Phenotyping of acute and persistent COVID-19 features in the outpatient setting: exploratory analysis of an international cross-sectional online survey

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Summary: In this survey study on non-hospitalized SARS-CoV-2-infected adults (Austria: n = 1157, Italy: n = 893) three phenotypically distinct manifestations of long COVID and post-acute sequelae of COVID-19 were characterized and linked to differing profiles of symptoms and recovery.

Abstract

BACKGROUND. Long COVID, defined as presence of COVID-19 symptoms 28 days or more after clinical onset, is an emerging challenge to healthcare systems. The objective of this study was to explore recovery phenotypes in non-hospitalized COVID-19 individuals.

METHODS.

A dual cohort, online survey study was conducted between September 2020 and July 2021 in the neighboring European regions Tyrol (TY, Austria, n = 1157) and South Tyrol (STY, Italy, n = 893). Data on demographics, comorbidities, COVID-19 symptoms and recovery adult outpatients were collected. Phenotypes of acute COVID-19, post-acute sequelae and risk of protracted recovery were explored by semi-supervised clustering and multi-parameter LASSO modeling.

RESULTS. Working age subjects (TY: 43 yrs (IQR: 31 – 53), STY: 45 yrs (IQR: 35 – 55)) and females (TY: 65.1%, STY: 68.3%) predominated the study cohorts. Nearly half of the participants (TY: 47.6%, STY: 49.3%) reported symptom persistence beyond 28 days. Two acute COVID-19 phenotypes were discerned: the non-specific infection phenotype and the multi-organ phenotype (MOP). Acute MOP symptoms encompassing multiple neurological, cardiopulmonary, gastrointestinal and dermatological complaints were linked to elevated risk of protracted recovery. The major subset of long COVID individuals (TY: 49.3%, STY: 55.6%) displayed no persistent hyposmia or hypogeusia but high counts of post-acute MOP symptoms and poor self-reported physical recovery.

CONCLUSION. The results of our two-cohort analysis delineated phenotypic diversity of acute and post-acute COVID-19 manifestations in home-isolated patients which needs to be considered for predicting protracted convalescence and allocation of medical resources.

Keywords: COVID-19, SARS-CoV-2, long-term sequelae, long-COVID, phenotyping

Introduction

Coronavirus disease 2019 (COVID-19) displays a broad clinical spectrum from asymptomatic to fatal courses and variable duration [1] . COVID-19 complaints present for more than four weeks, often described as 'long COVID', are a growing health concern and a new burden to health care systems [2] . The terms 'ongoing symptomatic COVID-19' for persistent post-infectious symptoms for 4 – 12 weeks and 'post-COVID-19 syndrome' or post-acute sequelae of COVID-19 (PASC) for symptoms lasting ≥ 12 weeks were introduced [3] . Long-lasting dyspnoea and fatigue are well characterized in hospitalized COVID-19 patients. The clinical phenotype of outpatients, who constitute the majority of COVID-19 cases, is still insufficiently described [4–6]. This subset, commonly classified as mild COVID-19, experiences prolonged symptoms including chronic cough, shortness of breath, chest tightness, cognitive dysfunction and fatigue [7–10] . Thus, identification of recovery patterns and subjects at risk of complicated convalescence following ambulatory COVID-19 is urgently needed to effectively allocate healthcare resources.

Herein we present results of a bi-national, two-cohort survey of non-hospitalized COVID-19 patients. Applying semi-supervised clustering, kinetic and risk modeling we explored patterns of acute and persistent manifestations, phenotypic heterogeneity of long COVID and PASC individuals and identified key risk factors of protracted recovery.

Methods

Study design and participants

The bi-national, two-cohort 'Health after COVID-19 in Tyrol' anonymized online survey (ClinicalTrials.gov: NCT04661462) was conducted in the neighboring European regions Tyrol (TY, Austria) and South Tyrol (STY, Italy) between the 30thSeptember 2020 and 5th July 2021 [11] . The participants were invited via public media calls (local broadcasters: ORF Tirol and RAI Südtirol, newspapers) and by general practitioners (STY). The inclusion criteria encompassed confirmed SARS-CoV-2 infection (PCR or seropositivity), TY/STY residency and age ≥ 16 (TY) or ≥ 18 years (STY). Analysis exclusion criteria were COVID-19-related hospitalization and the SARS-CoV-2 test – survey observation time < 28 days. PASC analyses was done in subsets with the observation time ≥ 90 days (**Figure 1**).

The study was performed in accordance with the Declaration of Helsinki. Each participant gave a digital informed consent at the survey start. The study protocol was approved by the institutional review boards of the Medical University of Innsbruck (TY, approval number: 1257/2020) and the Autonomous Province of South Tyrol/Bolzano (STY, 0150701).

Measures, definitions and variable stratification

Observation time was defined as the period between the positive SARS-CoV-2 test and survey participation. Respondents retrospectively assigned their symptoms (44 items) to pre-defined duration classes (absent, present for 1 – 3 days, ≤ 1 week, ≤ 2 weeks, ≤ 4 weeks, ≤ 3 months, ≤ 6 months and > 6 months). The symptoms were classified as (1) acute present in the first two weeks, (2) sub-acute present 2 – 4 weeks, (3) persistent present for ≥ 4 weeks. Long COVID was defined as at least one persistent symptom for ≥ 28 days, PASC was defined as at least one persistent symptom lasting ≥ 3 months.

Symptom relapse and subjective convalescence were surveyed as single yes/no questions each. Self-reported physical performance loss following COVID-19 was assessed with a 0 – 100 percent scale. Quality of life and overall mental health were measured with 4-point likert scales [12] . Stress was gauged with the PHQ psychosocial stress module [12,13] . For the detailed variable list and stratification, see **Supplementary Methods** and **Supplementary Table S1 – S2**.

Statistical analysis

Statistical analysis was performed with R 4.0.5. Differences between groups were compared with $\chi 2$, Mann-Whitney U or Kruskal-Wallis test. Symptom number kinetics was analyzed with mixed-effect Poisson regression [14] . Symptom phenotypes were defined by PAM (partitioning around medoids) clustering and simple-matching distance [15,16] . Subsets of long COVID and PASC subjects were defined by DBSCAN algorithm and Manhattan distance [17,18] in the training TY cohort and validated in the test STY collective [19] .

Univariate Poisson and logistic models were age- and gender-weighted and adjusted for observation time. Multi-parameter modeling was done with 50-fold cross-validated LASSO (least absolute shrinkage and selection operator) age- and gender-weighted Poisson or logistic regression in the training TY cohort [20] . LASSO model predictions in the test STY cohort were evaluated with receiver-operator characteristic (ROC). Multiple testing adjustment was

done with Benjamini-Hochberg method [21] . For statistical analysis details, see **Supplementary Methods**.

Results

Study population

3140 individuals (TY: n = 2065, STY: n = 1075) were recruited. After exclusion of hospitalized respondents (TY: n = 84, STY: n = 83) and questionnaires with an observation time < 28 days (TY: n = 741, STY: n = 56), 1157 TY and 893 STY surveys were eligible for analysis. For PASC phenotyping, subsets with an observation time ≥ 90 days (TY: n = 526, STY: n = 485) were utilized (**Figure 1**).

The median observation time was slightly shorter in the TY (79 days, IQR: 40 – 175) than in the STY collective (96 days, IQR: 60 – 138, $p = 1.5\times10^{-7}$) (**Table 1**). More STY (29.7%) than TY respondents (5.1%, $p = 1.9\times10^{-50}$) experienced a SARS-CoV-2 infection during the 2021 outbreaks caused mainly by alpha and beta variants of concern (**Table 3**) [22] .

Both collectives were predominantly of working age (TY: median 43 years, IQR: 31 – 53, STY: 45 years, IQR: 35 – 55) and elderly participants were under-represented (TY: > 65 years, 5.71% vs convalescents in Tyrol: 13.2%, $p = 9.9\times10^{-14}$; STY: > 60 years, 11.2% vs convalescents in Italy: 25.0%, $p = 3.8\times10^{-21}$). Furthermore, females (TY, 30 – 54 years, study: 65.7% vs convalescents in Tyrol: 50.6%, $p = 9.1\times10^{-14}$; STY, 30 – 60 years, study: 68.3% vs convalescents in Italy: 51.6%, $p < 10^{-16}$), healthcare employees (TY: 25.9% vs 10.9% in Austria, $p < 10^{-16}$; STY: 20.1% vs 6.56% in South Tyrol, $p < 10^{-16}$) and education workers (TY: 12.6% vs 6.73% in Austria, $p < 10^{-16}$; STY: 13.3% vs 3.55% in Italy, $p < 10^{-16}$) were over-represented (**Table 1, Supplementary Table S8**) [23–26]. Notably, the study collectives differed in multiple sociodemographic characteristics like employment or education structure (**Table 1**).

