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Health research in microgravity: a systematic literature mapping

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ABSTRACT

The state of microgravity, or more correctly micro-weightiness, exists in an orbital vehicle in a state of free fall, i.e. without any force acting on it except for gravitational forces. This results in a stress and strain-free state, in which fluids show an altered behavior, making microgravity experiments essential for research in space science. Therefore, this study aims to identify trends and research opportunities in this field of knowledge, reducing this gap in the literature through a systematic literature mapping study. Of the studies identified in the PubMed, ScienceDirect, and Wiley Online Library databases, 242 were selected by inclusion and exclusion criteria. The journals that publish the most and their countries of origin were highlighted, especially NPJ Microgravity and the United Kingdom. It was also observed that the number of publications in this area has been growing, with its peak in the year 2021. Among the forms of study in microgravity, research on board the International Space Station and, on Earth, through hindlimb unloading stands out. The health areas with the highest number of research are musculoskeletal health and cell biology. Through this research, those interested in the topic may have a first contact or deepen and update their knowledge, in addition to using the open results to carry out other in-depth studies through a systematic literature review.

Keywords: *Microgravity. Spaceflight. Health research. Microgravity research.*

Investigación en salud en microgravedad: un mapeo sistemático de la literatura

RESUMEN

El estado de microgravedad, o micropeso, existe en un vehículo en órbita en estado de caída libre, es decir, sin ninguna fuerza actuando sobre él, excepto las fuerzas gravitatorias. Esto da como resultado un estado libre de estrés y tensión en el que los fluidos exhiben un comportamiento alterado, lo que hace que los experimentos de microgravedad sean esenciales para la investigación en ciencias espaciales. Por lo tanto, este estudio tiene como objetivo identificar tendencias y oportunidades de investigación en este campo del conocimiento, reduciendo esta brecha en la literatura a través de un mapeo sistemático de la literatura. De los estudios identificados en las bases de datos PubMed, ScienceDirect y Wiley Online Library, 242 fueron seleccionados tras aplicar criterios de inclusión y exclusión. NPJ Microgravity y Reino Unido se destacaron como la revista que más publicó y su país de origen. También se observó que el número de publicaciones en esta área ha ido en aumento, con un pico en el año 2021. Entre las formas de estudio en microgravedad, la investigación a bordo de la Estación Espacial Internacional y, en la Tierra, a través de la descarga de patas traseras. Las áreas de la salud con más investigación son la salud musculoesquelética y la biología celular. A través de este artículo, los interesados en el tema pueden tener un primer contacto o profundizar y actualizar sus conocimientos, además de utilizar los resultados para realizar otros estudios en profundidad a través de una revisión sistemática de la literatura.

Palabras-clave: *Microgravedad. Vuelo espacial. Investigación en salud. Investigación en microgravedad.*

Pesquisa em saúde na microgravidade: um mapeamento sistemático da literatura

RESUMO

O estado de microgravidade, ou micro peso, existe em um veículo orbital em estado de queda livre, ou seja, sem nenhuma força atuando sobre ele, exceto as forças gravitacionais. Isso resulta em um estado livre de estresse e tensão, no qual os fluidos apresentam um comportamento alterado, tornando experimentos de microgravidade essenciais para a pesquisa em ciência espacial. Assim, este estudo visa identificar tendências e oportunidades de pesquisa neste campo do conhecimento, reduzindo esta lacuna na literatura por meio de um mapeamento sistemático da literatura. Dos estudos identificados nas bases de dados PubMed, ScienceDirect e Wiley Online Library, 242 foram selecionados após aplicação de critérios de inclusão e exclusão. Destacaram-se NPJ Microgravity e Reino Unido como o periódico que mais publicou e seu país de origem. Observou-se também que o número de publicações nessa área vem crescendo, com pico no ano de 2021. Entre as formas de estudo em microgravidade, destacam-se as pesquisas a bordo da Estação Espacial Internacional e, na Terra, por meio do descarregamento de membros posteriores. As áreas da saúde com maior número de pesquisas são a saúde musculoesquelética e a biologia celular. Por meio deste artigo, interessados no tema podem ter um primeiro contato ou aprofundar e atualizar seus conhecimentos, além de utilizar os resultados para realizar outros estudos aprofundados por meio de uma revisão sistemática da literatura.

Palavras-chave: *Microgravidade. Voo espacial. Pesquisa em saúde. Pesquisa em microgravidade.*

1 INTRODUCTION

The state of microgravity, or more correctly micro-weightiness, exists in an orbital vehicle in a state of free fall, i.e. without any force acting on it except for gravitational forces (Pletser, 2018). A microgravity environment is one in which the apparent weight of a system is small compared to its actual weight due to gravity, with a range from about one percent of Earth's gravitational acceleration to better than one part in a million (Rogers; Vogt; Wargo, 1997). This results in a stress and strain-free state, in which fluids show an altered behavior, making microgravity experiments essential for research in space science, but also valuable for research in biology, fluid mechanics, combustion, and material science (Breuninger *et al.*, 2016).

Demanding careful control, microgravity experiments can be conducted in environments such as that of the International Space Station (ISS), satellites, sounding rockets, drop towers, or aircraft during parabolic flight (Herranz *et al.*, 2013). Many scientific fields profit from the peculiarities of weightlessness to enlarge their field of investigations (Pletser; Russomano, 2020), including health sciences in a field called bioastronautics. The National Aeronautics and Space Administration (NASA) defines bioastronautics as the study of the biological and medical effects of spaceflight on living organisms (Charles, 2005).

