Hyposmia as a standalone persistent symptom of long COVID

Figures and Tables

Health after COVID-19 in Tyrol study team

2021-10-19

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Table 1: **Characteristic of the CovILD study cohort.**
Ambulatory, Moderate, Severe: severity of acute SARS-CoV-2 infection, Test: statistical test used for the comparison between the severity strata (KW: Kruskal-Wallis), Significance: test p value corrected for multiple comparisons with Benjamini-Hochberg method.

Parameter	Ambulatory	Moderate	Severe	Test	Significance
Sex	female: 72.2% (26) male: 27.8% (10) n = 36	female: 36.8% (28) male: 63.2% (48) n = 76	female: 27.3% (9) male: 72.7% (24) n = 33	χ^2	p = 0.00098
Age	mean(SD) = 45.8 (14) median(IQR) = 47.5 (37.5 - 55) range = 19 - 83 n = 36	mean(SD) = 61.8 (13.3) median(IQR) = 62 (52.8 - 73) range = 27 - 87 n = 76	mean(SD) = 59.4 (9.61) median(IQR) = 58 (53 - 65) range = 44 - 79 n = 33	KW	p = 7.2e-07
	up to 50: 58.3% (21) 51 - 65: 36.1% (13) over 65: 5.56% (2) n = 36	up to 50: 17.1% (13) 51 - 65: 40.8% (31) over 65: 42.1% (32) n = 76	up to 50: 18.2% (6) 51 - 65: 57.6% (19) over 65: 24.2% (8) n = 33	χ^2	p = 4.6e-06
Smoking	never: 77.8% (28) ex: 19.4% (7) active: 2.78% (1) n = 36	never: 48.7% (37) ex: 47.4% (36) active: 3.95% (3) n = 76	never: 69.7% (23) ex: 30.3% (10) active: 0% (0) n = 33	χ^2	p = 0.013
Comorbidity present	47.2% (17) n = 36	85.5% (65) n = 76	90.9% (30) n = 33	χ^2	p = 5.2e-05
Number of comorbidities (max. 17)	mean(SD) = 1.14 (1.96) median(IQR) = 0 (0 - 1.25) range = 0 - 10 n = 36	mean(SD) = 2.95 (2.11) median(IQR) = 3 (1 - 4) range = 0 - 9 n = 76	mean(SD) = 3.58 (2.05) median(IQR) = 3 (2 - 4) range = 0 - 8 n = 33	KW	p = 1.8e-07
BMI class	normal: 52.8% (19) obesity: 13.9% (5) overweight: 33.3% (12) n = 36	normal: 32.9% (25) obesity: 21.1% (16) overweight: 46.1% (35) n = 76	normal: 39.4% (13) obesity: 24.2% (8) overweight: 36.4% (12) n = 33	χ^2	ns
Cardiovascular comorbidity	8.33% (3) n = 36	46.1% (35) n = 76	60.6% (20) n = 33	χ^2	p = 2e-04
Hypertension	8.33% (3) n = 36	31.6% (24) n = 76	51.5% (17) n = 33	χ^2	p = 0.014
Pulmonary comorbidity	16.7% (6) n = 36	21.1% (16) n = 76	15.2% (5) n = 33	χ^2	ns
Endocrine or metabolic comorbidity	22.2% (8) n = 36	48.7% (37) n = 76	54.5% (18) n = 33	χ^2	p = 0.014

Table 1: **Characteristic of the CovILD study cohort.**
Ambulatory, Moderate, Severe: severity of acute SARS-CoV-2 infection, Test: statistical test used for the comparison between the severity strata (KW: Kruskal-Wallis), Significance: test p value corrected for multiple comparisons with Benjamini-Hochberg method. *(continued)*

Parameter	Ambulatory	Moderate	Severe	Test	Significance
Hypercholesterolemia	5.56% (2) n = 36	26.3% (20) n = 76	15.2% (5) n = 33	χ^2	p = 0.02
Diabetes	2.78% (1) n = 36	17.1% (13) n = 76	30.3% (10) n = 33	χ^2	ns
Malignancy	5.56% (2) n = 36	15.8% (12) n = 76	9.09% (3) n = 33	χ^2	ns
Symptomatic SARS-CoV-2 infection	97.1% (34) n = 35	98.7% (75) n = 76	100% (33) n = 33	χ^2	ns
Acute COVID-19 symptom number	mean(SD) = 5.34 (2.24) median(IQR) = 5 (4 - 7) range = 0 - 9 n = 35	mean(SD) = 5.22 (2.08) median(IQR) = 6 (3.75 - 6.25) range = 0 - 9 n = 76	mean(SD) = 5.91 (1.33) median(IQR) = 6 (5 - 7) range = 4 - 9 n = 33	KW	ns

Table 2: **Characteristic of the Health after COVID-19 in Tyrol study cohorts.**
Test: statistical test used for the comparison between the severity strata (U: Mann-Whitney U test), Significance: test p value corrected for multiple comparisons with Benjamini-Hochberg method.