48.9% of TY and 41.8% of STY participants reported comorbidities (p = 0.005), most frequently overweight (BMI 25 – 30 kg/m^2; TY: 28.4%, STY: 26.2%), hay fever (TY: 18%, STY: 11.4%), obesity (BMI > 30 kg/m^2, TY: 15.2%, STY: 9.08%), arterial hypertension (TY: 11.2%, STY: 9.41%), bruxism and depression or anxiety (**Table 2**).

Characteristics of acute COVID-19 and recovery trajectories

Rates of asymptomatic SARS-CoV-2 infection (TY: 8.3%, STY: 12.3%) were lower than estimates for Austria (16.5% - 26.9%) or Italy (≤ 50%) (**Table 3**) [24,27] . Almost half of the symptomatic subjects described acute COVID-19 as a condition 'not experienced before' (TY: 49.7%, STY: 47.8%), followed by 'common cold-', 'influenza-' and 'gastroenteritis-like' illness. In most participants (TY: 60%, STY: 52.8%), self-reported severe illness perception was limited to one week. However, nearly half of the individuals (TY: 47.6%, STY: 49.3%) suffered from long COVID defined as symptom presence for ≥ 28 days (**Figure 2A**) [3,8] . The self-reported relapse rate ranged from 20.9% (STY) to 31.9% (TY) collective (**Table 3**). Furthermore, over one third (TY: 40.7%, STY: 35.3%) of the subset with the observation time ≥ 90 days reported symptoms persisting for ≥ 3 months indicative of PASC (**Supplementary Figure S1A**) [3] .

The median acute symptom count (TY: 13, IQR: 9 – 18, STY: 13, IQR: 7 – 18) and the 35% weekly count reduction rate were comparable in the study collectives (**Figure 2B**, **Table 3**). Interestingly, long COVID (**Figure 2C**) or PASC individuals (**Supplementary Figure S1B**) had nearly twice the number of acute symptoms ($\beta_{\text{long COVID}}$ and β_{PASC}) and a 1.6 – 2.1 fold slower resolution rate ($\beta_{\text{interaction}}$) as compared to the participants with complete symptom recovery.

Prevalence of acute and persistent COVID-19 symptoms

Besides non-specific infection symptoms (fatigue, headache, joint pain, myalgia, diminished appetite, fever), respiratory manifestations: tachypnoea (TY: 57%, STY: 51%), chest pain (TY: 47%, STY: 41%) and dyspnoea (TY: 34%, STY: 28%) were frequent in acute COVID-19 outpatients (**Figure 3, Supplementary Figure S2 – S3**).

Frequencies of cold- or flu-like complaints declined significantly over time (**Figure 3**, **Supplementary Figure S2**, **Supplementary Table S3**). In contrast, resolution of fatigue (TY: 40%, STY: 46% of long COVID subjects), daytime tiredness (TY: 47%, STY: 46%), hyposmia/anosmia (TY: 47%, STY: 42%), taste disorder (TY: 35%, STY: 33%) and tachypnoea (TY: 35%, STY: 31%) were substantially delayed. Those features together with concentration (TY: 32%, STY: 38%) and memory deficits (TY: 27%, STY: 38%) represented the predominant manifestations of long COVID and PASC (**Figure 3**, **Supplementary Figures S2 – S3**).

Additionally, hair (TY: 13.7%, STY: 14.8%) and weight loss during convalescence were reported. One fourth (TY: 25.3%, STY: 23.8%) of the study collective rated the physical performance loss > 25% and more than one third (TY: 46%, STY: 36.7%) reported an incomplete recovery (**Table 3**).

Patterns of acute and persistent COVID-19 symptoms

By semi-supervised clustering, two acute COVID-19 symptom patterns were identified (**Supplementary Figure S4**) [15] . The 'non-specific infection phenotype' (NIP) encompassed symptoms of upper airway infections such as rhinitis, sore throat, dry cough and fatigue, along with smell and taste disorders. The 'multi-organ phenotype' (MOP) included manifold lower airway, neurological, gastrointestinal, cardiovascular and dermatological manifestations (**Figure 4, Supplementary Figure S5, Supplementary Table S4**). Of note, neither the NIP nor MOP symptom count differed between the study cohorts (**Table 3**).

By an analogical procedure, we found three phenotypes of long COVID and PASC symptoms: (1) 'hyposmia/anosmia phenotype' (HAP) encompassing closely co-occurring smell and taste disorder, (2) 'fatigue phenotype' (FAP) including fatigue, tiredness, memory and concentration deficits, and (3) 'multi-organ phenotype' (MOP) with pulmonary, gastrointestinal, neuro-cognitive and cardiovascular disorders **(Figure 5, Supplementary Figure S6 – S8, Supplementary Table S4)**.

Phenotypic diversity of long COVID and PASC

Next, we explored heterogeneity of protracted COVID-19 recovery based on the number of persistent HAP, FAP and MOP symptoms (**Supplementary Figure S9**) [17,19] . Three distinct clusters of long COVID and PASC individuals were characterized, the HAP-negative, -intermediate and -high subset, with differing counts of the HAP taste and smell disorders (**Figure 6AB, Supplementary Figure S10AB**). The largest, HAP symptom-negative subset comprising half of the long COVID and PASC individuals (TY: 49.1% in long COVID, 48.1% in PASC, STY: 55.5% in long COVID, 57.3% in PASC) demonstrated the highest count of FAP and MOP symptoms such as fatigue, tiredness, tachypnea, memory and concentration disorders. Contrastingly, these manifestations were expressed in the minor HAP-intermediate subset (TY: 18.9% in long COVID, 25.2% in PASC, STY: 13.4% in long COVID, 12.3% in PASC) at particularly low levels (**Figure 6BC, Supplementary Figure**

S10BC, Supplementary Figure S11). Although differences in demographic and clinical features between those subsets were minimal (**Table S5**), the HAP-high subgroup with co-occuring hyposmia and hypogeusia had the tendentially largest fraction of female and normal-weight participants (**Figure 7, Supplementary Figure 12**).

Subsequently, readouts of the acute disease, physical and mental recovery were compared. Acute COVID-19 symptom counts tended to be the lowest in the minor HAP-intermediate subgroup, especially in the STY cohort (**Figure 8A**, **Supplementary Figure S13A**). The same group was characterized by the lowest self-perceived physical performance loss following COVID-19, particularly in PASC, and tended towards the lowest psychosocial stress scoring. Notably, the worst performance rating was observed in the largest HAP-negative cluster. Differences in the remaining measures of quality of life, mental health impairment, convalescence rating and relapse rate were less evident (**Figure 8BC**, **Supplementary Figure S13BC, Table S6**).

Factors linked to acute COVID-19 severity and protracted recovery

Next, we analyzed pre-existing clinical factors affecting the severity of acute ambulatory COVID-19 (**Supplementary Table S7**). By univariate modeling (**Supplementary Tables S8 – S9**), multi-morbidity (≥ 3 conditions, TY: exp β = 1.34 [95%CI: 1.23 – 1.47], STY: 1.52 [1.33 – 1.72]), sleep disorders, high daily medication intake, frequent respiratory infections, depression or anxiety and obesity were associated with polysymptomatic acute COVID-19. Males displayed on average 20% symptoms less than females (**Supplementary Figure S14A**). In multi-parameter LASSO analysis, multi-morbidity (≥ 3 conditions, 13% more) and male sex (9% less) were identified as the most relevant co-variates of the symptom count (**Supplementary Figure S15**).

Finally, we analyzed association of pre-existing clinical features and acute COVID-19 symptoms with the risk of long COVID and PASC (**Supplementary Table S7**). In the univariate setting (**Supplementary Tables S8 – S9**), high overall count of acute symptoms (4^{th} quartile, long COVID, TY: OR = 8.11 [95%CI: 5.43 – 12.3], STY: 8.2 [5.05 – 13.6]) and of acute MOP complaints (4^{th} quartile, long COVID, TY: 7.53 [5.08 – 11.3], STY: 10.4 [6.31 – 17.4]) were found the strongest unfavorable risk-modifying factors. Additionally, acute MOP complaints: forgetfulness, confusion, palpitations and hand paresthesia were significantly linked with prolonged recovery. In turn, males had a 35 – 55% lower long COVID or PASC risk than females (**Supplementary Figure S14BC**).