As the development of counter measures for the purpose of preserving the health of space travelers are directly relevant to protecting the health and strength of all of us living on Earth (Vernikos, 2008), an understanding of the response of the human body to the environment of space at the systemic integration system level and at the molecular and cellular level is warranted (Blaber; Marçal; Burns, 2010). In addition, research on long-term space missions point to challenges such as the management of waste disposal systems, life-support systems, food and nutrition, medical care, and psychosocial health (Klein; Bluth; Wegmann, 1988; Williams, 2002; Horneck, 2008).

In this context of increasing relevance of the proposed theme, no previous study was identified in the literature that gathers and somehow evaluates the last five year's health research publications carried out in microgravity environments. Therefore, this study aims to identify trends and research opportunities in this field of knowledge, reducing this gap in the literature through a systematic literature mapping study. The following section explores the methodology used, followed by the results, discussion, and conclusion. In the end, the references of this research are presented.

2 METHODS

Mapping studies are intended to provide an overview of a broad topic area and identify both clusters of studies that might be suitable for more detailed systematic

reviews, and also areas where more primary studies might be required (Kitchenham; Brereton; Budgen, 2012). In a nutshell, systematic mapping deals with a broader research topic, opening the stage for systematic literature reviews that will deal directly with a specific research question narrowing the search for specific answers, and synthesizing studies' findings (Napoleão; Felizardo; Souza; Vijaykumar, 2017; Soaita; Serin; Preece, 2020).

This methodology can be construed as both a valuable research project in itself and an opening stage toward more focused evidence reviews (Soaita; Serin; Preece, 2020). Therefore, systematic mapping may be defined in two dimensions: (a) a time-limited, systematic search for literature related to a well-defined but still broad academic theme, (b) and the exploration and synthesis of key temporal, geographical, conceptual, and thematic features of this literature.

To obtain a more general perspective on the research, systematic mapping may be carried out, where important data will be returned regarding the number of types of research and the frequency of publications, as well as research-related trends (Garcia; Silva; Nascimento, 2018). This methodology requires the following steps: (a) definition of research questions; (b) conducting a search for primary studies; (c) screening of papers for inclusion and exclusion; (d) analysis of the works analyzed on the research questions; (e) conclusion of the study performed (Petersen *et al.*, 2008; Garcia; Silva; Nascimento, 2018).

All subsequent review activities derive from the research question, so defining it reliably to the topic you want to investigate is critical to the successful execution of a literature review or mapping (Dermeval; Coelho; Bittencourt, 2020). As this research is guided by the general aim of finding out what the characteristic trends of health studies in microgravity published in the last 5 years are, the specific research questions were organized and described in table 1:

Table 1 - Research questions

Questions (Q)	Research questions
Q1	What is the time distribution and trend of publication over the last 5 years?
Q2	What is the geographical distribution of publication of the studies?
Q3	What are the most adopted methodologies in microgravity for health research?
Q4	What are the most explored topics in health research?

Source: Organized by the authors (2022).

For the step of conducting a search for primary studies, 3 databases (PubMed, ScienceDirect, and Wiley Online Library) were elected. While PubMed is a database of international health literature, ScienceDirect is a website that provides access to

a large bibliographic database of scientific and medical publications of the Dutch publisher Elsevier and Wiley Online Library, a database that focuses on academic publishing that covers the full spectrum of humanities and life, health, physical, and social sciences.

A search for the descriptors "microgravity" and "health" was performed in each database, linked by the Boolean operator "AND". Search strings were used as inclusion criteria and are presented in Table 2, together with the exclusion criteria. The full mapping protocol can be found in Appendix A of this paper.

Table 2 - Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Being an article	Not having a microgravity methodology applied
Being published between 2017 and 2022	Not being about health research
Written in English, Portuguese, or Spanish	Having more than one copy in the search results
Being free and having full text available	Not being a primary study
	Not being a free available full article, although it is classified as such in the database
	Not being an article, although it is classified as such in a journal

Source: Organized by the authors (2022)

