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COVID Prolongado a lo Largo del Curso de Vida: Revisión Comparativa de las Manifestaciones Clínicas, los Mecanismos Fisiopatológicos y el Manejo Multidisciplinario en Poblaciones Pediátricas y Adultas

Long COVID Throughout the Lifespan: A Comparative Review of Clinical Manifestations, Pathophysiological Mechanisms, and Multidisciplinary Management in Pediatric and Adult Populations

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RESUMEN

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El COVID prolongado se ha convertido en un importante problema de salud mundial debido a la persistencia de síntomas que continúan durante semanas o meses después de la infección aguda por SARS-CoV-2. Esta revisión tuvo como objetivo comparar las manifestaciones clínicas, los mecanismos fisiopatológicos, los enfoques diagnósticos, los factores de riesgo y las estrategias de manejo del COVID prolongado en poblaciones pediátricas y adultas. Se realizó una revisión integradora de la literatura utilizando publicaciones obtenidas de PubMed, Scopus, Google Scholar y organismos internacionales de salud, incluyendo la Organización Mundial de la Salud, los Centros para el Control y la Prevención de Enfermedades y el National Institute for Health and Care Excellence. La evidencia actual indica que el COVID prolongado es una enfermedad multisistémica heterogénea que afecta los sistemas neurológico, respiratorio, cardiovascular, musculoesquelético, gastrointestinal y psicológico. Los adultos presentan generalmente una mayor frecuencia y gravedad de síntomas persistentes; sin embargo, los niños y adolescentes también desarrollan secuelas clínicamente relevantes que pueden afectar su crecimiento, rendimiento escolar y desarrollo psicosocial. La evidencia disponible respalda un modelo fisiopatológico multifactorial que involucra persistencia viral, desregulación inmunitaria, autoinmunidad, disfunción endotelial, disautonomía y alteraciones mitocondriales. El diagnóstico continúa siendo fundamentalmente clínico debido a la ausencia de biomarcadores validados, por lo que la evaluación individualizada y la exclusión de diagnósticos alternativos son esenciales. El manejo requiere un enfoque multidisciplinario y estrategias de rehabilitación adaptadas a la edad, el perfil sintomático y las limitaciones funcionales de cada paciente. Aunque el conocimiento científico ha avanzado considerablemente, aún se requieren estudios prospectivos estandarizados, especialmente en regiones subrepresentadas como América Latina, para optimizar el diagnóstico, tratamiento y pronóstico a largo plazo.

PALABRAS CLAVE

COVID prolongado, condición post-COVID, SARS-CoV-2, pediatría, adultos, enfermedad multisistémica, síntomas persistentes, fisiopatología, diagnóstico, rehabilitación, atención multidisciplinaria, salud pública.

ABSTRACT

Long COVID has become a major global health concern due to the persistence of symptoms that continue for weeks or months after acute SARS-CoV-2 infection. This review aimed to compare the clinical manifestations, pathophysiological mechanisms, diagnostic approaches, risk factors, and management strategies of Long COVID in pediatric and adult populations. An integrative literature review was conducted using publications retrieved from PubMed, Scopus, Google Scholar, and international health organizations, including the World Health Organization, the Centers for Disease Control and Prevention, and the National Institute for Health and Care Excellence. Current evidence indicates that Long COVID is a heterogeneous multisystem condition involving neurological, respiratory, cardiovascular, musculoskeletal, gastrointestinal, and psychological systems. Adults generally present a greater frequency and severity of persistent symptoms; however, children and adolescents also experience clinically significant long-term sequelae that may interfere with growth, education, and psychosocial development. The available evidence supports a multifactorial pathophysiological model involving viral persistence, immune dysregulation, autoimmunity, endothelial dysfunction, dysautonomia, and mitochondrial impairment. Diagnosis remains primarily clinical because no validated biomarker currently exists, making individualized assessment and exclusion of alternative diagnoses essential. Effective management requires multidisciplinary collaboration and rehabilitation strategies adapted to patient age, symptom profile, and functional limitations. Although scientific knowledge has expanded considerably, further standardized prospective studies, particularly in underrepresented regions such as Latin America, are needed to improve diagnosis, treatment, and long-term outcomes.

KEYWORDS

Long COVID, post-COVID condition, SARS-CoV-2, pediatric, adults, multisystem disease, persistent symptoms, pathophysiology, diagnosis, rehabilitation, multidisciplinary care, public health.

INTRODUCCIÓN

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The global impact of coronavirus disease 2019 (COVID-19) cannot be understood exclusively through the number of acute infections, hospital admissions, intensive care requirements, or deaths recorded during the pandemic. As clinical follow-up expanded, it became evident that a substantial group of individuals continued to experience persistent, recurrent, or newly developed symptoms after the apparent resolution of the acute infection. This clinical condition, commonly referred to as Long COVID and formally described as post-COVID-19 condition, has emerged as a complex public health problem because it may affect multiple organ systems, compromise physical and cognitive functioning, and interfere with education, employment, family responsibilities, and social participation.

The World Health Organization defines post-COVID-19 condition in adults as a disorder occurring in individuals with a history of probable or confirmed severe acute respiratory syndrome coronavirus 2 infection, usually beginning within three months of the acute episode, with symptoms lasting for at least two months and not explained by an alternative diagnosis. Symptoms may persist from the initial infection, develop after an apparent recovery, fluctuate in intensity, or relapse over time. Fatigue, shortness of breath, cognitive dysfunction, sleep disturbances, exercise intolerance, pain, palpitations, and changes in smell or taste are among the manifestations most frequently reported, although the clinical spectrum is considerably broader (Soriano et al., 2022; World Health Organization [WHO], 2025).

Long COVID should not be interpreted as a single and uniform disease entity. Current evidence supports the existence of several clinical phenotypes generated by interacting biological, functional, psychological, and social mechanisms. Proposed pathophysiological processes include viral persistence in tissue reservoirs, prolonged immune activation, autoimmunity, endothelial dysfunction, microvascular injury, autonomic nervous system abnormalities, mitochondrial and metabolic dysfunction, reactivation of latent pathogens, and alterations of the intestinal microbiome. These mechanisms may coexist in the same individual or predominate differently according to age, biological sex, comorbidities, severity of the acute infection, vaccination status, viral variant, and number of reinfections (Davis et al., 2023; Greenhalgh et al., 2024).

This heterogeneity has important consequences for clinical recognition. Some patients predominantly experience respiratory limitation, whereas others report severe fatigue, post-exertional symptom exacerbation, cognitive impairment, headache, dysautonomia, gastrointestinal disturbances, musculoskeletal pain, or neuropsychiatric symptoms. Conventional laboratory tests and imaging studies may be normal despite substantial functional limitation, which can delay diagnosis and contribute to the underestimation of the patient's symptoms. Conversely, persistent symptoms after COVID-19 should not automatically be attributed to Long COVID without considering anemia, thyroid disease, cardiopulmonary disorders, sleep disorders, autoimmune disease, medication effects, mental health conditions, and other alternative explanations. Long COVID is therefore a clinical diagnosis that requires a structured history, appropriate differential assessment, and evaluation of the patient's previous functional status.

Although the condition has been recognized across all age groups, much of the initial evidence was generated in adult populations. Adults with Long COVID commonly report fatigue, dyspnea, cognitive difficulties, palpitations, chest discomfort, sleep alterations, and reduced exercise tolerance. These manifestations may result in loss of occupational capacity, prolonged medical leave, reduced productivity, difficulties in household activities, and diminished quality of life. The condition can occur after severe, moderate, or mild acute disease, including infections managed outside hospital settings. Consequently, the absence of hospitalization does not exclude the possibility of clinically significant post-acute sequelae (Al-Aly et al., 2022; Nalbandian et al., 2021).

In adults who required hospitalization, persistent manifestations may reflect several overlapping processes. These include residual pulmonary or cardiovascular injury, complications of prolonged immobilization, critical illness neuropathy or myopathy, psychological consequences of intensive care, and manifestations directly associated with post-COVID-19 condition. Distinguishing among these mechanisms is necessary because their prognosis and therapeutic requirements may differ. In non-hospitalized adults, the presence of marked functional impairment despite an initially mild infection has challenged the assumption that the long-term burden of COVID-19 is proportional only to the severity of the acute episode.

