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

Tables and figures

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# Tables

Table 1: Baseline characteristic of the Austria (AT) and Italy (IT) survey study cohorts.

| **Variable** | **AT** | **IT** | **Significancea** | **Effect sizea** |
| --- | --- | --- | --- | --- |
| Sex | female: 67% (n = 320) male: 33% (n = 159) complete: n = 479 | female: 70% (n = 300) male: 30% (n = 127) complete: n = 427 | ns (p = 0.46) | V = 0.037 |
| Age, years | median: 43 [IQR: 32 - 53] range: 18 - 80 complete: n = 479 | median: 45 [IQR: 34 - 54] range: 18 - 95 complete: n = 427 | ns (p = 0.31) | r = 0.048 |
| BMI before COVID-19b | normal: 54% (n = 257) overweight: 28% (n = 135) obesity: 18% (n = 84) complete: n = 476 | normal: 66% (n = 278) overweight: 25% (n = 104) obesity: 8.8% (n = 37) complete: n = 419 | p = 0.0011 | V = 0.15 |
| Education | non-tertiary: 63% (n = 302) tertiary: 37% (n = 176) complete: n = 478 | non-tertiary: 59% (n = 250) tertiary: 41% (n = 177) complete: n = 427 | ns (p = 0.35) | V = 0.047 |
| Employment status | employed: 83% (n = 398) unemployed: 8.4% (n = 40) leave: 1.7% (n = 8) retired: 6.9% (n = 33) complete: n = 479 | employed: 81% (n = 348) unemployed: 9.4% (n = 40) leave: 1.9% (n = 8) retired: 7.3% (n = 31) complete: n = 427 | ns (p = 1) | V = 0.022 |
| Observation time | median: 180 [IQR: 130 - 220] range: 90 - 400 complete: n = 479 | median: 140 [IQR: 120 - 270] range: 90 - 390 complete: n = 427 | p = 0.0036 | r = 0.12 |
| Comorbidity | 49% (n = 237) complete: n = 479 | 43% (n = 185) complete: n = 427 | ns (p = 0.22) | V = 0.062 |
| Hypertension | 11% (n = 51) complete: n = 479 | 8.4% (n = 36) complete: n = 427 | ns (p = 0.46) | V = 0.038 |
| Cardiovascular disease | 2.1% (n = 10) complete: n = 479 | 3% (n = 13) complete: n = 427 | ns (p = 0.62) | V = 0.03 |
| Diabetes | 1.5% (n = 7) complete: n = 479 | 0.23% (n = 1) complete: n = 427 | ns (p = 0.26) | V = 0.065 |
| Pulmonary disease | 3.8% (n = 18) complete: n = 479 | 2.8% (n = 12) complete: n = 427 | ns (p = 0.67) | V = 0.026 |
| Gastrointestinal disease | 1.7% (n = 8) complete: n = 479 | 0.7% (n = 3) complete: n = 427 | ns (p = 0.46) | V = 0.044 |
| Malignancy | 2.1% (n = 10) complete: n = 479 | 4% (n = 17) complete: n = 427 | ns (p = 0.31) | V = 0.056 |
| Hay fever/allergy | 18% (n = 88) complete: n = 479 | 12% (n = 51) complete: n = 427 | p = 0.045 | V = 0.089 |
| Autoimmunityc | 6.7% (n = 32) complete: n = 479 | 6.3% (n = 27) complete: n = 427 | ns (p = 1) | V = 0.0072 |
| Freq. resp. infectionsd | 6.7% (n = 32) complete: n = 479 | 3.3% (n = 14) complete: n = 427 | ns (p = 0.1) | V = 0.077 |
| Freq. bact. Infections | 4.8% (n = 23) complete: n = 479 | 1.2% (n = 5) complete: n = 427 | p = 0.016 | V = 0.1 |
| Pre-CoV depression/anxiety | 5.4% (n = 26) complete: n = 479 | 5.2% (n = 22) complete: n = 427 | ns (p = 1) | V = 0.0061 |
| Pre-CoV sleep disorders | 3.5% (n = 17) complete: n = 479 | 4.7% (n = 20) complete: n = 427 | ns (p = 0.62) | V = 0.029 |
| Daily medication | absent: 62% (n = 295) 1 - 4 drugs: 37% (n = 175) 5 drugs and more: 1.9% (n = 9) complete: n = 479 | absent: 74% (n = 317) 1 - 4 drugs: 25% (n = 106) 5 drugs and more: 0.94% (n = 4) complete: n = 427 | p = 0.0024 | V = 0.14 |
| aCategorical variables: χ² test with Cramer V effect size statistic. Numeric variables: Mann-Whitney U test with wilcoxon r 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. | | | | |