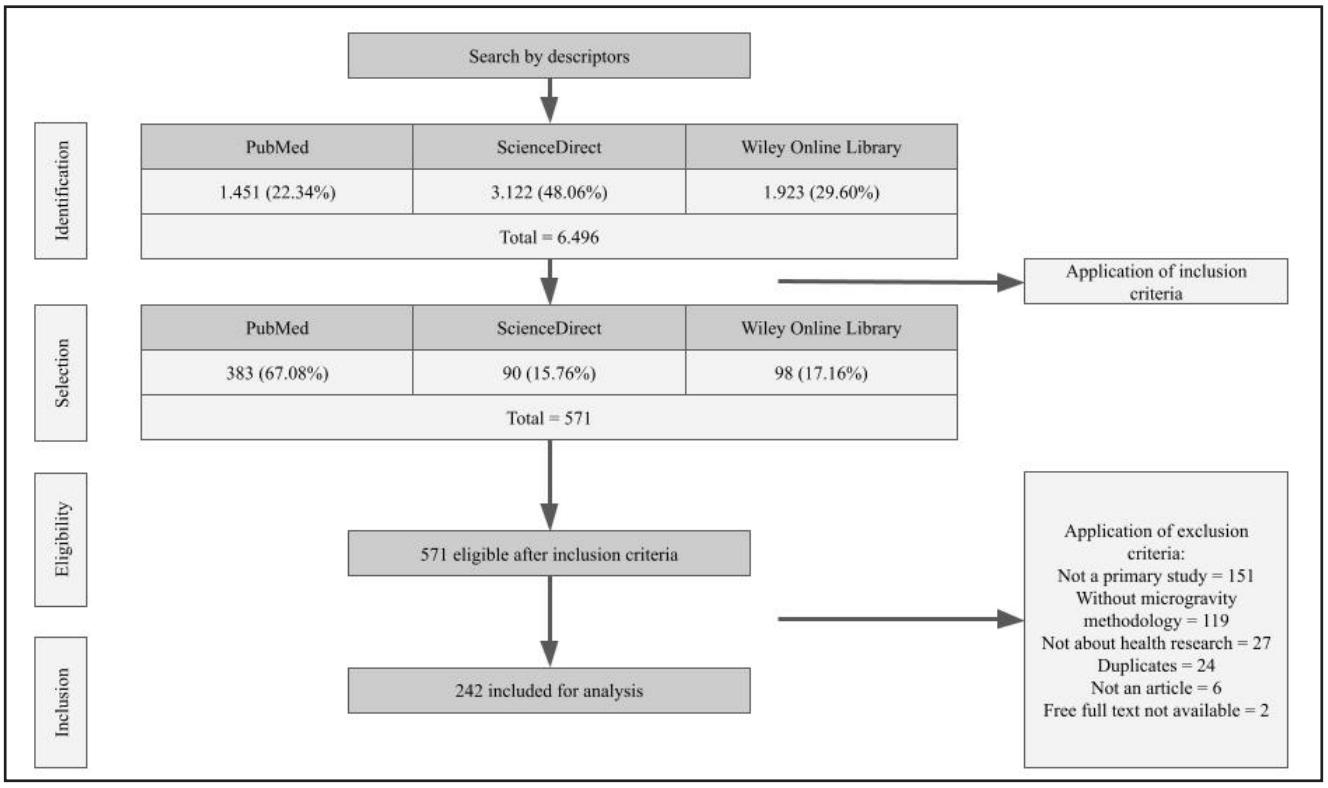
It was opted to include only full texts available because the information needed for analysis might not be available only in the abstract. After each identified result passed the inclusion and exclusion criteria, they had their data extracted and tabulated for analysis.

As additional exams, the analysis of frequency and a word cloud from the keywords of each study was made. The word cloud technique consists of interesting lexical analysis, in which it intends to present a graphical representation of the frequency or the occurrence of words (Camargo; Justo, 2013 *as cited in* Kreutz *et al.*, 2020). In the following section, the results of this research are presented.

3 RESULTS

According to the descriptors, 6,496 returns were obtained. After applying the inclusion criteria, we had 571 results that are presented in Image 1, divided by each portal. After applying the exclusion criteria, 242 articles were considered able to answer the research questions. Image 1 also shows the quantity of excluded research by each of the exclusion criteria, to clarify the selection process. The 242 articles resulting from the selection had their data extracted and analyzed.

Image 1 - Process of identification and selection of studies.



Source: Organized by the authors (2022).

The next section discusses the results of the articles included after applying the inclusion and exclusion criteria.

