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Clinical Research Study

Assessing the Relationship in Symptomology of Myalgic Encephalitis/Chronic Fatigue Syndrome and Long COVID

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ABSTRACT

The symptomology of Myalgic Encephalitis/Chronic Fatigue Syndrome (ME/CFS) shares many commonalities with Long COVID (LC). This study aimed to clearly define the comparison between ME/CFS and LC in terms of symptomology. A cross-sectional analysis of 27,651 interviewees from a National Health Interview Survey 2022 adult dataset was conducted. The data was controlled for subject's sex, race/ethnicity, age, life satisfaction, insurance coverage, poverty ratio, and comorbidities. A logistic regression was used to compare four groups: (1) LC individuals, (2) ME/CFS individuals, (3) LC with ME/CFS individuals, and (4) controls by symptoms of depression, anxiety, physical activity, fatigue, and memory. The results showed that subjects with both ME/CFS and LC were more likely to report memory issues, anxiety, depression, fatigue, and difficulty with physical activity followed by subjects with ME/CFS only, LC only, and the controls ($P < .01$). Our study suggests a synergistic mechanism between ME/CFS and LC in developing issues with anxiety, depression, fatigue, and physically activity in patients. The study's conclusions highlight the need to elucidate the possible overlap in pathophysiological mechanisms of ME/CFS and LC in the symptomology of patients.

Introduction

In a 2023 review article, information compared the symptoms of Long COVID (LC) and Myalgic EncephalitisChronic Fatigue Syndrome (ME/CFS), highlighting numerous similarities and some differences.[1] Out of the 25 symptoms, the authors found that LC and ME/CFS shared 20. ME/CFS is characterized by the sudden onset of an infectious-type illness, followed by chronic and debilitating fatigue, and postexertional malaise.[2] Many patients also experience recurrent fevers, pharyngitis, adenopathy, myalgias, sleep disorders, and cognitive impairment. On the other hand, LC (sometimes referred to as "post-acute sequelae of COVID-19") is a multisystemic condition with severe symptoms that manifest after a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[3] Several systematic reviews have documented patients globally experiencing a wide range of common ongoing symptoms after SARS-CoV-2 infection (in some cases over 60 physical and psychological symptoms), including fatigue, malaise, altered smell and taste, breathlessness, and cognitive impairments.[4,5]

As the authors of the systematic review argue, empirical data is still essential to thoroughly explore the relationship between LC and ME/CFS. Despite some clinical similarities, such as persistent fatigue and cognitive impairment, the precise nature and extent of the overlap between these two conditions remains unclear. Rigorous empirical studies are needed to investigate the underlying pathophysiological mechanisms, epidemiological patterns, symptomology, and potential shared biomarkers. Such data would enable researchers to differentiate between the conditions, understand any causal links, and identify effective treatment strategies. Additionally, empirical evidence can help clarify the prevalence and incidence of ME/CFS among LC patients, informing healthcare policies and resource allocation. This empirical approach is vital for developing targeted interventions and improving the quality of life for individuals affected by these debilitating conditions.

Our goal was to compare symptomology between ME/CFS and LC using data from the National Health Interview Survey (NHIS). The NHIS monitors the health of the civilian noninstitutionalized U.S. population through the collection and analysis of data on a broad range of

Abbreviations: ME/CFS, Myalgic Encephalitis/Chronic Fatigue Syndrome; LC, Long COVID; NHIS, National Health Interview Survey.

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health topics. A major strength of this survey lies in its ability to analyze health measures by many demographic and socioeconomic characteristics. During household interviews, NHIS obtains information on activity limitation, illnesses, injuries, chronic conditions, health insurance coverage (or lack thereof), utilization of health care, and other health topics.

As is argued in a meta-analysis of LC and ME/CFS, often-similar findings suggest that insights into each disorder will have implications for the other, and they may also enhance our understanding of both illnesses.[1] This article also helps to ensure that the future research is grounded in real-world observations and experiments, enhancing the validity and reliability of its conclusions. Furthermore, high-quality empirical data helps mitigate biases, increases the generalizability of findings, and supports evidence-based decision-making in various fields, from medicine to social sciences.

Objectives

Our study's objective is to assess the relationship between ME/CFS and LC symptomology, controlling for subject's sex, race/ethnicity, age, life satisfaction, insurance coverage, poverty ratio, and comorbidities using the NHIS database (Table 1). To investigate our study primary objective, we created a grouping variable (illness group) that included (1) LC individuals, (2) ME/CFS individuals, (3) LC with ME/CFS individuals, and (4) controls.

