

Introduction and Executive Summary of the Supplement, Role of Milk and Dairy Products in Health and Prevention of Noncommunicable Chronic Diseases: A Series of Systematic Reviews

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Premature death caused by noncommunicable chronic diseases (NCDs) remains one of the main health challenges we face in the 21st century. This problem affects all countries equally, including low- and middle-income countries, where >75% of deaths from NCDs take place (1, 2).

Cardiovascular disease (CVD), type 2 diabetes (T2D), cancer, and chronic respiratory diseases are the major NCDs, and are strongly influenced by modifiable risk factors such as smoking, alcohol abuse, nutritionally poor diets, and lack of physical activity. Unhealthy diets, inactivity and sedentarism, and alcohol consumption lead to overweight and obesity, increased blood pressure hyperlipidemia, and finally illness and premature death.

Among all the forms of malnutrition, poor dietary habits and low consumption of healthy foods are 2 of the main risk factors for mortality. Hence, the 2016–25 decade has been proclaimed the Decade of Action on Nutrition by the UN General Assembly (3).

Improving food habits, both at the societal and individual level, is essential to achieving a healthy diet and requires a population-based, multisectoral, multidisciplinary, and culturally relevant approach (4, 5). A well-balanced diet supplies adequate quantities of energy and nutrients in order to ensure health and well-being and allows us to meet nutrient recommendations and reference values, nutritional

targets, and adequate intake levels without exceeding the tolerable maximum intake levels. Overall evidence indicates that a healthy eating pattern is rich in vegetables, fruits, whole grains, seafood, low-fat or fat-free dairy products, legumes, and nuts. Moderating alcohol intake (among adults) and consuming only small amounts of red or processed meats, refined grains, and sugar-sweetened foods or drinks are also characteristics of healthy eating patterns (6).

The US Dietary Guidelines Advisory Committee has reported that many nutrients are underconsumed with respect to the estimated average requirements or adequate intake levels established by the Institute of Medicine (7). The following nutrients have been classified by the USDA as deficient: vitamins A, D, E, and C, folate, calcium, magnesium, potassium, and fiber. Furthermore, 3 of these nutrients (calcium, vitamin D, and potassium) are also categorized as nutrients of public health concern because, according to the scientific literature (6), their underconsumption has been associated with negative health effects.

Compared to the intake amounts recommended in the USDA Food Patterns, most people consume a poor intake of key food groups such as vegetables, fruits, whole grains, and dairy products, which are important sources of deficient nutrients, and exceed the consumption recommendations for sodium, saturated fats, refined grains, and added sugars (7). When considering the nutrients of public health concern (calcium, vitamin D, and potassium), achieving an adequate intake of dairy products seems very desirable (6).

Most dietary guidelines regarding the consumption of milk and dairy products recommend 2–4 servings/d depending on age and circumstances (6, 8, 9). However, the average intake of dairy products of most groups, classified by both age and sex, is well below recommendations (6); this low intake

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Abbreviations used: BMD, bone mass density; CAD, coronary artery disease; CRC, colorectal cancer; CVD, cardiovascular disease; MetS, metabolic syndrome; NCD, noncommunicable chronic disease; RCT, randomized controlled trial; T2D, type 2 diabetes.

of dairy is associated with lower intakes than recommended for calcium and other nutrients in a high percentage of individuals in Western countries (10–12).

Dairy products contain multiple nutrients and contribute significantly to meet the nutritional requirements for protein, calcium, magnesium, phosphorus, potassium, zinc, selenium, vitamin A, riboflavin, vitamin B-12, and pantothenic acid. This contribution of nutrients is difficult to obtain in diets that suppress dairy products (e.g. vegan diets) or that restrict dairy products for any reason. Many of the beneficial effects of milk and dairy products are likely due to interactions between the nutrients and not only to the action of each of these nutrients separately (13, 14).

The contribution of milk and dairy products as a source of calcium in Western countries is especially noteworthy (11, 13, 14). Between 50% and 65% of the calcium intake among the population in those countries is provided by dairy products, whereas dairy products only contribute 9–14% of the total energy consumed (15). Hence, milk and dairy products are nutrient-dense foods that provide high amounts of numerous nutrients (especially calcium) although are relatively low in caloric content.

