Upon publication of these papers, fully anonymised data will be placed on a research data repository with access given to researchers on request to the corresponding authors and subject to appropriate data sharing agreements.

### Extended data

Figshare: ReDIRECT study eCRF questionnaires screenshots. <https://doi.org/10.6084/m9.figshare.21270837> (Combet *et al.*, 2022).

Figshare: ReDIRECT Baseline Summary Tables and Figures. <https://doi.org/10.6084/m9.figshare.24602367> (Haag *et al.*, 2023b).

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](https://creativecommons.org/licenses/by/4.0/) (CC0 1.0 Public domain dedication).

## Acknowledgements

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Aspects of this paper were presented at the 30<sup>th</sup> European Congress on Obesity (Dublin, 2023) (Haag *et al.*, 2023a), the Nutrition Society Scottish Section Conference (Glasgow, 2023) (Haag *et al.*, 2023a), Scotland’s Health Research and Innovation Conference (Glasgow, 2023) ([link to online poster](#)), and the European Association for the Study of Obesity Winter School (Antalya, 2023).

## References

- Alah MA, Abdeen S, Kehyayan V, *et al.*: **Impact of staying at home measures during COVID-19 pandemic on the lifestyle of Qatar’s population: Perceived changes in diet, physical activity, and body weight.** *Prev Med Rep.* 2021; **24**: 101545.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Almandoz JP, Xie L, Schellinger JN, *et al.*: **Changes in body weight, health behaviors, and mental health in adults with obesity during the COVID-19 pandemic.** *Obesity (Silver Spring).* 2022; **30**(9): 1875–1886.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Ara R, Brazier JE: **Using Health State Utility Values from the General Population to Approximate Baselines in Decision Analytic Models when Condition-Specific Data are Not Available.** *Value Health.* 2011; **14**(4): 539–545.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Avenell A, Broom J, Brown TJ, *et al.*: **Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement.** *Health Technol Assess.* 2004; **8**(21): iii–iv, 1–182.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Bakaloudi DR, Barazzoni R, Bischoff SC, *et al.*: **Impact of the first COVID-19 lockdown on body weight: A combined systematic review and a meta-analysis.** *Clin Nutr.* 2022; **41**(12): 3046–3054.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Ballerling AV, van Zon SKR, Olde Hartman TC, *et al.*: **Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study.** *Lancet.* 2022; **400**(10350): 452–461.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Bernhardt V, Babb TG: **Weight loss reduces dyspnea on exertion in obese women.** *Respir Physiol Neurobiol.* 2014; **204**: 86–92.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Bestall JC, Paul EA, Garrod R, *et al.*: **Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease.** *Thorax.* 1999; **54**(7): 581–586.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Bonilla H, Peluso MJ, Rodgers K, *et al.*: **Therapeutic trials for long COVID-19: A call to action from the interventions taskforce of the RECOVER initiative.** *Front Immunol.* 2023; **14**: 1129459.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Brown DA, O’Brien KK: **Conceptualising Long COVID as an episodic health condition.** *BMJ Glob Health.* 2021; **6**(9): e007004.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Buchholz I, Janssen MF, Kohlmann T, *et al.*: **A Systematic Review of Studies Comparing the Measurement Properties of the Three-Level and Five-Level Versions of the EQ-5D.** *Pharmacoeconomics.* 2018; **36**(6): 645–661.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Byambasuren O, Stehlik P, Clark J, *et al.*: **Effect of covid-19 vaccination on long covid: systematic review.** *BMJ Med.* 2023; **2**(1): e000385.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Callard F, Perego E: **How and why patients made Long Covid.** *Soc Sci Med.* 2021; **268**: 113426.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Castanares-Zapatero D, Chalón P, Kohn L, *et al.*: **Pathophysiology and mechanism of long COVID: a comprehensive review.** *Ann Med.* 2022; **54**(1): 1473–1487.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Chalder T, Berelowitz G, Pawlikowska T, *et al.*: **Development of a fatigue scale.** *J Psychosom Res.* 1993; **37**(2): 147–153.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Christiansen T, Paulsen SK, Bruun JM, *et al.*: **Exercise training versus diet-induced weight-loss on metabolic risk factors and inflammatory markers in obese subjects: a 12-week randomized intervention study.** *Am J Physiol Endocrinol Metab.* 2010; **298**(4): E824–E831.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Combet E, Blane D, Haag L: **ReDIRECT study eCRF questionnaires screenshots.** *figshare.* Online resource. 2022.  
<http://www.doi.org/10.6084/m9.figshare.21270837.v4>
- Davis HE, Assaf GS, McCorkell L, *et al.*: **Characterizing long COVID in an international cohort: 7 months of symptoms and their impact.** *EclinicalMedicine.* 2021; **38**: 101019.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Davis HE, McCorkell L, Vogel JM, *et al.*: **Long COVID: major findings, mechanisms and recommendations.** *Nat Rev Microbiol.* 2023; **21**(3): 133–146.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Day HL: **Exploring Online Peer Support Groups for Adults Experiencing Long COVID in the United Kingdom: Qualitative Interview Study.** *J Med Internet Res.* 2022; **24**(5): e37674.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Evans RA, Leavy OC, Richardson M, *et al.*: **Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: a prospective observational study.** *Lancet Respir Med.* 2022; **10**(8): 761–775.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Flanagan EW, Beyl RA, Fearnbach SN, *et al.*: **The Impact of COVID-19 Stay-At-Home Orders on Health Behaviors in Adults.** *Obesity (Silver Spring).* 2021;

