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Trajectories of Health-Related Quality of Life 2 Years After Mild/Moderate Severe Acute Respiratory Syndrome Coronavirus 2 Infection in the Pre-Omicron Era

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Background. Individuals with postacute sequelae of coronavirus disease 2019 (COVID-19), or long COVID, experience substantial burden of illness many months after initial infection. Few studies have comprehensively and longitudinally assessed health outcomes for people with long COVID following mild/moderate infection. We applied the Wilson-Cleary model of health-related quality of life (HRQOL) to describe the impact of long COVID on multiple health dimensions up to 24 months following mild/moderate COVID-19.

Methods. Participants within the ADAPT post-COVID study (N = 172, 86% mild/moderate infection) completed structured patient-reported outcome measures at 4, 8, 12, 18, and 24 months postinfection. Following the Wilson-Cleary model, questionnaires assessed symptoms (anxiety/depression, chronic fatigue, breathlessness), return to pre-COVID-19 functioning, perceived health status (EuroQol Visual Analogue Scale), and wellbeing (EuroQol EQ-5D-5L, Personal Wellbeing Index). Temporal trends were assessed using general estimating equations and ordinal logistic regression, including time × long COVID interactions.

Results. Thirty-seven percent of participants were diagnosed with long COVID (≥1 new/persisting symptoms of chest pain, breathlessness, or fatigue/malaise at least 12 weeks after infection). Long COVID was associated with poorer health outcomes across all domains at first assessment. Over 2 years, participants with long COVID reported improvement in return to pre-COVID-19 work and Somatic and Psychological Health Report chronic fatigue but sustained impairment was observed in all other health domains, compared to participants recovered from COVID-19.

Conclusions. Substantial long-term impairment in various health domains were observed for individuals with long COVID following mild/moderate initial infection, with little improvement over time in most. Multimodal interventions must address impairment in multiple domains of HRQOL in individuals with long COVID.

Keywords. long COVID; patient-reported outcome measures; postacute sequelae of COVID-19; recovery; wellbeing.

Postacute sequelae of coronavirus disease 2019 (COVID-19), or long COVID, present an ongoing burden to a proportion of individuals exposed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), substantially limiting activities of daily living and adversely affecting health. A unified clinical definition of long COVID remains elusive; however, descriptions of long COVID typically depend on presence of symptoms persisting >12 weeks after index SARS-CoV-2 infection that were not present before initial infection and cannot be explained by other illness. An estimated 4%–6% of symptomatic SARS-CoV-2 infections in the general population result in long COVID during the pre-Omicron period, when accounting for presence of symptoms in individuals not exposed [1, 2]. Postacute symptoms commonly reported include fatigue, chest pain, and cognitive impairment [3, 4], most often occurring among people with severe initial SARS-CoV-2 infection, female sex at birth, and those with comorbid illnesses [5, 6]. The mechanisms underlying long COVID are not fully understood, but cluster analysis of symptoms in cross-sectional cohorts has suggested presence of subgroups related to pain/fatigue, breathlessness/chest pain, cardiovascular, and neuropsychiatric domains [7, 8].

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The long-term consequences of acute and chronic health conditions on wellbeing and quality of life are becoming widely recognized for respiratory pathogens and chronic illnesses but are not well understood for SARS-CoV-2 infection. Given the potential for broad impact on individuals, conceptual models of health and wellbeing are often used to understand the multidimensional impact of illness and guide health-related quality of life (HRQOL) research and practice [9]. For example, the Wilson-Cleary model of HRQOL conceptualizes individual health across five domains (biological and physiological factors, illness symptoms, functioning, general health perceptions, and overall quality of life) plus overarching environmental/individual characteristics to link clinical measures to broader health outcomes and to guide testing of direct causal relationships along the health domains [10]. The Wilson-Cleary model (and subsequent revision [11]) is the most commonly used conceptual model and has been used to in numerous chronic disease settings (eg, human immunodeficiency virus/AIDS, cardiovascular, respiratory, and cancer) [12, 13], but has not been widely applied in the context of post-COVID-19 illness. In the years following SARS-CoV-2 infection, self-reported recovery to pre-COVID-19 health in those with long COVID is often limited and HRQOL remains impaired despite reduction in the prevalence and severity of long COVID symptoms [14–16]. Individuals diagnosed with long COVID are more likely to experience prolonged impairment in HRQOL and poorer functioning compared to those who fully recovered after acute COVID-19 [17, 18]. While there is evidence of impaired health following SARS-CoV-2 infection, there is a lack of research that applies existing conceptual models of health and wellbeing to understand the impact of long COVID on patient-reported outcome measures.

This study aimed to use the Wilson-Cleary model of HRQOL to assess individual- and population-level trends in multiple domains (symptoms, functioning, general health perceptions, overall quality of life) in a cohort of individuals with mild/moderate initial SARS-CoV-2 infection up to 24 months postinfection. Temporal changes in patient-reported outcome measures reported at prescheduled visits for up to 24 months following initial infection, and the contribution of long COVID status to impairment, were assessed using generalized estimating equation regression and ordinal regression models.

METHODS

Patient Consent Statement

Written informed consent was obtained for all participants at enrollment. The study protocol was approved by the St Vincent's Hospital Human Research Ethics Committee (reference: 2020/ETH00964).

