Biopsychosocial and Economic Consequences of Long COVID: A Four-Year Longitudinal Analysis

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Ethical considerations: Not applicable – secondary analysis of publicly available, de-identified data (MEPS)

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Abstract

The multi-year trajectory of Long COVID is not fully understood. This study aims to examine the physical health, mental health, and long-term healthcare cost consequences of Long COVID in a nationally representative, longitudinal cohort.

We used a prospective longitudinal approach to examine 5,561 adults from the Medical Expenditure Panel Survey (MEPS). Participants were categorized into three strata: Long COVID (symptoms ≥3 months), COVID Recovered, and a No COVID reference group. We used hierarchical linear models to compare the four-year trajectories of perceived health, psychological distress (K6 scale), and inflation-adjusted healthcare expenditures, adjusting for demographic covariates, pre-pandemic health status, and insurance status.

After controlling for demographic characteristics and pre-pandemic health status, baseline differences in perceived health and psychological distress between the Long COVID and No COVID cohorts were found to be not statistically significant ($p = 0.4729$ and $p = 0.1065$, respectively). This suggests pre-existing health is associated with the major determinant of post-COVID health outcomes. In stark contrast, the trajectory of healthcare expenditures for the Long COVID group showed a significantly faster rate of increase over time compared to the reference group, confirmed by a highly significant time-by-group interaction ($p < .0001$).

The health and well-being impact of Long COVID is closely related to pre-pandemic health. However, infection is independently linked to an accelerating and cumulative economic expense within a multi-year period. These findings identify pre-pandemic health as a key vulnerability

Comment [A1]: Baseline difference : P > 0.05. Then “this suggests pre-existing health is associated with”. Need to report results to validate the suggestion.

Comment [A2]: Report results, P value, and CI to suggest that in the abstract.

Comment [A3]: The interpretation occasionally implies causal relationships (“infection is independently linked to…”) when only associations can be inferred. Wording should be adjusted throughout to avoid overstating causality.

and identify Long COVID's increased economic burden as its largest multi-year impact.

Keywords: health expenditures; psychological distress; hierarchical linear modeling; post-acute sequelae of COVID-19 (PASC); chronic illness.

List of Abbreviations: MEPS, PASC, HLM, K6, COVID

1. Introduction

The COVID-19 pandemic, initiated by the SARS-CoV-2 virus, has precipitated a global health crisis of unprecedented scale. Despite extensive research and public health responses to the acute phase, a massive secondary epidemic – Post-Acute Sequelae of SARS-CoV-2 infection (PASC), also known as Long COVID has followed in the footsteps of the acute epidemic (Nalbandian et al., 2021). It is characterized by a symptom profile of over 200 recurring and often recurring symptoms, including profound fatigue, neurocognitive impairment ("brain fog"), and cardiorespiratory dysfunction. Long COVID happens in a high percentage of individuals regardless of the severity of the initial illness (Davis et al., 2023; Sudre et al., 2021). This condition is not a simple and prolonged recovery, but a complex, multisystemic disease which is likely driven by several overlapping pathophysiological mechanisms, including viral persistence, immune dysregulation, autoimmunity, and endothelial dysfunction (Castanares-Zapatero et al., 2022; Davis et al., 2023).

A large body of literature has begun to outline the profound consequences of Long COVID. Cross-sectional and short-term cohort studies have consistently described its disproportionate impact across different domains. From a biological standpoint, Long COVID patients have high rates of new onset of chronic illness, including cardiovascular, metabolic, and neurologic disease, with substantially enhanced utilization of medical care (Al-Aly et al., 2022; Raman et al., 2022). Psychologically, the condition is strongly associated with elevated rates of depression, anxiety, and post-traumatic stress disorder, driven by the burden of chronic illness and uncertainty (Renaud-Charest et al., 2021). Socially and financially, Long COVID-caused work limitation has caused a huge loss of workforce participation, by the millions, due to the inability to work, creating tremendous economic insecurity on the family level, as well as financial instability on the broader level (Katie Bach; U.S. Department of Health and Human Services, 2022).

Comment [A4]: The manuscript should more explicitly clarify how this study extends existing longitudinal research (e.g., Al-Aly et al., 2022; Davis et al., 2023). Highlighting what is new about this four-year trajectory analysis (beyond duration) would strengthen the contribution.