29(2): 438–445.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Greenhalgh T, Sivan M, Delaney B, *et al.*: Long covid-an update for primary care. *BMJ*. 2022; **378**: e072117.

[PubMed Abstract](#) | [Publisher Full Text](#)

Haag L, Richardson J, Cunningham Y, *et al.*: The remote diet intervention to reduce Long COVID symptoms trial (ReDIRECT): protocol for a randomised controlled trial to determine the effectiveness and cost-effectiveness of a remotely delivered supported weight management programme for people with Long COVID and excess weight, with personalised improvement goals [version 2; peer review: 2 approved]. *NIHR Open Res*. 2022; **2**: 57.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Haag L, Richardson J, Haig C, *et al.*: The Remote Diet Intervention to Reduce Long Covid symptoms Trial (ReDIRECT)-dietary profile of the study participants at baseline. *Proc Nutr Soc*. 2023a; **82**(OCE3): E226.

[Publisher Full Text](#)

Haag L, Richardson J, Haig C, *et al.*: Baseline characteristics in the Remote Diet Intervention to Reduce long-COVID symptoms Trial (ReDIRECT).

In: *Obesity Facts*, 16 (S1) - 30th European Congress on Obesity (ECO 2023). Dublin, Ireland. 2023b; **16**: 320–321.

Hastie CE, Lowe DJ, McAuley A, *et al.*: Natural history of long-COVID in a nationwide, population cohort study. *Nat Commun*. 2023; **14**(1): 3504.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Hernández Alava M, Pudney S, Wailoo A: Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. *Pharmacoeconomics*. 2023; **41**(2): 199–207.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Höchstmann C, Dorling JL, Martin CK, *et al.*: Association between weight loss, change in physical activity, and change in quality of life following a corporately sponsored, online weight loss program. *BMC Public Health*. 2022; **22**(1): 451.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Horberg MA, Watson E, Bhatia M, *et al.*: Post-acute sequelae of SARS-CoV-2 with clinical condition definitions and comparison in a matched cohort. *Nat Commun*. 2022; **13**(1): 5822.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Janssen MF, Pickard AS, Shaw JW: General population normative data for the EQ-5D-3L in the five largest European economies. *Eur J Health Econ*. 2021; **22**(9): 1467–1475.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Jeffrey K, Woolford L, Maini R, *et al.*: Identifying Long Covid Using Electronic Health Records: A National Observational Cohort Study in Scotland. *P. w. T. Lancet*. 2023.

