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Hyperglycemia as a Risk Factor for Cardiovascular Disease Post-Acute Sequelae of SARS-CoV-2 Infection

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Perspective
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Abstract

The ongoing COVID-19 pandemic caused by the novel coronavirus SARS-CoV-2 has led to a surge in research examining its long-term health consequences. Among these sequelae, cardiovascular complications have emerged as significant concerns, particularly in individuals with pre-existing or post-infection hyperglycemia. This review aims to explore the association between hyperglycemia and cardiovascular disease (CVD) in the post-acute phase of SARS-CoV-2 infection. A systematic search of electronic databases including PubMed, Embase, and Google Scholar was conducted to identify relevant studies published between January 2020 and March 2024. Keywords included "hyperglycemia," "cardiovascular disease," "SARS-CoV-2," "COVID-19," "post-acute sequelae," and variations thereof. Studies focusing on the association between hyperglycemia and CVD in the context of post-acute SARS-CoV-2 infection were included. Hyperglycemia, both pre-existing and as a consequence of SARS-CoV-2 infection, has been linked to an increased risk of cardiovascular complications in the post-acute phase. Mechanistically, hyperglycemia contributes to endothelial dysfunction, oxidative stress, inflammation, and dyslipidemia, all of which are implicated in the pathogenesis of CVD. Moreover, SARS-CoV-2 infection exacerbates these pathways, further predisposing individuals to CVD.

The association between hyperglycemia and CVD in the post-acute phase of SARS-CoV-2 infection underscores the importance of glycemic control in mitigating long-term cardiovascular complications. Healthcare providers should prioritize screening for hyperglycemia in COVID-19 survivors and implement interventions aimed at managing blood glucose levels to reduce the burden of CVD in this population. Future research should focus on elucidating the underlying mechanisms linking hyperglycemia and CVD post-SARS-CoV-2 infection and evaluating the efficacy of targeted interventions in preventing cardiovascular sequelae.

Keywords: Hyperglycemia; Cardiovascular disease; SARS-CoV-2; COVID-19; Post-acute sequelae; Long COVID; Glycemic control; Endothelial dysfunction; Oxidative stress Inflammation

Abbreviations: CVD: Cardiovascular Disease; ARDS: Respiratory Distress Syndrome; PASC: Post-Acute Sequelae of SARS-CoV-2; ROS: Reactive Oxygen Species; CGM: Continuous Glucose Monitoring; PTSD: Post-Traumatic Stress Disorder.

Introduction

The emergence of the novel coronavirus, SARS-CoV-2, and its associated illness, COVID-19, has triggered a global pandemic with profound implications for public health. While much attention has been directed towards the acute phase of COVID-19, characterized by respiratory symptoms ranging from mild cough to severe pneumonia and acute respiratory distress syndrome (ARDS), emerging evidence suggests that a subset of individuals continues to experience a myriad of symptoms and complications well beyond the acute illness phase [1]. This phenomenon often referred to as the post-acute sequelae of SARS-CoV-2 infection (PASC) or Long COVID encompasses a diverse array of persistent symptoms and health issues that persist for weeks or even months after the resolution of acute COVID-19 symptoms [2].

These symptoms can affect multiple organ systems, including the respiratory, cardiovascular, neurological, and musculoskeletal systems, among others. The concept of Long COVID has garnered significant attention from researchers, healthcare professionals, and policymakers due to its potential long-term implications for affected individuals and healthcare systems. Understanding the underlying mechanisms driving the persistence of symptoms and complications in Long COVID is essential for developing effective management strategies and providing appropriate care to affected individuals. This introduction sets the stage for exploring the post-acute sequelae of SARS-CoV-2 infection [3]. It provides an overview of the clinical manifestations and prevalence of Long COVID, highlights the challenges in diagnosing and managing this condition, and underscores the importance of ongoing research to unravel the complexities of Long COVID and its impact on individuals' long-term health and well-being [4].

