CHARLES UNIVERSITY IN PRAGUE

FACULTY OF PHARMACY IN HRADEC KRALOVE

DEPARTMENT OF BIOLOGICAL AND MEDICAL SCIENCES

Diploma thesis (DT)

Mediterranean diet and prevention of diseases

Anastasia Vlasopoulou

Supervisor: Assoc. Prof. Miloslav Hronek, Ph.D.

HRADEC KRÁLOVÉ, 2021-2022

Acknowledgments

- For my family-

CONTENT

ABSTRACT

The Mediterranean diet (MD) is a well-known worldwide diet and is followed by many people. The fundamental reason is that the actual ingredients and the quantity of them used in this diet have been shown to help in the prevention of diseases. Everyday consumption of olive oil, vegetables, fruits, and whole grains, combined with the frequent intake of fish, dairy products, and controlled consumption of red meat and eggs have been associated with a substantial decrease in the incidence of many cardiovascular diseases (CVD). This has also been proven by either each component consumed acting individually or all the ingredients acting together, complimenting each other's influence. The MD seems to have occupied the scientific community a lot since it is proposed as the primary prevention against various diseases, especially heart diseases and their risk factors, such as diabetes mellitus (DM), atherosclerosis, obesity, and dyslipidemia. This paper (DT) analyzes the different types of food included in the Mediterranean pyramid, their effects on health, and the evidence that confirms the above assumption.

ABSTRAKT

Středomořská dieta (MD) je celosvětově známá dieta a dodržuje ji mnoho lidí. Základním důvodem je to, že skutečné ingredience a jejich množství použité v této dietě prokazatelně pomáhají v prevenci nemocí. Každodenní konzumace olivového oleje, zeleniny, ovoce a celozrnných výrobků v kombinaci s častým příjmem ryb, mléčných výrobků a kontrolovanou konzumací červeného masa a vajec byla spojena s podstatným snížením výskytu mnoha kardiovaskulárních onemocnění (KVO). To bylo také prokázáno tím, že buď každá spotřebovaná složka působí samostatně, nebo všechny složky působí společně a vzájemně se doplňují. Zdá se, že MD hodně zaměstnává vědeckou komunitu, protože je navržena jako primární prevence proti různým onemocněním, zejména srdečním chorobám a jejich rizikovým faktorům, jako je diabetes mellitus (DM), ateroskleróza, obezita a dyslipidémie. Tento dokument (DT) analyzuje různé druhy potravin obsažené ve středomořské pyramidě, jejich účinky na zdraví a důkazy, které potvrzují výše uvedený předpoklad.

1. INTRODUCTION

The MD is a modern nutritional habit, which is proven to have benefits and affect positively human health and well-being. According to sources, this diet is derived from the eating habits of people who lived in southern Italy and Crete. For this reason, the now known MD diet was firstly named the Cretan Diet. [1] In more extensive research, it was shown that the exact nutritional habits were not different from the rest of Greece and other Mediterranean counties so it was renamed the Mediterranean diet. In 1960 the World Organization of Health (WHO) in the so-called research of 7 countries recognize that the lowest mortality incidence of diseases like cardiovascular (CV), cancer and DM were found in citizens of these countries. Physiologist Ancel Keys invested the term, later in International Conference of Mediterranean nutrition it was decided what it is considered as healthy, and finally, in 1995 a team of researchers of Harvard University created the famous "Pyramid of Mediterranean Nutrition". [1,2]

This pyramid shows the foods that are included in the diet, as well as the sequence of their consumption. The pyramid's base is made up of plant-based meals. Typical dietary components of the diet are:

- Whole grains, fruits, and vegetables contain polyphenols and mainly flavonoids. Beverages, like a glass of red wine which is recommended to accompany a meal, tea, coffee, and dark chocolate
- Fish, all seafood, soybean oil, almonds, purslane, and olive oil which are considered healthy fats. These fats play a significant influence on the whole diet as they contribute to the confrontation of diseases, which will be discussed further in this paper. The two main groups of fats are long-chain ω-3 and ω-6 fatty acids
- Greek yogurt, cheese, and milk knead by probiotic bacteria
- Bioactive compounds and nutrients such as fibers, vitamins, phytosterols, antioxidants are found in smaller or bigger quantities in the above-mentioned foods [1,2]

Of course, these are not the only groups of healthy foods that participate in the diet. There are other ingredients, however, these are not recommended on a daily basis. Some ingredients even are not recommended more than once a week. These ingredients are sweets, potatoes, red meat, and beverages containing a lot of carbon dioxide and sugar as they are considered to have a bad influence on health. These however cannot be excluded, as people tend to like them immensely. Finally, it is crucial to cite the necessity of drinking water. The optimal intake of water on a daily basis is 1.5-2Lt. Proper hydration is essential to maintain the water equilibrium in a person's body, although intake can change according to the needs and exercise at each individual does on a daily basis. Only with the combination of a proper diet and balanced physical activity can a person achieve positive results. Below there is an example of the pyramid which gathers updated recommendations of quantities and qualities as it is designed by a group under the name of the Mediterranean Diet Foundation Expert Group. [3]

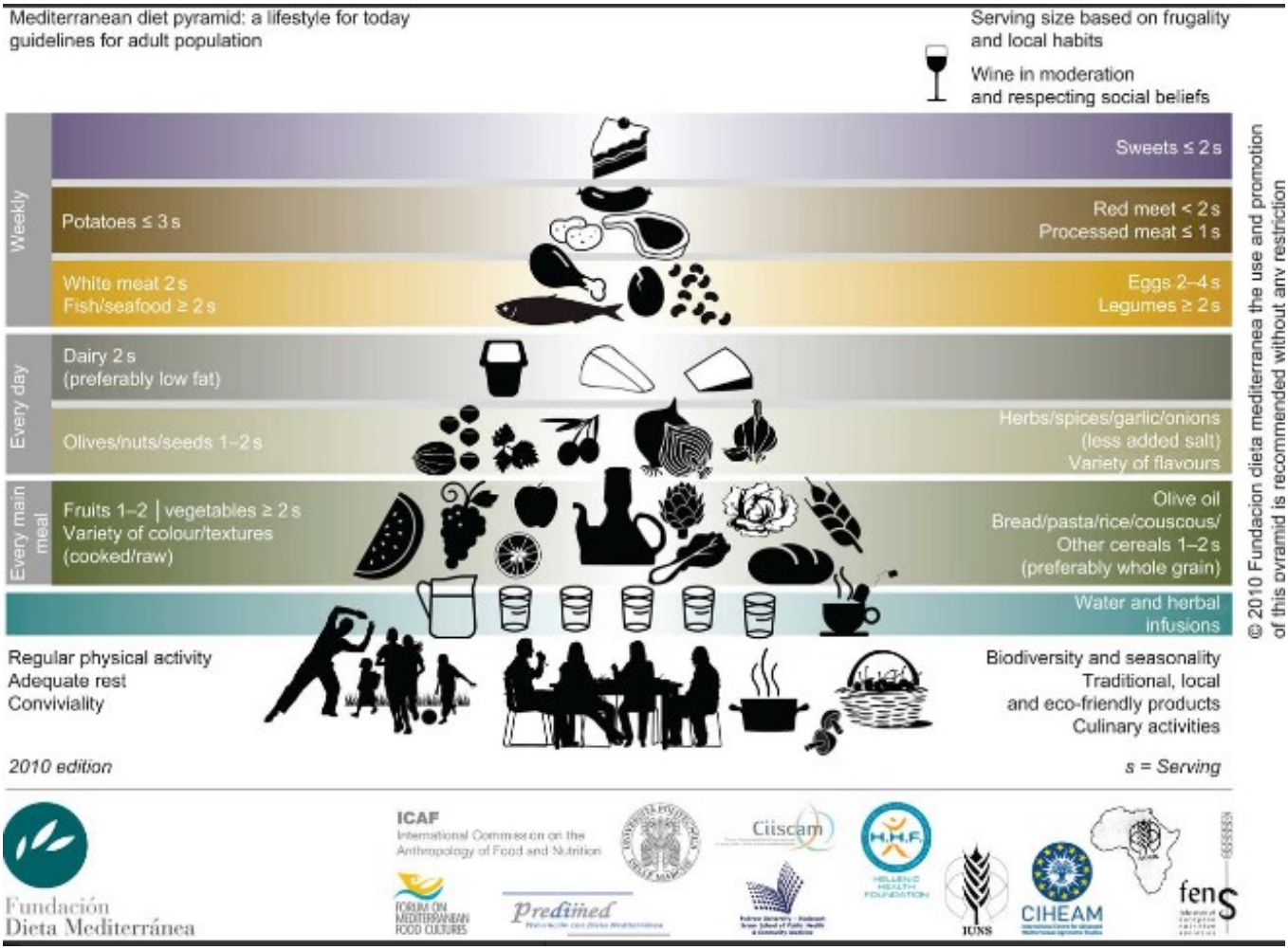


Figure 1:Mediterranean Pyramid **[3]** 10.1017/S1368980011002515

© 2010 Foundation diet Mediterranean: the use and promotion of this pyramid is recommended without any restriction

In the next chapters, there will be detailed described the main active components of the above-mentioned foods and the goal of the paper is to provide evidence that these foods can contribute to the prevention of several diseases.

2. "HEALTHY" FATS

Three main, essential, fatty acids are unable to be produced by the human body and therefore must be received from the diet. Mainly, the majority of dietary lipids are neutral fats and triglycerides, which are formed by three fatty acids esterified to a glycol molecule.

The most matter of importance is linoleic acid (LA, C18:2, n-6) and α-linolenic acid (ALA, C18:3, n3) responsible for the synthesis of larger ω-6 and ω-3 fatty acids. They are polyunsaturated fatty acids (PUFA) and their chemical structure consists of many double bonds, therefore structurally the difference between ω-3 and ω-6 is the number of carbons in the last double

bond. They are considered healthy fats and they replace less healthy fatty acids, such as saturated and trans fats, which contribute to the formation of CVD.

ALA is metabolized and finally, synthesized with the corporation of two enzymes Δ6 desaturase and elongase to longer ω-3 like eicosapentaenoic acid (EPA) and docosahexaenoic acid(DHA) but unfortunately, DHA is synthesized in a lower amount than the other. [4] It is also worth noting that there are also some fats like ω-7 and ω-9, which are monounsaturated fatty acids (MUFA) and synthesized from the body and consequently they are not considered essential, but they are contributing to the prevention of diseases. These fats are observed in some quantities in oils and salmon. The question is in which food the essential fatty acids are observed.

The main source of ω-3 is found in fish and fish oil, especially in salmon and mackerel. Ω-6 on the other hand is found in olive oil, corn oil, sunflower oil, and peanut oil. The major problem with the consumption of PUFAs is that the enzymes for elongation and desaturation act competitively. This leads us to why it is important to consume foods in equal amounts in order to have a balance between the two fatty acids. When we consume a higher amount of ω-6, this inhibits the metabolism of ω-3 and vice versa. [6] The importance of ω-3 acknowledges physiologist Hugh Sinclair, who in the 40s, noticed how many diseases were related to the lack of fats in the body, like atherosclerosis. He demonstrated his ideas in public in 1956, but back then, his thoughts were considered outrageous and he lost his position at Oxford University. After some years, his theory was confirmed and a unit was founded in the University of Reading about human nutrition (1995-2015). [5] Several sources of information mention that the western countries whose diet is rich in ω-6 and the big ratio between fats have shown pathogenesis to some diseases, including autoimmune, CV, and cancer. For example, some research has shown that a lower ratio prevents breast cancer in women, a ratio of 2-3:1 suppress inflammation of rheumatoid arthritis and a ratio of 4:1 is correlated with the decrease of 70% of total mortality in patients with CVD. [6] The ratios are different in each situation due to genetic predisposition. In each case, there has to be a balanced ratio of 1:1 or 4:1 which is considered optimal. In the MD, this ratio is succeeded due to the consumption of fish, two to three times a week.

3. OLIVE OIL

One of the most important components of the MD is olive oil. It is rich in antioxidants, especially Vitamin E, bioactive substances, such as carotenoids, polyphenols, flavonoids, and MUFAs. The LA that these substances contain is metabolized in arachidonic and with the corporation of cyclooxygenase (COX) and lipoxygenase synthesize eicosanoids, prostaglandins, leukotrienes, and thromboxane which are pro-inflammatory and contribute to the promotion of blood vessel constriction and pain signaling as well as help the inflammation and airway constriction. Olive oil can be divided into extra virgin (EVOO) and virgin with the first being the best choice due to the least processing it involves. What makes olive oil different from other oils is that it is the least processed oil and therefore keeps all its healthy compounds. Other oils that have been edited produce during the process bad products that can alert their

composition. Another benefit of olive oil is that it is very stable in high temperatures, especially when it comes to frying food, unlike other commonly used oils, such as corn oil. Fatty acids are prone to oxidize due to high temperatures and lead to the formation of peroxides, polymers, and products of peroxides cleavage, which can deteriorate health. The stability of olive oil is based on MUFAs like oleic acid and natural antioxidants. Furthermore, the presence of acrolein in other oils is related to the synthesis of acrylamide in starchy foods that are fried. This compound is considered carcinogenic and mutagenic. Furthermore, olive oil can be fried many times over, from four to five times even, but always after proper filtration. Additionally, olive oil consists of squalene, a substance that is a prodrug of sterols. Finally, fatty acids increase bile secretion by helping the digestion of other foods. The body is capable of absorbing a high proportion of nutrients due to the degree of digestion reaching 98%. [3]

3.1 MD and CV system

Studies have demonstrated that olive oils can provide health benefits to the CV system. Countries that follow the MD have shown lower mortality rates having CV diseases in comparison to other countries. According to Maria-Isabella Cova's studies at the University in Spain, people consuming olive oil are less likely to develop hypertension, stroke, hyperlipidemia, and thrombosis. [7] Moreover, Food and Drug Administration (FDA) and Europe Safety Authority recommended 20g of oil daily to prevent heart problems. Generally, it has anti- and pro-inflammatory, antioxidant, and anticoagulant effects resulting in the prevention of atherosclerosis and CVD. [8] Also, it has been shown to increase nitric oxide, which may help to reduce oxidative stress and have vasodilation properties. Arginine is catalyzed by some enzymes, one of which is produced in the endothelium. When arginine corporates with an enzyme it converts nitric acid to oxide which then dilates the arteries, improves blood circulation, lowers blood pressure, and helps the supply of oxygen and nutrients to tissues. [9]

Antioxidants contained in olive oil, especially phenols, can protect cells from damage due to the neutralization of free radicals, which if they are in high content, can cause oxidative stress and lead to cell damage and cancer. Olive oil increases high-density lipoproteins cholesterol (HDL-C) and reduces triglycerides and low-density lipoprotein cholesterol (LDL-C) ("bad" cholesterol). Oxidized forms of LDL can be more damaging than native and promote atherosclerosis, while the increase of oxidized form in blood circulation is a sign of developing coronary heart disease. [10]

Speaking of phenols, it is crucial to mention oleocanthin, which is present only in olive oil in ranges about 284-711 mg/kg and acts as an anti-inflammatory. It can reduce the production of elements that trigger inflammation like tumor necrosis factor alpha (α-TNP), interleukin, and thromboxane and inhibit the action of pro-inflammatory enzymes like COX-1 and COX-2. It can also reduce the action of C-reactive protein (CRP) and decrease the reactivity of arachidonic acid. In other words, oleocanthin can be compared with the action of non-steroidal anti-inflammatory drugs, which relieve inflammation and pain. The same action strengthens by vitamin E and especially from the substance a-tocopherol. [11]

3.2 Oil and prevention of other diseases

So, it is explained that the benefits mentioned above can also have a positive impact on metabolic syndrome due to a decrease in obesity, blood sugar, and LDL-C. In addition, there are some indications that MUFA's and phenols protect the human from diabetes mellitus type 2 (DMT2) and reduce the risk by 40% as they enhance pancreatic β-cells function and lower insulin resistance. [12] Also, there is mentioned evidence that olive oil, in combination with fish oil, helps rheumatoid arthritis due to its anti-inflammatory properties as they relieve joint pain and swelling. [13]

Another effect of oil is the antimicrobial and advantageous impact on gut microbiota. The consumption of oil can protect from Helicobacter pylori. This is a bacterium that can cause stomach ulcers by reducing the infection and attacking 8 strains of bacteria and reducing the risk by 10-40%. [14] Furthermore, consuming olive oil, first thing in the morning, on an empty stomach, can help with constipation, due to normalization of the intestine and an increase of water in the anal channel. [15] Last but not least, some studies have shown that substances like oleocanthal have antitumor effects as they protect cells from oxidation and apoptosis, reduce cell proliferation and increase activation of 5'AMP activated protein kinase. As a result, these compounds can protect the formation of breast, prostate, and colorectal cancer. However, many studies have to be made to confirm the above. [18] Finally, a study of Kaddoumi about oil has shown that oleocanthal can reduce the progression of Alzheimer's disease by reducing the development of beta-amyloid plaques in brain cells and neuroinflammation. Of course, for all mentioned diseases the impact of oil must be investigated further. [16]

4. FISH AND FISH OIL

Fish consumption is another very beneficial nourishment of MD. According to Balami et. al. (2019) fish is composed biochemically of 65-80% moisture, 15-20% protein, 5-20% fat and 0.5-2% ash. Ω-3 and more specifically DHA and EPA add high value to the beneficial role of fish along with vitamins and minerals. [17] High amounts of DHA have been found in the brain and retina making it important for memory, learning and brain development, especially for infants and children. The interesting fact is the research of Lucas et al. suggest that infants taking maternal milk are found to have greater IQ level, better short-term memory and are more concentrated at the age of 8 than those who received another type of milk. Crucial is also to define the appropriate dosages of fish and dosages related to a sensitive group of people like pregnant women and children, therefore according to FDA and Environmental Protection Agency suggested for pregnant and breastfeeding women 2-3 servings per week of low mercury level fish and for children 1-2 times per week adjusted doses according to their age and calories intake. Also, Dietary guidelines for Americans in 2015-2020 indicate to adults to take at least 8 ounces of fish per week according to the 2000 calorie diet. [4,18]

4.1 Fish and cardiovascular benefits

Seafood is known for its cardiovascular and anti-inflammatory benefits. A positive effect on the reduction of CV diseases is suggested to be the anti-inflammatory role of ω-3. Numerous epidemiological studies, clinical trials, and population-based cohort studies certified that the decrease of coronary mortality and risk of sudden death is caused by higher fish consumption. In the past, it was first observed that Inuit people, who consume more fish products, have 33-50% lower levels of LA and higher EPA compared to Danish indicators and generally to a Western way of life, which show that ω-3 and its function to inhibit the synthesis of thromboxane and prostacyclin can explain lower incidents of ischemic heart disease. According to research published in the Japan Public Health Center-Based Cohort I, middle-aged persons who consume marine items had a lower risk of nonfatal CVD (HR=0.43, 95%, 0.23-0.81). A meta-analysis of prospective studies made by Marckmann and Gronbaek showed that only high-risk populations benefit from the positive effects of fish. [4] In a cross-sectional study, which was held between April 2018 and August 2018 at the Healthy Planning Centre of Nihon University Hospital, 4,105 healthy people consuming fish on an average of 2.3+-1.3 days per week, were found to have a reduction in white blood cell counts. It was assumed that fish consumption may be related to healthier lifestyle choices, which may finally result in the prevention of atherosclerotic CVD and decrease the incidence of coronary artery disease. [19] Furthermore, 7 case indicators and 20 cross-sectional studies were combined in this meta-analysis made by Guo et al. showing that increasing levels of ω-3 were highly connected with reduced risk of metabolic syndrome (OR+0.63,95%CI:0.49-0.81). Another study by Eslick et al. showed that consuming fish approximately 3.25g of DHA/EPA can lead to the decrease of triglycerides (-0.34mmol/L,95%CI: -0.41 to -0.27) and a marginal rise of HDL (0.01mmol/L,95%CI:0.00 to 0.02). [20] In the Nurses' Health Study, fish consumption was also associated with decreased risk of death in 5,103 diabetic women. An important study of omega-3 supplementation in CV disease in 68,680 people found no connection between it and a lower risk of all-cause mortality in contrast to three prospective cohort studies(n=>53,00) from China, Japan, and the United States provided a correlation between fish intake and a reduction of all-cause mortality. [4,21]

5. VEGETABLES AND FRUITS

MD's mainstays are fruits and veggies. They are rich in vitamins, fibers, minerals, and phytochemicals making them an essential part of a balanced diet. Anh- Jarvis et al. categorize the dietary flavonoids into 4 classes based on their chemical structure. These groups are:

- flavonols (quercetin, kaempferol, myricetin) present in onions, tomatoes, broccoli, celery, grapes, and apples
- flavones (luteolin, apigenin) contained in parsley, celery, and thyme
- flavanones (cyanidin, malvidin, petunidin, pending) noticed in grapefruits, oranges, lemons, citrus peel, and fruits
- flav-3-ols which appear in green tea, red grapes, and red wine. [4]

