Article

The Effects of Ketogenic Diet on the Immune System: A Meta-Analysis

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Abstract: Healthcare systems are mindful of the importance of proper diet and nutrition in reducing the risk of various chronic diseases resulting in hospitalizations. In this regard, they are focusing on promoting the intake of foods comprising various diets with health benefits, such as the ketogenic diet. In this meta-analysis, a total of 20 research studies on the effect of the ketogenic diet on the immune system were analyzed. The research studies were obtained from three databases: Google Scholar, PubMed, and Science Direct. From the meta-analysis, the odd ratio of a similar outcome of an improvement in the strength of immunity between the intervention and control group was 0.76. On the other hand, the p-value for the studies was 0.09, with 15 out of the 20 being considered statistically significant. The heterogeneity between the studies was $I^2 = 15\%$, signifying a low variability in the findings that is not by chance. The Ketogenic diet indeed has positive effects on immunity. Nonetheless, it can also result in negative effects that may harm human health.

Keywords: Ketogenic diet; obesity; overweight; metabolism; energy low carb foods

1. Introduction

Many healthcare systems are recently focusing on promoting healthy and balanced diets among populations to decrease their risk of experiencing chronic non-communicable diseases. By promoting the consumption of foods that are rich in a wide range of nutrients, healthcare systems have decreased the risk of populations getting ill, thereby decreasing the costs incurred due to the provision of patient care services to manage diseases such as diabetes, cancer, and heart conditions among others [1], [2], [4], [21]. However, to achieve such a goal, healthcare systems must illustrate the effectiveness of various diets and nutritional intakes in contributing towards an improved human immune system. The ketogenic diet [17], which comprises foods such as cheese, fish, sea foods, poultry, and eggs, among others, is one such diet that has been considered to be necessary for the immune system since it results in low carbohydrates absorption by the human body and high saturated fats that can be metabolized into energy as shown in Figure 2 below [3], [5], [9]. Therefore, the purpose of the current meta-analysis study is to determine whether an intake of a ketogenic diet can improve the human immune system after a while by reducing the risk of various chronic and acute illnesses. The primary assessment of the research studies used in this meta-analysis revealed two main findings on the topic of interest that has been aforementioned. One of such findings was that the ketogenic diet improved the immune system since it is effective in decreasing the risk of uncontrolled epilepsy and various forms of cancer [1], [12], [13], [14], [15], [10], [18], [21]. Another finding is that the ketogenic diet may also negatively affect the immune system characterized by its high-fat content, especially unsaturated fat, which may result in a high risk of cardiovascular diseases [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [22]. Therefore, a controversial hypothesis

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on the topic is that the ketogenic diet is recommendable for the obese and overweight population due to its effectiveness in promoting weight loss [4], [8], [9]. However, a diverging hypothesis is that such a diet can lead to low energy levels in individuals because it requires the intake of low-carbohydrate foods, which makes it a less healthy strategy for promoting weight loss [4], [6], [13]. In this manner, this study will be significant in reducing hospitalization rates by promoting the making of informed nutritional decisions to populations especially older adults, due to their risk of developing specific diseases that can best be managed through an intake of a ketogenic diet. To achieve its purpose and significance, this study will entail an analysis of the findings of various research studies on the topic of *'the effects of the ketogenic diet on the immune system.'* It will also focus on determining the truth or falsity behind the hypothesis ketogenic diet is associated with positive effects on the human immune system taking into account the data and findings of studies related to that topic of interest. The main reason why it is an appropriate time to conduct the current meta-analysis is that there are increasing rates of overweight and obesity in diverse populations that can best be managed through education on the importance of the ketogenic diet. The other reason why it is an appropriate time to conduct the current study is because of the reluctance that many populations have towards healthy eating habits and proper nutrition [12], [15], [19], [20], [21], [22]. Healthy eating habits and proper nutrition can contribute towards an increase in quality of life and decreased rates of hospitalization, thus implying that the current study can be for decision-making processes on achieving such goals by diverse individuals and stakeholders within the medical health and nutritional sciences [16], [20]. Since the ketogenic diet decreases the risk of developing conditions such as cancer and diabetes by hastening the metabolism of consumed saturated fats into energy, it is associated with positive implications on the human immune system.

