Distinct smell and taste disorder phenotype of post-acute COVID-19 sequelae

Supplementary Material

Health after COVID-19 in Tyrol and CovILD study teams

2023-04-03

# Supplementary Methods

## Study procedures and variables

The complete list of study variables and stratification scheme is provided in **Supplementary Table S1** for the Health after COVID-19 in Tyrol survey study and in **Supplementary Table S2** for the observatory CovILD cohort.

### COVID-19 symptoms

A total of self-reported 42 symptoms were recorded in the survey study cohorts (**Supplementary Figure S2** and **Supplementary Table S1**). The symptom duration was coded as follows: absent: 0 days, 1 - 3 days: 3 days, up to 1 week: 7 days, up to 2 weeks: 14 days, up to 4 weeks: 28 days, up to or greater than 3 months: 3 months. Acute symptoms were defined as complaints present during the first 14 days after clinical onset of COVID-19.

In the observatory CovILD cohort, a total of self-reported 8 symptoms (reduced physical performance, olfactory dysfunction, dyspnea, sleep problems, cough, fever, night sweating, gastrointestinal symptoms) were recorded with a standardized questionnaire at each of 60-, 100-, 180- and 360-day post COVID-19 follow-up (**Supplementary Figure S4** and **Supplementary Table S2**). Acute COVID-19 symptoms were assessed retrospectively at the 60-day follow-up [1, 2].

### Rating of physical recovery, mental health and quality of life in the survey study

Self-perceived complete recovery, rehabilitation need and new medication since COVID-19 at the time of study participation were surveyed as single yes/no items. Percentage of physical performance loss as compared with the time before COVID-19 was rated with a 0 - 100% scale [3, 4]. Quality of life impairment (QoL) and overall mental health impairment (OMH) were rated with a 4 item Likert scale each (possible answers: “excellent,” “good,” “fair,” “poor,” scored: 0, 1, 2, and 3) [3, 4]. Anxiety (ANX) and depression (DPR) were assessed with the Patient Health Questionnaire (PHQ-4) [3–5]. Psychosocial stress was scored with a modified 7 item PHQ stress module as described before [3, 4, 6].

### Rating of olfactory dysfunction with sniffing stick test

Objective olfactory dysfunction at the 100-day and 360-day follow-up in the CovILD study participants was investigated with the 16-item sniffing stick test as described [7]. Clinically relevant olfactory dysfunction was defined as 12 correct answers [7, 8]. In the analysis, participants with the complete answers concerning self-reported olfactory dysfunction and complete test results were included.

## Statistical analysis

### Data transformation, descriptive statistic

Data transformation and statistical analysis was done with R version 4.2.0 with *tidyverse* data science environment [9]. Analysis results were visualized with *ggplot2* [10], *cowplot* [11] as well as in-house developed *ExDA* (<https://github.com/PiotrTymoszuk/ExDA>) and *figur* (<https://github.com/PiotrTymoszuk/figur>) packages.

Descriptive statistics including median with interquartile ranges and frequency of complete answers for numeric and categorical variables were calculated with base R functions and *ExDA* package.

### Statistical hypothesis testing

Since multiple study variables were non-normally distributed as assessed by Shapiro-Wilk test and visual assessment of their distribution (quantile-quantile plots), statistical significance for differences in outcome numeric variables were assessed with Mann-Whitney U test with r effect size statistic (two groups) or Kruskal-Wallis test with effect size statistic. Differences in frequency distribution for categorical outcome variables were assessed by test with Cramer V effect size statistic. Inter-rater assessment of self-reported and sniffing test olfactory dysfunction was accomplished with Cohen’s statistic [12]. significance () was estimated with Wald Z test. P values were adjusted for multiple testing with Benjamini-Hochberg method [13] separately for each analysis task and cohort. Packages *rstatix* [14], *vcd* [15] and *Exda* (<https://github.com/PiotrTymoszuk/ExDA>) were used for statistical hypothesis testing.

### Modeling of symptom recovery kinetic

To model recovery kinetics for binary symptom variables (0: absent, 1: present), second-order mixed-effect logistic (categorical features) modeling was applied (packages: *lme4*, *lmerTest* and development package *kinet* [<https://github.com/PiotrTymoszuk/kinet>]) [16–18]. Each model followed the general formula:

where indicates the random effect of the individual and and indicate the first- and second-order time effect terms. The first-order term estimate was interpreted as a measure of the recovery speed and the second-order term estimate was used to assess the plateau/rebound effect. Significance of the accuracy gain of the full second-order model compared with the nested null model was determined by likelihood ratio test (LRT) versus the nested first-order and null models, respectively. Likelihood ratio statistic (full versus null model) was used as an effect size measure. Individuals from the survey study or the CovILD cohort with the complete longitudinal symptom record were included in the kinetic modeling tasks. Results of the kinetic modeling were adjusted for multiple comparisons with Benjamini-Hochberg method [13].

### Symptom-symptom distances and multi-dimensional scaling

To assess co-occurrence or exclusivity of symptoms, simple matching distances between manifestations during the first 14 days, at 28 days and at 3 months after clinical onset in the survey study cohorts were calculated (package *scrime* and development package *clustTools* [<https://github.com/PiotrTymoszuk/clustTools>]) [19, 20]. Subsequently, the distance matrix was subjected to multi-dimensional scaling (MDS, k = 2 dimensions, package *stats*, function *cmdscale()*). Association of specific symptoms was assessed by visual analysis of MDS coordinate plots.

### Apriori analysis of COVID-19 symptoms in the survey study

Frequent combinations of symptoms during the first 14 days, at 28 days and at 3 months after clinical onset in the survey study cohorts were identified with the apriori algorithm (package *arules*) [21, 22] with the minimal support cutoff of 0.15, 2 - 10 item transaction length, confidence > 0.6 and lift > 2. The support statistic were used to estimate the symptom combination frequency. The confidence value was treated as an estimate of conditional probability of the symptom co-occurrence. The lift statistic was interpreted as a measure of the symptom dependence (lift = 1, symptoms are independent).

### Clustering analysis

COVID-19 recovery clusters of the training Autria (AT) survey cohort participants in respect to symptom-specific recovery times (**Figure 1A**) were defined with the PAM (partitioning around medoids) algorithm and Euclidean distance statistic (packages *cluster*, *philentropy* and development package *clustTools* [<https://github.com/PiotrTymoszuk/clustTools>]) [23, 24]. The set of participants with the complete clustering variable set was included in the analysis. The symptom recovery times were not subjected to any type of pre-processing. The choice of the clustering procedure was motivated by the analysis of the clustering variance (ratio of the total between-cluster to total sum of squares) and clustering structure stability in 10-fold cross-validation (metric: rate of correct cluster assignment, cluster assignment predicted by k = 5 nearest neighbors label propagation algorithm, package *clustTools*) [25, 26] for several clustering algorithms as presented in **Supplementary Figure S9A**. The optimal number of clusters was determined by the bend of the total within-cluster sum of squares curve (**Supplementary Figure S9B**, package *factoextra*) [27]. Permutation importance of specific clustering variables was investigated by calculating difference in clustering variance (ratio of total between-cluster sum of squares to total sum of squares) between the initial clustering object and the clustering object with the given variable reshuffled at random (package *clustTools*). Assignment of the Italy survey cohort participants to the recovery clusters was accomplished with k-nearest neighbors label propagation algorithm (k = 5) [26]. The clustering efficacy in the training AT cohort and the test IT cohort measured by clustering variance statistic defined above was similar (AT: 0.59, IT: 0.57).

## Data and source code availability

The raw data files will be made available upon request. The entire analysis pipeline was published at <https://github.com/PiotrTymoszuk/hyposmia_analsis_pipeline>.

# Supplementary Tables

Supplementary Table S1: Survey study variables.

| **Variable name** | **Variable label** | **Unit** | **Description** |
| --- | --- | --- | --- |
| ID | Patient ID |  | patient ID |
| cohort | Cohort |  | Study cohort |
| acute\_covid | Acute COVID-19 symptoms |  | Acute COVID-19 symptoms (first two weeks) |
| sex | Sex |  | participant’s sex |
| age | Age | years | Participant’s age at survey completion |
| bmi\_class\_before | BMI before COVID-19 |  | Body mass index class before COVID-19 |
| cohabitants | Household size | persons | Household size in persons |
| household\_size | Household size |  | Household size class: single, pair or bigger |
| education\_class | Education |  | Tertiary vs. non-tertiary education |
| employment\_before | Employment status |  | Employment status before COVID-19 |
| employment\_sector | Employment sector |  | Employment sector |
| obs\_time | Observation time |  | Observation time: test to survey completion |
| smoking | Smoking history |  | Smoking history before COVID-19 |
| comorb\_present | Comorbidity |  | At least one comorbidity present |
| comorb\_sum | Sum of co-morbidities |  | Sum of the co-morbidities queried in the survey |
| hypertension | Hypertension |  | Hypertension before acute COVID-19 |
| heart\_circulation | Cardiovascular disease |  | Cardiovascular disease before acute COVID-19 |
| diabetes | Diabetes |  | Diabetes before acute COVID-19 |
| lung | Pulmonary disease |  | Pulmonary disease before COVID-19 |
| gastrointenstinal | Gastrointestinal disease |  | Gastrointestinal disease before COVID-19 |
| malignancy | Malignancy |  | Malignancy before acute COVID-19 |
| hay\_fever | Hay fever/allergy |  | Hay fever or allergy before acute COVID-19 |
| autoimmunity | Autoimmunity |  | Autoimmune disease before acute COVID-19 |
| frequent\_flu\_like | Freq. resp. infections |  | Frequent upper respiratory tract infections (more than two per year) before COVID-19 |
| two\_plus\_infections\_antibiotics | Freq. bact. Infections |  | Frequent bacterial infections requiring antibiotic treatment (more than two per year) before COVID-19 |
| depression\_burnout | Pre-CoV depression/anxiety |  | Depression, anxiety or burnout before acute COVID-19 |
| insomnia | Pre-CoV sleep disorders |  | Sleep disorders before COVID-19 |
| night\_dyspnoe | Sleep apnea |  | Night apnea before COVID-19 |
| bruxism | Bruxism |  | Bruxism before COVID-19 |
| pins\_needles\_feet | Feet paresthesia |  | Feet/leg paresthesia before acute COVID-19 |
| daily\_medication | Daily medication |  | Daily medication class, number of drugs taken daily before COVID-19 |
| cov\_outbreak | SARS-CoV2 outbreak |  | Infection during the spring 2020, summer/fall 2020, winter/spring 2021 |
| illness\_feeling | Severe illness feeling |  | Subjective feeling of acute infection |
| sum\_symptoms\_acute | # acute symptoms |  | Sum of acute symptoms (first two weeks) |
| sum\_symptoms\_long | # persistent symptoms |  | Sum of persistent symptoms (4 weeks and longer) |
| weight\_loss\_kg | Weight loss | kg | Weight loss during/after acute COVID-19 |
| hair\_loss | Hair loss |  | Hair loss during/after acute COVID-19 |
| incomplete\_covelescence | Incomplete recovery |  | Self-perceived incomplete convalescence |
| perf\_impairment | Physical performance loss | percent | Percent loss of physical performance after COVID-19 as compared with the time before |
| new\_medication\_fup | New medication after COVID-19 |  | New medication after COVID-19 |
| rehabilitation\_fup\_needed | Subjective need for rehabilitation |  | Self-reported need for rehabilitation after COVID-19 |
| phq\_anxiety\_score | ANX score |  | Anxiety score |
| phq\_depression\_score | DPR score |  | Depression score |
| stress\_score | Stress score |  | Stress score |
| mental\_health\_score | OMH score |  | Overall mental health score |
| life\_quality\_score | QoL score |  | Quality of life score |
| fever | Fever |  | Fever |
| ague | Shivering |  | Shivering |
| sore\_throat | Sore throat |  | Sore throat |
| running\_nose | Running nose |  | Running nose |
| fatigue | Fatigue |  | Fatigue |
| dry\_cough | Dry cough |  | Dry cough |
| wet\_cough | Wet cough |  | Wet cough |
| breath\_short | Tachypnea |  | Tachypnea |
| dyspnoe | Dyspnea |  | Dyspnea |
| chest\_pain | Chest pain |  | Chest pain |
| tachycardia | Tachycardia |  | Tachycardia |
| extrasystole | Palpitations |  | Palpitations |
| joint\_pain | Joint pain |  | Joint pain |
| bone\_pain | Bone pain |  | Bone pain |
| muscle\_pain | Muscle pain |  | Muscle pain |
| abdominal\_pain | Abdominal pain |  | Abd. pain |
| nausea | Nausea |  | Nausea |
| vomiting | Vomiting |  | Vomiting |
| dim\_appetite | Dim. appetite |  | Dim. appetite |
| diarrhea | Diarrhea |  | Diarrhea |
| dizziness | Dizziness |  | Dizziness |
| anosmia | OD |  | Hyposmia/anosmia |
| taste\_loss | Hypogeusia/ageusia |  | Hypogeusia/ageusia |
| confusion | Confusion |  | Confusion |
| tingle\_feet | Tingling feet |  | Tingling feet |
| tingle\_hands | Tingling hands |  | Tingling hands |
| ache\_feet | Burning feet |  | Burning feet |
| ache\_hands | Burning hands |  | Burning hands |
| numb\_feet | Numb feet |  | Numb feet |
| numb\_hands | Numb hands |  | Numb hands |
| unhandiness\_walk | Imp. walk |  | Imp. walk |
| unhandiness\_micromotor | Imp. FMS |  | Imp. f. m. s. |
| sleep\_prob | Sleeplessness |  | Sleeplessness |
| fatigue\_day | Tiredness at day |  | Tiredness at day |
| imp\_concentration | Imp. concentration |  | Imp. concentration |
| forgetfulness | Forgetfulness |  | Forgetfulness |
| swelling | Swelling |  | Swelling |
| blue\_fingers | Blue fingers/toes |  | Blue fingers/toes |
| urticaria | Urticaria |  | Urticaria |
| blister\_rash | Blistering rash |  | Blistering rash |
| net\_rash | Marmorated skin |  | Bl. marm. skin. |
| red\_eyes | Red eyes |  | Red eyes |

