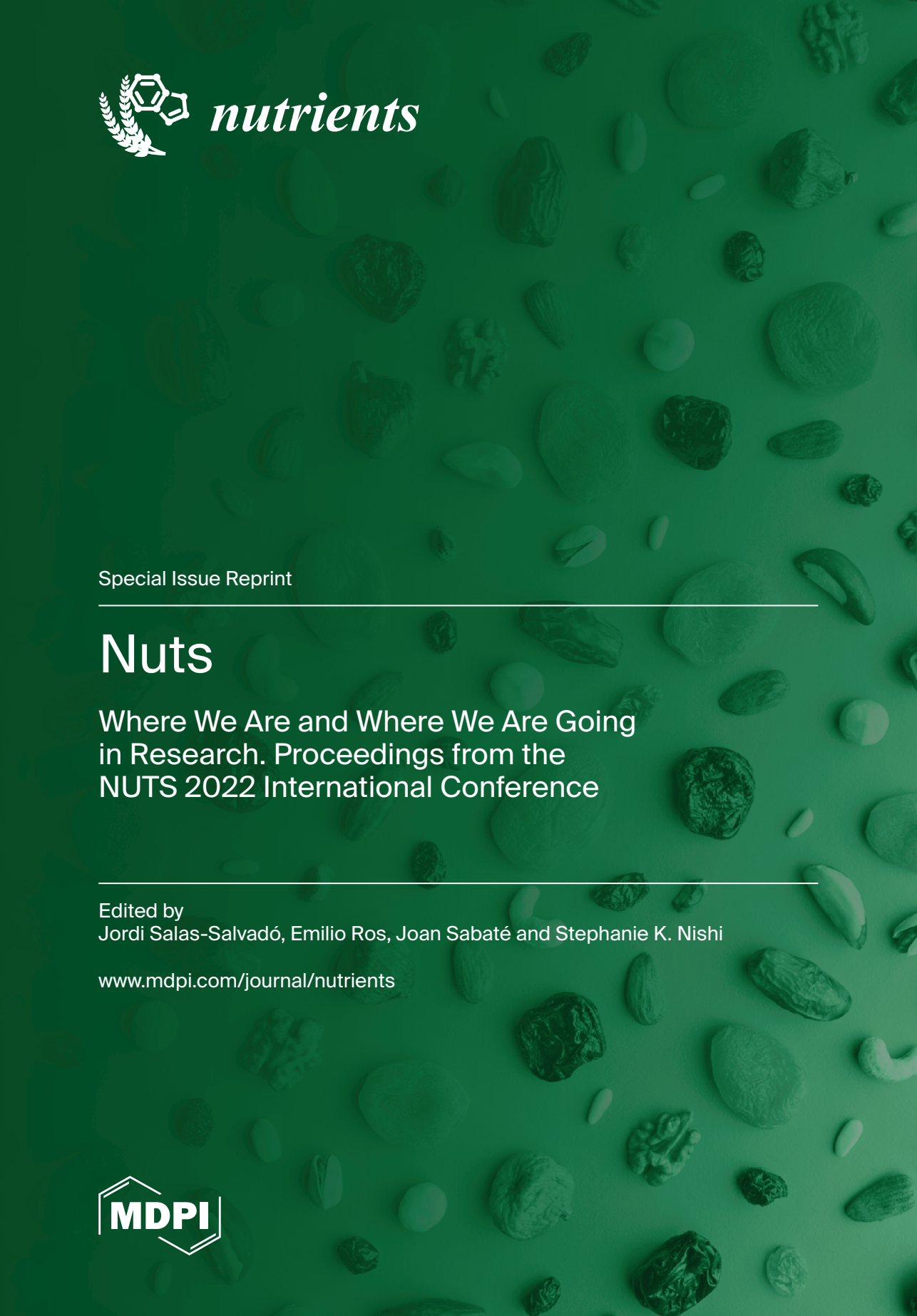

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Special Issue Reprint

Nuts

Where We Are and Where We Are Going in Research. Proceedings from the NUTS 2022 International Conference

Edited by
Jordi Salas-Salvadó, Emilio Ros, Joan Sabaté and Stephanie K. Nishi

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The International Nut and Dried Fruit Council

Contents

About the Editors

Jordi Salas-Salvadó

Jordi Salas-Salvadó MD, Ph.D., is a Distinguished Professor of Nutrition and ICREA Academia Researcher at Rovira i Virgili University; Director of the Food, Nutrition and Mental Health Research Group recognized by the Government of Catalonia; Principal Investigator of the CIBER Network Physiopathology of Obesity and Nutrition (CIBERobn) of the Carlos III Health Institute; Director of the Catalan Nutrition Centre of the Institute of Catalan Studies; Chairman of the Professorship Tree Nut World Forum for Nutrition Research and Dissemination; member of the Group of Experts of the Public Health Agency of Catalonia. Prof. Salas-Salvadó is an expert in clinical trials evaluating the effect of diets and dietary compounds on cardiometabolic health. He was a lead researcher of the PREDIMED study, a landmark trial evaluating the effect of the Mediterranean Diet on the primary prevention of cardiovascular diseases. He is currently the Director and Chair of the Steering Committee of the PREDIMED-Plus trial. He has published >700 scientific articles (h-index 81; >35,000 citations; 2018–2021 Clarivate Analytics "Highly Cited Researcher") and has received multiple awards and recognitions.

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Joan Sabaté

Joan Sabaté MD, Ph.D., is a Professor of Nutrition and Epidemiology at Loma Linda University School of Public Health and a board-certified physician in Internal Medicine. He was the principal investigator of a nutrition intervention trial that directly linked the consumption of walnuts to significant reductions in serum cholesterol, published in the New England Journal of Medicine in 1993. He is a co-investigator of Adventist Health Studies, the largest cohort of vegetarians relating dietary intake with health outcomes. For the past 25 years, he has been the principal investigator of many human nutrition intervention trials investigating the health effects of nuts, avocados, and other plant foods. Dr. Sabaté has authored >200 high-impact research articles (h-index of 65, >15,000 citations) and has contributed to public health, including being a member of the US 2020 Dietary Guidelines Advisory Committee. Dr. Sabaté directs the Environmental Nutrition research program at the Loma Linda University School of Public Health, which focuses on sustainable diets, explores the interrelationships between food choices' environmental and health impacts, and ultimately seeks to improve food systems' sustainability, health, and equity.

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Editorial

Where We Are and Where We Are Going in Nut Research

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Nuts have been part of the human diet for thousands of years [1]. Traditionally, nuts have been incorporated as an ingredient in many dishes, and over the years, nuts have been consumed in various forms from raw or minimally processed to more processed forms and eaten as snacks as well as included within recipes for main dishes.

In the last decades of the 20th century, the prevailing belief that dietary fat was harmful was at the basis of nuts being discouraged due to their high fat content. However, this perspective started to change following the first scientific studies demonstrating the potential health benefits of nut consumption. In 1992–1993, seminal publications from Loma Linda University showed that walnut consumption significantly reduced serum cholesterol [2] and that the frequency of nut consumption was inversely associated with coronary heart disease incidence according to data from the Adventist Health Study cohort [3]. Since then, many randomized clinical trials, epidemiological studies, and in vitro/in vivo mechanistic studies have explored and described the role of the consumption of different types of nuts on reduced incidence of cardiovascular disease and all-cause mortality, management of lipid disorders, and glycaemic control, without undue effects on body weight or overall adiposity, among other cardiometabolic and health-related risk factors and conditions [4]. More recently, several studies have examined the potential beneficial effects of nuts on the gastrointestinal system, cognitive performance, fertility, and different types of cancer, as well as the potential mechanisms implicated in the observed benefits. Importantly, landmark studies, such as the Adventist Health Study, the Nurses' Health Study, the Health Professionals Follow-up Study, the Physicians' Health Study, and the PREDIMED trial, have consistently reported that frequent nut consumption was associated with a lower risk of different cardiovascular outcomes [4] and all-cause mortality.

Based on the available scientific evidence, specific health claims have been accepted for nuts. Particularly, the Food and Drug Administration (FDA) has authorized qualified health claims for nuts in general and for walnuts and macadamias in particular concerning heart disease prevention when daily consuming one and one-half oz (42 g). However, the European Food Safety Authority (EFSA) has only agreed on a specific health claim for walnuts regarding beneficial effects on endothelial function. At the same time, nuts have been recommended over the last two decades by several health organizations and agencies worldwide.

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Due to the accumulating evidence on nut consumption and health outcomes, we thought it would be important to recapitulate and examine in detail what is well known and established, and what avenues of knowledge are still lacking in nut research. It is for this reason that we organized the NUTS 2022 Conference with the slogan: *Where we are and where we are going in nut research*.

The NUTS 2022 Conference offered the unique opportunity to bring together experts in the field of nut research from around the world with the following aims: (a) to summarize all the evidence related to the beneficial effects of nuts on health; (b) to identify new topics, needs, and opportunities in nut research; (c) to share knowledge with food industry and set new primary objectives for the future; and (d) to develop these scientific proceedings summarizing the current knowledge and new opportunities of research in the nut–health axis.

We believed it would be important and extremely useful to summarize and discuss future lines of nut research in the context of a multidisciplinary group of investigators with expertise in different fields for the benefit of: (1) the investigators, since it allows us to interact, share new ideas, and establish collaborations in the future; (2) the food industry, because they need to know that we know relatively little and that knowledge needs to be invested in; and (3) health agencies, because they need the most up-to-date knowledge to establish appropriate public health recommendations.

The NUTS 2022 Conference took place on 20–21 October 2022, and was organized in Reus by the University Rovira i Virgili together with Institut d'Investigació Sanitària Pere i Virgili (IISPV) and the Ciber Fisiopatología de la Obesidad y Nutrición (CIBEROBN) of Instituto de Salud Carlos III of Spain.

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Conflicts of Interest: J.S.-S. reports serving on the boards of the INC and receiving grant support from these entities through his institution. He has also received research funding (nuts for free to the PREDIMED participants) from the CWC; La Morella Nuts, Spain; and Borges SA, Spain. He has also received research funding (nuts for free to the PREDIMED-Plus participants) from the Almond Board of California, USA and Pistachio Growers of California, USA. He is a non-paid member of the Instituto Danone International and was a member of the executive committee of the Instituto Danone Spain. S.K.N. is a volunteer member of the not-for profit group Plant-Based Canada and has received a research grant from the INC (International Nut and Dried Fruit Council) through her institution. J.S. has received health research grant funding through his institution from several nut commodity boards. E.R. reports receiving grant support through his institution from the California Walnut Commission (Folsom, CA), in addition to personal funds for project supervision and advice, and serving as a non-paid member of its Scientific Advisory Committee; funds for travel and accommodation from the International Nut and Dried Fruit Council; and personal funds from Alexion for serving on the advisory committee.

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Review

Nuts, Energy Balance and Body Weight

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Abstract: Over several decades, the health benefits of consuming nuts have been investigated, resulting in a large body of evidence that nuts can reduce the risk of chronic diseases. The consumption of nuts, being a higher-fat plant food, is restricted by some in order to minimize weight gain. In this review, we discuss several factors related to energy intake from nuts, including food matrix and its impact on digestibility, and the role of nuts in regulating appetite. We review the data from randomized controlled trials and observational studies conducted to examine the relationship between nut intake and body weight or body mass index. Consistently, the evidence from RCTs and observational cohorts indicates that higher nut consumption does not cause greater weight gain; rather, nuts may be beneficial for weight control and prevention of long-term weight gain. Multiple mechanisms likely contribute to these findings, including aspects of nut composition which affect nutrient and energy availability as well as satiety signaling.

Keywords: energy; calories; mastication; appetite; food intake; body weight; obesity; nuts

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1. Introduction

Achieving and maintaining a healthy body weight is a difficult goal for many individuals. Obesity is a global health issue. According to the WHO [1], in 2016, almost 40% of the world's population were overweight and over 10% had obesity (among adults aged 18 years and older). Obesity is largely preventable, and at the simplest level, it is a matter of appropriate energy balance. To lose weight, energy intake must be less than energy expenditure, and to maintain weight, energy intake and expenditure must be equal. Within the constructs of this simple energy balance problem, there are many interdependent and complex factors that make body weight maintenance difficult. These factors include factors related to food and macronutrient composition, as well as the food matrix and energy availability. Appetite regulation is even more complex with a multitude of organ systems involved in making decisions multiple times, every day, about what to eat, when to eat, when to stop eating and how much to eat. Ultimately, interactions amongst food and its consumption determines energy intake.

In the early 1990s, research was beginning to show beneficial health effects associated with nut consumption [2]. With the emerging evidence, the 1995 Dietary Guidelines for Americans mentions including nuts in the diet but cautioned that foods, including nuts, high in fat should be used sparingly [3]. In the subsequent decades, much additional research has been conducted to better understand the health benefits of nuts, including the role nuts play in body weight maintenance. Herein, we review the state of the science in regard to how the food matrix of nuts effects energy availability, how nuts effect ingestive behavior and the literature on the relationship between nut intake and body weight maintenance.

2. Energy Availability

The plant cell wall significantly effects the bioavailability of energy and nutrients from nuts. Plant cell walls are complex extracellular matrices containing cellulose, hemicellulose, pectin and some proteins (usually enzymes that play a role in cell wall integrity). Lignin, which are polymers made of phenylpropanoid units, are additionally found in secondary cell walls [4]. Together, the cell wall components provide structural integrity for the plant, encapsulate the cell membrane to protect the individual cell and play a role in water and nutrient transport. Nutritionally, the plant cell wall is the source of dietary fiber which is resistant to mammalian digestive enzymes. Microbial anerobic fermentation or physical breakage of the plant cell wall is needed in order to release the cellular contents and make those contents available for absorption.

Among the first studies to report on the bioaccessibility of fat from nuts was a study of peanuts, peanut butter and peanut oil [5]. In this small study, subjects consumed each treatment, feces were collected and daily fecal fat excretion was determined. Consumption of peanuts resulted in increased fecal fat excretion compared to peanut butter and oil, and consumption of peanut butter resulted in increased excretion of fecal fat compared to peanut oil [5]. As seen in other studies, the absorption of lipids from oils is generally quite high in humans [6,7]. However, when the same fat is consumed in the plant matrix, bioaccessibility is decreased, resulting with increased fecal fat excretion.

2.1. Effect of Processing and Mastication on Almond Lipid Bioaccessibility

Microscopic analyses of nuts demonstrate that several factors contribute to breakage of the plant cell wall. Prior to that breakage, these microscopic analyses show that the lipid vacuoles remain intact, encased by the plant cell wall. Mastication is one factor which influences lipid bioaccessibility. In one study, subjects masticated and expectorated natural (unroasted) or roasted almonds [8]. Post-mastication, there were differences in the particle size distribution between the natural and roasted almonds, with larger particles (1700 to >3350 μm) being more prevalent in the natural almond samples and smaller particles (<1700 μm) being more prevalent in the roasted almond samples [8]. Lipid was identified on the surface of ruptured cells. In smaller particles (approximately 250 μm), free lipid was identified in all areas of the particles, not just the surface. In this study, roasting effected lipid bioaccessibility, which was greater in the roasted almonds compared to the natural almonds, and the higher lipid bioaccessibility was related to the increased proportion of smaller particles observed in the roasted almonds [8].

In a study of different forms of almonds (natural, roasted, roasted diced and almond butter (made from roasted almonds)), following simulated oral digestion, particle size distribution was similar for natural, roasted and chopped almonds (most particles having a size $\geq$1000 μm), whereas the particle size distribution of the almond butter resulted in mostly smaller particles (<850 μm) [9].

2.1.1. Effect of Roasting

Roasting changes the physical properties of almonds, and these changes contribute to the degree of cell ruptures. Using three-point bending to determine fracture force (N) at load failure, roasted almonds required less force for load failure than natural almonds [10]. The hardiness of roasted almonds, quantified by maximum force (N) required for failure during uniaxial compression, was also lower than natural almonds [10]. Upon fracture, 8-bit, binary digitized photos were used to quantify particle area and total number of fragments. The median particle area was smaller for roasted almonds compared to natural almonds, whereas there was a greater number of particles from roasted compared to natural almonds. The physical changes associated with roasting impact lipid bioaccessibility by increasing the ratio of surface area to volume and making more cellular contents available for digestion and absorption.

2.1.2. Effect of Mastication

Mastication is one of the physical processes which plays an important role in bioaccessibility of fat and energy. In a study of controlled mastication, subjects were provided 5 g of natural almonds and instructed to chew them for 10, 25 or 40 times and then expectorated [11]. The number of particles recovered was measured post-mastication, with more particles recovered after 10 chews compared to 25 or 40 chews [11]. Moreover, the mean particle size of the recovered particles was larger after 10 chews than 25 or 40 chews [11]. In a separate study with these subjects, they were allowed to chew the almonds and swallow after 10, 25 or 40 chews. Fecal samples were collected and fecal energy and fat were measured. Fecal energy and fat extraction were higher after 10 chews compared to 25 or 40 chews [11]. In this study, chewing almonds 10 times resulted in differences from chewing almonds for 25 or 40 times, but additional chewing of almonds beyond 25 times did not significantly change the particle size distribution, fecal energy or fat excretion.

2.1.3. Observations with Walnuts and Pistachios

Much of the research on the effects of processing and mastication has been conducted with almonds. One study [12] used walnuts (unsalted pieces) and pistachios (roasted) in addition to almonds (roasted and salted), and focused on in vitro gastrointestinal digestion. In undigested samples, walnuts had thinner cell walls compared to almonds and pistachios, whereas pistachios had smaller oil bodies than walnuts and almonds. Transmission electron microscopy revealed that in walnuts and almonds, the lipid was stored in a single, dense agglomerate, whereas the lipid in pistachios was observed in smaller and dispersed droplets within the cell [12]. Following mastication and in vitro digestion, cell walls from all nuts showed fissures and free lipids in the extracellular space. Thus, the effect of mastication and digestion (in vitro) of walnuts and pistachios also results in the breakage of cell walls, the release of lipids and increased bioaccessibility.

2.2. History of Determining the Energy Value of Foods

For food labeling purposes, the metabolizable energy value of the food is typically used. Metabolizable energy is the gross energy of the food corrected for energy losses in feces and urine. Gross energy of food, feces and urine are measured by bomb calorimetry. For food labeling, direct measures of metabolizable energy are not performed, but rather, the metabolizable energy is estimated using energy density factors which represent the energy, adjusted for incomplete digestion. The energy density factors, commonly known as the Atwater general factors, were based on research conducted by Atwater and colleagues [13]. Based on these studies, Atwater proposed that the metabolizable energy value of protein, fat and carbohydrate could be estimated as 4, 9 and 4 kcal/g, respectively. These factors were further refined based on food groups, more targeted to improve digestibility estimates of macronutrients. These refined energy density factors are commonly known as the Atwater specific factors.

While there is no evidence that Atwater performed studies with nuts, Jaffa performed studies with walnuts, Brazil nuts, pecans and almonds [14]. These studies were conducted with two to three men, involved simple diets usually containing a few items and lasted for a few days. While the intention of Jaffa's and Atwater's research was to provide information on the energy and nutrient availability of mixed diets, their results have been applied to individual foods. After the seminal work of Atwater and Jaffa, few additional studies have been reported focusing on measuring the energy value of individual foods or simple diets. While the state-of-the-art nature of Atwater's work has been the foundation for nutrition labeling, the approach is not without limitations. Some of the limitations have been reviewed [15] and include the small sample size, short duration of collections and measurement errors.

2.3. Recent Measures of the Metabolizable Energy Value of Nuts

In order to better measure the metabolizable energy value of an individual food while it is being consumed as part of a mixed diet, Novotny developed an approach [16] that overcomes the limitations of the Atwater approach [15]. Briefly, this approach requires a pair of diets—one without the food of interest and the other an identical diet with the food of interest. Using this approach, the metabolizable energy value of pistachios [17], almonds [16], walnuts [18] and cashews [19] was investigated. Additionally, a study of different forms of almonds was conducted [10].

In all of these studies, the measured metabolizable energy value of the nuts was lower than the energy value calculated using Atwater general or specific factors. The difference between the measured and calculated metabolizable energy values were 6% for pistachios (whole, lighted roasted and lightly salted) [17], 19% for almonds (whole, unroasted, unsalted) [16], 21% for walnuts (pieces) [18] and 6% for cashews (whole, roasted, lightly salted) [19]. In all of these studies, the amount of nuts included in the diet was 42 g/day (1.5 oz/day), and this amount was selected to be consistent with the US FDA qualified health claim for nuts [20,21]. Furthermore, with the study of pistachios and almonds, a second amount of 84 g/day was used to investigate dose effects. There was no change in the measured metabolizable energy value between the two doses [16,17].

3. Appetite as a Complex System

The regulation of appetite is complex and influenced by various biological, nutritional, physical and social factors. Humans are omnivores, allowing them to make food choices from a wide range of available options, but this versatility can also be a challenge. Appetite can be broadly divided into tonic and episodic components, which are generally represented by the drive to eat and food choice behavior. The key determinants of the drive to eat are the body's lean mass and resting metabolic rate, but these are unrelated to food choice [22]. Food hedonics, or the experienced pleasure derived from eating food, has a major influence on food choice. The consumption of chosen foods inhibit the drive to eat through the processes of satiation and satiety, which form part of the Satiety Cascade [23]. Satiety is the post-prandial inhibitory component of appetite control and is mediated by complex physiological processes. There is huge individual variability in the way people experience satiety, and the strength of satiety is heavily influenced by the diet selected.

The effect of nuts on appetite can be assessed by scientifically investigating their effects on the processes of satiation and satiety in relation to an individual's pattern of satiety control. When people freely consume nuts as part of their diet, either within or between meals, it is important to enquire what effects this will have on their overall energy intake and their pattern of food consumption. To investigate this issue, it is necessary to understand some features of the appetite system and the mechanisms that mediate the effects of ingested foods.

3.1. Appetite and Satiety (and Satiation)

Appetite is not the opposite of satiety; rather, satiety is an important component of appetite control. Appetite encompasses various processes that influence food consumption, including the initiation of eating and the duration and termination of eating episodes. Such processes include the level of hunger, food availability and choice, food hedonics, psychological traits, situational factors and social factors. Satiety refers to the reduction in hunger and eating following a meal. Satiation, on the other hand, is the termination of a meal and affects meal size. The period after a meal involves a complex series of physiological events in the digestive tract, including gastric activity and hormone release, which control the digestion and absorption of nutrients. These physiological events depend on the type of the foods consumed in the diet. As they accompany the state of satiety, they are often referred to as satiety signals. Whether these satiety signals are biomarkers of satiety or the cause of it is an area of debate in the field. However, it can be concluded that there is no single unique satiety signal [24]. As satiety is an inhibitory process, it

plays an important role in determining how much food is eaten and one's levels of hunger. Therefore, satiety may potentially influence body weight by either permitting or preventing overconsumption [25,26]. Weak satiety is seen as a major factor in obesity, while intensifying satiety through certain foods or drugs may support weight loss [27–29].

3.2. Foods and the Satiety Cascade

As omnivores, human beings have the capability to consume a vast variety of foods from around the world, leading to a range of unique dietary patterns. The foods chosen impact the levels of satiation and satiety felt. This phenomenon can be explained through the idea of the 'Satiety Cascade' (Figure 1) [23]. The satiety cascade provides a framework to understand the mechanisms involved in the short-term control of eating behavior.

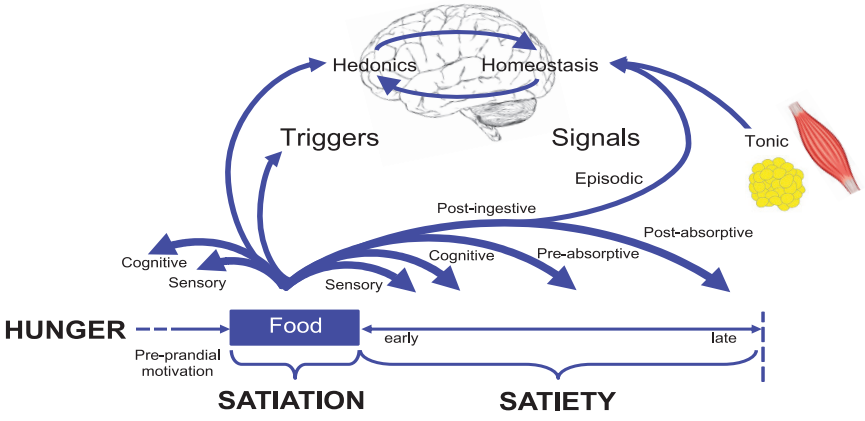

Figure 1. The Satiety Cascade depicts meal size and the time between meals is influenced by the processes of satiation and satiety. It also demonstrates the interaction between the homeostatic and hedonic influences on the processes of satiation and satiety. Adapted from Blundell and Finlayson [30].

The satiety cascade distinguishes between satiation and satiety and illustrates how a variety of signals, such as those arising from sensory, cognitive, post-ingestive and post-absorptive processes, affect the frequency and size of meals. The processes of satiation control meal size through their effect on the duration and termination of an eating episode. These processes, along with the nutritional content of the food consumed, determine the amount of energy consumed during the eating episode. Once the meal is finished, the desire to eat is temporarily suppressed by the physiological effects of the consumed food, especially in the stomach, and the hormones released by the gastrointestinal system during the digestion and absorption of food.

3.3. The Nature of Satiety Signals

After eating, the sensation of fullness (satiety) is produced by several features of the foods consumed, including volume, weight, sensory features (taste, texture, mouthfeel), enjoyment, appearance, nutritional composition, non-nutritional elements (such as fiber) and packaging/labeling. Therefore, satiety is a result of the combined effects of various components of the food consumed. Many studies have aimed to determine the specific characteristics of foods that have the most significant effect on satiety. Understanding these factors is crucial for the food industry in creating foods that can regulate hunger and enhance the feeling of fullness. There is evidence to suggest that high protein and fiber levels can increase satiety. However, energy density is a crucial factor, with low-energy-density diets producing stronger feelings of satiety [31].

Since the first investigations of satiety, it has been believed that the impact of food composition is influenced by post-meal physiological responses. These responses involve alterations in gastric distension, digestion and emptying, as well as the release of gastrointestinal peptides including cholecystokinin (CCK), glucagon-like peptide (GLP-1), peptide YY (PYY), insulin and others. For a long time, CCK was considered to be the sole satiety signal. It is important to note that all these peptides play important roles in the body's management of food through digestion and absorption processes, such as slowing down gastric emptying and releasing bile for fat emulsification. As a result, their impact on satiety may be secondary to their other functions. It remains a topic of discussion whether gut peptides are markers or the actual cause of satiety. The fact that different foods may have similar effects on satiety but produce distinct physiological profiles suggests that there is no uniform pattern behind satiety and that the same level of satiety may be linked to different post-prandial physiological changes [24]. In recent years, there has been considerable interest in the post-prandial physiological effects of raw foods compared with highly and ultra-processed foods [32].

3.4. A Note on (the Role of) Food Hedonics

Food is a reliable source of pleasure for most people, and the reward derived from food plays an important role in the initiation, maintenance and termination of an eating episode, in part through interaction with processes involved in hunger and satiety. Food hedonics is more than simply liking the taste of food or the experience of pleasure. Non-human animal research has demonstrated that the brain structures underpinning food hedonics comprise dissociable affective and motivational subcomponents, termed 'liking' and 'wanting', respectively. Liking refers to the sensory pleasure experienced while eating a food and is generated by the binding of opioids to specialized clusters of neurons in the reward pathway, particularly in the Nacc shell. Wanting refers to the process that assigns motivational value to finding and consuming a food and is mediated by the release of dopamine (DA) from the ventral tegmental area (VTA) to the nucleus accumbens (Nacc) and amygdala [33,34]. In human appetite research, the terms "liking" and "wanting" for food are often seen as explicit subjective states that correspond to their everyday meanings. Liking refers to the enjoyment of the sensory qualities of food that give it its hedonic impact, while wanting refers to a subjective state of desire or craving. People are generally good at estimating and reporting their liking for food, but are often inaccurate in their assessment of their implicit wanting for food, meaning why they are attracted to or craving a particular food over another [35,36].

After food is consumed, the sensory aspects of the food are registered by both cognitive and sensory processes before it is swallowed. Highly palatable food stimulates the reward pathways in the brain, causing the release of dopamine and endorphins. These reward pathways have connections to the hypothalamus, which triggers the release of hunger-inducing peptides such as NPY and orexins and suppresses the release of satiety-inducing peptides such as insulin, leptin and cholecystokinin. Thus, the consumption of highly palatable food can result in overeating, as the drive to eat is motivated by pleasure rather than actual hunger. The interplay between the hedonic and homeostatic systems of appetite regulation contributes to the overall pattern of eating behavior, and in an environment that promotes obesity, the hedonic drive to eat may have a stronger impact on food consumption compared to homeostatic mechanisms [29,37].

3.5. Individual Variability in Appetite Control and the Low Satiety Phenotype

The range of factors that contribute to a person's susceptibility to overconsume (and eventually weight gain and obesity) can include their genetics, physical and psychological characteristics, lifestyle habits and surrounding food and activity environment. Decades of research have pinpointed many aspects of the typical Western lifestyle and diet that interact with these factors, making it easier for people to overeat and gain weight. However, not everyone in a 'westernized' environment overconsumes food, and it is unlikely that

one single factor can account for why some are more vulnerable than others; this has implications for appetite control and the prevention of weight gain.

One approach to characterize individual susceptibility is through the identification and characterization of phenotypes. One such phenotype may be characterized by a weakened satiety response to food, which has been proposed as a possible marker of susceptibility to overeating [38–40]. Research has shown that under controlled conditions, appetite sensations are a valid and reliable method for measuring the subjective motivation to eat [41]. However, not everyone reports a good relationship between their sensations of appetite (hunger and fullness) and their eating behavior. A weakened satiety response to the feeling of satiety may play a role in a lack of control over one's appetite. Individuals with such a reduced response to food are referred to as the "low satiety phenotype" [42]. The low satiety phenotype has largely been observed in people with obesity, but evidence suggests that a weakened satiety response to food may lead individuals to be vulnerable to future weight gain. Research examining the low satiety phenotype has demonstrated that it is characterized by increased Three Factor Eating Questionnaire disinhibition and hunger scores, lower levels of craving control, greater food wanting and increased energy intake under laboratory conditions [42–44]. In terms of weight management, studies have shown that individuals with a low satiety responsiveness tend to lose less weight, experience smaller decreases in abdominal fat, report lower control over cravings and face more challenges in sticking to a diet compared to those with a high satiety responsiveness [44–46].

3.6. Nuts and Appetite Control: A Case Study with Almonds

Snacking between meals is a common behavior [47], and snack foods make a significant contribution to total daily food intake [48]. Snack foods are often characterized as being low in nutritional quality, primarily comprising fats and carbohydrates [49] that contribute to overconsumption. However, research suggests that frequent snacking can promote feelings of satiety throughout the day, which results in overall lower daily energy intake [50]. This suggests that snacking behavior itself is not undesirable and may present an opportunity for the addition of healthy foods, such as nuts, into the diet [51]. A recent meta-analysis of randomized clinical trials found that regular consumption of nuts was associated with increased daily energy intake and lower hunger but had no effect on weight or feelings of fullness [52]. The increase in daily energy intake was lower than the amount of energy consumed from the nuts, which may be due to the lower amount of available energy from nuts following digestion [16,53].

Almonds are a natural food product that are high in protein and fiber as well as fat, but lower in metabolizable energy compared to the predicted levels (using Atwater factors) [16]. It is well established that proteins and fibers have prominent effects on appetite control [54,55], and since they act via different mechanisms, their effects may be additive. The unique structural properties and macronutrient composition of almonds may be beneficial for the control of hunger, strength of satiety and subsequent energy intake relative to other foods. The addition of almonds to a meal has been shown to increase satiety and decrease blood glucose concentrations in those with and without impaired glucose tolerance [56–58]. Furthermore, when consumed as a snack, almonds have been shown to reduce feelings of hunger and desire to eat [59,60]. The consumption of almonds as a snack does not seem to cause an increase in total daily energy intake [61] or result in significant weight change over time [62–64]. A recent study compared the effect of consuming almonds as a mid-morning snack compared to an energy- and weight-matched comparator snack (crackers) and a zero-energy, weight-matched control (water) on measures of subjective appetite, food intake and food hedonics. It was found that overall hunger was lower in the almonds condition, and almonds were more satiating than the crackers (Figure 2). There was also a reduction in implicit wanting for high-fat food following almond consumption suggesting a beneficial effect on hedonic hunger. Further to this, participants' perceptions of the almonds were favorable, with almonds being perceived as healthy, filling and good for weight management [61].

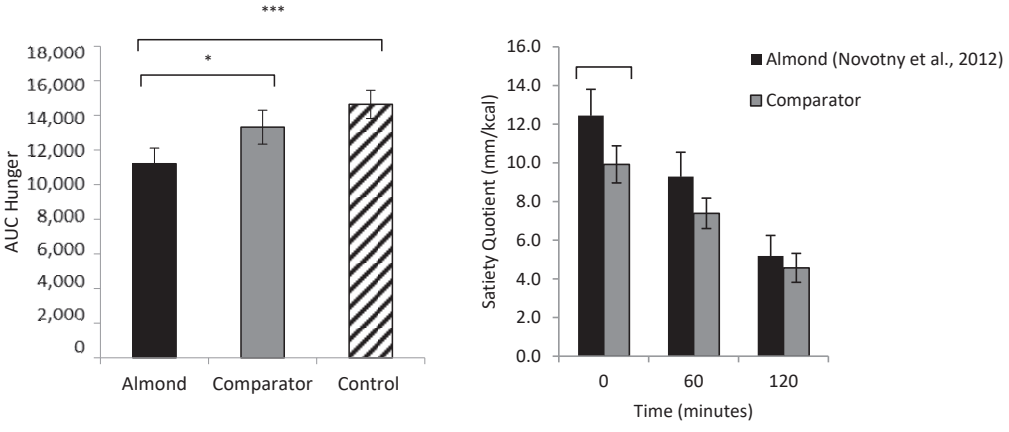

Figure 2. Left: Area under the curve hunger for the almonds condition, energy- and weight-matched comparator (crackers) and weight-matched comparator (water). Right: Satiating efficiency (measured by the Satiety Quotient) of the almonds compared to comparator for 120 min post-consumption [16]. Adapted from Hollingworth et al. [61]. Note: * $p < 0.05$; *** $p < 0.001$.

3.7. Nuts and the Low Satiety Phenotype

As outlined above, the low satiety phenotype is characterized by higher levels of hunger across the day, greater overall energy intake, increased liking and wanting for food, and poorer weight loss outcomes following structured weight management programs [42–46]. Foods that promote satiety have the potential to support individuals (in general and perhaps in particular those with a weakened satiety response to food) to control their appetite, eat fewer calories and manage their weight [65]. Research suggests that even when matched for calories, not all foods provide the same level of satiety [66], and a hierarchy of macronutrient satiating power has been established, with foods that are high in protein and fiber and low in energy density being more satiating [54,67–69]. The unique structural properties and macronutrient composition of nuts may be beneficial for the control of hunger, strength of satiety and subsequent energy intake relative to other foods; therefore, the consumption of nuts may support those with low satiety responsiveness in improving their appetite control.

Hollingworth [70] compared the effect of consuming almonds as a mid-morning snack compared to an energy- and weight-matched comparator snack food (crackers) on satiating efficiency, energy intake and feelings of hunger and fullness across the day in the low satiety phenotype compared to the high satiety phenotype. They found that almonds had a greater satiating efficiency, measured using the satiety quotient, in the low satiety phenotype compared to the comparator snack. In addition, when compared to the comparator food, almonds were perceived as being healthier, more filling and more favorable for weight management. Expectations about the satiating potential of food has been shown to play a role in expected satiety [71] and may present another mechanism by which almonds (and potentially other nuts) may support appetite control. Furthermore, while almonds and the comparator snack were rated as equally palatable, participants rated the almonds as more difficult to chew. The texture and chewiness of almonds may improve their satiating capacity, with evidence suggesting that oral processing plays an important role in food intake by affecting both satiation and satiety [72].

4. Overview of Nut Consumption and Body Weight

In order to understand the effects of almonds on appetite control, it is necessary to recognize the complex nature of human appetite as an emergent property of a complex system [73]. The act of food consumption in the real world is influenced by a diverse set of

biological and environmental variables, with a greater complexity than can be achieved in laboratory investigations. Recognizing this complexity, it can be shown that changes to the whole diet (for example, by changing energy density) can exert effects on meal sizes, daily energy intake and profiles of hunger [31]. With this in mind, we can ask what is the likely strength of effect on appetite of manipulating a single food in the diet? One systematic review with a meta-analysis of laboratory and field trials has noted that nuts in general do not exert consistent effects on food intake or hunger [52]. However, seeking general effects in an unselected cohort or population will be too insensitive to discriminate effects on people with varying existing degrees of appetite control (satiety phenotypes). An enhancement of satiety is more likely to occur in individuals showing poor appetite control. As shown above, almonds can improve satiety in the low satiety phenotype. This is important since such people are the most likely to benefit from an improvement in control over their appetites (hunger drive and meal size). This action demonstrates how a single food in the diet can exert a meaningful effect. When consumed by people with normal or strong appetite control (high satiety phenotype), the most likely outcome is the maintenance of the habitual eating pattern and a prevention of overconsumption. In achieving these outcomes, almonds (and other nuts) benefit from a range of food factors that influence satiety, including taste and texture, postprandial physiology as well as expectations about satiety. Therefore, in weighing up how nuts can influence appetite control, it is important to manage expectations and not to anticipate the same effect in all types of eaters. Actions can be expected to vary according to the strength of a person's natural appetite control. Different types of benefit can be expected in people with different forms of satiety control. This approach could form the basis for future investigations of the effect of nuts on appetite.

4.1. Evidence from Prospective Cohort Studies

Several prospective cohort studies have examined the association between nut consumption and long-term weight change and obesity risk. Bes-Rastrollo et al. [74] examined the long-term association between nut consumption and weight change over 8 years among 51,188 women aged 20–45 years from the Nurses' Health Study (NHS) II. The analysis prospectively evaluated the dietary intake of nuts reported in 1989 and subsequent weight changes from 1991 to 1999. After adjusting for age, BMI, alcohol consumption, physical activity, smoking, postmenopausal hormone use, oral contraceptive use and dietary factors, this study found that women who reported eating nuts $\geq$2 times/week experienced a slightly lower mean ($\pm$SE) weight gain (5.04 $\pm$ 0.12 kg) than did women who rarely ate nuts (5.55 $\pm$ 0.04 kg) (p-trend < 0.001). The findings were similar when nut consumption was subdivided into peanuts and tree nuts as well as for participants who are normal-weight, overweight and have obesity.

In an analysis of three prospective cohorts that included 120,877 US women and men with follow-ups ranging from 1986 to 2006 [75], each four-year weight change was inversely associated with a one-serving increment in the intake of nuts (−0.26 kg), fruit (−0.22 kg), vegetables (−0.10 kg), whole grains (−0.17 kg) and yogurt (−0.37 kg), whereas weight gain was positively associated with the intake of potato chips (0.77 kg), potatoes or fries (0.58 kg), sugar-sweetened beverages (0.45 kg), unprocessed red meats (0.43 kg) and processed meats (0.42 kg). These data suggest that specific dietary factors including nuts and overall diet quality influence long-term weight gain.

In a Spanish cohort study consisting of 8865 adult men and women [76], regular nut consumption was significantly associated with a reduced risk of weight gain of $\geq$5 kg. After adjustment for age, sex, smoking status, physical activity and other covariates, participants who ate nuts $\geq$2 times/week had a significantly lower risk of weight gain (OR: 0.69; 95% CI: 0.53, 0.90; p-trend = 0.006) compared with those who never or almost never ate nuts.

In a prospective analysis of 3092 young adults enrolled in the Coronary Artery Risk Development in Young Adults (CARDIA) study that assessed consumption of walnuts and other nuts three times during the follow-up [77], higher walnut consumption was significantly associated with higher HEI-2015, lower BMI, waist circumference, blood

pressure, and triglyceride concentration. Walnut consumers gained less weight since baseline than other nut consumers ($p \leq 0.05$).

Recently, Li and colleagues evaluated changes in total and different types of nut consumption and long-term weight change in three US cohorts [78]. These analyses included 27,521 men (Health Professionals Follow-up Study, 1986 to 2010), 61,680 women (Nurses' Health Study, 1986 to 2010) and 55 684 younger women (Nurses' Health Study II, 1991 to 2011) who were free of chronic disease at baseline in the analyses. The study found that increases in nut consumption, per 0.5 servings/day (14 g), was significantly associated with less weight gain per 4-year interval ($p < 0.01$ for all): −0.19 kg (95% CI −0.21 to −0.17) for total consumption of nuts, −0.37 kg (95% CI −0.45 to −0.30) for walnuts, −0.36 kg (95% CI −0.40 to −0.31) for other tree nuts and −0.15 kg (95% CI −0.19 to −0.11) for peanuts. In addition, increasing the intake of nuts, walnuts and other tree nuts was associated with a lower risk of obesity. In substitution analyses, substituting 0.5 servings/day of nuts for red meat, processed meat, French fries, desserts or potatoes and chips was associated with less weight gain ($p < 0.05$ for all) (Figure 3). This study provides further evidence that increasing daily consumption of total and different types of nuts is associated with less long-term weight gain and a lower risk of obesity in adults. More importantly, this study indicates that replacing "less healthful foods" with nuts may be an effective strategy to help prevent gradual long-term weight gain and obesity.

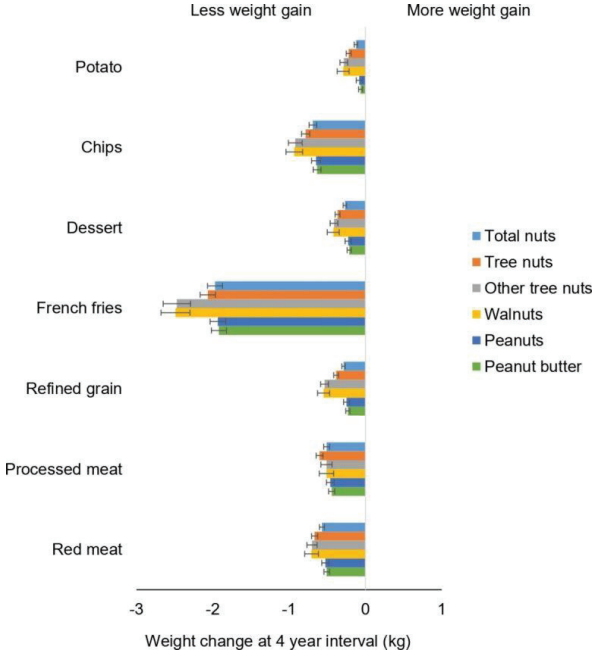

Figure 3. Association between weight change (kg) every 4 years and substitution of nuts and individual types of nuts, per 0.5 servings/day with equal serving of other food items among NHS, NHS II and HPFS. Weight changes are presented as solid bars; T bars represent 95% CI. Multivariate model was adjusted for age, menopausal status (pre- or postmenopausal) and hormone therapy use (never, past or current) in women; baseline BMI of every 4 years; hours of sleeping at baseline; changes in lifestyle factors: smoking status (never, former, current: 1 to 14, 15 to 24, or ≥25 cigarettes/day), physical activity (MET hours/week), hours of sitting (hours/week); and changes in dietary factors: fruits, vegetables, alcohol, snacks, dessert, French fries, red or processed meat, whole grain, refined grain products and sugar sweetened beverages.

Nishi et al. conducted a systematic review and meta-analysis of five prospective cohorts on nut consumption and weight gain and obesity among 520,331 participants [79]. It found that higher nut intake was associated with a decrease in overweight/obesity incidence (RR 0.93 [95% CI 0.88 to 0.98], $p < 0.01$; I2 = 90.0%, p-heterogeneity < 0.01). Similarly, higher nut consumption was associated with weight loss (MD 0.46 kg [95% CI 0.78 to 0.13 kg], $p < 0.01$; I2 = 95.9%, p-heterogeneity < 0.01) and reduced risk of weight gain ≥5 kg (RR 0.95 [95% CI, 0.94 to 0.96], $p < 0.01$; I2 = 46.7%, p-heterogeneity = 0.15). The certainty of evidence was rated moderate based on the GRADE criteria. In pooled analyses from models not adjusting for energy intake, higher nut consumption was associated with less weight gain (MD 0.64 kg [95% CI 1.12 to 0.15 kg]).

4.2. Evidence from RCTs

Few RCTs have specifically evaluated the role of nuts in weight loss and maintenance or obesity prevention. Wien et al. [80] evaluated the effect of an almond-enriched (84 g/day) or complex carbohydrate-enriched, formula-based, low-calorie diet (LCD) on anthropometric, body composition and metabolic parameters in a randomized 24-week trial among 65 adults with overweight and obesity (age: 27–79 y, BMI: 27–55). LCD supplementation with almonds, compared to complex carbohydrates, led to greater reductions in weight/BMI (−18 vs. −11%, $p < 0.0001$), waist circumference (WC) (−14 vs. −9%, $p < 0.05$), fat mass (−30 vs. −20%, $p < 0.05$), total body water (−8 vs. −1%, $p < 0.05$) and systolic blood pressure (−11 vs. 0%, $p < 0.02$). Ketone levels increased only in the almond-LCD group ($p < 0.02$). This study suggests that an almond-enriched LCD is beneficial for a sustained and greater weight reduction for the duration of the 24-week intervention.

Numerous small, short-term RCTs have examined the effects of nut-rich diets on a wide range cardiometabolic risk factors in which body weight or fatness were secondary outcomes. Fernández-Rodrígue et al. [81] conducted a systematic review and network meta-analysis on the relationship of tree nut and peanut consumption with adiposity measures including body weight (BW), BMI, waist circumference (WC) and body fat percentage (BF%). This study included a total of 105 RCTs with measures of BW (n = 6768 participants), BMI (n = 2918), WC (n = 5045) and BF% (n = 1226). Compared to a control diet, nut-enriched diets had no significant effects on the adiposity-related measures, except for a positive effect of hazelnut-enriched diets and an increase in WC. Moreover, almond-enriched diets significantly reduced WC compared to the control diet. In subgroup analyses with only RCTs designed to assess whether nut consumption affected weight loss, almond-rich diets significantly reduced BMI and walnut-rich diets significantly reduced %BF. This study provides evidence to supports that tree nut and peanut enriched diets do not increase adiposity. A similar conclusion was reached by a meta-analysis conducted by Nishi et al. [79], which found no adverse effect of nuts compared with control diets on body weight (105 trial comparisons involving 9655 participants, MD 0.09 kg, [95% CI 0.09 to 0.27 kg], $p = 0.34$; I2 = 63.2%, p-heterogeneity < 0.01).

In a systematic review and meta-analysis of 15 RCTs on almond consumption and cardiovascular risk factors [82], compared to control diets, almond-enriched diets significantly improved blood lipids and reduced inflammatory biomarkers. In the meantime, higher almond consumption of >42.5g/day significantly improved fasting blood glucose and reduced BMI.

In a systematic review and meta-analysis of 55 parallel-arm or crossover interventions of nuts (including mixed nuts, nut-based snack bar and individual nuts including almonds, cashews, hazelnuts, macadamia nut, peanut, pecan, pistachio and walnut) there was no change reported in body weight, BMI or waist circumference. The mean duration of these studies was 13.8 ± 21.5 weeks and the mean intake of nuts was 48.2 ± 20.8 g/d. The analysis included studies where no substitutions instructions were provided as well as studies which provided to the participants instruction on substitution. In the studies where substitution instructions were not provided, there was no change in body fat percentage.

In studies with dietary substitution instructions, there was a significant decrease in body fat percentage [83].

Only one long-term RCT examined the effects of a Mediterranean diet supplemented with nuts on body weight and waist circumference changes in the context of a Mediterranean dietary intervention and primary prevention of CVD [84]. The PREDIMED trial randomly assigned 7447 participants with high risk of CVD to one of three interventions: Mediterranean diet supplemented with extra-virgin olive oil (n = 2543); Mediterranean diet supplemented with mixed nuts including almonds, walnuts and hazelnuts (n = 2454); or a control diet (advice to reduce dietary fat; n = 2450). After a median 4.8 years of follow-up, participants in all three groups had marginally reduced bodyweight. After multivariable adjustment, the difference in 5-year changes in bodyweight in the olive oil group was −0.41 kg (95% CI −0.83 to 0.01; p = 0·06) and −0.02 kg (−0.45 to 0.42; p = 0.94) in the nut group compared with the control group. The adjusted difference in 5-year changes in waist circumference was −0.47 cm (−1.11 to 0.18; p = 0.15) in the olive oil group and −0.92 cm (−1.60 to −0.24; p = 0.008) in the nut group compared with the control group. This study provides strong evidence that diets supplemented with either extra-virgin olive oil or nuts had no adverse effects on body weight or WC. In contrast, these diets may have beneficial effects on adiposity measures compared to a lower-fat diet.

4.3. Methodological Issues in Observational Studies and RCTs

Both observational studies and RCTs of diet and body weight fraught with methodologic problems (see Chapter 14 in [85]). RCTs should provide some of the most rigorous evaluations of dietary intake and body weight. However, long-term dietary intervention studies are seldom feasible because of the high cost and lack of compliance by study participants. In addition, lack of compliance and high dropout rates are common in dietary intervention trials. Most RCTs on body weight and other CVD risk factors are of short-duration, small sample sizes and use different control groups. In most RCTs, adiposity measures such as weight or waist circumference changes were considered as secondary outcomes.

Observational studies of nut consumption and body weight are also complicated by several methodologic issues. In particular, residual confounding by other dietary and lifestyle factors cannot be ruled out because regular nut consumers tend to follow a healthier diet and lifestyle than non-consumers. Dietary assessment tools such as the 24 h recalls, dietary records and FFQs that are widely used in epidemiologic studies are prone to both random and systematic measurement errors. Although carefully validated FFQs that are administered repeatedly during follow-up are best-suited to the assessment of long-term patterns in intake, few large-cohort studies assessed diets repeatedly. In addition, no study has specifically examined the influence of food processing methods on body weight outcomes (i.e., salted, raw, roasted). Finally, most studies have been conducted in white or European populations, and thus the results may not be generalizable to other racial and ethnic groups.

5. Potential Components of Nuts That Contribute to Weight Control

Several mechanisms have been proposed to explain the potential benefits of nut consumption on body weight [86] (Figure 4). Nuts are rich in (1) proteins and (2) dietary fiber, which are associated with increased satiety, and in (3) unsaturated fats, which may increase oxidation that potentially decreases body fat accumulation [87]. High amounts of protein and fiber in nuts may also increase thermogenesis and resting energy expenditure. Dietary fiber (especially viscous fiber) in nuts delays gastric emptying and subsequent absorption that potentially suppresses hunger and promote healthy gut microbiome that improves energy metabolism. In addition, incomplete mastication of nuts may lead to increased energy loss via feces, which contributes to energy availability of nuts and thus a lower energy intake. Furthermore, consuming nuts at expense of red meat and refined carbohydrates may also contribute to less weight gain and lower risk of chronic diseases.

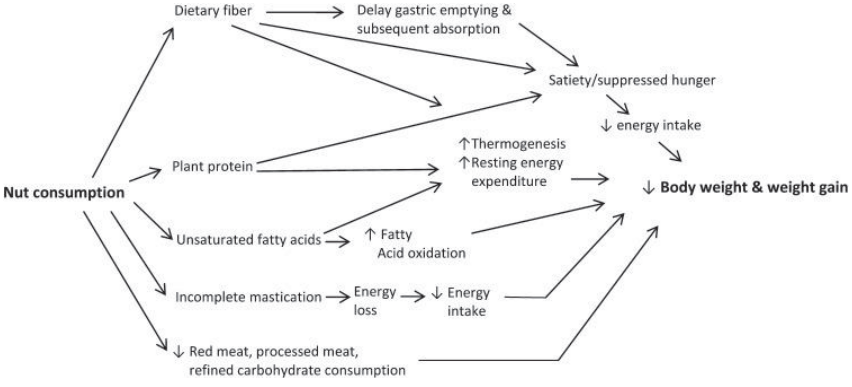

Figure 4. Conceptual framework of potential mechanisms linking nut consumption to decreased body weight and weight gain [86].

6. Clinical and Public Health Dietary Recommendations on Nuts and Weight Management

Cumulative evidence from long-term large cohort studies supports that an increased consumption of nuts, including total nuts and different types of nuts, is associated with less weight gain and lower risk of obesity, despite being calorically dense. The benefits to body weight are more pronounced when nuts are used to replace unhealthy foods such as red meat, processed meat, French fries, desserts or potato, chips. In addition, short-term RCTs suggest that nut-enriched diets had no adverse effects on body weight or other adiposity measures compared to control diets. There is some evidence that nuts may have beneficial effects on weight loss and maintenance, although more research is needed. Healthy dietary patterns rich in nuts, such as the Mediterranean diet, DASH diet and healthy plant-based diets, have been associated with age-related weight gain, although in these studies, the effects of nuts cannot be separated from other components of the dietary patterns [84].

7. Conclusions

To date, the plant cell wall factors that influence the energy available from nuts have mostly been investigated in almonds, with some research conducted in pistachios and walnuts. The effect of the plant cell wall, and its fermentation, on energy availability of other nuts has not been reported. Furthermore, the metabolizable energy value of nuts has been measured for almonds, walnuts, pistachios and cashews. Data from other nuts have not been reported. Additionally, the effect of processing on energy availability has only been investigated in almonds and peanuts. More information on dose response and individual variability may be useful to understand individual variability in energy intake, especially when trying to determine compensation of energy intake.

Evidence from RCTs and observational cohorts indicates higher nut consumption does not appear to cause greater weight gain; rather, nuts may be beneficial for weight control and prevention of long-term weight gain. Diet and lifestyle changes such as the replacement of less healthful food items (e.g., red or processed meats, refined grain products) with nuts and other healthy foods have the potential to reduce risk of obesity and obesity-related chronic diseases. In terms of future directions, more observational studies and RCTs are needed to examine the effects of nut consumption on different body depots, especially abdominal, visceral and liver fat. More studies are also needed to be conducted among individuals with type 2 diabetes, the metabolic syndrome and fatty liver disease and in diverse populations of different racial and ethnic groups and socio-economic status. Finally, research is needed to examine the role of nuts in healthy and sustainable eating patterns such as the Healthy Planetary Diet recommended by the Eat-Lancet Commission [88].

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nutrients

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Review

Nuts in the Prevention and Management of Type 2 Diabetes

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Abstract: Diabetes is a continuously growing global concern affecting >10% of adults, which may be mitigated by modifiable lifestyle factors. Consumption of nuts and their inclusion in dietary patterns has been associated with a range of beneficial health outcomes. Diabetes guidelines recommend dietary patterns that incorporate nuts; however, specific recommendations related to nuts have been limited. This review considers the epidemiological and clinical evidence to date for the role of nut consumption as a dietary strategy for the prevention and management of type 2 diabetes (T2D) and related complications. Findings suggest nut consumption may have a potential role in the prevention and management of T2D, with mechanistic studies assessing nuts and individual nut-related nutritional constituents supporting this possibility. However, limited definitive evidence is available to date, and future studies are needed to elucidate better the impact of nuts on the prevention and management of T2D.

Keywords: nuts; diabetes; glycemic control; insulin resistance

1. Introduction

Type 2 diabetes is one of the most globally challenging and prevalent metabolic disorders affecting an estimated 1 in 10 adults (10.5% of adults worldwide) [1]. Within the past 2 years, type 2 diabetes prevalence has risen by 16%, indicating an alarming growth rate [1]. Complications of diabetes, such as cardiovascular disease, chronic kidney disease, neuropathy, and retinopathy, and its high medical and other economic expenditures are a serious cause of concern [2]. Excluding mortality risks associated with COVID-19, approximately 12.2% of global adult deaths from all-cause are estimated to have occurred

due to diabetes or its complications in 2021 [2]. Further, 10.6% of adults worldwide have impaired glucose tolerance, placing them at high risk for developing type 2 diabetes (T2D) [2].