2. Materials and Methods

Search Strategy and Selection Criteria

In this research study, the focus of the researchers was to undertake an analysis of the results of a significant number of scientific research studies that had been undertaken on the topic of interest. The researchers were cognizant that the research studies were addressing a similar research question and that each study reported measurements that were expected to have a specific degree of error that did not necessarily affect the accuracy and credibility of the findings. The systematic assessment of the results of the chosen studies used for the current research aimed at deriving conclusions about the body of knowledge of consumption of the ketogenic diet on the human immune system. Therefore, the current research is only a meta-analysis since it only provides an overall statistical summary estimate from the available data on the topic of interest.

The data sources which were assessed were all health research studies that were obtained from various databases. Three main databases were used to search for such research studies. They include Google Scholar, PubMed, and Science Direct, as shown in chart 1 below. On the other hand, the exact date cut-offs for the search of the research studies from the three databases were between December 1, 2017, and December 1, 2022. The terms that were used for searching Google Scholar database for the research studies used in the current meta-analysis include '*ketogenic diet*,' '*weight loss and ketogenic diet*,' '*immune system and the ketogenic diet*,' '*ketogenic food benefits*,' '*low carb diet*' and '*low carb diet and immune system*.' In this manner, it was possible to identify a significant number of credible research studies which were essential in achieving the objectives of the current study.

To strengthen the researchers' understanding of the topic of interest to the current study, it was necessary to undertake thorough research by assessing specific grey literatures. Some grey literature sources assessed include blogs, podcasts, and YouTube videos on the ketogenic diet and its influence on the human immune system. However, the findings of such sources were not included in the current meta-analysis because they were

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non-peer-reviewed in nature. However, trial registries were not searched, and data was not obtained from unpublished research studies. To achieve the accuracy of the findings of the current meta-analysis study, only individual patient-level data were obtained from the included research studies. The literature search and data extraction processes were conducted by the researchers of this meta-analysis, who also double as its authors and have been mentioned above. Nevertheless, in case of conflicts among the researchers that arose over the inclusion of the research studies, two independent third parties acting as reviewers of the study made decisions on the studies with a conflict of interest. The inclusion criteria of the meta-analysis involved peer-reviewed research articles published in English during the last five years relevant to the topic of the ketogenic diet and improved immune system. Lastly, this meta-analysis does not have an online link for its study protocol.

Data Analysis

To achieve the accuracy of the data analysis process, it was necessary to undertake data extraction and appropriately deal with duplicate data. A logical method of data extraction was undertaken in that data was extracted from the source system, which was the databases. Specifically, full data extraction was undertaken in which the researchers obtained all relevant data related to the research topic from a single study before extracting more data from other studies. On the other hand, the researchers identified the level of the match of the data in each research study based on their research questions or hypotheses. After that, they excluded studies with a high level of similarity in their data and findings on the topic of interest. In this manner, it was possible to effectively deal with duplicate data which may have negatively affected the findings of the current meta-analysis.

The meta-analysis was conducted to obtain specific primary and secondary outcomes based on the data obtained from the included research studies. The primary outcome of the meta-analysis was the level of immunity attributed to the consumption of a ketogenic diet. The measure of effect used was odds ratio (OR) at a 95% Confidence Interval (CI). The OR was used due to the need to determine the odds of improved immunity by an intervention group consuming a ketogenic diet when compared with a control group consuming a non-ketogenic diet. The preplanned secondary outcomes include an improved innate immune system and a strong adaptive immune system. Lastly, no adverse event assessments were conducted in the current meta-analysis. Consequently, the researchers experienced a less complex data extraction and analysis process.

It was also necessary to undertake a risk of bias assessment after the identification of the research studies that met the aforementioned inclusion criteria for the current meta-analysis. The assessment of the risk of bias for the included studies was undertaken using the John Hopkins Nursing Evidence-Based Practice (JHNEBP) evidence level and quality guide toolkit. It was necessary to first identify the quality of evidence of the research studies using the such toolkit and categorize them as having high, good, or low-quality evidence. After that, studies with a low quality of evidence were considered to be having a high risk of bias, those with a good quality of evidence were considered to be having a moderate risk of bias, while those with a high quality of evidence were regarded to be having a low risk of bias. Finally, due to the numerical nature of the data collected from the research studies, sensitivity analyses were undertaken after excluding studies at high risk of bias. In this regard, it was possible to determine the influence that a change in the various variables of the studies had on each other.