Supplementary Table S2: CovILD study variables.

| **Variable name** | **Variable label** | **Unit** |
| --- | --- | --- |
| ID |  |  |
| time\_numeric | Time post diagnosis | days |
| sex | Sex |  |
| age | Age | years |
| weight\_class | Weight class |  |
| comorb\_present | Comorbidity present | % |
| no\_comorb | # comorbidities |  |
| endometabolic\_comorb | Metabolic disease | % |
| hypertension\_comorb | Hypertension | % |
| cardiovascular\_comorb | CVD | % |
| diabetes\_comorb | Diabetes | % |
| pulmonary\_comorb | Pulmonary disease | % |
| gastro\_comorb | GID | % |
| malingancy\_comorb | Malignancy | % |
| immdef\_comorb | Immune deficiency | % |
| cat\_WHO | COVID-19 severity |  |
| sleep\_sympt | Sleep problems | % |
| dyspnoe\_sympt | Dyspnea | % |
| cough\_sympt | Cough | % |
| fever\_sympt | Fever | % |
| night\_sweat\_sympt | Night sweat | % |
| gastro\_sympt | Gastrointestinal | % |
| anosmia\_sympt | OD | % |
| fatigue\_sympt | Reduced performance | % |

Supplementary Table S3: Demographic and baseline clinical characteristic at the COVID-19 onset of the survey study participants assigned to the recovery clusters, Austria (AT) cohort.

| **Variable** | **Cluster #1** | **Cluster #2** | **Cluster #3** | **Significancea** | **Effect sizea** |
| --- | --- | --- | --- | --- | --- |
| Sex | female: 79% (n = 77) male: 21% (n = 21) complete: n = 98 | female: 57% (n = 140) male: 43% (n = 106) complete: n = 246 | female: 76% (n = 103) male: 24% (n = 32) complete: n = 135 | p < 0.001 | V = 0.22 |
| Age, years | median: 42 [IQR: 30 - 50] range: 21 - 80 complete: n = 98 | median: 43 [IQR: 29 - 53] range: 18 - 77 complete: n = 246 | median: 48 [IQR: 38 - 53] range: 21 - 70 complete: n = 135 | p = 0.045 | η² = 0.012 |
| BMI before COVID-19b | normal: 62% (n = 60) overweight: 24% (n = 23) obesity: 14% (n = 14) complete: n = 97 | normal: 55% (n = 133) overweight: 29% (n = 70) obesity: 17% (n = 41) complete: n = 244 | normal: 47% (n = 64) overweight: 31% (n = 42) obesity: 21% (n = 29) complete: n = 135 | ns (p = 0.39) | V = 0.073 |
| Education | non-tertiary: 64% (n = 62) tertiary: 36% (n = 35) complete: n = 97 | non-tertiary: 63% (n = 154) tertiary: 37% (n = 92) complete: n = 246 | non-tertiary: 64% (n = 86) tertiary: 36% (n = 49) complete: n = 135 | ns (p = 0.99) | V = 0.012 |
| Employment status | employed: 87% (n = 85) unemployed: 7.1% (n = 7) leave: 3.1% (n = 3) retired: 3.1% (n = 3) complete: n = 98 | employed: 80% (n = 198) unemployed: 9.3% (n = 23) leave: 1.6% (n = 4) retired: 8.5% (n = 21) complete: n = 246 | employed: 85% (n = 115) unemployed: 7.4% (n = 10) leave: 0.74% (n = 1) retired: 6.7% (n = 9) complete: n = 135 | ns (p = 0.56) | V = 0.079 |
| Observation time | median: 180 [IQR: 130 - 210] range: 93 - 400 complete: n = 98 | median: 190 [IQR: 130 - 220] range: 90 - 400 complete: n = 246 | median: 180 [IQR: 140 - 220] range: 90 - 380 complete: n = 135 | ns (p = 0.85) | η² = -0.0029 |
| Comorbidity | 46% (n = 45) complete: n = 98 | 44% (n = 109) complete: n = 246 | 61% (n = 83) complete: n = 135 | p = 0.0095 | V = 0.15 |
| Hypertension | 9.2% (n = 9) complete: n = 98 | 10% (n = 25) complete: n = 246 | 13% (n = 17) complete: n = 135 | ns (p = 0.82) | V = 0.041 |
| Cardiovascular disease | 0% (n = 0) complete: n = 98 | 2.8% (n = 7) complete: n = 246 | 2.2% (n = 3) complete: n = 135 | ns (p = 0.36) | V = 0.076 |
| Diabetes | 2% (n = 2) complete: n = 98 | 1.6% (n = 4) complete: n = 246 | 0.74% (n = 1) complete: n = 135 | ns (p = 0.82) | V = 0.04 |
| Pulmonary disease | 0% (n = 0) complete: n = 98 | 4.5% (n = 11) complete: n = 246 | 5.2% (n = 7) complete: n = 135 | ns (p = 0.14) | V = 0.1 |
| Gastrointestinal disease | 1% (n = 1) complete: n = 98 | 2% (n = 5) complete: n = 246 | 1.5% (n = 2) complete: n = 135 | ns (p = 0.88) | V = 0.032 |
| Malignancy | 0% (n = 0) complete: n = 98 | 0.81% (n = 2) complete: n = 246 | 5.9% (n = 8) complete: n = 135 | p = 0.0025 | V = 0.17 |
| Hay fever/allergy | 13% (n = 13) complete: n = 98 | 17% (n = 41) complete: n = 246 | 25% (n = 34) complete: n = 135 | ns (p = 0.073) | V = 0.12 |
| Autoimmunityc | 7.1% (n = 7) complete: n = 98 | 4.1% (n = 10) complete: n = 246 | 11% (n = 15) complete: n = 135 | ns (p = 0.056) | V = 0.12 |
| Freq. resp. infectionsd | 5.1% (n = 5) complete: n = 98 | 5.3% (n = 13) complete: n = 246 | 10% (n = 14) complete: n = 135 | ns (p = 0.2) | V = 0.093 |
| Freq. bact. Infections | 1% (n = 1) complete: n = 98 | 3.7% (n = 9) complete: n = 246 | 9.6% (n = 13) complete: n = 135 | p = 0.01 | V = 0.15 |
| Pre-CoV depression/anxiety | 6.1% (n = 6) complete: n = 98 | 2.8% (n = 7) complete: n = 246 | 9.6% (n = 13) complete: n = 135 | p = 0.038 | V = 0.13 |
| Pre-CoV sleep disorders | 5.1% (n = 5) complete: n = 98 | 2.4% (n = 6) complete: n = 246 | 4.4% (n = 6) complete: n = 135 | ns (p = 0.53) | V = 0.063 |
| Daily medication | absent: 66% (n = 65) 1 - 4 drugs: 30% (n = 29) 5 drugs and more: 4.1% (n = 4) complete: n = 98 | absent: 66% (n = 162) 1 - 4 drugs: 33% (n = 80) 5 drugs and more: 1.6% (n = 4) complete: n = 246 | absent: 50% (n = 68) 1 - 4 drugs: 49% (n = 66) 5 drugs and more: 0.74% (n = 1) complete: n = 135 | p = 0.0092 | V = 0.13 |
| aCategorical variables: χ² test with Cramer V effect size statistic. Numeric variables: Kruskal-Wallis test with η² effect size statistic. P values corrected form multiple testing with Benjamini-Hochberg method. | | | | | |
| bBMI: body mass index, overweight > 25 kg/m², obesity > 30 kg/m², | | | | | |
| cFrequent respiratory infections, > 2 per year. | | | | | |
| dFrequent bacterial infections with antibiotic therapy, > 2 per year. | | | | | |

Supplementary Table S4: Demographic and baseline clinical characteristic at the COVID-19 onset of the survey study participants assigned to the recovery clusters, Italy (IT) cohort.