Lifestyle changes, such as those related to nutrition, underpin a general approach to diabetes risk minimization and management. Current diabetes guidelines recommend dietary patterns, such as Mediterranean and vegetarian patterns, which encourage the consumption of nuts [3–6]. Nuts, represented by tree nuts (almonds, Brazil nuts, cashews, hazelnuts, macadamias, pecans, pine nuts, pistachios, walnuts) and peanuts (technically a legume, but sharing a similar nutritional and culinary profile to tree nuts, hence, their inclusion in the "nuts" classification), are nutrient-dense foods with complex matrices providing unsaturated fatty acids, plant-protein, non-sodium minerals, phenolic and other bioactive compounds [7–9].

In this narrative review, we summarize the human evidence currently available ("Where we are") for the role of nuts in the prevention and management of T2D and discuss future directions ("Where we are going") in terms of what questions may still need to be addressed and how research may address and inform any knowledge gaps. For this narrative review, a comprehensive search of PubMed and Cochrane databases through November 2022 for English language articles of epidemiological, clinical studies, and the latest reviews and meta-analyses assessing nut consumption (tree nuts and peanuts) and their components on T2D and related risk factors was conducted. The present article is not a systematic review; thus, some studies may not have been identified; further, the possibility of publication bias should be acknowledged. Nonetheless, the authors independently conducted literature searches, and these findings were further shared and discussed among an assembly of experts in the field of nut and health research.

2. Effect of Nut Consumption on Measures of Glucose Metabolism

Few epidemiological studies have assessed the association between nut consumption and markers of glycemic control. Table 1 summarizes epidemiological and clinical findings related to nut consumption and measures of glucose metabolism. To our knowledge, there is a lack of prospective cohort studies that have analyzed markers of glucose metabolism in individuals with or without diabetes. One prospective population-based study, conducted within the framework of the Tehran Lipid and Glucose study (TLGS), presented fasting serum glucose measures following a median 6.2-year follow-up across tertiles of nut consumption. At 6.2 years, findings showed lower fasting serum glucose levels in the highest tertile of nut consumption (nut intake: median 8.7 g/week, IQR, 5.3 to 15.8 g/week; fasting glucose: 4.7 $\pm$ 0.1 mmol/L) compared to the lowest tertile (nut intake: median 1.6 g/week, IQR, 0.7 to 2.8 g/week; fasting glucose: 5.3 $\pm$ 0.1 mmol/L) (p = 0.02) [10]. However, there appears to be a shortage of evidence in relation to other glucose-metabolism-related biomarkers and in individuals with diabetes. Cross-sectional studies have shown an association between nut consumption and markers of glucose/insulin homeostasis. One cross-sectional study assessing data from 16,784 American adults (51.8% women, aged $\geq$18 years) participating in the National Health and Nutrition Examination Survey (NHANES, 2005–2010) evaluated the association between nut intake and markers of glycemic control [11]. The authors observed that higher nut intake was associated with significantly lower levels of all diabetes-related biomarkers, including fasting blood glucose, plasma insulin, homeostasis model assessment-insulin resistance (HOMA-IR), HOMA-β, glycated hemoglobin (HbA1c), and oral glucose tolerance test (OGTT) ($p < 0.001$). Another cross-sectional study analyzed the association between the frequency of nut consumption and insulin resistance, measured by HOMA-IR, in 379,310 Koreans [12]. In this study, nut consumption $\geq$5 servings/week (where 1 serving = 15 g) compared to <1 serving/month was associated with lower HOMA-IR (odds ratio [OR]: 0.90; 95% confidence interval [CI] 0.86 to 0.94). This association was observed to be more prominent in women, participants with normal glycaemia, and younger age (<40 years).

Table 1. Summary of findings related to nuts and diabetes related prevention and management.

Variables	Finding [1]	Level of Evidence [2]	Reference
Epidemiological Evidence			
Fasting blood glucose	↓	+	[11]
Plasma insulin	↓	+	
HOMA-IR	↓	+	[11,12]
HOMA-B	↓	+	[11]
HbA1c	↓	+	
OGTT	↓	+	
Diabetes incidence	↓/↔	+	[13,14]
Diabetes prevalence	↓/↔	+	[13,15–17]
CVD incidence in participants with T2D	↓	+	[18]
Diabetes mortality	↓	++	[19]
Clinical Trial Evidence			
Acute Trial Evidence			
In participants free of T2D:			
Postprandial glycemia	↓	++	[20–26]
Postprandial insulinemia	↓/↔	+	[21,27,28]
In participants with T2D:			
Postprandial glycemia	↓	+	[21,23,29,30]
Postprandial insulinemia	↓/↔	+	[21,29]
Glucose metabolic clearance rate	↑	+	[29]
Longer-term Trial Evidence			
In participants free of T2D at baseline:			
Diabetes incidence	↓/↔	+	[31–33]
In participants with T2D at baseline:			
Fasting glucose	↓	+	[30,34–39]
Fasting insulin	↔	+	
HbA1c	↓	+	
HOMA-IR	↔	+	
In participants with/without T2D at baseline:			
Fasting glucose	↔	+	[40]
Fasting insulin	↓	+	
HbA1c	↔	+	
HOMA-IR	↓	+	

Abbreviations: CVD, cardiovascular disease; HbA1c, glycated hemoglobin; HOMA, homoeostasis model assessment; IR, insulin resistance; OGTT, oral glucose tolerance test; T2D, type 2 diabetes mellitus. [1] Findings are based on the authors' review, and assessment of the noted literature, and hence could present some subjectivity. In general: ↓, majority of evidence indicated a decrease; ↑, majority of evidence indicated an increase; ↔, majority of evidence indicated no change observed; ↓/↔, majority of evidence was split between showing a decrease or no effect on the outcome. Where "majority of evidence" refers to the entirety of the evidence, if a relevant systematic review and meta-analysis was conducted these findings were used as the basis of this determination. [2] Level of Evidence is based on the authors' review and assessment and, hence, could present with some subjectivity. In general: +, limited and/or inconsistent evidence from few studies in the denoted type of study design; ++, consistent evidence in several studies in the denoted type of study design.

When considering evidence from clinical trials, consumption of nuts alone and when added to high glycemic index (GI) foods show a lowering in postprandial glycemia when compared to consumption of high GI foods alone. Several acute trials have assessed the effect of almond intake on postprandial glycemia. In healthy individuals, the consumption of almonds with white bread was shown to significantly lower the postprandial area under the insulin concentration vs. time curve when compared to a high GI meal (instant mashed potatoes) (n = 15) [41] and significantly lower the glucose peak height when compared

with white bread (n = 9) [27]. In another acute randomized crossover trial conducted in healthy participants (n = 100 with available data, n = 106 randomized), consumption of at least 10% of energy from raw almonds resulted in the mean area under the blood glucose response curve being significantly lowered when compared to consumption of biscuits [28]. Similar findings were shown for individuals at higher risk of diabetes. In an acute randomized five-arm crossover trial conducted in individuals with impaired glucose tolerance (n = 14), participants were randomized to consume whole almonds, almond butter, defatted almond flour, almond oil, or no almonds that were incorporated into a 75 g available carbohydrate-matched breakfast meal. Whole almonds significantly diminished the second meal and daylong blood glucose incremental area under the curve and elicited a greater second-meal insulin response [20]. Another acute randomized crossover trial conducted in individuals with good health (n = 12) and individuals with T2D (n = 7) showed consumption of 28 g of almonds with a test meal (bagel, juice, and butter) significantly reduced postprandial glycemia in participants with diabetes but not in participants without diabetes when compared to the test meal without almonds [21]. For pistachio intake, an acute trial conducted in healthy individuals (n = 10) showed consumption of pistachios alone and, when added to white bread at different doses (28 g, 56 g, 84 g), significantly lowered glycemic responses in comparison to white bread [42]. The addition of pistachios to other commonly consumed carbohydrate-rich foods (parboiled rice, pasta, potatoes) also resulted in reduced glycemic responses [42]. Similarly, in an acute trial conducted on individuals with metabolic syndrome (n = 20), the consumption of pistachios with white bread significantly lowered the glycemic response and increased insulin secretagogue levels when compared to white bread alone [22]. For mixed nuts, an acute trial conducted in individuals with good health (n = 14) and in individuals with T2D (n = 10) showed mixed nuts at three different doses significantly reduced the glycemic response in comparison to white bread. The addition of mixed nuts to white bread progressively reduced the glycemic response of the meal; however, in individuals with T2D, the reduction in glycemic response was half that seen in healthy individuals [23]. In another acute trial, adults with overweight/obesity (n = 54) were randomized to consume either mixed nuts or pretzels and showed pretzel consumption increased glucose and insulin, whereas, with mixed nuts, no elevation was detected at 60 min post snack consumption [24]. For peanut intake, an acute trial conducted in men with overweight/obesity (n = 65) who consumed a test meal of a shake containing conventional peanuts, high-oleic peanuts, or a control biscuit showed a quicker return of insulin to basal concentrations after consumption of the shakes containing conventional peanuts and high-oleic peanuts [25].

Several systematic reviews and meta-analyses (SRMAs) of randomized controlled trials (RCTs) with a duration of at least 3 weeks have been conducted assessing the effect of a tree nut(s) on markers of glycemic control in people with different health statuses (the effect of tree nuts on markers of glycemic control in people with diabetes is discussed in Section 5.2). In 2014, SRMA of 49 RCTs (n = 2226) was conducted to assess the effect of tree nuts on metabolic syndrome criteria, including fasting glucose. Twenty-six trials were included (n = 1360) for fasting glucose, which showed tree nuts significantly lowered fasting glucose compared with the controls (mean difference [MD] = −0.08 mmol/L; 95% confidence interval [CI] −0.16 to −0.01 mmol/L) [43]. In 2018, a network meta-analysis of RCTs assessed the effect of different food groups on intermediate disease markers in adults, including fasting glucose, HbA1c, and HOMA-IR [44]. The results showed nuts were more effective at reducing fasting blood glucose when compared to red meat and fruits and vegetables, as well as HOMA-IR when compared to eggs and dairy. No significant effects were shown for HbA1c. In 2019, another SRMA of 40 RCTs (n = 2832) was conducted to assess the effect of tree nut or peanut intake in adults on glycemic control, including fasting glucose, fasting insulin, HbA1c, and HOMA-IR. Nut intake showed a significant lowering in fasting insulin (28 RCTs; weighted mean difference [WMD]: −0.40 μIU/mL; 95% CI: −0.73, −0.07 μIU/mL; I^2 = 49.4%) and HOMA-IR (19 RCTs; WMD: −0.23; 95% CI: −0.40, −0.06; I^2 = 51.7%), with no significant effect on fasting glucose or HbA1c [40].

Subgroup analysis by nut type showed a significant reduction in fasting blood glucose with pistachio consumption compared with the control (WMD: −5.18 mg/dL; 95% CI: −8.76, −1.60 mg/dL; I^2 = 67%). This was supported by another SRMA of RCTs published in 2020, assessing the effect of pistachio intake on glycemic control in individuals with different health statuses (type 2 diabetes, prediabetes, and metabolic syndrome), which showed a significant reduction in fasting glucose and HOMA-IR but not HbA1c or fasting insulin [34]. Tindall et al. also identified a small number of studies that measured outcomes related to insulin production and HOMA-β cell function (7 studies), glucose concentrations after a 75-g OGTT (5 studies), insulin concentrations after a 75-g OGTT (2 studies), insulin sensitivity (3 studies) and short-term glucose control (2 studies) [40]. Due to a limited number of trials that measured these endpoints and the heterogeneity in the measurements, a meta-analysis was not performed. These studies showed no impact of nut intake on outcomes related to insulin concentrations after a 75 g OGTT and insulin sensitivity, whereas there were mixed findings for outcomes related to insulin production and HOMA-β cell function, glucose concentrations after a 75 g OGTT, and short-term glucose control [40]. Several other SRMAs of RCTs have been conducted between 2020 and 2022, assessing the effect of a specific nut type and/or the effect of nuts in a specific group of people. These SRMAs assessed the effect of different types of nuts in healthy adults with overweight/obesity (10 RCTs) [45], walnuts in middle-aged and older adults (17 RCTs) [46] and individuals with different health statuses (16 RCTs) [47], cashews (6 RCTs) [48], peanuts (11 RCTs) [49], and 2 SRMAs investigating almonds in individuals with different health statuses (24 RCTs [50], 15 RCTs [51]), all of which showed no impact on markers of glycemic status.

Since the publication of the above-mentioned SRMAs, more recent RCTs in people without diabetes have been published. In a 6-month RCT, 107 individuals who were overweight and at moderate or high risk of T2D were randomized to either an energy-restricted diet, including 70 g/d of peanuts or an energy-restricted low-fat diet, which showed no significant differences between groups in regard to HbA1c, fasting glucose, fasting insulin, 2 h glucose, and HOMA-IR [52]. In an 8-week RCT, 40 women were randomized to an energy-restricted diet without nuts or to an energy-restricted diet containing 45 g/d of nuts (15 g of Brazil nuts + 30g of cashew nuts), which also showed no significant differences in markers of glycemic status [53].

3. Nuts and Diabetes Prevention

Table 1 summarizes epidemiological and clinical findings related to nut consumption and diabetes prevention.

3.1. Epidemiological Evidence

Epidemiological studies conducted to date have shown inconsistent and inconclusive evidence related to nut consumption and the incidence of T2D. A number of SRMAs involving cross-sectional or prospective cohort studies have been published investigating associations between the frequency of nut consumption and the prevalence and/or the incidence of T2D risk. Most have not reported a significant association when comparing the highest to the lowest categories of nut consumption, nor were dose-response relationships observed [54–58]. Only one of these meta-analyses of prospective cohort studies showed a significant inverse association with the risk of T2D [59]. However, a key limitation is that most of these SRMAs included studies combining nuts with other plant foods as the exposure (i.e., peas, seeds, or legumes) and, therefore, the associations cannot be extrapolated specifically to the possible role of nuts per se [55,58,59]. Additionally, in some of the observational studies, the associations were adjusted for body weight or BMI, a potential mediator of the associations [11] and, therefore, possibly attenuating an association.

In 2021, an updated SRMA of cross-sectional (n = 3) and prospective (n = 5) studies, including only those with nuts alone as an exposure, was published [13]. The included studies were conducted in the United States (5 studies), Europe (3 studies), and Asia

(1 study). Findings from the meta-analyses of the cross-sectional studies (n = 72,559; 7559 cases of T2D) showed no significant association with diabetes prevalence when the highest compared to the lowest categories of total nut consumption was assessed (OR: 0.91; 95% CI: 0.83 to 1.01). When the prospective cohort studies were analyzed, no associations with risk of T2D were observed with consumption of total nuts (relative risk [RR]: 1.04: 95% CI: 0.94 to 1.15), tree nuts (RR: 0.98; 95% CI 0.87 to 1.11), or peanuts (RR: 0.95; 95% CI: 0.87 to 1.04). When peanut butter consumption was specifically assessed, it was shown to be inversely associated with T2D incidence (RR: 0.87; 95% CI: 0.77 to 0.98). Furthermore, there was no evidence of a linear dose-response or nonlinear dose-response gradient for the total nut or peanut consumption in prospective cohort studies. Of note, these analyses were adjusted for baseline BMI. Across all nut exposures evaluated, the certainty of the evidence was considered to be very low. The reduction in the risk of T2D seen in sensitivity analyses of this meta-analysis suggested that weight loss or decreased weight might mediate the reduction in risk, although appropriate statistical mediation analyses using repeated assessments are needed to confirm this assumption. It is important to highlight that in relation to the type of tree nuts, only one cross-sectional (n = 27,563) [15] and one prospective cohort (n = 137,956) study [14] had analyzed the association between the frequency of walnut consumption and T2D risk, reporting in both cases an inverse association with the prevalence and incidence of T2D, respectively. Of note, the largest prospective cohort study involving American adults participating in the Nurses' Health Study (NHS; 58,063 women aged 52–77 [1998–2008]) and NHS II (79,893 women aged 35–52 years [1999–2009]), free of diabetes, cardiovascular disease, or cancer at baseline, observed that consumption of $\geq$2 servings/week (where 1 serving = 28 g) of walnuts had a 24% (95% CI: 6–38%) lower risk of developing T2D than those that never or almost never consumed walnuts after adjustment for baseline BMI [14].

Following the publication of the 2021 SRMA by Becerra-Tomás and colleagues, two additional cross-sectional studies from Italy and Spain involving community-dwelling adults have been published. Both studies reported no association between nut consumption and the prevalence of T2D [16,17].

In view of the studies published to date, new research is needed that prospectively assesses differences in existing cohorts. Moreover, dose-response analyses are warranted in the future to determine the total amount of nuts associated with possible diabetes-related health benefits to better inform guidelines and practice.

3.2. Clinical Trial Evidence

Unfortunately, to date, no clinical trials have been conducted with the primary aim of testing the ability of nut supplementation to reduce or prevent the incidence of diabetes, probably because such types of trials are very expensive and difficult to perform. However, data is available in relation to a secondary analysis conducted in the context of the PREDIMED (PREvención con DIeta MEDiterránea) study, a randomized controlled trial aiming to assess the effect of a Mediterranean diet supplemented with virgin olive oil or nuts in comparison to a low-fat diet on primary prevention of cardiovascular disease [31].

A sub-analysis of this RCT conducted in participants from one of the 23 recruiting study centers (located in Reus, Spain) reported a beneficial effect of the Mediterranean diet enriched with 30 g/day of tree nuts (walnuts, almonds, and hazelnuts) on T2D prevention [31]. Results from the PREDIMED trial as a whole showed a non-significant decrease in the incidence of T2D when compared to participants in the group receiving the low-fat dietary advice [32,33]. It is important to recognize that due to the study design, it is not possible to quantify the beneficial effects secondary to the Mediterranean diet intervention or the nuts that participants consumed throughout the trial.

4. Nuts and Diabetes Management

Table 1 also summarizes epidemiological and clinical findings related to nut consumption and diabetes management.

4.1. Epidemiological Evidence

There is a lack of epidemiological evidence for the role of nut consumption in individuals with T2D for glucose control and the management of complications.

Of the available evidence, one prospective analysis including 16,217 men and women, from the Health Professionals Follow-up Study (HPFS, 1986–2014) and NHS (1980–2014), respectively, with diabetes mellitus at baseline or diagnosed during follow-up, showed that higher total nut consumption was associated with a lower risk of cardiovascular disease (CVD) incidence and mortality [18]. Specifically, for participants who consumed $\geq$5 servings of total nuts per week (1 serving = 28 g), compared to those who consumed <1 serving per month, multivariate-adjusted hazard ratios (HR; 95% CIs), showed reductions in total CVD incidence (HR = 0.83; 95% CI: 0.71–0.98; p trend = 0.01), coronary heart disease incidence (HR = 0.80; 95% CI: 0.67–0.96; p trend = 0.005), CVD mortality (HR = 0.66; 95% CI: 0.52–0.84; p trend < 0.001), and all-cause mortality (HR = 0.69; 95% CI: 0.61–0.77; p trend < 0.001). For specific types of nuts, higher tree nut consumption was associated with a lower risk of total CVD, coronary heart disease incidence, and mortality because of CVD, cancer, and all causes, whereas peanut consumption was associated with lower all-cause mortality only (all p trend <0.001). This study showed that higher consumption of nuts, especially tree nuts, may be associated with lower CVD incidence and mortality among participants with T2D.

A SRMA of four prospective cohort studies (n = 202,751) assessed the relationship of nut consumption with diabetes-related mortality, indicating higher nut intake to be associated with reduced risk of mortality from diabetes compared to the lowest intake [19]. A similar response was observed in the dose-response analysis, with a 39% reduction in the relative risk of diabetes mortality being observed with a one-serving/day (1 serving = 28 g) increase in nut consumption. Based on the findings of this SRMA and the assumption that the associations observed between nut consumption and diabetes mortality are causal, the authors estimated that for the regions assessed (i.e., North and South America, Europe, Southeast Asia, and Western Pacific), 139,000 deaths due to diabetes may be attributed to a nut intake below 20 g/day.

4.2. Clinical Trial Evidence

In clinical trials, consumption of nuts alone and when added to high GI foods show a lowering in postprandial glycemia when compared to the high GI food alone in people with diabetes. In an acute trial conducted in healthy individuals (n = 14) and in individuals with T2D (n = 10), mixed nuts at three different doses significantly reduced the glycemic response in comparison to white bread [23]. As previously noted, this trial also showed that adding mixed nuts to white bread progressively reduced the glycemic response of the meal. However, in individuals with T2D, the reduction in glycemic response was half that seen in healthy individuals. In a randomized crossover trial, the acute effects of almond intake were assessed in men with T2D (n = 7) randomized to consume a control (white bread, butter, cheese) and a test (white bread, almonds) meal. The test meal was found to be associated with lower postprandial glycemia and insulinemia, and an increased estimated glucose metabolic clearance rate [29]. Almonds were also assessed in another acute randomized controlled trial involving participants with (n = 7) and without (n = 12) diabetes [21]. Findings showed consumption of 28 g of almonds with a test meal, composed of a bagel, juice, and butter, significantly reduced postprandial glycemia in participants with diabetes but not those without diabetes when compared to the test meal without almonds.

Several SRMAs of RCTs have been conducted assessing the effect of tree nut(s) on markers of glycemic control in people with diabetes. In 2014, an SRMA of 12 RCTs assessing the effect of tree nuts on glycemic control in people with diabetes (n = 240) showed a significant lowering in fasting glucose (8 comparisons, MD = −0.15 mmol/L; 95% CI: −0.27, −0.02 mmol/L; I^2 = 35%) and HbA1c (8 comparisons, MD = −0.07%: 95% CI: −0.10, −0.03%; I^2 = 37%), with no significant effect on fasting insulin or HOMA-IR [35].

A 2019 SRMA of 40 RCTs (n = 2832) assessing the effect of tree nut or peanut intake in people with and without diabetes showed no significant effect on fasting glucose or HbA1c, and subgroup analyses by diabetes status showed no deviation from the main findings for either outcome [40]. There were a few differences in the inclusion/exclusion criteria between the 2014 and 2019 SRMAs. The 2019 SRMA [40] included trials using nut oil or peanuts as a treatment arm, non-isocaloric comparison arms, and studies published only in English. The 2014 SRMA [35] included only studies using whole tree nuts as the treatment arm, isocaloric comparison arms, and included studies that were not published in English. These differences may explain the discrepancy in findings. A more recent SRMA of RCTs published in 2021 (15 RCTs) assessed the effect of tree nuts on markers of glycemic control in individuals with T2D and showed no significant impact on fasting glucose, HbA1c, or postprandial glucose levels; however, the analysis only included RCTs with a follow-up period of 3 months or less [30]. Between 2020 and 2022 (present day), several other SRMAs of RCTs have been conducted assessing the effect of a specific nut type on markers of glycemic control in people with T2D. Two SRMA's assessed the effect of almond intake; the first SRMA (8 RCTs) showed a significant lowering in HbA1c but no impact on fasting glucose, insulin, or HOMA-IR [36], whereas the second SRMA (9 RCTs) showed no impact on markers of glycemic control, including HbA1c, fasting glucose, and insulin [37]. Another SRMA assessed the effect of pistachio intake in individuals with T2D, prediabetes, and metabolic syndrome (6 RCTs), which showed a significant lowering in fasting glucose and HOMA-IR, but not HbA1c or fasting insulin [34].

Since the publication of the above-mentioned SRMAs, more recent RCTs assessing the effect of nut consumption on glycemic control in people with diabetes have been published. In a 3-month RCT, 45 people with T2D were randomized to either an almond-based, low-carbohydrate diet group or a low-fat diet group. After 3 months, individuals in the almond-based, low carbohydrate diet group showed a significant improvement in HbA1c [38]. In another 3-month RCT, 204 individuals with stable coronary artery disease (~32% of which had diabetes) were randomized to one of three groups: a healthy diet, a healthy diet plus 30 g/d of pecans or a healthy diet plus 30 mL/d of EVOO. After 12-weeks there were no significant differences between groups in regard to fasting glucose, HbA1c, fasting insulin or HOMA-IR [39].

5. Possible Mechanisms of Action of Nuts in Diabetes Prevention and Management

While the possible protective role of nuts in diabetes prevention and management remains to be established with greater certainty, there is potential for a beneficial impact given the unique nutritional composition of nuts and the direct and indirect evidence to date relating relevant dietary constituents with diabetes prevention and management.

There are several proposed and speculative modulatory effects of the constituents of nuts in the prevention and management of T2D that may act synergistically (summarized in Figure 1).

Macronutrients, micronutrients, and other bioactive compounds found in nuts have been suggested to play a role in the regulation of postprandial glycemic and insulinemic levels. Furthermore, body weight management, control of cellular membrane fluidity and lipogenic gene expression, anti-inflammatory and antioxidant properties, and protection of β-cells against glucose toxicity and subsequent impacts on gene expression, microRNAs, and microbiota/metabolomics leading to regulation of postprandial glucose clearance, improving pancreatic insulin secretion, and decreasing insulin resistance have also been implicated with nut consumption or related factors. The following will briefly summarize available and relevant direct and indirect evidence for possible mechanisms for the impact of nut consumption on T2D related to macronutrients, micronutrients, other bioactive compounds, and resulting cellular and molecular mechanisms.

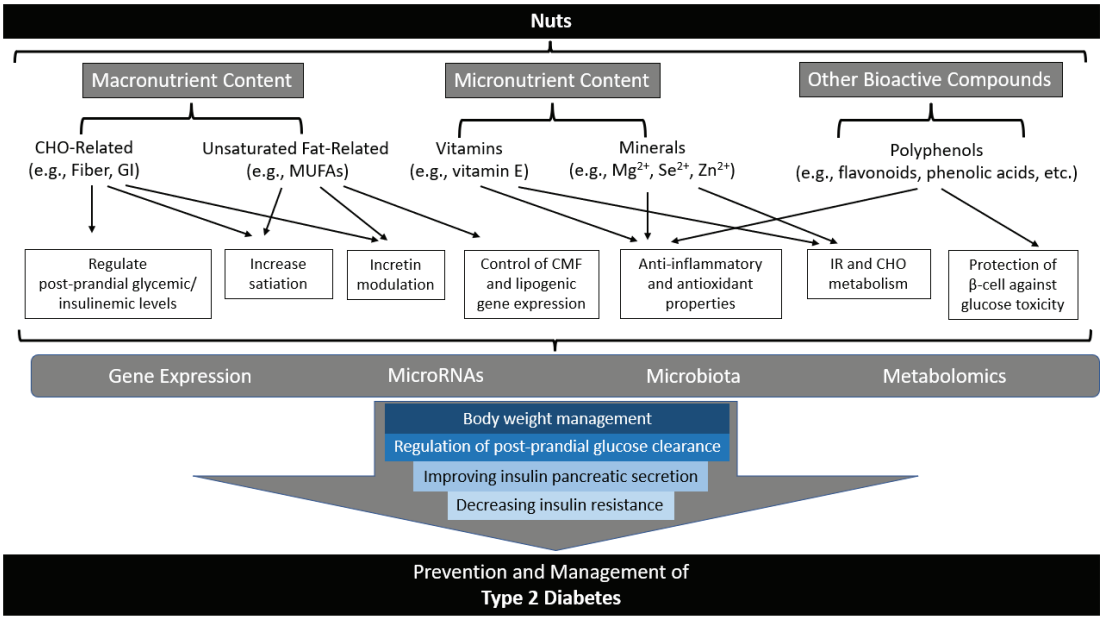

Figure 1. Summary of potential mechanisms of action for the role nuts may play in diabetes prevention and management. Adapted with permission from Ref. [60]. 2017, Hernández-Alonso et al. Abbreviations: CHO, carbohydrate; CMF, cellular membrane fluidity; GI, glycemic index; IR, insulin resistance; MUFAs, monounsaturated fatty acids; RNA, ribonucleic acid.

5.1. Related to Macronutrient Composition of Nuts

5.1.1. Low Glycemic Index and Fiber

Nuts contain low amounts of available carbohydrates, meaning they do not contribute significantly to postprandial glycemia [61,62]. However, when nuts are added to foods with a high available carbohydrate, they demonstrate a dose-dependent reduction in the glycemic index or relative glycemic response of the composite meal [27,42]. This is thought to be due to their fat and protein content, which are a source of additional energy when added to food with highly available carbohydrates [27,61]. Several studies conducted around 20 years ago demonstrated that an increase in energy density from high-fat, protein, and/or high-fiber containing foods decreases gastric emptying [27,42,63–65]. Therefore, as the dose of nuts is increased, the rate of gastric emptying decreases, which may increase feelings of satiety and would decrease the postprandial glycemic response [27].

Nuts are also a source of dietary fiber [8,9]. Soluble fiber has been shown to increase the viscosity of intestinal contents and slow down the absorption of nutrients in the gastrointestinal tract [66]. Consumption of meals/foods containing soluble fiber have been shown to lower postprandial glycemia [66].

Fiber has also been shown to be resistant to digestion by enzymes in the small intestine and, as a result, susceptible to fermentation by bacteria in the colon, which leads to the production of short-chain fatty acids (SCFA) [66]. SCFAs have been shown to reduce hepatic glucose output and stimulate the secretion of the incretin hormone glucagon-like peptide 1 (GLP-1) [67,68]. GLP-1, as well as other incretins such as gastric inhibitory polypeptide (GIP), promote the proliferation of beta-cells and their secretion of insulin, which favors the maintenance of blood glucose levels [69]. As such, the consumption of nuts may slow the absorption of carbohydrates and stimulate incretin secretion, which can positively impact glucose homeostasis.

Furthermore, repeated decreases in postprandial glucose peaks, such as that observed with nut consumption, have been hypothesized to contribute to decreased inflammation, oxidation processes, and mitochondrial toxicity, further contributing to reductions in the risk of diabetes [60].

5.1.2. Fatty Acids: Unsaturated vs. Saturated

Nuts have a high unsaturated fat content [8,9]. Substitution of carbohydrates or saturated fats (SFA) with unsaturated fats may be responsible for improvements in insulin sensitivity [40,70]. This was supported by an SRMA of 102 RCTs, which showed replacing carbohydrates or SFAs with monounsaturated or polyunsaturated fatty acids (MUFAs or PUFAs, respectively) improved markers of glycemic control, including HbA1c and HOMA-IR [70,71]. It should be noted that evidence involving the study of PUFAs tended to include a combination of these fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) along with alpha-linolenic acid (ALA); whereas, the PUFA found in nuts is ALA. Accordingly, additional investigation specific to ALA would better elucidate whether the PUFA content of nuts have the observed beneficial effects observed across overall PUFAs.

The quality of dietary fat can affect cell membrane composition and function, including membrane fluidity, insulin receptor binding/affinity, as well as facilitating the movement of the glucose receptor to the cell surface, which in turn can affect insulin sensitivity [72–75].

Dietary fat quality may also be involved in regulating gene expression and enzyme activity [72,76]. A diet high in unsaturated fatty acids, in particular, long-chain omega-6 and omega-3 polyunsaturated fatty acids, has been shown to lead to the suppression of lipogenic genes (genes of lipid synthesis) and induction of genes involved with fatty acid oxidation, which may reduce hepatic insulin resistance. Saturated fat and monounsaturated fat, on the other hand, do not appear to impact these same mechanisms. This was supported by a recent SRMA of 30 RCTs assessing the effect of omega-3 fatty acid supplementation on several cardiometabolic markers in people with T2D, which showed a significant lowering in HbA1c, fasting glucose and HOMA-IR [77].

Unsaturated fatty acids from nuts may also stimulate the secretion of GLP-1, which stimulates the secretion of insulin from beta-cells and promotes the proliferation of beta-cells and, therefore, improves beta-cell efficiency [70,78,79].

5.2. Related to Micronutrients and Other Bioactive Components of Nuts

A number of minerals, vitamins, and other bioactive components, which may be found within the nutritional composition of nuts, have been suggested to be protective against T2D and beneficial in the management of related complications.

5.2.1. Vitamins and Minerals

Nuts, depending on the type, contain relatively high amounts of vitamin E, magnesium, and selenium, among other nutrients [7–9]. While direct evidence does not appear to be currently available for the impact of the content of micronutrients from nut consumption specifically on the risk and management of T2D, there is evidence from epidemiological and oral micronutrient supplementation studies suggesting nutrients that are found in relatively high amounts in nuts may be beneficial.

Evidence from multiple SRMAs has supported the association of specific vitamins and minerals, analogous to those found in nuts, with markers of glycemic control and prevention of T2D [80–85]. When oral supplementation of antioxidant vitamins and minerals (such as those found in nuts: vitamin E, selenium, and zinc) were assessed in a SRMA of RCTs considering people with T2D, supplementation of zinc (30 to 660 mg/day) and vitamin E (200 to 800 IU/day) reduced HbA1c, and zinc reduced fasting blood sugar. None of the nut-associated micronutrient supplements were effective in the reduction of insulin, HOMA-IR, or HOMA-B, and all evidence was considered to be low certainty [85].

Magnesium has also been associated with beneficial effects on glycemic control. Imbalances in magnesium status, specifically hypomagnesemia, have been shown to inhibit glucose transporter type 4 translocation, increase insulin resistance, and affect lipid metabolism, oxidative stress, and the antioxidant system of endothelial cells [82]. A SRMA of 12 observational studies showed significantly lower circulating magnesium levels in people with prediabetes compared to individuals with good health [83]. Further, a 100 mg/day increase in oral magnesium intake has been associated with a 15% reduction in T2D risk (SRMA prospective cohort studies, n = 286,668). For perspective, a 100 mg amount of magnesium is approximately equivalent to the magnesium content in about $\frac{1}{4}$ cup of nuts, depending on nut type [8,9]. When considering individuals with T2D, oral magnesium supplementation, equivalent to just over $\frac{1}{2}$ cup of nuts, significantly improved glycemic control indicators, including HbA1c, IL, C-peptide, HOMA-IR, and HOMA-B and insignificantly decreased fasting blood glucose [86]. However, the impact of magnesium when consumed as a constituent of nuts may respond differently within the body compared to an oral magnesium supplement and further investigation may shed light on the possible role magnesium and/or other micronutrients from the consumption of nuts may have in the prevention and management of type 2 diabetes.

5.2.2. Phenolics and Other Bioactive Compounds

Nuts are composed of a matrix of other important bioactive compounds, including polyphenols of various types (e.g., flavonoids, phenolic acids, stilbenes, lignans, other polyphenols) and concentrations (e.g., 126 to 1576 mg total polyphenols per 100 g nuts) [87–89]. There have been a number of investigations into the polyphenol characteristics of nuts and, independently, a number of studies have assessed the role of polyphenols in diabetes progression and management. For example, polyphenols may improve HbA1c and insulin resistance, in addition to having anti-inflammatory and antioxidant properties such as superoxide dismutase (SOD)-like activity, 1,1-diphenyl-2-picrylhydrazyl (DPPH), and radical scavenging activity. In these ways, various polyphenols may lower the risk of developing diabetes and its complications. However, there is limited evidence confirming the role of polyphenols from nuts in glycemic control, insulin sensitivity, and ultimately in the prevention and management of diabetes [87,90,91]. Polyphenols in nuts may also be protective against diabetes by modifying the gut microbiota (discussed further in Section 5.4.1). Currently, nuts appear to provide only a small percentage of polyphenols in the diet based on cohort data and global average nut intake levels [88,89,92]. Yet, consumption of approximately 50 g/day of nuts could provide the polyphenol dose observed with reduced T2D incidence [88].

5.3. Related to Body Weight and Adiposity

Approximately 60% to 90% of T2D has been attributable to obesity or weight gain; moreover, elevated weight can increase the risk of complications and comorbidities in people with diabetes [93,94] While nuts appear to be relatively high in calculated total calories and fat, their consumption has not been associated with weight gain nor an increased risk of overweight or obesity [95]. Conversely, despite their high energy density, a SRMA of six prospective cohort studies (n = 569,910) and 86 RCTs (n = 5873) indicated nut intake was associated with lower incidence of overweight/obesity (RR 0.93; 95% CI: 0.88 to 0.98), had no effect on body weight, and meta-regression showed higher nut consumption to be related to reductions in body weight and body fat [95]. Furthermore, adiposity factors (i.e., body mass index (BMI) and waist circumference) have been shown to play a role in mediating the association between nut consumption and markers of glycemic control (i.e., fasting blood glucose, plasma insulin, HOMA-IR, HbA1c, and OGTT) suggesting a potential mechanism for the prevention of diabetes risk [11].

5.4. Related to Cellular and Molecular Mechanisms of Nuts

As briefly noted in Sections 3.1 and 3.2, the nutrient composition and bioactive compounds contained in nuts may play a role in preventing and managing diabetes through different cellular and molecular mechanisms, including the modulation of gut microbiota, modifying gene expression, or mediating gene expression through microRNAs (miRNAs). The following discusses evidence available explicitly related to nuts and these aspects.

5.4.1. Gut Microbiota

Within the complex nutrient matrix of nuts, some of the components, such as fiber and polyphenols, can reach the colon intact and interact with the gut microbial population changing its composition and function [66]. The microbial colonic fermentation of undigested fiber and other nutrients from nuts can lead to the production of metabolites, such as SCFA (e.g., butyrate and propionate), with well-demonstrated positive effects for gut microbial homeostasis and may serve as a prebiotic [96,97].

SCFAs can induce their beneficial effects on glucose homeostasis by reducing gut motility and appetite stimulating the expression of peptide YY via the G-protein-coupled receptors (Gpr41 and Gpr43) [98]. Additionally, SCFAs may activate Gpr41 and Gpr43 on L-cells subsequently triggering the secretion of GLP-1, which improves glucose homeostasis by increasing the secretion of insulin and decreasing the secretion of glucagon. The activation of Gpr43 inhibits insulin signalling in adipocytes and fat accumulation in adipose tissue. Butyrate and propionate promote intestinal gluconeogenesis, reducing the risk of T2D. Butyrate also suppresses the action of histone deacetylase (HDAC), which induces insulin resistance by acting in different molecular pathways [99].

Nuts are also rich in polyphenols [87–89], and undigested polyphenols are thought to exert a prebiotic effect by stimulating the growth and activity of some bacteria, such as Bifidobacteria, in the digestive tract [100]. Increased levels of fecal Bifidobacteria have been associated with improved glucose tolerance and diminished inflammatory markers such as the interleukins IL-6, IL-1α and IL-1β, tumor necrosis factor α, and monocyte chemoattractant protein-1 [101].

Considering specific nut types, the effects of almonds on gut microbiota, glycometabolism, and inflammatory parameters in individuals with T2D have been explored in a systematic review conducted by Ojo et al. [36]. The results suggest that an almond-based diet could promote the growth of SCFA-producing bacteria in the gut. Walnuts are also rich in polyphenols and ellagitannins, which are metabolized by intestinal bacteria into urolithins. It has been shown that walnut supplementation, even if short-term, can impact the metabolism of ellagitannins to urolithins via gut microbiota by increasing the production of SCFA (such as acetate, butyrate, and propionate) [102]. This may impact the risk of T2D, as it has been observed that propionate can reduce serum cholesterol and improve insulin resistance, as well as promote satiety [103].

5.4.2. Gene Expressions

Some nut components or their metabolites may act at the cellular level, modifying gene expression. Few studies have analyzed the impact of nut consumption on changes in gene expression in cells or tissues related to proteins that have important potential effects on carbohydrate metabolism, insulin resistance, or adiposity. The crossover EPIRDERM Study assessed the effect of pistachio intake (57 g/d for 4 months) versus a nut-free control diet on insulin resistance and T2D in participants with prediabetes (n = 54) showing changes in peripheral leukocyte gene expression and cellular glucose update [78]. Gene expression data showed that pistachio consumption, compared to control, significantly decreased the expression of interleukin-6 and resistin. Moreover, pistachio intake was shown to facilitate glucose transporter gene expression as assessed by SLC2A3 and SLC2A4 which showed different patterns. For instance, SLC2A4 appeared to be significantly increased in the control compared to pistachio phases. The percentage of change in cellular glucose transport activity also differed between the pistachio and control groups. Similarly, a

significantly increased SLC2A4 protein expression on the surface of lymphocytes has been described in both individuals with diabetes and impaired glucose metabolism [104]. Consistent with this, attenuation in the expression of glucose transporters, with pistachio consumption leukocytes, was observed to be significantly expressed in T2D. Therefore, these results suggest a potential mechanism by which pistachios could lead to an improved systemic inflammatory profile increasing insulin sensitivity, as has been observed in the EPIRDERM study.

In a clinical trial conducted in 24 healthy participants, the consumption of hazelnuts (40g/d for 6 weeks) did not lead to weight gain, possibly due to the improvement of the body's antioxidant capacity by the upregulation of genes [codifying superoxide dismutase 1 (SOD1), catalase (CAT), macrophage migration inhibitory factor (MIF), peroxisome proliferator-activated receptor gamma (PPAR-ɣ), vitamin D receptor (VDR) and methylenetetrahydrofolate reductase (MTHFR)] implied in oxidant reactions and inflammation [105]. Some of these genes have also been related to insulin resistance or diabetes.

5.4.3. MicroRNAs

Nuts may modulate the expression of genes related to glucose metabolism through the mediatory effect of nutrients on microRNAs (miRNAs), defined as small non-coding RNAs with 20 to 25 nucleotides that post-transcriptionally and negatively regulate gene expression.

In the EPIRDERM Study, seven human circulating miRNAs were selected for analysis, that are considered widely related to glucose metabolism, insulin resistance status, prediabetes status, and biomarkers of T2D. The miRNA expression data showed that of the seven miRNAs studied, after pistachio intervention, circulating miRNA-192 and 375 expressions were significantly lower than in the control phase [78]. Furthermore, changes in the circulating miRNA-192 and miRNA-375, were positively associated with plasma glucose, insulin, and HOMA-IR, indicating that an increase in these miRNA levels mirror an increase in insulin resistance.

Similarly, in another trial involving 10 healthy women, 8 weeks of following a PUFA-enriched (achieved via daily intake of 30 g of almonds and walnuts) normocaloric diet resulted in significant modifications to several common miRNAs [106]. Specifically, the authors found that changes in circulating PUFAs were associated with changes of plasma miRNA-106a; changes in plasma miRNA-130b and miRNA-221 were associated with changes in plasma C-reactive protein, and changes in plasma miRNA-125a-5p was associated with changes in plasma fasting triglycerides and adiponectin.

5.4.4. Metabolomics Modulation

Nutritional metabolomics is an emergent approach to obtaining deeper insights into diet–disease association that holds great promise in improving our understanding of the biological effects of nutritional factors and may help to identify potential novel markers of dietary intake and disease risk [107]. To date, a few studies have evaluated the impact of nut consumption on plasma or urinary metabolites [108].

Metabolomics has been used as an agnostic machine learning approach to identify plasma metabolites associated with walnut consumption using data from the PREvención con DIeta MEDiterránea (PREDIMED) study [109]. A metabolite profile including 19 metabolites (including lipids, purines, acylcarnitines, and certain amino acids) was associated with walnut consumption and with a lower risk of T2D incident in a Mediterranean population at high cardiovascular risk. These findings provide new insights into potential biological mechanisms explaining the effect of nut consumption on diabetes risk.

6. Current Strengths and Limitations

There are several strengths and limitations of the available evidence. Strengths, in general, include the relatively long follow-up duration of multiple years observed in the epidemiological studies and data from various countries allowing for potential general-

izability of the findings. However, the cross-sectional and prospective cohort studies are limited by the inability to determine causation. A cross-sectional study design is also limited by the lack of ability to assess a temporal relationship between the exposure and the outcome. Additionally, most studies included in this review tended to obtain intake data via food frequency questionnaires (FFQs). FFQs have inherent weaknesses as they are subject to possible measurement error and recall bias [110]. Further, data from these FFQs were limited by the questions asked, as they often assessed a combination of nuts rather than a specific nut type and did not provide data on their preparation, such as whether the nuts were salted, spiced, roasted, or raw. Tree nuts and peanuts were often grouped together in the FFQs and were sometimes also combined within a question, including seeds and/or legumes. The doses of nut intake studied were also relatively low, even in the highest quantile of the analyses (with estimated median nut intakes ranging from 0 to 213 g/week), or were not sufficiently described, being presented as times or servings per day without an equivalent gram amount noted. Moreover, the majority of prospective cohorts evaluated nut intake at baseline as the dietary exposure; however, dietary habits may have changed over the course of the study follow-up period. This could have potentially resulted in misclassification of the exposure to nuts, hence biasing results and possibly explaining null associations observed with T2D. Of note, only a few large cohort studies have collected repeated measures of nuts and other dietary factors; these include the Nurses' Health Study and Health Professionals' Follow-up Study [18], in which diet was assessed every 4 years over 3–4 decades of follow-up. These repeated measures not only represent long-term dietary habits, but also can reduce measurement errors. Finally, as aforementioned, some prospective studies assessing the association between the frequency of nut consumption and diabetes risk have adjusted the analyses for body weight, which is an important determinant of diabetes and, thus, may lead to an attenuation of potential associations. Future cohort studies should carefully evaluate the role of body weight in mediating the association between total and different types of nut consumption and the risk of T2D.

While evidence from both acute and chronic RCTs in individuals with diabetes suggests nut consumption may improve glycemic control via reductions in fasting glucose and HbA1c, the effect still needs to be confirmed by updated SRMAs studying individuals with and without diabetes separately and without mixing interventions of whole nuts with nut oils or other extracts from nuts. It would also be useful to better understand which foods should be replaced with nuts in the diet for the most beneficial impact, as the current trials vary in this regard—some prescribe proportional reductions to all foods, and some suggest replacing for carbohydrate- or saturated fat-rich foods. In contrast, others provide no specific instructions on food replacement. Glycemic control assessment methods are also limited, and there is a lack of direct evidence from clamp studies or from Bergman´s minimal model, which may provide a greater understanding of metabolic regulation [111]. Moreover, there is limited trial evidence for the effect of pecans, pine nuts, Brazil nuts, macadamias, or peanuts in this area. However, since most nut types have similar nutrient profiles, the findings and associated recommendations are likely to be able to be extended to include all types of nuts.

In addition to the limitations to the currently available evidence, there are also a few potential barriers to nut consumption, such as nut-related allergies, cost, dental or swallowing issues, especially in older adults, and lack of knowledge of health benefits by health professionals [112]. This, in conjunction with the limited research evidence to support knowledge and potential recommendations, could potentially explain the relatively low intake levels of nuts by individuals worldwide [92].

7. Future Directions

Future research is needed to better elucidate the impact of nuts on the prevention and management of T2D. Given the current research limitations and limited epidemiological

and clinical trial evidence available, there are several lines of research that could provide greater insight and better inform diabetes dietary guidelines.

Further investigation via prospective cohorts assessing the impact of nuts on diabetes incidence and pooled cohort analyses needs to be undertaken. Pooling data from currently conducted prospective cohorts may provide a relatively cost-effective and informative real-world way to explore the possible role of nuts in diabetes prevention and complications. Additionally, more studies in individuals with T2D are needed to demonstrate the impact of nuts on glycemic control (e.g., HbA1c, etc.). To determine a possible causal effect, conducting larger and longer RCTs (such as a multicentre RCT) evaluating markers of glycemic control as primary endpoints is needed in order to expand current knowledge to assess the effect of nuts on diabetes prevention in high-risk participants. Acutely, insulin sensitivity analysis testing the effect of nut consumption, such as replacing carbohydrates, using the Bergman Minimal Model of glucose regulation and clamps would aid in increasing the strength of available evidence.

Further explorations related to metabolomic and metagenomic signatures of nut consumption in clinical trials and assessing the association in long-term cohort studies of diabetes incidence and complications would additionally provide greater insights into a potential diet (nut)–disease (diabetes) association. Then a range of mechanistic molecular biological studies may be justified when a clear phenomenon, such as reduced insulin resistance and improved diabetes control, has been established.

8. Conclusions

Of the limited evidence currently available, overall findings suggest higher nut consumption may have beneficial effects on diabetes prevention and management. In particular, some but not all large cohort studies have found that higher consumption of total nuts, walnuts, and peanuts was significantly associated with a lower risk of T2D. Moreover, inclusion of nuts in the diets of individuals may have a beneficial effect on glycemic control and lower the risk of cardiovascular disease and mortality in those with T2D. In individuals with T2D, specifically, acute studies have demonstrated reductions in postprandial glucose levels, and long-term trials have indicated modest positive effects on blood glucose control, as shown by reductions in HbA1c and fasting blood glucose. Mechanistic pathways provide further promise for the potential role nut consumption may have in diabetes prevention and management. Despite all the potential diabetes-related health benefits nuts may pose, current evidence is not definitive, and there remains much opportunity for future research to address present weaknesses and limited data in this field to provide more conclusive evidence on the role of nuts in the prevention and management of diabetes.

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He is a founding member of the International Carbohydrate Quality Consortium (ICQC), Chair of the Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD), is on the Clinical Practice Guidelines Expert Committee for Nutrition Therapy of the EASD, and is a Director of Glycemia Consulting and of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. 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He is a member of the International Carbohydrate Quality Consortium (ICQC). His wife, Alexandra L Jenkins, is a director and partner of INQUIS Clinical Research for the food industry, his two daughters, Wendy Jenkins and Amy Jenkins, have published a vegetarian book that promotes the use of the foods described here, The Portfolio Diet for Cardiovascular Risk Reduction (Academic Press/Elsevier 2020 ISBN:978-0-12- 810510-8), and his sister, Caroline Brydson, received funding through a grant from the St. Michael's Hospital Foundation to develop a cookbook for one of his studies. 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Review

Effects of Nut Consumption on Blood Lipids and Lipoproteins: A Comprehensive Literature Update

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Abstract: In the present review, we provide a comprehensive narrative overview of the current knowledge on the effects of total and specific types of nut consumption (excluding nut oil) on blood lipids and lipoproteins. We identified a total of 19 systematic reviews and meta-analyses of randomized controlled trials (RCTs) that were available in PubMed from the inception date to November 2022. A consistent beneficial effect of most nuts, namely total nuts and tree nuts, including walnuts, almonds, cashews, peanuts, and pistachios, has been reported across meta-analyses in decreasing total cholesterol (mean difference, MD, −0.09 to −0.28 mmol/L), LDL-cholesterol (MD, −0.09 to −0.26 mmol/L), and triglycerides (MD, −0.05 to −0.17 mmol/L). However, no effects on HDL-cholesterol have been uncovered. Preliminary evidence indicates that adding nuts into the regular diet reduces blood levels of apolipoprotein B and improves HDL function. There is also evidence that nuts dose-dependently improve lipids and lipoproteins. Sex, age, or nut processing are not effect modifiers, while a lower BMI and higher baseline lipid concentrations enhance blood lipid/lipoprotein responses. While research is still emerging, the evidence thus far indicates that nut-enriched diets are associated with a reduced number of total LDL particles and small, dense LDL particles. In conclusion, evidence from clinical trials has shown that the consumption of total and specific nuts improves blood lipid profiles by multiple mechanisms. Future directions in this field should include more lipoprotein particle, apolipoprotein B, and HDL function studies.

Keywords: nuts; cholesterol; lipids; apolipoproteins

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1. Introduction

Cardiovascular diseases (CVD), specifically coronary heart disease (CHD) and stroke, are leading causes of death and disability-adjusted life years worldwide [1]. Dyslipidemia (elevated levels of low-density lipoprotein cholesterol (LDL-cholesterol) or triglycerides (TG) in blood, decreased levels of high-density lipoprotein cholesterol HDL-cholesterol, or other lipoprotein disturbances) is a well-documented risk factor for the development of atherosclerotic CVD [2]. CVD and its related risk factors are largely preventable. Therefore,

effective approaches for the prevention of CVD, including changes in lifestyle and diet, are key to reducing the consequences of dyslipidemia and the associated disease burden to improve population health.

Dietary interventions to lower blood cholesterol concentrations and modify blood lipoprotein levels are the cornerstone of prevention and treatment for CHD and other atherosclerotic diseases. Indeed, suboptimal dietary intake was responsible for an estimated one in five premature deaths globally from 1990 to 2016 [3]. In the United States (U.S.), suboptimal diets were associated with more deaths than any other risk factor. In 2016, dietary risk factors were responsible for an estimated 529,300 deaths, of which 84% were due to CVD [4]. Among individual dietary components, the largest estimated mortality was associated with an excessive sodium intake (9.5%) followed by the suboptimal consumption of nuts/seeds, among others [5]. In addition, in 2017 a diet low in nuts and seeds was the fourth leading risk factor for all-cause mortality globally, after a diet low in whole grains, a diet high in sodium, and a diet low in fruits [5].

Nuts and seeds, along with other plant foods such as whole grains, vegetables, fruits, and legumes, are key components of recommended healthy diet patterns worldwide such as the Mediterranean diet. Nuts are a good source of unsaturated fatty acids and are rich in fiber, minerals (potassium, calcium, and magnesium), vitamins (folate and vitamin E), phytosterols, and polyphenols. The fatty acid composition varies widely among different types of nuts [6]. Almonds, hazelnuts, pistachios, cashews, and peanuts are rich in monounsaturated fatty acids (MUFAs), whereas walnuts are rich in polyunsaturated fatty acids (PUFAs) [6,7].

In recent decades, an extensive body of evidence has linked nut consumption to a wide range of health benefits including reduced risk and prevention of cardiometabolic diseases [8], making them a key dietary recommendation for health promotion and disease reduction. In large prospective cohort studies, frequent nut consumption has been inversely associated with the risk of type 2 diabetes, metabolic syndrome, CVD, and total and cause-specific mortality [8]. These findings are consistent with the results of the PREvención con DIEta MEDiterránea (PREDIMED) study, a primary prevention trial that found a 28% reduction in incident cardiovascular events among participants randomly assigned to a Mediterranean diet supplemented with nuts [9]. In addition, short-term trials have demonstrated the beneficial effects of nut consumption on intermediate markers of CVD risk, including LDL-C [10]. Importantly, more than 60 human dietary intervention studies have been conducted investigating the effects of nut consumption on blood lipid levels. These studies differ in the type and quantity of the nuts consumed, placebo/diet control, study design, subject selection criteria, and duration.

In the present narrative review, we provide a comprehensive overview of the current knowledge on the effects of total and specific types of nut consumption (excluding nut oil) on blood lipids and lipoproteins in clinical trials, the potential mechanisms of the lipid effects of nuts, and the future directions for research in this area.

2. Effects of Nuts on Blood Lipids

We conducted a literature search in PubMed (https://pubmed.ncbi.nlm.nih.gov/, accessed on 22 December 2022) for systematic reviews and meta-analyses of randomized controlled trials (RCTs) that examined the effect of nut consumption on blood lipid biomarkers from the inception date through 20 November 2022. The search strategy was as follows: (nuts[MeSH] OR "tree nuts" OR nut OR almonds[MeSH] OR almond OR walnuts[MeSH] OR walnut OR cashews[MeSH] OR cashew OR pistachios[MeSH] OR pistachio OR peanuts[MeSH] OR peanut OR "peanut butter") AND (meta-analysis OR "systematic review") AND (English[lang]). We restricted the search to adult human trials and to articles published in English. Selected articles were required to focus on whole nuts or nuts-enriched food interventions, and to report on at least one lipid variable (TC, LDL cholesterol, HDL cholesterol, TGs, or apolipoproteins). We excluded articles that included nut oils as an intervention given their different nutrient matrix.

Numerous systematic reviews and meta-analyses of RCTs that evaluated nut consumption on blood lipid biomarkers have been published [11–29]. Table 1 summarizes 19 selected studies. Three focused on interventions of both nuts and peanuts together [11,12,21], three were on tree nuts [16,18,22], five on almonds [13,15,19,25,29], four on walnuts [17,23,24,26], two on cashews [20,28], one on pistachios [27] and one on peanuts including peanut butter [14]. The doses tested varied from 5 to 200 g/d and the study durations were from 4 days to 2 years.

