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Systematic review

Double trouble: Long COVID-19 and the onset of type 2 diabetes mellitus — a systematic review

Doble problema: COVID-19 prolongado e incidencia de diabetes mellitus tipo 2 — una revisión sistemática

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Abstract

Objective: This systematic review aims to clarify COVID-19's impact on the onset of T2D in adults. **Material and methods:** Following PRISMA guidelines, this systematic review sourced data from multiple databases from 2019 to April 20th, 2023. Two reviewers handled screening, with a third-party resolving disagreement. The focus was on COVID-19 cases with post-infection T2D symptoms persisting for two or more months. Exclusions included those outside the 18-70 age range, prior T2D history, pregnancy, and animal studies. Rayyan software facilitated article screening, STATA 18 performed meta-analysis, and bias was assessed using JBI tools. The study is registered in PROSPERO (ID: CRD42023414096). **Results:** A total of 173 articles were retrieved, of which 23 (11.6%) remained for extraction. 13 cohort studies with 11.551.026 participants were included for the meta-analysis, which found that the COVID-19 population had 1.4 greater risk of being diagnosed with T2D in comparison with the population without COVID-19or with other respiratory diseases. The other study designs were narratively analyzed, describing similar results as the meta-analysis. **Discussion:** New onset T2D is a potential consequence of LC. While T2D increases COVID-19 complications, the relationship appears bidirectional. Given the novelty of the topic and potential newer studies, further reviews are needed to understand LC's impact on chronic diseases like T2D globally. Further studies should be carried out on this specific topic that could raise the burden of T2D between all the other symptoms that may be caused by LC. In addition, it is necessary to adapt the interventions according to each country's possibilities.

Keywords: Diabetes mellitus II. New onset diabetes. Insulin resistance. Hyperglycemia. COVID-19. COVID-19 prolongado. Post-acute COVID-19 syndrome.

Resumen

Objetivo: El objetivo de esta revisión es aclarar el impacto del COVID-19 en nuevos diagnósticos de DM2. **Material y Métodos:** Esta revisión se elaboró en base a las guías PRISMA. Dos revisores realizaron una búsqueda en bases de datos, incluyendo artículos desde el 2019 hasta el 20 de abril de 2023 en adultos, diagnosticados al menos una vez con COVID-19, sin diagnóstico previo de DM2. Excluyeron: embarazadas, niños y diabetes mellitus I. Esta revisión se registró en PROSPERO (ID: CRD42023414096) el 6 de abril de 2023. **Resultados:** Un total de 173 artículos se obtuvieron luego de la búsqueda, de los cuales 23 (11,6%) quedaron para extracción. 13 estudios de cohorte con 11.551.026 participantes se incluyeron en el metaanálisis, que encontraron que la población que tuvo COVID tiene un 1,4 veces más riesgo de ser diagnosticados con DM2 en comparación a quienes no tuvieron el diagnóstico o fueron diagnosticados con otra patología respiratoria. Los diseños de estudio se describieron narrativamente, describiendo resultados similares a los del metaanálisis. **Discusión:** El nuevo diagnóstico de DM2 es una potencial consecuencia de LC. Mientras aumenta la DM2, aumentan las complicaciones de COVID-19, la relación aparenta ser bidireccional. Ya que estos hallazgos son medianamente recientes, no existe mucha evidencia disponible al respecto, por lo tanto, se requiere un mayor número de estudios al respecto, además de la creación de nuevas políticas de salud pública ad hoc a las posibilidades de cada país.

Palabras clave: Diabetes mellitus tipo II. Nueva aparición de diabetes. Resistencia a la insulina. Hiperglucemia. COVID-19. Long COVID-19. Síndrome post-agudo de COVID-19.

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Introduction

Mounting evidence has emerged since the 2019 coronavirus pandemic (COVID-19). Globally, COVID-19 has claimed nearly 7 million deaths as of 20th May 2023[1]. Although the World Health Organization (WHO) on May 5th, after more than three years of the pandemic, declared that this disease was no longer a Public Health Emergency of International Concern, the remaining comorbidities left by COVID-19, continue to rise[2].

Thousands of studies have emerged studying this respiratory disease, which helped to develop control measures as vaccines, which approximately 14 billion doses have been administered worldwide[1]. Nevertheless, the population is now living with the consequences that still linger after the virus. It is relevant to state that of the excess deaths, nearly 80% are not attributed directly to COVID-19, raising awareness of the collateral conditions that might have been developed during the virus, like kidney failure, obesity, heart failure and hyperglycemia or glycated hemoglobin (HbA1c) impairments[3].

The last four years, since the beginning of the COVID-19 pandemic, studies and trials have analyzed the consequences and symptoms that still prevail on patients who once were infected by COVID-19, which created new terminology: Long Haul Covid, Post-Acute SARS-CoV2 or Long COVID-19 (LC). According to the WHO (2023), nearly 10-20% of COVID-19 cases may develop LC. While the definition of LC has been established by the same institution, according to Delphi's criterion and coded since September 2020 in the ICD-10[4], the definition includes a wide range of symptoms, that may have a duration of two months or more after having the virus and cannot be explained by an alternative diagnosis. These symptoms may include: fatigue, shortness of breath, cognitive dysfunction and usually have an impact on everyday functioning and symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time[4].

