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MAJOR ARTICLE

Prevalence of Long-term Symptoms Varies When Using Different Post-COVID-19 Definitions in Positively and Negatively Tested Adults: The PRIME Post-COVID Study

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Background. Long-term symptoms after a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (ie, post–coronavirus disease 2019 [COVID-19] condition or long COVID) constitute a substantial public health problem. Yet, the prevalence remains currently unclear as different case definitions are used, and negatively tested controls are lacking. We aimed to estimate post-COVID-19 condition prevalence using 6 definitions.

Methods. The Prevalence, Risk factors, and Impact Evaluation (PRIME) post-COVID-19 condition study is a population-based sample of COVID-19-tested adults. In 2021, 61 655 adults were invited to complete an online questionnaire, including 44 symptoms plus a severity score (0–10) per symptom. Prevalence was calculated in both positively and negatively tested adults, stratified by time since their COVID-19 test (3–5, 6–11, or ≥12 months ago).

Results. In positive individuals (n = 7405, 75.6%), the prevalence of long-term symptoms was between 26.9% and 64.1% using the 6 definitions, while in negative individuals (n = 2392, 24.4%), the prevalence varied between 11.4% and 32.5%. The prevalence of long-term symptoms potentially attributable to COVID-19 ranged from 17.9% to 26.3%.

Conclusions. There is a (substantial) variation in prevalence estimates when using different post-COVID-19 condition definitions, as is current practice; there is limited overlap between definitions, indicating that the essential post-COVID-19 condition criteria are still unclear. Including negatives is important to determine long-term symptoms attributable to COVID-19.

Trial registration. ClinicalTrials.gov Identifier: NCT05128695.

Keywords. definitions; long-term symptoms; post-COVID-19 condition.

Globally, the number of individuals diagnosed with coronavirus disease 2019 (COVID-19) has risen to 660 million as of January 2023 [1]. Some infected individuals report long-term symptoms that may impede physical and mental functioning and lead to a loss in work productivity [2–4]. These long-term consequences embody a new and growing public health problem. However, the prevalence of long-term symptoms related to COVID-19 (ie, post-COVID-19 condition or long COVID) to date is unclear, partly due to the diverse terminology used to describe the condition and the lack of a uniform case definition [5].

To improve uniformity, the World Health Organization (WHO) proposed a definition [6], while several other health institutes, such as the UK National Institute for Health and Care Excellence (NICE) [7] and the US Centers for Disease Control and Prevention (CDC) [8] have proposed other definitions. Definitions used in clinical daily practice are often simplified toward criteria that are more feasible to assess in practice, such as presence of 1 or more symptoms since infection [9]. Recent studies have attempted to restrict the number of included symptoms, for example, only symptoms that were more present in positively than negatively tested people [10] or that were more severe [11]. Also, various durations since infection ranging from several weeks to months have been used [8, 12, 13]. It is unknown how the various definitions that are currently in practice relate to each other and to (more complex) post-COVID-19 condition definitions, such as that proposed by the WHO.

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To construct an adequate case definition, it is crucial to identify direct long-term consequences. It has proven challenging to successfully distinguish direct from possible indirect consequences provoked by the COVID-19 pandemic and preventive measures [14–16]. Furthermore, in scientific studies, data on symptoms before infection or in negative controls (as an estimate of background occurrence) are often lacking [17]. A Dutch study including test-negative and population controls revealed a substantial proportion of symptom experience (29.8% and 26.0% respectively) in controls, compared with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–positive cases (48.5%) [18].

This observational cohort study, called the Prevalence, Risk factors, and Impact Evaluation post-COVID study (PRIME post-COVID), aimed to reveal prevalence and variations in different case definitions. The results provide insight into the complexity of assessing post-COVID-19 condition, providing a reference for future research on long-term symptoms in COVID-19-infected individuals.

METHOD

Study Design

In November 2021, the PRIME post-COVID study, with both retrospective and prospective aspects, was initiated. The study design has been published previously [19]. In brief, a population-based sample of positively and negatively polymerase chain reaction (PCR)–tested adults was retrieved from the Dutch public health COVID-19 test registry. All adults with a positive test and a random selected sample of negatively tested adults were selected.

Participants

In total, 61 655 adults were invited by email to participate. Recorded adults (18 years and older) were invited when they had a valid test result (41 780 positives and 19 875 negatives) and e-mail address. To be classified as negative, no registered positive PCR test was allowed up to the time of participation. Negatively tested invitees were matched (1 for each 2 positives) on age, sex, municipality of residence, and year-quarter of the PCR test. Digital informed consent was obtained before data collection. Consent was also requested to link data on age, sex, and test result from the questionnaire to the public health registry data for certainty assessment [19].

Data Collection

Data were collected between November 2021 and January 2022 by self-administered questionnaires on the online MWM2 application of the market research platform Crowdtech (ISO 27001 certified). The questionnaire contained demographics (age, sex, comorbidities [per comorbidity, whether it was diagnosed before or after testing]), PCR tests (date, result), COVID-19 vaccination (number, date[s], type[s] of received vaccines], and experienced symptoms ["What complaints do you currently have?"], with severity scores ranging from 0 [no severe symptoms] to 10 [worst symptoms imaginable). There were 44 prelisted symptoms, based on existing literature [20, 21]. All positives were asked whether they felt recovered after infection.

Outcome Variables

The primary outcomes were 6 definitions of having long-term symptoms after PCR testing (Figure 1). Selection of the definitions was based on WHO recommendations, use in previous studies, and feasibility to be constructed by the study data. A participant was considered a case when reporting:

Definition 1: ≥1 of all 44 prelisted symptoms [9];
Definition 1a: >1 of all 44 prelisted symptoms;
Definition 2: ≥1 symptom that was significantly more often reported in positives than in negatives (in current data) [10];
Definition 3: ≥1 of the selected symptoms in definition 2 with a severity score of ≥5 points (cutoff of 5 was used according to the mean of scores) [11];
Definition 4: reflects the current WHO case definition: "a condition that occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually three months from the onset of COVID-19 with symptoms, that last for at least two months, and cannot be explained by an alternative diagnosis" [6]. A participant was considered a case when reporting ≥1 of the 44 prelisted symptoms AND the symptoms were present for ≥1 month AND the symptoms were not present before infection AND when no new comorbidities were reported after the test;
Definition 5: currently feeling unrecovered [22–25];
Definition 6: ≥1 of the 44 prelisted symptoms at 3 months [26], thus reflecting for each participant the same time period after positive test (ie, 3 months).

All definitions were constructed for positives, and definitions 1–4 also for negatives (as "background" occurrences).

Time Since PCR Test

The study population was divided into categories based on time since PCR test (3–5 ~ Delta variant, 6–11 ~ Alpha variant, and ≥12 months ~ Wuhan variant). Respondents who had a duration shorter than 3 months were excluded (ie, not indicative of long-term symptoms).