A significant reduction in LDL-C (mean differences, MD: −0.09 to −0.26 mmol/L; 10 of the 18 meta-analyses analyzing LDL-C) was most consistently reported across meta-analyses, followed by a reduction in triglycerides (TG; MD: −0.05 to −0.17 mmol/L; 9/19 meta-analyses) and total cholesterol (TC; MD: −0.09 to −0.28 mmol/L; 8/19). However, none reported an effect on HDL-C. Del Gobbo et al. (2018) further examined the effect of nuts, specifically tree nuts, on apolipoproteins (Apo) and found a significant reduction in Apolipoprotein B (ApoB) (−0.042 g/L (95% CI: −0.057, −0.026); 13 RCTs) [22]. In one meta-analysis that reported significance, the observed effect of nuts on LDL-C was comparable to up to $\frac{1}{4}$ of the effect of statin medication in populations including primary prevention, hemodialysis, CHD, diabetes, heart failure, and in those at low vascular risk [30,31].

Although the evidence supports a modest effect of nuts in lowering blood lipids/lipoproteins, it is unclear whether some types of nuts are more effective than others. Among tree nuts, walnuts are especially rich in linoleic acid (18:2n–6) and α-linolenic acid (18:3n–3) (ALA) [6]. The meta-analyses demonstrated the beneficial effects of walnuts on reducing TC, LDL-C, and TG [17,18,23,24]. This finding corroborates previous studies showing slightly reduced fasting serum TG [MD: −0.03 mmol/L (−0.11, −0.05)] with increasing ALA intake [32]. Pistachios are particularly rich in phytosterols and dietary fiber, and are high in MUFAs [33,34]. The only meta-analysis (of 12 RCTs) on pistachios found a significant effect of 32–126 g/d during 3–24 weeks in reducing TC (−0.19 mmol/L [95% CI: −0.33, −0.06]), LDL-C (−0.1 mmol/L [95% CI: −0.14, −0.06]), and TG (−0.13 mmol/L [95% CI: −0.16, −0.09]) [27]. Like pistachios, cashews have a high proportion of MUFAs but are lower in tocopherols, phytosterols, and dietary fiber. Few studies have examined the effect of cashew consumption on blood lipids. Two meta-analyses did not find any effect of 28–108 g cashews/d on lipid biomarkers in adult populations (3 RCTs; n = 384 to 392, duration: 4–12 weeks) [20,28]. These results were also confirmed in another meta-analysis [18]. The absence of an effect may be attributed to its differing food matrix or to limited available studies. Almonds are especially rich in alpha-tocopherol [34] and dietary fiber compared with other nuts. A consistent beneficial effect of almonds (10–168 g/d; 5–27 RCTs, n = 120–2,049 healthy or at risk of CVD individuals; 3–77 weeks duration) was reported in LDL-C (−0.15 to −0.18 mmol/L) [13,19,25], TC (−0.13 to −0.28 mmol/L) [19,25], and TG (−0.08 mmol/L) [25]. However, the evidence is less consistent in populations with type 2 diabetes [15,29]. Peanuts, although classified as a legume, have a comparable food matrix and fatty acid composition to those of tree nuts. The effect of 25–200 g/d peanuts or peanut butter consumption during 2–24 weeks on blood lipids was examined in a recent meta-analysis and demonstrated a significant reduction in TG [−0.13 mmol/L (95% CI: −0.2, −0.07)]; 9 RCTs, and 643 participants) [14].

To our knowledge, one RCT was published following the last meta-analysis on nuts and blood lipids that we summarize herein. The Brazilian Nut Study tested the effect of an energy-restricted diet with 45 g nuts (15 g Brazil nuts + 30 g cashews) and without nuts on various biomarkers including blood lipids in 40 women at risk of cardiometabolic disease [35]. After the 8-week intervention, the authors reported a decrease in TC and LDL-C in both groups, but no difference between groups; this is possibly due to the significant weight loss achieved in both the intervention (−3.5 +/−0.6 kg; $p < 0.001$) and the control (−1.8 ± 0.6; $p < 0.05$) groups at the end of the trial.

Table 1. Summary of meta-analyses on the effect of nuts and peanuts on lipid and lipoprotein biomarkers.

Publication	Search Dates	Population	Study Design	Sample Size	Duration of Intervention	Intervention	Control	Outcome Measures	Results Mean Change in mmol/L (95%CI)
Phung, 2009 [13]	through Jul 2008	Non-specified	RCTs with parallel or crossover design	5 RCTs 142 participants	4 weeks	Almonds 25–168 g/d	NCEP step II, usual diet, NCEP step I, high-fat diet, low-fat diet	Lipid profile: TC, LDL-C, HDL-C, TG, LDL/HDL; ApoA-I and apoB Lp(a)	↓LDL-C −0.18 (−0.34, −0.02) (5 RCTs)
Banel, 2009 [24]	through May 2008	All patient populations and age groups	RCTs with parallel or crossover design	13 RCTs 365 participants	4–24 weeks	Walnuts 15–108 g/d	Controlled diet, Western diet, Med diet, modified low-fat diet, habitual diet, low-fat diet, cholesterol lowering meals	Lipid profile: TC, LDL-C, HDL-C, TG	↓TC −0.27 (−0.38, −0.15) ↓LDL-C −0.24 (−0.34, −0.14) (11 RCTs)
Sabaté, 2010 [12]	1992–2004	No recent exposure to lipid-lowering medications	Controlled trials; duration of intervention ≥ 3 weeks; no body weight change between diets at the end of intervention	25 trials 583 participants (pooled analysis with individual participant data)	3–8 weeks	Tree nuts and peanuts 34–100 g/d	Western diet, Med diet, low total, and saturated fat	Lipid profile: TC, LDL-C, HDL-C, TG	↓TC −0.28 (−0.36, −0.2) ↓LDL-C −0.26 (−0.34, −0.19) (25 trials)
Mejia, 2014 [16]	through Apr 2014	Non-specified	RCTs; duration of intervention ≥ 3 weeks	47 RCTs 2211 participants	3 weeks–18 months	Tree nuts (almonds, Brazil nuts, cashews, hazelnuts, macadamia nuts, pecans, pine nuts, pistachios, walnuts, and mixed nuts) 30–85.5 g/d	Habitual diet, diet for diabetes, Western diet, low-fat diet, muffin, NCEP step I diet, AHA step 1 diet, ad libitum diet, NCEP step II diet, NCEP step II diet + muffin, cheese	At least one criterion of MetS (waist circumference, TG, HDL-C, blood pressure, glycemic control)	↓TG −0.06 (−0.09, −0.03) (43 RCTs)
Del Gobbo, 2015 [22]	through Mar 2013	Free of known CVD; Not receiving medication for diabetes, obesity, MetS, hypertension or hyperlipidemia; ≥18 yo	Randomized and nonrandomized controlled trials with parallel or crossover design	42 RCTs and 18 nonrandomized trials 2582 participants	3–26 weeks	Tree nuts 5–100 g/d	Habitual diet, healthy diet, low-fat diet, high-CHO diet, olive oil diet, habitual diet + red meat, low saturated fat diet with cereals and canola oil, AHA step 1 diet, American diet, isocaloric controlled diet, NCEP step 1 or 2 diet, salted pretzels, isocaloric high cholesterol diet, NCEP step 1, Med diet, AHA step 1 diet, ADA diet (with and without nuts)	Lipid profile: TC, LDL-C, HDL-C, TG; apolipoproteins	↓TC −0.09 (−0.11, −0.07) ↓LDL-C −0.11 (−0.13, −0.09) (38 RCTs) ↓ApoB (g/L) −0.042 (−0.065, −0.026) (13 RCTs)

Table 1. *Cont.*

Publication	Search Dates	Population	Study Design	Sample Size	Duration of Intervention	Intervention	Control	Outcome Measures	Results Mean Change in mmol/L (95%CI)
Guasch-Ferré, 2018 [23]	through Jan 2018	Adults	RCTs with a parallel or crossover design; Duration of intervention ≥ 3 weeks	26 RCTs 1059 participants	4 weeks–1 year	Walnuts 15–108 g/d	ad libitum control diet, Med diet, ADA diet, low-fat diet, habitual diet, controlled diet (walnut-free)	At least one of the lipid markers: TC, LDL-C, HDL-C, TG apolipoproteins	↓TC −0.18 (−0.24, −0.12) ↓LDL-C −0.14 (−0.2, −0.09) ↓TG −0.05 (−0.1, −0.01) (23 RCTs)
Lee-Bravatti, 2019 [19]	2015-June 2017 for lipid outcomes	Healthy or with CVD risk factors; ≥18 yo	RCTs; Duration of intervention ≥ 3 weeks	15 RCTs 534 participants	4–16 weeks	Almonds 37–113 g/d	NCEP step II diet, low-fat diet, high-fat diet custom diet, Med diet, NCEP step I diet, ADA diet	Lipid profile: TC, LDL-C, HDL-C, TG, TC/HDL, HDL/LDL; apolipoproteins, Lp(a)	↓TC −0.28 (−0.43, −0.12) ↓LDL-C −0.15 (−0.26, −0.05) (13 RCTs)
Morvaridzadeh, 2020 [28]	through June 2019	Non-specified	RCTs with a parallel or crossover design	3 RCTs 384 participants	4–12 weeks	Cashews 28–108 g	Isocaloric diet, baked potato chips	Lipid profile: TC, LDL-C, HDL-C, TG	No change
Liu, 2020 [18]	through June 2019	≥18 yo	RCTs; duration of intervention ≥ 3 weeks	34 RCTs 1677 participants	3–24 weeks	Tree nuts (walnuts, pistachios, hazelnuts, cashews, or almonds) 15–168 g/d	Control diet (nut-free)	Lipid profile: TC, LDL-C, HDL-C, TG	Walnut-enriched ↓LDL-C −0.09 (−0.12, −0.07) ↓TG −0.09 (−0.11, −0.07) (16 RCTs) Pistachio-enriched ↓LDL-C −0.17 (−0.28, −0.06) Hazelnut-enriched No change Almond-enriched No change
Jalali, 2020 [20]	through Nov 2019	≥18 yo	RCTs	3 RCTs 392 participants	4–12 weeks	Cashews 30–42 g/d	Diet for diabetes, isocaloric controlled diet (nut-free)	Lipid profile: TC, LDL-C, HDL-C, TG	No change
Hadi, 2021 [27]	through June 2019	≥18 yo	RCTs; duration of intervention ≥ 3 weeks	12 RCTs 771 participants	3–24 weeks	Pistachios 32–126 g/d	Control diet	Lipid profile: TC, LDL-C, HDL-C, TG	↓TC −0.19 (−0.33, −0.06) (10 RCTs) ↓LDL-C −0.1 (−0.14, −0.06) (12 RCTs) ↓TG −0.13 (−0.16, −0.09) (10 RCTs)

Table 1. *Cont.*

Publication	Search Dates	Population	Study Design	Sample Size	Duration of Intervention	Intervention	Control	Outcome Measures	Results Mean Change in mmol/L (95%CI)
Asbaghi, 2021 [25]	through Sept 2020	Healthy or otherwise; ≥18 yo	RCTs with a parallel or crossover design; Duration of intervention ≥ 3 weeks	27 RCTs 2049 participants	3–77 weeks	Almonds 10–168 g/d	No almond consumption or dietary substitutions containing no almond were used	At least one of the lipid markers: TC, LDL-C, HDL-C, TG	↓TC −0.13 (−0.2, −0.05) ↓TG −0.08 (−0.13, −0.02) (27 RCTs) ↓LDL-C −0.15 (−0.23, −0.07) (26 RCTs)
Wang, 2021 [29]	through Jan 2020	Adults with T2DB	RCTs with a parallel or crossover design; Duration of intervention ≥ 2 weeks	5 RCTs 120 participants	3–12 weeks	Almonds 30–60 g/d	Control diet, NCEP step II diet, peanuts, sunflower kernels	Lipid profile: TC, LDL-C, HDL-C, TG	No change
Xia, 2021 [11]	through June 2021	Patients with T2DB	RCTs	16 RCTs 1041 participants	6–52 weeks	Peanuts and tree nuts (walnuts, pistachios, macadamia nuts, pecans, cashews, almonds, hazelnuts, pine nuts, and Brazil nuts) 6–128 g/d	High-fat diet, low-fat diet, normal-fat diet, habitual diet, diet for diabetes, ADA meal plan (nut-free)	Lipid profile: TC, LDL-C, HDL-C, TG	↓TC −0.14 (−0.26, −0.02) (14 RCTs) ↓TG −0.1 (−0.17, −0.02) (12 RCTs)
Moosavian, 2022 [15]	through Mar 2021	Patients with T2DB; ≥18 yo	RCTs; Duration of intervention ≥ 3 weeks	9 RCTs 264 participants	4–12 weeks	Almonds 29–113g/d	NCEP step II diet, cheese, raw peanut with low carbohydrate diet, high-fat diet, low-fat diet, sunflower kernels with diabetic diet, custom diet (almond-free)	Lipid profile: TC, LDL-C, HDL-C, TG	↓LDL −0.14 (−0.26, −0.02) (8 RCTs)
Arabi, 2022 [26]	through Dec 2021	Diagnosed with MetS; ≥18 yo	RCTs with a parallel or crossover design	8 RCTs 506 participants	4–112 days	Walnuts (all forms, plain, or walnut-fortified food) 30 g–108 g/d	Standardized shakes, control diet, isocaloric white bread, ad libitum diet without walnuts, lifestyle counseling	Lipid profile: TC, LDL-C, HDL-C, TG	↓TG −0.17 (−0.32, −0.03) (5 RCTs)
Mates, 2022 [17]	through Nov 2021	Middle-aged and older adults ≥40 yo or mean age ≥50 yo	RCTs with a parallel or crossover design; Duration of intervention ≥ 3 weeks	17 RCTs 2466 participants	4 weeks-2 years	Walnuts (including plain or walnut-fortified food) 19.3–75 g/d	Med diet, modified low-fat diet, Western-type diet, habitual diet, CKD patients' diet (walnut-free)	Lipid profile: TC, LDL-C, HDL-C, TG	↓TC −0.13 (−0.2, −0.07) ↓LDL-C −0.15 (−0.2, −0.11) (12 RCTs) ↓TG −0.08 (−0.12, −0.04) (13 RCTs)

Table 1. *Cont.*

Publication	Search Dates	Population	Study Design	Sample Size	Duration of Intervention	Intervention	Control	Outcome Measures	Results Mean Change in mmol/L (95%CI)
Eslami, 2022 [21]	through Apr 2021	Overweight/obese (BMI: 25–40 kg/m^2); free of chronic diseases; ≥18 yo	RCTs with a parallel or crossover design; Duration of intervention ≥ one week	10 RCTS 711 participants	4–72 weeks	Peanuts and tree nuts (almonds, walnuts, hazelnuts, pistachios, cashews, macadamia nuts, Brazil nuts, pine nuts, pecans, mixed nuts) 20–60 g/d	Isocaloric nut-free diet	At least one of the following: Serum lipid profile: TC, LDL-C, HDL-C, TG	↓ TG −0.15 (−0.29, −0.01) (9 RCTs)
Parilli-Moser, 2022 [14]	through July 2021	Healthy or with MetS or at high risk of MetS	RCTs	9 RCTs 643 participants	2–24 weeks	Peanuts, peanut butter or high oleic acid peanuts 25–200 g/d	Hypocaloric diet, habitual diet, ADA meal plan, substitute snack (grain bar, white rice bar, candy, or almonds) (peanut-free)	Lipid profile: TC, LDL-C, HDL-C, TG	↓ TG −0.13 (−0.2, −0.07) (9 RCTs)

RCT, randomized controlled trial; NCEP, National Cholesterol Education Program; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; CHO, carbohydrates; ANDEAP, Academy of Nutrition and Dietetics Evidence Analysis Process; AHA, American Heart Association; ADA, American Diabetes Association; Med Diet, Mediterranean diet; BW, body weight; WC, waist circumference; BMI, body mass index; Lp (a), lipoprotein (a); MetS, metabolic syndrome; T2DB, type 2 diabetes. Units for blood lipids are presented as mmol/L, except for ApoB which is presented as g/L. Only lipid outcomes are reported.

2.1. Dose-Response Effects of Nuts on Blood Lipids

In eight of the 19 identified meta-analyses, dose-response analyses were conducted [12,16,22–25]. Some evidence suggests nuts dose-dependently improve TC, LDL-C, and TG. In a meta-analysis of 61 clinical trials, Del Gobbo et al. reported that tree nut intake lowered TC and LDL-C in a nonlinear manner such that stronger effects were observed in trials where >60 g/d of tree nuts were provided. For ApoB and TGs, linear dose-response effects were observed [22]. Similarly, Blanco Mejia et al. observed a borderline non-significant linear relationship between increasing tree nut doses and TG reductions; no dose-response relationship was observed for HDL-C [16]. In a pooled analysis of 25 RCTs, Sabaté et al. observed dose-dependent reductions in TC, LDL-C, and TG with higher consumption of tree nuts and peanuts [12].

In five meta-analyses, dose-response analyses were conducted to examine the relationship between the intake of a single nut type and lipid/lipoprotein responses [14,23–26]. In a meta-analysis of 24 clinical trials, higher walnut intake was dose-dependently associated with reductions in TC (−0.01 mmol/L per 1 g/d increase) [23]. A trend towards a dose-response relationship was observed for LDL-C (−0.01 mmol/L per 1 g/d increase), while no dose-response relationship was observed for TG or HDL-C. A recent meta-analysis of five studies conducted in cohorts with metabolic syndrome showed a non-linear association between walnut consumption and HDL-C whereby an intake of up to 50 g/d was associated with an increase in HDL-C [26]. Additionally, a trend toward a linear dose-response relationship was observed between the consumption of walnuts and TG reduction; no dose-response relationship was observed for TC or LDL-C. Less dose-response specific evidence is available for other nuts including almonds and peanuts. In a meta-analysis examining the effect of almond intake on lipids and lipoproteins, an inverse linear relationship was observed between almond dose and TG. TC, LDL-C, and HDL-C were not linearly related to almond intake dose [25]. A meta-analysis of nine RCTs showed no dose-response relationship between peanut intake and TC, LDL-C, HDL-C, or TG [14].

In 11 of the 19 included meta-analyses, subgroup analyses were conducted to examine the effect of higher vs. lower consumption of nuts on lipid/lipoprotein levels [11,13,15–17,19,21,23,25,26,29]. The highest consumption category was >63 g/d in one meta-analysis [26], ≥50 g/d in five meta-analyses [13,15,16,21,29], ≥45g/d in two meta-analyses [11,25], >42.5 g/d in one meta-analysis [19], ≥42 g/d in one meta-analysis [17], and ≥28 g/d in one meta-analysis [23]. In a meta-analysis of studies on healthy individuals, the consumption of ≥45 g/d of almonds lowered TC, LDL-C, and TG to a greater extent than <45 g/d [25]. Similarly, in a meta-analysis of five studies conducted in patients with type 2 diabetes, greater reductions in TC, LDL-C, HDL-C, and TG were observed with the consumption of ≥50 g/d of almonds [29]. In two meta-analyses including healthy participants and individuals at high risk for CVD, no effect modification by almond dose (≥50 g/d and >42 g/d) was observed [13,19].

Three meta-analyses examined the effect of walnut dose levels on changes in lipids and lipoproteins [17,23,26]. Guasch-Ferré et al. reported similar TC and LDL-C lowering with a walnut consumption of ≥28 g/d compared with <28 g/d [23]. However, greater reductions in TC and LDL-C were observed when walnut intake comprised 10–25% of total energy compared with 5–10% of total energy. No dose-related effect modification was observed for TG or HDL-C. In a meta-analysis of studies including middle-age and older adults, TC and TG reductions were only observed when walnut consumption was ≥42 g/d; LDL-C was lowered to a similar magnitude at both doses [17]. In a meta-analysis of studies including participants with metabolic syndrome, walnut dose (>63 g/d vs. ≤63 g/d) did not affect LDL-C differently [26].

Inconsistent findings were reported in three meta-analyses examining lipid/lipoprotein effect modification by doses of tree nuts and peanuts or tree nuts only [11,16,21]. A meta-analysis including studies involving patients with type 2 diabetes showed that higher tree nut and peanut consumption (≥45 g/d) lowered TC and LDL-C significantly, whereas lower consumption was not associated with TC and LDL-C lowering [11]. In contrast, in a

meta-analysis of 11 studies including participants with overweight/obesity, no difference in lipid responses by peanut and tree nut dose (≥50 g/d vs. <50g/d) was observed [21]. In a meta-analysis of studies conducted in participants that were healthy or had dyslipidemia, metabolic syndrome, or type 2 diabetes, TGs were reduced with a higher intake of tree nuts (≥50g/d); HDL-C findings were not different by the dose consumed and LDL-C and TC were not assessed [16].

Collectively, there is evidence supporting that nuts dose-dependently improve lipids and lipoproteins. However, many of the meta-analyses reviewed included a relatively small number of studies, which limits the statistical power to examine dose-response relationships. In addition, across the meta-analyses reviewed, higher vs. lower consumption was inconsistently defined, and limited rationale was provided in most cases for the cut points used.

2.2. Subgroup Analyses: Effects of Nuts on Blood Lipids

Across the meta-analyses reviewed, several subgroup analyses were conducted to assess the potential for sex, age, BMI, baseline lipid/lipoprotein concentrations, and health status to influence the effect of nuts on lipids and lipoproteins. Broadly, sex and age do not appear to be effect modifiers; BMI and baseline lipid/lipoprotein concentrations may influence the lipids/lipoprotein lowering effects of nuts.

2.2.1. Sex

In two of the included meta-analyses, subgroup analyses evaluating effect modification by sex were reported [12,22]. In both meta-analyses, no differences in the effect of nuts on lipids/lipoproteins were observed by sex [12] or by the proportion of the study sample that was men (≥50% or <50%) [22].

2.2.2. Age

Seven of the included meta-analyses conducted subgroup analyses to assess the effect of nuts on lipids/lipoproteins in different age categories [11,12,17,22,23,25,26]. Limited evidence suggests that TG lowering in response to tree nut intake may be greater in those aged <50 years; however, most of the evidence evaluated suggests age is not a strong effect modifier. In four meta-analyses, including studies examining the effect of tree nuts and peanuts [12], tree nuts only [22], and walnuts [23,26] on lipids and lipoproteins, effects did not differ across age categories. In two meta-analyses, TG reductions were only observed in response to almond [25] and walnut [17] consumption in the <50 y age category; no intervention effect was observed in ≥50 y age category. In both meta-analyses, no differences in TC or LDL-C were observed by age category. Xia et al., however, observed only TC lowering in response to tree nut and peanut consumption in the ≥55 y age category; there was no difference in LDL-C by age category [11].

2.2.3. BMI

Across the five meta-analyses that conducted subgroup analyses to evaluate effect modification by BMI, the evidence suggests nuts may induce greater lipid/lipoprotein improvements when BMI is <30 kg/m^2 [12,15,21,23,25]. Sabaté et al. observed greater improvements in the LDL-C/HDL-C ratio and TC/HDL-C ratio when BMI was <25 kg/m^2 and 25–30 kg/m^2 compared with BMI >30 kg/m^2 [12]. Similar trends were observed for LDL-C, TC, and TG. Eslami et al. reported TG lowering with the consumption of tree nuts and peanuts only when BMI was <30 kg/m^2; in this meta-analysis effect modification was not observed for TC, LDL-C, and HDL-C [21]. Guasch-Ferré et al. did not observe any difference in the effect of walnuts on lipids/lipoproteins in studies where BMI was <25 kg/m^2 vs. ≥25 kg/m^2 [23]. Similarly, Moosvian et al. reported that the effect of almonds on lipids and lipoproteins in studies including patients with type 2 diabetes did not differ by BMI category (<30 vs. ≥30 kg/m^2) [15]. Conversely, in a meta-analysis including studies conducted in generally healthy populations, reductions in TC and LDL-C were

only observed with almond consumption in individuals with overweight; no differences in TG or HDL-C were observed across BMI categories [25].

2.2.4. Baseline Lipids/Lipoprotein Concentrations

In nine of the included meta-analyses subgroup analyses were conducted to examine effect modification by baseline lipid/lipoprotein concentrations or hyperlipidemia/dyslipidemia status [12,13,15,16,22–25,27]. Evidence suggests greater improvements in lipids and lipoproteins in response to nut consumption when the baseline TC and/or LDL-C is higher [12,25,27] or in participants with hyperlipidemia or dyslipidemia [13]. However, in meta-analyses that examined effect modification by baseline TG concentrations, reductions in TGs were only observed when the baseline TG concentrations were lower (<1.69 mmol/L) [16,25,27]. In four meta-analyses, no effect modification was observed by the baseline lipid/lipoprotein level or the hyperlipidemia/dyslipidemia status [15,22–24]. Across the evaluated meta-analyses, inconsistent cut points were used to define higher vs. lower baseline lipid/lipoprotein concentrations and dyslipidemia/hyperlipidemia, which likely contributes to the variability observed.

2.2.5. Health Status

Across the six meta-analyses that conducted subgroup analyses to assess effect modification by health status (healthy vs. metabolic impairment), inconsistent findings were reported, with no clear pattern of effect modification by health status [14,17,19,22,25,27]. In the largest meta-analysis including 61 trials, no heterogeneity in the effect of tree nuts on TC, LDL-C, HDL-C, or TG was observed by disease status (healthy, type 2 diabetes, metabolic syndrome, high cholesterol, obesity) [22]. In this analysis, ApoB reductions were greater in those with type 2 diabetes (−0.115 g/L, 95% CI −0.162, −0.068) compared with healthy populations (−0.025 g/L; 95% CI −0.047, −0.003). Given the variation in the methodology used in these meta-analyses and the aggregate nature, subgroup analyses have limited power to identify true differences between subgroups. To further explore effect modification by health status, individual participant data meta-analyses are needed.

2.3. Effects of Nut Processing on Blood Lipid Profile

Few investigations of the effect of nut processing on lipids/lipoproteins have been conducted. The available evidence from RCTs suggests almond [36,37], hazelnut [38], and peanut [14,39,40] processing (i.e., roasting, or production of oil or butter) does not alter lipid and lipoprotein responses. In an RCT including adults with normolipidemia, the consumption of ~14% of energy from almond oil or whole almonds for 6 weeks improved TC, LDL-C, HDL-C, and TG with no difference in almond processing [36]. Similarly, in a study of individuals with hypercholesterolemia, the consumption of 100 g/d of roasted salted almonds, roasted almond butter, or raw almonds improved TC and LDL-C after 4 weeks and the magnitude of the effect was not impacted by almond processing [37]. Comparable findings were observed in an RCT whereby the intake of 30 g/d of either raw or dry roasted, lightly salted hazelnuts for 4 weeks did not differentially affect TC and LDL-C [38].

Findings from three RCTs suggest peanut processing does not influence lipid/lipoprotein changes [14,39,40]. In a five-arm randomized trial, the intake of 56 g of whole raw unsalted peanuts, whole roasted unsalted peanuts, whole roasted salted peanuts, whole honey roasted peanuts, or peanut butter for 4 weeks did not affect TC, LDL-C, HDL-C, or TG differently [40]. This is consistent with findings from crossover RCTs where the intake of a diet enriched with peanut butter/peanuts similarly improved TC, LDL-C, TG, and ApoB compared with an average American diet [39]. Similar findings were observed in a 6-month RCT examining the intake of 25 g/d of skin-roasted peanuts, two tablespoons (32 g)/day of peanut butter, or two tablespoons (32 g)/day of peanut oil [14]. In this trial, no differences in TC, LDL-C, HDL-C, or TG were observed per peanut form. Thus, from the limited evidence available, nut processing does not appear to alter lipid/lipoprotein responses.

3. Proposed Mechanisms of Action of Cholesterol-Lowering by Nuts

Nuts are a good source of MUFAs and PUFAs, and they also contain dietary fiber, phytosterols, and polyphenols. In isolation, all these nutrients and bioactive compounds may have a modest cholesterol-lowering effect; however, when these molecules combine in the matrix of nuts and synergize to potentiate cardiometabolic pathways, they have the capacity to reduce LDL-cholesterol beyond the effects predicted by equations based solely on fatty acid profiles [41]. Figure 1 summarizes the potential mechanisms for the beneficial effects of nuts consumption on lipid metabolism with the ensuing reduction of the atherogenic lipid/lipoprotein profile.

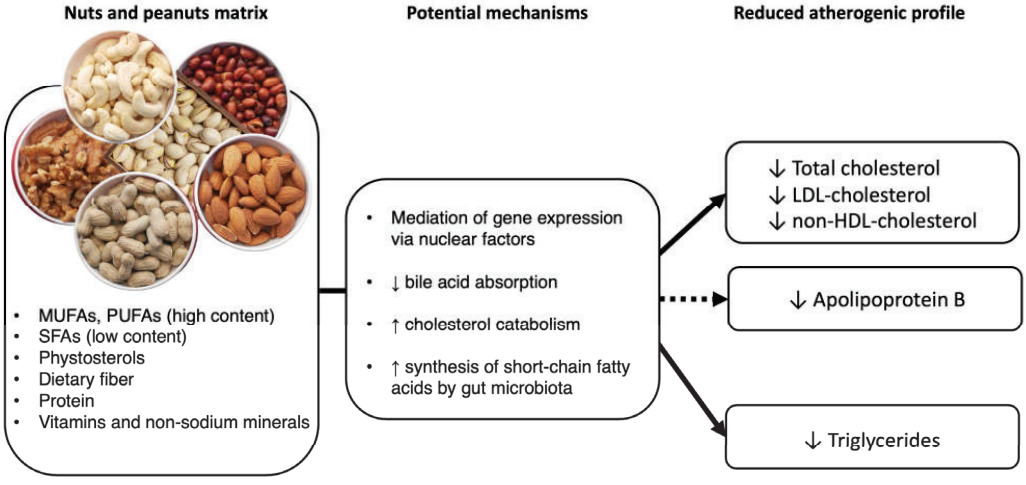

Figure 1. Potential mechanisms by which tree nuts and peanuts reduce atherogenic lipid/lipoprotein profile. A plain arrow indicates a strong level of evidence to support the effect, whereas a dashed arrow indicates a lower level of evidence. LDL, low density lipoprotein; HDL, high density lipoprotein.

Specifically, nuts have favorable effects on serum lipids primarily because of their high content of unsaturated fatty acids (both MUFAs and PUFAs), while they have a low content of saturated fatty acids (SFAs; 4 to 15%) [42]. The unique fatty acid profile of nuts facilitates a favorable shift in the dietary fatty acids when nuts are substituted for foods that are high in SFAs or carbohydrates. Dietary PUFAs have been shown to reduce ApoB while MUFAs increase ApoA1, which mediates the efflux of cholesterol associated with HDL particles [41]. Experimental and clinical studies have shown that the intake of unsaturated fatty acids enhances the hepatic receptor-dependent clearance of LDL and concomitantly reduces plasma LDL-C levels [43]. Unsaturated fats from nuts replacing SFA in lipid bilayers increase membrane fluidity, flexibility, and elasticity, while reducing membrane thickness [44]; these physical changes impact the interaction of membrane-bound receptors with their ligands, such as the affinity of LDL receptors for ApoB-100 in LDL particles, thus enhancing LDL-C uptake. Additionally, PUFA can mediate the expression of several genes involved in lipid metabolism via nuclear factors, including the peroxisomal proliferator-activated nuclear receptors gamma (PPARγ), liver X-receptor (LXR), hepatocyte nuclear factor-(HNF)-4α, nuclear factor kappa B (NFκB), and sterol-regulatory element binding proteins (SREBPs) [45]. Particularly, PUFAs downregulate the expression of SREBPs and enzymes for cholesterol synthesis, thus decreasing the body cholesterol pool [45].

Improvement in blood lipids is attributable mainly to the favorable fatty acid profile of nuts, but other nut components, namely dietary fiber, and plant sterols [42], may also play a significant role. Nuts contain ~7 g/100 g dietary fiber, of which ~25% is soluble fiber [46]. In a meta-analysis of 67 clinical trials to quantify the cholesterol-lowering effect of dietary

fiber, 2–10 g/d of soluble fiber was associated with modest but significant reductions in total cholesterol and LDL-C [47]. According to a recent umbrella meta-analysis, total dietary fiber (independently of type) also has cholesterol-lowering properties [48]. Dietary fiber, particularly soluble fiber, exerts its hypocholesterolemic effect through several mechanisms: (1) increased intestinal viscosity, which reduces bile acid absorption and promotes cholesterol catabolism; (2) enhanced synthesis of short-chain fatty acids by gut microbiota, particularly butyrate and propionate, which reduce de novo cholesterol synthesis via 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibition; and (3) interference with micelle formation in the intestinal lumen and enhanced fecal excretion of fat, cholesterol, and bile acids [48].

Like all plant foods, nuts are cholesterol-free, but their fat fraction contains chemically related plant sterols or phytosterols [42]. The phytosterol content is variable ranging from approximately 72 to 272 mg/100 g with pistachios, almonds, and walnuts containing the most. These compounds play a structural role in their cell membranes just as cholesterol does in animal cell membranes [49]. Phytosterols interfere with cholesterol absorption in the intestinal lumen and thus help lower blood cholesterol. Interestingly, evidence has demonstrated that phytosterols contribute to the cholesterol-lowering effect of nut consumption [50]. In a systematic review and meta-analysis of 61 trials with 2582 participants, with nut intakes from 0.2 to 3.5 servings/d (equivalent to about 5 to 100 g/d) and phytosterol doses ranging from 4.8 to 279 mg/d, the total phytosterol dose from nuts was inversely correlated with a decrease in LDL-C ($r = -0.60$) [50]. Of note was that the predominant LDL-C lowering effect was due to the quantity of nuts consumed; hence representing a greater quantity of both phytosterols and unsaturated fat consumed. A review by Cofan and Ros [51] summarized the LDL-C lowering effects of phytosterols and reported that one meta-analysis [52] concluded that the cholesterol-lowering effects were greater when phytosterols were consumed with fat in the food matrix. Collectively, the evidence suggests that the LDL-C lowering effects of nuts are primarily due to their fatty acid profile but also due to the effects of dietary fiber and plant sterols, as well.

Finally, beyond LDL-C lowering, nuts contain highly bioactive polyphenols, representing one of the richest food sources [42,53]. Although data from clinical studies are few and inconclusive, the lipid effects of polyphenols appear to be limited to reducing LDL oxidation [54], which concurs with the well-known antioxidant and anti-inflammatory properties of these phytochemicals and likely contributes to their atheroprotective role. Oxidized LDL (oxLDL) is important because it is involved in several steps of atherogenesis (endothelial injury, leukocyte recruitment/retention, foam cell formation, etc.) [55,56]. However, the evidence for the benefits of nut consumption on oxLDL and other biomarkers of LDL oxidation is inconsistent, as shown in a recent review of 12 RCTs using a variety of nuts and showing results for changes in blood oxidation markers, usually as secondary outcomes [56].

Another important consideration of the mechanisms to explain the health benefits of nuts pertains to their effects on reverse cholesterol transport, an important mechanism whereby cholesterol is removed and transported from peripheral tissues by HDL to the liver for disposal. A recent review on the role of HDL in atherosclerotic disease notes the shift from measuring HDL-C concentrations to focusing on the more functional measures of HDL (e.g., HDL particle number and cholesterol efflux capacity), which is more predictive of future atherosclerotic CVD events [57]. There is evidence that nuts increase HDL function (i.e., increased cholesterol efflux capacity). This has been demonstrated for walnuts, pistachios, and mixed nuts (walnuts, almonds, and hazelnuts) [58–60]. Nut consumption may shift HDL distribution to improve reverse cholesterol transport. A shift, or increase, in large HDL particles, could indicate increased reverse cholesterol transport due to their affinity to sequester cholesterol that effluxes from macrophages via ATP Binding Cassette Subfamily G Member 1 (ABCG1) [61]. Although the evidence is limited and the underlying mechanisms are not completely understood, nut intake may increase the reverse

cholesterol transport capacity of HDL leading to increased removal of cholesterol from peripheral tissues.

Lipoprotein(a) [Lp(a)] is an independent, causal, risk factor for atherosclerotic CVD [62]. Lp(a) concentrations are primarily genetically predetermined with minimal effects from dietary interventions [62]. Several RCTs have assessed the effects of diets enriched with nuts at doses of 1.5 servings (42.5 g)/d or more compared with control diets in various populations (healthy, type 2 diabetes, hyperlipidemia, at risk of CVD). The results have been inconsistent, with modest reductions of Lp(a) in three trials using walnuts [63], pecans [64], or almonds [65], and no discernible effect in four further trials, two with almonds [66,67] and two with walnuts [68,69].

3.1. Emerging Evidence of the Effects of Nuts on Lipoprotein Particle Size

Lipoproteins, assessed by nuclear magnetic resonance, are categorized by particle sizes and densities, or lipoprotein subclasses, and many of these subclasses are associated with CVD outcomes [63]. A review by Qiao et al. on the role of LDL-C and LDL particles in atherogenesis concluded that LDL particles/density (e.g., oxLDL and small dense LDL) may be superior to LDL-C for predicting atherosclerotic CVD risk [64]. In fact, all ApoB-containing lipoproteins are atherogenic, and the small dense LDL particles are even more proatherogenic than larger LDL particles. In the Women's Health Initiative, large very low-density lipoprotein (VLDL) particles increased CVD risk more so than small VLDL particles [65]. Interestingly, lipoprotein particle sizes are being evaluated in diet and nut studies. Observational studies and clinical trials have demonstrated a consistent relationship between improved diet quality and less atherogenic lipoprotein subclass profiles (lower large VLDL, small HDL, and small dense LDL) [66–68]. Moreover, the evidence to date indicates beneficial effects of nut consumption on lipoprotein profiles including particle sizes.

A cross-sectional and longitudinal analysis was conducted with 196 participants in the PREDIMED-Reus center to evaluate the associations of dietary intake (assessed by food frequency questionnaire [FFQ]) and plasma lipoprotein profiles at baseline and 1 year of follow-up [69]. Nut consumption for tertile 3 (highest nut consumption) was 26 g/d (total nuts); 14 g/d (walnuts); and 15 g/d (non-walnut nuts). The authors reported that the increased consumption of total nuts, walnuts, and non-walnut nuts was associated with decreased total and medium LDL particles, very large VLDL, and LDL-C; and decreased VLDL particle size, as well as increased HDL particles and HDL-C.

The Walnuts and Healthy Aging Study (WAHA), a multicenter study conducted in Spain and the U.S. with 628 participants (average age = 69 years) evaluated the effects of walnut consumption (15% of energy and 30 to 60 g/d) for two years on lipid and lipoproteins, including lipoprotein particle sizes [70]. The authors reported that the walnut diet decreased total LDL particles and small LDL particle numbers by 4.3% and 6.1%, respectively. In addition, the walnut diet significantly decreased total cholesterol, LDL-C, and intermediate-density lipoprotein cholesterol by 4.4%, 3.6%, and 16.8%, respectively. The take-home message from the WAHA Study is that the decrease in total LDL particles and small LDL particle number provides mechanistic insight into their cardiovascular benefit beyond changes in the conventional lipid/lipoprotein profile.

Several smaller clinical studies have shown similar benefits of tree nuts on lipoprotein particle size; however, likely because of the smaller sample sizes (and lower statistical power), significant diet effects were not consistently observed [59,71,72]. A study conducted with almonds (42.5 g/d) and dark chocolate (18 g cocoa power; 43 g dark chocolate/d) for four weeks reported that the almond diet significantly decreased LDL_{1+2}, and the dark chocolate plus almond diet significantly decreased LDL_{3+4} compared with the average American diet [71]. In another study conducted by Tindall et al. [72], a diet that provided 18% energy from walnuts (57–99 g/d) tended ($p < 0.1$) to decrease LDL subclasses LDL_{1+2} and LDL_4 compared with a fatty acid-matched diet and a diet where oleic acid was substituted for ALA in the comparator diets. Moreover, in a study conducted with pistachios [59]

there was a significant decrease in small and dense LDL particles in response to a diet that provided 20% energy from pistachios (63–126 g/day) versus a diet with 10% of energy from pistachios as well as a lower-fat (25% of energy), low saturated fat (<8% of energy) control diet after 4 weeks. In addition, based on analysis of variance, there was a trend for an increase in α-1 and α-2 HDL (i.e., larger HDL particles) with the inclusion of pistachios. However, in a study conducted by Hernández-Alonso et al. [73] in participants with pre-diabetes, pistachios (57 g/d) increased small HDL particles and decreased medium and large HDL particles. The differences reported between the studies conducted by Holligan et al. [59] and Hernández-Alonso et al. [73] may be explained by differences in the study populations (i.e., healthy vs. pre-diabetes) and the known effects of elevated glucose levels on HDL function and HDL-C levels [74].

While research is still emerging about the effects of nuts on lipoprotein subparticle distribution and concentration, it is becoming clear that nuts favorably affect the conventional lipoprotein profile (i.e., reduced atherogenicity) with a consequent decreased risk of CVD. These findings are expanding our understanding of how tree nuts modulate lipoprotein metabolism and lower CVD risk.

3.2. Effects of Nut Consumption on Adiposity

Nuts are energy-dense foods containing high amounts of fat, a reason why there has been concern that their consumption may lead to weight gain and obesity. However, there is consistent evidence from large prospective studies, scientifically sound RCTs, and meta-analyses thereof that incorporation of substantial amounts of nuts into healthy diets do not lead to weight gain or increase the risk of abdominal obesity, and may even help promote weight loss and reduce waist circumference [75–78]. Several mechanisms explain the lack of the fattening effect of nuts, ranging from the effort required at mastication and chewing to increased satiety and the promotion of fullness due to delayed gastric emptying by the high fat and fiber content. Furthermore, the efficiency of energy absorption from nuts is reduced due to incomplete mastication and fat encasement within the unbroken cell walls in nut particles, thus limiting the bioaccessibility of fat from nuts in the intestine, with an ensuing increase in fecal fat losses [79].

4. Future Directions for Research on Nut Consumption and Blood Lipids

Non-communicable diseases such as CVD have multiple interacting dietary determinants, thus the effects of diet are likely to be dependent on the combination of foods rather than a single food [80]. Nevertheless, dyslipidemia remains a major risk factor contributing to CVD and the evidence supporting the effects of nut consumption on blood lipids and lipoproteins is compelling. Nut consumption improves lipid profiles by multiple mechanisms, and this understanding lays the groundwork for further research.

One of the challenges for this research is to integrate understanding at the level of key nutrients, foods, and dietary patterns. For example, a recent prospective study in the Coronary Artery Risk Development in Young Adults (CARDIA) study showed that individuals with higher walnut consumption also had higher diet quality (measured with Healthy Eating Index 2015), but also lower body mass index, waist circumference, blood pressure, and triglyceride concentration, and gained less weight since baseline than other nut consumers [81]. From a nutrient perspective, nuts make important contributions of unsaturated fatty acids, tocopherols, phytosterols, and dietary fiber. The relative composition varies by nut type, and this may explain inconsistencies in the research results. Separate studies may be required for mechanistic studies at the nutrient level, for example, on the role of PUFAs from nuts on gene expression related to lipid metabolism [44]. Further exploration of the effect of nut consumption on lipid particle number and size may need to focus on differences in fatty acid profiles and the varying doses of phytosterols and fiber provided by different nuts. This may be the case as the research progresses from the study of basic lipid profiles to sub-fractions, HDL function studies, and investigations around changes in ApoB.

Variations in results remain a problem for meta-analyses but this is often due to differences in study design, including dietary methodology. While age and sex do not appear to influence the effects of nut consumption on lipids, weight changes can confound results, so total diets are important. Likewise, studies may show that the processing of nuts does not appear to influence their relationship to blood lipids, but it may influence weight, due to the increased available energy from processing [82], so food form remains a consideration.

Other study design issues relate to the need for greater power in studies (larger sample sizes), further investigation of the linearity of effects (and determination of cut points), and study populations' health status. Given the multifaceted effects on blood lipids and the variations in disease profiles of study participants, more individual participant data meta-analyses may be required.

Further studies evaluating the association between nut consumption and the microbiome are needed [83,84], a new horizon for research with the potential to add to our knowledge of how nuts influence lipid profiles. Preliminary reports indicate little change, but modulatory effects are emerging. On the other hand, plasma metabolomics are providing a useful innovative path for research linking nut consumption with CVD risk [85] and providing insights into the underlying mechanisms. This provides added support for the growing evidence of the effects of nut consumption on lipids and lipid fractions.

5. Conclusions

In conclusion, evidence from clinical trials has shown that the consumption of total nuts and specific types of nuts improves blood lipid profiles by multiple mechanisms, as discussed herein. Specifically, nut-enriched diets are associated with lowering total cholesterol, LDL-C, and TG compared with control diets. Some RCTs have also shown benefits in reducing ApoB levels and improving the lipoprotein subparticle profile. The major determinant of cholesterol-lowering appears to be nut dose rather than nut type.

As summarized in Figure 1, many bioactive compounds of nuts might explain the beneficial effects of nut consumption on blood lipids and lipoproteins. Improvement in blood lipids is attributable mainly to the favorable fatty acid profile of nuts, but other nut components, namely dietary fiber, phytosterols, and bioactive polyphenols play a role.

Although more research is needed to better understand the biological mechanisms of cardiometabolic protection by nuts, increasing their consumption as part of a healthy diet improves cardiovascular risk factors and helps to reduce the risk of CVD in the general population as well as in individuals at high CVD risk. It goes without saying that an integral step for increasing nut consumption is to effectively educate consumers about the health benefits of nuts and, importantly, communicate how to substitute them for unhealthy foods in the diet to achieve the greatest possible CVD benefits.

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Abbreviations

ALA: α-linolenic acid; Apo, apolipoproteins; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular diseases; FFQ, food frequency questionnaire; HDL, high-density lipoprotein cholesterol; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; HNF-4α, hepatocyte nuclear factor; LDL, low-density lipoprotein cholesterol; Lp(a), Lipoprotein(a); LXR, liver-X-receptor; MD, mean difference; MUFA, monounsaturated fat; NFκB, nuclear factor kappa B; PPARγ, peroxisomal proliferator-activated nuclear receptors gamma; PREDIMED, PREvención con DIeta MEDiterránea; PUFA, polyunsaturated fat; RCT, randomized controlled trial; SFA, saturated fat; SRBPs, sterol-regulatory element binding proteins; TG, triglycerides; TC, total cholesterol; VLDL, very low-density lipoprotein; WAHA, Walnuts and Healthy Aging Study.

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Effect of Nuts on Gastrointestinal Health

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Abstract: Nuts are high nutrient-dense foods containing healthy lipids, dietary fiber, and bioactive phytochemicals, including vitamins and minerals. Although the beneficial effect of nut consumption on different chronic diseases has been well documented, especially in relation to their cardiometabolic benefits, less scientific evidence is available on their possible beneficial effects on gastrointestinal health. In this narrative review, we summarize the most important findings and new research perspectives in relation to the importance of nut consumption on gastrointestinal health. The integrity of the cell wall structure, cell size and particle size after mastication are known to play a crucial role in energy, nutrient and bioactive release from nuts during digestion, therefore affecting bioaccessibility. Other mechanisms, such as cell wall composition, thickness and porosity, as well as stability of the membranes surrounding the oil bodies within the cell, are also important for energy extraction. As the undigested nutrients and phytochemicals are delivered to the colon, effects on gut microbiota composition are predicted. Although the overall effect of nut consumption on microbial alpha- and beta-diversity has been inconsistent, some scientific evidence suggests an increase in fecal butyrate after almond consumption, and a beneficial role of walnuts on the prevention of ulcerative colitis and protection against the development of gastric mucosal lesions.

Keywords: nuts; gut health; microbiota; digestion

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1. Introduction

Nuts, including peanuts, are nutrient dense foods containing healthy lipids, beneficial phytonutrients and a range of essential vitamins and minerals [1,2]. After cereals, nuts are the plant food group highest in dietary fiber, which results in unique microstructure and physical properties. Since nuts resist digestion in the upper GI tract, their cellular structure retains intact lipids and polymerized polyphenols and plays a key role in how they are metabolized by gut microbiota in the colon to form bioactive molecules which could benefit human health [3]. The role for specific foods and dietary patterns in modifying gut microbiota and fecal metabolites and their impact on various aspects of human health is well known. Research to understand the composition and function of the microbiota has expanded dramatically in recent years with the development of increasingly sensitive analytical techniques. These tools have facilitated data mining to better understanding the relationship of the microbiome to physiology and health [4].

There are now four tree nuts (almond, cashews, pistachios, walnuts) for which human clinical trials have clearly shown that the measured (metabolizable) energy value is 5–25% lower that the calculated values used in food labelling [5]. Considering these nuts have varying cellular structures and macro, micro, and phytonutrient contents, the mechanisms for digestion and microbiota changes are not fully understood, although the evidence for

lipid encapsulation is compelling [6]. Some studies have shown that an optimized diet rich in nuts may be an intervention that promotes a healthy microbial population and thereby improves overall physiology, but clinical trials to date are inconclusive.

In 2020, a systematic review [7] and meta-analysis [8] of a total of 10 randomized, controlled trials (RCTs) assessed the effects of various nuts on fecal microbiota for over 600 adults consuming western diets, with 40–100 g nuts daily, in the U.S.A., Germany, Italy and Spain. Fitzgerald et al. [7] concluded from nine RCTs (four almond, three walnut, one each hazelnut and pistachio) that the overall gut health benefits of nuts may be due, in part, to their unique composition and physical structure. However, the exact mechanisms by which nuts exert these modest modulatory effects on gut microflora remain unclear. Since specific microbial alterations were evident, but often inconsistent, the authors recommended future studies designed to address the baseline habitual dietary patterns and microbial composition to minimize inter-individual composition of the gut microflora. Creedon et al. [8] found the strength of evidence from their meta-analysis from nine RCTs (five almond, three walnut and one pistachio) to be generally inconclusive. Nut consumption affected gut microbiota composition at the genus level, but not at a phyla level nor on the diversity of the microbiome. However, nut type and, to some extent, their duration of consumption influenced the overall effects. They concluded that further parallel design RCTs, powered to detect changes in fecal microbiota and that incorporate functional and clinical outcomes, are still needed. Mead et al. [9] performed a systematic review of four studies that included children between the ages of 3 and 18 years (one almond, two hazelnut, one Brazil nut) who consumed between 15–30 g nuts daily for 8–16 weeks. Although they found nut consumption improved overall diet quality in this young population, there were inconsistent effects on gut health. They concluded that further studies were needed, with consideration given to higher doses and longer intervention periods.

Dietary pattern analysis has emerged as an alternative approach to study the relation between nutrition and disease. Nuts are typically included in different healthy food patterns, and, as part of the Mediterranean Diet (MedDiet), a dietary pattern widely recognized as a nutritional strategy that improves cardiometabolic health [10]. In Spain, Galie et al. [11] examined whether following a MedDiet modified gut microbiota composition and fecal metabolomics profiles, as well as cardiometabolic risk factors, compared with a non-MedDiet supplemented with 50 g nuts daily. They reported for the first time that the 50 participants with metabolic syndrome following the MedDiet, compared with a non-MedDiet diet supplemented with nuts, significantly changed specific microbial genera and fecal metabolites. However, it was concluded that further intervention studies were needed to understand the effects of different healthy dietary patterns on gut microbiota composition and functionality. In a separate study, Israeli researchers used a different approach to augment the MedDiet. In these studies, conducted in Spain and Italy, Rinott et al. [12] showed that within a 6 month controlled-feeding trial of 294 subjects, a green MedDiet, that included 28 g walnuts per day as well daily polyphenol-rich green tea and Mankai aquatic plant, led to more prominent compositional change in the gut microbiota.

They found both MedDiets induced substantial changes to the community structure of the gut microbiome, with the green MedDiet leading to more prominent compositional changes, largely driven by the low-abundant, "non-core", microorganisms [12]. They concluded that the diet microbiome–host interaction should be further explored in future studies that may guide the implementation of novel beneficial modifications of existing dietary patterns.

An overview on the digestibility of nut nutrients and phytochemicals and the impact of food matrices and processing on digestion in the upper gastrointestinal (GI) tract is provided. In addition, the effect of nuts on the composition and diversity of the gut microbiota and their impact on the production of microbially-derived short chain fatty acids and bile acids, as well as recent reports describing the prevention of gastrointestinal diseases associated with nut consumption, is described in this review.

2. Food Matrix and Digestion

2.1. Microstructure and Cell Properties

The great diversity of species, as well as of varieties within the same species, the cultivation methods, and the climatic characteristics where tree nuts are cultured, combine to exert profound effects on the chemical composition of nuts. The geometrical properties of nut shells and kernels, including length, width, thickness, density, surface area, volume, and specific gravity, influence the quality of nut products in the post-harvest process. Nut structure can influence lipid digestibility [13]. We have previously demonstrated that individual raw almond cells separated by the chelating agent CDTA are small (less than 50 µm in diameter) and the lipid is still within oleosomes (Figure 1), surrounding the protein bodies [14]. Roasting has an effect liberating the lipid from the oil bodies, which will then form large lipid droplets in unstained and Sudan IV-stained cells.

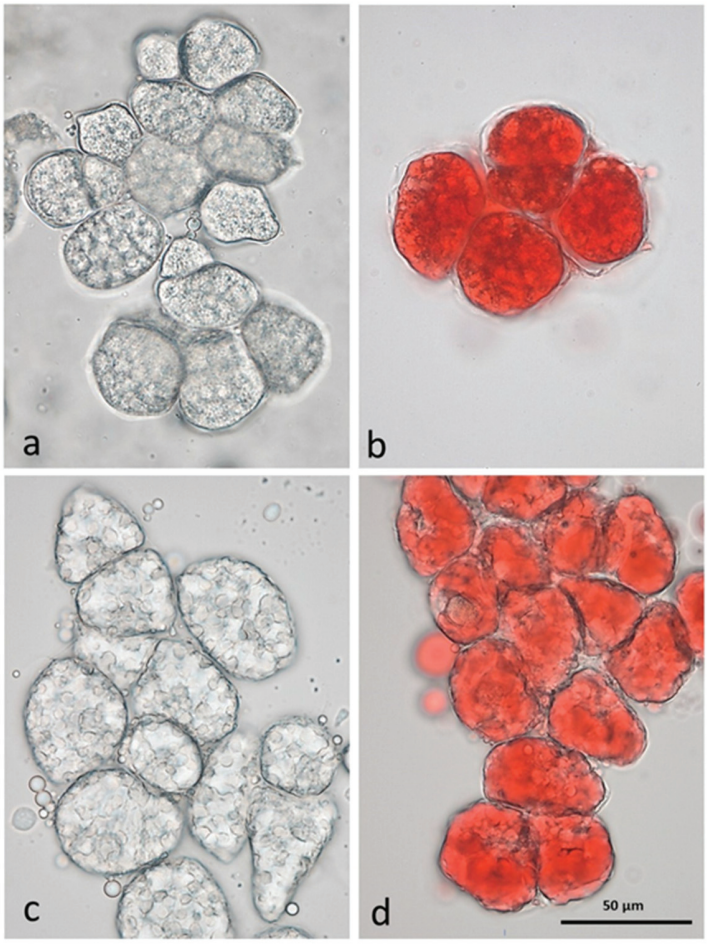

Figure 1. CDTA-separated cells of baseline natural raw almonds (**a**) unstained, (**b**) lipid stained with Sudan IV; and roasted almonds (**c**) unstained, (**d**) lipid stained with Sudan IV, showing lipid coalescence in the cells following roasting [14].

The physicochemical properties of the cell walls (e.g., dietary fiber), as well as their composition, mainly comprised of non-starch polysaccharides, are factors known to influ-

ence nutrient digestibility [15]. In addition, phospholipids and proteins can also limit the access of hydrolytic enzymes.

