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Reappraisal of the scientific evidence linking consumption of foods from specific food groups to non-communicable diseases

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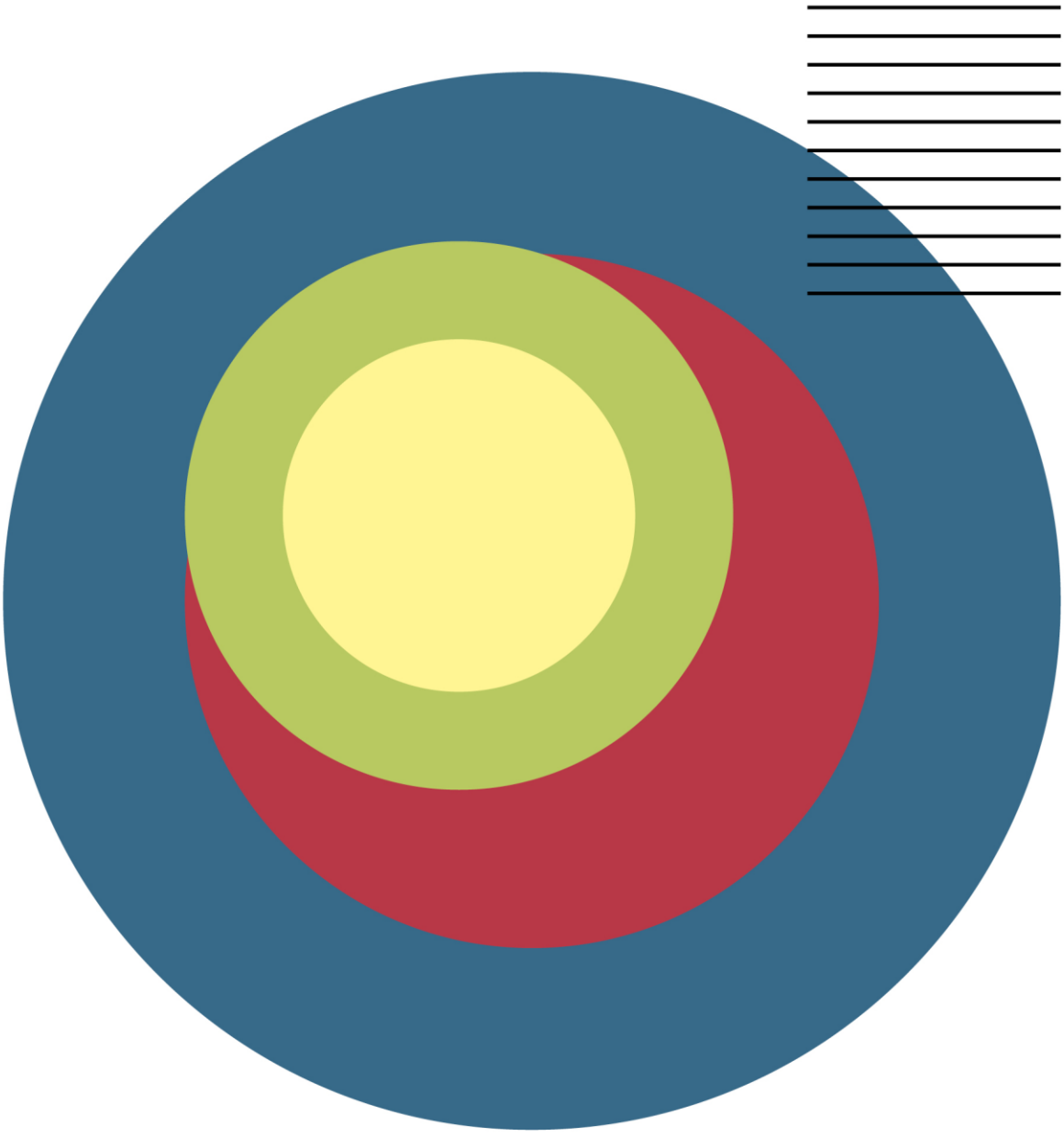

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Conflicts of interest

Luc Tappy has received research support from Soremartec Italia srl, Italy and speaker's fees from Soremartec Italia srl, Italy and Nestlé SA, Switzerland.

Kim-Anne Lê is employed by Nestlé Research.

Adoption of the report

The final version of the report was adopted by a majority of the Federal Commission for Nutrition on the 23rd of December 2019.

Preface

A varied, well-balanced and generally healthy diet has a very important influence on the health of the Swiss population. However, the definition of a standardized "healthy diet" is difficult and depends on various factors, such as the quality and type of individual food components, their quantity and the distribution within the menu. Furthermore, the definition of a "healthy diet" differs between various population groups - depending on age, weight and state of health, as well as accompanying diseases. For example, the consumption of a piece of chocolate can be considered healthy. However, as Paracelus already described in 1538 ("All things are poison, and nothing is without poison; only the dose makes a thing not be a poison"), chocolate also has a similar dosage/effect ratio as most foods, such as meat, coffee and many more. This complex issue raises the question of how to provide the Swiss population with generally valid recommendations for a healthy diet, which can be implemented in everyday life and reflect the latest findings from scientific studies. This is the objective of the Swiss Food Pyramid which provides recommendations for a balanced diet for healthy adults and illustrates in a simple and understandable way how much of which food group is needed.

