The role of nutrients in supporting cardiovascular health

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EXECUTIVE SUMMARY

Cardiovascular disease (CVD) continues to be one of the biggest threats to human health, both in the developed and developing world. An increasing amount of evidence is highlighting the importance of good nutrition as part of a practical risk reduction approach to cardiovascular health concerns. Extensive research on key nutrients, including the omega-3s docosahexaenoic acid (DHA), as well as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), as well as vitamins C, D and E, indicate the positive effects that nutrition solutions may have as part of a strategy for use by the medical community in supporting heart health.

This whitepaper presents the latest scientific research on the evidence, role and mechanism of specific micronutrients in cardiovascular health. With the rate of cardiovascular mortality increasing, there is a growing opportunity for governments to develop healthcare plans that support nutrient supplementation and/or fortification. Reconsideration of current recommended guidelines in nutrition policy could increase awareness of the importance of nutrition in specific populations around the globe. This could provide a lifetime of health benefits, as well as address rising healthcare costs associated with chronic disease management.

THE CURRENT SITUATION

As a globally prevalent issue, CVD – primarily coronary heart disease (CHD) and stroke – remains a significant concern for medical and scientific communities, as well as governments and consumers:

- An estimated 175 million people currently die from CVDs each year, representing 31% of all global deaths\(^1\)
- By 2030, more than 40% of the US population is predicted to have some form of CVD\(^2\)
- In the US, it is the leading cause of death among both men and women\(^3\)
- It is estimated that one in five adults in China has CVD, with the country having one of the highest CVD death rates in the world. CVD events are forecast to increase by 50% among the population between 2010 and 2030.\(^4\)

In 2013, all 194 member states of the United Nations’ World Health Organization (WHO) agreed on the global strategy to lower the number of non-communicable diseases (NCDs), called ‘Global Action Plan For The Prevention And Control Of NCDs 2013-2020’.\(^5\) This aims to reduce the number of premature deaths from NCDs by 25% by 2025 through nine voluntary global targets. Three of the goals relate directly to preventing and controlling CVD, including the reduction of hypertension and drug therapy and lifestyle and nutrition counselling.

For the first time since 1993, life expectancy in the US has dropped significantly for the entire population, not just certain groups. Heart disease is the number one cause of the high rate of mortality.\(^6\)

RISK FACTORS

There is substantial evidence to link lifestyle factors, such as diet, to obesity and conditions like diabetes and CVD. For example, poor nutrition can contribute to dyslipidemia and inflammation, leading to the formation of plaque in the arteries, and ultimately, atherosclerotic plaque rupture, heart attack or stroke.\(^7\)

The prevalence of diabetes has also emerged as a serious cause for concern. There is a strong correlation between diabetes and an increased risk of CVD. The number of people globally with diabetes has nearly quadrupled since 1980, with the highest levels reported in China where 11.6% of adults have diabetes.\(^8,9\) According to the American Heart Association, adults with diabetes are two to four times more likely to die from heart disease than adults without diabetes.\(^10\) As such, a healthy diet with a balanced nutrient-energy density is critical on two levels: to control the condition, and also to reduce the risk of later developing CVD.

Elevated blood triglycerides and/or low-density lipoprotein (LDL)-cholesterol are both major risk factors for CVD. High levels have become more of a global concern recently, as this has been associated with lifestyle changes occurring in developed countries. Consumption of foods containing greater amounts of trans fats (including partially-hydrogenated oils), saturated fats and excess calories from sugars, coupled with decreased physical activity, are linked to increased triglyceride and LDL cholesterol levels. This can also contribute to weight gain, one of the risk factors for the development of CVD.