Today's literature lacks a comprehensive longitudinal analysis of health, financial stability, employment, and disability outcomes despite this background information. Currently, most studies are based on one year or less of follow-up, and thus, much of the condition's multi-year development remains unmapped. ~~Currently, most studies are based upon one year or less of follow-up, and thus, much of the condition's multi-year development remains unmapped.~~ We do not yet know if the health and financial losses linked to Long COVID are fixed, get better, or, more alarmingly, get worse over time. Knowing this answer is not just an intellectual exercise; it

Comment [A5]: Duplication

Comment [A6]: Kind of repetition

is necessary for predicting future healthcare requirements, planning efficient social support networks, and determining the actual, long-term societal cost of the pandemic.

This study fills this crucial knowledge gap through one of the first multi-year, nationally representative, longitudinal studies of the outcomes of Long COVID. Using four years of Medical Expenditure Panel Survey (MEPS) data, we go beyond short-term, static measures. We use hierarchical linear modeling to specifically model and compare over time the paths of physical health, psychological distress, and healthcare spending for three different groups: persons with Long COVID, persons who recovered from acute COVID, and a No COVID control group. By doing so, we aim to characterize the long-term burden of Long COVID, determining whether its impact represents a persistent deficit, a gradual recovery, or an accelerating crisis.

Comment [A7]: Perceived?

Comment [A8]: aimed

2. Materials and Methods

2.1. Research Design and Data Source

This research used a prospective longitudinal cohort study design to examine the MEPS Panel 24 data. MEPS is a national representative survey of Americans. Panel 24 is particularly well-suited to this investigation because the data collection for the panel (2019-2022) dates covers the pre-pandemic (2019, baseline), emergence of COVID-19, and post-pandemic, so there is a powerful pre-post test.

2.2. Study Population and Cohort

The study population included all adult respondents (aged 18 and older) from MEPS Panel 24. Participants were stratified into three mutually exclusive cohorts based on their responses to survey questions regarding COVID-19 history:

1. The Long COVID Cohort: Individuals who reported a history of COVID-19 with symptoms lasting three months or longer.
2. The COVID-19 (Recovered) Cohort: Individuals who reported a history of COVID-19 but did not report symptoms lasting three months or more.
3. The No COVID Cohort: Individuals who did not report a history of COVID-19 infection during the study period. This cohort serves as the reference group.

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All analyses were weighted using the MEPS longitudinal weights to ensure that the results are nationally representative.

2.3. Measures

The primary Independent Variable is the Cohort status: (Long COVID, COVID Recovered, and No COVID).

Primary Dependent Variables are:

1. Perceived Health Status: Measured on a 5-point Likert scale (1=Excellent, 5=Poor).
2. Psychological Distress: Measured using the Kessler-6 (K6) scale, a continuous score where higher values indicate greater distress. The K6 was selected since it is a well-validated and widely used instrument for assessing non-specific psychological distress in population health surveys.
3. Total Healthcare Expenditures: The inflation adjusted log-transformed healthcare expenditures, per individual. The log-transformation of the cost was to normalize the distribution and stabilize variance.

Comment [A10]: Add a brief description of it. Validity?

Comment [A11]: Ref?

Comment [A12]: Ref? Add an example of a question to the manuscript for the readers

Covariates: We used demographic variables known to influence health outcomes (age, sex, and race/ethnicity). To strengthen association inference, models also control for time-varying insurance status and pre-pandemic health status, using the Year 1 (2019) measure of perceived health.

Comment [A13]: What? Add a brief description

2.4. Statistical Analysis: Hierarchical Linear Modeling

Comment [A14]: The definition relies on self-reported symptom duration (≥3 months), which may introduce heterogeneity and misclassification bias. The manuscript mentions this limitation but should include sensitivity analyses or subgroup checks (e.g., by symptom type or duration beyond 6 months) if feasible.

To analyze the longitudinal data, we employed Hierarchical Linear Modeling (HLM), also known as mixed-effects modelling, using SAS (Version 9.4, SAS Institute Inc., Cary, NC). This approach is optimal for analyzing changes over time as it accounts for the nested structure of the data (i.e., repeated measurements nested within individuals).

The analysis was conceptualized as a two-level model:

Level 1: Within-person Change

$$Y_{ti} = \pi_{0i} + \pi_{1i}\left(\text{Time}_t\right) + e_{ti} \quad (1$$

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Where Y_{ti} is the outcome for person i at time t,

π_{0i} is the baseline outcome,

π_{1i} is the annual rate of change, and

e_{ti} is the residual error.