Table 2: Baseline characteristic of the CovILD study cohort and the study participants stratified by COVID-19 severity.

| **Variable** | **Entire cohort** | **Ambulatory CoV subset** | **Moderate CoV subset** | **Severe CoV subset** | **Significancea** | **Effect sizea** |
| --- | --- | --- | --- | --- | --- | --- |
| Sex | female: 41% (n = 44) male: 59% (n = 64) complete: n = 108 | female: 67% (n = 18) male: 33% (n = 9) complete: n = 27 | female: 35% (n = 19) male: 65% (n = 36) complete: n = 55 | female: 27% (n = 7) male: 73% (n = 19) complete: n = 26 | p < 0.001 | V = 0.31 |
| Age, years | median: 56 [IQR: 49 - 68] range: 19 - 87 complete: n = 108 | median: 47 [IQR: 38 - 55] range: 19 - 70 complete: n = 27 | median: 62 [IQR: 53 - 72] range: 27 - 87 complete: n = 55 | median: 56 [IQR: 52 - 64] range: 44 - 79 complete: n = 26 | p < 0.001 | η² = 0.21 |
| BMI at CoV onsetb | normal: 39% (n = 42) overweight: 43% (n = 46) obesity: 19% (n = 20) complete: n = 108 | normal: 56% (n = 15) overweight: 33% (n = 9) obesity: 11% (n = 3) complete: n = 27 | normal: 29% (n = 16) overweight: 51% (n = 28) obesity: 20% (n = 11) complete: n = 55 | normal: 42% (n = 11) overweight: 35% (n = 9) obesity: 23% (n = 6) complete: n = 26 | p < 0.001 | V = 0.17 |
| Comorbidity present | 75% (n = 81) complete: n = 108 | 41% (n = 11) complete: n = 27 | 85% (n = 47) complete: n = 55 | 88% (n = 23) complete: n = 26 | p < 0.001 | V = 0.46 |
| Metabolic disease | 42% (n = 45) complete: n = 108 | 19% (n = 5) complete: n = 27 | 49% (n = 27) complete: n = 55 | 50% (n = 13) complete: n = 26 | p < 0.001 | V = 0.27 |
| Hypertension | 27% (n = 29) complete: n = 108 | 7.4% (n = 2) complete: n = 27 | 27% (n = 15) complete: n = 55 | 46% (n = 12) complete: n = 26 | p < 0.001 | V = 0.31 |
| Cardiovascular disease | 40% (n = 43) complete: n = 108 | 7.4% (n = 2) complete: n = 27 | 47% (n = 26) complete: n = 55 | 58% (n = 15) complete: n = 26 | p < 0.001 | V = 0.39 |
| Diabetes | 15% (n = 16) complete: n = 108 | 3.7% (n = 1) complete: n = 27 | 15% (n = 8) complete: n = 55 | 27% (n = 7) complete: n = 26 | p < 0.001 | V = 0.23 |
| Pulmonary disease | 19% (n = 20) complete: n = 108 | 11% (n = 3) complete: n = 27 | 22% (n = 12) complete: n = 55 | 19% (n = 5) complete: n = 26 | p = 0.031 | V = 0.11 |
| Gastrointestinal disease | 13% (n = 14) complete: n = 108 | 0% (n = 0) complete: n = 27 | 20% (n = 11) complete: n = 55 | 12% (n = 3) complete: n = 26 | p < 0.001 | V = 0.24 |
| Malignancy | 9.3% (n = 10) complete: n = 108 | 3.7% (n = 1) complete: n = 27 | 15% (n = 8) complete: n = 55 | 3.8% (n = 1) complete: n = 26 | p < 0.001 | V = 0.19 |
| Immune deficiency | 5.6% (n = 6) complete: n = 108 | 0% (n = 0) complete: n = 27 | 3.6% (n = 2) complete: n = 55 | 15% (n = 4) complete: n = 26 | p < 0.001 | V = 0.25 |
| aComparison of ambulatory, moderate and severe COVID-19 individuals. Categorical 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, | | | | | | |