While these findings and symptom definitions may seem quite clear, alterations such as hyperglycemia or new onset T2D mellitus remain deprioritized. T2D in 2019 was the sixth cause of death worldwide. Some authors have stated that this situation may act as a bidirectional pandemic, since T2D was declared a risk factor for exacerbations of COVID-19, but now the reverse is also true, since being infected by COVID-19 may cause persistent inflammation, hence have a diabetogenic effect, causing high blood glucose levels or even a new diagnosis of T2D[5].

Although certain theories may help explain why COVID-19 infection may cause an increased rate of T2D[6], the rationale of conducting this systematic review is to find out how much did the COVID-19 pandemic impact on the onset diagnosis of T2D. The objective of this systematic review is to analyze the relation between LC diagnosis, based on the WHO definition and new onset diagnosis of T2D or other related glucose impairments as insulin resistance.

Material and methods

This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Review and meta-analysis (PRISMA) guidelines[7,8]

The study was registered in PROSPERO (registration ID: CRD42023414096) on April 6th 2023.

Eligibility criteria

The eligibility criteria for this systematic review were based on: (a) study type, observational studies and reviews, (b) study participants: individuals over 18 years to 70 years old, any gender or nationality. There was at least one exposure to COVID-19, based on the International Classification of Diseases (ICD-10) codes (U0.71-U0.72),[3] the outcome of interest was diagnosis of new onset T2D (fasting plasma glucose ≥126 mg/dL, glycated hemoglobin (HbA1c ≥ 6.5%) or insulin resistance (HOMA ≥ 3), hyperglycemia or prediabetes (fasting plasma glucose ≥100 mg/dL; HbA1c ≥ 5.7%).[3] Language: all languages were included. Exclusion criteria: those with no COVID-19 diagnosis, those with a history of T2D prior to COVID-19 diagnosis, and those > 70 years. Studies of pregnant or nursing women were excluded as were animal studies.

Information sources and search strategy

This review comprised exhaustive research of electronic databases: PubMed Central (PMC), Cochrane Library, Lilacs, Embase. Grey Literature from Open Grey and hand search articles from Google Scholar, were included, until April 20th, 2023. Additionally, all the references from the included full texts were consulted to identify other relevant evidence about the topic. Articles, reports, study cases or institutional documents, published from 2019 to April 20th 2023, included keywords as "Long-Covid," "post-acute SARS-CoV2 syndrome," "Diabetes mellitus II," "hyperglycemia," "insulin resistance," and "incidence."

Selection and data collection process

All relevant articles were retrieved in the Rayaan free version[9]. In the first phase, two investigators (CA and AC) independently screened through title and abstract of the retrieved articles and selected them according to the inclusion and exclusion criteria. If there were any disagreements between the investigators, a third party (MH) was included to solve them. The potentially relevant articles for extraction were read full text by two investigators (CA and AC) and again, if there was any conflict, the third reviewer resolved them (MH).

Methodological quality

Critical appraisal was carried out using the Joanna Briggs Institute (JBI) assessment tools for each study design[10], hence to avoid confounders and risk of bias.

Data extraction

Data extraction took place according to a standardized format by the three investigators (CA, AC and MH). The research team piloted and tested the designed matrix and adjusted it according to the feedback obtained from this phase. The data extracted included the article's main characteristics and specific aspects according to the objective of this review. The topics extracted were: first author, year of publication, country, study design, population, number of individuals, baseline characteristics of population (COVID-19 previous diagnosis), follow-up, outcome (including statistical

analysis) and funding sources or potential conflicts of interests of the authors.

Data analysis and effect measures

For each included study, we extracted the number of newly diagnosed T2D, hyperglycemia, insulin resistance in individuals with COVID-19. Cohort studies were analyzed using a comprehensive meta-analysis, using a random effect model, represented visually with forest plots using 95% confidence intervals (CI). The forest plots were done separately for population studies, hospital-based studies and then plotted them all together; given the sample size difference and selection processes which may also affect the overall effect. Since not all studies had a comparator, those studies, which analyzed only incidence of new onset T2D, were pooled in other groups. (**Figure 2, Figure 3, Figure 4**).

Sensitivity analyses were performed to evaluate each cohort's influence on the pooled estimate by sequentially omitting one cohort at a time on the cohorts included in the meta-analysis.

Moreover, a narrative description of those studies other than a cohort was performed. Conducting a meta-analysis on one hand, and a narrative synthesis on the other, corresponds to a strategic methodological decision that reinforces the robustness and relevance of the findings. The diversity in study designs, which includes both observational studies and reviews, makes it possible to capture a broader spectrum of evidence, offering a multidimensional view of the impact of long COVID-19 and the development of Diabetes.

Risk of bias assessment

Risk of publication bias was assessed by using a funnel plot done in STATA 18 (**Figure 6**) including the cohort studies analyzed in the meta-analysis and selection bias was assessed with the Joanna Briggs risk of bias assessment tools for each included study of the narrative review[11].

Results

The search yielded 193 articles; after 20 (10.3%) duplicates were removed, 173 (89.7%) titles and abstracts were screened, and 28 (16.2%) of them remained for full text revision, of which 2 (1%) were retrieved after backward reference search. After the full text articles and reports were reviewed 23 (82%) remained for extraction (**Figure 1: PRISMA flow diagram**).

