Hyposmia as a standalone persistent symptom of long COVID

Methods, Results, Figures and Tables

Health after COVID-19 in Tyrol study team

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Contents

Methods

Study design and approval

Data generated in the 'Health After COVID-19 in Tyrol' (HACT, ClinicalTrials.gov: NCT04661462) online survey[1,2] and in the longitudinal, multi-center cohort observation CovILD study CovILD study (ClnicalTrials.gov: NCT04416100, acute COVID-19 and 60-, 100- and 180-day post-COVID-19 follow-up data)[3–5] were re-analyzed in the current report. The studies were conducted in accordance with the Declaration of Helsinki and European Data Policy. The participant's data were analyzed in anonymized form. All participants gave digitally signed or written informed consent prior to enrollment. The study protocols were reviewed and approved by the institutional review boards of the Medical University of Innsbruck (HACT, Austria cohort, approval number: 1257/2020, CovILD: 1103/2020) and of the Autonomous Province of Bolzano - South Tyrol (HACT Italy cohort, approval number: 0150701).

The HACT study encompassed two independently recruited cohorts of ambulatory COVID-19 convalescents in the Tyrol state in Austria and the South Tyrol province in Italy. The study exclusion criterion was hospitalization because of COVID-19. The study inclusion criteria were laboratory-confirmed SARS-CoV-2 infection (PCR or seropositivity), adult age (Austria: $\geq$ 16 years, Italy: $\geq$ 18 years) and residence in the study regions.[1,2] The analysis inclusion criterion was a minimal observation time of 90 days between the positive SARS-CoV-2 test and the survey completion (**Figure 1**). A total of 1011 questionnaires was eligible for the current analysis (Austria: n = 526, Italy: 485).

The CovILD cohort consists of longitudinally investigated multi-center collective of convalescents of ambulatory (WHO categories 1 - 3, n = 36), moderate (WHO categories 4 - 5, n = 76) and severe COVID-19 (WHO categories 6 - 9, n = 33) recruited at the Department of Internal Medicine II at the Medical University of Innsbruck (Austria), St. Vinzenz Hospital in Zams (Austria) and the acute rehabilitation facility in Muenster (Austria) (**Figure 1**).[3–5]

Procedures and definitions

In the HACT study, the duration classes of 44 symptoms of COVID-19 were surveyed ('absent', 'present for 1 - 3 days', 'present for up to 1 week', 'present for up to 2 weeks', 'present for up to 3 months', 'present for up to 6 months' or 'present for more than 6 months') and duration of individual symptoms was calculated.[1] In the CovILD study, 9 self-reported symptoms were surveyed at each follow-up visit.[4] For both studies, detailed characteristic of demography, socioeconomic status, medical history before COVID-19 as well as the disease course and recovery was recorded as described.[1–5] The full list of the variables available for the current analysis is provided in **Supplementary Table S1**.

Self-reported symptoms were classified as acute when present for $\geq$ 14 days, persistent when present $\geq$ 28 days and long-term persistent complaints when lasting for $\geq$ 3 months post clinical onset (HACT) or present at the 100-day follow-up visit (CovILD). Numeric variables (symptoms, anti-SARS-CoV-2 S1/S2 antibody titers) were stratified by quartiles, laboratory parameters recorded during the CovILD visits were binarized with standard cutoffs as described.[1–5] Assessment of hyposmia by the sniffing stick test, lung CT imaging and lung function measurements were conducted as reported before.[3–5] Details on study variables and their stratification are provided in **Supplementary Methods** and **Supplementary Table S1**.

Statistical analysis

Statistical analysis was performed with R 4.0.5.[6–8] Statistical significance for differences in numeric variables between analysis groups as determined by Mann-Whitney U and Kruskal-Wallis test, as appropriate. Statistical significance for differences in frequency of categorical variables was assessed by χ^2 test. Concordance between self-reported hyposmia and the results of sniffing stick test was measured with Cohen's κ statistic.[9] Overlap between symptoms was expressed as cosine similarity coefficient.[10] Modeling of symptom resolution

was accomplished by mixed-effect second-order logistic regression (random effect of the individual); model term and odds ratio estimate significances were assessed by likelihood ratio and Wald Z test, respectively.[11–13] Clustering of the HACT study participants in respect to long-term persistent symptoms was done with a combined self-organizing map and hierarchical clustering approach.[2,14–16] Univariable modeling of long-term persistent hyposmia risk was done with a series of logistic regression models. In the HACT study, the risk models included age and sex weights and the stratified diagnosis - survey time as a confounder.[1,2] Statistical testing results were corrected for multiple testing with Benjamini-Hochberg method.[17] Details of the statistical analysis are provided in **Supplementary Methods**.