# Figures

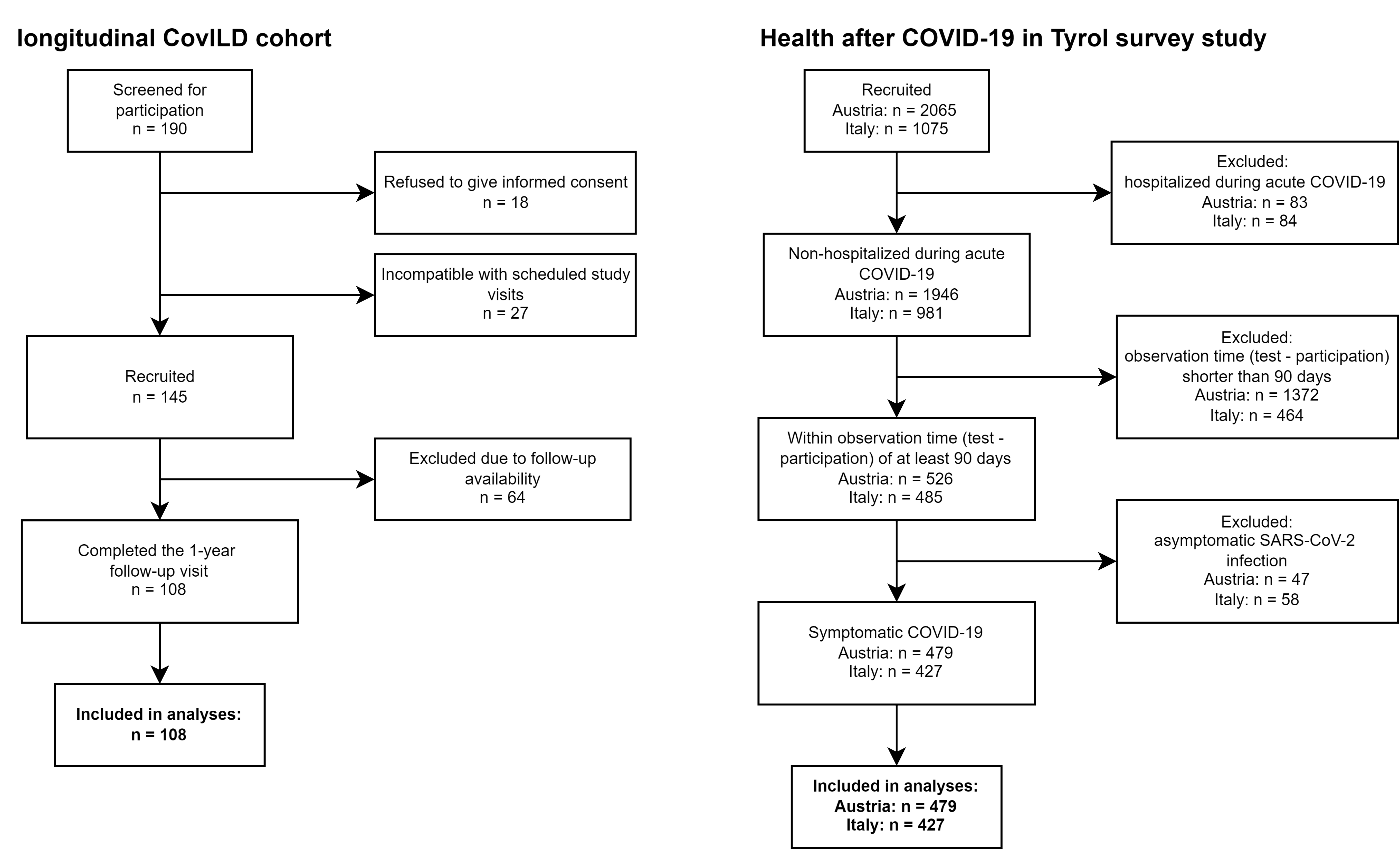


Figure 1: Flow diagram of the analysis inclusion process for the longitudinal CovILD cohort and the Health after COVID-19 survey study.