Statistical Analysis

To improve the likelihood for representativeness of the study population relative to the invitees, data were weighted by age categories, sex, and year-quarter of PCR test (positives and

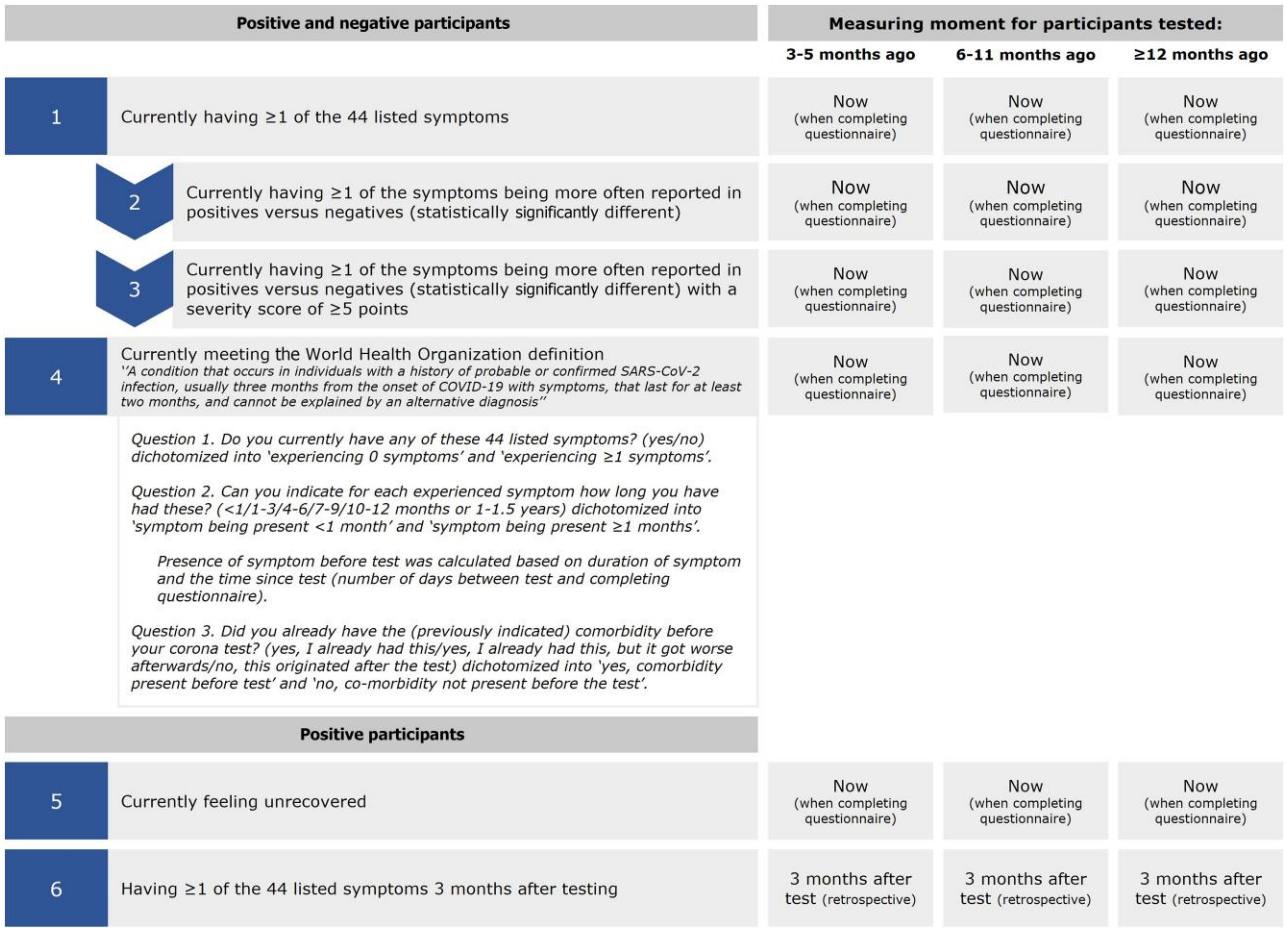

Figure 1. Six definitions of long-term symptoms based on currently experienced symptoms, severity of symptoms, the clinical case definition of post-COVID-19 condition (World Health Organization), currently feeling unrecovered, and experiencing symptoms 3 months after testing, with measuring moments for participants tested 3–5, 6–11 and ≥12 months ago, used in the PRIME post-COVID study. Abbreviation: COVID-19, coronavirus disease 2019.

negatives separately). Unweighted numbers and percentages (u%) and weighted percentages (w%) were presented. Chi-square tests were used to compare symptoms between all positives and negatives and positives and negatives who met definitions 1 and 4 (definitions 2 and 3 are not representative of all 44 prelisted symptoms, and definitions 5 and 6 were unavailable for negatives). The proportion of participants with each outcome (for each definition separately) was estimated, and 95% CIs were calculated, stratified by time since the test: 3–5, 6–11, and ≥12 months ago. The range of prevalence estimates was presented for the 3 test window groups. Logistic regression analyses were performed to test whether the presence of long-term symptoms differed between the test window groups. The proportion of long-term symptoms potentially attributable to a positive SARS-CoV-2 test (as an estimate for direct rather than indirect impact) was calculated by subtracting the observed prevalence in negatives from the observed prevalence in positives. We stress "potentially attributable" as we acknowledge that we cannot rule out that (some) negatively tested participants might have been infected but not included in the registry. In sensitivity analyses, negatively tested participants reporting SARS-CoV-2 antibodies (type not specified) before vaccination were excluded. To compare inter-relations between the definitions used in practice (definitions 1, 5, and 6 were selected for clarity and readability) and the WHO case definition, 3 Venn diagrams were constructed for each of the 3 test window groups. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS; version 27.0; IBM, Armonk, NY, USA). A P value <.001 was considered statistically significant, applying Bonferroni correction due to multiple testing [27].

Ethical Statement

The Medical Ethical Committee of Maastricht University Medical Centre+ waived this study (METC2021-2884), as the Medical Research Involving Human Subjects Act (WMO) did not apply. This study was registered at Clinical Trials.gov Protocol Registration and Results System (NCT05128695).

