UNIVERSITÄTSMEDIZIN HALLE

Medizinische Fakultät der Martin-Luther-Universität Halle-Wittenberg

The Role of SARS-CoV-2 Variant in Post-COVID Recovery: Results from a Population-Based Cohort Study

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September 25, 2024

WCE WORLD CONGRESS OF EPIDEMIOLOGY 2024

Outline

- **Background**
  - **The DigiHero study**
  - What is Post-COVID?
  - Risk factors for Post-COVID
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  - Proportion recovered
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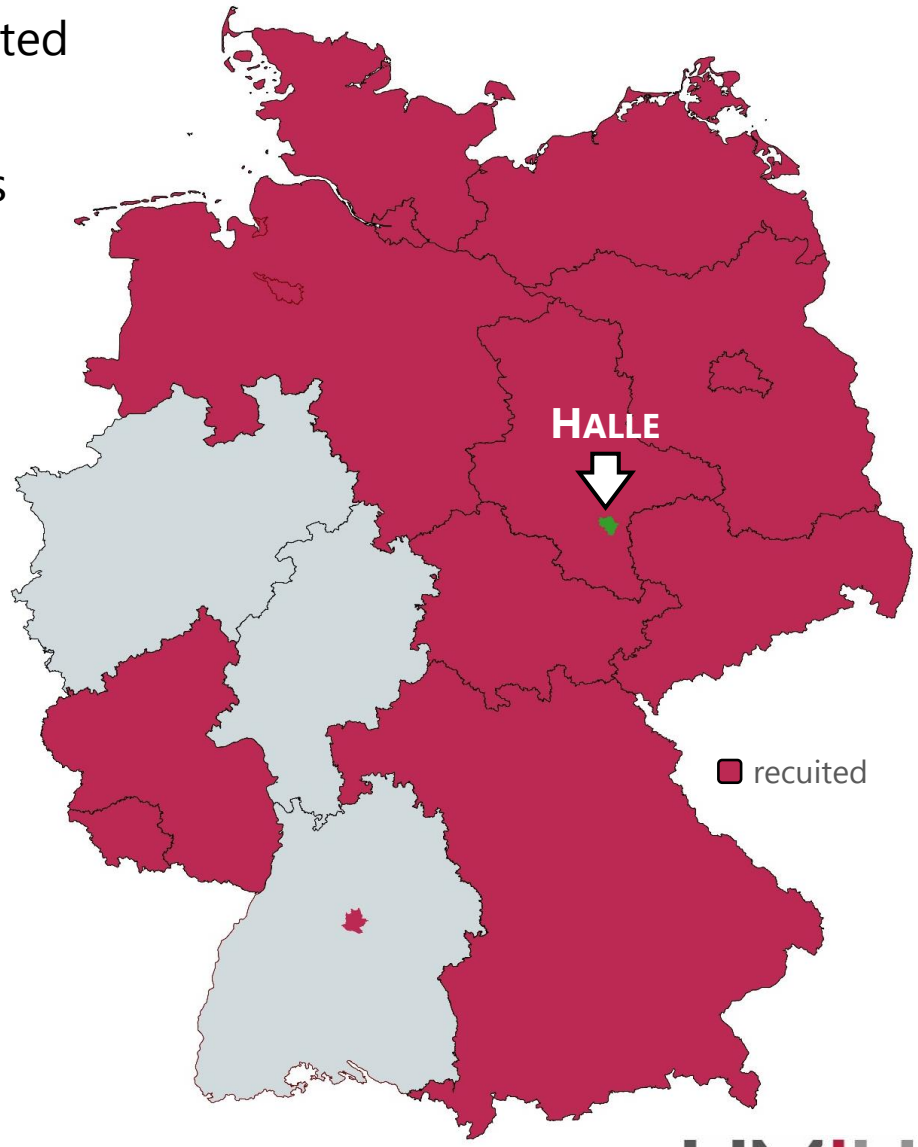
Study for Digital Health Research in Germany (DigiHero)

- Population-based prospective cohort study, initiated in Halle (Germany)
- By now over 90.000 people from 14 federal states have been recruited
- Online surveys
  - Baseline: Sociodemographic factors
  - Surveys on specific topics

  → Late symptoms after COVID-19

  → initiation of a **Post COVID-registry**



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STUDY FOR DIGITAL HEALTH RESEARCH IN GERMANY (DIGIHERO)

WCE WORLD CONGRESS OF EPIDEMIOLOGY 2024

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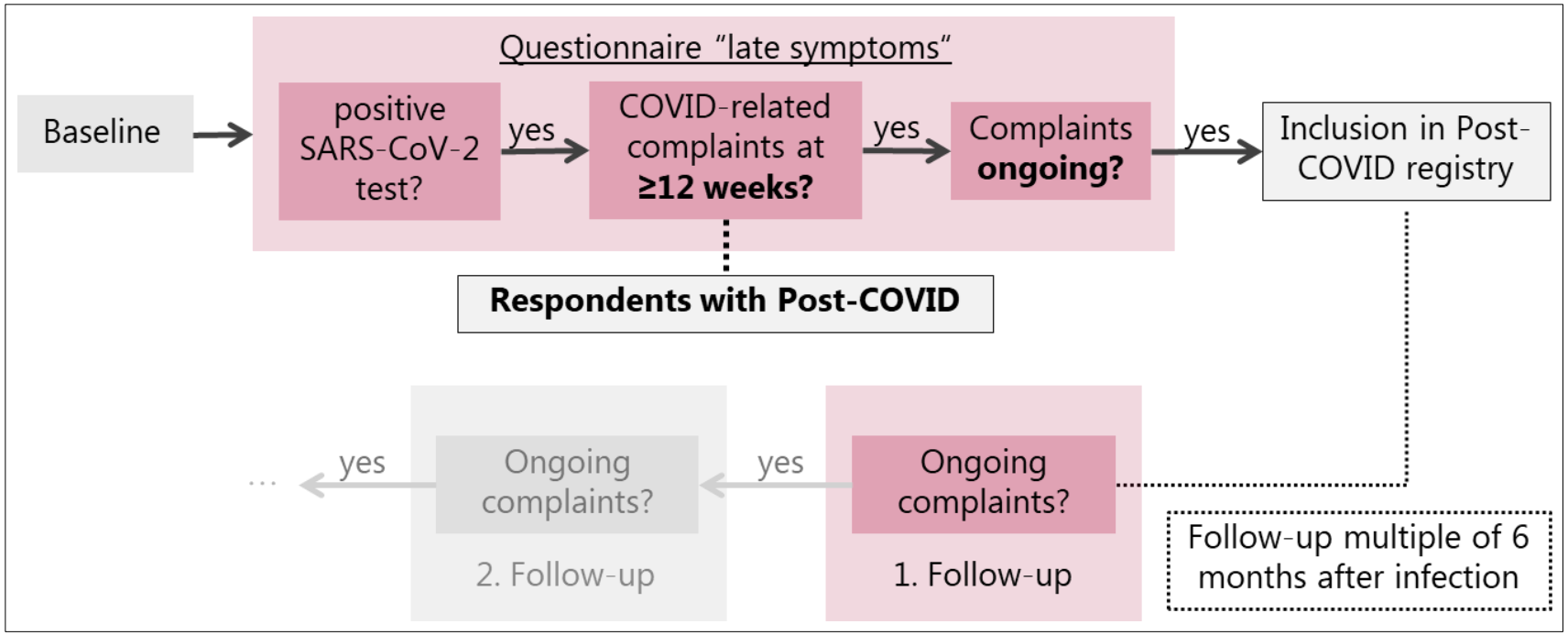

