COVID-19 lockdown consequences on body mass index and perceived fragility related to physical activity: A worldwide cohort study

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Abstract
Background: This paper is a follow-up study continuing the COVISTRESS network previous research regarding health-related determinants.
1 | INTRODUCTION

In previous years, global pandemics have occurred, including COVID-19, with severe consequences for world populations.\(^1\)\(^2\) The COVID-19 outbreak effects could be divided into two main areas of analysis. The first regards medical measures, which include identifying the genome sequence characteristics of the virus, finding adequate treatment for those infected, new research on discovering new diagnosis tools and COVID-19 vaccine development strategies.\(^3\)\(^4\) The second aspect is connected to the worldwide lockdown imposed by authorities in order to break the chain of infection and prevent further spread of the virus.\(^5\)\(^7\) Although lockdown constraints were different among countries and not simultaneously implemented, some regulations were mandatory worldwide: home confinement, closing down cultural and social events, teleworking, online schooling, restricted displacements, social distancing or restricted Physical Activity.\(^8\) These safety measures represented at the same time health-related risk factors for Body Mass Index (BMI), Physical Activity (PA) and Perceived Fragility and risk of getting infected.

Evidence indicates that increased BMI is highly related to developing severe complications of COVID-19.\(^9\) Authors documented a U-shaped infection rate among overweight and underweight elderly,\(^10\) revealing that obesity is also implicated in impaired immune responses.\(^11\) It was emphasized that when examining the degree of association between higher BMI and the need of hospitalization, obesity was acknowledged as predicting a poor clinical prognosis in patients with COVID-19.\(^12\)\(^13\) Both obesity and underweight are proven to be important health-related risk factors for various pathologies, including COVID-19.\(^9\)\(^14\) Research established causal mechanisms between overweight/obesity and the risk of developing severe symptoms of COVID-19 in all age groups, especially in the elderly.\(^15\) Authors developed a risk prediction model for hospital admission and death rate from coronavirus in large cohort studies, including variables such as age, Body Mass Index, ethnicity, deprivation and a range of comorbidities.\(^16\)

Studies examined the global changes in daily PA, revealing that the global trend emphasizes a drastic decline in PA levels across different countries and ages during the confinement period.\(^17\) This evidence needs formalization of PA guidelines comprising main recommendations in the areas of exercise and PA.\(^18\) Even if the lockdown was expected to protect against the virus, vulnerable people, namely the elderly and those with chronic medical conditions, were impacted by sedentary behaviour.\(^19\)\(^20\) The evidence-based consequences for the elderly during this pandemic highlight the importance of their perceived frailty, resulting from multiple...


comorbidities.\textsuperscript{21} Still, authors like Spiegelhalter (2020)\textsuperscript{22} discussed the slight difference between the normal risk of death and the COVID-19 similar rate in England and Wales; before the pandemic, the fatality risk doubled every seven years of extra age, while in 2020 during a 16-week pandemic period this risk doubled for every 5 to 6 years of extra age.

According to UN,\textsuperscript{23} there are more than 700 million people aged over 65 years worldwide, considered to be at higher risk for severe prognosis concerning COVID-19,\textsuperscript{24} unless muscle function, cardiovascular fitness, immune function and overall well-being\textsuperscript{25,26} are preserved. A wide understanding of fragility in the elderly requires a holistic vision including multiple causes: biological, psychological and social aspects, which render seniors more vulnerable to chronic illnesses, emotional stress or limited activities of daily living.\textsuperscript{27}

Moreover, increased loneliness and reduced family interactions, along with PA restriction, are likely to produce health issues\textsuperscript{28,29} that could be explained by alterations in the adaptive and innate immune systems.\textsuperscript{30}

Regarding the meanings of the term ‘fragility’ from a biological perspective, meta-analysis also addresses this concept as an individual trait greatly influenced by diverse physical and psychological stressors along with the diminished health system capacity to provide medical care.\textsuperscript{31} Fragility was described as a myriad of conditions such as decreased physiological reserve, emaciation or overweight, susceptibility to injuries and diminished stress resilience.\textsuperscript{32,33}

Moreover, specialists emphasize that the fragility syndrome is a more severe health status related to the simultaneous presence of two or more comorbidities.\textsuperscript{34,35} Authors like Mello et al (2014)\textsuperscript{36} correlate the fragility syndrome with different characteristics, namely age, female gender, extreme BMI values, depressive symptoms and self-evaluation health risks.

