1   **Multi-organ impairment in low-risk individuals with long COVID**

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41 **Multi-organ impairment in low-risk individuals with long COVID**

42 **Abstract**

43 **Background:** Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection

44 has disproportionately affected older individuals and those with underlying medical

45 conditions. Research has focused on short-term outcomes in hospital, and single organ

46 involvement. Consequently, impact of long COVID (persistent symptoms three months post-

47 infection) across multiple organs in low-risk individuals is yet to be assessed.

48 **Methods:** An ongoing prospective, longitudinal, two-centre, observational study was

49 performed in individuals symptomatic after recovery from acute SARS-CoV-2 infection.

50 Symptoms and organ function (heart, lungs, kidneys, liver, pancreas, spleen) were assessed

51 by standardised questionnaires (EQ-5D-5L, Dyspnoea-12), blood investigations and

52 quantitative magnetic resonance imaging, defining single and multi-organ impairment by

53 consensus definitions.

54 **Findings:** Between April and September 2020, 201 individuals (mean age 44 (SD 11.0)

55 years, 70% female, 87% white, 31% healthcare workers) completed assessments following

56 SARS-CoV-2 infection (median 140, IQR 105-160 days after initial symptoms). The

57 prevalence of pre-existing conditions (obesity: 20%, hypertension: 6%; diabetes: 2%; heart

58 disease: 4%) was low, and only 18% of individuals had been hospitalised with COVID-19.

59 Fatigue (98%), muscle aches (88%), breathlessness (87%), and headaches (83%) were the

60 most frequently reported symptoms. Ongoing cardiorespiratory (92%) and gastrointestinal

61 (73%) symptoms were common, and 42% of individuals had ten or more symptoms.

62 There was evidence of mild organ impairment in heart (32%), lungs (33%), kidneys (12%),

63 liver (10%), pancreas (17%), and spleen (6%). Single (66%) and multi-organ (25%)

64 impairment was observed, and was significantly associated with risk of prior COVID-19

65 hospitalisation ($p < 0.05$).

66 **Interpretation:** In a young, low-risk population with ongoing symptoms, almost 70% of

67 individuals have impairment in one or more organs four months after initial symptoms of

68 SARS-CoV-2 infection. There are implications not only for burden of long COVID but also

69 public health approaches which have assumed low risk in young people with no

70 comorbidities.

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77 **Introduction**

78 Early in the COVID-19 pandemic, research and clinical interest in SARS-CoV-2 (Severe

79 acute respiratory syndrome-coronavirus 2)-induced organ damage was predominantly

80 focused on the respiratory system(1). There have been indirect effects on other organ

81 systems and disease processes, such as cardiovascular diseases and cancers, through

82 changes in health systems or behaviours of patients and health professionals(2-4). In

83 addition, beyond an acute systemic inflammatory response, evidence for direct COVID-19-

84 related effects on multiple organs is accumulating, with potential long-term impacts for

85 individuals as well as health systems(5-8). However, no study to-date has included detailed

86 characterisation of all major organ systems following SARS-CoV-2 infection.

87

88 COVID-19 represents a convergence of an infectious disease, under-treated non-

89 communicable diseases and social determinants of health, as a "syndemic"(9). Pre-existing

90 non-communicable diseases and risk factors are important predictors of poor COVID-19

91 outcomes, whether intensive care admissions or mortality(2). Research has focused on the

92 acute phase of SARS-CoV-2 infection, in hospitalised patients, and on individuals that have

93 died from COVID-19(10-12). It is clear that COVID-19 can have longer multiple symptoms

94 and long-term effects(13), but "long-COVID" is yet to be fully defined(14-15), partly due to

95 lack of understanding of medium- and long-term pathophysiology across organ systems.

96

97 Long COVID in low-risk individuals, who represent up to 80% of the population(2), has public

98 health importance in terms of burden of disease and healthcare utilisation, and therefore has

99 urgent policy relevance across countries. However, in the UK, government policies have

100 emphasised excess risk of mortality in moderate- and high-risk conditions, including

101 "shielding"(2) and commissioning of a risk calculator to identify those at highest risk of

102 COVID-19 severity and mortality(16). As the pandemic progresses, there is growing concern

103 regarding prolonged isolation strategies for people with vulnerable conditions and at highest

104 risk of severe COVID-19 outcomes(17). These approaches have assumed low risk of SARS-

105 CoV-2 infection in younger individuals without underlying conditions, based on their low

106 excess mortality, but without knowledge of the chronic pulmonary and extrapulmonary

107 effects of COVID-19.

108

109 In order to better understand the long-term impact of COVID-19 and ultimately inform

110 preventive measures at health system level, we performed a pragmatic, prospective study in

111 low-risk individuals with symptom assessment, multi-organ magnetic resonance imaging

112   (MRI) and blood investigations for inflammatory markers at three months post-COVID-19

113   diagnosis.