UMH

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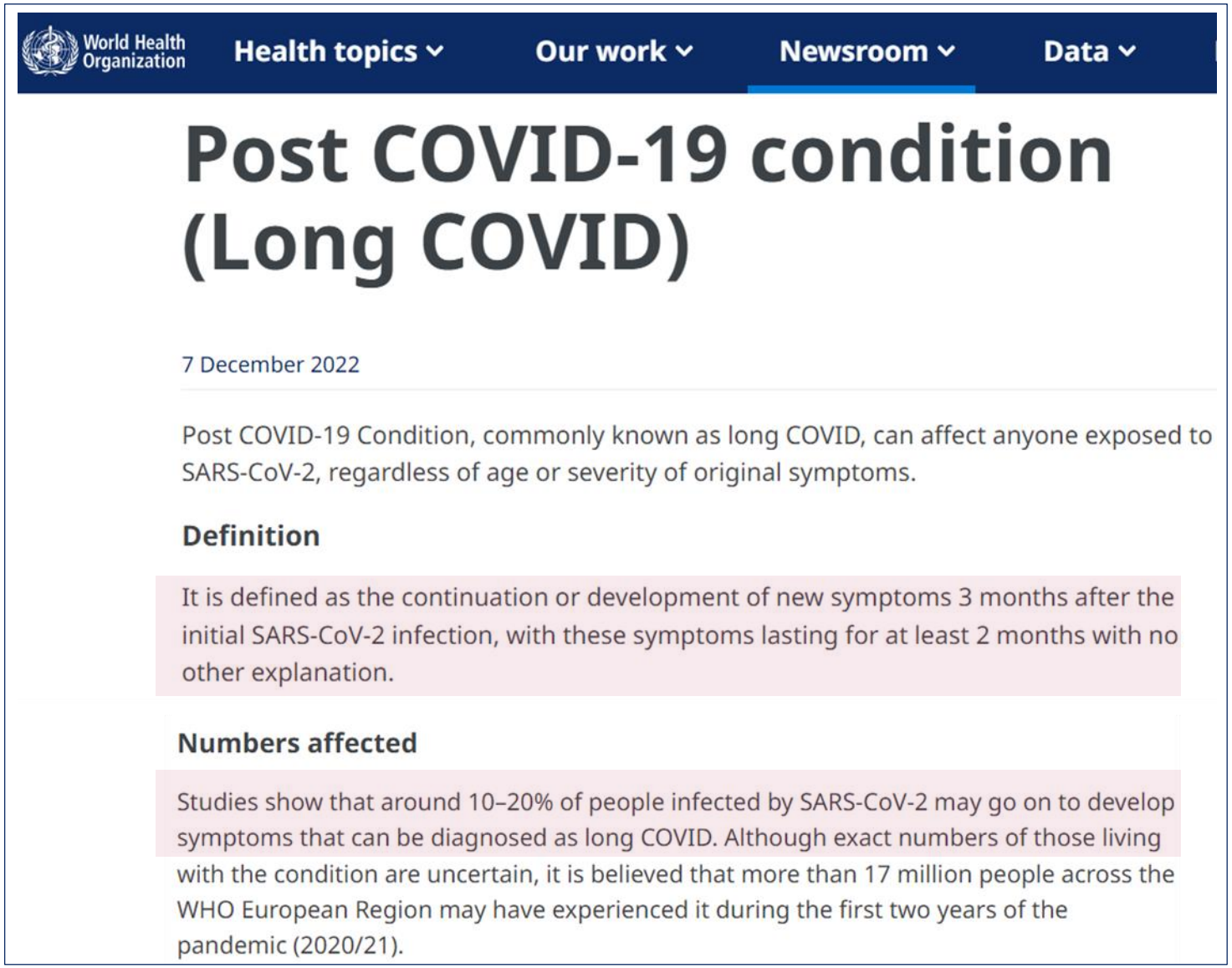
WHAT IS POST-COVID?



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Post COVID-19 condition (Long COVID)

7 December 2022

Post COVID-19 Condition, commonly known as long COVID, can affect anyone exposed to SARS-CoV-2, regardless of age or severity of original symptoms.

Definition

It is defined as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation.

Numbers affected

Studies show that around 10–20% of people infected by SARS-CoV-2 may go on to develop symptoms that can be diagnosed as long COVID. Although exact numbers of those living with the condition are uncertain, it is believed that more than 17 million people across the WHO European Region may have experienced it during the first two years of the pandemic (2020/21).

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RISK FACTORS FOR POST-COVID

WCE WORLD CONGRESS OF EPIDEMIOLOGY 2024

JAMA Internal Medicine | Original Investigation

Risk Factors Associated With Post–COVID-19 Condition
A Systematic Review and Meta-analysis

Vasiliki Tsampasian, MD, MSc; Hussein Elghazaly, MBBS; Rahul Chattopadhyay, MBBS, MSc; Maciej Debski, MD, PhD; Thin Kyi Phyu Naing, MBBS; Pankaj Garg, PhD; Allan Clark, PhD; Eleana Ntatsaki, MD(Res), MA; Vassilios S. Vassiliou, MBBS, PhD

RESULTS The initial search yielded 5334 records of which 255 articles underwent full-text evaluation, which identified 41 articles and a total of 860 783 patients that were included. The findings of the meta-analysis showed that female sex (OR, 1.56; 95% CI, 1.41-1.73), age (OR, 1.21; 95% CI, 1.11-1.33), high BMI (OR, 1.15; 95% CI, 1.08-1.23), and smoking (OR, 1.10; 95% CI, 1.07-1.13) were associated with an increased risk of developing PCC. In addition, the presence of comorbidities and previous hospitalization or ICU admission were found to be associated with high risk of PCC (OR, 2.48; 95% CI, 1.97-3.13 and OR, 2.37; 95% CI, 2.18-2.56, respectively). Patients who had been vaccinated against COVID-19 with 2 doses had a significantly lower risk of developing PCC compared with patients who were not vaccinated (OR, 0.57; 95% CI, 0.43-0.76).

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- Some more recent studys could not confirm a protective effect of vaccination for Post-COVID [3-9]
- Lower risk for Post-COVID for Omicron, compared to the earlier variants [3, 5, 8, 10-13]
- "Vaccination was strongly (negatively) associated with the post-COVID condition (⋯), however, the association was not present in the multivariate model, which included virus types." [9]

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STUDY AIM

We investigated factors associated with Post-COVID recovery, focusing on virus variants and vaccination status.

- Some more recent studys could not confirm a protective effect of vaccination for Post-COVID [3-9]
- Lower risk for Post-COVID for Omicron, compared to the earlier variants [3, 5, 8, 10-13]
- "Vaccination was strongly (negatively) associated with the post-COVID condition (…), however, the association was not present in the multivariate model, which included virus types." [9]

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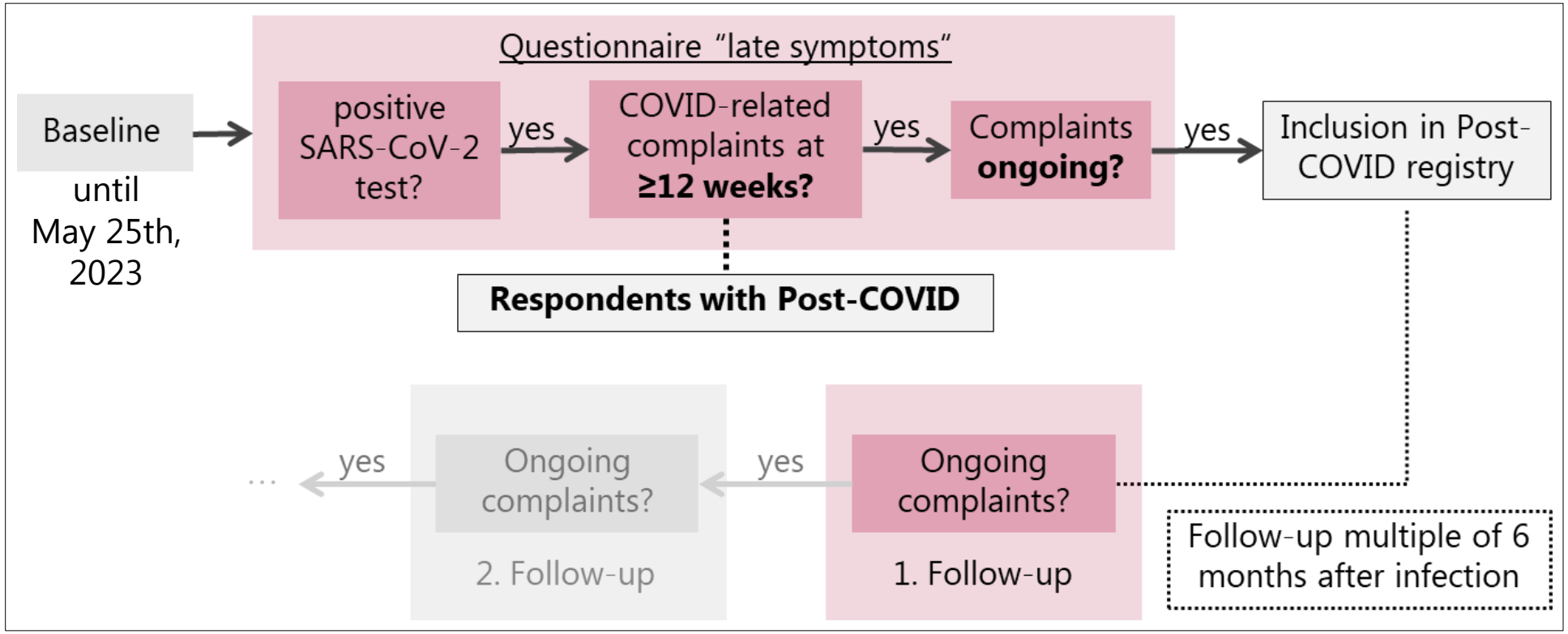
METHODS



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METHODS

- Descriptive analyses
- Illustration of „**proportion recovered**“ at different time-points post-infection (nonparametric maximum likelihood estimate)
- **Cox-regression for interval-censored data**
  → dependent variable: time to PCC-recovery
  1. including vaccination status, not variant
  2. including vaccination status, stratified by variant
  3. including variant, not vaccination status

  → Adjusted for: sex, age, income, education level
- Sensitivity analyses:
  1. including severity of acute course
  2. only considering those with at least one severe PCC-symptom

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DESCRIPTION OF THE STUDY SAMPLE

- **N = 4,529 respondents with Post-COVID** participated in baseline until May 25, 2023 and had complete information in relevant variables
- Most respondents are women (72.6%), the median age is 50 years (IQR =20)

RESPONDENT CHARACTERISTICS		N	%
Dominant virus variant at time of infection	SARS-CoV-2 wildtype	709	*15.7*
	Alpha	651	*14.4*
	Delta	605	*13.4*
	Omicron	2,564	*56.6*
COVID-19 vaccination status prior to infection	not vaccinated	1,593	*35.2*
	one dose	136	*3.0*
	two doses	692	*15.3*
	three or more doses	2,108	*46.5*
Information on Post-COVID-19 condition	recovered between 12 weeks & "late symptoms assessment"	1,346	*29.7*
	recovered between "late symptoms assessment" & follow-up	374	*8.3*
	right censored at "late symptoms assessment"	1,113	*24.6*
	right censored at follow-up	1,696	*37.4*