[Publisher Full Text](#)

Khubchandani J, Kandiah J, Saiki D: The COVID-19 Pandemic, Stress, and Eating Practices in the United States. *Eur J Investig Health Psychol Educ*. 2020; **10**(4): 950–956.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Khubchandani J, Price JH, Sharma S, *et al.*: COVID-19 pandemic and weight gain in American adults: A nationwide population-based study. *Diabetes Metab Syndr*. 2022; **16**(1): 102392.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Kim Y, Bae S, Chang HH, *et al.*: Long COVID prevalence and impact on quality of life 2 years after acute COVID-19. *Sci Rep*. 2023; **13**(1): 11207.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Lean MEJ, Leslie WS, Barnes AC, *et al.*: Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet*. 2018; **391**(10120): 541–551.

[PubMed Abstract](#) | [Publisher Full Text](#)

Loosen SH, Jensen BEO, Tanislav C, *et al.*: Obesity and lipid metabolism disorders determine the risk for development of long COVID syndrome: a cross-sectional study from 50,402 COVID-19 patients. *Infection*. 2022; **50**(5): 1165–1170.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Lopez-Leon S, Wegman-Ostrosky T, Perelman C, *et al.*: More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Sci Rep*. 2021; **11**(1): 16144.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Marfella R, Esposito K, Siniscalchi M, *et al.*: Effect of weight loss on cardiac synchronization and proinflammatory cytokines in premenopausal obese women. *Diabetes Care*. 2004; **27**(1): 47–52.

[PubMed Abstract](#) | [Publisher Full Text](#)

Marjenberg Z, Leng S, Tascini C, *et al.*: Risk of long COVID main symptoms after SARS-CoV-2 infection: a systematic review and meta-analysis. *Sci Rep*. 2023; **13**(1): 15332.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Mason MR, Hudgins JH, Campbell MS, *et al.*: Changes in physical activity during the initial stages of the COVID-19 pandemic. *J Sports Sci*. 2022; **40**(1): 116–124.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Messier SP, Resnik AE, Beavers DP, *et al.*: Intentional Weight Loss in Overweight and Obese Patients With Knee Osteoarthritis: Is More Better? *Arthritis Care Res (Hoboken)*. 2018; **70**(11): 1569–1575.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Moeller K, Ostermann AI, Rund K, *et al.*: Influence of weight reduction on blood levels of C-reactive protein, tumor necrosis factor- $\alpha$ , interleukin-6, and oxylipins in obese subjects. *Prostaglandins Leukot Essent Fatty Acids*. 2016; **106**: 39–49.

[PubMed Abstract](#) | [Publisher Full Text](#)

Nguyen LH, Drew DA, Graham MS, *et al.*: Risk of COVID-19 among front-line health-care workers and the general community: a prospective cohort study. *Lancet Public Health*. 2020; **5**(9): e475–e483.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Peluso MJ, Lu S, Tang AF, *et al.*: Markers of Immune Activation and Inflammation in Individuals With Postacute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 Infection. *J Infect Dis*. 2021; **224**(11): 1839–1848.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Peter RS, Nieters A, Brockmann SO, *et al.*: Association of BMI with general health, working capacity recovered, and post-acute sequelae of COVID-19. *Obesity (Silver Spring)*. 2023; **31**(1): 43–48.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Reilly MC, Zbrozek AS, Dukes EM: THE VALIDITY AND REPRODUCIBILITY OF A WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT INSTRUMENT. *Pharmacoeconomics*. 1993; **4**(5): 353–365.

[PubMed Abstract](#) | [Publisher Full Text](#)

Riddle DL, Stratford PW: Body weight changes and corresponding changes in pain and function in persons with symptomatic knee osteoarthritis: A cohort study. *Arthritis Care Res (Hoboken)*. 2013; **65**(1): 15–22.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Robertson C, Archibald D, Avenell A, *et al.*: Systematic reviews of and integrated report on the quantitative, qualitative and economic evidence base for the management of obesity in men. *Health Technol Assess*. 2014; **18**(35): v-vi, xxiii-xxix, 1–424.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Russell D, Spence NJ, Chase JAD, *et al.*: Support amid uncertainty: Long COVID illness experiences and the role of online communities. *SSM Qual Res Health*. 2022; **2**: 100177.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Sach TH, Barton GR, Doherty M, *et al.*: The relationship between body mass index and health-related quality of life: comparing the EQ-5D, EuroQol VAS and SF-6D. *Int J Obes (Lond)*. 2007; **31**(1): 189–196.