Level 2: Between-person Differences in change

This level models how the individual intercepts and slopes from Level 1 are predicted by the independent variables. The expanded equations are:

$$\pi_{0i} = \beta_{00} + \beta_{01}\left(\text{LongCOVID}_i\right) + \beta_{02}\left(\text{Age}_i\right) + \beta_{03}\left(\text{Sex}_i\right) + \beta_{04}\left(\text{Race}_i\right) + \beta_{05}\left(\text{Insurance}_i\right) + \beta_{06}\left(\text{Baseline\_Health}_i\right) r_{0i} \quad (2$$

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$$\pi_{1i} = \beta_{10} + \beta_{11}\left(\text{LongCOVID}_i\right) + \beta_{12}\left(\text{Age}_i\right) + \beta_{13}\left(\text{Sex}_i\right) + \beta_{14}\left(\text{Race}_i\right) + \beta_{15}\left(\text{Insurance}_i\right) + \beta_{16}\left(\text{Baseline\_Health}_i\right) r_{1i} \quad (3$$

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Here, β_{01} reflects baseline differences between the Long COVID and No COVID groups, while β_{11} captures differences in rates of change (time-by-group interaction). Random effects r_{0i} and r_{1i} represent unexplained variability in intercepts and slopes.

Missing data were addressed using Full Information Maximum Likelihood (FIML), the method that retains all cases by using all available observed data under the Missing at Random (MAR) assumption, reducing bias compared to listwise deletion. By maximizing the likelihood across all participants, FIML yields less biased and more efficient parameter estimates, ensuring that findings are robust and representative of the national sample (McDougall et al., 2016).

Comment [A15]: Level of significance?

3. Results

Comment [A16]: Consider including effect sizes (e.g., Cohen's d) or confidence intervals for interpretation of practical significance.

The final weighted, nationally representative sample consisted of 336.8 million individuals from the MEPS Panel 24 longitudinal file. The population was stratified into three cohorts based on COVID-19 history (Table 1). The largest cohort comprised individuals with no history of COVID-19 (63.24%). Those who had contracted and recovered from COVID-19 without long-term symptoms represented 31.84% of the sample. The Long COVID cohort constituted 4.91% of the population.

Table 1: Weighted Populated Frequency by COVID-19 Status Group

Group	Frequency	Weighted Frequency	Percent	95% CI for Percent
Long COVID	279	16548565	4.91	[4.122, 5.71]
No Long COVID	1601	107238612	31.84	[29.76, 33.93]
No COVID	3681	212981219	63.25	[61.11, 6537]
Total	5561	336940627	100.00	

Comment [A17]: 6537?

3.1. Longitudinal Trajectories of Health and Economic Outcomes

Longitudinal mixed-effect models were used to examine the trajectories of three primary outcomes: perceived health status (Model 1), psychological distress (Model 2), and inflation adjusted log-transformed healthcare expenditures (Model 3), adjusting for demographics and pre-pandemic health status. Table 2 below represents the summary of the estimates from the models.

1. Perceived Health and Psychological Distress:

We adjusted for pre-pandemic health status and the insurance status, the main effect of belonging to the Long COVID group was not statistically significant for either perceived health status (β = 0.0506, p = 0.4729) or psychological distress (β = 0.3807, p = 0.1065). This indicates that the poorer self-reported health and well-being in the Long COVID group may largely be attributed to pre-existing health disparities and socioeconomic factors rather than a direct, long-term consequence of the infection itself. For both outcomes, the trajectories over the four-year period were almost parallel across three groups, with non-significant time-by-group interactions

(Figures 1 & 2).