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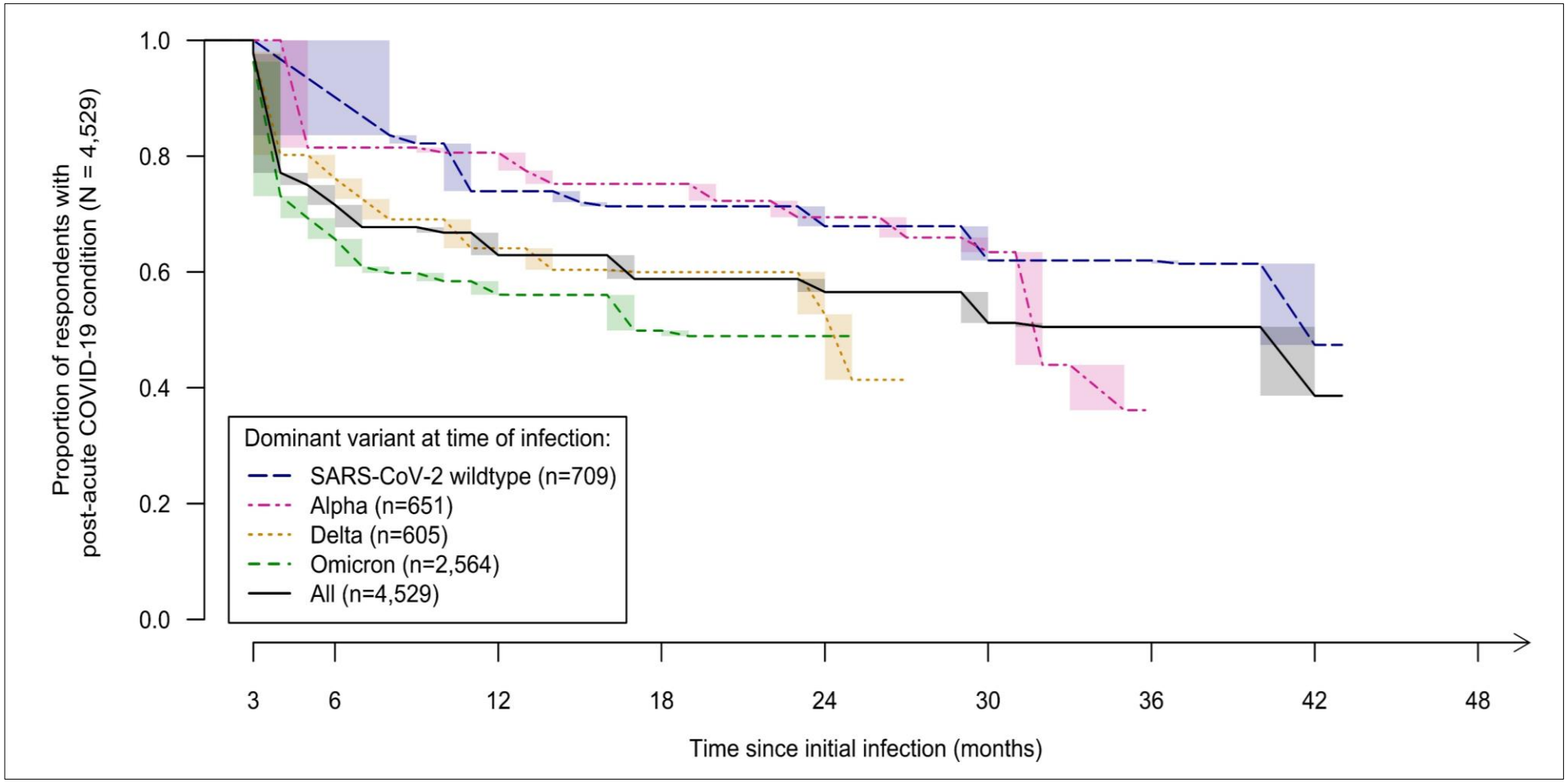
PROPORTION RECOVERED



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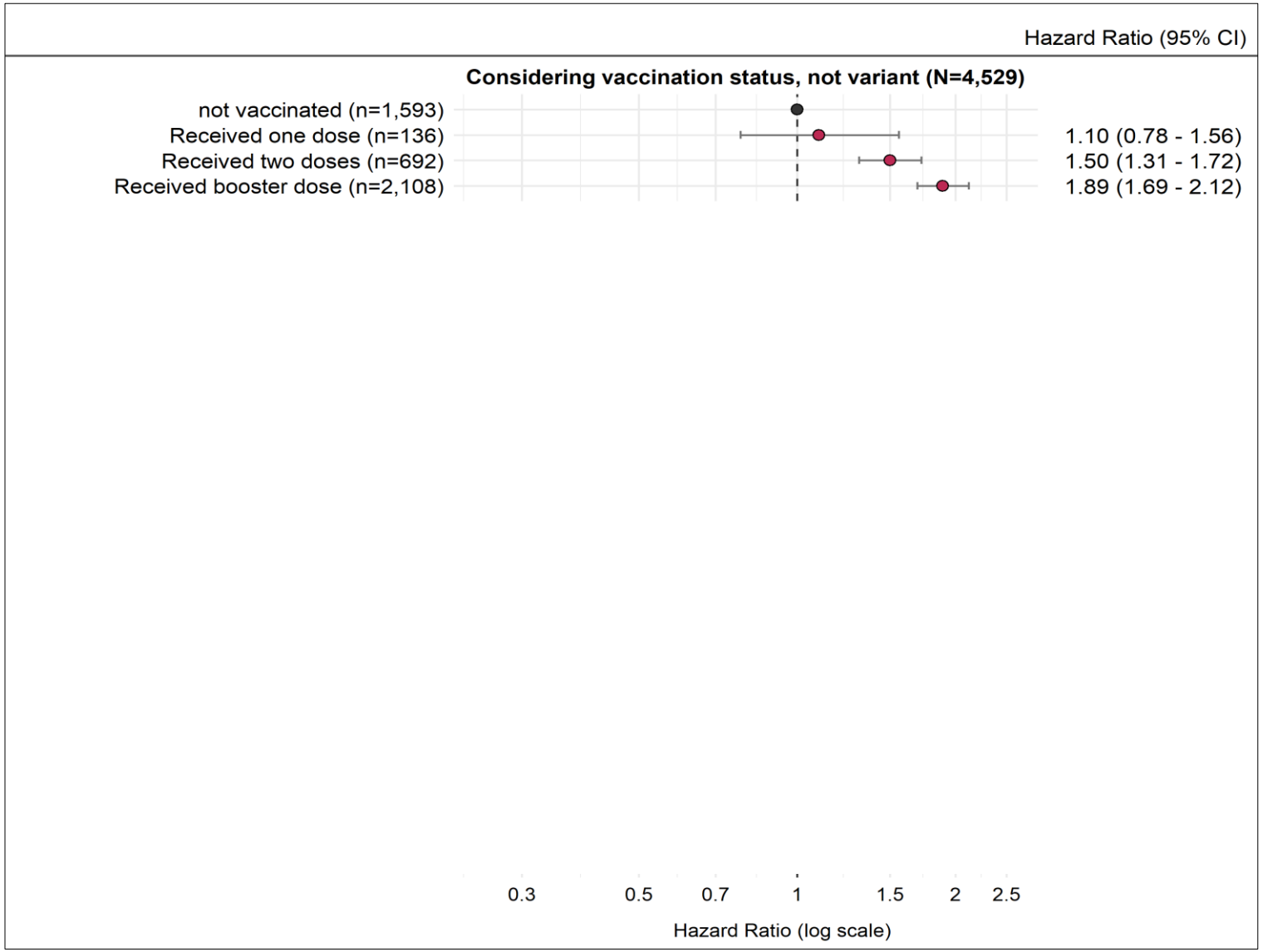
MULTIVARIABLE ANALYSIS OF TIME TO RECOVERY



Note. All analyses are adjusted for age, sex, net household income, and education level