Data from the research studies were extracted from a wide range of variables related to the topic of interest. Such variables include the weight of the participants, the strength of the participants' immune systems, and the daily carbohydrate intake of the participants. However, since the level of data that was sought by the researchers was individual-patient level data and not summary estimates, no summary measures were used for the current meta-analysis study. Heterogeneity was used to establish the variability between

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the included research studies. It involved assessing the inconsistency between the findings of the studies and describing it as a percentage of the variation across such studies that do not result from chance. The percentage was then noted as an I^2 statistic and served as a measure of the extent to which the findings of the research studies included in this meta-analysis differed. The studies were combined based on the similarity of their research questions or hypotheses. Research studies whose research questions or hypotheses appeared to have a high level of similarities were considered to be having almost similar data findings. On the other hand, a fixed-effects model was used for the current study and involved assessing the differences in the studies' methodologies during the data analysis and extraction process. The analysis of the data obtained from the studies was undertaken using Statistical Package for Social Sciences (SPSS) with version number 1.0.0.1406. Lastly, since the study protocol of the current meta-analysis is not yet available online, it lacks a study registry number and name.

Role of the Funding Source

The financial cost of conducting the current meta-analysis study was fully settled by its researchers, who are also its authors. In essence, no funder had a role in providing financial assistance for the completion of any activity of this study, such as study design, data collection, analysis and interpretation, and the report writing process. Resultantly, this meta-analysis study did not have a funding source.

3. Results

For the current meta-analysis, a total of 120 research articles were identified by searching the three aforementioned databases. However, a total of 10 additional research articles were also identified through other sources distinct from the above-stated grey literature sources. After removing duplicated and irrelevant research articles based on the inclusion criteria, a total of 80 research articles on the topic of interest were left and screened for relevance based on their title and abstracts. The researchers further excluded 58 research articles for their lack of full texts or institutional access requirements, implying that only 22 full-text research articles were assessed. Lastly, two full-text articles were further excluded since they did not use randomized controlled trials. Resultantly, the current meta-analysis includes a total of 20 research articles. Consider the study selection figure following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines in Chart 2 in the Appendix below.

Various criteria were considered for the 20 research articles to be included; the inclusion of the relevant research studies was considered. Firstly, only studies that had been undertaken between December 1, 2017, and December 1, 2022, were used for the meta-analysis. Secondly, the chosen studies were only published in English language only. Thirdly, the research studies which were used in the current meta-analysis were focused on populations that were obese or overweight and were intending to use dietary restrictions as a strategy for achieving weight loss. Finally, all the studies used in the current meta-analysis used randomized controlled trials to achieve their study aims and objectives. In this regard, the accuracy of the research studies was guaranteed due to the randomized sampling process of participants.

The included research studies had different characteristics that were assessed by the researchers of this study to determine their effectiveness in achieving their goals and objectives. Firstly, all the research studies used a randomized controlled trial design which implies that their samples of participants were randomly selected. In this regard, none of the research studies were at risk of experiencing sampling bias that would have negatively affected the accuracy and relevancy of their findings. Secondly, the research studies were either population cohort or retrospective studies. In essence, they were either focused on a single population to assess a specific exposure (intake of ketogenic diet) and outcome (increased or decreased strength of immune system) or a group of individuals with specifically distinct characteristics (such as obese, overweight, and normal weight

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individuals) but have a similar characteristic (intake of ketogenic diet). Lastly, all the studies used adult populations for their research process, as illustrated by the distinct age groups for each of them shown in Table 1 below. Due to the similarities in such characteristics, the research studies used in the current meta-analysis study were considered appropriate and relevant for achieving its objectives.

Table 1. Main Characteristics of the Studies Used in the Meta-Analysis.

	Main Characteristics	
Research Studies	**Nature of study**	**Age Groups of Samples of Participants**
Alsharairi et al., 2022	Population Cohort	18-67
Chyra et al., 2021	Retrospective Cohort	18-45
Ellerbroek et al., 2018	Retrospective Cohort	19-50
Falsaperla et al., 2020	Retrospective Cohort	20-55
Fan et al., 2019	Retrospective Cohort	21-87
Ferrere et al., 2021	Population Cohort	18-80
Gangitano et al., 2021	Population Cohort	20-67
Goldberg et al., 2020	Retrospective Cohort	25-80
Kamepalli et al., 2020	Retrospective Cohort	18-66
Kong et al., 2021	Population Cohort	19-65
Licha et al., 2019	Population Cohort	20-65
Murakami et al., 2022	Population Cohort	20-70
Paoli et al., 2020	Population Cohort	20-80
Pardo, 2020	Population Cohort	18-55
Polito et al., 2021	Population Cohort	18-65
Shaw et al., 2021	Population Cohort	21-75
Valente et al., 2022	Retrospective Cohort	21-70
Weber et al., 2021	Retrospective Cohort	25-75
Wright and Simone, 2019	Retrospective Cohort	18-50
Yang et al., 2022	Population Cohort	19-45