Data availability

The study data is available at reasonable request to the corresponding authors. The source code of the R analysis pipeline is available at GitHub (https://github.com/PiotrTymoszuk/hyposmia_analsis_pipeline).

Results

Characteristic of the study collective

Post-COVID-19 hyposmia is a long-term persistent symptom

In order to delineate the recovery kinetics, overlap of hyposmia and other COVID-19 symptoms and risk factors for delayed long-term post-COVID-19 olfactory disorders, we first re-analyzed data gathered in the population of ambulatory COVID-19 convalescents enrolled in the bi-national 'Health After COVID-19 in Tyrol' study (HACT).[1,2] By means of mixed-effect logistic modeling of the recovery curves[13] for 44 COVID-19-related complaints (**Supplementary Table S2**) gauged by the online HACT survey,[1] we identified a set of symptoms characterized by a highly significant second-order time term suggestive of strong 'plateauing' effect and hence a substantial chronicity potential. This set of candidate chronic manifestations was highly consistent in both Austria and Italy HACT cohorts and included among others headache, muscle and joint pain, tiredness and fatigue as well as olfactory and taste disorders (**Figure 2A**, **Supplementary Figure S1**, **Supplementary Table S2**). Among them, tiredness, fatigue and self-reported hyposmia were the symptoms with the longest median recovery times (14 days) still present in at least 25% of the participants beyond 28 days post clinical onset (**Figure 2B**). Of note, whereas the duration of non-specific infection symptoms like fever or shivering in course of COVID-19 was virtually limited to the first two weeks of the disease (**Supplementary Figure S2**), fatigue, tiredness and taste disorders were still present in more than 10% the Austria or Italy HACT cohort 3 months post clinical onset (**Supplementary Figure S3**). Importantly, an analogically retarded recovery was observed for self-declared hyposmia in these collectives (**Figure 3A**). To explore, if a similar hyposmia kinetic may be observed in individuals hospitalized during acute COVID-19, we resorted to the longitudinally investigated CovILD cohort.[3–5] Surprisingly, self-reported smell disorders displayed nearly complete resolution in the subset of severe COVID-19 survivors (WHO class 6 - 9) within 180 days post COVID-19 diagnosis. However, this disease symptom was still reported by 13 to 15% of ambulatory (WHO class 1 - 3) and moderate (WHO class 4 - 6) COVID-19 patients at the 180-day follow-up (**Figure 3B**). Hence, hyposmia persisting beyond the contraction of the non-specific acute infection and acute upper airway symptoms belongs to the complaints most frequently declared by ambulatory and moderate COVID-19 convalescents.

Sniffing stick test detected hyposmia is far more frequent than self-reported olfactory disorders

Next, we sought to investigate the strike differences in self-perceived olfactory deficits between the survivors of severe, moderate and ambulatory COVID-19 in the CovILD cohort at the 100-day post-COVID-19 follow-up. As shown in **Supplementary Figure S4A**, the frequency of moderate-to-severe hyposmia defined by < 13 points in the 16-point sniffing stick test was way higher that the self-reported smell disorders. In particular, up to 44.4% of the severe COVID-19 survivors declaring no hyposmia, were affected by at least moderate olfactory impairment suggestive of a distorted symptom perception (**Supplementary Figure S4A**). Notably, the prevalence of severe hyposmia characterized by < 8 test points was detected only in a minute fraction of the participants (up to 10.4% in the moderate COVID-19 subset, **Supplementary Figure S4B**). In general, the concordance between the test-detected moderate-to-severe long-term hyposmia and the self-perceived symptom was fair for the moderate ($\kappa = 0.349$) and weak ($\kappa = 0.226$) for the severe COVID-19 convalescent subset.[9] No statistically valid overlap was observed for the severe COVID-19 survivors ($\kappa = 0.00567$) (**Supplementary Figure S4C**). Collectively, the true prevalence of hyposmia may be greatly underestimated by the patient's report, especially in severe COVID-19

Limited co-occurrence of hyposmia and other persistent symptoms in long-term COVID-19 recovery