114   **Methods**

115   *Patient population and study design*

116   In an ongoing, prospective study, 201 participants were enrolled at two UK sites

117   (Perspectum, Oxford and Mayo Clinic Healthcare, London) between April 2020 and August

118   2020 and completed baseline assessment by 14 September 2020 (**Figure 1**). Participants

119   were eligible for enrolment if they tested positive by the oro/nasopharyngeal throat swab for

120   SARS-CoV-2 by reverse-transcriptase-polymerase-chain reaction (n=62), a positive antibody

121   test (n=63), or had typical symptoms and were determined to have COVID-19 by two

122   independent clinicians (n=73). Exclusion criteria were symptoms of active respiratory viral

123   infection (temperature >37.8°C or three or more episodes of coughing in 24 hours);

124   discharged from hospital in the last 7 days; and contraindications to MRI, including implanted

125   pacemakers, defibrillators, other metallic implanted devices; claustrophobia. The study

126   protocol was approved by a UK ethics committee (20/SC/0185), registered

127   (https://clinicaltrials.gov/ct2/show/NCT04369807) and all patients gave written informed

128   consent.

129

130   **To assess the burden of multi-organ involvement after SARS-CoV2 infection**

131   Organ function was assessed by patient-reported validated questionnaires, fasting blood

132   investigations (as listed below) and multi-organ MRI. MRI was the chosen imaging modality

133   (as in UK Biobank) because it is: (1) safe, with no radiation exposure, no need for

134   intravenous contrast, minimal contact with the radiographer; (2) quantitative, repeatable and

135   robust, with >95% acquisition and image processing success rate; (3) informative through a

136   repository of digital data which can be shared in the research community for independent

137   analysis and research; (4) rapid and scalable, i.e. a 35-minute scan can phenotype the lung,

138   heart, kidney, liver, pancreas and spleen. At time of MRI, we completed (i) questionnaires for

139   quality of life(EQ-5D-5L(18)), addressing mobility, self-care, usual activity, pain and anxiety,

140   and breathlessness (Dyspnoea-12(19)) and (ii) full blood count, serum biochemistry (sodium,

141   chloride, bicarbonate, urea, creatinine, bilirubin, alkaline phosphatase, aspartate transferase,

142   alanine transferase, lactate dehydrogenase, creatinine kinase, gamma-glutamyl

143   transpeptidase, total protein, albumin, globulin, calcium, magnesium, phosphate, uric acid,

144   fasting triglycerides, cholesterol (total, HDL, LDL), iron, iron-binding capacity (unsaturated

145   and total) and inflammatory markers (erythrocyte sedimentation rate, ESR; high sensitivity-

146   C-Reactive Protein, CRP) (TDL laboratories, London).

147

148   **Magnetic Resonance Image Analysis**

149   Multi-organ MRI data were collected at both☐study sites (Oxford:☐MAGNETOM Aera 1.5T,

150   Mayo Healthcare London:☐MAGNETOM Vida 3T; both from☐Siemens Healthcare Erlangen,

151   Germany). The COVERSCAN Multiparametic MRI assessment typically required 35mins per

152   patient, including lungs, heart, liver, pancreas, kidneys and spleen by standardised

153   methodology (**Supplementary methods**).

154

155   **Definition of organ impairment**

156   MRI-derived measurements from the heart, lungs, kidney, liver, pancreas and spleen were

157   compared with established reference ranges (**Table S1**) to determine impairment for each

158   organ. An individual organ was classified as impaired if at least one of the metrics calculated

159   for that organ was outside the reference range. Excessive organ fat was not considered as

160   an indicator of impairment on the assumption that this was likely pre-existing and thus

161   treated separately. Organ impairment was defined for each metric according to established

162   cut-offs (Table S1) and was grouped by evidence of: borderline or low ejection fraction and

163   evidence of myocarditis in the heart; reduced pulmonary dynamic measurements in the

164   lungs; elevated cortical T1 in the kidneys; borderline or definite inflammation in the liver and

165   pancreas; and splenomegaly from spleen length.

166

167   **Statistical analysis**

168   All statistical analyses were performed using R software (version 3.6.1) with a p-value less

169   than 0.05 considered statistically significant. Descriptive statistics were used to summarise

170   baseline participant characteristics. Mean and standard deviation (SD) were used to

171   describe normally distributed-continuous variables, median with interquartile range (IQR) for

172   non-normally distributed, and frequency and percentage for categorical variables.

173

174   Mean difference in quantitative organ metrics between hospitalised versus not hospitalised

175   were compared using the Wilcoxon test, and difference in the counts of the binary outcomes

176   of those with evidence of organ abnormalities compared using Fisher's test. Multi-organ

177   impairment was defined as impairment to ≥2 organs. Associations between multi-organ

178   impairment and symptoms, comorbidities and pre-existing risk factors were assessed using

179   Spearman's correlation. Based on the observed differences between hospitalised and non-

180   hospitalised groups, multivariate logistic regression models were used to assess risk factors

181   for COVID-19 hospitalisation.