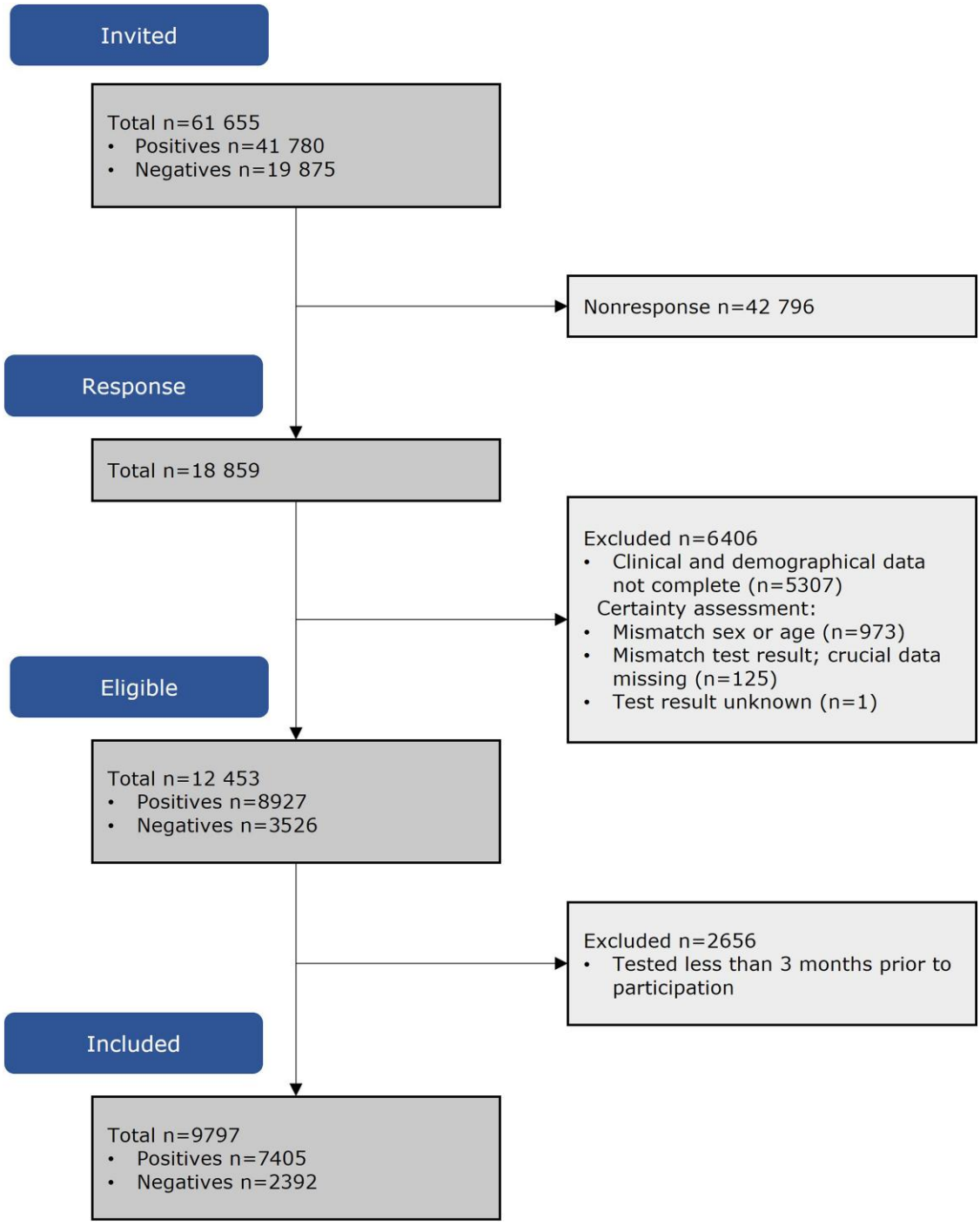

Figure 2. Flowchart of invitees, respondents, exclusion criteria, participants eligible for inclusion, and study population included in the analysis of the PRIME post-COVID study. Abbreviation: COVID-19, coronavirus disease 2019.

RESULTS

Of the 61 655 invitees, 12 453 (20.2%) participants provided the minimal data, 9797 (78.7%) of whom were PCR tested ≥3 months previously and thereby eligible for inclusion (Figure 2).

Of the included participants, 7405 (75.6%) had tested positive, 2392 (24.4%) negative, and 1367 (14.0%) were tested 3–5 months ago, 6402 (65.3%) 6–11 months ago, and 2028 (20.7%) ≥12 months ago (Table 1). The share of positives was 61.9%, 80.0%, and 71.0% for the test window groups, respectively. For participants tested ≥6 months ago, negatives were more often men compared with positives ($P < .001$) (Table 1). Overall, negatives were older than positives ($P < .001$).

Table 1. Participant Characteristics for the Positively and Negatively Tested Adults Stratified by Time Since Test

	Positives (n = 7405)									Negatives (n = 2392)								
	Tested 3–5 Months Ago (n = 846)			Tested 6–11 Months Ago (n = 5119)			Tested ≥12 Months Ago (n = 1440)			Tested 3–5 Months Ago (n = 521)			Tested 6–11 Months Ago (n = 1283)			Tested ≥12 Months Ago (n = 588)		
	n	u%	w%	n	u%	w%	n	u%	w%	n	u%	w%	n	u%	w%	n	u%	w%
Sex																		
Men	352	41.6	50.6	2052	40.1	44.1	569	39.5	43.9	256	49.1	53.4	647	50.4	50.6	296	50.3	53.2
Women	494	58.4	49.4	3067	59.9	55.9	871	60.5	56.1	265	50.9	46.6	636	49.6	49.4	291	49.5	46.5
Unknown	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	0	0
Age	43 (17) | 35 (16)			51 (15) | 45 (17)			52 (15) | 46 (17)			54 (17) | 44 (18)			59 (15) | 51 (18)			57 (15) | 49 (17)		
18–20 y	70	8.3	18.1	92	1.8	5.9	23	1.6	4.2	12	2.3	7.7	14	1.1	3.3	3	0.5	2.2
21–30 y	194	22.9	36.3	503	9.8	20.3	157	10.9	21.6	53	10.2	24.1	65	5.1	14.7	35	6.0	17.2
31–40 y	111	13.1	14.1	699	13.7	16.6	182	12.6	16.1	51	9.8	14.6	91	7.1	13.5	48	8.2	15.3
41–50 y	128	15.1	11.5	888	17.3	16.7	219	15.2	15.4	68	13.1	14.5	130	10.1	12.9	89	15.1	17.0
51–60 y	192	22.7	12.1	1498	29.3	21.5	407	28.3	21.4	117	22.5	16.4	328	25.6	21.3	129	21.9	18.2
61–70 y	110	13.0	5.4	1016	19.8	12.5	325	22.6	14.7	140	26.9	13.8	391	30.5	20.0	178	30.3	18.5
71–80 y	37	4.4	2.0	380	7.4	5.5	117	8.1	5.9	65	12.5	6.4	230	17.9	11.4	95	16.2	10.0
81+ y	4	0.5	0.5	43	0.8	1.0	10	0.7	0.7	15	2.9	2.5	34	2.7	2.8	11	1.9	1.5

Abbreviations: u%, unweighted percentage; w%, weighted percentage.

The majority of all participants had received at least 1 vaccine dose (80.6%, 91.3%, and 91.7% of positives and 98.0%, 96.9%, and 97.1% of negatives, for the test window groups, respectively).

The proportion of negatives who experienced ≥1 symptom around the moment of their test was lower ($P < .001$) compared with positives. In total, 19.6% (n = 1450) of positives reported >10 symptoms, and 1.3% (n = 99) were hospitalized during acute infection. Comorbidities reportedly present before the PCR test were overall comparable between positives and negatives. Current comorbidities were reported more often in negatives than positives, tested 3–5 months ago (44.3% negatives, 32.5% positives; $P < .001$).

Description of Symptoms Significantly More Often Reported in Positives Than Negatives

Of the 44 prelisted symptoms, 24 were more often reported in positives than in negatives, including amnesia, brain fog, chest tightness, concentration difficulties, confusion, cough, dizziness, fatigue, hair loss, headache, heart palpitations, increased resting heart rate, irritability, joint pain, loss/change of smell, loss/change of taste, mucus, muscle pain and weakness, pain between shoulder blades, pain or burning sensation in the lungs, shortness of breath, sleeping problems, tinnitus, and voice difficulties. These symptoms were used in definitions 2 and 3 (see "Methods").

Reported Symptoms in Positives and Negatives who Met the Case Definitions

Negatives who met case definition 1 or 4 significantly more often experienced general cold symptoms (ie, earache, sneezing, runny nose, cold), vomiting, and dreariness/depression, compared with positives who met definition 1 or 4 (Table 2). Symptoms significantly more often reported in positives than negatives meeting definition 1 or 4 were chest pressure, hair loss, amnesia, loss/change of taste, loss/change of smell, shortness of breath, concentration difficulties, and fatigue (Table 2). The proportion who experienced loss/change of smell (20.2% for definition 1% and 24.1% for definition 4) and fatigue (16.8% for definition 1 and 8.2% for definition 4) demonstrated the largest difference between positives and negatives (Table 2).

The most reported symptoms in positives who met definitions 5 and 6 were fatigue, loss/change of smell, shortness of breath, concentration difficulties, change/loss of taste, and sleeping problems (Table 2).