The first food pyramid was published in 1998 by the former Swiss Association for Nutrition (SVE, now Swiss Society for Nutrition), modelled on the American food pyramid of the United States Department of Agriculture of 1992. In order to take account of new scientific findings and evolving design expectations, the food pyramid was revised twice in 2005 and 2011. In recent years, new findings from epidemiological studies have been summarised in the form of systematic reviews and meta-analyses, prompting the Federal Nutrition Commission (EEK) to mandate a further revision of the scientific basis for the food pyramid under the leadership of Prof Luc Tappy and eight other authors. The revision focuses on the evaluation of the current recommendations from the point of view of the prevention of non-communicable diseases. The different levels of the pyramid were revised, based on selected food groups such as fluids, incl. coffee, fruit and vegetables, sweetened beverages, starch-containing products, dairy products, vegetable proteins, fats and oils and nuts. Some new findings have emerged, such as the preventive role of nuts, hence the recommendation to reclassify them at the level of fruits and vegetables.

Many people in Switzerland are motivated to follow a healthy diet, i.e. a diet that will keep them healthy. This FCN (EEK) report summarises current scientific knowledge and is intended to provide the basis for a revision of the nutritional recommendations, which can be translated into a revised food pyramid, as an aid to making healthy dietary choices. The pyramid should provide valuable nutritional recommendations in simple form. Furthermore, the pyramid should offer objective information to interested readers about the potential health benefits and risks of individual food groups. In this way the pyramid can be a tool in fulfilling one of the goals of the Federal Nutrition Strategy, i.e. to increase the nutritional competence of the population.

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1 Introduction

Noncommunicable diseases (NCDs), such as cardiovascular diseases, type 2 diabetes mellitus, or cancers are highly prevalent in Switzerland as in most countries worldwide. These NCDs not only strain affected individuals and their relatives, but also have also important consequences on work productivity and overall economy, and represent a major burden on our health care system. It is well documented that a wide range of factors, including genetic, environmental, and life style factors determines the risk of developing NCDs. Among the latter protective behavioural factors are abstention from smoking, maintaining an adequate level of physical activity and body weight and ensuring an adequate intake of foods and essential nutrients. This implies that the incidence and prevalence of NCDs may be significantly reduced, and the age at which NCDs develop may be significantly delayed by interventions aimed at improving the lifestyle at population level. The main primary prevention intervention at nutritional level relies on the Swiss Food pyramid as a tool to inform the generally healthy adult population of what constitutes a healthy food pattern. The pyramid depicts recommended food intakes based on the frequency of consumption of basic food groups, e.g. beverages, fruits and vegetables, grain, potatoes and pulses, etc., and was last updated in 2016. The Federal Commission for Nutrition (FCN) was asked by the Swiss Federal Food Safety and Veterinary Office (FSVO) to reappraise the scientific evidence linking consumption of foods from specific food groups to NCDs, and to assess whether changes to the Swiss Food Pyramid are warranted based on recent scientific evidence.

There is strong evidence that nutritional factors are closely linked to the development of NCDs, and international and national food agencies continuously monitor scientific progress made in this field and periodically revise specific dietary guidelines. Several recent FCN reports have thus addressed the relationships that exist between red meat intake (https://www.blv.admin.ch/blv/de/home/das-blv/organisation/kommissionen/eek/gesundheitliche-aspekte-des-fleischkonsums.html), or dietary fats intake (https://www.blv.admin.ch/blv/de/home/das-blv/organisation/kommissionen/eek/fette-in-der-ernaehrung1.html) and health. Each year new scientific evidence on the association between nutrition and health is published. Publications encompass a broad range of approaches, including studies aimed at assessing the mechanisms underlying foods biological effects, surveys documenting the level of intakes of foods in the populations, observational studies assessing the relationship which exists between the consumption of specific food classes or nutrients and risk of NCDs, and clinical trials documenting the effects of controlled changes in food intake on health outcomes. The FCN has therefore mandated a group of experts to recover and analyse the recent scientific literature (from 2012 to 2017) pertaining to the relationships between consumption of each food groups represented on the Swiss Food Pyramid and the risk for NCDs, and to formulate the scientific basis linking dietary guidelines for each food groups and NCDs. The mandate was explicitly limited to effects on NCDs and NCDs risk markers, and did not extend to dietary macro- or micronutrients deficiencies.

2 Methods used to assess the relationship between food groups' consumption and NCDs

Author: Luc Tappy

A working group constituted by Murielle Bochud, Sabine Rohrmann and Luc Tappy coordinated the expertise. It was structured to address specific food groups represented in the current Swiss Food Pyramid, i.e. fluids and beverages, fruits and vegetables; cereals and starchy foods; dietary protein sources, including milk and dairy products, meat and fish, pulses and vegetable proteins; and fats and nuts. An additional food group constituted of sweet and salted snacks and industrial food was initially included to evaluate whether it was possible and relevant to provide specific health-related information and or propose dietary guidelines regarding these foods. It was however recognized that the scientific literature was both too scarce and not recent enough to make a meaningful analysis, and this additional group was therefore not included in the final recommendations.

Each of the 5 food groups was addressed in one specific chapter, which was written by one or several experts.