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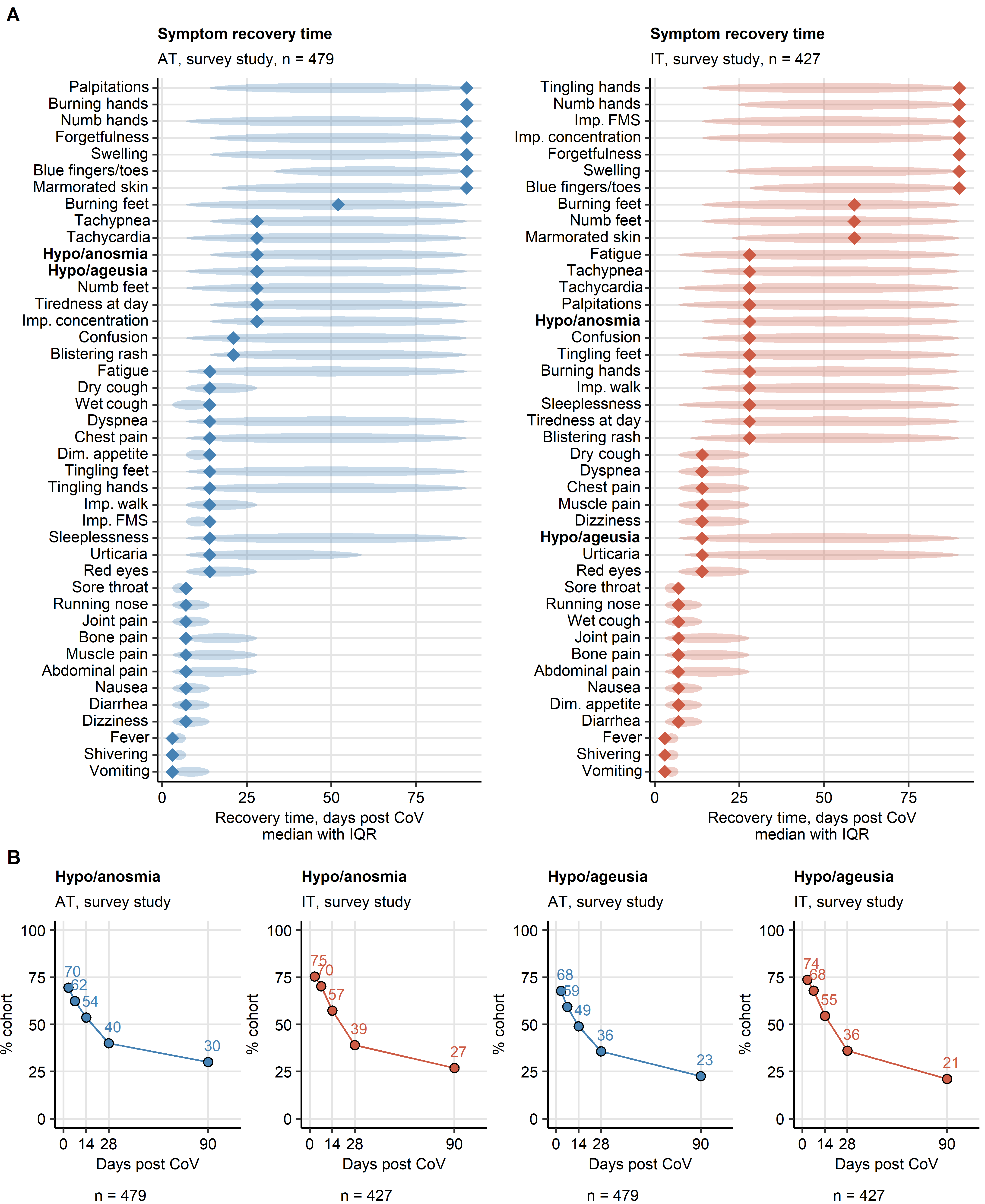


Figure 2: Symptom-specific recovery times in ambulatory COVID-19 survey study.

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*Symptom-specific recovery times were calculated for each participants of the survey study cohorts (Austria: AT, Italy: IT).*

*(A) Distribution of the recovery times in the individuals with the indicated symptoms present during acute COVID-19 (first 14 days after clinical onset). Diamonds represent median recovery times, tinted ellipses code for interquartile ranges. Numbers of complete observations are indicated in the plot captions.*

*(B) Percentages of individuals with smell and taste disorders 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.*