This analysis utilized the ADAPT Study, a longitudinal cohort of people with predominantly mild/moderate COVID-19 in an urban area of Australia [19]. As previously described, individuals (N = 198) with nasopharyngeal swab polymerase chain reaction–confirmed SARS-CoV-2 infection were enrolled between 14 May 2020 and 16 February 2022 to complete structured laboratory and clinical assessments and patient-reported outcomes at scheduled study visits (4, 6, 12, 18, and 24 months following index infection). Given differences in disease severity and clinical outcomes by SARS-CoV-2 variants [20], we restricted analysis to infections acquired prior to Omicron being the major variant of concern (ie, date of diagnosis before 17 December 2021). Index SARS-CoV-2 infection experience (eg, symptoms, severity, comorbidities) and sociodemographic factors (ie, age, sex, housing status, employment status) were recorded at enrollment. At each follow-up visit, patient-reported outcome measures and respiratory infection status (eg, recurrent SARS-CoV-2 or other respiratory infection, new COVID-19 symptom) were recorded. Additionally, non-COVID-19 control cases (ie, exposed to respiratory virus other than SARS-CoV-2 or epidemiological contact of SARS-CoV-2 infection) enrolled between 18 August 2020 and 14 December 2020 completed patient-reported outcome measures 4 and 12 months after a confirmed negative SARS-CoV-2 RNA test.

Patient-Reported Outcome Measures. In line with the Wilson-Cleary model of HRQOL (Supplementary Figure 1), patient assessments were prospectively completed for the following domains:

Biological Function. Long COVID was defined as per the classification from prior ADAPT Study analyses: patient reporting new or persisting symptom of chest pain, shortness of breath, or fatigue/malaise at the participant's first study visit occurring ≥12 weeks after their index SARS-CoV-2 infection [19]. Participants who did not report new or persistent symptoms at this assessment visit were considered recovered, and participants who did not complete a study visit ≥12 weeks after index SARS-CoV-2 infection (n = 26) were excluded from the current analysis. Long COVID status was the primary exposure in the analysis and was time-invariant during follow-up.

Symptoms. Psychological and physiological impairment was assessed at each visit using subscales of the validated Somatic and Psychological Health Report (SPHERE), specifically symptoms of anxiety and depression (SPHERE anxiety/depression; 14 items) and chronic fatigue (SPHERE chronic fatigue; 10 items) [21]. Each item was measured using a Likert scale (3-level; "never/some of the time" to "most of the time") and sum scores generated for each subscale (range: 0–28 for anxiety/depression, 0–20 for chronic fatigue). Breathlessness was

assessed at 8-, 12-, 18-, and 24-month visits using the modified Medical Research Council (MRC) dyspnea scale (5-level; "only with strenuous exercise"; "when hurrying on the level or up a slight hill"; "when walking at own pace on the level"; "when walking 100 yards or for a few minutes"; "at rest") [22]. Given low endorsement, the 2 top levels were collapsed into a single level.

Functioning. Perceived COVID-19–related functioning was assessed at 8-, 12-, 18-, and 24-month visits for 4 domains: (1) fully recovered from COVID-19; (2) confident returning to pre-COVID-19 work; (3) return to usual activities of daily living; and (4) return to normal exercise levels. Each question was measured on a Likert scale (6-level; "strongly disagree" to "strongly agree").

Global Health Perception. Perceived global health was assessed using the EuroQol Visual Analogue Scale (EQ-VAS) tool [23]. Participants rate their current perceived health on a scale of 0 ("worst health you can imagine") to 100 points ("best health you can imagine").

Overall Quality of Life. Participants reported their health state in 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) at each visit using the EuroQol 5-dimension 5-level (EQ-5D-5L) tool [23]. The EQ-5D-5L health states were converted into a single health utility score based on the Australian value-set [24]. The utility scores mostly lie between 0 and 1, where 0 represents death and 1 represents perfect health. Negative utility scores are also possible, which indicates a health state worse than death. Health status was defined as "poor" if EQ-5D-5L utility scores were below the lower 95% confidence interval (CI) of age- and sex-matched normative values from the general population in Australia [25]. Subjective wellbeing was assessed at 8-, 12-, 18-, and 24-month visits using the Personal Wellbeing Index (PWI) [26], a validated tool that assesses 7 life domains (standard of living, health, achieving, relationships, safety, community, future). Each item was scored on an 11-point scale ("no satisfaction at all" to "completely satisfied"), and the sum of 7 items was converted into the standard 0–100 scale.

Statistical Analysis

Continuous Outcomes. To assess population-mean changes in continuous HRQOL outcomes (ie, EQ-5D-5L utility score and EQ-VAS scores, SPHERE, PWI) over time, generalized estimating equation (GEE) linear regression models were used, with the effect of time since index infection on outcome estimated using β-coefficients and 95% CI. Time effect was assessed in incremental study visits, irrespective of the duration between study visits. GEE models were adjusted for baseline covariates (age, sex, education, date of initial SARS-CoV-2 infection, smoking history, number of comorbid conditions, and premorbid psychiatric conditions) and time-updating covariates (eg, hospitalization since last visit, recurrent SARS-CoV-2 or other respiratory infection) that may impact outcomes independent from long COVID status. Additional models assessed the interaction between time and long COVID status.