Fruits and vegetables mainly consist of anti-inflammatory, antioxidant, and electrolytic properties and contain functional characteristics like glycemic load and energy density. They also work as metal chelators and can regulate cell signaling and gene expression. Fruits and vegetables differ quantitatively and qualitatively between their antioxidants and bioavailability, making unclear which the optimal portions per day are or whether they must be consumed fresh, processed, or dried. Recently, dietary guidelines from the US Department of Agriculture in 2010 suggest an optimal quantity of 9 servings per day, 4 fruits (2cups), and 5 vegetables (2,5 cups) based on a 2000kcal diet. [22]

5.1 Preventing CVD with fruits and vegetables

As demonstrated previously, the development of CVD is strongly related to the existence of numerous risk variables. The consumption of fruits and vegetables can follow many preventive strategies, like reducing blood pressure and oxidative stress. Their consumption may improve the lipid profile of a person and add anti-inflammatory action as well as antithrombotic action to the body. This will result in a decrease in obesity and shift a person to a healthier dietary pattern. [27,28] In a randomized clinical trial, over a period of 12 months, Epstein et al. observed that overweight people following the advice to eat fruits and vegetables had obesity decreased by 12% compared to people that were obliged to restrict the intake of fat and sugar, which was only 3,9%. Also in a 12-year follow-up study by Nurses' Health Study, it was observed that an increase in fruits and vegetables decreases the possibility of obesity Body Mass Index (BMI>30) by 26%. However, many can be the potential ways of this decrease. For example, higher water and fiber content intake or low energy density, can promote weight control by increasing satiety or substituting food with high energy density and modulation of metabolic pathways as insulin action. [23]

5.1.1 The role of fruits and vegetables in the prevention of DM

Another health risk for the development of CVD can be DM, as evidenced by cross-sectional and prospective studies the consumption of fruits and vegetables can lower the risk of DM. Of course, not all of them confirm the relationship of fruits and vegetables with the reduction of DM due to the overall impact of other foods and healthy diet as well as there is a need for trials to specify the fruits and vegetables that would help. A 6-year follow-up study from Iowa Women's Health Study showed no correlation between fruits and vegetables and DMT2. Other studies, like Williamses et al., show that people eating salad and raw vegetables constantly had a reduced incidence of DMT2 and impaired glucose tolerance than those who did not eat fruit and vegetables (OR 0.18, 95% CI, 0.04 to 0.81). Furthermore, 5996 middle-aged women and men without knowing to have DM were studied to see if there was a link between fruits and vegetables and glycosylated hemoglobin levels. Attendees who were eating fruits and cruciferous veggies had a reduced mean percent of glycosylated Hemoglobin A1c (HbA1c) (5.34% SE of 0.01) than others eating little or none (5.41% SE of 0.03, p=0.046). [23] In a cross-sectional study of 4774 Iranian participants, an association was found between intake of potato, diabetes, fasting, blood sugar and low serum HDL (OR 1.38,95% CI,1.14-1.67, p<0.001;

OR 1.40, 95% CI,1.17-1.68, p<0.001; OR 0.10, 95% CI, 1.01-1.20, p=0.02). In another, cross-sectional study of women consuming more than 10 servings of tomato-based goods each week, there was an improvement in their total cholesterol (TC) 5.38mmol/L, HDL-C ratio of 4.08 and HbA1c 5.02%, compared to women consuming less than 1.5 servings per week (5.51mmol/L, p=0.029; 4.22, p=0.046; 5.13%, p<0.001). [24]

5.1.2 Fruits and vegetables decrease hypertension

A cross-sectional study was made, involving 3995 participants. These participants lived in the Mediterranean area and were at high CV risk. The study was based on the consumption of gazpacho - a soup based on vegetables containing many phytochemicals. The study showed that there was a decrease in both systolic and diastolic blood pressure (BP) for those who consumed the soup in moderation rather than to the higher amount (1-19g/day to up to 20g/day). The participants that consumed a higher amount intake, approximately 250g/week, showed greater incidences of decrease in hypertension compared to the control group (OR 0.85, 95%CI: 0.73-0.99 and OR 0.73, 95% CI: 0.55-0.98). [24] Approaches to Stop Hypertension, (DASH) observed among 459 adults with systolic BP lower than 160mmHg and diastolic BP between 80 and 95mmHg, showed that participants who consume a diet full of vegetables and fruits for 8 weeks had a reduction of systolic BP by 2.8mmHg(p<0.001) and diastolic BP by 1.1mm Hg (p=0.07). In addition, they showed a reduction of 5.5 and 3.0 mm Hg in participants who followed a combination diet full of fruits vegetables and low-fat dietary products. [23] Also, the results of this study show constant levels of body weight and sodium intake. It was also reported in a three-armed clinical trial, that participants in behavioral intervention, such as weight loss, salt reduction, regular physical activity, and consumption of a restricted amount of alcohol, show a lower reduction of BP compared to participants in behavioral intervention including DASH (fruits and vegetables). However, both show better results for participants having only the advice to follow these habits. [22,23]

Toledo and Martinez-Gonzales summarized nutritional epidemiological studies in Western countries, China and Japan, and discovered a connection between higher consumption of fruits and vegetables with reduced incidences of CVD. Moreover, Miller and colleagues in a systematic review including 95 epidemiological studies(n=226.910-2123415) from 18 countries reported that moderate consumption of fruits, vegetables, and legumes eliminated the risk of cardiovascular events and stroke by 27%-39% and reduction of mortality by 35% compared with smaller intake (1serving per day). Potential beneficial components can be fibers, potassium, magnesium, and folate. When compared to the usual American diet, fruits and veggies in the DASH diet enhance potassium and magnesium levels by around 3 times. [4] A randomized control trial has shown that supplementation with potassium reduces BP in hypertensive persons as well as in normotensive. In two, randomized crossover trials, made by the same teamwork, it was found that 10 healthy male participants receiving a low potassium diet had increased systolic BP by about 4 mmHg p<0.05. In 12 hypertensive participants, an observation of both increments in systolic and diastolic BP was about 7mmHg, p=0.01, and 6mmHg, p=0.04

each consuming a low dietary potassium intake. So it can be suggested by evidence that a diet high in fruits and vegetables with high potassium intake can be protective against stroke via decreasing the risk of high BP or directly lowering the risk of stroke and CVD. In southern California, Khaw and Barrett-Connor observed a strong inverse relationship between potassium consumption and stroke mortality among 859 female and male retirees. This evidence confirmed also Ascherio et al. in a cohort study of 43.738 male health professionals. In another way, dietary and serum folate levels are suggested to have associations with lower mortality rates from coronary heart disease, as folic acid and B12 are key enzymes and cofactors in the metabolism of homocysteine. Recently, in a representative adult population from the US was observed an inverse connection between intake of folate and stroke as well as a randomized trial the supplementation with folic acid and B6 decreases significantly the markers of endothelial dysfunction and development of atherosclerosis. [23]

5.2 Juices containing fruits and vegetables

There is a big dilemma and many discussions on the proper form fruits and vegetables have to be consumed. Large amounts of evidence showed that juices, being popular all over the world, as a part of a balanced diet can give beneficial results concerning cancer, neurodegenerative diseases, and CVD. The consumption of vegetable and fruit juice was identified to assist in achieving the recommended daily intake according to Dietary Guidelines and DASH. In the tables below there are studies concerning the influence of juices on pressure and blood lipids. [25]

Effects of juices on blood pressure.

Juices	Effective Components	Subjects	Study Types	Results
		Fruit juices		
Sweetie fruit juice	Naringin	Stage I hypertension	Cross-over	Decrease in systolic blood pressure (SBP) dose-dependent decrease in diastolic blood pressure (DBP)
Pomegranate juice	Ellagitannins and anthocyanins	Hypertensive	Randomized controlled	Decrease in SBP and DBP
Grapefruit juice	Flavanones	Healthy postmenopausal women	Randomized, controlled, crossover	No effect
Orange juice	-	Persons with hypercholesterolemia and hypertriglyceridemia	Randomized controlled	No effect
Clear and cloudy apple juices	Polyphenols	Healthy persons	Randomized crossover	No effect
Guava fruit juice	-	Healthy volunteers	Randomized, controlled	Decrease in SBP and DBP
Cherry juice	Anthocyanin	Healthy volunteers	Crossover	Decrease in SBP and DBP
Polyphenol-rich juices [1]	Polyphenols	Healthy individuals	Randomized, controlled	Decrease in SBP and DBP
Purple grape juice	Anthocyanin	Smokers	Pilot	Decrease in DBP
		Vegetable juices		
Commercial vegetable juice [2]	Minerals and vitamins	Healthy persons	Randomized, controlled, parallel-arm	Decrease in BP
Beetroot juice	Nitrate	Healthy persons	Randomized crossover, Randomized, controlled	Decrease in BP
		Persons with type 2 diabetes	Randomized, crossover	No effect
		Hypertensive subjects	Randomized, crossover	Decrease in BP
		Hypertensive individuals	Randomized controlled	No effects
Carrot juice	Fiber, potassium, nitrates, and vitamin C	Persons with elevated Plasma cholesterol and Triglyceride levels	Pilot	Decrease in SBP
Commercial vegetable juice [2]	Vitamin C and potassium	Persons with metabolic syndrome	Randomized, controlled, parallel-arm	No effects
Yam bean root juice	nitrate	Healthy volunteers	Randomized, controlled	Decrease in DBP
		Mixture juice		
Fruit and vegetable powder juice [3]	-	Healthy persons	Pilot	Decrease in SBP and DBP

[1] Juice based on cherries, chokeberries, red grapes, bilberries, and blackcurrant; [2] Commercial vegetable juice (V8®; Campbell Soup Company, Camden, NJ, USA) that provided Vitamin A, Vitamin C, calcium and iron; [3] Encapsulated juice powder containing acerola cherry, apple, beet, tomato, etc.

Figure 2:Fruits and vegetable juices' effects and mechanisms on CV disease[25] **https://doi.org/10.3390/ijms18030555**

The table shows the impact of fruit and vegetable juices, specifically for individual kinds of food, on blood pressure and different studies that have been made to confirm or deny this effect. Also are reported the active components for this effect and the subjects used for each trial. As it is observed some juices have the opportunity to decrease both systolic and diastolic BP and some trials have also controversial results example beetroot juice which has shown no effect on hypertensive individuals but a decrease in BP for hypertensive subjects [25]

Effects of juices on blood lipids.

Juices	Effective Components	Subjects	Study Types	Results
Fruit juices				
Pomegranate juice	Ellagitannins and anthocyanins	Hypertensive	Randomized controlled	No effect
Orange juice	Vitamin C, folate, and potassium	Persons with hypercholesterolemia and hypertriglyceridemia	Randomized controlled	No effect
		Persons with normal and moderately high cholesterol blood levels	Cross-sectional	TC, LDL-C, apo B and LDL/HDL ratio were all significantly lowered [1]
Apple juice	Polyphenols	Healthy persons	Randomized crossover	Lower serum LDL-C for cloudy juice, no effect for clear juice
	Vitamin C	Healthy persons	Randomized crossover	Decreased trend in total cholesterol
Acai berry juice	Polyphenols	Junior hurdlers	Pilot	Improvement in lipid profile
Cranberry juice	Polyphenols	Healthy persons	Cross-sectional, association	A tendency of lower levels of cholesterol
Chokeberry juice	-	Healthy volunteers	Pilot	No significant effect
Vegetable juices				
Carrot juice	Carotenoid, anthocyanin	Healthy persons	Pilot	No effect
Tomato juice	Lycopene, minerals	Healthy persons	Randomized controlled	Decrease in serum cholestol, increase in adiponectin and triglyceride
Tree tomato juice	-	Persons with hypercholesterolemia	Randomized, controlled	Decrease in TC and LDL-C
Mixture juices				
Mixture of vegetables and fruits juice [2]	Minerals, vitamins, and polyphenols	Prehypertensive and hypertensive	Pilot	Decrease in HDL-C and apo A
Fruit and komatsuna juice [3]	Minerals, vitamins. and polyphenols	Healthy persons	Randomized controlled	Decrease in TC and LDL-C

[1] TC, total cholesterol; LDL-C, low-density lipoprotein–cholesterol; LDL/HDL ratio, low-density lipoprotein/high-density lipoprotein ratio; [2] It an encapsulated juice powder containing acerola cherry, apple, beet, tomato, etc.; [3] The fruit includes banana and apple.

Figure 3:Fruits and vegetables juices influence CV disease and their mechanism[25]
https://doi.org/10.3390/ijms18030555

The second table also shows a correlation of different kinds of fruits and vegetable juices but on blood lipids [25]

5.3 Management and prevention of kidney stones

Many studies have shown that a diet rich in fruits and vegetables may have a protective function in the management of kidney stones. Antioxidant phytochemicals like catechin, epicatechin, diosmin, epigallocatechin-3-gallate, rutin, hyperoside, quercetin, and curcumin can help with the prevention of urolithiasis, with a diuretic, antispasmodic and antioxidant role. Some small-scale investigation has demonstrated that people consuming a plant-based diet full of plant-sourced protein can see improvement of metabolic acidosis and decrease of glomerular filtration rate and for people suffering from chronic kidney disease improvement with further nephropathy progression. In addition, it has been identified that a plant diet can increase pH and volume of urine and quantities of stone inhibitors like phytate, citrate, potassium, and magnesium, which are connected with the supersaturation of calcium oxalate and uric acid. Specifically, natural food induces alkali load raising urinary citrate, which can prevent kidney stones. Phytate, being a source of phosphate, can develop insoluble complexes with calcium in the gut suppressing crystal formation, and dietary fibers, which connect with minerals and fats in the gastrointestinal tract (GIT), can suppress the excretion of oxalate and calcium. Parsley and oregano (Origanum vulgare) well used in Mediterranean dishes have some evidence that it efficiently helps with urolithiasis. In experimental studies parsley, due to its significant content of chlorophyll and magnesium-despite other components like flavonoids, carotenoids, coumarins, tocopherol, ascorbic acid- found to inhibit calcium oxalate and regulate the pH of urine in levels at which oxalate crystals could be left as dispersed particles and the excretion of them could have succeeded more easily. Oregano is known as a diuretic and antispasmodic ingredient. The aqueous-methanolic extract of its aerial part is shown in vitro activity in the nucleation and aggregation of calcium oxalate crystals, according to experimental studies in rats with ethylene glycol and ammonium chloride-induced urolithiasis. Furthermore, pomegranate, which contains antioxidant components, polyphenols, alkaloids, and anthocyanins, is very beneficial as if all components have something to add to its positive action. Pomegranate seeds are used to control urine discharge and provide relief from painful urination, seed oil, juice, flower, and peel are used to prevent nephrotoxicity and extracts are utilized for renal failure and renal arteries. Finally, a human study investigating the connection of fruits and vegetables and the probability of getting urolithiasis in women found no history of kidney stones, and the results were compared to stone recurrence in women who had previously had kidney. The results showed that fruits and vegetables contributed to the reduction of the risk of urolithiasis. [26]

6. ALCOHOL AND WINE

The history of alcohol creation begins many years ago. A beverage comprised of rice, honey, and grape-hawthorn fruit was identified in ancient China at approximately 7000 BC. Phoenicians, Greeks, and Roman established the diffusion of grapes making wine one of the Mediterranean diet's most common ingredients. Wine contains more than 500 compounds, 160 of them are esters, and the rest are water, ethanol (10-13%),

organic acids, such as acetic acid, malic, lactic acid, which control pH, sugar and essential component like polyphenols. Polyphenols are divided into non-flavonoids and flavonoids like quercetin, catechin, and resveratrol and specifically in red wine anthocyanin and tannins. To ecological studies, the content of polyphenols in white wine is 50-400 mg/L and for red much higher, 900-1400mg/L, therefore the intake of 250ml of white wine per day have 60mg of polyphenols and a glass of red wine 210mg, proving that red wine is more beneficial. [32] All the time, it is crucial to mention that a high intake of alcohol, especially heavy drinks as well beer, will not lead to desirable effects but the opposite, it will lead to risk for many diseases. In fact, 1 in 10 deaths among people aged 20-64 in the US is caused by an abnormally high intake of alcohol. In addition, it is critical to point out that although the preventive effects of wine, it is not recommended to non-drinkers for prevention but for people who have the habit to drink alcohol. Alcohol guidelines vary between countries, for example, the recommendation of the U.S is 1 drink for women and 2 for a man per day containing 14 gr pure alcohol and 14 units of alcohol per week for both men and women in the United Kingdom, with one unit comprising 10 mL pure alcohol. [4,27,28,]

6.1 Wine in the prevention of CVD and risk factors

Wine is considered to have profitable effects because of ethanol's influence on HDL-cholesterol, platelets, and coagulation, but not only, alcohol-free red wine due to polyphenols content considered to have antioxidant effect and scavenging of peroxidation which lead to prevention of oxidation of low-density lipoproteins and defend endothelial cells. Red wine suppresses platelet aggregation and eicosanoids formation, which can lead to incensement of prostacyclin and reduction of thromboxane and add vasodilation effect by acting properly on endothelial cells and influencing the production of nitric oxide, which is dependent on calcium. In research including 101 alcohol users aged approximately 60 who consumed small amounts of red wine on a regular basis, Da Luz et al, discovered greater HDL levels and reduced coronary incidence when compared to 104 non-alcohol consumers. More than 60 prospective studies considered that perceived alcohol consumption (1-2 drinks per day) can have a coronary protective effect and a meta-analysis of 13 studies revealed that wine can reduce vascular risk (RR 0.68,95% CI:0.59-0.77) when compared to nondrinkers. Beer was also found to be protective in 15 studies but without clear evidence. [4] Levantesi et al. studied the link between wine and incidence of a cardiovascular event and total mortality after myocardial infarction, using 11,248 Italian patients who have recently had myocardial infarction divided into groups never, up to 0.5L per day and over the amount of wine consumption. She observed that moderate wine consumption was connected to a decreased risk of cardiovascular events when compared to abstainers and the total mortality was lower with the intake of wine up to 0.5L per day. [34]

6.2 Alcohol and stroke

According to the Copenhagen City Heart Research, drinking wine alone can lower the risk of stroke. In 2014, a meta-analysis of five studies noticed a nonlinear, J-shaped relation between

alcohol consumption and stroke occurrence. Low levels of alcohol intake (<15g per day) were correlated with a reduction of stroke (RR0.85,95%CI,0.75-0.95) and moderate intake (15-30gr per day) was not implicated as the cause of stroke (RR 1.01,95%CI,0.93-1.09) compared to nondrinkers. [36] North Manhattan Study among a multiethnic population of moderate drinkers found a reduction of ischemic heart stroke by about 44% (HR 0.56,95%CI:0.39-0.81) and a follow-up study during 9.2 years assumed that intake of 1-6 drinks per week was linked to a slight reduction in the risk of ischemic stroke (RR 0.75,95%CI:0.53-1.06). Finally, brain-imaging studies revealed that alcohol consumption ranging from light to moderate could lead to a decline in the rate of silent strokes and white matter lesions. [4]

6.3 Wine and cognition

A systematic review verified the protective benefits of mild to moderate drinking for Alzheimer's disease and vascular dementia. [4] Possible mechanism of action suggested to be antioxidant and anti-amyloid beta-peptide (anti-Aβ) effect of polyphenols, with current models, propose that anti-Aβ therapies are effective in prevention or delay of development of Alzheimer disease or even to a patient having the disease in asymptomatic phase. [4,31]

Clinical Sample	Dose/Type/Experimental Models	Main Results
12,326 individuals from the Swedish Twin Registry	Beer, wine, or 6 cL of 80-proof spirits/questionnaire	>12 g of alcohol per day may increase risk of dementia.
589 multi-ethnic community residents of New York aged ≥65 years	Beer, wine, or liquor/FFQ	Protective effect of wine on brain
2613 participants, aged 43–70 years	Beer, wine (red, white and rosé), fortified wine and spirits/FFQ	Only moderate red wine consumption, associated with less strong cognitive decline
360 patients with early AD in New York, Boston, Baltimore and Paris	Alcohol intake/FFQ	Wine did not affect the rate of cognitive decline
5505 high-risk middle aged and elderly men and women	Beer, wine, spirits/FFQ	2–7 units of wine per week, associated with 32% lower risk of depression, yet heavy drinking can increase the risk of depression
1572 adults living in southern Italy	Dietary intakes of polyphenols/questionnaire	Higher dietary intake of flavonoid may be inversely associated with depressive symptoms.

FFQ, Food Frequency Questionnaire; RW, red wine; WW, white wine.