A theoretical model has been developed to predict lipid release from almonds in the gut: using simple geometry and data on cell dimensions and particle size, the number of ruptured cells in cut almond cubes was calculated [16]. The model has the potential to accurately predict nutrient bioaccessibility in a broad range of edible plants, based on their particle size and cell diameter. Grassby et al. [17] have also demonstrated that test meals containing almonds of different particle sizes behaved differently in the gut. Using a theoretical model, Creedon et al. [18] revealed a greater lipid bioaccessibility for ground almonds than whole almonds after mastication (10.4% ± 1.8% vs. 9.3% ± 2.0%, respectively; $p = 0.017$).

2.2. Bioaccessibility of Nutrients and Phytochemicals in the Upper Gastrointestinal Tract

During the multistage processing that occurs in the digestive system, mechanical and chemical mechanisms promote the breakdown of food molecules into smaller moieties, which can then be absorbed by the body. With the term "bioaccessibility", we refer to the proportion of nutrients and/or phytochemicals released from the upper GI tract, thereby becoming potentially available for absorption [19]. The physicochemical properties of nuts significantly affect the bioaccessibility of their constituent nutrients and phytochemicals [20,21].

2.2.1. Nutrient Bioaccessibility

Studies on almond digestion have shown that mechanical trituration or chewing breaks down a large fraction of the first outer layer of cells, while the majority of parenchyma cells, in which lipids and proteins are encapsulated, remains intact [19,22]. In a study with ileostomy volunteers, we showed that the lipids present in the intact cells located under the fractured layers appeared to 'leach' from the intact cells only after a protracted incubation in the upper GI tract [23]. This may be due to the increased porosity of the cells and to the degradation and solubilization of pectic compounds present in the cell wall and middle lamella [24]. The fractured surface may account for the lipid release that occurs after prolonged incubation in the GI tract. Although it is unclear to what extent lipolysis occurs inside almond cells and whether the lipids leave the cells as triacylglycerol molecules or hydrolyzed products, certainly mechanical processing (mainly grinding) or mastication is necessary for the cells to rupture and allow intracellular lipid and other nutrients (e.g., proteins) to be made available for digestion. Ellis et al. [19] observed the presence of almond tissues (cotyledon and testa) in fecal material after ingestion of almond kernels; some cells were still intact, whereas other cells had partially or totally lost their intracellular lipid. Recently, McArthur and Mattes [21] have subjected masticated samples of almonds, pistachios and walnuts obtained from healthy adults to a static model of gastric and intestinal digestion. While there was no significant difference in the total lipid release between the three nuts after intestinal digestion, walnuts produced a significantly larger particle size after chewing compared with almonds. Furthermore, the particle size after digestion was larger for walnuts compared with pistachios and almonds, indicating additional mechanisms, such as cell wall fissures and lipid storage properties, as relevant for energy extraction from nuts.

2.2.2. Phytochemicals Bioaccessibility

One of the main factors affecting the beneficial potential of polyphenols is their bioaccessibility and absorption in the upper GI tract, followed by their metabolism by the gut microbiota [25]. Polyphenols are a heterogeneous group of compounds characterized by complex structures and polymerization [26]. It is believed that only about 5–10% of the total polyphenol intake could be absorbed in the small intestine, mostly low molecular-weight polyphenols, starting with the removal of the sugar moiety from the glycoside [27]. The chemical structures and associated constituents largely influence their overall absorption, determining whether the polyphenols will be absorbed in the small intestine, or

subsequently enter the colon where they could be metabolized by the colonic microbiota. Generally, hydrophobic forces and molecular hindering mechanisms are involved in the in vitro bioaccessibility of lipophilic phenolics, while hydrogen bonding and ionic forces are involved in the bioaccessibility of hydrophilic compounds [28].

We have demonstrated that polyphenols from pistachios are bioaccessible in the upper GI tract, with small differences between raw unsalted and roasted, salted pistachios [29]. It is believed that lutein and zeaxanthin bioavailability from pistachios are enhanced by the presence of fatty acids.

Clinical studies on the bioavailability of almond polyphenols are available. Urpi-Sarda et al. [30] analyzed the polyphenols and their metabolites in the plasma and urine of healthy human subjects after consumption of almond skin polyphenols. Products (O-methyl glucuronide, sulfate, glucuronide and O-methyl sulfate derivatives) of naringenin, (epi)catechin and isorhamnetin were identified in plasma and urine samples in the nanomolar range, together with the glucuronide and sulfate forms of 5-(dihydroxyphenyl)-γ-valerolactone and 5-(hydroxymethoxyphenyl)-γ-valerolactone. Bartolomé et al. [31] identified O-methyl glucuronide, O-methyl sulfate, sulfate and glucuronide derivatives of (epi)catechin, the glucuronide conjugates of isorhamnetin and naringenin, and sulfate conjugates of isorhamnetin, together with conjugates of hydroxyphenylvalerolactones and several products of microbial metabolization in plasma and urine samples. Garrido et al. [32] reported a maximum urinary excretion of naringenin and (epi)catechin conjugates between 2 and 6 h after consumption of almond skin polyphenols, while conjugated metabolites of isorhamnetin and hydroxyphenylvalerolactones reached their maximum levels between 10 and 24 h after consumption.

2.2.3. Effect of Processing and Food Matrix on Digestion

The type of nut and related processing methods greatly influences the damage incurred to the cell wall of the parenchyma, and, thus, the general bioaccessibility, the intracellular diffusion and lipase access to the oil bodies. Verghese et al. [33] have reviewed the effects of processing on the bioavailability of phytochemicals from a range of foods, including nuts, in relation to health benefits of bioactive compounds.

Amongst nut processing methods, dehydration through air or oil roasting can cause microstructural changes, such as lipid coalescence and chemical variations, which affects the integrity and structure of cell walls [34]. Roasting causes textural changes making nut mastication more efficient, which may be explained by the fact that tissues are more brittle when dehydrated. On the other hand, various types of roasting can influence the number of required chews before swallowing [24]. In a recent study, roasting of macadamia nuts changed the appearance of the cell walls and disrupted the oil body membrane, resulting in oil droplet coalescence [35].

Fewer studies have examined the influence of blanching on lipid digestibility, presumably due to the relatively mild process compared with roasting [13]. Oliveira et al. [36] reported that bioactive compounds and antioxidant activities increased with roasting and decreased with blanching. Both processing treatments positively affected the sensorial characteristics, increasing the content of polyunsaturated fatty acids, while saturated fatty acids, monounsaturated fatty acids and several health lipid indices decreased [36].

We have previously reported that incorporating natural and roasted salted pistachios in a food matrix (muffin) decreased the bioaccessibility of certain bioactive compounds, such as protocatechuic acid and luteolin, during in vitro gastric and duodenal digestion [29].

Different food matrices had a significant impact on bioaccessibility of polyphenols from almond skin using a dynamic gastric model. Use of full-fat milk lowered polyphenol recovery, influenced the free total phenols and associated antioxidant status, indicating that phenolics could bind protein within the matrix [37].

A pilot walnut supplementation study of urolithin bioavailability in healthy human volunteers demonstrated that ellagitannin (e.g., punicagalin) metabolism produced a highly

variable profile of nine different urolithin metabolites in the urine [38]. Furthermore, the concentration of glucuronidated urolithins in blood and urine did not correlate with antioxidant capacity [39].

Overall, the available literature demonstrated that nutrient and phytochemical release from nuts during digestion is limited and influenced by several factors. Food matrix has an impact on bioaccessibility.

3. Effect of Nuts on Gastrointestinal Health

3.1. Microbiota Composition and Diversity

Understanding the importance of the gut microbiota (the collection of microorganisms present in a fecal sample) and the gut microbiome (genomes present in the fecal sample) is rapidly advancing. In healthy humans, gut microbiota and microbiome are usually assessed using fecal samples collected after dietary interventions. In these samples, microbial diversity and products of microbial metabolism are typically measured. Microbial end-products of metabolism can also be measured in other biospecimens such as blood or urine. There are many polyphenolic compounds (flavonoids and non-flavonoids) found in nuts. Although these compounds are generally poorly absorbed, they have a wide range of anti-bacterial, anti-inflammatory and anti-carcinogenic effects [40]. These anti-bacterial properties are of interest in how they may affect the host gut microbiota. For example, based on serving size, walnuts are the seventh largest source of total polyphenols among commonly consumed foods and beverages [41,42]. The phenolic profiles and antioxidant activities of free, esterified and bound phenolics in the walnut kernel reveal the presence of a remarkable array of phenolic compounds, including phenolic acids, flavonoids, tannins, phenolic lignans and stilbene-derivatives [43]. The main polyphenol found in walnuts is pedunculagin, an ellagitannin that has a wide range of antioxidant and anti-inflammatory properties [42]. After ingestion, ellagitannins are hydrolyzed to release ellagic acid, which is converted by the gut microflora into the urolithins [42]. With respect to nuts, analyses of microbial diversity, microbiota and microbial end-products have been performed in only a few studies, with more data becoming available as methodologies evolve and analytical costs decrease.

Alpha-diversity is the diversity within a defined microbial community. Typical measures of alpha-diversity are those that account for total species number (species richness) and the relative abundance of species (species evenness). One common measure of species richness is Chao-1, and measures of species richness and evenness include the Shannon index and Simpson index [44]. Chao-1 counts the number of different taxonomic groups (typically genus or species) in a sample, but does not take into account the abundance or relative distributions of the taxa. On the other hand, the Simpson index does consider relative abundance by weighing. Increased alpha-diversity is associated with improved health outcomes [45,46].

Studies of walnuts [47,48], almonds [49–51], and pistachios [51] have reported the effect on alpha-diversity of adding these nuts to the diet (intervention type, study design, sample size, dose and study duration are summarized in Table 1). In one study comparing the consumption of almonds or graham crackers as a snack, significant changes were reported in the Chao-1 index and Shannon index [52]. In this study, the snacks were provided for 8 weeks. The authors suggested that the 8 week provision of snacks was longer than many of the other studies, which typically last 3 weeks [47,49,51], and that perhaps these shorter interventions were not of sufficient length to affect alpha-diversity. On the other hand, an additional 8 week intervention of walnuts did not change the Simpson index [53]. Thus, it is unclear what length of feeding is important to affect alpha-diversity, and if tree nut dietary interventions have a substantial effect on alpha-diversity.

Table 1. Summary of studies evaluating nut intake and microbial changes.

Study Number (REF)	Intervention Nut	Study Design	Sample Size	Dose	Study Duration	Diversity Changes	Microbial Composition Change
[47] (Holscher et al., 2018)	Walnut	Crossover, controlled diet	18	42 g/d	3 wk	No effect on α diversity; β diversity, weighted principal coordinates analysis of UniFrac distances between samples based on their 97% OTU composition and abundances showed that bacterial communities were affected by walnut consumption.	Compared with after the control period, walnut consumption resulted in higher relative abundance of Faecalibacterium, Clostridium, Dialister, and Roseburia and lower relative abundances of Ruminococcus, Dorea, Oscillospira, and Bifidobacterium.
[48] (Tindall et al., 2020)	Walnut	Crossover, controlled diet	42	18% of energy	6 wk	No effect on α diversity; β diversity, weighted principal coordinates analysis of UniFrac distances between samples based on their 97% OTU composition and abundances showed that bacterial communities were affected by walnut consumption.	Compared with after the control period, walnut consumption resulted in higher relative abundance of Faecalibacterium, Clostridium, Dialister, and Roseburia and lower relative abundances of Ruminococcus, Dorea, Oscillospira, and Bifidobacterium.
[49] (Holscher et al., 2018)	Almond (whole, whole roasted, chopped roasted, butter)	Crossover, controlled diet	18	42 g/d	3 wk	No effect on α and β diversity.	Almond consumption increased the relative abundances of *Lachnospira*, *Roseburia*, and *Dialister*. Comparisons between control and the four almond treatments revealed that chopped almonds increased *Lachnospira*, *Roseburia*, and *Oscillospira* compared with the control; whole almonds increased *Dialister* compared with the control. There were no differences between almond butter and the control.
[50] (Burns et al., 2016)	Almond	Crossover, free-living	50	40 g/g	6 wk	No differences in overall microbiota diversity measures (Shannon diversity index and inverse Simpson diversity index).	Targeted qPCR analysis did not show almond intake-associated changes in the quantities of Bifidobacteria spp or lactic acid bacteria. When individual OTUs from 16S rRNA were combined at the phylum level, there were no significant differences in abundances correlating with almond intake. Some changes in the prevalence of various bacterial signatures at the genus and species levels were observed with the almond intervention at final vs. baseline.
[51] (Ukhanova et al., 2014)	Almond	Crossover, controlled diet	18	42 g/d and 84 g/d	18 d	α-diversity was not affected by the intake of almonds.	Numbers of bifidobacteria were not affected by the consumption of almonds.

Table 1. *Cont.*

Study Number (REF)	Intervention Nut	Study Design	Sample Size	Dose	Study Duration	Diversity Changes	Microbial Composition Change
[51] (Ukhanova et al., 2014)	Pistachio	Crossover, controlled diet	16	42 g/d and 84 g/d	18 d	α-diversity was not affected by the intake of pistachios.	Numbers of bifidobacteria were not affected by the consumption of pistachio. Pistachio consumption appeared to decrease the number of lactic acid bacteria.
[52] (Dhillon et al., 2022)	Almond	Parallel arm, free-living	73	57 g/d	8 wk		Microbial amino acid biosynthesis, and amino sugar and nucleotide sugar metabolism pathways were differentially enriched at the end of the intervention.
[53] (Bamberger et al., 2018)	Walnut	Crossover, free-living	142	43 g/d	4 wk	Supplementing walnuts in the diet did not significantly affect bacterial diversity measured by Shannons effective, and Simpsons effective counts. There was no significant difference in evenness as well as in richness for the walnut diet compared with the control diet. Beta-diversity increased with walnut consumption.	The abundance of Ruminococcaceae and Bifidobacteria increased significantly while Clostridium sp. cluster XIVa species (Blautia; Anaerostipes) decreased significantly during walnut consumption.
[54] (Dhillon et al., 2019)	Almond	Parallel arm, free-living	73	57 g/d	8 wk	Almond snacking resulted in 3% greater quantitative alpha-diversity (Shannon index) and 8% greater qualitative alpha-diversity (Chao1 index) than the cracker group.	Almond snacking decreased overall Bacteroides fragilis relative abundance by 48%.
[55] (Sapp et al., 2022)	Peanut	Crossover, controlled diet	50	28 g/d	6 wk	No between-condition differences in alpha- or beta- diversity were observed.	Following peanut intake, Ruminococcaceae were significantly more abundant compared with a lower-fat higher-carbohydrate snack. Metatranscriptomics showed increased expression of the K03518 (aerobic carbon-monoxide dehydrogenase small subunit) gene following peanut intake, and Roseburia intestinalis L1-82 was identified as a contributor to the increased expression.
[56] (Choo et al., 2021)	Almond	Parallel arm, free-living	69	56 g/d	8 wk	In the almond intervention group, there were significant increases in bacterial community richness, evenness and diversity.	Increases in both the relative and absolute abundance of operational taxonomic units in the Ruminococcaceae family, including Ruminiclostridium, Ruminococcaceae NK4A214, and Ruminococcaceae UCG-003 were the principal drivers of microbiota-level changes.

Beta-diversity is the diversity among different communities. For some approaches, such as UniFrac distances, qualitative plots are created to show beta-diversity. On the other hand, weighted UniFrac distances are quantitative. Both approaches have been used to measure beta-diversity [44,57]. Increased beta-diversity is associated with improvement in some health outcomes and reduction in BMI.

In four studies of almonds, two studies have reported no effect of almond consumption on beta-diversity using weighted and unweighted UniFrac distances [49,54], one study reported an increase in beta-diversity using unweighted UniFrac distances [51], and one study reported that beta-diversity was measured, but no data were presented [50].

In three studies of walnuts, two studies reported an increase in beta-diversity using weighted principal coordinates analysis of UniFrac distances [47,53]. Additionally, Bamberger et al. also measured beta-diversity with unweighted UniFrac distances, which was also significantly changed with walnut consumption [53]. One study [48] of walnuts used weighted UniFrac distances and did not report significant effects of the walnut diet compared with diets that were matched in fatty acid composition, but did not contain walnuts, or a diet replacing alpha-linolenic acid with oleic acids (also not containing walnuts) after 6 weeks of consuming each diet. The results observed in this study [48] may reflect the similarity of the composition of the diets, and that primarily fatty acid concentrations were manipulated. In one study of pistachios, beta-diversity was reportedly increased [53], and in one study of peanuts, changes in beta-diversity were unchanged between the peanut-containing diet and the control diet [55].

Overall, the effect of nut consumption on alpha- and beta-diversity was inconsistent. Reasons for these reported inconsistencies may be the variability in the length of intervention, the amount of nuts fed, dietary control of the intervention, comparator diets and sample size. The length of intervention for these various studies was 3 to 8 weeks. Since diversity was not a primary outcome, these studies may not have been designed or powered sufficiently to detect changes in diversity. The optimal length of feeding for these types of dietary interventions is unknown. Furthermore, a limited number of studies use provisioned diets which provide all the food consumed by the research volunteers, whereas other studies provide dietary guidance. The latter will likely result in more diet heterogeneity and variability which are two factors that may independently impact microbial diversity. Overall, the amount of nuts offered ranged from 42 to 99 g/d. The differences in these dose levels will likely affect substrate availability for fermentation in the large intestine, given the decreased digestibility of macronutrients in nuts and hence the associated increase in substrate reaching the large intestine [58–62]. Finally, the beta-diversity measured among diets will depend upon the differences in the composition of the diets, and perhaps some of the inconsistencies observed in beta-diversity is a reflection of the similarity of diet comparisons.

3.1.1. Changes in Relative Proportion at the Phyla Level

Changes in the relative abundance of bacteria can be determined at different phylogenetic levels. In a meta-analysis of nut studies, seven interventions investigated phlya-level changes in *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, *Proteobacteria*, and *Verrucomicrobia* [47,49,50,54]. Additionally, two studies reported changes in relative abundance of the phyla *Tenericutes* [50,54]. Additional data were published but were not included in this meta-analysis [8]. Across these interventions, there were no significant effects of nut intake (five almond randomized control trials and one walnut RCT) on the relative abundance of these phlya. In fact, there was only one study in which any of these phyla were altered—with a significant change in the standard mean difference of *Proteobacteria* [50].

3.1.2. Changes in Relative Proportion at the Genus Level

At the genera-level, changes in the relative abundance of 19 phyla have been reported in several interventions [8]. Combining these data, the relative abundance of *Clostridium*, *Dialister*, *Lachnospira*, *Parabacteroides*, and *Roseburia* have been reported [8]. Nut consump-

tion increased the relative abundance of *Clostridium*, *Dialister*, *Lachnospira*, and *Roseburia*. Further nut consumption decreased the relative abundance of *Parabacteroides*. These data represented five almond randomized control trials and one walnut RCT. When the data from the walnut trial were excluded from the meta-analysis, the effect of nut consumption on the relative abundance of *Clostridium* was no longer statistically significant. All of these studies were cross-over designed studies except one, the Dhillon study [54] which was a parallel arm intervention. When the parallel arm study (using almonds) was not included in the meta-analysis, the effect of nut consumption on the relative abundance of *Dialister*, *Lachnospira*, and *Parabacteroides* was no longer significant [8]. For many of these findings, there was heterogeneity, especially related to study duration (studies < 4 weeks vs. studies > 4 weeks), amount of nut consumed (<45 g/d vs. >45 g/d) and nut type (almond vs walnut). While the results of individual studies, and the results obtained from meta-analyses are intriguing, the total number of studies reported is limited, especially when it is likely that overall dose, nut type, and duration of intervention may all affect changes in relative abundance at the genera-level.

3.2. Effect of Nuts on Microbial End Products

3.2.1. Short Chain Fatty Acids

Short chain fatty acids (or volatile fatty acids) include acetate, butyrate and propionate. They are a microbial end-product of anerobic fiber fermentation. These short chain fatty acids can be used as an energy substrate by the microbes or host. Short chain fatty acids can block inflammatory processes via activation of G-protein-coupled receptors that are present within colonocytes [63]. These molecular alterations can subsequently activate intracellular signaling pathways that dampen NF-kB activation, modify downstream inflammatory mediators, and increase epithelial barrier function [64]. Species within the genera *Dialister*, *Lachnospira*, and *Roseburia* are known butyrate producers [65]. As mentioned above, the relative abundance of these genera has been shown to be increased with nut consumption.

Specific nut intervention studies that have measured the concentration of fecal short chain fatty acids are limited. In one such study, 87 subjects received 56 g/d of whole almonds or ground almonds (or no almonds as a control) for 4 weeks [18]. Compared with the baseline, there was no change in the fecal concentration of short chain fatty acids (acetate, butyrate, propionate, isobutyrate, valerate or isovalerate) in either the control diet or in subjects consuming either form of almond. However, when the data from the two forms of almonds were combined, there was a higher concentration in fecal butyrate compared with the controls. In a study of 69 subjects also receiving 56 g/d of whole almonds for 8 weeks, there was no observed effect of almond consumption on fecal concentrations of short chain fatty acids [66]. In a study of 63 subjects fed 25 g/d of peanuts, 32 g/d of peanut butter or 32 g/d of control butter made with peanut oil for 6 months, consumption of peanuts and peanut butter increased the fecal concentration of acetate, propionate and butyrate compared with baseline, with no changes in the control group fed butter [56]. In a crossover study of 50 subjects fed 28 g/d of dry roasted, unsalted peanuts or a lower-fat, higher-carbohydrate peanut-free snack for 6 weeks, short chain fatty acids were not measured; however, meta-transcriptomics analysis found that there was an increase in the expression of the bacterial K03518 gene that is directly involved in butyrate production [55]. In a recent short-term study of walnuts, a 3 day consumption in healthy individuals was found to modify the gut microbiome, while also increasing short chain fatty acid levels [67]. Importantly, these effects were dependent upon the composition of the individual microbiome [68]. Walnuts were found to modify the microbiome in an urolithin metabolite-dependent manner. Microbiota analysis further showed significant increases in two bacterial species, namely, *Coprococcus* and *Anaerostipes*, each established producers of butyrate [69]. In addition, *Phascolarbacterium*, a known producer of acetate and propionate, was also increased by walnut consumption [65]. Finally, this study identified significant variability in the metabolism of the polyphenols, differences that were present between the distinct urolithin metabotypes [68].

3.2.2. Bile Acids

The primary bile acids (cholic acid and chenocholic acid) are produced in the liver, while the secondary bile acids (lithocholic acid and deoxycholic acid) are produced in the large intestine by bacterial metabolism. Many bacteria are involved in the conversion of primary to secondary bile acids, including *Bifidobacterium*, *Lactobacillus*, *Clostridium*, *Enterococcus*, *Bacteroides*, *Eubacterium*, and *Escherichia* [70]. The microbially-produced secondary bile acids can bind to nuclear and membrane-bound receptors, activating a complex network of signaling cascades [71,72]. Through these cellular mechanisms, the secondary bile acids have been implicated in various disease etiologies, including several types of cancer, inflammatory bowel disease, cardiovascular disease and non-alcoholic fatty liver disease [72].

In a study of 18 subjects fed 42 g/d of walnuts or an identical control diet without walnuts for 3 weeks, fecal bile acids were measured at the end of each treatment [47]. There were no differences in the concentration of the primary bile acids measured between the two diets. However, after consumption of the diet containing walnuts, the concentration of the secondary bile acids was significantly lower [47]. These walnut-mediated changes in bile acid concentration raise the possibility that walnuts can affect multiple cell-signaling pathways, and possibly disease outcomes, through these microbially-derived end-products [47].

3.3. Walnut Consumption and Gastrointestinal Disease

Extensive research has been undertaken to determine whether walnuts may contribute to the mitigation of gastrointestinal disease, particularly with respect to ulcerative colitis and cancer. Walnut constituents contribute to decreased inflammation within the intestinal mucosa, related in part, to the microbial conversion of walnut-derived ellagitannins into a complex family of anti-inflammatory molecules, the urolithins [73]. Of course, walnuts also contain alpha-linolenic acid, a fatty acid that can be readily converted into eicosapentaenoic acid and docosahexaenoic acid, both associated with anti-inflammatory properties [74]. Studies in animal models and in several cell culture systems have uncovered a variety of health benefits that may be attributed to walnuts. A unifying mechanism is likely to involve at least some aspect of effects on immune-related and inflammatory cells. Defining the health benefits of dietary walnut consumption and the influence of its phytochemical composition may stimulate further research into underlying mechanisms that account for disease prevention.

In a preclinical animal model designed to recapitulate the pathology of ulcerative colitis (UC), ellagic acid was found to inhibit disease progression, while reducing associated intestinal inflammation in treated mice [75]. Furthermore, urolithin A, a microbial metabolite of ellagic acid, and its potent synthetic analogue, UAS03, were also found to mitigate DSS-induced intestinal inflammation, with reduced oxidative tissue damage and enhanced intestinal barrier function repair [76]. Both urolithin A and UAS03 provided significant protection against both acute and chronic colitis. This protection was caused by a number of distinct molecular mechanisms, including direct effects on inflammatory mediators, up-regulation of the ligand-activated transcription factor, AhR, and the remarkable ability of these compounds to enhance barrier function by eliciting an up-regulation of claudin 4, a critical tight junction protein [76]. These investigators also evaluated the effects of urolithin A on the direct activation of murine CD4-positive T cells and found a significant repression of their proliferative capacity that was associated with increased miR-10a-5p levels and down-regulation of Orai1/STIM1/STIM2 expression [76]. Koh et al. tested a walnut phenolic extract in both acute and chronic colitis models in mice [77]. This extract was found to inhibit NF-κB signaling, an effect directly associated with reduced expression of pro-inflammatory mediators [78]. Furthermore, Koh et al. also reported that their walnut phenolic extract inhibited colitis-associated colon cancer induced by treatment with the colon carcinogen, azoxymethane, followed by three cycles of 2% DSS for 5 days [77]. Overall, the therapeutic potential of walnuts to positively impact the

severity of inflammatory diseases and possibly even inflammation-associated cancer has been established. Finally, Bartoszek et al. have tested the ability of walnut oil to stabilize tight junction proteins and to reduce the levels of pro-inflammatory cytokines commonly present within the inflamed mouse colon following treatment with the ulcerogenic agent, dextran sodium sulfate (DSS) [78]. Promising data from this research group have shown that walnut oil improves overall disease activity and restores normal ion transport and colonic wall permeability [78].

Nakanishi et al. used a similar mouse model to evaluate dietary supplementation with walnuts on colonic mucosal injury induced by DSS [74]. Mice were fed a "Total Western Diet" supplemented with walnuts (ranging from 0 to 14 g walnuts/100 g diet) for two weeks prior to DSS administration. After DSS administration, walnut supplementation significantly protected the colonic mucosa 10 days post-injury. Based on this observed protection against experimentally-induced colitis by walnuts, a follow-up study was conducted to determine the effect of walnuts on metabolites present in the colon [74]. Fecal and colonic samples were analyzed using discovery-based metabolite profiling two weeks post-walnut consumption. Nakanishi et al. found that walnuts caused a significant increase in fecal polyunsaturated fatty acids, including DHA and 9-oxo-10(E),12(E)-octadecadienoic acid (9-oxoODA), as well as kynurenic acid. In the colon, there was a significant increase in S-adenosylhomocysteine and betaine, two important mediators of fatty acid β-oxidation. Together, these findings suggest that metabolic changes caused by walnut consumption may contribute to protection against DSS-induced inflammatory tissue injury [74]. Additional studies are needed to confirm these findings and to better define the precise role of these metabolic changes on colonic inflammation.

Finally, walnut fractions have been found to protect against the development of gastric mucosal lesions, including gastritis, gastric ulcer, and gastric carcinoma [79]. Liu reported gastro-protective and cancer preventive effects of walnut constituents on alcohol-induced inflammation, with fewer gastric lesions and decreased gastric inflammation associated with decreased inflammatory cytokines [80]. Park tested the anti-inflammatory and anti-tumorigenic effects of walnuts in an *H. pylori* gastric cancer model [81]. Mice were infected with *H. pylori* and fed a high-salt diet to promote gastric cancer, and were supplemented with walnuts for nine months. Walnut supplementation caused a significant reduction in gastric cancer frequency with markedly reduced levels of PGE2 and COX-2, important pro-inflammatory mediators that play a key role in tumor promotion [80,81].

Overall, we have demonstrated that, although some nutrients and phytochemicals from nuts are absorbed in the upper GI tract and will reach the colon, clinical studies on their effect on the gut microbiota are still inconclusive. There is literature available on the beneficial effect of walnuts on the prevention of ulcerative colitis and gastric mucosal lesions.

4. Conclusions

In the present review, we have outlined the physiological processes that contribute to the digestion of tree nuts. Cell wall composition, thickness and porosity, as well as lipid encapsulation, may slow down or completely prevent some enzymes from entering the cell. It is clear that some fraction of nutrients and phytochemicals present in the nut are not digested in the upper GI tract and could reach the colon, where they may be fermented by the gut microbiota. Although some studies have demonstrated that nut consumption promotes a healthy microbiota, clinical trials are still inconclusive. Importantly, research focused on how nut consumption may affect microbial communities is at an early stage, is further confounded by the wide variability in overall quality of trial design, research methods used, age and health status of subjects, and the amount, type, and duration of nut intake.

5. Research Gaps and Future Directions

Future clinical trials must include key measures of microbial community structure, such as species diversity and composition, as well as changes to the microbiome that may

be directly related to human health and disease risk. This information will be useful for comparing the beneficial effects of nut consumption across the population. While certain nuts have been investigated more than others for their impact on the GI transit, limited literature is available on the effects of regular consumption of mixed nuts. Research with additional types of nuts is needed to understand their broader effects.

To more accurately assess the health benefits and functionality associated with nut consumption, further studies are needed to better define the mechanisms responsible for their limited energy extraction during digestion, and how the physical structure of individual nuts may ultimately affect bioavailability. Clearly, epidemiological and clinical studies analyzing the potential beneficial effects of nut consumption on prevalent gastrointestinal diseases are warranted in the future.

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nutrients

MDPI

Review

Effect of Nuts on Markers of Inflammation and Oxidative Stress: A Narrative Review

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Abstract: Oxidative stress and inflammation are mediators in the pathophysiology of several non-communicable diseases (NCDs). Tree nuts and peanuts lower risk factors of cardiometabolic disease, including blood lipids, blood pressure and insulin resistance, among others. Given their strong antioxidant/anti-inflammatory potential, it is plausible that nuts may also exert a favorable effect on inflammation and oxidative stress. Evidence from systematic reviews and meta-analyses of cohort studies and randomized controlled trials (RCTs) suggest a modest protective effect of total nuts; however, the evidence is inconsistent for specific nut types. In this narrative review, the state of evidence to date is summarized for the effect of nut intake on biomarkers of inflammation and oxidative stress, and an attempt is made to define the gaps in research while providing a framework for future research. Overall, it appears that some nuts, such as almonds and walnuts, may favorably modify inflammation, and others, such as Brazil nuts, may favorably influence oxidative stress. There is a pressing need for large RCTs with an adequate sample size that consider different nut types, and the dose and duration of nut intervention, while evaluating a robust set of biomarkers for inflammation and oxidative stress. Building a stronger evidence base is important, especially since oxidative stress and inflammation are mediators of many NCDs and can benefit both personalized and public health nutrition.

Keywords: inflammation; non-communicable diseases; oxidative stress; peanuts; tree nuts

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1. Introduction

Non-communicable diseases (NCDs) are related to lifestyle factors including smoking, sedentary habits, and an unhealthy dietary pattern [1]. Oxidative stress and low-grade chronic inflammation are common mediators in the pathophysiology of many age-related NCDs, including obesity, cardiovascular disease (CVD), type-2 diabetes (T2D), some cancers, and neurodegenerative diseases [2]. Diet and lifestyle modification strategies are cornerstones for preventing NCDs. The evidence supports the role of plant-based diet patterns and plant foods such as tree nuts and peanuts in preventing NCDs and comorbidities, thereby favorably modifying the incidence and mortality of these diseases [3–7].

Reactive oxygen species (ROS) and nitrogen oxidative species (NOS) are part of the normal cellular processes, but the oxidative stress induced by the imbalance of antioxidant systems triggers chronic low-grade inflammation (Figure 1) that contributes to the development of atherosclerosis, CVD, and insulin resistance-related diseases [2,8,9]. In the setting of oxidative stress there is the activation of the regulatory transcription factor, nuclear factor kappa beta (NFκβ), resulting in the release of pro-inflammatory cytokines and the inhibition of nuclear factor-erythroid factor 2-related factor 2 (Nrf2), all leading to more inflammation [10,11]. Plant foods like nuts are rich in phytochemicals and other

antioxidant nutrients, with a potential to counteract oxidative stress and inflammation. Tree nuts and peanuts lower major risk factors of cardiometabolic disease, including blood lipids/lipoproteins, blood pressure, endothelial dysfunction and insulin resistance [12–15]. Given their strong antioxidant/anti-inflammatory potential, nuts may also exert a favorable effect on other risk factors of cardiometabolic disease, such as inflammation and oxidative stress.

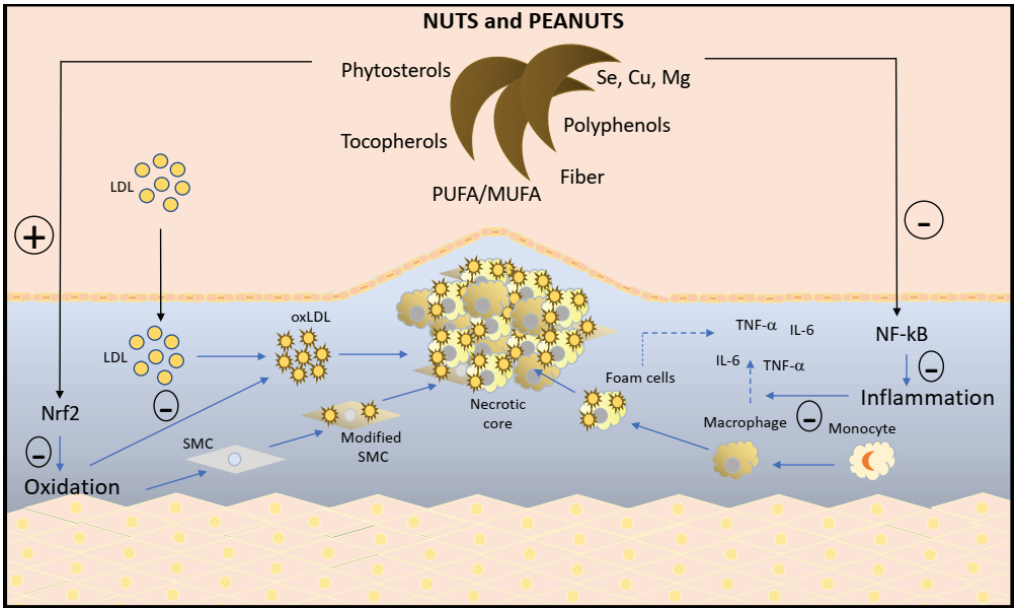

Figure 1. Inflammatory and oxidative processes modulated by nutrients and bioactive substances in tree nuts and peanuts. Fiber, phytosterols, PUFA/MUFA and mineral antioxidants such as Se, Cu, and Mg in tree nuts and peanuts can improve lipid metabolism through a cholesterol-lowering effect on low-density lipoprotein (LDL). Additionally, antioxidants (polyphenols and tocopherols) quench free radicals, avoiding the oxidative modification of LDL (oxLDL). Together, this process prevents monocyte migration and macrophage differentiation, and the consequent endocytosis of oxLDL by macrophages and the formation of foam cells. Increased levels of free radicals in the sub endothelial space stimulate changes in the smooth muscle cell (SMC) phenotype, favoring uptake of oxLDL. This complex process is essential to induce and maintain the low-grade inflammation characterized by the continuous synthesis of inflammatory cytokines (TNF-α, IL-6, and other markers) common in atherosclerosis and present in many other chronic diseases. Tree nuts and peanuts rich in bioactive substances can modulate multiple inflammation and oxidation pathways. Additionally, nut antioxidants can directly quench reactive oxygen species produced in the cell, reduce oxidative stress, and suppress NFκβ expression and downstream pro-inflammatory cytokine generation. Nut antioxidants are cofactors of several antioxidant enzymes. They can increase their activity, upregulate the gene expression of Nrf2, and increase the expression of antioxidant response element gene expression.

Tree nuts (almonds, Brazil nuts, cashew, hazelnuts, macadamia, pecans, pine nuts, pistachios, and walnuts) and peanuts (classified as a legume but considered a nut due to its similar nutrient profile and health benefits) are plant foods that offer a unique combination of macronutrients, micronutrients, and phytonutrients. They are rich in unsaturated fat, which includes polyunsaturated fat (PUFA), both linoleic and α-linolenic acid (ALA), and monounsaturated fat (MUFA). Walnuts and pine nuts have a significant amount of PUFAs,

while all nuts are high in MUFAs. Nuts also have a plethora of powerful antioxidant and anti-inflammatory bioactives, including tocopherols, selenium, zinc, magnesium, fiber, phytosterols, and polyphenols [16–19]. Many of these nutrients and non-nutrients present in nuts exert antioxidant and anti-inflammatory effects independently [18,19], but their presence in a whole food matrix may promote synergistic effects.

Early nut intervention trials primarily observed a lipid-lowering effect of nuts; interestingly, the CVD risk reduction was greater than predicted based on low-density lipoprotein cholesterol (LDL-C) lowering alone [12–14,19,20]. To gain a deeper understanding of the other mechanisms beyond blood lipids that might contribute to the overall CVD risk reduction, the effect of nuts on biomarkers of inflammation and oxidative stress were evaluated mostly as secondary outcomes. This narrative review summarizes the current understanding of the role of tree nuts and peanuts on oxidative stress and inflammation biomarkers, identifies the gaps in this area, and provides a framework for future research. This review was presented at an international conference, "NUTS 2022, Where we are and where we are going in research", in the session on "nuts, inflammation and oxidation". While not exhaustive, this review has considered all relevant systematic reviews, cohort studies and randomized controlled trials (RCTs) published to date.

2. Nuts and Inflammation and Oxidative Stress

This section explores evidence from cohort studies and RCTs on the association or effect, respectively, of the various tree nuts and peanuts on markers of inflammation and oxidative stress. Serum markers of inflammation frequently assayed include *C*-reactive protein (CRP), tumor-necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interleukin-1β (IL-1β), as well as adhesion molecules E-selectin, intercellular (ICAM-1), and vascular cell adhesion (VCAM-1) molecules. Enzymes play an integral part in managing antioxidant and oxidant homeostasis, from which superoxide dismutase (SOD) converts superoxide into hydrogen peroxide and dioxygen [21], while glutathione S-transferase (GST) participates in the phase II detoxification process [22]. The markers of oxidative stress frequently assessed in studies are oxidized LDL (oxLDL), lipid peroxides malondialdehyde (MDA), DNA damage marker, 8-hydroxy deoxy guanine (8-OHdG), antioxidant enzyme activity, and antioxidant capacity. The evidence to date from cohort studies and RCTs is presented below.

2.1. Evidence from Cohort Studies

Systematic reviews and meta-analyses of prospective cohort studies investigated the association between nut consumption and coronary heart disease (CHD) risk, stroke, hypertension, and T2D [5,6,23–25]. Irrespective of follow-up time (3.8 to 26 years), geographical regions, and variation in cohort size (175,000 to >300,000), higher nut intake was inversely associated with CHD risk (relative risk [RR] = 0.81; 95% CI = 0.72–0.91, heterogeneity [I^2] = 56.8%, p = 0.018) [6]. In cohort studies of hypertension cases versus control, a marginal association between higher nut intake and reduced risk of hypertension was noted (RR = 0.66; 95% CI = 0.44–1.00, I^2 = 75.9%, p = 0.006) but no association was observed for T2D or stroke risk. With respect to nut consumption and colorectal cancer risk, the pooled relative risk for the highest versus lowest (never) categories of nut consumption was 0.91 (95% CI = 0.79–1.05, I^2 = 49.1%, p = 0.08). In case–control studies, there was a significant reduction in colorectal cancer risk (RR = 0.84; 95%CI = 0.71–0.99) with nut consumption [6].

The association of nuts and peanuts on the incidence of total mortality, mortality related to CVD, cancer and all-cause among T2D subjects was evaluated in a cross-sectional sample from the Nurses' Health Study (NHS) (1980–2014) and Health Professionals Follow-Up Study (HPFS) (1986–2014) cohorts including 16,217 men and women with T2D at baseline or diagnosed during follow-up [24]. Nuts were associated with a significant reduction in the incidence of total CVD (hazard ratio [HR] = 0.80; 95% CI = 0.70–0.92), and CHD (HR = 0.77; 95% CI = 0.65–0.79), and CVD-specific mortality (HR = 0.61; 95% CI = 0.49–0.79), cancer mortality (HR = 0.73; 95% CI = 0.60–0.90) and all-cause mortality

(HR = 0.67; 95% CI = 0.60–0.74). However, peanuts were associated only with a decrease in all-cause mortality. Collectively, the cohort studies, which have considered many relevant covariates (age, BMI, physical activity, smoking, alcohol, energy intake) in their statistical models, confirmed the positive relationship of nuts and peanuts on mortality incidence; however, neither oxidative stress nor inflammation outcomes were considered.

The cohort studies that have determined the association of nuts and peanut intake on inflammatory markers and their role in risk, incidence, and mortality from NCDs are presented in Table 1. Li et al. [25] examined the association between nut consumption and incident CVD in a subsample from the NHS composed of 6309 women with T2D. From a semi-quantitative food frequency questionnaire (FFQ), habitual nut consumption was grouped into four categories based on the number of servings (serving size, 28 g (1 ounce) for nuts and 16 g for peanut butter): mostly never, 1–3 servings/month to 1 serving/week, 2–4 servings/week, or ≥5 servings/week. Although a higher consumption of nuts and peanuts was associated with lower CVD risk in women with T2D, it was not significantly associated with the inflammatory markers, including tumor necrosis factor receptor 2 (TNFR), ICAM-1, E-selectin, CRP, or fibrinogen. A cross-sectional study from the NHS cohort including 987 women with diabetes assessed the adherence level to the Mediterranean dietary (MedDiet) pattern on a 9-point scale. The higher (6–9 score) adherence level to the MedDiet was associated with higher adiponectin level in comparison to individuals in the lower category of adherence (0–3 score), independent of age, total energy intake, BMI, waist circumference, physical activity, and smoking status. To investigate which food groups in the MedDiet were able to explain the improvement in adiponectin level, using an age and energy-adjusted model, women with diabetes in the highest quintile of nut consumption had adiponectin levels significantly higher, by 23%, than those in the lowest quintile, and this remained significant even when adjusted for BMI, smoking status, activity level, and waist circumference [26].

Table 1. Cohort Studies: Associations between nuts and inflammatory biomarkers.

Reference	Study Country	Sample Size Gender	Follow-Up	Nut Type Amount	Outcome	Inflammatory Biomarkers
Li et al., 2009 [25]	NHS, USA	6.309 Female	1989–1990	Peanuts and mixed nuts Almost never or ≥5 servings/week (Portion size—28 g/day for nuts and 16 g/day for peanut butter)	Incident CVD	TNFR-2, ICAM-1, E-selectin, CRP, and fibrinogen (No changes)
Jiang et al., 2006 [27]	MESA, USA	6.080 Female, Male	Baseline	Mixed nuts, seeds, or peanuts/peanut butter Never/rare or ≥5 times/week (Portion size—no data)	Inflammation biomarkers	↓CRP, ↓IL-6 and ↓fibrinogen
Mantzoros et al., 2006 [26]	NHS, USA	987 Female	1989–1990	Mixed nuts Quintile of nuts intake (Portion size—no data)	Adipocytokine	↑Adiponectin
Bonaccio et al., 2015 [28]	Moli-sani Study, Italy	19,386 Female, Male	4.3 years	Walnuts, hazelnuts, almonds, and peanuts Never or ≥8 times/month (Portion size—no data)	Total and specific mortality	↓CRP, ↓platelet count and ↓neutrophil to lymphocyte ratio
Yu et al., 2016 [29]	NHS HPFS, USA	NHS (3654) HPFS (1359) Female, Male	NHS (1989–1990) HPFS (1993–1995)	Peanuts, mixed nuts, and peanut butter Almost never or ≥5 times/week (Portion size—28 g/day)	Inflammatory biomarkers	↓TNFR-2, ↓CRP and ↓IL-6

NHS—Nurses' Health Study; MESA—Multiethnic study of atherosclerosis; HPFS—Health professional follow-up study; CVD—cardiovascular disease; TNFR—Tumor necrosis factor receptor; CRP—C-reactive protein; IL-6—Interleukin 6. ↓—higher consumption of nuts associated with lower levels of the inflammatory markers; ↑—higher consumption of nuts associated with higher levels of the anti-inflammatory marker.

In the Multi-Ethnic Study of Atherosclerosis cohort, when compared to those with lower total tree nut consumption (never/rarely), a higher consumption (≥5 times/week; portion size not shown) was associated with lower levels of inflammatory biomarker CRP (1.98 vs. 1.69 mg/L). For peanuts and peanut butter, a higher level of consumption (≥5 times/week) compared to never/rarely consumed was associated with lower IL-6 (1.11

vs. 1.24 pg/mL) [27]. The same cohort also investigated the influence of anthropometric measures (BMI and waist-to-hip ratio (WHR)) and ethnicity on the relationship between total nuts and seed consumption and inflammatory markers. Lower levels of CRP and IL-6 and WHR < 0.94 cm were observed in groups with higher nut and seed consumption, while individuals with BMI $\geq$ 28 kg/m^2 and WHR $\geq$ 0.94 cm had lower fibrinogen values. Regarding ethnicity, lower CRP, IL-6, and fibrinogen levels were found in the Caucasian population with higher total nut and seed consumption.

Cross-sectional data from the NHS and HPFS demonstrated that higher nut consumption ($\geq$5 times/week; portion size—28 g/day) was associated with lower CRP (OR = 0.84; 95% CI = 0.74–0.95; *p* trend = 0.006) and IL-6 (OR = 0.88; 95% = 0.79–0.99; *p*-trend = 0.016) [27], but not TNFR-2 [29]. In addition, the Moli-Sani Study cohort [28] with a follow-up of 4.3 years showed that individuals with higher nut consumption ($\geq$8 times/month; portion size not shown) had lower levels of low-grade inflammation (CRP, platelet count, and neutrophil-to-lymphocyte ratio). Higher nut consumption was also associated with all-cause and cancer mortality when inflammatory markers were combined with other variables. Compared with those who reported never consuming nuts, participants with regular nut consumption had a 34% lower risk of all-cause mortality and a 36% reduction in cancer mortality.

In summary, although tree nuts and peanuts are rich in antioxidants and other bioactive components, cohort studies have not consistently considered the association between oxidative stress and inflammatory markers and the risk of fatal and non-fatal disease outcomes when diet evaluations occurred at baseline. Thus, we rely on evidence from RCTs (albeit inconclusive currently) to clarify the relationship between nut consumption and oxidative stress and inflammation.

2.2. Evidence from RCTs

A few systematic and narrative reviews and meta-analyses have summarized findings from RCTs on the role of nut consumption (almonds, Brazil nuts, hazel nuts, pistachios, walnuts) on inflammatory biomarkers [30–36]. There is some evidence, although inconsistent, that nuts may ameliorate inflammation.

When considering inflammatory markers, a meta-analysis on almond consumption [32] mainly noted a significant decrease in serum CRP. This effect was observed more consistently among adults free of obesity and generally healthy than those with metabolic disorders [37–39], and when the intervention was at least 12 weeks. Among other inflammatory cytokines assessed, almond consumption seemed to lower IL-6 significantly in some [40,41], but not all studies [38,42], with no significant changes in TNF-α or endothelial adhesion molecules [32]. The decrease in serum IL-6 attenuated when adjusted for weight loss [42]. Whether almond consumption affects adhesion molecules is unknown, since these markers have not been measured in studies conducted thus far. The evidence appears to primarily suggest a modest lowering of serum CRP with almond intake [32]. However, it is critical to highlight that CRP levels may be associated with numerous factors, including infections, trauma, and non-dietary lifestyle factors [43]. Consequently, researchers should assess multiple inflammatory parameters and adjust for potential confounding variables.

In contrast, a meta-analysis of nine RCTs [33] on walnut intake on CRP that ranged in duration from four weeks to twelve months, with comparators varying from protein foods (eggs, meat), dietary fat (olive oil) to a walnut-free habitual diet, revealed only a non-significant change. The effects of walnuts on other inflammatory cytokines such as IL-6, TNF-α, and IL-1β are inconsistent, mainly tending towards a null effect [33], except when the duration exceeded 24 weeks [44]. Regarding adhesion molecules, although the meta-analyses concluded no significant effect on walnuts (331), individual RCTs suggest a somewhat favorable effect on adhesion molecules [45–47]. The discrepancies in the findings may be partly attributed to the small sample size and short duration of most of these RCTs [33]. Meta-analyses performed with a small number of studies that vary in study design, duration, and subject characteristics, and are limited in sample size, may introduce

sampling error that leads to bias in reporting [48]. A key consideration is the intensity and duration of the intervention, which was two years in the Walnuts and Healthy Aging (WAHA) study [44]. This significantly exceeded even the longest trial of 24 weeks cited in the meta-analysis on walnuts [33], highlighting the relevancy of the exposure period. In the WAHA study, the daily ingestion of walnuts over two years in healthy older adults significantly reduced several inflammatory biomarkers including E-Selectin, IL-6, TNF-α, granulocyte-macrophage colony stimulating factor, interferon-γ and, most strikingly, IL-1β (which are associated with CHD).

In a recent systematic review of hazelnut consumption on cardiometabolic risk factors [36], only a few studies assessed the outcomes of inflammation and/or oxidative stress markers and revealed null effects. The seemingly favorable effect on CRP and VCAM-1 was from a study that utilized a less rigorous sequential or single intervention design, and/or combined hazelnuts with cocoa as the intervention [49]. Similarly, for oxidative stress markers, oxLDL decreased and antioxidant enzyme gene expression increased, but only post-prandially [50] or was noted only in uncontrolled studies [36]. The impact of other tree nuts (Brazil nuts, cashews, macadamias, pecans, pine nuts, pistachios) and peanuts on inflammatory biomarkers has been explored less [30,31,34,35]. However, many of these nuts are rich in phytochemicals and other anti-inflammatory compounds similar to walnuts and almonds [16] and warrant further exploration.

Collectively, the evidence on the effect of nuts and inflammation indicates a significant gap in research. Overall, there is a trend towards modest reductions in CRP and IL-6 with almond intake, although this is attenuated when adjusted for weight loss for IL-6 [32]. Short-term studies ($\leq$24 weeks) with walnuts mostly suggest a significant reduction in endothelial adhesion molecules [33]. For other tree nuts and peanuts, conclusions cannot be drawn due to either insufficient data or inconclusive evidence. However, these inconsistencies and seeming null effects on inflammatory biomarkers may be explained by the study designs implemented, since favorable changes on multiple inflammatory biomarkers were noted when the exposure to a single nut was longer, as was seen with walnuts when consumed for two years [44].

A systematic review of 16 RCTs showed an overall favorable effect of nuts on oxidative stress markers [17,51,52]. However, the strength of the evidence is weak, due mostly to the variations in the markers assessed. A modest beneficial effect was specifically observed for almonds, Brazil nuts and mixed nuts. Almonds at doses ranging from 37 g/d to 74 g/d for at least four weeks consistently lowered oxLDL levels, especially in adults with hyperlipidemia and T2D [53], but other lipid peroxidation products such as MDA, or antioxidant capacity, were not responsive to almond intervention. In a recent meta-analysis on Brazil nuts [35], five RCTs that examined the effect on antioxidant enzyme activity noted a positive effect on the selenium-containing glutathione peroxidase activity (GPx) and the increased expression of Nrf2 [54,55]. Brazil nuts have high selenium content [16,35], which is reflected in high serum selenium levels following the intake of just one Brazil nut a day [54]. Another significant marker of oxidative stress, 8-OHdG, reflecting DNA damage, was reduced as a result of Brazil nut intervention in hemodialysis patients [56], indicating that individuals with this disease state may have amplified oxidative stress. For walnuts specifically, there seems to be a positive impact on oxidative stress markers such as oxLDL and antioxidant capacity, but only postprandially following the ingestion of a walnut meal [57]. In the short term ($\leq$12 weeks), walnuts had no effect on oxLDL [51] unless provided along with almonds and hazelnuts, in which case they lowered the urinary excretion of 8-OHdG following a 12-week intervention in those with metabolic syndrome [58]. For other tree nuts (cashew, pecan, pistachio) and peanuts there are mostly null findings concerning oxidative stress markers, largely because $\leq$ 2 RCTs have evaluated these markers for these nut types [51].

An increase in one or more of the antioxidant enzymes has been noted for some nuts [51], although mostly among adults with metabolic conditions accompanied by a heightened state of oxidative stress [53,56]. Dose and duration may be more important

than the type of nuts, since studies of 8 weeks or longer, and at least 40–60 g/d (except for Brazil nuts, with just 1 unit/d) seem to have some clinically relevant impacts on antioxidant enzymes. A less common assay for antioxidant capacity is the ferric-reducing antioxidant property (FRAP), which has been used in a few studies and is increased with nut intervention [57]. Different forms of a nut, specifically walnuts, (whole, skin, oil, defatted) improve FRAP acutely [59]. However, the defatted walnuts have the least effect, suggesting that some of the polyphenol antioxidants may be removed during the fat removal, lowering the antioxidant potential. Inconsistencies across studies on the choice of biomarkers or analytical processes used to measure antioxidant capacity and oxidative stress preclude drawing any conclusions.

The evidence from the various meta-analyses and systematic reviews discussed in this section, and the authors' interpretations of the current knowledge and gaps in research, are summarized in Table 2. The discrepant findings for most nut types on oxidative stress markers illustrate several shortcomings in these studies, including small sample size, short duration of the intervention (mostly $\leq$ 8 weeks), varied nut dose (<10 g/d to >100 g/d), form of the nut (whole nut, nut butter, nut oil), participant characteristics (age, smoking status, health status e.g., healthy, presence of diabetes, metabolic disorders, high CVD risk), and the control diet choice (habitual nut free diet, specific high fat or high protein food, low-fat or MedDiet). While there are several limitations, the most significant current gap in knowledge is the lack of assessment of a more robust profile of oxidative stress biomarkers.

Table 2. Nuts and inflammation and oxidative stress biomarkers—current evidence from randomized controlled trials and research gaps.

Nut Type Reference [#]	CRP	IL-6	TNF-α	Adhesion Molecules	OxLDL	Antioxidant Enzymes	Oxidized Metabolites
Almonds [32,51]	↓	↓	↔	↔	↓	-	↔
Brazil nuts [35,51]	↔	-	-	-	↔	↑	↔
Hazelnuts [36,51,52]	↔	-	-	-	-	-	-
Pistachios [34,51]	↔	-	-	-	↔	-	-
Walnuts * [33,44,51,52]	↔	↓	↓	↓	↔	-	↔
Other ** [30,31,51]	-	-	-	-	-	-	-

Adhesion molecules (E-selectin, ICAM-1, VCAM-1); antioxidant enzymes include glutathione peroxidase or catalase, superoxide dismutase activity or gene expression; oxidized metabolites include 8-hydroxy deoxy guanine, urinary isoprostane, MDA. ↑ Significant increase; ↓ Significant decrease; ↔ Null impact or conflicting findings; - Not sufficient evidence (i.e., gaps in research) * Walnuts affect inflammatory biomarkers while mostly null according to a meta-analysis [33]; exposure to walnuts for two years produced a more robust anti-inflammatory effect [44], which is reflected in this table. ** Other tree nuts (cashews, macadamia, pecans, pine nuts) and peanuts.