For each food group or subgroup, the following elements were presented:

1. A generic definition of the food group, whenever possible referring to the Swiss food legislation and a brief summary of its nutritional properties
2. A recall of its present position in the Swiss Food Pyramid and current data on levels of intake in the Swiss population or other comparable populations
3. A summary of the putative mechanisms linking foods from this group to NCDs
4. A review of literature 2012-2017
5. Recommendations from the chapter's author (intake, further research etc.)

For the critical appraisal of recent scientific evidence, a complete de novo analysis of the whole literature and the performance of independent meta-analyses, as performed by large international or national food agencies could not be done within the time-frame and budget allowed. The following strategy was therefore proposed. Only human data from prospective cohort studies (PCSs) and randomized controlled trials (RCTs) were considered. Cross-sectional epidemiological studies were exceptionally included if felt adequate. Ecological studies, non-controlled clinical trials, narrative reviews, animal studies, and data available in non-peer-reviewed medical literature (i.e.: theses, abstracts in congresses, grey literature) were not considered relevant for the analysis. The literature search aimed at retrieving meta-analyses of PCSs or RCTs, either published between 2012 and 2017 in peer reviewed medical journals or produced and released by international/national food agencies in the same period. The selected endpoints of these meta-analyses were incidence of specific NCDs (obesity, type 2 diabetes, cardiovascular diseases; cancers); mortality associated with NCDs; markers of risk for NCDs; others as defined by experts. Information from these meta-analyses was extracted and reported in tables. When no meta-analysis was available to address one specific question, primary research reports of PCSs or RCTs were considered and their main findings was summarized. Primary reports of PCS and RCTs which were too recent to be already included in meta-analyses were also considered and their main findings were summarized in the results section of the chapter. For meta-analyses, level of heterogeneity was taken into consideration.

When available, meta-analyses with a low level of between-studies heterogeneity and providing a dose-response evaluation were favored. The experts and the working group considered that RCTs provided information on effects of foods on NCDs incidence or NCDs-related outcomes (progression, risk factors….), and that some RCTs or experimental controlled studies provided plausible mechanisms linking foods consumption and NCDs. They also considered that PCSs provided information on associations between foods' consumption and NCDs incidence or NCDs-related outcomes (progression, risk factors….)

To evaluate the levels of evidence, it was considered that randomized controlled trials (RCTs) provided the highest level of evidence with respect to causality, but that observational studies, when adequately conducted, provided valuable information on causality, in particular when associations are strong and results replicated across different settings.

These methodological guidelines were applied when possible by each expert in charge of the evaluation of one food group/subgroup; due to the fact that availability of published studies, and type of studies available showed considerable variations between food groups/subgroups, experts were entitled to use alternate approaches as required, and mentioned specific methods used in their report. For the meat, fish, egg and tofu food groups, the working group considered that the association between red meat, resp. cured meat, and NCDs had been comprehensively addressed in the 2014 FCN report, and that novel additional knowledge was unlikely to alter the conclusion of this report; it was also felt that there was little novel scientific evidence regarding fish and eggs consumption and NCDs. It was therefore decided to provide a short summary of the present dietary guidelines as an introduction to the expert reports on other protein-rich foods, i.e. milk and dairy products and pulses and vegetable proteins.

A summary of major findings for each food groups and recommendations was prepared by the working group and was reviewed by the members of FCN. Final conclusions and recommendations are summarized in the final chapter of this report, as well as in separate management summaries.

3 Beverages

In general, beverages regroup all liquids consumed during the day, whether or not they contain calories (water, coffee, tea, sodas, etc.), with the exception of milk, which is included in the dairy products food groups.

Beverages are in general the main source of the nutrient “water”, which plays a major role in fluid and mineral homeostasis. In addition to water intake from beverages, about 1500 ml of water is consumed daily with foods or produced through the oxidation of macronutrients (i.e. metabolic water, endogenic source). At the time being, the scientific evidence for specific recommendations for beverages is weak, in part because of a lack of international consensus on the methods to be used to assess water intake and hydration status. Water balance is characterized by dynamic complexity with constantly changing, vastly integrated regulatory mechanisms [1]. In this chapter, the topic of hydration will be briefly mentioned in chapter 3.1 (water), other beverages discussed are sugar-sweetened beverages, including coffee (chapter 3.2) and juices (chapter 3.3), the latter two being included in this chapter.

3.1 General fluid intake, water

Authors: Murielle Bochud, Angeline Chatelan

3.1.1 Definition of water

Water of drinking quality is defined in the Swiss food legislation as either mineral water, i.e. microbiologically irreproachable water from underground layers or deposits and is extracted from a source accessible through one or more natural or artificial outlets, or as spring water. This is water of subterranean origin which is marketed while preserving its original state.

3.1.2 Recommendations and intake data

Water has a special position as it can be seen both as a nutrient and as a food group. Most data on recommended fluid intake are based on water as a hydrating nutrient.

Summary box recommendations and intake

WATER	Definition	Quantity
Daily recommendations current Swiss Food Pyramid [2]	preferably in the form of sugar-free drinks, e.g. tap/mineral water or fruit/herbal tea. Beverages containing caffeine, such as coffee, black and green tea, can contribute to liquid intake	1-2 L
Daily Intake in Switzerland [3]* Total / male / female	Water	1.2 L / 1.2 L / 1.2 L

*Data are mean values of two 24-hour recalls protocols, weighted and corrected for seasonality and weekdays.