Parameter	Austria	Italy	Test	Significance
Observation time	mean(SD) = 182 (61.8) median(IQR) = 182 (131 - 217) range = 90 - 400 n = 526	mean(SD) = 180 (87.7) median(IQR) = 136 (118 - 271) range = 90 - 387 n = 485	U	p = 0.00022
	up to 100 days: 7.41% (39) 100 - 180 days: 41.8% (220) more than 180 days: 50.8% (267) n = 526	up to 100 days: 10.9% (53) 100 - 180 days: 57.3% (278) more than 180 days: 31.8% (154) n = 485	χ^2	p = 6.8e-09
Sex	female: 65.6% (345) male: 34.4% (181) n = 526	female: 69.1% (335) male: 30.9% (150) n = 485	χ^2	ns
Age	mean(SD) = 43.3 (13.4) median(IQR) = 43.5 (32 - 53) range = 17 - 80 n = 526	mean(SD) = 44.6 (13.3) median(IQR) = 45 (34 - 55) range = 18 - 95 n = 485	U	ns
	young: 22.2% (117) middle-aged: 73.4% (386) elderly: 4.37% (23) n = 526	young: 18.8% (91) middle-aged: 77.1% (374) elderly: 4.12% (20) n = 485	χ^2	ns
Smoking	never: 59.9% (315) former: 31.6% (166) active: 8.56% (45) n = 526	never: 66.4% (322) former: 23.3% (113) active: 10.3% (50) n = 485	χ^2	p = 0.013
Comorbidity absent	50% (263) n = 526	57.5% (279) n = 485	χ^2	p = 0.02
Number of comorbidities (max. 25)	mean(SD) = 0.926 (1.67) median(IQR) = 1 (0 - 1) range = 0 - 24 n = 526	mean(SD) = 0.68 (0.999) median(IQR) = 0 (0 - 1) range = 0 - 6 n = 485	U	p = 0.0046
BMI class	normal: 55.4% (289) overweigth: 27.6% (144) obesity: 17% (89) n = 522	normal: 66.2% (315) overweigth: 25.4% (121) obesity: 8.4% (40) n = 476	χ^2	p = 5.4e-05
Cardiovascular comorbidity	2.09% (11) n = 526	3.09% (15) n = 485	χ^2	ns
Hypertension	11% (58) n = 526	8.25% (40) n = 485	χ^2	ns
Pulmonary comorbidity	3.8% (20) n = 526	2.47% (12) n = 485	χ^2	ns

Table 2: **Characteristic of the Health after COVID-19 in Tyrol study cohorts.**
Test: statistical test used for the comparison between the severity strata (U: Mann-Whitney U test), Significance: test p value corrected for multiple comparisons with Benjamini-Hochberg method. *(continued)*

Parameter	Austria	Italy	Test	Significance
Hay fever/allergy	18.8% (99) n = 526	11.3% (55) n = 485	χ^2	p = 0.0013
Diabetes	1.52% (8) n = 526	0.619% (3) n = 485	χ^2	ns
Malignancy	1.9% (10) n = 526	3.71% (18) n = 485	χ^2	ns
Symptomatic SARS-CoV-2 infection	91.1% (479) n = 526	88.2% (427) n = 484	χ^2	ns
Acute COVID-19 symptom number	mean(SD) = 13.2 (7.71) median(IQR) = 13 (8 - 18) range = 0 - 42 n = 526	mean(SD) = 13.2 (8.24) median(IQR) = 13 (7 - 19) range = 0 - 38 n = 484	U	ns
	1Q: 26.8% (141) 2Q: 28.1% (148) 3Q: 20.3% (107) 4Q: 24.7% (130) n = 526	1Q: 25.6% (124) 2Q: 26.2% (127) 3Q: 26% (126) 4Q: 22.1% (107) n = 484	χ^2	ns