By multi-parameter LASSO logistic modeling, acute MOP manifestations: forgetfulness (long COVID: OR_{LASSO} = 1.92, PASC: OR_{LASSO} = 1.50), sleeplessness (long COVID: 1.22, PASC: 1.07), palpitations (long

COVID: 1.08, PASC: 1.5) along with smell (long COVID: 1.33, PASC: 1.52) and respiratory disorders were identified as independent unfavorable correlates of long COVID and PASC in the TY cohort (**Supplementary Figure S16A**). Importantly, the multi-parameter models demonstrated an accuracy at predicting long COVID and PASC > 72% (ROC, area-under the curve) both in the training TY and the test STY collective (**Supplementary Figure S16B**).

Discussion

The leading acute COVID-19 manifestations in our study included fatigue, headache, hyposmia/anosmia/dysgeusia, joint pain, dry cough, myalgia, rhinitis and fever shared by multiple upper-respiratory infections and subsumed under the 'non-specific infection phenotype' (NIP). In turn, the 'multi-organ phenotype' (MOP) comprised of wide-ranged neurological, gastrointestinal, cardiovascular and dermatological manifestations, which pertain to acute 'atypical' and multi-systemic complaints reported in large-scale studies [7,8,28] Supposedly, high MOP density reflects severe ambulatory COVID-19 correlating with the need of professional medical support, as suggested for abdominal pain and confusion classified here as MOP symptoms [28]. Importantly, t**he MOP was detectable in post-acute sequelae**. **Mechanistically, diversity and persistence of MOP symptoms may involve viral pneumonia and encephalopathy, hyper-inflammatory immune response and/or pathological coagulation [29] .**

Clinically, 50% of participants suffered from long COVID and over 35% of the long-term observation subjects had PASC defined by symptom persistence ≥ 28 days and ≥ 3 months, respectively [3] . This frequency is located within the reported range of long COVID (13-76%) depending on sample size and study design [7,8,29,30] . As reported recently, both the long COVID and PASC subset was linked to an elevated acute symptom count and a halved resolution pace [8,10] . Specifically, fatigue, tiredness, smell and taste disorders, tachypnea and MOP manifestations such as forgetfulness, tachycardia and confusion showed a delayed resolution and represented a congruent signature of post-acute sequelae as described previously [5,8,10,29]. Additionally, acute MOP symptoms like neuro-cognitive deficits, sleeplessness and cardiopulmonary abnormalities were found independent prognostic factors of long COVID and PASC. In accord with previous reports, males sex had a lower risk of perturbed convalescence [5,8]. This effect, however, was not independent in the multi-parameter analysis, which be explained by the lower overall acute symptom count in males in the study collectives.

Machine learning-based classification of long COVID and PASC individuals unraveled three subsets differing in profiles of persistent manifestations. The largest, hyposmia- and hypogeusia-free subset demonstrated high density of MOP complaints, fatigue, respiratory abnormalities and poor self-perceived physical recovery. By contrast, a small group affected by either hyposmia or hypogeusia was characterized by a better clinical, physical and mental recovery. Notably, no clear set of clinical parameters could be associated with those clusters. This suggests, that the phenotypic diversity of the post-acute sequelae may rather depend on the individual biological vulnerability to the SARS-CoV-2 pathogen. Furthermore, it needs to be clarified, how the three post-acute subsets differing in taste and smell disorders reflect the distorted self-perception of olfactory stimuli in COVID-19 described recently [31].

Our study bears limitations. Over-representation of symptomatic cases, long COVID, females and health care workers indicates a selection bias towards health-aware individuals particularly affected by acute COVID-19 and incomplete recovery. The retrospective, cross sectional design precluded detailed tracking of particular symptom kinetic and relapses. Such selection and recall bias confounds a precise determination of long COVID and PASC prevalence and risk modeling even if partly addressed by model adjustment. Hence, predictive statistics presented here call for a prospective validation. Additionally, the questionnaire had not been validated before. In turn, the large numbers of participants with post-acute sequelae enabled us to explore phenotypic diversity of long COVID and PASC in detail. Finally, our approach employing two independently recruited cohorts differing in multiple demographic, socioeconomic and clinical paramaters allowed us to delineate features of COVID-19 convalescence with high confidence.

Conclusion

The results of our two-cohort survey indicate that both acute COVID-19 and its post-acute sequelae in non-hospitalized patients are multi-faceted conditions with possible multi-organ involvement, differing symptom profiles and recovery rates. Especially the phenotypically diverse subsets of long COVID and PASC patients may require different therapeutic approaches and allocation of medical resources.

Notes

Author Contribution

GW, RH, RBW, HB, BSU, GN, SS, VR, AP, MA, KC, BB, and JLR designed the study. SS, PT, PW, DA, GR, BH and GP collected the data. PT and DA performed data analysis. PT, SS, DA, AP, VR, KH, KK, GW, RBW, HB, AB, TS, SK, CW, BSU, GP, AH, RH, IT and JLR interpreted the data. SS, PT, DA, VR, AP, IT, GW, RH and JLR wrote the manuscript. All authors critically reviewed the final version of the manuscript.

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Data sharing

Anonymised data and the study protocol are available at request to judith.loeffler@i-med.ac.at. For the analysis pipeline, see https://github.com/PiotrTymoszuk/health-after-COVID19-analysis-pipeline.

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Conflict of interest

PT owns the Data Analytics As a Service data science enterprise; PT is (from May 2021 on) a freelance data scientist working in his own enterprise. He received an honorary for the study data management, curation and analysis and minor manuscript work.. GR has intellectual property rights to the CHES software tool used for data collection. KH received a speaker

honorary from Tiroler Ärztekammer and research grants from Austria Wirtschaftsservice GmbH and the State of Tyrol for unrelated COVID-19 projects. KH reports data analysis and writing of parts of the

manuscript related to statistics from Piotr Piotr Tymoszuk, Data Analytics As a Service.Tirol.

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Table 1. Sociodemographic characteristics of the study cohorts

Characteristic	Tyrol	South Tyrol	P value
Total, n	1157	893	NA
Median age (IQR), years	43 (31 – 53)	45 (35 – 55)	0.002[A]
Sex, n (%)			
Male	404 (34.9)	283 (31.7)	<0.001[B]
Female	753 (65.1)	610 (68.3)	
Observation time, n (%)			
> 60 days	492 (42.5)	230 (25.8)	<0.001[B]
61-120 days	234 (20.2)	316 (35.4)	
121-180 days	164 (14.2)	193 (21.6)	
> 180 days	267 (23.1)	154 (17.2)	
Smoking history, n (%)			
Active	106 (9.16)	90 (10.1)	0.006[B]
Former	361 (31.2)	215 (24.1)	
Highest education, n (%)			
Secondary	505 (43.8)	575 (64.5)	<0.001[B]
Apprenticeship	164 (14.2)	NA[C]	
Elementary	41 (3.6)	2 (0.2)	
Tertiary	444 (38.5)	315 (35.3)	
Mother tongue, n (%)			
German	1157 (100)	493 (55.3)	<0.001[B]
Italian	0 (0)	327 (36.7)	
Ladin	0 (0)	58 (6.5)	
Other	0 (0)	14 (1.6)	
Employment, n (%)			
actively employed	939 (81.2)	728 (81.5)	ns[B]
Employment sector, n (%)			
Health services	296 (25.9)	175 (20.1)	<0.001[B]

Administration/office	222 (19.4)	245 (28.2)	
Education	144 (12.6)	116 (13.3)	
Gastronomy/Tourism	101 (8.8)	72 (8.29)	
Industry	65 (5.7)	43 (5.0)	
Construction	34 (3.0)	245 (28.2)	
Other	283 (24.7)	191 (22.0)	