Recommendations for water intake

Water requirement varies between individuals and depends on environmental conditions, such as air temperature, humidity, as well as on physical activity. Recommendations for water intake therefore need to specify to which conditions the recommendations apply.

Recommendations of adequate total fluid intake have been proposed by the European Food Safety Authority (EFSA), with the publication of a scientific opinion of dietary reference values for water in 2010. EFSA distinguishes “total water intake” (from beverages and foods) and “total available water intake” (from beverages, foods and metabolically produced water) [4]. According to EFSA, the reference values for total water intake should include water from drinking water, beverages of all kinds and from food moisture [4].

The EFSA recommendation is based on a combination of observed water intakes in 13 European countries, with ranges of intake varying from 720 to 2621 mL/day [5]. Taking into account (a) observed intakes in several European populations, (b) desirable urinary osmolarity levels, as well as (c) desirable water volumes per energy unit consumed, the EFSA currently considers that adequate intake (AI) of water for adult women is 2.0 L/day (percentile 95 = 3.1 L/day) and 2.5 L/day (percentile 95 = 4.0 L/day) for men, with similar AIs for the elderly [4]. Pregnant women should consume 300 mL/day of water in addition to what is recommended for non-pregnant women and, for lactating women, additional 700 mL/day of water are recommended [4]. These AIs of water include water from beverages, water ingested with foods, and water produced from the metabolism of macronutrients, and are intended for moderate environmental temperature and moderate physical activity levels (PAL 1.6) [4]. AIs is 100-190 mL/kg/day for infants between 0 and 6 months, 800-1000 mL/day for those between 7 and 12 months, 1100-1200 mL/day for children aged between 1 and 2 years, 1300 mL/day for those aged 2-3 years; 1600 mL/day for those aged between 4-8 years.

Levels and characteristics of water intakes in the population

Total water intake substantially differs across countries and regions of the world. Average water intake from beverages and foods among adult men and women were 2.3 L and 2.1 L in France (NutriNet-Santé Dataset), 1.7 L and 1.6 L in Spain (ANIBES), 1.7 L and 1.7 L in Italy (INCAN-SCAI dataset), respectively [6]. In Ireland, total water intake was 2.3 L in men and 2.1 L in women, with lower intakes in elderly people as well as in people with low education, physical inactivity and higher BMI [7]. In the UK National Diet and Nutrition Survey (NDNS 2000/2001) including 1724 adults aged 19 to 64 years, total water intake averaged 2.5 L in men and 2.0 L in women [8]. In the first Swiss national nutrition survey, menuCH, mean [median] water intake from beverages and foods among 2000 adults aged 18 to 75 years, were 3.1 [3.0] L in men and 2.9 [2.8] L in women, with differences across linguistic regions (unpublished data). According to menuCH data, total water intake is higher in Switzerland than reported in prior population-based surveys across Europe. Important differences across Swiss regions also exist for 24-hour urine volume, with higher volumes in the German-speaking part of Switzerland, as illustrated in the population-based SKIPOGH cohort including adults aged 18 to 90 years randomly selected from the general population of three Swiss regions, Lausanne, Geneva and Bern [9–14]. The regional differences observed in SKIPOGH, in both men and women, may reflect cultural differences related to diet as well as different mixes of urban-rural settings across these regions: Geneva is a primarily urban canton, whereas the canton of Bern includes a large rural part. The Lausanne sample comes primarily from people living in the city of Lausanne and, to a lesser extent, people living in settings that are more rural. This confirms prior observations from the Swiss Survey on Salt, including data on 1300 participants with 24-hour urine collections across the three main linguistic regions of Switzerland [15].

Part of these country and regional differences likely reflects differences in methodology, but the observation of relevant regional differences within Switzerland (i.e. using the same method) suggests that total water intake also depends on the cultural context.

The amount of water in non-liquid foods strongly varies across food groups, ranging from 70-80% for selected fruits and vegetables to 0% for oils and sugars [16]. Overall, food contributed to 32% of total water intake in Spain, 38% in France and 45% in Italy [6]. In another study, the contribution of water from foods was 27% in UK (UK Nutritional Survey NDNS 2008/2009-2011/2012) and 36% in France (French Nutritional Survey – CCAF 2013) [17].

The percentage of water consumption in the beverage category was 48% and 47% in French women and men, respectively, 46% and 43% in Italian women and men, respectively and 46% and 41% in Spanish women and men, respectively [6]. Water hence represents, by far, the largest proportion of total fluid intake, in these three European countries. In Spain, only

13% men and 22% of women followed EFSA recommendations for adequate intake of 2.5 L (men) and 2.0 L (women) total water intake, whereas the corresponding percentages were 11% and 24% in Italy and 30% and 51% in France [6]. Furthermore, 29% of men and 42% of women followed the above 1 criterion for the ratio between total water intake and total energy intake in Spain, whereas 13% of men and 27% of women in Italy, and 46% of men and 66% of women in France fulfilled this criteria [6]. These results highlight the difficulty to follow EFSA recommendations for water consumption among European adults as well as the important differences in total water intake across European cultures.