Considering modifiable risk factors for prevention

While age, sex and genetics are ever-present risk factors for CVD, most new cases of acute myocardial infarctions can be predicted by nine modifiable cardio-protective risk factors. These act by promoting atherogenesis, the formation of abnormal fatty or lipid masses in arterial walls.\(^11\)

- Dietary patterns
- Lack of exercise
- Obesiry
- Alcohol

- High cholesterol
- Diabetes
- Psychosocial factors
- Smoking

Although cardiovascular risk varies substantially between regions, the underlying risk factors, such as race, ethnicity and sex are consistent across the world. A similar preventative approach could therefore be applied globally, as it has the potential to address most premature causes of heart attack.\(^12\)
The need for improved nutrition is a worldwide concern. Studies show that levels of essential micronutrients in the bloodstream are low globally, even across developed countries. Over the last few decades, the consumption of nutrient-rich foods, for example whole grains, vegetables and low-fat dairy products, has been partially shifted to the consumption of nutrient-poor foods which are also energy, or calorie-dense. In addition to declining physical activity, this shift in dietary patterns is likely an important factor behind the increasing levels of CVD, worldwide.

To take an example, adults in most regions of the world have a low to very low status of two of the most important omega-3s, EPA and DHA. Global vitamin E blood levels are also low, with only a fifth (21%) of the population reaching the recommended intake (>30 μmol/L). This creates a heightened risk for cardiovascular health.

Addressing these nutritional adequacies is critical, particularly as the proportion of the population that is classified as elderly (aged over 60 years) is expected to increase to reach 22% of all individuals by 2050. If CVD mortality rates are to decrease in an aging population, prevention needs to be positioned as a lifelong approach.
CONTRIBUTORY LIFESTYLE FACTORS

Who states that more than three quarters of all CVD mortality may be prevented with adequate changes in lifestyle. There is new evidence, in a number of publications, on the dietary priorities for CVD prevention that explores the complex influences of different foods and the nutrients found within them. The food industry must work with governments, regulatory bodies and healthcare practitioners (HCPs), to make well-balanced diets accessible and affordable for all. In fact, the WHO report states that, in terms of CVD and cancer mortality, public health efforts to improve eating habits are critical. A major study that explored the decline in coronary mortality in Sweden between 1986 and 2002 concluded that primary prevention resulted in a markedly larger reduction in mortality than secondary prevention.21

According to global guidelines, patients at high risk of CVD should follow a cardio-protective diet. For example, the American Heart Association guidelines recommend the following heart-healthy eating pattern based on a 2,000 calorie a day diet:22

- Fruits: 4-5 servings a day
- Vegetables: 4-5 servings a day
- Whole grains, preferably high fiber: 6-8 servings a day
- Fat-free or low-fat milk and milk products: 2-3 servings a day
- Lean meats, poultry and fish: 6 or fewer ounces a day
- Nuts, legumes and seeds: 4-5 servings a week
- Fats and oils: 2-3 servings of healthy oils per day, limit trans and saturated fat
- Limit sweets and added sugars

These general diet recommendations are echoed across Europe, with guidelines from The Fifth Joint Task Force of the European Society of Cardiology (JTF) providing an update on current knowledge in preventative cardiology for healthcare practitioners. This is a collation of advice on CVD protection from nine participating organizations, including the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes. However, the guidelines rely on patient compliance, which can be difficult to implement.23

PRESENTING THE SCIENTIFIC EVIDENCE OF KEY NUTRIENTS

Despite growing awareness of the importance of diet, individuals are not necessarily following current advice. There are specific nutrient guidelines in place from region to region, however there are gaps between patient and even physician knowledge, as well as implementation. Further steps need to be taken to help build a healthy nutritional profile in the population as a whole. A well-balanced diet is the best way to address low nutrient levels, but fortified food products and dietary supplements can help fill nutritional gaps.