3. Nuts: Antioxidant and Anti-Inflammatory Mechanisms

Inflammation and oxidative stress, two of the common mediators of NCDs, result from a dysregulation caused by an increased production of reactive oxygen species (due to an imbalance in oxidative and antioxidative pathways in the cell), producing pro-inflammatory cytokines [2,8]. These processes are regulated by two transcriptional factors, NFκβ and Nrf2, the former induced when oxidative stress is high and resulting in a pro-inflammatory state, and the latter responsible for mitigating the state of inflammation and oxidative stress. The plethora of bioactive compounds in nuts, such as unsaturated fatty acids, tocopherol, selenium, copper, fiber, phytosterols, polyphenols, and other phytonutrients, independently

and synergistically modulate inflammation and oxidative stress by influencing one or more of the pathways involving these two nuclear factors (Figure 1).

With respect to oxidation, PUFAs act as a pro-oxidant whereas MUFAs are mostly neutral or do not contribute to oxidative stress. Nuts predominantly have MUFAs, except walnuts, which are high in PUFAs. Studies of nuts lowering oxLDL have mostly been observed with hazelnuts, almonds, and Brazil nuts, but not walnuts [51]. Importantly, no adverse effects have been reported, possibly due to the presence of other powerful antioxidants that might counteract the oxidant potential of PUFAs [16,17]. Some of the phytochemicals in nuts (phytosterols, and polyphenols), as well as selenium, can up-regulate the Nrf2 pathway which stimulates the antioxidant response element (ARE) gene transcription and the various antioxidant enzymes it encodes, including GPx, superoxide dismutase and catalase [60]. When Nrf2 is activated, it directly counteracts the NFκβ pathway, and reduces the pro-inflammatory state [60,61]. Antioxidants such as γ-tocopherol and phytonutrients directly inhibit the NFκβ pathway and suppress the pro-inflammatory state [62]. Unsaturated fatty acids, particularly ALA found in walnuts, may exhibit anti-inflammatory activity, potentially via the modulation of cyclooxygenase and lipoxygenase pathways [63]. Vitamin E (tocopherols), polyphenols, phytosterols and selenium are powerful antioxidants that are mostly responsible for the antioxidant capacity of tree nuts and peanuts [16–18]. Selenium and copper, notedly high in some nuts (such as Brazil nuts), are cofactors of antioxidant enzymes, including GPx that suppresses oxidative stress [58]. Overall, the bioactive compounds in the nut matrix, both independently and synergistically, may be exerting antioxidant and anti-inflammatory effects.

4. Scope for the Future

Routine tree nut and peanut consumption improves health and reduces the risk of NCDs through multiple pathways, including a reduction in inflammation and oxidative stress [6,7,12–15]. Although the relationship between inflammation and oxidative stress is well recognized, cohort studies conducted to date have only evaluated the association between nut intake and inflammatory biomarkers, not oxidative markers, or their association with disease outcomes. Thus, future cohort studies could consider both oxidative stress and inflammatory markers as intermediate mediators between exposure and disease outcomes. Furthermore, cohort studies should include repeated measures of diet during the follow-up to reduce bias associated with changes that may be made in lifestyle behaviors over time.

The comprehensive evidence from RCTs on the role of nuts on inflammation and oxidative stress biomarkers remains unresolved, although there is evidence of beneficial effects for some nuts such as almonds and walnuts on select markers of inflammation, and for Brazil nuts on oxidative stress. Historically, RCTs have considered inflammation and oxidative stress biomarkers as secondary outcomes [30,31]. However, in nut intervention trials, the CVD risk reduction achieved was greater than predicted only by the LDL-C lowering [19]. This indicates that other mechanisms could contribute to the overall CVD risk reduction, which perhaps encouraged the evaluation of inflammation and oxidative biomarkers to explain this gap. These studies were likely underpowered to assess these biomarkers, as they were not a prespecified primary outcome. Well-designed RCTs with a large sample size, evaluating inflammation and oxidative stress biomarkers as primary outcomes, are vital to clarify some of the inconsistencies that exist at present. These RCTs should consider the duration ($\geq$24 weeks), dose (40–60 g/d), how nuts are incorporated (added to the habitual diet, substitution for nutrient/food or displacement), the comparator diet (habitual nut-free diet or high carbohydrate snack, or other fat source), potential confounders (including age, sex, genotype and lifestyle factors), and the participants' health status (healthy, high risk for T2D or CVD, obesity).

One of the major confounders in studies assessing the association between nut intake and inflammation and oxidative stress biomarkers is body weight. While most studies adjust for weight or BMI, the exposure's effect may differ among those with and without obesity [30–36]. In addition, studies show that nuts, when part of a low-calorie diet

(LCD), may produce similar weight loss compared to a nut-free LCD [64]; however, nut-enriched LCD may have additional benefits, as in favorably modifying inflammatory biomarkers. This implies that nuts may influence inflammatory biomarkers independent of body weight, but future studies have to untangle the complex connections between body weight, inflammation and nut consumption.

The biggest gap in this area of nut research is the apparent lack of evaluation of multiple markers of inflammation and oxidative stress. No single biomarker is ideal, as each marker may be associated with different metabolic conditions (high CRP associated with CVD, for example) or originate from different processes (8-OHdG for DNA damage, F2 isoprostanes for lipid peroxidation). The current consensus summarized in Table 2 is that for some nuts there are few to no RCTs that have evaluated these outcomes. For others, comparing outcomes from different studies is challenging, since they have not always measured the same markers, or have used different study designs, sometimes of less rigor [30–36]. In the WAHA study, one of the strengths besides the long duration (two years) of exposure to walnuts was the inclusion of ten inflammatory biomarkers [44], where six showed a favorable modification with walnut consumption. There is also a concern that there may be large inter- and intra-individual variability for these biomarkers, that would make it difficult to detect any real change caused by diet modification [65]—this makes a case for including a large sample size. The validity of measuring these markers only in a fasting state, which is currently the practice [30–36], is considered insensitive, especially in healthy individuals. Instead, the use of inflammatory challenges has been proposed [66] and much work is needed in this area before considering for future studies on diet and inflammation/oxidative stress. In addition, metabolomic signatures that better represent low-grade inflammation could be identified and may be more useful than single markers.

Along with assessing multiple biomarkers, it would be useful to explore other mechanisms by which nuts influence inflammation and oxidative stress. Genetics, epigenetics, and omics would be relevant considerations for the future [67]. We have limited evidence that Brazil nuts increase the gene expression of antioxidant enzymes and suppress the NFκβ pathway [55], and that pistachios lower IL-6 gene expression [68]. This needs to be verified with more well-designed studies that include other nut types. Epigenetic changes can also modify inflammatory genes, as demonstrated in a cohort study of high CVD-risk patients following a MedDiet with mixed nuts [67]. While DNA methylation assays are expensive, they may be well worth the investment as plant food bioactives seem to favorably modify inflammation and oxidative stress through DNA methylation changes [69]. Finally, the connection between the gut microbiome, whole-body inflammation, and oxidative stress cannot be ignored. Given the beneficial role of nuts on the gut microbiome [70], future studies should include the inter-relationships between the gut axis and immune system in nut exposure studies.

In secondary prevention trials of CVD and type-2 diabetes, new frontiers to explore would include inflammation and oxidative stress. One would expect patients with NCDs to have elevated inflammation, and thus have a better response to an intervention. Although a small study in adults with CHD failed to show any change in inflammation with 30 g/d of pecans [71], another study showed that a mixed nuts or extra virgin olive oil enriched MedDiet was associated with increased atheroma plaque stability and reduced vascular inflammation compared to a low-fat MedDiet [72]. Thus, in healthy individuals with normal values of these biomarkers it may be challenging to see the intervention effect, and hence choosing individuals with elevated inflammation and oxidative stress as an inclusion criterion may be a better option.

Cardiometabolic disease is often associated with non-alcoholic fatty liver disease (NAFLD), with oxidative stress and inflammation considered mediators of this condition [2]. Preliminary evidence suggests that frequent nut consumption ($\geq$1 time/week) is inversely associated with NAFLD, at least in men [73]. Additionally, other polyphenol-rich plant foods (green tea, fruits, and spices) have been shown to protect against fatty liver [74]. With NAFLD becoming a significant public health problem, and given that nuts have

abundant polyphenols and other anti-inflammatory nutrients, a critical next step would be to determine if nut intake could lower liver fat fraction in those with NAFLD. Alongside the nut type, duration and dose, such studies must carefully consider the background diet, include nuts in the context of LCDs, and use accurate techniques such as magnetic resonance imaging. Alongside NAFLD, future research can build on preliminary work highlighting a beneficial role for nuts in inflammatory/oxidative stress indices in women with polycystic ovary syndrome (PCOS) and bone health [75,76]. Another emerging trend since the COVID-19 pandemic has been research focused on identifying plant foods to boost the immune system. Oxidative stress and inflammation are potent modulators of the immune response [77] and, thus, evaluating the role of nuts in bolstering the immune response would be timely and critical.

Shifting our approach from utilizing biomarkers to assessing inflammation and oxidative stress, future studies could consider a dietary approach such as the dietary inflammatory index (DII). In the absence of a significant decrease in serum inflammatory markers, a lowering of the DII score may be a surrogate that implies an anti-inflammatory effect. In a six-month dietary intervention study (MedDiet versus low-fat control), a decrease in DII scores was observed with the MedDiet [78], pointing to the anti-inflammatory potential of the MedDiet. Studies exploring the DII of a diet with a single food (nut) intervention may thus be valuable to the overall understanding of the role of nuts in lowering inflammation. Moreover, higher DII scores seem to correlate with CVD and related adverse clinical events [79].

5. Conclusions

In conclusion, the current evidence from cohort studies and randomized clinical trials suggest that tree nuts and peanuts packed with potent bioactive nutrients (MUFAs, PUFAs, vitamin E, selenium and copper) and non-nutrients (fiber, polyphenols and phytosterols) have the potential to reduce inflammation and oxidative stress. However, the evidence is only modest for some, inconsistent for few, and has not been evaluated for many nut types. This creates excellent opportunities for future research to focus on well-designed RCTs that consider many of the limitations described in this narrative review, to further our understanding of the role of nuts in reducing inflammation and oxidative stress. A strong consensus is that including nuts in the habitual diet can help mitigate the risk of several chronic diseases. However, the evidence base for nuts in this area must be expanded to promote food (nut)-based strategies, to lower inflammation and oxidative stress for precision and public health nutrition.

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nutrients

MDPI

Review

Nuts and Cardiovascular Disease Outcomes: A Review of the Evidence and Future Directions

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Abstract: Nuts are nutrient-rich foods that contain many bioactive compounds that are beneficial for cardiovascular health. Higher consumption of nuts has been associated with a reduced risk of several cardiovascular diseases (CVD) in prospective cohort studies, including a 19% and 25% lower risk of CVD incidence and mortality, respectively, and a 24% and 27% lower risk of coronary heart disease incidence and mortality, respectively. An 18% lower risk of stroke mortality, a 15% lower risk of atrial fibrillation, and a 19% lower risk of total mortality have also been observed. The role of nuts in stroke incidence, stroke subtypes, peripheral arterial disease and heart failure has been less consistent. This narrative review summarizes recommendations for nuts by clinical practice guidelines and governmental organizations, epidemiological evidence for nuts and CVD outcomes, nut-containing dietary patterns, potential mechanisms of nuts and CVD risk reduction, and future research directions, such as the use of biomarkers to help better assess nut intake. Although there are still some uncertainties around nuts and CVD prevention which require further research, as summarized in this review, there is a substantial amount of evidence that supports that consuming nuts will have a positive impact on primary and secondary prevention of CVD.

Keywords: tree nuts; peanuts; nutrition; cardiovascular diseases; review

1. Introduction

Cardiovascular diseases (CVD) are the leading cause of death worldwide and a major cause of premature mortality, causing an estimated 31% of all deaths globally [1]. Major modifiable risk factors for CVD include smoking, harmful alcohol use, physical inactivity, unhealthy diets, abdominal obesity, hypertension, dyslipidemia, high fasting glucose and diabetes, and kidney dysfunction [2]. Furthermore, there are many downstream complications of CVD that can significantly impact quality of life and cause disability and death, including dementia, peripheral arterial disease (PAD), heart failure (HF), kidney disease, frailty and poor aging, among others [3].

Despite a decline in CVD in several regions around the globe, it remains a major threat to public health as the absolute numbers continue to increase, with prevalent cases of total CVD nearly doubling from 1990 to 2019 [4]. These numbers are expected to increase even further in upcoming years due to population growth and aging. For example, a recent analysis in the United States projects large future increases in CVD risk factors and CVD prevalence (e.g., 31% increase in ischemic heart disease and 34% increase in stroke) by 2060 [5]. According to the Global Burden of Diseases (GBD) Study, unhealthy diets are the greatest contributor to premature morbidity and mortality worldwide, including CVD mortality [6]. The main dietary risk factors attributable to the global burden of diseases include diets low in whole grains, fruit, nuts/seeds, and vegetables and diets high in sodium and processed meat [7]. Tree nuts and peanuts, one of the top dietary risk factors noted by the GBD study, may be particularly beneficial for CVD prevention due to their bioactive components. Of note, peanuts are botanically defined as legumes; however, they have a similar nutrient composition and culinary use as tree nuts and are, therefore, usually included as nuts when estimating total nut intake [8]. The bioactive components of tree nuts and peanuts include their macronutrient, fat-soluble bioactive, fiber, vitamin, mineral and phenolic content [9]. Specifically, fat-soluble bioactives such as their fatty acid content (monounsaturated and polyunsaturated fatty acids), fiber, magnesium, tocopherols and tocotrienols, phytosterols, sphingolipids, carotenoids, chlorophylls and alkyl phenols, and phenolic compounds (including flavonoids, phenolic acids, stilbenes, lignans, among others) all likely contribute to their cardiovascular health-promoting effects [9].

In this narrative review, we describe the importance given to nuts in clinical practice guidelines, the evidence we have in relation to the beneficial effects of frequent consumption of nuts in the prevention of CVD, as well as the possible mechanisms involved. However, we also emphasize the gaps that exist in the literature and discuss the possible studies that we should develop in the future to increase the level of evidence and establish recommendations.

2. Nuts in Clinical Practice Guidelines for Cardiovascular Risk Reduction

Given their cardiovascular health-promoting properties, tree nuts and peanuts are recognized by several international health organizations for cardiovascular risk reduction for both primary and secondary prevention. Table 1 highlights the recommendations from cardiovascular clinical practice guidelines (CPGs), including the Canadian Cardiovascular Society, Joint British Societies for the Prevention of Cardiovascular Disease, the Australian Heart Foundation, the American Heart Association and the European Society of Cardiology [10–14]. Nuts are recommended as a healthy plant protein and fat source that should be frequently consumed to lower low-density lipoprotein cholesterol (LDL-C), improve the overall lipoprotein profile and decrease CVD risk.

Table 1. Examples of Recommendations for Nuts in CVD Clinical Practice Guidelines.

Guideline Association	Nuts Recommendation
American Heart Association 2021 [10]	"Choose healthy sources of protein, mostly protein from plants (legumes and nuts)"

Table 1. *Cont.*

Guideline Association	Nuts Recommendation
European Society of Cardiology and European Atherosclerosis Society 2019 [11]	"Food choices to lower low-density lipoprotein cholesterol and improve the overall lipoprotein profile are nuts and seeds"
Canadian Cardiovascular Society 2016 [12]	"We suggest that all individuals be encouraged to moderate energy (caloric) intake to achieve and maintain a healthy body weight (Conditional Recommendation; Moderate-Quality Evidence) and adopt a healthy dietary pattern to lower their CVD risk: Dietary patterns high in nuts (30 g/day) (Conditional Recommendation; Moderate-Quality Evidence)"
Joint British Society Consensus for prevention of Cardiovascular Disease 2014 [13]	"Consider regular consumption of whole grains and nuts"
Heart Foundation Australia 2019 [14]	"Eating patterns for heart health are based on: • A variety of healthy protein sources including fish, seafood, lean meat and poultry, legumes, nuts and seeds • Healthy fat choices with nuts, seeds, avocadoes, olives and their oils for cooking"

Abbreviations: CVD = cardiovascular disease.

3. Regulated Nut Health Claims Allowed for Cardiovascular Risk Reduction

To encourage the consumption of foods that may be beneficial for health, governmental agencies review the evidence and approve health claims that can provide consumers with reliable information about the relationship between the consumption of food and a specific health benefit. Several regulated disease risk reduction health claims have been approved for nuts and CVD by the U.S. Food and Drug Administration (FDA), the European Food Safety Authority (EFSA) and Food Standards Australia New Zealand (FSANZ), as shown in Table 2 [15,16]. Health Canada has not approved a disease risk reduction claim for nuts. The FDA and FSANZ both approved a health claim regarding nuts and CVD risk reduction, particularly for the LDL-C lowering effects of nuts. However, EFSA did not approve this type of claim and noted that, specifically for walnuts, the evidence provided did not establish that the consumption of walnuts had an effect on LDL-C beyond what could be expected from their fatty acid composition [17]. EFSA, however, established that a cause-and-effect relationship between the consumption of walnuts and the improvement of endothelium-dependent vasodilation exists and has approved a health claim for this finding (Table 2) [17].

Table 2. Examples of Regulated Health Claims for Nuts and CVD Risk Reduction.

FDA	EFSA	FSANZ
1.5 ounces per day of nuts, as part of a diet low in saturated fat and cholesterol and not resulting in increased intake of saturated fat or calories may reduce the risk of CHD [15]	30 g per day of walnuts may improve endothelium-dependent vasodilation [17]	General level health claim around heart health without causing weight gain allowed for tree nuts, peanuts, ground nuts/butters/pastes [16]

Abbreviations: EFSA = European Food Safety Authority; FDA = Food and Drug Administration; FSANZ = Food Standards Australia New Zealand.

4. Nuts and Cardiovascular Disease Outcomes

The scientific study of the role of nuts in preventing CVD started over 30 years ago, first with a discovery that individuals in the Adventist Health Study who consumed nuts more frequently (more than four times per week) had fewer coronary heart disease (CHD) events compared to those who consumed nuts less than once per week [18]. Investigators believed that this CHD risk reduction might be related to the favorable fatty acid profile of nuts. Researchers from the same group then assessed if consuming walnuts (20% of calories through replacing other fatty foods, meat and oils, margarine and butter) would

affect blood lipids in healthy individuals [19]. They found that incorporating a moderate amount of walnuts in the diet decreased levels of total cholesterol (TC) and LDL-C [19]. The favorable modification of the lipid profile by frequent nut consumption has been confirmed in additional trials and systematic reviews and meta-analyses [20]. The role of nuts in preventing CVD outcomes in prospective cohort studies has also been extensively studied. Below we describe this evidence related to total CVD, CHD, stroke, HF, atrial fibrillation (AF), PAD and total mortality. The definition of nuts includes tree nuts, peanuts and seeds (sunflower, pumpkin, etc.) as a culinary definition for this review. An overview of the pooled summary data for each outcome is included in Figure 1.

Outcome	Studies	Cases	n	RR (95% CI)	Pooled RR (95% CI)
Cardiovascular Disease					
Incidence	11	18,655	376,228	0.81 (0.74, 0.89)	
Mortality	16	19,574	524,610	0.75 (0.71, 0.79)	
Coronary Heart Disease					
Incidence	11	12,331	315,397	0.76 (0.69, 0.84)	
Mortality	13	10,083	429,833	0.73 (0.67, 0.80)	
Stroke					
Incidence	7	12,646	302,888	1.00 (0.92, 1.09)	
Mortality	12	4396	449,293	0.82 (0.73, 0.92)	
Ischemic	7	8401	302,423	0.99 (0.89, 1.10)	
Hemorrhagic	2	5454	194,307	1.53 (0.97, 2.41)	
Heart Failure	2	4253	53,887	1.00 (0.86, 1.16)	
Atrial Fibrillation	2	10,867	53,965	0.85 (0.73, 0.99)	
Peripheral Arterial Disease*	3	6018	233,883	1.03 (0.96, 1.09)	
Total Mortality	15	85,870	819,448	0.81 (0.77, 0.85)	

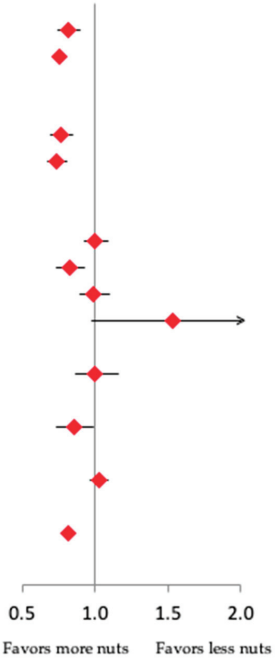

Figure 1. Summary of the pooled effect estimates of prospective cohort studies assessing the association between high and low consumption of nuts and risk of cardiovascular disease outcomes and total mortality. Figure adapted from Figure 2 in [21]. Pooled risk estimate is represented by the diamond. * To obtain summary estimates for peripheral arterial disease, we used generic inverse variance (fixed effects) to pool the natural log-transformed RRs of the extreme quantiles. Abbreviations: CI = confidence intervals; RR = relative risk.

4.1. Total Cardiovascular Disease

Total CVD is a composite outcome of CVD incidence (including only nonfatal or a combination of nonfatal and fatal outcomes of different CVD outcomes) or may include CVD mortality outcomes only, which is a composite of different fatal CVD endpoints. A recent systematic review and meta-analysis of prospective cohort studies that were commissioned to update the clinical practice guidelines for nutrition therapy for the European Association for the Study of Diabetes (EASD) found that in three cohort comparisons (including 210,839 participants and 14,136 events), high consumption of nuts was associated with a 15% lower risk of CVD incidence (relative risk [RR] = 0.85, 95% confidence intervals

[CI]: 0.80–0.91) compared to low consumption [22]. In 15 cohort comparisons (including 413,797 participants and 14,475 events), high consumption of nuts was associated with a 23% lower risk of CVD mortality (RR = 0.77, CI: 0.72–0.82) compared to low consumption [22]. The certainty of the evidence was assessed using the Grading Recommendations Assessment, Development and Evaluation (GRADE). The GRADE for CVD incidence was low quality due to a downgrade for indirectness (i.e., how applicable the evidence is to the general population) but an upgrade for a dose-response gradient. The GRADE for CVD mortality was moderate quality due to an upgrade for a dose-response gradient. The dose-response analysis showed that the reduction in risk of CVD incidence was observed up to 10 g/day with no further reduction in risk for higher consumption. For CVD mortality, there was a greater reduction in risk at 15–20 g/day, with no further reduction with higher consumption. When assessing different types of nuts, tree nuts, peanuts and walnuts were all associated with a 13–19% lower risk of CVD incidence, whereas the association for peanut butter was not significant (RR = 0.98, CI: 0.93–1.03). For CVD mortality, only peanuts have been analyzed, and higher consumption was associated with a lower risk of CVD mortality compared to low consumption [22]. The lack of association with peanut butter may be in part because many peanut butters on the market have added salt, fully hydrogenated oils or oils such as palm oil that can increase the saturated fat content, which could negatively impact their health benefits as compared with whole sources of peanuts; further research on natural peanut butter may provide additional insight into this hypothesis.

A more recent 2022 umbrella review assessing the role of nuts in preventing several chronic diseases found similar associations with CVD incidence and mortality [21]. For CVD incidence, 11 cohort comparisons were assessed (including 376,228 participants and 18,655 events), and a 19% lower risk was observed comparing high to low consumption (RR = 0.81, CI: 0.74–0.89) and 21% lower risk when assessing associations per serving (28 g/day) (RR = 0.79, CI: 0.70–0.89). For CVD mortality, 16 cohort comparisons were included (524,610 participants and 19,574 cases), and a 25% lower risk comparing high to low consumption (RR = 0.75, CI: 0.71, 0.79) was observed and a 6% lower risk when assessing nut intake by 28 g/day (RR = 0.94, CI: 0.93, 0.96) [21]. This umbrella review also assessed dose-response relationships with CVD mortality and found that the optimal intake levels of nuts are ~15–20 g/day and that there were limited further benefits of consuming up to one serving (28 g/day), similar to the earlier meta-analysis [22]. However, it should be mentioned that the high end of nut consumption across most cohorts is typically one serving (28 g)/day, and little is known about the dose-response relationship with higher intakes.

4.2. Coronary Heart Disease

Similar to total CVD, CHD incidence may include fatal and nonfatal events, whereas CHD mortality includes CHD mortality outcomes only. The systematic review and meta-analysis conducted to update the EASD nutrition therapy guidelines assessed 7 cohort comparisons (including 275,812 participants and 12,654 cases) and found that high nut consumption was associated with an 18% lower risk of CHD incidence (RR = 0.82, CI: 0.69–0.96) compared to low consumption [22]. For CHD mortality, 13 cohort comparisons were included (396,014 participants and 7877 cases), and high consumption of nuts was associated with a 24% lower risk (RR = 0.76, CI: 0.67–0.86) compared to low consumption. The certainty of evidence using GRADE was very low for CHD incidence owing to downgrades for inconsistency (i.e., unexplained heterogeneity), indirectness and imprecision (i.e., the minimally important difference for the clinical benefit [considered RR = 0.95 in this meta-analysis]), and an upgrade for a dose-response gradient. The certainty of the evidence was moderate for CHD mortality, owing to an upgrade for a dose-response gradient. When assessing different types of nuts, tree nuts, peanuts and walnuts were all associated with a 15–23% lower risk of CHD incidence, and similar to CVD incidence, no association was reported for peanut butter consumption (RR = 1.00, CI: 0.94–1.07). The findings were also similar between CVD and CHD mortality, where peanut consumption was inversely asso-

ciated with the risk of CHD mortality. Comparable to CVD mortality, the CHD mortality dose-response analysis showed greater reductions in risk at around 15–20 g/day [13,22]. The 2022 umbrella review showed that for CHD incidence (including 12 cohort comparisons with 315,397 participants and 12,331 events), there was a 24% lower risk comparing high to low consumption (RR = 0.76, CI: 0.69–0.84) and 25% lower risk when assessing per servings associations of 28 g/day (RR = 0.75, CI: 0.64–0.88) [21]. For CHD mortality, 13 cohort comparisons were included (429,833 participants and 10,083 cases), and a 27% lower risk comparing low to high consumption (RR = 0.73, CI: 0.67, 0.80) was observed and a 6% lower risk when assessing nut intake by 28 g/day (RR = 0.94, CI: 0.93, 0.96) [21].

4.3. Stroke

Stroke outcomes include stroke incidence and mortality, and the main stroke subtypes, ischemic and hemorrhagic stroke. The association between nut consumption and stroke risk has been less consistent than that observed for total CVD and CHD. For stroke incidence, the EASD systematic review and meta-analysis included 7 cohort comparisons (of 302,888 participants and 12,646 events) and found no associations when comparing high to low consumption (RR = 1.00, CI: 0.92–1.09) [22]. In contrast, for stroke mortality, 12 cohort comparisons were analyzed (including 351,618 participants and 2332 cases) and comparing high vs. low categories of nut consumption was associated with a 17% lower risk (RR = 0.83, CI: 0.75–0.93). The certainty of evidence using GRADE was very low for stroke incidence owing to downgrades for indirectness and imprecision, and low for stroke mortality, owing to downgrades for imprecision but an upgrade for a dose-response gradient. Regarding specific types of nuts, peanut consumption was associated with a lower risk of stroke incidence and mortality, but other nut types and peanut butter were not significantly associated with either outcome. For stroke subtypes, no associations were seen with ischemic stroke (RR = 0.99, CI: 0.89–1.10 in 7 cohort comparisons including 302,423 participants and 8401 cases) or hemorrhagic stroke (RR = 1.02, CI: 0.77–1.34 in 5 cohort comparisons including 188,750 participants and 3088 cases) [22].

Another meta-analysis including 11 cohort studies (9272 stroke cases) and 396,768 participants also reported an inverse association in the high vs. low analysis (RR = 0.89, CI: 0.82–0.97), but not in the linear dose-response analysis (RR = 0.93, CI: 0.83–1.05); however, there was some indication of a non-linear J-shaped association with a reduction in risk up to approximately 10–15 g/day, but a slight positive association at 30 g/day [23]. There was no indication of an increased risk at high intakes when stroke incidence and stroke mortality were analyzed separately, suggesting that the direct association at high nut doses observation could be an artefact. When subtypes of nuts were examined, no association was observed for tree nuts in relation to the risk of stroke in the high vs. low and dose-response analyses, while slight inverse associations were observed for peanuts [23], which were both similar to those reported in the EASD meta-analysis [22]. It is unclear whether these differences in results between subtypes are real or simply because of chance variation due to the few studies available. Given largely overlapping confidence intervals between summary estimates, it is possible that chance variation is playing a role; therefore, further studies are needed. The 2022 umbrella review findings were also similar: no association was seen with stroke incidence (RR = 1.00, CI: 0.92–1.09) in 7 cohort comparisons, including 302,888 participants and 12,646 cases, with an inverse association seen with stroke mortality (RR = 0.82, CI: 0.73–0.92) in 12 cohort comparisons including 449,293 participants and 4398 events [21]. Although results regarding nut consumption and stroke risk have been more variable than for CHD, it seems there may be a modest inverse association between higher nut intake and stroke risk. Most of the individual studies may not have been sufficiently powered to detect an association. Nonetheless, a possible reason for the weaker association between nut consumption and stroke than for CHD could be the fact that many nuts are salted. Dietary salt consumption is one of the main determinants for elevated blood pressure, and it is possible that adding salt to nuts could dilute some of the

benefits they have, particularly for stroke, similar to the possible reasons for no association seen with peanut butter and several CVD outcomes.

4.4. Heart Failure

Few prospective cohort studies have assessed the role of nut consumption in preventing one of the major complications of CVD, HF. The EASD systematic review and meta-analysis included two cohort studies with 53,877 participants and 4253 cases, and for high vs. low categories of nut consumption, the RR was 1.00 (CI: 0.86–1.16) [22]. The certainty of evidence by GRADE was very low for HF, owing to downgrades due to the risk of bias (i.e., study quality as assessed by the Newcastle Ottawa Scale), indirectness and imprecision. Similarly, the 2022 umbrella review included the same cohorts, and the same effect estimates were observed [21]. Interestingly, a large prospective Swedish Cohort study of 61,364 adults observed a non-linear inverse association with the risk of HF and a 12% reduction in risk (HR = 0.88, CI: 0.79–0.99) with consumption of nuts 1–2 times per week with 17 years of follow-up [24].

4.5. Atrial Fibrillation

Similar to HF, fewer prospective cohort studies have examined the role of nuts in preventing this important risk factor for stroke and HF. The EASD systematic review and meta-analysis assessed two prospective cohort studies, including 53,965 participants and 10,867 cases [22]. Comparing high vs. low consumption of nuts, there was a 15% lower risk of AF (RR = 0.85, CI: 0.73–0.99), similar to the 2022 umbrella review [21]. The certainty of the evidence was very low, owing to downgrades due to indirectness and imprecision [22]. Similar to HF, the Swedish Cohort study also found a non-linear inverse relationship with the risk of AF and consumption of nuts 3 or more times per week was associated with an 18% reduced risk of AF [24].

4.6. Peripheral Arterial Disease

Few studies have assessed the association between nut consumption and the risk of PAD [25]. In the Atherosclerosis Risk in Communities Study, 14,082 men and women were followed for 20 years, and 1569 incident cases of PAD were identified. There was no clear association between the frequency of nut consumption and the risk of PAD, and the HR was 1.04 (CI: 0.89–1.23) when comparing an intake of ≥2/week vs. almost never [26]. In an analysis from the Women's Health Initiative, including 138,506 postmenopausal women and 1036 PAD cases identified during 19 years of follow-up, there was no association between higher consumption of nuts and seeds and PAD (highest vs. lowest quartile of nuts and seeds consumption was 0.93 [CI: 0.78–1.10]) [27]. Similarly, in a combined analysis of 38,823 women in the Swedish Mammography Cohort and 45,472 men in the Cohort of Swedish Men (aged 45–83 years) with 22 years follow-up and 3413 PAD cases, there was no clear association between intake of nuts and PAD risk, and the HR was 1.05 (CI: 0.89–1.24) for the highest vs. lowest category of intake [28]. We pooled the data from the 3 cohorts, and the RR was 1.03 (CI: 0.96–1.09), also highlighting no clear association between nut consumption and the risk of PAD (Figure 1). However, we cannot exclude the possibility that there may be a U-shaped association between nut consumption and PAD.

4.7. Total Mortality

The 2022 umbrella review also assessed the association between nut consumption and overall total mortality. In 16 cohort comparisons (including 819,448 participants and 85,870 deaths), both high vs. low categories of nut consumption (RR = 0.81, CI: 0.77, 0.85) and per serving (28 g/day, RR = 0.78, CI: 0.72, 0.84) were associated with lower risk of total mortality [21]. Similar to total CVD, the dose-response analyses indicated optimal intake levels were approximately ~15–20 g/day, with limited further benefits up to 28 g/day. In addition, a meta-analysis of 15 cohort studies indicated that 4.4 million premature deaths

in the Americas, Europe, Southeast Asia and Western Pacific would be attributable to a nut intake below 20 g/day [23].

4.8. Change in Nut Intake and Substitution Analyses

Changes in nut intake over time and the substitution of nuts for other dietary factors have also been associated with a lower risk of CVD. For instance, Liu et al. examined the association between 4-year changes in nut consumption and risk of CVD outcomes in the subsequent 4 years in the Health Professionals Follow-up Study (HPFS) and Nurses' Health Study (NHS) I and II [29]. They found that a per 1/2 serving/day increase in total nut consumption was associated with a lower risk of CVD (HR = 0.92, CI: 0.86–0.98), CHD (HR = 0.94, CI: 0.89–0.99) and stroke (HR = 0.89, CI: 0.83–0.95) and those that decreased their nut consumption over time had an increased risk of CVD, CHD and stroke. The 1/2 serving/day increase in consumption for a different type of nuts showed that most nut types were associated with a lower risk of CVD outcomes, with walnuts showing the strongest association and peanut butter showing no association. The researchers also examined the substitution effect per 1/2 serving/day of nuts and found that replacing red meat, processed meat, refined grains, French fries and dessert with nuts was associated with a lower risk of CVD, CHD and stroke [29]. In another analysis of HPFS and NHS, substituting both unprocessed and processed red meat for nuts was associated with the greatest reduction in total mortality [30].

5. Healthy Dietary Patterns That Contain Nuts

Several healthy dietary patterns that are recommended in CVD clinical practice guidelines contain nuts as a key food component. These include dietary patterns such as the Mediterranean, Nordic, Dietary Approaches to Stop Hypertension (DASH), vegetarian and Portfolio diets. Each of these dietary patterns has been shown to lower important CVD risk factors in RCTs and is associated with a lower risk of CVD in prospective cohort studies [31–38]. A healthy Mediterranean diet including nuts was also assessed with CVD endpoints in the landmark Prevención con Dieta Mediterránea (PREDIMED) trial. In this trial, over 7000 high-risk individuals for CVD were randomly assigned to an energy-unrestricted Mediterranean diet supplemented with either extra virgin olive oil (EVOO) or mixed nuts or the control diet (advice to curtail all types of fat) [39]. After approximately 5 years, both the Mediterranean diet groups supplemented with EVOO and nuts had a 30% reduction in CV events, mainly through reductions in stroke. Further analyses of the PREDIMED study also found a reduced risk of PAD both in the EVOO (HR = 0.36, CI: 0.21–0.65) and in the nuts group (HR = 0.54, CI: 0.32–0.92) when compared to the control group [40]. Due to the design of the PREDIMED study, it is not possible to separate the impact of nuts (or EVOO) from that of other dietary recommendations given to increase adherence to a Mediterranean diet, as well as with other healthy dietary patterns, and it is possible that other components of the diet could contribute in part to these findings.

6. Mechanisms Related to Nuts and Cardiovascular Risk Reduction

There are several mechanisms by which nuts can lower the risk of developing CVD, such as through positively impacting intermediate cardiovascular risk factors, including blood lipids, blood pressure, inflammation, and markers of glycemic control, among others. Nuts are rich in unsaturated fatty acids, plant protein, phytosterols, fiber, some minerals (including potassium, calcium and magnesium), vitamins (vitamin E and B6) and phenolic and bioactive compounds, all of which may contribute to their CV health-promoting benefits [9]. A systematic review and meta-analysis of 61 trials of tree nut consumption found that at a median dose of 56 g/day, TC, LDL-C, apolipoprotein B (ApoB) and triglycerides were significantly lowered, with no effect on high-density lipoprotein-cholesterol (HDL-C). A dose-dependent effect was also reported, with stronger effects seen for TC and LDL-C with nut intake over 60 g/day [20]. Importantly, the type of nut did not appear to be important for the cholesterol-lowering results observed [20]. The effects

on blood pressure and inflammation have been less consistent than those observed for blood lipids, with the same systematic review and meta-analysis finding no significant effects of tree nut consumption on blood pressure and C-reactive protein [20]. Other meta-analyses have conversely shown that nut consumption, particularly pistachios, does have a modest blood pressure lowering effects in people without type 2 diabetes [41], with another meta-analysis finding that almond consumption lowered diastolic blood pressure [42]. This finding of stronger effects on blood lipids than on blood pressure is consistent with the studies showing that LDL-C and ApoB are causal in the development of CHD [43], while elevated blood pressure is a greater risk factor for stroke [44] and may explain the more consistent finding with a lower risk of CHD than with stroke seen in the prospective cohort studies described earlier. Furthermore, a systematic review and meta-analysis that included 12 trials found that tree nuts at a median dose of 56 g/day can improve markers of glycemic control in individuals with type 2 diabetes (including lowering HbA1c and fasting glucose) [45]. Another systematic review and meta-analysis of 40 RCTs at a median dose of 52 g/day, including diverse populations of adults (including healthy, those with type 2 diabetes or with CVD risk factors), found that tree nuts or peanuts improved markers of insulin sensitivity, however, the effect on fasting blood glucose and HbA1c was not significant [46]. Other potential mechanisms include their role in adiposity [47], possibly due to their satiating effect, increased efforts and/or time of mastication and hence incomplete digestion in the intestines, and alpha-linolenic acid content of nuts, especially walnuts, which might increase membrane fluidity of endothelial cells with the enhancement of nitric oxide synthesis and ensuing improvement of endothelial function [48,49]. Overall, there is good evidence that nut consumption consistently lowers atherogenic blood lipids and may improve insulin sensitivity and endothelial function, with less consistent effects on blood pressure, without adversely impacting adiposity. Regarding adiposity, a recent systematic review and meta-analysis highlighted that the median nut intake in the trials included in their analyses, as well as in the health claims noted in Table 2, that a dose of 42.5 g/day could be integrated into a daily dietary pattern without contributing to weight gain [47].

7. Future Directions

The evidence for nut consumption and total CVD and CHD is more consistent in prospective cohort studies compared to other CVD outcomes, with low to moderate certainty of evidence using the GRADE criteria. The GRADE criteria, however, may not be the best grading system to use when evaluating the certainty of evidence from observational studies, particularly in the field of nutritional epidemiology [50]. Future pooled analyses that assess the certainty of evidence should consider integrating ROBINS-I to assess the risk of bias [51] or consider also applying the NutriGrade system [52], both of which do not provide excessive downgrading of observational evidence. In addition, given the scarcity and sometimes conflicting results among studies, more studies are needed to clarify the role of nut consumption in stroke, particularly stroke subtypes, HF, AF and PAD. Further research on the type of nuts will eventually provide further insight into their role in CVD prevention, including studies of peanut and other nut butters (including natural) and salted vs. unsalted nuts. New analyses on nut intake should also report quantities of nut intake (i.e., grams/day) so that these data can be used in updated meta-analyses. The quantity of nuts is also more translatable for guiding dietary recommendations compared to high vs. low categories. Individual cohort pooled meta-analyses would also be useful to ensure consistency in analyses across cohort studies. Although RCTs of nut consumption and blood lipids support the results from observational cohort studies showing reduced CVD and CHD risk, there is some discrepancy between what doses of nuts have been shown to reduce blood lipids in RCTs and what doses lower CVD and CHD risk in observational cohort studies. For example, in a meta-analysis of RCTs, there was a steeper reduction in total and LDL-C between 50–100 g/d than at lower levels of intake [20], while in the observational cohort studies, maximum risk reductions have been observed around

15–20 g/d (approximately 4–5 servings/week) [21–23]. However, the highest nut intakes reported in cohort studies have typically been around one serving/day (28 g/d), and it is unknown whether CVD or CHD risk is reduced further with higher intakes. Considering that relatively few people consume more than one serving of nuts per day in most populations [23,53], pooled analyses may also be needed to explore, with sufficient statistical power, whether higher intakes are associated with further reductions in hard endpoints. Further studies are also needed to clarify if other mechanisms than reductions in lipids (e.g., antioxidant or anti-thrombotic effects) may contribute to the vascular benefits observed at the more modest nut consumption levels reported in the observational studies. Another important consideration related to the discrepancy of nut levels consumed in trials and cohort studies is the dietary assessment tool used, as food frequency questionnaires (FFQ) commonly administered in cohort studies may not be as accurate in quantifying absolute intake compared to trials, where diet records are typically used, and intervention groups are usually provided nuts to guarantee the desired consumption. As diet records are not feasible in large cohort studies, repeated measurements of FFQs will be important to represent long-term dietary habits and reduce measurement error, as well as allow assessment of change in nut consumption in relation to health outcomes. FFQs should also consider including more nut categories (walnuts, almonds, peanuts, seeds, etc.) to provide more detailed information on nuts and nut types.

Using objective biomarkers of nut consumption alongside dietary intake assessment methods will additionally be important in the future, as they are less prone to measurement error from FFQs or 24-h recalls [54]. For example, in the PREDIMED study, plasma alpha-linolenic acid (a polyunsaturated fatty acid that abounds in walnuts) levels were measured to confirm adherence in the group receiving mixed nuts alongside an FFQ [39]. Novel approaches, such as multi-omics, will likely play a larger role in the future for both assessing adherence to diet and precision nutrition [55]. Metabolomics, in particular, is a promising technique to help identify objective dietary biomarkers by providing a comprehensive representation of overall dietary intake by measuring the metabolites in biological samples (such as blood or urine). In prospective cohort studies, several metabolites, mainly lipid-related, have been found to be markers of nut intake in general [56] or of specific types of nuts, such as walnuts, and these metabolites have likewise been associated with a lower risk of CVD [57]. The metabolites associated with nut consumption may be helpful in identifying potential objective biomarkers of exposure to nuts in large prospective cohort studies, as well as in clarifying underlying mechanisms implicated in disease risk. Importantly though, these metabolomic profiles associated with nut consumption are not highly correlated with self-reported nut consumption and also reflect the metabolic response to consumption and are therefore not completely sensitive or specific markers. Many of these metabolites may also not be able to distinguish between different types of nuts. Thus, dietary intake assessment methods such as FFQs will still be important to determine more specific information on nut consumption.

Other future directions include undertaking large CV outcome trials of nut-containing dietary patterns, as was previously done with PREDIMED [39] and the current ongoing PREDIMED-Plus trials [58] (both primary CVD prevention trials) and the CORDIOPREV trial (a secondary CVD prevention trial) [59]. One limitation of these trials is that they cannot separate the effect of the Mediterranean diet from that of nuts on health outcomes. Thus, any further trials in this setting could benefit from having an additional intervention group on a Mediterranean diet only (without nuts). Large trials should also consider long-term measurements of renal function, as this area has been given insufficient attention and kidney dysfunction has been causally related to CHD risk [60], therefore highlighting the need for preventative approaches to also preserve renal function. Furthermore, determining metabolomic signatures that can reflect adherence and metabolic response to these nut-containing dietary patterns should be included within these types of trials. This method was previously assessed using the Mediterranean diet in the PREDIMED study, where a metabolic signature that robustly reflected adherence and metabolic response to the diet

was determined [61]. The metabolic signature was then used to assess associations with CVD risk and showed stronger inverse associations with CVD risk compared to dietary intake alone in a Spanish and three US cohorts. Mendelian randomization analyses also showed that the genetically inferred metabolic signature was significantly associated with a lower risk of CHD and stroke [61]. These novel approaches hold promise for an objective and complete evaluation of both adherence and metabolic responses to diet, including nuts, and may allow more effective and individualized approaches to dietary interventions in the future; however, further research is also needed in this area. Overall, a combination of efforts, including well-conducted large prospective cohort studies, large RCTs of hard CV endpoints and incorporation of multi-omics approaches and genetics, will help us better understand the role of nuts in the primary and secondary prevention of CVD.

8. Summary and Conclusions

The overall findings and conclusions from this review are that nuts are a beneficial food for CVD risk reduction, with consistent findings for the benefit for total CVD and CHD in prospective cohort studies and likely benefits for stroke and AF, but additional research is needed for HF, AF, PAD and stroke subtypes. Considering all evidence from mechanistic studies, RCTs of intermediate risk factors and CV events, and prospective cohort studies, at least one serving per day of nuts should be considered for CV risk reduction, although further research on the optimal dose is needed. The type of nut may not be important, though more research is needed to confirm this finding. However, a general nut recommendation will provide more variety of options and be important for any availability and affordability concerns for consumers.

In conclusion, future research is urgently needed as outlined above, particularly for stroke subtypes, PAD and HF, and include individual cohort pooled analyses, large RCTs of nut-containing dietary patterns and using -omics methodologies to better capture adherence and metabolic responses to diet, including the consumption of nuts.

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He is also a vegan. **CWCK** has received grants or research support from the Advanced Food Materials Network, Agriculture and Agri-Foods Canada (AAFC), Almond Board of California, Barilla, Canadian Institutes of Health Research (CIHR), Canola Council of Canada, International Nut and Dried Fruit Council, International Tree Nut Council Research and Education Foundation, Loblaw Brands Ltd., the Peanut Institute, Pulse Canada and Unilever. He has received in-kind research support from the Almond Board of California, Barilla, California Walnut Commission, Kellogg Canada, Loblaw Companies, Nutrartis, Quaker (PepsiCo), the Peanut Institute, Primo, Unico, Unilever, WhiteWave Foods/Danone. 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Pulse Canada, Sun-Maid, Tate and Lyle, Unilever and White Wave Foods/Danone. He has served on the scientific advisory board for the International Tree Nut Council, International Pasta Organization, McCormick Science Institute and Oldways Preservation Trust. He is a founding member of the International Carbohydrate Quality Consortium (ICQC), Chair of the Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD), is on the Clinical Practice Guidelines Expert Committee for Nutrition Therapy of the EASD and is a Director of Glycemia Consulting and the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. **JLS** has received research support from the Canadian Foundation for Innovation, Ontario Research Fund, Province of Ontario Ministry of Research and Innovation and Science, Canadian Institutes of health Research (CIHR), Diabetes Canada, PSI Foundation, Banting and Best Diabetes Centre (BBDC), American Society for Nutrition (ASN), INC International Nut and Dried Fruit Council Foundation, National Dried Fruit Trade Association, The Tate and Lyle Nutritional Research Fund at the University of Toronto, The Glycemic Control and Cardiovascular Disease in Type 2 Diabetes Fund at the University of Toronto (a fund established by the Alberta Pulse Growers), and the Nutrition Trialists Fund at the University of Toronto (a fund established by an inaugural donation from the Calorie Control Council). He has received in-kind food donations to support a randomized controlled trial from the Almond Board of California, California Walnut Commission, American Peanut Council, Barilla, Unilever, Unico/Primo, Loblaw Companies, Quaker, Kellogg Canada, and WhiteWave Foods. He has received travel support, speaker fees and/or honoraria from Diabetes Canada, Mott's LLP, Dairy Farmers of Canada, FoodMinds LLC, International Sweeteners Association, Nestlé, Pulse Canada, Canadian Society for Endocrinology and Metabolism (CSEM), GI Foundation, Abbott, Biofortis, ASN, Northern Ontario School of Medicine, INC Nutrition Research and Education Foundation, European Food Safety Authority (EFSA), Comité Européen des Fabricants de Sucre (CEFS), and Physicians Committee for Responsible Medicine. He has or has had ad hoc consulting arrangements with Perkins Coie LLP, Tate and Lyle, and Wirtschaftliche Vereinigung Zucker e.V. He is a member of the European Fruit Juice Association Scientific Expert Panel and Soy Nutrition Institute (SNI) Scientific Advisory Committee. He is on the Clinical Practice Guidelines Expert Committees of Diabetes Canada, European Association for the study of Diabetes (EASD), Canadian Cardiovascular Society (CCS), and Obesity Canada. He serves or has served as an unpaid scientific advisor for the Food, Nutrition, and Safety Program (FNSP) and the Technical Committee on Carbohydrates of the International Life Science Institute (ILSI) North America. He is a member of the International Carbohydrate Quality Consortium (ICQC), Executive Board Member of the Diabetes and Nutrition Study Group (DNSG) of the EASD, and Director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. His wife is an employee of AB InBev. All other authors have no conflicts of interest to report.

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nutrients

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Review

Impact of Nut Consumption on Cognition across the Lifespan

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Abstract: Cognitive health is a life-long concern affected by modifiable risk factors, including lifestyle choices, such as dietary intake, with serious implications for quality of life, morbidity, and mortality worldwide. In addition, nuts are a nutrient-dense food that contain a number of potentially neuroprotective components, including monounsaturated and polyunsaturated fatty acids, fiber, B-vitamins, non-sodium minerals, and highly bioactive polyphenols. However, increased nut consumption relates to a lower cardiovascular risk and a lower burden of cardiovascular risk factors that are shared with neurodegenerative disorders, which is why nuts have been hypothesized to be beneficial for brain health. The present narrative review discusses up-to-date epidemiological, clinical trial, and mechanistic evidence of the effect of exposure to nuts on cognitive performance. While limited and inconclusive, available evidence suggests a possible role for nuts in the maintenance of cognitive health and prevention of cognitive decline in individuals across the lifespan, particularly in older adults and those at higher risk. Walnuts, as a rich source of the plant-based polyunsaturated omega-3 fatty acid alpha-linolenic acid, are the nut type most promising for cognitive health. Given the limited definitive evidence available to date, especially regarding cognitive health biomarkers and hard outcomes, future studies are needed to better elucidate the impact of nuts on the maintenance of cognitive health, as well as the prevention and management of cognitive decline and dementia, including Alzheimer disease.

Keywords: nuts; cognitive performance; brain health; dementia; lifespan; aging; epidemiological studies; clinical trials

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1. Introduction

Cognitive health is a key component of healthy aging. Age-related cognitive decline and neurodegenerative disorders, such as dementia, which are a consequence of population aging and an increased lifespan, are a growing public health concern [1]. Dementia, with Alzheimer's Disease (AD) as the most common type, is currently one of the top ten leading causes of mortality among all diseases and one of the major causes of disability and dependency among older people worldwide [1]. As cognitive decline and dementias have

physical, psychological, social, and economic impacts, not only for the people directly affected, but also for their caregivers, families, and society at large, it is a key public health concern to address [1].

While neurodegenerative disorders tend to occur at older ages, brain development and cognitive health are impacted across the lifespan, from the fetus stage in pregnancy through adulthood [2]. Increasing evidence indicates that a high cognitive reserve, a healthy lifestyle, and the control of modifiable cardiovascular risk factors may reduce the risk of developing cognitive decline and dementia, including AD [3]. Of the lifestyle components influencing brain health, nutrition holds much potential. Nutrition may directly affect the brain or indirectly influence risk factors shared by cardiovascular and neurodegenerative diseases, thereby possibly having a substantial influence on cognition and the risk of dementia [4,5]. For instance, oxidative stress and inflammation are thought to play a major role in the initiation and progression of AD and other neurodegenerative disorders [6]. Antioxidant-rich foods and dietary patterns are potential strategies to counteract cognitive decline and AD and promote healthy aging. As proof, evidence is accumulating from both prospective studies and randomized controlled trials (RCTs) that adherence to plant-based dietary patterns rich in antioxidant foods, such as vegetables, fruits, whole grains, legumes, and nuts, is associated with a delay in age-related cognitive decline among older adults from diverse populations, as summarized in recent systematic reviews [7,8].

The Mediterranean diet (MedDiet) has been by far the most investigated dietary pattern for associations with brain health outcomes, with findings suggesting a protective association with cognitive decline [9–11]. Neuroimaging studies have further supported the association between increasing adherence to the MedDiet and greater brain volumes, lesser changes of brain atrophy, and the preservation of structural connectivity in healthy older adults. Within these investigations, higher intake of specific nutrients such as unsaturated fatty acids, antioxidant vitamins, and polyphenols has been linked to larger brain volumes [12]. More limited research on other healthy plant-based diets, such as the dietary approach to stop hypertension (DASH) diet, the Mediterranean-DASH diet, the intervention for neurodegenerative delay (MIND) diet, and other anti-inflammatory diets, has shown beneficial associations with cognitive health in older adults as well [13,14].

Given the available evidence, the World Health Organization (WHO) guidelines for risk reduction of cognitive decline and dementia included nutrition-related recommendations relating to the MedDiet and healthy, balanced, plant-based dietary patterns, all of which included nuts [15]. In addition, the WHO guidelines state that unsaturated fats, such as those found in nuts, are preferred over saturated fats for brain health and that consumption of nuts has been associated with a reduced risk of cognitive impairment [15].

Nuts (i.e., tree nuts, including almonds, Brazil nuts, cashews, hazelnuts, macadamias, pecans, pine nuts, pistachios, and walnuts; and peanuts) are an integral part of plant-based diets and have an optimal nutrient profile, being particularly abundant in anti-inflammatory and antioxidant molecules, such as unsaturated fatty acids, non-sodium minerals, vitamins, and polyphenols; moreover, their frequent consumption is associated with a consistent reduction in the risk of cardiovascular disease (CVD) [16]. Due to the fact that cardiovascular risk factors and CVD have well-established links to neurodegeneration and unhealthy aging, nut consumption, already well known to benefit vascular function, has been hypothesized to also favor cognition and overall brain health [17].

The present narrative review aims to present up-to-date evidence regarding the association between nut consumption and cognitive health during different stages of life. Specifically, it reports on the proceedings from the "Nuts 2022, Where we are and where we are going in research" international conference session titled "Nuts, Ageing, and Cognition." In this session, epidemiological, clinical, and mechanistic evidence regarding nut consumption and cognition in different age groups was presented and discussed. This review is not a systematic review, and thus limitations should be acknowledged in that all studies may not have been identified. However, this review summarizes the available

literature from independently conducted searches, and findings were further shared and discussed among the ensemble of experts in the field of nut and health research.

2. Nut Consumption and Neurodevelopment in Early Life (Gestation to Young Adulthood)

The early life years are critically important for cognitive development. Generally, brain development begins a few weeks after conception and is thought to be complete by early adulthood. The basic structure of the brain is believed to be shaped primarily during the prenatal period and early childhood, with the formation and refinement of neural networks and modification of functional abilities continuing over the long term [2]. Nutrition during each of the life stages of pregnancy, lactation, childhood, and adolescence can have a fundamental influence on development [18,19].

2.1. Nut Consumption and Prenatal Cognitive Development

The period of in-utero growth during gestation is considered to be particularly important for neurodevelopment since the brain undergoes several uniquely intense and complex processes [20,21]. Human brain development begins soon after conception with the inception of the formation of the neural tube and continues into early adulthood. The fetal brain begins to develop during the third week of gestation. By the end of the embryonic period (gestational week 10), the basics of the neural system are established. All the structures continue to develop throughout the fetal period and early childhood. By 6 years of age, the brain has reached 90% of its adult volume [22]. During this period of brain development, essential nutrients, such as the omega-3 fatty acid alpha-linolenic acid (ALA), which can be found in nuts, particularly walnuts, may alter the epigenetic control of neural processes, neuron formation, migration, axon and dendritic growth, synaptogenesis, and myelination [23]. In the long term, adequate nutrition that promotes neurodevelopment during the in-utero period may benefit a child's neuropsychological development, school performance, and future professional success [21]. Yet, the possible protective effects of nut consumption on cognitive health have hardly been explored in child neurodevelopment. At present, there is limited evidence from epidemiological and clinical studies assessing nut consumption and brain function during pregnancy, childhood, or adolescence.