As suggested by our previous report, isolated smell and/or taste disorders were sole long COVID symptoms in a substantial fraction of ambulatory COVID-19 convalescents.[1] In acute COVID-19, self-reported hyposmia co-occurred with numerous other manifestations in the HACT study cohorts (20 of 44 symptoms with cosine similarity coefficient > 0.5) and in the CovILD study (ambulatory: 8, moderate: 6, severe: 5 symptoms of 9 features surveyed with cosine similarity coefficient > 0.5) including non-specific infection symptoms such as fever, muscle and joint pain and fatigue or respiratory manifestations like tachy- and dyspnea (**Figure 4**, **Supplementary Table S3**). However, in course of recovery, the association with the majority of symtoms with faster resolution kinetic (**Figure 2**, **Supplementary Figure S1**) was lost and solely self-reported taste disorders showed moderate co-occurrence (cosine similarity coefficient > 0.5) with self-reported hyposmia in the HACT cohort (**Figure 4A**, Supplementary Figure S4A). In the ambulatory and moderate COVID-19 subsets of the CovILD study, such moderate association could by discerned only for dyspnea (ambulatory) and pain (moderate) at the 180-day follow-up (**Figure 4B**, Supplementary Figure S4B).

Of interest, two other highly persistent symptoms frequently reported during the long-term COVID-19 recovery: fatigue and tiredness (**Figure 2**, **Supplementary Figure S1** and **S3**) demonstrated only a weak-to-fair co-existence with self-reported hyposmia in the HACT (90-day Austria, fatigue: cosine similarity = 0.28, tiredness: 0.35, Italy, fatigue: cosine similarity = 0.28, tiredness: 0.38) and CovILD study (100-day follow-up, fatigue, ambulatory: cosine similarity = 0.4, moderate: 0.42) (Supplementary Figure S4).

To corroborate this hypothesis we resorted to an association analysis of the HACT participants with long-term persisting COVID-19 symptoms beyond 3 months post clinical disease onset in respect to the most frequent long COVID manifestations (present in at least 25% of the participants at ≥ 28 days post symptom onset: impaired concentration, tachypnea, hypogeusia, hyposmia, fatigue, tiredness and forgetfulness) (**Figure 2B**). By applying a combined self-organizing map and hierarchical clustering algorithm,[2,14,15] three subsets of the participants could be discerned, further referred to as 'non-specific', 'hyposmia' and 'neuro/fatigue' clusters (**Figure 5A**, **Supplementary Figure S5**). The hyposmia cluster comprising approximately one-third of the individuals affected by the highly protracted COVID-19 recovery (Austria: 35.1%, Italy: 29.9%) was characterized by a 100% prevalence and of self-reported hyposmia, approximately 60% frequency od taste disorders and, remarkably, by minimal occurrence of other symptoms (up to 12.2% for tiredness) (**Figure 5B**). In summary, the results of the overlap and association analyses strongly suggest that in the late course of COVID-19 recovery, self-reported hyposmia may pose the sole protracted disease symptom occurring independently of post-COVID-19 fatigue, tiredness, memory and concentration deficits.

Male sex is associated with lower risk of persistent long-term hyposmia

Finally, we intended to find demographic and clinical features identifiable during acute disease and early recovery which correlate with the risk of development of long-term persistent hyposmia present for 3 months or longer post clinical COVID-19 onset. By means of logistic risk modeling, hyposmia and taste disorders in the course of acute COVID-19 were identified as the strongest correlates of the long-term hyposmia risk (**Figure 6**). Furthermore, in the HACT study, highly poly-symptomatic acute disease (50 - 100$^{\text{th}}$ symptom count percentile) was linked to a substantially higher protracted hyposmia risk. As demonstrated above (**Figure 3B**), severe acute COVID-19 was associated with an 80% lower risk of hyposmia present at the 100-day follow-up in the CovILD cohort, however, this effect was not significant when adjusted for multiple testing (**Figure 6A**). Of note, independently of the investigated study, male sex was a significant favorable co-variate associated with over 50% lower risk of long-term hyposmia (**Figure 6**).

A more detailed investigation and modeling of recovery from post-COVID-19 hyposmia in female and male participants of the HACT study revealed no significant differences in pace of the resolution and comparable 'plateauing' effect between the sex strata in both the Austria and Italy cohort (**Supplementary Figure S7AB**). Furthermore, no differences in the median recovery time in females and males suffering from olfactory deficits during acute COVID-19 could be observed (**Supplementary Figure S7C**). Instead, the prevalence of hyposmia during acute COVID-19 was significantly higher in females than in males in both HACT cohorts

(χ^2 test; Austria, females: 75.7%, males: 48.6%, p = 8.4×10^{-10}; Italy, females: 74.9%, males: 58.7%, p = 4.6×10^{-4}) (**Supplementary Figure S7A**).