Assessing the heterogeneity and risk of bias of the studies used in the current meta-analysis was significant in obtaining accurate and relevant findings on the topic of interest. The heterogeneity score, I^2 of the studies, was 15% which implied a lower level of variability that was not due to chance in their findings and statistical estimates. In this manner, many of the studies used had similar findings on the research topic of interest based on their research questions and hypotheses. From the risk of bias assessment of the studies that were used, 17 research studies were established to have a high quality of evidence, one was established to be having a good quality of evidence, and two had a low quality of evidence based on the JHNEBP toolkit. For that reason, the 17 research articles with high-quality evidence had a low risk of bias. In contrast, the one research study with a good quality of evidence had a moderate risk of bias, as shown in Table 2 below. The two research studies with a piece of low-quality evidence had a high risk of bias. Since many of the studies used in this meta-analysis had a hh quality evidence, its findings on the research topic of interest were considered highly accurate and credible.

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Table 2. Risk of Bias Assessment of the Studies.

Research Studies	Main Characteristics	
	Level of Evidence According to the JHNEBP toolkit	Risk of Bias
Alsharairi et al., 2022	High	Low
Chyra et al., 2021	High	Low
Ellerbroek et al., 2018	High	Low
Falsaperla et al., 2020	High	Low
Fan et al., 2019	High	Low
Ferrere et al., 2021	High	Low
Gangitano et al., 2021	Good	Moderate
Goldberg et al., 2020	High	Low
Kamepalli et al., 2020	High	Low
Kong et al., 2021	High	Low
Licha et al., 2019	Low	High
Murakami et al., 2022	High	Low
Paoli et al., 2020	High	Low
Pardo, 2020	High	Low
Polito et al., 2021	High	Low
Shaw et al., 2021	High	Low
Valente et al., 2022	Low	High
Weber et al., 2021	High	Low
Wright and Simone, 2019	High	Low
Yang et al., 2022	High	Low

The statistical analysis of the quantitative data collected from the research studies used in this meta-analysis established various aspects of their outcome measures. Consider Figure 1, shown in the Appendix section below, which illustrates a forest plot for the meta-analysis of the included research studies. The odds ratio (OR) for the research studies was 0.76, with 17 out of the 20 having statistically significant ORs indicating a protective effect of the ketogenic diet on the human immune system. That is to say, the meta-analysis revealed reduced odds of the exposure (intake of ketogenic diet) having a similar outcome (improved immune system) on both the intervention and the control groups of the research studies. Consequently, the studies suggest that there is potential for an increase in the strength of the intervention groups' immune systems due to the intake of the ketogenic diet, unlike the control group. Finally, the average p-value of the research articles was $p = 0.09$, with 15 out of the 20 studies being considered as statistically significant in that that they had p values less than 0.05 at 95% CI [1], [2], [3], [4], [10], [11], [12], [13], [14], [15], [16], [19], [20], [21], [22]. For that reason, more than half of the research studies used in the current meta-analysis failed to reject their null hypotheses that the ketogenic diet had a positive effect on the human immune system.

4. Discussion

The research studies included in this meta-analysis each had several valid and credible findings on the effects of the ketogenic diet on the immune system. Since many people are focused on the strengths of their immune systems characterized by decreased risk of sickness and quick healing of wounds, the current study is significant in making healthcare decisions related to individual diet intakes [1], [2], [3], [4], [5], [6], [7], [8], [9], [10], [11]. From an analysis of the findings of the research studies, it was established that the ketogenic diet involves eating foods that have high fat but low carbohydrate content. By doing so, the body can easily break down the fats into ketones which are then used for energy generation, thereby promoting a fastened weight loss process [1], [2], [3], [4], [5], [6], [7], [8], [9], [10], [11]. In this regard, the researchers of the studies that were analyzed

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consider such diet to be mainly effective for individuals who are obese or overweight in nature.