Ordinal Outcomes. To assess population-level functional status change over time, ordinal regression models were used with the effect of time since index infection on functional status score estimated using odds ratios (ORs) and 95% CIs [27]. Ordinal linear regression models were adjusted for baseline and time-updating covariates as above.

For all analyses, statistically significant differences were assessed at a .05 level; *P* values were 2-sided. All analyses were performed using Stata version 14.2 software (StataCorp LLC, College Station, Texas).

RESULTS

In total, 172 participants were recruited in the ADAPT Study and completed long COVID assessment ≥12 weeks after index SARS-CoV-2 infection, completing an average of 3.9 study visits over 24 months. Participants were most often assigned male at birth, White/Caucasian ethnicity, and completed higher education, with median age 48 years (interquartile range [IQR], 35–58 years) (Table 1). Comorbid medical conditions were reported by 74 (43%) participants, with the most common conditions being chronic respiratory disease, hypertension, immunological suppression, and psychiatric conditions. Most participants had mild/moderate index SARS-CoV-2 infection, with 24 (14%) participants hospitalized and 6 (3%) admitted to the intensive care unit (ICU). The median time from index infection to long COVID assessment was 132 days (IQR, 116–154 days), with 64 (37%) participants meeting this definition. Most participants had their initial SARS-CoV-2 infection during April–May 2020 (n = 111 [65%]), with 15% vaccinated before enrollment and 60% vaccinated by 12 months postinfection. During follow-up, recurrent SARS-CoV-2 infection was reported at 47 study visits in 45 individuals and all-cause hospitalization was reported at 50 study visits in 40 individuals.

The EQ-5D-5L tool demonstrated acceptable psychometric performance in this cohort of people with predominantly mild/moderate index SARS-CoV-2 infection (Supplementary Table 1). For participants with long COVID, the mean EQ-5D-5L utility score was 0.90 (standard deviation [SD], 0.11) at 4 months, 0.91 (SD, 0.11) at 12 months, and 0.93 (SD, 0.7) at 24 months postinfection (Figure 1; Supplementary Table 2). In comparison, for recovered participants the mean EQ-5D-5L utility score was 0.97 (SD, 0.06) at 4 months, 0.96 (SD, 0.07) at 12 months, and 0.96 (SD, 0.04) at 24 months

Table 1. Baseline Characteristics of Participants Enrolled in the ADAPT Study Who Completed Assessment for Long COVID

Characteristic	Recovered and Long COVID Total (n = 172)	Long COVID Status		Non-COVID-19 Controls (n = 51)
		Recovered (n = 108)	Long COVID (n = 64)	
Age, y, median (IQR)	48 (35–59)	45 (34–58)	51 (39–60)	45 (32–60)
Sex at birth				
Female	74 (43)	41 (38)	33 (52)	28 (55)
Male	98 (57)	67 (62)	31 (48)	23 (45)
White/Caucasian ethnicity				
No	23 (13)	14 (13)	9 (14)	7 (14)
Yes	149 (87)	94 (87)	55 (86)	44 (86)
Completed higher education				
No	36 (21)	21 (19)	15 (23)	11 (22)
Yes	136 (79)	87 (81)	49 (77)	40 (78)
Employment status				
Not full-time employed	96 (56)	61 (57)	35 (55)	28 (54)
Full-time employed	76 (44)	47 (44)	29 (45)	23 (45)
Smoking status				
No smoking	99 (58)	60 (56)	39 (61)	…
Current or past smoking	73 (42)	48 (44)	25 (39)	…
Preexisting psychiatric condition	18 (11)	10 (9)	8 (13)	…
Preexisting physical comorbidities				
No. of conditions, median (IQR)	1 (0–1)	1 (0–1)	1 (0–2)	1 (0–1)
Body mass index >30 kg/m^2	35 (20)	16 (15)	19 (30)	0 (0)
Chronic respiratory disease	22 (13)	12 (11)	10 (16)	5 (10)
Chronic cardiac disease	12 (7)	9 (8)	3 (5)	2 (4)
Diabetes mellitus	10 (6)	3 (3)	7 (11)	0 (0)
Cancer/malignant neoplasm	10 (6)	7 (7)	3 (5)	0 (0)
Hypertension	20 (12)	15 (14)	5 (8)	8 (16)
Chronic kidney disease	4 (2)	2 (2)	2 (3)	1 (2)
Immunological suppression	18 (11)	8 (7)	10 (16)	4 (8)
Date of initial SARS-CoV-2 infection				
Apr 2020–May 2020	111 (65)	72 (67)	39 (61)	…
July 2020–Dec 2020	25 (15)	18 (17)	7 (11)	…
June 2021–Jan 2021	36 (21)	18 (17)	18 (27)	…
Hospitalization during initial SARS-CoV-2 infection				
No	148 (86)	100 (93)	48 (75)	…
Yes	24 (14)	8 (7)	16 (25)	…
Vaccination status[a]				
At enrollment	21 (15)	10 (11)	11 (20)	…
At 12 mo	88 (61)	48 (53)	40 (74)	…
Hospitalization during follow-up				
No	132 (77)	91 (84)	41 (64)	42 (82)
Yes	40 (23)	17 (16)	23 (36)	9 (18)
Recurrent SARS-CoV-2 infection				
No	127 (74)	79 (73)	48 (75)	…
Yes	45 (26)	29 (27)	16 (25)	…