Tables

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

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
Endocrine or metabolic comorbidity	22.2% (8) n = 36	48.7% (37) n = 76	54.5% (18) n = 33	χ^2	p = 0.014
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

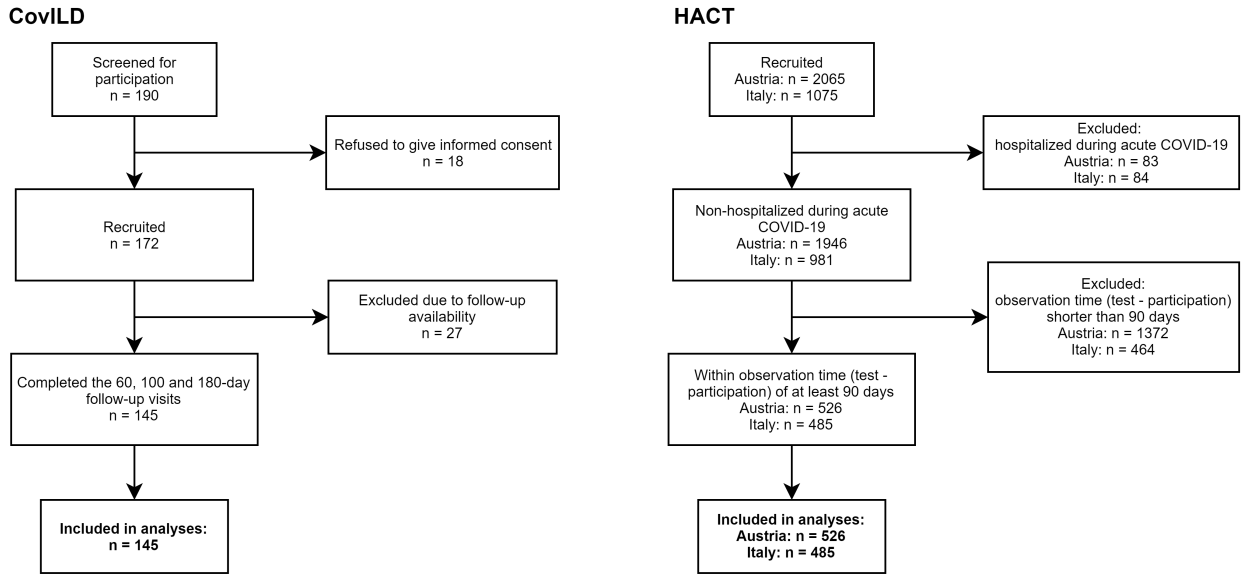

Figure 1: CONSORT flow diagrams for the CoVILD and HACT study cohorts.