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Results

190   The mean age was 44.0 (SD: 11.0) years. 70% of individuals were female, 87% were white,

191   31% were healthcare workers, 18% had been hospitalised with COVID-19. Assessment

192   (symptoms, blood and MRI) was a median 140 (IQR 105-160) days after initial symptoms.

193   Relevant past medical history included smoking (3%), asthma (18%), obesity (20%),

194   hypertension (6%), diabetes (2%) and heart disease (4%). The hospitalised group were

195   older (p=0.001), had a higher proportion of non-white participants (p=0.038), and were more

196   likely to report 'inability to walk' (p=0.01) than non-hospitalised individuals. There were no

197   other significant differences between risk factors or symptoms reported between the groups.

198   The most commonly reported on-going symptoms (regardless of hospitalisation status) were

199   fatigue (98%), muscle ache (88%), shortness of breath (87%) and headache (83%) (**Table 1,**

200   **Figure 2(a)**). Ongoing cardiorespiratory (92%) and gastrointestinal (73%) symptoms were

201   common. 99% of individuals had four or more and 42% had ten or more symptoms. 52% of

202   patients reported persistent moderate problems undertaking usual activities (level 3 or

203   greater in the relevant EQ-5D-5L question). 20% reported Dyspnoea-12 ≥15 (equivalent to

204   ~3 on the MRC dyspnoea grade).

205

Blood investigations

207   Triglycerides (p=0.002), cholesterol (p=0.021), LDL-cholesterol (p=0.005) and transferrin

208   saturation (p=0.005) were more likely to be abnormal in hospitalised versus non-hospitalised

209   individuals. Mean corpuscular haemoglobin concentration (26%), alanine transferase (14%),

210   lactate dehydrogenase (16%), triglycerides (12%) and cholesterol (42%) were all abnormally

211   high in ≥10% of all individuals (without separation by hospitalisation status). ESR (13%),

212   bicarbonate (13%), uric acid (16%) and high-sensitivity CRP (13%) were abnormally high in

213   in ≥10% of individuals in the hospitalisation group. Bicarbonate (10%), phosphate (13%), uric

214   acid (11%), and transferrin saturation (19%) were abnormally low in ≥10% of individuals

215   (without separation by hospitalisation status) (**Table S2**).

216

Single and multi- organ impairment

218   Impairment was present in the heart in 32% (myocarditis in 11%; systolic dysfunction in

219   23%), lungs in 33%, kidneys in 12%, liver in 10%, pancreas in 17%, and 6% had evidence of

220   splenomegaly (**Table 2, Figure 2(b)**). 66% of individuals had impairment in one or more

221   organ systems. There was evidence of multi-organ impairment in 25% of individuals, with

222   varying degrees of overlap across multiple organs (**Figure 1 and 3**). Organ impairment was

223   more common in hospitalised versus non-hospitalised individuals. Measures of inflammation

224   in the kidneys and pancreas, and ectopic fat in the pancreas and liver, were also higher in

225   hospitalised individuals (all p <0.05)(**Figure 2(b)**).

226

227   *Association between symptoms, blood investigations and organ impairment*

228   **Figure 4** shows the percentage of reported symptoms in those with organ impairment (per

229   organ). Multi-organ involvement was associated with more serious symptoms (fatigue,

230   breathlessness etc), but no clear pattern was observed linking symptoms to organ

231   impairment. Regression analysis did not show any association between specific organ

232   impairment and specific symptoms or blood investigations. Increasing age (OR: 1.06 [CI:

233   1.02-1.10], p< 0.01), increased liver volume (OR: 1.18 [CI: 1.06-1.30], p<0.001) and having

234   multi-organ impairment (OR: 2.75 [CI:1.22-6.22], p <0.05), all significantly increased the

235   likelihood of being hospitalized, adjusting for gender and BMI.

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Discussion

In the first study to-date evaluating medium-term impairment across multiple organs following SARS-CoV2 infection, we had three major findings. First, in young individuals, largely without risk factors, pre-existing disease or hospitalisation, there was significant symptom burden and evidence of heart, lung, liver and pancreas impairment four months post-COVID-19. Second, symptoms and blood investigations predicted neither organ impairment nor hospitalisation. Third, cardiac (myocarditis and systolic dysfunction) and lung impairment have similar prevalence in low-risk individuals with long COVID.

The short-term symptoms likely to predict COVID-19(20) persist four months post-infection, particularly fatigue, shortness of breath, myalgia, headache and arthralgia. In this young cohort with low prevalence of comorbidities, the extent of symptom burden and organ impairment is concerning. Models of population COVID-19 impact have been based on age, underlying conditions and mortality, excluding morbidity or potential for multi-organ impairment and chronic diseases(21, 22). Moreover, studies highlighting extrapulmonary COVID-19 manifestations emphasised acute phase of illness(20). Although we describe mild rather than severe organ impairment, the pandemic's scale and high infection rates in lower risk individuals (by age and underlying conditions), suggest a medium- and longer- term impact of SARS-CoV-2 infection which cannot be ignored in healthcare or policy spheres.