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Among 145 participants with COVID-19 vaccination records.

postinfection. A greater proportion of participants with long COVID had EQ-5D-5L utility scores below the lower 95% CI of population norms at all visits (12%–26%) compared to recovered participants (0.0–5%). Similarly, with global perceived health, participants with long COVID had consistently lower EQ-VAS scores compared to recovered participants at the 4-month (76 vs 85, respectively), 12-month (76 vs 84, respectively), and 24-month (77 vs 84, respectively) study visits (Figure 1; Supplementary Table 2). A greater proportion of participants with long COVID had EQ-5D-5L utility scores below the lower

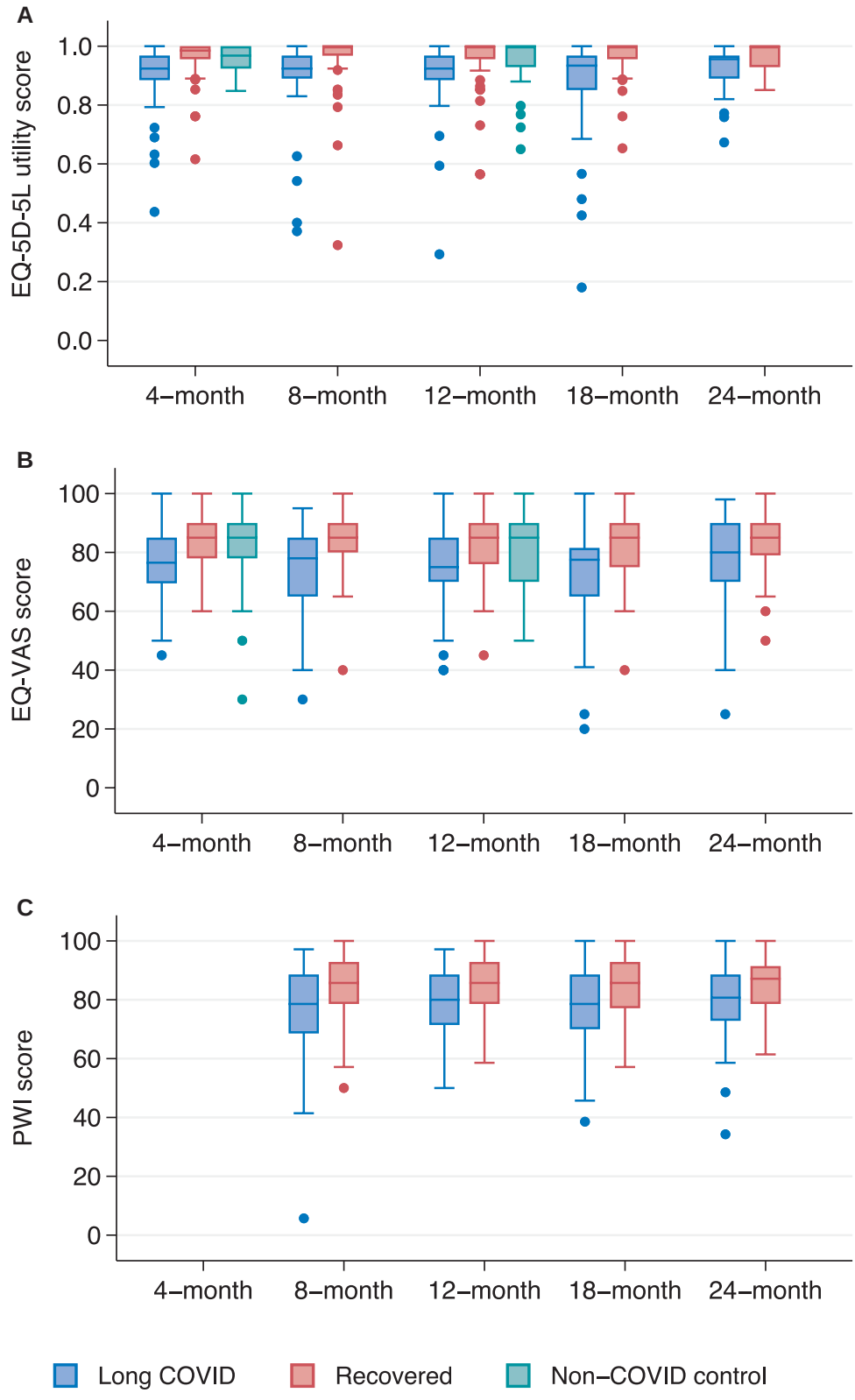

Figure 1. Trends in patient-reported quality of life and personal wellbeing over 24 months following index severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection among ADAPT study participants, stratified by long COVID status. Generic quality of life was assessed using the EuroQol 5-dimension 5-level (EQ-5D-5L) utility score (*A*) and EuroQol Visual Analogue Scale (EQ-VAS) (*B*), and overall subjective wellbeing was assessed using the Personal Wellbeing Index (PWI) (*C*). Long COVID status was defined as presence of new/persistent symptom of chest pain, shortness of breath, or fatigue/malaise at least 12 weeks following index SARS-CoV-2 infection. Non-COVID controls were exposed to respiratory virus other than SARS-CoV-2 or had epidemiological contact of SARS-CoV-2 infection with prior confirmed negative SARS-CoV-2 test. Data are presented as box plots showing the median, 25th to 75th percentiles with whiskers (±1.5 times interquartile range), and outliers.

