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	Significance[a]	Effect size[a]
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-19[b]	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

Variable	AT	IT	Significance[a]	Effect size[a]
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
Autoimmunity[c]	6.7% (n = 32) complete: n = 479	6.3% (n = 27) complete: n = 427	ns (p = 1)	V = 0.0072
Freq. resp. infections[d]	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

[a]Categorical variables: χ^2 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.

[b]BMI: body mass index, overweight > 25 kg/m^2, obesity > 30 kg/m^2.

[c]Frequent respiratory infections, > 2 per year.

[d]Frequent 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	Significance[a]	Effect size[a]
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	$p < 0.001$	$\eta^2 = 0.21$
BMI at CoV onset[b]	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	$p = 0.031$	$V = 0.11$

Variable	Entire cohort	Ambulatory CoV subset	Moderate CoV subset	Severe CoV subset	Significance[a]	Effect size[a]
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	$p < 0.001$	$V = 0.25$

[a]Comparison of ambulatory, moderate and severe COVID-19 individuals. Categorical variables: χ^2 test with Cramer V effect size statistic. Numeric variables: Kruskal-Wallis test with η^2 effect size statistic. P values corrected form multiple testing with Benjamini-Hochberg method.

[b]BMI: body mass index, overweight > 25 kg/m^2, obesity > 30 kg/m^2,

Figures

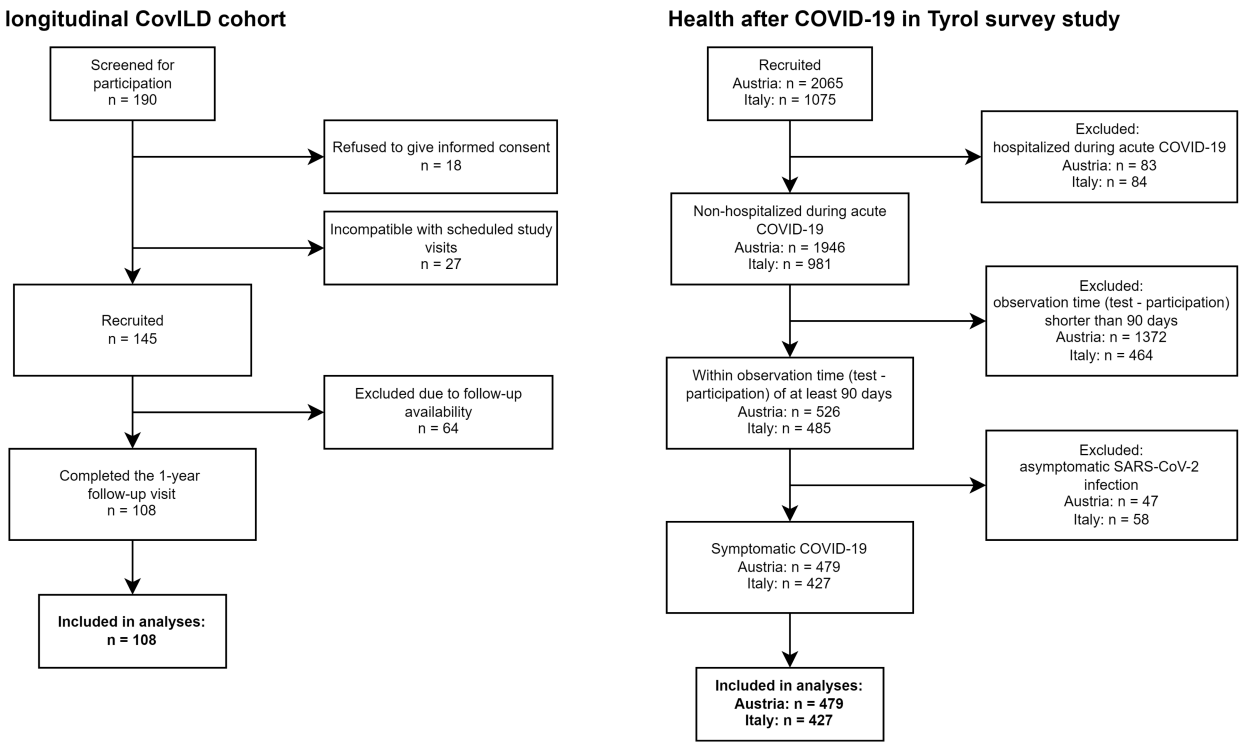

Figure 1. Flow diagram of the analysis inclusion process for the longitudinal CovILD cohort and the Health after COVID-19 survey study.