Figure 4: Studies about alcohol consumption [28] https://doi.org/10.3390/diseases6030073

As it is observed from the table, a cross-sectional study was made involving 589 elderly residents of New York from different ethnicities. By using a high-resolution structural MRI to assess the effect of alcohol on the anatomy of the brain, a dose-response association was found between wine and brain volume. There was a display of a protective role of wine on the brain but none of the other drinks. In the Doetinchem Cohort Study, including 2,613 participants at the beginning of the disease, it was observed during 10 years of study that red wine consumption was found to be connected with a deterioration in cognitive performance, flexibility, and memory with the best results shown for 1.5 glasses of red wine. Furthermore, a study proposes that 2 to 7 drinks of wine per week can be associated with a 32% reduction in the incidence of depression. [28] In Washington Heights- Columbia Aging Project in New York City a study with participants belonging to the age group higher than 65 (n=980) in 4 years' duration found that drinking less or equal 3 servings of wine exclusively can reduce in half the risk of Alzheimer disease. An interesting fact suggested by Kawas, is that moderate alcohol intake with additional benefits to cardiovascular and cerebrovascular can provide social engagement, which contributes to the maintenance of cognitive functions, especially to older people. [4]

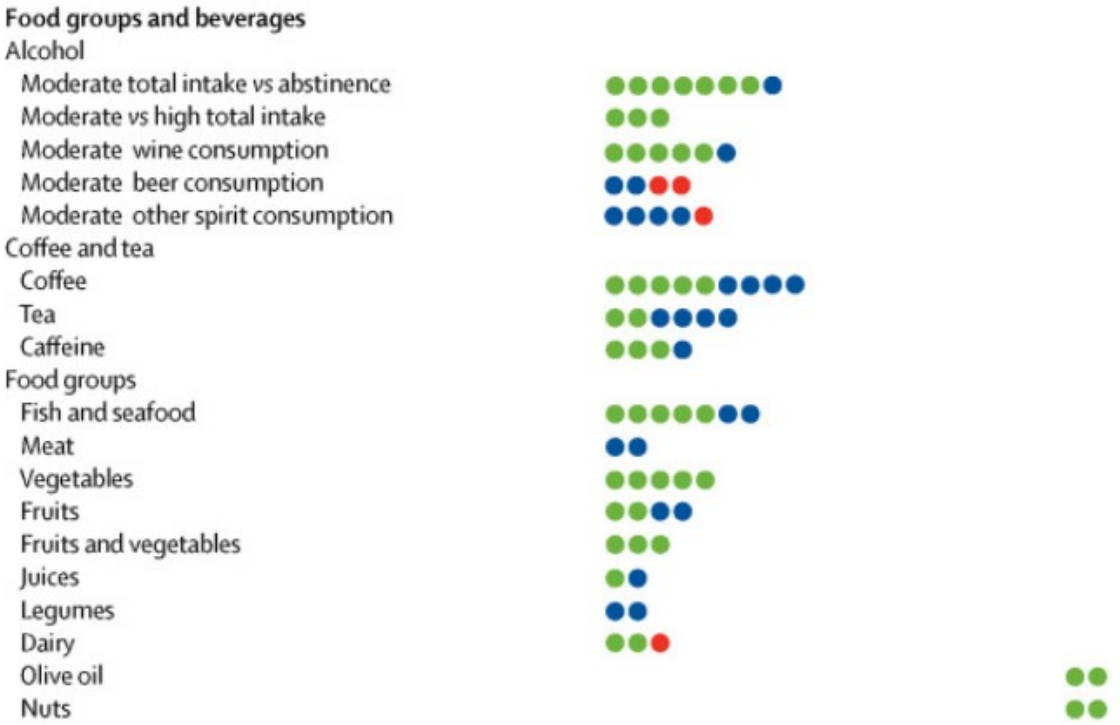


Figure 5:Studies about food and beverages in relation to cognition [30] https://doi.org/10.1016/S1474-4422(18)30338-7

In the first line there are observed observational studies and on the second one clinical trials about different kinds of food including alcohol and containing polyphenols related to cognition.

The meaning of the green circle is a protective effect, blue is considered to be neutral, with no significant effect, and the red circle has a harmful effect. [30]

6.4 Wine polyphenols influence gut microbiota

Moderate intake of wine is considered to have positive effects on gut microflora. The microbiota in the gut has a role in the metabolism of polyphenols and the metabolites strengthen the growth of bacteria and in this way prevent pathogenic bacteria. The metabolic pathway of polyphenols begins in the mouth continues to the gastrointestinal tract and ends up in the colon where they are broken down by gut microbiota releasing aglycones which are might be absorbed and produce other metabolites with greater activity and higher polyphenol bioavailability. Non-absorbed polyphenols and metabolites are assumed to influence gut development by modifying the variety of microorganisms. Specifically, flavan-3-ols and proanthocyanidins present in red wine have great evidence that helps the development of beneficial bacteria, as they produce more potent, active metabolites. [32] In conclusion, it is considered that polyphenols can act as probiotics empowering gut microbiota and defense system. [28]

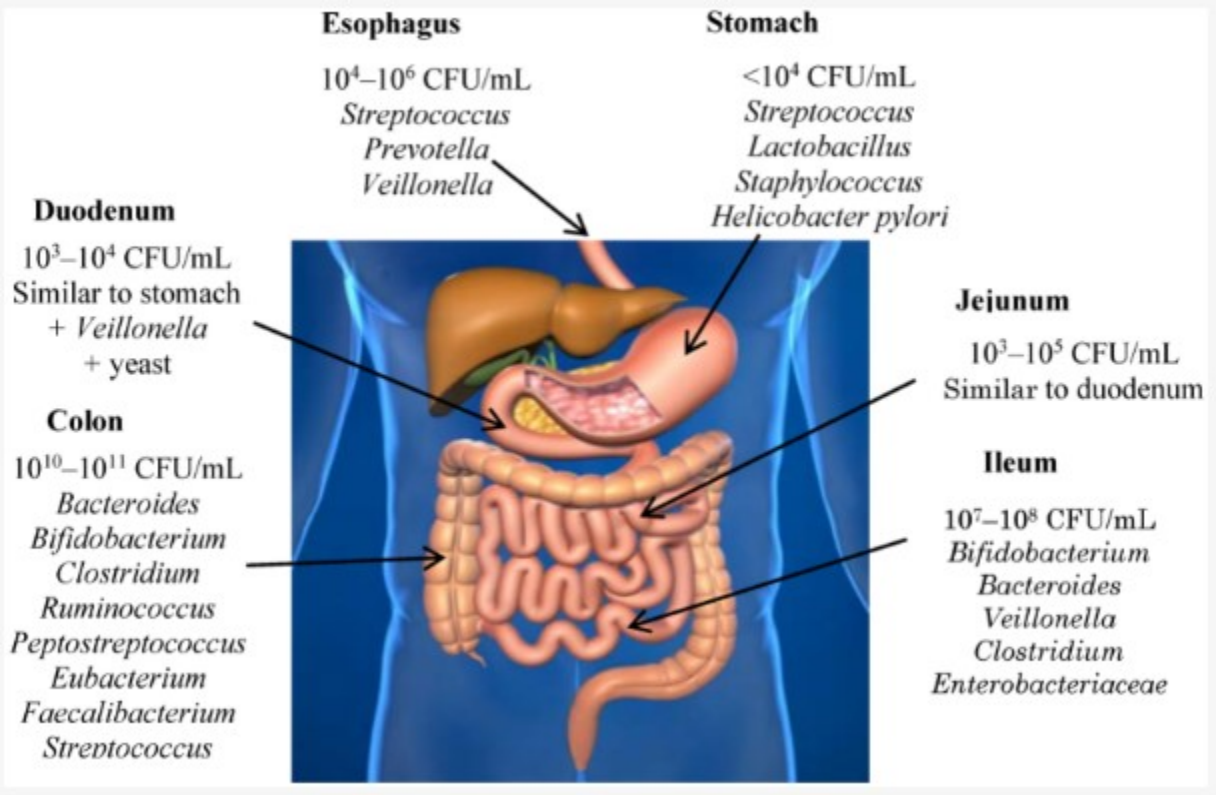


Figure 6:Composition of bacteria in GIT [32] https://doi.org/10.3390/antiox4010001

The picture shows the composition of bacteria present in different areas of the gastrointestinal tract [32]

Some studies explored the effect of different polyphenols contained in red wine using batch cultural fermentation and gastrointestinal stimulator. The aim is to determine the effect of polyphenols on bacterial proliferation or inhibition. (Fig6) [32]

Studies Using Batch Culture Fermentation

Fecal Concentration	Phenolic Compound/Food	Dose	Time of Incubation	Microbial Technique	Growth Enhancement	Growth Inhibition	No Effect
10%, w/v	(+)-Catechin	150 mg/L, 1000 mg/L	<48 h	FISH	*Lactobacillus–Enterococcus* spp.; *Bifidobacterium* spp.; *C. coccoides–E. Rectale* group *E. coli*	*C. histolyticum* group	
10%, w/v	Malvidin-3-*O*-glucoside Anthocyanidins mixture	20 mg/L and 200 mg/L 4850 mg/L and 48,500 mg/L	<24 h	FISH	*Lactobacillus–Enterococcus* spp.; *Bifidobacterium* spp.; *C. coccoides–E. rectale* group		
10%, w/v	Grape seed extract fractions	300–450 mg/L	<48 h	FISH	*Lactobacillus–Enterococcus* spp.	*C. histolyticum* group	
1% w/v	Red wine extract	600 mg/L	48 h	FISH		*C. histolyticum* group	*Lactobacillus–Enterococcus spp.*
	Red wine extract	500 mg/L	48 h	qPCR	*Lactobacillus* spp.; *Bifidobacterium* spp.; *Bacteroides* spp.; *Ruminococcus* spp.		
20% w/v	Red wine/grape extract	500–1000 mg/L	72 h	HITChip			

Figure 7: Effects of polyphenols in different kind of bacteria [32]
https://doi.org/10.3390/antiox4010001

Clostridium coccoides- Eubacterium rectale growth promotes the production of large amounts of butyrate, a short-chain fatty acid having anti-inflammatory and antineoplastic properties. [32]

Studies Using a Gastrointestinal Simulator							
Simulator	Phenolic Compound/Food	Dose	Time	Microbial Technique	Population Increase	Population Decrease	No Effect
Twin-SHIME	Red wine-grape extract	3 × daily dosing (1000 mg polyphenols as total daily dose)	2 weeks	Plate count qPCR PCR-DGGE; Pyrosequencing	*Klebsiella* spp.; *Alistipes* spp.; *Cloacibacillus* spp.; *Victivallis* spp.; *Akkermansia* spp.	Bifidobacteria; *Blautia coccoides* group; *Anaeroglobus* spp.; *Subdoligranulum* spp. *Bacteroides*	

Figure 8:Effects of red wine grape using a gastrointestinal stimulator [32]
https://doi.org/10.3390/antiox4010001

The effect also of wine was observed in human models. Queipo-Ortuno et al. in a randomized, crossover controlled trial conducted by 10 volunteers investigate the impact of wine, dealcoholized red wine, and gin revealing that only red wine has beneficial outcomes. (Fig7) [32]

Human Intervention Studies							
Volunteer Numbers	Phenolic Compound/Food	Dose	Treatment Duration	Microbial Technique	Population Increase	Population Decrease	No Effect
9	Proantocyanidin-rich extract from grape seeds	0.5 g/day	6 weeks	Plate count	*Bifidobacterium* spp.	*Enterobacteriaceae*	
10	Red wine	272 mL/day	20 days	qPCR	*Enterococcus* spp.; *Prevotella* spp.; *Bacteroides Bifidobacterium* spp.; *Bacteroides uniformis Eggerthella lenta Blautia coccoides–E. rectale* group	*Clostridium* spp.; *C. histolyticum* group	Actinobacteria

Figure 9:Human studies on the effects of wine on various types of bacteria [28]
https://doi.org/10.3390/diseases6030073

Finally, the connection between the red wine, inflammation, oxidation and fecal microbes was studied in 8 volunteers who intake 100 mL of red wine per day. There was observed lower serum concentration of malondialdehyde (increased production is a marker of oxidative stress), Bifidobacterium coccoides, Clostridium leptum, and Lactobacillus. [28]

7. VITAMINS

7.1 Vitamin D

Every person can produce vitamin D in the skin based on cholesterol precursor 7-dehydrocholesterol with the support of sunlight. The active form of vitamin D is calcitriol or 1,25-dihydroxy-D3 produced after exposure of skin to UVB light and through metabolic

processes in the liver and kidney. Vitamin D has an affinity to nuclear vitamin D receptor (VDR) present in many tissues like the intestine, parathyroid, osteoblast, tumor cells, T and B-lymphocytes, keratinocytes, ovarian cells and brain. Also, vitamin D can be consumed by food but in smaller quantities. [4,34]

As the table show marine products, not all of them but some kinds like cod liver oil, salmon, tuna, and sardines contain a high level of vitamin D as well as some other products like mushrooms, eggs, and dairy products, which sometimes are enhanced with vitamin. Vitamin D's function is to guarantee calcium and phosphorus absorption and maintain bone homeostasis. [35]

Food	Micrograms (mcg) per serving	International Units (IU) per serving	Percent DV*
Cod liver oil, 1 tablespoon	34.0	1,360	170
Trout (rainbow), farmed, cooked, 3 ounces	16.2	645	81
Salmon (sockeye), cooked, 3 ounces	14.2	570	71
Mushrooms, white, raw, sliced, exposed to UV light, ½ cup	9.2	366	46
Milk, 2% milkfat, vitamin D fortified, 1 cup	2.9	120	15
Soy, almond, and oat milks, vitamin D fortified, various brands, 1 cup	2.5-3.6	100-144	13-18
Ready-to-eat cereal, fortified with 10% of the DV for vitamin D, 1 serving	2.0	80	10
Sardines (Atlantic), canned in oil, drained, 2 sardines	1.2	46	6
Egg, 1 large, scrambled**	1.1	44	6
Liver, beef, braised, 3 ounces	1.0	42	5
Tuna fish (light), canned in water, drained, 3 ounces	1.0	40	5
Cheese, cheddar, 1 ounce	0.3	12	2
Mushrooms, portabella, raw, diced, ½ cup	0.1	4	1
Chicken breast, roasted, 3 ounces	0.1	4	1
Beef, ground, 90% lean, broiled, 3 ounces	0	1.7	0
Broccoli, raw, chopped, ½ cup	0	0	0
Carrots, raw, chopped, ½ cup	0	0	0
Almonds, dry roasted, 1 ounce	0	0	0
Apple, large	0	0	0
Banana, large	0	0	0
Rice, brown, long-grain, cooked, 1 cup	0	0	0
Whole wheat bread, 1 slice	0	0	0
Lentils, boiled, ½ cup	0	0	0
Sunflower seeds, roasted, ½ cup	0	0	0
Edamame, shelled, cooked, ½ cup	0	0	0

* DV = Daily Value. The FDA developed DVs to help consumers compare the nutrient contents of foods and dietary supplements within the context of a total diet. The DV for vitamin D is 20 mcg (800 IU) for adults and children aged 4 years and older [26]. The labels must list vitamin D content in mcg per serving and have the option of also listing the amount in IUs in parentheses. Foods providing 20% or more of the DV are considered to be high sources of a nutrient, but foods providing lower percentages of the DV also contribute to a healthful diet.

** Vitamin D is in the yolk.

Figure 10:Content of Vitamin D varies among different types of food [35]
https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/

According to the National Institute of health, this table shows a variety of foods and their vitamin D levels. [35]

7.1.1 Vitamin D and CV system

Vitamin D deficiency has been correlated to hypertension because its active components behave as a negative endocrine regulator of renin gene expression influencing the renin-angiotensin system. [4] Another mechanism suggested to be the reduction of BP and improvement of blood glucose levels in diabetic people, because β-cells express the vitamin D receptor to convert pro-insulin to insulin. [41] Some epidemiological studies found inverse associations between calcitriol levels in plasma and risk of myocardial infarction. Furthermore, VDR activation can protect against ischemic brain damage due to the influence in extracellular signal-regulated kinase 1 and 2. [4] Moreover, Gadheri et al. found that the supplementation with 50,000 IU vitamin D every 2 weeks for a period of 3 months could reduce the levels of triglyceride and LDL-C, helping the risk factors of hypertension. [41]

7.1.2 The role of vitamin D in cancer prevention

Many clinical and preclinical studies have linked the increased risk of different types of cancer with vitamin D deficiency. Inflammation is considered to be, one of the hallmarks of cancer, and vitamin D has a significant impact on the inflammatory system's regulation. First, Garland et al. proposed that lower levels of calcitriol are implicated with a greater possibility of developing collateral cancer. That was also confirmed by other studies. Gorham et al. suggested that vitamin D dosage in excess of 1000 IU per day can decrease colorectal cancer by 50% for people receiving less than 100 IU per day and Ma et al. found that increased serum levels of 25(OH)/D lessen the danger of colorectal cancer by 33%. Moreover, there is a link between vitamin D insufficiency and prostate and breast cancer, according to research. The study suggested that with a 20ng/mL increase of serum 25(OH)D levels, the risk of breast cancer is less likely to occur by 26% and a meta-analysis by Kim et al.- found every 100 IU per day increase of vitamin D levels can lead to a reduction of incidence of breast cancer by 2%. In addition, a meta-analysis of 17,332 cancer patients indicated that a 10nmol/L rise in calcitriol led to a 4% decline in overall mortality of cancer patients, and another case-cohort study made by Japan Public Health revealed that high vitamin D levels might reduce the risk of total cancer. Although even if a lot of mechanisms have been identified to prevent cancer via a high amount of vitamin D, additional search is required. [36]

7.1.3 COVID-19 prevention with vitamin D

Coronavirus is an illness that affects the respiratory system driven by Severe Acute Pulmonary Syndrome Coronavirus 2 (SARS-CoV-2). Nowadays, it is suggested that lack of vitamin D is linked with a higher prevalence of COVID infection, because vitamin D is an important anti-inflammatory micronutrient and has been reported to protect against respiratory infections and influenza [37,38]. Vitamin D strengthens the defense system of the body by inducing peptides like cathelicidum and b-defensin which induce pro-inflammatory cytokines, stimulate

chemotaxis and remove pathogens by apoptosis and autophagy, induction of it depends on plasma levels of calcitriol. [40] From 318 records, only 14 confirm that when compared to vitamin D- sufficient individuals, vitamin D insufficiency can increase the probability of COVID-19 infections by as much as 80% (OR 1.80,95% CI: 1.72,1.88) A study made in England in hospitalized patients with COVID-19 observed that vitamin D shortage was connected to higher disease severity and another study in Belgium suggested that vitamin D deficiency is a hazard indicator for life-threatening infection. Maghbooli et al. found that higher than 30ng/mL levels of 25(OH)D are connected to the reduction of the severity of COVID-19 infection-related clinical consequences. Moreover, a retrospective cohort study in Switzerland found that individuals being positive for COVID-19 had markedly less 26(OH)D levels compared to negative patients and D'Avolio et al. suggested that supplementation with vitamin D3 could be also efficacious in the therapy of COVID-19 by reducing the severity of symptoms and the presence of the virus. However, there are studies like the UK biobank that observed no connection between vitamin D levels and coronavirus. [38]

7.2 Vitamins and cognitive impairment

Important is the contribution of vitamin B, C, D, and E to cognitive balance in elderly people. Vitamin C and E (a-tocopherol) are strong antioxidant vitamins that provide protection against lipid peroxidation, mitochondrial damage, DNA mutations, neurodegeneration, and Aβ deposition. The brain is very susceptible to oxidative stress and low antioxidant activity can lead to the progression of dementia. Two studies are showing that people aged 55 years with higher vitamin C intake and 65 years old individuals with higher consumption of vitamin C together with vitamin D were found to have a lower rate of Alzheimer's disease. [30] On the other hand, nutritional epidemiological studies, propose that a combination of a-tocopherol and g-tocopherol can be associated with a postponement of cognitive deterioration in the elderly and lower the risk of Alzheimer's disease. (4) Possible mechanism of action may be the prevention of hyperphosphorylation of tau protein dysfunction and reduction of Aβ protein. [4,33]

	Major dietary sources
B vitamins	
B6[11]	Grains (wholegrain corn or maize, brown rice, sorghum, quinoa, and wheat germ), pulses, nuts and seeds, meat, liver and meat products, and fish
B12[12]	Animal products (dairy products, eggs, meats, fish, and liver), foods that contain yeast or have been exposed to microbial fermentation (eg, beer), and fortified foods (eg, ready-to-eat cereals)
Folate[13]	Dark-green leafy vegetables, legumes, oranges and grapefruit, peanuts and almonds, offal (liver and kidney), and baker's yeast
Antioxidants	
Vitamin C[14]	Fruits (berries, citrus fruits, kiwis, lychees, and papayas), vegetables (Brussels sprouts, cauliflowers, cabbages, sweet peppers, and tomatoes), and herbs and spices (parsley, sorrel, and chives)
Vitamin E[15]	Vegetable oils and fat spreads from vegetable oils, nuts and seeds, some fatty fish (eg, sardines, salmon, herring, swordfish, and trout), egg yolk, and wholegrain cereals
Carotenes[16]	Yellow or orange vegetables (sweet potatoes, carrots, and pumpkins), dark leafy vegetables (spinach, broccoli, and endives), and yellow or orange fruits (apricots, peaches, mangoes, and melons)
Flavonoids[17]	Fruits (mainly citrus fruits, bananas, and berries), vegetables (parsley and onions), tea (black and brewed)
Vitamin D[18]	Fish (especially fatty fish) and fish liver, full-fat dairy products (or fortified low-fat ones), egg yolk, meat and meat products, and offal (particularly liver)
n-3 fatty acids[19]	Fish (for eicosapentaenoic acid and docosahexaenoic acid) and some vegetable oils and nuts (eg, linseeds, rapeseed oil, and walnuts for α-linolenic acid)