Methods

Data Source

This study is a retrospective cross-sectional analysis of data from the 2022 NHIS.[6] The NHIS is a cross-sectional household interview survey providing health information on the civilian noninstitutionalized population in the U.S. The National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) collects the data annually.[6] The employment of a complex sampling design using stratification and clustering ensures a nationally representative sample. The survey consists of a core set of interview questions that gathers baseline demographics, socioeconomic, and health status characteristics for each member of the household. We used the adult dataset of which 27,651 individuals were interviewed.

Statistical Analysis

Summary statistics were calculated for all study variables. The first analysis compared the four groups using either a Welch ANOVA or a Pearson chi-square statistic with the Rao and Scott second-order correction, on the covariates sex, race/ethnicity, life satisfaction, education level, insurance coverage, age, poverty ratio, and number of comorbidities. In the second analysis we conducted logistic regression analysis to compare the four illness groups on the symptoms anxiety, depression, fatigue, memory issues, and physical activity. All logistic models controlled for subjects' age, number of comorbidities, and poverty ratio. Stata 18.1 was used for all data analysis. Statistical significance was found at $P < .05$ and 95% confidence intervals were calculated and presented for all statistical tests Table 1.

Results

Differences were found across all covariates. Refer to Table 2 and Figures 1–4 for details. Specifically, a greater proportion of women were part of the ME/CFS with LC, ME/CFS only, or LC only groups compared to the controls. A greater percentage of individuals in the ME/CFS or with ME/CFS LC reported dissatisfaction with life than the LC or controls. ME/CFS LC individuals were older, more educated, more likely to

Table 1
NHIS Variable Definitions and Coding.

Independent Variable	NHIS Question	Project Coding
Illness	ME/CFS: Ever had chronic fatigue syndrome?	Yes vs no
	Long COVID: Did you have any symptoms lasting 3 months or longer that you did not have prior to having coronavirus or COVID-19?	Yes vs no
	ME/CFS and Long COVID: Positive response to both ME/CFS and Long COVID NHIS questions.	Yes vs no
	Control: Negative response to both ME/CFS and Long COVID NHIS questions.	Yes vs no
Covariates	**NHIS Question**	**Project Coding**
Sex		Male vs female
Race/ethnicity		Hispanic vs non-Hispanic White vs non-Hispanic Black vs non-Hispanic Other
Life satisfaction	In general, how satisfied you with your life?	Satisfied vs dissatisfied
Education		<high school vs high school vs some college vs bachelor's degree vs graduate degree
Insurance coverage		Insurance vs no insurance
Age		Continuous
Poverty ratio		The poverty ratio is a ratio of the family's income to the appropriate Federal poverty threshold
Comorbidities	Hypertension, cancer, cholesterol, cardiovascular, asthma, diabetes, COPD, arthritis, dementia.	Count of nine comorbidities
Dependent Variables	**NHIS Question**	**Project Coding**
PHQ (depression)	Summary of the eight-item patient health questionnaire depression scale (PHQ-8)	No (none/minimal) vs yes (mild, moderate, severe)
GAD (anxiety)	Summary of the seven-item generalized anxiety disorder scale (GAD-7)	No (none/minimal) vs yes (mild, moderate, severe)
Physical activity	Moderate physical activity	None (unable or never) vs yes (frequency per-day, per-week, per-month, per-year)
Fatigue	How often tired, past 3 months	Never vs yes (some days, most days, every day)
Memory issues	Do you have difficulty remembering or concentrating?	No (no difficulty) vs yes (some difficulty, a lot of difficulty, cannot do at all)

Table 2
Summary Statistics and Bivariate Analysis for Covariates.