These articles were from 2019 until 20th April 2023. The mean age of the included population was 46 years old, ranging from 18 to 85 years old and 34% were female. The follow-up period ranged from 31 days to 1 year since the COVID-19 diagnosis. The time diagnosis of T2D was diverse, since some participants were diagnosed during hospi-

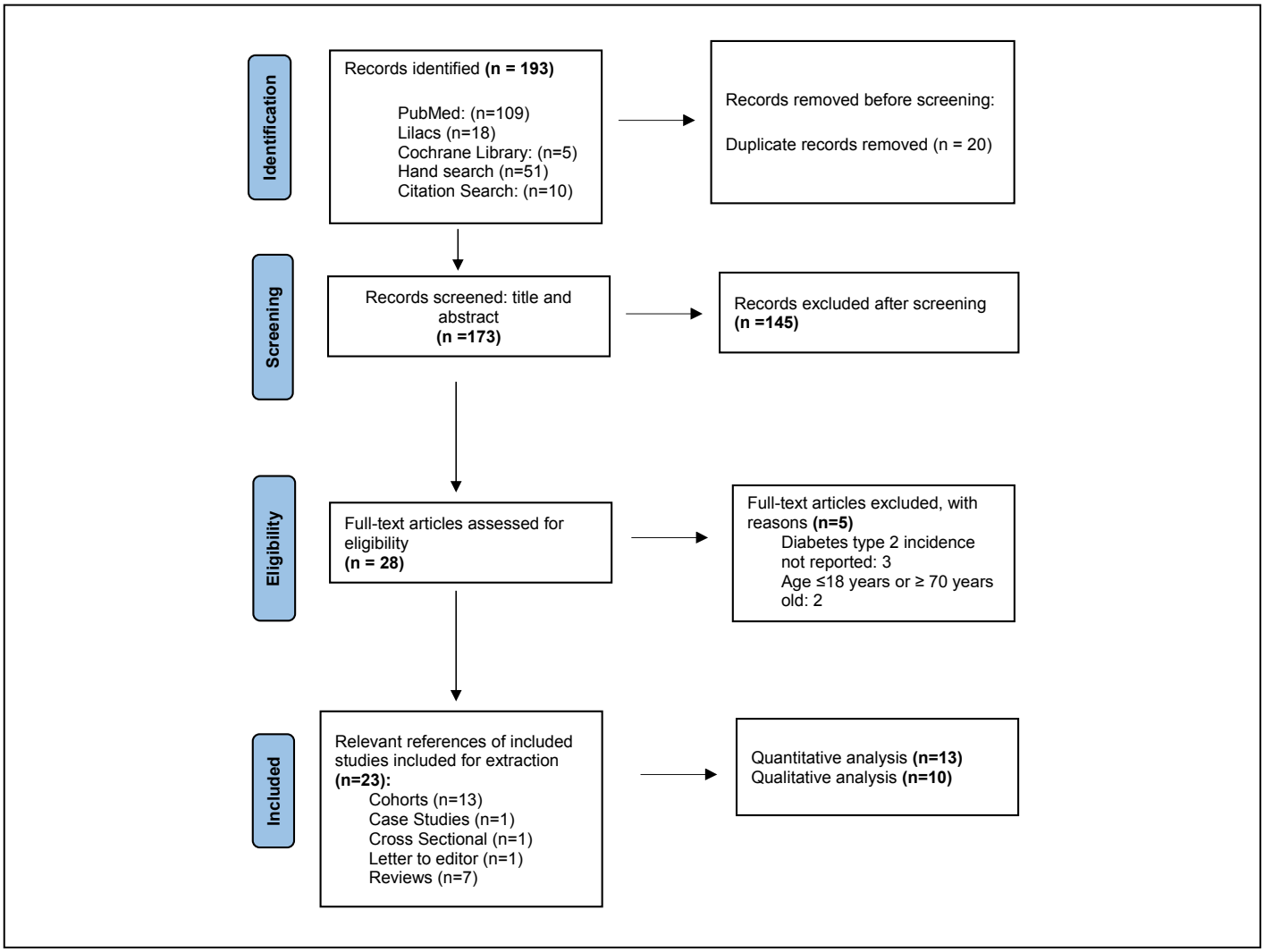

Figure 1. PRISMA flow diagram.

tal admission and the disease remained chronic[12] and in other cases the diagnosis of T2D was made after months of COVID-19 recovery, since it was not possible to compensate for the hyperglycemia[13].

Of these, 13 (56.5%) were cohorts[13–22], 8 (34.7%) were reviews[12,23–28], 1 (4.3%) was a case study[29], and 1 (4.3%) was a cross sectional study[30].

The 13 cohorts were included in the meta-analysis, 6 (46%) of the 13 studies were from United States[14–19], 2 (15%) from Italy[31,32], 2 (15%) from England[13,22], 1 (7.7%) from Germany[21] and 1 (7.7%) from Bosnia Herzegovina[20]. Among the COVID-19 participants included in the cohorts, over 3.5 million persons were included and nearly 8 million persons were included as part of the cohort studies. From the 13 cohorts included, two were from veterans' data from the United States[18,19].