Figures

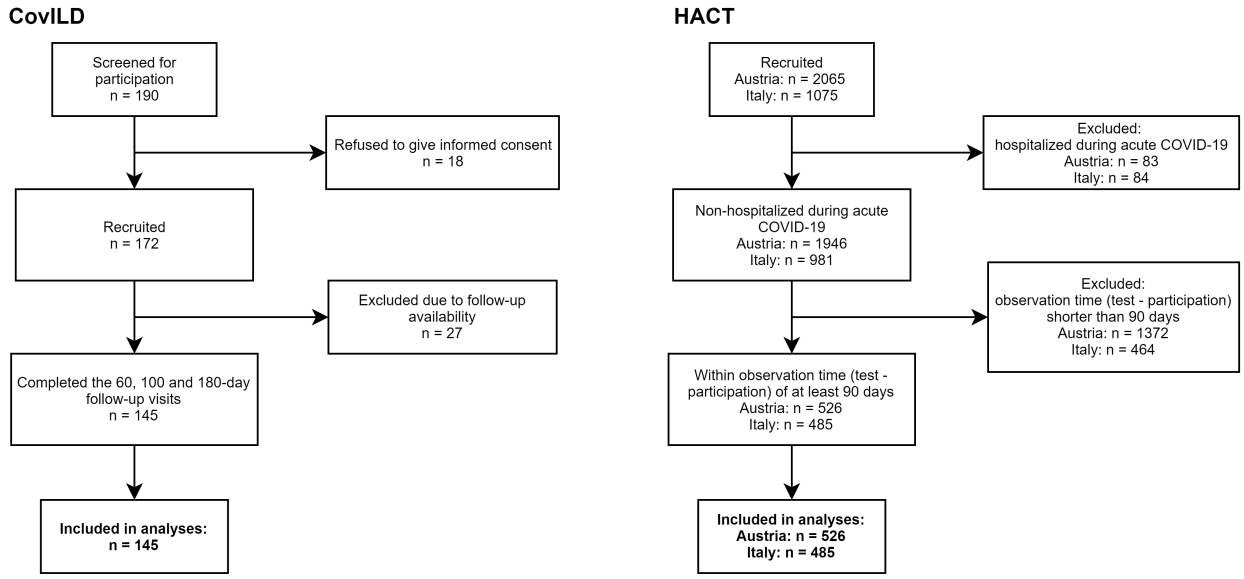

Figure 1: CONSORT flow diagrams for the CoVILD and HACT study cohorts.