| **Variable** | **Cluster #1** | **Cluster #2** | **Cluster #3** | **Significancea** | **Effect sizea** |
| --- | --- | --- | --- | --- | --- |
| Sex | female: 83% (n = 54) male: 17% (n = 11) complete: n = 65 | female: 63% (n = 150) male: 37% (n = 87) complete: n = 237 | female: 77% (n = 96) male: 23% (n = 29) complete: n = 125 | p = 0.0032 | V = 0.18 |
| Age, years | median: 46 [IQR: 34 - 55] range: 18 - 71 complete: n = 65 | median: 43 [IQR: 32 - 53] range: 18 - 77 complete: n = 237 | median: 48 [IQR: 38 - 56] range: 19 - 95 complete: n = 125 | p = 0.024 | η² = 0.016 |
| BMI before COVID-19b | normal: 82% (n = 53) overweight: 12% (n = 8) obesity: 6.2% (n = 4) complete: n = 65 | normal: 67% (n = 155) overweight: 26% (n = 61) obesity: 6.5% (n = 15) complete: n = 231 | normal: 57% (n = 70) overweight: 28% (n = 35) obesity: 15% (n = 18) complete: n = 123 | p = 0.0077 | V = 0.14 |
| Education | non-tertiary: 57% (n = 37) tertiary: 43% (n = 28) complete: n = 65 | non-tertiary: 57% (n = 135) tertiary: 43% (n = 102) complete: n = 237 | non-tertiary: 62% (n = 78) tertiary: 38% (n = 47) complete: n = 125 | ns (p = 0.6) | V = 0.05 |
| Employment status | employed: 80% (n = 52) unemployed: 11% (n = 7) leave: 3.1% (n = 2) retired: 6.2% (n = 4) complete: n = 65 | employed: 79% (n = 188) unemployed: 11% (n = 27) leave: 2.5% (n = 6) retired: 6.8% (n = 16) complete: n = 237 | employed: 86% (n = 108) unemployed: 4.8% (n = 6) leave: 0% (n = 0) retired: 8.8% (n = 11) complete: n = 125 | ns (p = 0.27) | V = 0.1 |
| Observation time | median: 140 [IQR: 120 - 280] range: 92 - 370 complete: n = 65 | median: 140 [IQR: 110 - 260] range: 90 - 390 complete: n = 237 | median: 140 [IQR: 120 - 300] range: 90 - 380 complete: n = 125 | ns (p = 0.21) | η² = 0.0045 |
| Comorbidity | 35% (n = 23) complete: n = 65 | 38% (n = 89) complete: n = 237 | 58% (n = 73) complete: n = 125 | p < 0.001 | V = 0.2 |
| Hypertension | 7.7% (n = 5) complete: n = 65 | 6.8% (n = 16) complete: n = 237 | 12% (n = 15) complete: n = 125 | ns (p = 0.28) | V = 0.083 |
| Cardiovascular disease | 0% (n = 0) complete: n = 65 | 3.4% (n = 8) complete: n = 237 | 4% (n = 5) complete: n = 125 | ns (p = 0.34) | V = 0.077 |
| Diabetes | 0% (n = 0) complete: n = 65 | 0% (n = 0) complete: n = 237 | 0.8% (n = 1) complete: n = 125 | ns (p = 0.34) | V = 0.075 |
| Pulmonary disease | 3.1% (n = 2) complete: n = 65 | 2.1% (n = 5) complete: n = 237 | 4% (n = 5) complete: n = 125 | ns (p = 0.6) | V = 0.051 |
| Gastrointestinal disease | 0% (n = 0) complete: n = 65 | 0.42% (n = 1) complete: n = 237 | 1.6% (n = 2) complete: n = 125 | ns (p = 0.37) | V = 0.071 |
| Malignancy | 6.2% (n = 4) complete: n = 65 | 2.5% (n = 6) complete: n = 237 | 5.6% (n = 7) complete: n = 125 | ns (p = 0.28) | V = 0.083 |
| Hay fever/allergy | 7.7% (n = 5) complete: n = 65 | 11% (n = 27) complete: n = 237 | 15% (n = 19) complete: n = 125 | ns (p = 0.34) | V = 0.076 |
| Autoimmunityc | 6.2% (n = 4) complete: n = 65 | 4.6% (n = 11) complete: n = 237 | 9.6% (n = 12) complete: n = 125 | ns (p = 0.25) | V = 0.089 |
| Freq. resp. infectionsd | 0% (n = 0) complete: n = 65 | 1.3% (n = 3) complete: n = 237 | 8.8% (n = 11) complete: n = 125 | p < 0.001 | V = 0.2 |
| Freq. bact. Infections | 0% (n = 0) complete: n = 65 | 0.42% (n = 1) complete: n = 237 | 3.2% (n = 4) complete: n = 125 | ns (p = 0.071) | V = 0.12 |
| Pre-CoV depression/anxiety | 4.6% (n = 3) complete: n = 65 | 3% (n = 7) complete: n = 237 | 9.6% (n = 12) complete: n = 125 | p = 0.044 | V = 0.13 |
| Pre-CoV sleep disorders | 3.1% (n = 2) complete: n = 65 | 1.7% (n = 4) complete: n = 237 | 11% (n = 14) complete: n = 125 | p < 0.001 | V = 0.2 |
| Daily medication | absent: 75% (n = 49) 1 - 4 drugs: 25% (n = 16) 5 drugs and more: 0% (n = 0) complete: n = 65 | absent: 81% (n = 191) 1 - 4 drugs: 19% (n = 45) 5 drugs and more: 0.42% (n = 1) complete: n = 237 | absent: 62% (n = 77) 1 - 4 drugs: 36% (n = 45) 5 drugs and more: 2.4% (n = 3) complete: n = 125 | p = 0.0032 | V = 0.14 |
| aCategorical variables: χ² test with Cramer V effect size statistic. Numeric variables: Kruskal-Wallis test with η² effect size statistic. P values corrected form multiple testing with Benjamini-Hochberg method. | | | | | |
| bBMI: body mass index, overweight > 25 kg/m², obesity > 30 kg/m², | | | | | |
| cFrequent respiratory infections, > 2 per year. | | | | | |
| dFrequent bacterial infections with antibiotic therapy, > 2 per year. | | | | | |

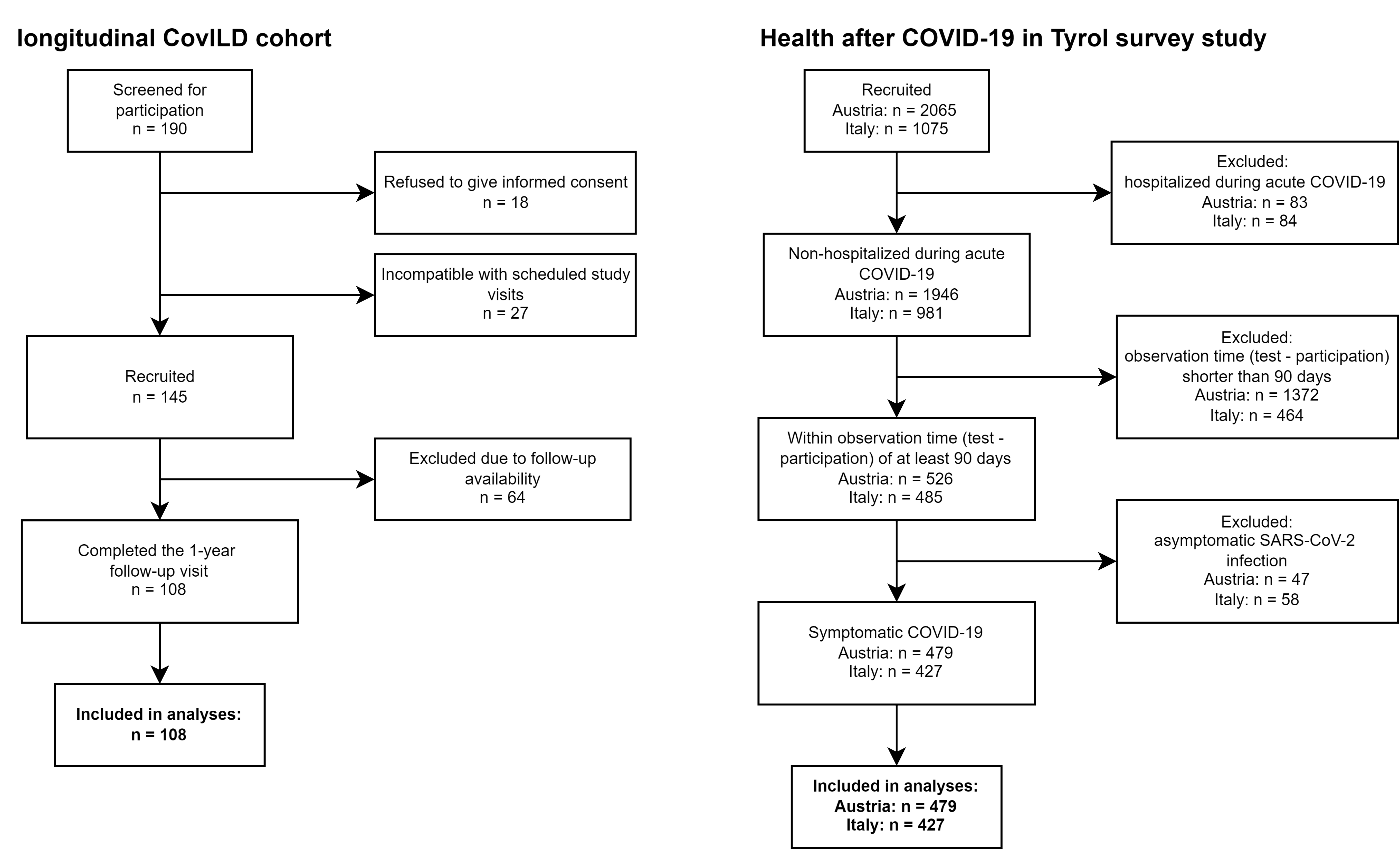
Supplementary Table S5: COVID-19 course and recovery in the survey study participants assigned to the recovery clusters, Austria (AT) cohort.