In spite of the nutritional and dietary importance of milk and dairy products, consumption is decreasing and moving away from the advised level in many countries. Furthermore, for some time, the potential benefits of milk and dairy products for health have come under question (14, 16). Although milk consumption has been related to a reduction in the risk for osteoporosis and possibly colorectal cancer (CRC) and T2D, high dairy consumption has been associated with other NCDs such as CVD and prostate cancer (14). Among the studies that have questioned the benefits of dairy products to health is that of Michaëlsson et al. (17), whose results found that elevated milk consumption was related to higher mortality in a cohort of women and in another cohort of men. This work also shows a positive relation between milk intake and incidence of fractures in women. However, the authors point out that, given the design of observational studies with their intrinsic possibilities of residual confusion and reverse causality, a prudent interpretation of the results is recommended. In another study, Brouwer-Brolsma et al. (18) reported direct associations between consumption of whole and unfermented dairy products and newly detected T2D and prediabetes. This study also found an inverse relationship between the consumption of fat-free dairy products and prediabetes.

Currently, there is growing skepticism in the population about the beneficial health effects of dairy products, which translates into an increased intake of vegetable drinks derived from soy, rice, almonds, or oats. Generally, these vegetable drinks are of low nutritional density, contain proteins of relatively lower biological value, and have a low micronutrient content and large amounts of added sugars (16, 19). From the nutritional point of view, it should be noted that vegetable drinks and cow's milk are totally different foods and, consequently, the established recommendations for dairy products cannot be extrapolated

to plant-based beverages (16). Vitoria (19) recently reviewed the composition of 164 vegetable drinks used in infant and childhood feeding and concluded that the nutritional quality of vegetable drinks is lower than that of cow's milk and infant formulas. Therefore, vegetable drinks are not an adequate nutritional alternative, and their predominant or exclusive use can lead to serious nutritional risks in infancy and early childhood. In fact, Vitoria indicates at least 30 published cases of children with nutritional pathology associated with almost exclusive consumption of vegetable drinks (19).

Although there are studies, as mentioned above, that question the health benefits of dairy products, numerous studies report health benefits associated with dairy consumption. Recently, Denghan et al. (20) reported that dairy consumption is associated with lower risk of mortality and major CVD events in a large multinational cohort study from 21 countries in 5 continents. Additionally, the meta-analysis conducted by Gijsbers et al. (21) found that the total intake of dairy products (especially yogurt) was inversely associated with the risk of T2D.

Most meta-analyses report no or a weak inverse association between dairy intake and CVD and related intermediate outcomes. There is some suggestion that dairy consumption was inversely associated with stroke incidence, and yogurt consumption was associated with lower risk of T2D. Odd-chain fatty acids found primarily in dairy (15:0 and 17:0) appear to be inversely associated with cardiometabolic risk, although causation is uncertain (15).

There is high-quality evidence supporting an inverse association between the total intake of dairy products and the risk of hypertension, and between the intake of low-fat dairy products and yogurt and the risk of T2D. There is also evidence of moderate quality suggesting an inverse association between the intake of total milk products, low-fat dairy products, cheeses, and fermented milk products and the risk of stroke; between the intake of low-fat dairy and milk and the risk of hypertension; between total dairy and milk consumption and the risk of metabolic syndrome (MetS); and between the total dairy and cheese intake and the risk of T2D. In addition, data from this study show that the consumption of different forms of dairy products is associated in either a favorable or neutral way with clinical aspects related to cardiovascular health (22).

Dairy products are an important source of many nutrients, but they can be high in saturated fats (23). Indeed, most dietary guidelines recommend the consumption of low-fat dairy (6). However, the scientific rationale behind this recommendation is still under debate (14, 15, 24), an issue that is also addressed in the present supplement. To reduce coronary artery disease (CAD), dietary guidelines generally recommend reducing the intake of SFAs (21). Nevertheless, recent studies have questioned the role of SFAs in CVD. It has been found that substitution of SFAs in the diet with ω -6 (n-6) polyunsaturated fatty acids (abundant in vegetable oils) can lead to an increased risk of death from CVDs and CAD unless these are balanced with ω -3 polyunsaturated fat

(13). Similarly, it has been shown that replacing SFAs with high-glycemic-index carbohydrates is also associated with a higher risk of CAD (13, 25).