		ME/CFS (N = 114) Weighted Percent (95% CI)	Long COVID (N = 1708) Weighted Percent (95% CI)	ME/CFS with Long COVID (N = 87) Weighted Percent (95% CI)	Controls (N = 7024) Weighted Percent (95% CI)	P Value
Sex	Male	27.19 (20.00,35.82)	36.15 (33.91,38.45)	21.84 (14.37,31.75)	46.02 (44.84,47.2)	$P < .001$
	Female	72.81 (64.18,80.00)	63.85 (61.55,66.09)	78.16 (68.25,85.63)	53.98 (52.8,55.16)	
Race/ethnicity	Non-Hispanic White	64.91 (55.68,73.15)	66.98 (64.82,69.07)	73.56 (63.50,81.65)	65.82 (64.76,66.86)	$P = .046$
	Hispanic	17.54 (11.40,26.02)	18.15 (16.48,19.95)	12.64 (7.22,21.21)	16.59 (15.79,17.41)	
	Non-Hispanic Black	7.02 (3.53,13.48)	8.96 (7.70,10.40)	9.20 (4.64,17.42)	9.30 (8.60,10.04)	
	Non-Hispanic Other	10.53 (6.14,17.47)	5.91 (4.88,7.15)	4.60 (1.72,11.70)	8.30 (7.69,8.95)	
Life satisfaction	Satisfied	82.46 (74.14,88.51)	94.55 (93.35,95.54)	80.00 (70.01,87.27)	96.99 (96.58,97.35)	$P < .001$
	Dissatisfied	17.54 (11.49,25.86)	5.46 (4.46,6.65)	20.00 (12.73,29.99)	3.011 (2.651,3.419)	
Education	<High school	12.28 (7.40,19.69)	9.77 (8.44,11.27)	11.49 (6.40,19.78)	7.93 (7.34,8.56)	$P < .001$
	High school	24.56 (17.39,33.49)	21.41 (19.42,23.55)	17.24 (10.82,26.35)	20.74 (19.80,21.72)	
	Some college	32.46 (24.48,41.60)	33.71 (31.58,35.90)	51.72 (41.60,61.70)	28.23 (27.21,29.27)	
	Bachelor's degree	19.30 (13.06,27.58)	22.18 (20.32,24.15)	14.94 (9.01,23.77)	26.81 (25.79,27.86)	
	Graduate degree	11.40 (6.74,18.64)	12.94 (11.49,14.54)	4.60 (1.72,11.72)	16.29 (15.39,17.22)	
Insurance coverage	No insurance	4.39 (1.84,10.12)	7.97 (6.76,9.38)	1.15 (0.16,7.77)	7.26 (6.67,7.90)	$P = .026$
	Insurance	95.61 (89.88,98.16)	92.03 (90.62,93.24)	98.85 (92.23,99.84)	92.74 (92.10,93.33)	
		Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	
	Age	57.8 (49.6, 56.1)	48.8 (48.0, 49.5)	53.0 (49.7, 56.4)	47.2 (46.8, 47.6)	$P = .003$
	Poverty ratio	3.51 (3.02, 4.00)	4.01 (3.88, 4.14)	2.91 (2.42, 3.40)	4.63 (4.56, 4.70)	$P < .001$
	Comorbidities	2.57 (2.25, 2.90)	1.53, (1.46, 1.60)	2.81 (2.40, 3.22)	1.16 (1.13, 1.20)	$P < .001$

Significant differences were found between illness groups for all variables.

be non-Hispanic white with health insurance, with the lowest poverty ratio, and the highest number of comorbidities compared to all other groups ($P < .01$).

Results from the logistic regression models showed that subjects with ME/CFS and LC are most likely to report an experiencing memory issues, anxiety, depression, fatigue, and difficulty with physical activity, followed by subjects with ME/CFS, LC only, and lastly, controls ($P < .01$). Refer to Table 3 and Figure 5 for more details. Specific results show adjusted odds ratios.

Memory issues

- Compared to controls, individuals with ME/CFS and LC are 6.21 times more likely to report memory issues [95% CI: 3.90, 9.87]. Individuals with ME/CFS only are 3.79 times more likely to report memory issues [95% CI: 2.55, 5.61], and individuals with LC only are 1.68 times more likely to report memory issues [95% CI: 1.48, 1.90].

Anxiety

- Compared to controls, individuals with ME/CFS and LC are 7.11 times more likely to report anxiety (95% CI: 4.23, 11.95). Individuals with ME/CFS alone are 4.18 times more likely to report anxiety (95% CI: 2.76, 6.33), and those with LC alone are 1.84 times more likely to report anxiety (95% CI: 1.62, 2.08).

Depression

- Compared to controls, individuals with ME/CFS and LC are 11.29 [95% CI: 5.91, 21.56] times more likely to report depression, individuals with ME/CFS only are 8.67 [95% CI: 5.50, 13.67] times more likely to report depression, and individuals with LC only are 1.94 [95% CI: 1.73, 2.18] times more likely to report depression.