Since individuals who are obese or overweight are at high risk of developing various chronic diseases such as cancer and diabetes, the researchers aimed to determine how their intake of the ketogenic diet can reduce their risk of such diseases. The intake of the ketogenic diet results in a high metabolism process within the body since the process of converting ketones to energy is faster when compared with that of converting glucose to energy [7], [8], [9], [10], [11]. In this regard, there is a low risk of increased adiposity, which in turn leads to a low risk of uncontrolled epilepsy and various forms of cancer, thereby justifying an improvement in the human immune system [7], [8], [9], [10], [11]. Even though the consumption of a ketogenic diet can result in a decreased risk of uncontrolled epilepsy and cancer, the researchers also established that it could lead to an increased risk of the development of heart diseases. That is because when unsaturated fats are consumed at high levels, they may block a person's blood vessels which may result in heart conditions such as myocardial infarction and high blood pressure [12], [13], [14], [15], [16]. Therefore, in such cases, a ketogenic diet would have negatively affected a person's immune system by becoming a precipitating factor in the development of such chronic illnesses.

Based on the above-stated research findings while undertaking the meta-analysis study, it was established that some of the researchers compared the ketogenic diet with other diets, such as the Mediterranean, Dukan, and Vegan diets, among others. From a comparison of such diets, the researchers established that various diets are more effective in improving the human immune system than the ketogenic diet [12], [13], [14], [15], [16]. That is because they mainly comprise a combination of foods such as vitamins and proteins, which are essential in the production of white blood cells, which boosts the immune system [12], [13], [14], [15], [16]. Since many foods with unsaturated fats, such as avocado, meat, and cheese, do not contribute positively towards increased white blood cells production, ketogenic foods were considered to be less effective in improving the human immune system by the researchers of the analyzed studies [14], [15], [16], [19], [20], [21], [22]. For that reason, the researchers suggested that there is a need to supplement ketogenic foods with foods from other diets to improve their effectiveness in decreasing the risk of various chronic diseases and enhancing the strength of the immune system.

The current meta-analysis was associated with two main limitations. One of them was that it included studies that used randomized controlled trials only for the collection of quantitative data on the topic of interest. In this regard, this meta-analysis may not capture the changing perceptions of specific stakeholders and interest groups within the health sciences and nutrition field on the topic of the ketogenic diet and its effects on the immune system. The other limitation of the study is that it used relatively few numbers of research articles to achieve its objectives, mainly because of the lack of access to full articles that required subscription or institutional access. For that reason, the study would have entailed more research articles had it received funding for accessing a wide range of databases and literature sources.

Two main strengths are attributed to the current meta-analysis. Firstly, this meta-analysis includes research studies published only in English. In this manner, it has an international significance in making decisions related to the intake of the ketogenic diet. Secondly, this meta-analysis includes research studies that were published within the last five years. Therefore, there is a high level of confidence in the relevancy of its findings based on the current nature of such studies. Nonetheless, the source of bias of one of the research studies that had a low level of evidence according to the JHNEBP toolkit was a publication bias in that the results that were published by the authors of such study contradicted the findings that had been made in favor of positive results by previous research studies on the topic of interest. Consequently, the fact that only one study that was included in the current meta-analysis had a high risk of bias justifies the fact that its findings are highly accurate and credible based on its purpose.

Meta-analyses often trigger controversies that may not necessarily be identified by the individual researchers of the studies they include. One of the controversies raised by

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the current study is whether the ketogenic diet mainly impacts the adaptive or innate human immune system both positively and negatively. The other controversy is the positive and negative effects of relying on a ketogenic diet for weight loss among obese and overweight individuals. However, despite such controversies, the current meta-analysis does not have any discrepancies with other systematic reviews or meta-analyses conducted previously and related to its topic of interest. Finally, from the controversies that have just been mentioned above, it is necessary that future meta-analysis research studies should focus on analyzing studies that have focused solely on the effect of a ketogenic diet on both the adaptive and innate human immune systems. Additionally, future meta-analyses should focus on the analysis of the findings of studies on the effects of the ketogenic diet in achieving weight loss among obese and overweight individuals. By focusing on such topics, such meta-analyses will enhance the significance of the findings of the current one in achieving improved health and nutritional decision-making processes among populations.