[A] Mann-Whitney U test, Benjamini-Hochberg correction for multiple testing

[B] χ^2 test, Benjamini-Hochberg correction for multiple testing

[C] not applicable to Italy

Table 2. Pre-existing comorbidities and medication in the study cohorts

Characteristic	Tyrol	South Tyrol	P value[D]
Comorbidities, n (%)			
Comorbidity present	566 (48.9)	373 (41.8)	0.005
Metabolic			
Overweight[A]	327 (28.4)	231 (26.2)	<0.001
Obesity[B]	175 (15.2)	80 (9.1)	<0.001
Diabetes	18 (1.6)	7 (0.8)	ns
Gastrointestinal	34 (2.9)	9 (1.0)	ns
Cardiovascular and pulmonary			
Cardiovascular	34 (2.9)	26 (3.0)	ns
Arterial hypertension	130 (11.2)	84 (9.4)	ns
Thromboembolism	32 (2.8)	7 (0.8)	0.006
Pneumological	48 (4.2)	23 (2.6)	ns
Immunological			
Autoimmunity	67 (5.8)	45 (5.0)	ns
Frequent respiratory infections	51 (4.4)	26 (2.9)	ns
Frequent bacterial infections[C]	45 (3.9)	12 (1.3)	0.003
Hay fever/allergy	23 (2.6)	102 (11.4)	<0.001
Neurologic/psychiatric			
Bruxism	83 (7.2)	47 (5.3)	ns
Sleep disorders	53 (4.6)	36 (4.0)	ns
Sleep apnea	22 (1.9)	10 (1.1)	ns
Stroke	8 (0.7)	4 (0.5)	ns
Depression/anxiety	69 (6.0)	41 (4.6)	ns
Chronic kidney disease	17 (1.5)	7 (0.8)	ns
Malignancy	28 (2.4)	26 (3.0)	ns
Daily medication, n (%)			
1-4 drugs	440 (38.0)	231 (25.9)	<0.001

≥ 5 drugs	29 (2.5)	13 (1.46)	<0.001
Corticosteroids	16 (1.4)	9 (1.0)	ns
Anticoagulation	54 (4.7)	21 (2.4)	0.021
ACE inhibitor	122 (10.7)	75 (8.5)	ns
Analgesic treatment	85 (7.4)	55 (6.2)	ns
Immunosuppression	17 (1.5)	15 (1.7)	ns

[A] defined as BMI >25

[B] defined as BMI >30

[C] defined as indication for antibiotic therapy >2 times per year

[D] χ^2 test, Benjamini-Hochberg correction for multiple testing

Table 3. Characteristics of acute and post-acute COVID-19 course

Characteristic	Tyrol	South Tyrol	P value
Acute COVID-19			
Contact with an infected person, n (%)	712 (61.7)	593 (66.6)	0.03[A]
Period of SARS-CoV-2 infection, n (%)			
Spring 2020	309 (26.7)	144 (16.1)	<0.001[A]
Summer/Fall 2020	789 (68.2)	484 (54.2)	
Winter/spring 2020/21	59 (5.1)	265 (29.7)	
Subjective perception of acute COVID-19, n (%)			
Common cold-like	289 (25.4)	248 (28.3)	<0.001[A]
Influenza-like	235 (20.7)	147 (16.8)	
Gastroenteritis-like	47 (4.1)	62 (7.1)	
Not-experienced before	565 (49.7)	418 (47.8)	
Weight loss, n (%)	555 (48)	355 (39.8)	ns[A]
Contact with physician during quarantine, n (%)	482 (41.8)	463 (51.8)	<0.001[A]
Symptomatic COVID-19 therapy, n (%)			
None	864 (74.7)	593 (66.4)	<0.001[A]
Anti-pyretic	259 (22.4)	257 (28.8)	0.003[A]
Anbtibiotic	83 (7.2)	94 (10.5)	0.02[A]
Acute symptom number, median (IQR)			
Overall	13 (9-18)	13 (7-18)	ns[B]
NIP[C]	8 (6-10)	8 (6-10)	ns[B]
MOP[D]	3 (1-5)	3 (1-6)	ns[B]
Symptom persistence, n (%)			
absent	96 (8.3)	110 (12.3)	0.012[A]
1-3 days	43 (3.7)	28 (3.1)	
< 1 week	66 (5.7)	58 (6.5)	
< 2 weeks	130 (11.2)	92 (10.3)	
< 4 weeks	272 (23.5)	165 (18.5)	
≥ 4 weeks	550 (47.6)	440 (49.3)	
Post-acute COVID-19			
Presence of persistent COVID-19 symptoms, n (%)	550 (47.6)	440 (49.3)	ns[A]
Symptom relapse, n (%)	368 (31.9)	86 (20.9)	<0.001[A]
Rehabilitation after COVID-19, n (%)	14 (1.2)	7 (0.8)	ns[A]
Subjective need for rehabilitation, n (%)	196 (17.0)	117 (13.2)	0.044[A]

Subjective complete convalescence, n (%)	624 (54.0)	563 (63.3)	<0.001[A]
Subjective physical performance loss, n (%)			
0-25%	860 (74.7)	674 (76.2)	ns[A]
26-50%	202 (17.5)	145 (16.4)	
51-75%	72 (6.3)	54 (6.1)	
76-100%	17 (1.5)	11 (1.2)	
Persistent symptom number, median (IQR)			
Overall	0 (0-3)	0 (0-3)	ns[B]
HAP[E]	1 (0-2)	0 (0-2)	ns[B]
FAP[F]	1 (0-3)	1 (0-3)	ns[B]
MOP[D]	1 (0-4)	1 (0-4)	ns[B]

[A] $\chi 2$ test, Benjamini-Hochberg correction for multiple testing

[B] Mann-Whitney U test, Benjamini-Hochberg correction for multiple testing

[C] Non-specific infection phenotype

[D] Multi-organ phenotype

[E] Hypo-/anosmia phenotype

[F] Fatigue phenotype

Figure legends

Figure 1. CONSORT flow diagram for the study populations.

Figure 2. Kinetic of symptom resolution.

(A) Percentages of symptomatic participants in time. Statistical significance was determined by $\chi 2$ test for trend. P values are shown in the plot caption.

(B, C) Symptom number trajectories in the entire study cohorts (B) and in the subsets with or without long COVID. Thin gray lines: individual symptom number trajectories, thick color line: median symptom count, color ribbon: IQR. Statistical significance was determined by mixed-effect Poisson modeling. Model estimates (β) with 95% CI and p values are indicated in the plot.

Numbers of complete cases are indicated under the plots. TY: Tyrol, STY: South Tyrol cohort.

Figure 3. Symptom frequency in acute and sub-acute COVID-19, long COVID and PASC.

Symptom frequencies were expressed as percentages of the individuals with symptoms at the indicated time points after clinical onset. Point size and color represents the percentage. Numbers of complete observations are indicated below the plot.

tired. day: tiredness at day, imp.: impaired, conc.: concentration, abd. pain: abdominal pain, dim.: diminished, f.m.s: fine motor skills, bl.: blue, marm. skin: marmorated skin, TY: Tyrol, STY: South Tyrol cohort.

Figure 4. Clustering of acute COVID-19 symptoms.

Clusters (phenotypes) of acute COVID-19 symptoms, the non-specific infection (NIP) and multi-organ phenotype (MOP), were defined in the training Tyrol (TY) cohort by simple matching distance (SMD) and PAM (partitioning around medoids) algorithm. The phenotype assignment scheme was applied to the test South Tyrol data set (Supplementary Figure S5). SMD values for symptom pairs in the TY cohort are presented as a heat map. The number of complete observations is indicated under the plot.

tired. day: tiredness at day, imp.: impaired, conc.: concentration, abd. pain: abdominal pain, dim.: diminished, f.m.s: fine motor skills, bl.: blue, marm. skin: marmorated skin.

Figure 5. Clustering of persistent COVID-19 symptoms.

Clusters (phenotypes) of long COVID symptoms, the hypo/anosmia (HAP), fatigue (FAP) and multi-organ phenotype (MOP), were defined in the training Tyrol (TY) cohort with simple matching distance (SMD) and PAM algorithm. The phenotype assignment scheme was applied to the test South Tyrol data set (Supplementary Figure S6). SMD values for symptom pairs in the TY cohort are presented as a heat map. The number of complete observations is indicated under the plot.

tired. day: tiredness at day, imp.: impaired, conc.: concentration, abd. pain: abdominal pain, dim.: diminished, f.m.s: fine motor skills, bl.: blue, marm. skin: marmorated skin.

Figure 6. Subsets of long COVID individuals defined by HAP, FAP and MOP phenotype symptoms.

Hypo/anosmia-negative (HAP-), intermediate (HAPi) and high (HAP+) subsets of long COVID individuals were defined in the training Tyrol (TY) cohort with Manhattan distance and DBSCAN clustering according to the counts of hypo/anosmia (HAP), fatigue (FAP) and multi-organ phenotype (MOP) symptoms. The subset assignment in the test South Tyrol (STY) cohort was done with the k-nearest-neighbor label propagation algorithm.