3.1.3 Putative mechanisms linking water intake and NCDs

Physiology of water balance

Water intake is essential for life and for human health. In the adult human body, water represents 60% of body weight in men and about 50-55% in women [4]. In new-born children, water represents 75% of body weight [4]. The water content of the body is distributed into the intracellular and extracellular compartments. A balance needs to be achieved between water inputs and water losses for each compartment. The main sources of water inputs are water intake (around 1000 mL from beverages), water content from foods (around 1200 mL) and water metabolically produced in the human body (about 300 mL per day). Water losses may occur in the kidney (urine [about 1500 mL per day, depending on fluid intakes]), the intestine (faeces [about 100 mL per day]), the skin (sweat and perspiration) and the lung (evaporation via respiration [about 900 mL per day]). Water homeostasis is regulated by multiple feedback systems, including the hypothalamus, the hypophysis and the kidney [18]. Water balance is a complex and highly dynamic process [1, 19]. Human beings must replenish water every day by ingestion of beverages and foods. A tight regulation of the hydration status of the human body is essential for life. Given the complexity of total body water turnover, it is clear that no single biomarker of hydration status exists and that the ideal biomarker, or set of biomarkers, depend on the question being asked [19]. Under steady-state conditions, hydration status can be split into hypohydration, euhydration and hyperhydration [18, 20]. Yet, there is no internationally accepted laboratory method to define the hydration status of an individual [20]. Dehydration occurs when water losses are greater than water intakes. Mild dehydration has been defined as a 1% to 2% loss of body weight as a result of fluid loss [20]. A loss of 10% of body water may be fatal. Reduction in body weight of 2 to 3% are considered to impair cognitive performances [21], although the literature is inconsistent with some studies indicating that a dehydration level of 1% may already affect cognitive performances [22], impair exercise performance and increase the risk of kidney stones [23]. Fluid intake following dehydration was found to improve exercise performance, whereas evidence for improved cognitive performance was limited [24].

Mechanisms linking water intake and NCD’s

For many years, scientific studies in the field of water metabolism focused mainly on the extremes of severe dehydration and water intoxication [16]. There is growing evidence that chronic mild hypo-hydration may influence multiple health outcomes, including the risk of common chronic diseases [1, 16] (see section 4). This field of study is however suffering from the lack of consensus on a “gold standard” for hydration biomarkers [1, 16]. There is convincing evidence that increased urine volume from increased fluid intake reduces the risk of kidney stones [16, 25–27]. This probably results from diluted urine concentration and decreased urine acidity. Vasopressin, the primary water-regulating hormone, influences glucose metabolism in the liver (gluconeogenesis, glycogenolysis) and pancreas (insulin or glucagon production) as well as NO-mediated vasodilation in vascular smooth muscle cells [1]. These latter biological functions may explain a link between water intake and risk of cardiometabolic disorders.

The association of water intake with body weight maintenance likely results from a combination of mechanisms: reduced total energy intake (e.g. if water replaces caloric beverages), increased satiety, and/or reduced feeling of hunger [30].

3.1.4 Review of literature

Water intake and health outcomes

Identifying appropriate studies was made difficult by the ambiguity in use of terms “water”, “fluids”, and “beverages”. In the following review, the terms are reported as used by the authors. Water is increasingly being identified as playing a key role in chronic disease prevention [16, 28], in particular for chronic kidney disease [29, 30], nephrolithiasis [29], cardiovascular disease [31], obesity [32, 33] and type 2 diabetes [34]. High circulating vasopressin levels are associated with higher risk of type 2 diabetes, metabolic syndrome, cardiovascular disease and premature mortality in population-based observational studies [34]. Although the evidence is still low, a systematic review found that increased water intake in adults on weight losing diet or weight maintenance programs is associated with weight reduction [32]. Findings are similar for children and adolescents [33]. Of note, there is, to date, no published major long-term randomized controlled trial on the effect of increased water intake on health.

A recently published report found no association between total daily fluid intake and all-cause and CVD mortality nor with rapid renal function decline in 1055 women aged 70 years or older followed-up for 10 years [35]. High total water intake was not associated with improved survival after a median follow-up of 11 years in 25’000 participants to the NHANES 1988-1994 and 1999-2004 surveys [36].

Water intake and diet quality

In the French INCA2 survey, water drinking was associated with higher diet quality, when considering mean adequacy ratios of several nutritional indices or the probability of adequate intakes (PANDiet) [28]. The majority of French adults (72% of men and 46% of women) were below the EFSA recommended adequate water intakes [28].

3.1.5 Recommendations

Daily water needs vary across individuals depending on climate, physical activity, diet and cultural factors [37]. Total water intake data substantially vary from one population to the other, both within and across countries. Part of these differences are clearly attributable to methodological issues [38]. Current recommendations for total water intake are based on AIs in temperate climates at moderate physical activity levels and not on estimated average requirement (EAR) nor on Recommended Dietary Allowance (RDA) [38]. To date, recommendations for water intakes have been established from population intake data and not from studies having linked long-term water intake with health outcomes [37]. Given the limited amount of current evidence linking total water intake to health outcomes, further data would be needed to guide evidence-based recommendations on water intake. In particular, scientific evidence on the levels of long-term water intake needed to reduce the risk of common chronic diseases is currently limited.

3.2 Coffee

Author: Idris Guessous

Worldwide, coffee and tea are among the most widely consumed beverages and caffeine is ubiquitous in beverages. In 2015, the European Food Safety Authority published a report on

the effects of caffeine on health [39]. The report concluded that daily caffeine intakes from all sources up to 400 mg per day do not raise safety concerns for adults in the general population.