95% CI of population norms at all visits (32%–39%) compared to recovered participants (8%–19%). Among non-COVID-19 control participants (ie, epidemiological contact or non-COVID-19 respiratory infection; n = 51), the mean EQ-5D-5L utility score was 0.96 (SD, 0.05) at 4 months and 0.95 (SD, 0.08) at 12 months after confirmed negative SARS-CoV-2 RNA test, and mean EQ-VAS score was 83 (SD, 13.7) at 4 months and 81 (SD, 12.6) at 12 months (Figure 1; Supplementary Table 2).

In an adjusted GEE model, long COVID status was associated with significantly lower EQ-5D-5L utility scores at the 4-month visit (Supplementary Table 3; β-coefficient: −.06 [95% CI, −.02 to −.09; $P < .001$) and those with long COVID did not significantly improve over time relative to recovered participants (ie, no significant interaction between long COVID status and time). Similarly, perceived overall health (as measured by EQ-VAS) score did not change significantly over time (Supplementary Table 3). Long COVID status was associated with a lower EQ-VAS score at 4-month follow-up (β-coefficient: −9.68 [95% CI, −5.85 to −13.51; $P < .001$); however, there was no significant interaction between long COVID status and time since infection. In an adjusted GEE model, PWI scores did not change significantly over time; however, long COVID status was associated with significantly lower PWI score at the 8-month visit (Supplementary Table 3; β-coefficient: −7.2 [95% CI, −.02 to −.09; $P < .001$). There was no significant change in PWI scores over time for participants with long COVID in the interaction term between long COVID and study visit. Sensitivity analyses excluding participants hospitalized during index SARS-CoV-2 infection produced similar results (Supplementary Table 3).

Return to pre-COVID-19 daily functioning was assessed in 4 life domains (ie, full recovery, return to work, return to usual activities, and return to exercise) at 8-, 12-, 18-, and 24-month follow-up visits (Figure 2; Supplementary Table 4). At 8 months postinfection compared to recovered participants, a smaller proportion of participants with long COVID agreed that they had fully recovered (47% vs 93%), returned to work (76% vs 97%), returned to usual activities (77% vs 96%), and returned to exercise (55% vs 88%). At 24 months, the proportion of participants with long COVID agreeing with return to pre-COVID-19 functioning remained below that of recovered participants: fully recovered (51% vs 91%), returned to work (81% vs 97%), returned to usual activities (81% vs 96%), and returned to exercise (60% vs 89%). In adjusted ordinal regression analyses, participants with long COVID had lower odds of agreeing with returning to pre-COVID functional status at 8 months postinfection with respect to full recovery (OR, 0.07 [95% CI, .03–.13]; $P < .001$), return to work (OR, 0.08 [95% CI, .03–.17]; $P < .001$), return to usual activities (OR, 0.12 [95% CI, .06–.24]; $P < .001$), and return to exercise (OR, 0.14 [95% CI, .07–.28]; $P < .001$) compared to recovered participants (Supplementary Table 5). There was no significant interaction between time and return to pre-COVID-19 functional status for full recovery, return to usual activities, or return to exercise, suggesting sustained impairment in functional status over 2 years; however, at later visits a greater proportion of participants with long COVID agreed with return to work (Supplementary Table 5). Sensitivity analyses excluding participants hospitalized during index SARS-CoV-2 infection produced similar results (Supplementary Table 5).

Participants with long COVID had consistently higher average SPHERE anxiety/depression scores compared to recovered participants at the 4-month (4.4 vs 1.7, respectively), 12-month (3.8 vs 1.5), and 24-month (3.6 vs 1.6) study visits (Figure 3*A*; Supplementary Table 2). In the adjusted GEE model, long COVID status was associated with higher SPHERE anxiety-depression subscale score at 4 months postinfection (β-coefficient: 2.61 [95% CI, 1.64–3.58]; $P < .001$; Supplementary Table 6), but there was no significant interaction between long COVID status and time for anxiety/depression symptoms. Participants with long COVID had consistently higher average SPHERE anxiety/depression scores compared to recovered participants at the 4-month (3.6 vs 1.3, respectively), 12-month (2.7 vs 1.2), and 24-month (2.8 vs 1.4) study visits (Figure 3*B*; Supplementary Table 2). In adjusted GEE models, long COVID status was associated with higher SPHERE chronic fatigue subscale score at 4 months postinfection (β-coefficient: 2.16 [95% CI, 1.44–2.88]; $P < .001$; Supplementary Table 6). Significant interaction between long COVID status and time in the SPHERE chronic fatigue subscale identified reduction in fatigue-related symptoms for participants with long COVID through to 24 months postinfection. Participants with long COVID were consistently more likely to report some breathlessness compared to recovered participants at the 8-month (69% vs 19%, respectively), 12-month (64% vs 13%), and 24-month (66% vs 27%) study visits (Figure 3*C*; Supplementary Table 7). In the adjusted ordinal logistic regression model, the odds of reporting more severe breathlessness was 6.87 (95% CI, 3.37–13.99; $P < .001$; Supplementary Table 6) for participants with long COVID compared to recovered participants, with no interaction between long COVID status and time since infection. Non-COVID control participants had similar SPHERE anxiety/depression scores (4 months: 2.4 vs 1.7; 12 months: 2.0 vs 1.5) and SPHERE chronic fatigue scores (4 months: 1.9 vs 1.7; 12 months: 2.0 vs 1.5) compared to recovered participants (Figure 3*A* and 3*B*; Supplementary Table 2). Sensitivity analyses excluding participants hospitalized during index SARS-CoV-2 infection produced similar results (Supplementary Table 6).