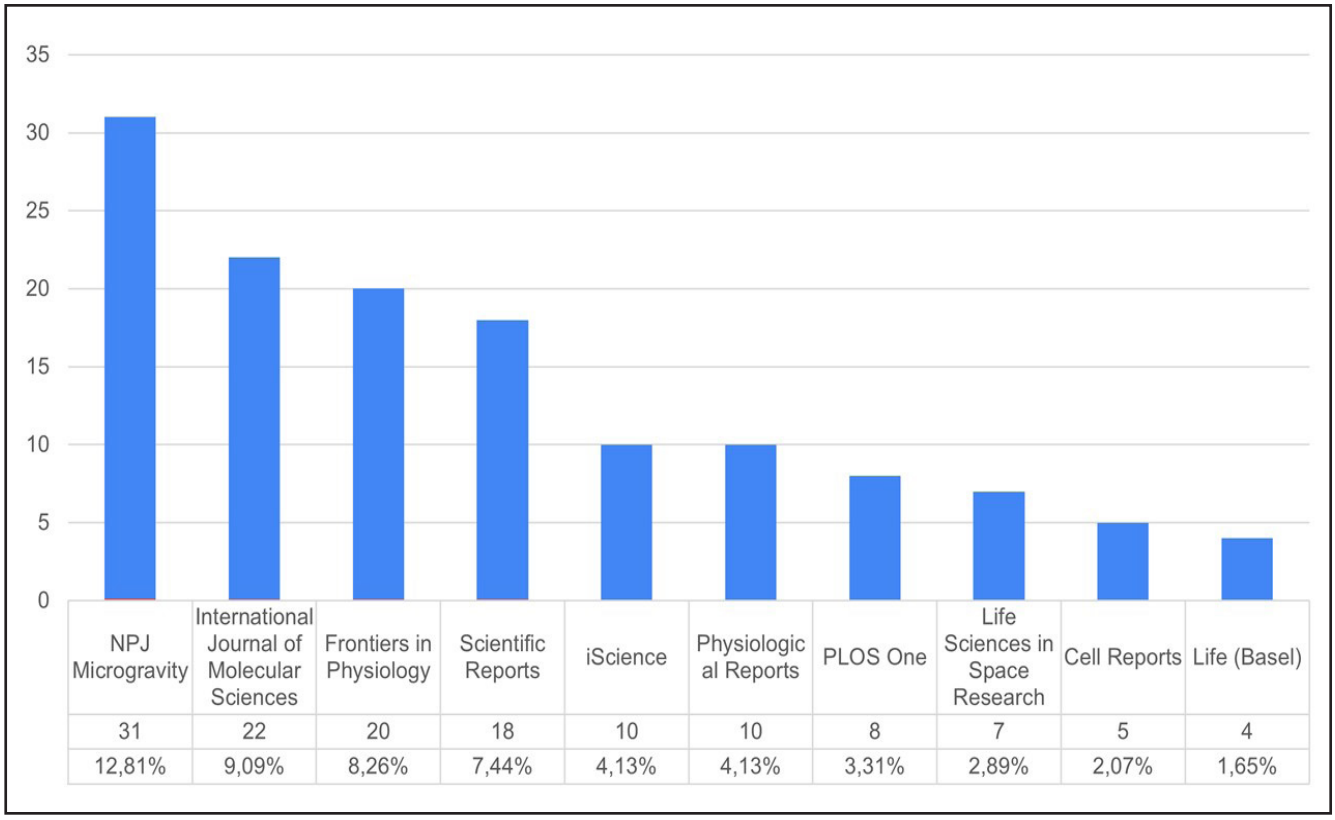
4 DISCUSSION

Here, the extracted results will be discussed in three segments. They are (1) data analysis of journal, year, and country of publication; (2) analysis of microgravity simulation methodologies and health areas addressed; and (3) analysis and word cloud with the keywords found.

4.1 Journal, year, and country of publication

Of the 92 journals responsible for publishing the 242 results of this article, the distribution among the 10 most relevant ones was as follows: NPJ Microgravity; International Journal of Molecular Sciences; Frontiers in Physiology; Scientific Reports; iScience; Physiological Reports; PLOS One; Life Sciences in Space Research; Cell Reports; Life (Basel). The relationships by the quantity of publication can be seen in Image 2. Other journals with less than 4 publications, or 1.5% of presence in the results will not be mentioned by name.

Image 2 - Journals with the most publications.



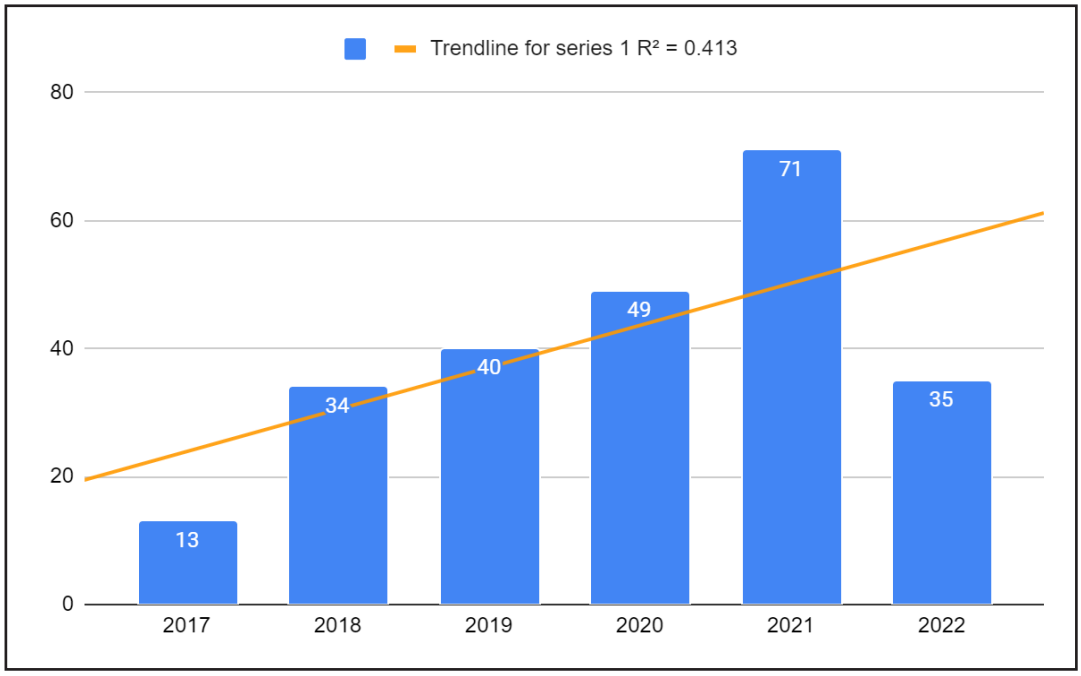
NPJ Microgravity	International Journal of Molecular Sciences	Frontiers in Physiology	Scientific Reports	iScience	Physiological Reports	PLOS One	Life Sciences in Space Research	Cell Reports	Life (Basel)
31	22	20	18	10	10	8	7	5	4
12,81%	9,09%	8,26%	7,44%	4,13%	4,13%	3,31%	2,89%	2,07%	1,65%

Source: Organized by the authors (2022).