Figure 11:Vitamins and where they are contained [30] https://doi.org/10.1016/S1474-4422(18)30338-7

7.3 Folic acid and Vitamin B

Folic acid, vitamin B6 and B12 deficiencies contribute to increasing the risk of cognitive impairment in elderly people. [33] The metabolism of homocysteine is mediated by folic acid, vitamin B6 (pyridoxine) through B6-dependent cystathionine-β-synthase and B12 (cobalamin) through B12-dependent methionine synthase. Methylenetetrahydrofolate reductase (MTHFR) gene mutation is relevant to age-related memory decline and late-onset of Alzheimer disease,

according to Roman, whereas cystathionine-γ-lyase gene mutation causes the rise of total homocysteine. That considered being a potential risk of dementia for adults over the age of 60, due to lower vitamin B12 absorption and cobalamin deficiency as we age, and to coronary disease, peripheral vascular disease, stroke as well as thrombosis due to oxidative stress. Evidences showed that vitamin B could decrease shrinkage up to 30% in elderly subjects with a high risk of dementia. However, there are other studies of the recent meta-analysis that showed minor or no effect in the prevention of dementia. In conclusion, studies proposed that the key factor of vitamin B therapy is the B12 and the elderly should have higher doses. According to Spencer et al. investigating the response of people to vitamins, found that patients receiving a higher amount of B12 have the greatest responses and vice versa. [4]

8. CEREALS

Grain cereals are classified into several kinds including wheat, corn, barley, rice sorghum, oats, rye, and millet. They are a good source of proteins, dietary fiber, antioxidants, carbohydrates, phytoestrogens, lignans, phytic acid vitamins such B-group and vitamin E and minerals (Fe, K, Mg, Zn, Se). Many of these components are eliminated during the milling process, and thus grains are better to be produced by wholegrain cereals, which their content is greater. Wholegrain cereals contain all the 3 parts of grain, bran, germ, and endosperm with the first two promoting health due to the additive and synergistic effect of their components. [4,42,43]

8.1 Cereals in the prevention of CVD and stroke

After ten to twelve years of studying 337 subjects, Morris et al. concluded that the consumption of cereal fiber was correlated with a reduction of CVD incidence. In addition, an analysis of cohort studies on dietary fiber showed that dietary fiber intake from grains and fruits was shown to be inversely related to the risk of coronary disease. In the Finnish study, there were examined 21,930 men-who smoked aged 50-69 years- for 6,1 years and the results showed that the increase of products containing rye lead to the reduction of risk of CVD. Also, a study by Rimm et al. amongst 43,757 health professionals, aged 40-75, in the USA, was made. This study showed, that cereal fiber is connected with reduced risk of myocardial infarction, with a 0.71 decline in risk per 10g increase in the ingestion of cereal fiber. [42] Two recent, prospective cohort studies revealed, that the increased intake of whole-grain cold breakfast cereal and bran was possibly connected with a decreased risk of ischemic stroke. [4] In the following table, many studies are shown investigating different kinds of cereals and if they benefit coronary artery disease, stroke, and CVD. Results reveal that generally refined grain, white bread, and total rice are not favorable to decrease the risk of diseases. [43]

Type of grain	High *v* low analysis				Dose-response analysis				
	No of studies	RR* (95% CI)	I^2	P value†	Dose (g/day)	No of studies	RR* (95% CI)	I^2	P value†
Coronary heart disease									
Whole grain bread	7	0.83 (0.75 to 0.92)	0	0.64	90	5	0.83 (0.76 to 0.92)	0	0.53
Whole grain breakfast cereals	4	0.72 (0.64 to 0.82)	0	0.92	30	4	0.81 (0.75 to 0.88)	0	0.69
Rye products	2	0.81 (0.70 to 0.94)	0	0.47	30	2	0.97 (0.91 to 1.05)	54	0.14
Added bran	3	0.78 (0.63 to 0.95)	65	0.06	10	2	0.72 (0.58 to 0.89)	34	0.22
Germ	2	0.73 (0.33 to 1.64)	65	0.09	2	2	0.88 (0.76 to 1.03)	0	0.65
Refined grains	4	1.16 (0.84 to 1.59)	48	0.12	90	5	1.13 (0.90 to 1.42)	57	0.05
White bread	2	1.07 (0.86 to 1.34)	50	0.16	90	2	0.96 (0.53 to 1.76)	86	0.007
Refined grain breakfast cereals	2	1.15 (0.79 to 1.67)	70	0.07	30	2	1.14 (0.75 to 1.73)	72	0.06
Total rice	4	0.98 (0.90 to 1.07)	0	0.44	100	4	0.99 (0.95 to 1.03)	7	0.36
Total grains	3	1.07 (0.91 to 1.25)	0	0.47	90	2	1.07 (0.88 to 1.30)	0	0.40
Stroke									
Whole grain bread	2	0.88 (0.75 to 1.03)	0	0.89	90	1	0.88 (0.72 to 1.07)	—	—
Whole grain breakfast cereals	2	0.99 (0.53 to 1.86)	77	0.04	30	2	1.07 (0.69 to 1.64)	78	0.03
Refined grains	4	0.95 (0.78 to 1.14)	23	0.28	90	5	0.91 (0.81 to 1.02)	29	0.23
Total rice	4	1.02 (0.94 to 1.11)	0	0.95	100	4	1.00 (0.97 to 1.03)	0	0.87
Total grains	4	0.89 (0.79 to 1.00)	6	0.36	90	5	0.93 (0.85 to 1.02)	62	0.03
Cardiovascular disease									
Whole grain bread	4	0.83 (0.75 to 0.92)	0	0.78	90	3	0.87 (0.80 to 0.95)	0	0.71
Whole grain breakfast cereals	2	0.74 (0.65 to 0.84)	4	0.31	30	2	0.84 (0.78 to 0.90)	0	0.82
Bran	3	0.82 (0.76 to 0.88)	0	0.64	10	2	0.85 (0.79 to 0.90)	0	0.37
Germ	2	1.06 (0.97 to 1.16)	0	0.41	2	2	1.05 (0.96 to 1.15)	0	0.41
Refined grains	2	1.02 (0.91 to 1.14)	16	0.27	90	3	0.98 (0.90 to 1.06)	56	0.11
Total breakfast cereals	2	0.80 (0.70 to 0.90)	55	0.14	30	3	0.80 (0.68 to 0.93)	73	0.03
Total rice	3	0.96 (0.90 to 1.03)	0	0.54	100	3	0.98 (0.95 to 1.00)	0	0.47
Total grains	3	0.94 (0.84 to 1.06)	0	0.47	90	1	0.83 (0.70 to 1.00)	—	—

Figure 12:Different types of grains and their influence on different diseases [43] 10.1136/bmj.i2716

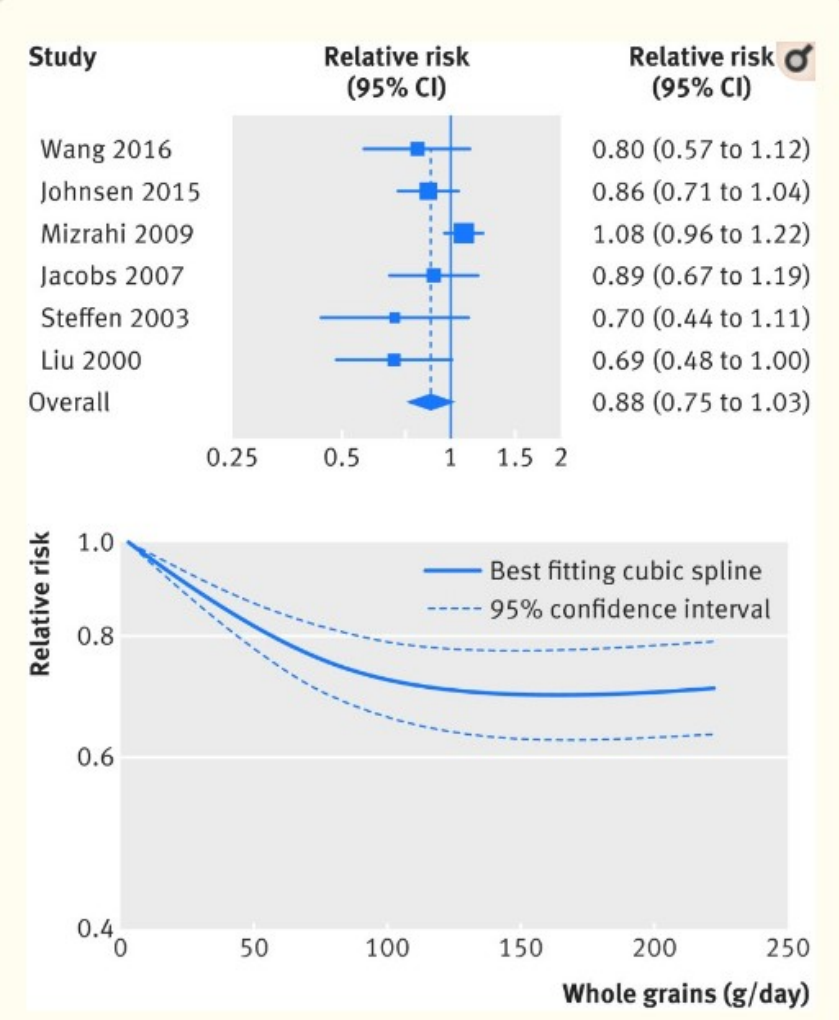


Figure 13:Trial about the association between intake of whole grain and stroke [43] 10.1136/bmj.i2716

The analysis of wholegrain diet and stroke risk comprised 2334 cases and 245012 individuals from six cohort studies. The evidence showed a good association between stoke and whole-grain intake but was also found non-linearity ($p<0.001$) and there was no reduction in risk above 120-150 g/day. [43]

8.2 Cereals in the prevention of DM

High consumption of wholegrain cereals and their derivatives, such as whole-wheat bread has been proven in several epidemiological studies to reduce the incidence of DM by 20-30%. Most cereals contain carbohydrates in different proportions but not only the quantity is important to add value to the type of cereal but also the rate at which it is assimilated. This is influenced by the kind of carbohydrate (glucose, fructose, sucrose, lactose), the origin of the starch (amylose, amylopectin), the method of preparation, degree of processing, and additional components such as slow-digesting pectin, phytates, and tannins. Pereira et al. assumed that whole-grain cereal increases insulin tissue responsiveness in overweight or obese people after analyzing hyperinsulinemic participants who were fat. 11 were participating, giving them 2 diets identical to each other with the difference that one of the refined cereals and bread were replaced with

whole grain products, each for 6 weeks. During the fasting state, the insulin was 10% lower by following the diet with whole grain products making it a possible mechanism of reducing diabetes and cardiac diseases. In research of postmenopausal women, Juntunen et al. discovered that the acute response of insulin was higher during the period of rye bread consumption than during the period of white wheat bread intake. Finally, Jensen et al. among 938 healthy men and women observed that the intake of whole-grain cereals was inversely relevant to plasma markers of glycemic control such as peptide-C, glycosylated HbA1c, and insulin during the fasting state. [42]

8.3 Grains in the prevention of cancer

Also, studies are assuming that eating wholegrain cereals lowers the incidence of some forms of GIT malignancies such as collateral cancer, polyps, digestive tract tumors, and pancreatitis. A review of 40 studies on gastrointestinal cancers found that people who consume substantial amounts of wholegrain products have a reduced risk of 21% to 43% compared to those who consume less. [42]

Total cancer									
Whole grain bread	3	0.89 (0.78 to 1.01)	42	0.18	90	3	0.91 (0.85 to 0.96)	0	0.63
Brown rice	3	1.07 (0.91 to 1.26)	27	0.26	100	3	0.98 (0.92 to 1.04)	0	0.61
Refined grains	1	0.98 (0.82 to 1.16)	—	—	90	2	0.94 (0.90 to 0.99)	0	0.60
White rice	3	0.87 (0.76 to 1.01)	53	0.12	100	3	0.98 (0.92 to 1.05)	49	0.14
Total breakfast cereals	1	0.90 (0.86 to 0.95)	—	—	30	2	0.90 (0.82 to 1.00)	36	0.21
Total rice	4	0.95 (0.88 to 1.02)	65	0.03	100	4	0.98 (0.95 to 1.01)	55	0.08
Total grains	1	0.92 (0.80 to 1.06)	—	—	90	2	0.97 (0.96 to 0.99)	0	0.51

Figure 14:Relationship of different types of whole-grain and cancer [43] 10.1136/bmj.i2716

There was an inverse association between wholegrain bread and total cancer, weaker for refined grains and total grains but no association for brown rice, white rice, total breakfast cereals [43]

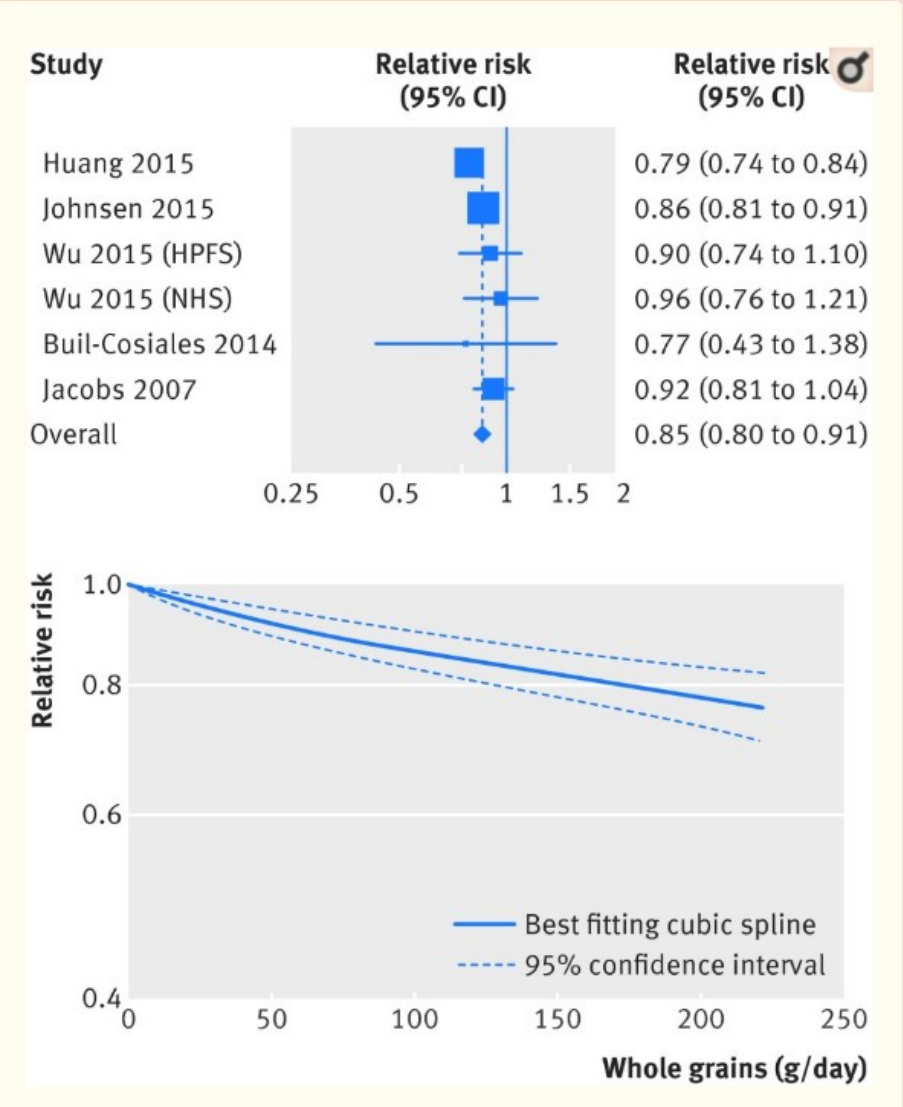


Figure 15:Studies about overall cancer and intake of whole-grains [43] 10.1136/bmj.i2716

The analysis of wholegrain consumption and overall cancer risk comprised six cohort studies, all of which showed a dose-response relationship [43]

9. DAIRY PRODUCTS

Milk, cheese, and yogurt are considered to be the most known dairy products with good evidence for preventing chronic diseases. Years ago, there were perceptions that dairy products are harmful to health, but in the last 10 years, the most cited general review highlighted their benefits of them. Many guidelines suggested an optimum intake of milk and other dairy products about 2-4 servings per day depending on age and sex, but still, the intake of these products is shown to move away from recommended levels in many countries. Dairy products are a good source of protein, vitamins, minerals and fatty acids. The exact levels and

components of dairy products are shown in the following table according to USDA- National Nutrient Database. [2,44]

	milk, 3.25% fat, vitamin D added	Cheddar cheese	yogurt, plain low-fat
proximates (g/100 g)			
protein	3.15	24.90	5.25
lipid	3.25	33.14	1.55
carbohydrate	4.80	1.28	7.04
minerals (mg/100 g)			
calcium	113	721	183
copper	0.025	0.031	0.013
iron	0.03	0.68	0.08
magnesium	10	28	17
manganese	0.004	0.010	0.004
phosphorus	84	512	144
potassium	132	98	234
selenium	0.0037	0.0014	0.0031
sodium	43	621	70
zinc	0.37	3.11	1.51
vitamins (µg/100 g)			
A	46	265	14
B_1 (thiamin)	46	27	44
B_2 (riboflavin)	169	375	214
B_3 (niacin)	89	80	114
B_6 (pyridoxine)	36	74	49
B_9 (folate)	5	18	11
B_{12} (cobalamin)	0.45	0.83	0.56
C	0	0	0.8
D	1.3	0.6	0
E	70	290	30
K_1	0.3	2.8	0.2

Figure 16:Milk, cheddar cheese, and yogurt constituents [44] https://doi.org/10.1021/jf5042454

9.1 Proteins

Proteins of dairy products are divided into two categories. α_{s1}-, α_{s2}-, β-, and κ-caseins make up 80% of the protein in the milk, while whey proteins such α-lactalbumin, β-lactoglobulin, and serum albumin make up the remaining 20%. The digestibility ratings of milk protein (95%) and casein alone (94.1%) are greater than those of soy, pea, wheat, and rapeseed proteins (84-91.5%), according to the Digestible Indispensable Amino Acid Score. [44] Casein and whey proteins are precursors of a large number of biologically active peptides, which are dormant and require enzymatic proteolysis to release bioactive fragments from protein precursors. The way, in which fragments can release, is during gastrointestinal digestion or food processing like fermentation with bacteria, Lactobacillus helveticus. [45] Bioactive molecules present mostly in research include IIe-Pro-Pro and Val-Pro-Pro. These peptides are in the group of angiotensin-converting enzyme inhibitory proteins and blocking the conversion of angiotensin I to angiotensin II can reduce BP. [44] Aihara et al. performed a 4-week research in which she provided powdered, fermented milk pills (12g) or placebo tablets to 40 participants with high-normal BP and 40 moderate hypertensives. A decrease in both systolic BP by 3.2 mmHg and diastolic by 5.0 mmHg ($p<0.05$) was observed in high-normal people, while in mild hypertensive people the results were better 11.2 mmHg ($p<0.05$) and 6.5 mmHg ($p=0.055$) respectively. Mizuno et al. performed a 6-week study including 40 people with high-normal BP and 83 mild hypertensives by giving them casein hydrolase (3,6mg/d) or placebo tablets. In the high normal group, no significant changes were observed but in the mild hypertensive persons, there was a reduction in BP by 11.8 mmHg and in diastolic 2.9 mmHg. [45] Another study, including 2500 Welsh men and over a duration of 22.8 years revealed that a high intake of milk (>586 mL/day) is associated with the decrease of systolic BP by 10.4 mmHg and lowers the rigidity of arteries. In addition, another study, including 2200 Rotterdam residents at least 55 years old showed that low-fat dairy products were connected with a 20% decrease in the incidence of hypertension. [44] Additionally, a recent placebo-controlled trial in 135 mild hypertensive people by Engberink et al. revealed no impact of milk-derived peptides on BP or angiotensin-converting enzyme activity after 8 weeks, questioning the bioavailability of the peptides and angiotensin-converting enzyme-inhibitory peptide amount in non-enriched milk products. [45]

Moreover, the high satiating effect helps to avoid over-consumption of energy and reduces body fat stores as well as helps to maintain the metabolically active muscles mass during weight loss and weight maintenance due to essential amino acids, which aid in muscle protein synthesis. It is typical for old people to consume below half of the daily protein needed, which perhaps progress to sarcopenia. The ingestion of whey proteins from 15 people around 60-85 years old has been discovered to enhance skeletal muscle. [44]