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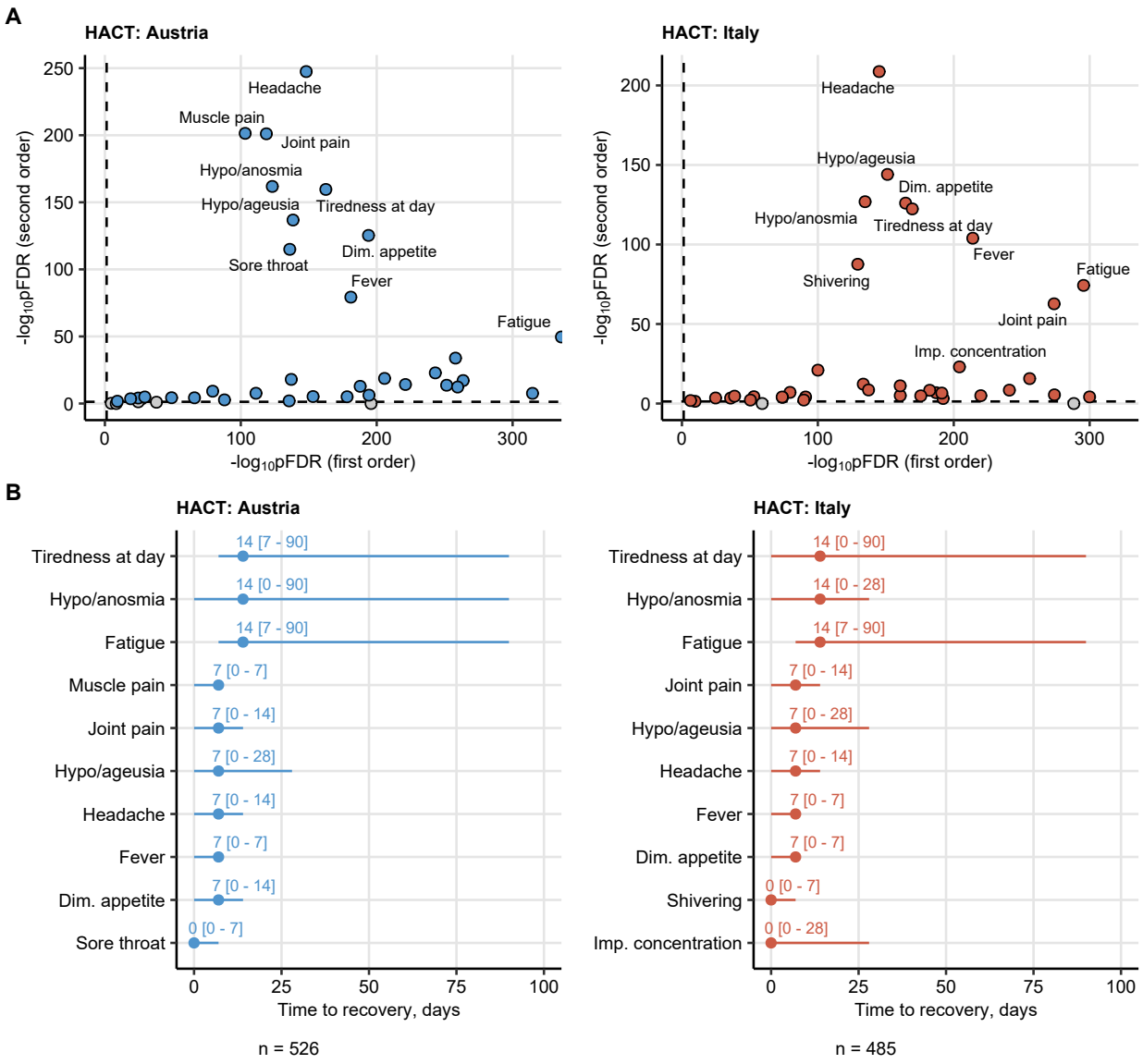

Figure 2: Second order kinetic modeling of symptom recovery course in the HACT study.

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Symptom frequency during acute COVID-19 and recovery in the Austria and Italy HACT cohorts (0, 7, 14, 28 and 90 days post symptom onset) were modeled with mixed-effect logistic regression (**Supplementary Table S2**). Significance of the first and second order model terms was determined by step-wise likelihood ratio test (LRT). P values were corrected for multiple comparisons with Benjamini-Hochberg method. N number of complete observations is provided under the plots in (**B**). Dim.: diminished, imp.: impaired.

(A) Significance of the first and second order model term in LRT test. Points represent single symptoms, color codes for significance (gray: non-significant). Top 10 symptoms with the most significant second order terms as candidate long-term persistent features are labeled with their names.

(B) Median recovery times for top 10 symptoms with the most significant second order terms as candidate long-term persistent features. Whiskers represent interquartile ranges.