Although there may be an immunologic basis for variations in progression and severity of SARS-CoV-2 infection in different individuals(24), prediction models to-date have high rates of bias and poor performance(25). We found clustering of cardiorespiratory and gastrointestinal symptoms with evidence of impairment in heart, liver and pancreas respectively, but blood investigations were not associated with particular patterns of organ impairment as determined by COVERSCAN multi-organ assessment. Neither symptoms nor blood investigations were predictive of organ impairment. In acutely unwell patients, the focus has been on recognition of respiratory dysfunction and early provision of ventilatory support, but chronic multi-organ function has not been described systematically. Ongoing studies are considering chronic impact of COVID-19(26) but excluding non-hospitalised, low-risk individuals with and without organ impairment, which we will be investigating further in the longer term. As well as interest in specialist long COVID clinical services(27), there is a role for multi-organ assessment and ongoing evaluation, including low-risk, non-hospitalised individuals, perhaps even in the absence of symptoms.

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298   Acute myocarditis and cardiogenic shock have been described[28], as well as high

299   prevalence of myocarditis in hospitalised COVID-19 patients[29]. In American athletes,

300   although recent COVID-19 was associated with myocarditic changes, many non-infected

301   patients also showed these changes[30]. We now add that one third of low-risk individuals

302   with long COVID syndrome have cardiac impairment in the form of mild systolic dysfunction

303   or myocarditis three months following SARS-CoV-2 infection. Whilst causality cannot be

304   attributed, cardiac function can be viewed as a risk factor for severe infection and an

305   explanation of persistent symptoms in long COVID. As longitudinal data across organs

306   become available, potential significance of our findings in the liver, kidney and pancreas

307   needs to be explored.

308   *Implications for research*

309   Our findings at four months post-infection and future findings have three research

310   implications. First, as countries face second pandemic waves, models of the pandemic's

311   impact must include long COVID, whether quality of life, healthcare utilisation, productivity

312   and economic effects. Second, there is urgent need for further multi-organ assessment,

313   including blood and imaging analysis in the COVID-19 context, as well as linkage with

314   primary and secondary care data, so that long COVID can be properly defined. Third, further

315   longitudinal investigation of clustering of symptoms and organ impairment will inform health

316   services research to plan multidisciplinary care pathways.

317   *Implications for clinical practice and public health*

318   There are three implications for COVID-19 management. First, as well as highlighting the

319   potential for MRI across organ systems following SARS-CoV-2 infection, our findings signal

320   the need for monitoring and follow-up in at least the medium- and longer-term, especially for

321   extrapulmonary sequelae. Second, as the search for effective COVID-19 vaccines and

322   treatments continues, potential and real long-term multi-organ consequences of SARS-CoV-

323   2 infection in low-risk individuals reinforce the central importance of minimising infection

324   through social distancing, wearing of masks, physical isolation and other population-level

325   measures. Third, both in terms of managing baseline risk, and monitoring and treating

326   complications across organ systems, long COVID requires management across specialities

327   (e.g. cardiology, gastroenterology) and disciplines (e.g. communicable and non-

328   communicable diseases).

329   *Strengths and limitations*

330   Our study is an ongoing, prospective, longitudinal cohort study with detailed blood and

331   imaging characterisation of organ function, despite limited clinical examination with video

332   consultations in the era of COVID-19. By recruiting ambulatory patients after infection with

333   broad inclusion criteria (e.g. SARS-CoV-2 testing by virus RNA, antibody or antigen), we

334   focus on individuals at lower risk of severity and mortality from acute SARS-CoV-2 infection.

335   Our cardiac MRI protocol excluded gadolinium contrast as concerns regarding COVID-19-

336   related renal complications remain. We relied on native T1 mapping to detect and

337   characterise myocardial inflammation, allowing non-invasive tissue characterisation which

338   was previously evaluated as superior to gadolinium MRI for acute myocarditis(31).

339

340   We report baseline findings following SARS-CoV-2 infection. In our pragmatic study design,

341   the diagnosis of COVID-19 was by multiple methods, partly limited by access to laboratory

342   testing during the pandemic. Causality of the relationship between organ impairment and

343   infection cannot be deduced, but may be addressed by longitudinal follow-up of individuals

344   with organ impairment. Our study population was limited by ethnicity despite

345   disproportionate impact of COVID-19 in non-white individuals. Pulse oximetry and spirometry

346   were added later to the protocol and follow up; they were not included from the outset to limit

347   interaction and exposure between trial team and patients. We did not include healthy

348   controls or MRI assessment of brain or muscle function.