9.2 Obesity and DMT2

An important risk factor of DM is obesity. Furthermore, uncontrolled body weight may be a potential risk for other disorders including osteoporosis (underweight) and osteoarthritis (overweight). There is evidence that dairy products reduce body fat but not weight since lean

body mass is preserved. A meta-analysis of 14 randomized controlled trials (RCTs) including 883 adults showed that dairy consumption, at recommended doses without following caloric restrictions, had a smaller effect on weight loss. In addition, there was a decrease in fat mass and waist circumference and an increase in lean body mass. It was greater in participants following energy restriction, like modest benefit on weight reduction (-0.61kg,95% -1.29 to 0.07 p=0.08) greater reduction in fat mass (-0.72 kg, 95%CDI -1.29 to -0.14, p=0.01) and waist circumference (-2.19cm,95% CI -3.42 to -0.96, p<0.001), compared with indicators. In a study, among 22,557 men and 98,320 women in the USA, it was identified over a 4 years that yogurt intake was linked to a substantial decrease in weight gain. These results were in agreement with a cohort study among 8,516 Mediterranean men and women. This study showed that high (~7 servings/week) consumption of complete and whole-fat yogurt was attributed to a decreased prevalence of obesity in comparison to lower intake (0-2 servings/week). [46] A meta-analysis among preschool and elementary pupils showed no relation between dairy products and adiposity, but a modest protective effect among adolescence. Lu et al. in a recent meta-analysis found that children consuming high levels of dairy products when compared to the group that consumed modest quantities of fat, were 38% less likely to become overweight or obese. A one-serving increase in dairy consumption was associated with a 0.65% decrease in body fat and a 13% decrease in the risk of obesity. A recent meta-analysis including 22 cohort studies with a total of 579,832 people and 43,118 with DMT2 showed an inverse association between total dairy and yogurt intake and risk of DM, but no associations with milk intake. Several trials have shown that whey protein could decrease postprandial plasma glucose values in diabetic subjects due to leucine which has been demonstrated to stimulate insulinotropic polypeptides that are glucose-dependent, leading to higher insulin response and a decrease in blood sugar levels. [47] As shown in the following table, there are studies that contain dose-response analysis for the intake of dairy products by category. For the overall intake of dairy products, there is an association between them and DM for 200-400 g/d and 200g/d low-fat products but none for high-fat products. In addition, for milk intake, high in fat no significant effect was observed. However, one out of three studies pointed out the effect of 200g/d low-fat milk with RR 0.89. For cheese consumption, RR ranged from 0.80-1.00 with significant outcomes in 2 out of 3 studies, 50g/d (RR=0.92) and 30g/d (RR=0.80). [48]

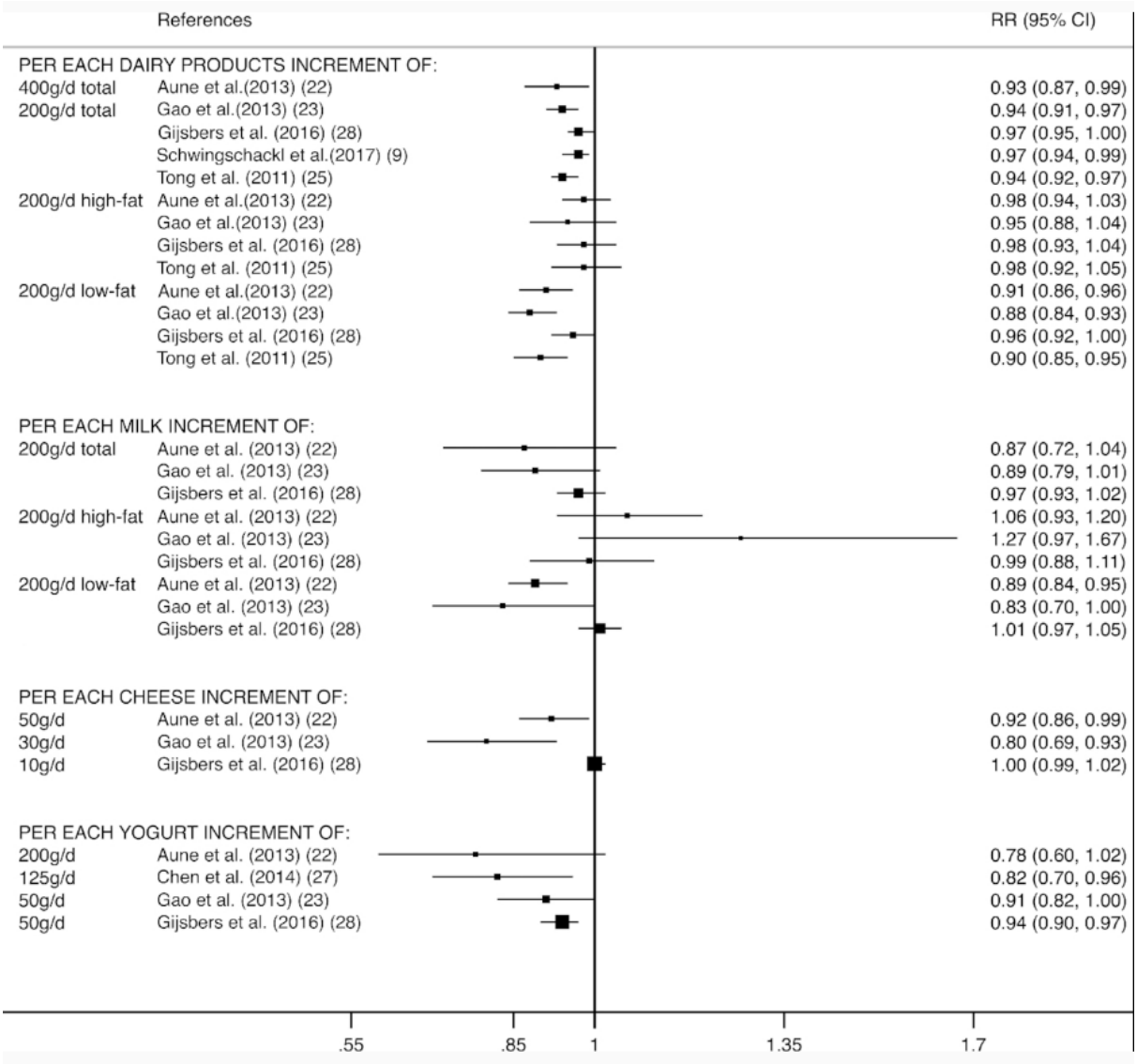


Figure 17:Dose-response dairy products consumption with risk of DM [48]
https://doi.org/10.1093/advances/nmy097

9.3 Minerals and cholesterol-lowering mechanisms

Many are the elements consist in dairy products. All of them contribute to the maintenance of the body, however, calcium (Ca) possess the most important component. Ca assist enhance of mineral density during skeletal development and prevent bone loss and osteoporotic fracture if consumed in sufficient amounts, especially in risky populations like senior and postmenopausal women. In addition, Ca is considered to help with the reduction of metabolic diseases including obesity, glucose intolerance, hypertension, and dyslipidemia. Higher consumption of dairy products was correlated to a healthier metabolic profile over a 5-year period in French research of 288 males aged 28-60 years, and higher intake of calcium was linked to a lower BMI and waist circumference. [44] More specifically, Ca is known to increase serum HDL-C and decrease

LDL-C as well as TC and improvement in HDL: LDL ratio. In 223 postmenopausal women were given 1g Ca daily as calcium citrate or placebo and was found that HDL and HDL: LDL ratio increased by 0.13mmol/L and 0.06mmol/L respectively, but significant results were shown for total cholesterol and LDL. A potential mechanism is described by which Ca influence lipoprotein metabolism. Blocking of fat absorption in the gut is one proposed method, as Ca interferes with SFA (increase total and LDL cholesterol) to form Ca-fatty acid soaps, which increase fecal fat excretion. [45]

Dairy food (food code)	Calcium (mg)	Potassium (mg)	Phosphorus (mg)	Magnesium (mg)	Zinc (mg)	Protein (g)
Milk, full-fat 3.7 % (01078)	119	151	93	13	0.38	3.3
Milk, skimmed (01151)	122	156	101	11	0.42	3.4
Yogurt, plain low-fat (01117)[a]	183	234	144	17	0.89	5.3
Yogurt, fruit low-fat (01122)[a]	169	216	133	16	0.82	4.9
Cheddar cheese (01009)	721	98	512	28	3.11	24.9
Cottage cheese, non-fat (01014)	86	137	190	11	0.47	10.3
Ice cream, vanilla (19095)	128	199	105	14	0.69	3.5

Source Compiled from U.S. Department of Agriculture, Agricultural Research Service. 2013. USDA National Nutrient Database for Standard Reference, Release 26. Available from: Nutrient Data Laboratory Home Page: http://www.ars.usda.gov/ba/bhnrc/ndl [14]

[a] A higher content of calcium and protein may be found in American yogurts compared with those found in Europe, as milk powder is added to thicken the consistency. In Europe, the calcium and protein contents of yogurts are similar to those of milk

Figure 18:Nutrient content per 100g of different types of dairy product [46] 10.1007/s00223-015-0062-x

Food	Standard serving size[a] (g)	Calcium content/ serving (mg)	Calcium absorbed/ serving (mg)	Servings needed to equal 240 ml milk
Milk	240	300	96	1.0
Yogurt	240	300	96	1.0
Cheddar cheese	42	303	97	1.0
Tofu with calcium	126	258	80	1.2
Bok choy	85	79	43	2.3
Kale	85	61	30	3.2
Broccoli	71	35	21	4.5
Spinach	85	115	6	16.3
Red beans	172	41	10	9.7
White beans	110	113	25	3.9
Pinto beans	86	45	12	8.1
Rhubarb	120	174	10	9.5

Source Adapted from Weaver 1999 [20]

[a] 1 serving = 240 ml milk; 42 g (1.5 oz) cheese; 85 g green leafy vegetables

Figure 19:A comparison of the amount of Ca that is available for absorption in calcium-rich meals [46] 10.1007/s00223-015-0062-x

Another method involves bacterial hydrolases de-conjugating bile acids, small-intestine probiotics binding cholesterol, cholesterol conversion to coprostanol, and decrease of cholesteryl esters in LDL particles. Yogurt eating was found to lower total cholesterol and LDL by 4% and 5%, respectively, in a meta-analysis of short-term trials. Probiotics, according to

Cochrane collaborations, have been reported to be useful in regulating bowel activity and control of pathogens such as Campylobacter jejuni, Clostridium difficile, and Helicobacter pylori. [4] Irritable bowel syndrome patients with constipation were given fermented milk containing Bifidobacterium lactis, S. thermophiles, L. bulgaricus, and Lactococcus lactis for four weeks in a 28 cohort research. It was found that positive changes were made in the gut microbiome and restoration of butyrate-producing bacteria took place, which is beneficial for gut health. Clinical trials have shown that it can help with diarrhea caused by antibiotics, travelers' diarrhea, and rotavirus eating other fermented milk products including yogurt. [49]

10. EGGS

Chicken eggs are a great source of many macro and micronutrients. Their consumption has been increased over the years as they are rich in ingredients, especially in proteins, and they are an affordable choice for consumers. However, many studies and discussions have been made over the years concerning their consumption and their negative impact on cardiovascular and metabolic diseases, due to their high content in cholesterol. [50] Recently, the Dietary Guidelines for Americans (2015-2020) replaced prior recommendations from 2010-2015 that recommended limiting dietary cholesterol consumption to "not more than 300 mg/day" and instead advised people to consume "as little as possible", while following a balanced dietary pattern. Furthermore, the American Heart Association and the American College of Cardiology suggested limiting the intake of eggs for better prevention of rising cholesterol, despite the lack of evidence. Nowadays, the Therapeutic Lifestyle Changes and the DASH for the reduction of hypertension and hypercholesterolemia suggested no specific restrictions but follow an overall healthy dietary lifestyle pointing to Mediterranean patterns. Many experimental, observational and clinical trials have shown no evidence associating dietary cholesterol with the increase of blood cholesterol. However, in contrast, it is suggested that eggs can add a nutritive value and benefit adults, children, and the elderly with some restrictions to groups with underlying diseases. [52]

Source	*Recommendation*
Danish Technical University, FOOD[87]	Eat up to seven eggs a week, no limit for consumption of dietary cholesterol
Dietary Guidelines for Americans 2015[6]	Eat as little cholesterol as possible
French National Nutrition and Health Program[88,89]	1–2 servings of egg per day. No specific recommendations for consumption of dietary cholesterol
Mayo Clinic[11]	Consume no more than 300 mg of cholesterol a day
Mediterranean Diet Pyramid (Spain)[88]	Consume eggs 2-4 times weekly, serving size 50-100 g. No specific recommendations for consumption of dietary cholesterol
Nordic Nutrition Recommendations 2012[9]	No upper limit for either egg or dietary cholesterol
The Italian Dietary Guidelines[89]	No specific recommendations for eggs or dietary cholesterol

Figure 20:Recommendations of egg consumption from different sources and guidelines [53] 10.1038/ejcn.2017.153

Source	Recommendation
American Heart Association[15]	No upper limit for either egg or dietary cholesterol.
Australian Heart Foundation[85]	Up to six eggs per week can be included as part of a varied and healthy diet
British Heart Association[16,90]	Eggs are a part of a balanced diet
Danish Heart Association (Hjerteforeningen)[91]	Eggs are a good source of protein and vitamins and can be included as part of a varied and heart-friendly diet, but be aware in that the egg yolk has is high in both fat and cholesterol
European Society of Cardiology[92]	When guidelines are followed to lower saturated fat intake, this usually also leads to a reduction in dietary cholesterol intake. Therefore, some guidelines (including this one) on healthy diet do not give specific guidelines on the intake of dietary cholesterol; others recommend a limited intake of, 300 mg/day
German Heart Association (Deutsche Herzstiftung)[12]	Do not exceed 250–300 mg cholesterol daily and no more than two eggs a week
Mayo Clinic 2016[11]	Limit cholesterol to maximum 200 mg daily
New Zealand Heart Foundation[86]	Up to six eggs per week can be included as part of a heart friendly diet
Swedish Heart Association (Hjärt-lungfonden)[93]	No upper limit for either egg or dietary cholesterol

Figure 21:Recommendations of egg consumption from different sources and guidelines [53] 10.1038/ejcn.2017.153

10.1 Nutritive value of eggs

An egg is divided into egg white and egg yolk. Water occupies the biggest part of the egg, about 76,1%. The major components of an egg are stable and depend on the proportion of egg white and yolk. The minor nutrients are affected by the nutrition of the hen. On a whole, raw egg proteins are allocated between white and yolk in contrast with lipids, vitamins, and minerals, which are the main components of yolk. Egg white protein concentration is estimated to be around 110mg/mL and it contains fibrous structured proteins called ovomucins, glycoproteins called ovalbumin and protease inhibitors, antibacterial proteins like lysozymes, and finally peptides. On the other hand, the yolk contains 68% of LDL,16% of HDL, 10% of livetins and 4% phosvitins with apolipoprotein B, apovitellenin-1, vitellagenins, serum albumin, immunoglobulins, ovalbumin, and ovotransferrin occupy 80% of total proteins of egg yolk. Moreover, egg yolk contains lipids that are considered stable. They range from 8.7 to 11.2 per 100g of a whole egg, while the concentration of fatty acids depends on the hen's diet. In addition, eggs are rich in vitamins except for vitamin C and eating two eggs per day answers to 10% to 30% of daily vitamin requirements. Egg white concentrates high amounts of vitamin A, D, E, K, B1, B5, B6, B9, B12, while yolk contains vitamins B2, B3, B5, B1, B6, B8, B9, B12 with liposoluble vitamins strongly depending on hen's diet. Furthermore, egg yolk contains a high amount of choline in an amount of 680mg per 100g, with the boiled egg being the second bigger source of choline after beef liver, considered a very important component for neurotransmission. Moreover, egg yolk contains minerals with a higher amount of calcium and phosphorus. [51,52]

10.2 Association of dietary cholesterol from eggs and risk of CVD

The egg is well known for its high content in cholesterol, approximately 200mg in large egg yolk, being the biggest source of cholesterol in the Western diet. The Framingham Heart Study, which analyzed first the effect of cholesterol on CV problems suggested that dietary cholesterol was responsible for the elevation of lipids which led to atherosclerosis and heart diseases, but

there was no evidence to support this hypothesis. However, some studies show that the diabetic population may be negatively impacted by high egg intake, but interestingly not from its content in cholesterol, since it has been discovered that diabetics, obese people, and insulin-resistant people absorb it more poorly. It is hypothesized that phosphatidylcholine is responsible for the promotion of atherosclerosis as phosphatidylcholine generates trimethylamine N-oxide (TMAO) in the gut, a metabolite found in cohort studies to promote atherosclerosis. In a randomized long-term dietary intercession, healthy volunteers were participating and were consuming zero to up to 6 egg yolks within 24 hours. The outcome showed that intake of more than two eggs increases plasma TMAO, but none of the markers of CV risk was changed, for example, oxidized LDL-C and high-sensitivity CRP. Even so, the intake of 2-3 eggs per day does not elevate fasting TMAO concentrations in healthy young adults and even decreases postprandial TMAO in healthy men. [51,52]

10.2.1 Evidence involving healthy individuals

Bergel et al. performed a systematic review and a meta-analysis of 17 cohort studies and found that there is no significant correlation between dietary cholesterol and ischemic and hemorrhagic stroke or heart disease. Moreover, in 19 interventional studies which deal with the association of lipid responses to dietary cholesterol from eggs, Bengel et al. concluded that cholesterol could elevate significantly both serum LDL-C and HDL-C, which will lead to only a slight increase of the LDL/HDL ratio. The optimal ratio is lower than 2.5 (above that number there is an increase in the risk of developing cardiomyopathy). In crossover studies in which the cholesterol level of kids and adults was measured, it was found that LDL-C and HDL-C levels were both increased after 30 days of eating 2-4 eggs per day compared to a yolk-free replacement with no difference in the ratio. As it is known eggs are appropriate food for weight maintenance and loss giving a feeling of satiety. Eggs also are known to offer higher energy to individuals who exercise, because of their high content in proteins. Researchers, comparing a breakfast with 2 eggs per day and an isocaloric breakfast without eggs concluded that the first diet does not affect blood lipid amount in contrast with an egg-free breakfast. Moreover, studies including middle-aged men and premenopausal women consuming 3 eggs per day as well as adults and postmenopausal women taking 1 or 3 eggs per day for a month failed to change LDL-C and HDL-C concentrations. [52] Alexander et al. in a meta-analysis of 14 studies including healthy individuals found that eating one egg per day lead to a lower risk of stroke (0.88 CI:95% 0.81-0.97) about 12% and no risk of developing coronary heart disease (0.97 CI:95% 0.88-1.07) compared with individuals consuming lower than two eggs per week. Larsson et al. discovered that daily egg consumption was not related to myocardial infarction or stroke in a prospective cohort study involving approximately 3770 male and 32800 female individuals, but eating more than one egg daily was associated with an increased risk of heart failure in men (RR 1.30 95% CI: 1.01, 1.67) in contrast to women. In another study, Robbins et al. included healthy subjects from the National Heart, Lung, and Blood Institute. No connection between egg intake and risk of coronary artery calcium content was found. Oppositely, Choi et al. conducted a cross-sectional study, including 23417 healthy South Korean individuals. It was

found that subjects who eat seven or more eggs per day have a greater risk of developing coronary artery calcium compared to individuals eating less than one per week (1.80 95% CI: 1.14-2.83). In conclusion, it was found that egg consumption can lead to atherosclerosis due to high content in cholesterol with more intense outcomes in a population with excessively high BMI and consumption of small portions of vegetables. Also, Djousse et al. in a meta-analysis of 12 cohort studies including only US studies concluded that the uptake of three or more eggs per day increases the risk of DMT2. [53]

Egg consumption can also alter lipoprotein particle characteristics like size. Bigger particles of HDL-C are considered to be more protective against the formation of atherosclerosis and other heart diseases, while smaller particles of LDL-C are more prone to oxidation and thus contribute more to the development of atherosclerosis. There are some studies including healthy individuals during weight maintenance conditions, which are dealing with the correlation of dietary cholesterol from eggs with lipoprotein characteristics. In a crossover study including healthy subjects, Herron et al. found that by consuming 3 eggs per day versus consuming an egg substitute for a month, there was an increase in the concentration of large LDL particles. However, there was no change of oxidized LDL, while Greene et al. in a crossover study with the same parameters but including elderly individuals found an increase in the concentration of large LDL and HDL particles and an increase of the size of HDL. Ballesteros et al. including healthy children eating 2 eggs per day vs egg substitute found an increase in large LDL particle concentration and size and decrease of small LDL. [51]