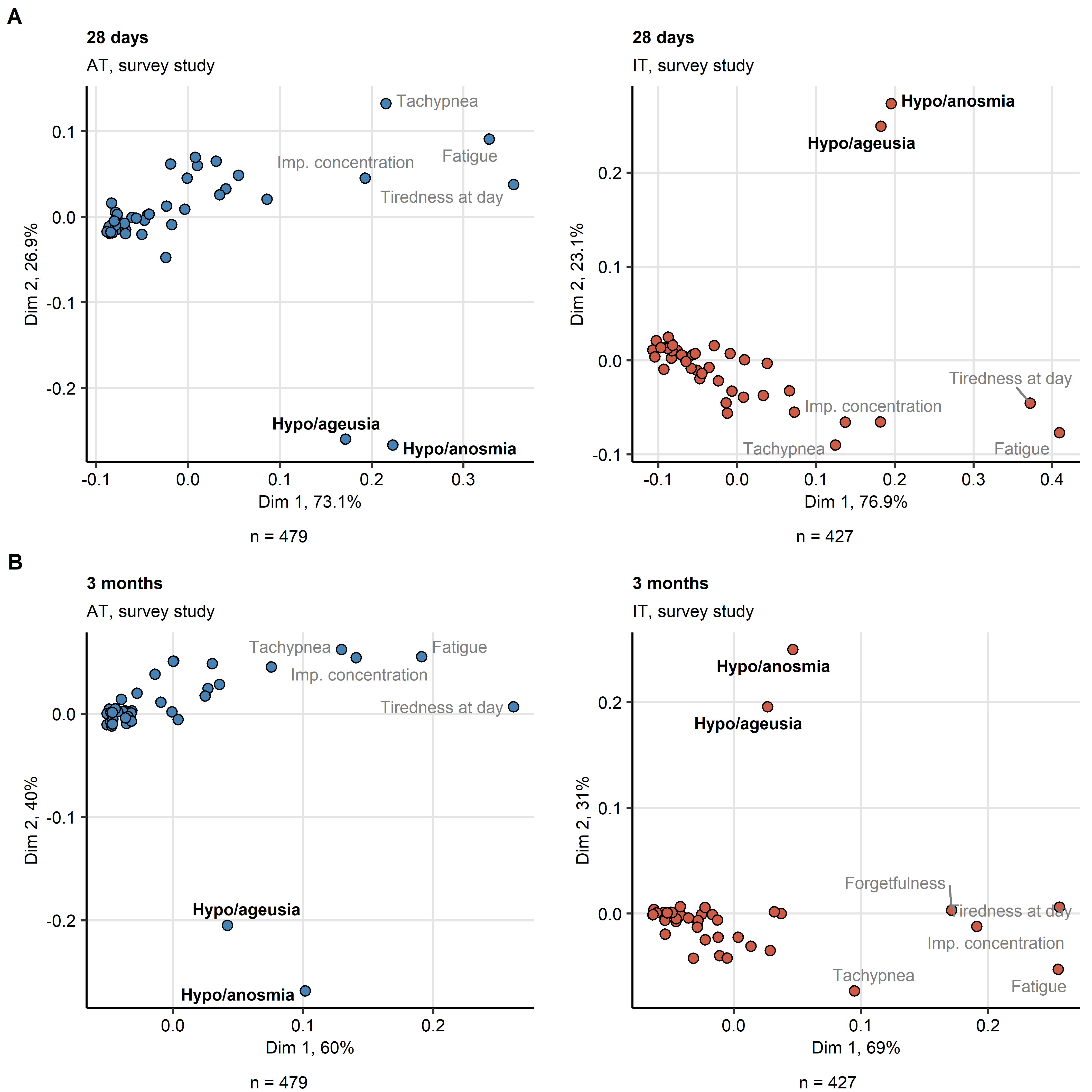


Figure 3: Self-reported smell and taste disorders are isolated persistent symptoms of COVID-19.

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*Symptom data during at 28 days (A) and 3 moths (B) 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.*