NPJ Microgravity is a cross-disciplinary, open-access journal that serves as a novel platform for scientific exchange by capturing the discoveries made not only in the reduced gravity environment of spaceflight but also in the normal gravity of Earth using spaceflight analogue systems (Nickerson, 2015). Our results show that NPJ Microgravity has stood out within our selection criteria and in the last 5 years as the journal with the highest number of publications on the topic of health research using simulated microgravity. His most studied health area was musculoskeletal health, with 6 articles, and Hindlimb unloading (HU), Rotary cell culture system (RCCS), and research aboard the International Space Station (ISS) as the most common methodologies for microgravity simulation.

Musculoskeletal health was also the most prominent area in the year with the most publications, 2021. In addition, research in eye and vision care, immune system and cardiac health stood out. The proportion of studies per year can be seen in Image 3.

Image 3 - Publications per year, in the last 5 years.



Source: Organized by the authors (2022).

It is noticeable, by the trend line, the growing importance of this area in the literature. The R^2 standard relies on one particular reference model, namely the model with just a constant as an explanatory variable (Bartels, 2015) usually with a result between 0 and 1, where the closer to 1, the better, more reliable the result. Despite the result below 0.5 of the trend line in Image 3, it is worth remembering that this research has been carried out since mid-year 2022. Thus, even if at the end of the year the number of publications is not greater than that of 2021, the result R^2 will be closer to 1.

As for the country of origin of the publication, here are the numbers, in alphabetical order: Brazil (1), Canada (1), China (4), Denmark (1), Germany (2), Greece (1), India (2), Iran (1), Japan (1), Netherlands (14), Poland (2), Singapore (1), Switzerland (64), United Arab Emirates (1), United Kingdom (UK) (71), United States of America (USA) (69). In addition to these, 6 publications without a defined country of origin were considered international.

In the United Kingdom, the place with the highest number of publications, research in the areas of musculoskeletal health, eye and vision care, circadian cycle, and immune system stands out. In addition to the main microgravity simulation method of HU and aboard the ISS, research on space shuttles and clinostat rotation is also highlighted. While in the United States the Head down tilt bed rest (HDBR) method stands out, in Switzerland dry immersion and parabolic flights are also widely used. The proportion of publications by country can be better visualized in Image 4.

Image 4 - Publication proportion by country.

Source: Organized by the authors (2022).

It is worth emphasizing that these are the countries of origin of the journals, not necessarily where the research is carried out, something that is also valid to be evaluated in future studies. The next section will delve into some of the concepts cited here as areas of health research and study methods in microgravity.

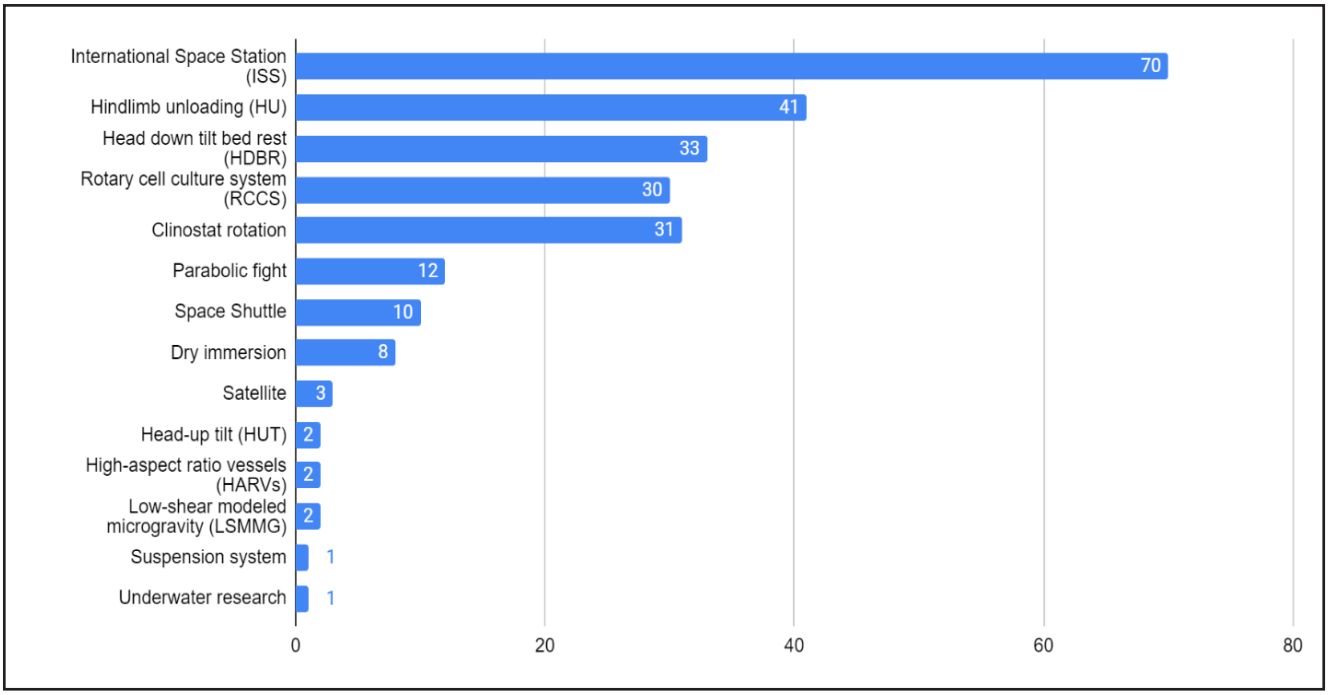
4.2 Simulated microgravity methodologies and health researched areas