| **Variable** | **Cluster #1** | **Cluster #2** | **Cluster #3** | **Significancea** | **Effect sizea** |
| --- | --- | --- | --- | --- | --- |
| SARS-CoV2 outbreak | spring 2020: 55% (n = 54) summer/fall 2020: 43% (n = 42) winter/spring 2021: 2% (n = 2) complete: n = 98 | spring 2020: 63% (n = 156) summer/fall 2020: 35% (n = 87) winter/spring 2021: 1.2% (n = 3) complete: n = 246 | spring 2020: 53% (n = 71) summer/fall 2020: 47% (n = 64) winter/spring 2021: 0% (n = 0) complete: n = 135 | ns (p = 0.16) | V = 0.09 |
| Weight loss, kg | median: 0.5 [IQR: 0 - 3] range: 0 - 8 complete: n = 98 | median: 0 [IQR: 0 - 2.1] range: 0 - 11 complete: n = 244 | median: 2 [IQR: 0 - 4.5] range: 0 - 15 complete: n = 134 | p < 0.001 | η² = 0.039 |
| Hair loss | 19% (n = 19) complete: n = 98 | 9.3% (n = 23) complete: n = 246 | 30% (n = 41) complete: n = 135 | p < 0.001 | V = 0.24 |
| Incomplete recoveryd | 62% (n = 61) complete: n = 98 | 22% (n = 55) complete: n = 245 | 73% (n = 98) complete: n = 135 | p < 0.001 | V = 0.47 |
| Physical performance loss, percent | median: 10 [IQR: 4 - 25] range: 0 - 69 complete: n = 98 | median: 3.5 [IQR: 0 - 14] range: 0 - 100 complete: n = 244 | median: 25 [IQR: 15 - 42] range: 0 - 92 complete: n = 134 | p < 0.001 | η² = 0.26 |
| New medication after COVID-19 | 7.1% (n = 7) complete: n = 98 | 7.3% (n = 18) complete: n = 246 | 24% (n = 32) complete: n = 135 | p < 0.001 | V = 0.23 |
| Subjective need for rehabilitation | 13% (n = 13) complete: n = 98 | 6.5% (n = 16) complete: n = 246 | 42% (n = 56) complete: n = 134 | p < 0.001 | V = 0.4 |
| ANX scoree | median: 0 [IQR: 0 - 2] range: 0 - 5 complete: n = 98 | median: 0 [IQR: 0 - 1] range: 0 - 6 complete: n = 246 | median: 1.5 [IQR: 0 - 2] range: 0 - 6 complete: n = 134 | p < 0.001 | η² = 0.11 |
| DPR scoref | median: 1 [IQR: 0 - 2] range: 0 - 6 complete: n = 98 | median: 0 [IQR: 0 - 2] range: 0 - 6 complete: n = 246 | median: 2 [IQR: 1 - 3] range: 0 - 6 complete: n = 135 | p < 0.001 | η² = 0.15 |
| Stress score | median: 3.5 [IQR: 2 - 6] range: 0 - 19 complete: n = 98 | median: 3 [IQR: 1 - 5] range: 0 - 16 complete: n = 246 | median: 5 [IQR: 3 - 9] range: 0 - 16 complete: n = 135 | p < 0.001 | η² = 0.064 |
| OMH scoreg | median: 1 [IQR: 0 - 1] range: 0 - 3 complete: n = 98 | median: 1 [IQR: 0 - 1] range: 0 - 3 complete: n = 246 | median: 1 [IQR: 1 - 2] range: 0 - 3 complete: n = 135 | p < 0.001 | η² = 0.072 |
| QoL scoreh | median: 1 [IQR: 1 - 1] range: 0 - 3 complete: n = 98 | median: 1 [IQR: 0 - 1] range: 0 - 3 complete: n = 246 | median: 1 [IQR: 1 - 2] range: 0 - 3 complete: n = 135 | p < 0.001 | η² = 0.052 |
| aCategorical variables: χ² test with Cramer V effect size statistic. Numeric variables: Kruskal-Wallis test with η² effect size statistic. P values corrected form multiple testing with Benjamini-Hochberg method. | | | | | |
| dSelf-reported incomplete recovery. | | | | | |
| eANX: anxiety. | | | | | |
| fDPR: depression. | | | | | |
| gOMH score: overall mental health impairment score | | | | | |
| hQoL score: quality of life impairment score | | | | | |

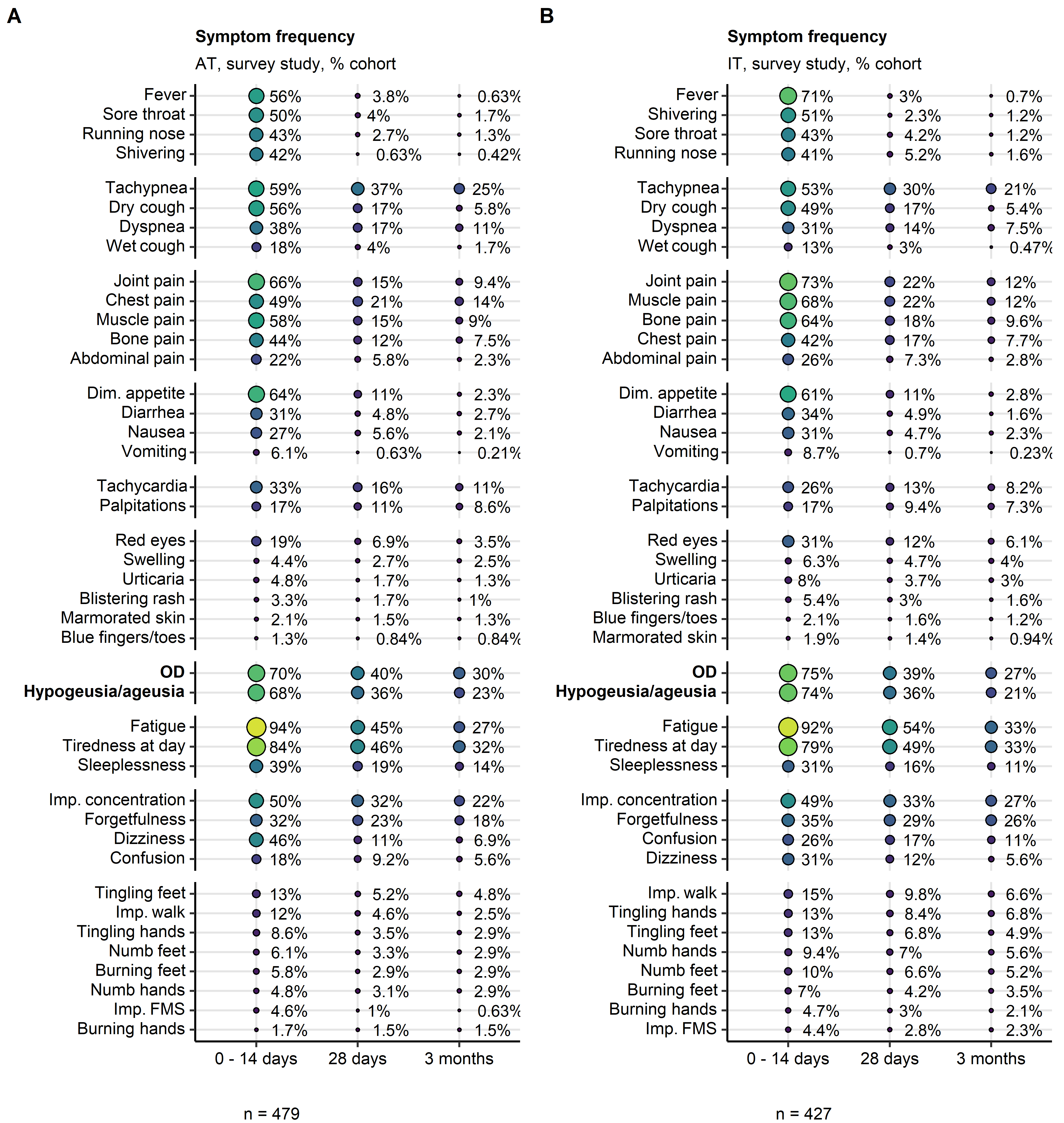
Supplementary Table S6: COVID-19 course and recovery in the survey study participants assigned to the recovery clusters, Italy (IT) cohort.

| **Variable** | **Cluster #1** | **Cluster #2** | **Cluster #3** | **Significancea** | **Effect sizea** |
| --- | --- | --- | --- | --- | --- |
| SARS-CoV2 outbreak | spring 2020: 34% (n = 22) summer/fall 2020: 65% (n = 42) winter/spring 2021: 1.5% (n = 1) complete: n = 65 | spring 2020: 28% (n = 67) summer/fall 2020: 71% (n = 169) winter/spring 2021: 0.42% (n = 1) complete: n = 237 | spring 2020: 32% (n = 40) summer/fall 2020: 68% (n = 85) winter/spring 2021: 0% (n = 0) complete: n = 125 | ns (p = 0.55) | V = 0.062 |
| Weight loss, kg | median: 0 [IQR: 0 - 2] range: 0 - 5 complete: n = 65 | median: 0 [IQR: 0 - 2] range: 0 - 8 complete: n = 236 | median: 2 [IQR: 0 - 4] range: 0 - 15 complete: n = 124 | p < 0.001 | η² = 0.049 |
| Hair loss | 25% (n = 16) complete: n = 65 | 9.7% (n = 23) complete: n = 237 | 31% (n = 39) complete: n = 125 | p < 0.001 | V = 0.25 |
| Incomplete recoveryd | 55% (n = 35) complete: n = 64 | 18% (n = 43) complete: n = 235 | 65% (n = 81) complete: n = 125 | p < 0.001 | V = 0.45 |
| Physical performance loss, percent | median: 10 [IQR: 1 - 20] range: 0 - 58 complete: n = 65 | median: 5 [IQR: 0 - 16] range: 0 - 60 complete: n = 231 | median: 29 [IQR: 20 - 50] range: 0 - 93 complete: n = 124 | p < 0.001 | η² = 0.29 |
| New medication after COVID-19 | 13% (n = 8) complete: n = 63 | 8.2% (n = 19) complete: n = 231 | 20% (n = 25) complete: n = 123 | p = 0.0092 | V = 0.16 |
| Subjective need for rehabilitation | 17% (n = 11) complete: n = 65 | 3.8% (n = 9) complete: n = 235 | 34% (n = 42) complete: n = 124 | p < 0.001 | V = 0.37 |
| ANX scoree | median: 1 [IQR: 0 - 2] range: 0 - 6 complete: n = 65 | median: 0 [IQR: 0 - 2] range: 0 - 6 complete: n = 237 | median: 2 [IQR: 1 - 4] range: 0 - 6 complete: n = 125 | p < 0.001 | η² = 0.14 |
| DPR scoref | median: 2 [IQR: 0 - 2] range: 0 - 6 complete: n = 65 | median: 1 [IQR: 0 - 2] range: 0 - 6 complete: n = 236 | median: 2 [IQR: 2 - 4] range: 0 - 6 complete: n = 125 | p < 0.001 | η² = 0.16 |
| Stress score | median: 4 [IQR: 1 - 6] range: 0 - 13 complete: n = 65 | median: 3 [IQR: 1 - 6] range: 0 - 14 complete: n = 235 | median: 6 [IQR: 4 - 9] range: 0 - 15 complete: n = 125 | p < 0.001 | η² = 0.11 |
| OMH scoreg | median: 1 [IQR: 0 - 1] range: 0 - 2 complete: n = 65 | median: 1 [IQR: 0 - 1] range: 0 - 3 complete: n = 237 | median: 1 [IQR: 1 - 2] range: 0 - 3 complete: n = 125 | p < 0.001 | η² = 0.1 |
| QoL scoreh | median: 1 [IQR: 1 - 1] range: 0 - 3 complete: n = 65 | median: 1 [IQR: 0 - 1] range: 0 - 3 complete: n = 237 | median: 1 [IQR: 1 - 2] range: 0 - 3 complete: n = 125 | p < 0.001 | η² = 0.095 |
| aCategorical variables: χ² test with Cramer V effect size statistic. Numeric variables: Kruskal-Wallis test with η² effect size statistic. P values corrected form multiple testing with Benjamini-Hochberg method. | | | | | |
| dSelf-reported incomplete recovery. | | | | | |
| eANX: anxiety. | | | | | |
| fDPR: depression. | | | | | |
| gOMH score: overall mental health impairment score | | | | | |
| hQoL score: quality of life impairment score | | | | | |