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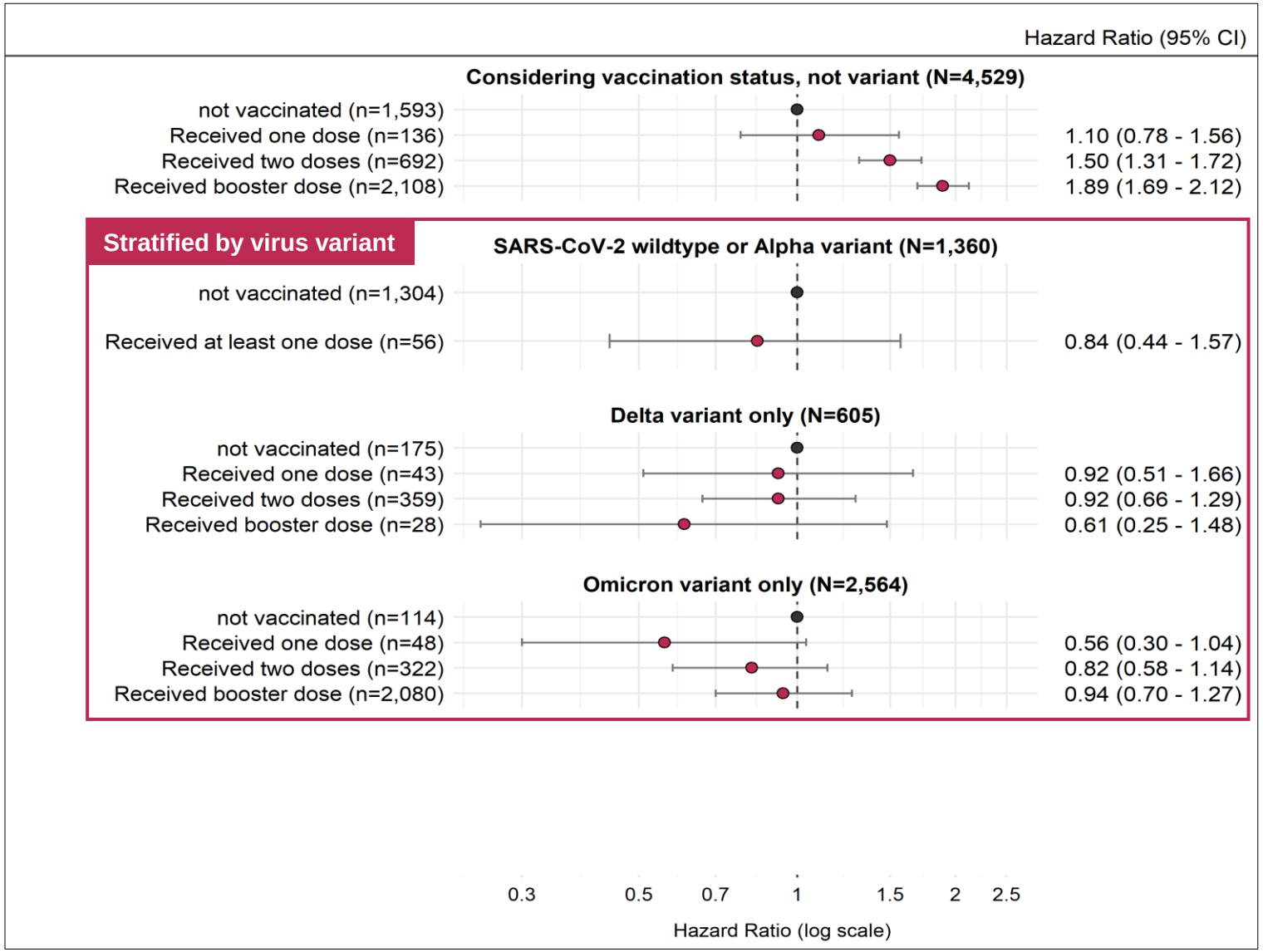

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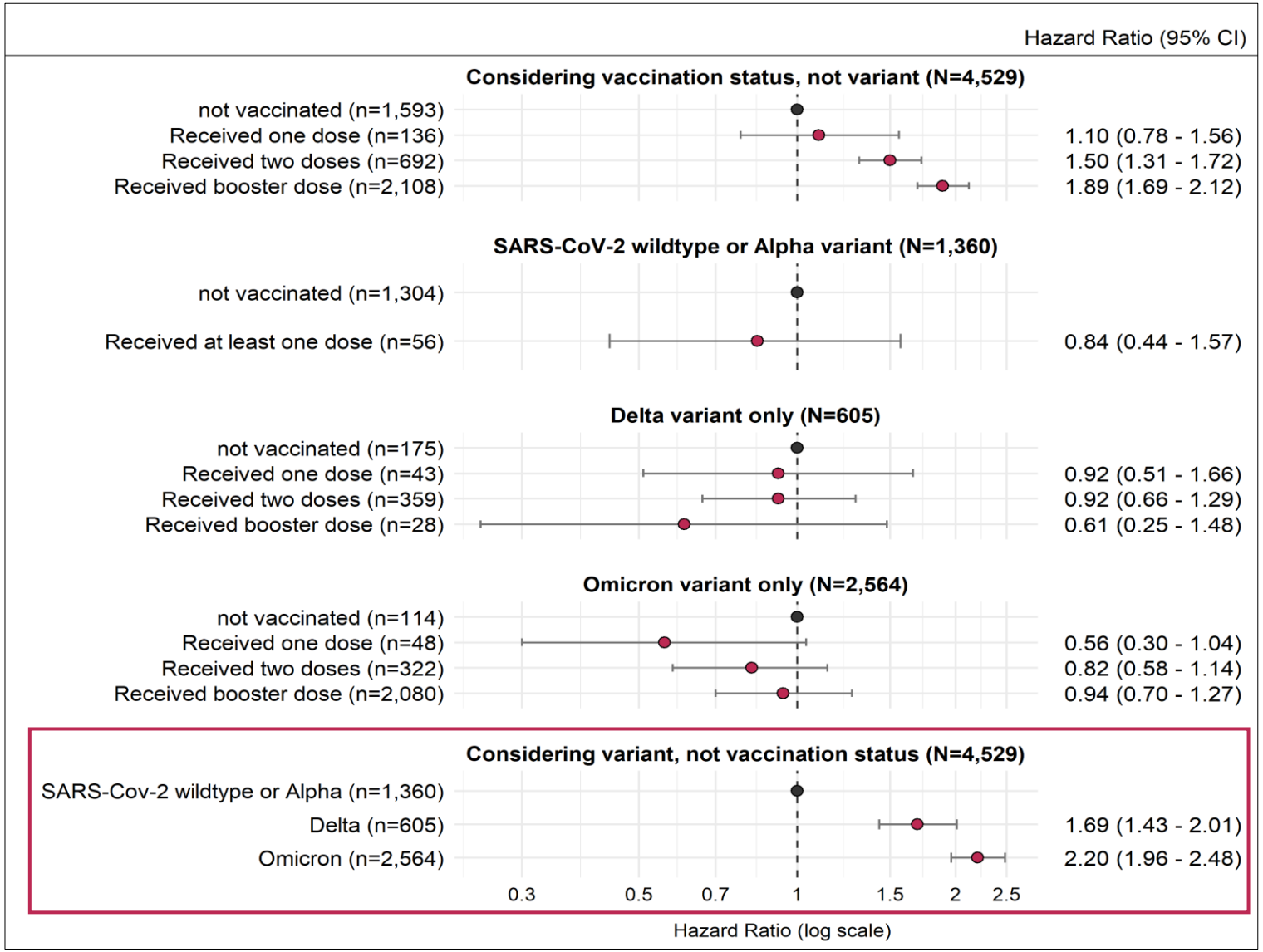
Multivariable Analysis of Time to Recovery



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DISCUSSION

- **Results in accoradace with**
  - Research describing a lower Post-COVID risk for Omicron [3, 5, 8, 10-13]
  - Morello et al. (2023): faster Post-COVID recovery in children infected with Omicron [14]
  - Atchison et al. (2023): prolonged Post-COVID for those infected with the SARS-CoV-2 wildtype [10]

- Results strengthen our assumption that recovery depends on the virus variant and probably not on vaccination status.
  → However, **Vaccination status might be influencing both Post-COVID risk and the recovery-rate via protection against severe infection** [10,12]

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Discussion: Limitations (selection)

- All data are based on **self-reports**
- Dominant variant at time of infection as an estimate for virus variant
- **Generalizability**: initial response in DigiHero is between 3% and 5% depending on region. Women and those with a higher socio-economic status are overrepresented

Conclusion and Outlook

- **Post-COVID recovery was faster for the newer virus variants, vaccinations preceding infection were not independently associated with recovery**.