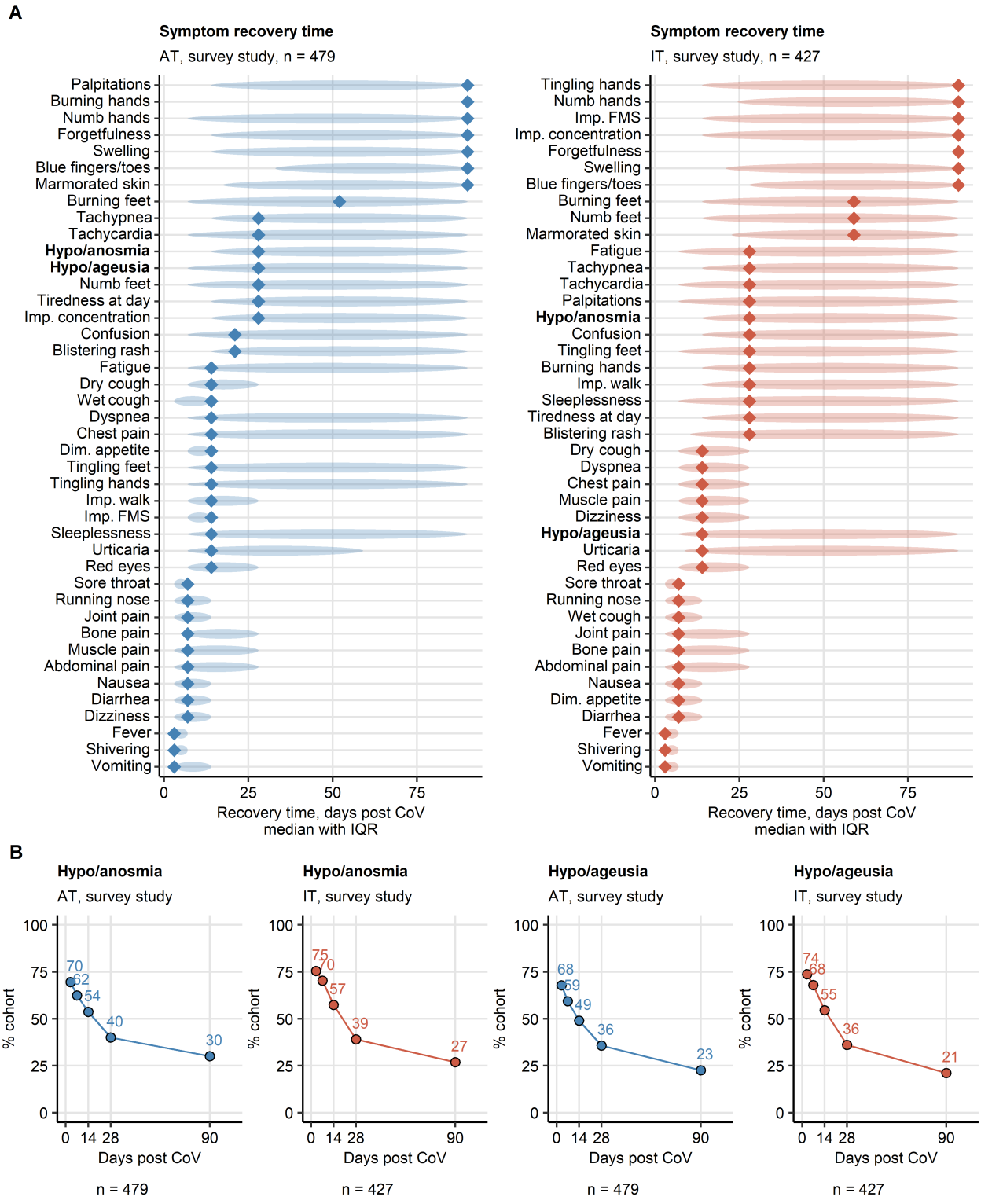

Figure 2. Symptom-specific recovery times in ambulatory COVID-19 survey study.