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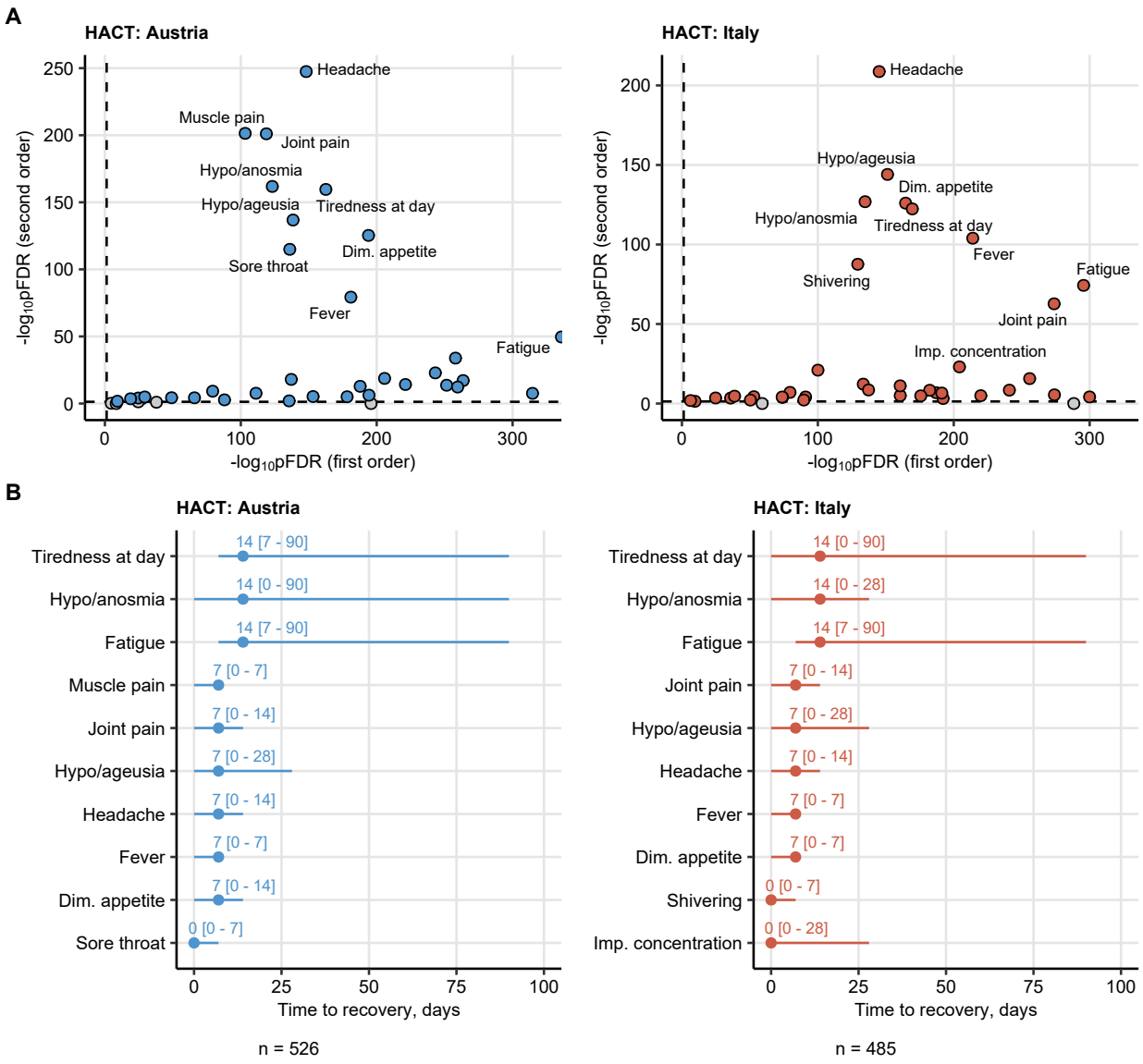

Figure 2: Second order kinetic modeling of symptom recovery course in the HACT study.

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

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.