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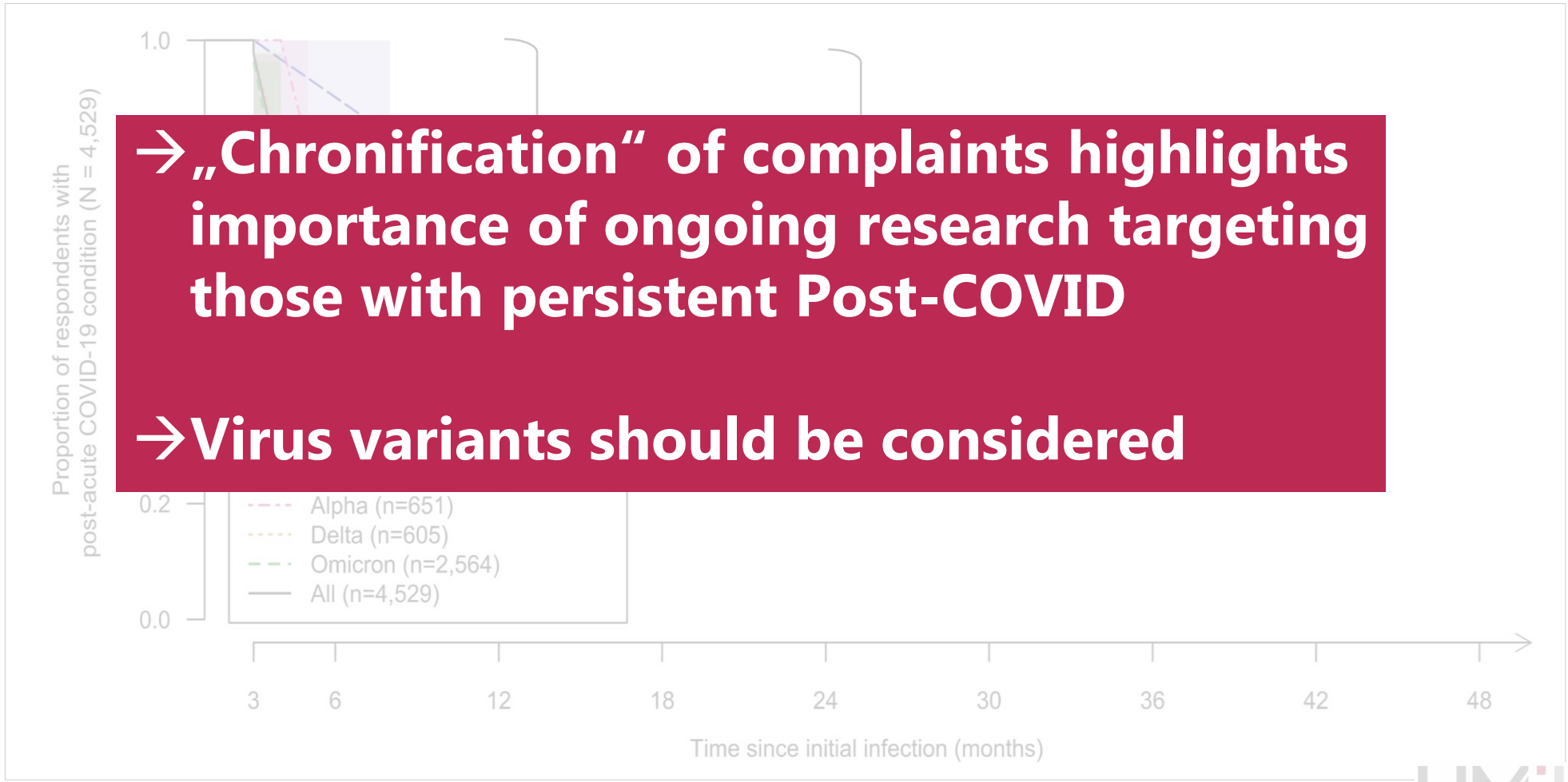

→„Chronification“ of complaints highlights importance of ongoing research targeting those with persistent Post-COVID

→Virus variants should be considered

Acknowledgements

DigiHero Team at the Institute for Medical Epidemiology, Biometry and Informatics (IMEBI), Medical Faculty of the Martin Luther University Halle-Wittenberg, Germany:

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Rafael Mikolajczyk

Research associates

Project Management

Data Management

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Dr. PH Irene Moor
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Prof. Dr. med. Michael Gekle

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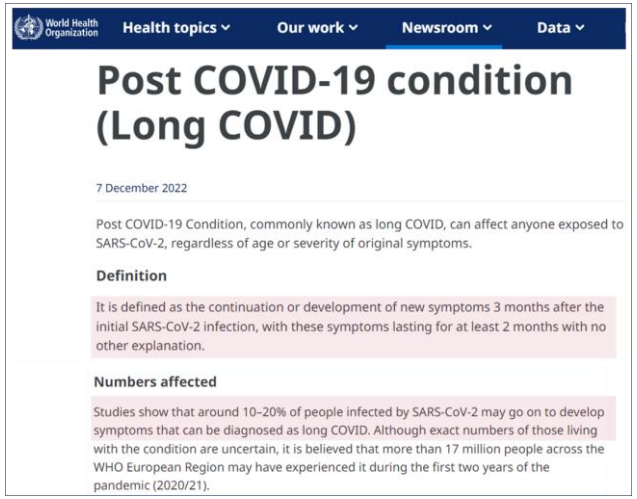
SUPPLEMENT

WCE
WORLD CONGRESS OF EPIDEMIOLOGY 2024

Supplement: What is Post-Covid?



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7 December 2022

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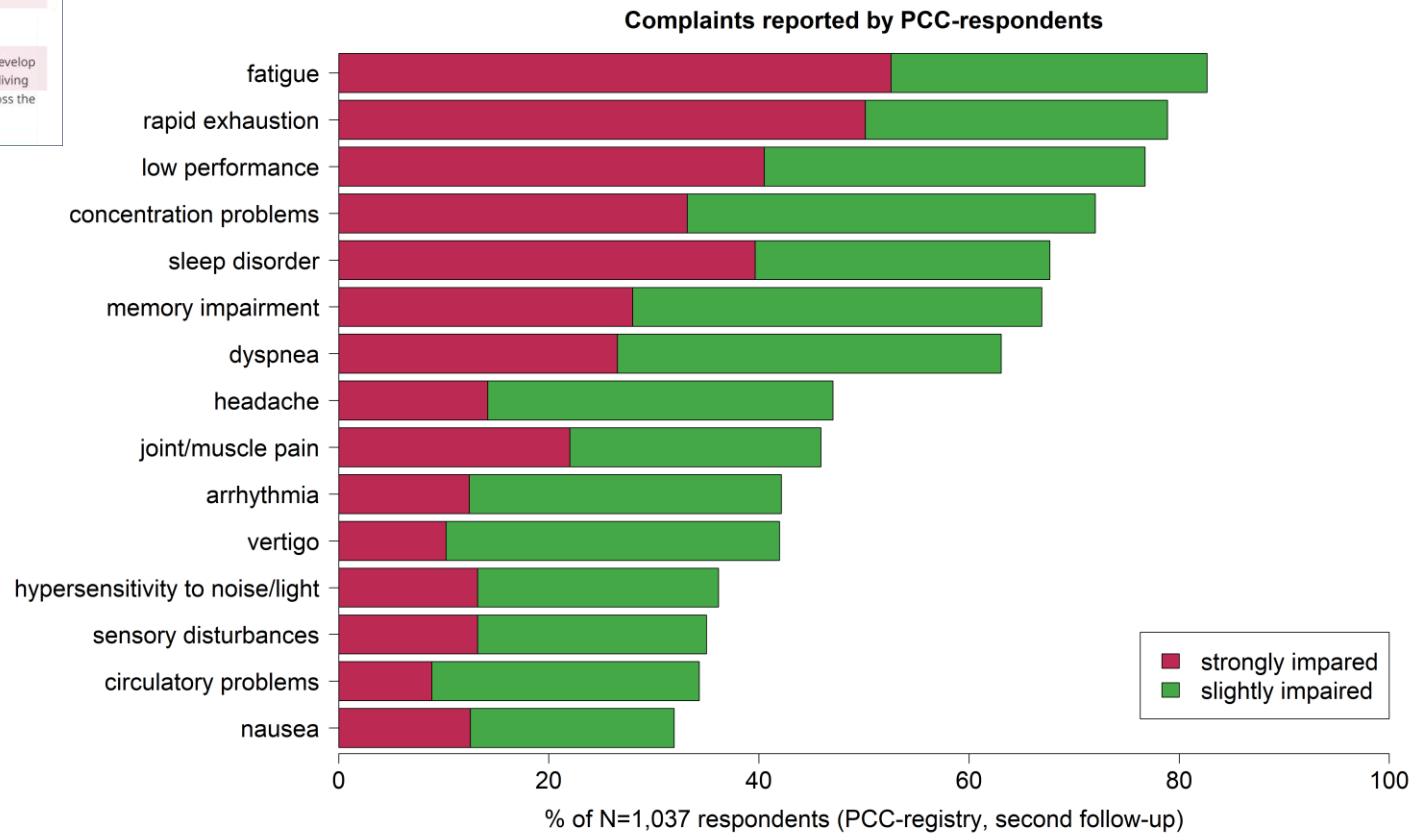
Definition

It is defined as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation.

Numbers affected

Studies show that around 10–20% of people infected by SARS-CoV-2 may go on to develop symptoms that can be diagnosed as long COVID. Although exact numbers of those living with the condition are uncertain, it is believed that more than 17 million people across the WHO European Region may have experienced it during the first two years of the pandemic (2020/21).

"This meta-analysis revealed that almost 30% of subjects who had been infected by SARS-CoV-2 experienced post-COVID symptoms two-years after an acute SARS-CoV-2 infection. **Fatigue, cognitive impairments, and pain** were the most prevalent post-COVID symptoms two-years after"
(Fernandez-de-las-Peñas, 2023)



SUPPLEMENT: WHAT IS POST-COVID?

Table 1 Potential post-acute COVID-19 condition symptoms at ≥12 weeks post-infection available for selection

	not at all	very mild	mild	moderate	severe	do not know
Fever						
Swelling of lymph nodes						
Smell and taste disorders						
Joint, muscle or limb pain						
Tiredness, fatigue (with a normal amount of sleep)						
Sleep disorder						
Night sweats						
Cognitive impairments (concentration difficulties, memory loss, confusion)						
Anxiety						
Depression						
Headache						
Common cold						
Conjunctivitis						
Earache or ringing in the ears (tinnitus)						
Shortness of breath						
Sore throat						
Cough						
Tightness in the chest/ chest pain						
Heart problems such as palpitations or arrhythmia						
Vertigo						
Stomach ache						
Gastrointestinal complaints/ diarrhea						
Nausea						
Premenstrual syndrome (PMS)/ menstrual cramps						

Note. The list was presented to DigiHero respondents at the infections-assessment (roll-out: August, 2021).