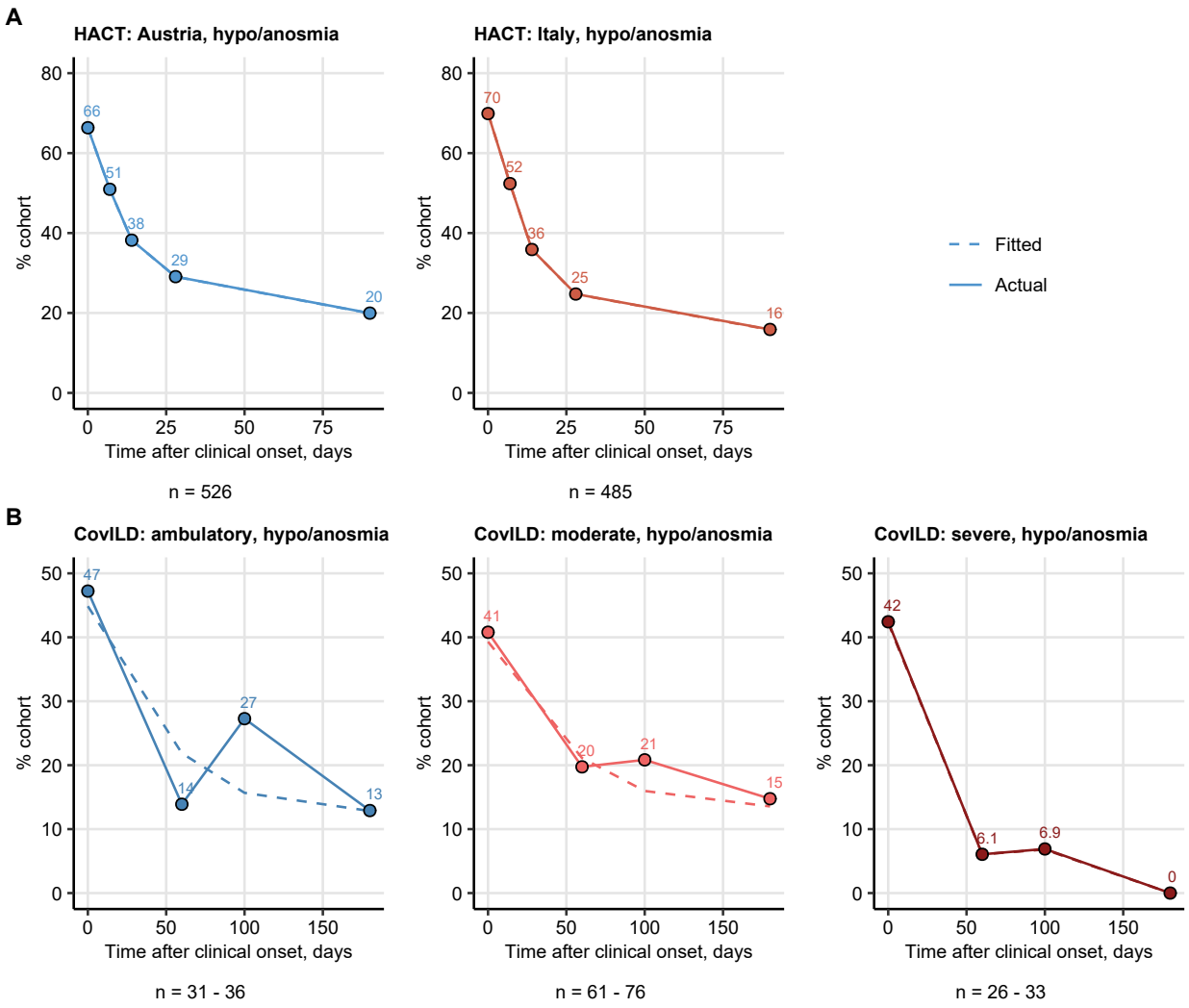

Figure 3: Actual and predicted frequency of self-reported hyposmia in course of COVID-19 recovery.

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Frequency of self-reported hyposmia during acute COVID-19 and recovery in the HACT study (**A**, 0, 7, 14, 28 and 90 days post symptom onset) and severity subsets of the CovILD cohorts (**B**, acute COVID: 0, 60-, 100 and 180-day follow-up visits) was modeled with mixed-effect logistic regression (**Supplementary Table S2**). Points and solid lines represent the actual frequencies. The model predictions are displayed as dashed lines. The ranges of complete observations per time point are shown under the plots.