In relation to the pregnancy period, to our knowledge, only one study has been published assessing the association between cognitive health and nut consumption during early development. This study involved the Spanish Childhood and Environment (Infancia y Medio Ambiente, INMA) Project, a large prospective, multicenter, population-based cohort of 2208 mother-child pairs, conducted in several regions of Spain [24]. Mothers were followed during pregnancy (first and third trimesters), and their children were enrolled at birth and followed until the age of 8 years. Twice during pregnancy and at the children's ages of 1.5, 5, and 8 years, dietary intake questionnaires and neuropsychological assessments were administered. The mean nut consumption among mothers in the first trimester of pregnancy was 41 g/week (standard deviation [SD], 74 g/week), and the median was 17 g/week (interquartile range [IQR]: 0 to 46 g/week), with a third of the total participants being non-consumers (n = 860, 33.5%). Overall, the authors found that higher maternal consumption of nuts in early pregnancy was associated with enhanced cognitive development in their children, compared to non-consumers, at 1.5, 5, and 8 years of age [24].

2.2. Nut Consumption and Early Life (Childhood and Adolescence) Cognitive Development

Nutrition during childhood is particularly important, as this is a period of relatively rapid brain development, and nutrients aid the brain in the creation of new synaptic connections during learning processes at school and in home environments [18]. While the structural components of the brain and the foundations of basic sensation and perception systems are fully developed by the time children reach kindergarten age, other systems such as those involved in memory, decision-making, and emotion continue to develop well into childhood. The foundations of many of these abilities, however, are constructed

during the early years. Whereas the functional aspects of the brain can have varying developmental time frames and patterns, adolescence is an important period of brain development and remodeling to functionally develop for thinking and processing [2]. The brain reorganizes during this developmental stage with functional and structural changes resulting from the re-emergence of gonadotropin-releasing hormone, triggering a cascade of hormone-dependent processes. Other biological processes involve epigenetic factors, which are highly sensitive to the environment and may therefore make this period of growth more vulnerable to external insults [25]. Moreover, the prefrontal cortex, which carries out important functions such as internally guided behaviors (control of emotion), logical thinking, working memory, and organizing skills (executive function), is the last region of the brain to mature (in the early twenties). The synaptic plasticity of the prefrontal cortex is accentuated during adolescence, a process that involves loss of grey matter density and an increase in white matter volume, cerebral blood flow, and synaptic pruning. Adolescence is also a time of refinement of brain connectivity and complex behaviors [26]. It is widely recognized that the synaptic plasticity of the brain decreases with age [25,26], but this pattern does not seem to follow a linear trend, and adolescence is an important period during which brain development can be enhanced and protected from environmental hazards, from air pollution to unhealthy diets, with long-term consequences.

Considering the importance of brain structural and functional development during childhood and adolescence, very few studies have assessed the association between nut consumption and cognitive health during these life stages. One cross-sectional study conducted in 317 Korean children and adolescents (167 girls and 150 boys) with a mean age of 11.8 (range, 6 to 18) years and no prior diagnosis of neurologic or psychiatric disorders assessed the consumption of nuts, among other healthy foods estimated from diet questionnaires, in relation to cognitive performance [27]. Nut consumption was related to improved cognitive reaction time consistency and attention function as measured by the symbol-digit modality test (SDMT). However, no associations were observed with the other neuropsychological measures, specifically the verbal and visual memory tests, the shift attention test, the reasoning test, and the digit span forward and backward tasks, assessed as part of a computerized cognitive assessment battery. A limitation of this study is that the authors did not adjust the data for covariables known to influence cognitive performance in youth, such as parental social class, parity, type of delivery, breastfeeding, birthweight, maternal intellectual quotient (IQ), maternal mental health, maternal smoking and alcohol intake during pregnancy, clinical history during pregnancy, overall dietary pattern, and stress events [27].

While there is currently a lack of RCTs, there is promise for further evidence as a protocol for a RCT (the WALNUT study [WSS]) aiming to assess the effect of daily walnut consumption (30 g) over 6 months on cognitive function among nearly 700 healthy adolescents from several high schools in Barcelona, Spain, was recently published [28]. The results of this study will eventually fill a gap in our knowledge of the effect of nut consumption on cognitive health in adolescence.

Linking the previous findings relating the consequences of increased nut consumption by mothers during pregnancy to the later neuropsychological traits of their children [24], and further applying public health recommendations to an entire population, for example, recommending pregnant women to consume a daily serving of nuts throughout the prenatal period, might be hypothesized to increase the population mean IQ score by a few points. This is not clinically significant at the individual level; still, the impact on the IQ distribution at the population level might represent a significant reduction in the proportion of children with learning problems or low IQ scores [24,29]. Depending on the findings of future research, this could be a potentially impactful health promoting message for the population, possibly akin to the promotion of long-term breastfeeding and/or the recommendation to stop smoking during pregnancy.

2.3. Nut Consumption and Cognitive Health in Young Adulthood

As adolescence transitions into young adulthood, complex cognitive behaviors are refined. It is during this life stage that myelination of regions involved in higher cognitive abilities, such as the prefrontal cortex, is considered to be complete [2]. This process of myelination ultimately involves the axons of neurons being wrapped in fatty cells, which facilitates neuronal activity and communication for the transmission of electrical signals.

Nutrition, and particularly fatty acids, are critical for brain development. Essential fatty acids are long-chain polyunsaturated acids (LC-PUFAs) that the body cannot synthesize and must be obtained from the diet (mainly from oily fish, seeds, and nuts). LC-PUFAs are involved in the function and architecture of the central nervous system throughout the various life stages. It has been shown that the LC-PUFA docosahexaenoic acid (DHA) regulates neurotransmission systems such as serotonergic, dopaminergic, norepinephrinergic, and acetylcholinergic systems [23,30].

The omega-3 PUFA ALA, which is particularly abundant in walnuts, has been associated with cognitive function in older people [31]. However, it has been scarcely studied at younger ages. In a recent cross-sectional study of 332 healthy adolescents, the red blood cell proportions of ALA (an objective biomarker of walnut consumption) were inversely associated with impulsivity (a usually detrimental psychological trait and a key feature of many psychiatric disorders) [32]. The findings from this study support the hypothesis that nuts, particularly walnuts, could have a beneficial impact on cognition.

Additionally, to date, the only known RCT specifically investigating the effect of nut consumption on cognitive health in youth was that conducted by Pribis and colleagues in young adults aged 18 to 25 years [33]. In a crossover investigation, the consumption of 60 g of walnuts for 8 weeks by college students (n = 47) was associated with better critical thinking abilities as measured by the Watson-Glaser Critical Thinking Appraisal. However, no differences were observed for verbal reasoning, as measured by Raven's advanced progressive matrices, or memory, as assessed by the Wechsler Memory Scale, when compared with the placebo group. The authors acknowledged that these findings may be limited by the short duration of the intervention as well as by the fact that participants were college students, whose baseline cognitive functioning may be higher than that of the general population and hence may impact cognitive findings.

Early-life structural and functional development of the brain and the potential influence of dietary intake are important, yet little research has been conducted to assess the impact of nut consumption on cognitive health during childhood and adolescence. Although preliminary research is promising, further investigations are warranted to better determine the efficacy of consuming nuts on neurodevelopment, especially during life stages of growth and development.

3. Nut Consumption and Cognitive Performance in Adulthood

An essential component of healthy aging is normal cognitive function, which critically affects functional independence and health-related quality of life. Increased life expectancy and subsequent population aging entail a rising prevalence of age-associated cognitive impairment, a major public health concern given its frequent transition to mild cognitive impairment (MCI) and dementia, including AD [34]. Indeed, many older adults experience deteriorating cognitive function, usually with declining episodic memory and executive function that parallel volume losses in critical brain structures such as the hippocampus [35]. Cognitive domains that can be interrogated with specific neuropsychological tests include memory, executive function, attention, language, and visuospatial skills. The neuropsychological test most commonly used in epidemiologic studies is the Mini-Mental State Examination (MMSE), a brief test (it takes 7 to 10 min to complete) that is very useful to detect dementia when it is grossly abnormal but is limited in its ability to provide insight into subtler and much more frequent cognitive deficits [36]. A telephone-adaption of the MMSE (the TICS, or Telephone Interview for Cognitive Status) to assess overall cognitive performance has also been frequently used in the absence of more comprehensive tests.

While these screening instruments may offer an opportunity for cognitive comparisons, their accuracy in detecting cognitive impairment is a limitation in neurocognitive studies. MCI is said to be present when there is objective evidence at cognitive testing that one or more of these cognitive domains is impaired. As opposed to individuals with dementia, those with MCI maintain their independence in functional abilities and have no significant impairment in social or occupational functioning [37].

3.1. Epidemiological Studies Examining the Association of Nut Consumption with Cognitive Performance

In the review of epidemiological evidence evaluating nut consumption and cognitive performance, 15 studies were identified, including 7 cross-sectional and 8 prospective cohort studies. Table 1 lists these investigations by date of publication and summarizes their findings. Briefly, these observational studies involved men and women, with the majority aged ≥50 years, from Australia, China, Italy, the Netherlands, Norway, Spain, and the United States, with the prospective cohorts ranging from 3 to 20 years in duration and assessing quantiles of nut intake comparing none or low to higher intake dosages. The known factors influencing cognitive performance in adulthood, namely age, sex, educational level, body mass index, cardiovascular risk factors (smoking, hypertension, dyslipidemia), physical activity, overall dietary pattern, and depression [3], were treated as confounders and adjusted for in analyses of data from epidemiological studies.

Table 1. Epidemiological studies examining the association of nut consumption with cognitive performance.

Author, Year	Study Design (Source)	N	Age (Years)	Participant Characteristics	Neuro-Psychological Tests	Nut Dose/Day (Range)	FU (Years)	Outcome
Nurk, 2010 [38]	Cross-sectional (Hordaland Health Study)	2031	70–74	Men & women, general population	Complete battery	No consumption to high consumption	NA	No association
Nooyens, 2011 [39]	Prospective (Doetinchem cohort)	2613	43–70	Men & women, general population	Tests of memory, information processing, cognitive flexibility—sum of test scores (global cognition)	Quintiles of consumption	5	Higher nut consumption associated with cognitive flexibility and global cognition at baseline and trend to delayed cognitive decline at follow-up.
Valls-Pedret, 2012 [40]	Cross-sectional (PREDIMED study)	447	55–80	Men & women at high cardiovascular risk	Comprehensive battery	Total nuts (0–60) Walnuts 1 g (0–30)	NA	Walnuts, but not total nuts, associated with better working memory.
Samieri, 2013 [41]	Prospective (Women's Health Study)	6174	65+	Women	Comprehensive battery, including TICS	Quintiles of nut consumption within the Mediterranean diet	4	No association of nuts with cognitive changes
O'Brien, 2014 [42]	Prospective (Nurses' Health Study)	15,467	Mean 74	Women from a selected cohort of nurses	TICS	From never/<1/ month to ≥5 servings/week	6	Higher long-term total nut intake associated with better average cognitive status for all cognitive outcomes.
Arab, 2015 [43]	Cross-sectional (NHANES)	5562 and 2975	2 groups: 20–59 ≥60	Men and women, general population	Various cognitive tests	Walnuts with high certainty/walnuts with other nuts	NA	Walnut consumption positively associated with cognitive function in the two groups.

Table 1. *Cont.*

Author, Year	Study Design (Source)	N	Age (Years)	Participant Characteristics	Neuro-Psychological Tests	Nut Dose/Day (Range)	FU (Years)	Outcome
Dong, 2016 [44]	Cross-sectional	894	50 to >80	Men and women from a population cohort	MoCa test	Tertiles of consumption	NA	Higher nut consumption associated with delayed memory. Cognitively healthy adults consumed more nuts than those with MCI.
De Amicis, 2018 [45]	Cross-sectional	279	>65	Men and women attending Nutrition center	MMSE	Highest vs. lowest nut consumption within the Mediterranean diet	NA	OR = 0.30; 95% CI, 0.13–0.69 of low MMSE
Li, 2019 [46]	Prospective	4822	>55	China Health and Nutrition survey	TICS	Consumers of nuts (mainly peanuts)	15	Nuts >10 g/d: OR 0.60, 95% CI 0.43–0.84) of poor cognition
Rabassa, 2020 [47]	Prospective	119	>65	InChianti population study	MMSE	Consumers vs. non-consumers	3	OR: 0.78; 95% CI: 0.61–0.99 of low MMSE
Tan, 2021 [48]	Cross-sectional (NHANES)	1848	60+	Men and women, general population	CERAD total, delayed recall, animal fluency and digit-symbol substitution test	4 groups, from no consumers to consumers meeting recommendations (>30 g/d)	NA	Cognitive scores higher from moderate intake (15.1–30.0 g/d), same in high intake
Jiang, 2021 [49]	Prospective	16,737	Mean 53,5	Singapore Chinese Health Study	MMSE	Nuts <1 serv/mo, 1–3 serv/mo, 1 serv/wk, and =>2 serv/wk	20	3 highest categories: 12% (CI 2–20%), 19% (CI 4–31%) and 21% (CI 2–36%) lower risk of cognitive impairment
Bishop, 2021 [50]	Prospective	3632	65+	Health and Retirement & Health Care and Nutrition studies	TICS	None, low or moderate intake of walnuts	4	Any walnut consumption had greater scores at baseline. No association with cognitive changes.
Chen, 2021 [51]	Cross-sectional	819	70–90	Sydney Memory and Ageing Study:	Comprehensive battery	Consumption of nuts and legumes	NA	Higher consumption related to global cognition (β = 0.117; CI: 0.052–0.181), visuospatial function (β = 0.105; CI: 0.047–0.163), and language (β = 0.113; CI: 0.038–0.189).
Li, 2022 [52]	Prospective	9028	Mean 69	Zhejiang Ageing and Health Cohort Study	MMSE (repeated)	None, <70 g/week, or =>70 g/week	6	Less cognitive impairment (RR = 0.83, 95% CI 0.75–0.91) for highest nut intake group

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CI, confidence interval; FU, follow-up; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; mo, month; MoCa, Montreal cognitive assessment (short-term memory recall ability, visuospatial abilities, executive functions, phonemic fluency ability, verbal abstraction ability, attention, concentration and working memory, language, and orientation); N, number of study participants; NA, not applicable; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; PREDIMED, PREvención con DIeta MEDiterránea; TICS, Telephone Interview for Cognitive Status, a telephone-adaption of the MMSE to assess overall cognitive status; serv, serving.

Out of a total of 15 observational studies, 13 showed a positive association between nut consumption and cognitive performance; however, beneficial relationships were not observed among all cognitive assessments conducted in each study. For instance, in a

prospective Dutch study of middle-aged adults, cognitive performance was assessed at baseline and after a 5-year follow-up in relation to quintiles of consumption of plant foods. The highest nut intake was associated with better cognitive function (i.e., memory, speed, flexibility, and global cognitive function) at baseline but not lesser cognitive decline at follow-up when data were adjusted for cardiovascular risk factors [39]. In a cross-sectional study of Chinese adults, higher consumption of fruit, vegetables, and nuts was associated with delayed memory, while all other cognitive domains were unaffected; moreover, cognitively healthy participants consumed more nuts than those with MCI [44].

Further cross-sectional analyses have presented significant beneficial relationships between nut consumption and cognitive health. A cross-sectional study of nut consumption and cognitive performance was nested within a sub-cohort of the Prevención con Dieta Mediterránea (PREDIMED) study. This was a landmark 5-year RCT in which a MedDiet supplemented with either extra-virgin olive oil or mixed nuts (30 g/day: 15 g walnuts, 7.5 g almonds, and 7.5 g hazelnuts) versus a control diet (advice to follow a low-fat diet) resulted in nearly a 30% reduction in CVD events in older individuals at high cardiovascular risk [53]. The cross-sectional sub-study assessed the association of consumption of various foods with cognitive function. Of all the foods considered, only olive oil, coffee, wine, and walnuts—but not total nuts—were related to better cognitive function independently of known risk factors for cognitive decline, other food consumption, and energy intake. Of note, total urinary polyphenol excretion, an objective biomarker of intake of polyphenol-rich foods, was directly associated with working memory function [40]. In addition, within the context of the MedDiet, consumption of 1 serving of nuts (30 g)/week by older Italian adults was cross-sectionally associated with a reduced risk of low MMSE [45]. Cross-sectional analyses of the U.S. National Health and Nutrition Examination Survey (NHANES) indicated beneficial associations between nut consumption and cognition, determined based on 24-h dietary recalls [43,48]. Findings from the most recent relevant NHANES analyses of participants aged 65 and older who consumed nuts 15 to 30 g/d or met recommendations by consuming >30 g/day (either group accounting for 10% of the cohort) had better cognitive scores than non-consumers or low consumers [48]. A moderately sized cross-sectional study within the Sydney Memory and Ageing Study related consumption of different food groups to cognitive performance and found that higher consumption of nuts and legumes together related to higher global cognition, visuospatial function, and language [51].

Furthermore, prospective cohort analyses have demonstrated a potential beneficial relationship between nut consumption and cognitive function. In brief, a U.S. prospective study of a large sub-cohort of older women from the Nurses' Health Study (NHS) assessed total nut consumption in relation to cognitive function and found an association with better average status for all cognitive outcomes analyzed. The difference in the global composite score between women consuming at least 5 servings of nuts/week and non-consumers was equivalent to the mean difference observed in cognitive status between women 2 years apart in age [42]. Another sizable U.S. cohort framed within an observational study of an aging population found that participants with any walnut consumption had greater cognitive scores at baseline, but no association with 4-year cognitive change was observed. However, only 13% of the sample had moderate walnut consumption of around 1/2 oz (14 g) per day [50]. Along similar lines, three large Asian prospective cohort studies showed favorable associations between nut intake and cognitive function. A prospective large 15-year Chinese study of participants in a nutrition survey aged 55 years or more found that consumers of nuts (mostly peanuts), which made up only 17% of the cohort, had less cognitive decline, as measured with the telephone version of the MMSE, than those not consuming any nuts [46]. The large prospective Singapore Chinese Health Study, in which nut consumption was determined at baseline and cognitive function was measured by the MMSE after 20 years of follow-up, reported an inverse association between graded nut consumption and reduction of cognitive function [49]. However, adjustment for intake of unsaturated fatty acids attenuated the association to non-significance, suggesting mediation of the cognitive effect

by this key nut component. Finally, a large Chinese cohort study assessed nut consumption at baseline and in relation to changes in the MMSE, administered one to three times during a 6-year follow-up; the results showed that higher nut consumption related to a lower risk of cognitive impairment [52]. Conversely, possibly due to the shorter duration, a small prospective Italian study reported that baseline nut consumers versus non-consumers had a borderline reduced rate of developing a low MMSE after follow-up for 3 years [47].

Regarding specific types of nuts in general, walnuts appeared to be the type most studied and reported to be associated with better cognitive function when compared to low or non-consumers [41,43,47]. However, most of the studies assessed the total nut consumption as a whole and did not or could not delineate the analyses by the different types of nuts.

Two of the 15 studies did not show statistically significant associations between nut consumption and cognitive performance. Specifically, in a cross-sectional investigation of an older Norwegian cohort, nuts were non-significantly associated with better cognitive performance, although only 16% of the participants were nut consumers [38]. Additionally, a large U.S. prospective cohort, the Women's Health Study, found no association for changes in cognitive performance in relation to quintiles of total nut consumption over a 4-year follow-up [41].

Overall, the epidemiological evidence suggests nut consumption may be positively associated with cognitive health. Still, the quality of the evidence from these epidemiological studies, which cannot determine causation, may be considered low for several reasons. First, six of the 13 studies with positive results were cross-sectional, and in four investigations reporting a beneficial association between increased exposure to nuts and cognitive performance, the outcome was assessed with the MMSE, exclusive of more precise neuropsychological tests. Second, most studies obtained exposure data from food frequency questionnaires (FFQs) or diet recalls, which have inherent weaknesses with regard to possible measurement error and recall bias [54]. Third, most prospective studies have an additional problem, i.e., nut exposure is assessed only once at baseline, thus missing the effect of any changes in consumption during follow-up. Fourth, tree nut and peanut data were also often reported in combination in the assessments, and information on nut preparation (salting, roasting, etc.) was lacking. Fifth, based on the available data, the prevalence of nut consumers was usually low, with some cohorts reporting only 13 to 30% of the study population consuming at least 1 serving (28 g)/week. Only 2 studies evaluated cohorts that met nut consumption recommendations of 30 or more g/d compared to non-consumers [44,45]. Finally, the amounts of nuts consumed by consumers tended to be relatively low (e.g., 2.9 g/d to $\geq$20 g/d) or were not sufficiently described to be able to provide comprehensive assessments and interpretations to help inform practice.

3.2. Randomized Controlled Trials of Nuts with Outcomes on Cognitive Performance

The results of scientifically sound RCTs are critical for formulating evidence-based dietary recommendations. However, few RCTs have examined the effects of nuts on cognitive outcomes in adults, and even fewer had sufficient statistical power or an intervention period lasting more than 6 months (Table 2). Hence, the level of evidence is still fragmentary.

Table 2. Randomized controlled trials of nuts with outcomes on cognitive performance in adults.

Author, Year	Study Design (Source)	N	Age (Years)	Participant Characteristics	Neuro-Psychological Tests	Nut Dose/Day (Range)	FU	Outcome
Martinez-Lapiscina, 2013 [55]	Parallel (Sub-sample of PREDIMED study)	522	55–80	Men & women at high cardiovascular risk	MMSE and Clock Drawing Test (Administered once at the end of the study)	Mixed nuts, 30 g with MedDiet	6.5 years	MedDiet + nuts: better global cognition compared to control diet.

Table 2. *Cont.*

Author, Year	Study Design (Source)	N	Age (Years)	Participant Characteristics	Neuro-Psychological Tests	Nut Dose/Day (Range)	FU	Outcome
Valls-Pedret, 2015 [56]	Parallel (Sub-sample of PREDIMED study)	334	55–80	Men & women at high cardiovascular risk	Tests of memory, executive function, global cognition (Administered at baseline and end of study)	Mixed nuts, 30 g with MedDiet	4.1 years	MedDiet + nuts: better memory and a tendency to improved executive function and global cognition compared to control diet.
Barbour, 2017 [57]	Crossover	61	Mean 65	Men and women with over-weight/obesity	Tests of memory, executive function, and processing speed	High-oleic acid peanuts, 56–84 g	12 weeks	Short-term memory and verbal fluency improved with the peanut diet compared to control diet.
Dhillon, 2017 [58]	Parallel	86	Mean 31	Men and women with over-weight/obesity	Tests of memory and attention	Almonds, dry-roasted at 15% energy	12 weeks	Cognition similarly improved with the almond and control diets.
Sala-Vila, 2020 [59]	Parallel (WAHA study)	708	63–79	Cognitively healthy	Complete test battery	Walnuts at 15% energy	2 years	No effect on cognitive scores in the whole cohort.
Mustra Rakic, 2022 [60]	Parallel	60	50–75	Healthy adults	CANTAB	Almonds/day: 1.5 oz, 3 oz or 3.5 oz snacks	6 months	No among-group changes in cognitive measures.

Abbreviations: CANTAB, Cambridge neuropsychological test automated battery: taps several cognitive domains, including memory, processing speed, and attention; FU, follow-up; MedDiet, Mediterranean diet; MMSE, Mini-Mental State Examination; N, number of study participants; PREDIMED, PREvención con DIeta MEDiterránea. WAHA, Walnuts And Healthy Aging trial.

Additionally, two of the largest RCTs with the longest follow-up were sub-studies of the PREDIMED trial. In a study conducted in the Navarra recruiting center, two neuropsychological tests assessing general cognition were administered [55]. However, these tests were only administered at the end of the study, following a median 6.5-year intervention period, thus changes over time were not evaluated. The results indicated that the two MedDiets (enriched with olive oil or mixed nuts) were associated with better cognitive outcomes compared to the control diet. In another PREDIMED sub-study carried out in the Barcelona center, a comprehensive cognitive battery was administered both at baseline and at the end of the trial after a median follow-up of 4.1 years [56]. The results showed that values for all cognitive domains declined in participants randomized to the control diet, while composites of memory performance, executive function, and global cognition improved above baseline with the two MedDiets. However, the improvement in executive function and global cognition observed with the nut diet did not reach statistical significance compared to the control diet. The findings demonstrated that a MedDiet supplemented with mixed nuts could delay the age-related decline of memory function.

Two small, short-term RCTs investigated the effect of peanuts [57] and almonds [58] on outcomes of cognitive performance in individuals with overweight or obesity. Surprisingly, given the intervention only lasted 12 weeks, in the study of Barbour et al. [57], the diet enriched with high-oleic acid peanuts resulted in improvements in short-term memory and verbal fluency compared to the control diet. In this trial, blood flow velocity in the middle cerebral artery was measured non-invasively with transcranial Doppler, and results showed that the peanut diet increased cerebrovascular reactivity (i.e., improved endothelial function of brain arteries). On the other hand, in the study by Dhillon et al. [58], almond consumption had no effect on cognitive performance compared to the control diet. In this trial, acute experiments examined whether a high-fat lunch rich in almonds would influence the well-known post-lunch dip in alertness, memory, and vigilance. The findings revealed

that, compared with a high-carbohydrate meal, almond consumption at lunch counteracted in part the postprandial decline in memory, but not that of attention performance [58].

The large walnuts and healthy aging (WAHA) trial tested the 2-year effects of walnut consumption at 15% of daily energy on cognitive performance in healthy older adults from two sites, Barcelona (Spain) and Loma Linda (CA, USA) [59]. The WAHA study failed to find any differences in neurocognitive test scores for perception, language, memory, and frontal function domains or in a composite score of global cognition compared to the control diet. However, post hoc analyses by site revealed improved cognition in participants allocated to the walnut diet in Barcelona, who were more at risk of cognitive impairment than their California counterparts due to lower educational levels and more smoking. Functional brain magnetic resonance imaging (MRI) in a subset of the Barcelona cohort supported the benefit of walnuts on cognition [59]. Finally, a recent small RCT using different doses of almonds for 6 months in cognitively healthy middle-aged and older adults assessed with a complete neuropsychological test battery at baseline, 3 months, and 6 months found no differences in cognitive measures over time [60].

In summary, the findings of the two well powered, long-term, PREDIMED sub-studies examining the effects of MedDiets supplemented with nuts on cognitive performance indicated a beneficial effect in older individuals at high risk of CVD (thus, also at high risk of cognitive impairment and dementia); however, improved cognitive health might not be entirely attributable to nuts, as other components of the MedDiet changed in these studies [55,56]. Nevertheless, the MedDiet enriched with nuts reduced the relative risk of stroke by nearly 50% in the PREDIMED trial [39], which further supports the neuroprotective effect of nuts. Indeed, preventing stroke, post-stroke cognitive impairment, and dementia is critical for achieving optimal brain health [61]. The large, 2-year WAHA trial uncovered a salutary cognitive effect of walnuts only in participants at higher risk of cognitive impairment [59]. These findings concur with data collected in large multi-domain trials suggesting that individuals at high risk of cognitive impairment or who already have memory complaints, or MCI, are those who should be targeted for preventive interventions because they might obtain the largest benefit [62]. Clearly, larger and longer-term studies with nuts in populations at risk of dementia are warranted.

4. Potential Mechanisms of Action of Nuts in Cognitive Health

Normal aging involves many structural and functional brain changes. There are several hallmarks of cerebral atrophy (ventricular enlargement, cortical thinning, sulcal widening, and volume loss [63]), which are observed in parallel with declines in processing speed and certain memory, language, visuospatial, and executive function abilities [64]. Ageing is the primary risk factor for late-onset Alzheimer's disease (AD; occurring in people aged 65 and over) [65]. However, AD should not be considered part of normal aging [66]. What determines the transition from normal aging to AD remains to be elucidated, but there is a long-standing consensus supporting the view of AD as a multifactorial disease [67], with pathological brain changes taking place years (even decades) before symptomatology is present. However, knowledge of AD is rapidly evolving. For many years, AD was conceived as a clinical-pathological construct, defined by the presence of symptoms/signs. The advent of cost-effective biomarkers prompted the re-definition of AD as a clinical-biomarker construct, referring to an aggregate of neuropathologic changes that can be identified in vivo much before clinical symptoms appear [68]. This preclinical phase of AD represents a therapeutic window for preventive strategies, which are of utmost importance, as highlighted by several international organizations [69,70].

Evidence is accumulating on the many diet components that might have a significant impact on the progression and prevention of AD (reviewed in [71]). As discussed, nuts are rich in compounds with anti-inflammatory, antioxidant, and hypolipidemic effects, thereby reducing the risk of CVD [16]. Given that CVD and AD share many risk factors, particularly hypertension, obesity, type 2-diabetes, and smoking [3], it is reasonable to assume that regular nut consumption might also protect against AD. Abundant experimental research

supports this hypothesis (reviewed in [72]). As summarized in the preceding section, epidemiologic evidence, albeit generally of low quality, also concurs with this view, while RCTs of nuts for cognitive outcomes are incipient and confined to changes in cognitive performance after short- or medium-term supplementations. In this section, we will summarize possible mechanisms underlying the putative effects of nut bioactives on the two major hallmarks of AD, namely the buildup in the brain of amyloid-beta (Aβ) plaques and neurofibrillary tangles. We will review experimental research involving either nuts, nut extracts, or nut bioactives given on their own. Additionally, and concurrently with the current needs for research on diet and dementia [73], we will also focus on how available biomarkers might help in better selecting participants to be included in RCTs, and/or as intermediate endpoints, allowing for the detection of subtle changes after short-term interventions.

4.1. Nuts and Extracellular Plaque Deposits of Aβ

4.1.1. Pathophysiologic Overview

According to the amyloid hypothesis [74], derangements in the production, accumulation, or disposal of Aβ are the main cause of AD. Aβ is a ~4 kDa peptide derived from the so-called β-amyloid precursor protein (APP), which is a transmembrane molecule. The enzymatic processes involving the metabolism of APP to Aβ involve a sequential cleavage by two membrane-bound endoproteases, β- and γ-secretase. In the first step, believed to be the rate limiting one, β-secretase (also known as BACE1) cleaves APP to release a large, secreted derivative (soluble peptide APPβ), while a 99-amino acid fragment (C99, also known as the carboxy-terminal fragment of beta [CTFβ]) remains bound to the fatty acid membrane. C99 undergoes a second cleavage by the action of γ-secretase, generating different species of Aβ, those ending at positions 40 (Aβ40) and 42 (Aβ42) being the most abundant ones (~80–90%, and ~5–10%, respectively) (reviewed in [75]). Aβ42 is more hydrophobic than Aβ40 and rapidly aggregates to form monomers and then mature fibrils and dense fibril meshes (senile plaques), the best-known hallmark of AD. However, soluble dimers, trimers, and small oligomeric Aβ42 aggregates other than monomers are increasingly believed to be more neurotoxic than Aβ42 mature fibrils [76]. Aβ deposition spreads from temporobasal and frontomedial areas to the remaining associative neocortex, primary sensory-motor areas, and the medial temporal lobe [77,78].

4.1.2. Nuts and Aβ

Nut bioactives could hamper Aβ plaque build-up by targeting BACE1, γ-secretase, and/or Aβ aggregation (Figure 1A). To the best of our knowledge, while there has been exploration of the association between adherence to the MedDiet and AD biomarkers [79], there has been no assessment of nut consumption and AD, and there are no available clinical nut supplementation studies on this specific topic. In a cellular model of early AD (human SH-SY5Y cells transfected with APP695), treatment with 10 μg/mL of a lipophilic walnut kernel extract for 24 h resulted in a significant reduction in Aβ40 levels when compared to control cells [80]. In line with this finding, in a study testing the in vitro inhibitory effects against BACE1 of 18 different hydroalcoholic ethnomedicinal plant extracts (1 g per 5 mL), leaves (nuts were not tested here) from *Juglans regia* (walnut tree) were found to display a BACE1 inhibitory activity in a concentration-dependent manner [81]. In another in vitro study, the methanolic extract of walnut kernels (4 g per 10 mL) was found to inhibit Aβ fibril formation and defibrillate preformed Aβ fibrils [82]. Finally, reduced Aβ burden was described in experimental studies testing isolated bioactives found in nuts, including oleic acid [83,84], linoleic acid [84], ALA [85], beta-sitosterol [86], nicotinamide [87], ellagic acid [88–90], epigallocatechin [91], myricetin [92,93], caffeic acid [94], and an array of other polyphenols [93].

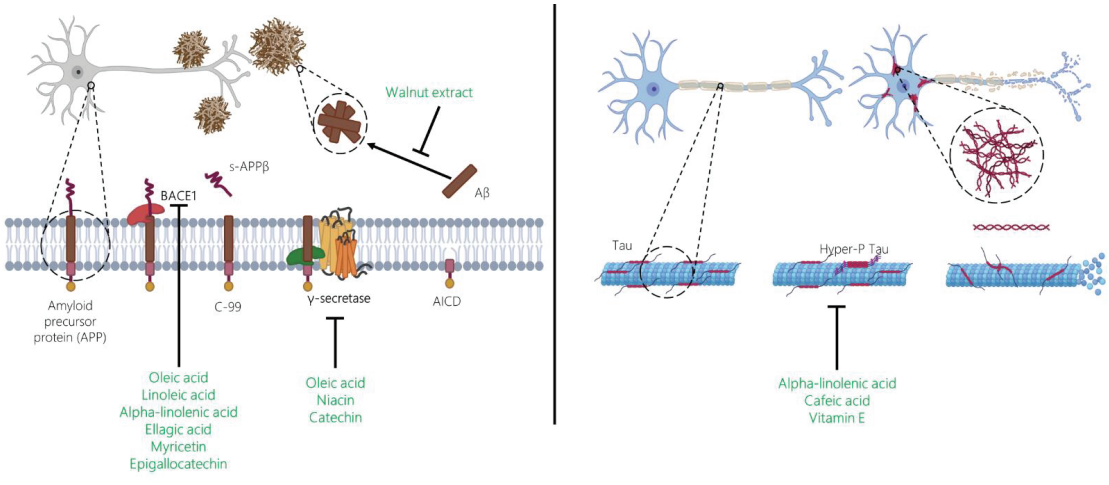

Figure 1. Alzheimer´s Disease Hallmarks (**A**) amyloid-beta (Aβ) deposition and (**B**) neurofibrillary tangles of hyperphosphorylated tau. Effects of nut bioactives on critical pathways are shown.

4.1.3. Potential of Aβ Biomarkers in Future Research on the Neuroprotective Properties of Nuts

The accumulation of Aβ is considered the first detectable change of AD in the brain. It follows that an accurate determination of Aβ is relevant for the etiological diagnosis and for monitoring disease progression. Importantly, it might be a useful tool to identify changes in the rates of amyloid deposition without requiring long-term dietary interventions. Cerebrospinal fluid (CSF) analyses can indicate the presence of amyloid pathology in its earliest stages, although there is growing pressure to develop and validate less invasive blood-based biomarkers. A characteristic feature of AD is the reduction in CSF Aβ42 [95], which becomes evident about 15 years before clinical symptoms appear [96], although it plateaus relatively early in the AD continuum. The ratio Aβ42/Aβ40 in CSF has been repeatedly proven to improve prediction of clinical progression better than Aβ42 alone [97]. On the other hand, positron emission tomography (PET) imaging enables the non-invasive, in vivo assessment and quantification of continued build-up of amyloid burden beyond the CSF plateau, as well as providing information on the spatial distribution of the pathology in the brain [98]. Despite the potential interest of the Aβ42/Aβ40 ratio in CSF (or blood) and amyloid-PET imaging, none of them have been used as secondary outcomes in RCTs of nut supplementation with cognitive changes as primary outcomes.

4.2. Nuts and Neurofibrillary Tangles

4.2.1. Pathophysiologic Overview

The second histopathologic hallmark of AD is the presence of neurofibrillary tangles, which are entirely made up of hyperphosphorylated tau protein. Tau is a microtubule-associated protein that promotes the formation of axonal microtubules, stabilizing them [99]. Tau might undergo phosphorylation at over 70 potential sites [100]. In AD, there is an abnormal tau hyperphosphorylation, which decreases the capacity of the protein to bind microtubules, promoting the destabilization of axons. Hyperphosphorylation also contributes to the detachment of tau, which self-aggregates to form paired helical and straight filaments, leading to the formation of intracellular neurofibrillary tangles [101]. These tangles are initially found in the entorhinal region and subsequently progress to the limbic system and neocortical regions, greatly correlating with cognitive decline [102].

4.2.2. Nuts and Neurofibrillary Tangles

There is a current need to identify interventions capable of reducing tau aggregation by means of stabilizing microtubules, inhibiting tau phosphorylation, or inhibiting fibrillization. As in the case of Aβ, there is no clinical research on nut consumption and tau protein, while experimental research has tested only the bioactives that are present in nuts in isolation. Figure 1B presents the potential impact of specified nut bioactives on tau hyperphosphorylation. One of the most investigated is ALA, the vegetable omega-3 PUFA abundant in walnuts [16,31], which was found to inhibit tau aggregation in an in vitro study [103]. Furthermore, N9 (microglia) cells exposed to ALA increased their ability to better target [104], phagocyte, and degrade extracellular tau [105]. Another bioactive present in nuts tested in relation to tau is caffeic acid. In a study conducted in high-fat diet-induced hyperinsulinemic rats, the administration of caffeic acid (30 mg/kg body weight/day) for 30 weeks significantly reduced the expression of phosphorylated-tau protein in the hippocampus [94]. Similarly, pretreatment of P12 cells with caffeic acid prior to challenge with Aβ attenuated tau phosphorylation [106]. Finally, in a study including both in vitro (primary culture of cortical neurons) and in vitro (APP/PS1 double transgenic mice of AD), exposure to vitamin E reduced the formation of hyperphosphorylated tau through the inhibition of p38MAPK [107].

4.2.3. How Biomarkers Can Help in Future Research

Akin to the use of biomarkers to quantify amyloid burden, the tau landscape is rapidly evolving, with ultrasensitive immunoassays allowing the reliable measurement of tau biomarkers in blood, while second-generation tau-PET tracers are being developed [108]. Patients with AD show increased levels of total-tau and phosphorylated-tau in CSF and blood when compared to healthy controls. Phosphorylated-tau is a more specific AD biomarker than total-tau, which can be increased in neurodegenerative diseases other than AD. Phosphorylation at threonine 181 (so-called p-tau181) is the most widely used tau biomarker, although other tau species, including those phosphorylated in other mid-domain residues (threonine 217, threonine 231), are increasingly used [95]. However, to the best of our knowledge, no RCTs have assessed changes in these biomarkers using nut supplementation.

5. Summary and Future Directions

Epidemiological, clinical, and mechanistic evidence, while limited and inconclusive, suggests a possible role for nuts in the maintenance of cognitive health and prevention of cognitive decline in individuals across the lifespan, particularly in older adulthood. Given the potential beneficial impact of nuts on cognitive health, their consumption within a healthy dietary pattern may offer a simple public health strategy for the prevention of cognitive decline in most individuals.

Still, the limitations of the presently available evidence should be acknowledged and considered for future research. There is a dearth of research on nuts and cognition, especially in individuals under 60 years of age, and no study has examined whether nut containing diets influence hard clinical outcomes (e.g., dementia or AD) [109]. On the basis of the strength of the evidence on nut/walnut consumption and heart disease, the US Food and Drug Administration issued qualified health claims for nuts in 2003 [110] and for walnuts in 2004 [111], stating that "supportive but not conclusive research shows that eating 1.5 ounces per day of nuts/walnuts, as part of a low saturated fat and low cholesterol diet and not resulting in increased caloric intake, may reduce the risk of coronary heart disease". Research in the last two decades has indeed confirmed this beneficial effect for total nuts and walnuts [16], and more recently, a similar qualified health claim was issued for macadamia nuts [112]. Given the shared risk factors between common heart and brain diseases and the manifold salutary effects and safety of nut consumption, and pending additional evidence, this recommendation may also be applied for the prevention of cognitive decline and dementia.

Future large RCTs among healthy pregnant women, children or adolescents, and, particularly, older adults at risk of cognitive decline could provide a new and important public health dimension about simple nutritional recommendations for an entire population. There is a need to develop the area of research on nut consumption and neurodevelopment with a special focus on windows of vulnerability and opportunity, such as the pregnancy, childhood, and adolescence periods, as even if only a small positive cognitive effect is found, this may have significant implications at the population level from a public health perspective. Concerning the evidence currently available, a key methodological limitation is the low accuracy of the screening instruments commonly used to assess cognitive function, such as the MMSE, which compromises the ability to draw firm conclusions. Given that experimental research has tested only bioactives that are present in nuts in isolation, studying the build-up of Aβ plaques and neurofibrillary tangles may provide an avenue to address the limitations of neuropsychological tests. There is a current need to clinically identify if nut interventions may reduce Aβ plaque build-up and tau aggregation by stabilizing microtubules, inhibiting tau phosphorylation, or inhibiting fibrilization. Further research is warranted to elucidate the impact of nut consumption on brain health and better inform cognitive health-related practices and guidelines.

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nutrients

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Review

Dried Fruits, Nuts, and Cancer Risk and Survival: A Review of the Evidence and Future Research Directions

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Abstract: Dried fruits and nuts contain high amounts of nutrients and phytochemicals—all of which may have anticarcinogenic, anti-inflammatory, and antioxidant properties. This narrative review summarizes the evidence for dried fruits and nuts and cancer incidence, mortality, and survival and their potential anticancer properties. The evidence for dried fruits in cancer outcomes is limited, but existing studies have suggested an inverse relationship between total dried fruit consumption and cancer risk. A higher consumption of nuts has been associated with a reduced risk of several site-specific cancers in prospective cohort studies, including cancers of the colon, lung, and pancreas, with relative risks per 5 g/day increment equal to 0.75 (95% CI 0.60, 0.94), 0.97 (95% CI 0.95, 0.98), and 0.94 (95% CI 0.89, 0.99), respectively. A daily intake of total nuts of 28 g/day has also been associated with a 21% reduction in the rate of cancer mortality. There is also some evidence that frequent nut consumption is associated with improved survival outcomes among patients with colorectal, breast, and prostate cancer; however, further studies are needed. Future research directions include the investigation of additional cancer types, including rare types of cancer. For cancer prognosis, additional studies with pre- and postdiagnosis dietary assessment are warranted.

Keywords: dried fruits; tree nuts; peanuts; cancer; cancer survivors; mortality; review

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1. Introduction

Globally, an estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred in 2020 [1]. In the next two decades, the cancer burden is projected to increase by 47% to 28.4 million new cancer cases in 2040 [1]. This estimate is solely based on the growth and aging of the population and may be further exacerbated by an increasing prevalence of risk factors in many parts of the world [1].

Factors such as consuming a healthful diet, being physically active, avoiding tobacco use, and maintaining a healthful weight can have a strong influence on cancer prevention [2]. It has been estimated that approximately 50% of cancer cases can be prevented [3]. However, international cancer statistics continue to show that up to 80% of the cancer burden in high-income countries could be preventable in principle [4]. Therefore, there is considerable interest in studying the impact of lifestyle changes, in particular, the impact of changes

in diet, on cancer development and progression [3]. There is compelling evidence that nutrition has substantial effects on the incidence and progression of cancer [5].

This narrative review summarizes the evidence for dried fruits and nuts and cancer incidence, mortality, and survival and their potential anticancer properties. In addition, the gaps that exist in the literature and recommendations for future research are discussed. The steps of study selection are described in Supplementary Figure S1.

2. Dietary Strategies to Prevent Cancer

Few countries have optimal diets for cancer prevention [6]. For example, analysis of diets by the Alternate Healthy Eating Index reveals suboptimal global levels due to either a relatively high consumption of red meat, added sugars, and transfat or a relatively low consumption of fruits, vegetables, nuts, and whole grains [7]. Suboptimal diets are estimated to cause 1.6 million preventable cancer deaths annually [7].

Nearly every authoritative health body recommends increased fruit intake for preventing cancer and chronic disease risk. The International Agency for Research on Cancer/World Health Organization (IARC/WHO) Report estimated that ~5% of cancer deaths in the U.S. are due to low fruit and vegetable consumption [6]. The U.S. Dietary Guidelines for Americans recommends 2 cups of fruit equivalents/day per 2000 kcal where $\frac{1}{2}$ cup of dried fruit is 1 equivalent [8]. The U.S. Food and Drug Administration (FDA) also allows for a fruit and cancer claim provided the fruit meets the nutrient content requirements for a "good source" of at least vitamin A, vitamin C, or dietary fiber [9]. The model wording of the claim reads, "*Development of cancer depends on many factors. Eating a diet low in fat and high in fruits and vegetables, foods that are low in fat and may contain vitamin A, vitamin C, and dietary fiber, may reduce your risk of some cancers. Oranges, a food low in fat, are a good source of fiber and vitamin C*" [9]. The IARC/WHO European Code Against Cancer recommends the consumption of whole grains, pulses, vegetables, and fruits for cancer prevention [10].

Nuts, encompassing tree nuts and compositionally related peanuts, are also widely recommended for consumption as nutrient-dense foods [6,8,11]. The World Cancer Report associates dietary patterns containing high intakes of fruits and nuts with the reduction of colorectal cancer risk [6]. Several FDA-qualified claims about diet and cancer risk are relevant to the components found in dried fruit and nuts. Furthermore, other agencies have highlighted the importance of dietary bioactives in cancer prevention. The American Cancer Society guidance for consumers states, "Fruit and non-starchy vegetables contain a large number of potential anti-tumorigenic agents, such as dietary fiber, carotenoids" [11,12]. The World Cancer Research Fund International has published, "Fruit and non-starchy vegetables contain a large number of potential anti-tumorigenic agents", among dietary guidance for cancer prevention [13].

3. Dried Fruits and Cancer

Many types of dried fruits are consumed worldwide. Globally, the most common dried fruits are raisins, dates, prunes, apricots, and figs [14]. However, other specialty dried fruits are produced, including sweetened-dried cranberry and high-value, freeze-dried fruits and powders. Globally, the Middle East and Europe account for half of dried fruit consumption [14]. In the U.S., dried fruit contributes <4% of total fruit intake, whereas juice and fresh or other nondried forms are more commonly consumed [15]. For this review, we mainly focus on cancer prevention through the most common dried fruits.

3.1. Preclinical Studies Relating Dried Fruits and Cancer

Cancer develops through many mechanisms. Preclinical studies have revealed that dried fruit may prevent cancer at the stage of initiation through the induction of detoxification enzymes and reducing the impact of carcinogens and environmental stress; during promotion by inhibiting oxidative stress and inflammation; and at the stage of progression by inducing apoptosis [16]. Mechanistic data from in vitro studies are available for raisins [17,18], apricots [19,20], figs [21,22], prunes [23,24], and dates [25,26] and in vivo for

figs [27], dates [28], prunes [29], and apricots [30]. As reviewed elsewhere, these studies cover gastric, colon, breast, liver, bone, prostate, renal, and testicular cancers [16]. Furthermore, fruit bioactives have a direct impact on cancer-related factors, including antioxidant and anti-inflammatory activity and improved gut immune function in preclinical studies [16,31–33]. These functionalities may reduce cancer by inhibiting the risk of cancer initiation and progression and by improving survival.

Dried fruits contain fiber, micronutrients, and bioactives that may contribute to cancer chemoprevention, as summarized in a companion article [34]. Dried fruits contain a diverse number of bioactives, including phenolics, carotenoids, and terpenoids [16]. The drying process itself impacts the profile, abundance, and possibly the bioaccessibility of bioactives in dried fruits. For example, freeze-drying may retain bioactives more so than forced-air or sun-drying processes [35]. Heat can increase the formation of melanoidins, especially during the production of raisins [36]. Fruit melanoidins are poorly described but function as antioxidants and accumulate polyphenols into complex polymers. Thermal processing of dried fruits (and nuts) also increases the content of advanced glycation endproducts (AGEs) as compared to unprocessed fruits and nuts [37]. AGEs may play a role in carcinogenesis [38]. However, a large, multinational, prospective cohort study across 20 anatomical cancer sites reported that a higher intake of dietary AGEs was not associated with an increased risk of overall cancer and most cancer types studied. A nonlinear, weak positive association was observed between higher AGE intake and the risk of prostate cancer [38]. The addition of sulfites during processing inhibits melanoidin formation [39] and therefore may alter the profile of bioactives when used in the fruit drying process.

Drying may also impact the structure and accessibility of soluble fibers and bioactives from fruit. In vitro digestion of different dried fruits may increase or decrease the release of antioxidants [40]. In mice, the consumption of nonextractable phenolics from dried berries increases colonic polyphenol content more so than the consumption of freely extractable polyphenols [41]. Therefore, drying may also impact the accessibility of fiber-associated phenolics and other bioactives that could subsequently affect the gut microbiota and intestinal immune system. Further studies are needed to link dried fruit processing parameters to cancer prevention activities.

3.2. Human Intervention Studies of Dried Fruits and Cancer

The evidence from human intervention studies for cancer prevention by dried fruit consumption is very limited. Thus far, human intervention studies with dried fruits have focused on cardiometabolic health or other chronic diseases [42–44]. Some evidence is available for the function of high-value, freeze-dried berry products in healthy individuals and those with colorectal, oral, and prostate cancers [45–50]. However, these forms of dried fruit are not commonly consumed and have a profile of bioactives similar to fresh fruits, which differs from more commonly available and consumed dried fruits produced via processes that utilize heat during drying.

3.3. Epidemiological Studies of Dried Fruits and Cancer

3.3.1. Cancer Incidence (or Risk)

Few epidemiological studies have directly assessed the relationship between dried fruits and cancer risk. A systematic review of observational studies published through 2018 found insufficient studies to perform a meta-analysis [51]. The review identified 16 studies with 12,732 cases from 437,298 participants that assessed cancer risk and the intake of total dried fruits or specifically raisins, prunes, dates, or figs [51]. Among the prospective studies, there was an inverse relation between total dried fruit consumption and cancer incidence in seven studies with a significant, dose-response trend identified in three studies on pancreatic cancer, prostate cancer, and colorectal polyps [51]. Among the case–control studies, there were inverse associations of cancer incidence with total dried fruits, raisins, or dates, with five of seven studies reporting significant associations [51]. Among these studies, dried fruit intake was associated with reduced stomach cancer,

pancreatic cancer, and colorectal cancer incidence (for dates but not other dried fruits), nasopharyngeal cancer incidence (raisins but not dried figs, which increased risk), and bladder cancer incidence [51]. Where dried fruit intakes were compared with fresh fruit intakes, dried fruit was more protective than fresh fruit in five of seven prospective studies and three of four case–control studies [51].

Prospective cohort studies conducted in the Netherlands have shown no association between total dried fruit intake and urothelial [52], stomach [53], and prostate [54] cancer incidence. In contrast, consumption of prunes was associated with increased colorectal cancer risk in the Nurses' Health Study and Health Professionals' Follow-up Study (RR (95% CI) for women: 1.46 (0.93, 2.31) and for men: 1.73 (1.20, 2.50)) [55]. Several prospective analyses conducted in cohorts of Californian Seventh Day Adventists have shown that the frequency of dried fruit intake is associated with a lower risk of cancer [56–58]. In the Adventists Health Study 1, intake of raisins, dates, and other dried fruits ≥3 times/week was associated with a 65% reduction (relative risk (RR) (95% CI): 0.35 (0.17, 0.73)) in the relative risk of fatal pancreatic cancer compared to intake less than once per month [56]. In an analysis of the Adventists Health Study 1 and 2, dried fruit intake ≥3 times/week was associated with 24% lower odds of rectal/colon polyps (odds ratio (OR) (95% CI): 0.76 (0.58, 0.99)) compared to intake less than once per week [57]. Finally, intake of raisins, dates, or other dried fruits ≥5 times/week was associated with a lower relative risk of prostate cancer after adjustment for age ((RR (95% CI): 0.51 (0.31, 0.85)) compared to intake <1 time/week; however, the relationship was attenuated after further adjustment for education and other dietary factors (RR (95% CI): 0.62 (0.36, 1.06)) [58]. In an analysis of Adventist Health Study 1, no association was observed between dried fruit intake and lung cancer [59].

Recent epidemiological studies in other populations have investigated dried fruit intake and cancer risk (Table 1).

Table 1. Epidemiological studies assessing the association between dried fruit intake and cancer risk published since 2019.

Study Type	Participants	Cancer Type	Outcome (95% CI)	Reference
Systematic review	*n* = 437,298 from 16 studies	Pancreatic, prostate, colorectal polyps	Dose-response trend from prospective studies	Mossine et al., 2020 [51]
		Stomach, pancreatic, colorectal, nasopharyngeal, bladder	Total dried fruit, raisins, or dates reduced incidence from case–control studies	
Cohort	UK Women's Cohort Study (*n* = 35,372 women aged 35–69 in England, Wales, and Scotland)	Breast	HR 1.04 (0.98,1.13)	Dunneram et al., 2019 [60]
		Endometrial	HR 0.60 (0.37, 0.97)	
		Ovarian	HR 1.06 (0.89, 1.26)	
Prospective cohort	National Institutes of Health-American Association of Retired Persons Diet and Health Study (*n* = 485,403 men and women aged 50–71 at baseline in the United States)	Liver	HR (Q5 vs. Q1) 0.73 (0.60, 0.89)	Zhao et al., 2022 [61]

Table 1. *Cont.*

Study Type	Participants	Cancer Type	Outcome (95% CI)	Reference
Mendelian randomization	UK Biobank (*n* ~500,000 men and women aged 49–69 in the United Kingdom)	Oral cavity/pharyngeal	IVW OR 0.17 (0.04, 0.69)	Jin et al., 2022 [62]
		Lung	IVW OR 0.33 (0.17, 0.64)	
		Squamous cell lung	IVW OR 0.23 (0.09, 0.60)	
		Breast	IVW OR 0.47 (0.32, 0.68)	
		Pancreatic	IVW OR 0.03 (0.001, 0.68)	
		Cervical	IVW OR 0.99 (0.9897, 0.9998)	
		Lung adenocarcinoma, endometrial, thyroid, prostate, bladder, brain	IVW OR not significant	

Abbreviations: HR, Hazard ratio; IVW, Inverse variance weighted; OR, Odds ratio.

The risk of breast, endometrial, and ovarian cancer was assessed in the prospective UK Women's Cohort study of *n* = 35,372 women [60]. After 18 y of follow-up in participants aged 35–69, total dried fruit intake was associated with reduced risks of endometrial cancer (hazards ratio (HR) (95% CI): 0.60 (0.37, 0.97)) and postmenopausal endometrial cancer (HR (95% CI) 0.55: (0.31, 0.98)). Total dried fruit intake was not related to breast or ovarian cancer risks; total fruit intake was not associated with breast, endometrial, or ovarian cancer risks.

Dried fruit intake and cancer risk were evaluated in the National Institutes of Health-American Association of Retired Persons Diet and Health study, which included 485,403 participants who were 50–71 years old [61]. In this study, dried fruit intake was associated with lower RR (95% CI) of both liver cancer (0.73 (0.60, 0.89)) and chronic liver disease mortality (0.59 (0.48, 0.73)) [61].

A two-sample Mendelian randomization study utilized ~500,000 samples from the UK Biobank database to investigate dried fruit intake and cancer risk [62]. In this data set, for one standard deviation increase in genetically predicted dried fruit intake, a reduced risk was observed for oral cavity/pharyngeal cancer, lung cancer, squamous cell lung cancer, breast cancer, pancreatic cancer, and cervical cancer [62].