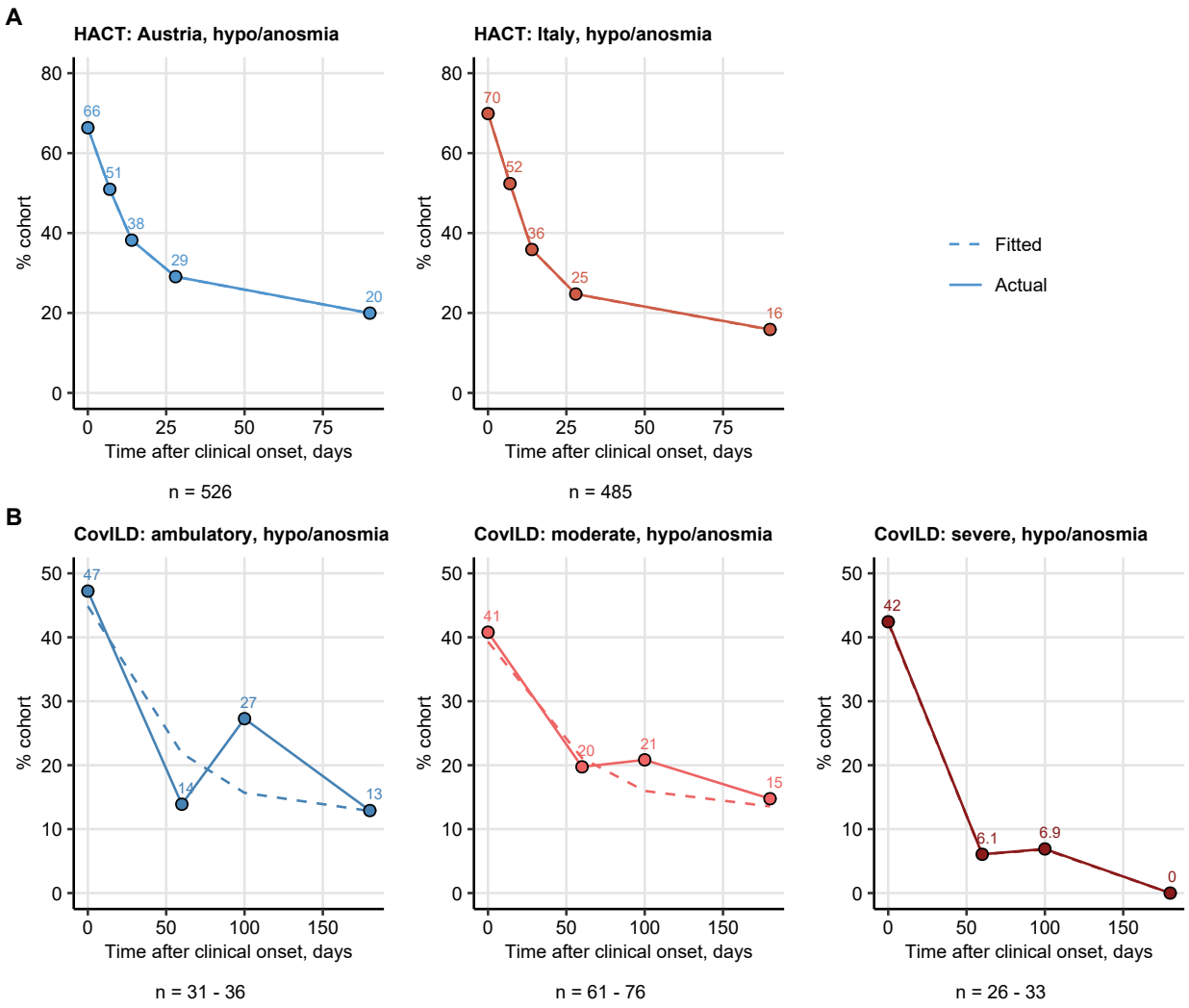

Figure 3: Actual and predicted frequency of self-reported hyposmia in course of COVID-19 recovery.

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

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.