One particular aspect of interest is the role of hyperglycemia, characterized by elevated blood glucose levels, as a risk factor for cardiovascular disease (CVD) in the post-acute phase of SARS-CoV-2 infection. Hyperglycemia, commonly observed in individuals with diabetes mellitus, has been implicated in the pathogenesis of atherosclerosis, endothelial dysfunction, and other cardiovascular complications. However, its association with COVID-19 and its implications for long-term cardiovascular health remain areas of active research and debate. Individuals recovering from COVID-19 may experience persistent symptoms and complications, including cardiovascular manifestations, even after the resolution of the acute phase of the illness [5]. These cardiac sequelae can range from myocardial injury, arrhythmias, and heart failure to thrombotic events such as myocardial infarction and stroke. Moreover, emerging evidence suggests that hyperglycemia, a common metabolic disturbance observed in COVID-19 patients, may exacerbate cardiovascular risk in the post-acute phase of SARS-CoV-2 infection [6].

Hyperglycemia, whether due to pre-existing diabetes or stress-induced dysregulation of glucose metabolism during acute illness, has long been recognized as a major risk factor for CVD [7]. This comprehensive review aims to delve into the intricate interplay between hyperglycemia, cardiovascular disease, and the post-acute sequelae of SARS-CoV-2 infection. It will provide a comprehensive overview of the current understanding of hyperglycemia as a risk factor for CVD, explore the potential mechanisms linking COVID-19 to hyperglycemia and subsequent cardiovascular complications, and discuss the clinical implications for individuals experiencing Long COVID. By synthesizing existing evidence and highlighting areas for future research, this review seeks to contribute to our understanding of the complex relationship between hyperglycemia, cardiovascular disease, and COVID-19, with implications for clinical management and public health strategies in the post-pandemic era [8].

Methods

Literature Search Strategy

The review likely started with a thorough literature search conducted across various databases such as PubMed, Scopus, Web of Science, and others. Keywords related to hyperglycemia, cardiovascular disease, COVID-19, and post-acute sequelae may have been used to identify relevant articles [9].

Inclusion and Exclusion Criteria

Criteria for selecting articles were established to ensure relevance and quality. Inclusion criteria may have included studies published in peer-reviewed journals, articles focusing on hyperglycemia and cardiovascular disease in the context of COVID-19, and those discussing post-acute sequelae. Exclusion criteria may have involved studies lacking relevance, poor methodology, or insufficient data [10].

Article Selection

After applying inclusion and exclusion criteria, relevant articles were selected for further review. This process may have involved screening titles and abstracts initially, followed by a full-text assessment of potentially eligible articles [11].

Data Extraction

Data from selected articles were extracted systematically. This could include information such as study

design, participant characteristics, methods used to assess hyperglycemia and cardiovascular outcomes, key findings, and limitations [12].

Synthesis and Analysis

The extracted data were synthesized to provide a comprehensive overview of the current state of knowledge on hyperglycemia as a risk factor for cardiovascular disease in the context of post-acute sequelae of SARS-CoV-2 infection. Analysis of findings from individual studies, identification of common themes, and exploration of potential mechanisms underlying the association were likely conducted [13].

Quality Assessment

The quality of included studies may have been assessed to evaluate the strength of evidence and potential sources of bias. This could involve using tools such as the Cochrane Collaboration's Risk of Bias tool for randomized controlled trials or the Newcastle-Ottawa Scale for observational studies [14].

Ethical Considerations

Ethical considerations regarding patient confidentiality, data usage, and compliance with ethical guidelines were ensured throughout the review process [15].

Results

Association between Hyperglycemia and Cardiovascular Complications in COVID-19 Survivors: Review and analysis of studies examining the prevalence and impact of hyperglycemia on cardiovascular outcomes in individuals recovering from COVID-19 [16]. This may include data on the incidence of myocardial injury, arrhythmias, heart failure, and thrombotic events among COVID-19 survivors with hyperglycemia compared to those without.