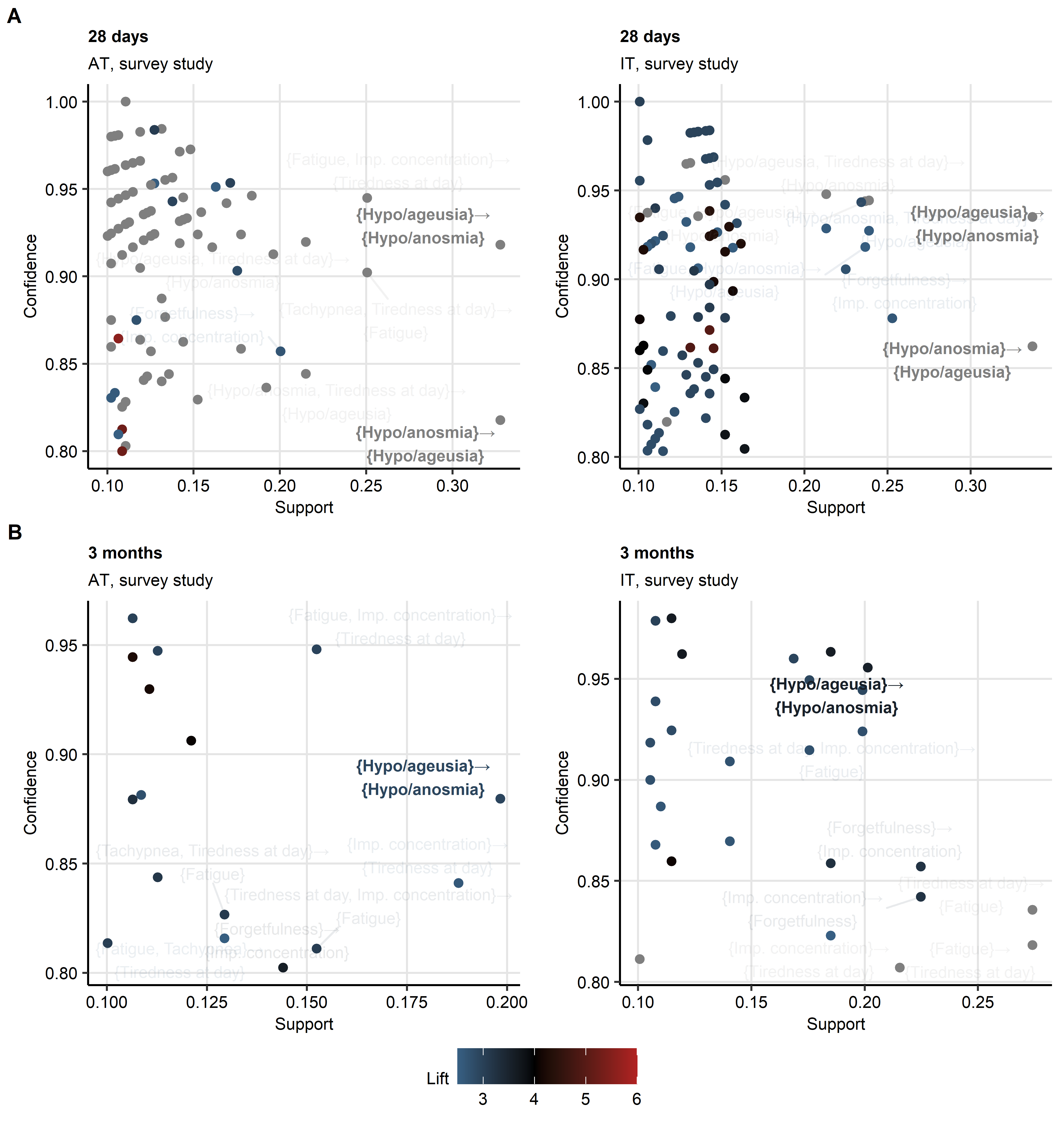


Figure 4: Co-occurrence of smell and taste disorders in post-acute COVID-19 sequelae.

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*Frequent combinations of symptoms at 28 days (A) and 3 months (B) after clinical onset in the Austria (AT) and Italy (IT) survey study cohorts were identified with the apriori algorithm. Symptom combination support and confidence are presented in the plots. Point color codes for lift statistic values. The hypo/anosmia and hypo/ageusia combinations are labeled.*