Over the last few decades, several methods to simulate microgravity have been developed, according to the possibilities and needs of each test. According to Morey-Holton and Globus (2022), these are the steps followed to establish a way of simulating microgravity:

> The process includes 1) defining the physiological response(s) to weightlessness that the model is intended to mimic, 2) designing and developing the system to study those aspects, 3) collecting and analyzing data from the model, 4) comparing the data with spaceflight studies, 5) defining those aspects of spaceflight that the model most closely mimics, and 6) defining limitations of the model (Morey-Holton; Globus, 2002, p. 1368).

The following methods stood out as the most used for health research in microgravity: aboard the ISS, hindlimb unloading (HU), head down tilt bed rest (HDBR), rotary cell culture system (RCCS), and clinostat rotation. The proportion by all identified methods can be seen in Image 5.

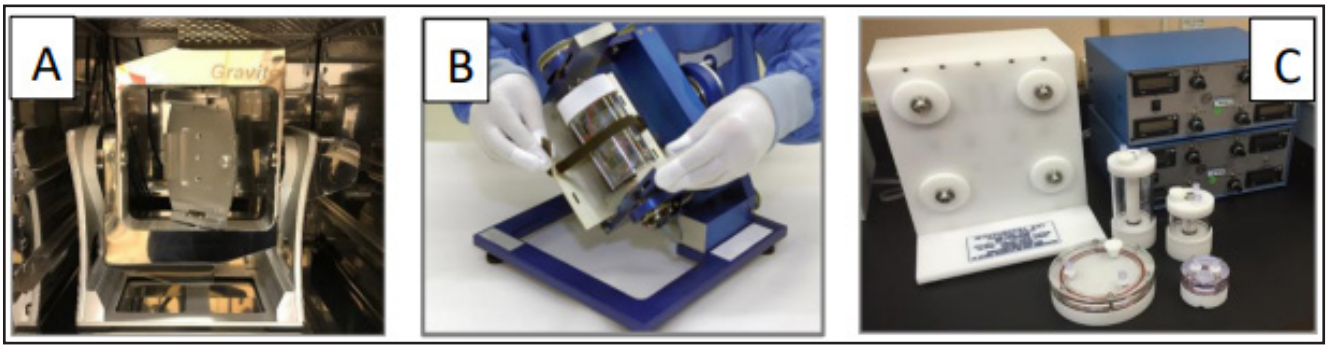
Image 5 - Identified microgravity methodologies



Source: Organized by the authors (2022).

A Clinostat is an experimental instrument used to simulate microgravity or to remove the effect of gravity, existing three types: 1D, 2D, and 3D, which is also called a Random Positioning Machine (RPM) (Oluwafemi; Fatoki; Ibraheem, 2020). Other studies used the rotary cell culture system. The rotational motion of this system prevents sedimentation by randomization of the gravity vector, creating an optimized suspension culture capable of supporting 3-D cell growth on microcarrier bead scaffolds (Riwaldt et al., 2015 as *cited in* Xu *et al.*, 2018). These types of equipment were widely used, by the results of this study, in cancer cells and immune system research. Image 6 illustrates the equipment described.

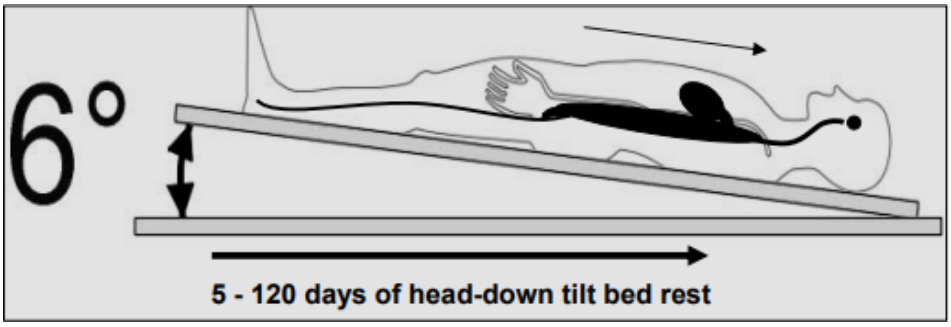
Image 6 - 3D clinostat (a), Random Positioning Machine (b), and rotary cell culture system (c) units.



Source: Richards *et al.*, 2021

Head-down tilt bed simulates the effects on humans of microgravity, such as cranial volume shift and physical deconditioning, being one of the wellestablished analog and groundbased model for simulating the microgravity of space (Anasuya; Deepak; Jaryal, 2021; Orter *et al.*, 2021), as illustrated in Image 7. Recent studies were found to be focused on head-down bed rest of different durations for exploring the headward fluid shifts and the cardiovascular adaptations akin to those found in spaceflight and microgravity (Hargens; Vico, 2016). In this research, this methodology was widely used to study musculoskeletal health, circadian cycle, and cardiac health.