[PubMed Abstract](#) | [Publisher Full Text](#)

Schultheiss C, Willscher E, Paschold L, *et al.*: Liquid biomarkers of macrophage dysregulation and circulating spike protein illustrate the biological heterogeneity in patients with post-acute sequelae of COVID-19. *J Med Virol*. 2023; **95**(1): e28364.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Schultheiss C, Willscher E, Paschold L, *et al.*: The IL-1 $\beta$ , IL-6, and TNF cytokine triad is associated with post-acute sequelae of COVID-19. *Cell Rep Med*. 2022; **3**(6): 100663.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Shabnam S, Razieh C, Dambha-Miller H, *et al.*: Socioeconomic inequalities of Long COVID: a retrospective population-based cohort study in the United Kingdom. *J R Soc Med*. 2023; **116**(8): 263–273.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Soriano JB, Murthy S, Marshall JC, *et al.*: A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis*. 2022; **22**(4): e102–e107.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Spadoni GF, Stratford PW, Solomon PE, *et al.*: The evaluation of change in pain intensity: a comparison of the P4 and single-item numeric pain rating scales. *J Orthop Sports Phys Ther*. 2004; **34**(4): 187–93.

[PubMed Abstract](#) | [Publisher Full Text](#)

Stenius-Aarniala B, Poussa T, Kvarnström J, *et al.*: Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. *BMJ*. 2000; **320**(7238): 827–832.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Stubbs RJ, Morris L, Pallister C, *et al.*: Weight outcomes audit in 1.3 million adults during their first 3 months' attendance in a commercial weight management programme. *BMC Public Health*. 2015; **15**: 882.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Su Y, Yuan D, Chen DG, *et al.*: Multiple early factors anticipate post-acute COVID-19 sequelae. *Cell*. 2022; **185**(5): 881–895.e20.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Subramanian A, Nirantharakumar K, Hughes S, *et al.*: Symptoms and risk factors for long COVID in non-hospitalized adults. *Nat Med*. 2022; **28**(8): 1706–1714.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Sudre CH, Murray B, Varsavsky T, *et al.*: Attributes and predictors of long COVID. *Nat Med*. 2021; **27**(4): 626–631.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

The-nCoV Outbreak Joint Field Epidemiology Investigation Team, Li Q: An Outbreak of NCIP (2019-nCoV) Infection in China - Wuhan, Hubei Province, 2019-2020. *China CDC Wkly*. 2020; **2**(5): 79–80.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Thompson EJ, Williams DM, Walker AJ, *et al.*: Long COVID burden and risk factors in 10 UK longitudinal studies and electronic health records. *Nat*

*Commun.* 2022; **13**(1): 3528.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Tran VT, Perrodeau E, Saldanha J, *et al.*: **Efficacy of first dose of covid-19 vaccine versus no vaccination on symptoms of patients with long covid: target trial emulation based on ComPaRe e-cohort.** *BMJ Med.* 2023; **2**(1): e000229.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Tsampasian V, Elghazaly H, Chattopadhyay R, *et al.*: **Risk Factors Associated With Post-COVID-19 Condition: A Systematic Review and Meta-analysis.** *JAMA Intern Med.* 2023; **183**(6): 566–580.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Tudor K, Tearne S, Jebb SA, *et al.*: **Gender differences in response to an opportunistic brief intervention for obesity in primary care: Data from the BWeL trial.** *Clin Obes.* 2021; **11**(1): e12418.