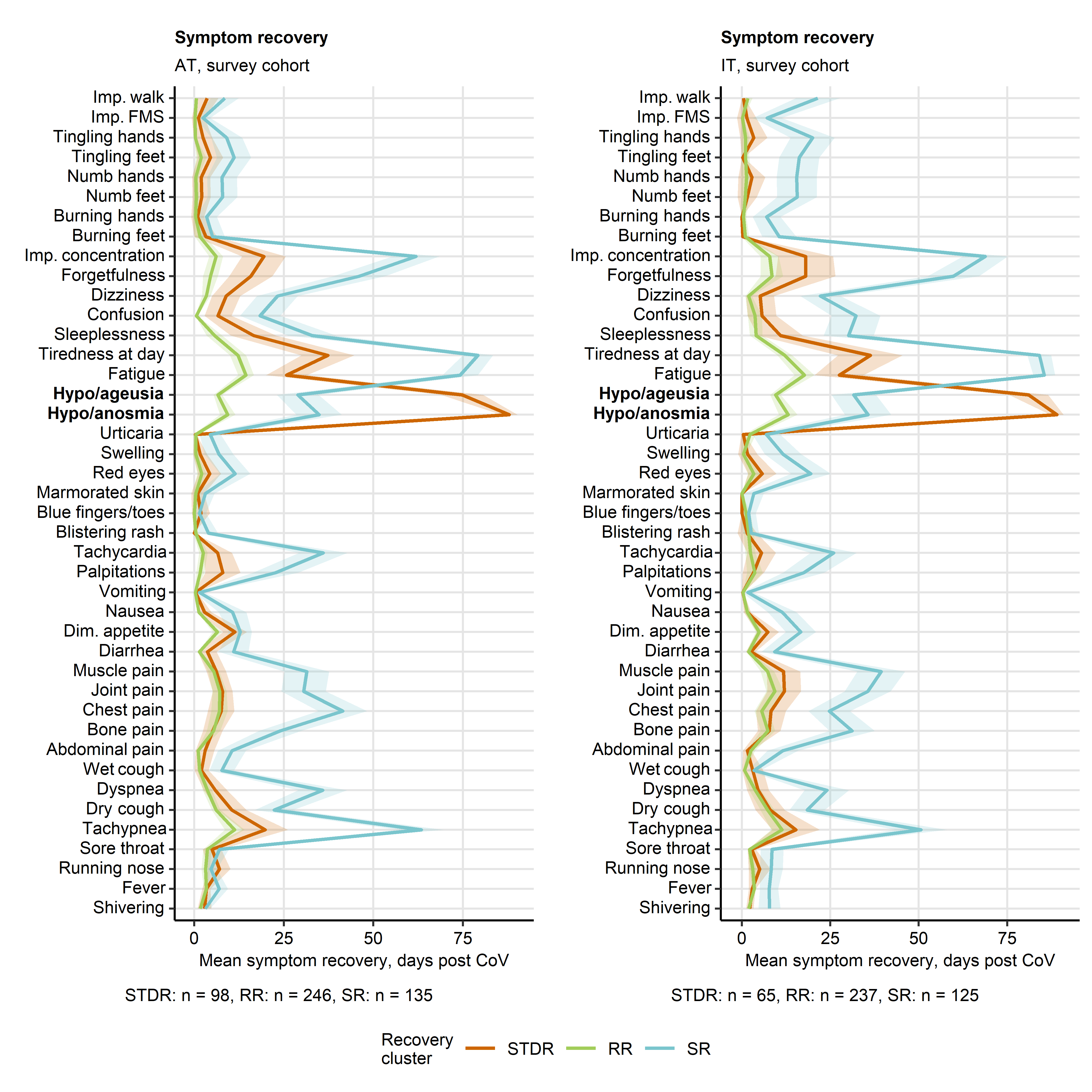


Figure 5: Differing duration of neurocognitive and respiratory symptoms, fatigue, smell and taste disorders defines the COVID-19 recovery clusters.

**Figure 5. Differing duration of neurocognitive and respiratory symptoms, fatigue, smell and taste disorders defines the COVID-19 recovery clusters.**

*The smell and taste disorder recovery (STDR), rapid recovery (RR) and slow recovery (SR) clusters of the survey study participants were identified by semi supervised PAM clustering (partitioning around medoids, Euclidean distance, training cohort: Austria [AT], test cohort: Italy [IT]). Mean recovery times in the recovery clusters are presented as lines, 2 SEM intervals are displayed as tinted regions. Numbers of individuals assigned to the recovery clusters are indicated under the plots.*

*Dim. appetite: diminished appetite, Imp. concentration: impaired concentration, Imp. walk: impaired walk, Imp. FMS: impaired fine motor skills.*