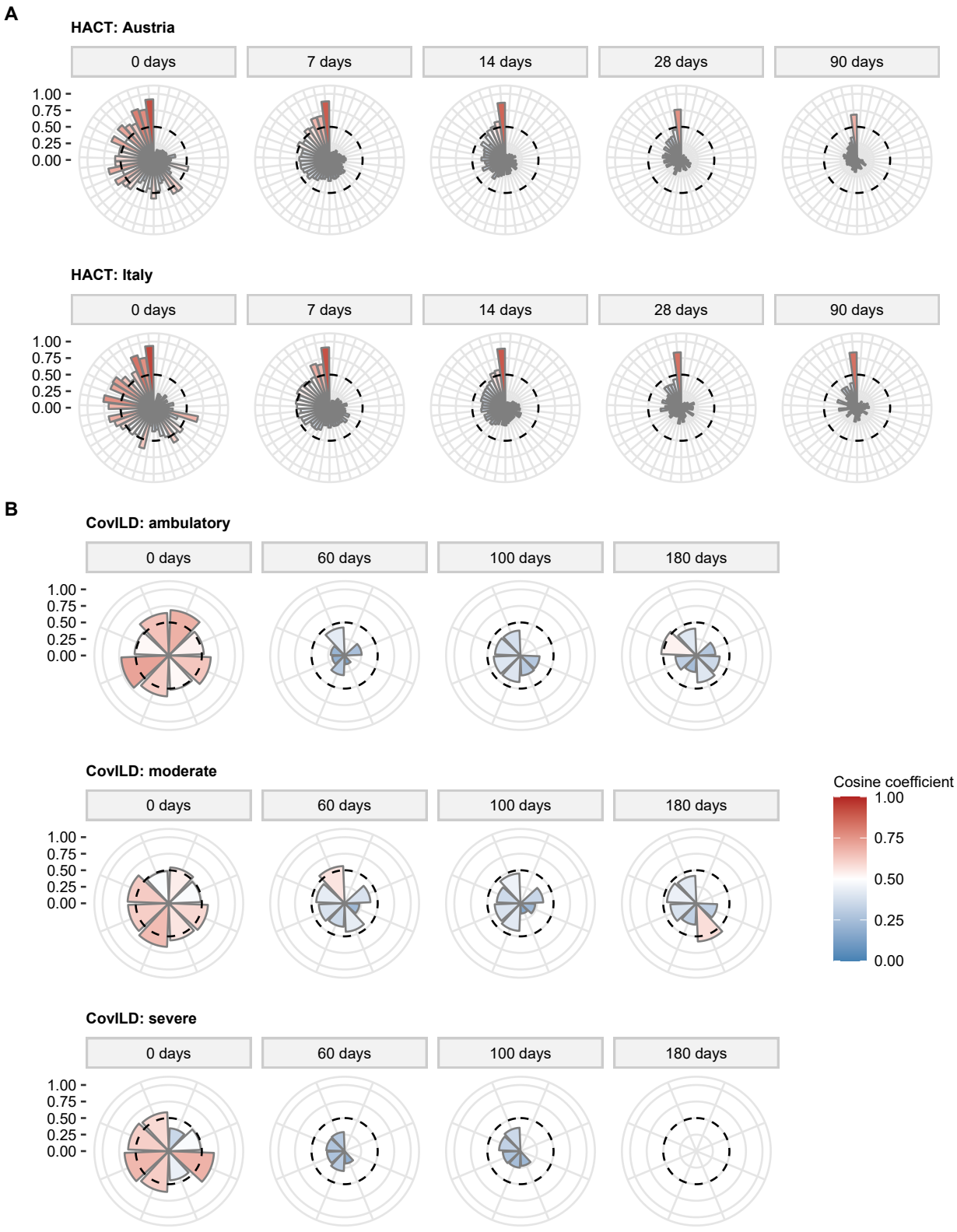

Figure 4: Co-occurrence of self-reported hyposmia and other symptoms in course of COVID-19 recovery.

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recovery.

Cosine similarity coefficients between hyposmia and other self-reported symptoms of COVID-19 in the HACT (**A**, 44 symptoms in total, Austria: n = 526, Italy: 485) and COVILD study (**B**, 9 symptoms, ambulatory: n = 36, moderate: n = 76, severe COVID-19: 33) were calculated for the indicated time points (**Supplementary Table S3**) and presented in radial plots. Each bar represents a single symptom. Bar length and color code for the value of Cosine similarity coefficient. Dashed lines represent cosine similarity coefficient of 0.5.