[PubMed Abstract](#) | [Publisher Full Text](#)

Walker AJ, MacKenna B, Inglesby P, *et al.*: **Clinical coding of long COVID in English primary care: a federated analysis of 58 million patient records in situ using OpenSAFELY.** *Br J Gen Pract.* 2021; **71**(712): e806–e814.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Whitaker M, Elliott J, Chadeau-Hyam M, *et al.*: **Persistent COVID-19 symptoms in a community study of 606,434 people in England.** *Nat Commun.* 2022; **13**(1): 1957.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Zhang JY, Whalley JP, Knight JC, *et al.*: **SARS-CoV-2 infection induces a long-lived pro-inflammatory transcriptional profile.** *Genome Med.* 2023; **15**(1): 69.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Zigmond AS, Snaith RP: **The Hospital Anxiety and Depression Scale.** *Acta Psychiatr Scand.* 1983; **67**(6): 361–370.

[PubMed Abstract](#) | [Publisher Full Text](#)

# Open Peer Review

Current Peer Review Status:    

## Version 1

Reviewer Report 19 August 2024

<https://doi.org/10.3310/nihropenres.14676.r32176>

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**Yessica Abigail Tronco Hernández** 

University of Plymouth, Plymouth, England, UK

This is a good article that attempts to cover comprehensively the health profile of people with long Covid to deliver a dietary intervention. Some suggestions to improve follow:

### ABSTRACT

It is worth mentioning in the methods section that the work was conducted in the UK or only in England and Scotland

Mention what kind of data analysis was conducted

It is not clear whether they gained weight which led to obesity or if they had obesity before they had their first covid infection

From the abstract it is not clear whether this is a protocol or the trial finalised. This should be clarified to avoid misleading the reader. The title says baseline characteristics but this is not clear in the abstract

The lay summary suggests it is a protocol, but the study seems to be a trial when looking at some results.

If an acronym is used for long covid, which is the main interest variable, then why not using one for covid-19?

### Introduction

End of paragraph 2, define what you mean by long term

6<sup>th</sup> paragraph, Is Bakaloudi reporting UK populations? And how do you discard those who had obesity pre pandemic to present figures? Need to clarify

### Methods

Please provide a reference for the GRIPP2

It is not clear whether participants received any compensation for their time

Need to clarify what is your rationale for selecting the tools for XYZ symptoms, on the other hand to clarify whether these tools were selected after participants answered the baseline questionnaire and selected the most burdensome symptoms. The first paragraph of page 8 does not explicitly say this.

## RESULTS

Need to specify for those decreased work hours whether this was due to their own disease or due to lockdown conditions or other reasons, to avoid cofounders or speculation

## DISCUSSION, limitations and conclusions

This is the section I enjoyed the most as you reviewed several papers. More data on the influence of the pandemic on health and wellbeing during lockdowns (Tronco Hernandez et al, 2021) as well as experiences reported by people with long COVID and lessons for professionals and researchers (Tronco Hernandez et al. 2023) would provide more breadth to this body of evidence

Good to acknowledge the major limitation self reports and lack of training to self-measure weight and blood pressure

The burden of the questionnaire on participants needs to be considered too

In general, researchers studied a lot of variables, some may be cofounders and lead to spurious assumptions. I suggest you divide them into primary (weight, blood pressure, etc) and secondary variables (e.g. socioeconomic status, vaccination status) otherwise there is too much data hence the main aim can get easily lost for readers or they could make erroneous assumptions

## References

1. Tronco Hernández YA, Parente F, Faghy MA, Roscoe CMP, et al.: Influence of the COVID-19 Lockdown on the Physical and Psychosocial Well-being and Work Productivity of Remote Workers: Cross-sectional Correlational Study. *JMIRx Med.* 2021; **2** (4): e30708 [PubMed Abstract](#) | [Publisher Full Text](#)
2. Tronco Hernández Y, Anderson L, Weekes L, Julian A, et al.: Providing optimal nutritional care to patients with long-COVID. *Primary Health Care.* 2023; **33** (4): 30-35 [Publisher Full Text](#)

### **Is the work clearly and accurately presented and does it cite the current literature?**

Partly

### **Is the study design appropriate and is the work technically sound?**

Yes

### **Are sufficient details of methods and analysis provided to allow replication by others?**

Partly

### **If applicable, is the statistical analysis and its interpretation appropriate?**

I cannot comment. A qualified statistician is required.