349

350   *Conclusions*

351   Long COVID has a physiological basis, with measurable patient-reported outcomes and

352   organ impairment. Medium- and long-term evaluation and monitoring of multi-organ function

353   beyond symptoms and blood investigations is likely to be required, even in lower risk

354   individuals. Health system responses should emphasise suppression of population infection

355   rates, as well as management of pre- and post-COVID-19 risk factors and chronic diseases.

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389 Study design: AD, SK, RB, JA, SR

390 Patient recruitment: SK, RB, COVERSCAN team

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398 care (SK); healthcare management (JA).

409

410 **Research in Context**

411

412 ***Evidence before this study***

413 We searched PubMed, medRxiv, bioRxiv, arXiv, and Wellcome Open Research for peer-
414 reviewed articles, preprints, and research reports on long COVID syndrome and medium-
415 and long-term impact of coronavirus disease 2019 (COVID-19), using the search terms
416 "coronavirus", "COVID-19", and similar terms, "organ impairment", "organ function" and
417 "morbidity", up to September 30, 2020. We found no prior studies of medium- or long-term
418 multi-organ impairment due to COVID-19. Prior studies have considered acute phase of
419 illness and hospitalised patients, focusing on "high-risk" individuals based on age and
420 underlying conditions. Without longer term data including lower risk individuals, full
421 population impact of the pandemic cannot be assessed and health system responses cannot
422 be planned.

423

424 ***Added value of this study***

425 In 201 individuals with low risk for COVID-19 severity and mortality (mean age 44 years,
426 20% obesity, 6% hypertension, 2% diabetes and 4% heart disease, 18% hospitalised), we
427 assessed symptoms, blood investigations and multi-organ magnetic resonance imaging
428 across organ systems, four months following SARS-CoV-2 infection. 99% and 42% had ≥4
429 and ≥10 symptoms respectively. Mild organ impairment was present in at least one organ in
430 66% and in 2 or more organs in 25% of individuals. Multi-organ impairment was associated
431 with hospitalisation.

432

433 **Implications of all the available evidence**

434 These analyses support strategies to suppress and minimise the infection rate in the
435 population; medium- and long-term follow-up after SARS-CoV-2 infection with detailed
436 evaluation across organ systems; and management of underlying conditions and risk factors
437 before and after infection. For the first time, we provide multi-organ assessment in young,
438 low-risk individuals with long COVID to inform healthcare and policy responses.

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596 **Figures and Tables**

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598   Table 1: Baseline demographics and symptoms in 201 low-risk individuals with long-COVID.

599   Table 2: Evidence of organ impairment in 201 low-risk individuals with long-COVID.

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601   Figure 1: Natural history of long COVID, the COVERSCAN study in low-risk individuals
602   (n=201) and policy recommendations.

603   Figure 2: Proportion of low-risk individuals with long-COVID by hospitalisation (n=201) for (a)
604   symptoms; and (b) evidence of organ impairment.

605   Figure 3: Multi-organ impairment in low-risk individuals with long COVID by gender and
606   hospitalisation (n=201).

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608   Figure 4: Clustering of reported symptoms and organ impairment for individuals with long-
609   COVID (n=201).

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629 Table 1: Baseline demographics and symptoms in 201 low-risk individuals with long-COVID.*