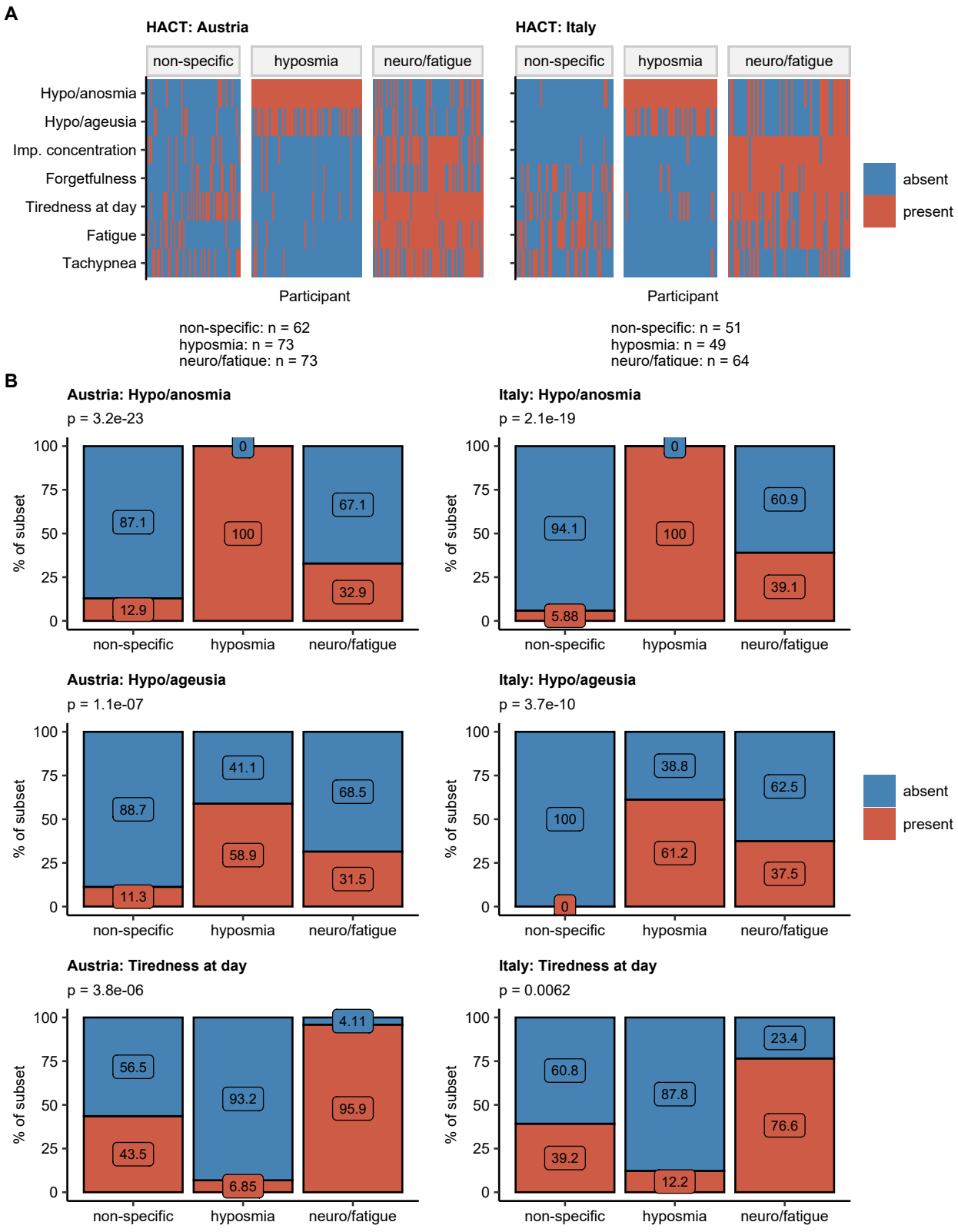

Figure 5: Long-term COVID-19 recovery phenotypes in the HACT study.

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HACT participants with COVID-19 symptoms present for at least three months post clinical onset (Austria: n = 208, Italy: n = 164) were clustered in respect to manifestations present in at least 25% of the cohort for 28 days or longer with a combined algorithm employing self-organizing map (4×4 hexagonal units, Jaccard distance) and hierarchical clustering (Ward D2 algorithm, Euclidean distance). Numbers of individuals assigned to particular clusters are presented under the plot in (**A**). Imp.: impaired.

(**A**) Presence of the features used for cluster definition in the participants assigned to the 'non-specific', 'hyposmia' and 'neuro/fatigue' subset.

(**B**) Frequency of self-reported hyposmia, taste disorders and tiredness at day in the participant subsets. Statistical significance of the frequency differences was assessed with χ^2 test corrected for multiple comparisons with Benjamini-Hochberg method. P values are presented in the plot captions.