Indeed, the consumption of milk or dairy products has been inversely related to the incidence of CVDs in observational studies (15, 22). Moreover, the consumption of dairy products has been suggested to ameliorate characteristics of MetS, including some risk factors such as insulin resistance, increased blood pressure, dyslipidemia, and abdominal obesity, which together markedly increase the risk of diabetes and CVD (13). Some studies found similar results regarding the consumption of dairy products as a protective factor against certain pathologies such as T2D and CVDs (15), regardless of whether these dairy products were low or high fat (22). A benefit associated with the consumption of low-fat dairy in relation to T2D and the risk of stroke has also been shown by other authors (20, 22). In addition, when SFAs are consumed as part of complex food matrices, such as those in milk, cheese, yogurt, and other dairy foods, the potential detrimental effects could be counteracted (21). Considering the aforementioned studies as well as the current recommendations to consume low-fat dairy, further research is urgently needed to compare the impact of low-fat with regular- and high-fat dairy on cardiovascular-related clinical outcomes (22).

It is prudent to consider that in the dairy group there are different products, and results should be considered within the context of this heterogeneity (18, 20, 22). Finally, it should be noted that the observed effect of dairy consumption may be different between individuals with different characteristics and metabolic conditions (overweight/obese individuals, hypercholesterolemia, hypertension, T2D, etc.) (15); dairy consumption within the context of a globally healthy diet should also be considered (2, 6, 8).

However, there remain doubts about the effects of dairy on health by a part of the general population and by some health professionals. Some of these doubts are based on beliefs that are not scientifically sound, but in other cases, current knowledge about the mechanisms of these effects justify doubts raised by people with a high level of scientific knowledge. Therefore, it is necessary to analyze the scientific information published so far regarding the association between the consumption of milk and dairy products and health concerns such as growth and development, the promotion of health, and the prevention and control of several NCDs.

On February 28, 2018, a conference on the “Role of milk and dairy products in health and prevention of noncommunicable chronic diseases” was held in Madrid, coordinated by Prof. Angel Gil, University of Granada and Prof. Rosa Ortega, Complutense University of Madrid, Spain, with financial support from the EU H2020-funded project no. 734451 entitled “Program for the promotion of milk and dairy products within the framework of good dietary practices” [“Programa de promoción de la leche y los productos lácteos en el marco de unas prácticas dietéticas adecuadas”] and the aid of a grant from the Interprofessional Dairy Organization (INLAC), Spain.

The present supplement, based on that conference, aims to assess and summarize scientific evidence regarding the impact of dairy intake on health and all-cause mortality, and on the prevention and control of diverse chronic diseases, mainly from meta-analyses of observational studies and randomized controlled trials (RCTs).

By paying attention to the importance of an adequate consumption of dairy products to the health of different population groups, Achón et al. (26) evaluated the influences of maternal milk and dairy consumption on pregnancy and lactation outcomes in healthy women. Due to the high density of nutrients in milk and dairy products, these foods are potentially key to meeting the high nutrient demands of pregnancy and lactation. In this sense, most studies have assessed the impact of the consumption of small amounts of dairy products, paying attention to different stages of pregnancy/lactation. The authors concluded that although the number and types of studies provide insufficient evidence to form definite conclusions, there seem to be trends of positive associations between moderate maternal milk intake during pregnancy and both infant birth weight and length. However, there are too few studies to draw conclusions about other aspects related to the health of mother and child (preterm deliveries, spontaneous abortion, and lactation).

Milk and dairy products are particularly rich in certain nutrients (protein, calcium, and vitamin D) critical to growth and development, the highest rates of which occur in the pediatric population. De Lamas et al. (27) have analyzed the available evidence associating dairy product intake with linear growth and bone mineral content in childhood and adolescence. The authors conclude that supplementing the usual diets with dairy products significantly increases bone mineral content during childhood. However, the results regarding a possible relation between dairy consumption and linear growth are inconclusive.

Cavero-Redondo et al. (28) have conducted an overview of existing systematic reviews and meta-analyses to examine the association between dairy product consumption and the risk of mortality from all causes. The number of included studies in each meta-analysis ranged from 6 to 26 cohort studies, which reported data from 6 to 28 populations with the sample sizes varying across studies from 24,466 participants reporting 5092 mortality cases to 938,817 participants reporting 126,759 mortality cases. Analysis of the differences between high and low dairy consumption and for dose-response found no association between dairy product consumption and risk of all-cause mortality.