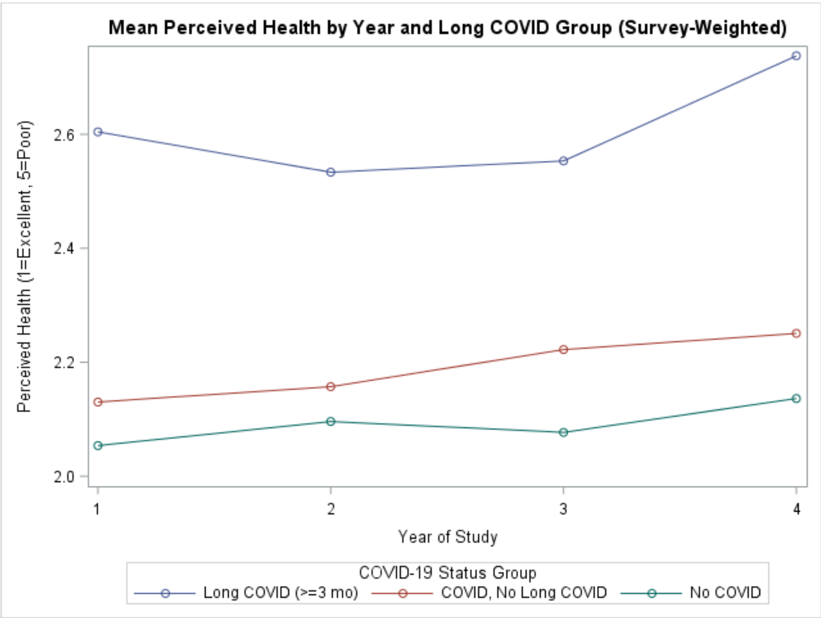

Figure 1: Trajectory of Mean Perceived Health Status (1=Excellent, 5=Poor) over four years, stratified by COVID-19 status group.

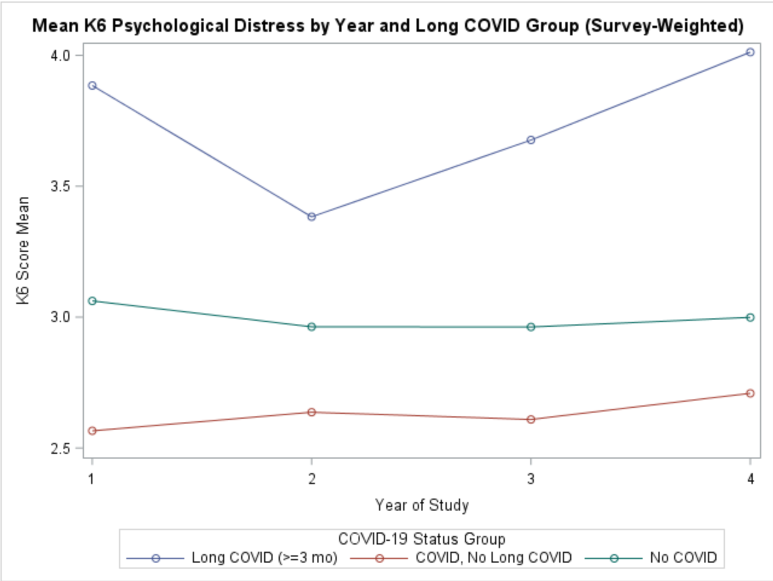

Figure 2: Trajectory of Mean Psychological Distress (K6 Score) over four years, stratified by COVID-19 status group.

2. Accelerating Financial Burden: An Independent Consequence of Long COVID

The analysis of inflation-adjusted healthcare expenditures revealed a robust and independent effect of Long COVID. A highly significant interaction was found between time and the Long COVID group ($F(2, 1E4) = 15.11$, $p < .0001$), this finding that was robust to controlling for pre-pandemic health and insurance status. The rate of increase in healthcare expenditure was significantly higher for the Long COVID group compared to the other two groups ($\beta = 0.3159$, $p < .0001$). This demonstrates a divergent, accelerating economic burden that is a direct consequence of the illness itself (Figure 3).

Comment [A18]: The manuscript highlights an "accelerating" cost trajectory; however, this is based on a significant interaction term. A visualization of predicted expenditures with 95% CIs would better support this claim.

Comment [A19]: Clarify whether expenditures include out-of-pocket costs only or total healthcare system expenditures.