Prevalence of Six Long-term Symptom Definitions in Positives and Negatives

In positives, the prevalence of long-term symptoms ranged between 26.9% and 64.1% for all definitions (Figure 3): The prevalence ranged (by test window group) from 47.6%–53.1% for definition 1 (≥1 of all symptoms), 34.9%–39.2% for definition 1a (Supplementary Table 1), 41.1%–47.0% for definition 2 (different symptoms in positives/negatives), 33.4%–37.9% for definition 3 (different symptoms in positives/negatives plus severity), 34.7%–39.0% for definition 4 (WHO), 26.9%–34.4% for definition 5 (unrecovered), and 47.4%–64.1% for definition 6 (≥1 of all symptoms at 3 months). In negatives, the prevalence was from 29.0%–32.5%, 18.5%–22.6%, 14.0%–18.8%, and 11.4%–19.3%, for definitions 1–4, respectively (Figure 3). Excluding negatives with SARS-CoV-2 antibodies before vaccination (n = 95) showed comparable results (Supplementary Table 2).

Table 2. Proportion of Symptoms Experienced by Positives and Negatives Meeting Four Long-term Symptom Definitions

	Definition 1. (≥1 of All Symptoms) n = 4488[a]			Definition 4. (WHO) n = 3095[a]			Definition 5. (Unrecovered) n = 2428[a]	Definition 6. (≥1 of All Symptoms at 3 Months) n = 4438[a]
Experienced Symptoms, w%	Negatives (n = 721)	Positives (n = 3767)	Diff.	Negatives (n = 345)	Positives (n = 2322)	Diff.	Positives	Positives
Loss/change of smell	3.1	23.3	20.2[b]	3.5	27.6	24.1[b]	28.3	19.2
Fatigue	31.9	48.7	16.8[b]	45.2	53.4	8.2	57.8	38.7
Shortness of breath	8.1	20.7	12.6[b]	9.0	22.1	13.1[b]	27.9	16.6
Concentration difficulties	10.6	23.0	12.4[b]	15.4	24.8	9.4[b]	30.4	19.0
Loss/change of taste	3.3	15.7	12.4[b]	3.5	18.3	14.8[b]	20.4	12.9
Amnesia	4.7	11.7	7.0[b]	6.1	12.3	6.2[b]	15.4	9.5
Chest pressure	2.4	6.9	4.5[b]	2.6	6.9	4.3	9.3	5.5
Hair loss	3.6	7.4	3.8[b]	6.1	8.6	2.5	8.3	5.9
Headache	13.2	16.4	3.2	18.9	16.3	–2.6	19.0	12.6
Brain fog	5.0	8.2	3.2	6.1	8.4	2.3	10.9	6.7
Pain between shoulder blades	4.7	7.0	2.3	5.8	7.3	1.5	8.8	5.5
Palpitations	4.3	6.4	2.1	6.1	6.4	0.3	8.4	5.2
Increased resting heart rate	2.6	4.7	2.1	3.8	4.8	1.0	6.6	3.7
Confusion	1.2	2.9	1.7	1.2	2.9	1.7	4.1	2.3
Pain or burning sensation in the lungs	1.2	2.8	1.6	1.2	3.0	1.8	4.0	2.2
Irritability	8.3	9.9	1.6	13.0	9.9	–3.1	13.1	8.1
Muscle pain or weakness	9.7	11.0	1.3	13.7	11.2	–2.5	14.0	8.6
Voice difficulties	3.6	4.5	0.9	5.2	4.6	–0.6	5.7	3.3
Diarrhea	1.9	2.7	0.8	2.9	2.8	–0.1	3.4	2.1
Elevated body temperature	0.7	1.1	0.4	0.6	0.9	0.3	1.5	0.8
Heat flushes	1.4	1.8	0.4	2.6	1.9	–0.7	2.0	1.5
Fever	0.1	0.2	0.1	0.0	0.0	0.0	0.2	0.1
Sudden weight loss	0.8	0.9	0.1	1.7	0.9	–0.8	1.2	0.8
Burning sensation in the trachea	2.1	2.1	0.0	2.3	2.4	0.1	3.0	1.7
Stomach ache	2.9	2.6	–0.3	3.5	2.8	–0.7	3.0	2.1
Dizziness	7.1	6.8	–0.3	10.2	6.9	–3.3	9.1	5.5
Sleeping problems	16.6	16.3	–0.3	20.3	16.8	–3.5	20.3	13.1
Loss of appetite	2.6	2.2	–0.4	4.1	2.3	–1.8	3.1	1.8
Tinnitus	8.5	8.1	–0.4	7.8	7.8	0.0	8.5	6.3
Skin rash/red spots on toes or feet	1.5	1.0	–0.5	2.9	0.9	–2.0[b]	1.1	0.8
Nerve pain	3.3	2.8	–0.5	4.4	2.9	–1.5	3.6	2.2
Vomiting	0.8	0.2	–0.6[b]	1.4	0.1	–1.3[b]	0.2	0.1
Fear	5.1	4.4	–0.7	6.7	3.7	–3.0	5.7	3.5
Eye difficulties	5.8	5.0	–0.8	7.2	5.5	–1.7	6.4	4.0
Nausea	3.5	2.7	–0.8	4.4	2.3	–2.1	3.2	2.1
Joint pain	11.4	10.4	–1.0	12.5	10.1	–2.4	12.0	8.2
Coughing up mucus	11.1	10.0	–1.1	12.2	9.6	–2.6	10.4	6.5
Sore throat	9.0	7.6	–1.4	9.3	6.4	–2.9	7.2	4.9
Earache	3.3	1.8	–1.5	4.6	1.6	–3.0[b]	2.0	1.4
Other	5.3	3.6	–1.7	5.8	3.3	–2.5	3.8	2.9
Coughing	17.4	14.0	–3.4	17.7	12.1	–5.6	13.1	8.9
Dreariness/depression	12.5	9.1	–3.4	15.7	8.5	–7.2[b]	10.2	7.2
Sneezing	15.8	7.7	–8.1[b]	15.7	6.5	–9.2[b]	6.3	4.8

Table 2. Continued

Experienced Symptoms, w%	Definition 1. (≥1 of All Symptoms) n = 4488[a]			Definition 4. (WHO) n = 3095[a]			Definition 5. (Unrecovered) n = 2428[a]	Definition 6. (≥1 of All Symptoms at 3 Months) n = 4438[a]
	Negatives (n = 721)	Positives (n = 3767)	Diff.	Negatives (n = 345)	Positives (n = 2322)	Diff.	Positives	Positives
Cold	30.0	19.7	−10.3[b]	26.1	15.6	−10.5[b]	14.0	11.9
Runny nose	23.3	11.9	−11.4[b]	23.5	9.7	−13.8[b]	8.3	7.6

Definition 1. Currently reporting ≥1 of the 44 prelisted symptoms. Definition 4. World Health Organization post-COVID-19 condition case definition. Definition 5. Currently feeling unrecovered since PCR test. Definition 6. Reporting ≥1 of the 44 prelisted symptoms 3 months after testing. Diff = difference calculated by subtracting the proportion of the experienced symptoms in the negatives from the proportion of the experienced symptoms in the positives. Negative values represent symptoms more often present in negatives; positive values represent symptoms more frequently reported in positives.

Abbreviations: COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction; w%, weighted percentage; WHO, World Health Organization.

[a]Number of participants meeting the definition.

[b]Significantly different between positives and negatives meeting the definitions ($P \leq .001$).