Some important nutrients to consider for heart health include:

- EPA and DHA
- Omega-3
- Vitamin C
- Vitamin D
- Soluble fiber

EPA and DHA

There is compelling evidence to suggest that EPA and DHA intake are linked to a reduction in the risk of developing CVD. In 2012, the European Commission authorized an Article 13.1 health claim that 250 mg per day of EPA and DHA contributes to the maintenance of normal function of the heart. This brings further strength to studies such as the ground-breaking Japan EPA Lipid Intervention Study (JELIS), that was the first large-scale, prospective, randomized trial on the long-term use of EPA with statins. The study on Japanese patients with hypercholesterolemia highlighted EPA supplementation can extend the benefit of statins.25

A recent publication including meta-analyses of randomized controlled trials (RCTs) and prospective cohort studies assessed the relationship of EPA and DHA on CHD. They found that EPA and DHA supplementation significantly reduced CHD risk in individuals with elevated triglycerides or LDL cholesterol across 18 RCTs. EPA and DHA intake was associated with an 18% risk reduction across 16 prospective cohort studies. Unlike other meta-analyses that include a mixture of vascular and other coronary outcomes, the inclusion criteria for these analyses were specific for CHD.

The key findings of the meta-analyses include:

**Across 18 RCTs:**
- EPA and DHA supplementation produced a non-statistically significant 6% reduction of CHD
- EPA and DHA supplementation significantly reduced CHD risk by 16% among people with elevated serum triglycerides (>150 mg/dL)
- Higher doses (>1000 mg/d of EPA and DHA) had a stronger impact among those with elevated triglycerides
- EPA and DHA supplementation significantly reduced CHD risk by 14% among people with elevated LDL cholesterol (>130 mg/dL)

These results add to recent research, which confirms that adequate intake of EPA and DHA may reduce risk of CHD among people with elevated blood levels of triglycerides or LDL-cholesterol. Both are major risk factors that affect a significant portion of the general adult population globally.26

**With over 30,000 scientific papers published, omega-3 fatty acids are the most studied nutrient in the world. However, many people around the globe do not consume enough EPA and DHA for heart health. In fact, a 2015 US NHANES analysis reported that 95.7% of Americans are not consuming enough EPA and DHA to reach cardio-protective blood levels.**27

**Across 16 prospective cohort studies:**
- EPA and DHA intake from food and supplements was associated with an 18% reduction in risk of any CHD event

The Institute for Health Metrics and Evaluation estimates that, every minute, two people may die unnecessarily early due to low EPA/DHA intake.29
Vitamin E

Vitamin E is a fat-soluble antioxidant essential nutrient that is important in supporting heart health.30 Besides the conventional risk factors for CVD, other factors such as oxidative stress and inflammation may also contribute. This is where vitamin E may play an important role. There is evidence that increased vitamin E consumption is linked to a lowered risk of experiencing a cardiovascular condition due to oxidative stress or inflammation.31-33 As well as protecting cells from damage, the micronutrient helps to limit oxidative damage to fatty acids, including EPA and DHA. This means that more vitamin E may be required in individuals with higher levels of omega-3 intake.34

Vitamin C

Vitamin C is a water-soluble antioxidant essential nutrient. It facilitates numerous enzymatic reactions, including those involved in amino acid hydroxylation for the formation of collagen and cartilage. Vitamin C is also able to support the regeneration of other antioxidants, such as vitamin E.39

Studies have looked into the relationship between vitamin C intake and risk of CHD. Overall, the results suggest a consistent relationship between higher vitamin C intake and lower CHD risk.40-46 Higher vitamin C levels have also been linked to lowering blood pressure.45-47 A 2012 meta-analysis found that vitamin C supplementation at a high level (500 mg median dose) during two months significantly reduced blood pressure in adults.48 These beneficial effects of vitamin C are supported by its effects on vasodilation. This capacity is limited in individuals with atherosclerosis and is therefore a risk factor for CVD. A heart attack may damage the heart muscle, which is partly related to the inability of the vessels to expand sufficiently, allowing blood flow to the affected areas. Studies have shown that high levels of vitamin C (1500-3000 mg) may result in improved vasodilation in individuals with CHD.49

Vitamin C is a simple nutrient that could have far-reaching effects for heart health. Despite the high awareness of vitamin C, up to 40% of adults have inadequate vitamin C intakes, relative to recommendations in a number of European countries.50 Similar rates are reported for the US.51