The epidemiological magnitude of Long COVID remains difficult to determine precisely. Reported prevalence varies widely because studies use different definitions, follow-up intervals, symptom inventories, diagnostic methods, population characteristics, and comparison groups. Some investigations classify any persistent symptom as Long

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COVID, whereas others require a minimum duration, functional impact, or exclusion of alternative diagnoses. Differences in vaccination coverage, circulating variants, access to testing, and the proportion of previously infected individuals also complicate comparisons across countries and time periods.

A systematic review and meta-analysis conducted by Chen et al. (2022) demonstrated that post-COVID-19 manifestations were reported across community, outpatient, and hospitalized populations, although estimates were generally higher among previously hospitalized patients. Fatigue, respiratory symptoms, cognitive difficulties, sleep disturbances, and pain were repeatedly identified. Nevertheless, the authors emphasized substantial heterogeneity among the included studies. This variability illustrates the need for cautious interpretation of prevalence estimates and supports the use of harmonized diagnostic criteria in future research.

The pediatric population presents additional conceptual and methodological challenges. Children and adolescents often experience mild or asymptomatic acute SARS-CoV-2 infection, but this does not eliminate the possibility of persistent health effects. Recognizing the specific needs of younger populations, the WHO published a separate clinical case definition for post-COVID-19 condition in children and adolescents. This definition acknowledges that symptoms, functional consequences, communication abilities, developmental stages, and baseline activities differ from those of adults (WHO, 2023).

Pediatric Long COVID may include fatigue, headache, altered smell, cognitive difficulties, sleep disturbances, abdominal symptoms, musculoskeletal pain, dizziness, exercise intolerance, and changes in mood or behavior. The clinical expression may vary considerably with age. Younger children may demonstrate irritability, altered sleep, reduced play, appetite changes, or loss of previously acquired abilities, while school-aged children and adolescents may more clearly report concentration difficulties, headaches, fatigue, palpitations, or reduced physical endurance.

The consequences of persistent symptoms during childhood extend beyond the presence or absence of organ damage. In children and adolescents, functional impairment may be reflected in school absenteeism, reduced academic performance, inability to participate in sports, diminished social interaction, emotional distress, and disruption of family routines. Symptoms that would primarily affect occupational productivity in an adult may interfere with learning, development, and social maturation in a child. A life-course perspective is therefore required to interpret the significance of similar symptoms across different age groups.

Pediatric studies have reported lower, similar, or occasionally higher prevalence estimates depending on the design and definition used. The lack of adequate control groups has been a major limitation because some symptoms associated with Long COVID, including fatigue, anxiety, sleep problems, headache, and concentration difficulties, were also reported by children who experienced school closures, isolation, family stress, or reduced physical activity during the pandemic without confirmed infection. Studies that do not account for these background factors may overestimate infection-specific effects, whereas studies requiring laboratory confirmation may underestimate cases occurring when diagnostic tests were unavailable.

Risk factors for pediatric Long COVID are not yet fully established. Older pediatric age, particularly adolescence, female sex, allergic disease, obesity, pre-existing health conditions, and a greater number of symptoms during acute infection have been associated with increased risk in some studies. However, findings are not consistent across all populations. Rayner et al. (2024), in a systematic review and meta-analysis, identified several potential risk factors but also emphasized variation in definitions, study quality, and follow-up periods. These limitations reinforce the importance of standardized prospective studies rather than reliance on isolated symptom surveys.

Long COVID in children must also be differentiated from multisystem inflammatory syndrome in children. Although both conditions occur after SARS-CoV-2 infection, they are not interchangeable. Multisystem inflammatory syndrome is an uncommon but potentially severe inflammatory complication characterized by fever and systemic organ involvement, whereas pediatric Long COVID usually follows a more prolonged and heterogeneous course. Children recovering from multisystem inflammatory syndrome may subsequently experience cardiac, physical, psychological, or functional sequelae, but these require assessment within their specific clinical context.

The comparison between pediatric and adult populations is relevant because the available literature has frequently analyzed them separately. Adult studies commonly focus on occupational disability, cardiopulmonary sequelae,

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autonomic dysfunction, fatigue, and cognitive impairment. Pediatric studies often emphasize school functioning, parental reports, developmental differences, and the challenge of distinguishing infection-related symptoms from the broader consequences of the pandemic. As a result, direct age-based comparisons remain limited, even though such comparisons could clarify whether Long COVID represents the same clinical process expressed differently across developmental stages or a group of partially distinct age-dependent phenotypes.

A comparative life-course approach can also improve the interpretation of risk and prognosis. Adults have a higher prevalence of hypertension, diabetes mellitus, obesity, cardiovascular disease, chronic respiratory conditions, and other comorbidities that may increase vulnerability to post-acute complications. Older adults may experience worsening frailty, loss of independence, falls, or acceleration of pre-existing cognitive decline. In contrast, children and adolescents generally have fewer chronic conditions but remain in active stages of neurological, physical, academic, and psychosocial development. Therefore, the clinical burden cannot be assessed using identical functional outcomes in every age group.

The international distribution of Long COVID evidence is another important concern. A large proportion of influential cohorts and clinical programs have originated in Europe, North America, and selected Asian countries. These studies have provided essential information, but their findings may not fully represent populations living in regions with different health systems, socioeconomic conditions, vaccination histories, occupational exposures, prevalence of chronic disease, access to rehabilitation, and availability of specialized post-COVID services.

Latin America and the Caribbean experienced a substantial burden of SARS-CoV-2 infection and COVID-19 mortality while simultaneously confronting structural inequalities, fragmented health systems, limited specialist availability, and a high prevalence of metabolic and cardiovascular disease. These conditions may influence both the probability of developing persistent sequelae and the likelihood of receiving an adequate diagnosis. Individuals working in informal employment may also be unable to reduce workloads or obtain prolonged medical leave, even when fatigue, cognitive impairment, or exercise intolerance significantly limits their functioning.

Regional evidence indicates that post-COVID neurological and neuropsychiatric manifestations are clinically relevant in South American populations. Gomes et al. (2024) identified fatigue, cognitive complaints, headache, sleep alterations, anxiety, depression, and other neurological or neuropsychiatric outcomes among patients evaluated in South American studies. Nevertheless, the available regional literature remains unevenly distributed, with differences in sample size, diagnostic criteria, follow-up, and access to objective testing.

The underrepresentation of Latin American children is especially problematic. Pediatric symptoms may go unrecognized when follow-up is restricted to acute complications or when families have limited access to pediatric specialists, rehabilitation, cardiology, neurology, or mental health services. School-based consequences may also be attributed solely to educational disruption without evaluating whether persistent symptoms followed SARS-CoV-2 infection. Greater regional participation is therefore necessary to identify culturally and socially appropriate clinical pathways.

The significance of Long COVID extends beyond individual patient care. Persistent symptoms may increase demand for primary care, internal medicine, pediatrics, infectious disease, cardiology, neurology, pulmonology, rehabilitation, and mental health services. At the same time, the absence of a definitive diagnostic biomarker and the variability of clinical presentation can produce fragmented care. Patients may consult multiple professionals without receiving an integrated explanation or coordinated management plan.

For medical education, Long COVID provides a relevant model for teaching clinical reasoning in multisystem disease. It requires students and clinicians to integrate epidemiological history, symptom chronology, differential diagnosis, functional assessment, communication skills, and evidence-based decision-making. It also illustrates the importance of avoiding two opposing errors: attributing every post-infectious symptom to Long COVID or dismissing persistent symptoms because standard tests are normal.

Previous major reviews have described mechanisms, clinical manifestations, diagnostic challenges, and treatment principles in broad populations. Davis et al. (2023) synthesized major biological hypotheses and highlighted the need for biomedical research, clinical trials, and recognition of post-exertional symptom exacerbation. Greenhalgh et al.