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.

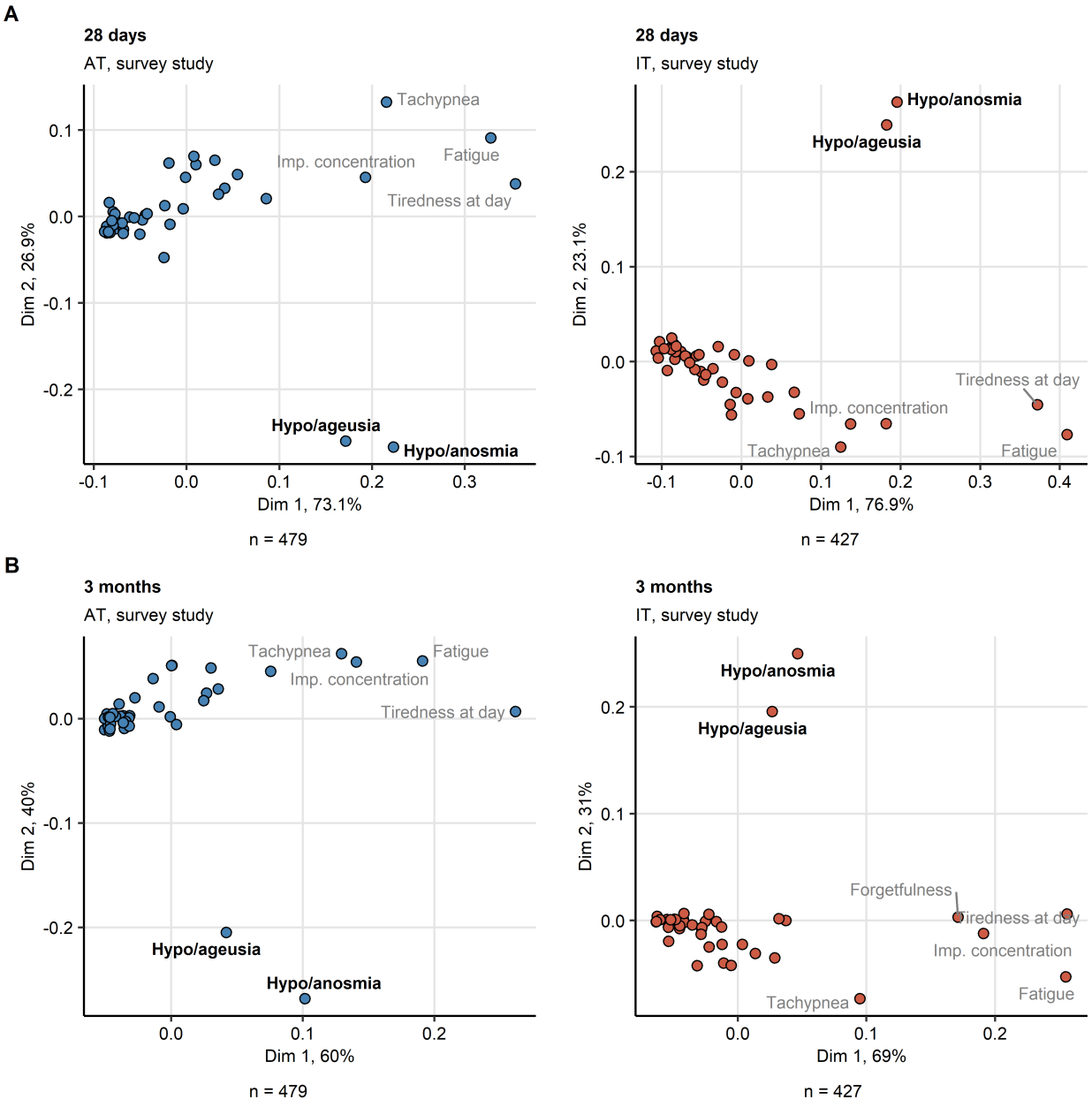

Figure 3. Self-reported smell and taste disorders are isolated persistent symptoms of COVID-19.