DISCUSSION

This study provides detailed, prospective longitudinal characterization of the trajectories of HRQOL and wellbeing among a cohort of 172 people with predominantly mild/moderate index SARS-CoV-2 infection between 2020 and 2022 in Sydney, Australia. Participants with long COVID had substantially

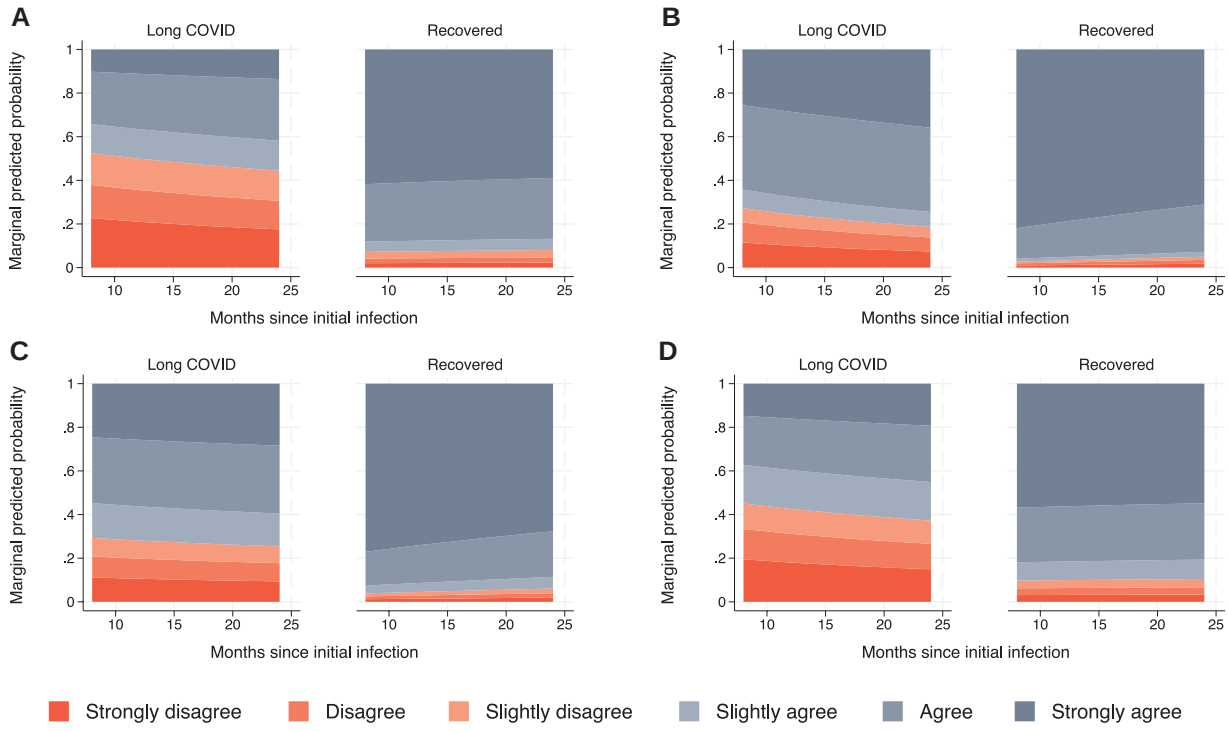

Figure 2. Trends in patient-reported functional impairment over 24 months following index severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection among ADAPT study participants, stratified by long COVID status. Participants reported their agreement with full recovery from coronavirus disease 2019 (COVID-19) (*A*), return to pre-COVID-19 work (*B*), return to usual activities of daily living (*C*), and return to normal exercise level (*D*). Long COVID status was defined as presence of new/persistent symptom of chest pain, shortness of breath, or fatigue/malaise at least 12 weeks following index severe acute respiratory syndrome coronavirus 2 infection. Data are presented as marginal predicted probability of the outcome.

impaired HRQOL scores as measured by EQ-5D-5L and Personal Wellbeing Index compared to recovered participants, with no improvement in mean scores over the duration of the study, and a substantial proportion had HRQOL scores lower than the population norm data in Australia. Additionally, long COVID status was associated with impairments in daily functioning (eg, work, usual activities, exercise) and a higher burden of physical and psychiatric symptoms compared to recovered participants. Although participants with long COVID reported slight improvement in return to work and fatigue scores, these improvements in health status were inconsistent with most other patient-reported outcomes. Hence, the natural history of long COVID in individuals following mild/moderate infection reflects that seen in cohorts of individuals with severe COVID-19, with a substantial proportion of individuals with impaired functioning and quality of life remaining impacted.