### **Are all the source data underlying the results available to ensure full reproducibility?**

Partly

### **Are the conclusions drawn adequately supported by the results?**

Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** I am a postdoctoral researcher who has published several papers on the effects of covid on people and how to best support professionals and employers delivering wellbeing and dietary strategies to patients with Long covid

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Reviewer Report 08 July 2024

<https://doi.org/10.3310/nihropenres.14676.r32175>

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**Jessica Campbell** 

Auckland University of Technology, Auckland, New Zealand

Agreeing with peer reviewer 1, this is a well written and interesting paper which I enjoyed reading. It would however benefit from some clarification regarding the aim of the paper. In particular, when reading the abstract, it was not initially clear that results would not be presented, though the title of the paper is clear. Additionally, below are a few comments/suggestions for the authors to consider.

1. Add details regarding which version of R was used.
2. Clarify the use of statistical tests. For example, were Mann-Whitney tests chosen due to data failing the assumptions of parametric testing, or was this always intended to be the test of choice?
3. Throughout the paper it would be helpful to make a clearer distinction between acute Covid-19 infection and Long Covid. If the authors have data, it would be interesting to see more detailed information about when LC started (rather than just how long individuals had been experiencing LC symptoms). Data are presented relating to the dates of each acute Covid-19 infection and about these infections in relation to vaccination; however, it would have been nice to see these events in relation to LC. For example, was LC more likely after the first or second infection? Was it more likely before or after vaccination? This wasn't entirely clear.
4. Similar to point 3, there is discussion throughout the paper about changes after Covid-19 (for example, weight gain). It would be good to clarify whether this relates to LC specifically, or to the first acute infection, the second acute infection, etc. In some cases, this may be difficult to determine, but acknowledgment of this would be beneficial.
5. I suggest changing 'vegan' to 'plant-based' given that the former is an ethical stance related to broader changes in lifestyle, whereas the latter refers specifically to a diet which may be adopted for health reasons (as is more appropriate in this context).
6. It is perhaps worth noting or clarifying that some of the changes that occurred post-Covid may be related to more general pandemic responses rather than being (only) related to illness. For example, weight gain and reductions in exercise were widely reported due to

- lockdown measures even in otherwise healthy individuals. If it is possible to rule this out, a comment noting this would be beneficial.
7. While (online) LC support groups were undoubtedly helpful for many, it may be worth noting the downsides of these groups e.g. (Turner J., 2017)
  8. While the limitations section notes that self-report measures were used, this could be explained more explicitly.
  9. The discussion mentions that several patients who reported infection before testing was widely available became aware of LC within 7 to 14 months post-infection. This point may need further elaboration. Rather than focusing on the lack of testing, consider discussing the significant time gap between infection and the onset of LC symptoms. This delay makes it challenging to ascertain whether the symptoms are genuinely related to Covid-19 or if they might be idiopathic.

### References

1. Turner J: Online Support Groups: The Good, the Bad, and the Motivated. *Journal of Consumer Health on the Internet*. 2017; **21** (1): 11-25 [Publisher Full Text](#)

### Is the work clearly and accurately presented and does it cite the current literature?

Yes

### Is the study design appropriate and is the work technically sound?

Yes

### Are sufficient details of methods and analysis provided to allow replication by others?

Yes

### If applicable, is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

### Are all the source data underlying the results available to ensure full reproducibility?

Yes

### Are the conclusions drawn adequately supported by the results?

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** I have previously published research on Covid-19 and currently focus on studying the effects of nutritional interventions. My work involves exploring how diet and lifestyle changes can impact health outcomes, particularly in the context of chronic disease.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Reviewer Report 04 July 2024

<https://doi.org/10.3310/nihropenres.14676.r32173>

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**Teresa Maria Tomasa-Irriguible** 

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### **Reviewer Comments. Baseline Characteristics in the Remote Diet Intervention to REduce long-COVID Symptoms Trial (ReDIRECT)**

#### **ABSTRACT**

- Methods section:
  - Does not reflect what the paper is about. What is the objective/s? “Baseline Characteristics”? You could write this sentence: “Here, we describe the baseline characteristics of ReDIRECT participants, focusing on socioeconomic and demographic factors as well as dietary and medical history, including LC diagnosis and symptoms”.
- Conclusions.
  - Does not answer the title “**Baseline Characteristics**” as no objectives are described at M&M...