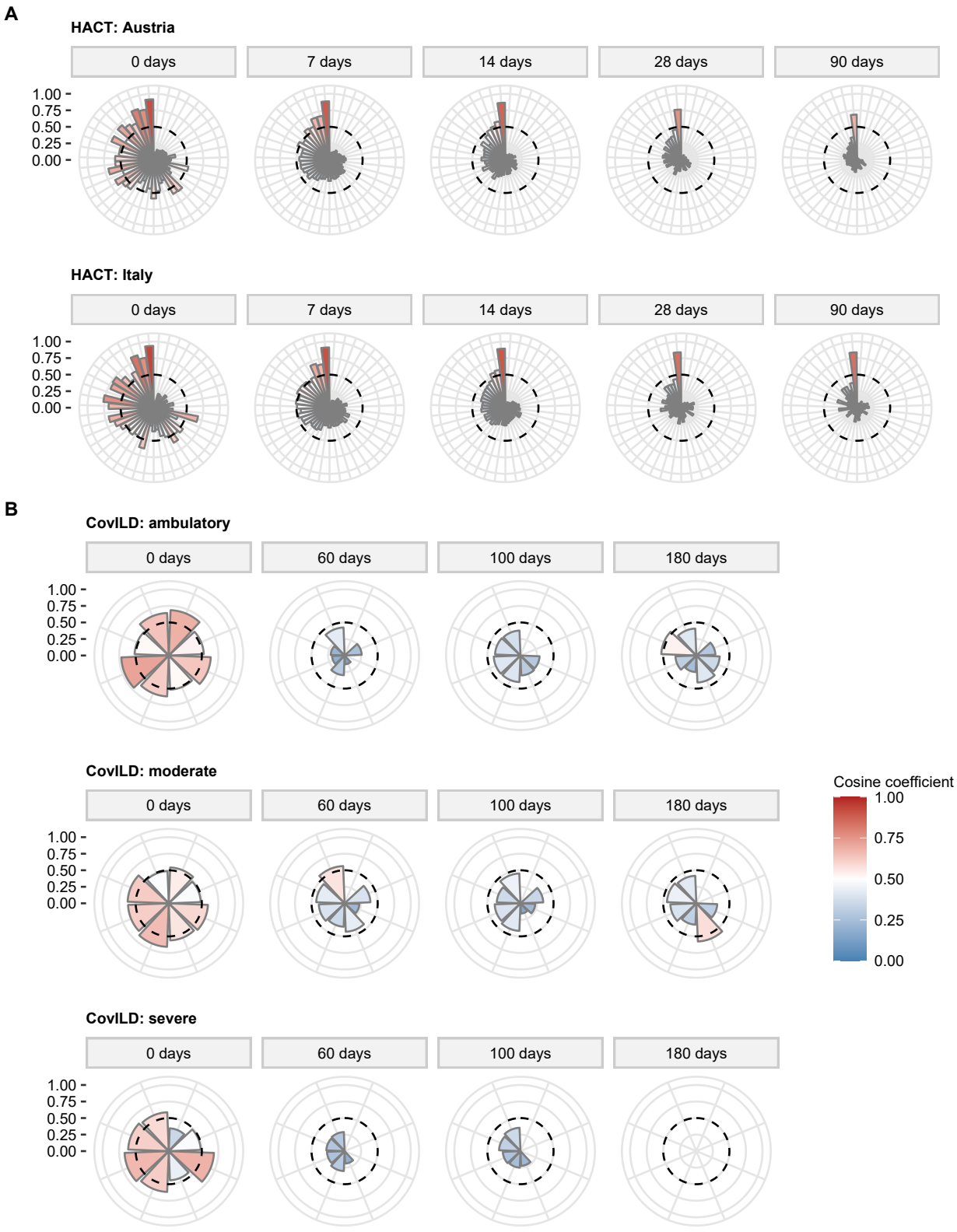

Figure 4: Co-occurrence of self-reported hyposmia and other symptoms in course of COVID-19 recovery.

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

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.

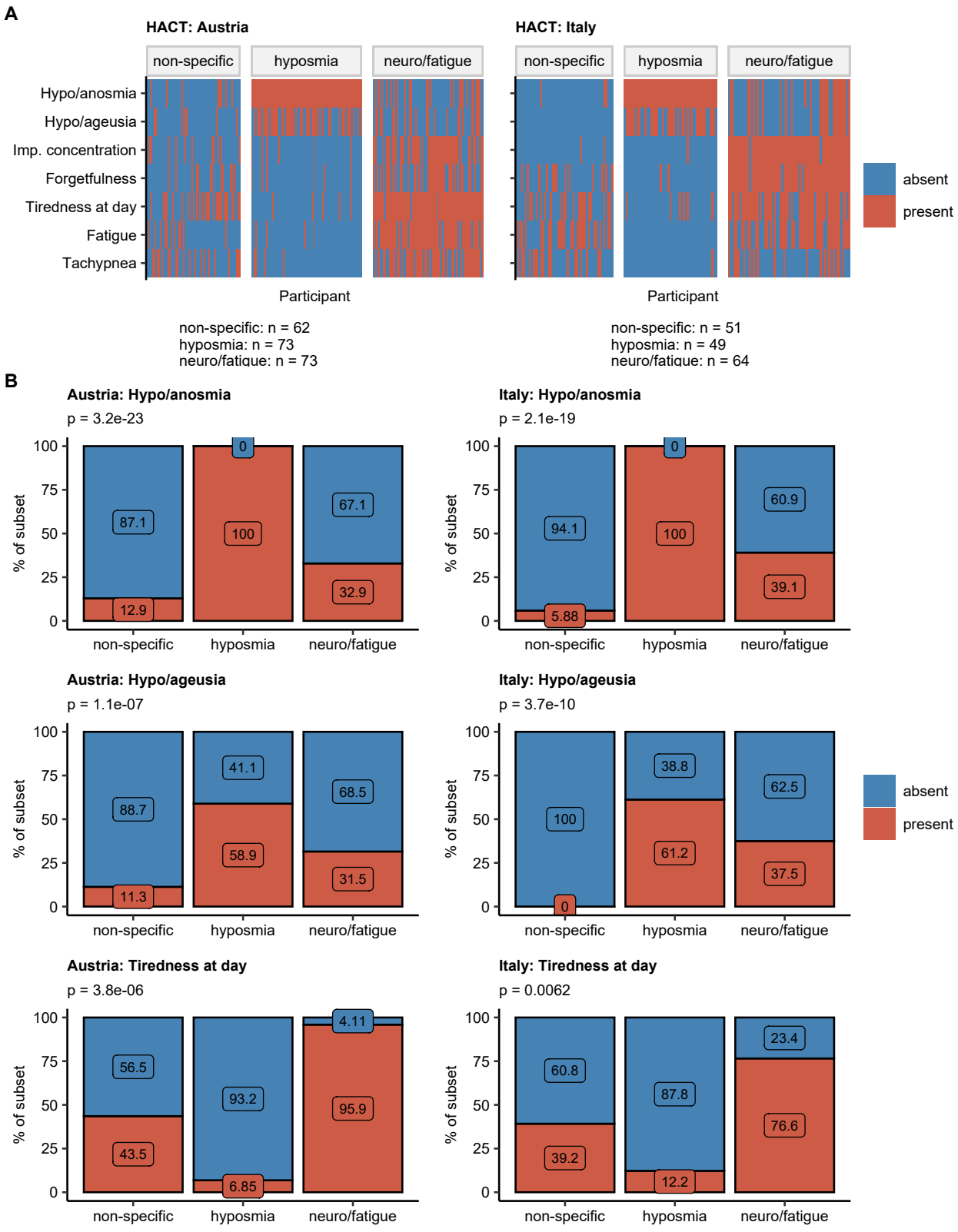

Figure 5: Long-term COVID-19 recovery phenotypes in the HACT study.