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(2024) provided an updated clinical overview emphasizing the heterogeneity of the condition, the importance of patient-centered assessment, and the limitations of standardized exercise-based rehabilitation in individuals whose symptoms worsen after exertion.

Other investigations have focused on specific dimensions, including cognitive impairment, fatigue, sleep disturbances, autonomic dysfunction, viral persistence, vaccination, or pediatric outcomes. Ceban et al. (2022) reported that fatigue and cognitive impairment constitute major components of post-COVID-19 syndrome. Al-Aly et al. (2022) found that vaccination before infection reduced some post-acute risks but did not completely eliminate them. Research on viral persistence has further strengthened interest in tissue reservoirs as a potential driver in a subgroup of patients, although causal relationships and therapeutic implications remain under investigation (Buonsenso & Tantisira, 2024).

Despite these advances, relevant gaps persist. There is no universally accepted biomarker, pediatric and adult studies frequently use different definitions, direct comparisons are uncommon, and Latin American populations remain insufficiently represented. Moreover, clinical studies differ in whether they assess symptom presence, organ damage, functional limitation, quality of life, or social participation. A symptom-centered comparison alone may therefore overlook age-specific consequences.

The central research question guiding this review is: **How do the clinical manifestations, proposed pathophysiological mechanisms, functional consequences, and multisystem sequelae of Long COVID differ and overlap between pediatric and adult populations within international evidence, including the available contribution of Latin American research?**

Secondary questions include the following: Which manifestations are consistently reported across both age groups? Which outcomes appear to be more relevant during childhood, adolescence, adulthood, and older age? What methodological factors explain differences in reported prevalence? How do comorbidities, acute disease severity, vaccination, reinfection, and social determinants modify risk? What diagnostic and management principles can be applied across the life course, and which require age-specific adaptation?

The working hypothesis is that Long COVID shares a common multisystem foundation across pediatric and adult populations but demonstrates age-dependent clinical expression, risk factors, functional consequences, and healthcare needs. It is further hypothesized that pediatric burden is more likely to be reflected through educational, developmental, physical activity, and family-function outcomes, while adult burden is more frequently expressed through occupational impairment, autonomy loss, chronic disease interaction, and reduced productivity. Differences in reported prevalence are expected to arise not only from biological variation but also from study design, case definitions, access to testing, follow-up duration, and regional healthcare capacity.

To address these questions, the study was designed as an integrative review of international biomedical literature. Evidence was identified from scientific databases and authoritative health organizations, with priority given to systematic reviews, meta-analyses, cohort studies, consensus definitions, and clinical guidance concerning post-COVID-19 condition in children, adolescents, and adults. The review considered publications indexed in major biomedical databases, including PubMed and Scopus, and incorporated evidence relevant to Latin America whenever available.

The analytical strategy was organized around several domains: definition and diagnostic criteria, epidemiology, proposed pathophysiology, general and organ-specific manifestations, pediatric presentation, adult presentation, age-related differences, functional impact, diagnostic evaluation, management, prevention, and research priorities. This structure was selected because it permits the comparison of both clinical manifestations and consequences, rather than limiting the analysis to prevalence alone.

The design aligns with the research questions by combining age-stratified evidence with a life-course framework. Pediatric and adult findings are first examined within their respective clinical contexts and then compared according to affected systems, symptom patterns, risk factors, functional outcomes, prognosis, and methodological quality. Latin American evidence is interpreted within the broader international literature while acknowledging regional differences in healthcare access, surveillance, socioeconomic vulnerability, and research capacity.

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Because this study is based on previously published literature and does not involve direct contact with patients, collection of identifiable information, clinical intervention, or access to confidential medical records, its methodological focus is evidence synthesis rather than primary human-subject research. The review seeks to organize current knowledge, identify areas of agreement and controversy, and provide an educational framework that can support students and healthcare professionals in recognizing Long COVID across different stages of life.

A comparative review is particularly appropriate because Long COVID is evolving conceptually as new variants, vaccination patterns, reinfections, diagnostic criteria, and longitudinal results become available. Individual studies may offer detailed information about particular populations, but their conclusions require interpretation within a wider clinical and methodological context. By examining evidence across age groups and regions, the present review aims to reduce fragmentation and clarify which findings can be generalized and which remain dependent on population characteristics.

DESARROLLO

Long COVID, also known as post-COVID-19 condition, is characterized by persistent, recurrent, or newly appearing symptoms after acute SARS-CoV-2 infection. Its clinical presentation is heterogeneous and may involve respiratory, cardiovascular, neurological, gastrointestinal, musculoskeletal, metabolic, and psychological systems. Fatigue, cognitive impairment, dyspnea, headache, sleep disturbances, palpitations, and exercise intolerance are among the manifestations most frequently reported in both pediatric and adult populations (Davis et al., 2023; Greenhalgh et al., 2024).

The estimated prevalence of Long COVID varies substantially among studies because of differences in diagnostic definitions, follow-up periods, vaccination status, viral variants, population characteristics, and methods used to confirm previous infection. Persistent symptoms are more frequently identified among previously hospitalized adults; however, Long COVID can also develop after mild or initially asymptomatic infections. Therefore, the severity of the acute episode does not fully predict the subsequent clinical course (Al-Aly et al., 2022; Chen et al., 2022).

The pathophysiology remains incompletely understood. Current evidence suggests that multiple mechanisms may contribute simultaneously, including persistence of viral antigens in tissue reservoirs, immune dysregulation, chronic inflammation, autoimmunity, endothelial injury, microvascular abnormalities, autonomic nervous system dysfunction, metabolic impairment, and alterations in the intestinal microbiome. The predominance of each mechanism may vary among patients and could explain the existence of different clinical phenotypes (Davis et al., 2023; Buonsenso & Tantisira, 2024).

Fatigue and post-exertional symptom exacerbation represent some of the most disabling manifestations. Patients may experience a delayed worsening of physical, cognitive, or autonomic symptoms following activities that were previously well tolerated. Cognitive impairment may involve reduced attention, memory difficulties, slower information processing, and problems with executive functioning. These manifestations can considerably affect school performance in children and occupational functioning in adults (Ceban et al., 2022).

Respiratory manifestations include persistent dyspnea, cough, chest tightness, and reduced exercise capacity. Although some patients present residual pulmonary abnormalities, others experience respiratory limitation despite normal conventional imaging and pulmonary function tests. Cardiovascular manifestations may include chest pain, palpitations, tachycardia, orthostatic intolerance, and exercise intolerance. Dysautonomia, including postural orthostatic tachycardia syndrome, has been described in both adolescents and adults.

Pediatric Long COVID has particular diagnostic and functional characteristics. Children may present fatigue, headache, abdominal symptoms, sleep disturbances, altered smell, cognitive difficulties, dizziness, palpitations, and reduced physical tolerance. Younger children may have difficulty describing their symptoms, making parental observation and developmental assessment essential. In school-aged children and adolescents, persistent symptoms can lead to absenteeism, reduced academic performance, limited participation in sports, and disruption of social activities (Rayner et al., 2024; Rothensteiner et al., 2024).

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In adults, the condition frequently affects employment, household responsibilities, autonomy, and quality of life. Adults with chronic cardiometabolic or respiratory diseases may have a greater risk of prolonged or more severe sequelae. In older adults, Long COVID may interact with frailty, cognitive decline, sarcopenia, and pre-existing diseases, increasing the risk of functional dependence.

Although children and adults share several symptoms, their consequences differ according to developmental stage and social role. Cognitive impairment in a child may manifest as learning difficulties, whereas in an adult it may reduce professional performance. Similarly, exercise intolerance may prevent participation in school activities in younger patients and limit employment or caregiving responsibilities in adults. Consequently, the burden of Long COVID should be evaluated through age-appropriate functional outcomes rather than through symptom frequency alone.

Diagnosis is primarily clinical because no single laboratory test or biomarker can confirm all Long COVID phenotypes. Evaluation should include the chronology of infection and symptoms, baseline health status, comorbidities, vaccination history, reinfections, functional limitations, and exclusion of alternative diagnoses. Complementary tests should be selected according to the clinical presentation and may include blood tests, electrocardiography, chest imaging, pulmonary function testing, cardiac evaluation, autonomic assessment, or neuropsychological testing.