The literature review focused on caffeine and coffee on health; it did not review the literature on tea, caffeinated sugar-sweetened beverages, “energy drinks” or weight loss and sports supplements.

Disentangling the effects of caffeine versus sugar in caffeinated sugar-sweetened beverages is challenging and beyond the scope of this section. In addition, governmental recommendation on sugar-sweetened beverages intake is likely to be straightforward (e.g., “no intake” or “as little as possible”), independently of the presence or not of caffeine. Finally, chapter 3.3 on sugar-sweetened beverages might cover, at least in part, the literature on caffeinated sugar-sweetened beverages.

We performed a Medline literature search for human meta-analysis and critical reviews of studies (interventional or observational studies) that evaluated the associations of caffeinated-beverages, with specific focus on coffee, on major non-communicable diseases incidence and outcomes. The review covered the 2014-2017 period. The search was started in 2014 to cover the year preceding the publication of the 2015 European Food Safety Authority “Scientific Opinion on the safety of caffeine” [39]. Studies were included if they focused on associations with or effects of chronic caffeinated-beverages intake and non-communicable diseases among adult men and non-pregnant women from the general population (“healthy general population”). Articles focusing on gene-caffeine interaction, tea, and methylxanthines others than caffeine were not included. When multiple meta-analyses on a given health outcome were published, only the latest meta-analysis was generally included.

Finally, this review focused on associations between caffeinated beverages intake and chronic diseases in adult men and non-pregnant women, from the general population; specific associations in particular population subgroups (e.g., adults with disease or risk factors for specific diseases, pregnant women, etc.) were not evaluated. Some of this information is however presented by other agencies/expert panels reports [39].

3.2.1 Current recommendations and intake data

Currently the recommendations are cautious, stating that “caffeinated drinks like coffee, black and green tea can contribute to covering fluid needs”. Not specific serving sizes are given (e.g. highest tolerable levels), nor are there any restrictions made for specific population groups.

Several authorities have published scientific statements regarding the safety of caffeine. The 2015 European Food Safety Authority concluded that daily caffeine intakes from all sources up to 400 mg per day do not raise safety concerns for adults in the general population, except for pregnant women (200 mg per day). Although caffeine concentration might differ according to the type of coffee preparation, one cup of coffee contains typically about 100mg of caffeine. These recommendations are in line with those released by other food authorities (2012 Belgium’s Superior Health Council [40], Health Canada [41] The European Food Safety Authority concluded for example that any diuretic effects resulting from chronic caffeine consumption are unlikely to have adverse health consequences for the healthy general population.

This review does not include the specific effects of tea on health. Different dietary guidelines such as the 2015 Dutch food-based dietary guidelines have reviewed this topic. Green and black tea and appeared to reduce blood pressure in interventional studies and the consumption of tea was associated with a lower risk of stroke in cohort studies. The consumption of black tea and green tea was also associated with a lower risk of type 2 diabetes. Based on this evidence, the 2015 Dutch food-based dietary guidelines recommend up to three cups of tea daily [42].

Summary box recommendations and intake

COFFEE	Definition	Quantity
Daily recommendations current Swiss Food Pyramid [2]	Beverages containing caffeine, such as coffee, black and green tea, can contribute to liquid intake.	1-2 L total, with coffee for variety
Daily Intake in Switzerland [3]* Total	coffee	2.6 dl coffee / day, with regional, gender and age-based differences

*Data are mean values of two 24-hour recalls protocols, weighted and corrected for seasonality and weekdays

3.2.2 Putative mechanisms

Caffeine (1,3,7-Trimethylxanthine) is a purine alkaloid, with coffee being the major dietary source (more than 70 %) [43]. Coffee bean extract is a complex mixture of thousands of chemicals and includes potentially bioactive components such as caffeine, polyphenols (e.g., chlorogenic acid), fatty acid esters of diterpenoids (e.g. cafestol, kahweol) [44].

Several of these coffee components may affect health. For example, chlorogenic acids, the most abundant polyphenols in coffee, are known to function as antioxidants and may improve glucose metabolism and inhibit formation of advanced glycation end products [45] Two major natural diterpenoids found in coffee, cafestol and kahweol, have been associated with an elevation of cholesterol [46]. In addition, caffeine can influence blood pressure and other factors related to cardiovascular health via its impact on renal segmental tubular sodium handling, smooth muscle relaxation, arterial stiffness and phosphodiesterase inhibition [47].

The acute and chronic effects of coffee or caffeine intake on non-communicable diseases are different; this review focused only on the chronic effect of caffeinated-beverages. Caffeine is metabolized by the liver CYP1A2 enzyme to paraxanthine (about 80 %), theobromine (about 12 %) and theophylline (about 4%); others (about 4%).

3.2.3 Review of literature

This review focusses on the effects of caffeine per se, not on that of its metabolites.

