

## 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 rather than 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].

| 7 Databases        |                                                       | Design                                                                      |
|--------------------|-------------------------------------------------------|-----------------------------------------------------------------------------|
| Health research    | PubMed, Embase, CINAHL, AMED, CENTRAL                 | <b>P</b> Persisting symptom(s) after acute COVID-19 illness.                |
|                    |                                                       | <b>I</b> Any nutrition intervention aimed at treating one or more symptoms. |
| Specialist sources | Nutrition Evidence [12], Living Map of Long-COVID [9] | <b>C</b> Healthcare                                                         |
|                    |                                                       | <b>O</b> Any                                                                |
|                    |                                                       | <b>S</b> Peer-reviewed primary clinical research. English                   |

## FINDINGS AND DISCUSSION

- 39 studies were found in addition to the 5 previously reported [7] indicating the high research incidence on this topic and marked increase in the evidence-base.
- Some trends maintained and gained evidence depth since the 2023 paper [7]:
  - greater focus on supplements than dietary approaches;
  - the most often reported vitamins were C, D, B<sub>6</sub> and B<sub>1</sub>, and minerals were magnesium, zinc, and selenium.
- Personalised diets were more often implemented than specific diets, i.e., Mediterranean or anti-inflammatory diets, and focused on increasing protein and calorie intake relative to routine dietary recommendations.
- Supplements also favoured protein intake, with a focus on specific amino acids, followed by fatty acids.
- Evidence has broadened to fill knowledge gaps previously identified [7], i.e., cysteine, alpha-lipoic acid, omega-3, co-enzyme Q<sub>10</sub>, quercetin, and the Mediterranean and anti-inflammatory diets, and beyond to other nutritional components. Although many of the latter were implemented in 3 or fewer studies, indicating limited knowledge depth.
- 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].
- Findings reinforce 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:

- Broad engagement with the evidence-base as study designs often excluded in other systematic reviews were included [10].

### Limitations:

- 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

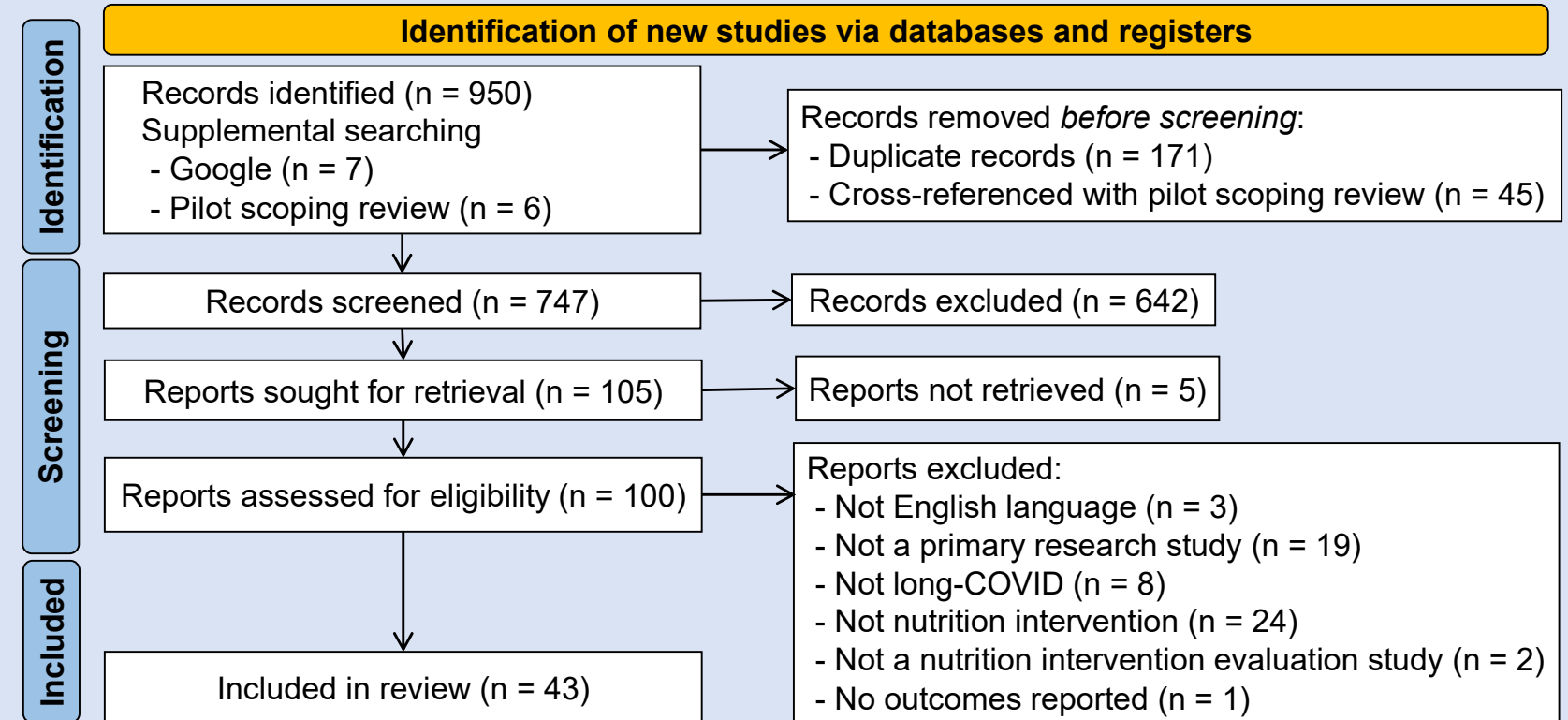
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## RESULTS