In the context of the COVID-19 pandemic, the multidimensional fragility concept reveals to be even more relevant due to the increased threats for the individual health and a hindered stress response.\textsuperscript{37} Thus, feeling insecure and being worried about risk of infection are both consequences of a fragility status.

Fragility is also conceptualized by global entities like OECD as a complex political, economic and societal reality, requiring a distinct policy agenda and being largely influenced in the last year by the COVID-19 pandemic. This reminded of the great disparities among countries in terms of health-care systems.\textsuperscript{38}

The aim of this study was to identify the main consequences of the COVID-19 lockdown on BMI and Perceived Fragility, as relevant aspects related to PA as part of an active lifestyle. Conceived as a cross-cultural study, this paper addressed different age, gender and weight categories, providing large-scale information originating from numerous countries worldwide. It was not the intention of the authors to delineate specific national characteristics as to how the pandemic acted upon the individuals’ health outcomes. The research questions were the following: Were the COVID-19 lockdown consequences equally distributed across different categories of individuals? Which of these categories were impacted the most by the restrictions linked to physical activities?

## METHODS

### 2.1 Sample

This study involved 10 121 participants originating from 67 countries worldwide, which were analysed as a whole. They were asked to complete an online questionnaire linked to the COVID-19 consequences on BMI, PA and Perceived fragility and risk of getting infected. The inclusion criteria for participants were the ability to complete this open-access tool available at covistress.org.\textsuperscript{39} The recruitment of participants was achieved by self-selection, using snowball sampling techniques via social media invitations (Facebook, Twitter, LinkedIn), where the aim, procedure and consent for participation were explained. No exclusion criteria were applied. All data were anonymized. The participants willingly gave their informed consent once they accessed the survey, having the possibility to withdraw at any time and/or partially complete the items, without giving reasons. Ethical approval for the research protocol was granted by the Research Ethics Commission of a University Hospital in Europe (Nos Ref.: 2020/CE 06, March 2020), the procedures applied complying with the Declaration of Helsinki. Each National representative institution provided Ethical approval.

### 2.2 Procedure

Our study encompassed the first COVID-19 lockdown (March–May 2020), when severe regulations were applied in most countries experiencing different timings and durations for the lockdown. Data were collected from March to June 2020, allowing all participants to undergo COVID-19 constraints. This research was a joint effort of universities, university hospitals and scientific research centres from France, Australia, Austria, Canada, Chile, China, Denmark, Indonesia, Italy, Iran, Norway, Portugal, Tunisia, Taiwan, Scotland, Switzerland, Romania and United States, all being part of an international research team. This COVISTRESS network (http://covistress.org/contacts.html) created an assessment tool intended to investigate the lifestyle and stress characteristics experienced by populations worldwide during the COVID-19 pandemic. Concretely, a questionnaire was disseminated in different national languages, by means of REDCap\textsuperscript{®} application (Research Electronic Data Capture) specifically designed to create and manage online surveys.\textsuperscript{40,41} The COVISTRESS questionnaire included 45 items divided into different sections: sociodemographic, epidemiological context, stress and worries, occupation and professions, parenthood and family, isolation and impact of coronavirus and health coverage.\textsuperscript{42} These items focused on collecting general information available worldwide with a common understanding of the aspects addressed, without making references to different countries. The completion of the questionnaire was estimated at 20 minutes. Within the current study, specific items were selected from the COVISTRESS questionnaire, as a stand-alone approach, including the items relating to BMI, PA and Perceived fragility and risk of getting infected. The first two items

<table>
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referred to the prior pandemic period and to the first lockdown. Unlike BMI and PA, the Perceived fragility and risk of getting infected item made reference only to the lockdown period. Therefore, an accurate assessment of the situation at that time became possible. In order to identify the most vulnerable populations by age, the participants were divided into three categories: youth and young adults aged between 18 and 35 years old, adults aged between 36 and 65 years old and elderly aged over 65 years old. Depending on their BMI, the participants of most interest were the underweight and the overweight individuals. For the PA item, participants were requested to mention the number of hours of PA performed per week, before and during the isolation. For Perceived Fragility, the participants had to choose the intensity level of this measured outcome, from a 0 to 100 mm scale (Visual Analogue Scale). This scale has been used by different authors to assess perceived stress, mental and physical fatigue. The task for the participants was to establish their level of Perceived Fragility and risk of getting infected on a horizontal line of 100 mm, ranging from very low (0), to very high (100).