5. Conclusion

In conclusion, the fact that the ketogenic diet facilitates the metabolism process of consumed saturated fats into energy which in turn decreases the risk of chronic conditions such as cancer and diabetes, suggests that it has positive implications for the human immune system. However, to prove such a hypothesis, the current meta-analysis study involved researching research relevant to the topic of interest and synthesizing their findings. 20 relevant research articles were identified based on a specific inclusion criteria from three databases: Google Scholar, PubMed, and Science Direct. The research articles were either population or retrospective cohort studies and entailed a sample of participants who were adults. The JHNEBP was used to undertake a risk assessment of the studies, which revealed that 17 of them had a high quality of evidence, thus implying that many of the studies included in this meta-analysis had a low risk of bias. The meta-analysis revealed that the ketogenic diet is mainly effective for obese and overweight since it promotes weight reduction. Furthermore, such a diet can result in improved immunity since the conversion of ketones to energy is faster than that of carbohydrates to energy, thus implying that it can reduce the risk of cancer and uncontrolled epilepsy. Nevertheless, some researchers claim that it may also increase the risk of cardiovascular conditions such as hypertension and myocardial infarction. In this regard, to realize the effectiveness of such a diet in achieving proper health among populations, it should be supplemented with other diets, such as the Mediterranean and the Dukan diets.