10.2.2 Evidence involving individuals with underlying diseases

Herron et al. in a crossover study including 25 healthy men and 15 hyper-responders consuming 3 eggs per day vs. egg substitute, concluded that the ratio of LDL-C to HDL-C has risen, but still remained within the optimal range. Similar outcomes were conducted from Knopp et al. including hypercholesterolemic and combined hyperlipidemic individuals consuming 2 eggs per day vs egg substitute for 84 days resulting in an elevation in HDL-C with no alterations in LDL-C for hypercholesterolemic individuals and an overall rise in both LDL-C and HDL-C for combined hyperlipidemic individuals. Another crossover study by Knopp et al. contrasted lean insulin-resistant and obese insulin-resistant individuals eating 4 eggs per day for 28-day vs egg substitute and found that LDL-C and HDL-C were both increased in lean individuals in comparison to egg substitute, but only HDL-C was found to be elevated in obese individuals. Many studies suggest that diabetic people or overweight individuals following a diet with low calories for weight loss show no association with the rising of lipoproteins or their ratio. In fact, it is suggested that by lowering carbohydrate intake in obese people and by consuming a whole egg there may be an increase in HDL-C. Furthermore, this may even help the health of the heart. For example, Fuller et al. compared diabetic individuals consuming 12 eggs per week with individuals consuming lower than two. No changes in lipoprotein concentration were found. For 84 days, Blesso et al. compared eating 3 eggs per day to an egg replacement in men and women with metabolic syndrome. A small increase of HDL-C was found. In addition, there

seemed to be a lower number of the ratio, while LDL-C concentration was unchanged. [51] Moreover, in a crossover study including insulin resistant, sensitive, and obese subjects, it was observed that plasma concentration of HDL-C was increased after the intake of 4 eggs per day for 4 weeks. At the same time, LDL-C was also raised compared with HDL-C. In a study, people with metabolic syndrome who ate three eggs every day during a carbohydrate restriction were observed to have an elevation in HDL-C, LDL size, and decrease in triglycerides and fasting plasma concentration of α-TNF and CRP in contrast with individuals having an egg-free diet. [54] Overweight and obese people with DMT2 were not detected with impaired glucose metabolism in a randomized trial while eating 3 eggs per day for 12 weeks and restricting carbohydrates. The same applied to those eating 2 eggs per day for 12 weeks and being on an energy-restricted high protein diet and to those consuming 2 eggs per day for 6 weeks and being on a diet maintaining the weight. A prospective study including 4000 men and women from the Cardiovascular Health Study from 1989 to 2007 discovered no link between egg intake and the development of DMT2, but there are also studies claiming the opposite. Researches from Zutphen Study were associating egg intake with fasting glucose, while a prospective study involving 60000 people found a link between egg cholesterol and DMT2. Moreover, a meta-analysis conducted by Shin et al. including 7549 diabetic patients found that egg consumption was shown to be unrelated to CV mortality, although patients who consumed more than one egg per day were 1.69 times more likely to have CV comorbidities than patients who consumed less than one egg. (HR 1.69 95%CI: 1.09-2.62) [53] Djousse et al. made a cross-sectional study including 4568 African-American people not diagnosed with TM2 with the majority being women. In this study, it was suggested that egg intake at the time of measure was positively associated with DM2 but in a prospective study for 7.3 follow up years of 3564 people of the same nationality but diagnosed with DM2 he claimed that egg was not connected with DM2 development. [53]

11. MEAT

Meat is an essential element of the diet due to the nutrients it contains, but its widespread consumption nowadays has sparked many discussions about its negative impact on chronic diseases and the environment. These issues are considered to concern more red and processed meat derived from mammals and less white meat derived from poultry. A working committee from International Agency for Research on Cancer detected processed meat as a “carcinogen to humans” and red meat as “probably carcinogenic to humans” for collateral cancer but the moderation of its consumption does not seem to raise health concerns. It is therefore critical to note the nutritive value of meat and its necessity, ways we can improve their perception as well as studies which show that meat can lead to some diseases and therefore the need for reducing its quantity. [55]

11.1 Nutritive value of meat and benefit to human health

Eating meat gives the body many important sources of proteins, fatty acids with the most important content of ω-3 PUFAs, vitamin A and B-complex, and micronutrients such as iron,

zinc, selenium, potassium. Their concentrations vary according to the breed, type of feeding, and meat part. [58]

11.1.1Proteins

Proteins and their essential amino acids provide adequate nutrition for the growth and maintenance of the body in adults and children and excess protein gives energy, a feeling of satiety, and helps individuals to reduce their weight. [56] Older people due to aging and loss of skeletal muscle mass, a disease called sarcopenia of sarcopenic obesity - a very common disease in the UK among elder people, is important to consume high-quality proteins to prevent the disease. However, the current recommendations of consuming meat do not allow the prevention of sarcopenia at the optimal levels, the branched-chain of amino acids with leucine, isoleucine, and valine which is crucial for the proteins synthesis, is higher in red meat than in plant origin goods, suggesting that meat could have a more preventive role on physical disability problems [56]

11.1.2 Fats

The biggest source of energy are fats and are derived according to the feed of animals, the type of meat, the cut, and the degree of trimming of meat products. Fatty acids are derived from saturated SFA which can harm health and led to CVD and to unsaturated like ω-3 and ω-6 which possess a preventive role to many CVD. Lean meats have a higher amount of PUFAs and lower SFA with visible fat-containing 37gof SFA per 100gr of meat. Although fish products are the primary source of ω-3 fatty acids it is estimated that meat accounts for up to 20% of ω-3 intake. [58] Fatty acid composition is affected by a ruminant intrinsic digestive system with microbial enzymes that enhance the isomerization and hydrolysis of unsaturated fat, affecting the stearic acid concentration with higher amounts reaching the small intestine which is the primary absorption site. Ruminants have high-saturated fatty acid absorption and hence a greater capability of bile salts and the lysophospholipid system to solubilize fatty acids. On the other hand, in the duodenum and jejunum, the low pH presents there about 3-6 can lead to a smaller amount of hydrogen carbohydrate, reduction in SFA conversion to insoluble Ca salts which will be not internalized by enterocytes. Thinking this process despite the amount of LA and ALA present in the meat the biggest fatty acid leaving rumen is stearic acid, which can be converted further to oleic acid. Also, trans-fatty acids are formed by hydrolysis of unsaturated fatty acids by rumen bacteria. This evidence has demonstrated the good effects on human health, in obesity, prevention of CVD and DM, but unfortunately, it is also mentioned that the concentration in beef is minimal, 1 g per 100 g and 10-46mg per 100 gr of trimmed fat meat. [58,59]

11.1.3 Minerals

Furthermore, meat is an important source of minerals with higher amounts of zinc, selenium, phosphorus, and iron. [59] Most importantly, iron plays a very crucial part in a child's development and growth. It is found in two varieties, heme-iron, and non-heme iron, with the

first one coming from animal sources from hemoglobin and myoglobin and is it easily absorbed from the intestine in contrast with non-heme iron coming from vegetables like spinach and legumes but with low bioavailability in the body from 2 to 20%. So it turns out, the bioavailability of iron from meat is two to three times more since 15-35% is absorbed from the body and also heme-iron can contribute to the absorption of non-heam iron from cereals and vegetables. [56] Studies report that 26.2 to 75.60% of the iron in meat is heme-iron, with beef having the highest amounts of iron, in lean about 45% to 77.58% with average values being about 58.10%. Chicken is reported to have lower amounts than beef with dark meat heme-iron around 39.20% and light meat up to 26.15%. Pork heme-iron values are between beef and chicken with studies reporting ranging from 38% to 60%. It is worth mentioning that meat consumption can provide up to 18% of a person's daily iron needs and thus prevent nutritional deficiencies but excessive consumption can lead also to toxicity. More detailed, high amounts of iron can hurt the intestinal mucosa and promote the production of free radicals, which will result in the disruption of tissues, collateral cancer, inflammations, CV diseases, infections, and neurodegenerative diseases. For this reason, the intake of iron must be balanced with the highest amount set at 45mg per day in the USA, an amount that will not cause any adverse effect to the organism. Other minerals have also their role in the human body. Zinc intake is important because it is responsible for enzymatic processes like cell division and growth, gene expression and immune defense functions and its deficiency can promote the risk of infections and oxidative stress. Selenium on the other hand, although found in fish products, meat can also contribute to daily consumption. it is the component of selenoproteins that are shown to have antioxidant effects and regulate the glutathione peroxide activity, a very essential enzyme in detoxification, mechanisms which can protect from CVD and cancer diseases. [56,59]

11.1.4 Vitamins

Red meat involves a number of vitamins like riboflavin (B2), niacin(B3), B6, thiamin(B1), pantothenic acid, vitamin A, folic acid, and B12. It is reported that red meat can contribute to 25% of recommended daily requirements of these vitamins per 100 gr of meat with B12 to be covered in 2/3 of the daily intake. Although some studies suggest that cooking meat alter the concentration of vitamin B due to the characteristic of the vitamin. Vitamin B complexes are water-soluble and susceptible to high temperatures so boiling and longtime cooking will increase the losses of vitamin B.

11.2 Lipid peroxidation and the role of the ingredients of MD

Studies have demonstrated that meat can cause CV diseases and collateral cancer, due to the high content of fats, which can oxidize during cooking or GIT digestion and generate toxic compounds bad for the organism. The mechanism which free radicals generate is the creation of hydroxyl and perhydroxyl radicals and the production of perferylmioglobin-containing peptides as well as the contribution of ferrous iron which catalyzes the H2O2 decomposition to hydroxyl radicals and formation of volatile and non-volatile compounds known as end–products of advanced lipoxidation. It is suggested that lipid hydroperoxides can be minimized with the

concomitant intake of vegetables, in a study, which the group found associations between salad ingredients and grilled turkey in vitro co-digestion. The research of in-vitro digestion seems to apply to the in vivo situation. The Mediterranean salad was made from 200g of tomato, 25g of pink onion, 25g of black olives, 10g of EVOO, and 5g of fresh basil in relationship with the amount of meat, which was 100g. The inhibitory effect of the formation of lipid peroxides of every single component of the salad when co-digested with turkey breast meat was excellent for onion and EVOO represented by 100% inhibition duo to undetectable amounts of lipid hydroperoxides. Lower effect but still significant is the effect of tomato with 75% inhibition although present with the highest amount among other ingredients. Black olives were found with a 62% inhibitory effect while fresh basil when added to meat had no significant effect. However, Van Hecke et al. (2017) in another study discovered that dried basil when added in amounts 1% or 0.5% with beef shows better lipid peroxidation inhibitory activity due to the better release of its antioxidant compounds. Further in the study, phenolic fractions were removed from the ingredients and were digested alongside with turkey. The results were the same as with the results of the whole ingredients except tomato where the effects were less observed with inhibitory effect in 58%. The following table indicates the presence of phenolic classes in salad vegetables, as well as the proportion of the strongest phenolic group found in the salad. [60]

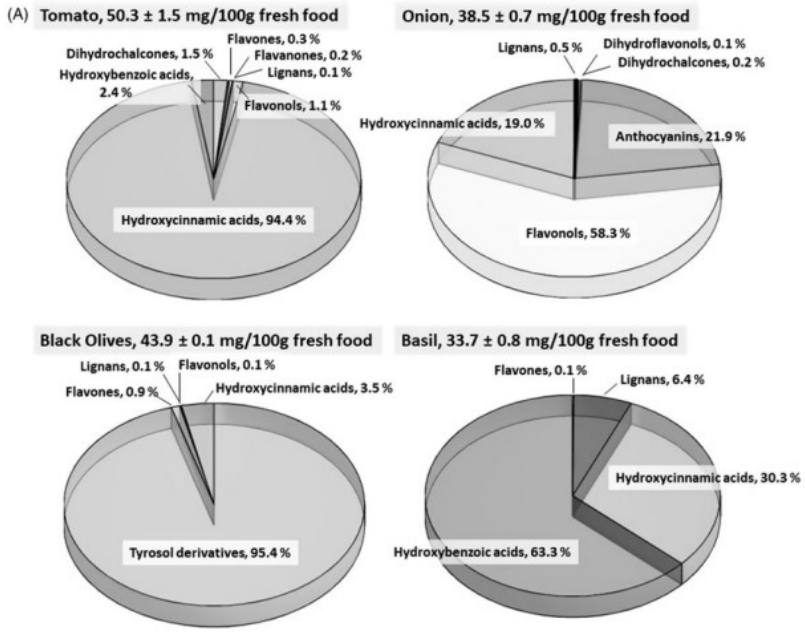


Figure 22:Content of phenolic classes in tomato, onion, black olives, and basil [60]
10.1080/09637486.2019.1677570

Each ingredient is strongly linked with antioxidant activity. For example, black olives and onion being rich in quercetin, cyaniding and hydroxytyrosol derivatives containing 3', 4'-dihydroxy structure in the B-ring are considered to have the highest total radical scavenging capacity

(ABTS) and hydroxyl scavenging activity. Tomato contains a high amount of hydroxycinnamic, responsible for its activity, shown to have superoxide scavenging and ferric reducing properties. In addition, differences were observed between black olives and EVOO, as the second showed lower ABTS and hydroxyl scavenging activity probably because of the presents of non-phenolic compounds like oleoside in the oil. [60]

	μmol ascorbic acid equivalent/mg of total phenolic compounds[a]				% chelation[b]
	ABTS radical scavenging	Hydroxyl radical scavenging	Superoxide anion scavenging	Fe^{3+} reducing properties	Fe^{2+} chelating ability
Tomato	1.60 ± 0.05^{c}	0.89 ± 0.05^{c}	2.77 ± 0.45^{a}	2.04 ± 0.07^{b}	4.65 ± 1.14^{c}
Fresh basil	1.69 ± 0.01^{c}	0.89 ± 0.02^{c}	0.11 ± 0.01^{c}	1.49 ± 0.08^{b}	54.72 ± 6.29^{a}
Onion	2.97 ± 0.20^{a}	1.56 ± 0.07^{b}	1.04 ± 0.05^{b}	1.03 ± 0.02^{c}	6.90 ± 2.98^{c}
Black olives	2.70 ± 0.04^{b}	1.78 ± 0.08^{a}	0.14 ± 0.04^{c}	1.47 ± 0.04^{b}	43.53 ± 1.86^{b}
EVOO	1.61 ± 0.07^{c}	0.87 ± 0.07^{c}	0.27 ± 0.01^{c}	0.63 ± 0.02^{d}	7.54 ± 1.61^{c}

[a]Data expressed as μmol ascorbic acid equivalent normalised for the total phenolic content as determined by mass spectrometry experiments.
[b]% of chelated Fe^{2+} by 100 μg of phenolic compounds.

Figure 23:Different antioxidant properties of each ingredient of MD salad [60]
10.1080/09637486.2019.1677570

11.3 Red and processed meat increases the chance of developing a variety of ailments

Last century dietary habits of people have been changed worldwide and the increased consumption of meat up to 500% during 1992-2016 has raised concerns about the impact of red and processed meat on health and the environment. Following the statement by IRAC that red meat is a potential carcinogen to people; the daily intake has been set at 50-100 g with more than 200g being considered an increased amount. [61,62] Red meat in the meaning of beef, veal, pork, lamb, and mutton have been shown in studies to increase the risk of total mortality, DMT2, stroke, CVD, and cancer. In the figure, there are illustrated relative risk (RR) from meta-analyses of cohort studies and single cohort studies of the connection between unprocessed and processed red meat intake and the occurrence of several diseases. For example, Feskens et al. in 11/21 cohort studies of unprocessed/ processed meat intake found 1.15(0.99-1.33) RR (95% CI) for unprocessed meat consumption of 100g per day and 1.32 (1.19-1.48) for processed meat intake of 50g per day. A similar pattern was also for Kaluza et al. in cohort studies investigating the association between stroke and meat. He found among 329,495 participants and 10,630, 6,420 and 1,276 cases for total, ischemic and hemorrhagic stroke respectively relative risk for unprocessed red meat 1.11 (1.03-1.2) for total, 1.13(1.00-1.27) for ischemic and 1.08 (0.84-1.39) for hemorrhagic and for processed 1.13(1.03-1.24) for total, 1.15(1.06-1.24) for ischemic and 1.16(0.92-1.46). [62]

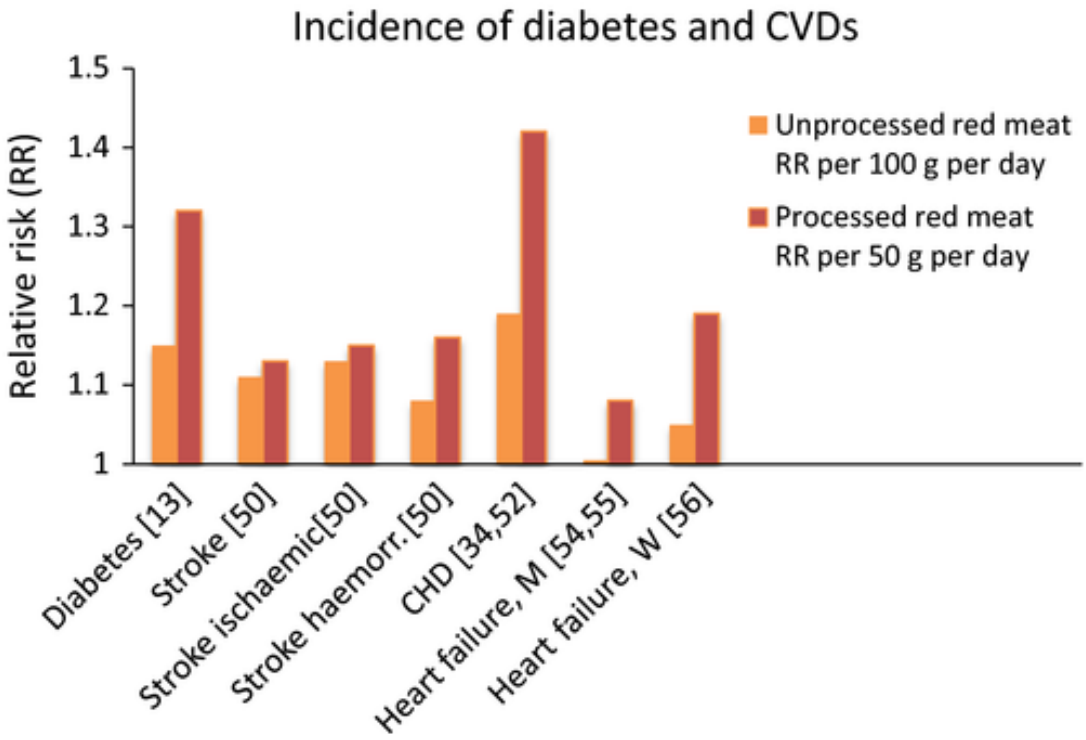


Figure 24:RR between consumption of unprocessed/processed meat and prevalence of DM and CV diseases [62] https://doi.org/10.1111/joim.12543

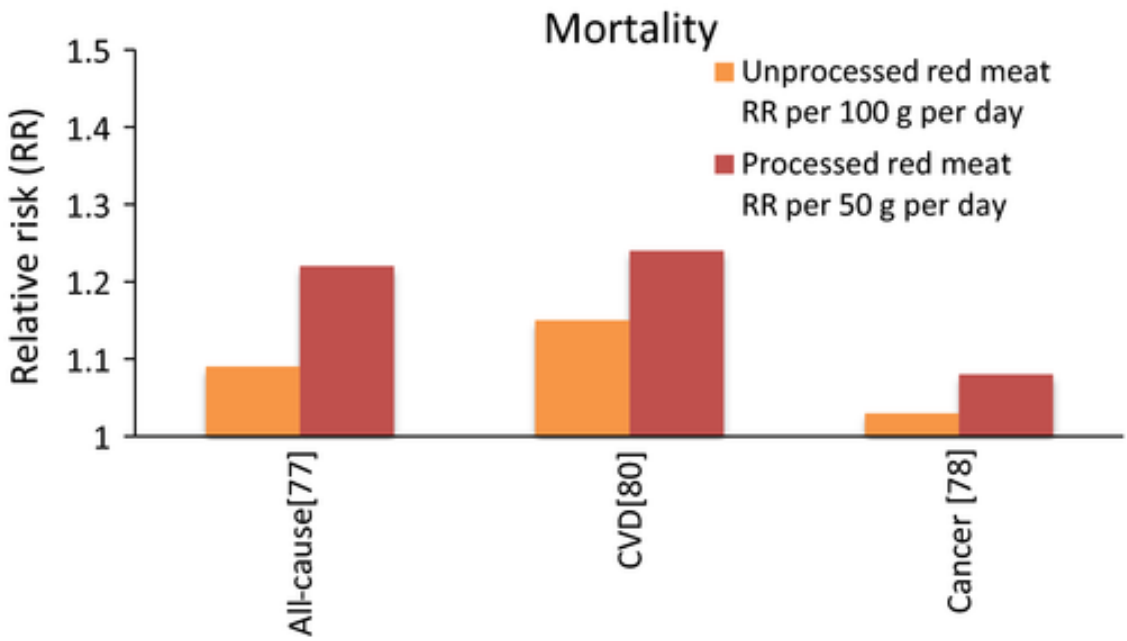


Figure 25:Data from meta-analysis analyzing the connection between all-cause, CV disease and cancer with the intake of meat [62] https://doi.org/10.1111/joim.12543

Processed meat was interconnected to all-cause mortality in a recent meta-analysis of nine cohort studies involving 1,330,352 people from Europe, the United States, and China and 137,376 all-cause fatalities with RR (1.23, 95% CI 1.17-0.28). A dose-response analysis from 4 cohort studies including US participants found that every serving of unprocessed meat per day was linked to an increased risk of all-cause deaths RR (1.15, 95% CI, 1.12-1.19), but in the summary of cohorts from Europe and Asian did not display significant associations. Bellavia et a. made a cohort study including 74,645 Swedish men and women out of which 16,683 deaths took place. Over the 15 years of the follow-up study, it was found that increased consumption of processed meat (75g per day) compared with no consumption was associated with shorter life expectancy (HR 1.47, 95% CI 1.13-1.90 while moderate and excessive consumption of unprocessed red meat when taken with unprocessed was associated with shorter survival. Nevertheless, it was also mentioned that no associations between shorter survival and intake of red meat were found in the consumption of processed is 65-100g per day and lower that 20 g per day for unprocessed.