Prevalence estimates for definitions 1–5 did not differ between test window groups. However, for definition 6 (≥1 of all symptoms at 3 months), the prevalence was significantly higher in positives tested 6–11 months (61.9%) and ≥12 months (64.1%) ago compared with positives tested 3–5 months (47.4%) ago.

Long-term Symptoms Potentially Attributable to COVID-19

The long-term symptoms proportion difference between positives and negatives—thus, the long-term symptoms potentially attributable to COVID-19—ranged between 17.9% and 26.3% for all definitions: 17.9%–21.9% for definition 1 (≥1 of all symptoms), 22.8%–26.3% for definition 2 (different symptoms in positives/negatives), 18.2%–23.7% for definition 3 (different symptoms in positives/negatives plus severity), and 21.4%–23.3% for definition 4 (WHO) (Figure 4).

Overlap Between Case Definitions in Positives

In total, 519 (61.4%), 3567 (69.7%), and 1043 (72.4%) positives tested 3–5, 6–11, and ≥12 months ago, respectively, met at least 1 of the 6 outcome case definitions.

Of these, the majority of the participants with long-term symptoms met definition 1 (≥1 of all symptoms; 80.5% tested 3–5 months ago, 76.4% tested 6–11 months ago, and 75.7% tested ≥12 months ago) and definition 6 (≥1 of all symptoms at 3 months; 85.2% tested 3–5 months ago, 91.7% tested 6–11 months ago, and 91.3% tested ≥12 months ago) (Figure 5).

About half of the participants with long-term symptoms met definitions 4 (WHO) and 5 (unrecovered) (Figure 5). The overlap between the definitions depicted in the Venn diagrams was similar for the different test window groups.

The proportion of participants who met the WHO definition and would also meet definitions used in clinical practice (definitions 1, 5, and 6) was 100.0%, 67.9%, and 93.4% for definitions 1, 5, and 6, respectively. The proportion of participants not meeting the WHO definition (definition 4), and similarly not meeting definitions 1, 5, and 6, was 76.4%, 85.4%, and 56.5%, respectively (Table 3).

DISCUSSION

The results of the PRIME post-COVID cohort study demonstrate that loss/change of smell, fatigue, loss/change of taste, shortness of breath, and concentration difficulties reflect the most pronounced long-term symptoms. Prevalence estimates of long-term symptoms after PCR-positive testing show a large range from 26.9% to 53.1%, depending on the definition used in science and care. Variation was also recorded by moment of report, demonstrating 64.1% based on retrospective assessment of symptoms present 3 months after testing. Participants who tested negative also reported symptoms, with substantial proportions ranging from 11.4% to 32.5%. Accounting for symptoms in negatives, the prevalence of long-term symptoms potentially attributable to a SARS-CoV-2 infection ranged from 17.9% to 26.3%.

Including negatives enables an estimation of the proportion of direct consequences of COVID-19 infection. Yet, we acknowledge that we cannot rule out that (some) tested negatives might have been infected (eg, due to undiagnosed infection at the time of questionnaire completion), but unknown in our data set. Despite the varying prevalence estimates when using different definitions, the prevalence potentially attributable to COVID-19 is within a reasonable range across the various case definitions (between 17.9% and 26.3%). These findings suggest that the inclusion of a control group of negatively tested participants can be of great value when estimating post-COVID-19 condition prevalence, independent of definition used.

Comparing the prevalence estimates of our study with previous literature is challenging due to unstandardized definitions of relevant symptoms after testing or infection. Prevalence estimates from previous studies ranged from 6.0% to 80.0% in positives and 26.0% to 53.4% in negatives, and the proportion

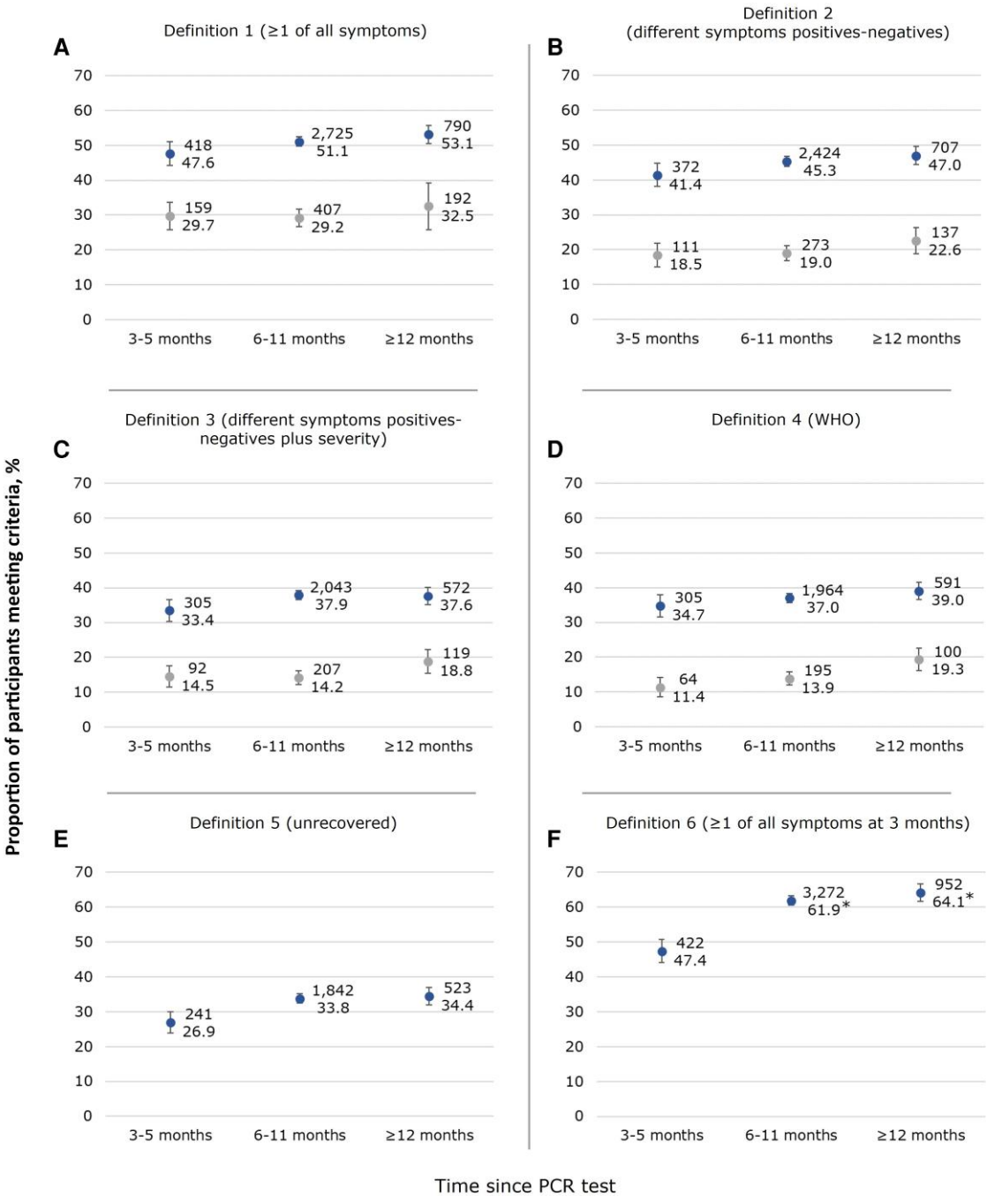

Figure 3. Weighted prevalence estimates and 95% confidence intervals for 6 long-term symptom definitions in positives and negatives stratified for time since PCR test. *A*, Definition 1. Currently reporting ≥1 of the 44 prelisted symptoms. *B*, Definition 2. Currently reporting ≥1 of the 24 symptoms more often reported in positives than negatives. *C*, Definition 3. Reporting ≥1 of the 24 symptoms more often reported in positives than negatives with a severity score of ≥5. *D*, Definition 4. Meeting the World Health Organization definition. *E*, Definition 5. Currently feeling unrecovered since PCR test. *F*, Definition 6. Reporting ≥1 of the 44 prelisted symptoms 3 months after testing. *Significant differences in prevalence estimates compared with participants tested 3–5 months ago. Dominant virus variants in overlapping periods were Wuhan strain between March and December 2020, Alpha strain between December 2020 and July 2021, and Delta strain between July and December 2021. Abbreviations: PCR, polymerase chain reaction; WHO, World Health Organization.

attributable to COVID-19 ranged from 12.7% to 25.2% [10, 11, 25, 28–31]. The range in estimated attributable symptoms is comparable to our findings.