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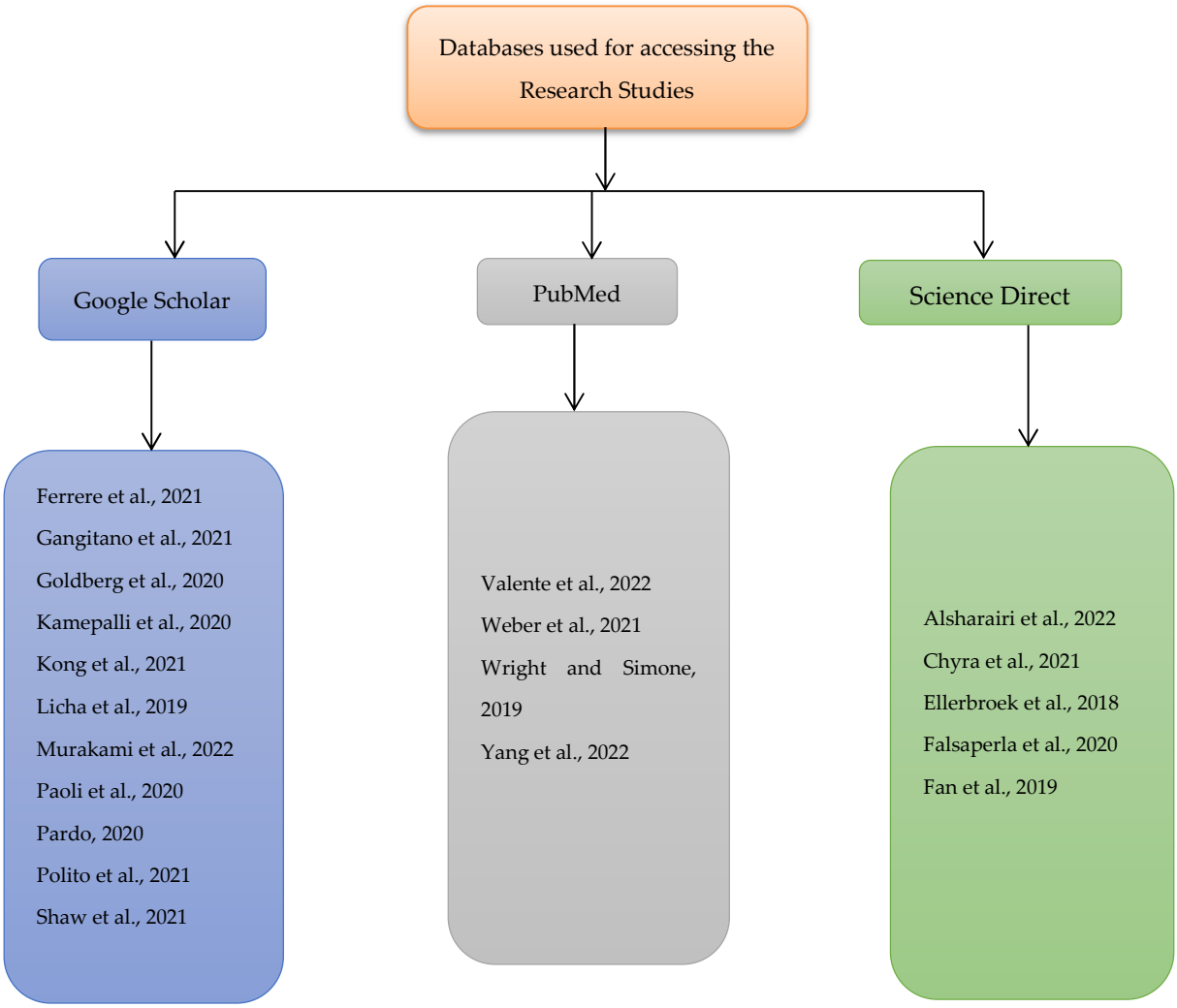
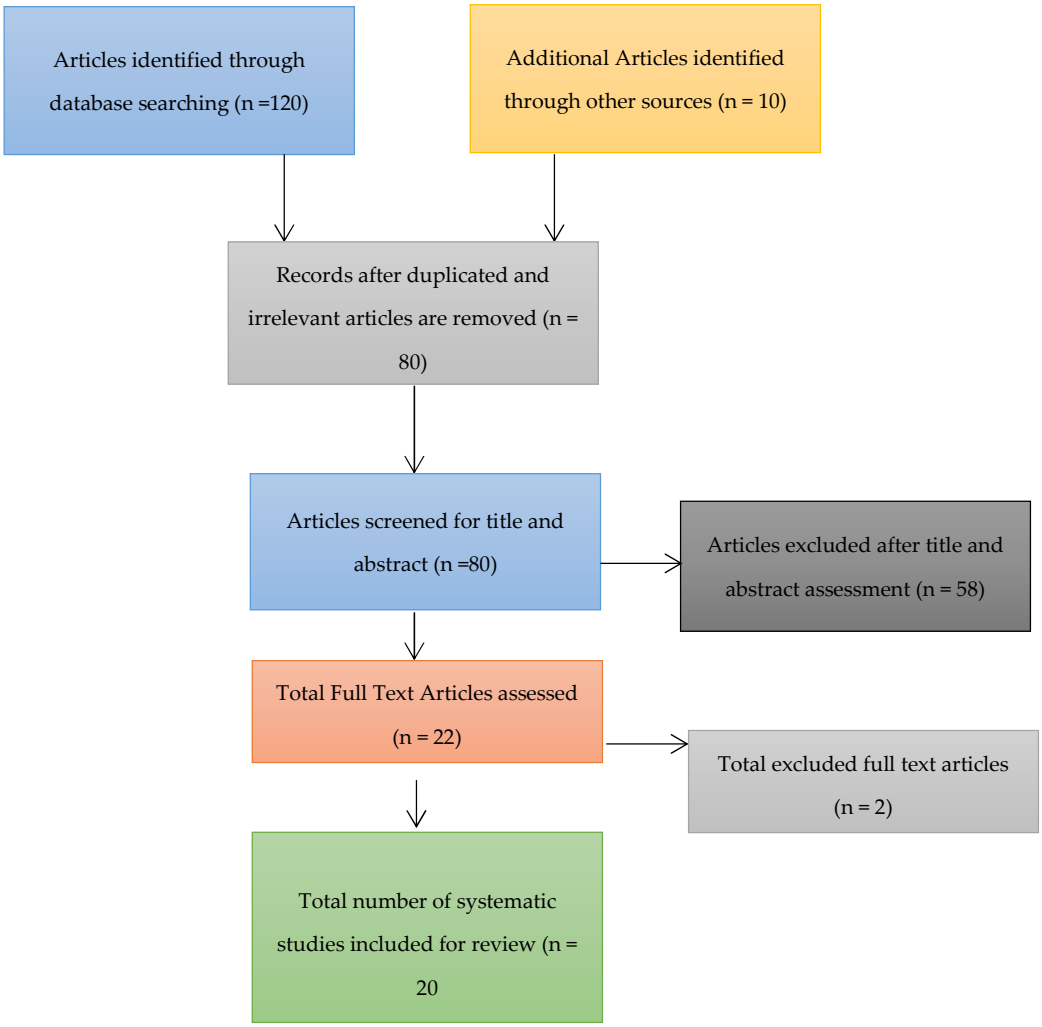
Appendix

Chart 1: Databases Used and their respective research studies



 doi:10.20944/preprints202212.0395.v1

Chart 2: The Study Selection Figure for the Meta-Analysis (PRISMA Flow Chart for the Meta-Analysis Study).