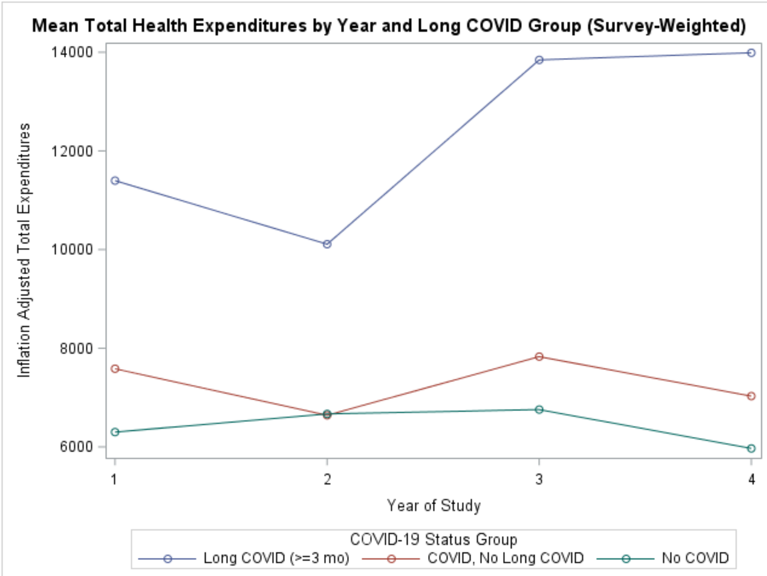

Figure 3: Trajectory of Mean Inflation-Adjusted Total Health Expenditures (2024 USD)

Table 2: Fixed Effect Estimates for the models

Predictor	Perceived Health Status (β, SE)	Psychological Distress (β, SE)	Log Health Expenditures (β, SE)
Intercept	0.3106 (0.0356)***	2.5034 (0.3952)***	4.9701 (0.2015)***
Long COVID	0.0506 (0.0709)	0.3807 (0.2326)	0.2642 (0.1609)
No Long COVID	−0.0097 (0.0336)	−0.4208 (0.1264)***	0.1245 (0.0763)
Baseline Health	0.7891 (0.0057)***	1.2144 (0.0519)***	0.3421 (0.0315)***
Insured (vs. Uninsured)	−0.2093 0.0189)***	−0.4728 (0.1009)***	0.3592 (0.0652)***
Time	0.0416 (0.0060)***	0.0125 (0.0323)	−0.1425 (0.0194)***
Time × Long COVID	0.0033 (0.0212)	0.0101 (0.0964)	0.3159 (0.0689)***
Time × No Long COVID	−0.0063 (0.0102)	0.0142 (0.0505)	0.1066 (0.0331)**
Age	0.0028 (0.0003)***	−0.0194 (0.0031)***	0.0427 (0.0015)***
Male (vs. Female)	−0.0031 (0.0110)	−0.5739 (0.1111)***	−0.5776 (0.0661)***
White (vs. Multiple races)	0.000022 (0.02939)	-0.9768(0.3450)**	-0.6532(0.1722)***
Black (vs. Multiple races)	0.01725 (0.03241)	-1.2432(0.3706)***	-1.1476 (0.1875)***
Am. Indian/Alaska Native (vs. Multiple)	-0.06263 (0.08741)	-1.1355 (0.7798)	-1.6230 (0.4819)***
Asian/Native Hawaiian (vs. Multiple)	-0.04205 (0.03592)	–1.6442(0.4092)**	-1.1820 (0.2141)***

Note: Values are unstandardized coefficients with standard errors in parentheses. p < 0.05 (*), p < 0.01 (**), p < 0.001 (***).

4. Discussion

Comment [A20]: Although pre-pandemic health is controlled, potential unmeasured confounders (e.g., socioeconomic status, vaccination status, comorbidities) should be acknowledged in the discussion. n

This multi-year, nationally representative longitudinal analysis provides an in-depth, quantitative exploration of the long-term consequences of Long COVID. The report establishes a complex interrelation between pre-existing frailty and the direct, incremental disease-specific economic impact. Our study clarifies the distinct challenges that Long COVID poses to public health by highlighting these factors.

A primary finding of this study is that pre-pandemic health status is a powerful determinant of post-infection well-being. The initial, significant deficits in perceived health and psychological distress observed in the Long COVID cohort were largely attenuated after controlling for baseline health. This suggests that Long COVID would not create a new health deficit *de novo* in a previously healthy population, but rather that pre-existing health vulnerabilities make one more susceptible to developing severe and prolonged sequelae following SARS-CoV-2 infection. This would be in line with a developing body of literature that has found pre-existing medical conditions, such as autoimmune disease, diabetes, and prior mental health disorders, to be significant PASC risk factors (Notarte et al., 2022; Thaweethai et al., 2023). Our findings solidify this view, reframing the narrative from a universal chronic illness to one that disproportionately impacts and exacerbates the conditions of those with prior health challenges. This finding also aligns with the public health concept of allostatic load, where the cumulative physiological burden of pre-existing conditions reduces an individual's capacity to recover from a new health condition like a SARS-CoV-2 infection (McEwen, 1998). These attenuations persisted after additionally controlling for insurance status, underscoring baseline health as the dominant driver of perceived health and distress outcomes.