The type of symptoms and the proportion of positives and negatives who reported experiencing those symptoms can be very different when using different case definitions. For

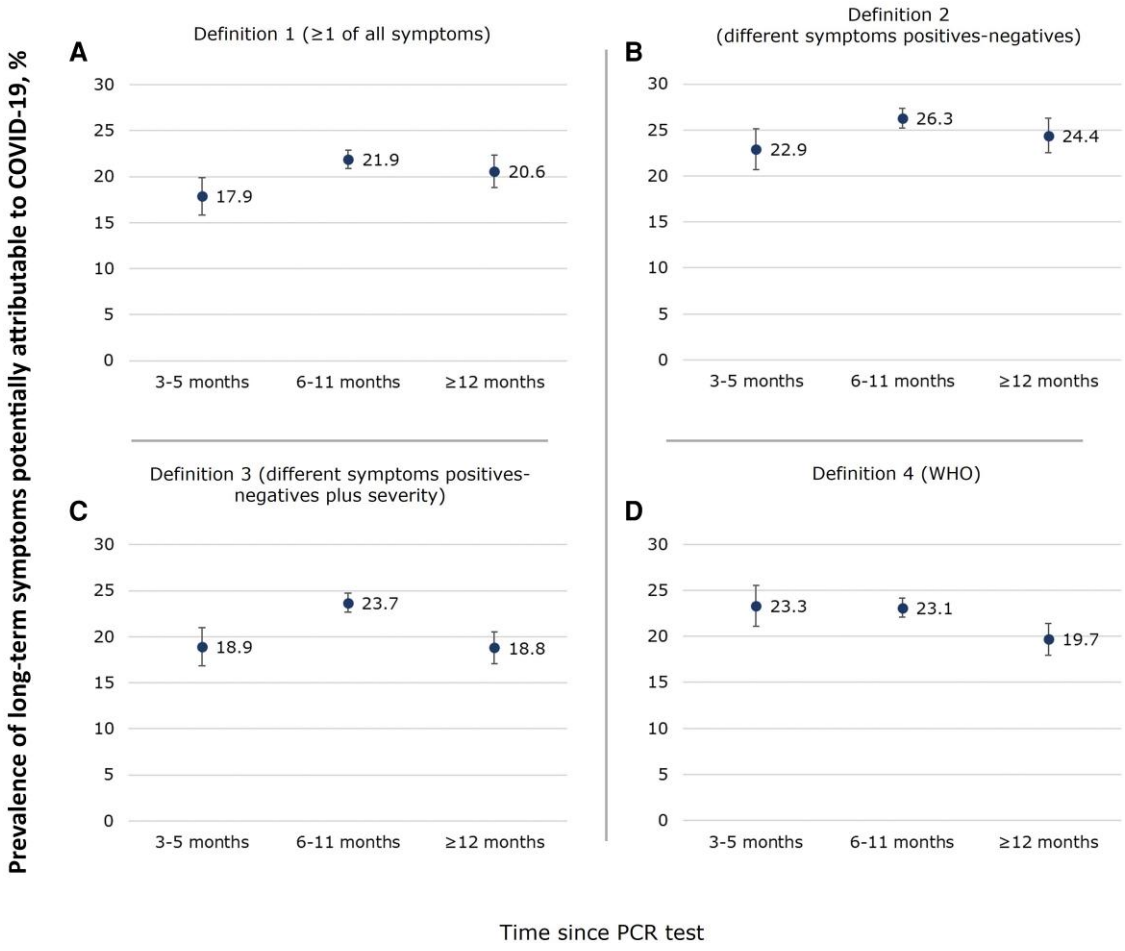

Figure 4. Weighted prevalence estimates and 95% confidence intervals for long-term symptoms potentially attributable to COVID-19 using 4 definitions, stratified for time since PCR test. *A*, Definition 1. Currently reporting ≥1 of the 44 prelisted symptoms. *B*, Definition 2. Currently reporting ≥1 of the 24 symptoms more often reported in-positives than negatives. *C*, Definition 3. Reporting ≥1 of the 24 symptoms more often reported in positives than negatives with a severity score of ≥5. *D*, Definition 4. Meeting the World Health Organization definition. Potentially attributable prevalence was calculated by subtracting the observed prevalence in negatives from the observed prevalence in positives. Abbreviations: COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction; WHO, World Health Organization.

example, the difference between experiencing fatigue in positively vs negatively tested participants meeting definition 1 (≥1 of all symptoms) was twice as high compared with the difference in experiencing fatigue between positively and negatively tested participants who met definition 4 (WHO). This clearly illustrates the difficulty of defining a core set of symptoms, which is needed to reach the desired consensus.

The results of our study suggest that defining the presence of long-term symptoms based on any symptoms likely overestimates the prevalence of post-COVID-19 condition. Selecting only symptoms significantly more often reported in positives than negatives and including a degree of severity results in lower prevalence estimates. While this might result in more realistic estimates, it should be noted that such a definition also might still be an underestimation due to potentially relevant unmeasured symptoms. Recent studies have included symptom severity in the case definition [10, 11], suggesting that this might have added value when studying post-COVID-19 condition. Our results provide a range of prevalence estimates based on different definitions, highlighting the complexity of this condition and measurements and providing a point of reference for future research. Focusing on a single definition will cause cases to be missed, as exemplified in our Venn diagram and comparison with the WHO definition. Only including the WHO definition when studying post-COVID-19 condition will identify about half (55.1% to 58.8% for different test window groups) of all likely cases (based on definitions 1–3, 5, and 6). Thereby, we were able to compare simpler (in practice) definitions with each other and the current WHO definition. Yet, this also indicates that the search for an adequate case definition is not complete, and finding the essential criteria for defining post-COVID-19 condition is still a challenge.