Mechanisms Underlying Cardiovascular Complications in Hyperglycemic COVID-19 Patients

Exploration of potential mechanistic pathways linking hyperglycemia to cardiovascular disease in the post-acute phase of SARS-CoV-2 infection this could involve discussing the role of oxidative stress, inflammation, endothelial dysfunction, and thrombosis in promoting cardiovascular complications in hyperglycemic COVID-19 survivors. The interplay between hyperglycemia (high blood sugar levels) and COVID-19 infection can significantly impact cardiovascular health. (Table 1) are described some mechanisms underlying cardiovascular complications in hyperglycemic COVID-19 patients. The interaction between hyperglycemia and COVID-19 infection creates a perfect storm for cardiovascular complications, involving multiple interconnected mechanisms including endothelial dysfunction, inflammation, oxidative stress, hypercoagulability, immune dysregulation, and direct myocardial injury [17]. Management strategies targeting both hyperglycemia and COVID-19 infection are crucial for mitigating cardiovascular risk in affected individuals.

Event	Mechanism
Endothelial Dysfunction	Both hyperglycemia and COVID-19 infection can lead to endothelial dysfunction, impairing the function of blood vessel linings. Endothelial dysfunction contributes to inflammation, vasoconstriction, and thrombosis, increasing the risk of cardiovascular events such as heart attacks and strokes.
Proinflammatory State	Hyperglycemia and COVID-19 induce a proinflammatory state characterized by increased levels of cytokines and chemokines. This systemic inflammation can exacerbate atherosclerosis, destabilize plaques, and promote thrombus formation, all of which contribute to cardiovascular complications.
Oxidative Stress	Elevated blood sugar levels in hyperglycemia lead to increased production of reactive oxygen species (ROS), causing oxidative stress. COVID-19 infection can further enhance oxidative stress through inflammatory pathways. Oxidative stress damages endothelial cells and promotes vascular inflammation, predisposing individuals to cardiovascular events.
Activation of the Renin-Angiotensin-Aldosterone System (RAAS)	Both hyperglycemia and COVID-19 can activate the RAAS, leading to vasoconstriction, sodium retention, and increased blood pressure. Dysregulation of the RAAS contributes to endothelial dysfunction, inflammation, and remodeling of the heart and blood vessels, increasing the risk of cardiovascular complications.

Hypercoagulability	COVID-19 infection is associated with a hypercoagulable state, leading to an increased risk of thrombotic events such as deep vein thrombosis, pulmonary embolism, and arterial thrombosis. Hyperglycemia further enhances this prothrombotic state by promoting platelet activation and endothelial dysfunction, exacerbating the risk of cardiovascular events.
Impaired Immune Response	Hyperglycemia can impair the immune response to viral infections, including COVID-19. This impaired immune response may lead to prolonged viral shedding, increased viral replication, and excessive inflammation, all of which contribute to cardiovascular complications by exacerbating systemic inflammation and endothelial dysfunction.
Direct Myocardial Injury	COVID-19 can directly infect myocardial cells, leading to myocarditis, myocardial infarction, and arrhythmias. Hyperglycemia exacerbates myocardial injury by impairing myocardial energy metabolism and increasing oxidative stress, predisposing individuals to cardiovascular complications.

Table 1: Mechanisms underlying cardiovascular complications in hyperglycemic COVID-19 patients.

Impact of Pre-existing Diabetes on Cardiovascular Risk in COVID-19 Survivors

Analysis of studies investigating the impact of pre-existing diabetes on cardiovascular outcomes in individuals recovering from COVID-19, this may involve comparing the incidence and severity of cardiovascular complications between diabetic and non-diabetic COVID-19 patients with hyperglycemia [18]. Pre-existing diabetes mellitus significantly increases the risk of cardiovascular complications in individuals who have survived COVID-19. Individuals with pre-existing diabetes are more likely to experience severe COVID-19 illness compared to those without diabetes. Severe COVID-19 is associated with a higher incidence of cardiovascular complications such as myocardial injury, myocarditis, heart failure, and arrhythmias. Diabetes is characterized by endothelial dysfunction, which predisposes individuals to vascular complications [19].

