Nutritional interventions for long-COVID: a systematic quantitative literature review

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BACKGROUND

Long-COVID (coronavirus disease 2019) is anticipated to cause significant and long-term healthcare strain [1,2]. New treatments are needed [1-3]. Nutritional interventions may be helpful [4,5], but recommendations are based on expert opinion not empirical evidence [2,6].

A 2023 scoping review found 5 studies implementing nutritional interventions for long-COVID [7]. Frequent surveillance is appropriate for this new and high-incidence topic [8]. Quantitative mapping can identify research clusters and opportunities that can guide research and coordination to benefit long-COVID patients [9]. This update review [8] explored what nutritional interventions have been investigated for long-COVID.

AIMS AND OBJECTIVES

- To identify and quantitatively summarise what nutritional interventions have been investigated for long-COVID.
- To contribute to the research priorities to identify candidate non-pharmaceutical therapeutics for long-COVID.
- To benefit long-COVID researchers, clinicians, and patients.

METHODOLOGY AND METHODS

This trans-methodological, mapping-like systematic quantitative literature review [10] collated, categorised, and quantitatively summarised:

- nutrition interventions investigated for long-COVID (breadth); and
- number of primary clinical studies investigating each of these (depth) [11].

Ethical approval: 05/2023. Searching conducted: 11-18/09/2023. Optional quality appraisal was not conducted [10,11].

Design	
P	Persisting symptom(s) after acute COVID-19 illness.
I	Any nutrition intervention aimed at treating one or more symptoms.
C	Healthcare
O	Any
S	Peer-reviewed primary clinical research.
	English

7 Databases	
Health research	PubMed, Embase, CINAHL, AMED, CENTRAL
Specialist sources	Nutrition Evidence [12], Living Map of Long-COVID [9]

RESULTS

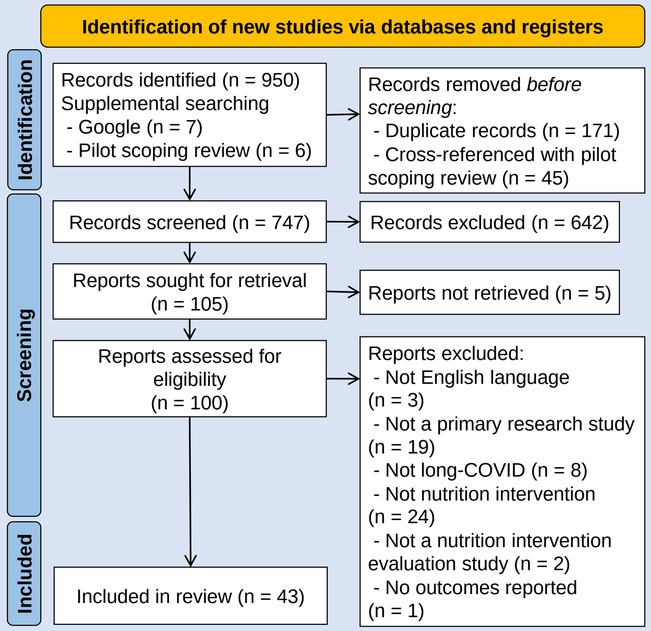

Table 1: Dietary interventions	Papers (n)
All	11
Personalised	9
Macronutrients	6
Protein-rich	6
High carbohydrate	1
Low carbohydrate	1
Calories	5
Hypercaloric	2
3 Specific diets	3
Low histamine, anti-inflammatory	1
Mediterranean	1
Pevsner (protein-rich, high carbohydrate, low fat, hypercaloric, vitamin-enriched, high salt; exclude: spicy, difficult to digest foods)	1

Table 2: Supplement interventions	Papers (n)
All	37
Macronutrients	21
Protein	14
12 Amino Acids	12
Arginine	8
Cysteine	3
3 Fatty acids	6
Palmitoylethanolamide	4
Alpha-lipoic acid	1
Omega-3	1
17 Multi-component Supplements	19
Glialia®	3
Apportal®	2
Bioarginina® C	2
25 Micronutrients	16
12 Vitamins	16
6 B vitamins	9
Vitamin B_6	4
Vitamin B_1	3
Vitamin C	6
Vitamin D	5
Vitamin A	2
13 Minerals	6
Magnesium	4
Zinc	4
Iron	3
Selenium	3
9 Compounds	10
8 Organic compounds	9
Coenzyme Q_{10}	3
Carnitine	3
Malic acid	2
8 Plant extracts	6
Eleutherococcus senticosus	3
Panax ginseng	2
4 Polyphenols	6
2 Flavonoids	5
Luteolin	3
Quercetin	2
14 Biotics	4
6 Probiotics	3
8 Prebiotics	2
8 Enzymes	2
Bromelain	2

DISCUSSION

- 39 studies were found in addition to the 5 previously reported [7], demonstrating a marked increase in the evidence-base. One study included in [7] did not meet the inclusion criteria for this study.
- Tables 1 and 2 show, consistent with previous findings [7], supplements were more often implemented than diet.
- Table 2 shows the evidence is deeper for vitamins C, D, B_6 and B_1 and minerals magnesium, zinc, and selenium. This is consistent with previous trends [7].
- Evidence has broadened to fill knowledge gaps previously identified [7] for cysteine, alpha-lipoic acid, omega-3, co-enzyme Q_{10}, quercetin, and the Mediterranean and anti-inflammatory diets.
- Some nutritional components of the same family were more frequently implemented than those previously suggested [7], such as the amino acid arginine, fatty acid palmitoylethanolamide, and flavonoid luteolin versus cysteine, alpha-lipoic acid and omega-3, and quercetin, respectively [7].
- Turmeric and liposomal glutathione continue to be absent in the evidence [7].
- Rather than specific diets, such as the Mediterranean and anti-inflammatory diets, Table 1 shows personalised dietary increases in protein and calorie intake were more often implemented.
- Many additional nutritional components have been investigated indicating broad expansion of the evidence-base. However, many were implemented in 3 or fewer studies, indicating limited knowledge depth and research coordination.
- This reinforces calls for improved coordination to achieve research aims that ultimately benefit long-COVID patients [13].
- Scoping reviews of identified knowledge clusters with quality appraisal could verify suitability for further primary studies.