The remaining 10 (43.5%), were analyzed narratively, 4 (17.4%) were from the United States[25,26,29,33], 1 (4.3%) from the United Kingdom[27], one (4.3%) from Spain[30], one (4.3%) from Italy[12], one (4.3%) from Netherlands[23], one (4.3%) from the United Arab Emirates[24] and one (4.3%) from Guatemala[28]. And of these, eight (34.7%) were reviews[12,23–28,33], one (4.3%) was a case study[29], one (4.3%) a cross-sectional study[30].

Meta-analysis

According to the study characteristics the cohort studies were meta-analyzed according to the study setting and study and control groups, using random effect model, with DerSimonian-Laird estimate of tau^2.

The first meta-analysis analyzed the cohort studies in hospital-based setting finding a Risk Ratio of 1.79 (1.17-2.73 95%CI), with a p-value= 0.007, hence the risk of developing T2D or hyperglycemia after being hospitalized because of COVID-19 was not significant. The heterogeneity measures resulted in a Mantel-Haenszel value of 65.45 (df=3 and p-value=0.000), I^2= 95.4%. Modified H^2= 20.792 and tau^2= 0.1556 (**Figure 2**)

The second meta-analysis evaluated the cohort studies in a population-based setting, finding a Risk Ratio of 1.36 (1.02-1.81 95%CI) and a p-value= 0.034, which means that in population-based settings, the risk of developing new onset T2D is 36% times higher than the control population. The heterogeneity measures resulted in a Mantel-Haenszel value of 1554.10 (df=5 and p-value=0.000), I^2= 99.7%. Modified H^2= 304.274 and tau^2= 0.1253 (**Figure 3**).

Then both groups, population and hospital-based were pooled together. Resulting in an overall risk ratio of 1.45 (1.2-1,86 95%CI) and a p-value=0.000, which means that the overall risk of developing new onset T2D is 45% higher than the control group. The heterogeneity measures resulted in a Mantel-Haenszel value of 1675.0 (df=9 and p-value=0.000), I^2= 99.5%. Modified H^2= 182.883 and tau^2= 0.1137 (**Figure 4**).

The other group was analyzed separately, since they did not have control groups. They were analyzed with a proportion meta-analysis and analyzed COVID-19cases, not comparing it with controls as the groups above. Resulting on an Effect Size of 0.081 (0.01-0.17 95%CI) p-value= 0.00000. Heterogeneity chi^2 80.813 (df=2 p=0.000 I^2 variation in ES attributable to heterogeneity 97.53%. Estimate of between study variance tau^2=0.005. test of ES=0: z= 2.1 p=0.04 (**Figure 5**).

Given the heterogeneity of the resulting meta-analysis, the funnel plot may appear asymmetrical. Besides, certain studies have small effects, hence larger variability in their effect estimates. Additionally, the funnel plot was done with the ten studies included in the meta-analysis, which