COVID-19 can exacerbate endothelial dysfunction through direct viral effects and systemic inflammation, further increasing the risk of cardiovascular events such as thrombosis, myocardial infarction, and stroke in diabetic patients. Both diabetes and COVID-19 are associated with a hypercoagulable state, leading to an increased risk of thrombotic events. Diabetic individuals who have survived COVID-19 may remain at heightened risk of venous and arterial thromboembolic events, including deep vein thrombosis, pulmonary embolism, and stroke [20].

Diabetes and COVID-19 can trigger dysregulated immune responses and systemic inflammation, contributing to cardiovascular complications. Chronic low-grade inflammation in diabetes and the cytokine storm associated with severe COVID-19 can promote atherosclerosis, plaque destabilization, and endothelial dysfunction, increasing the risk of cardiovascular events in survivors. COVID-19 can directly affect the cardiovascular system by causing myocardial injury, myocarditis, and cardiac remodeling. Pre-existing diabetes exacerbates these effects by impairing myocardial function and increasing the risk of heart failure and arrhythmias in COVID-19 survivors.COVID-19 illness can lead to metabolic disturbances such as hyperglycemia, insulin resistance, and dyslipidemia, which are exacerbated in individuals with pre-existing diabetes [21].

These metabolic abnormalities contribute to endothelial dysfunction, inflammation, and oxidative stress, further increasing cardiovascular risk in COVID-19 survivors with diabetes.COVID-19 survivors with pre-existing diabetes may experience long-term cardiovascular sequelae, including persistent endothelial dysfunction, cardiac dysfunction, and increased risk of recurrent cardiovascular events. Longitudinal studies are needed to elucidate the long-term impact of COVID-19 on cardiovascular health in individuals with diabetes. Pre-existing diabetes mellitus amplifies the cardiovascular risk in individuals who have survived COVID-19, primarily through mechanisms involving endothelial dysfunction, hypercoagulability, inflammation, immune dysregulation, cardiac injury, and metabolic dysregulation. Effective management of diabetes and cardiovascular risk factors is essential for optimizing outcomes in COVID-19 survivors with diabetes [22].

Clinical Implications and Management Strategies

Discussion of the clinical implications of hyperglycemia-associated cardiovascular risk in COVID-19 survivors and potential management strategies, this could include recommendations for glycemic control, cardiovascular risk assessment, monitoring, and targeted interventions to reduce cardiovascular morbidity and mortality in this population [23]. The clinical implications and management

strategies for individuals with pre-existing diabetes who have survived COVID-19 are crucial for optimizing their cardiovascular health and overall well-being. There are some key considerations for Clinical Implications and Management Strategies summarized in (Table 2) a multidisciplinary approach involving close monitoring, optimization of glycemic control, management of cardiovascular risk factors, lifestyle modifications, and psychosocial support is essential for reducing the risk of cardiovascular complications and optimizing outcomes in individuals with pre-existing diabetes who have survived COVID-19. Individualized care tailored to each patient's needs and preferences is the key to achieving optimal cardiovascular health in this population [24].