Fatigue

- Compared to controls, individuals with ME/CFS and LC are 30.45 [95% CI: 4.23, 219.41] times more likely to report fatigue, individuals with ME/CFS only are 5.75 [95% CI: 2.70, 12.25] times more likely to report fatigue, and individuals with LC only are 1.95 [95% CI: 1.71, 2.23] times more likely to report fatigue.

Physical activity

- Compared to controls, individuals with ME/CFS only are 2.39 [95% CI: 1.64, 3.48] times more likely to report no physical activity. While not significantly different at an alpha of 5%, individuals with LC are 1.12 [95% CI: 0.99, 1.27, $P = .056$] times more likely to report no physical activity, and individuals with ME/CFS and LC are 1.23 [95% CI: 0.79, 1.93, $P = .343$] times more likely to report fatigue.

We also identified significant covariate effects. For instance, as the poverty ratio increased (indicating a higher ratio of income to the Federal poverty threshold), the likelihood of reporting a symptom decreased. Moreover, as the number of comorbidities increased, so did the likelihood of reporting a symptom. Interestingly, apart from physical activity, the likelihood of reporting a symptom decreased as the age of the subjects increased. This information can be found in Table 3.

Discussion

Findings

This study aimed to assess the relationship between ME/CFS and LC symptomology by grouping illness variables including (1) LC individuals, (2) ME/CFS individuals, (3) LC with ME/CFS individuals, and (4) controls. Across our variable groups, our findings demonstrated that

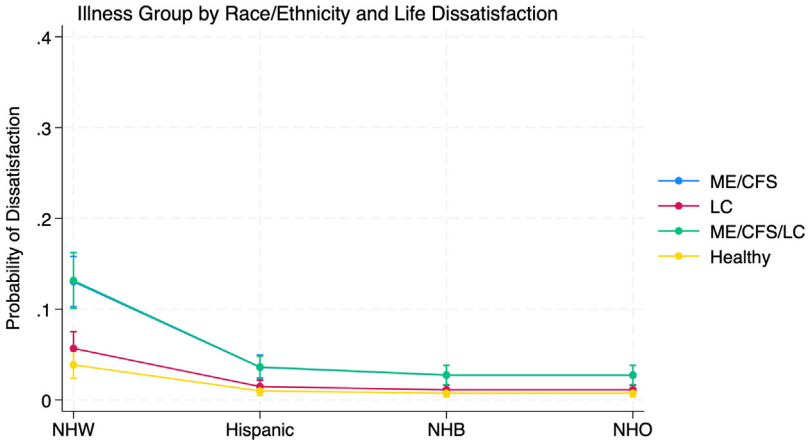

Figure 1. Illness group by race/ethnicity and life dissatisfaction.

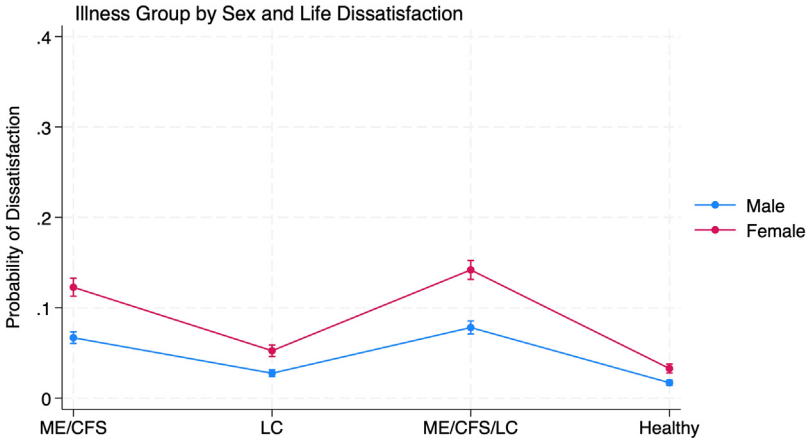

Figure 2. Illness group by sex and life dissatisfaction.

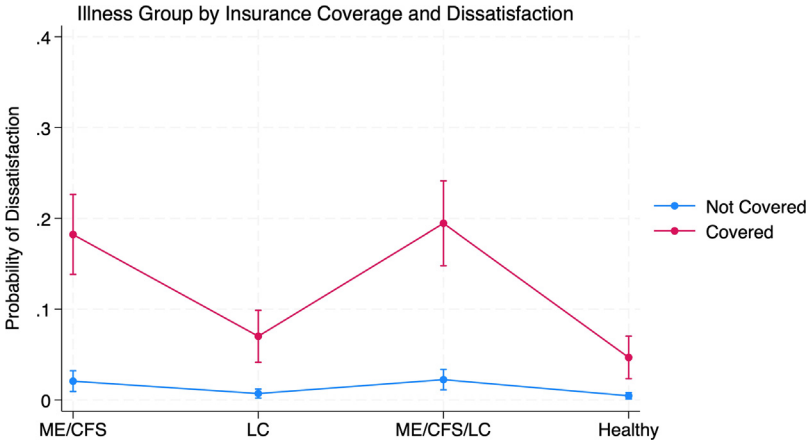

Figure 3. Illness group by insurance coverage and dissatisfaction.