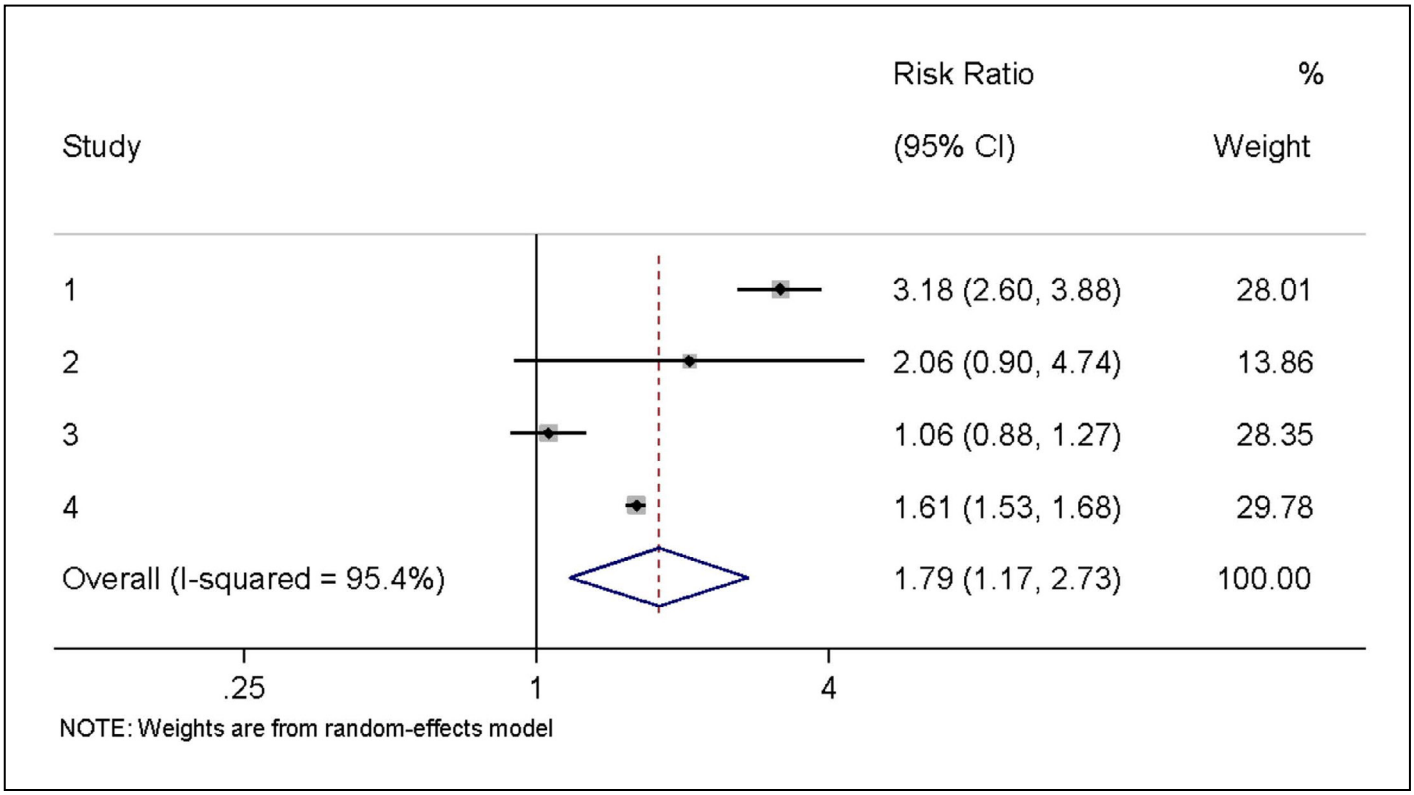

Figure 2. Forest Plot Hospital-Based New Onset T2D after COVID-19 positive diagnosis.

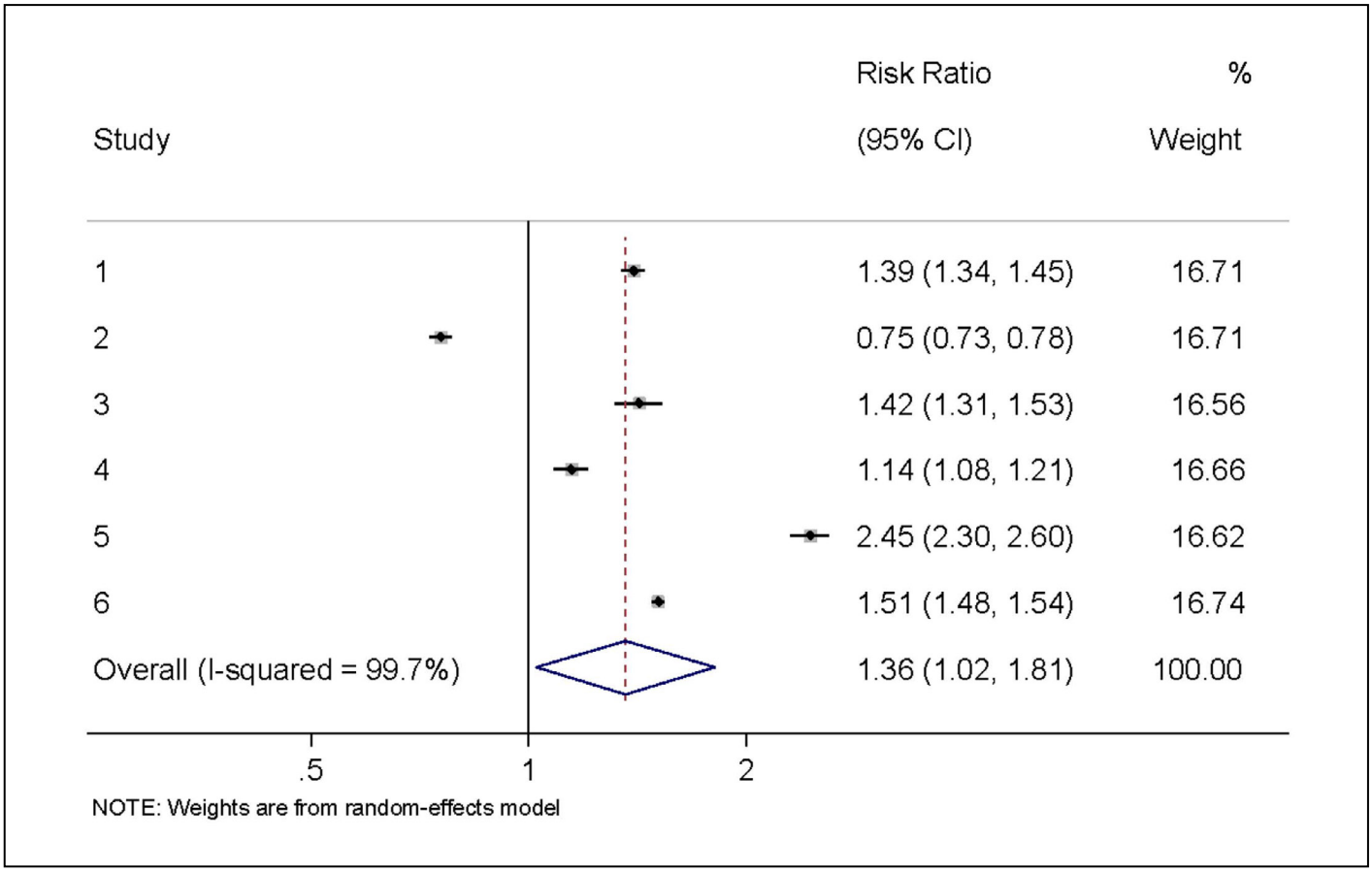

Figure 3. Forest Plot Population-Based New Onset T2D after COVID-19 positive diagnosis.