(A) Two-dimensional principal component analysis (PCA) score plot with the long COVID participant subset assignment. Percent variances associated with principal components (PC) are indicated in the plot axes. Numbers of subset individuals are indicated under the plots.

(B) Minimum/maximum-normalized counts of HAP, MOP and FAP symptoms in the long COVID participant subsets. Differences between the participant subsets were investigated by Kruskal-Wallis test.

(C) Occurrence of the 10 most frequent HAP, FAP and MOP long COVID symptoms (Supplementary Figure S3) in the long COVID participant subsets presented as a heat map.

imp. conc.: impaired concentration, tired. day: tiredness at day.

Figure 7. The most relevant demographic and clinical features of the long COVID participant subsets.

Differences in demographic and clinical features (Supplementary Table S5) between the hypo/anosmianegative (HAP-), intermediate (HAPi) and high (HAP+) subsets of long COVID individuals were investigated by $\chi 2$ test. Comparison results for the most differentiating features: sex (A), body mass index class (B) and number of comorbidities (C) are presented. Raw and multiple testing-adjusted significance (pFDR) p values are presented in the plot captions. Numbers of subset individuals are indicated under the plots.

TY: Tyrol, STY: South Tyrol.

Figure 8. Acute symptom count, rating of physical, quality of life and mental impairment in the long COVID participant subsets.

(A) Numbers (#) of acute COVID-19 symptoms in the hypo/anosmia-negative (HAP-), intermediate (HAPi) and high (HAP+) subsets of long COVID individuals. Statistical significance was assessed with Kruskal-Wallis test. Raw and multiple testing-adjusted significance (pFDR) p values are presented in the plot captions. Numbers of subset individuals are indicated under the plots.

(B) Minimum/maximum-normalized scores of physical performance (phys. imp), quality of life (QoL), overall mental health (OMH) impairment and stress in the subsets of long COVID individuals. Statistical significance was assessed with Kruskal-Wallis test. Multiple testing-adjusted significance are presented in the plots.

(C - D) Frequencies of self-reported complete convalescence (B) and symptom relapse (C) in the long COVID participant subsets. Statistical significance was assessed by $\chi 2$ test. Raw and multiple testing-adjusted significance (pFDR) p values are presented in the plot captions.

TY: Tyrol, STY: South Tyrol.

Figure 1

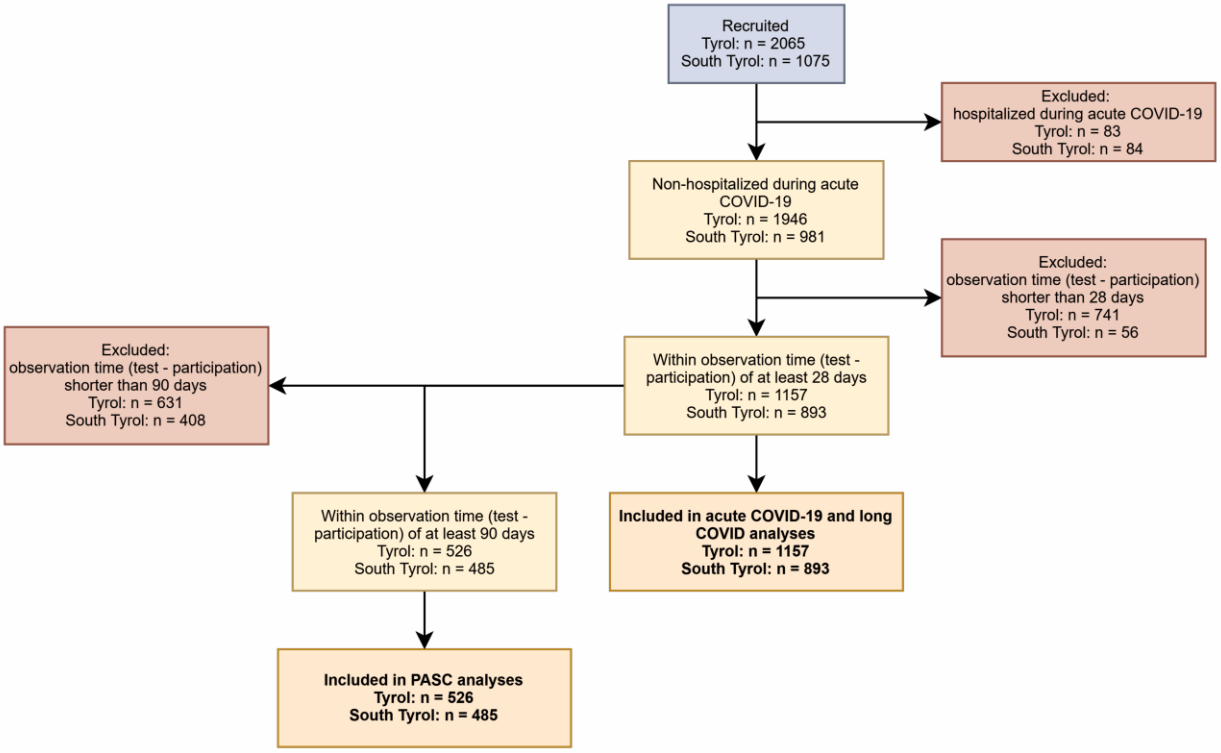

Recruited
Tyrol: n = 2065
South Tyrol: n = 1075
Excluded:
hospitalized during acute COVID-19
Tyrol: n = 83
South Tyrol: n = 84
Non-hospitalized during acute COVID-19
Tyrol: n = 1946
South Tyrol: n = 981
Excluded:
observation time (test - participation) shorter than 28 days
Tyrol: n = 741
South Tyrol: n = 56
Excluded:
observation time (test - participation) shorter than 90 days
Tyrol: n = 631
South Tyrol: n = 408
Within observation time (test - participation) of at least 28 days
Tyrol: n = 1157
South Tyrol: n = 893
Within observation time (test - participation) of at least 90 days
Tyrol: n = 526
South Tyrol: n = 485
Included in acute COVID-19 and long COVID analyses
Tyrol: n = 1157
South Tyrol: n = 893
Included in PASC analyses
Tyrol: n = 526
South Tyrol: n = 485