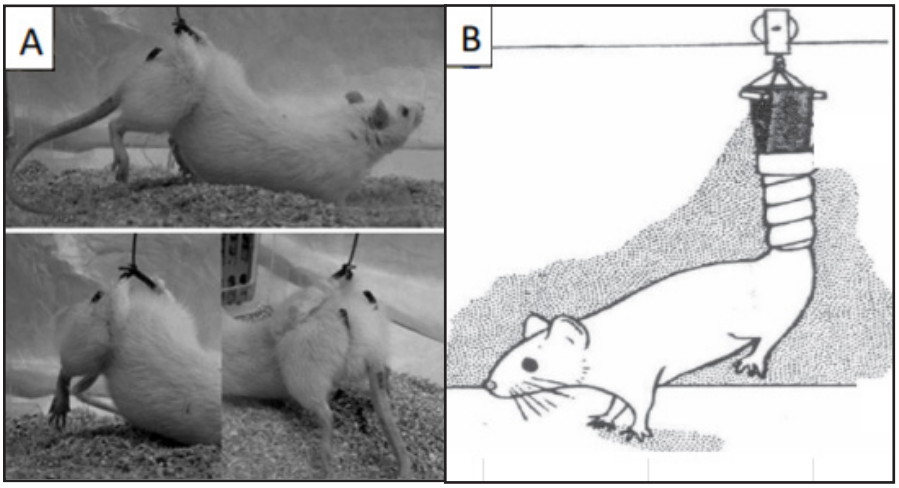
Image 7 - The minus 6 Head-down tilt bed rest model.



Source: Blottner *et al.*, 2006.

As the second most used method in the searches found is hindlimb unloading. In HU, individual mice are suspended by the tail at, usually, 15 or 30-degree head-down tilt with no load bearing on the hindlimb (Zhou et al., 2012). The HU technique has been approved by the NASA ARC Animal Care and Use Committee as a rat model for simulating spaceflight, based on data showing that indicators of stress in hindlimb-unloaded animals are not markedly different from those in control animals (Morey-Holton; Globus, 2022). Image 8 demonstrates two forms of research with HU. Among the areas studied with this technique are cognitive function, gene expression, intestinal flora, and liver metabolism.

Image 8 - Pelvic hindlimb suspension technique (a) and rat's tail suspension model of hindlimb unloading (b).



Source: Chowdhury *et al.*, 2013 (left) and Barbosa *et al.*, 2011 (right).

As the last research methodology in microgravity presented, there is the research carried out on board the ISS. NASA's research activities on the ISS span several scientific fields, including exploration technology development, microgravity research in the physical and biological sciences, human research for exploration, Earth science and education (Evans; Robinson; Tate-Brown, 2009). Image 9 illustrates a non-invasive fundus retinal photography being performed on the ISS, as part of research on anemia monitoring during long-duration spaceflight.

Image 9 - Non-invasive fundus retinal photography onboard the ISS.

Source: Waisberg *et al.*, 2022.

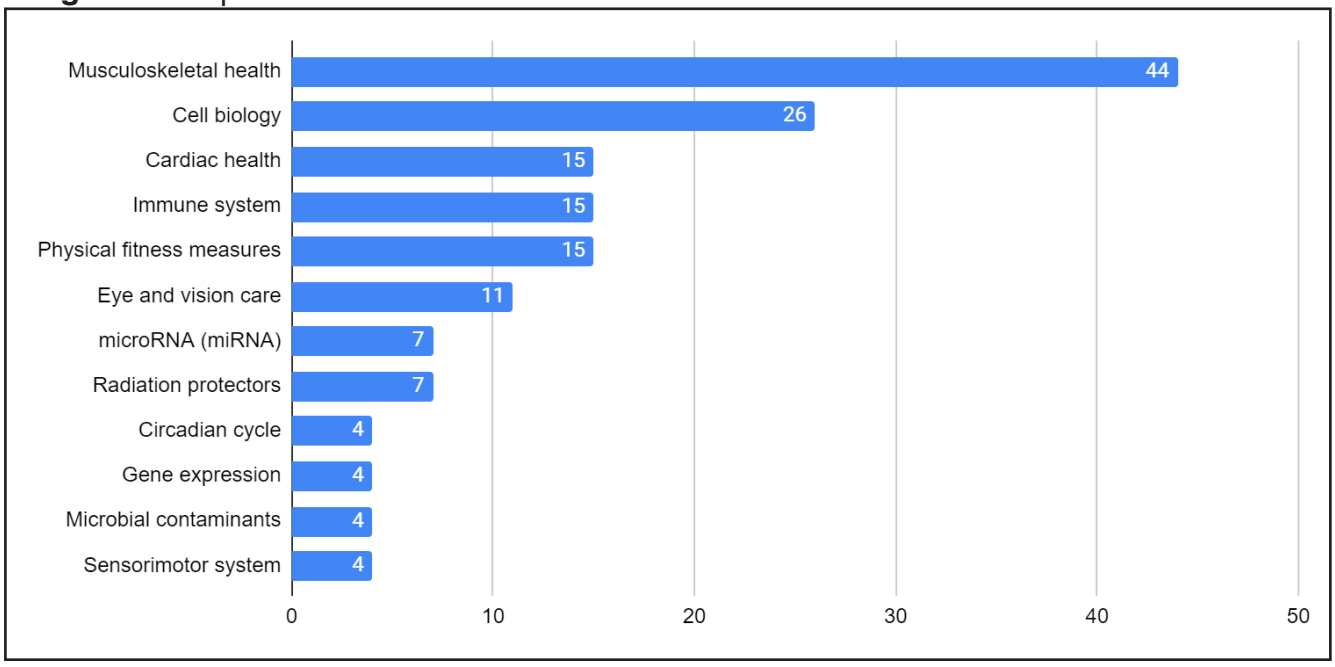
As NASA's first human mission to the vicinity of Mars is expected for the mid-2030s, and a human landing on the Martian surface is anticipated for the 2040s (Axpe *et al.*, 2020), researchers are focusing on understanding the pathological causes of bone loss in a space environment, including microgravity (Zhang *et al.*, 2018). The loss of bone mass and alteration in bone physiology during space flight are one of the major health risks for astronauts (Shanmugarajan *et al.*, 2017), and the aim to reduce the risks in this area was evidenced by the results of this research since musculoskeletal health was the most searched topic in the last 5 years.