2.3 | Statistics

Data analysis was performed using SPSS software, v20. The normality of the data distribution was ascertained using Skewness and Kurtosis coefficients. Skewness coefficient in absolute values was not exceeding a value of 3 for Skewness and 8 for Kurtosis. t tests were applied in order to determine the significant differences between prior and during sets of data. Significance was set at P < .05. According to Cohen, if d = 0.8 the effect size is strong, if d = 0.5, the effect size is medium, while for d = 0.2, the effect size is small. For the homogeneity of the variances, Levene’s test was used. When the homogeneity condition was not met, an analysis of variance (ANOVA) was applied. Given the multiple comparisons performed on measured outcomes and the need to control the type 1 errors in null hypothesis, the powerful Hochberg test was applied. Correlational analysis was applied using either Spearman’s or Pearson’s coefficients. The correlations were considered to be very strong (r > .8), moderate (r = .6-.8), fair (r = .3-.6) and poor (r = .1-.3).

3 | RESULTS

3.1 | Socio-demographic analysis

Out of the 10 121 participants who accessed the COVISTRESS questionnaire, 8124 totally or partially responded to the selected items. From the whole group, 5603 were female participants, with a mean age of 41.42 ± 12.97 years old, 2498 were male participants, with a mean age of 44.38 ± 14.28 years old, whereas 23 participants did not mention their sex. The subjects were divided into three age groups, namely 2759 youth and young adults aged between 18 and 35 years old, 4924 adults aged between 36 and 65 years old, 387 elderly aged over 65 years old, whereas 54 participants did not mention their age. All selected outcome measures had a normal distribution for the whole group by applying the Skewness and Kurtosis coefficients.

3.2 | Body Mass Index analysis

Mean BMI value before isolation was 24.71 ± 5.04 kg/m² and increased significantly from a statistical standpoint during isolation to 24.78 ± 5.03 kg/m². t test value was t(7099) = 5.64, at P < .001, with a very small effect size (d = 0.01). The whole group of subjects fell into the healthy weight category. In females, mean BMI value before isolation was 24.32 ± 5.27 kg/m² (Skewness 1.60 (std. error 0.04) and Kurtosis 4.10 (std. error 0.07)) and increased significantly during isolation to 24.39 ± 5.26 kg/m² (Skewness 1.58 (std. error 0.04) and Kurtosis 3.99 (std. error 0.07)). t test value was t(4840) = 6.29, at P < .001, with a small effect size (d = 0.01). Both mean values expressed a slightly overweight category for the female participants. From the total number of participants completing this item, 457 were underweight (below 18.5 kg/m²), 492 were overweight and obese (25-29.9 kg/m²; 30-39.9 kg/m²), 6151 were healthy weight (18.5-24.9 kg/m²). For the underweight, the mean BMI value before isolation was 18.06 ± 0.71 kg/m², (Skewness −0.86 (std. error 0.11) and Kurtosis 0.09 (std. error 0.23)) and increased significantly from a statistical standpoint during the isolation to 18.16 ± 0.87 kg/m², (Skewness −0.47 (std. error 0.11) and Kurtosis 0.62 (std. error 0.23)). t test value was t(456) = 3.88, at P < .001, with a very small effect size (d = 0.13). For the obese subjects, the mean BMI value before isolation was 36.78 ± 3.46 kg/m², (Skewness 0.99 (std. error 0.11), Kurtosis 0.45 (std. error 0.22)) and decreased significantly from a statistical viewpoint during isolation to 36.66 ± 3.60 kg/m², (Skewness 0.78 (std. error 0.11) and Kurtosis 0.51 (std. error 0.22)). t test value was t(491) = 2.14, at P = .033, with a very small effect size (d = 0.03). Both mean values referred to class II obesity. It is a common fact that obesity status most frequently leads to severe consequences for health outcomes. In general, the effect size, either small or very small, underlines the reduced differences between means. These differences were not likely to influence changes in health outcomes in the short term, during the first lockdown, although the value itself was highly concerning.