Mortality

Since the 2012 landmark publication showing that coffee consumption (caffeinated or decaffeinated) was inversely associated with total and cause-specific mortality [48], we identified additional articles reporting on this association. Two meta-analyses were published in 2014 with more than 990,000 participants included in each of them. One meta-analysis reported a nonlinear association between coffee consumption and mortality from all causes and cardiovascular disease (CVD) mortality; the largest risk reductions were observed with an intake of 4 cups/day for all-causes mortality (16% 95% CI 0.82, 0.87) and 3 cups/day for CVD mortality (21% 95% CI 0.74, 0.84) [49]. Coffee consumption was not associated with cancer mortality. The other meta-analysis separated the associations of coffee and caffeine [50]. The relative risk of death for the high *versus* low category of coffee consumption was 0.86 (95% CI 0.80, 0.92). The pooled relative risk for studies using ≥ 2-4 cups/d as a cut-off for the high category was similar to that for studies using ≥ 5-9 cups/d as the cut-off. High consumption of decaffeinated coffee was also found to be associated with a lower risk of death.

Cardiovascular disease (including kidney diseases and metabolic diseases and the metabolic syndrome)

The associations between caffeinated-beverages intake and CVD risk were investigated in several observational studies and summarized in 13 meta-analyses since 2014. The subdomains include peripheral arterial disease (PAD), metabolic syndrome, coronary artery disease, stroke, hypertension or blood pressure, and CVD in general [51–63]. In general, caf-

feinated-beverages intake was associated with lower risk of incident PAD, metabolic syndrome, hypertension, and stroke. Coffee consumption was associated with lower blood pressure and higher estimated glomerular filtration rate (eGFR) [51, 61]. Coffee consumption was not associated with increased risk of atrial fibrillation [64]. The Italian-arm of the EPICOR prospective study (EPICOR) found an increased risk of coronary heart disease [59], while another prospective study found no association with cardiovascular events or coronary artery calcium progression (although caffeine intake was marginally inversely associated with coronary artery calcium progression) [54]. A 2014 meta-analysis of 36 prospective cohort studies (1,279,804 participants included) found a nonlinear association between coffee consumption and CVD risk; moderate coffee consumption was inversely significantly associated with CVD risk, with the lowest CVD risk at 3 to 5 cups per day, and heavy coffee consumption was not associated with elevated CVD risk [58]. Data on the separate associations with coffee and caffeine were generally not provided.

Cancer

We identified several studies reporting the association between caffeinated-beverages consumption and cancer, including 10 meta-analyses [65–74]. Studies included a very broad type of cancers. In general, caffeinated-beverages consumption was associated with a lower risk of gallbladder cancer [53], melanoma [75], brain tumor [76], colorectal cancer [77, 78], oral cancer [69], breast cancer [79], liver cancer [80], endometrial cancer [71], and ovarian cancer [81].

The lower risk of leukaemia among regular coffee consumers, initially reported by a few small-sized studies, was not confirmed in a 2017 larger retrospective study on 2,422 subjects [82]. There was no significant association between coffee consumption and thyroid cancer risk [68].

A 2014 meta-analysis including about 480,000 participants found that a high (e.g., highest ≥ 4 or 5 cups/day) caffeinated-beverages intake was associated with a significant reduced risk of overall prostate cancer and with fatal and high-grade prostate cancer compared to no intake [72].

A 2016 meta-analysis reported that every one-cup increase in daily caffeinated-beverage intake was associated with a 1% increase in pancreatic cancer risk [73]. Another meta-analysis found a significantly increased risk of gastric cardia cancer associated with coffee consumption (RR = 1.50, 95% CI: 1.09-2.07). However, these associations were no more observed after adjusting for smoking or body mass index [67]. Caffeinated-beverage intake was associated with an increased risk of lung cancer in a meta-analysis of 5 cohorts and 12 case-control studies (N=120,000 participants) [74].

Using the data of the Prostate, Lung, Colorectal, and Ovarian (PLCO) cohort prospective screening study (N=97334), investigators found that coffee intake was not associated with the risk of all cancers combined [83].

The specific associations between coffee intake and caffeine-intake and cancer were reported in 6 studies. Intake of caffeinated coffee was inversely associated with non-melanoma skin risk, but there was no such association for intake of decaffeinated coffee [66]. In a prospective study of about 10,000 participants in Israel, coffee consumption was associated with lower odds of developing colorectal cancer and the inverse association was also observed for decaffeinated coffee consumption alone [78]. Thus, both coffee intake and decaffeinated intake were associated with a reduced risk for colorectal cancer. No association between coffee or decaffeinated coffee and bladder cancer risk was found [84]. No association between total, caffeinated, or decaffeinated coffee intake and pancreatic cancer were found in a very large cohort study conducted in the US [85]. In a very large meta-analysis (N=1,534,039 participants), the overall relative risk of endometrial cancer for caffeinated and decaffeinated coffee were 0.66 (95% CI: 0.52-0.84) and 0.77 (95% CI: 0.63-0.94), respectively. The risk decreased

by 5% for every 1 cup per day of coffee intake, 7% for every 1 cup per day of caffeinated coffee intake, 4% for every 1 cup per day of decaffeinated intake of coffee, and 4% for every 100mg of caffeine intake per day [71]. Higher caffeinated coffee intake was associated with lower risk of postmenopausal breast cancer, while decaffeinated coffee intake was not [86].