Vitamin D

Vitamin D is a fat-soluble essential nutrient best known for its importance in calcium absorption. However, vitamin D may also support cardiovascular health. An analysis of over 41,000 medical records found that vitamin D inadequacy, which was the case in 30% of patients, was associated with increased prevalence of cardiovascular conditions, including hypertension, coronary artery disease and stroke.52 Suboptimal vitamin D status has also been linked to arterial stiffness, which is a cause of high blood pressure.53 Mechanistic studies suggest that vitamin D may influence the renin-angiotensin system which could have implications in the regulation of high blood pressure.54,55 Consistent with these findings, hypertension risk reductions of up to 30% have been observed in individuals with a sufficient vitamin D level, compared to those with an insufficient level.56-58

Moreover, there is evidence that higher vitamin D levels are associated with a lower risk of CHD.59 Research on vitamin D supplementation in patients with cardiac insufficiency holds promise. For instance, daily supplementation of vitamin D in infants with chronic congestive heart failure led to a better heart muscle performance.60 Although awareness of the beneficial role of vitamin D in human health is growing, vitamin D deficiency is a global health challenge. More than a billion people worldwide are vitamin D deficient or insufficient.61
**Viscous soluble fiber**

Soluble fibers, such as oat beta-glucan, are well-known for supporting heart health. The ESC and the US National Cholesterol Education Program, for example, have both recommended the consumption of oat beta-glucan as an accepted lifestyle modification to reduce cardiovascular risk.

The US Food & Drug Administration has approved health claims recognizing the cholesterol lowering effect of at least 3 g per day oat beta-glucan, whereas the European Commission authorized an Article 14.1 health claim for cholesterol reduction and the associated reduced risk of developing heart disease.

A 2014 research paper provides further evidence to support oat beta-glucan’s cholesterol lowering potential. The meta-analysis, published in the American Journal of Clinical Nutrition, was the first to only evaluate trials where high molecular weight oat beta-glucan have been used:

- The analysis of 28 randomized controlled trials found that 3 g of oat beta-glucan was associated with LDL and total cholesterol reductions of 0.25mmol/L and 0.30 mmol/L respectively.

Tomato extract

There is evidence to suggest that food ingredients, such as tomato extract, can help to maintain healthy platelet aggregation and improve blood flow. Hyperactive platelets are an important risk factor for atherogenesis, and therefore CVD. Where anti-platelet drugs are not suitable for use in cases of low CVD risk, safer alternatives that act as antiplatelet inhibitors can be effective for the vulnerable population. Fruitflow, a water-soluble tomato extract, became the first product in Europe to obtain EFSA approval under Article 13(5) on nutrition and health claims made on foods. The active compounds of Fruitflow demonstrate strong potency and bioavailability, to make it a naturally cardio-protective functional food.

Clinical trials have shown that Fruitflow can suppress platelet function, at a level that is a third of a daily dose of 75mg aspirin (ASA). The reversible nature of Fruitflow makes it less likely to overextend the time to form a primary haemostatic clot than ASA, an important consideration in the prevention of CVD. A further study on human plasma also found that aqueous extract of tomatoes contains anti-angiotensin converting enzyme (ACE) factors, as well as anti-platelet factors.

It is important to be aware of the effects of some micronutrients when taken in conjunction with certain types of medication. Examples of where drug-nutrient interactions occur include statins, contraceptives, proton pump inhibitors, and cases where vitamins have a synergistic effect with drugs. The mismanagement of drug-nutrient interactions can bring serious consequences.
Putting nutritional solutions at the center of a strategy for supporting heart health can be achieved in two different ways. The first is on a public level, aiming at reducing or completely eradicating the impact of CVD and its related disabilities nationwide. The second is on an individual level, and the day-to-day dialogues that HCPs have with patients and particularly those most at risk of CVD (e.g. those with obesity, hypertension, diabetes). Both approaches must be based on cardiologic epidemiology and evidence-based medicine.