Considering that aging may potentially modify nutritional requirements, Cuesta-Triana et al. (29) investigated the effectiveness of dairy product intake in the prevention of frailty, sarcopenia, and cognitive decline in the elderly. They concluded that the consumption of dairy products in older subjects may reduce the risk of frailty, especially in those who consume a high quantity of low-fat milk and yogurt, and that skeletal muscle mass may improve with the addition of milk protein to the regular diet, thus decreasing the risk for sarcopenia. However, the studies concerning cognitive

decline show contradictory findings. A higher consumption of dairy desserts and ice cream was associated with cognitive decline in women. However, after adjustment for saturated fat intake, a high consumption of milk during midlife was negatively associated with some cognitive decline as measured by verbal memory.

Dairy products have been implicated in changes in bone mass density (BMD) and the increased fracture risk associated with aging. Matía-Martín et al. (30) have analyzed the evidence regarding the influence of dairy intake on osteoporotic fracture risk and prospective BMD evolution in Europeans and in non-Hispanic whites from North America. The results regarding BMD change were heterogeneous and the evidence did not allow the researchers to definitively state whether or not dairy intake influenced BMD. The selected studies described a 1.7–3% lower hip BMD in young and postmenopausal women with poor intake of milk during youth, a positive relationship between baseline milk ingestion and the percentage of trochanteric BMD change in elders, and a positive correlation between milk intake and BMD change in the radius in women aged >65 y. The authors also concluded that the highest consumption of dairy products did not show a clear association with total osteoporotic fracture and hip fracture risk; however, a diminished risk of vertebral fracture was found.

Mena-Sánchez et al. (31) have analyzed the associations between consumption of dairy products and their subtypes and the incidence of MetS. The results from the systematic review and meta-analysis of prospective studies suggest that total and low-fat dairy consumption, total yogurt (and its different subtypes) consumption, and total milk consumption are associated with a reduced risk of developing MetS. Furthermore, consumption of whole-fat dairy was not associated with the incidence of MetS. Due to the alarming prevalence of MetS, new dietary strategies to prevent this syndrome are imperative and dairy products should not be excluded.

Fontecha et al. (32) have conducted an overview of systematic reviews and meta-analyses of cohort studies, and an overview of meta-analyses involving RCTs to evaluate the evidence regarding the influence of dairy product consumption on the risk of major cardiovascular-related outcomes and how various doses of different dairy products (total dairy, milk, cheese, fermented dairy, cream, and butter) affect the responses, as well as on selected biomarkers of CVD risk, i.e., blood pressure and blood lipids. The study concluded that current evidence supports the hypothesis that consumption of dairy products does not adversely affect the risk of cardiovascular outcomes (CVD, coronary heart disease, heart failure, and stroke) and may even have a subtle protective effect. Moreover, evidence has been provided of an inverse association between the consumption of dairy products and ischemic heart disease and myocardial infarction. Furthermore, meta-analyses of the RCTs confirmed that dairy product consumption does not adversely affect the development of CVD, as evidenced by the nonadverse effects on risk biomarkers such as blood pressure (systolic

and diastolic) and plasma lipids (total cholesterol and LDL cholesterol).

The aim of the systematic review and meta-analysis by Álvarez-Bueno et al. (33) was to examine the scientific literature available on the association between dairy product consumption and T2D risk. The evidence suggests that dairy consumption, particularly low-fat dairy and yogurt (80–125 g/d), is associated with a lower risk of T2D. This is important from a public health point of view because the results may inform the recommendations of practitioners, policymakers, and relevant scientific associations. Dose-response analysis showed lower T2D risk at 200–400 g/d of total dairy product consumption, 200 g/d of low-fat dairy product consumption, and 80–125 g/d of yogurt consumption. The association with cheese was moderate. Moreover, dose-response analyses showed that the risk of T2D decreased incrementally as units of consumption of total dairy products and low-fat dairy products increased. However, the evidence is still null or weak regarding high-fat dairy, and more research is warranted to differentiate fat content in dairy products (high/low), and fat and sweetener content of yogurt, and studies with the ability to adjust for other food components and conduct substitution analyses may provide the strongest evidence given the lack of RCTs.