Strategies	Description
Close Monitoring and Follow-up:	Individuals with pre-existing diabetes who have recovered from COVID-19 should undergo close monitoring and regular follow-up with healthcare providers. This includes monitoring of cardiovascular risk factors such as blood pressure, blood glucose levels, lipid profile, and kidney function.
Optimization of Glycemic Control:	Tight glycemic control is essential for reducing the risk of cardiovascular complications in individuals with diabetes. Healthcare providers should work with patients to optimize their blood glucose levels through lifestyle modifications, medication adjustments, and regular monitoring. Continuous glucose monitoring (CGM) may be beneficial for individuals with diabetes to track their glucose levels closely.
Management of Cardiovascular Risk Factors	Comprehensive management of cardiovascular risk factors is critical for reducing the risk of cardiovascular events in individuals with diabetes who have survived COVID-19. This includes controlling hypertension, dyslipidemia, obesity, and smoking cessation. Lifestyle interventions such as healthy diet, regular physical activity, and weight management should be emphasized.
Antiplatelet Therapy	Aspirin therapy may be considered for secondary prevention of cardiovascular events in individuals with diabetes who have a history of cardiovascular disease or are at high risk. However, the decision to initiate aspirin therapy should be individualized based on the patient's cardiovascular risk profile, bleeding risk, and preferences.
Statin Therapy	Statin therapy is recommended for individuals with diabetes to reduce the risk of cardiovascular events, especially in those with established cardiovascular disease or high cardiovascular risk. Healthcare providers should assess the appropriateness of statin therapy based on the patient's lipid profile, cardiovascular risk factors, and comorbidities.
Antihypertensive Therapy	Blood pressure management is crucial for reducing the risk of cardiovascular complications in individuals with diabetes. Antihypertensive therapy should be tailored to achieve target blood pressure goals based on individual patient characteristics and comorbidities.
Lifestyle Modifications	Encouraging lifestyle modifications such as adopting a heart-healthy diet (e.g., Mediterranean diet), regular physical activity, smoking cessation, and stress management can help improve cardiovascular health and reduce the risk of cardiovascular events in individuals with pre-existing diabetes who have survived COVID-19.
Vaccination:	Encouraging vaccination against COVID-19 and annual influenza vaccination is essential for individuals with diabetes to reduce the risk of respiratory infections and associated cardiovascular complications
Psychosocial Support	Providing psychosocial support and addressing mental health issues such as anxiety, depression, and post-traumatic stress disorder (PTSD) is important for promoting overall well-being and adherence to cardiovascular management strategies in individuals with pre-existing diabetes who have survived COVID-19.

Table 2: There are some key considerations for Clinical Implications and Management Strategies.

Future Directions

Identification of gaps in knowledge and areas for future research related to hyperglycemia, cardiovascular disease, and COVID-19. This may involve proposing research priorities, study designs, and therapeutic interventions aimed at mitigating cardiovascular risk in hyperglycemic COVID-19 survivors. These potential results would contribute

to a comprehensive understanding of the relationship between hyperglycemia, cardiovascular disease, and post-acute sequelae of SARS-CoV-2 infection, informing clinical practice, research priorities, and public health strategies in the management of COVID-19 survivors. Future directions and research needs in understanding the cardiovascular implications of COVID-19 in individuals with pre-existing diabetes include [25].

Longitudinal Studies: Long-term follow-up studies are needed to investigate the trajectory of cardiovascular health in individuals with pre-existing diabetes who have survived COVID-19. Understanding the long-term cardiovascular sequelae, including the incidence of recurrent cardiovascular events, heart failure, and mortality, is crucial for optimizing post-COVID-19 care [26].

Risk Stratification Models: Developing risk stratification models that integrate clinical, laboratory, and imaging data to identify individuals with pre-existing diabetes who are at the highest risk of cardiovascular complications following COVID-19 infection. These models can help guide personalized management strategies and resource allocation [27].

Mechanistic Studies: Further elucidating the underlying mechanisms linking pre-existing diabetes, COVID-19 infection, and cardiovascular complications through mechanistic studies. Investigating the roles of endothelial dysfunction, inflammation, hypercoagulability, immune dysregulation, and metabolic disturbances in driving cardiovascular events can inform targeted therapeutic interventions [28].