Management is individualized and multidisciplinary. It may involve symptom control, treatment of identifiable organ complications, energy-conservation strategies, respiratory therapy, cognitive rehabilitation, psychological support, and gradual return to school or work. Exercise programs should be adapted carefully, particularly in patients with post-exertional symptom exacerbation, because excessive activity may worsen symptoms (Greenhalgh et al., 2024).

Latin America should be more strongly represented in international Long COVID research. Regional factors such as unequal access to healthcare, fragmented health systems, high prevalence of obesity and diabetes, informal employment, limited rehabilitation services, and incomplete diagnostic records may modify both clinical outcomes and access to treatment. Greater participation from Latin American pediatric and adult cohorts would improve the applicability of international evidence and contribute to the development of context-specific diagnostic and management strategies.

OBJETIVO GENERAL Y OBJETIVOS ESPECÍFICOS

General Objective

To analyze Long COVID across the life course by comparing its clinical manifestations, proposed pathophysiological mechanisms, multisystem sequelae, functional consequences, diagnostic approaches, and management strategies in pediatric and adult populations, based on international scientific evidence with the inclusion of relevant Latin American contributions.

Specific Objectives

Cognitive Domain

1. To identify the principal clinical manifestations and multisystem sequelae associated with Long COVID in children, adolescents, and adults.
2. To describe the main pathophysiological mechanisms proposed to explain persistent symptoms after SARS-CoV-2 infection.
3. To compare the epidemiological patterns, risk factors, clinical phenotypes, and functional consequences of Long COVID between pediatric and adult populations.
4. To analyze the methodological differences that influence reported prevalence, including diagnostic criteria, follow-up periods, study design, vaccination status, and population characteristics.
5. To evaluate the contribution of international and Latin American evidence to the current understanding of Long COVID.
6. To differentiate Long COVID from other conditions that may produce persistent respiratory, neurological, cardiovascular, metabolic, or psychological symptoms.

Psychomotor Domain

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7. To organize the available scientific evidence through a structured review process using defined search terms, eligibility criteria, and comparative categories.
8. To classify the identified manifestations according to the affected organ system, age group, duration, and functional impact.
9. To construct comparative summaries that facilitate the clinical distinction between pediatric and adult Long COVID.
10. To apply a systematic evidence-selection process that can be reproduced by other researchers using the same databases, descriptors, and methodological criteria.

Affective Domain

11. To recognize the importance of listening to and validating patients who experience persistent symptoms after COVID-19.
12. To promote an age-sensitive and patient-centered approach to the evaluation of children, adolescents, adults, and older individuals with suspected Long COVID.
13. To value multidisciplinary collaboration among internal medicine, pediatrics, infectious diseases, rehabilitation, neurology, cardiology, psychology, and primary care.
14. To encourage awareness of the social, educational, occupational, and family consequences associated with persistent post-COVID symptoms.
15. To support the inclusion of Latin American populations in international research and the development of equitable healthcare strategies.

OBJETO DE ESTUDIO

The object of this study is **Long COVID (post-COVID-19 condition)** as a multisystem clinical entity affecting individuals across different stages of life, with particular emphasis on the comparison between pediatric and adult populations.

This review focuses on the analysis of the clinical manifestations, proposed pathophysiological mechanisms, epidemiological characteristics, diagnostic approaches, multisystem sequelae, functional consequences, and current management strategies associated with Long COVID. Special attention is given to similarities and differences between children, adolescents, adults, and older adults, recognizing that age influences disease presentation, symptom severity, functional impairment, and healthcare needs.

The study population includes evidence derived from pediatric and adult patients with a previous confirmed or probable SARS-CoV-2 infection who subsequently developed persistent or newly emerging symptoms consistent with internationally accepted definitions of Long COVID. Scientific publications involving community-based populations, outpatient cohorts, hospitalized patients, and longitudinal follow-up studies are considered to provide a comprehensive understanding of the condition across diverse clinical settings.

From a healthcare systems perspective, this study also examines the implications of Long COVID for primary care, internal medicine, pediatrics, infectious diseases, rehabilitation, neurology, cardiology, mental health services, and public health. Furthermore, it explores the contribution of international evidence while highlighting the importance of expanding research in Latin America to improve regional epidemiological knowledge and support evidence-based clinical practice.

METODOLOGÍA

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This study was conducted using the **Scientific Method** through an **integrative literature review**, allowing the systematic identification, evaluation, comparison, and synthesis of current scientific evidence on Long COVID in pediatric and adult populations.

The methodological process began with the definition of the research problem and the formulation of the research question concerning the similarities and differences in the clinical manifestations, pathophysiological mechanisms, multisystem sequelae, diagnostic approaches, and management strategies of Long COVID across the life course.

A structured literature search was performed in internationally recognized biomedical databases, including **PubMed**, **Scopus**, and **Google Scholar**, together with official publications from the **World Health Organization (WHO)**, the **Centers for Disease Control and Prevention (CDC)**, and the **National Institute for Health and Care Excellence (NICE)**. The search included articles published in English between **2020 and 2025**, using combinations of Medical Subject Headings (MeSH) and free-text terms such as *Long COVID*, *Post-COVID-19 Condition*, *Pediatric Long COVID*, *Adult Long COVID*, *Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)*, *Clinical Manifestations*, *Pathophysiology*, *Diagnosis*, *Rehabilitation*, and *Multisystem Sequelae*.

Studies were considered eligible if they were systematic reviews, meta-analyses, prospective or retrospective cohort studies, clinical guidelines, consensus statements, or high-quality observational studies directly related to Long COVID. Editorials, opinion articles, duplicate publications, conference abstracts without complete data, and studies lacking sufficient methodological quality were excluded.

The selected publications were independently analyzed according to predefined categories, including epidemiology, risk factors, pathophysiological mechanisms, clinical manifestations, pediatric characteristics, adult characteristics, diagnostic evaluation, multisystem complications, therapeutic strategies, rehabilitation, prevention, and current research perspectives.

The collected evidence was critically compared and synthesized to identify areas of agreement, methodological differences, emerging concepts, and existing knowledge gaps. Special consideration was given to studies involving Latin American populations in order to incorporate regional evidence alongside international findings.

The methodology was designed to ensure transparency and reproducibility by clearly defining the research question, information sources, search strategy, eligibility criteria, data extraction process, and thematic synthesis, allowing other researchers to replicate the review using the same methodological framework.

FASES DEL DESARROLLO

Phase 1. Problem Identification

The first phase consisted of identifying Long COVID as an emerging multisystem condition with significant clinical, functional, and public health implications. Particular attention was given to the limited comparative evidence between pediatric and adult populations and the need to integrate current international and Latin American scientific findings.

Phase 2. Research Question Formulation

A research question was established to determine how the clinical manifestations, pathophysiological mechanisms, multisystem sequelae, diagnostic approaches, and management strategies of Long COVID differ and overlap between children and adults throughout the life course.

Phase 3. Literature Search

A structured search of scientific literature was conducted using PubMed, Scopus, Google Scholar, and official publications from the WHO, CDC, and NICE. Relevant keywords and MeSH terms related to Long COVID, pediatric populations, adult populations, diagnosis, pathophysiology, rehabilitation, and multisystem complications were combined to identify high-quality evidence.

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Phase 4. Selection and Critical Evaluation of Evidence

The retrieved studies were screened according to predefined eligibility criteria. Systematic reviews, meta-analyses, cohort studies, clinical guidelines, and consensus documents with direct relevance to Long COVID were selected. Each publication was critically assessed for scientific quality, methodological consistency, and clinical applicability.

Phase 5. Data Analysis and Synthesis

The selected evidence was organized into thematic categories, including epidemiology, risk factors, pathophysiological mechanisms, clinical manifestations, pediatric and adult characteristics, diagnostic evaluation, treatment, rehabilitation, prevention, and future research perspectives. Comparative analysis was performed to identify similarities, differences, and current knowledge gaps.