# Supplementary Figures



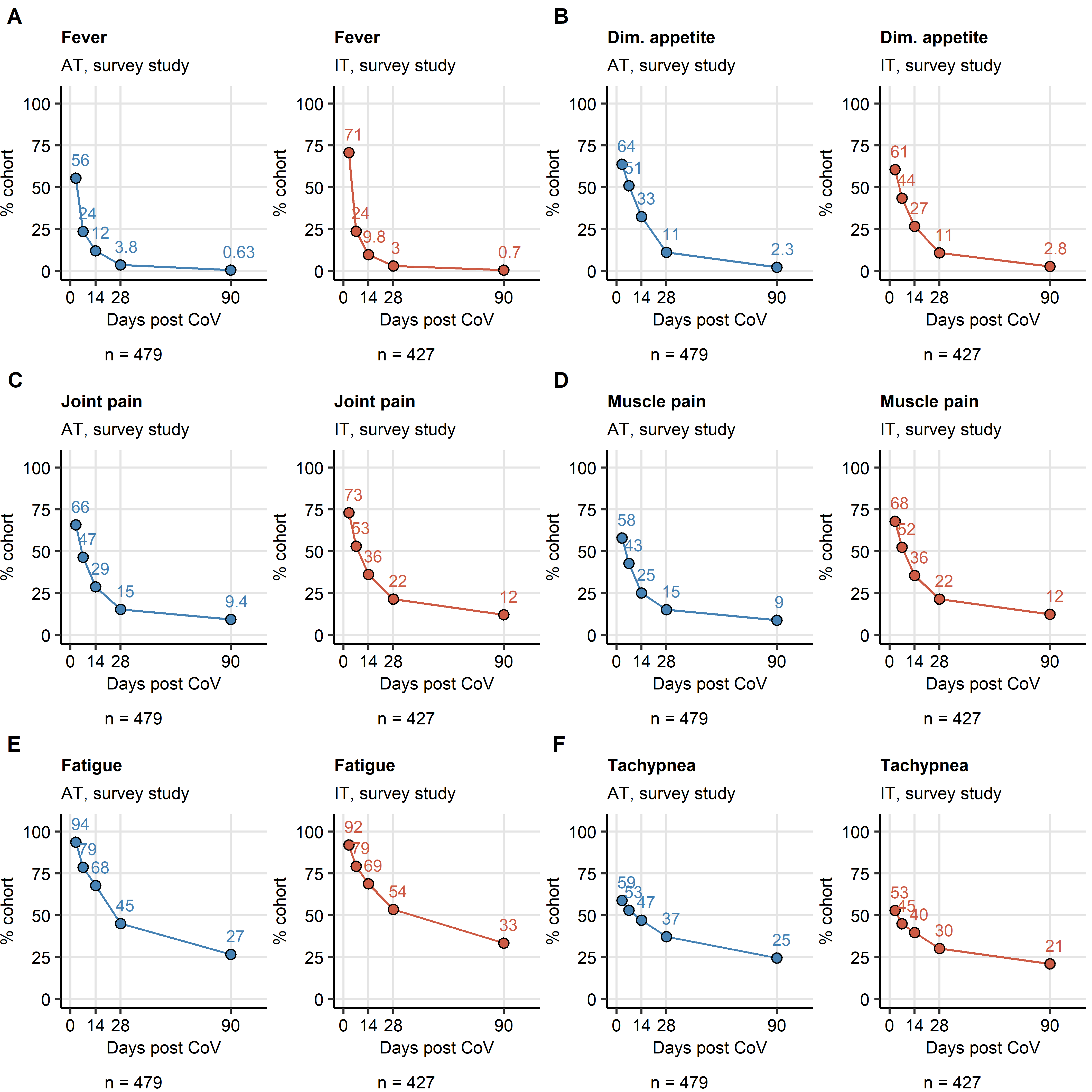
**Supplementary Figure S1. Flow diagram of the analysis inclusion process for the longitudinal CovILD cohort and the Health after COVID-19 survey study.**



**Supplementary Figure S2. Frequency of COVID-19 symptoms in the survey study.**

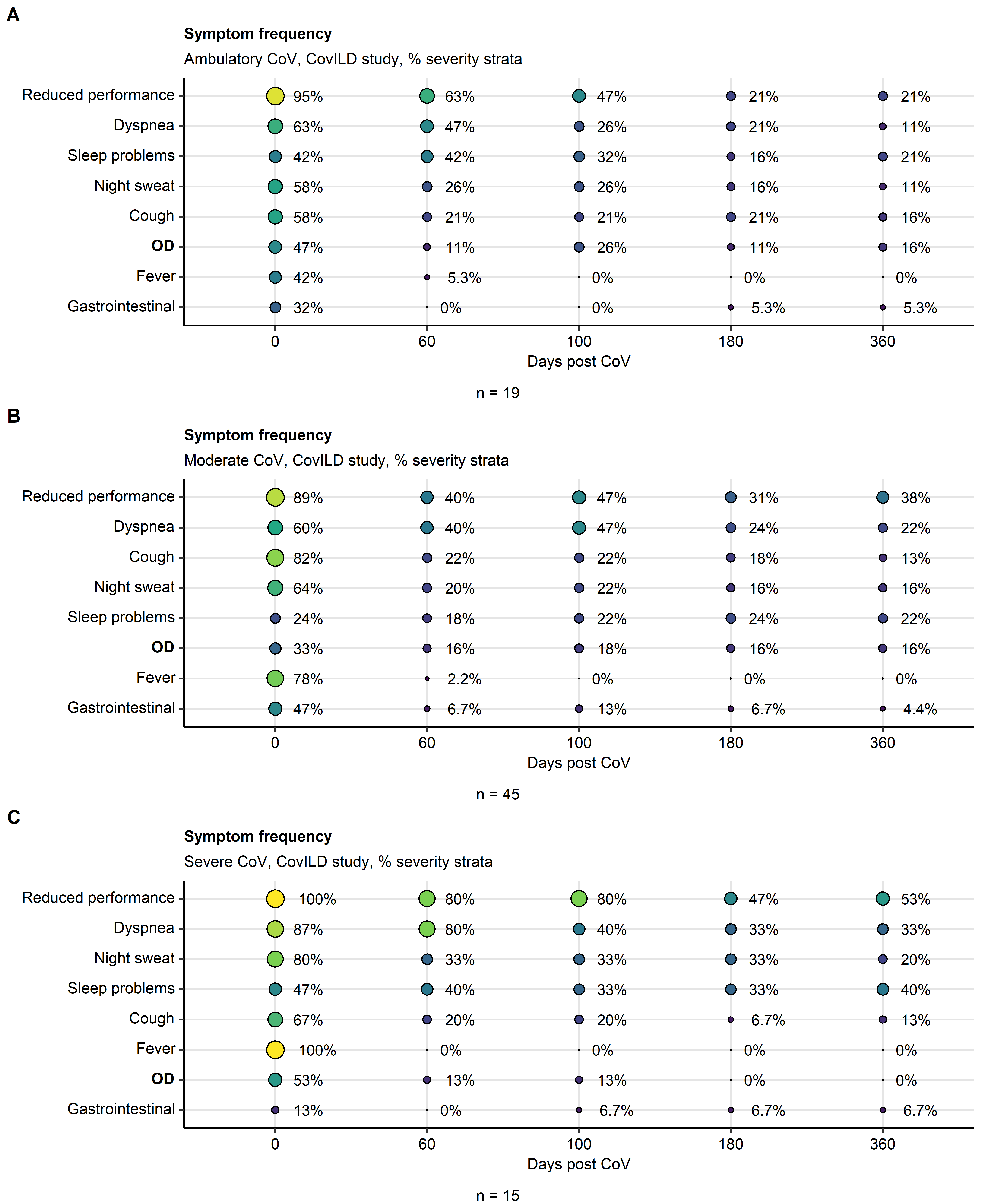
*Frequency of symptoms in first 14 days, 28 days and 3 months after clinical onset of COVID-19 in the Austria (AT, A) and Italy (IT, B) survey study cohorts expressed as percentages of the cohort. Point size and color represents the percentage. Numbers of complete observations are indicated under the plot.*

*OD: self-reported olfactory dysfunction, Dim. appetite: diminished appetite, Imp. concentration: impaired concentration, Imp. walk: impaired walk, Imp. FMS: impaired fine motor skills.*



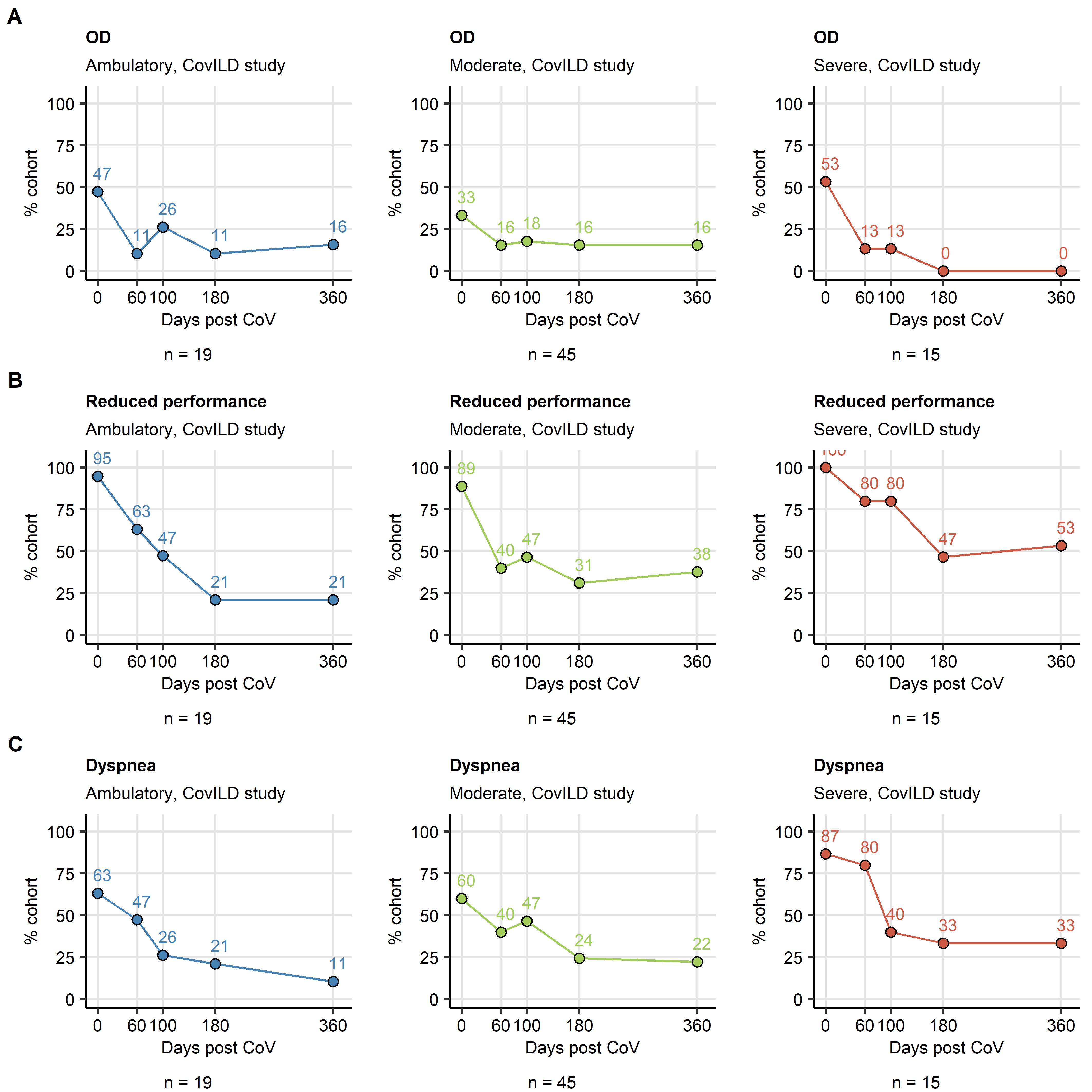
**Supplementary Figure S3. Kinetic of recovery from leading acute COVID-19 symptoms in the survey study.**