Figure 2

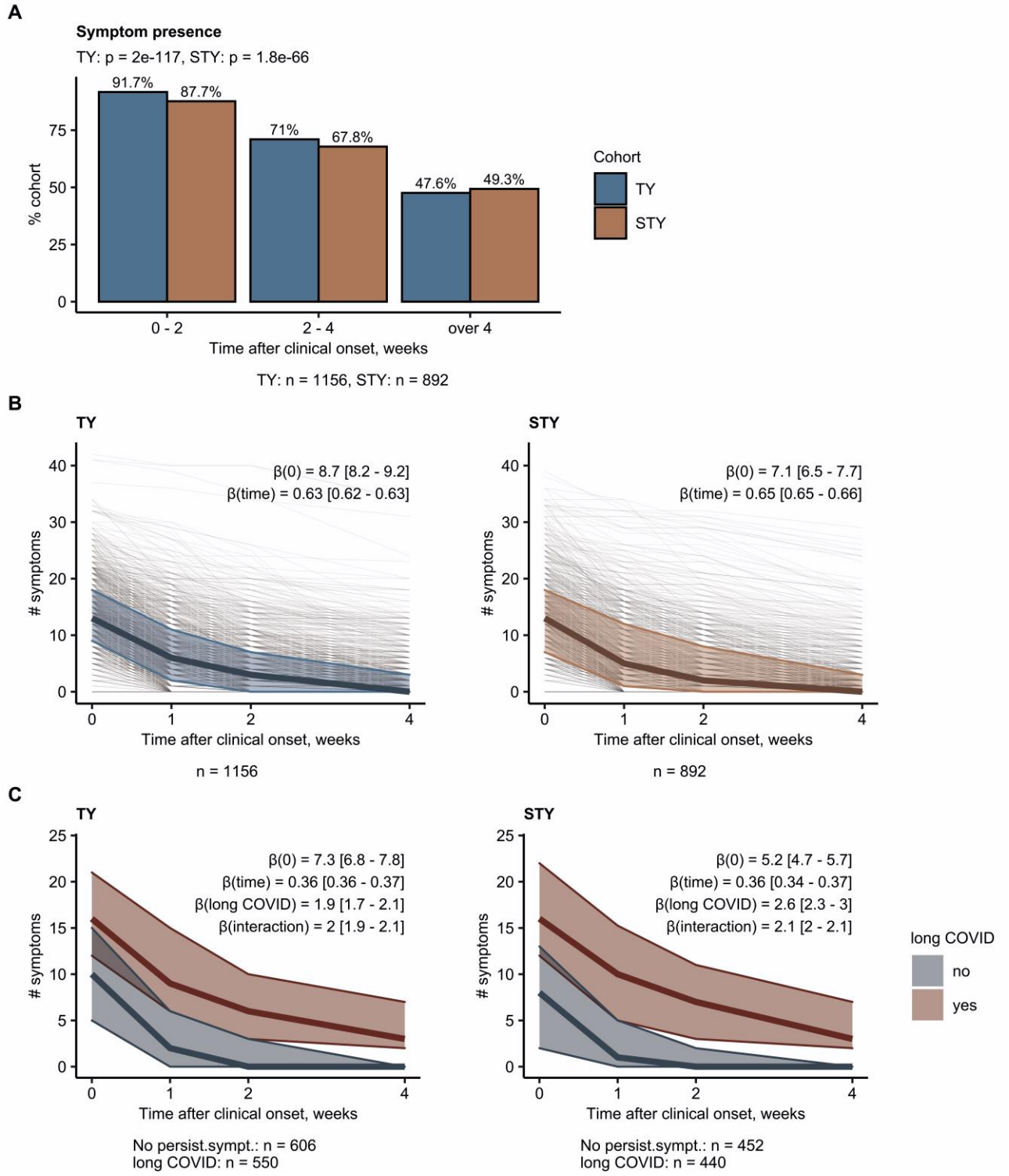
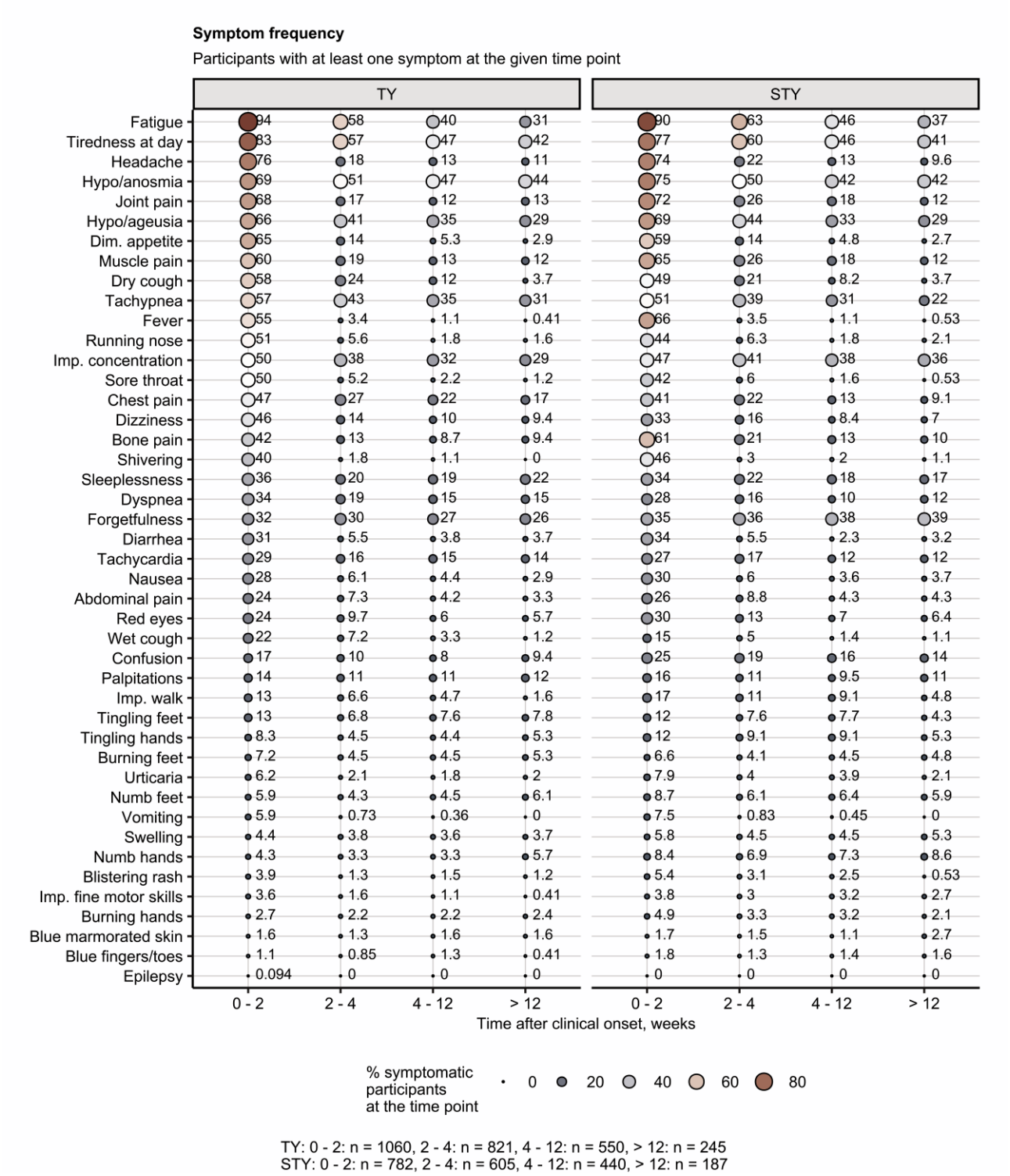

A
Symptom presence
TY: p = 2e-117, STY: p = 1.8e-66
91.7%
87.7%
71%
67.8%
47.6%
49.3%
% cohort
Cohort
TY
STY
0 - 2
2 - 4
over 4
Time after clinical onset, weeks
TY: n = 1156, STY: n = 892
B
TY
β(0) = 8.7 [8.2 - 9.2]
β(time) = 0.63 [0.62 - 0.63]
symptoms
Time after clinical onset, weeks
n = 1156
STY
β(0) = 7.1 [6.5 - 7.7]
β(time) = 0.65 [0.65 - 0.66]
symptoms
Time after clinical onset, weeks
n = 892
C
TY
β(0) = 7.3 [6.8 - 7.8]
β(time) = 0.36 [0.36 - 0.37]
β(long COVID) = 1.9 [1.7 - 2.1]
β(interaction) = 2 [1.9 - 2.1]
symptoms
Time after clinical onset, weeks
No persist.sympt.: n = 606
long COVID: n = 550
STY
β(0) = 5.2 [4.7 - 5.7]
β(time) = 0.36 [0.34 - 0.37]
β(long COVID) = 2.6 [2.3 - 3]
β(interaction) = 2.1 [2 - 2.1]
symptoms
Time after clinical onset, weeks
No persist.sympt.: n = 452
long COVID: n = 440
long COVID
no
yes

Figure 3



TY: 0 - 2: n = 1060, 2 - 4: n = 821, 4 - 12: n = 550, > 12: n = 245
STY: 0 - 2: n = 782, 2 - 4: n = 605, 4 - 12: n = 440, > 12: n = 187