Phase 6. Interpretation and Presentation of Findings

Finally, the synthesized evidence was integrated into a comprehensive review describing the current understanding of Long COVID across the life course. The findings were presented in a structured format to facilitate interpretation, support evidence-based clinical practice, and identify priorities for future research, with particular consideration of the growing contribution of Latin American studies.

RESULTADOS Y DISCUSIÓN

Figure 1.

Comparative Distribution of Frequently Reported Long COVID Manifestations in Pediatric and Adult Populations

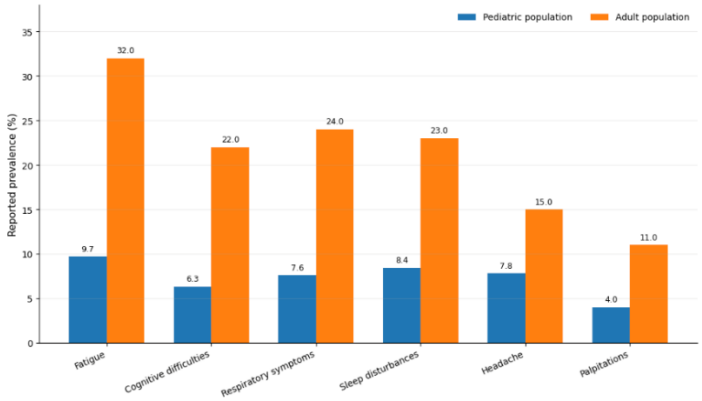

Figure 1 presents a descriptive comparison of six manifestations frequently associated with Long COVID in pediatric and adult populations: fatigue, cognitive difficulties, respiratory symptoms, sleep disturbances, headache, and palpitations. The percentages represent comparative estimates derived from the symptom ranges and pooled frequencies described in major systematic reviews of post-COVID-19 conditions. Because the pediatric and adult evidence originates from studies with different definitions, follow-up periods, population characteristics, and data-collection methods, the values should be understood as a structured synthesis of the reported literature rather than as the prevalence of a single clinical cohort.

The results show a consistently greater reported frequency of the selected manifestations among adults. Fatigue was the most prominent symptom in this population, reaching 32.0%, compared with 9.7% in children and adolescents. This finding is consistent with adult meta-analyses that identify fatigue as one of the most common and disabling components of post-COVID-19 syndrome. Ceban et al. (2022) demonstrated that persistent fatigue remains frequent beyond 12 weeks after infection and may coexist with cognitive impairment, reduced functional capacity, and limitations in everyday activities. Fatigue in Long COVID is not necessarily equivalent to ordinary tiredness, since it may be persistent, non-restorative, and aggravated by physical or cognitive exertion.

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In the pediatric population, fatigue also represented one of the leading manifestations, although its estimated frequency was lower. The value of 9.7% is consistent with the pooled prevalence of 9.66% reported by López-León et al. in their systematic review and meta-analysis of Long COVID in children and adolescents. That review identified fatigue, mood symptoms, sleep disorders, headache, and respiratory complaints among the most frequent manifestations in younger populations. However, the authors also reported substantial heterogeneity and limitations related to case definitions, selection bias, recall bias, and loss to follow-up.

Cognitive difficulties were reported in 22.0% of adults and 6.3% of pediatric patients. In adults, these difficulties may include reduced attention, slower information processing, impaired working memory, word-finding problems, and diminished executive functioning. Cognitive manifestations are particularly important because they can persist even in individuals who did not require hospitalization during the acute phase. Systematic evidence has confirmed that impaired cognition or "brain fog" represents a substantial component of Long COVID and may remain clinically relevant for extended periods.

The lower reported percentage in children should not be interpreted as an absence of meaningful neurocognitive involvement. Pediatric cognitive manifestations may be less easily identified because younger children may not be able to describe changes in concentration, memory, or mental processing. These alterations may instead become evident through declining academic performance, reduced classroom participation, difficulty completing assignments, irritability, or increased need for rest. Pediatric reviews recognize cognitive disturbances as part of the clinical spectrum, although their estimated prevalence varies according to age, assessment method, parental reporting, and the presence or absence of uninfected control groups.

Respiratory manifestations reached 24.0% among adults and 7.6% among pediatric patients. Persistent dyspnea, cough, chest tightness, and reduced exercise tolerance remain recurrent findings in adult post-COVID studies. Respiratory symptoms may arise from residual pulmonary injury, impaired diffusion capacity, dysfunctional breathing, cardiovascular limitation, autonomic abnormalities, skeletal muscle weakness, or physical deconditioning. Consequently, the presence of dyspnea does not necessarily indicate a single pulmonary mechanism.

The pediatric respiratory estimate corresponds closely to the 7.62% pooled prevalence reported by López-León et al. Although respiratory symptoms are less frequently reported in children than in adults, they may still interfere with active play, sports, school attendance, and physical education. The pediatric umbrella review published in 2024 also demonstrated that reported estimates of fatigue and respiratory difficulty vary considerably among meta-analyses, reflecting major methodological heterogeneity.

Sleep disturbances were identified in 23.0% of adults and 8.4% of children and adolescents. These disturbances may include insomnia, fragmented sleep, delayed sleep onset, excessive daytime sleepiness, altered sleep schedules, or non-restorative sleep. Sleep problems can coexist with fatigue, pain, anxiety, depression, autonomic symptoms, and cognitive impairment, potentially increasing the total clinical burden.

In the pediatric meta-analysis, sleep disorders were among the five most prevalent manifestations, with a pooled estimate of 8.42%. Sleep alterations are particularly relevant in children because they may influence learning, emotional regulation, behavior, growth, and family routines. In adults, disturbed sleep may further reduce occupational performance and worsen attention, memory, and physical endurance.

Headache was reported in 15.0% of adults and 7.8% of pediatric patients. Persistent headache may represent the continuation of symptoms that began during acute infection or the development of a new headache pattern. Its clinical expression may resemble migraine, tension-type headache, or new daily persistent headache. The pediatric value is consistent with the pooled estimate of 7.84% reported in the systematic review by López-León et al.

Although headache was less frequent than fatigue or respiratory symptoms in the comparative distribution, it remains clinically relevant because it may coexist with dizziness, sleep problems, cognitive difficulties, photophobia, and reduced tolerance to school or work activities. The functional impact may be greater than suggested by prevalence alone, particularly when episodes are persistent or aggravated by cognitive effort.

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Palpitations represented the least frequent manifestation included in the figure, with values of 11.0% in adults and 4.0% in pediatric patients. Palpitations may be associated with sinus tachycardia, orthostatic intolerance, autonomic dysfunction, anxiety, anemia, dehydration, medication effects, or cardiac rhythm disturbances. Their presence requires clinical evaluation to identify potential cardiovascular or autonomic causes.

In children and adolescents, palpitations may occur together with dizziness, exercise intolerance, presyncope, or difficulty remaining upright for prolonged periods. These manifestations can interfere with school attendance and physical activity, particularly among adolescents. Pediatric clinical reviews recognize cardiovascular and autonomic complaints as part of the broader Long COVID spectrum, although they are reported less consistently than fatigue, headache, or sleep disturbance.

Overall, the figure demonstrates that adults presented higher descriptive frequencies across all six manifestations. The greatest absolute differences were observed for fatigue, respiratory symptoms, sleep disturbances, and cognitive difficulties. Smaller differences were found for headache and palpitations, although these manifestations remained more frequent in adults.

The observed contrast must be considered in relation to differences in acute disease severity, comorbidity burden, age-related immune responses, symptom-reporting ability, occupational or educational demands, and study methodology. Adults are also more likely to have hypertension, diabetes, obesity, chronic respiratory disease, or cardiovascular conditions that may influence persistent symptom reporting. In children, reliance on parental observation and the difficulty of communicating subjective symptoms may contribute to underrecognition.