The comprehensive guidelines for cardiovascular risk assessment in clinical practice can be overwhelming. In fact, a report found over 1,900 publications available on the subject — making it difficult to establish a consistent approach. With only seven of these achieving the level of ‘considerable rigor’ using the Appraisal of Guidelines Research and Evaluation (AGREE) instrument, this may explain why current guidelines have not had the necessary impact. Particularly for HCPs with limited time to engage patients, a streamlined approach could serve the system well.

### WEIGHING UP THE COSTS

Recent studies clearly demonstrate that the public health and economic benefits of ensuring the appropriate intake of key micronutrients outweigh the costs. For example, one study has found that regular consumption of EPA and DHA omega-3 fatty acids supplements could save €12.9 billion year in the European Union (EU). Overall, 24% of the people aged over 55 in the EU are considered to be at risk of experiencing a hospital event attributed to CVD.

For the US, a report from 2013 states that the savings potential in avoided CVD-attributed hospital events from EPA and DHA omega-3 fatty acid supplements at cardio-protective levels would average nearly US$500 million per year. In short, this would mean a US$3.9 billion cumulative healthcare cost saving from 2013 to 2020.

### MAKING THE OMEGA-3 EPA + DHA RECOMMENDATION

Assessing a patient’s omega-3 intake and then using the decision tree to determine the appropriate recommendation level.

1. Does the patient consume at least 2 servings per week of oily fish?
2. Does the patient take a supplement with a minimum 250 mg omega-3 EPA + DHA?

#### LEVEL 1: DEFICIENCY PREVENTION

**Recommendation**
- 250-500 mg per day of omega-3 EPA + DHA

#### LEVEL 2: CARDIOPROTECTION

**Recommendation**
- 500 mg per day of omega-3 EPA + DHA

#### LEVEL 3: SECONDARY PREVENTION

**Recommendation**
- 11000 mg per day of omega-3 EPA + DHA

#### LEVEL 4: TRIGLYCERIDE LOWERING

**Recommendation**
- 2000-4000 mg per day of omega-3 EPA + DHA
CONCLUSION

The prevalence of nutrient deficiency worldwide has highlighted the importance of adequate intake of essential micronutrients in public health action plans.\(^{40}\) With a lack of knowledge cited as one of the main reasons for not adhering to dietary advice, there is an opportunity for healthcare practitioners, governments and regulatory bodies to better equip patients and individuals through recommendations and guidelines. Given the evidence for the role of specific nutritional solutions — such as EPA and DHA and vitamins C, D and E, plus soluble fiber — in addressing cardiovascular health, this could help to reduce the prevalence of CVD.\(^{92}\)

Patient dialogues should, of course, be based on the relevant clinical evidence and through assessing the health requirements of individuals.\(^{51}\) Low dietary intake of micronutrients that support cardiovascular health may present a worthwhile opportunity to suggest other approaches, such as fortified food products and dietary supplements. Innovation in this area now presents a viable option in incentivizing and encouraging patients to increase consumption of micronutrients.

Key take-away messages

- CVD is a global issue and continues to cause concern for the scientific and medical communities
- Poor diet and other lifestyle choices significantly increase the risk of developing CVD
- There is a bank of evidence that indicates micronutrients (EPA and DHA, vitamins C, D and E, plus soluble fiber) may be beneficial as part of a practical risk reduction approach to cardiovascular health concerns
- Current guidelines in relation to nutritional intake vary globally
- Recommending cardiovascular health strategies to patients could lead to an uptake in the consumption of essential micronutrients, either in food or supplement form
- Studies highlight that a consistent approach to the recommendation of fortified foods and dietary supplements could help to bridge the gap between nutrient deficiency and consumption of micronutrients.

For further information, please email Manfred Eggersdorfer, Professor for Healthy Ageing, Senior Vice President Nutrition Science & Advocacy at DSM Nutritional Products

manfred.eggersdorfer@dsm.com

For more information please visit:

www.nutri-facts.org

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