Average HRQOL and wellbeing scores were stable over the 2-year follow-up, with consistently worse outcomes on average for participants with long COVID compared to recovered participants. A substantial subgroup of participants with long COVID had EQ-5D-5L utility scores (19%) and EQ-VAS (38%) scores that were below the lower 95% CI of the Australian population norm. While a substantial proportion of participants with long COVID had impaired HRQOL scores, the overall ADAPT cohort had higher mean scores compared to population normative values for both HRQOL (EQ-5D-5L utility score: 0.86 vs 0.95 in population and ADAPT cohorts, respectively; EQ-VAS: 73 vs 82, respectively) and wellbeing (PWI: 75 vs 82, respectively) scores [25, 26]. Higher values in the ADAPT cohort may reflect social factors, with the cohort largely drawn from a higher socioeconomic advantage urban area of eastern Sydney. Our findings are supported by the current literature on HRQOL after SARS-CoV-2 infection, where HRQOL measures remain impaired among people with long COVID up to 2 years following infection [17, 28]. Furthermore, distinct long COVID phenotypes derived from persistent symptoms appear to be differentially associated with impaired HRQOL over time, with greater impairment experienced by those with high burden of symptoms [29, 30]. Given sustained impairment in HRQOL and wellbeing 2 years after infection—including among individuals with mild/moderate infection—the development of effective interventions tailored to individual patient need are urgently needed.

Illness symptoms and activities in daily functioning that underpin higher-level HRQOL and wellbeing are significantly impaired in individuals with long COVID compared to those who recover after acute infection. Sustained presence of symptoms