	All (n=201) N (%)	Not hospitalised (n=164) N(%)	Hospitalised (n=37) N(%)	p
Patient characteristics				
Age (yrs, mean; sd)	44(11.0)	43(10.9)	50(10.0)	0.001
Female (No, %)	140(69.7)	117(71.3)	23(62.2)	0.208
BMI (kg.m^{-2}, median; IQR)	25.7(22.7,28.1)	25.3(22.6,27.7)	27.2(23.1,31.0)	0.162
Ethnicity White	174(86.6)	146(89.0)	28 (75.7)	0.408
Mixed	3(1.5)	3(1.8)	0 (0)	
South Asian	8(4.0)	5(3.0)	3 (8.1)	
Black	5(2.5)	3(1.8)	2 (5.4)	
Comorbidities and risks				
Smoking Never	132 (65.7)	108 (65.9)	24 (64.9)	0.945
Current	6 (3.0)	6 (3.7)	0 (0.0)	
Ex	63 (31.3)	50 (30.5)	13 (35.1)	
Health care worker	62 (30.8)	49 (29.9)	13 (35.1)	0.537
Asthma	36 (17.9)	33(20.1)	3 (8.1)	0.099
BMI ≥25 kg/m^2	112 (56.3)	87 (53.7)	25 (67.6)	0.144
≥30 kg/m^2	40 (20.1)	28 (17.3)	12 (32.4)	0.103
Hypertension	12 (6.0)	10 (6.1)	2 (5.4)	1
Diabetes	4 (2.0)	4 (2.4)	0 (0.0)	1
Previous heart disease	8 (4.0)	7 (4.3)	1 (2.7)	1
Symptoms				
Fatigue	197 (98.0)	160 (97.6)	37 (100.0)	1
Muscle ache	176 (87.6)	145 (88.4)	31 (83.8)	0.408
Shortness of breath	175 (87.1)	140 (85.4)	35 (94.6)	0.177
Headache	166 (82.6)	139 (84.8)	27 (73.0)	0.097
Joint pain	157 (78.1)	128 (78.0)	29 (78.4)	1
Fever	151 (75.1)	127 (77.4)	24 (64.9)	0.14
Chest pain	147 (73.1)	116 (70.7)	31 (83.8)	0.15
Cough	148 (73.6)	119 (72.6)	29 (78.4)	0.54
Sore throat	143 (71.1)	120 (73.2)	23 (62.2)	0.228
Diarrhoea	119 (59.2)	92 (56.1)	27 (73.0)	0.086
Abnormal pain	108 (53.7)	91 (55.5)	17 (45.9)	0.362
Wheezing	97 (48.3)	74 (45.1)	23 (62.2)	0.097
Inability to walk	81 (40.3)	59 (36.0)	22 (59.5)	0.01
Runny nose	68 (33.8)	55 (33.5)	13 (35.1)	0.85
Time interval				
Initial symptoms-to-assessment (days: median, [IQR])	(n=1 missing) 140 (105, 160)	(n=1 missing 140 (106, 162)	138 (97, 150)	0.782
COVID-19 positive-to-assessment (days: median, [IQR])	(n=3 missing) 70 (42, 112)	(n=3 missing) 67 (39, 109)	105 (59, 126)	0.405

*Continuous data presented as means (SD) for normally distributed data and median (IQR) for non-normally distributed data and categorical as count (%). Comparisons between patients man

679   *aged at home vs hospitalised were conducted using Wilcoxon Rank sum test for continuous data and*
680   *Fisher exact test for categorical data.*
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685   Table 2: Evidence of organ impairment in 201 low-risk individuals with long-COVID.

Measurement	All (n=201) N(%)	Not hospitalised (n=164) N(%)	Hospitalised (n=37) N(%)	p
HEART				
Left ventricular ejection fraction (%)				
• Normal (>55%)	155 (77.1)	129 (78.7)	26 (70.3)	
• Borderline impairment (50-55%)	38 (18.9)	31 (18.9)	7 (18.9)	0.079
• Definite impairment (<50%)	8 (4.0)	4 (2.4)	4 (10.8)	
Left ventricular end diastolic volume (ml)				
• >214ml in M; >178ml in W	27 (13.4)	18 (11.0)	9 (24.3)	0.057
Evidence of myocarditis				
• ≥ 3 segments with high T1 (≥1264ms at 3T; ≥1015ms at 1.5T)	22 (10.9)	18 (11.0)	4 (10.8)	1
LUNGS				
Deep Breathing Fractional area change	(n= 11 missing)	(n= 8 missing)	(n= 3 missing)	
• < 39%	63 (33.2)	47 (30.1)	16 (47.1)	0.071
KIDNEYS				
Kidney cortex T1	(n= 12 missing)	(n= 8 missing)	(n= 4 missing)	
• Normal (<1610 ms at 3T; <1191ms at 1.5T)	175 (88.4)	146 (90.7)	29 (78.4)	0.046
• Definite impairment (≥1610ms at 3T; ≥1191ms at 1.5T)	23 (11.6)	15 (9.3)	8 (21.6)	
PANCREAS				
Pancreatic inflammation (T1 in ms)				
• Normal (<800ms)	157 (83.1)	136 (87.2)	21 (63.6)	
• Borderline (800-865ms)	20 (10.6)	11 (7.1)	9 (27.3)	0.003
• Significant (>865ms)	12 (6.3)	9 (5.8)	3 (9.1)	
Pancreatic fat	(n= 6 missing)	(n= 4 missing)	(n= 2 missing)	
• Normal (<5%)	126 (64.6)	111 (69.4)	15 (42.9)	
• Borderline (5-10%)	44 (22.6)	33 (20.6)	11 (31.4)	0.005
• Significant(>10%)	25 (12.8)	16 (10.0)	9 (25.7)	
LIVER				
Liver Inflammation (cT1 in ms)	(n= 1 missing)	(n= 1 missing)		
• Normal (<800ms)	181 (90.5)	150 (92.0)	31 (83.8)	
• Borderline (800-825ms)	5 (2.5)	5 (3.1)	0 (0.0)	0.040
• Significant (>825ms)	14 (7.0)	8 (4.9)	6 (16.2)	
Liver fat				
• Normal (<5%)	162 (80.6)	138 (84.1)	24 (64.9)	
• Borderline (5-10%)	18 (9.0)	12 (7.3)	6 (16.2)	0.025
• Definite (>10%)	21 (10.4)	14 (8.5)	7 (18.9)	
SPLEEN				
Splenic length (mm)	(n= 10 missing)	(n= 10 missing)		
• Normal **(Table S1)**	179(9.4)	144(9.5)	35 (9.5)	
• Borderline **(Table S1)**	12 (6.3)	10 (6.5)	2 (5.4)	1