An interesting secondary finding was the significantly lower baseline psychological distress in the "COVID-19 Recovered" group compared to the No COVID reference group. This unexpected result may be explained in several different ways. It may be a "healthy survivor" effect, in that individuals with greater levels of psychological resilience would be more likely to recover. It may also be a "relief effect" or a post-traumatic growth, in that recovery from an acute disease has led to temporarily enhanced mental well-being (Tedeschi & Calhoun, 2004). Importantly, this lower level of distress remained significant after adjustment for baseline health and insurance coverage.

The most robust finding of this study is the diverging and accelerating pattern of healthcare expenditure for the Long COVID group. This rising financial burden has the connotation that the disease process requires more medical attention over a prolonged period. This finding adds to existing literature, which has identified high healthcare utilization in the first year following infection (Al-Aly et al., 2022), by revealing that this spending burden continually becomes more adverse for a multi-year period.

In the fully adjusted model, inflation-adjusted spending declined in the No COVID group (≈13%

per wave), was roughly flat to slightly declining in the COVID-19 Recovered group (≈3–4% per wave), and increased in the Long COVID group (≈18–19% per wave), consistent with a positive Time × Long COVID interaction. Insurance coverage was, as expected, strongly associated with higher expenditures; however, adjusting for insurance did not eliminate the upward Long COVID spending slope.

This trajectory follows the theories of pathophysiology involving chronic or low-grade inflammation that could catalyze the onset of new health conditions or worsening of pre-existing conditions over time (Davis et al., 2023; Perumal et al., 2023). The accelerating trajectory of healthcare costs is similar to that seen in other chronic illnesses characterized by secondary complications over time, such as diabetes or congestive heart failure. This increasing cost has significant repercussions, tallying a likely unsustainable long-term cost for the healthcare system, insurers, and households, and underscores a clear need for policy intervention.

Comment [A21]: The discussion appropriately links results to pre-existing health disparities and the concept of allostatic load. However, the section could benefit from more specific public health implications: e.g., what interventions or policy responses should address the financial burden?

Strengths and Limitations

Comment [A22]: The limitations section is well-addressed but could expand slightly on the issue of self-selection and attrition bias across the four-year MEPS panel.

One of the major strengths of this study is its use of a large, nationally representative, multi-year longitudinal dataset with a pre-pandemic baseline, allowing for robust and generalizable conclusions about the trajectories of change. However, this study is not without limitations. First, the reliance on self-reported data from MEPS is subject to recall and reporting biases. Furthermore, the definition of Long COVID was based on a single self-reported item regarding symptom duration rather than a formal clinical diagnosis. This approach introduces the potential for misclassification bias, as individuals with pre-existing conditions may misattribute their ongoing symptoms to Long COVID. Future research using electronic health records with formal diagnostic codes could further strengthen these findings.

A further strength is the explicit inflation adjustment of expenditures and inclusion of insurance status to mitigate confounding by coverage and access; nonetheless, insurance may provide health-seeking behavior, so some residual confounding in cost models is possible.

Conclusion

This study provides definitive evidence that while the long-term health and well-being impact of Long COVID is strongly associated with pre-pandemic health status, the condition independently triggers an accelerating and cumulative financial burden over a multi-year period. The distinct findings demonstrate that having existing health conditions before contracting COVID is the main vulnerability factor, and the growing financial burden is the most serious long-term impact of Long COVID. This emphasizes the need for socioeconomic policy interventions that curtail the escalating financial burden of the condition. This may include ensuring access to disability benefits, creating efficient workplace accommodation, and developing insurance frameworks that account for people with long-term care costs. By addressing the patient's pre-existing vulnerabilities and the independent economic consequences of the disease, healthcare systems and policymakers can more effectively address the profound and lasting societal impact of Long COVID.

Crucially, these conclusions hold in models that adjust for insurance status and use inflation-adjusted, log-scaled expenditures, reinforcing Long COVID's economic burden independence and persistence. Policy responses should be explicitly insurance-aware (e.g., out-of-pocket caps, disability support, workplace accommodations, etc.) to buffer households from documented multi-year cost accumulation.

Acknowledgements

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