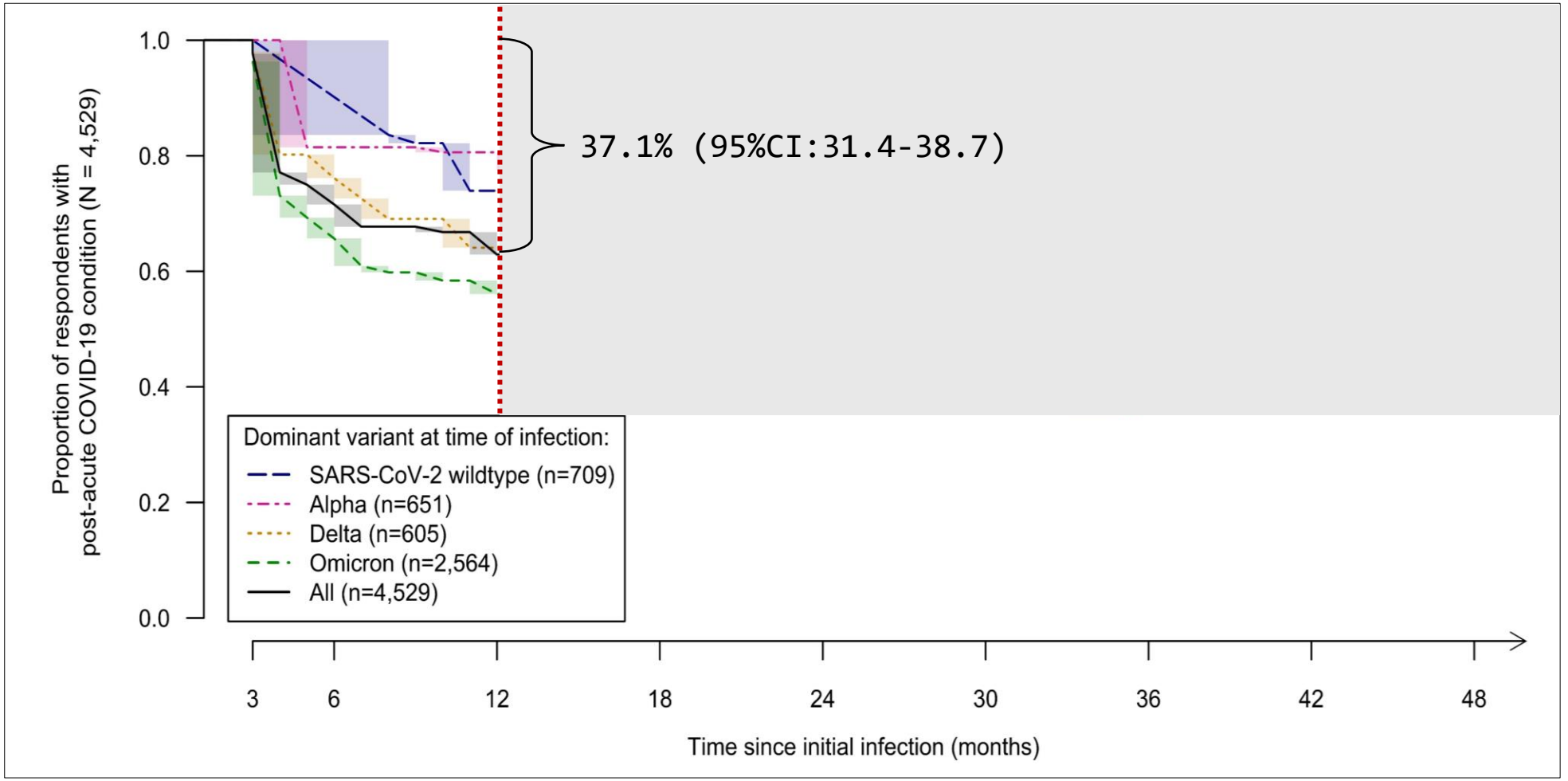
Supplement: Description of the Study Sample

Respondent characteristics		Included in analyses (N = 4,529)		Excluded (N = 1,041)	
		n	%	n	%
Sex	male	1,239	*27.4*	323	*31.0*
	female	3,290	*72.6*	710	*68.2*
	diverse	-	-	3	*0.3*
	not available	-	-	5	*0.5*
Age	<30	499	*11.0*	130	*12.5*
	30-39	737	*16.3*	191	*18.3*
	40-49	956	*21.1*	255	*24.5*
	50-59	1,328	*29.3*	276	*26.5*
	60-69	763	*16.8*	127	*12.2*
	≥70	246	*5.4*	37	*3.6*
	not available/ implausible	-	-	25	*2.4*
Dominant virus variant at time of infection	SARS-CoV-2 wildtype	709	*15.7*	273	*26.2*
	Alpha	651	*14.4*	206	*19.8*
	Delta	605	*13.4*	144	*13.8*
	Omicron	2,564	*56.6*	404	*38.8*
	not available	-	-	14	*1.3*
COVID-19 vaccination status prior to infection	not vaccinated	1,593	*35.2*	410	*39.4*
	one dose	136	*3.0*	33	*3.2*
	two doses	692	*15.3*	105	*10.1*
	three or more doses	2,108	*46.5*	250	*24.0*
	not available/ implausible	-	-	243	*23.3*
Education level[a]	low	155	*3.4*	43	*4.1*
	medium	1,738	*38.4*	419	*40.2*
	high	2,555	*56.4*	557	*53.5*
	not available	81	*1.8*	22	*2.1*
Net household income in €	<2.250	918	*20.3*	219	*21.0*
	2.250 to <4.000	1,680	*37.1*	365	*35.1*
	≥4.000	1,519	*33.5*	345	*33.1*
	not available	412	*9.1*	112	*10.8*
Course of acute infection	no symptoms/ mild course	746	*16.5*	149	*14.3*
	moderate course	1,144	*25.3*	252	*24.2*
	severe course	385	*8.5*	94	*9.0*
	not available	2,254	*49.8*	546	*52.5*
Information on self-reported Post-COVID-19 condition	recovered between 12 weeks and IA	1,346	*29.7*	65	*6.2*
	recovered between IA and FU	374	*8.3*	70	*6.7*
	right censored at FU	1,696	*37.4*	287	*27.6*
	right censored at IA	1,113	*24.6*	83	*8.0*
	not available	-	-	536	*51.5*

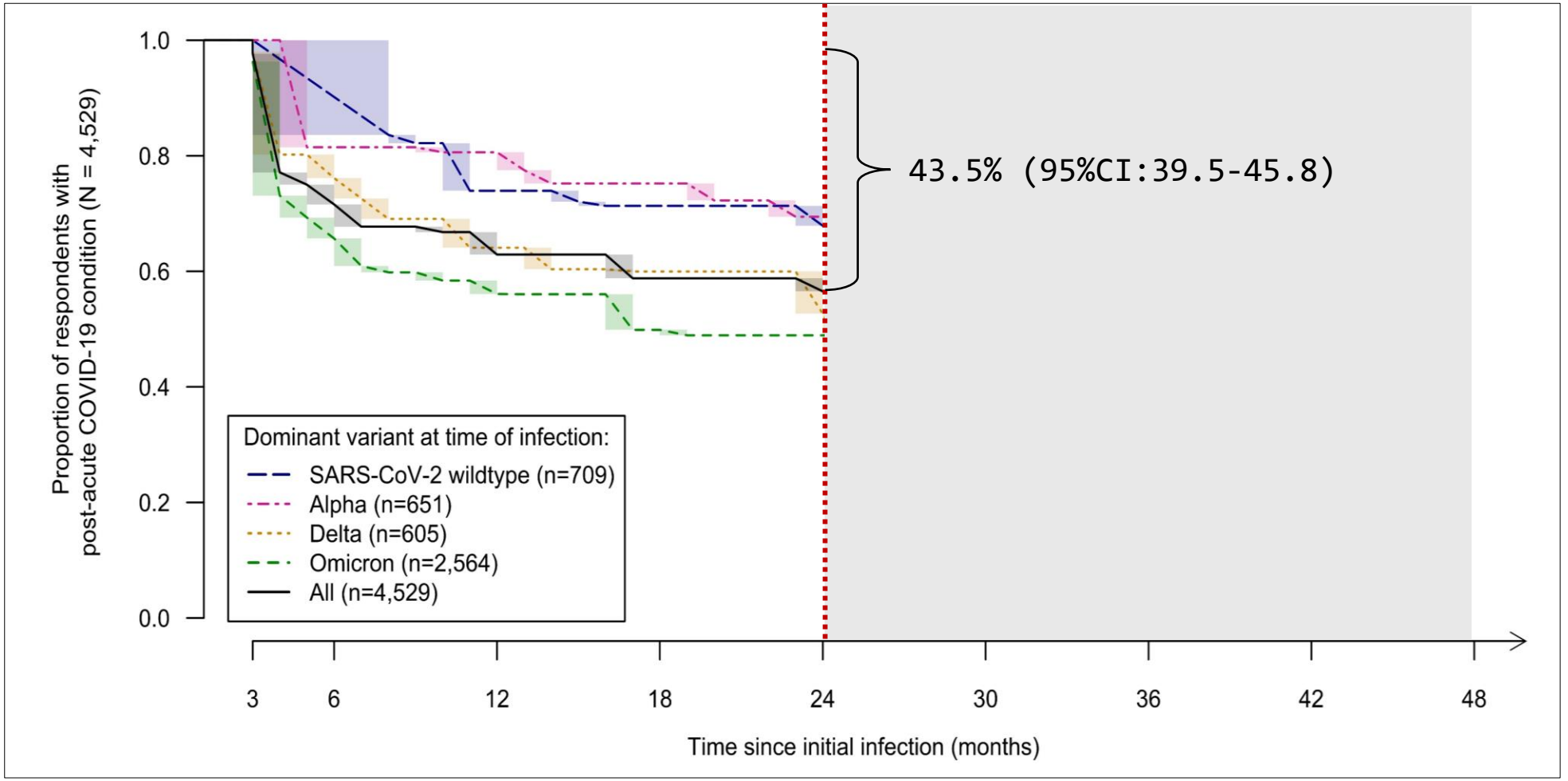
Estimation of virus variant based on dominant VOC at time of infection:

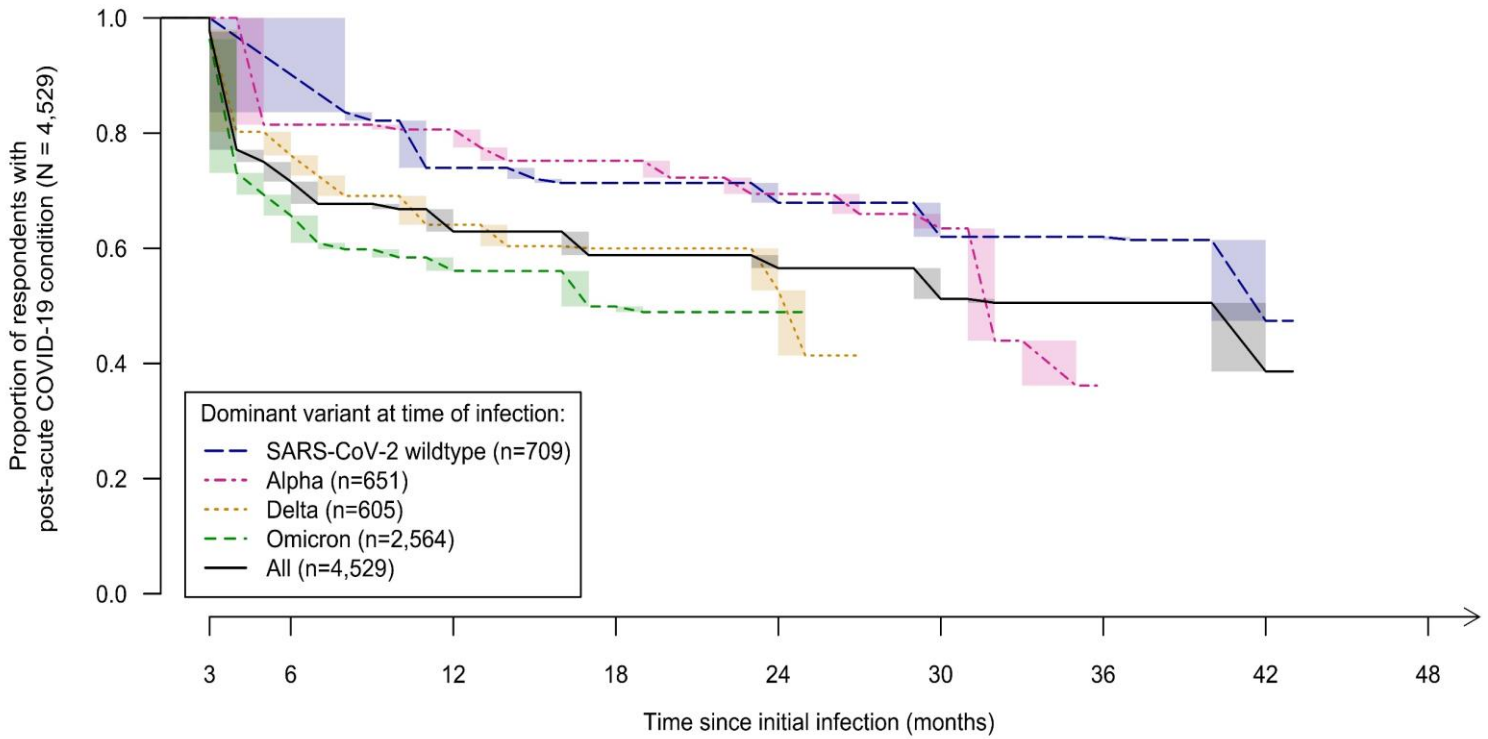
- **SARS-CoV-2 wildtype**: < January 1st, 2021
- **Alpha**: January 1st, 2021 to June 31st, 2021
- **Delta**: July 1st, 2021 to December 20th, 2021
- **Omicron**: ≥ December 21st, 2021

SUPPLEMENT: PROPORTION RECOVERED



SUPPLEMENT: PROPORTION RECOVERED





SARS-CoV-2 wildtype	Nr. at risk	592[a]	524	505	481	439	439	336
	% recovered (95%CI)	16.4 (0.0-25.1)	26.1 (19.7-30.4)	28.7 (23.0-32.7)	32.1 (25.3-35.6)	38.0 (28.6-42.0)	38.0 (33.6-43.6)	52.6 (34.4-68.2)
Alpha	Nr. at risk	530	524	489	452	412	234	
	% recovered (95%CI)	18.5 (0.0-22.0)	19.4 (15.3-25.9)	24.8 (18.8-29.9)	30.5 (23.9-34.3)	36.6 (27.8-43.7)	63.9 (35.5-1.0)	
Delta	Nr. at risk	460	387	362	318	250[b]		
	% recovered (95%CI)	23.9 (14.2-30.1)	35.9 (29.7-40.6)	40.0 (35.3-45.2)	47.3 (35.5-54.7)	58.6 (37.4-84.9)		
Omicron	Nr. at risk	1,684	1,437	1,278	1,254			
	% recovered (95%CI)	34.3 (26.5-38.4)	43.9 (38.7-46.2)	51.1 (42.1-53.2)	51.1 (48.3-56.3)			
Total	Nr. at risk	3,242	2,849	2,663	2,561	2,318	2,288	1,750
	% recovered (95%CI)	28.4 (22.4-31.0)	37.1 (31.4-38.7)	41.2 (37.7-42.9)	43.5 (39.5-45.8)	48.8 (41.9-51.1)	49.5 (46.0-53.1)	61.3 (46.9-72.6)

[a] Nr. at risk and proportion recovered at 8 months
[b] Nr. at risk and proportion recovered at 25 months

Supplement: Multivariable Analysis of Time to Recovery

C. Considering variant, not vaccination status (N=4,529)	crude HR	95%CI		adjusted HR	95%CI	
Dominant virus variant at time of infection (ref: SARS-Cov-2 wildtype or Alpha, n=1,360)						
Delta (n=605)	1.63	1.37	1.94	1.69	1.43	2.01
Omicron (n=2,564)	2.24	1.99	2.52	2.20	1.96	2.48
Sex (ref: male; n=1,239)						
Female (n=3,290)				0.81	0.73	0.90
Age (ref: <30; n=499)						
30-39 (n=737)				0.79	0.66	0.94
40-49 (n=956)				0.59	0.48	0.72
50-59 (n=1,328)				0.60	0.50	0.72
60-69 (n=763)				0.64	0.52	0.78
≥70 (n=246)				0.62	0.46	0.82
Education level (ref: high; n=2,555) [b]						
Low (n=155)				0.99	0.74	1.34
Medium (n=1,738)				0.91	0.82	1.01
Not available (n=81)				0.72	0.46	1.13
Net household income in € (ref: <2.250; n=918)						
2.250 to <4.000 (n=1,680)				1.06	0.93	1.21
≥4.000 (n=1,519)				1.24	1.08	1.42
Not available (n=412)				1.05	0.87	1.26

Note. Crude Hazard ratios (HR) as well as adjusted HR and respective 95% confidence intervals (95%CI) are shown. Panel C also depicts the HR for each variable included in the multivariable analysis, while in Panel A and B the HR for the variables sex, age, education level, and household income are not shown.

[a] Analyses adjusted for age, sex, education level, and household income.