individuals with both ME/CFS and LC are most likely to report memory issues, anxiety, depression, and fatigue. In contrast, the LC individuals were least likely to report memory issues, anxiety, depression, and fatigue across our variable groups. Although individuals with both ME/CFS and LC were most likely to report many of the parameters investigated in this study, individuals with ME/CFS alone were more likely to report memory issues, anxiety, depression, and fatigue compared to those with LC alone.

The results are consistent with past research. For example, a meta-analysis conducted in 2021 found that 25 out of 29 known ME/CFS symptoms were reported by at least one selected LC study.[7] This included fatigue, reduced daily activity, and postexertional malaise.[7] In a recent population-based study, researchers found that among persons with LC, ME/CFS-like illness symptoms including significant impairment in physical, mental, emotional, social, and occupational functioning were present.[8] Similar to our study, research has demonstrated that postinfectious fatigue syndromes, while evident in both LC, ME/CFS persons, is more pronounced in ME/CFS patients.[9]

In terms of recovery recent research shows that compared to ME/CFS, LC sufferers initially were more symptomatic for the immune and orthostatic domains, but over time, evidenced significantly less severe symptoms than those with ME/CFS, except in the orthostatic domain.[10] A recent scoping review concluded that future studies should examine pacing to support individuals with varying symptom severity

Table 3
Adjusted Odds Ratios [95% Confidence Intervals] for Regression Model Variables.

	Memory	Anxiety	Depression	Fatigue	No Physical Activity
Control	Reference Group	Reference Group	Reference Group	Reference Group	Reference Group
Long COVID	1.68	1.84	1.94	1.95	1.13
	[1.49, 1.90]†	[1.62, 2.08]†	[1.73, 2.18]†	[1.71, 2.23]†	[0.99, 1.28]
ME/CFS	3.79	4.18	8.67	5.75	2.39
	[2.56, 5.62]†	[2.76, 6.33]†	[5.50, 13.67]†	[2.70, 12.25]†	[1.64, 3.48]†
ME/CFS and Long COVID	6.21	7.11	11.29	30.45	1.24
	[3.91, 9.88]†	[4.23, 11.95]†	[5.91, 21.56]†	[4.23, 219.41]†	[0.80, 1.93]
Poverty ratio	0.88	0.93	0.90	0.98	0.85
	[0.86, 0.90]†	[0.91, 0.95]†	[0.89, 0.92]†	[0.97, 1.00]†	[0.84, 0.87]†
Comorbidities	1.37	1.39	1.46	1.29	1.19
	[0.99, 1.00]†	[1.32, 1.46]†	[1.39, 1.53]†	[1.22, 1.35]†	[1.13, 1.25]†
Age	1.00	0.96	0.97	0.97	1.02
	[0.99, 1.00]	[0.94, 0.98]†	[0.96, 0.98]†	[0.95, 0.98]†	[1.01, 1.03]†

Healthy individuals served as the reference group for comparing illness groups in the regression models. Covariates in the regression models included the continuous variables poverty ratio, comorbidities, and age.
$^{**}P < .01$. $^{*}P < .05$ refer to statistically significant results.
† $P < .001$.

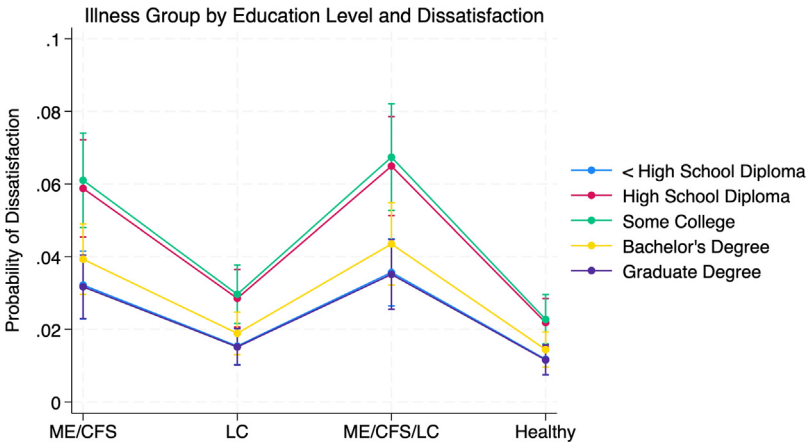

Figure 4. Illness group by education level and dissatisfaction.