Strengths	Limitations
Broad engagement with the evidence-base as study designs often excluded in other systematic reviews were included [10].	Conducted by a sole researcher for academic award, it is limited to a 'systematised' standard [14].
	Heterogeneity in long-COVID clinical definitions challenged search strategy sensitivity and specificity [15] and external validity [16,17].

CONCLUSION

This study contributes to research priorities to identify long-COVID candidate therapeutics and non-pharmaceutical interventions [3]. Intervention clusters indicate suitability for scoping reviews with quality analysis to extend findings. An annual update review could track and guide knowledge advancement to benefit long-COVID patients and their clinicians [8,9,13].

REFERENCES

[1] National Institute for Health Research. Living with COVID19: second review 2021. https://evidence.nihr.ac.uk/themedreview/living-with-covid19-second-review/ (accessed September 25, 2022).

[2] World Health Organization. Clinical management of COVID-19: living guideline 2023. https://www.who.int/teams/health-care-readiness/post-covid-19-condition (accessed January 29, 2023).

[3] Carson G; Long Covid Forum Group. Research priorities for Long Covid: refined through an international multi-stakeholder forum. BMC Med 2021;19(1):84. https://doi.org/10.1186/s12916-021-01947-0.

[4] Gérard M, Mahmutovic M, Malgras A, Michot N, Scheyer N, Jaussaud R, et al. Long-term evolution of malnutrition and loss of muscle strength after COVID-19: a major and neglected component of Long COVID-19. Nutrients 2021;13(11):3964. https://doi.org/10.3390/NU13113964.

[5] Leal-Martínez F, Abarca-Bernal L, Garcia-Perez A, González-Tolosa D, Cruz-Cázares G, Garcia MM, et al. Effect of a nutritional support system to increase survival and reduce mortality in patients with COVID-19 in stage III and comorbidities: a blinded randomized controlled clinical trial. Int J Environ Res Public Health 2022;19(3):1172. https://doi.org/10.3390/ijerph19031172.

[6] Hernandez YAT, Julian A, Weekes EC, Murphy J, Frost G, Hickson M. Developing a consensus to support health and social care professionals and patients manage nutrition in the context of COVID-19 recovery. J Hum Nutr Diet 2023; 36(6):1242-52.

[7] Bradbury J, Wilkinson S, Schloss J. Nutritional support during long COVID: a systematic scoping review. J Integr Complement Med 2023;29(11):695-704.

[8] Garner P, Hopewell S, Chandler J, MacLehose H, Schünemann HJ, Akl EA, et al. When and how to update systematic reviews: consensus and checklist. BMJ 2016; 354:i3507. https://doi.org/10.1136/BMJ.I3507.

[9] Evidence for Policy and Practice Information and Co-ordinating (EPPI) Centre. COVID-19: a living systematic map of the evidence 2023. https://eppi.ioe.ac.uk/cms/Projects/DepartmentofHealthandSocialCare/Publishedreviews/COVID19Livingsystematicmapoftheevidence/tabid/376/Default.aspx (accessed June 26, 2023).

[10] Pickering CM, Grignon J, Steven R, Guitart D, Byrne J. Publishing not perishing: how research students transition from novice to knowledgeable using systematic quantitative literature reviews. Studies in Higher Education 2015;40:1756-69.

[11] Clapton J, Rutter D, Sharif N. SCIE Systematic mapping guidance 2009. http://www.scie.org.uk/publications/researchresources/rr03.pdf.

[12] Nutrition Evidence. What is Nutrition Evidence? 2023. https://www.nutrition-evidence.com (accessed February 27, 2023).

[13] Norton A, Bucher A, Antonio E, Advani N, Grund H, Mburu S, et al. Living mapping review for COVID-19 funded research projects 2022. https://www.ukcdr.org.uk/resource/living-mapping-review-covid19funded-research-projects/ (accessed June 25, 2023).

[14] Grant MJ, Booth A. A typology of reviews: an analysis of 14 review types and associated methodologies. Health Info Libr J 2009;26(2):91-108.

[15] Salvador-Oliván JA, Marco-Cuenca G, Arquero-Avilés R. Errors in search strategies used in systematic reviews and their effects on information retrieval. J Med Libr Assoc 2019; 107(2):210-21.

[16] Høeg TB, Ladhani S, Prasad V. How methodological pitfalls have created widespread misunderstanding about long COVID. BMJ Evid Based Med 2023;bmjebm-2023-112338. https://doi.org/10.1136/bmjebm2023-112338.

[17] Huerne K, Filion KB, Grad R, Ernst P, Gershon AS, Eisenberg MJ. Epidemiological and clinical perspectives of long COVID syndrome. Am J Med Open 2023;9:100033. https://doi.org/10.1016/j.ajmo.2023.100033.