3.3 | Physical Activity analysis

Regarding the number of hours of PA before isolation across three age groups, the data exhibited normal distribution. Despite this,
the conditions of homogeneity of variances were not met, Levene’s test indicated $F(2,7198) = 53.24$, $P < .001$, and as a result, the ANOVA test was applied. It was demonstrated that the subjects from the three age groups showed significantly different results ($F(2,7198) = 0.41$, $P < .001$) for PA before isolation, the effect size being small ($\eta^2_p = .015$). Hochberg test showed significant differences among the age groups (alpha = 0.05). The effect size was small ($d = 0.07$) between 18-35 years and 36-65 years; over medium ($d = 0.60$) between 36-65 years and over 65 years; and under medium ($d = 0.44$) between 18-35 years and over 65 years. In terms of PA during isolation across three age groups, the data exhibited normal distribution. Despite this, the condition of homogeneity of variances were not met, Levene’s test indicating $F(2,7176) = 14.71$, $P < .001$, so the ANOVA test was applied. It was shown that the subjects from the age groups registered significantly different results ($F(2,7198) = 30.06$, $P < .001$) for PA during isolation, the effect size being small ($\eta^2_p = .008$). Applying the Hochberg test, there were significant differences between the 18 and 35 years and over 65 years, as well as between 36 and 65 years and over 65 years, at alpha = 0.05. The effect size was almost medium ($d = 0.43$) for both 36-65 years and over 65 years and between 18 and 35 years and over 65 years ($d = 0.41$) (Table 1).

### 3.4 Analysis for Perceived Fragility and risk of getting infected

Statistics corresponding to the whole group for Perceived Fragility and risk of getting infected revealed a mean value of $34.94 \pm 32.02$ on a scale from 0 to 100, with $36.33 \pm 32.65$ for males (Skewness 0.58 (std. error 0.03) and Kurtosis −0.98 (std. error 0.07)) and $31.71 \pm 30.33$ for the male participants (Skewness 0.76 (std. error 0.05) and Kurtosis −0.65 (std. error 0.10)). $t$ test value was $t_{adj} = 4.880$, at $P < .001$, with a small effect size ($d = 0.14$). With respect to the age groups, the mean value for the 18-35 years was $27.12 \pm 29.69$ (Skewness 1.06 (std. error 0.05) and Kurtosis −0.02 (std. error 0.10)), $37.54 \pm 32.09$ for the 36-65 years group (Skewness 0.53 (std. error 0.04) and Kurtosis −1.02 (std. error 0.07)) and $57.77 \pm 31.49$ for the over 65 years group (Skewness −0.38 (std. error 0.13) and Kurtosis −1.07 (std. error 0.25)). ANOVA emphasized that the participants from the three age groups registered significant different results ($F(2,7710) = 198.3$, $P < .001$). The effect size was under medium ($\eta^2_p = .049$). Hochberg test demonstrated significant differences among all three age groups. The effect size was small ($d = 0.33$) between 18-35 years and 36-65 years; over medium ($d = 0.63$) between 36-65 years and over 65 years; and large ($d = 1.02$) between 18-35 years and over 65 years.

### 3.5 Correlations among BMI, PA and Perceived Fragility and risk of getting infected

For the whole group, there were statistically significant correlations: a small positive correlation between BMI before and Perceived Fragility and risk of getting infected ($r = .25$); a very small negative correlation between BMI before and PA before ($r = -.08$); a small positive correlation between BMI during isolation and Perceived Fragility and risk of getting infected ($r = .25$); a small negative correlation between BMI during and PA during ($r = .07$). For female participants, there were statistically significant correlations: a small positive correlation between BMI before isolation and Perceived Fragility and risk of getting infected ($r = .26$); a very small negative correlation between BMI before isolation and PA before ($r = -.13$); a small positive correlation between BMI during and Perceived Fragility and risk of