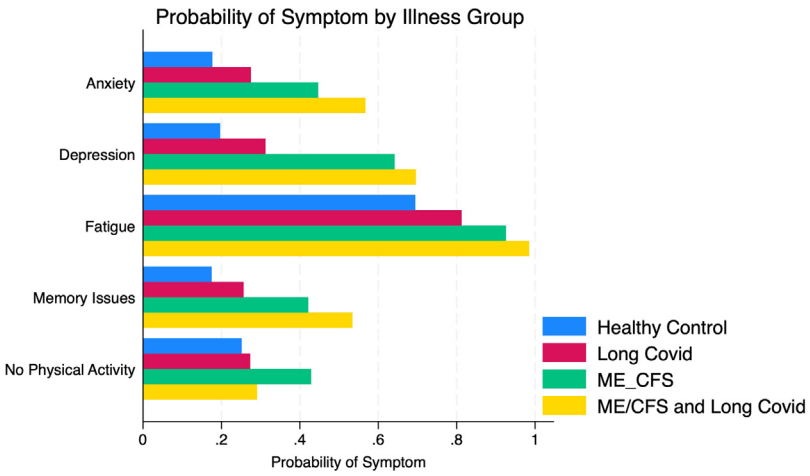

Figure 5. Probability of symptom by illness group.

and personalized support. This would improve accessibility and reduce selection bias, in addition to improving scalability of interventions.[11]

Implications

These findings suggest that ME/CFS and LC may have synergistic effects in increasing the likelihood of anxiety, depression, and fatigue. While a past meta-analysis suggests that LC and ME/CFS present with similar symptoms, our study reveals that LC and ME/CFS together may be stronger in contributing to overlapping symptoms of memory issues, anxiety, depression, and fatigue than either condition alone. Furthermore, our study suggests that subjects with ME/CFS only are more likely to develop memory issues, anxiety, depression, and fatigue when compared to subjects with LC only. This indicates that the pathophysiology of ME/CFS may have a stronger impact on the development of these symptoms within a synergistic relationship between ME/CFS and LC.

Limitations

While the use of the NHIS-derived dataset allowed us to control for subject's sex, race/ethnicity, age, life satisfaction, insurance coverage, poverty ratio, and comorbidities; the retrospective study design and the

interview-based nature of the NHIS data was a limitation of this study. This study has a few important limitations. First, it mainly relied on people's own reports about their health, without having confirmation from doctors or official medical records. Even though self-reported symptoms are essential for understanding long-term COVID, having a more detailed account from healthcare providers would give a clearer picture of the issue. Second, the study didn't include information on when the initial COVID-19 infection happened or any other related factors, which means it couldn't explore many possible risk factors. Lastly, the way LC was defined in the survey was quite limited, as it didn't clearly mention that symptoms need to last for at least 2 months or more. And weak control on the variables. Other factors that could affect recall bias are the participant's age, disease status, education, socioeconomic status, pre-existing beliefs, and how important the event being recalled is to the participant. Thus, in future investigations, a prospective design may be considered to strengthen the validity of findings.

Conclusions

Our study supports the increased likelihood that patients with both ME/CFS and LC are more likely to develop problems with memory, anxiety, depression, and fatigue when in comparison to either disease alone. These conclusions highlight the necessity to further investigate the possible synergistic relationship between LC and ME/CFS in developing memory issues, anxiety, depression, and fatigue. Better understanding of the pathophysiology of LC and ME/CFS and the relationship between both processes can lend to development of stronger preventative and treatment methods for symptomology.

Declaration of competing interest

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

CRediT authorship contribution statement

Nikitha Garapaty: Writing – review & editing, Validation, Methodology, Conceptualization. **Kristina M. Reyes:** Writing – review & editing, Writing – original draft. **Lily Tehrani:** Writing – review & editing, Writing – original draft. **Maximiliano Barbosa Mendoza:** Writing – review & editing, Validation, Formal analysis. **Patrick Hardigan:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ajmo.2024.100085.

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