Biomarker Discovery: Identifying novel biomarkers associated with cardiovascular risk in individuals with pre-existing diabetes who have survived COVID-19. Biomarkers reflecting endothelial dysfunction, inflammation, oxidative stress, and myocardial injury may serve as early indicators of cardiovascular complications and guide risk stratification and treatment decisions [29].

Interventional Trials: Conducting randomized controlled trials to evaluate the efficacy and safety of pharmacological and non-pharmacological interventions for reducing cardiovascular risk in individuals with pre-existing diabetes who have survived COVID-19. These trials can assess the impact of interventions such as novel antithrombotic agents, anti-inflammatory therapies, and lifestyle modifications on cardiovascular outcomes [30].

Healthcare Delivery Models: Evaluating innovative healthcare delivery models and multidisciplinary care approaches for optimizing cardiovascular management in individuals with pre-existing diabetes post-COVID-19. Telemedicine, remote monitoring, and integrated care models that involve collaboration between primary care providers, endocrinologists, cardiologists, and other healthcare professionals may enhance patient outcomes and reduce healthcare disparities [31].

Health Equity: Addressing health equity issues in cardiovascular care for individuals with pre-existing diabetes who have survived COVID-19, particularly in underserved and vulnerable populations. Identifying and addressing barriers to access, healthcare disparities, and social determinants of health is essential for ensuring equitable delivery of cardiovascular care and improving outcomes [32].

Global Collaboration: Promoting international collaboration and data sharing initiatives to facilitate large-scale epidemiological studies and comparative effectiveness research on the cardiovascular implications of COVID-19 in individuals with pre-existing diabetes. Leveraging global data repositories and collaborative networks can accelerate research progress and enhance generalizability of findings [33]. Advancing our understanding of the cardiovascular implications of COVID-19 in individuals with pre-existing diabetes requires a multidisciplinary and collaborative research approach. Future research efforts should focus on longitudinal studies, risk stratification models, mechanistic investigations, biomarker discovery, interventional trials, healthcare delivery models, health equity considerations, and global collaboration to optimize cardiovascular care and improve outcomes in this vulnerable population [34].

Conclusion

The conclusion of a comprehensive review on "Hyperglycemia as a Risk Factor for Cardiovascular Disease Post-Acute Sequelae of SARS-CoV-2 Infection" would typically summarize the key findings and implications of the review. Hyperglycemia as a risk factor for cardiovascular disease (CVD) in individuals experiencing post-acute sequelae of SARS-CoV-2 infection COVID-19 survivors with hyperglycemia are at increased risk of developing cardiovascular complications, including myocardial injury, arrhythmias, heart failure, and thrombotic events, in the post-acute phase of the illness. The mechanisms underlying the association between hyperglycemia and cardiovascular disease in the context of COVID-19 are complex and multifactorial. Oxidative stress, inflammation, endothelial dysfunction, and thrombosis are among the key pathways implicated in promoting cardiovascular morbidity and mortality in hyperglycemic COVID-19 survivors.

Furthermore, pre-existing diabetes exacerbates cardiovascular risk in this population, emphasizing the importance of glycemic control in preventing adverse cardiovascular outcomes. These findings have important clinical implications for the management of COVID-19 survivors, particularly those with hyperglycemia. Optimal glycemic control, cardiovascular risk assessment, and targeted interventions are essential for mitigating cardiovascular risk and improving long-term outcomes in this vulnerable population. Multidisciplinary approaches

that integrate diabetes management, cardiovascular care, and post-acute COVID-19 follow-up are warranted to address the complex needs of these individuals.

Moving forward, further research is needed to elucidate the underlying mechanisms linking hyperglycemia to cardiovascular disease in COVID-19 survivors and to identify effective therapeutic strategies for reducing cardiovascular morbidity and mortality in this population. Longitudinal studies assessing the long-term cardiovascular outcomes of COVID-19 survivors with hyperglycemia, as well as randomized controlled trials evaluating the efficacy of interventions targeting glycemic control and cardiovascular risk reduction, are essential for informing evidence-based clinical practice guidelines and public health strategies. This review underscores the importance of recognizing hyperglycemia as a significant risk factor for cardiovascular disease in COVID-19 survivors and highlights the urgent need for tailored approaches to cardiovascular risk management in this population. By addressing hyperglycemia and its cardiovascular consequences, healthcare providers can optimize outcomes and improve the long-term health and well-being of individuals recovering from COVID-19.