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$^aR$ Squared = 0.015 (adjusted $R$-squared = 0.014)–regression analysis.
getting infected \( r = .27 \); a very small negative correlation between BMI during and PA during isolation \( r = -.12 \). For male participants, statistically significant correlations were also found: a small positive correlation was identified between BMI before isolation and Perceived Fragility and risk of getting infected \( r = .24 \); also, a small negative correlation between BMI before isolation and PA before isolation \( r = -.05 \) and a small positive correlation between BMI during isolation and Perceived Fragility and risk of getting infected \( r = .23 \) were revealed. For the underweight group, statistically significant correlations were identified: a small negative correlation was identified between the BMI before isolation and Perceived Fragility and risk of getting infected \( r = -.11 \). Statistically significant correlations were emphasized for the obese group as well: a small positive correlation between BMI before isolation and Perceived Fragility and risk of getting infected \( r = .20 \); a small negative correlation between BMI before isolation and PA before isolation \( r = -.10 \); a small positive correlation between BMI during isolation and Perceived Fragility and risk of getting infected \( r = .22 \); a small negative correlation between BMI during isolation and PA during isolation \( r = -.16 \).

With regard to the comparative analysis for underweight and obese in terms of Age, Perceived Fragility and PA, the age mean values were 36.10 years for underweight and 44.03 years for the obese; for fragility, the mean values were 28.63 for the underweight and 57.20 for the obese; for PA before isolation, the mean values were 9.71 hours/week for the underweight and 7.08 hours/week for the obese; for PA during isolation, the mean values were 6.60 hours/week for the underweight and 5.06 hours/week for the obese. t test (Table 2) revealed significant differences between underweight and obese, in terms of age \( t_{\text{adj}}(890.4) = 9.49, P < .001 \). The effect size was over medium \( (d = 0.62) \). The same test emphasized significant differences between underweight and obese in terms of Perceived Fragility and risk of getting infected \( t_{\text{adj}}(889.7) = 13.3, P < .001 \). The effect size was large \( (d = 0.89) \). The Perceived Fragility and risk of getting infected were more intense in obese, compared with underweight: 57.2 ± 34.08 vs 28.63 ± 30.16. t tests also revealed significant differences between underweight and obese in terms of PA before isolation \( t_{\text{adj}}(856.7) = 5.01, P < .001 \), with a small effect size \( (d = 0.33) \). Prior to isolation, obese participants exercised less, compared with underweight: 7.08 ± 7.05 vs 9.71 ± 8.71. Regarding the PA during isolation, there were significant differences between underweight and obese \( t_{\text{adj}}(853.9) = 3.8, P < .001 \), with a small effect size \( (d = 0.25) \). During the isolation, the obese participants exercised less, compared to underweight participants: 5.06 ± 5.44 vs 6.6 ± 6.74.

### 4 DISCUSSION

This paper is a continuation of our previous research regarding COVID-19 consequences on different health-related components, as conceptualized by the COVISTRESS network. This study emphasized a thematic sequence of this methodology, as complementary information to similar data collected by this team.
4.1 | BMI

Despite the reduced BMI differences, which would not influence optimal health status in general, the statistical tools nonetheless revealed that for the whole group this outcome slightly varied before and during isolation. In the long term, an ascending trend for BMI, predictable under the circumstances of a prolonged pandemic, might represent a serious health risk for the participants. Similar results were reported for an Italian population of all ages and genders, exploring body weight changes during the lockdown. Our findings showed that female participants exhibited healthy weight BMI values both before and during isolation, while the male participants were slightly overweight both prior and during the lockdown. Although BMI registered a very small increase during isolation for both categories, female participants remained in the healthy weight category, while male participants remained slightly overweight. Weight gain, often correlated to its contributing factors, analysed during the pandemic, was confirmed in multiple studies for both genders, all of them raising awareness about the importance of nutritional status for a healthy lifestyle. Taking into consideration the extreme weight categories as being linked to risk of severe COVID-19 complications, we noticed that 13.11% of the total sample fell into these vulnerable categories. Severe COVID-19 patients had overweight or obesity syndromes, reported as an 'independent risk factor', because enhanced adiposity diminishes pulmonary function.

4.2 | Physical Activity

According to recent studies, although the World Health Organization established the minimum duration of PA per day for a healthy person, the COVID-19 pandemic has drastically restricted PA in all age groups, in all countries. In this study, statistical results provided insights about PA patterns before and during the isolation for different age groups. In all three age categories, the number of hours per week decreased by 31.25% for youth and young adults, by 26.05% for the adults and by 30.27% for the elderly, during the lockdown. Also, the participants over 65 years old were the most active before isolation, followed by the youth and young adults. During the lockdown, the young people were the most deprived, followed by the elderly and the adults. Active behaviour decreased also in the Italian young population and in the French elderly, due to severe restrictions regarding physical daily living activities.