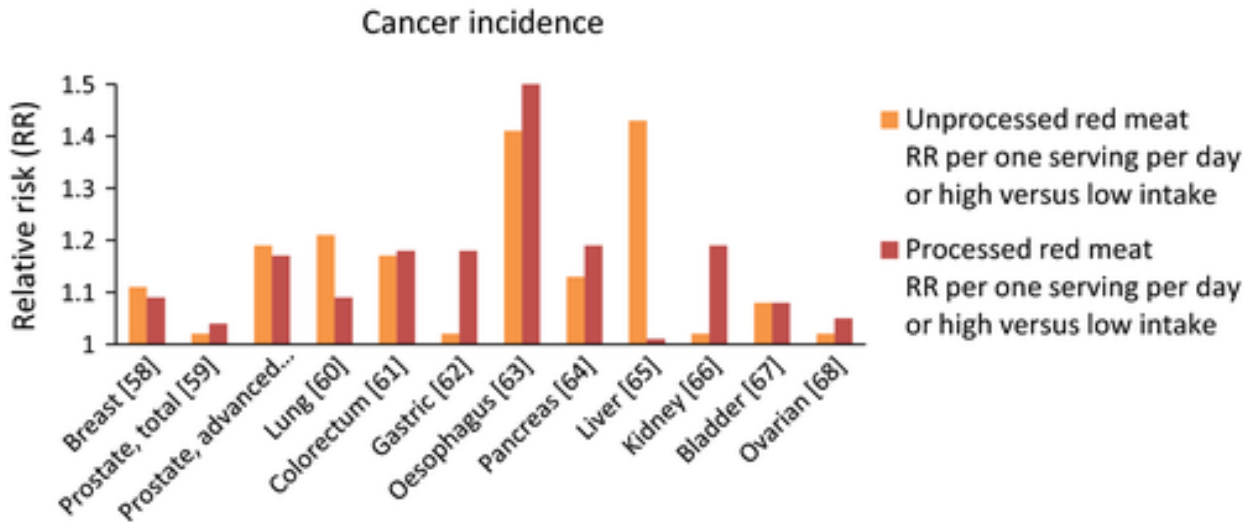


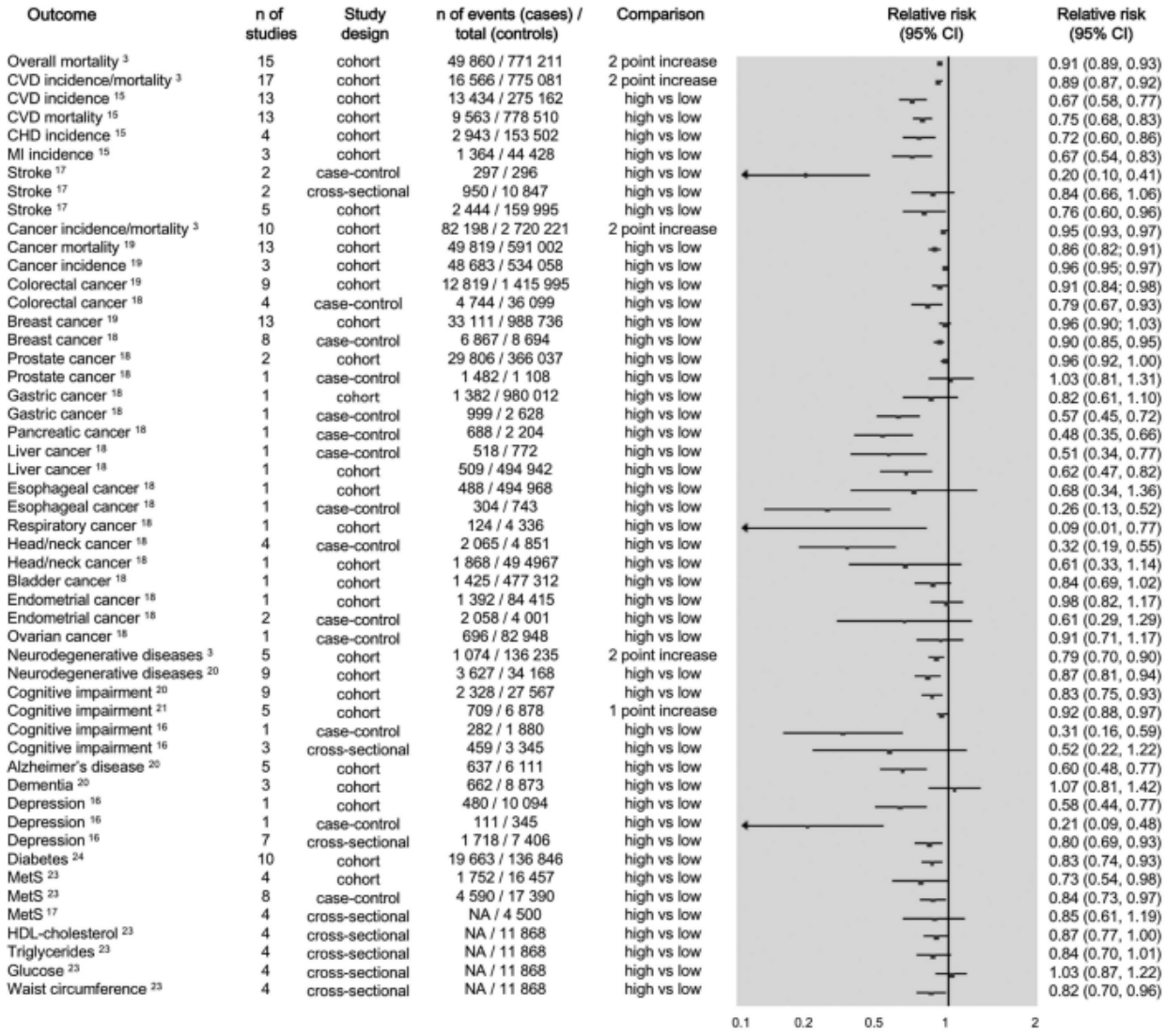
Figure 26:Results from meta-analysis examining the link between processed/unprocessed meat [62]
https://doi.org/10.1111/joim.12543

The table above shows the association of cancer with red meat with the results showing the significant risk of esophagus cancer. Free iron provided in red meat is thought to play a role in the formation of free radicals, particularly H2O2, which can induce inflammation, cytotoxicity, and genetic alterations. Furthermore, intake of red meat promotes modifications in DNA and leads to the peroxidation of lipids and production of N-nitroso compounds, which are more produced when the meat is fire drying. [62]

12. ADHERENCE TO MD AND OUTCOMES

Many meta-analyses have been conducted gathering information from observational studies, cohort, and RCT about the overall impact of MD in human health. As shown in the tables below

much evidence support that MD prevents many CVD but further investigations must be done to have more strong evidence about the prevention of cognitive diseases. [63]



Outcome	n of studies	Study design	n of events (cases) / total (controls)	Comparison	Relative risk (95% CI)
Overall mortality [3]	15	cohort	49 860 / 771 211	2 point increase	0.91 (0.89, 0.93)
CVD incidence/mortality [3]	17	cohort	16 566 / 775 081	2 point increase	0.89 (0.87, 0.92)
CVD incidence [15]	13	cohort	13 434 / 275 162	high vs low	0.67 (0.58, 0.77)
CVD mortality [15]	13	cohort	9 563 / 778 510	high vs low	0.75 (0.68, 0.83)
CHD incidence [15]	4	cohort	2 943 / 153 502	high vs low	0.72 (0.60, 0.86)
MI incidence [15]	3	cohort	1 364 / 44 428	high vs low	0.67 (0.54, 0.83)
Stroke [17]	2	case-control	297 / 296	high vs low	0.20 (0.10, 0.41)
Stroke [17]	2	cross-sectional	950 / 10 847	high vs low	0.84 (0.66, 1.06)
Stroke [17]	5	cohort	2 444 / 159 995	high vs low	0.76 (0.60, 0.96)
Cancer incidence/mortality [3]	10	cohort	82 198 / 2 720 221	2 point increase	0.95 (0.93, 0.97)
Cancer mortality [19]	13	cohort	49 819 / 591 002	high vs low	0.86 (0.82; 0.91)
Cancer incidence [19]	3	cohort	48 683 / 534 058	high vs low	0.96 (0.95; 0.97)
Colorectal cancer [19]	9	cohort	12 819 / 1 415 995	high vs low	0.91 (0.84; 0.98)
Colorectal cancer [18]	4	case-control	4 744 / 36 099	high vs low	0.79 (0.67, 0.93)
Breast cancer [19]	13	cohort	33 111 / 988 736	high vs low	0.96 (0.90; 1.03)
Breast cancer [18]	8	case-control	6 867 / 8 694	high vs low	0.90 (0.85, 0.95)
Prostate cancer [18]	2	cohort	29 806 / 366 037	high vs low	0.96 (0.92, 1.00)
Prostate cancer [18]	1	case-control	1 482 / 1 108	high vs low	1.03 (0.81, 1.31)
Gastric cancer [18]	1	cohort	1 382 / 980 012	high vs low	0.82 (0.61, 1.10)
Gastric cancer [18]	1	case-control	999 / 2 628	high vs low	0.57 (0.45, 0.72)
Pancreatic cancer [18]	1	case-control	688 / 2 204	high vs low	0.48 (0.35, 0.66)
Liver cancer [18]	1	case-control	518 / 772	high vs low	0.51 (0.34, 0.77)
Liver cancer [18]	1	cohort	509 / 494 942	high vs low	0.62 (0.47, 0.82)
Esophageal cancer [18]	1	cohort	488 / 494 968	high vs low	0.68 (0.34, 1.36)
Esophageal cancer [18]	1	case-control	304 / 743	high vs low	0.26 (0.13, 0.52)
Respiratory cancer [18]	1	cohort	124 / 4 336	high vs low	0.09 (0.01, 0.77)
Head/neck cancer [18]	4	case-control	2 065 / 4 851	high vs low	0.32 (0.19, 0.55)
Head/neck cancer [18]	1	cohort	1 868 / 49 4967	high vs low	0.61 (0.33, 1.14)
Bladder cancer [18]	1	cohort	1 425 / 477 312	high vs low	0.84 (0.69, 1.02)
Endometrial cancer [18]	1	cohort	1 392 / 84 415	high vs low	0.98 (0.82, 1.17)
Endometrial cancer [18]	2	case-control	2 058 / 4 001	high vs low	0.61 (0.29, 1.29)
Ovarian cancer [18]	1	case-control	696 / 82 948	high vs low	0.91 (0.71, 1.17)
Neurodegenerative diseases [3]	5	cohort	1 074 / 136 235	2 point increase	0.79 (0.70, 0.90)
Neurodegenerative diseases [20]	9	cohort	3 627 / 34 168	high vs low	0.87 (0.81, 0.94)
Cognitive impairment [20]	9	cohort	2 328 / 27 567	high vs low	0.83 (0.75, 0.93)
Cognitive impairment [21]	5	cohort	709 / 6 878	1 point increase	0.92 (0.88, 0.97)
Cognitive impairment [16]	1	case-control	282 / 1 880	high vs low	0.31 (0.16, 0.59)
Cognitive impairment [16]	3	cross-sectional	459 / 3 345	high vs low	0.52 (0.22, 1.22)
Alzheimer's disease [20]	5	cohort	637 / 6 111	high vs low	0.60 (0.48, 0.77)
Dementia [20]	3	cohort	662 / 8 873	high vs low	1.07 (0.81, 1.42)
Depression [16]	1	cohort	480 / 10 094	high vs low	0.58 (0.44, 0.77)
Depression [16]	1	case-control	111 / 345	high vs low	0.21 (0.09, 0.48)
Depression [16]	7	cross-sectional	1 718 / 7 406	high vs low	0.80 (0.69, 0.93)
Diabetes [24]	10	cohort	19 663 / 136 846	high vs low	0.83 (0.74, 0.93)
MetS [23]	4	cohort	1 752 / 16 457	high vs low	0.73 (0.54, 0.98)
MetS [23]	8	case-control	4 590 / 17 390	high vs low	0.84 (0.73, 0.97)
MetS [17]	4	cross-sectional	NA / 4 500	high vs low	0.85 (0.61, 1.19)
HDL-cholesterol [23]	4	cross-sectional	NA / 11 868	high vs low	0.87 (0.77, 1.00)
Triglycerides [23]	4	cross-sectional	NA / 11 868	high vs low	0.84 (0.70, 1.01)
Glucose [23]	4	cross-sectional	NA / 11 868	high vs low	1.03 (0.87, 1.22)
Waist circumference [23]	4	cross-sectional	NA / 11 868	high vs low	0.82 (0.70, 0.96)

Figure 27:Summary of meta-analysis from observational studies showing the effects of MD [63] 10.1038/ejcn.2017.58

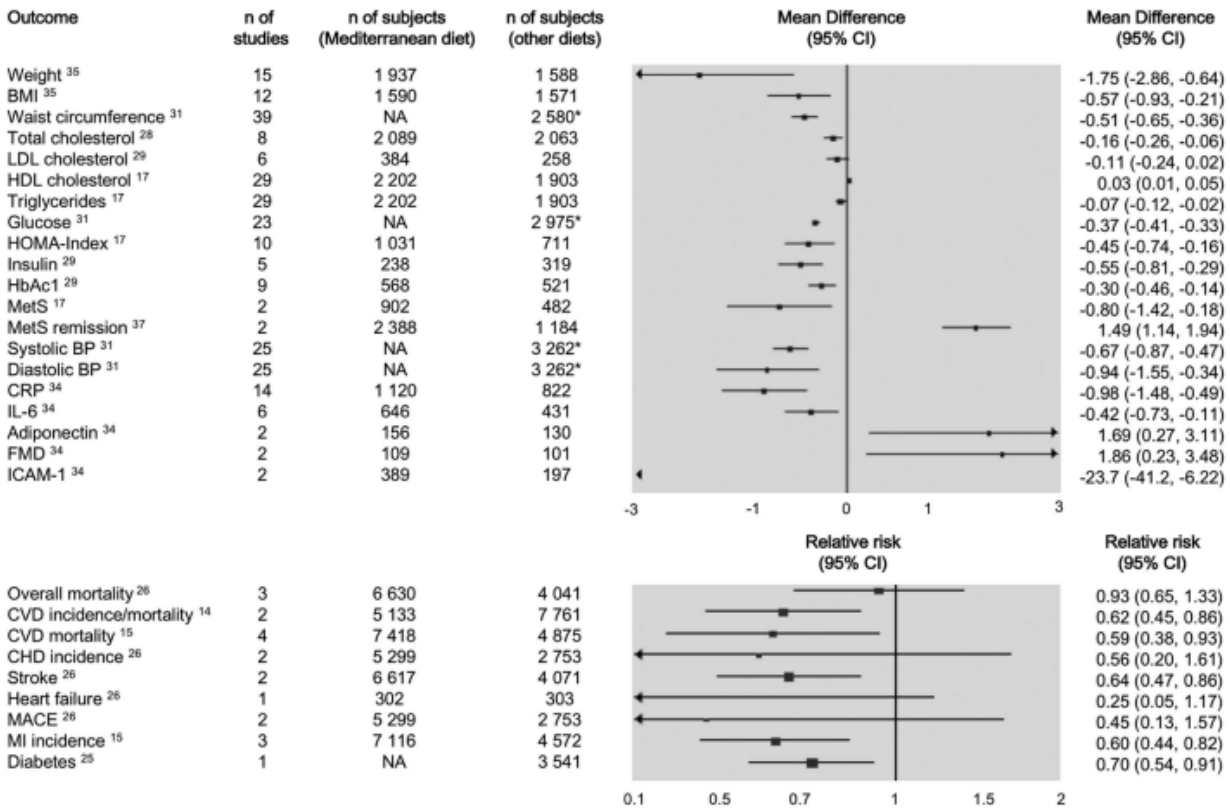


Figure 28:Summary of meta-analysis of RCT reporting the health outcomes following MD [63] 10.1038/ejcn.2017.58

As it is observed from a meta-analysis of observational and RCT studies, most outcomes confirm the positive effects of MD to CV incidence mortality, stroke, myocardial infarction incidence, many types of cancer, and their risk factors. These may be the reduction of weight, control of BMI, and reduction of LDL-C, triglycerides, and HbA1c leading to prevention of DMT2, dyslipidemia, atherosclerosis, and coronary heart diseases.

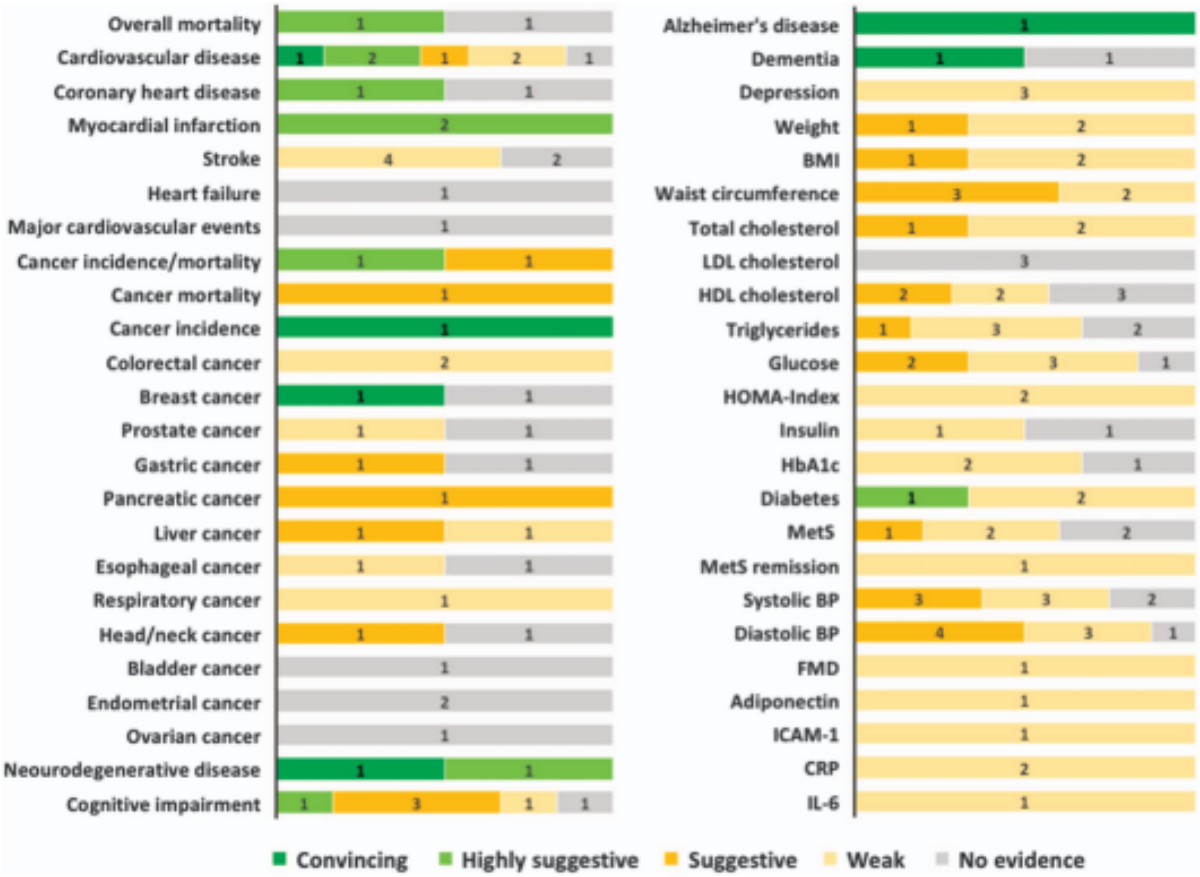


Figure 29:Strength and number of evidence from different types of cancer [63] 10.1038/ejcn.2017.58

The table shows the strength of evidence used in the above tables and the number indicates the number of meta-analyses that were included [63]

Brain function and diseases accompanied by cognitive decline, dementia, depression, Alzheimer's and Parkinson's diseases are topics, which should be investigated more. The evidence for meta-analysis came mainly from observational studies and lesser from RCT. Evidence from a meta-analysis of observational studies including normal individuals showed that following MD was connected with decreased possibility of mild cognitive impairment (HR=0.73, 95% CI: 0.56, 0.89) and Alzheimer's disease (HR=0.64, 95% CI: 0.46, 0.89). In a meta-analysis conducted after the first one, the findings of the previous meta-analysis reporting were confirmed with similar effects and findings (RR 0.79, 95% CI:0.70, 0.90). Furthermore, the meta-analysis from the Singapore Chinese Health Study, including 16,948 individuals for 20 years, the European Prospective Investigation into Cancer and Nutrition including 8,009 elderly individuals for 13 follow up years and the Coronary Artery Risk Development in Young Adults for 20 years confirmed the positive association between MD and cognitive impairment. 50 cohort studies including 41,492 individuals and 2 RCTs with 309 and 162 participants were analyzed and showed the beneficial effect of MD in cognition and other studies analyzed 56 articles that reported a consistent body of evidence. A study of Whitehall II, which analyzed the impact of 3

different diets including MD, on recurrence of depressive symptoms in 9,949 individuals for 13 follow-up years did not find strong coloration of MD with depression. In contrast with the SUN study which included 15,980 adults without depression for 10.4 follow-up years, suggesting that the impact was attributed to eating fruits and nuts and avoidance of food high in fats. Finally limited are the evidence about the effects of MD on Parkinson's disease, with Greek researchers in a population-based cohort study of 1,731 elderlies without Parkinson's, suggesting that MD can possibly decrease by 2% the chance of developing Parkinson's. [64]

CONCLUSION

In summary, MD is found to be beneficial to human health. PUFAs and their derivatives, derived mainly from fish and olive oil having the optimal proportions benefit the health by reducing CVD and cognitive decline. Polyphenols, like flavonoids derived from olive oil, vegetables, fruits, and wine have strong antioxidant and anti-inflammatory effects, similarly, like different types of vitamins, which have antioxidant effects and essential actions in the body like B12 found in meat. Strong evidence is found confirming the effect of each component of the pyramid and overall diet to decrease the risk of developing CVD, cancer, and cognitive decline. Even though more studies must be conducted and more information must be gathered to explain the mechanisms of the food, the proportions, and the cooking techniques that must be followed to maintain the beneficial components of foods.