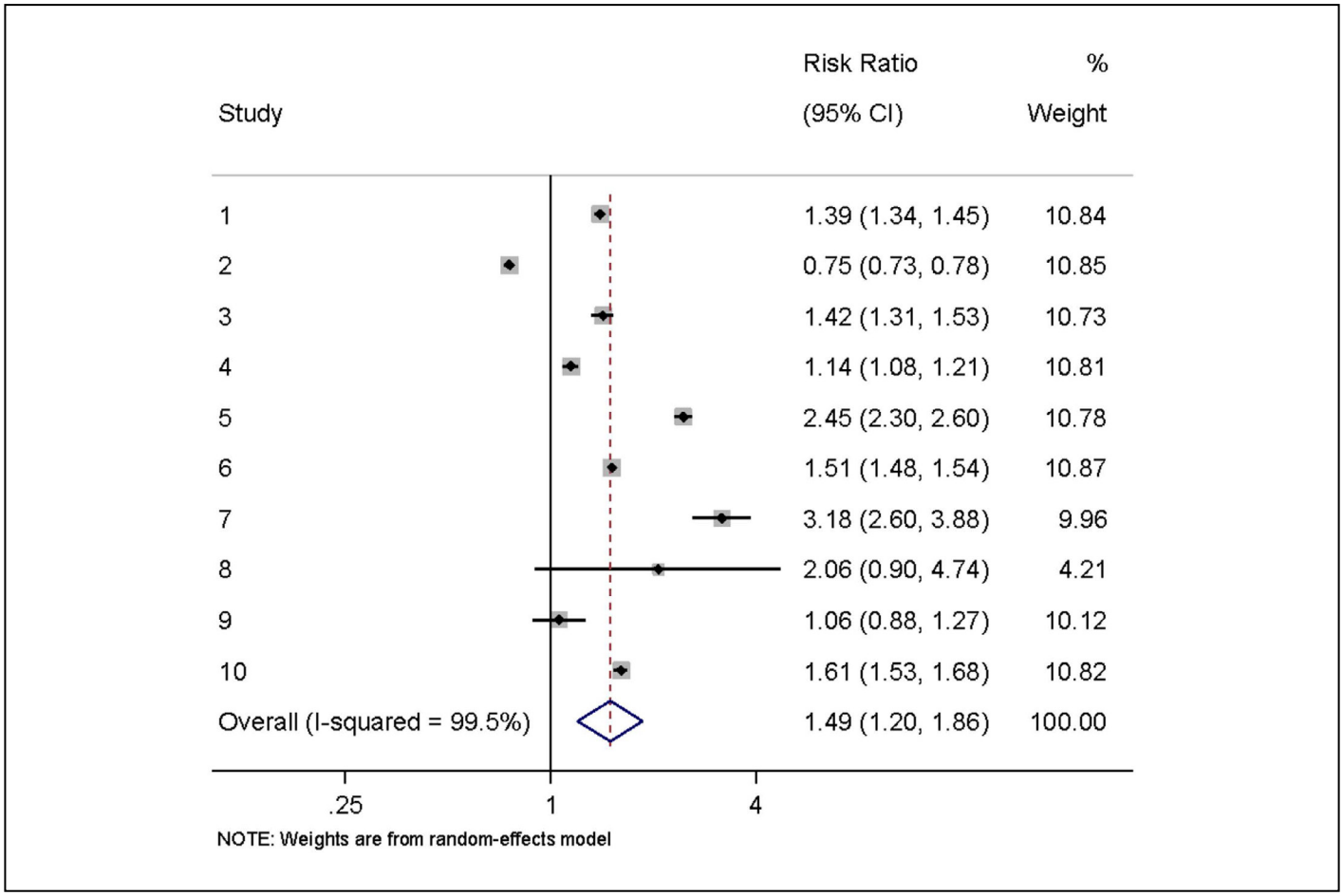

Figure 4. Forest Plot Population and Hospital-Based New Onset T2D after COVID-19 positive diagnosis.