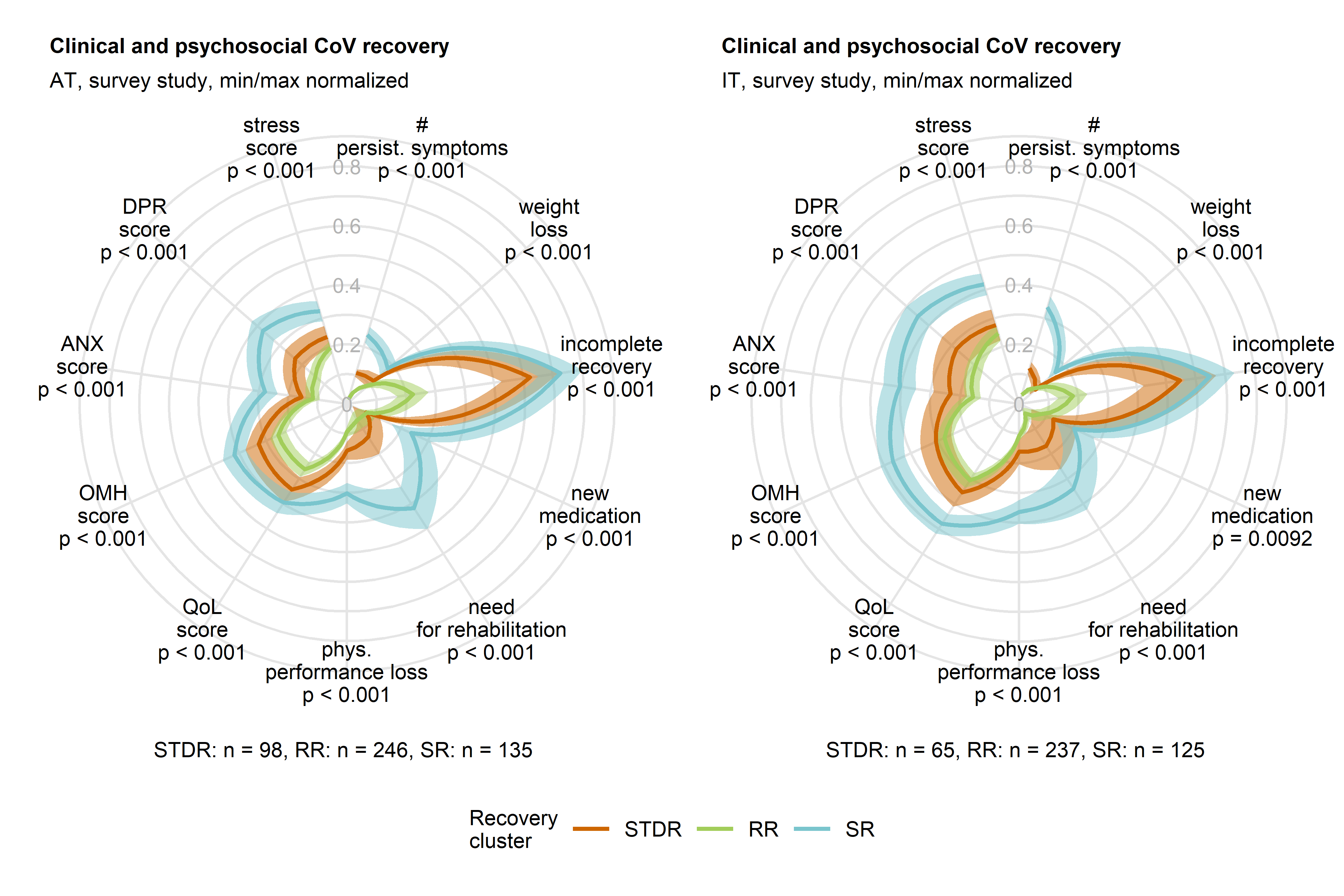


Figure 6: Good clinical and mental health status and quality of life at the survey completion in individuals with persistent smell and taste disorders.

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*Differences in minimum/maximum scaled readouts of clinical and physical recovery, mental health and quality of life at the time of survey completion in the recovery clusters (STDR: smell and taste disorder recovery, RR: rapid recovery, SR: slow recovery) in the Austria (AT) and Italy (IT) survey study cohorts. Dichotomous items (incomplete convalescence, weight loss, new medication and need for rehabilitation) were binarized (yes: 1, no: 0) prior to visualization. Statistical significance for differences between the clusters was assessed by Kruskal-Wallis (numeric readouts) or test (dichotomous readouts). P values were corrected for multiple testing with Benjamini-Hochberg method. Lines represent mean values, 2 SEM intervals are displayed as tinted regions. Numbers of individuals assigned to the recovery clusters are indicated under the plots.*

*incomplete recovery: self-reported incomplete recovery, # persist. symptoms: number of symptoms at 28 days after clinical onset, phys. performance loss: physical performance loss as compared with the time before COVID-19, QoL score: quality of life impairment score, OMH score: overall mental health impairment score, ANX score: anxiety score, DPR: depression score.*