*Percentages of individuals with fever (A), diminished appetite (B), joint pain (C), muscle pain (D), fatigue (E) and tachypnea (F) in the AT (Austria) and IT (Italy) survey study cohorts at particular time points after clinical onset. Numbers of complete observations are indicated under the plots.*



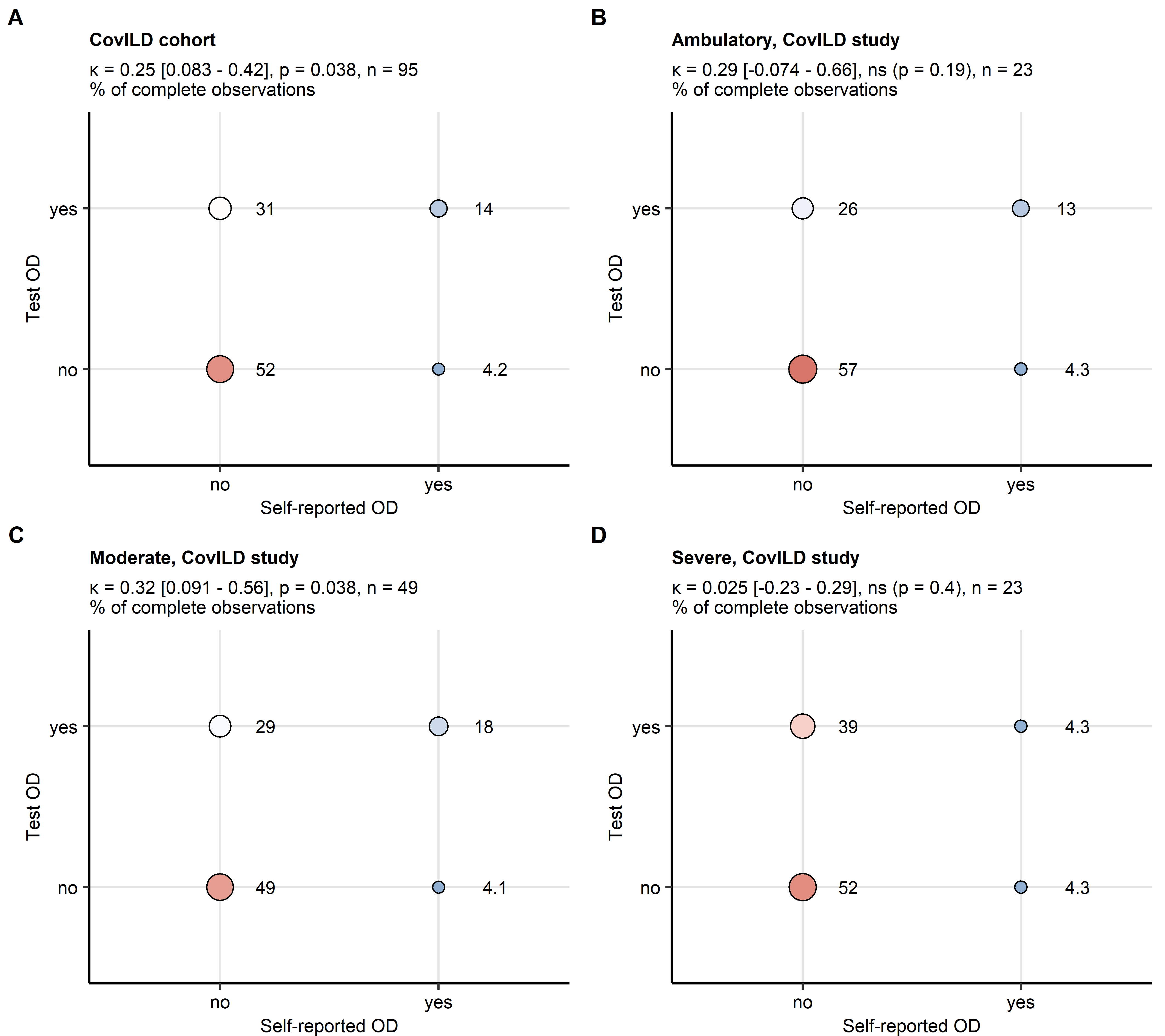
**Supplementary Figure S4. Symptom frequency in ambulatory, moderate and severe COVID-19 subsets of the CovILD study.**

*Frequency of symptoms during acute COVID-19 and at the 60-, 100-, 180- and 360-day follow-ups in ambulatory (A), moderate (B) and severe COVID-19 (C) participants expressed as percentages of individuals with the complete longitudinal data set. Point size and color represents the percentage. Numbers of complete observations are indicated under the plots.*



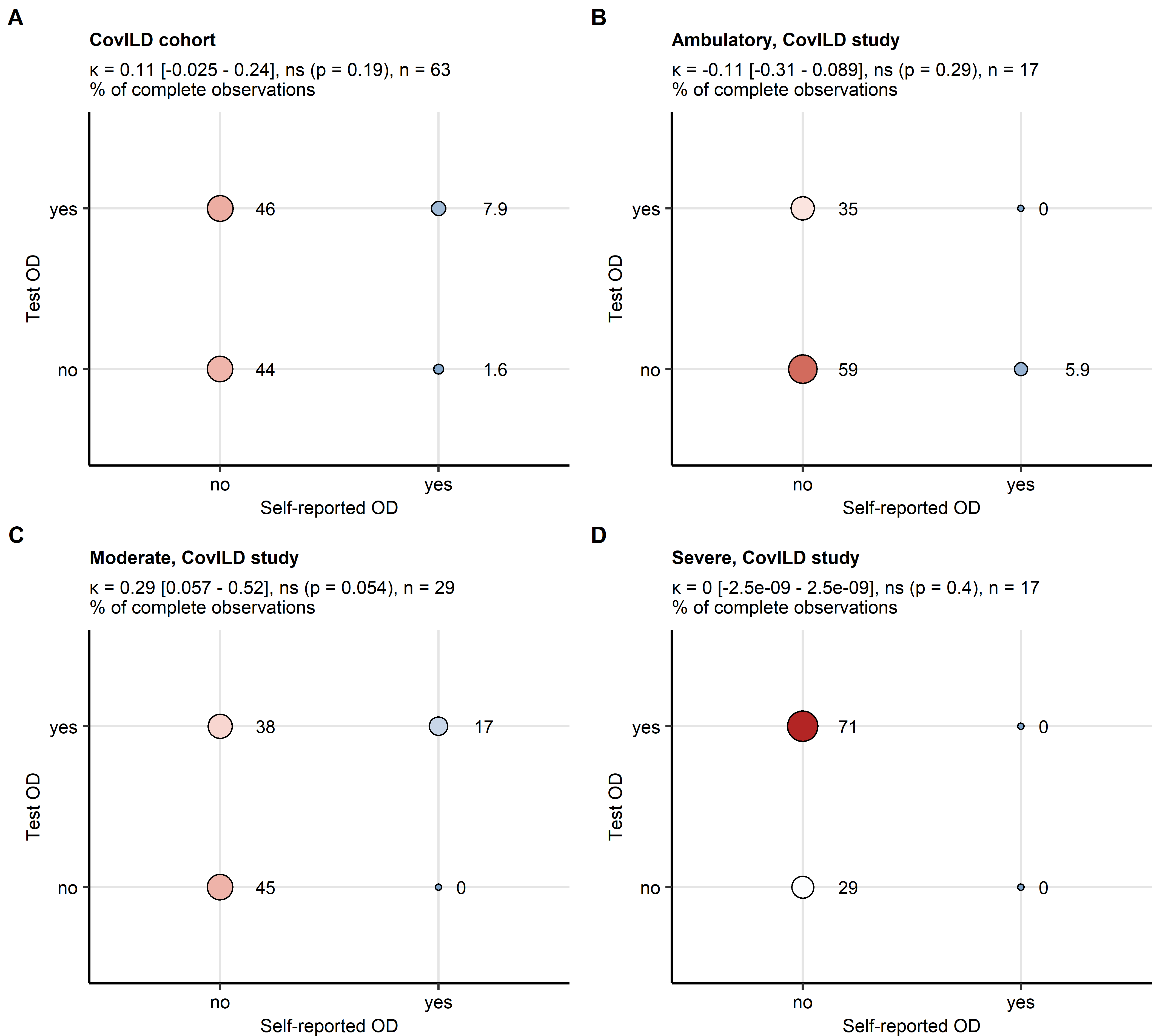
**Supplementary Figure S5. Kinetic of recovery from olfactory dysfunction, reduced performance and dyspnea in ambulatory, moderate and severe COVID-19 subsets of the CovILD study.**

*Percentages of individuals with the complete longitudinal data set suffering from olfactory dysfunction (OD) (A), reduced physical performance (B) and dyspnea (C) in the ambulatory, moderate and severe COVID-19 subsets during acute COVID-19 and at the 60-, 100-, 180- and 360-day follow-ups. Numbers of complete observations are indicated under the plots.*