[b] The education level was defined based on the International Standard Classification of Education (ISCED-97)[23]

Supplement: Sensitivity Analysis I – Including Acute Course of COVID-19

A. Considering vaccination status, not variant (N=2,275)	crude HR	95%CI		adjusted HR[a]	95%CI	
(ref: not vaccinated, n=1,176)						
Received one dose (n=80)	1.10	0.75	1.63	1.06	0.72	1.55
Received two doses (n=417)	1.54	1.26	1.88	1.46	1.19	1.79
Received booster dose (n=602)	1.75	1.43	2.15	1.57	1.27	1.94
B. Analyses stratified for virus variant	**crude HR**	**95%CI**		**adjusted HR[a]**	**95%CI**	
B.1 Omicron variant only (N=796)						
Vaccination status prior to infection (ref: not vaccinated, n=52)						
Received one dose (n=21)	0.64	0.09	4.61	0.62	0.08	4.59
Received two doses (n=141)	1.17	0.72	1.90	1.12	0.66	1.90
Received booster dose (n=582)	0.92	0.60	1.41	0.88	0.57	1.37
B.2 Delta variant only (N=434)						
Vaccination status prior to infection (ref: not vaccinated, n=127)						
Received one dose (n=20)	0.99	0.43	2.29	0.65	0.26	1.65
Received two doses (n=267)	0.77	0.53	1.11	0.62	0.41	0.96
Received booster dose (n=20)	0.68	0.26	1.79	0.41	0.15	1.13
B.3 Alpha variant only (N=508)						
Vaccination status prior to infection (ref: not vaccinated, n=460)						
Received at least one dose (n=48)	0.86	0.46	1.60	0.92	0.45	1.87
B.4 SARS-CoV-2 wildtype or Alpha variant (N=1,045)						
Vaccination status prior to infection (ref: not vaccinated, n=997)						
Received at least one dose (n=48)	0.83	0.42	1.67	0.94	0.46	1.91

Supplement: Sensitivity Analysis I – Including Acute Course of COVID-19

C. Considering variant, not vaccination status (N=2,275)	crude HR	95%CI		adjusted HR	95%CI	
Dominant variant at infection (ref: SARS-Cov-2 wildtype or Alpha, n=1,045)						
Delta (n=434)	1.67	1.35	2.06	1.68	1.36	2.07
Omicron (n=796)	2.32	1.85	2.90	2.13	1.71	2.65
Sex (ref: male; n=582)						
Female (n=1,693)				0.79	0.67	0.94
Age (ref: <30; n=248)						
30-39 (n=385)				0.86	0.63	1.18
40-49 (n=498)				0.64	0.46	0.87
50-59 (n=696)				0.70	0.51	0.95
60-69 (n=354)				0.72	0.51	1.02
≥70 (n=94)				0.75	0.49	1.15
Education level (ref: high; n=1,293)[b]						
Low (n=80)				0.96	0.58	1.59
Medium (n=853)				0.91	0.79	1.06
Not available (n=49)				0.65	0.31	1.36
Net household income in € (ref: <2.250; n=472)						
2.250 to <4.000 (n=900)				1.06	0.84	1.34
≥4.000 (n=711)				1.19	0.94	1.51
Not available (n=192)				1.09	0.78	1.53
Course of acute disease (ref: no symptoms/mild course; n=746)						
moderate course (n=1,144)				0.68	0.59	0.79
severe course (n=385)				0.33	0.24	0.44

Note. The first sensitivity analysis considered DigiHero respondents with post-acute COVID-19 condition at the infections-assessment who provided complete information on the acute course of their COVID-19 disease (N = 2,275). Hazard ratios (HR) and 95% confidence intervals (95%CI) are shown.

[a] Analyses adjusted for age, sex, educational level, household income, and course of acute COVID-19 disease.

[b] The education level was defined based on the International Standard Classification of Education (ISCED-97) [1]

Supplement: Sensitivity Analysis II – Only Those with ≥1 severe Complaint

A. Considering vaccination status, not variant (N=2,177)	crude HR	95%CI		adjusted HR[a]	95%CI	
(ref: not vaccinated, n=745)						
Received one dose (n=67)	0.84	0.41	1.72	0.85	0.41	1.77
Received two doses (n=310)	1.42	1.05	1.92	1.39	1.03	1.88
Received booster dose (n=1,055)	2.21	1.80	2.72	2.13	1.72	2.64
B. Analyses stratified for virus variant	**crude HR**	**95%CI**		**adjusted HR[b]**	**95%CI**	
B.1 Omicron variant only (N=1,292)						
Vaccination status prior to infection (ref: not vaccinated, n=51)						
Received one dose (n=28)	0.34	0.00	91.96	0.28	0.00	77.67
Received two doses (n=166)	0.82	0.46	1.48	0.68	0.38	1.25
Received booster dose (n=1,047)	1.08	0.66	1.80	0.95	0.56	1.59
B.2 Delta variant only (N=247)						
Vaccination status prior to infection (ref: not vaccinated, n=79)						
Received at least one dose (n=168)	0.69	0.39	1.22	0.62	0.34	1.14
B.3 Alpha variant only (N=313)						
Vaccination status prior to infection (ref: not vaccinated, n=290)						
Received at least one dose (n=23)	0.51	0.00	672.87	0.54	0.00	819.68
B.4 SARS-CoV-2 wildtype or Alpha variant (N=638)						
Vaccination status prior to infection (ref: not vaccinated, n=615)						
Received at least one dose (n=23)	0.50	0.00	962.84	0.49	0.00	1055.44

Supplement: Sensitivity Analysis II – Only Those with ≥1 severe Complaint

C. Considering variant, not vaccination status (N=2,177)	crude HR	95%CI		adjusted HR	95%CI	
Dominant variant at infection (ref: SARS-Cov-2 wildtype or Alpha n=638)						
Delta (n=247)	1.68	1.18	2.38	1.81	1.27	2.58
Omicron (n=1,292)	2.61	2.04	3.32	2.57	2.00	3.30
Sex (ref: male; n=514)						
Female (n=1,663)				0.91	0.76	1.11
Age (ref: <30; n=276)						
30-39 (n=363)				0.75	0.56	1.01
40-49 (n=456)				0.42	0.31	0.58
50-59 (n=634)				0.51	0.38	0.67
60-69 (n=338)				0.59	0.42	0.84
≥70 (n=110)				0.52	0.33	0.83
Education level (ref: high; n=1,135)[c]						
Low (n=82)				1.06	0.68	1.65
Medium (n=915)				0.96	0.82	1.12
Not available (n=45)				0.84	0.43	1.63
Net household income in € (ref: <2.250; n=487)						
2.250 to <4.000 (n=804)				1.16	0.93	1.45
≥4.000 (n=683)				1.58	1.25	1.99
Not available (n=203)				1.07	0.76	1.50

Note. The second sensitivity analysis considered DigiHero respondents with post-acute COVID-19 condition at the infections-assessment who indicated experincing at least one post-acute COVID-19 symptom they rated as "severe" (N = 2,177). Hazard ratios (HR) and 95% confidence intervals (95%CI) are shown.

[a] Analyses adjusted for age, sex, educational level, and household income

[b] Analyses adjusted for age, sex, and household income

[c] The education level was defined based on the International Standard Classification of Education (ISCED-97) [1]

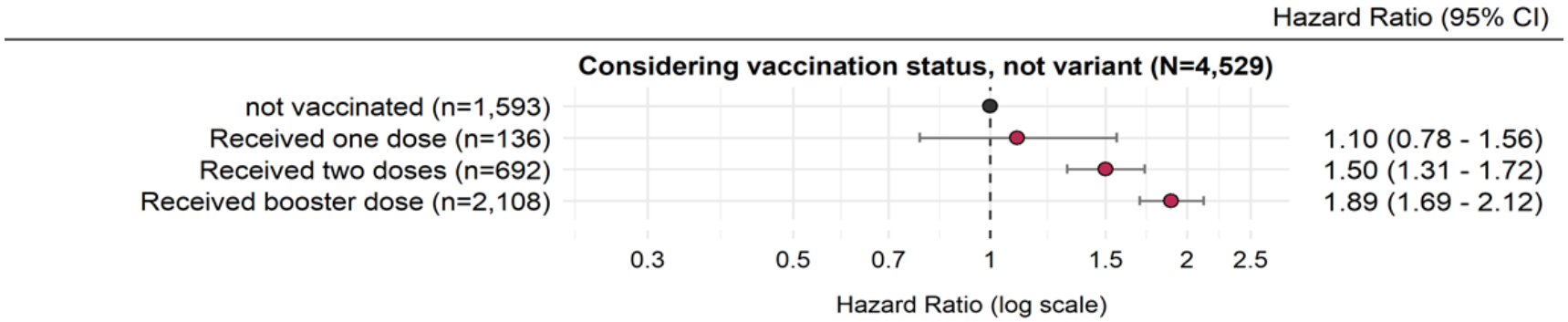
Supplement: Contingency Table of Vaccination Status and Variant

Contingency table of COVID-19 vaccination status prior to infection and dominant SARS-CoV-2 variant at infection in the DigiHero post-acute COVID-19 cohort included in analyses (N = 4,529)

COVID-19 vaccination status prior to infection	**Dominant SARS-CoV-2 variant at time of infection**							
	SARS-CoV-2 wildtype		Alpha		Delta		Omicron	
Not vaccinated	709	100%	595	91.4%	175	28.9%	114	4.4%
One dose	-	-	45	6.9%	43	7.1%	48	1.9%
Two doses	-	-	11	1.7%	359	59.3%	322	12.6%
Three or more doses	-	-	0	-	28	4.6%	2,080	81.1%
Total	709	100%	651	100%	605	100%	2,564	100%

Note. The correlation between the two variables is r = 0.86 (Spearman correlation).

Supplement: Analysis Stratified by Vaccination Status, not Variant



D. Analyses stratified for vaccination status	adjusted HR[a]	95%CI	
D.1 Received at least one dose (N=2,936)			
Dominant virus variant at time of infection (ref: SARS-Cov-2 wildtype or Alpha, n=56)			
Delta (n=430)	2.12	1.14	3.95
Omicron (n=2,450)	2.87	1.54	5.36
D.2 Not vaccinated (N=1,593)			
Dominant virus variant at time of infection (ref: SARS-Cov-2 wildtype or Alpha, n=1,304)			
Delta (n=175)	1.81	1.38	2.37
Omicron (n=114)	2.47	1.75	3.50

Note. Crude Hazard ratios (HR) as well as adjusted HR and respective 95% confidence intervals (95%CI) are shown.

[a] Analyses adjusted for age and sex.