The aim of the systematic review of epidemiologic studies carried out by Barrubés et al. (34) was to update and examine the associations between the consumption of specific types of dairy products and CRC incidence and location. No significant associations with CRC were found for the consumption of low-fat dairy products, whole milk, fermented dairy products, and cultured milk. However, high consumption of total dairy products and total milk is associated with a lower risk for all locations of CRC development. Evidence suggests that low-fat milk consumption could decrease the risk of colon cancer. An inverse association between cheese consumption and CRC as well as proximal colon cancer risk was also detected. No harm was observed related to the consumption of any type of dairy, including whole-fat dairy products. Therefore, the consumption of dairy products and especially low-fat milk and cheese may seem to be an appropriate practice in relation to CRC.

Milk and dairy products have been frequently associated with an increase in prostate cancer risk. However, various discrepancies have been observed in the literature. The relationship between dairy and prostate cancer risk is a highly debated topic and has generated much commentary. This is the topic investigated in the systematic search of López-Plaza et al. (35), which found that although there are some data indicating that higher dairy product consumption could increase prostate cancer risk, the total evidence generated to date is still inconclusive, due mainly to statistical heterogeneity, the number of studies included in each analysis, and the weak control of confounding factors in primary studies, all of which generate uncertainty in the observed results. Therefore, there is currently insufficient evidence to justify a reduction in daily milk and dairy product consumption. Hence, daily intake of milk and dairy products should follow

the dietary recommendations promulgated by the competent authorities of each country.

The meta-analysis from Bermejo et al. (36) pooled the results of 26 cohort and case-control studies to determine the association between milk and dairy products and bladder cancer. Overall, medium compared with low consumption of total dairy products, milk, and fermented dairy products was significantly associated with lower pooled risk for bladder cancer. The inverse association for milk consumption was stronger in Asia and for cohort study designs. However, high compared with low consumption of whole milk was significantly associated with a higher risk for bladder cancer, although statistical heterogeneity was considerable, and these results should be interpreted with caution.

The systematic review by Ulven et al. (37) evaluated the scientific evidence gathered from RCTs in the past 5 y regarding the effects of milk and dairy products on inflammatory biomarkers. The authors concluded that the consumption of milk or dairy products did not show a proinflammatory effect on healthy subjects, overweight/obese individuals, or individuals with other metabolic abnormalities. The evidence from long-term supplementation showed a subtle anti-inflammatory effect in both healthy and metabolically abnormal subjects. However, the evidence from acute or short-term interventions is scarce and, therefore, inconclusive.

It is interesting to extend the investigation to the role of functionally fortified dairy products in improving nutrition and health, and preventing risk factors associated with NCDs, in particular CVDs. In relation to this topic, Soto-Méndez et al. (38) have analyzed the effects of consuming fortified dairy products as functional foods on biomarkers of cardiometabolic risk. The most relevant aspects of the investigation were that fortification of dairy products with phytosterols and ω -3 fatty acids seems to be a good approach to improve cardiometabolic risk biomarkers, and because of their characteristics, dairy products appear to be good vehicles to deliver these compounds to the general population. However, there is a need for further RCTs with similar and well-designed methodologies, greater numbers of subjects, and longer durations to confirm the findings of the potential effect of functional fortified dairy products on cardiometabolic health.

In summary, although there is great heterogeneity in the designs of the studies, all conclude that the consumption of dairy products does not adversely affect mortality. In most cases, regarding the NCDs included in this supplement, there is a benefit associated with dairy product consumption, sometimes described for total dairy consumption and sometimes for a particular type of dairy product.

A limitation of some of these studies is the need to control for possible changes in the consumption of other foods, which can occur with an intervention that increases the consumption of milk or dairy products. Although all the investigators point out the need for further research and indicate interpretation of the results should be made with caution, the systematic reviews and meta-analyses

carried out in the present supplement support adequate milk consumption at various stages of life and in the prevention/control of various NCDs. In some cases, the effect of dairy product intake on a specific condition is neutral. However, even in these cases it is not possible to ignore the nutritional importance of dairy products within the context of a well-balanced diet.

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