Excluded Research Articles and Reasons for their Exclusion

Rawat K, Singh N, Kumari P, Saha L. A review on preventive role of ketogenic diet (KD) in CNS disorders from the gut microbiota perspective. Reviews in the Neurosciences. 2021 Feb 1;32(2):143-57.

Reason for exclusion: *It did not use a randomized controlled trial.*

Fell B, Volek J, Kraemer W. The Potential Therapeutic Role of the Ketogenic Diet in Multiple Sclerosis.

Reason for exclusion: *It did not use a randomized controlled trial.*

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Figure 1: A Meta-analysis Forest Plot for the Included Studies

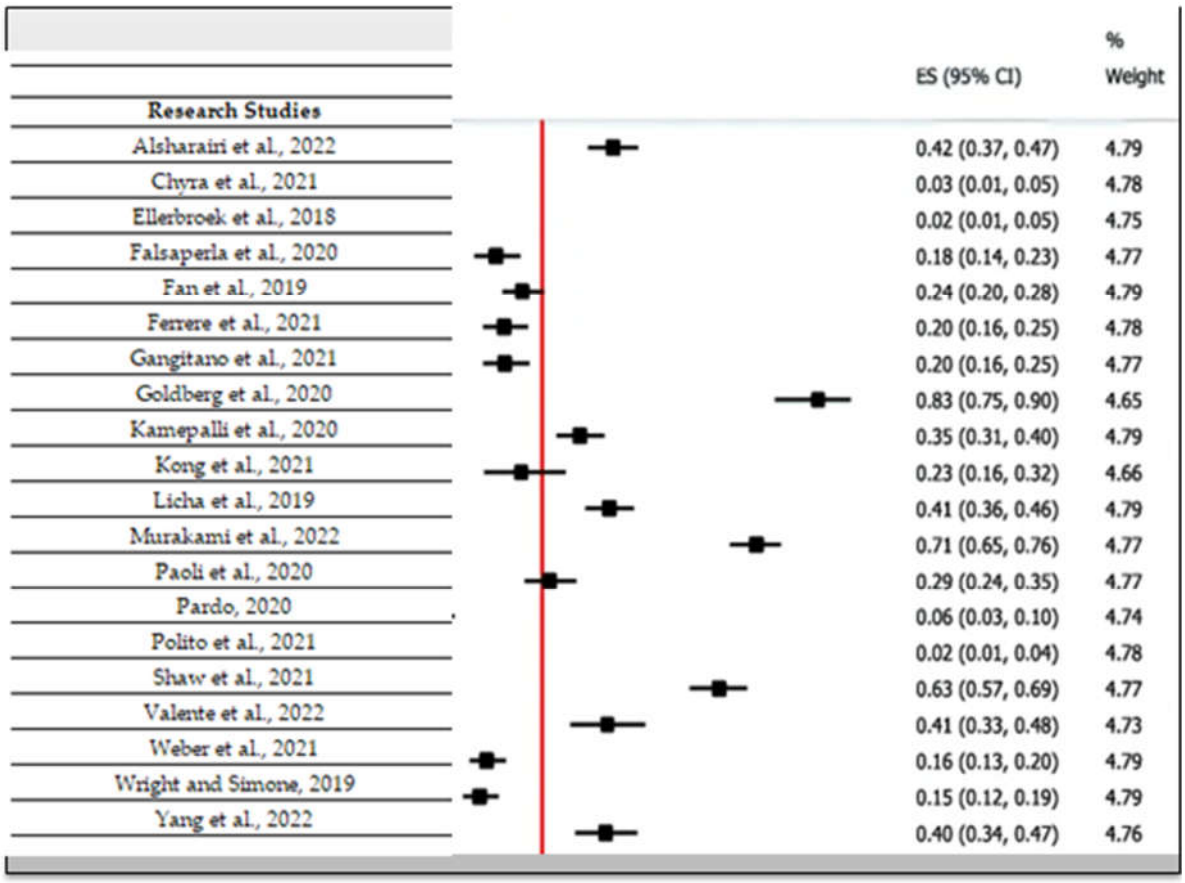

Figure 2: Composition of Ketogenic Diet