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

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.

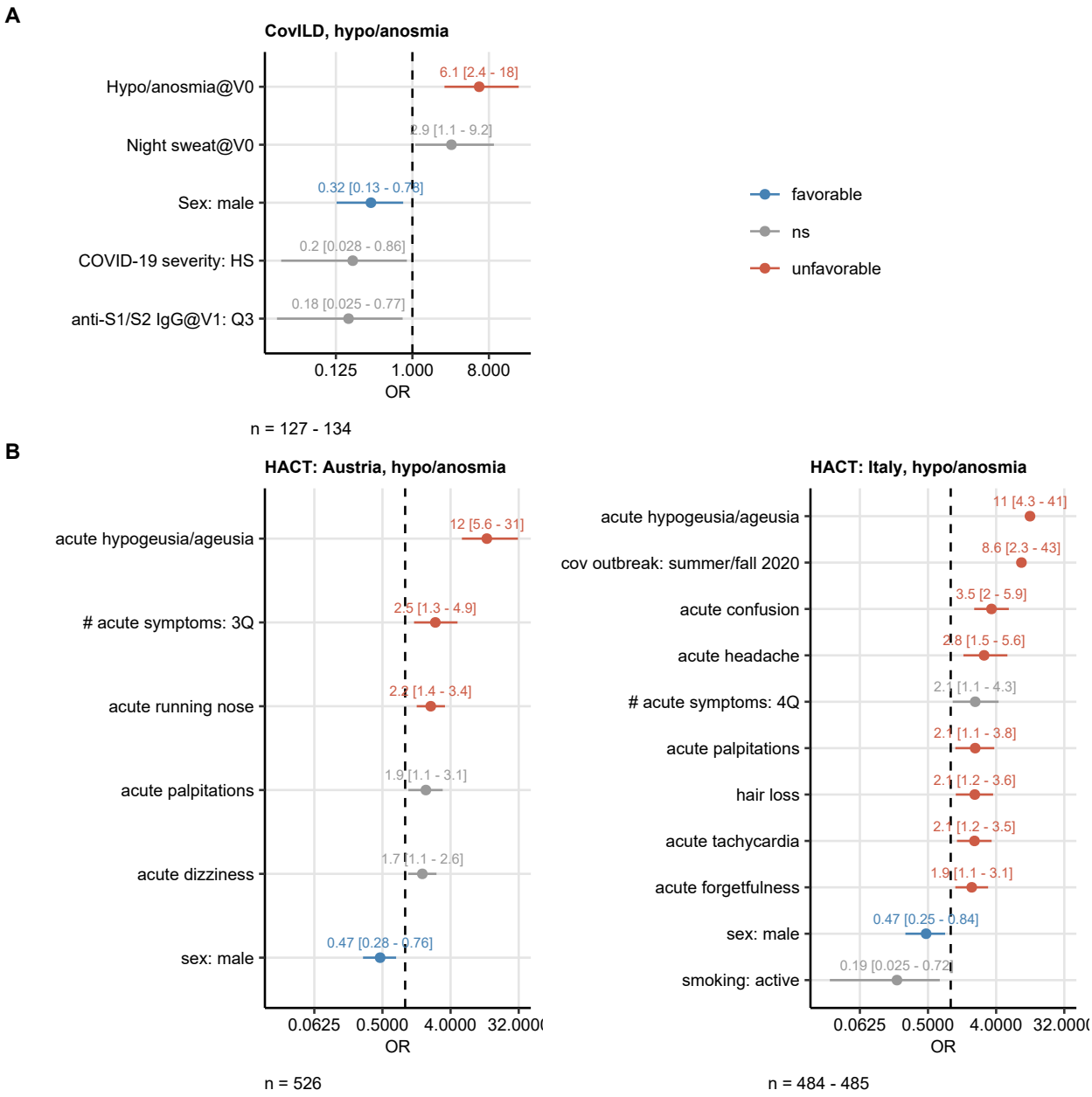

Figure 6: Risk factors for long-term persistent self-reported post-COVID-19 hyposmia.

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.

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