The second major focus of research found is cell biology. These studies are focused on different types of cells, such as cell-free DNA, embryonic stem cells, endometrial stromal cells, endothelial cells, epidermal stem cells and cancer cells. In these studies, the concern is not only with life in space but also with the quality

of life on Earth. Like the experiment by Schulz *et al.*, (2022) which by observing cancer cells in parabolic flights, sought to observe the alternating gravitational stimulus and place them in context with carcinogenesis and cancer progression to finally obtain new and rapid biomarkers that alter expression for the diagnosis of prostate cancer.

As for the other most researched health areas, the results of the 12 most relevant were summarized in Image 10.

Image 10 - Proportion of most studied health areas.



Source: Organized by the authors (2022).

The next section will analyze the word cloud created using the study keywords.

4.3 Keywords word cloud

As a visual way of summarizing the search results, the word cloud made by analyzing the frequency of each keyword was done by the website https://www.wordclouds.com/. The result reveals words like *"simulated microgravity"*, *"spaceflight"* and *"space"* among the main ones. This suggests a good alignment between each objective of this study and the search methodology used.

As seen in Image 11, other words with high frequency, such as *"hindlimb unloading"* and *"bed rest"*, highlight some of the main methodologies of microgravity study identified. Finally, terms such as *"atrophy"*, *"muscle"*, *"bone"* and *"cells"* refer to the areas of health obtained as the most studied in the last 5 years with microgravity methodologies, that is, musculoskeletal health and cell biology.

Image 11 - Keywords word cloud.

Source: WordClouds website - https://www.wordclouds.com/

5 RELEVANCE AND LIMITATIONS

Research under the conditions of microgravity during space missions has contributed greatly to our knowledge of the impact of gravity on biological processes, gravity sensing mechanisms, and gravity-mediated orientation of organisms in their spatial environment (Herranz *et al.*, 2013). In the current scenario of planning long missions in space, it is essential to understand the effects of microgravity on human metabolism. At the same time, research in this area helps in innovations for treatments on Earth.

Through this research, those interested in the topic can have a first contact or deepen and update their knowledge, in addition to using the open results to carry out other in-depth studies through a systematic literature review. Its limitations are the use of only 3 databases, with open access articles, and only results in the English language. For future research, it is suggested the analysis by country or laboratory that performed the research, analysis of the quality of articles, analysis by author and by citation relevance.

6 CONCLUSIONS

In recent years, the endeavor to understand the implications of microgravity on health has seen a significant upsurge, as evidenced by the systematic literature

mapping undertaken in this study. Spanning the last five years, this mapping has provided a panoramic view of the developments in the field, pinpointing journals and regions that are at the forefront of these research efforts. Notably, NPJ Microgravity emerged as a prominent publication outlet, with the United Kingdom leading the charge in terms of countries of origin. This underscores the global interest and the collaborative efforts in place to unravel the mysteries of microgravity and its impact on health.

The trajectory of research in this area has been on a consistent incline. This surge is indicative of the growing recognition of the importance of microgravity research, especially in the health domain. The methodologies adopted to simulate and study microgravity conditions vary, yet some approaches clearly dominate. Among them, research conducted onboard the International Space Station (ISS) is of paramount importance. Concurrently, on Earth, hindlimb unloading has emerged as a pivotal technique to simulate these conditions, further broadening the scope of studies and insights that can be garnered.

Diving deeper into the specific health sectors that are the focal points of these microgravity studies, two areas stand out: musculoskeletal health and cell biology. The preponderance of research in these domains underscores their criticality. The musculoskeletal system's response to microgravity conditions, for instance, can offer insights into potential health risks for astronauts during prolonged space missions. Similarly, understanding cellular behaviors and changes in a microgravity environment can pave the way for breakthroughs in therapeutic interventions and drug development. In conclusion, as we continue to push the boundaries of space exploration, it becomes imperative to deepen our understanding of microgravity's effects. As the academic community continues to delve into these areas, the synthesized knowledge promises to augment our comprehension of life in space and potentially revolutionize health strategies for future space missions.

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Contribuições dos autores:

Marcelo Kratz Mendes foi responsável pela conceituação, metodologia, curadoria de dados, administração do projeto, supervisão, além de escrever o rascunho original, revisar e editar o trabalho. Roger de Bem Jarger contribuiu na conceituação, desenvolveu a metodologia, analisou os dados e participou na escrita, revisão e edição da versão final do artigo.

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