Nutritional interventions were clustered into categories and quantified by category size and intervention frequency. Tables 1 and 2 report most frequently reported interventions.

| Table 1: Dietary interventions                                                                                                           | Papers (n) |
|------------------------------------------------------------------------------------------------------------------------------------------|------------|
| <b>All</b>                                                                                                                               | <b>11</b>  |
| <b>Personalised</b>                                                                                                                      | <b>9</b>   |
| <b>Macronutrients</b>                                                                                                                    | <b>6</b>   |
| Protein-rich                                                                                                                             | 6          |
| High carbohydrate                                                                                                                        | 1          |
| Low carbohydrate                                                                                                                         | 1          |
| <b>Calories</b>                                                                                                                          | <b>5</b>   |
| Hypercaloric                                                                                                                             | 2          |
| <b>3 Specific diets</b>                                                                                                                  | <b>3</b>   |
| 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) |
|---------------------------------------|------------|
| <b>All</b>                            | <b>37</b>  |
| <b>Macronutrients</b>                 | <b>21</b>  |
| <b>Protein</b>                        | <b>14</b>  |
| 12 Amino Acids                        | 12         |
| Arginine                              | 8          |
| Cysteine                              | 3          |
| <b>3 Fatty acids</b>                  | <b>6</b>   |
| Palmitoylethanolamide                 | 4          |
| Alpha-lipoic acid                     | 1          |
| Omega-3                               | 1          |
| <b>17 Multi-component Supplements</b> | <b>19</b>  |
| Gliaia®                               | 3          |
| Apportal®                             | 2          |
| Bioarginina® C                        | 2          |
| <b>25 Micronutrients</b>              | <b>16</b>  |
| <b>12 Vitamins</b>                    | <b>16</b>  |
| 6 B vitamins                          | 9          |
| Vitamin B <sub>6</sub>                | 4          |
| Vitamin B <sub>1</sub>                | 3          |
| Vitamin C                             | 6          |
| Vitamin D                             | 5          |
| Vitamin A                             | 2          |
| <b>13 Minerals</b>                    | <b>6</b>   |
| Magnesium                             | 4          |
| Zinc                                  | 4          |
| Iron                                  | 3          |
| Selenium                              | 3          |
| <b>9 Compounds</b>                    | <b>10</b>  |
| <b>8 Organic compounds</b>            | <b>9</b>   |
| Coenzyme Q <sub>10</sub>              | 3          |
| Carnitine                             | 3          |
| Malic acid                            | 2          |
| <b>8 Plant extracts</b>               | <b>6</b>   |
| <i>Eleutherococcus senticosus</i>     | 3          |
| <i>Panax ginseng</i>                  | 2          |
| <b>4 Polyphenols</b>                  | <b>6</b>   |
| 2 Flavonoids                          | 5          |
| Luteolin                              | 3          |
| Quercetin                             | 2          |
| <b>14 Biotics</b>                     | <b>4</b>   |
| 6 Probiotics                          | 3          |
| 8 Prebiotics                          | 2          |
| <b>8 Enzymes</b>                      | <b>2</b>   |
| Bromelain                             | 2          |