Case–control analyses conducted in Australia, Jordan, Spain, and Turkey showed relationships between dried fruit intake and cancer incidence. An Australian case–control analysis reported that individuals with pancreatic cancer (cases) had a significantly lower intake of raisins than controls [63]. In a case–control study conducted in Jordan, a daily intake of dates (OR (95% CI): 0.52 (0.27, 0.98)) was associated with lower odds of colorectal cancer; total dried fruit intake was not associated with colorectal cancer risk [64]. In a case–control analysis conducted in Spain, a higher intake of dried fruits was associated with lower odds of gastric cancer (OR (95% CI): 0.40 (0.20, 0.80)) [65]. Likewise, in a Turkish case–control study, a higher intake of dried fruit was associated with a lower risk of gastric cancer [66].

3.3.2. Cancer Mortality and Survival

Increased fruit intake is associated with reduced cancer mortality. A meta-analysis of 26 cohort studies reported that an intake of five servings of fruits and vegetables relative to the reference level of two servings had a hazard ratio (HR) (95% CI) of 0.90 (0.86, 0.95) for cancer mortality [67]. Few studies have directly analyzed dried fruits and cancer mortality.

A meta-analysis published in 2017 identified only two studies on dried fruit and total cancer mortality risk and found a nonsignificant association (RR (95% CI): 0.89 (0.61, 1.30)) [68].

3.4. Research Gaps, Needs, and Priorities Related to Dried Fruits and Cancer

Although fruits are currently recommended for cancer prevention, more research is needed to understand the specific contributions and mechanisms of dried fruit intake and cancer prevention. Additional epidemiological studies are needed to assess dried fruit intake and additional cancer types. Dried fruit is often not treated as a separate subcategory of total fruit intake when assessing dietary intake, which hinders the ability to assess cancer risk and dried fruit intake in epidemiological studies [51]. Sufficient dried fruit intake in a study population should be considered. Although the intake on a g/day basis may be low, higher frequency intake of 3+ to 5+ times/week, such as in the AHS [57], may be considered reasonable intake frequencies to detect inverse associations between dried fruit consumption and cancer risk. At lower frequencies of intake, e.g., less than weekly, associations may be more difficult to detect. Furthermore, dried fruit intake is also difficult to describe since the composition and methods used to process dried fruit vary. Therefore, new assessment tools or biomarkers are needed to accurately assess intake.

Additional preclinical and mechanistic studies are needed. However, greater attention to the design of nutritionally relevant studies is needed considering that many fruit bioactives are metabolized before reaching tissues and organs [69]. Identifying specific mechanisms by which dried fruit may impact cancer risk can inform the design of mechanistic intervention studies. Relating specific bioactives in dried fruits to preventive mechanisms is desirable. For example, the World Cancer Report links the intake of fruit carotenoids with a reduced risk of estrogen receptor-negative breast tumors [6,70]. Additional human studies are needed to understand how other bioactives in dried fruits affect cancer risk and survival. Assessing dried fruit bioactives and their metabolites in tissues and plasma in human studies can lead to new mechanistic insights and dietary recommendations. Lastly, future human intervention studies are needed to clarify the role of dried fruit in primary prevention, secondary prevention, or improving the quality of life in cancer patients.

4. Tree Nuts, Peanuts, and Cancer

A holistic view of the evidence shows that most diets that are protective against cancer are rich in foods of plant origin [2]. Relatively unprocessed foods of plant origin are rich in nutrients and dietary fiber. Higher consumption of these foods instead of processed foods and sugars could protect against weight gain, overweightness, and obesity [71] and therefore protect against obesity-related cancers, such as postmenopausal breast, colorectum, liver, thyroid, pancreas, endometrium, and kidney cancer [2]. A higher consumption of nuts has been associated with less weight gain in adults as summarized in a systematic review and meta-analysis of prospective cohorts and randomized controlled trials [72]. Nuts, including tree nuts (almonds, hazelnuts, and walnuts) and peanuts, contain high amounts of nutrients such as unsaturated fats, protein, vitamins (e.g., α-tocopherol, folate, and niacin), nonsodium minerals (e.g., magnesium, calcium, and potassium), and phytochemicals—all of which may have anticarcinogenic, anti-inflammatory, and antioxidant properties. Nuts, and walnuts, in particular, have also been shown to modulate the microbiota by increasing gut microbial diversity [73], and new mechanistic hypotheses on diet and cancer relationships include interactions between host and environmental factors in selecting the microbiota that in turn influence carcinogenesis [74].

4.1. Preclinical Studies Related to Nuts and Cancer

In vitro and in vivo studies to determine whether nuts can help combat cancer are instrumental to understanding potential mechanisms and whether results are coherent with studies in humans.

Preclinical studies for breast cancer have demonstrated reduced growth and multiplicity of breast cancer tumors in relation to walnuts or the main compounds characteristic of

walnuts, such as melatonin [75,76]. Potential mechanisms for cancer prevention include the suppression of proliferation, alterations in cell signaling pathways involved in cell differentiation and apoptosis, and selective inhibition of some cyclooxygenase and lipoxygenase activities [75–77].

Preclinical studies for colon cancer suggest that consumption of mixed nuts, walnuts, and almonds inhibits DNA damage and tumor growth through the suppression of angiogenesis, proliferation, and inflammation, as well as increased apoptosis and favorable alterations to the gut bacteria and enterotype-like clusters [78–83]. In line with the latter, a cross-sectional study among 222 Koreans showed that a healthy dietary pattern characterized by higher intakes of nuts/seeds was related to higher α-diversity reflecting gut microbial health [84].

In vivo and in vitro models for prostate cancer suggest that diets containing walnuts and almonds may reduce the risk of prostate cancer through declines in plasma levels of IGF-1, resistin, LDL-cholesterol, oxidative stress, and inflammation, and increased expression of tumor suppressors [85–87].

Bioactives in nuts with anticancerogenic potential that have been studied in preclinical studies include lipid-associated components [82], such as ellagic acid, which is a dietary flavonoid polyphenol abundant in walnuts and pecans [80], and melatonin found in walnuts along with polyunsaturated fatty acids, which are abundant in nuts in general [76]. Another bioactive nutrient in nuts is selenium, for which Brazil nuts are one of the richest known food sources [88]. In a 2023 preclinical study in mice, selenium-rich Brazil nuts and selenomethionine dietary supplementation reduced mammary tumor growth [89]. Another aspect to highlight is that differences in the composition of bioactives across various types of nuts likely translate into different potential anticancer properties.

These potential anticancer properties of nuts based on preclinical studies are summarized in Table 2.

Table 2. Potential anticancer properties of nuts based on preclinical studies.

Author Year	Cancer Model	Putative Mechanism of Nuts Dietary Factor	Dietary Factor
Breast Cancer-Related Studies			
Hardman and Ion 2008 [90]	Human breast cancer tumors in nude mice	Suppression of cell proliferation or suppression of metastasis	18% of dietary calories from walnuts
Hardman et al., 2011 [75]	C(3)1 TAg transgenic mice, breast cancer	Alterations in cell signaling related to proliferation, differentiation, and apoptosis	Walnuts in the diet
Garcia et al., 2015 [76]	Implanted mammary gland adenocarcinoma in BALB/c mouse model	Inhibition of cyclooxygenase and lipoxygenase	6% walnut oil or 6% walnut flour containing phytomelatonin
Chen et al., 2015 [77]	Breast cancer cells	Growth inhibition of breast cancer cells through cell cycle arrest and inhibition of proliferation	Ellagic acid that is abundant in walnuts
Colorectal Cancer-Related Studies			
Hong et al., 2022 [78]	Colonic cell proliferation, apoptosis, and gene expression in rat model	Reduced DNA damage possibly via downregulation of RelA inflammation gene expression without changes to colonic cell proliferation and apoptosis	Mixed nuts in the diet

Table 2. *Cont.*

Author Year	Cancer Model	Putative Mechanism of Nuts Dietary Factor	Dietary Factor
Chen et al., 2020 [79]	Mouse tumor bioassay after colonotropic carcinogen exposure	Favorably altering the gut microbiota	Walnuts in a Western diet
Nagel et al., 2012 [80]	HT-29 human colon cancer cells in nude mice	Inhibition of tumor growth rate through suppression of angiogenesis	Walnut and flaxseed oil
Nakanishi et al., 2016 [81]	Mice treated with organotropic colon carcinogen	Tumor suppression associated with alterations in gut bacteria	Dietary walnut of up to 15% of total caloric intake
Davis and Iwahashi 2001 [82]	Aberrant crypt foci (ACF) in rats treated with azoxymethane	ACF and cell turn over reduced	Whole almond-, almond meal- or almond oil-containing diet
Prostate Cancer-Related Studies			
Davis et al., 2012 [85]	Transgenic adenocarcinoma of the mouse prostate (TRAMP)	Reduced TRAMP mouse prostate cancer growth and size; declines in plasma IGF-1, resistin, and LDL	Whole almonds as part of a high-fat diet
Kim et al., 2014 [86]	TRAMP	Reduced TRAMP mouse prostate cancer growth and size; improved insulin sensitivity and effects on cellular energy status, tumor suppression	Whole walnuts, walnut oil
Reiter et al., 2013 [87]	Implanted tumor model in nude mice	Reduced number and growth of LNCaP human prostate cancer cells; decreased oxidative stress	Standard mouse diet supplemented with walnuts

4.2. Human Intervention Studies of Nuts and Cancer

Several nuts have been evaluated in human intervention studies for cancer-relevant outcomes. These studies have illustrated that both long- (>2 months) and shorter-term (≤8 weeks) consumption of nuts may modulate biochemical pathways relevant to cancer prevention and reduce cancer progression.

In a randomized, controlled trial involving 4282 women aged 60 to 80 years at high cardiovascular disease risk, a Mediterranean diet supplemented with mixed nuts (30 g/d: 15 g walnuts, 7.5 g hazelnuts, and 7.5 g almonds) vs. the advice to follow a low-fat diet was associated with a risk reduction of first invasive breast cancer with a hazard ratio of 0.59 (95% CI: 0.26 to 1.35) [91]. However, this association was not significant, most likely due to a small number of incident cases (n = 35) during the relatively short follow-up of 4.8 years [91].

In a randomized clinical trial involving 32 participants (>50 years of age), Hu et al. found that a 6-week intervention with Brazil nuts (6 nuts/day) or green tea extract alone affected gene expressions associated with selenoproteins, WNT signaling, inflammation, and DNA methylation comparing baseline to end levels after 6 weeks [88], all of which are genetic and epigenetic biomarkers related to colorectal cancer development. Brazil nuts are also an excellent source of selenium, and there is evidence from observational studies in humans that selenium intake/status may play a protective role in colorectal cancer development in European populations where selenium status is lower as compared to the USA [92]. However, a large prevention trial (SELECT) in North America failed to show any reduction in cancer incidence, cancer mortality overall, or for specific cancers, including prostate, lung, or colorectal cancer with selenium supplementation [93].

In a randomized crossover study in 40 middle-aged men, no significant difference between mean prostate-specific antigen (PSA) levels at the conclusion of the 6-month walnut-supplemented diet phase (1.05 mu g/L, 95% CI [0.81, 1.37]) and the conclusion of the 6-month Western-type control diet phase (1.06 mu g/L, 95% CI [0.81, 1.38]) (p = 0.86) was observed [94].

In contrast, in an 8-week walnut supplementation time course experiment to examine the effects of walnuts on serum tocopherols (T) and PSA in 21 men, a significant decrease in the α-T: γ-T ratio with an increase in serum γ-T and a trend towards an increase in the ratio of free PSA: total PSA was observed, which suggests that walnuts may improve biomarkers of prostate and vascular status [95].

Jia et al. investigated the effects of almond consumption on DNA damage and oxidative stress among thirty regular cigarette smokers randomly divided into three groups [96]. After four weeks, lower levels of urinary 8-hydroxy-2′-deoxyguanosine (8-OH-dG) and single-strand DNA breaks and lower malondialdehyde levels, a surrogate oxidative stress marker, were observed in the two almond-treated groups compared with the control group that did not receive any almonds [75].

In addition, emerging evidence based on randomized, controlled trials suggests that nut consumption has a favorable impact on the gut microbiota [73]. A meta-analysis of randomized controlled trials including 9 trials (almonds, n = 5; walnuts n = 3; and pistachios, n = 1) showed that nut consumption significantly increased the relative abundances of butyrate-producing bacteria, such as *Clostridium*, *Lachnospira*, and *Roseburia*, that have been associated with the prevention of cardiometabolic diseases and certain cancers, such as colorectal cancer. For example, in a randomized, controlled crossover study in healthy Caucasian adults (n = 194), 8 weeks of walnut consumption (43 g/day) compared to a nut-free diet significantly enhanced gut microbial diversity [97].

4.3. Epidemiological Studies of Nuts and Cancer

4.3.1. Cancer Incidence

In a 2021 systematic review and dose-response meta-analysis, a higher intake of total nuts (per 5 g/day increment) was associated with a lower incidence of cancers of the colon, lung, pancreas, and breast with relative risks equal to 0.75 (95% CI 0.60–0.94), 0.97 (95% CI 0.95–0.98), 0.94 (95% CI 0.89–0.99), and 0.98 (95% CI 0.96–0.99), respectively [98]. A lower incidence of several other types of cancer was also observed comparing the highest vs. lowest intake of total nuts, including cancers of the esophagus, stomach, rectum, liver, ovaries, endometrium, and leukemia; however, the relative risk estimates were imprecise and included the null; hence, no firm conclusions for these cancers can be drawn yet. In addition, for some cancer sites (e.g., colon, breast), results from case–control studies (which are more likely to be affected by recall and selection biases than cohort studies) were combined with those from cohort studies in this meta-analysis [98]; thus, additional prospective cohort studies are needed. These findings are largely similar to a 2020 meta-analysis of prospective studies with the exception of breast cancer where no association with intake of total nuts was observed [99]. A 2023 meta-analysis that included only prospective studies reported an inverse association between total nut intake (highest vs. lowest) and the risk of cancers of the lung and stomach with pooled relative risks equal to 0.86 (CI: 0.81–0.91) and 0.79 (95% CI: 0.68–0.91), respectively [100]. The few cohort studies that investigated the association between nut consumption and total cancer incidence in cohorts from Europe and the USA with more than 20 years of follow-up and more than a total of 60,000 incident cancer events reported no clear association of 5+ times per week vs. never/or almost never consuming a serving of nuts [101–103].

4.3.2. Cancer Mortality and Survival

In an umbrella review of epidemiological evidence that included 49,161 cancer deaths, a daily intake of 28 g/d nuts was inversely associated with cancer mortality with an RR of 0.89 (95% CI: 0.83–0.94) [104]. The proportion of variability due to between-study heterogeneity was low (I^2: 23%), and the strength of the evidence was rated as moderate (AMSTAR-2) [104]. The authors reported slightly stronger inverse associations with cancer mortality for tree nuts than for peanuts [104]. These findings are in line with previous systematic reviews and meta-analyses of prospective studies [100,105–108]. For example, Chen et al. [105] estimated a summary RRs for high (5+ servings/week) compared with low nut (never/almost never) consumption of 0.87 (95% CI: 0.80–0.93) for cancer mortality (11 studies 21,353 deaths), while Aune et al. reported a summary estimate of 0.83 (95% CI: 0.75–0.92) per 28 g/d for cancer mortality [106]. When updating the latter analysis by adding results from 6 additional cohort studies that have since been published [109–114] (Supplementary Table S1), the summary estimate was 0.87 (95% CI: 0.81–0.94, I^2 = 60%, n = 13) per 28 g/d (Figure 1A) based on data from 13 cohort studies (12 publications), and there was evidence of nonlinearity ($P_{\text{nonlinearity}}$ = 0.005) with most of the reductions in risk observed with an intake of 15–20 g/day (Figure 1B).

There is also evidence that among patients with cancer, frequent consumption of nuts may be linked to lower mortality from all causes. In the Health Professionals Follow-up Study, frequent nut intake (5 or more times per week; serving size: 28 g) among patients with prostate cancer was associated with a lower risk of dying from prostate cancer and from all causes by more than 30 percent compared to the men who ate nuts once or less a month [115].

In a prospective study among 3449 long-term breast cancer survivors with 374 deaths, including 252 breast cancer deaths, total nut intake $\geq$ 17 g/week compared to nonconsumption was inversely associated with overall survival (OS) (HR (95% CI): 0.74 (0.52, 1.05)) and disease-free survival (DFS) (0.48 (0.31, 0.73)), and these associations did not vary by nut type [116].

Among 826 patients with stage III colon cancer in a prospective, observational study, compared to nonconsumers, patients who consumed $\geq$ 2 servings of nuts (1 oz per serving) per week had an HR (95% CI) of 0.43 (0.25, 0.74) for OS, of 0.58 (0.37, 0.92) for DFS, and 0.70 (0.42, 1.16) for recurrence-free survival (RFS) compared to nonconsumers [117]. When cumulative averages of nut consumption before and after diagnosis were used for the statistical analysis, the corresponding HRs (95% CIs) were 0.43, (0.30–0.61), 0.45 (0.33–0.62), and 0.46 (0.32–0.64), respectively, suggesting the importance of repeated dietary assessments [110]. Subgroup analyses showed that the beneficial effects of nut intake were particularly attributable to tree nut intake [117]. Similarly, in a prospective, observational study among 1404 long-term colorectal cancer survivors, compared to the lowest nut intake (1st quintile), the highest nut intake (5th quintile) postdiagnosis was inversely associated with OS (HR (95% CI): 0.48 (0.31, 0.75) [118].

4.4. Research Gaps, Needs, and Priorities Related to the Study of Nuts and Cancer

Considering the current evidence of the relationship of nut consumption with cancer risk and mortality where nut consumption is often only assessed at baseline, and potential changes in consumption patterns over time are missed, more research with improved exposure assessment is warranted. This should include repeated assessment of the intake of specific types of nuts and improved quantification. Better biomarkers of nut consumption would also help to further investigate the promising observations of the putative chemopreventive effect of nuts in cancer development, including secondary and primary cancer outcomes. Furthermore, there is a need to investigate additional cancer types, including thyroid, kidney, or head and neck, and outcome-wide analyses across cancer sites could provide answers relatively quickly. The multifaceted nature of cancer risk and the variety of cancer chemopreventive mechanisms suggest that nuts may have different effects among

cancer subtypes. To address the heterogeneity across studies and investigate rare types of cancer, a pooling of prospective cohorts could be a way forward.

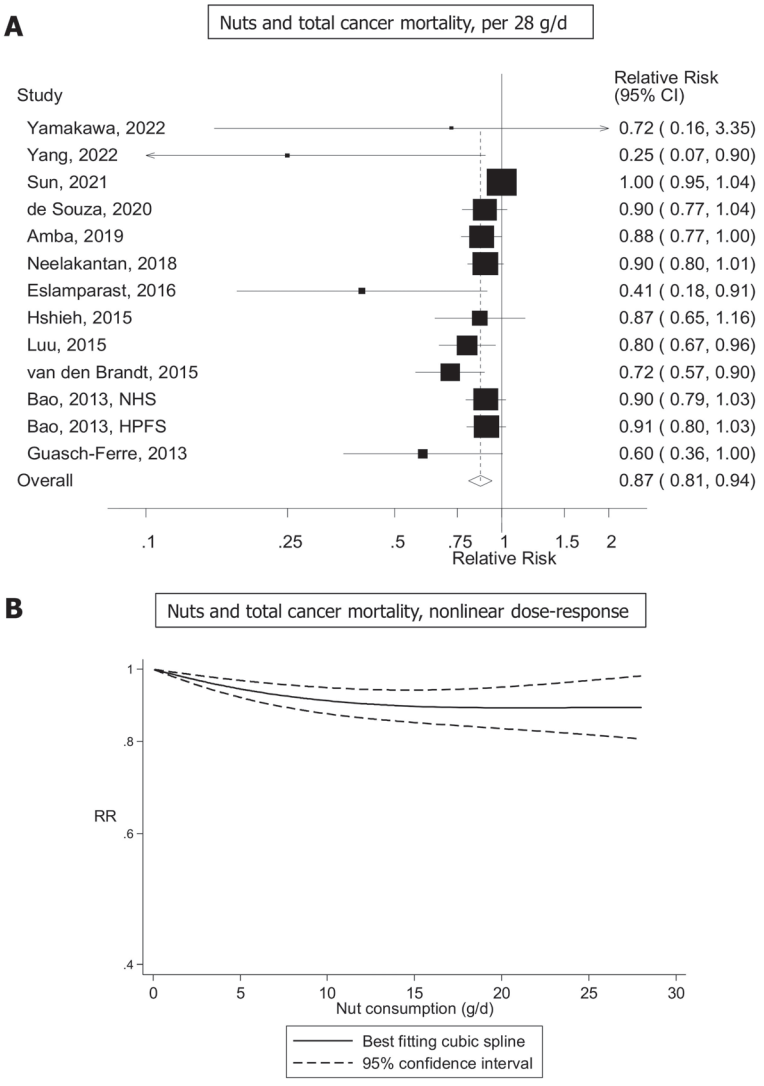

Figure 1. Nuts and total cancer mortality, linear (**A**), and nonlinear (**B**) dose-response analysis (updated analysis based on Aune et al.) [106,110–114,119–124].

For cancer prognosis, additional studies with pre- and postdiagnosis dietary assessment are warranted. It is likely that distinguishing the timing of nut consumption could provide a greater understanding of how nuts may modify risks during different stages of cancer development.

Few studies have addressed the impact of nuts on the co-occurrence of cancer and other long-term chronic diseases (e.g., diabetes) in an individual. For example, in a multinational cohort study, we showed that greater adherence to the Mediterranean diet was inversely associated with cardiometabolic multimorbidity after a first primary cancer [125].

5. Summary and Recommendations

The degree of evidence for dried fruit consumption and cancer prevention is more limited than what has been established for nuts. Preliminary studies have been promising and have begun to establish mechanistic links between bioactives and chemopreventive pathways. Commonly consumed dried fruits have different profiles of bioactives than their fresh counterparts. Several studies suggest that dried fruit intake is associated with a greater reduction of risk than that of fresh fruit. As with nuts, improved methods to track intake and document consumption across multiple types of dried fruit are needed to improve epidemiological studies for diet and cancer prevention.

Evidence from multiple lines of research encompassing cell line studies, animal models, observational studies, interventional studies, and meta-analyses is suggestive that a higher consumption of nuts is inversely associated with the risk of certain cancers and of dying from cancer. Among the 12 cancer sites investigated in the literature (i.e., esophagus, stomach, colorectum, liver, pancreas, lung, breast, ovary, endometrium, leukemia, prostate, and lymphomas), inverse associations were most consistent across studies for the incidence of colorectal cancer and, more specifically, with colon cancer. Studies differentiating between tree nuts and peanuts tend to report stronger inverse associations between tree nuts and cancer incidence and cancer mortality than for peanuts. There is limited, inconclusive evidence for an inverse association with the incidence of cancers of the pancreas, stomach, and lungs, while the most recent studies on breast cancer are null. Evidence is largely missing for other types of cancer; however, there is consistent evidence that nut consumption is associated with reduced total cancer mortality. Potential mechanisms include suppression of angiogenesis, proliferation, and inflammation, as well as increased apoptosis and favorable induced changes in gut bacteria. Indirectly, a higher consumption of nuts may be linked to a reduced risk of certain cancers or dying from cancer through reduced weight gain during adult life. Nuts in the diet may also have a role in tertiary prevention in cancer survivors where a higher nut intake was consistently related to better survival of cancers of the colorectum, breast, and prostate. Considering the observation that nut consumption appears to be more consistently associated with reduced total cancer mortality than total cancer incidence, it is also possible that an association with cancer is driven more so by improvements in survival after a cancer diagnosis than reductions in cancer incidence, but further studies are needed to clarify this, as the number of studies on total cancer incidence is limited.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/nu15061443/s1, Figure S1: PRISMA Flow Diagram of Study Selection; Table S1: Prospective cohort studies on total nut consumption and total cancer mortality. References [126,127] are cited in the supplementary materials.

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Review

Dried Fruits: Bioactives, Effects on Gut Microbiota, and Possible Health Benefits—An Update

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Abstract: Dried fruits contain many bioactive compounds broadly classified as phytochemicals including phenolics, flavonoids, carotenoids, proanthocyanidins, stilbenes, chalcones/dihydrochalcones, and phytoestrogens. These compounds have antioxidant effects that may benefit health. Dried fruits are also a diverse group of foods with varying fibre contents. The evaluation of the biological activity of these bioactive compounds, including their bioaccessibility and bioavailability, may contribute to the understanding of the health effects of dried fruits. Limited evidence suggests that dried fruits (raisins, cranberries, dates, and prunes) affect human gut microbiota composition in a potentially beneficial manner (in terms of effects on *Bifidobacteria*, *Faecalibacterium prausnitzii*, *Lactobacillus*, *Ruminococcaceae*, *Klebsiella* spp., and *Prevotella* spp.). There is little epidemiological evidence about the association of dried fruit consumption with cardiovascular disease incidence and mortality, as well as the risk of type 2 diabetes or obesity. Clinical trial evidence for the effects of dried fruit consumption on cardiovascular risk factors, including glycaemic control, is mixed. Clinical trial evidence suggests prunes might preserve bone mineral density in postmenopausal women. Consumption of dried fruits is associated with higher-quality diets. Studies are needed to increase our understanding of the health effects of dried fruits and the underlying biological mechanisms.

Keywords: dried fruits; gut health and microbiome; cardiometabolic diseases; bone health; dietary guidance

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1. Introduction

Dried fruits are enjoyed by populations worldwide as a shelf-stable, convenient alternative to fresh fruit. Epidemiological evidence suggests dried fruit consumption is associated with lower risk of cardiovascular disease (CVD), type 2 diabetes (T2D), as well as obesity, various cancers, and other chronic diseases, although the evidence is limited and sometimes contradictory. Nonetheless, dried fruits are nutrient dense and a good source of bioactives/phytochemicals [1].

The biological action of bioactives/phytochemicals in dried fruits is dependent on the food matrix release (e.g., bioaccessibility), bioavailability, and metabolism by colonic microbiota [2]. In 2014, the European Food Safety Authority (EFSA) authorized a health claim for dried plums/prunes and gastrointestinal health [3]. This claim states that "*Dried plums/prunes can contribute to normal bowel function*". To obtain the claimed effect, about 100 g/day (~8–12 prunes, depending on their size) of prunes should be consumed. More recently, the effects of dried fruits and the constituent phytochemicals on microbiota composition and functionality have been active areas of investigation. It is now recognized that microbiota contributes to metabolic health and, when aberrant, the development of cardiometabolic diseases. Thus, identifying dietary strategies to promote metabolic health through microbial modulation is a priority.

Evidence from epidemiological and clinical studies suggests that dried fruit intake may improve glucose metabolism and other cardiovascular risk factors, as well as a lower risk for osteoporosis [4,5]. The intake of dried fruits has also been proposed as a strategy to meet fruit recommendations, improve diet quality, and address nutrient deficiencies [6,7].

This review summarizes evidence on the relationship between dried fruit intake and gastrointestinal (GI) health. Bioactive/phytochemical composition and bioaccessibility and bioavailability of dried fruits are also highlighted. We also discuss the association between dried fruit intake and cardiometabolic diseases, bone health, and diet quality as well as the potential mechanisms involved. This is an emerging area of science, and current evidence suggests that the effects of dried fruits on the microbiome, cardiometabolic disease risk, bone health, and diet quality warrant further investigation.

2. Methodologies

To write this narrative review, a detailed literature review was conducted (via sources such as Web of Science, PubMed, SCOPUS, MEDLINE, and Google Scholar). Articles related to the following topics were included: (1) bioactives/phytochemicals present in most commonly consumed dried fruits, (2) bioaccessibility and bioavailability of compounds in dried fruits, (3) GI effects (gut health and microbiota) of dried fruits in animals (in vivo) or human clinical trials, (4) epidemiological evidence about the association of dried fruit consumption with CVD, T2D, and adiposity, (5) cardiometabolic and bone health effects of dried fruit consumption, (6) dietary guidance for dried fruits and benefits on diet quality, and finally, (7) potential mechanisms involved in the observed biological effects. To ensure that current and recent research was presented in this review, only articles published from 2000 onward were included (with a few exceptions due to the relevance of the work), with preference given to articles published between 2015 and 2022 in order to improve contemporary relevance.

Selected articles were examined in detail, and then the bioactives/phytochemicals, bioaccessibility and bioavailability of compounds, gut health and microbiota, epidemiological evidence, cardiometabolic diseases, bone health, and potential mechanisms involved for health benefits as well as diet quality and dietary recommendations for dried fruits were compiled and evaluated. This review is not a systematic review. The most innovative aspect of this review is the update of GI health and cardiometabolic effects of commonly consumed dried fruits (in vivo and in vitro studies). In addition, the update on bioactives/phytochemicals, potential mechanisms involved in the observed biological effects, recommendations for dried fruit consumption, and benefits on diet quality contribute to the novelty of this review.

3. Bioactives/Phytochemicals, Dietary Fibre, and Antioxidant Activity in Dried Fruits

Dried fruits contain a variety of bioactive compounds/phytochemicals such as flavonoids (anthocyanins, flavan-3-ols, flavonols, and flavones), proanthocyanidins (dimer, trimer, 4–6 m, and 7–10 m), phenolic acids (hydroxycinnamic acids and hydroxybenzoic acids), carotenoids (α-carotene, β-carotene, β-cryptoxanthin, lutein, and zeaxanthin), and stilbenes as well as phytoestrogens (isoflavones, lignans, and coumestan) and chalcones/

dihydrochalcones [1,8,9]. Among these bioactive phytochemicals, phenolic compounds are the major group (Table 1). Alasalvar et al. [9] reported various phenolic compounds (anthocyanins, flavan-3-ols, flavonols, flavones, phenolic acids, proanthocyanidins, chalcones/dihydrochalcones, and stilbenes) in nine dried fruits (apples, apricots, cranberries, dates, figs, peaches, pears, prunes, and raisins). Some dried fruits (such as apricots, cranberries, dates, figs, prunes, and raisins) have the most diverse phenolic profiles. Little information is available about the exact phenolic profiles of dried apples, peaches, and pears. With regard to carotenoids, which are plant pigments responsible for yellow, orange, and bright red hues in many fruits and vegetables, α-carotene, β-carotene, β-cryptoxanthin, and lutein + zeaxanthin are present in dried fruits except raisins (seedless), albeit in varying quantities. Of these, β-carotene is the most abundant in apricots (2163 μg/100 g), peaches (1074 μg/100 g), and prunes (394 μg/100 g) [10]. Phytoestrogens consist of isoflavones, lignans, and coumestans. Apricots, dates, prunes, and raisins have been reported to contain phytoestrogens. Total phytoestrogen content ranged from 30.3 μg/100 g in raisins (seedless) to 445 μg/100 g in apricots. No phytoestrogens have been reported in dried apples, cranberries, figs, and peaches (Table 1) [11]. Detailed quantitative analysis on different classes of phenolic compounds, carotenoids, and phytoestrogens in different forms and varieties of dried fruits are needed.

Dried fruits are a good source of dietary fibre (3.7–9.8 g/100 g) (Table 1). Consumption of dried fruits (around 20–30 g per/day recommended by many countries) provides 10–16% of the recommended daily intake of fibre (14 g/day), depending on the fruit [10,12,13].

The oxygen radical absorbance capacity (ORAC), a measure of antioxidant activity, of dried fruits is relatively high, although it varies by dried fruit type as well as by cultivar/variety (Table 1). For example, raisins (seedless) have the lowest ORAC values (3037 μmol trolox equivalents (TE)/100 g), whereas raisins (Golden seedless) have the highest ORAC value ((10,450 μmol TE)/100 g). Similarly, ORAC values vary appreciably for dates cultivars of Deglet noor and Medjool [14].

Table 1. Reported bioactives/phytochemicals, dietary fibre, and antioxidant activity in selected dried fruits.

	Phenolics	**Carotenoids (μg/100 g)**	**Phytoestrogens (μg/100 g)**	**Dietary Fibre (g/100 g)**	**Antioxidant Activity (μmol of TE/100 g)** [a]
Apples	Flavan-3-ols Flavonols Phenolic acids Chalcones/ dihydrochalcones	Lutein + zeaxanthin (18)	-	8.7	6681
Apricots	Flavan-3-ols Flavonols Flavones Phenolic acids Chalcones/ dihydrochalcones	β-Carotene (2163)	Isoflavones (39.8) Lignans (401) Coumestan (4.2)	7.3	3234
Cranberries	Anthocyanins Flavan-3-ols Flavonols Phenolic acids Proanthocyanidins	β-Carotene (27) Lutein + zeaxanthin (138)	-	5.3	-
Dates	Anthocyanins Flavonols Phenolic acids Proanthocyanidins	β-Carotene (6) Lutein + zeaxanthin (75)	Isoflavones (5.1) Lignans (324) Coumestan (0.8)	8.0	2387–3895 [b]

Table 1. *Cont.*

	Phenolics	Carotenoids (μg/100 g)	Phytoestrogens (μg/100 g)	Dietary Fibre (g/100 g)	Antioxidant Activity (μmol of TE/100 g) [a]
Figs	Anthocyanins Flavan-3-ols Flavonols Flavones Phenolic acids Proanthocyanidins	β-Carotene (6) Lutein + zeaxanthin (32)	-	9.8	3383
Peaches	Anthocyanins Flavan-3-ols Flavonols Phenolic acids	α-Carotene (3) β-Carotene (1074) β-Cryptoxanthin (444) Lutein + zeaxanthin (559)	-	8.2	4222
Pears	Flavan-3-ols Phenolic acids Chalcones/ dihydrochalcones	β-Carotene (2) Lutein + zeaxanthin (50)	-	7.5	9496
Prunes	Flavan-3-ols Flavonols Phenolic acids	α-Carotene (57) β-Carotene (394) β-Cryptoxanthin (93) Lutein + zeaxanthin (148)	Isoflavones (4.2) Lignans (178) Coumestan (1.8)	7.1	8578
Raisins	Anthocyanins Flavan-3-ols Flavonols Flavones Phenolic acids Stilbenes	-	Isoflavones (8.1) Lignans (22) Coumestan (0.2)	3.7	3037–10,450 [c]
References	[1,9]	[10]	[11]	[10]	[14]

[a] Based on oxygen radical absorbance capacity (ORAC). [b] Between Deglet noor and Medjool cultivars. [c] Among white, seedless, and Golden seedless raisins.

Several studies have reported the bioactive compounds and antioxidant activities of dried fruits are higher than those of their corresponding fresh counterparts [15–18]. This is due to bioactive compounds and antioxidants becoming concentrated after the drying process. However, losses (e.g., carotenoids and anthocyanins) or changes in some compounds occur during drying and storage. Therefore, drying types and duration, as well as storage and packaging are of great importance in terms of functional/nutritional quality and flavour (taste and aroma) of the final product for consumption.

4. Bioaccessibility and Bioavailability of Compounds in Dried Fruits

The bioaccessibility and bioavailability of compounds in dried fruits have been investigated using in vitro models. These models mimic human in vitro GI digestion (e.g., mouth (oral or salivary digestion), stomach (gastric digestion), small intestine (intestinal digestion), and colon or large intestine (colonic digestion)) [19–22]. Bioaccessibility refers to the level of a compound released from the food matrix during GI digestion that becomes available for absorption (bioavailability) in the intestine [23]. To exert health effects, ingested compounds, including phytochemicals and micronutrients (vitamins and minerals) contained in food, must be released from the food matrix in the GI tract and become bioavailable [21].

Evidence suggests that the phenolics contained within dried fruits are bioaccessible. Recently, Scrob et al. [24] investigated the bioaccessibility of constituents in six dried fruits (dates, raisins, coconuts, cranberries, prunes, and bananas) and demonstrated the highest bioaccessibility of phenolics was observed in prunes and the lowest in cranberries and dates. Total sugars content increased after in vitro digestion of coconuts, dates, and raisins, but it decreased for bananas, cranberries, and prunes. In vitro digestion led to an increase in

the antioxidant activity for most dried fruits. This study showed prunes, coconuts, bananas, and raisins are sources of high bioaccessible phenolics. However, the contribution of dried fruit consumption to the recommended dietary allowances (%) was less considering the bioaccessible fraction compared to the total content.

Polar phenol bioaccessibility of dates using a static model of in vitro digestion was also investigated by Panagopoulou et al. [22]. Simulated GI digestion revealed date polar phenols were found to be bioaccessible to an extent depending on the polar phenol class, the nature of the polar phenols, and the specific date matrix. A 37–70% release was observed post-oral digestion, in terms of total phenolic content, which further increased post-gastric digestion (>100%).

Ma et al. [20] investigated the biological activities of kiwifruits and kiwifruit products including dried slices under simulated GI in vitro digestion. Dried slices showed the lowest biological activity compared to those of other kiwifruit products (such as raw fruit, juice, vinegar, wine, yogurt, and jelly). However, dried slices and jam had the highest quantity of minerals (per unit weight). Thus, consuming dried slices and jam could supply more mineral elements than other forms of the fruit [20].

The impact of GI digestion on the total phenolic content (TPC) and antioxidant activities of dried apricots, figs, and raisins was evaluated by Kamiloglu et al. [25]. There was an increase in TPC (0.4–4.5-fold) for all samples after the gastric digestion. The antioxidant activities of dried apricots and figs were increased as determined by various antioxidant activity assays.

In conclusion, in vitro GI digestion studies have some advantages including being fast and inexpensive, without human ethics concerns. However, these digestion systems (static and dynamic) might not completely mimic human physiology. In vitro models need to be compared with in vivo models (particularly, human intervention studies) to better understand the biological effects. These comparative data are essential for demonstrating the biological relevance of bioactive compounds in the context of nutrition and human health [1,25].

5. Dried Fruits, Gut Health, and Microbiota

Diet is an important modulator of the gut microbiota and its metabolite production. The multiple interactions between food components and gut microbiota as well as the modification of the gut microbiota composition and activities by food components contribute to human health [26,27]. To the best of our knowledge, few studies have investigated the effects of dried fruit intake on gut microbiota. Recent findings from animal and human studies are reviewed.

5.1. In Vivo Animal Studies

A recent chapter by Muñoz and Lamuela-Raventós [28] reviewed the effects of different dried fruits on gut health and microbiota composition using in vitro and in vivo studies. These in vivo studies were conducted using rat, fish, or broiler chick models. The effects of dried fruits on the modulation of gut microbiota from preclinical studies published following the chapter by Muñoz and Lamuela-Raventós [28] are discussed in this section. Among dried fruits, gut health and the microbiota data are available for goji berries, prunes, and dried cranberries.

In a recent study conducted by Cremonesi et al. [29], New Zealand white rabbits fed chow with 3% goji berries had enrichment of *Ruminococcaceae*, *Lachnospiraceae*, *Lactobacillaceae*, and the genus *Lactobacillus*, all of which are considered to be beneficial bacteria, compared to a control group fed regular chow. In addition, the supplementation of goji berries enhanced lactic acid fermentation that contributes to the caecal fermentation [29]. Similarly, in a 10-week study involving mice, Tian et al. [30] demonstrated that supplementation of goji berries at 1.5 or 3% modulated the gut microbiota composition by enhancing the growth of beneficial bacteria such as *Verrucomicrobia*, *Bacteroidetes*, *Bacteroidales S24-7* group, *Anaerotruncus*, *Coprococcus 1*, *Ruminococcaceae UCG-014*, and *Akkermansia*, while

suppressing the growth of harmful bacteria such as *Firmicutes*, *Helicobacter*, *Bacteroides*, and *Mucispirillum*. Meanwhile, administration of goji berries promoted the growth of short-chain fatty acid (SCFA)-producing bacteria, increasing the production of SCFAs [30]. Finally, Kang et al. [31] studied interleukin (IL)-10-deficient mice and showed feeding with goji berries (1% of dry feed weight) for 14 days enhanced the abundance of *Bifidobacteria* and butyrate-producing bacteria, *Clostridium leptum*, and its dominant constituent *Faecalibacterium prazusnitzii,* compared to control chow fed mice. This resulted in an increase in faecal butyrate content [31].

In another study, the effects of freeze-dried cranberries in dextran sodium sulphate-treated (DSST) male CD-1 mice (to induce colitis) were evaluated [32]. This study showed supplementation with 1.5% (*w*/*w*) freeze-dried cranberries (equivalent to 7.5 g of whole cranberry powder) alleviated colitis in DSST mice by reducing the levels of numerous pro-inflammatory cytokines. In addition, treatment with freeze-dried cranberries alleviated the reduced α-diversity of the gut microbiota induced by DSST [32]. Specifically, treatment with freeze-dried cranberries enhanced the abundance of beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus* while reducing the abundance of harmful bacteria, such as *Suterella* and *Bilophila* [32].

5.2. Human Clinical Trials

Wijayabahu et al. [33] conducted a human clinical trial evaluating the effect of three servings (28.3 g per serving) of sun-dried raisins daily for 14 days on gut microbiota composition in healthy adults. Overall gut microbiota composition was not different after raisin consumption, but specific operational taxonomic units (OTUs) were affected. For example, OTUs matching *Faecalibacterium prausnitzii* and *Ruminococcaceae* were significantly enhanced, while OTUs matching *Klebsiella* spp. and *Prevotella* spp. were reduced significantly. These taxa, *Faecalibacterium prausnitzii* and *Ruminococcaceae*, are important for the breakdown of complex carbohydrates in the gut microbiota [33]. Meanwhile, the reduction in OTUs matching *Klebsiella sp.* and *Prevotella sp.* indicated a reduced risk for urinary tract infections and chronic inflammation, respectively [34].

In another randomized, double-blind, cross-over, controlled trial, healthy adults consumed 30 g/day of freeze-dried whole cranberry powder or a placebo for 5 days [35]. Cranberry powder consumption decreased the abundance of *Firmicutes*, while increasing the abundance of *Bacteroidetes*. In addition, the consumption of freeze-dried cranberry powder reduced the production of secondary bile acids and prevented the reduction in SCFAs, relative to the control [35]. Bekiares et al. [36] demonstrated that intake of 42 g/d of sweetened dried cranberries (SDC) for 14 days increased the *Firmicutes*:*Bacteroidetes* ratio and the relative abundance of *Akkermansia*. The authors recommended that further studies be conducted using well-controlled study designs and larger sample sizes to better understand the effect of cranberries on the relative abundance of *Akkermansia* [36].

The effect of prunes on bowel function has also been investigated [37]. Healthy adults (n = 120) consumed either 80 g or 120 g of prunes daily for 4 weeks, with stool weight and frequency as the primary study outcomes. Participants who consumed both 80 g and 120 g of prunes daily had higher stool weight and frequency than the control group. Supplementation with prunes significantly enhanced the relative abundance of *Bifidobacteria* compared to the control group. However, supplementation of prunes did not affect the levels of SCFA or stool pH in the subjects studied. The authors postulated that the effect of prunes on the gut microbiota could be mediated by fibre content, sorbitol, or phytochemicals in prunes [37]. Hence, more research should be carried out to confirm this result. A recent randomized, open-label, controlled trial evaluated the effects of prune consumption in adult women after undergoing benign gynaecologic surgery [38]. Participants (n = 77) consumed 12 prunes with 100 g docusate sodium (widely used as medicine as laxative and as stool softener) twice daily vs. docusate alone for 3 days. Participants who consumed 12 prunes twice daily had an increased likelihood of a bowel movement and earlier hospital discharge than the control group [38].

Dates have also been tested in a randomized, controlled, cross-over, clinical trial for gut microbiota, and GI function [39]. Healthy adult participants consumed 50 g of dates per day or maltodextrin-dextrose as a control for 21 days, with a 14-day washout period. Adults who consumed prunes daily had higher stool weight and bowel movement frequency than the control group. Supplementation with dates did not cause any significant alterations in the SCFA levels or in the growth of selected bacteria [39].

Most studies conducted to date have examined the effects of dried fruits on microbiota composition, whereas studies on metabolite production and functionality are scarce. Figure 1 summarises the potential mechanisms by which intake of dried fruits may modulate gut microbiota to influence health. Phytochemicals from dried fruits undergo significant biotransformation by gut microbiota, and the resulting metabolites may influence health [40]. Future studies, including in vitro, animal, human, and mechanistic studies are needed to address this research gap.

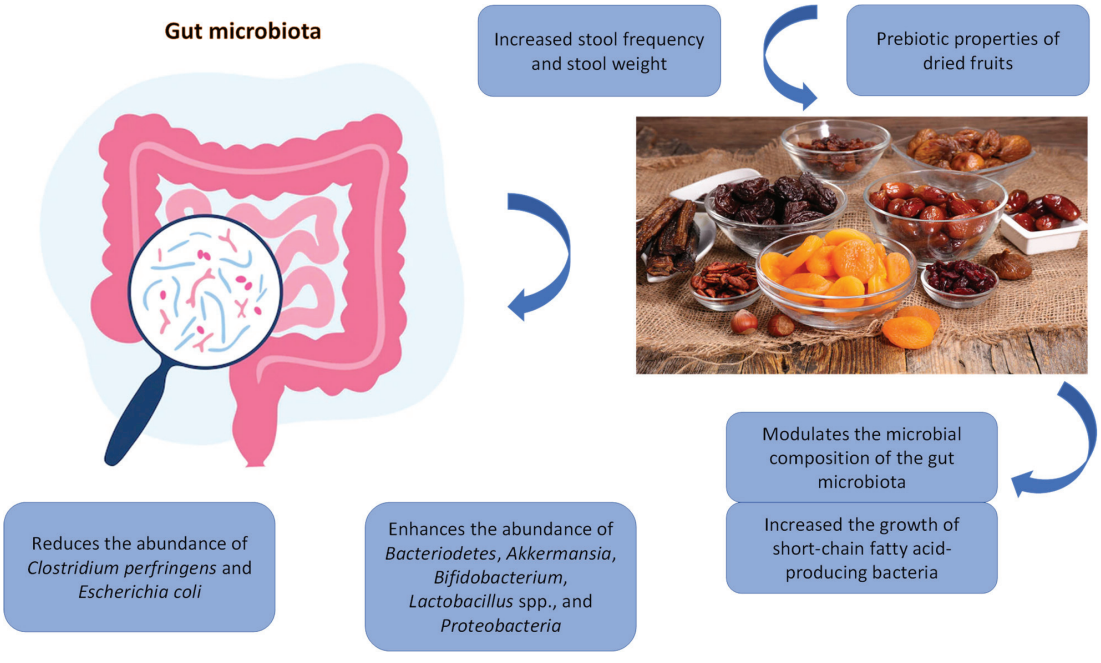

Figure 1. Potential mechanisms of action of dried fruit-related gut microbiota modulation.

6. Epidemiological Evidence for Health Benefits of Dried Fruits

6.1. CVD

CVDs are the leading cause of death worldwide [41]. A suboptimal diet is a major contributor to cardiovascular mortality, with low fruit intake ranked among the top three global dietary risk factors for cardiovascular deaths [42]. Individuals consuming dried fruits within the context of healthy dietary patterns generally have a healthier cardiometabolic risk profile, with lower lipid concentrations, blood glucose, and blood pressure [43–45]. However, there is limited evidence regarding the impact of dried fruit consumption on cardiovascular risk factors, CVD incidence, and mortality. Intake of grapes and raisins (queried together) ≥4 servings/week was associated with an 8% lower risk of hypertension in the Nurses' Health Study and Health Professionals Follow-Up Study cohorts, which included 187,453 individuals. Dried plum intake was not associated with incident hypertension after adjusting for other cardiovascular risk factors (including body mass index—BMI) and lifestyle and dietary factors [46]. Dried fruit consumption

(≥1 vs. <1 serving/day) was not associated with cardiovascular mortality in the Massachusetts Health Care Panel Study, though few people (~5%) consumed more than 1 serving of dried fruit daily [47]. In the UK Women's Cohort Study, combined fresh and dried fruit intake was associated with a lower risk of CVD mortality (8% lower risk per 80 g/day) [48]. However, just dried fruit intake was not significantly associated with cardiovascular mortality.

6.2. T2D

In the Nurses' Health Study and Health Professionals Follow-Up Study cohorts after adjusting for demographic, lifestyle, dietary factors, and diabetes-related risk factors including BMI, every three servings/week of grapes and raisins was associated with a 12% lower risk of T2D [49]. Greater dried plum intake was not associated with T2D incidence. Substituting equivalent portions (three servings/day) of dried plums or grapes and raisins for fruit juice was associated with an 18–19% lower diabetes risk [49]; however, the association may be attributable to fibre intake rather than dried fruit intake per se.

6.3. Body Weight

Observational evidence suggests that dried fruit intake is associated with a lower risk of excess adiposity. Based on the most recent cross-sectional analysis of data from the National Health and Nutrition Examination Survey (NHANES; from 2007 to 2016), dried fruit consumers had a lower mean BMI (−0.8, 99% CI −1.4 to −0.2; $p = 0.002$) and waist circumference (−2.6 cm, 99% CI −4.2 to −0.9 cm; $p < 0.001$) than non-consumers [50]. Mean dried fruit intake in US adults was 0.04 ± 0.001 cup-equivalents/day, which represented 3.7% of total daily fruit intake. In an earlier NHANES analysis (from 1999 to 2004), dried fruit consumers (≥1/8 cup-equivalent per day) had lower body weight (78.2 ± 0.6 vs. 80.7 ± 0.3 kg; $p < 0.01$) and BMI (27.1 ± 0.2 vs. 28.1 ± 0.2 kg/m^2; $p < 0.01$) than non-consumers [51]. In another NHANES analysis (from 2001 to 2012), raisin consumption (defined as having any amount during the first 24 h dietary recall) was associated with a lower body weight (−4.2%), BMI (−5.2%), and waist circumference (−3.8%) [52]. Raisin consumers were 39% less likely to have overweight or obesity.

In summary, few epidemiological studies report favourable associations between dried fruit and CVD, T2D, and body weight, but health benefits are not consistently shown. Observed associations between dried fruit intake and CVD, T2D, and body weight may be confounded by overall diet quality as well as other health-promoting behaviours. While many studies adjust for some foods and nutrients, the specific dietary components included in models vary widely. More comprehensive adjustment for dietary and lifestyle factors may strengthen future epidemiological studies investigating dried fruit consumption. In addition, the ability to detect associations between dried fruit intake and health may be limited by low observed consumption in these study populations. Investigating health associations in populations that routinely consume greater amounts of dried fruits could yield stronger evidence.

7. Clinical Trial Evidence for Dried Fruits and Health

7.1. Cardiometabolic Diseases

In several clinical studies, dried fruit intake has improved cardiovascular risk factors, including cholesterol, blood pressure, and glycaemic control (Table 2). However, the effects are inconsistent, which may be attributable to differences in the bioactive phytochemical and nutrient profiles of dried fruits, as well as differences in trial designs.

Table 2. Clinical trials reporting cardiometabolic effects of routine (≥4 weeks) dried fruit consumption.

References	Study Design	Duration (Week)	Participants (*n*)	Fruit (Dose)	Comparator	Findings
Sullivan et al. [45]	Crossover	4	Men and women with BMI 25–36 kg/m^2 and ≥1 additional cardiometabolic risk factor, *n* = 55	Equal parts (~28 g each) dried plums, Mission figs, Deglet Noor dates, and raisins totalling 3/4 cups/day	Energy-matched processed snacks (animal crackers and fruit snack gummies)	Dried fruits increased LDL-C (0.10 mmol/L) and non-HDL-C (0.12 mmol/L) and reduced HDL-C (−0.05 mmol/L) compared to baseline. Dried fruits increased fasting glucose compared to control (0.08 mmol/L). No between-group or within-group differences in total cholesterol, TAG, blood pressure, or insulin.
Tinker et al. [53]	Crossover	4	Men with elevated total cholesterol (5.2–7.5 mmol/L), *n* = 41	Dried plums, ~100 g/day (12 plums)	360 mL grape juice	Dried plums reduced LDL-C compared to grape juice (−0.17 mmol/L). No difference in total cholesterol, HDL-C, or TAG.
Clayton et al. [54]	Parallel	8	Men and women with BMI ≥ 25 kg/m^2, *n* = 45	Dried plums, ~84 g/day	Energy-matched portion (200 kcal) of low-fat muffins	Dried plums reduced LDL-C compared to low-fat muffins (−24.5 mg/dL). Dried plums increased C-peptide compared to baseline (+1.56 ng/mL). No between-group or within-group differences in total cholesterol, HDL-C, blood pressure, TAG, insulin, or glucose.
Alalwan et al. [55]	Parallel	16	Men and women with T2D, *n* = 96	Dates (Khudary cultivar, tamar stage), 3 dates/day	Usual diet	Dates reduced total cholesterol compared to baseline (−0.209 mmol/L). No between-group or within-group differences in HbA1c, TAG, HDL-C, or LDL-C.
Shishehbor et al. [56]	Parallel	5	Men and women with elevated total cholesterol (>200 mg/dL) or TAG (>200 mg/dL), *n* = 38	Raisins, 90 g/day	Usual diet	Raisins reduced DBP compared to control group (−1.56 mm Hg). Raisins reduced LDL-C (−0.68 mmol/L) and total cholesterol (−0.72 mmol/L) compared to baseline. No between-group or within-group differences in SBP, HDL-C, or TAG.
Kanellos et al. [57]	Parallel	24	Men and post-menopausal women with T2D, *n* = 48	Corinthian raisins, 36 g/day	Usual diet	Raisins reduced DBP compared to the control group (−6 mm Hg). No between-group or within-group differences in SBP, total cholesterol, LDL-C, HDL-C, TAG, fasting glucose, or HbA1c.

Table 2. *Cont.*

References	Study Design	Duration (Week)	Participants (*n*)	Fruit (Dose)	Comparator	Findings
Anderson et al. [58]	Parallel	12	Men and women with BMI 25–34.9 kg/m^2, blood pressure >120/80 mm Hg, and fasting glucose 90–150 mg/dL, *n* = 46	Raisins, 3 ounces/day	Energy-matched pre-packaged processed snacks (three 100 kcal packages)	Raisins reduced SBP (−5.4 mmHg vs. baseline; −6.3 mmHg vs. snacks), DBP (−5.5 mmHg vs. baseline; −3.6 mmHg vs. snacks), HDL-C (−3.6 mg/dL vs. baseline), and HbA1c (−0.12% vs. baseline; −0.08% vs. snacks). No between-group differences in total cholesterol, LDL-C, TAG, or fasting glucose.
Bays et al. [59]	Parallel	12	Men and women with T2D and BMI 25–50 kg/m^2, *n* = 46	Raisins, 3 ounces/day	Energy-matched pre-packaged processed snacks (three 100 kcal packages)	Raisins reduced SBP compared to snacks (−8.7 mm Hg). No between-group differences in fasting glucose, HbA1c, DBP, total cholesterol, LDL-C, HDL-C, or TAG.
Peterson et al. [60]	Crossover	5 (per arm)	Men and women with LDL-C 100–189 mg/dL and BMI 18.5–35 kg/m^2, *n* = 102	Dried California Mission figs (~120 g/day, 12–15 figs)	Usual diet	Figs increased total cholesterol compared to control (6 mg/dL). No difference in LDL-C, HDL-C, or TAG.

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; T2D, type 2 diabetes; TAG, triacylglycerols.

Two studies reported improved low-density lipoprotein cholesterol (LDL-C) after prune consumption compared to energy-matched control foods. In a randomized crossover trial, LDL-C was 0.17 mmol/L (~6.6 mg/dL) lower after 41 hypercholesterolemic men consumed 12 (~100 g) prunes vs. a 360 mL portion of grape juice daily for 4 weeks [53]. In a parallel design trial, adults with overweight and obesity randomized to consume two daily 100-calorie prune snacks (~84 g/day) for 8 weeks had lower LDL-C (−24.5 mg/dL) compared to the control arm randomized to consume low-fat muffins [54]. In two other parallel design studies, cholesterol reductions were observed in participants who consumed dried fruits, but the changes did not differ relative to the control group. Consumption of three dates/day for 16 weeks reduced total cholesterol (−0.209 mmol/L) in adults with T2D, while changes in LDL-C and high-density lipoprotein cholesterol (HDL-C) were not significant [55]. Among adults with hyperlipidaemia, consuming 90 g/day of raisins for 5 weeks reduced total cholesterol (−0.72 mmol/L) and LDL-C (−0.68 mmol/L) [56]. In all four of these studies, diet records confirmed that participants maintained constant energy intakes across the study periods that were consistent with baseline intakes, and three of the four studies confirmed that weight remained stable throughout the study duration [54–56].