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.

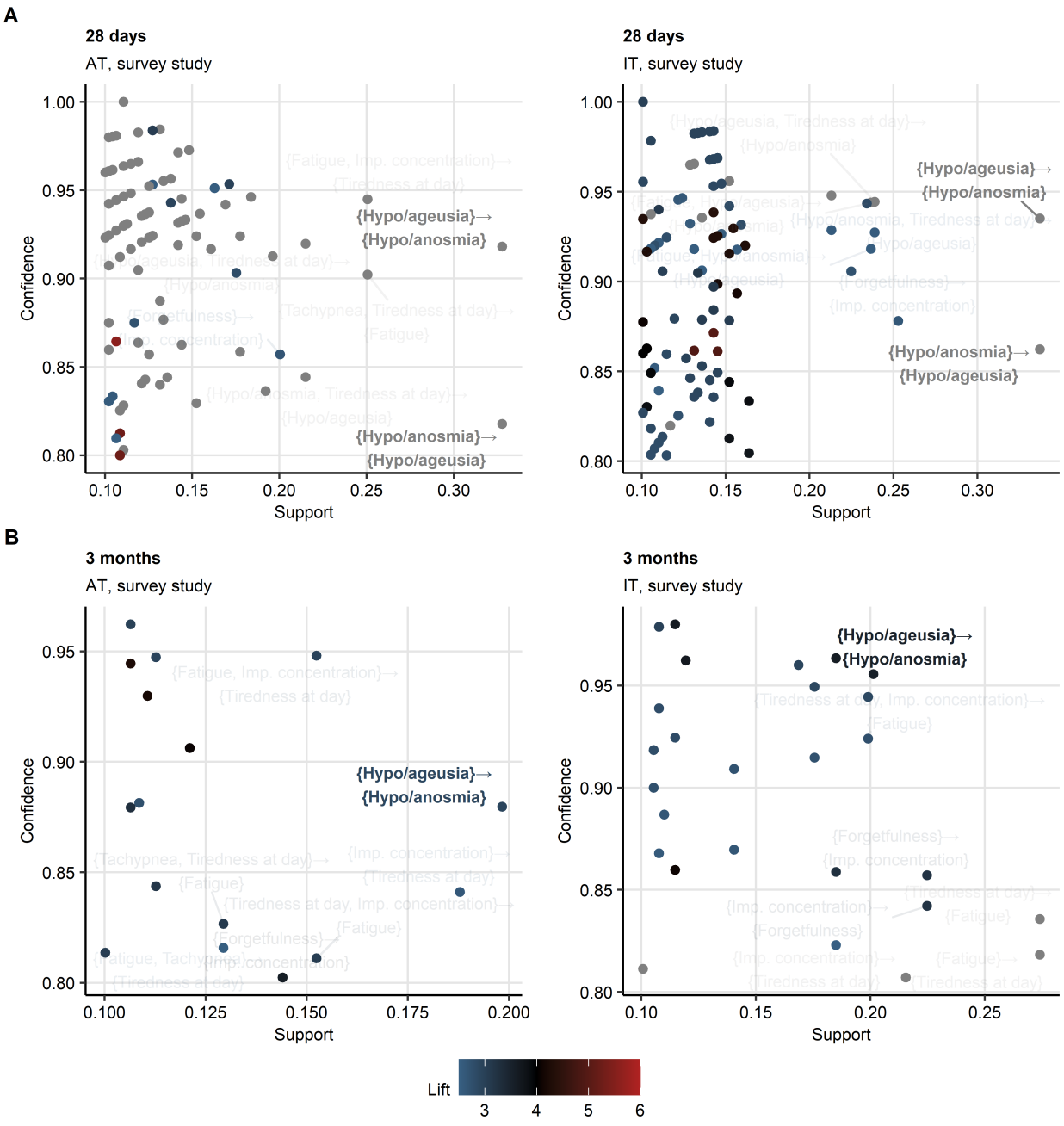

Figure 4. Co-occurrence of smell and taste disorders in post-acute COVID-19 sequelae.

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.