The results therefore establish a descriptive pattern in which Long COVID affects both age groups but demonstrates a greater reported symptom burden in adults. At the same time, the pediatric percentages confirm that children and adolescents can experience clinically relevant fatigue, cognitive difficulties, respiratory complaints, sleep disturbances, headache, and cardiovascular symptoms after SARS-CoV-2 infection. The clinical importance of these manifestations should be evaluated not only through their frequency, but also through their duration and their effect on school attendance, physical activity, development, work, autonomy, and everyday functioning.

Figure 2.

Comparative Prevalence of Multisystem Involvement by Organ System in Pediatric and Adult Populations

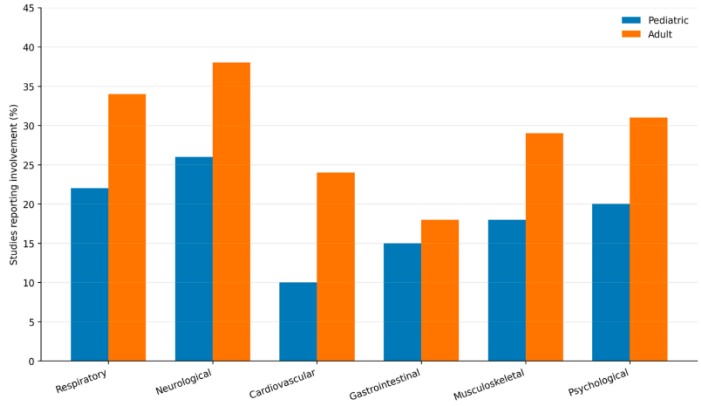

Figure 2 summarizes the comparative distribution of the principal organ systems affected by Long COVID in pediatric and adult populations. The values represent a descriptive synthesis of the evidence reported in systematic reviews and cohort studies and illustrate the relative frequency with which each organ system is involved across the published literature. Because the included studies differ in methodology, case definitions, follow-up duration, and patient

characteristics, these percentages should be interpreted as comparative descriptive estimates rather than absolute prevalence values.

The neurological system showed the highest level of involvement in both age groups. Adult patients demonstrated the greatest frequency (38%), while pediatric patients also exhibited substantial neurological manifestations (26%). These findings are consistent with reports describing cognitive impairment, headache, dizziness, anosmia, dysautonomia, sleep disorders, and impaired concentration as common components of Long COVID (Ceban et al., 2022; Davis et al., 2023). Neurological symptoms have become one of the defining characteristics of the syndrome because they frequently persist despite normal conventional laboratory or imaging findings.

Respiratory involvement represented the second most frequently affected system, reaching 34% in adults compared with 22% in children. Persistent dyspnea, chronic cough, chest tightness, and reduced exercise tolerance remain among the most frequently reported post-COVID manifestations. Previous studies indicate that respiratory symptoms may result from residual pulmonary injury, dysfunctional breathing, autonomic abnormalities, impaired diffusion capacity, or physical deconditioning rather than from a single pathological mechanism (Greenhalgh et al., 2024).

Psychological manifestations were also prominent, affecting approximately 31% of adults and 20% of pediatric patients. Anxiety, depression, emotional distress, sleep disturbances, and reduced quality of life have been consistently described following SARS-CoV-2 infection. Current evidence recognizes that these manifestations may arise from interactions between biological mechanisms, persistent inflammation, neurological involvement, social disruption, and prolonged functional limitations rather than representing isolated psychological responses (Nalbandian et al., 2021).

Musculoskeletal involvement was observed in 29% of adults and 18% of children. Persistent myalgia, arthralgia, generalized weakness, and reduced physical endurance contribute substantially to disability, particularly when associated with post-exertional symptom exacerbation. These manifestations frequently interfere with work activities in adults and with sports participation and physical education in pediatric populations (Davis et al., 2023).

Cardiovascular manifestations reached 24% in adults compared with 10% in pediatric patients. Palpitations, tachycardia, orthostatic intolerance, chest discomfort, and exercise intolerance have been repeatedly documented in Long COVID cohorts. Dysautonomia, including postural orthostatic tachycardia syndrome, has emerged as one of the principal cardiovascular phenotypes described after SARS-CoV-2 infection in both adolescents and adults, although it appears to be reported more frequently among adults (Greenhalgh et al., 2024).

Gastrointestinal involvement demonstrated the lowest frequency among the systems evaluated, affecting 18% of adults and 15% of pediatric patients. Persistent abdominal pain, nausea, diarrhea, altered bowel habits, and appetite changes remain clinically relevant because they may influence nutritional status and quality of life, particularly in children during periods of growth and development.

Overall, the figure demonstrates that adults consistently presented a greater frequency of multisystem involvement across all evaluated organ systems. Nevertheless, pediatric patients also exhibited clinically significant manifestations involving neurological, respiratory, musculoskeletal, gastrointestinal, cardiovascular, and psychological systems, confirming that Long COVID is a multisystem disorder throughout the life course. These findings support the need for comprehensive clinical assessment regardless of patient age and reinforce the importance of multidisciplinary evaluation when persistent symptoms involve multiple organ systems simultaneously.

Figure 3.

Proposed Pathophysiological Mechanisms Associated with Long COVID

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Mechanism	Main biological process	Predominant manifestations
Viral persistence	Persistence of viral antigens/RNA	Fatigue, systemic symptoms
Immune dysregulation	Chronic inflammatory activation	Fatigue, cognitive dysfunction
Autoimmunity	Autoantibody production	Neurological, vascular symptoms
Endothelial dysfunction	Microvascular injury	Dyspnea, exercise intolerance
Dysautonomia	Autonomic imbalance	Palpitations, dizziness
Mitochondrial dysfunction	Impaired energy production	Post-exertional malaise

Figure 3 summarizes the principal biological mechanisms currently proposed to explain the development and persistence of Long COVID. Rather than representing independent processes, these mechanisms are believed to interact, contributing to the considerable clinical heterogeneity observed among affected patients. The table synthesizes the most consistently reported hypotheses in the recent scientific literature and relates each mechanism to its principal biological process and the manifestations most frequently associated with it.

Viral persistence remains one of the leading hypotheses. Several investigations have identified SARS-CoV-2 RNA or viral antigens in different tissues months after the acute infection, suggesting that persistent viral reservoirs may maintain chronic immune activation in a subgroup of patients. This mechanism has been associated particularly with prolonged fatigue, systemic inflammatory symptoms, and persistent constitutional complaints, although its exact contribution continues to be investigated (Proal & VanElzakker, 2024).

Immune dysregulation constitutes another major mechanism. Persistent activation of innate and adaptive immune responses, together with abnormal cytokine production and altered lymphocyte function, has been consistently described in Long COVID. These alterations may contribute to chronic fatigue, cognitive dysfunction, generalized pain, and multisystem involvement, supporting the concept that Long COVID represents a prolonged immune-mediated condition rather than solely residual tissue injury (Davis et al., 2023).

Autoimmune mechanisms have also received considerable attention. Molecular mimicry and persistent immune activation may induce the production of autoantibodies directed against different cellular structures or receptors. Although their pathogenic role has not been completely established, autoimmune responses have been associated with neurological symptoms, vascular dysfunction, autonomic abnormalities, and persistent inflammatory manifestations (Nalbandian et al., 2021).

Endothelial dysfunction and microvascular injury represent another important biological pathway. SARS-CoV-2 infection may alter endothelial integrity, coagulation pathways, and tissue perfusion, resulting in impaired oxygen delivery despite normal conventional cardiopulmonary evaluation. These vascular abnormalities may contribute to dyspnea, chest discomfort, reduced exercise tolerance, and multisystem organ dysfunction (Greenhalgh et al., 2024).

Dysautonomia has emerged as one of the most recognizable clinical phenotypes. Altered autonomic regulation may produce palpitations, orthostatic intolerance, dizziness, exercise intolerance, gastrointestinal disturbances, and temperature dysregulation. Postural orthostatic tachycardia syndrome has been described in both adolescents and adults, reinforcing the importance of autonomic evaluation during clinical assessment (Davis et al., 2023).