No differences in prevalence estimates were observed in the test window groups. Only for definition 6 (constructed by

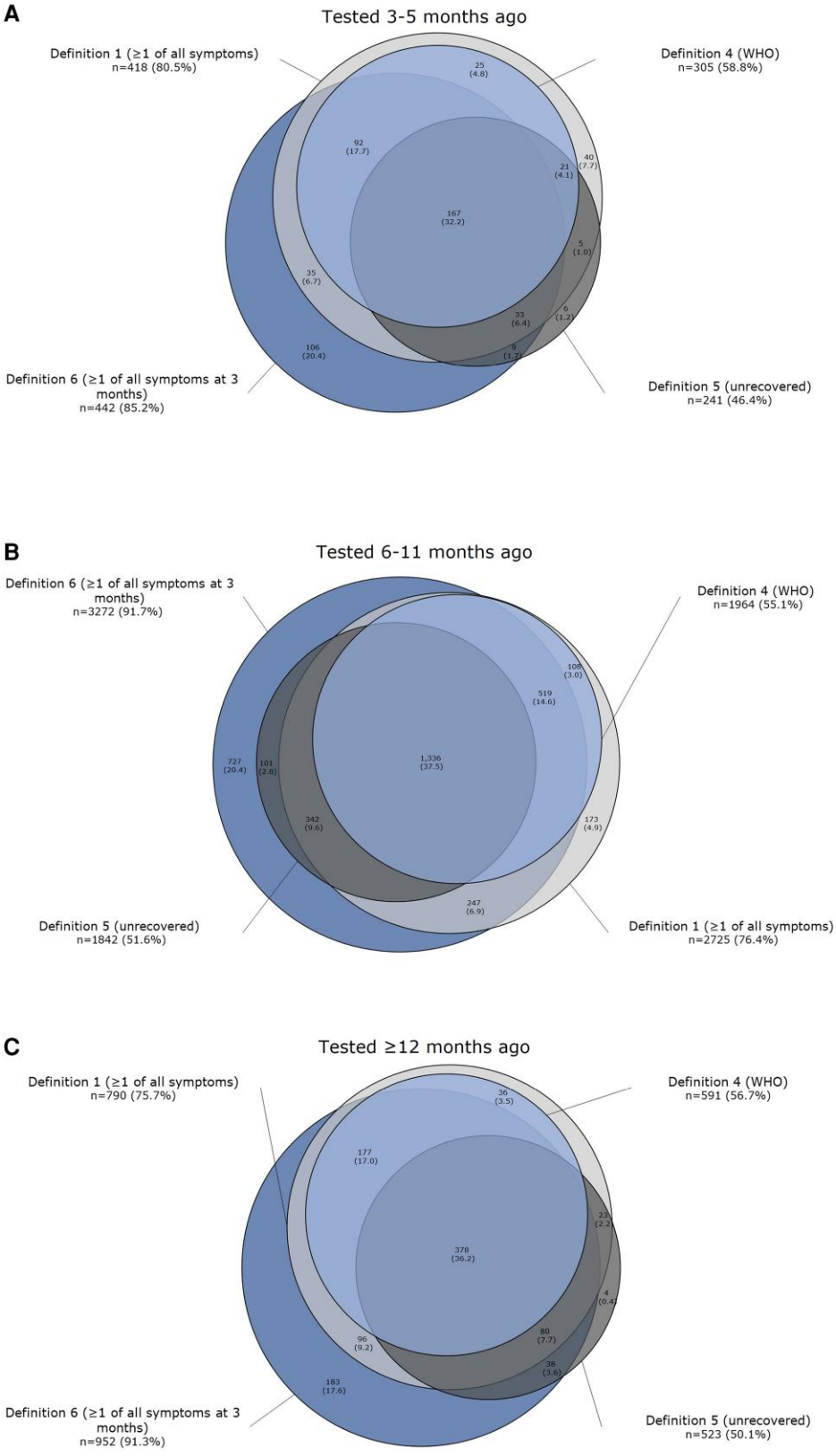

Figure 5. Venn diagrams of 4 long-term symptom definitions in positively tested participants, stratified for time since PCR test. A, tested 3-5 months ago. B, tested 6-11 months ago. C, Tested ≥12 months ago. Definition 1. Currently reporting ≥1 of the 44 prelisted symptoms. Definition 4. Meeting the World Health Organization definition. Definition 5. Currently feeling unrecovered since PCR test. Definition 6. Reporting ≥1 of the 44 prelisted symptoms 3 months after testing. Percentages represent the proportion of participants meeting the definitions compared with all positives who met at least 1 of the definitions (n = 519 for participants tested 3–5 months ago, n = 3567 for participants tested 6–11 months ago, and n = 1043 for participants tested ≥12 months ago). Abbreviations: PCR, polymerase chain reaction; WHO, World Health Organization.

Table 3. Comparison Between the Definitions Used in Daily Clinical Practice (Definitions 1, 5, and 6) and the WHO Definition

		Definition 4 (WHO)	
Tested 3–5 Months Ago (n = 846)		Met Definition (n = 305)	Did Not Meet Definition (n = 541)
Definition 1 (≥1 of all symptoms)	Met definition (n = 418)	100.0%	…
	Did not meet definition (n = 428)	…	79.1%
Definition 5 (unrecovered)	Met definition (n = 241)	61.6%	…
	Did not meet definition (n = 605)	…	90.2%
Definition 6 (≥1 of all symptoms at 3 mo)	Met definition (n = 422)	84.9%	…
	Did not meet definition (n = 424)	…	69.9%
Tested 6–11 mo ago (n = 5119)	…	(n = 1964)	(n = 3155)
Definition 1 (≥1 of all symptoms)	Met definition (n = 2725)	99.9%	…
	Did not meet definition (n = 2394)	…	75.9%
Definition 5 (unrecovered)	Met definition (n = 1842)	69.4%	…
	Did not meet definition (n = 3277)	…	84.8%
Definition 6 (≥1 of all symptoms at 3 mo)	Met definition (n = 3272)	94.5%	…
	Did not meet definition (n = 1847)	…	55.1%
Tested ≥12 mo ago (n = 1440)	…	(n = 591)	(n = 849)
Definition 1 (≥1 of all symptoms)	Met definition (n = 790)	100.0%	…
	Did not meet definition (n = 650)	…	76.6%
Definition 5 (unrecovered)	Met definition (n = 523)	66.0%	…
	Did not meet definition (n = 917)	…	84.3%
Definition 6 (≥1 of all symptoms at 3 mo)	Met definition (n = 952)	93.9%	…
	Did not meet definition (n = 488)	…	53.2%

Percentages represent proportion of participants who met definition 4 (WHO) and also met definitions 1 (≥1 of all symptoms), 5 (unrecovered), and 6 (≥1 of all symptoms at 3 months) OR the proportion of participants who did not meet definition 4 (WHO) and also did not meet definitions 1 (≥1 of all symptoms), 5 (unrecovered), and 6 (≥1 of all symptoms at 3 months).

Abbreviations: WHO, World Health Organization.

retrospective reporting; ≥1 of all symptoms at 3 months) was prevalence significantly higher in participants tested 6–11 and ≥12 months ago, compared with participants tested 3–5 months ago. Whether this is due to potential (recall) bias, virus variant (overlapping with the time periods since test used in the current study), or vaccination status must be further explored. Currently, only data from the baseline recruitment (cross-sectional) are available, eliminating the opportunity to study prevalence estimates in more recent calendar times and individual trajectories over time. Future analysis using longitudinal data collected within the PRIME post-COVID study will provide more insight into this issue.

Strengths and Limitations

The major strength of this study is the population-based sample, also including positives who experienced a mild infection. Additionally, we were able to include a considerable portion of negatives, creating the opportunity to study long-term symptoms experienced in the general population and the proportion of long-term symptoms potentially attributable to COVID-19. Nevertheless, negatives might have been infected, but not tested, due to limited test possibilities in the beginning of the pandemic, lack of indication for testing (ie, asymptomatic nature of the infection), or lack of intention to test. This might have affected our comparison of symptoms and prevalence estimates between positives and negatives, possibly leading to some overcorrection. Nevertheless, sensitivity analyses excluding negatives with SARS-CoV-2 antibodies before vaccination showed comparable results. Regarding the validity, we were able to check questionnaire data with public health registry data, resulting in more confirmed certainty of our data (ie, age, sex, test result, and test date).