#### **MAIN SECTIONS**

##### **INTRODUCTION**

- **4<sup>th</sup> paragraph, 1<sup>st</sup> sentence.** Reference missing. This point is important as your hypothesis states that obesity is a risk factor for LC.
- **5<sup>th</sup> paragraph, 1<sup>st</sup> sentence** Reference missing. This point is important, as your hypothesis is whether a dietary modification may influence LC.
- **Last paragraph.** This is the real M&M. This text should also be at the abstract at introduction and M&M sections.

##### **METHODS**

- **2<sup>nd</sup> paragraph, 1<sup>st</sup> sentence.** I think that could be a problem, since they may not offer a fairness judgment.
- **Ethical approval. 3<sup>rd</sup> paragraph.** Think about moving this paragraph to 3 paragraphs below, in *Study design and participants* before “A total of 240 participants...”
- **Study design and participants. Last paragraph, last sentence.** One question: “Further support is provided through in-app weekly monitoring and nudges, personalized messaging, and group support” this was also done with the control group in the first 3 months and until de year?

##### **RESULTS**

- **Long COVID**
  - **1<sup>st</sup> paragraph, 2<sup>nd</sup> sentence.** This is a very important epidemiological finding! Hence, think about writing this finding in the abstract and conclusions sections.
  - **7<sup>th</sup> paragraph, 2<sup>nd</sup> sentence. Regarding cognitive impairment.** This is also a



relevant epidemiological finding; Moreover, this symptom does not depend a priori on the patient's weight and other confusing symptoms. Think about writing this finding in the abstract and conclusions sections.

- **8<sup>th</sup> paragraph, 2<sup>nd</sup> sentence.** This is also a very important epidemiological finding. Think about writing this finding in the abstract and conclusions sections.
- **Weight management and diet. 1<sup>st</sup> and 2<sup>nd</sup> paragraphs.** Some of these findings are relevant and should be in the abstract and conclusion section. In addition, as you mentioned along the manuscript, median weight gain of 11.5 kg by itself can cause fatigue, dyspnea and depression. Hence, you would argue this thing in the discussion section.
- **Weight management and diet. 6<sup>th</sup> paragraph.** These findings are relevant and should be in the abstract and conclusion section.

## DISCUSSION

- **2<sup>nd</sup> paragraph.** This paragraph is already in the Results section. No comparison is done with other studies. This paragraph could be removed from here.
- **6<sup>th</sup> paragraph.** This is also in the Results section. No comparison is made with other studies. This paragraph could be removed from here, too.
- **7<sup>th</sup> paragraph.** This is also in the Results section. No comparison is made with other studies. This paragraph could be removed from here, too.
- **One question for the sentence at the end of 8<sup>th</sup> paragraph.** What was the average age in the Office for National Statistics UK Health Indicators, 2022?
- **10<sup>th</sup> paragraph.** This is also in the Results section. No comparison is made with other studies. This paragraph could be removed from here, too.
- **11<sup>th</sup> paragraph.** This is also in the Results section. No comparison is made with other studies. This paragraph could be removed from here, too.
- Instead of this paragraphs, you could discuss something about this other issues in **Long COVID** results:
  - **1<sup>st</sup> paragraph, 2<sup>nd</sup> sentence.** This is a very important epidemiological finding! Hence, think about writing this finding in the abstract and conclusions sections.
  - **7<sup>th</sup> paragraph, 2<sup>nd</sup> sentence. Regarding cognitive impairment.** This is also a relevant epidemiological finding; Moreover, this symptom does not depend a priori on the patient's weight and other confusing symptoms. Think about writing this finding in the abstract and conclusions sections.
  - **8<sup>th</sup> paragraph, 2<sup>nd</sup> sentence.** This is also a very important epidemiological finding. Think about writing this finding in the abstract and conclusions sections.
  - **Weight management and diet. 1<sup>st</sup> and 2<sup>nd</sup> paragraphs.** Some of these findings are relevant and should be in the abstract and conclusion section. In addition, as you mentioned along the manuscript, median weight gain of 11.5 kg by itself can cause fatigue, dyspnea and depression. Hence, you would argue this thing in the discussion