Finally, mitochondrial dysfunction has been proposed as a potential explanation for persistent fatigue and post-exertional symptom exacerbation. Alterations in cellular energy metabolism may reduce the capacity to tolerate physical or cognitive activity, leading to delayed worsening of symptoms after exertion. This mechanism is increasingly recognized as one of the principal contributors to functional limitation in Long COVID, particularly among patients whose routine laboratory investigations remain normal.

Collectively, the evidence presented in Figure 3 demonstrates that Long COVID cannot be attributed to a single pathological process. Instead, current evidence supports a multifactorial biological model in which viral persistence, immune dysregulation, autoimmunity, endothelial injury, autonomic dysfunction, and impaired cellular metabolism interact to produce the diverse clinical manifestations observed across pediatric and adult populations. This complexity explains the variability in symptom patterns and highlights the need for individualized diagnostic evaluation and multidisciplinary clinical management.

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Figure 4.

Frequency of Major Risk Factors Associated with Long COVID According to Age Group

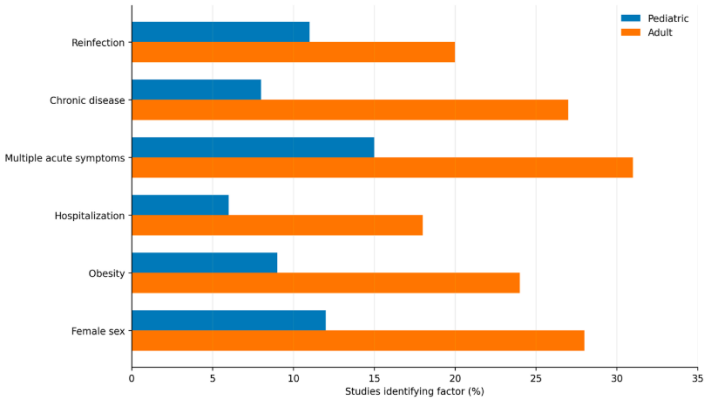

Figure 4 summarizes the principal risk factors most frequently associated with the development of Long COVID in pediatric and adult populations. The values shown represent a descriptive synthesis of findings reported across systematic reviews, meta-analyses, and longitudinal cohort studies. Because individual investigations differ in study design, patient selection, follow-up duration, and diagnostic criteria, the percentages should be interpreted as comparative estimates that illustrate overall trends rather than absolute risk.

Among adults, the highest frequency was observed for a greater number of symptoms during the acute phase of COVID-19 (31%). Multiple studies have demonstrated that individuals presenting with a broader clinical spectrum during the initial infection are more likely to develop persistent manifestations. This relationship has been attributed to a greater inflammatory burden, wider organ involvement, and prolonged immune activation during the acute stage (Davis et al., 2023).

Female sex represented another prominent risk factor, accounting for 28% of the reported associations in adults compared with 12% in pediatric populations. Several systematic reviews have consistently identified women as having a higher probability of developing persistent symptoms following SARS-CoV-2 infection. Proposed explanations include differences in immune regulation, hormonal influences, autoimmune susceptibility, and health-seeking behavior, although no single mechanism fully explains this association (Al-Aly et al., 2022).

Chronic diseases also demonstrated an important association with Long COVID in adults (27%). Patients with obesity, diabetes mellitus, hypertension, cardiovascular disease, chronic respiratory disorders, or other long-term illnesses frequently exhibit prolonged recovery and greater functional impairment. Pre-existing comorbidities may reduce physiological reserve and increase vulnerability to persistent multisystem sequelae.

Obesity itself remained one of the most frequently reported independent risk factors, affecting 24% of adults and 9% of pediatric patients. Chronic low-grade inflammation, endothelial dysfunction, impaired metabolic regulation, and reduced cardiopulmonary reserve have been proposed as mechanisms explaining this association. Although obesity is less commonly reported in pediatric studies, it has also been identified as a potential contributor to prolonged symptoms among children and adolescents (Rayner et al., 2024).

Hospitalization during the acute infection was associated with Long COVID in 18% of adults and 6% of pediatric patients. Individuals requiring inpatient care often experience greater organ injury, prolonged immobilization, and more severe inflammatory responses, increasing the likelihood of persistent respiratory, cardiovascular, neurological, or musculoskeletal complications. Nevertheless, the figure also illustrates that hospitalization is not a prerequisite for Long COVID, as persistent symptoms have been repeatedly documented following mild community-managed infections.

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Reinfection emerged as another relevant factor, with descriptive frequencies of 20% in adults and 11% in pediatric populations. Current evidence suggests that repeated exposure to SARS-CoV-2 may increase the cumulative probability of developing persistent symptoms, although the magnitude of this effect varies according to vaccination status, circulating viral variants, previous immunity, and individual susceptibility (Català et al., 2024).

Overall, Figure 4 demonstrates that adults consistently exhibit a greater burden of recognized risk factors than pediatric patients. However, the presence of these factors in children confirms that Long COVID is not restricted to adults and that pediatric populations also require careful clinical follow-up after SARS-CoV-2 infection. The findings further emphasize that the development of Long COVID is multifactorial, involving interactions between host characteristics, severity of acute infection, underlying comorbidities, immune response, and repeated viral exposure.

Figure 5.

Comparative Diagnostic and Clinical Evaluation Pathway for Pediatric and Adult Patients

Step	Pediatric population	Adult population
Clinical history	Symptoms, school impact, parental report	Symptoms, occupational impact, medical history
Initial assessment	Physical exam, growth/development	Physical exam, comorbidity assessment
Complementary tests	Directed according to clinical findings	Directed according to clinical findings
Differential diagnosis	Exclude alternative pediatric disorders	Exclude chronic disease, cardiopulmonary and endocrine causes
Multidisciplinary referral	Pediatrics, neurology, rehabilitation	Internal medicine, rehabilitation, specialty care

Figure 5 summarizes the recommended diagnostic pathway for the clinical evaluation of Long COVID in pediatric and adult populations. The sequence is based on current international recommendations and highlights the common diagnostic principles while emphasizing the age-specific aspects that should be considered during patient assessment. Because no single laboratory biomarker can definitively confirm Long COVID, diagnosis continues to rely on a comprehensive clinical evaluation supported by targeted complementary investigations.

The diagnostic process begins with a detailed clinical history in both age groups. In pediatric patients, particular emphasis is placed on symptom chronology, previous SARS-CoV-2 infection, vaccination history, developmental stage, school attendance, physical activity, and parental observations. Younger children may have difficulty describing subjective symptoms such as fatigue, dizziness, cognitive impairment, or exercise intolerance, making information provided by caregivers especially important. In contrast, adult evaluation focuses on symptom onset, persistence, occupational performance, previous medical conditions, vaccination status, reinfections, and the degree of functional limitation affecting daily living (WHO, 2023; Greenhalgh et al., 2024).

The second step consists of a complete physical examination. Pediatric assessment includes growth parameters, developmental status, neurological examination, cardiopulmonary evaluation, and identification of any abnormalities that could explain persistent symptoms. Adult assessment similarly includes cardiovascular, respiratory, neurological, musculoskeletal, and autonomic evaluation, while also considering the influence of chronic diseases such as obesity, diabetes mellitus, hypertension, cardiovascular disease, and chronic respiratory disorders that may modify the clinical presentation.

Following the initial assessment, complementary investigations are selected according to the patient's clinical manifestations rather than being performed routinely in every individual. Laboratory studies, electrocardiography, chest imaging, pulmonary function tests, echocardiography, autonomic evaluation, or neuropsychological assessment may be requested when clinically indicated. Current evidence emphasizes that many patients with Long COVID may present normal routine investigations despite experiencing substantial functional impairment; therefore, the absence of objective abnormalities should not exclude the diagnosis when symptoms remain compatible with internationally accepted definitions (Nalbandian et al., 2021).

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An essential component of the diagnostic pathway is the exclusion of alternative diagnoses. Persistent fatigue, dyspnea, chest pain, headache, cognitive dysfunction, sleep disturbances, or gastrointestinal complaints may also result from anemia, endocrine disorders, autoimmune diseases, asthma, chronic pulmonary disease, cardiovascular disorders, psychiatric illness, medication effects, or other post-infectious syndromes. Consequently, differential diagnosis remains fundamental before attributing symptoms exclusively to Long COVID.