First, possible limitations in generalizability have to be discussed. As all positively tested adults in the registry were invited, the invitees were representative of all positives recorded in the Dutch public health test registry (in our study region). Nevertheless, the generalizability of the individuals in the registry regarding all positive adults in the population might not be optimal. For example, the number of individuals suffering severe illness was limited, possibly resulting in an underestimation of post-COVID-19 condition in our sample [32]. Additionally, a limited number of asymptomatic positives were included due to lack of motivation for testing and thus no registration in the public health registry. Still, some positively and negatively tested participants did not experience any symptoms when tested, meaning that testing—as well as registration—was probably indicated by other factors (eg, source and contact tracing). It is expected that the lack of asymptomatic positives has a limited effect, as post-COVID-19 condition prevalence is estimated to be very limited in this population.

Negative invitees were comparable to positive invitees in key characteristics, however, not necessarily to all negatives in the registry. Among invited negatives, there were fewer women (50.1% vs 55.6%), fewer adults tested in the second quarter of 2020 (18.3% vs 23.4%), and more adults aged 51–70 years (34.1% vs 24.1%), compared with all negatives in the registry. We acknowledge the limited generalizability of negative participants to negatives in the registry, but recognize the value of comparable characteristics between positive and negative invitees.

Second, there is a possibility of selection bias overall, as not all invitees participated. Elderly individuals who are less digitally skilled were probably more likely to decline participation, resulting in an underrepresentation of these participants. However, we tried to limit the influence of selection bias on our results by weighing participants back to invitees on key characteristics (age, sex, year-quarter of testing, test result). Nevertheless, we observed negatives to be more often men (when tested ≥6 months ago) and older, which we will take into account in future analyses.

In conclusion, prevalence estimates of long-term symptoms after infection vary widely, between 26.9% and 53.1% when using different definitions based on current symptoms (ie, measuring moment now) and 64.1% when using a definition based on retrospective assessment of symptoms (ie, 3 months after PCR test) in positives. This highlights the importance of formulating an adequate post-COVID condition definition to reliably estimate the prevalence of long-term symptoms attributable to a positive SARS-CoV-2 test. Taking severity of experienced symptoms into account facilitates specification of prevalence estimates by only including symptoms that have at least a moderate impact. Negatives or population controls are important to determine long-term symptoms attributable to COVID-19, preventing overestimation of prevalence. Furthermore, there is limited overlap between different long-term symptom definitions, indicating that the essential criteria for defining post-COVID-19 condition are still unclear. Future studies should focus on risk factors predisposing certain individuals to help focus on relevant subgroups in practice for the clinic or the general population.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

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Author contributions. D.P., C.v.B., S.B., M.V.H., K.K., C.d.H., H.t.W., M.S., C.H., and N.D. designed the study. D.P., C.v.B., and S.B. actively participated in data collection. D.P. performed the data analysis and wrote the first draft of the manuscript. C.v.B., M.V.H., K.K., C.d.H., and N.D. supervised data analysis and collection. All authors were involved in data interpretation, revised the manuscript critically for important intellectual content, approved the final version, and agreed to be accountable for all aspects of the manuscript.

Data availability. Data cannot be shared publicly because the data contain potentially identifying patient information. Data are available on request from the head of the data-archiving South Limburg Public Health Service (contact via helen.sijstermans@ggdzl.nl) for researchers who meet the criteria for access to confidential data.

Participant consent. The Medical Ethical Committee of Maastricht University Medical Centre+ waived this study (METC2021-2884), as the Medical Research Involving Human Subjects Act (WMO) did not apply. Written digital informed consent was obtained before questionnaire completion.

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Potential conflicts of interest. All authors: no reported conflicts.

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0% (n=0/615)||,¶,#,8,9
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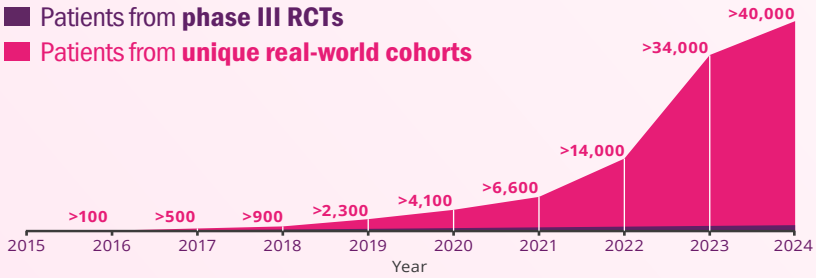

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ABBREVIATIONS

3TC, lamivudine; **CD4,** cluster of differentiation 4; **DTG,** dolutegravir; **FDA,** United States Food and Drug Administration; **FTC,** emtricitabine; **HIV,** human immunodeficiency virus; **ITT-E,** intention-to-treat exposed; **NRTI,** nucleoside/nucleotide reverse transcriptase inhibitor; **RCT,** randomised controlled trial; **RNA,** ribonucleic acid; **TAF,** tenofovir alafenamide fumarate; **TDF,** tenofovir disoproxil fumarate; **XTC,** emtricitabine.

FOOTNOTES

*Data extracted from a systematic literature review of DTG+3TC real-world evidence. Overlap between cohorts cannot be fully excluded.

**The reported rate reflects the sum-total of resistance cases calculated from GEMINI I and II (n=1/716, through 144 weeks), STAT (n=0/131, through 52 weeks), and D2ARLING (n=0/106, through 24 weeks).[5–7]

†GEMINI I and II are two identical 148-week, phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority, controlled clinical trials testing the efficacy of DTG/3TC in treatment-naïve patients. Participants with screening HIV-1 RNA ≤500,000 copies/mL were randomised 1:1 to once-daily DTG/3TC (n=716, pooled) or DTG + TDF/FTC (n=717, pooled). The primary endpoint of each GEMINI study was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).[13]

‡STAT is a phase IIIb, open-label, 48-week, single-arm pilot study evaluating the feasibility, efficacy, and safety of DTG/3TC in 131 newly diagnosed HIV-1 infected adults as a first line regimen. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 24.[6]

§D2ARLING is a randomised, open-label, phase IV study designed to assess the efficacy and safety of DTG/3TC in treatment-naïve people with HIV with no available baseline HIV-1 resistance testing. Participants were randomised in a 1:1 ratio to receive DTG/3TC (n=106) or DTG + TDF/XTC (n=108). The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48.[7] Results at week 24 of the study.

||The reported rate reflects the sum-total of resistance cases calculated from TANGO (n=0/369, through 196 weeks) and SALSA (n=0/246, through 48 weeks).[8,9]

¶TANGO is a randomised, open-label, trial testing the efficacy of DOVATO in virologically suppressed patients. Participants were randomised in a 1:1 ratio to receive DOVATO (n=369) or continue with TAF-containing regimens (n=372) for up to 200 weeks. At Week 148, 298 of those on TAF-based regimens switched to DOVATO. The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL (virologic non-response) as per the FDA Snapshot category at Week 48 (adjusted for randomisation stratification factor).[8,13]

#SALSA is a phase III, randomised, open-label, non-inferiority clinical trial evaluating the efficacy and safety of switching to DTG/3TC compared with continuing current antiretroviral regimens in virologically suppressed adults with HIV. Eligible participants were randomised 1:1 to switch to once-daily DTG/3TC (n=246) or continue current antiretroviral regimens (n=247). The primary endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).[9]

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