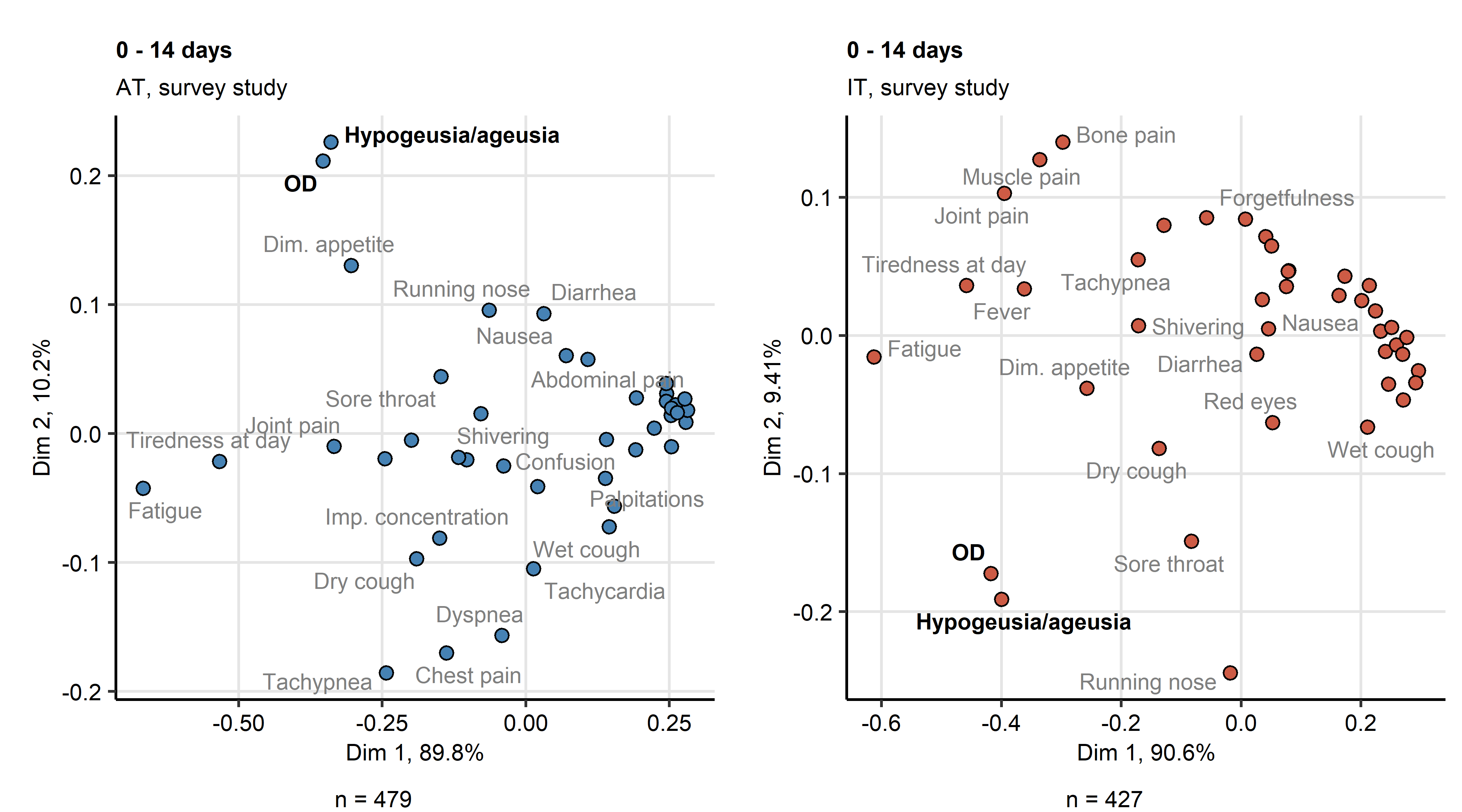
**Supplementary Figure S6. Rates of self-reported olfactory dysfunction and olfactory dysfunction in the sniffing stick test at 3-month post COVID-19 follow-up in the ambulatory, moderate and severe COVID-19 subsets of the CovILD study.**

*Association of self-reported and sniffing stick test rates of olfactory dysfunction (OD) was investigated with Cohen’s statistic. Statistical significance was assessed with Wald’s Z test corrected for multiple testing with Benjamini-Hochberg method. Percentages of individuals with self-reported and test OD within the entire cohort (A), the ambulatory (B), moderate (C) and severe (D) COVID-19 subsets are presented in bubble plots. Point size and color represents the percentage. values with 95 confidence intervals, p values and numbers of complete observations are indicated in the plot captions.*

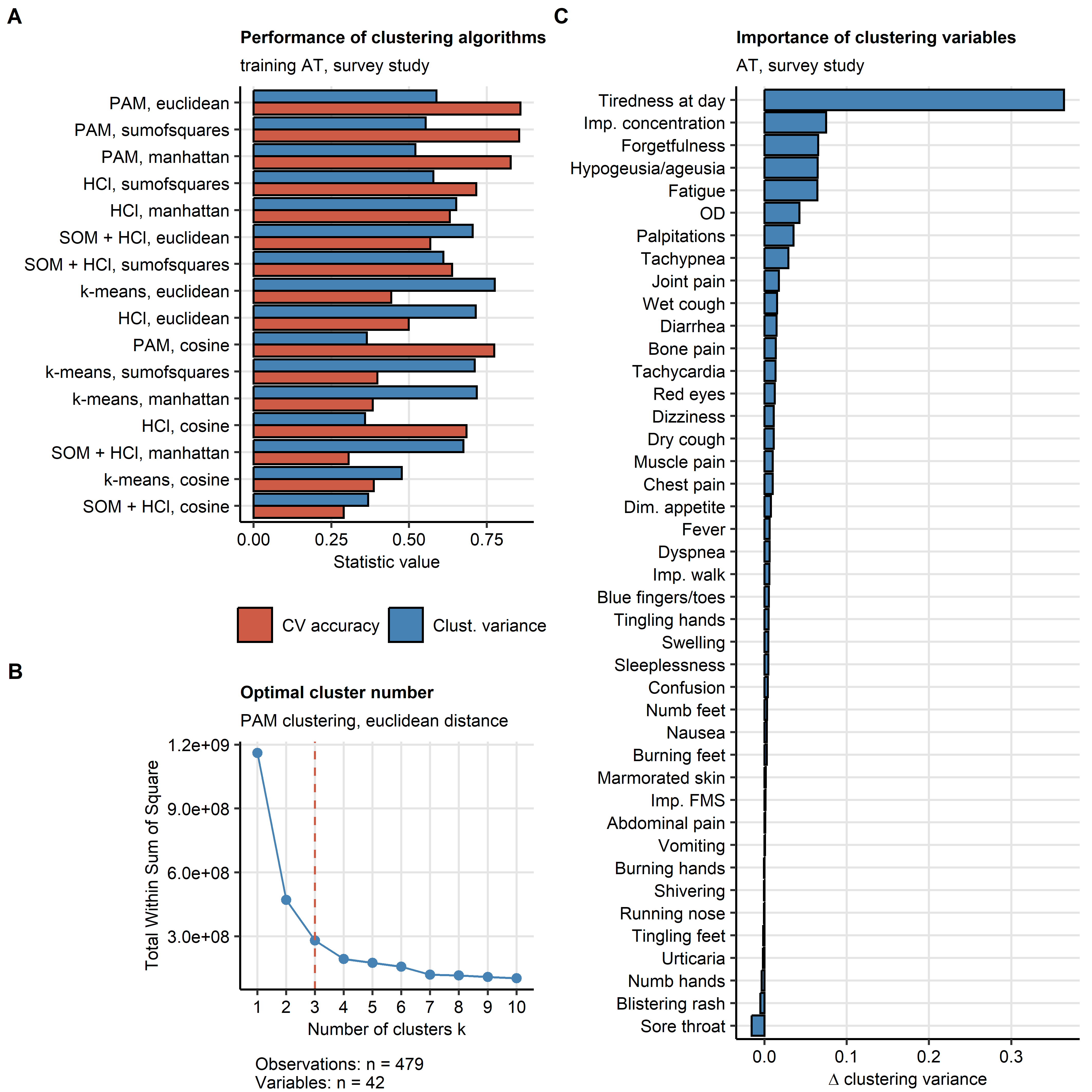


**Supplementary Figure S7. Rates of self-reported olfactory dysfunction and olfactory dysfunction in the sniffing stick test at 1-year post COVID-19 follow-up in the ambulatory, moderate and severe COVID-19 subsets of the CovILD study.**

*Association of self-reported and sniffing stick test rates of olfactory dysfunction (OD) was investigated with Cohen’s statistic. Statistical significance was assessed with Wald’s Z test corrected for multiple testing with Benjamini-Hochberg method. Percentages of individuals with self-reported and test OD within the entire cohort (A), the ambulatory (B), moderate (C) and severe (D) COVID-19 subsets are presented in bubble plots. Point size and color represents the percentage. values with 95 confidence intervals, p values and numbers of complete observations are indicated in the plot captions.*



**Supplementary Figure S8. Multi-dimensional scaling analysis of acute COVID-19 symptoms in the survey study.** *Symptom data for acute COVID-19 (first 14 days after clinical onset) in the Austria (AT) and Italy (IT) survey study cohorts were subjected to two-dimensional multi-dimensional scaling (MDS) with simple matching distance (SMD) between the symptoms. MDS coordinates are presented in point plots. Selected data points are labeled with the symptom names. Percentages of the data set variance associated with the MDS dimensions are indicated in the plot axes. Numbers of complete observations are indicated under the plots. OD: self-reported olfactory dysfunction.*



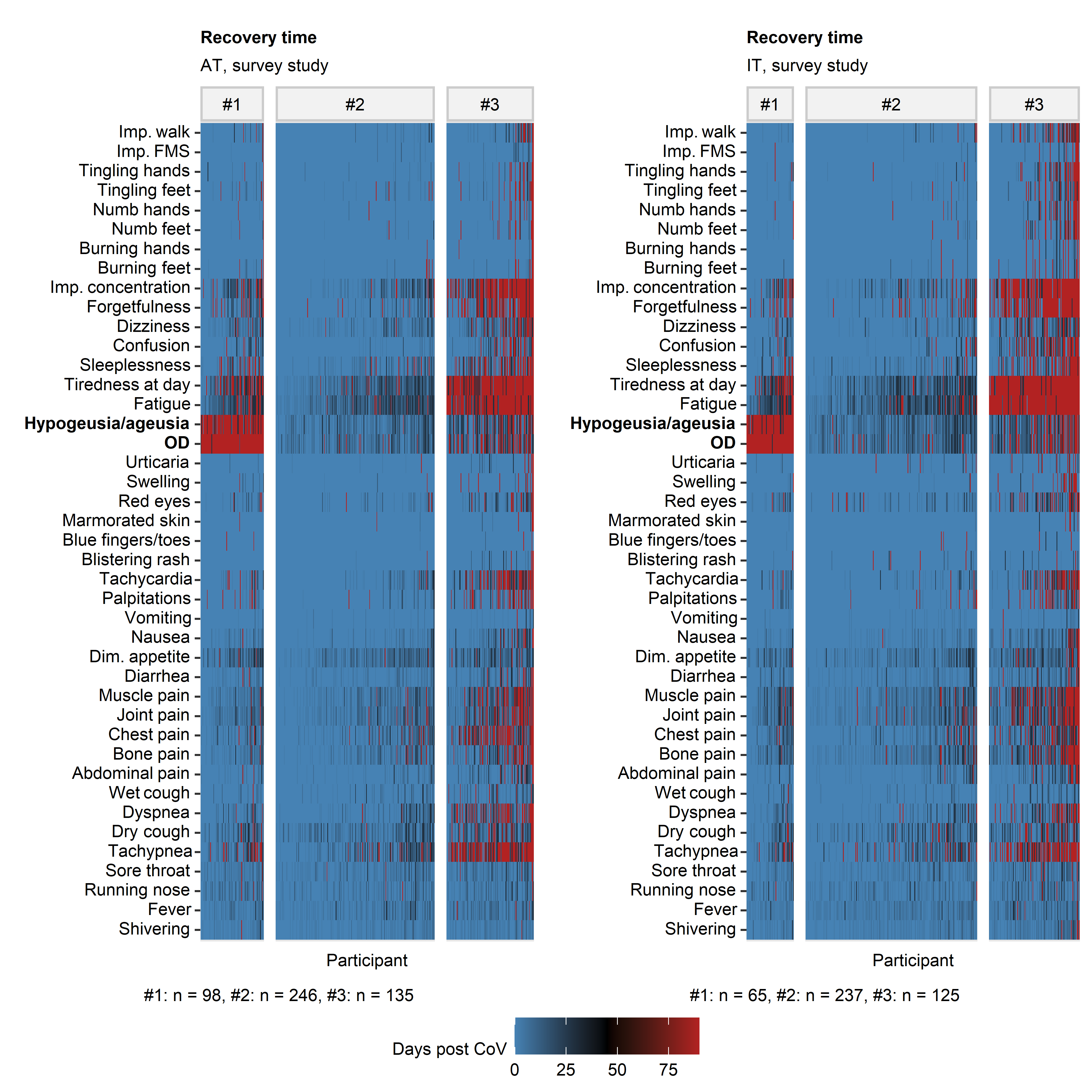
**Supplementary Figure S9. Definition of the COVID-19 recovery clusters and clustering feature importance in the survey study.**