Figure 4

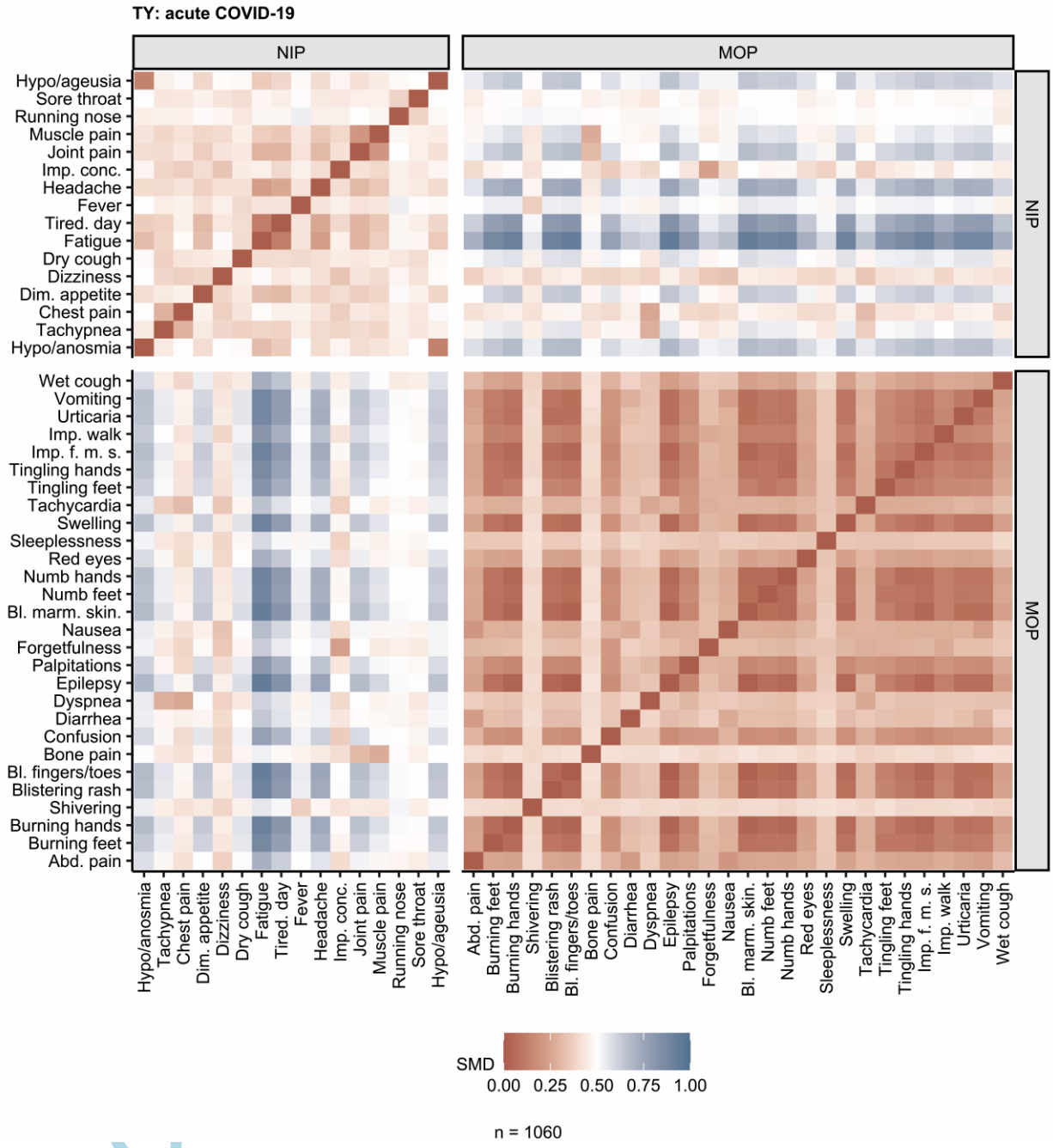

TY: acute COVID-19
NIP
MOP
Hypo/ageusia
Sore throat
Running nose
Muscle pain
Joint pain
Imp. conc.
Headache
Fever
Tired. day
Fatigue
Dry cough
Dizziness
Dim. appetite
Chest pain
Tachypnea
Hypo/anosmia
Wet cough
Vomiting
Urticaria
Imp. walk
Imp. f. m. s.
Tingling hands
Tingling feet
Tachycardia
Swelling
Sleeplessness
Red eyes
Numb hands
Numb feet
Bl. marm. skin.
Nausea
Forgetfulness
Palpitations
Epilepsy
Dyspnea
Diarrhea
Confusion
Bone pain
Bl. fingers/toes
Blistering rash
Shivering
Burning hands
Burning feet
Abd. pain
SMD
0.00 0.25 0.50 0.75 1.00
n = 1060

Figure 5

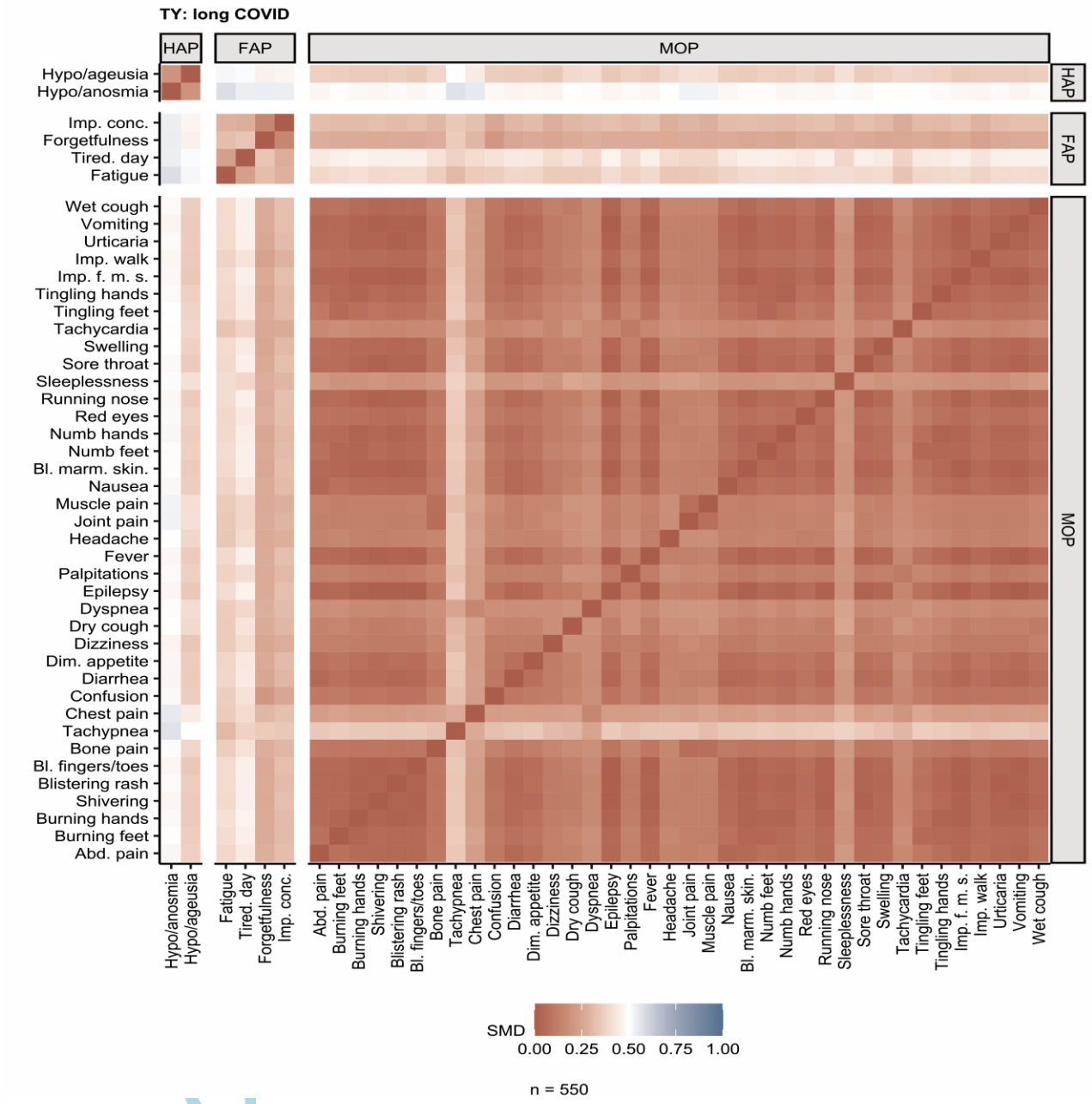

TY: long COVID
HAP
FAP
MOP
Hypo/ageusia
Hypo/anosmia
Imp. conc.
Forgetfulness
Tired. day
Fatigue
Wet cough
Vomiting
Urticaria
Imp. walk
Imp. f. m. s.
Tingling hands
Tingling feet
Tachycardia
Swelling
Sore throat
Sleeplessness
Running nose
Red eyes
Numb hands
Numb feet
Bl. marm. skin.
Nausea
Muscle pain
Joint pain
Headache
Fever
Palpitations
Epilepsy
Dyspnea
Dry cough
Dizziness
Dim. appetite
Diarrhea
Confusion
Chest pain
Tachypnea
Bone pain
Bl. fingers/toes
Blistering rash
Shivering
Burning hands
Burning feet
Abd. pain
SMD
0.00 0.25 0.50 0.75 1.00
n = 550