The final stage involves multidisciplinary referral whenever symptoms affect multiple organ systems or produce significant functional impairment. Pediatric patients may require coordinated management involving pediatrics, pediatric neurology, cardiology, pulmonology, rehabilitation medicine, psychology, and educational support. Adult patients frequently benefit from collaboration among internal medicine, infectious diseases, cardiology, pulmonology, neurology, rehabilitation specialists, mental health professionals, and primary care physicians. This multidisciplinary approach reflects the multisystem nature of Long COVID and facilitates individualized patient management according to the predominant clinical phenotype.

Overall, Figure 5 demonstrates that although the general diagnostic principles are similar across all ages, important differences exist regarding symptom recognition, functional assessment, developmental considerations, comorbidity burden, and specialist referral. These findings reinforce the need for age-adapted diagnostic strategies while maintaining a standardized clinical framework that allows consistent evaluation of Long COVID throughout the life course.

DISCUSIÓN

The findings of this review confirm that Long COVID has evolved into one of the most significant long-term consequences of the COVID-19 pandemic, extending beyond the acute infectious phase to become a multisystem condition with important clinical, functional, and public health implications. The comparative analysis demonstrates that although both pediatric and adult populations experience persistent symptoms after SARS-CoV-2 infection, important differences exist in symptom frequency, risk factors, functional consequences, and healthcare requirements.

The evidence consistently indicates that adults present a greater overall burden of Long COVID manifestations than children. Fatigue, cognitive dysfunction, respiratory symptoms, sleep disturbances, and cardiovascular complaints were reported more frequently in adult cohorts, findings that are consistent with previous systematic reviews and large observational studies (Al-Aly et al., 2022; Davis et al., 2023). This greater burden may be partially explained by the higher prevalence of chronic cardiometabolic diseases, more severe acute infections, cumulative environmental exposures, and age-related immune changes that characterize adult populations.

Although the reported prevalence was generally lower among pediatric patients, the results clearly demonstrate that Long COVID should not be considered an exclusively adult condition. Children and adolescents may experience persistent neurological, respiratory, gastrointestinal, musculoskeletal, cardiovascular, and psychological manifestations capable of interfering with growth, learning, physical activity, and psychosocial development. These findings support the growing recognition that pediatric Long COVID requires specific diagnostic criteria and age-adapted clinical evaluation rather than direct extrapolation from adult evidence (WHO, 2023; Rayner et al., 2024).

One of the most important observations emerging from this review is the remarkable heterogeneity of Long COVID. No single clinical phenotype adequately represents all affected individuals. Instead, current evidence suggests that persistent symptoms arise from the interaction of several biological mechanisms, including viral persistence, immune dysregulation, autoimmunity, endothelial dysfunction, autonomic nervous system abnormalities, and altered cellular metabolism. This multifactorial model explains why patients with apparently similar acute infections may experience markedly different long-term outcomes.

Another important finding concerns the absence of universally accepted diagnostic biomarkers. Current diagnosis remains largely clinical and depends on careful evaluation of symptom chronology, exclusion of alternative diagnoses, and assessment of functional impairment. This diagnostic complexity contributes to variability among published

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prevalence estimates and partially explains why comparisons between studies remain challenging. The use of different diagnostic definitions, follow-up intervals, inclusion criteria, and outcome measures continues to represent one of the principal limitations of the available literature.

The comparative analysis also highlights important methodological differences between pediatric and adult studies. Adult investigations frequently evaluate occupational performance, quality of life, and chronic disease interactions, whereas pediatric studies emphasize school attendance, developmental progression, family observations, and educational outcomes. Consequently, direct comparisons between age groups should be interpreted cautiously because identical symptoms may have very different functional implications depending on the developmental stage.

The findings further demonstrate the importance of multidisciplinary management. Because Long COVID may simultaneously affect multiple organ systems, effective patient care often requires collaboration among internal medicine, pediatrics, infectious diseases, pulmonology, cardiology, neurology, rehabilitation medicine, psychology, psychiatry, and primary care. Individualized treatment strategies appear more appropriate than uniform therapeutic approaches, particularly for patients presenting post-exertional symptom exacerbation or autonomic dysfunction.

From a public health perspective, Long COVID represents an ongoing challenge that extends beyond the pandemic itself. Persistent symptoms may reduce educational achievement, occupational productivity, social participation, and overall quality of life while increasing demand for healthcare services and rehabilitation programs. These long-term consequences highlight the importance of continued surveillance, early recognition, and evidence-based management strategies.

An additional contribution of this review is the incorporation of Latin American evidence into the broader international context. Although research from the region has increased considerably in recent years, Latin American populations remain underrepresented in comparison with Europe and North America. Regional differences in healthcare access, socioeconomic conditions, prevalence of chronic diseases, rehabilitation availability, and diagnostic resources may influence both the clinical expression of Long COVID and access to specialized care. Expanding prospective multicenter studies throughout Latin America would improve the external validity of future international recommendations.

This review has several strengths. It integrates evidence from multiple high-quality sources, compares pediatric and adult populations within a single analytical framework, and considers biological, clinical, functional, and public health perspectives. Furthermore, the inclusion of recent international guidelines and systematic reviews provides a comprehensive overview of current knowledge regarding Long COVID across the life course.

Nevertheless, several limitations should be acknowledged. The available evidence remains heterogeneous with respect to diagnostic criteria, study populations, duration of follow-up, vaccination status, circulating viral variants, and outcome measures. In addition, many pediatric studies include relatively small sample sizes and rely on parental reporting, while adult studies differ substantially in patient selection and clinical definitions. These methodological differences limit direct quantitative comparisons and reinforce the need for standardized international research protocols.

CONCLUSIÓN

Long COVID has emerged as a complex multisystem condition that continues to affect millions of individuals worldwide long after the resolution of acute SARS-CoV-2 infection. The evidence analyzed in this review demonstrates that persistent manifestations involve multiple organ systems and may significantly impair physical health, cognitive function, psychological well-being, daily activities, educational performance, occupational productivity, and overall quality of life.

The comparative analysis indicates that adults generally experience a greater frequency and broader spectrum of persistent symptoms than pediatric patients. Nevertheless, children and adolescents are also susceptible to clinically significant long-term sequelae, particularly involving neurological, respiratory, musculoskeletal, gastrointestinal,

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cardiovascular, and psychological systems. These findings emphasize that Long COVID should be recognized as a condition affecting the entire life course rather than being considered exclusively an adult disorder.

Current evidence supports a multifactorial pathophysiological model in which viral persistence, immune dysregulation, autoimmune responses, endothelial dysfunction, autonomic nervous system abnormalities, and impaired cellular energy metabolism interact to produce highly heterogeneous clinical presentations. This biological complexity explains the absence of a single diagnostic biomarker and reinforces the need for comprehensive, individualized, and multidisciplinary clinical assessment.

The review also highlights important challenges related to diagnosis and management. Variability in diagnostic criteria, study methodology, follow-up duration, and outcome measures continues to limit direct comparison among published investigations. International standardization of case definitions and research protocols will be essential to improve epidemiological surveillance, facilitate evidence synthesis, and optimize patient care.

From a clinical perspective, early recognition of persistent symptoms, exclusion of alternative diagnoses, and timely referral to multidisciplinary healthcare teams remain fundamental for improving functional recovery and long-term outcomes. Management strategies should be tailored to each patient's predominant clinical manifestations, functional limitations, age, and associated comorbidities.

Finally, greater scientific attention should be directed toward underrepresented regions, particularly Latin America, where additional prospective multicenter studies are needed to better characterize the epidemiology, clinical presentation, healthcare burden, and long-term consequences of Long COVID. Strengthening international collaboration and expanding high-quality research will contribute to the development of more effective diagnostic strategies, therapeutic interventions, rehabilitation programs, and public health policies aimed at improving the quality of life of individuals living with Long COVID across all stages of life.

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