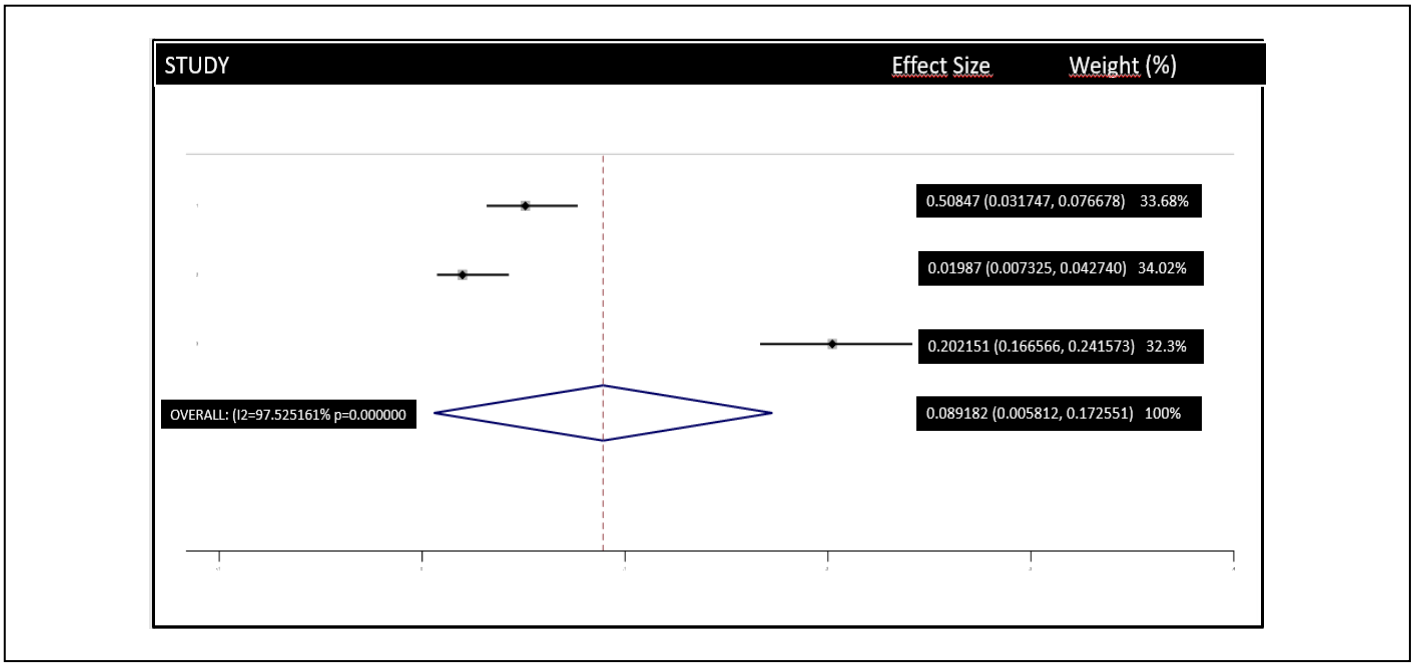

Figure 5. Forest Plot Incidence New Onset T2D after COVID-19 positive diagnosis (no control group).

makes the population more variable and it is possible that this could be due to chance.

In the sensitivity analysis, it was found that no individual estimate significantly influenced the overall effect. The pooled estimate remained robust, with tau^2 (P = 0.016).

Qualitative analysis

Given the nature of the remaining 10 (43.5%) articles, these were described narratively.

Although it is highly plausible to develop hyperglycemia after an infection, in COVID-19 the relation is quite different, since this hyperglycemic condition lingers and it may remain chronic, generating not only hyperglycemia, but affecting directly the β-cells affecting the insulin production of the pancreas, hence T2D. Another explanation, stated by Scherer *et al,*[26] is that the virus of SARS CoV2 persists in the adipose tissue, which explains why the obese population was determined as a high-risk population for COVID-19 infection.

Although some authors stated that T2D is a high-risk worsening factor of COVID-1919[23,27] the condition of new onset T2D caused by COVID-19 has even worse prognosis for COVID-19, than even having T2D previously[27]. Additionally, it is key to identify hyperglycemia promptly, since there is a high risk of developing diabetic ketoacidosis (DKA), which may cause several chronic impairments or even death[12]. Nalbandian *et al.,*[33] states that it is likely that COVID-19 associated with T2D, if developed during the acute phase, probably will not resolve afterwards, due to LC. Furthermore, non-hospitalized patients have 1.4 times higher risk of developing new onset T2D[26].

Other authors[30,31] have tried to explain the mechanism of development of T2D; this particular virus infects the pancreatic islets, hence causes chronic dysfunction. There is no specific predisposition for new onset T2D during COVID-19, although it is more probable in vulnerable populations, at younger ages, and it is more common to be diagnosed in the non-Hispanic white population[28].

Discussion

Based on the results of this systematic review and meta-analysis, involving a population of nearly 12 million of participants, there is a significant associated risk on being diagnosed with T2D after a COVID-19 infection, resulting in a 40% higher risk of new onset T2D than the control group.

This shows that this particular diagnosis should not be underestimated as part of the characteristics of LC, a condition that has been highly prevalent in the years after the pandemic, affecting between 10-20% of the individuals with a previous diagnosis of COVID-19, although not as well studied as warranted[33].

Many authors have tried to explain the relation between the new diagnosis of T2D and COVID-19, Fadini *et al.,*[31] stated that since the pandemic there have been fewer visits to health institutions, hence, fewer diagnoses of LC or T2D, which explains the fact that newly diagnosed diabetes had a stronger association with ICU admissions.

Metformin or other drugs to treat hyperglycemia have been shown to be a positive contribution on the recovery of diabetic patients with COVID-19[3] which may help new onset diabetic patients in their recovery, hence more studies should be carried out to see that affect long term[29].

Other authors suggest that new onset diabetes debuts with a decompensated hyperglycemia and ketoacidosis[12], nevertheless can be a confounder, since when a respiratory disease is decompensated, it highly possible to have an unbalanced acid-basic relation, hence developing new onset hyperglycemia or T2D.

Compared to other similar systematic reviews, this study shows certain similarities, since there is a clear association

between new onset T2D as a consequence of COVID-19, hence LC. Additionally, a cross sectional study found out similar results as the ones obtained in this systematic review, which pointed out that there was a 1.3% incidence of T2D in 543 patients after hospital discharge[30].