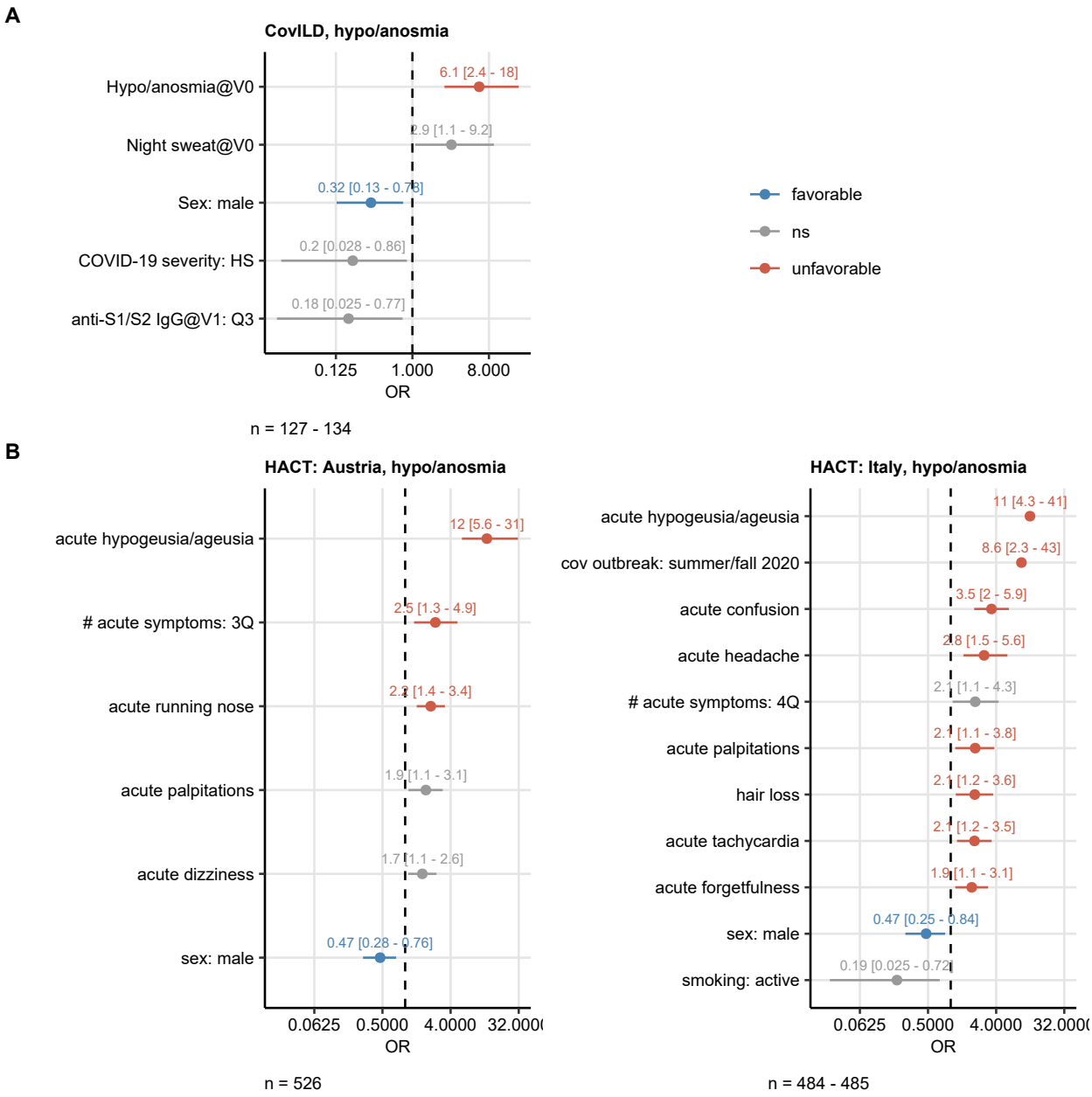

Figure 6: Risk factors for long-term persistent self-reported post-COVID-19 hyposmia.

Figure 6. Risk factors for long-term persistent self-reported post-COVID-19 hyposmia.

Association of candidate risk factors (**Supplementary Table S1**) with long-term persistent self-reported hyposmia in the CovILD (**A**, hyposmia declared at the 100-day follow-up visit) and HACT cohorts (**B**, self-reported hyposmia present for at least three months post clinical onset) was investigated with univariable logistic regression (**Suppmenetary Table S4**). For the HACT cohorts, the models were weighted for age and sex distribution in the general COVID-19 convalescent populations and included stratified the observation time variable as a confounder. Significance of model estimates (odds ratio, OR) was determined by Wald Z test corrected for multiple comparisons with Benjamini-Hochberg method. OR estimate values with 95% confidence intervals for significant and nearly significant (adjusted $p < 0.1$) co-variates are presented as points and whiskers in the Forest plots. The ranges of complete observations per time point are shown under the plots.