Figure 6

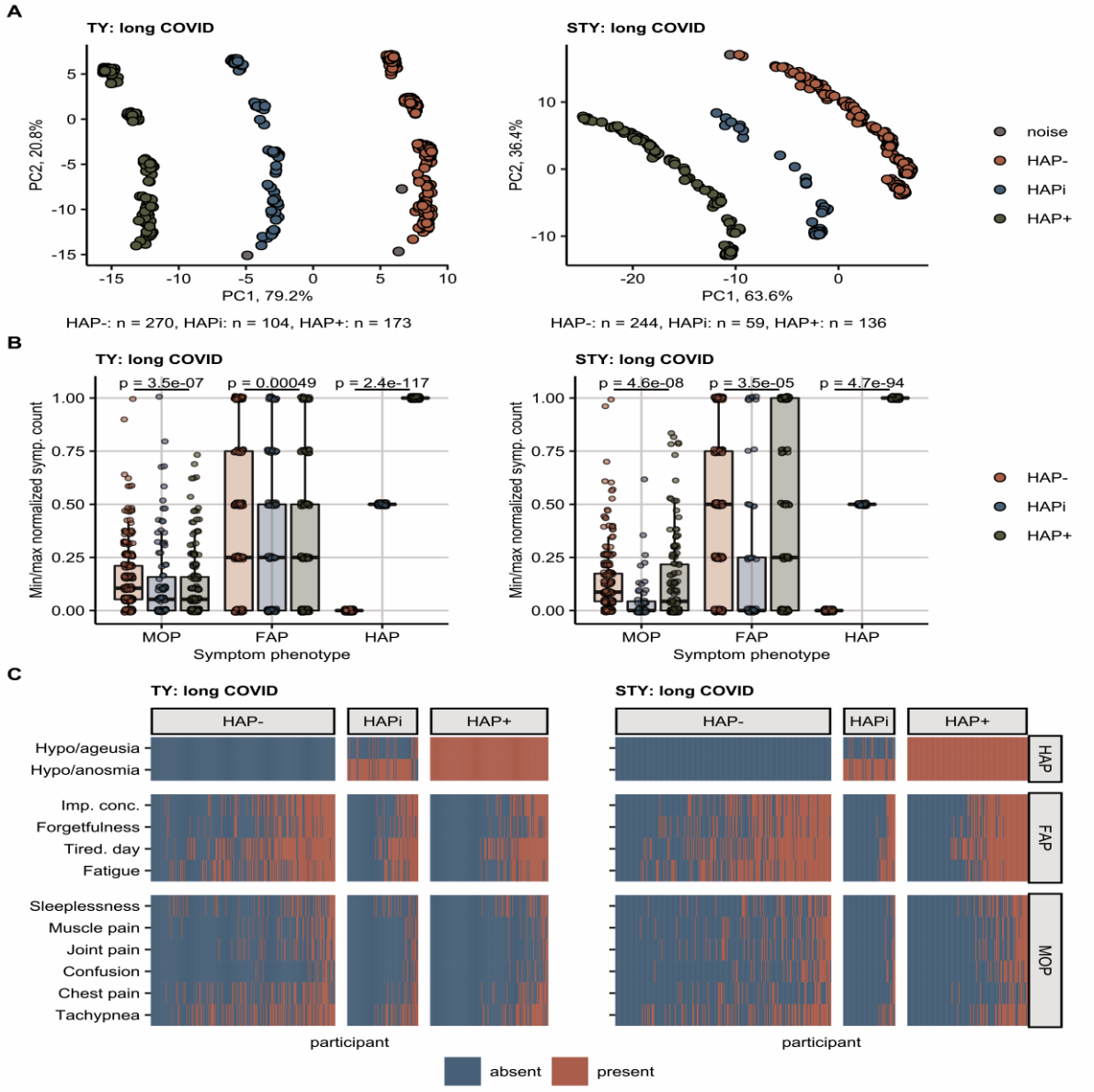


Figure 7

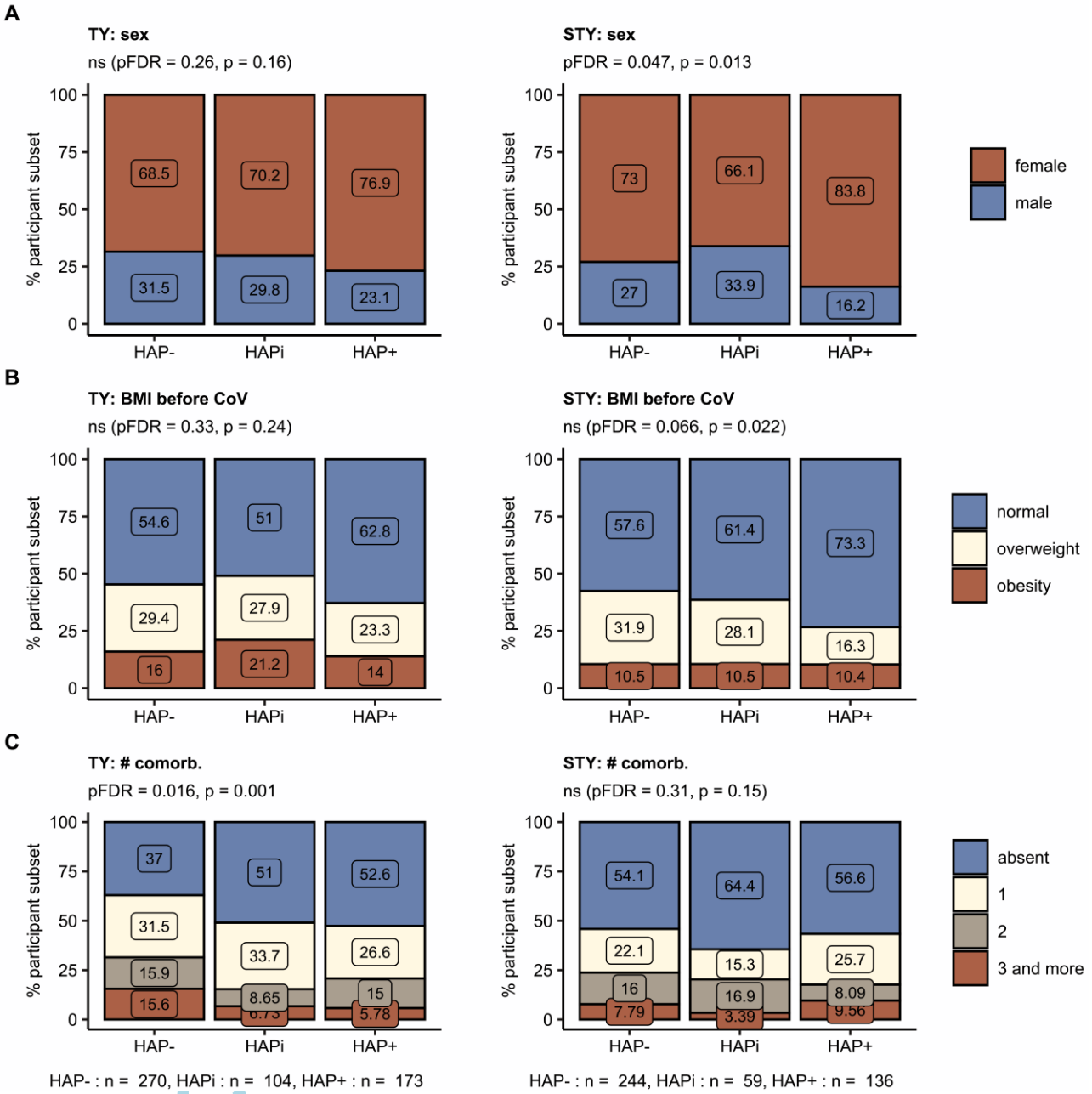

A
TY: sex
ns (pFDR = 0.26, p = 0.16)
STY: sex
pFDR = 0.047, p = 0.013
% participant subset
100
75
50
25
0
68.5
31.5
70.2
29.8
76.9
23.1
73
27
66.1
33.9
83.8
16.2
HAP-
HAPi
HAP+
female
male
B
TY: BMI before CoV
ns (pFDR = 0.33, p = 0.24)
STY: BMI before CoV
ns (pFDR = 0.066, p = 0.022)
54.6
29.4
16
51
27.9
21.2
62.8
23.3
14
57.6
31.9
10.5
61.4
28.1
10.5
73.3
16.3
10.4
normal
overweight
obesity
C
TY: # comorb.
pFDR = 0.016, p = 0.001
STY: # comorb.
ns (pFDR = 0.31, p = 0.15)
37
31.5
15.9
15.6
51
33.7
8.65
52.6
26.6
15
5.78
54.1
22.1
16
7.79
64.4
15.3
16.9
3.39
56.6
25.7
8.09
absent
1
2
3 and more
HAP- : n = 270, HAPi : n = 104, HAP+ : n = 173
HAP- : n = 244, HAPi : n = 59, HAP+ : n = 136

Figure 8