REFERENCES

[1] Davis, C., Bryan, J., Hodgson, J., & Murphy, K. (2015). Definition of the Mediterranean diet; a literature review. *Nutrients*, *7*(11), 9139-9153. https://doi.org/10.3390/nu7115459

[2] Altomare, R., Cacciabaudo, F., Damiano, G., Palumbo, V. D., Gioviale, M. C., Bellavia, M., ... & Monte, A. I. L. (2013). The mediterranean diet: a history of health. *Iranian journal of public health*, *42*(5), 449.

[3] Bach-Faig, A., Berry, E. M., Lairon, D., Reguant, J., Trichopoulou, A., Dernini, S., ... & Serra-Majem, L. (2011). Mediterranean diet pyramid today. Science and cultural updates. *Public health nutrition*, *14*(12A), 2274-2284. 10.1017/S1368980011002515

[4] Román, G. C., Jackson, R. E., Gadhia, R., Román, A. N., & Reis, J. (2019). Mediterranean diet: The role of long-chain ω-3 fatty acids in fish; polyphenols in fruits, vegetables, cereals, coffee, tea, cacao and wine; probiotics and vitamins in prevention of stroke, age-related cognitive decline, and Alzheimer disease. *Revue neurologique*, *175*(10), 724-741. https://doi.org/10.1016/j.neurol.2019.08.005

[5] Lovegrove, J. A., Commane, D. M., Jackson, K. G., Karani, V., Kennedy, O. B., Kuhnle, G. G., ... & Yaqoob, P. (2015). The Hugh Sinclair Unit of Human Nutrition–20 years of research 1995–2015.https://doi.org/10.1111/nbu.12176

[6] Simopoulos, A. P. (2003). The importance of the ratio of omega-6/omega-3 essential fatty acids. *Alternative Medicine Review*, *8*(1), 83-84. 10.1016/s0753-3322(02)00253-6

[7] Marrugat, J., Covas, M. I., Fitó, M., Schröder, H., Miró-Casas, E., Gimeno, E., ... & Farré, M. (2004). Effects of differing phenolic content in dietary olive oils on lipids and LDL oxidation. *European journal of nutrition*, *43*(3), 140-147. 10.1007/s00394-004-0452-8

[8] Santangelo, C., Vari, R., Scazzocchio, B., De Sanctis, P., Giovannini, C., D'Archivio, M., & Masella, R. (2018). Anti-inflammatory activity of extra virgin olive oil polyphenols: which role in the prevention and treatment of immune-mediated inflammatory diseases. *Endocrine, Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders)*, *18*(1), 36-50. https://doi.org/10.2174/1871530317666171114114321

[9] Storniolo, C. E., Roselló-Catafau, J., Pintó, X., Mitjavila, M. T., & Moreno, J. J. (2014). Polyphenol fraction of extra virgin olive oil protects against endothelial dysfunction induced by high glucose and free fatty acids through modulation of nitric oxide and endothelin-1. *Redox Biology*, *2*, 971-977. https://doi.org/10.1016/j.redox.2014.07.001

[10] Covas, M. I., Konstantinidou, V., & Fitó, M. (2009). Olive oil and cardiovascular health. *Journal of cardiovascular pharmacology*, *54*(6), 477-482. 10.1097/FJC.0b013e3181c5e7fd

[11] Parkinson, L., & Keast, R. (2014). Oleocanthal, a phenolic derived from virgin olive oil: A review of the beneficial effects on inflammatory disease. *International journal of molecular sciences*, *15*(7), 12323-12334. https://doi.org/10.3390/ijms150712323

[12] Jurado-Ruiz, E., Álvarez-Amor, L., Varela, L. M., Berná, G., Parra-Camacho, M. S., Oliveras-Lopez, M. J., ... & Martín, F. (2019). Extra virgin olive oil diet intervention improves insulin resistance and islet performance in diet-induced diabetes in mice. *Scientific reports*, *9*(1), 1-13.

[13] Rodríguez-Romero, B., & Carballo-Costa, L. (2014). Importance of nutritional treatment in the inflammatory process of rheumatoid arthritis patients; a review. *Nutricion hospitalaria*, *29*(2), 237-245. 10.1002/art.1780330607

[14] Borzì, A. M., Biondi, A., Basile, F., Luca, S., Vicari, E. S. D., & Vacante, M. (2019). Olive oil effects on colorectal cancer. *Nutrients*, *11*(1), 32. 10.3390/nu11010032

[15] Pang, K. L., & Chin, K. Y. (2018). The biological activities of oleocanthal from a molecular perspective. *Nutrients*, *10*(5), 570. https://doi.org/10.3390/nu10050570

[16] Abuznait, A. H., Qosa, H., Busnena, B. A., El Sayed, K. A., & Kaddoumi, A. (2013). Olive-oil-derived oleocanthal enhances β-amyloid clearance as a potential neuroprotective mechanism against Alzheimer's disease: in vitro and in vivo studies. *ACS chemical neuroscience*, *4*(6), 973-982. https://doi.org/10.1021/cn400024q

[17] Mishra, S. P. (2020). Significance of fish nutrients for human health. *Int. J. Fish. Aquatic Research*, *5*(3), 47-49.

[18] Anonymous. (2017). FDA and EPA Issue Fish Consumption Advice. U.S. Food & Drug Administration [online]. [cit.2-05-2017]. Available from: **https://www.fda.gov/food/cfsan-constituent-updates/fda-and-epa-issue-fish-consumption-advice**

[19] Tani, S., Kawauchi, K., Atsumi, W., Matsuo, R., Ashida, T., Imatake, K., ... & Okumura, Y. (2021). Association among daily fish intake, white blood cell count, and healthy lifestyle behaviours in an apparently healthy Japanese population: implication for the anti-atherosclerotic effect of fish consumption. *Heart and Vessels*, *36*(7), 924-933. 10.1007/s00380-020-01769-9

[20] Clifton, P. (2019). Metabolic syndrome—role of dietary fat type and quantity. *Nutrients*, *11*(7), 1438. 10.3390/nu11071438

[21] Rousseau, G. (2021). Microbiota, a New Playground for the Omega-3 Polyunsaturated Fatty Acids in Cardiovascular Diseases. *Marine Drugs*, *19*(2), 54. https://doi.org/10.3390/md19020054

[22] Alissa, E. M., & Ferns, G. A. (2017). Dietary fruits and vegetables and cardiovascular diseases risk. *Critical reviews in food science and nutrition*, *57*(9), 1950-1962. https://doi.org/10.1080/10408398.2015.1040487

[23] Bazzano, L. A., Serdula, M. K., & Liu, S. (2003). Dietary intake of fruits and vegetables and risk of cardiovascular disease. *Current atherosclerosis reports*, *5*(6), 492-499. 10.1007/s11883-003-0040-z

[24] Tang, G. Y., Meng, X., Li, Y., Zhao, C. N., Liu, Q., & Li, H. B. (2017). Effects of vegetables on cardiovascular diseases and related mechanisms. *Nutrients*, *9*(8), 857. https://doi.org/10.3390/nu9080857

[25] Zheng, J., Zhou, Y., Li, S., Zhang, P., Zhou, T., Xu, D. P., & Li, H. B. (2017). Effects and mechanisms of fruit and vegetable juices on cardiovascular diseases. *International Journal of Molecular Sciences*, *18*(3), 555. 10.3390/ijms18030555

[26] Nirumand, M. C., Hajialyani, M., Rahimi, R., Farzaei, M. H., Zingue, S., Nabavi, S. M., & Bishayee, A. (2018). Dietary plants for the prevention and management of kidney stones: preclinical and clinical evidence and molecular mechanisms. *International journal of molecular sciences*, *19*(3), 765. 10.3390/ijms19030765

[27] Snopek, L., Mlcek, J., Sochorova, L., Baron, M., Hlavacova, I., Jurikova, T., ... & Sochor, J. (2018). Contribution of red wine consumption to human health protection. *Molecules*, *23*(7), 1684. https://doi.org/10.3390/molecules23071684

[28] Pavlidou, E., Mantzorou, M., Fasoulas, A., Tryfonos, C., Petridis, D., & Giaginis, C. (2018). Wine: an aspiring agent in promoting longevity and preventing chronic diseases. *Diseases*, *6*(3), 73. https://doi.org/10.3390/diseases6030073

[29] Lakkur, S., & Judd, S. E. (2015). Diet and stroke: recent evidence supporting a Mediterranean-style diet and food in the primary prevention of stroke. *Stroke*, *46*(7), 2007-2011. https://doi.org/10.1161/STROKEAHA.114.006306

[30] Scarmeas, N., Anastasiou, C. A., & Yannakoulia, M. (2018). Nutrition and prevention of cognitive impairment. *The Lancet Neurology*, *17*(11), 1006-1015. https://doi.org/10.1016/S1474-4422(18)30338-7

[31] Golde, T. E., Schneider, L. S., & Koo, E. H. (2011). Anti-Aβ therapeutics in Alzheimer's disease: the need for a paradigm shift. *Neuron*, *69*(2), 203-213. 10.1016/j.neuron.2011.01.002

[32] Dueñas, M., Cueva, C., Muñoz-González, I., Jiménez-Girón, A., Sánchez-Patán, F., Santos-Buelga, C., ... & Bartolomé, B. (2015). Studies on modulation of gut microbiota by wine polyphenols: from isolated cultures to omic approaches. *Antioxidants*, *4*(1), 1-21. https://doi.org/10.3390/antiox4010001

[33] Bruins, M. J., Van Dael, P., & Eggersdorfer, M. (2019). The role of nutrients in reducing the risk for noncommunicable diseases during aging. *Nutrients*, *11*(1), 85. 10.3390/nu11010085

[34] Anjum, I., Jaffery, S. S., Fayyaz, M., Samoo, Z., & Anjum, S. (2018). The role of vitamin D in brain health: a mini literature review. *Cureus*, *10*(7). 10.7759/cureus.2960

[35] Anonymous. VitaminD. National Institutes of Health [online] [cit.17-08-2021] Available from: https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/

[36] Liu, W., Zhang, L., Xu, H. J., Li, Y., Hu, C. M., Yang, J. Y., & Sun, M. Y. (2018). The anti-inflammatory effects of vitamin D in tumorigenesis. *International journal of molecular sciences*, *19*(9), 2736. https://doi.org/10.3390/ijms19092736

[37] Razdan, K., Singh, K., & Singh, D. (2020). Vitamin D levels and COVID-19 susceptibility: is there any correlation. *Medicine in drug discovery*, *7*, 100051. https://doi.org/10.1016/j.medidd.2020.100051

[38] Teshome, A., Adane, A., Girma, B., & Mekonnen, Z. A. (2021). The impact of vitamin D level on COVID-19 infection: systematic review and meta-analysis. *Frontiers in Public Health*, *9*, 169. 10.3389/fpubh.2021.624559

[39] Ilie, P. C., Stefanescu, S., & Smith, L. (2020). The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. *Aging clinical and experimental research*, *32*(7), 1195-1198. https://doi.org/10.1007/s40520-020-01570-8

[40] Mado, H., Reichman-Warmusz, E., Dudek, D., & Warmusz, O. (2021). Is Vitamin D Supplementation Protective against Coronavirus Disease 2019 (COVID-19). Electron J Gen Med. 2021; 18 (2): em283. https://doi.org/10.29333/ejgm/9762

[41] Melguizo-Rodríguez, L., Costela-Ruiz, V. J., García-Recio, E., Luna-Bertos, D., Ruiz, C., & Illescas-Montes, R. (2021). Role of Vitamin D in the Metabolic Syndrome. *Nutrients*, *13*(3), 830. https://doi.org/10.3390/nu13030830

[42] Gil, A., Ortega, R. M., & Maldonado, J. (2011). Wholegrain cereals and bread: a duet of the Mediterranean diet for the prevention of chronic diseases. *Public health nutrition*, *14*(12A), 2316-2322. https://doi.org/10.1017/S1368980011002576

[43] Aune, D., Keum, N., Giovannucci, E., Fadnes, L. T., Boffetta, P., Greenwood, D. C., ... & Norat, T. (2016). Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: systematic review and dose-response meta-analysis of prospective studies. *bmj*, *353*. 10.1136/bmj.i2716

[44] Tunick, M. H., & Van Hekken, D. L. (2015). Dairy products and health: recent insights. *Journal of agricultural and food chemistry*, *63*(43), 9381-9388. https://doi.org/10.1021/jf5042454

[45] Van Meijl, L. E., Vrolix, R., & Mensink, R. P. (2008). Dairy product consumption and the metabolic syndrome. *Nutrition research reviews*, *21*(2), 148-157. https://doi.org/10.1017/S0954422408116997

[46] Rozenberg, S., Body, J. J., Bruyere, O., Bergmann, P., Brandi, M. L., Cooper, C., ... & Reginster, J. Y. (2016). Effects of dairy products consumption on health: benefits and beliefs—a commentary from the Belgian Bone Club and the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases. *Calcified tissue international*, *98*(1), 1-17. DOI 10.1007/s00223-015-0062-x

[47] Thorning, T. K., Raben, A., Tholstrup, T., Soedamah-Muthu, S. S., Givens, I., & Astrup, A. (2016). Milk and dairy products: good or bad for human health? An assessment of the totality of scientific evidence. *Food & nutrition research*, *60*(1), 32527. https://doi.org/10.3402/fnr.v60.32527

[48] Matía-Martín, P., Torrego-Ellacuría, M., Larrad-Sainz, A., Fernández-Pérez, C., Cuesta-Triana, F., & Rubio-Herrera, M. Á. (2019). Effects of milk and dairy products on the prevention of osteoporosis and osteoporotic fractures in Europeans and non-Hispanic Whites from North America: a systematic review and updated meta-analysis. *Advances in Nutrition*, *10*(suppl_2), S120-S143. https://doi.org/10.1093/advances/nmy097

[49] Shah, N. P. (Ed.). (2017). *Yogurt in health and disease prevention*. Academic Press.

[50] Réhault-Godbert, S., Guyot, N., & Nys, Y. (2019). The golden egg: nutritional value, bioactivities, and emerging benefits for human health. *Nutrients*, *11*(3), 684. 10.3390/nu11030684

[51] Blesso, C. N., & Fernandez, M. L. (2018). Dietary cholesterol, serum lipids, and heart disease: are eggs working for or against you. *Nutrients*, *10*(4), 426. 10.3390/nu10040426

[52] Clayton, Z. S., Fusco, E., & Kern, M. (2017). Egg consumption and heart health: A review. *Nutrition*, *37*, 79-85. doi: https://doi.org/10.1016/j.nut.2016.12.014

[53] Geiker, N. R. W., Larsen, M. L., Dyerberg, J., Stender, S., & Astrup, A. (2018). Egg consumption, cardiovascular diseases and type 2 diabetes. *European journal of clinical nutrition*, *72*(1), 44-56. 10.1038/ejcn.2017.153

[54] Richard, C., Cristall, L., Fleming, E., Lewis, E. D., Ricupero, M., Jacobs, R. L., & Field, C. J. (2017). Impact of egg consumption on cardiovascular risk factors in individuals with type 2

diabetes and at risk for developing diabetes: a systematic review of randomized nutritional intervention studies. *Canadian journal of diabetes*, *41*(4), 453-463. 10.1016/j.jcjd.2016.12.002

[55] De Smet, S., & Vossen, E. (2016). Meat: The balance between nutrition and health. A review. *Meat Science*, *120*, 145-156. https://doi.org/10.1016/j.meatsci.2016.04.008

[56] Wyness, L. (2016). The role of red meat in the diet: nutrition and health benefits. *Proceedings of the Nutrition Society*, *75*(3), 227-232. https://doi.org/10.1017/S0029665115004267

[57] Bohrer, B. M. (2017). Nutrient density and nutritional value of meat products and non-meat foods high in protein. *Trends in Food Science & Technology*, *65*, 103-112. https://doi.org/10.1016/j.tifs.2017.04.016

[58] Arshad, M. S. (Ed.). (2018). *Meat science and nutrition*. BoD–Books on Demand.

[59] Pereira, P. M. D. C. C., & Vicente, A. F. D. R. B. (2013). Meat nutritional composition and nutritive role in the human diet. *Meat science*, *93*(3), 586-592. https://doi.org/10.1016/j.meatsci.2012.09.018

[60] Martini, S., Conte, A., Bottazzi, S., & Tagliazucchi, D. (2020). Mediterranean diet vegetable foods protect meat lipids from oxidation during in vitro gastro-intestinal digestion. *International journal of food sciences and nutrition*, *71*(4), 424-439. 10.1080/09637486.2019.1677570

[61] Qian, F., Riddle, M. C., Wylie-Rosett, J., & Hu, F. B. (2020). Red and processed meats and health risks: how strong is the evidence. *Diabetes Care*, *43*(2), 265-271. 10.2337/dci19-0063

[62] Wolk, A. (2017). Potential health hazards of eating red meat. *Journal of internal medicine*, *281*(2), 106-122. https://doi.org/10.1111/joim.12543

[63] Dinu, M., Pagliai, G., Casini, A., & Sofi, F. (2018). Mediterranean diet and multiple health outcomes: an umbrella review of meta-analyses of observational studies and randomised trials. *European journal of clinical nutrition*, *72*(1), 30-43. 10.1038/ejcn.2017.58

[64]) Sánchez-Sánchez, M. L., García-Vigara, A., Hidalgo-Mora, J. J., García-Pérez, M. Á., Tarín, J., & Cano, A. (2020). Mediterranean diet and health: A systematic review of epidemiological studies and intervention trials. *Maturitas*, *136*, 25-37. https://doi.org/10.1016/j.maturitas.2020.03.008

LIST OF FIGURES

LIST OF ABBREVIATIONS

ABST	Radical scavenging capacity
ALA	α-linolenic acid
α-TNF	Tumor necrosis factor alpha
BMI	Body mass index
Ca	Calcium
CI	Confident interval
COX	Cyclooxygenase
CRP	C-reactive protein
CV	Cardiovascular
CVD	Cardiovascular disease
DASH	Dietary Approach to Stop Hypertension
DHA	Docosapentanoic acid
DM	diabetes mellitus
DMT2	Diabetes mellitus type 2
DT	Diploma thesis
EPA	Eicosapentanoic acid
EVOO	Extra virgin olive oil
FDA	Food and Drug Administration
GIT	Gastrointestinal tract
HbA1c	Glycosylated Hemoglobin A1c
HDL-C	High-density lipoprotein
HR	Hazard ratio
LA	Linoleic acid
LDL-C	Low-density lipoproteins
MD	Mediterranean diet
MUFA	Monounsaturated fatty acids
OR	Odds ratio
p	p-value
PUFA	Polyunsaturated fatty acids
RCT	Randomized controlled trial
RR	Relative ratio
SFA	Saturated fatty acids
TC	Total cholesterol
TMAO	Trimethyl N-oxide
VDR	Nuclear vitamin D receptor
WHO	World Organization of Health