*Individuals of the training Austria (AT) study survey cohort were subjected to clustering in respect to symptom-specific recovery times with the PAM (partitioning around medoids) algorithm and Euclidean distance measure.*

*(A) Comparison of performance of various algorithms (HCl: hierarchical clustering, SOM + HCl: combined self-organizing map and hierarchical clustering, k-means) and distance statistic in clustering of the training data set investigated by clustering variance (ratio of total between-cluster sum of squares to total sum of squares) and cluster assignment accuracy in 10-fold cross-validation (CV).*

*(B) Determination of the optimal cluster number in the PAM clustering of the training cohort by the bend of the total within-cluster sum of squares curve.*

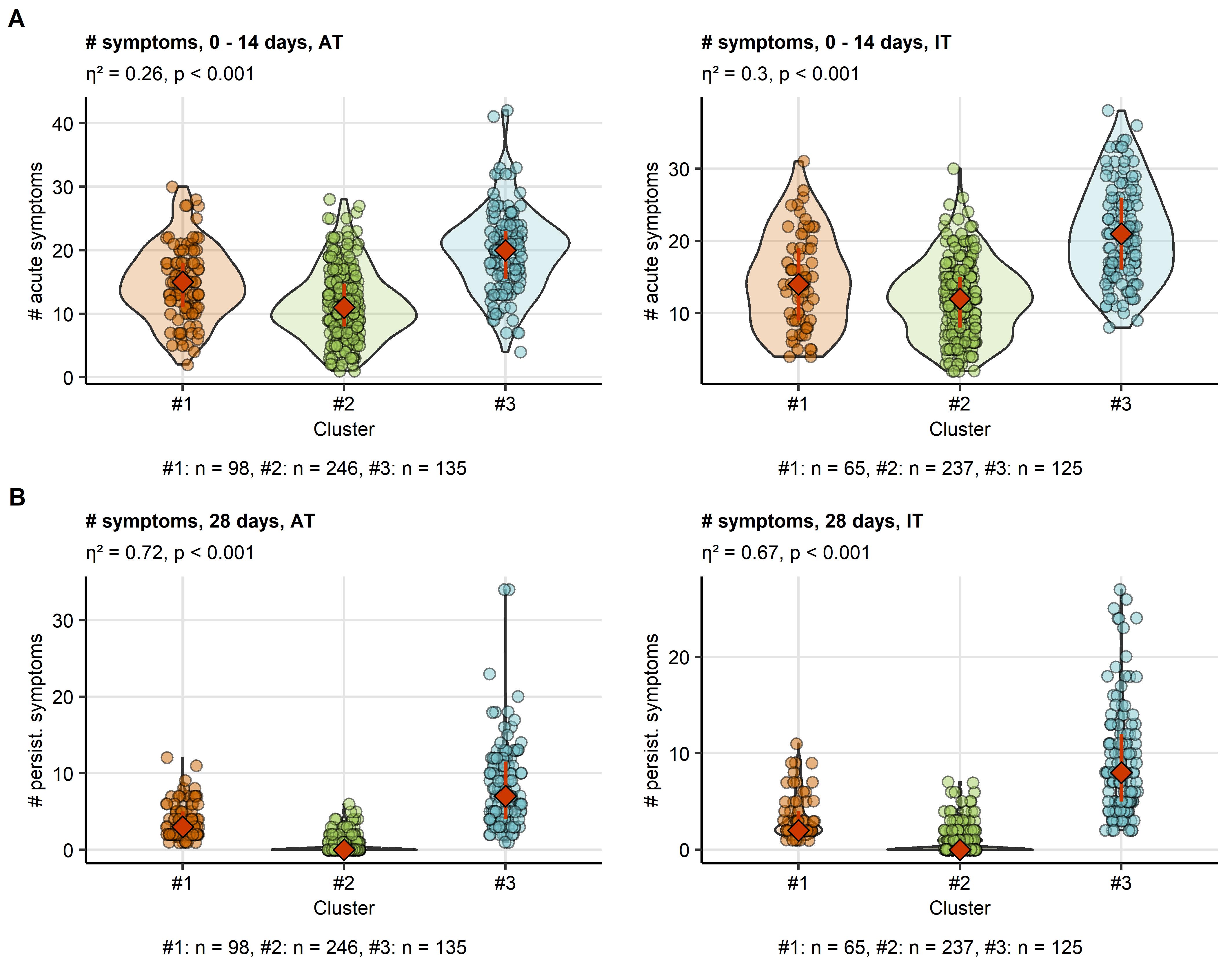
*(C) Permutation importance of the clustering features (symptoms) for clustering of the training cohort expressed as the difference in clustering variance (ratio of total between-cluster sum of squares to total sum of squares) between the initial clustering object and the clustering object with the given variable reshuffled at random. Imp. concentration: impaired concentration, OD: self-reported olfactory dysfunction, Dim. appetite: diminished appetite, Imp. walk: impaired walk, Imp. FMS: impaired fine motor skills.*



**Supplementary Figure S10. Clustering of ambulatory COVID-19 individuals by symptom-specific recovery times.**

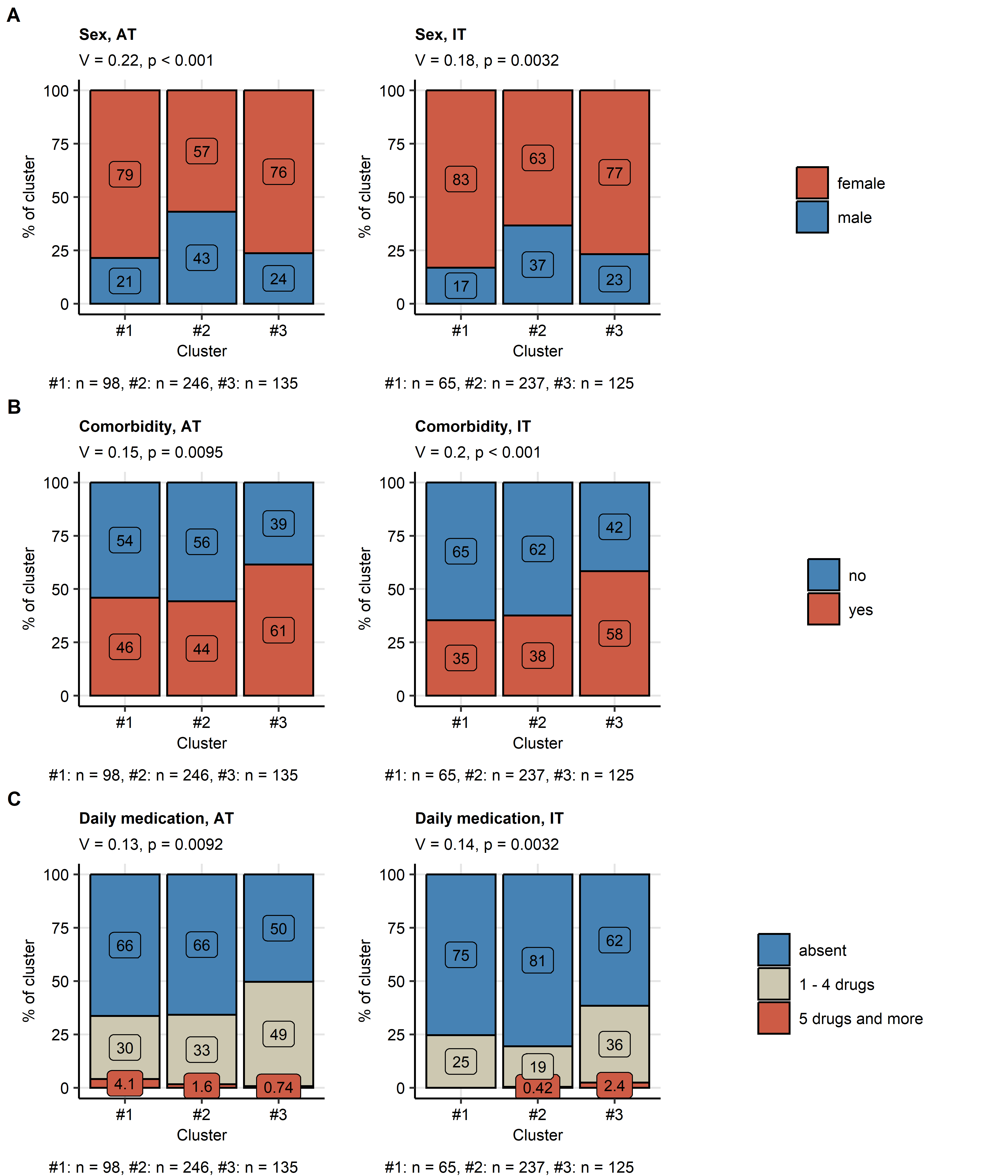
*Individuals of the training Austria (AT) survey study cohort were subjected to clustering in respect to symptom-specific recovery times with the PAM (partitioning around medoids) algorithm and Euclidean distance measure (Supplementary Figure S9). Cluster assignment in the test Italy (IT) survey cohort was done with k-NN label propagation algorithm. Recovery times for particular COVID-19 symptoms in the COVID-19 recovery clusters are presented as heat maps. Numbers of individuals assigned to the recovery clusters are indicated under the plots.*

*OD: self-reported olfactory dysfunction, Dim. appetite: diminished appetite, Imp. concentration: impaired concentration, Imp. walk: impaired walk, Imp. FMS: impaired fine motor skills.*



**Supplementary Figure S11. Numbers of COVID-19 symptoms in the survey study clusters.**

*Clustering of the survey study participants in respect to symptom-specific recovery times was done by the semi-supervised PAM algorithm (partitioning around medoids, Euclidean distance, training cohort: Austria [AT], test cohort: Italy [IT]). Differences in numbers of symptoms in the first 14 days (A) and at 28 days (B) after clinical onset between the clusters were assessed by Kruskal-Wallis test and effect size statistic. P values were corrected for multiple testing with Benjamini-Hochberg method. Symptom counts are presented in violin plots. Points represent single observations, orange diamonds with whiskers code for medians and interquartile ranges. Effect size statistics and p values are indicated in the plot caption. Numbers of complete observations are displayed under the plots.*



**Supplementary Figure S12. COVID-19 recovery clusters differ in sex distribution, comorbidity and daily medication rates.**

*Clustering of the survey study participants in respect to symptom-specific recovery times was done by the semi-supervised PAM algorithm (partitioning around medoids, Euclidean distance, training cohort: Austria [AT], test cohort: Italy [IT]). Differences in sex distribution (A), frequency of comorbidity (B) and daily medication (C) between the recovery clusters were assessed by test with Cramer V effect size statistic. P values were corrected for multiple testing with Benjamini-Hochberg method. The frequencies are presented as bar plots. Effect size statistics and p values are indicated in the plot caption. Numbers of complete observations are displayed under the plots.*

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