section.

- **Weight management and diet. 6<sup>th</sup> paragraph.** These findings are relevant and should be in the abstract and conclusion section.

## CONCLUSIONS

**2<sup>nd</sup> sentence.** You did exclude the thin patients by design of the study. This sentence cannot be a conclusion of this **Baseline Characteristics** epidemiological study.

Instead of this sentence, you could conclude something more concrete about this **Long COVID** results:

- ○ **1<sup>st</sup> paragraph, 2<sup>nd</sup> sentence.** This is a very important epidemiological finding! Hence, think about writing this finding in the abstract and conclusions sections.
- **7<sup>th</sup> paragraph, 2<sup>nd</sup> sentence. Regarding cognitive impairment.** This is also a relevant epidemiological finding; Moreover, this symptom does not depend a priori on the patient's weight and other confusing symptoms. Think about writing this finding in the abstract and conclusions sections.
- **8<sup>th</sup> paragraph, 2<sup>nd</sup> sentence.** This is also a very important epidemiological finding. Think about writing this finding in the abstract and conclusions sections.
- **Weight management and diet. 1<sup>st</sup> and 2<sup>nd</sup> paragraphs.** Some of these findings are relevant and should be in the abstract and conclusion section. In addition, as you mentioned along the manuscript, median weight gain of 11.5 kg by itself can cause fatigue, dyspnea and depression. Hence, you would argue this thing in the discussion section.
- **Weight management and diet. 6<sup>th</sup> paragraph.** These findings are relevant and should be in the abstract and conclusion section.

**Is the work clearly and accurately presented and does it cite the current literature?**

No

**Is the study design appropriate and is the work technically sound?**

No

**Are sufficient details of methods and analysis provided to allow replication by others?**

Partly

**If applicable, is the statistical analysis and its interpretation appropriate?**

Not applicable

**Are all the source data underlying the results available to ensure full reproducibility?**

Partly

**Are the conclusions drawn adequately supported by the results?**

No

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** ORCID <https://orcid.org/0000-0001-8033-8527>

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Reviewer Report 31 May 2024

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**Hiyam Al-Jabr** 

University of Keele, Keele, UK

This is a well-written exciting paper, thank you for writing this.

I have few comments for authors to consider:

1. The aim is not clear in the abstract. Please add the aim of the study to the abstract.
2. Please clarify aim on page 4, I was confused whether the paper is going to talk about the impact of the intervention on listed outcomes or just describe characteristics of the study population, please clarify the exact aim of the paper.
3. Please define abbreviations of "UoG" and "PPI" on page 4.
4. On page 5, you could remove the section that starts with "The REC favorable opinion...." to "except where explicitly specified otherwise". this is by default a requirement by ethics whenever an NHS site is included.
5. Could you please whether the answers to the "living situation" in table 2 is "select all that applies" as total number for this part exceeds 234 participants.
6. on page 16, the sentence "To our knowledge, this is the first study to investigate a dietary management approach to improve LC symptoms". the paper only reports baseline characteristics of included participants, thus I'm not sure this line fits with this paper, especially that no impacts are mentioned related to the use of the intervention.

**Is the work clearly and accurately presented and does it cite the current literature?**

Yes

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

I cannot comment. A qualified statistician is required.

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** I'm a research Fellow with experience of conducting research in Long COVID.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

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