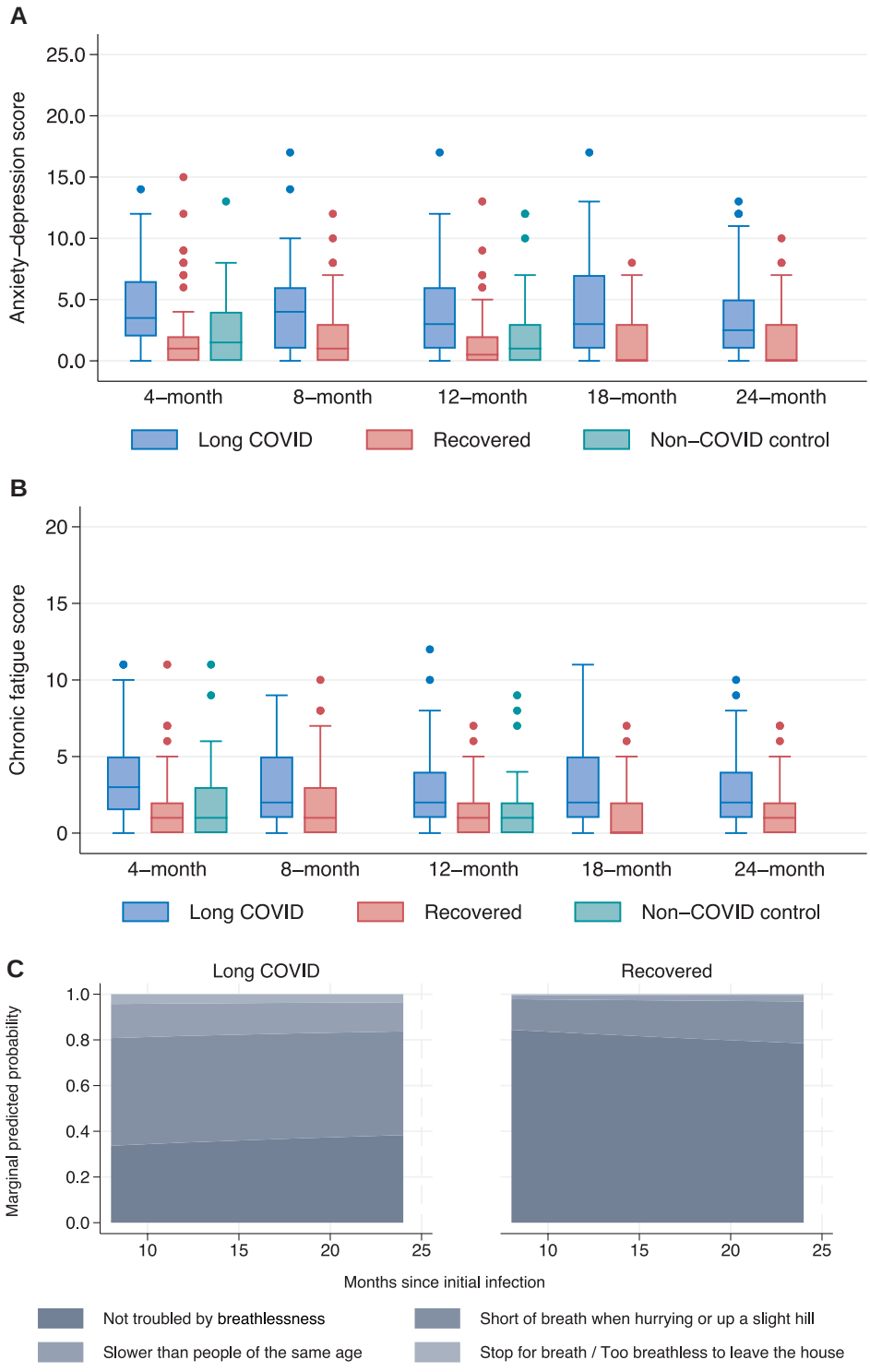

Figure 3. Trends in patient-reported psychological and physiological impairment over 24 months following index severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection among ADAPT study participants, stratified by long COVID status. Symptoms of psychological impairment were assessed using the Somatic and Psychological Health Report (SPHERE) anxiety/depression (*A*) and SPHERE chronic fatigue (*B*) measures, and symptoms of breathlessness were assessed using the modified Medical Research Council (MRC) dyspnea scale (*C*). Long COVID status was defined as presence of new/persistent symptom of chest pain, shortness of breath, or fatigue/malaise at least 12 weeks following index severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Non-COVID controls were those with a previously confirmed negative SARS-CoV-2 test with either exposure to respiratory virus other than SARS-CoV-2 or epidemiological contact of SARS-CoV-2 infection. SPHERE data are presented as box plots showing the median, 25th to 75th percentiles with whiskers (±1.5 times interquartile range), and outliers, while modified MRC dyspnea data are presented as marginal predicted probability of the outcome.

(anxiety/depression, chronic fatigue, breathlessness) and impaired functioning (return to work, exercise, and usual activities) for individuals with long COVID in the current study validates large cross-sectional cohort studies in comparable high-income countries [18, 31, 32]. A limitation of these other studies is that most are cross-sectional [33], have short follow-up duration [34, 35], or do not assess long COVID status in longitudinal analysis [15]. ADAPT data add and extend to these prior findings. In qualitative studies, common themes of concern among people with long COVID include severe disruption to life, uncertainty of the illness trajectory, access to treatment, understanding from others, and changes to self-identity [36, 37]. Additionally, individuals with long COVID are conscious of experiencing stigma and discrimination related to their illness and may be hesitant engaging with health services to avoid negative experiences [38]. Given the lack of effective pharmacological interventions for long COVID, development of appropriate support mechanisms and therapeutic interventions should consider holistic approaches that address the multisystemic nature of long COVID, address impairment in activities of daily living and wellbeing, and be created in collaboration with people with lived experience [39].

This study has several limitations. The ADAPT cohort is an observational cohort located in a relatively wealthy urban setting and findings may not be generalizable to other settings. Outcome measurement may have been biased if retention was differential by long COVID status, although this was not overtly the case in ADAPT (62% and 59% completed 24-month visits for recovered and long COVID participants, respectively). Our definition of long COVID was developed internally due to absence of international consensus at the time of first ADAPT analyses (mid-2020). This definition was retained to align with ADAPT cohort previous analyses and includes persisting symptoms (ie, chest pain, dyspnea, fatigue/malaise) commonly reported by other cohorts examining long COVID following mild/moderate initial infection. The EQ-5D-5L utility score is a generic measure of HRQOL and may be impacted by other health factors not related to long COVID; however, its use globally across disease settings allows comparison and contrast of disease impact. Given the rapid initiation of the ADAPT cohort early in the COVID-19 pandemic, validated instruments to assess long COVID-related HRQOL were not available and the generic instrument EQ-5D-5L was selected. The predominant initial ADAPT recruitment in 2020 also means that the outcomes are largely in the context of an unvaccinated population. Both prevalence of long COVID and its impact on HRQOL may differ in the vaccinated population. Patient-reported outcome measures are susceptible to bias (eg, detection, interviewer, recall, and confirmation bias), and we cannot exclude whether these biases influenced the results in unknown directions. Health status (ie, psychological and physiological impairment, and perceived quality of life and wellbeing) prior to SARS-CoV-2 infection may confound these measures during follow-up, especially if these factors are associated with acquiring COVID-19. The design of the ADAPT cohort precluded collection of preinfection health status; however, patient-reported psychiatric and physical comorbidities were recorded at enrollment and included as covariates in the longitudinal analyses to address this potential confounding.

In conclusion, this study demonstrated sustained impairment in multiple domains of health up to 2 years in a subset of patients after mild/moderate SARS-CoV-2 infection. On average, individuals with long COVID had poorer health states at time of long COVID assessment (ie, ≥12 weeks after initial infection) and had showed little improvement in most health domains over time. This study adds to extant literature reporting sustained health impairment in patients following severe initial infection and uniquely applies the Wilson-Cleary model of HRQOL to extend knowledge of long COVID–related outcomes. Given that most SARS-CoV-2 infections globally had mild/moderate severity, the scale of impaired health states after infection will likely be vast if not addressed. Translation of the study results to clinical practice may include development of multidisciplinary models of care (to address multiorgan impairment) or production of patient education materials (to inform patients on expected return to health). Continued efforts to describe mechanisms of persisting symptoms and limited functioning are necessary to develop patient-centered clinical and behavioral interventions.

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.

Notes

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