Additionally, the literature on LC and its potential association with incident T2D can be confusing due to the interchangeable use of terms such as 'diabetes,' 'T2D' (Type 2 Diabetes Mellitus), 'T1D' (Type 1 Diabetes Mellitus), 'hyperglycemia,' and after the pandemic the new concept of 'new-onset diabetes.' These terms are not always used consistently, leading to misunderstandings about the specific conditions being discussed. Understanding that T1D is an autoimmune condition, resulting in insulin deficiency. T2D, as it has been explained throughout the article, on the other hand, is characterized by insulin resistance and relative insulin deficiency. Hyperglycemia refers to high blood sugar levels, which can occur in both T1D and T2D, as well as in other conditions. However, in this review the authors were particularly strict in the inclusion and exclusion criteria in order to include only new onset T2D and hyperglycemia, only related to T2D impairments[35,36]. Therefore, readers should be cautious and seek clarification when encountering these terms in the literature to ensure a clear understanding of the conditions being studied.

Another fact which was not overlooked, was incorporating the observation regarding the varying aggressiveness of COVID-19 across the pre- and post-vaccine periods into our discussion. The significance of delineating these distinct periods and its potential impact on the outcomes assessed in our meta-analysis. While our meta-analysis and narrative review encompasses studies published from 2019 onwards, it is pertinent to note that the vaccination status of individuals included in these studies may vary. In this systematic review, we attempted to extract and analyze data regarding vaccination status wherever available. However, due to the evolving nature of vaccination campaigns and reporting practices across different regions and time frames, comprehensive data on vaccination status may not be consistently reported or available across all included studies. In fact, some authors declared that they did not include the impact of vaccination in their analysis so as to avoid the influence of later variants and vaccinations, and to only those with PCR test results[16]. Additionally, other authors described the socioeconomic and ethnic backgrounds disparities that may impact on the access to vaccines[17], but not in the impact of pre and post vaccination severity of COVID-19.

Nevertheless, we recognize the importance of considering this factor in the interpretation of our findings, hence it is crucial for further reviews to explore deeper the pre and post vaccination periods and the aggressiveness of COVID-19.

In fact, there are preliminary results of a LC study called *"Caracterización sintomatología Condición post COVID-19 en la población de dos ciudades de Chile"* by Molina X, Awad C, *et al.,* (2023) in the Center of Epidemiology and Health Policy (CEPS in Spanish), Faculty of Medicine Universidad del Desarrollo, Santiago Chile, where of 83 participants which reported LC symptoms 8.5% reported having a newly diagnosed T2D which has persisted after two months after the COVID-19 virus[1].

Finally, Cutler *et al.*, stated that LC not only affects population health, but also economics. The three economic costs of LC were estimated according to three main pillars of economic problems in health: higher spending on medical care, loss of earnings, and loss of life quality, which was estimated as approximately US$3.7 trillion spent on LC consequences[37].

Strengths and limitations

This is still a relatively new topic coming from the consequences of the pandemic. In addition, this systematic review has an inclusion criterion, which is specific for the association of T2D and LC. It also has a quantitative and qualitative analysis of the findings, represented by a meta-analysis and a narrative of other study designs.

Nevertheless, it is important to point out that it is difficult in terms of analysis to separate the different types of diabetes mellitus, since when identifying incident diabetes, some authors used the term indistinctly for T2D and T1D, which as we know are completely different diseases.

Another caveat we must acknowledge, is the scarcity of available literature on this specific topic and it is indeed a notable challenge to conduct a comprehensive review. To address potential selection bias, the reviewers meticulously employed systematic search strategies across multiple databases, encompassing various publication types and languages, to capture as much relevant data as possible. Additionally, we adhered strictly to predefined inclusion and exclusion criteria explained in the methods, so as to ensure the selection of studies with robust methodologies and pertinent outcomes. Despite these efforts, we acknowledge the possibility of inherent biases due to publication trends, language restrictions, and study design preferences. The analysis presented, aims to transparently document these limitations and interpret the findings within this context to provide a comprehensive understanding of the current evidence landscape regarding COVID-19 and T2D.

Furthermore, since the topic has not much evidence yet and there still remains residual confounding and bias. Moreover, it is crucial to point out that there is heterogeneity shown in the forest plots as well. This may be justified by the variability of the diagnosis of LC, the differences of the population demographics and their comorbidities, the number of the included population in each study. Nevertheless, given the limited information and variability, this study gives evidence on the identification of this particular risk of developing new onset T2D after the infection with COVID-19, which is valuable for clinical practice and for health policies.

Although all the studies were assessed using the JBI assessment tool for critical appraisal, it is difficult to standardize the diagnostic method of COVID-19 between the studies, which may impact the results. Since at the beginning of the pandemic, more cases were registered on the healthcare systems, however, now, not all cases are reported, since there is more availability of home-tests, which are not adequately reported at any registry, hence many cases could

have been left out as well. Finally, part of the infected COVID-19 population may have been left out, since they were not aware of the diagnosis or they did not get tested and they might have developed T2D without knowing that they could be associated with COVID-19.

Conclusion

This year, awareness of LC and its association with T2D has increased significantly. A notable example is the ongoing CoviDiab Registry[38], an international initiative aimed at characterizing the demographics of patients diagnosed with T2D following a COVID-19 infection. However further research on this particular topic is needed, and if possible, interventions adapted to each country's possibilities of implementation[39].

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Conflict of interests

The authors declare no conflict of interest.

Author contributions

The authors have equally contributed to the conception, design, collection, analysis, and/or interpretation of data, and have contributed to the writing and intellectual content of the article.

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