In contrast, several studies have shown either no change or increased cholesterol after dried fruit consumption. Three studies reported no effect of raisins on total or LDL-C compared to the usual diet [57] or energy-matched processed snacks [58,59]. In a randomized crossover trial in adults with above optimal or high LDL-C (100–189 mg/dL; *n* = 102), daily consumption of 120 g of dried Mission figs for 5 weeks increased total cholesterol compared to usual diet, though neither LDL-C nor HDL-C significantly differed between conditions [60]. Energy intake was approximately 200 kcal greater on the fig condition, resulting in a small statistically non-significant 0.4 kg weight gain. Among adults

with overweight and obesity, average total and LDL-C did not differ after 4 weeks of daily consumption of 3/4 cup of mixed dried fruits (comprising equal parts raisins, dates, prunes, and dried figs) compared to calorie- and carbohydrate-matched processed snacks, though LDL-C increased 0.10 mmol/L (~4 mg/dL) from baseline after dried fruit consumption [45]. While no diet records were collected, small (0.3–0.4 kg) weight gains were observed after both conditions, suggesting that study foods were not completely substituted for other dietary energy sources. Differences in energy balance may be an important explanatory factor distinguishing trials that demonstrate the cholesterol-lowering effects of dried fruits vs. those that do not.

Several studies have demonstrated blood pressure-lowering effects of raisins, but not other dried fruits. Both systolic and diastolic blood pressure (SBP and DBP) were reduced in adults with overweight or obesity who consumed three 1-ounce portions of raisins (84 g) daily for 12 weeks, compared to energy-matched processed snack foods [58]. SBP decreased with raisin consumption in a similarly designed study among adults with T2D [59], while a 36 g portion of Corinthian raisins consumed daily for 24 weeks improved DBP in adults with T2D, compared to the control arm consuming their usual diets [57]. Daily consumption of 90 g of raisins for 5 weeks also reduced DBP in adults with hyperlipidaemia, compared to the usual diet control arm [56]. In contrast, 3/4 cup of mixed dried fruits did not improve resting brachial, 24 h ambulatory, or central blood pressure compared to processed snacks in adults with overweight or obesity [45]. Prune consumption (84 g/day for 8 weeks) also did not reduce blood pressure compared to processed snacks [54].

The effect of dried fruit intake on glycaemic control is important given that they are high in natural sugars. Acutely, dried fruits have a low-to-moderate glycaemic index and can attenuate glycaemic response when substituted for refined carbohydrates [61,62], likely due to partial displacement of glucose with fructose. A lower glycaemic index diet has been associated with a lower risk of CVD and mortality [63].

Several studies have shown that routine dried fruit consumption does not adversely affect glycaemic control. In adults with overweight and obesity, a daily intake of 3 ounces of raisins for 12 weeks reduced haemoglobin A1c (HbA1c) (−0.08%) compared to energy-matched processed snacks, while fasting glucose was unchanged [58]. Among adults with T2D, daily consumption of 3 ounces/day of raisins for 12 weeks did not alter HbA1c or fasting glucose compared to calorie-matched snacks [59]. Similarly, compared to the usual diet, daily consumption of dates (3 g/day for 16 weeks) [55] or Corinthian raisins (36 g/day for 24 weeks) [57] did not affect HbA1c in adults with T2D.

In contrast, two studies showed adverse effects of dried fruits on glycaemic control. Daily prune intake (84 g) for 8 weeks increased C-peptide, which is released during insulin production [54]. However, fasting glucose and insulin concentrations were not altered, and the increase in C-peptide did not significantly differ from the control arm. In adults with overweight and obesity, a small increase in fasting glucose (0.08 mmol/L, ~1.4 mg/dL) was observed after 4 weeks of consuming 3/4 cup/day of mixed dried fruits compared to calorie- and carbohydrate-matched processed snacks [45]. Since glycaemic measures were not the primary focus of the trial, these findings should be interpreted with caution and require replication.

Overall, the evidence is mixed regarding the effect of dried fruit consumption on cardiovascular risk factors. While several clinical studies show reductions in cholesterol and blood pressure, without harm to glycaemic control, benefits are not consistently observed. Additional well-designed randomized controlled trials that account for the potential confounding effect of changes in energy intake and body weight are needed to confirm the cardiovascular benefits of dried fruit consumption.

7.2. Bone Health

Preclinical studies conducted in rodent models of osteopenia or osteoporosis show prune supplementation prevents and reverses bone loss by modulating oxidative and inflammatory pathways [64–66]. Inflammation and oxidative stress enhance bone resorption

by increasing osteoclast function and suppress bone formation through reducing osteoblast function [64]. These preclinical findings are generally supported by evidence from clinical trials. Other dried fruits have not been linked improved bone health.

Five clinical trials have been conducted in postmenopausal women and provide suggestive evidence that intake of prunes (50 or 100 g/day) for 3 to 12 months may have osteoprotective effects [67–71]. Four trials conducted by one research group show potential antioxidant and anti-inflammatory effects [67–69], as well as improvements in markers of bone formation [70] and resorption [67,68]. Hooshmand et al. [67] showed 100 g/day of prunes increased bone mineral density (BMD) of the ulna and spine compared to 75 g of dried apple after 12 months; no change in neck of femur, total hip, or total body BMD was observed. In a subsequent study, this group demonstrated 50 and 100 g/day of prunes attenuated loss of total BMD compared to the control group after 6 months; no effects were observed for total hip, L_1–L_4 lumbar vertebra, or ulna BMD [68]. In a recent, single-centre, parallel-arm 12-month randomized controlled trial, 50 g/day of prunes preserved total hip BMD (–0.3 $\pm$ 0.2%) compared to the control group (–1.1 $\pm$ 0.2%) in postmenopausal women. An intake of 100 g/day of prunes did not affect BMD; however, the dropout rate was 41% for this group, suggesting limited feasibility of this dose [71]. This large, well-conducted randomized controlled trial is generally confirmatory of previous trials, and the totality of the evidence suggests intake of 50 g/day of prunes might be an efficacious, non-pharmacological intervention to preserve BMD in postmenopausal women.

Recently, two small studies examining the effect of prune intake on markers of bone metabolism in older men have been conducted [72,73]. In a 3-month randomized controlled trial of men 55–80 years with mild bone loss, 50 g/day and 100 g/day of prunes had limited and inconsistent effects on markers of bone turnover compared to the control group [72]. In a subsequent 12-month study by the same group, 100 g/day of prunes did not affect total body, spine (L1–L4), hip, and ulna BMD [73]. The findings of these studies should be cautiously interpreted given the small sample sizes examined limiting statistical power.

8. Dried Fruits and Diet Quality

Individuals who consume dried fruits tend to have higher-quality diets, overall. Based on an analysis of NHANES data from 2007–2016, adult consumers of dried fruits had higher Healthy Eating Index (HEI)-2015 scores, representing better adherence to the 2015–2020 Dietary Guidelines for Americans [50]. Specifically, they had higher intakes of fruits, vegetables, whole grains, legumes, seafood, and plant proteins, and they had lower intakes of (and thus higher HEI-2015 component scores for) sodium, refined grains, and saturated fats (Figure 2) [50]. Consumed as snacks or incorporated into meals, dried fruits can contribute to a healthy dietary pattern. In US adults, dried fruit consumption adds to total fruit intake, rather than displacing other forms of fruit, and contributes to greater intakes of dietary fibre and potassium [50]. Thus, increasing dried fruit intake could be an effective strategy to increase intakes of fruit, fibre, and potassium.

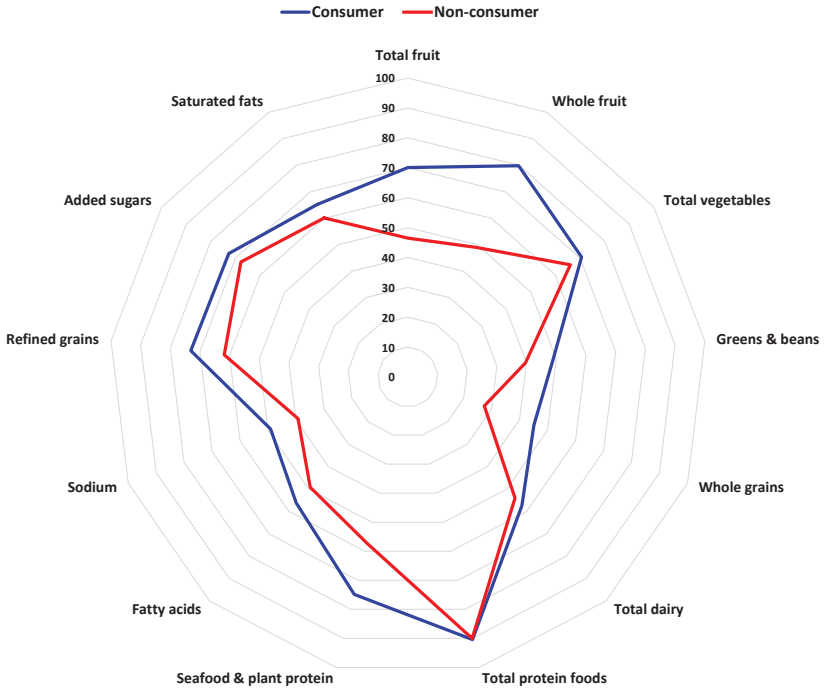

Figure 2. HEI-2015 component scores for dried fruit consumers and non-consumers, NHANES 2007–2016. Dried fruit consumers reported ≥1/4 cup-equivalent dried fruit intake on at least one of two 24 h diet recalls. Component scores are represented as percentages of maximum score. Data from [50]. Copyright Elsevier (2021).

9. Dietary Recommendations for Dried Fruit Consumption

A suboptimal diet is a leading cause of morbidity and mortality globally, and a suboptimal fruit intake is a major contributor to CVD, diabetes, and neoplasms [42]. A healthy dietary pattern that includes fruits is the basis for current dietary recommendations made by many organizations globally. In 2020, the World Health Organization recommended a healthy diet that includes the following: at least 400 g (e.g., five portions) of fruit and vegetables per day, excluding potatoes, sweet potatoes, cassava, and other starchy roots [74]. The 2020–2025 US Dietary Guidelines for Americans recommends two cup equivalents of fruits per day (per 2000 calories), which is equal to four servings per day [6]. With respect to dried fruits, 1/4 cup is equal to a 1/2 cup serving of fruit. The European Commission (the European Union as well as Iceland, Norway, Switzerland, and the UK) recommends two to three servings per day of fruit [7]. According to the Global Burden of Disease Study 2017, fruit consumption (94 g per day) falls short of current (two to three servings per day) dietary recommendations for fruit [42]. Similarly to the US, some European countries include dried fruit in the fruit recommendations, whereas others have specific recommendations for dried fruit in the range of 20–30 g per day [7]. According to 2020–2021 data from International Nuts Council, annual global per capita dried fruit consumption is about 1.2 g per day [75].

10. Potential Mechanisms Involved for Health Benefits of Dried Fruits

Among dried fruits, prunes are an excellent source of vitamin K, providing about 28 µg of vitamin K per serving of five prunes (47.5 g), which is 23% of the recommended dietary allowances for men and 31% for women [2,10]. Although no bioavailability studies have been conducted for vitamin K in prunes, vitamin K absorption is significantly increased in

the presence of some dietary fat. Thus, consuming prunes in the absence of fat, for example, alone as a snack, may result in relatively low absorption of their vitamin K [2]. In general, vitamin K plays a role in blood clotting, bone metabolism, and regulating blood calcium levels. Dried fruits are a good source of potassium [10]. It is likely that potassium is well absorbed from dried fruits and therefore would be a significant dietary source of the mineral. It has been reported that a high sodium:potassium ratio is associated with a significant increase in the risk of CVD and all-cause mortality in a US population [76]. Increased consumption of dried fruits would provide a means to reduce the sodium-potassium ratio, therefore potentially reducing CVD risk.

Dried fruits are rich in bioactives/phytochemicals, such as phenolic compounds, phytoestrogens, and carotenoids with potent antioxidant capacities [1,8,9]. These compounds scavenge free radicals and hence alleviate the oxidative stress that causes tissue damage, aging, and other chronic diseases [9]. Studies using simulated in vitro GI track digestion models indicate that there is little absorption of bioactives/phytochemicals from dried fruits after intestinal digestion. It has been hypothesized that unabsorbed bioactives/phytochemicals might be active in the digestive tract, rather than systemically. Because the digestive tract is a major organ involved in the immune response, effects within it may still contribute significantly to its overall health indirectly. In the colon, bioactives/phytochemicals are metabolized by the gut microbiota to form a wide range of metabolites, some of which would be responsible for health benefits attributed to the parent compounds. Therefore, measuring nutrient bioavailability from dried fruits is an open area of investigation [2]. Furthermore, the consumption of dried fruits modulates the diversity of gut microbiota by enhancing the relative abundance of beneficial microbes while reducing the relative abundance of harmful microbes [31,32]. Modulation of the gut microbiota by dried fruit consumption alleviated chronic inflammation, which in turn reduces the severity of metabolic disorders, such as CVD, T2D, and obesity [34].

In vitro and in vivo studies have been conducted to elucidate the mechanisms by which dried fruits may promote improvement in glycaemic control and insulin sensitivity. In human studies, dried fruits have a low-to-moderate glycaemic index. Mechanisms that may help to explain the benefits of dried fruits may relate to their relatively lower glycaemic index and insulin index potential, high mineral content of potassium and magnesium, and increased fibre content, as well as high levels of antioxidant and bioactives/phytochemicals [77].

Obesity is a disease characterized by chronic accumulation of excessive fat in adipose tissues, which leads to the production of pro-inflammatory cytokines. Chronic inflammation causes endothelial dysfunction, accompanied by insulin resistance. In addition, obesity, high blood pressure, high glucose levels, abnormal lipids/lipoproteins [total cholesterol, LDL-C, and triacylglycerols (TAG)], and chronic inflammation are major risk factors for atherosclerosis. Inhibition of inflammatory pathways by numerous bioactives/phytochemicals contained in dried fruits may beneficially affect inflammation-related diseases (e.g., metabolic disorders, such as CVD and T2D) [45,54].

Evidence suggests that prunes both prevent and reverse bone loss in postmenopausal women and potentially in men. Dried fruits, in general, contain several bioactives/phytochemicals (including but not limited to resveratrol, kaemferol, proanthocyanidins, quercetin, cholorogenic acid, and catechin) with potential osteoprotective effects; however, the mechanisms by which these effects occur remain unclear [5].

In short, the potential of dried fruit to be a therapeutic strategy to prevent the severity of numerous chronic metabolic diseases warrants further investigation.

The relationships between bioactive compounds/phytochemicals present in dried fruits and health outcomes are summarized in Figure 3.

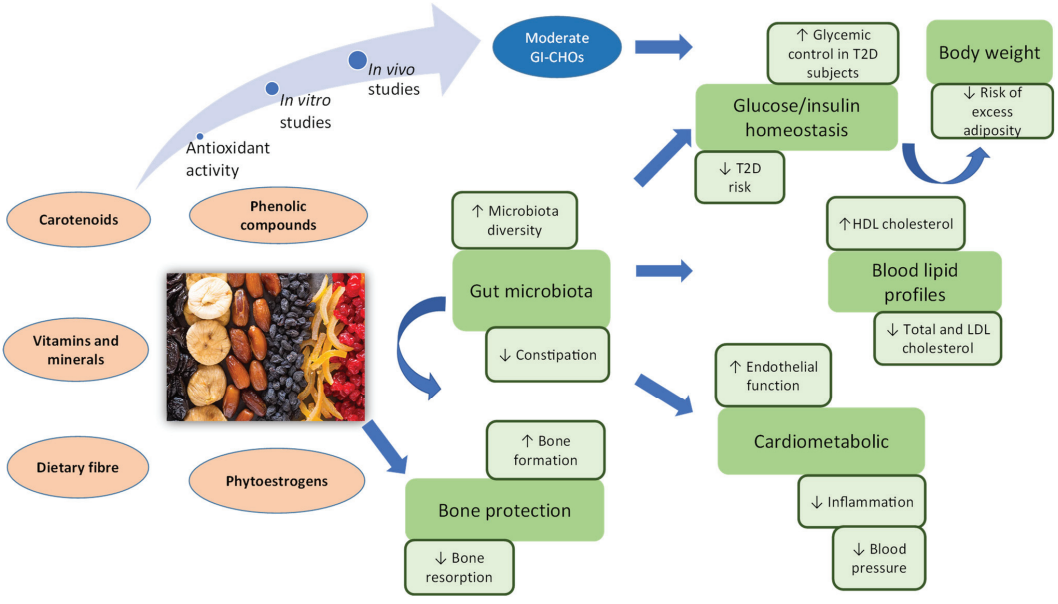

Figure 3. Summary of the health benefits ascribed to dried fruits. Frequent consumption of dried fruits benefits cardiovascular, gut microbiota, and bone health due to their unique composition of nutrients, bioactives/phytochemicals, and fibre. Abbreviations: CHOs, carbohydrates; HDL, high-density lipoprotein; GI, glycaemic index; LDL, low-density lipoprotein; T2D, type 2 diabetes.

11. Limitation of Studies in Dried Fruits and Future Recommendations

The bioactives/phytochemicals, gut microbiota, and bioavailability as well as health benefits of dried fruits have been less explored compared to their fresh counterparts. Although the bioactive/phytochemical profiles of some dried fruits (such as apricots, cranberries, dates, figs, prunes, and raisins) are well known, limited evidence is available for dried berries and tropical/non-tropical dried fruits. In addition, information about the bioavailability of minerals, vitamins, and bioactives/phytochemicals from dried fruits is scarce [1,8,9]. Measuring bioavailability of nutrients and bioactives/phytochemicals is an active area of research. More research needs to be conducted to determine circulating metabolite profiles after ingestion of dried fruits compared to fresh fruit counterparts [2]. Few studies have investigated the effect of dried fruits on gut microbiota, and further research is needed to understand the health implications of dried fruit related gut microbiota modulation [28]. Further research is also needed to clarify the extent to which bioactives/phytochemicals are altered by processing and whether this affects their bioactivity. Elucidating the mechanisms and bioactives/phytochemicals responsible can also help to identify processing techniques (such as sun-drying vs. heat-drying vs. freeze-drying) or particular fruits that best promote cardiometabolic and bone health [78]. Finally, evidence suggests that prunes have beneficial effects on bone health and may prevent osteoporosis. Further research is needed to examine the effectiveness of this potential non-pharmacological intervention given the side effects of pharmacological therapy for osteopenia [5].

12. Conclusions

Research about the health benefits (e.g., specifically related to the microbiota, cardiometabolic diseases, and bone health) of dried fruits is in its early stages. The phytochemical profiles of different dried fruits have been investigated; however, our understanding of their bioaccessibility and bioavailability is not well understood. Furthermore, a better

understanding of the biological effects of dried fruits and their bioactive compounds on cardiometabolic diseases, their risk factors, bone health, and the microbiome is needed. Despite this, we have an understanding that is evolving about the health benefits of some of the bioactive compounds in dried fruits and also the many health benefits of fresh fruits and juices. The encouraging results from the studies with both dried fruits, as well as fresh fruits and juices, justify further research. Additional scientific investigations will provide a better understanding of the biological effects of dried fruits on major chronic diseases and their biological mechanisms of action will be useful for future dietary guidance for dried fruits.

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nutrients

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Review

Novel Lines of Research on the Environmental and Human Health Impacts of Nut Consumption

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Abstract: Nuts have formed part of human diets throughout the ages. In recent decades, research has shown they are key foods in dietary patterns associated with lower chronic disease risk. The current state of climate change, however, has introduced an imperative to review the impact of dietary patterns on the environment with a shift to plant-based diets. Nuts emerge as a significant source of protein in plant-based diets and are a minimally processed and sustainable food. Research in this area is evolving to drive better production methods in varying climate conditions. Nevertheless, nut consumption remains an important contributor to human health. The mechanisms of action can be explained in terms of the nutrients they deliver. Studies of nut consumption have linked components such as monounsaturated fatty acids, plant omega-3 fatty acids, antioxidants, and plant sterols to improved lipoprotein profiles, lower blood pressure, and reduced cardiovascular disease risk. Preliminary research also indicates possible beneficial effects of nut consumption on reproductive health. In any case, the ultimate effects of foods on health are the results of multiple interactive factors, so where nuts fit within dietary patterns is a significant consideration for research translation. This has implications for research methodologies, including categorization within food groups and inclusion in Healthy Dietary Indices. The aim of this narrative review is to outline new focal points for investigation that examine the environmental and some novel human health impacts of nut consumption and discuss future directions for research.

Keywords: nuts; environment; sustainability; reproduction; sexual function; diet; dietary patterns

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1. Introduction

As naturally occurring edible and nutritious foods, nuts have been part of the human diet throughout the ages [1]. Modern nutrition science provides evidence of their health benefits, but foods have not always been the object of nutrition research, with a focus in past decades on nutrients contained in foods. At the same time, the industrialization of the food supply saw the emergence of chronic lifestyle-related diseases, such as obesity, cardiovascular disease (CVD), and type 2 diabetes. Research identified so-called 'negative' components of the diet including dietary fat and excess energy consumption [2], which

translated to dietary advice and created an ambiguous position for nuts as a high-energy, high-fat food.

Population-based dietary guidelines appeared in the 1980s aimed at providing adequate nutrition and preventing chronic disease. Early guidelines referred to staple food groups, with advice to avoid foods high in fat, sugar, and salt [2]. The position of nuts in food groups was variable, but the value of naturally occurring foods, captured in the concept of food synergy [3], and an appreciation of the relationship between nutrients, foods, and dietary patterns [4] led to today's guidelines having a greater focus on dietary patterns. Research on nuts followed this direction, expanding beyond their nutritional contributions to nuts as a significant food in healthy dietary patterns. Direct clinical evidence of health effects came from trials involving at-risk populations. Basic science research provided insights into the molecular pathways underlying health effects, and epidemiological studies confirmed that associations between nut consumption and health outcomes occurred in the broader population. Each of these types of research were important in building the body of evidence, despite challenges in providing timely and consistent studies to support nutrition policy and practice [5–7]. At the same time, clinical evidence review methodology has developed further to consider the quality as well as quantity of research. This development recognized that research practices and study designs require sufficient scrutiny to assure confidence in results and valid translation to practice [8].

Today, evidence supporting nut consumption is extensive. It goes beyond chronic disease prevention to other forms of human health—including reproductive health—and then to the planet's health. The environmental impact of healthy dietary patterns is part of the evidence analysis, as nuts are significant foods in plant-based diets. The global imperative to address climate change calls for additional research methodologies that address the environmental impact of foods [8]. Today, there are strong calls to combine imperatives for human health with that of the environment [9].

The aim of this narrative review is to outline new focal points for research that examine the environmental and novel human health impacts of the consumption of nuts and discuss future directions.

2. Nuts and Environmental Sustainability

Environmental sustainability is one of the most pressing new areas of research on food today. Food production and consumption face unprecedented scrutiny as their impact on the natural environment and human health becomes more evident. How foods are grown (including water use), processed, sold, prepared, cooked, consumed, and disposed of is crucial. In studying nuts and environmental sustainability, all these stages of production and consumption (the 'food system') must be considered.

The global food system produces enough calories for a growing world population. However, about half of the population is malnourished with almost 1 billion people not consuming enough food and experiencing hunger, and almost 2 billion overconsuming foods low in nutritional quality associated with micronutrient and phytonutrient deficiencies, obesity, and increased incidence of chronic disease. Globally, the non-optimal intake of foods in the diet is estimated to account for approximately 22% of all deaths among adults and 15% of disability-adjusted life-years [10]. At the same time, agriculture uses ~70% of the global freshwater [11]. The food supply chain is responsible for ~26% of global greenhouse gas emissions (GHGe), occupies ~43% of habitable land, causes ~78% of the ocean and freshwater eutrophication, and ~32% of terrestrial acidification worldwide [12].

Several strategies have been proposed to decrease the environmental pressures exerted by the food systems. These include (1) improving agricultural technologies to enhance productivity and reduce harmful emissions; (2) reducing food loss and waste to decrease food production requirements and waste emissions in landfills; and (3) shifting to the production and consumption of foods that support human and planetary health [13–16]. Thus, the type and amount of food produced and consumed are major determining factors in promoting human health within planetary boundaries [17,18]. Research can identify

where nuts fit within these parameters. Addressing the environmental impacts of the lifecycle of nuts (LCA, Lifecycle Analysis), from production to consumption, is one way to approach this.

According to the Food and Agriculture Organization (FAO), environmentally sustainable diets are "those diets with low environmental impacts which contribute to food and nutrition security and to healthy life for present and future generations (. . .) while optimizing natural and human resources [19]." We have previously identified four determinants for, or dimensions of, a sustainable diet from the consumer's perspective. These dimensions are based on the ratios of dietary characteristics. They are (1) the proportion of foods in the diet of animal versus plant origin, (2) the proportion of processed versus whole foods, (3) the proportion of seasonal/locally sourced foods versus out-of-season/context, and (4) the proportion of foods consumed versus wasted [18] (Figure 1).

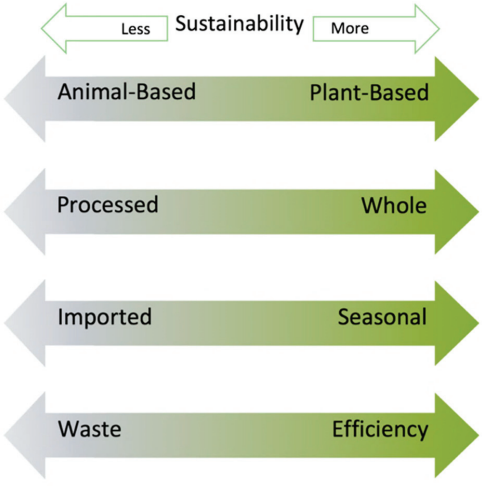

Figure 1. Characteristics of foods in a diet that determines its sustainability. The graphic illustrates that a sustainable diet has a higher proportion of foods that are plant-based, whole, in-season, and consumed with no or minimal waste [18].

Most diets (and most meals) have a mix of foods, each having different characteristics. The inclusion of nuts in the diet is variable. The larger the amount and proportion of foods in a meal or diet whose constituent foods are animal-sourced, processed, out of season or context (requiring transportation or refrigeration for storage), and wasted, the less sustainable the diet is. Reciprocally, the higher the proportion of foods of plant origin consumed, minimally processed, in season, and locally sourced, the more sustainable the diet is. Thus, nuts would appear to have a place in sustainable diets.

2.1. Nuts as Sustainable Foods

At the consumption level, nuts are plant foods consumed whole or very minimally processed; they have a "long season" (since they do not require refrigeration for storage, can be transported and stored with minimal energy use), and have little waste. Thus, nuts appear to be sustainable foods.

At the production level, however, concerns have been raised regarding the high water usage and chemical inputs in the production of nuts under intensive agricultural practices. Importantly, this is not the case when nuts are grown in extensive or traditional agricultural practices.

2.1.1. Life Cycle Analysis

There is a relative paucity of published data from Lifecycle Analysis (LCA) on nuts. Environmental impacts of foods can be measured using various units, including, per weight (of edible amount), per serving, or, depending on the nutritional contribution of each food, per grams of protein or energy (kcal) [20–22]. This can be problematic for some foods such as nuts. For example, many food comparisons regarding environmental impacts have been based on edible amounts (by weight), giving nuts mixed results. A commonly recommended nut serving size is small (approximately 30 g) compared to other foods (often 50–120 g or even 240 g for most beverages). However, nuts are also energy-dense foods (less than 5% water) whose main nutrients are fat and protein. As a result, the environmental impacts of certain nuts measured per grams of protein are very low compared to other animal-sourced protein-rich foods.

We conducted a LCA of five common food sources of protein: legumes, nuts, eggs, poultry, and red meat—specifically, kidney beans (*Phaseolus* sp.), almonds (*Prunus dulcis*), eggs, chicken, and beef as produced in Californian agricultural practices [23]. When using beans as the reference (legumes are nature's most efficient production of protein), almond protein is the second best ranked after beans for most environmental parameters except for pesticides (Figure 2).

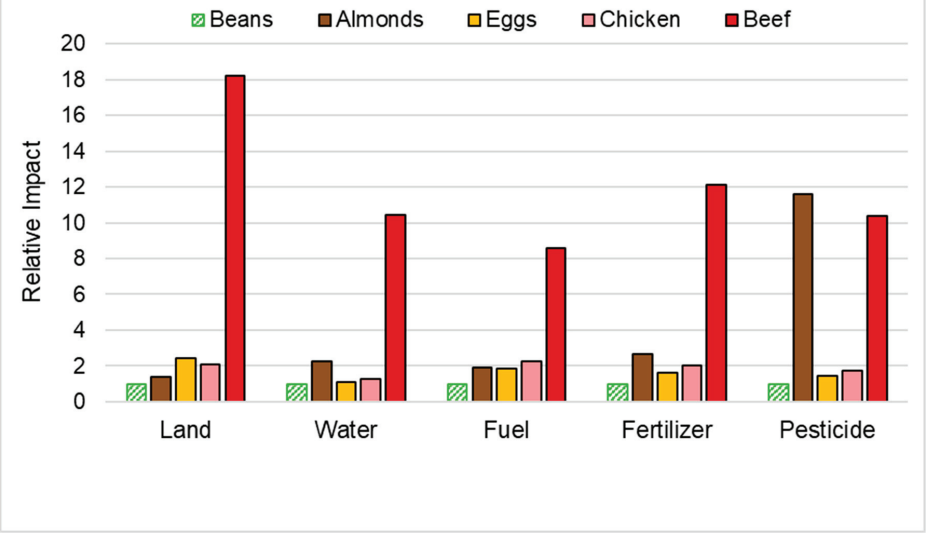

Figure 2. Relative Environmental Impacts of Protein Food Sources in relation to protein from beans [23].

Clark and colleagues [24] analyzed LCA data from meta-analyses to determine the impact of fifteen foods on environmental depreciation, encompassing five components: plausible acidification, eutrophication, GHGe, land use, and scarcity-weighted water use. Of the fifteen analyzed foods, red meat (100 g), chicken (100 g), eggs (50 g), legumes (50 g dried weight; DW), and nuts (28 g) represent protein sources [25]. Each food was depicted in a radar plot, illustrating the rank-ordered impingement on designated environmental parameters per daily food serving. When comparing nuts, eggs, and red meat, nuts performed relatively well on all environmental parameters except water use. The environmental impact per serving of eggs per day serves as an intermediate. Red meat received the highest or most detrimental rank in all five environmental parameters, thus corresponding with previous research [23].

The foods were rank-ordered from least to most environmentally impactful per serving produced [24]. Nuts ranked lowest (least harmful) for GHGe among all fifteen foods. Among the five protein food sources, nuts ranked lowest in eutrophication potential and second lowest in acidification and land use. However, in conjunction with previous scholarly [26] and media [27,28] critiques on nut production and water use, nuts ranked second highest in scarcity-weighted water use, only exceeded by red meat. These findings imply that the environmental impact of a 28 g serving of nuts is less aggravating than that of a 100 g serving of red meat, although water use is of concern.

2.1.2. Water Footprint

The situation for nuts requires further examination of the term 'water use'. This complex issue may be better addressed by considering distinct 'water footprints' referring to 'blue water' (surface plus groundwater, often used in irrigation [29]) and 'green water' (rainwater consumed with agricultural production [26]). Mekonnen and Hoekstra calculated the water footprints of nuts [26] and farm animals [30] from 1996 to 2005. Vanham and colleagues [31] applied the water footprint computations to demonstrate the blue and green water footprint of nuts and animal proteins (beef, eggs, chicken, pig meat, and sheep meat) in liters per kilogram and liters per gram of protein. In the context of liters per kilogram, shelled cashew (*Anacardium occidentale*) nuts have the most prominent combined blue and green water footprint among all nuts and triple that of beef. The water footprints of almonds and pistachios are also considerable, exceeding 10,000 L per kilogram. Among the selected animal proteins, eggs have the lowest water footprint. When comparing the water footprint by food weight, the sustainability of nuts appears unfavorable; however, as previously mentioned, protein is a sizable component of nuts' nutrients, suggesting that water footprint expressed per gram of protein may be a more accurate representation for this environmental impact.

Further clarification on the position of different types of nuts is seen through the water footprint articulated in liters per gram of protein. Accordingly, the water footprint of cashews remains higher than that of beef, whereas that of peanuts is lower than all five animal proteins [31]. Moreover, the average green and blue water footprint of almonds, hazelnuts (*Corylus* sp.), pistachios (*Pistacia vera*), and walnuts (*Juglans* sp.), combined, remain lower than beef's water footprint when based on liters per gram of protein. Comparing the environmental impact of foods based on protein content rather than weight may be valuable from a nutritional perspective, as eating patterns focus on nutrient levels rather than weight.

Researchers must also address the location of nut production, as agricultural production in water-scarce areas may have a greater impact on water footprint than locations with greater water availability. Indeed, water stress, defined as the ratio of water used to available water [32], varies according to region. For example, in California, the powerhouse of almond production [33], high water stress [31] and water demand [34] are evident even though the carbon footprint is relatively low [35]. Agricultural practices, including intensive versus extensive agriculture [36], require further consideration because these determine the magnitude of resource utilization.

2.2. Future Research on Nuts and Sustainability

First and foremost, future research should prioritize collecting data on nut production and sustainability using environmental parameters beyond water and GHGe. Although data regarding acidification and eutrophication potency are available [24], they are limited, and this confines the current comprehension of the environmental impact of producing nuts. Furthermore, collecting and comparing data on the environmental impact of nut production according to agricultural methods (intensive versus extensive), climate setting, and location may clarify whether previous critiques of nut production and sustainability are consistently reasonable across varied agricultural conditions.

Certainly, an increase in the production and consumption of nuts, as recommended by the EAT–Lancet Commission [9], a global initiative on food and planetary health, beckons the question of whether eating more nuts is more sustainable than "healthier" diets. If "healthier" diets were to incorporate conventional meat analogs, it would be necessary to compare their sustainability with that of nuts. This would require quantifying the LCA of nuts versus conventional meat analogs in isocaloric and isoprotein conditions. Additional modeling or use of diet records can be useful in describing the environmental impact of nuts in previously defined dietary patterns.

The future of nuts in the diet may even involve replacing well-known meat analogs, including texturized vegetable protein (TVP) [37], with nut-based meat analogs. Notably, this implies assessing and comparing the sustainability of nut-based meat analogs with current TVPs using the parameters discussed above.

In addition, nuts are an excellent source of fat, almost entirely unsaturated. They contain mainly monounsaturated fatty acids (MUFAs) and some polyunsaturated fatty acids (PUFAs), mostly *n*-6 PUFAs, while walnuts are a good source of vegetable *n*-3 PUFAs [38]. Given the importance of these essential and healthy fats, relevant research could include the computation of LCA environmental inputs relative to the different food sources of unsaturated fats, including *n*-3 PUFAs.

Unsustainable and unhealthy foods harm both planetary health and human well-being. Further research is required demonstrating and quantifying the environmental sustainability of nuts. Specifically, more needs to be known about the efficient use of natural resources and environmental protection in the production, preparation, and disposal of nuts. Consumption needs to be addressed in terms of nuts as a single food, as an alternative to other foods, and in the context of healthy dietary patterns.

3. Nuts and Male Reproductive Health

From environmental concerns to effects on human biology, research on the health effects of nuts has extended beyond the scope of chronic non-communicable diseases to the support of human growth and development. One particularly novel area is that of infertility, defined as the incapacity to conceive after one year or longer of unprotected intercourse. Infertility affects approximately 15% of the world's population [39]. Male factors are responsible for 40–50% of infertility cases, and an evident decline in semen quality parameters has been reported over the last fifty years [40–43]. A recent meta-regression analysis, including 185 studies and more than 42,000 men without known fertility problems, estimated a 50–60% decrease in sperm counts between 1973 and 2011 [44]. Accordingly, despite the multicausal nature of male infertility, the examination of the factors negatively affecting semen quality is warranted to develop novel strategies to prevent, diagnose, and treat male infertility disorders [45]. Several etiologies of male infertility have been uncovered over the years, such as specific lifestyle factors, congenital/genetic disorders, hormonal imbalances, or sexually transmitted diseases [45,46]. Among all male (in)fertility-associated factors, lifestyle habits are modifiable factors highly associated with sperm quality, which plays a key role in reproductive health [47].

Dietary patterns, specific foods, and their nutrient components have been reported as essential factors for proper sperm function and male fertility [48]. The adherence to a healthy diet [49–57], including the consumption of fruits and vegetables, nuts, fish, seafood, and whole-grain cereals, while avoiding excessive intake of processed high-fat products, alcoholic beverages, caffeine, and sugary drinks [49,58–61] have been positively associated with sperm quality (Figure 3).

In this regard, adhering to unhealthy dietary habits could exert a negative impact on semen quality, thus impairing the function of male gametes and reducing or preventing fecundability [45]. This warrants the study of novel dietary habits contributing to improving sperm quality and thereby reducing male-factor infertility.

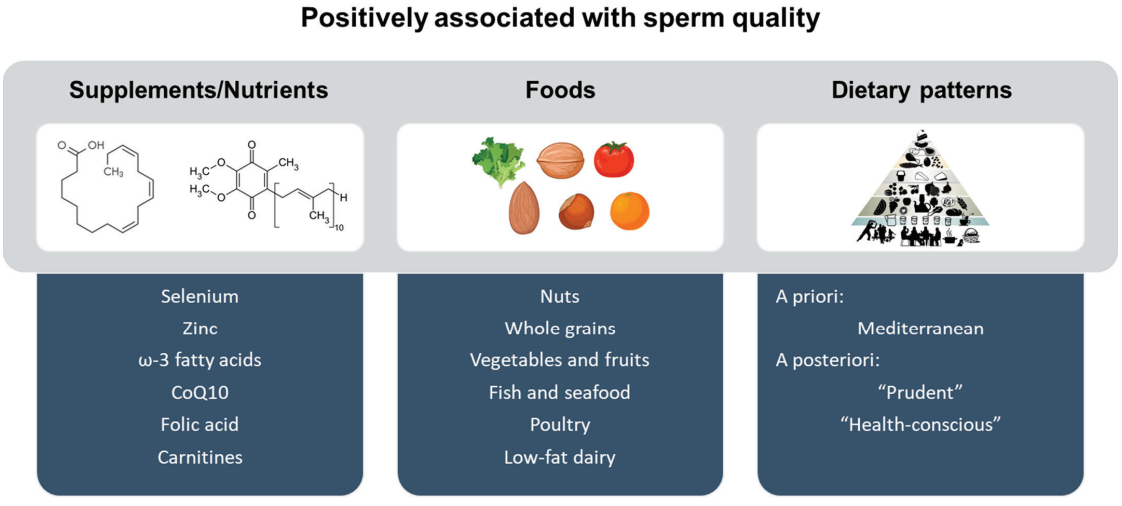

Figure 3. Supplement/nutrient intake, food consumption, and dietary pattern adherence positively associated with sperm quality parameters [61].

Recognized as a component of healthy dietary patterns, nuts are nutrient-dense foods rich in unsaturated fatty acids, fiber, minerals, vitamins (among them, tocopherols), phytosterols, polyphenols, and other antioxidants. Nuts deserve special attention for their potential role in male reproductive health, given the general beneficial impact on several health outcomes [38,62–64]. The next section of the review examines the potential impact of nut consumption on sperm quality and functionality, as well as on sexual function.

3.1. Nuts and Sperm Quality and Functionality

Animal models have demonstrated possible benefits of nut consumption for sperm quality and functionality. Two recent articles focused on the effects of hazelnut [65] and cashew [66] supplementation. In one study, Kara et al. randomized a group of rats into a control (ad libitum laboratory standard diet) and hazelnut-supplemented feed group, with a daily dose of 3 g hazelnut kg^{-1} bodyweight. The authors reported that the supplementation corresponded to 5.5% of hazelnut in the diet and equated to 30 g day^{-1} in humans. Following a thirty-day intervention, the inclusion of hazelnuts significantly improved sperm vitality. Moreover, the hazelnut intervention also significantly improved the Johnsen's testicular histologic score, a system conventionally used to evaluate the completeness of testicular spermatogenesis, and reduced apoptotic indices [65]. In another study, Akomolafe et al. investigated the effect of cashew nut supplementation on fertility in rats. The rats were randomly divided into six diet groups with varying cashew nut (10 to 20%) and clomiphene citrate composition in the diets. The combination of cashew nut supplementation and clomiphene citrate significantly increased epididymal sperm count, vitality, and motility, and decreased total sperm abnormalities in comparison to the control [66]. These findings suggest that the inclusion of nuts (e.g., hazelnuts or cashews) may be useful to treat male partners suffering from sperm quality problems and infertility issues.

The effects of nut consumption on sperm quality have been tested in humans in two randomized clinical trials (RCT) [67,68]. Robbins and collaborators were the first to report substantial improvements in sperm vitality, motility, and morphology after the inclusion of 75 g day^{-1} of walnuts for 12 weeks by 117 healthy men following Western-style diets [67]. The authors attributed these improvements to the increase in blood *n*-6 PUFAs and alpha-linolenic acid (ALA), the vegetable *n*-3 PUFA, hypothesizing on potential

mechanisms of action (ALA is a well-established biomarker of walnut consumption [69,70]). In a second study, the FERTINUTS trial, Salas-Huetos et al. evaluated the effect of chronic consumption of mixed nuts (almonds, hazelnuts, and walnuts) on changes in conventional semen parameters, implicating several potential mechanisms. A total of 119 healthy reproductive-age men consuming a Western-style diet were randomized and allocated to two diet groups, one enriched with 60 g mixed nuts day^{-1} and the other devoid of nuts. The inclusion of nuts significantly improved total sperm count and sperm cell vitality, motility, and morphology, and these findings were explained in terms of a reduction in sperm DNA fragmentation [68]. Nut consumption was also associated with a reduction in the micro-RNA hsa-miR-34b-3p expression level [68] and with differential methylation in 36 genomic regions between the baseline and the end of the trial [71]. These studies suggest that sperm epigenome mechanisms can respond to diet.

3.2. Nuts and Sexual Function

Erectile function and sexual desire are directly influenced by lifestyle factors such as diet through the vascular and nervous systems. For example, Esposito et al. described a direct association between Mediterranean diet adherence and erectile function [72,73], but few authors have studied the most relevant food groups. One early prospective study on nuts involved 17 male patients with erectile dysfunction in an intervention provided with 100 g of pistachios per day for 3 weeks. The authors demonstrated for the first time that a pistachio-supplemented diet improved several of the scores in the International Index of Erectile Function (IIEF), including those related to sexual desire, orgasmic function, and erectile function, among others [74]. However, this was a non-randomized clinical study with outcomes measured before and after the intervention only, which detracts from its quality and casts doubt on the findings. On the other hand, using data from the FERTINUTS trial, Salas-Huetos et al. demonstrated that 60 g day^{-1} of mixed nuts (walnuts, hazelnuts, and almonds) during 14 weeks positively modulated erectile function and sexual desire scores [75]. However, these studies failed to show that these improvements resulted from changes in peripheral levels of nitric oxide or E-selectin, two of the main endothelial function markers. Highlighting the limitations of this research, the authors called for equivalence trials with defined primary outcomes to demonstrate these effects.

3.3. Future Research on Nuts and Reproductive Health

Although investigations have begun in this fascinating area, questions remain largely open. In general, more observational studies of good quality and RCTs with larger sample sizes and well-defined inclusion/exclusion criteria are needed to make any recommendations for the general population. We need a better understanding of the mechanisms of action that modulate fertility status and sexual function. Consuming nuts may help to improve the main parameters of semen quality, but there are no current RCTs addressing the effect of paternal and maternal nut consumption and fecundability outcomes. Well-designed intervention and prospective studies in preconception cohorts will help understand the role of nuts in fecundability rates.

4. Nuts as Components of Healthy Dietary Patterns

Research involving nuts that addresses the pressing needs of environmental sustainability and novel areas of health, such as reproductive health, both come back to the question of how nuts fit within healthy dietary patterns. This level of research is also evolving, with particular implications for methodological development and translation to policy and practice. While there is a strong history of cultural use of nuts in the human diet, particularly in the Mediterranean regions [1], their broad inclusion in dietary guidance reflects advances in nutrition science. In the last century, there was a focus on nutrients as the basis for providing this guidance [2], but this has evolved to dietary patterns as the burden of disease has shifted to chronic lifestyle-related disease. These non-communicable diseases have multiple and interacting dietary determinants, which

best reflect a pattern of food consumption and the synergy that exists between nutrients in foods and foods in a diet [4]. Dietary patterns are now listed among research priorities in a number of authoritative nutrition-related areas, including the US National Institutes of Health "https://dpcpsi.nih.gov/onr/strategic-plan (accessed on 12 February 2023)", The Australian Academy of Science "https://www.science.org.au/files/userfiles/support/reports-and-plans/2019/2019-nutrition-decadal-plan.pdf (accessed on 12 February 2023)", and the European collaboration reflected in the EAT–Lancet papers [9].

As naturally occurring plant foods, nuts have a unique nutritional composition characterized by significant proportions of unsaturated fatty acids, fiber and phytosterols, key micronutrients (such as vitamin E and selenium), and polyphenols. Importantly, this reflects the biochemistry of the nut as a living organism, with an interdependence of the nutrients contained therein [76]. Not surprisingly, research has shown that nuts form part of healthy dietary patterns. This last section of the review outlines the research on nuts in healthy dietary patterns, issues relating to their positioning, and directions for future research.

4.1. Nuts in Healthy Dietary Patterns

Nut consumption is a key component of numerous dietary patterns known to be associated with a range of health benefits [77]. For instance, nuts feature prominently in diet quality indices such as the Healthy Eating Index (HEI), Alternate Healthy Eating Index (AHEI), and Dietary Approaches to Stop Hypertension (DASH) score, all of which have been associated with a significant reduction in risk of all-cause mortality and incidence of chronic diseases such as (CVD), type 2 diabetes, and cancer [78]. The Mediterranean diet, which has been consistently associated with reduced risk of chronic diseases [79], has regular consumption of nuts as a key feature. Furthermore, examination of a posteriori dietary patterns identified in prospective cohort studies observed that 'prudent diets' were associated with reduced risk of coronary heart disease and included a range of beneficial foods, including nuts [80].

Clinical trials have confirmed the beneficial effects of including nuts as components of healthy dietary patterns. For example, the PREDIMED trial, which examined the effect of a Mediterranean diet supplemented with either mixed nuts or olive oil, found a range of health benefits, including reduced incidence of cardiovascular events, when compared to advice on a low-fat diet [62]. A network meta-analysis comparing the effects of consumption of foods and markers of disease in RCTs found that, of the food groups examined, increased consumption of nuts, legumes, and whole grains resulted in the greatest improvements in intermediate risk markers for CVD, nuts being particularly beneficial for reducing LDL cholesterol [81]. Similarly, the inclusion of 30 g of walnuts a day in addition to an interdisciplinary intervention (inclusive of dietary support) for 12 months was found to result in greater weight loss in overweight participants compared to a control diet [82]. These findings are particularly relevant given that nuts are an energy-dense food, with consumers reporting concern regarding the effects of nuts on body weight [83,84]. However, recent meta-analyses have demonstrated that nut consumption does not result in weight gain or increased abdominal adiposity [85], regardless of whether nuts are advised or not to be substituted for other foods [86]. Taken together, these results suggest that nut consumption plays an important role in healthy dietary patterns, with no adverse effects on body weight.

Given the recognized importance of nuts in healthy dietary patterns, regular consumption of nuts is recommended in dietary guidelines globally [87]. While some dietary guidelines [88,89] classify nuts as a food group, many others categorize them with other foods, typically either protein foods [90–95] or fats and oils [96–98], and some guidelines include nuts in both food groups [99–101]. Quantitative recommendations for nut consumption vary between guidelines and appear based on recommendations for the food group, which includes nuts, although the serving size provided in guidelines typically ranges from 15 to 30 g. While approaches to food categorization tend to reflect the protein

and fat composition of nuts, variations in food group allocations present challenges when comparing population intakes to recommendations.

Despite the current inclusion in dietary guidelines, population intakes do not appear to meet recommended levels for nut consumption. The 2017 Global Burden of Disease Study noted that global consumption of nuts was approximately 12% of the optimal intake of nuts and seeds (considered to be 21 g per day) [10]. Results from national surveys similarly highlight a common issue of low nut consumption. For instance, a secondary analysis of a subset of the 2005–2018 National Health and Nutrition Examination Survey (NHANES) from the United States of America found 12.9% of adult males and 9.1% of adult females met recommendations to consume 30 g or more of nuts per day [102]. Analysis of the 2011–2013 National Nutrition and Physical Activity Survey in Australia found 5.6% of individuals consuming nuts met the recommendation to eat 30 g of nuts per day [103]. Of note, under 40% of Australians reported consuming nuts during the survey, despite nut consumption including nuts in mixed dishes such as breakfast cereals or muesli bars. Similarly, the European Prospective Investigation into Cancer and Nutrition (EPIC) study found that on the day of the 24 h recall, less than 30% of respondents consumed nuts from any source, although it should be noted that nut intake did vary substantially among countries [104]. These results suggest that population intakes globally do not match current recommendations for nut consumption and highlight the need for increased nut consumption as part of a healthy dietary pattern.

4.2. Positioning Nuts in the Diet

Translating the evidence supporting nuts in healthy dietary patterns requires an understanding of nut consumption with other foods and within meals. The lack of congruence between recommendations and actual intakes suggests more work is required in that area. Nuts can serve as snack foods, and while research has exposed their impact on diet quality when substituted for poor-quality snacks [105], positioning them as snacks can align them with incidental, non-staple foods. In addition, theoretical positions of nuts in trials of healthy dietary patterns does not always translate to their inclusion as a staple food. For example, nuts were critical foods in the PREDIMED study, which demonstrated the CVD-preventive effects of the Mediterranean diets supplemented with extra-virgin olive oil or mixed nuts [62], but were less obvious in a study of staple foods in the context of food insecurity in the USA [106]. On the other hand, nuts are emerging as key foods in sustainable diets [107].

Behind this issue lies the question of collecting and managing research data on nuts. One suggestion is to create a separate food group of nuts, possibly with seeds as contemporaries [108]. This would clarify measurement in dietary surveys, albeit with a need to address the name of the group, serving size, and frequency of consumption. There are also implications for how nuts might be included in dietary indices that evaluate diet quality and how they might fit within a cuisine pattern. Even if this were the case, there have been major shifts away from naming food groups in terms of actual foods, with a greater focus on degree of processing.

The NOVA system of food categorization [109] places nuts favorably in the desired 'unprocessed or minimally processed' food category. This position is consistent with accompanying research that indicates a risk to cardiovascular health with ultra-processed foods, explainable through the loss of natural food synergy, displacement of healthy foods, and high content of saturated fat, sugar, and salt [110]. There is substantial debate on this methodological development, arguing the issue of misclassification with the NOVA system, the lack of associated conventional research, and the adequacy of current nutrient scoring systems [111]. Nevertheless, the minimally processed food category is consistent with staple foods recommended in dietary guidelines [112], which may assist in better compliance. The debate has brought into question not just food groupings, but food classification systems in general used in the review of dietary guidelines [113]. Whether these are nutrient-based rating or scoring systems, or food categories based on processing

(such as NOVA), or dominant nutrient contribution (as in dietary guidelines), there is wide variation in agreement in the way they present the health potential of individual foods.

Healthy dietary patterns tend to be investigated using forms of diet quality indices or scores (for example, Mediterranean diet scores) [114]. They address the whole of diet relationships with health outcomes, such as CVD risk, and take various approaches to the consumption of foods and nutrients and/or dietary patterns/cuisines. It is important to note, however, that they also serve various purposes: from health promotion activity to food labeling requirements and from measuring relationships in observational studies to effects seen in intervention trials. The positioning of nuts in instruments that address dietary patterns would need to take into consideration the purpose of the research activity.

4.3. Future Research on Nuts in Healthy Dietary Patterns

The ability to discern the impact of nuts in a dietary pattern, as with any food, will depend on how they are categorized and treated in the analysis [77]. Of the two main analytical approaches: a posteriori (looking for groups, identifying and naming patterns), or a priori (using pre-determined dietary patterns), those using an Index (a priori approach) are the commonest, followed by Factor or Principal Component Analysis (a posteriori approaches) [115]. This is also a developing area, with varying applications and reporting systems, as well as attention to foods and/or nutrients. Building an argument that deals with the interrelationship between foods and nutrients, however, strengthens the evidence of food effects. For example, using Principal Component Analysis in a study of baseline relationships between nutrients, foods, and dietary patterns with blood pressure, the dietary pattern categorized by nuts, seeds, fruit, and fish was significantly associated with lower blood pressure and with lower sodium:potassium ratio (a nutrient ratio related to blood pressure) [116]. In this case, the analyses based on healthy foods and intervening nutrients produced congruent outcomes.

Building the evidence base for nuts in healthy dietary patterns continues to rely on epidemiology to provide evidence of associations, clinical trials to demonstrate effects, and experimental laboratory studies to expose explanatory mechanisms [4]. Systematic reviews, meta-analyses, and quality assessments add rigor to the process, but this is a dynamic system requiring regular updates, oversight, and dedicated funding [7]. The purpose of building the evidence base will also inform the nature of the research, and this includes a consideration of transitional issues such as consumer communications. For example, research has shown the presence of health claims influences consumer purchasing, but there is more to do around how consumers understand and act on health claims in relation to meal contexts and overall dietary patterns [117].

5. Conclusions

Nuts are healthy foods: they are a source of important micronutrients, unsaturated fatty acids, protein, fiber, and plant sterols, and they form part of recognized healthy dietary patterns. Today, however, there is an imperative to review the impact of dietary patterns on the environment. This has led to a shift to plant-based diets, where nuts emerge as a significant source of protein. Health perspectives see nuts as a minimally processed and sustainable food, but research at the production level is evolving. Given their high nutritional value, environmental research is likely to drive better nut production methods in varying climate conditions. Nuts remain an important contributor to human health, with the mechanisms of action explained in terms of the nutrients they deliver. Studies have linked nut consumption to better blood lipoprotein profiles and lower CVD risk, but early research is now indicating possible beneficial effects of nut consumption at the other end of the life spectrum, namely reproductive health. This is a novel and interesting area of new research with many questions open for further investigation. Whether we consider the production of nuts or their consumption, the position of nuts in the dietary pattern remains an issue. The ultimate effects of food on health are the results of multiple interactive factors, so where nuts fit within dietary patterns is a significant consideration for research

translation. There are implications for research methodologies, including categorization within food groups and inclusion in Healthy Dietary Indices.

One of the most significant issues for research translation is that the consumption of nuts in many jurisdictions across the globe does not meet evidence-based recommendations. New areas of research, such as reproductive health discussed here, may help to increase the recognition of nuts as important foods in the diet. Likewise, their role in plant-based diets aimed at addressing environmental as well as health concerns may be casual. While continuing to build the evidence base on the health benefits of nuts, a focus should remain on methodology affecting the positioning of nuts in dietary assessment instruments, which may, in turn, influence forms of communication to consumers.

In dietary surveys, a separate category of nuts (and possibly seeds) may address the problem, as could the inclusion of nuts in healthy diet indices. Translational targets also require clarity of purpose in research. The nutrition science community recognizes the diversity of research methods to 'advance discovery, interpretation and application of knowledge' [118]. This includes an appreciation of how different layers of knowledge create the evidence base that enables appropriate (dietary) recommendations. In research on the health benefits of nuts, expanding the scope of interest to health throughout the lifecycle, especially in the area of reproductive health, and integrating research on environmental issues and sustainable diets represent very positive ways forward.

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