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687   [*]*Data are presented as count (%). Comparisons between patients managed at home vs hospitalised*
688   *were conducted using Fisher exact test.*
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690   Figure 1: Natural history of long COVID, the COVERSCAN study in low-risk individuals (n=201) and policy recommendations.
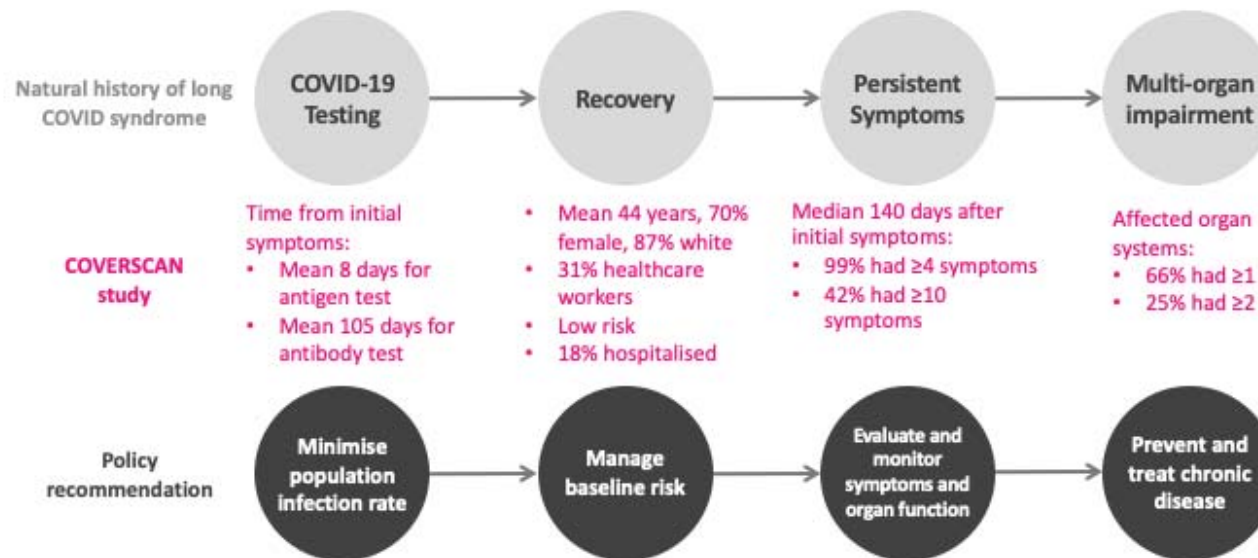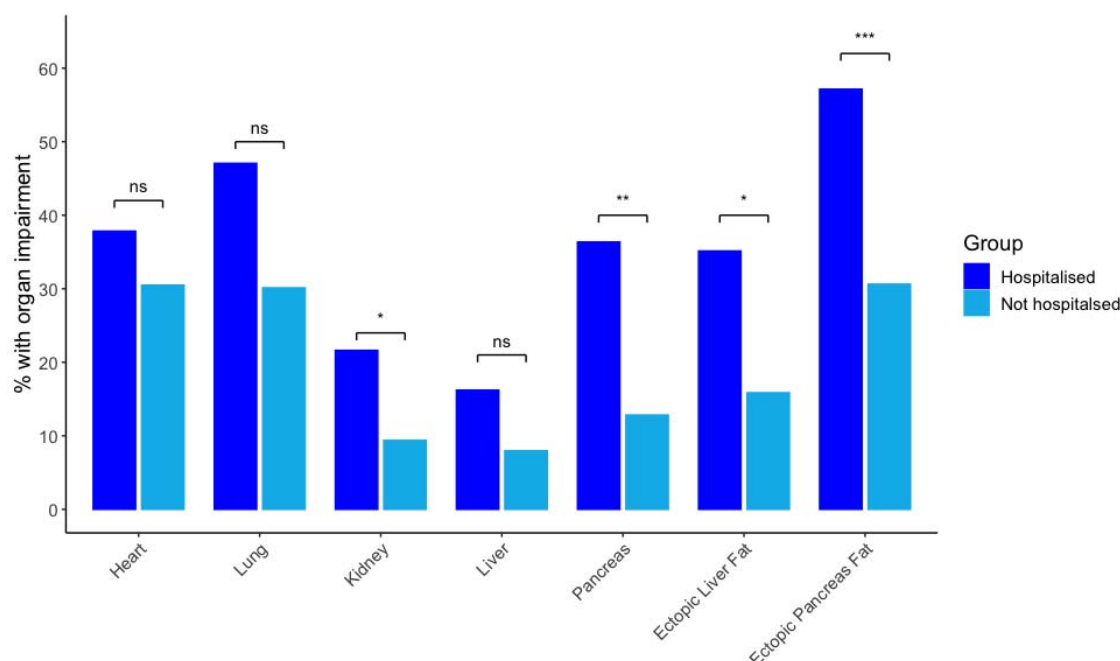