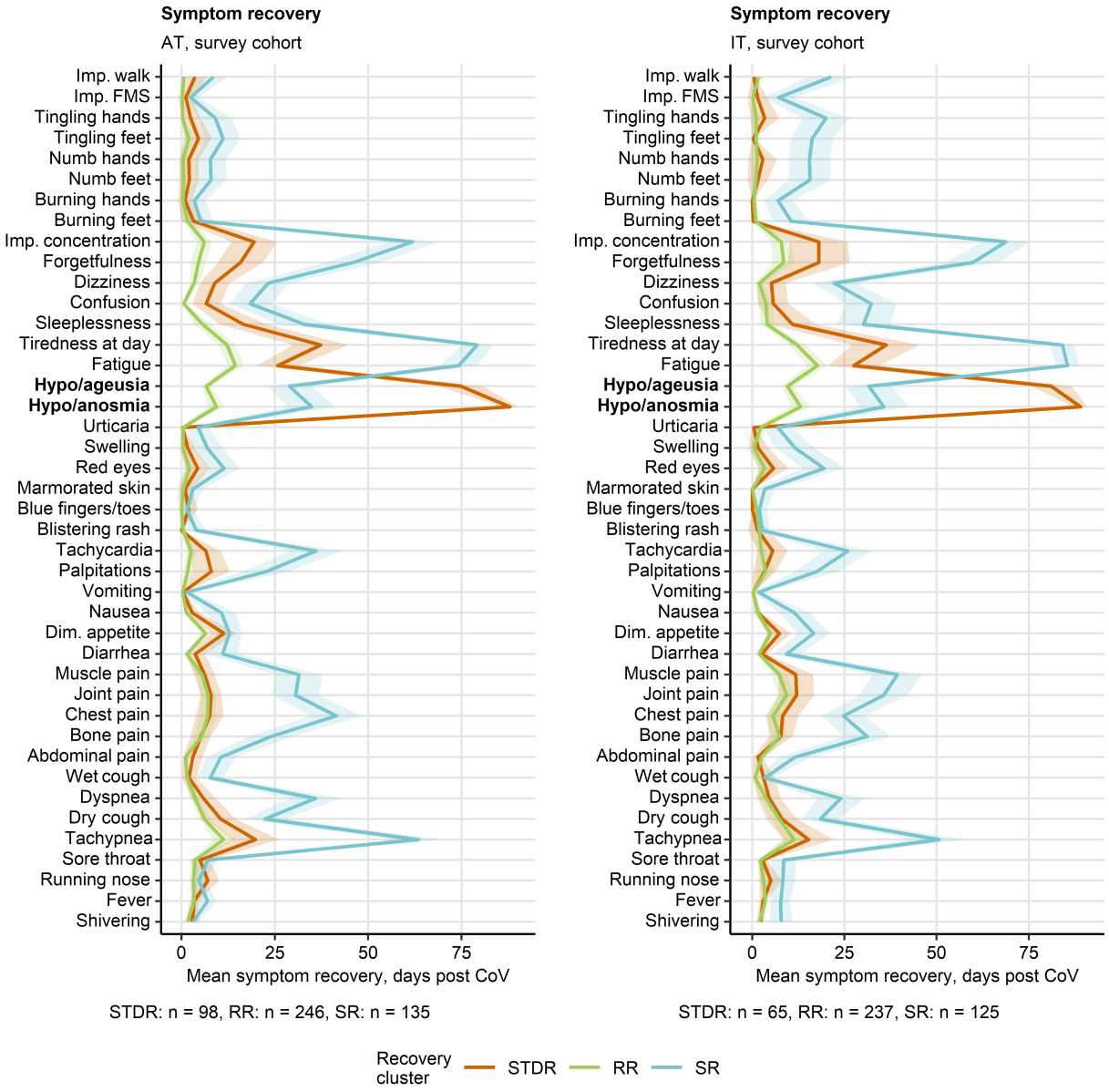

Figure 5. Differing duration of neurocognitive and respiratory symptoms, fatigue, smell and taste disorders defines the COVID-19 recovery clusters.

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.

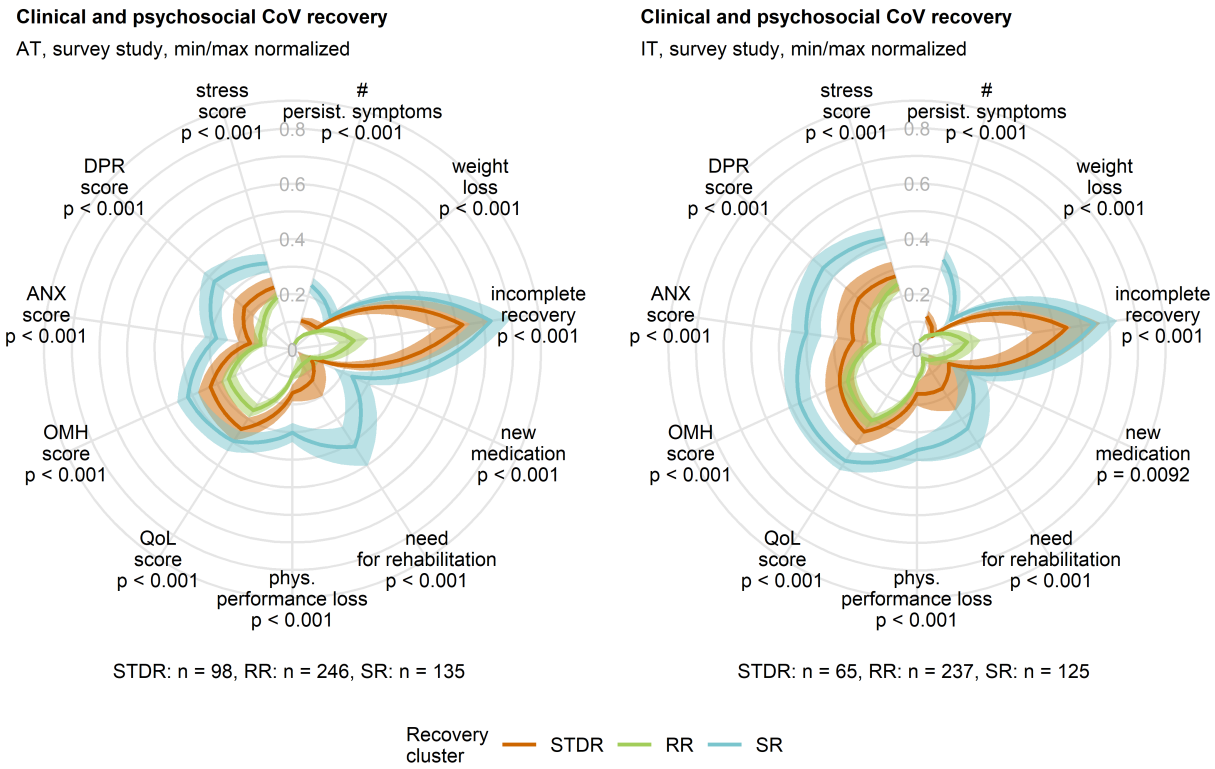

Figure 6. Good clinical and mental health status and quality of life at the survey completion in individuals with persistent smell and taste disorders.

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 χ^2 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.