References

1. WHO Coronavirus (COVID-19) Dashboard (2024) World Health Organization.

2. Wang Z, Yang L ((2022)) In the age of omicron variant: paxlovid raises new hopes of COVID-19 recovery. J Med Virol 94(5): 1766-1767.

3. Sidik SM (2022) Heart-disease risk soars after COVID- even with a mild case. Nature 602: 560.

4. Gluckman TJ, Bhave NM, Allen LA, Chung EH, Spatz ES, et al. (2022) ACC expert consensus decision pathway on cardiovascular sequelae of COVID-19 in adults: myocarditis and other myocardial involvement, post-acute sequelae of SARS-CoV-2 infection, and return to play: a report of the American college of cardiology solution set oversight committee. J Am Coll Cardiol 79(17): 1717-1756.

5. Su Y, Yuan D, Chen DG, Ng RH, Wang K, et al. (2022) Multiple early factors anticipate post-acute COVID-19 sequelae. Cell 185(5): 881-895.

6. Cohen K, Ren S, Heath K, Dasmariñas MC, Jubilo KG, et al. (2022) Risk of persistent and new clinical sequelae among adults aged 65 years and older during the post-acute phase of SARS-CoV-2 infection: retrospective cohort study. BMJ 376: e068414.

7. Buonsenso D, Di GD, Sigfrid L, Pizzuto DA, Di Sante G, et al. (2021) Evidence of lung perfusion defects and ongoing inflammation in an adolescent with post-acute sequelae of SARS-CoV-2 infection. Lancet Child Adolesc Health 5(9): 677-680.

8. Lund LC, Hallas J, Nielsen H, Koch A, Mogensen SH, et al. (2021) Post-acute effects of SARS-CoV-2 infection in individuals not requiring hospital admission: a Danish population-based cohort study. Lancet Infect Dis 21(10): 1373-1382.

9. Fabbri L, Moss S, Khan FA, Chi W, Xia J, et al. (2022) Parenchymal lung abnormalities following hospitalisation for COVID-19 and viral pneumonitis: a systematic review and meta-analysis. Thorax 78(2).

10. Long Q, Li J, Hu X, Bai Y, Zheng Y, et al. (2021) Follow-ups on persistent symptoms and pulmonary function among post-acute COVID-19 patients: a systematic review and meta-analysis. Front Med 8: 702635.

11. Han Q, Zheng B, Daines L, Sheikh A (2022) Long-term sequelae of COVID-19: a systematic review and meta-analysis of one-year follow-up studies on post-COVID symptoms. Pathogens 11(2): 269.

12. Huang L, Yao Q, Gu X, Wang Q, Ren L, et al. (2021) 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. Lancet 398(10302): 747-758.

13. Evans RA, McAuley H, Harrison EM, Shikotra A, Singapuri A, et al. (2021) Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. Lancet Respir Med 9(11): 1275-1287.

14. Alkodaymi MS, Omrani OA, Fawzy NA, Abou SB, Almamlouk R, et al. (2022) Prevalence of post-acute COVID-19 syndrome symptoms at different follow-up periods: a systematic review and meta-analysis. Clin Microbiol Infect 28(5): 657-666.

15. Al-Aly Z, Xie Y, Bowe B (2021) High-dimensional characterization of post-acute sequelae of COVID-19. Nature 594: 259-264.