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694   Figure 2: Proportion of low-risk individuals with long-COVID by hospitalisation (n=201) for (a)
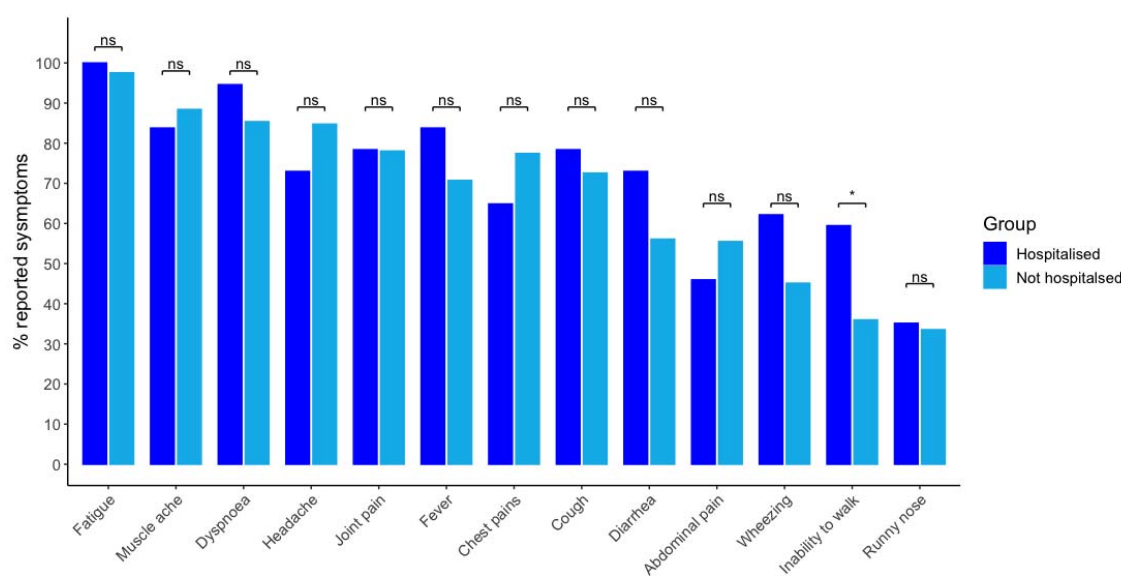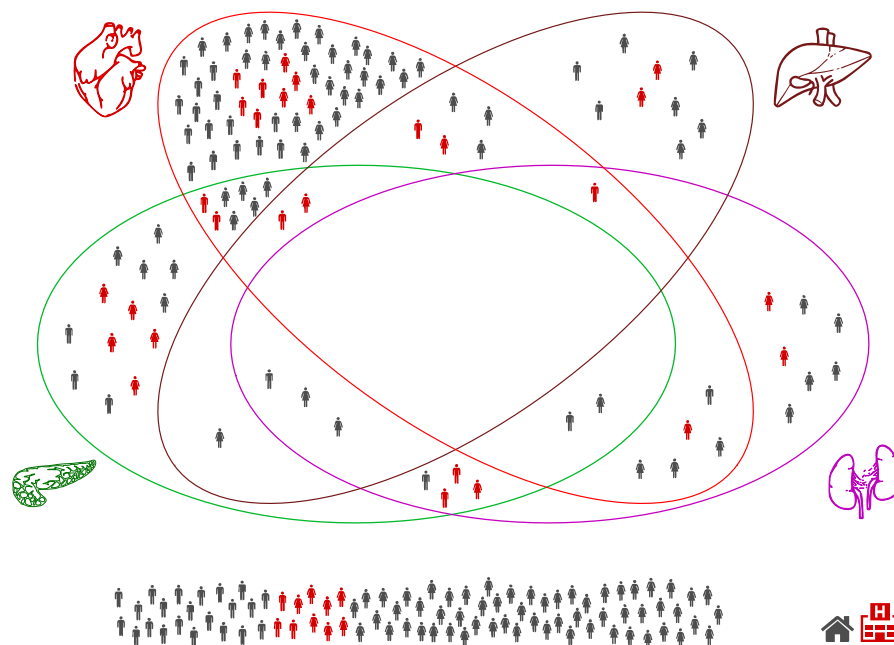695   symptoms; and (b) evidence of organ impairment.

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704 Figure 3 Multi-organ impairment in low-risk individuals with long COVID by gender and
705 hospitalisation (n=201).

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727 Figure 4: Clustering of reported symptoms and organ impairment for individuals with long-
728 COVID (n=201).

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