4.3 | Perceived Fragility and Risk of getting infected

This study emphasized a high level of Perceived Fragility and risk of getting infected for female participants, compared to the surveyed male population, which is also confirmed by different statistics. The most striking differences regarding Perceived fragility and risk of getting infected were identified among the three age groups. Perceived fragility and risk of getting infected gradually increased along with the age category. Thus, the over 65-year participants had the most significant fragility score, most probably associated with their health status and fear of getting infected. Given the elderly multiple comorbidities, perceived risk was more than twice than that of the young. That is why the restrictive measures are more relevant when elderly subjects are involved. Seniors facing great deprivation of family contact and social life in general will be able to cope with this new reality by adhering to COVID-19 safety measures.

4.4 | Correlations among measured outcomes

According to statistical correlations, it was demonstrated that BMI influenced Perceived Fragility and had a cause-effect relationship with PA performed before and during the isolation. BMI relating to physical self positively influences self-confidence and empowerment, so that the individual feels less fragile in coping with COVID-19. Regarding the same correlation applied to female and male subject outcomes, there were similar cause-effect relationships between BMI, Perceived Fragility and the amount of PA, both before and during the lockdown, with the exception of the correlation between the male BMI and PA during isolation. With respect to the above-mentioned correlations, it was obvious that for obese subjects, BMI related to their Perceived Fragility before and during the lockdown. The predicted relationship between BMI and the amount of PA was emphasized, both before and during lockdown, revealing the well-known positive effects of exercise on physical appearance. Similar results regarding the benefits of Physical Activity on losing weight in obese patients were found on a regular basis before the pandemic onset. The results acknowledge that obese populations are at a higher risk of feeling physically fragile and prone to develop severe COVID-19 symptoms if becoming infected.

4.5 | Limitations

The research team was not able to control the severity of the restrictions or the time differences across countries. Also, different criteria for lockdown metrics were not taken into consideration for the surveyed countries, nor the differences between their economic status. The self-selection procedure for participants did not meet the requirements of the typical sampling techniques, but the great number of participants compensated for this limitation. The number of respondents varied to a great extent by country, the data being analysed as a whole, without underlining country-specific aspects.

The present questionnaire did not include information about the exercise intensity or the type of PA performed. In terms of Perceived Fragility, further specific assessment tools are likely to add complementary information about the fragility syndrome in the elderly.
5 | CONCLUSIONS

This study examined the main consequences of the first lockdown on different outcomes related to Physical Activity as part of an active lifestyle. Based on the research questions, the findings highlighted that the elderly, females and obese participants are more impacted by the COVID-19 restrictions, especially regarding PA.

The current results extend and confirm previous research concerning vulnerable populations that are more likely to be at risk, by experiencing weight variations or an enhanced Perceived Fragility. We can conclude that physical and health-related components might be impacted in the long term, by the changes in the daily routines imposed by the pandemic.

Vulnerable populations are more susceptible to developing different health conditions, without adequate counteracting measures to alleviate the physical and psychological curfew constraints. Despite the lockdown, individuals need to maintain an active lifestyle in order to tackle the pandemic challenges and to develop more resilient mechanisms to COVID-19 infections.

To sum up, the health-related findings in this paper reveal the current and potential effects upon long-term health status, mostly triggered by the prolonged psychological pandemic stressors and diminished Physical Activity. In this context, health-care professionals and also educators should focus on preventing sedentary lifestyle and providing psychological counselling as necessary interventions to mitigate some of the COVID-19 consequences.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

The authors contributed equally to this work. CU and AB contributed to conceptualization; CU, AB and UCU contributed to methodology; MD, AB and CU contributed to software design; FD, MC, NA and YG validated the study; CU, AB, UCU and BP made formal analysis; CU, AB, UCU, BP and JSB made investigation; FD, DT, NA and KK contributed to resources; KK, YG, KR, NA and BP involved in data curation; CU and AB contributed to writing—original draft preparation; UCU, JSB, MD and RB contributed to writing—review & editing; FD and RB made visualization; FD and MC made supervision; FD and MC involved in project administration, and FD acquired funding. All authors have read and agreed to the published version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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