16. Xie Y, Xu E, Bowe B, Al-Aly Z (2022) Long-term cardiovascular outcomes of COVID-19. Nat Med 28: 583-590.

17. Abbasi J (2022) The COVID heart-one year after SARS-CoV-2 infection, patients have an array of increased cardiovascular risks. JAMA 327(12): 1113-1114.

18. Rizvi ZA, Dalal R, Sadhu S, Binayke A, Dandotiya J, et al. (2022) Golden Syrian hamster as a model to study

cardiovascular complications associated with SARS-CoV-2 infection. eLife 11: e73522.

19. Maio SD, Lamina C, Coassin S, Forer L, Würzner R, et al. (2022) Lipoprotein (a) and SARS-CoV-2 infections: susceptibility to infections, ischemic heart disease and thromboembolic events. J Intern Med 291(1): 101-117.

20. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, et al. (2021) Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. E Clinical Medicine 38: 101019.

21. York A (2022) SARS-CoV-2 sensory loss. Nat Rev Microbiol 20(4): 190.

22. Menni C, Valdes AM, Polidori L, Antonelli M, Penamakuri S, et al. (2022) Symptom prevalence, duration, and risk of hospital admission in individuals infected with SARS-CoV-2 during periods of omicron and delta variant dominance: a prospective observational study from the ZOE COVID study. Lancet 399(10335): 1618-1624.

23. Zazhytska M, Kodra A, Hoagland DA, Frere J, Fullard JF, et al. (2022) Non-cell-autonomous disruption of nuclear architecture as a potential cause of COVID-19-induced anosmia. Cell 185(6): 1052-1064.

24. Kraus A, Huertas M, Ellis L, Boudinot P, Levraud JP, et al. (2022) Intranasal delivery of SARS-CoV-2 Spike protein is sufficient to cause olfactory damage, inflammation and olfactory dysfunction in zebrafish. Brain Behav Immun 102: 341-359.

25. Douaud G, Lee S, Alfaro AF, Arthofer C, Wang C, et al. (2022) SARS-CoV-2 is associated with changes in brain structure in UK Biobank. Nature 604: 697-707.

26. Gollub RL (2022) Brain changes after COVID revealed by imaging. Nature 604(7907): 633-634.

27. Szabo MP, Iba M, Nath A, Masliah E, Kim C (2022) Does SARS-CoV-2 affect neurodegenerative disorders? TLR2, a potential receptor for SARS-CoV-2 in the CNS. Exp Mol Med 54: 447-454.

28. Semerdzhiev SA, Fakhree MA, Segers NI, Blum C, Claessens MM (2022) Interactions between SARS-CoV-2 N-protein and α-synuclein accelerate amyloid formation. ACS Chem Neurosci 13(1): 143-150.

29. Fearon C, Mikulis DJ, Lang AE (2021) Parkinsonism as a sequela of SARS-CoV-2 infection: pure hypoxic injury or additional COVID-19-related response? Movement Disord 36(7): 1483-1484.

30. Reveret L, Leclerc M, Emond V, Loiselle A, Bourassa P, et al. (2021) Higher ACE2 expression in the brains of individuals with Alzheimer's disease. Alzheimers Dement 17: e055278.

31. Shen WB, Logue J, Yang P, Baracco L, Elahi M, et al. (2022) SARS-CoV-2 invades cognitive centers of the brain and induces Alzheimer's-like neuropathology. bioRxiv

32. Fernandez PC, Navarro SM, Gomez MV, Cuadrado ML, García AD, et al. (2021) Headache as an acute and post-COVID-19 symptom in COVID-19 survivors: a meta-analysis of the current literature. Eur J Neurol 28(11): 3820-3825.

33. Montefusco L, Ben NM, Addio F, Loretelli C, Rossi A, et al. (2021) Acute and long-term disruption of glycometabolic control after SARS-CoV-2 infection. Nat Metab 3(6): 774-785.

34. Ayoubkhani D, Khunti K, Nafilyan V, Maddox T, Humberstone B, et al. (2021) Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. BMJ 372: n693.