Type 2 Diabetes

A meta-analysis of 28 prospective cohort studies on the association between coffee consumption (caffeine versus decaffeinated) and type 2 diabetes risk was published in 2014 [87]. Compared with no or occasional coffee consumption, the relative risk for type 2 diabetes was reduced to 0.92 (0.90-0.94), 0.85 (0.82-0.88), 0.79 (0.75-0.83), 0.75 (0.71-0.80), 0.71 (0.65-0.76), and 0.67 (0.61-0.74) with daily intake of 1, 2, 3, 4, 5, and 6 cups/day, respectively. The relative risk of type 2 diabetes for a 1 cup/day increase was 0.91 (0.89-0.94) for caffeinated coffee and 0.94 (0.91-0.98) for decaffeinated coffee.

Interestingly, data from the Health Professionals Follow-Up Study (HPFS) and the Nurses' Health Studies (NHS) showed that participants who increased their coffee consumption by more than 1 cup/day over a 4-year period had an 11% (95% CI 3%, 18%) lower risk of developing type 2 diabetes during the subsequent 4 years, compared with those who made no changes in consumption. Participants who decreased their coffee intake by more than 1 cup/day had a 17% (95% CI 8%, 26%) higher risk for type 2 diabetes [88].

Depression

A 2016 meta-analysis of 23 studies including more than 355,000 participants found that compared to individuals with lower coffee consumption, those with higher intakes had pooled relative risk of depression of 0.76 (95% CI: 0.64, 0.91) [89]. Significant results were found only for caffeinated-coffee consumption not decaffeinated coffee. Dose-response effects suggested a nonlinear J-shaped relation between coffee consumption and risk of depression with a peak of protective effect for 400mL/day.

Cognitive function

Data on the association between coffee consumption and cognitive decline and dementia are available. Coffee consumption has been significantly associated with a lower risk of incident dementia in a very large prospective cohort of 131,337 elderly adults in Japan [90]. However, the most recent meta-analysis of 11 prospective studies reported that high coffee consumption was not associated with cognitive decline or dementia (subgroup analyses suggested a significant inverse association between highest coffee consumption and the risk for Alzheimer disease [summary relative risk, 0.73; 95% CI, 0.55-0.97]) [91]. This null finding is in line with a 2015 meta-analysis on dementia [92].

3.2.4 Conclusions / recommendations

This review of the literature published between 2014 and 2017 suggests that coffee consumption is safe and may in fact exert protective effects against some non-communicable diseases. While large interventional studies on the long-term health effects of coffee/caffeine are still missing, data from very large prospective cohort studies with long follow-up are available. Determining causality and identifying the bioactive components of coffee involved in health effects (e.g. caffeine, chlorogenic acid, cafestol, kahweol, etc.) or association with other foods commonly consumed with coffee (e.g. milk, etc.) is not possible from the current review of the literature. Evidence from large observational studies is generally compatible with a protective effect of coffee consumption, including decaffeinated coffee consumption, on many health outcomes. A clear distinction between the health effects of caffeinated and decaffeinated coffee is difficult based on the current data. Our update of the literature identified 17 studies that included comparative data on the health effects of caffeinated and decaffeinated-coffee. Similar decreased risk of overall mortality, colorectal cancer, endometrial cancer, type 2 diabetes, and depression were reported for caffeinated and decaffeinated coffee. Caffeinated but not

decaffeinated coffee was associated with decreased risk of cardiovascular disease, melanoma, non-melanoma skin, hepatocellular carcinoma, and postmenopausal breast cancer. Overall however, evidence suggests that caffeine contributes to the beneficial effects of coffee consumption on health.

Our review of literature showed that coffee consumption has been associated with lower mortality (caffeine and decaffeinated coffee), lower overall risk of cardiovascular events, cancer, and lower risk of type 2 diabetes. Yet, the data being observational and often limited, it is not possible to unequivocally assert that coffee consumption causally protects from these outcomes.

Data on cognitive function and depression are scarce, but coffee consumption appeared to be associated with lower risk of depression whereas no clear association was found with cognitive function.

In summary, it is reasonable to conclude that both caffeinated- and decaffeinated-coffee appeared to be safe up to 4 cups a day for healthy men and non-pregnant women and that both might provide some health benefits.

3.3 Sugar-sweetened beverages

Author: Luc Tappy

3.3.1 Introduction

The need for specific recommendations for sugar intake, including specific recommendations for sugar-sweetened beverages (SSBs), has become of high importance in the present Swiss and world-wide nutritional context. It has indeed been observed that consumption of refined sugars has increased markedly since the 1960s, and that sugar intake exceeds 10-15% of average total energy intake in many countries throughout the world [93–96]. It has further been recognized that, in many countries, consumption of SSB make a major contribution to total sugar intake [97–100]. In addition, it has been suggested that high sugar consumption may play a prominent role in the pathogenesis of metabolic and cardiovascular diseases and of cancers [101–103].

3.3.2 Definitions and scope

Sugars

Sugars are defined as mono and disaccharides i.e. glucose, fructose, galactose, lactose and sucrose and maltose. They are naturally present in fruits and some vegetables, in honey, and in dairy products, but the most important source of dietary sugars is sucrose from refined beet or cane sugar. Since the 1970s, refined sucrose has been replaced in part by high fructose corn syrup (HFCS), which is a mixture of glucose 58-45% and fructose (42-55%) industrially prepared from cornstarch. Similar glucose-fructose syrups prepared from plant starch is also consumed in some European countries under the name of “isoglucose”, or glucose-fructose syrups. Sugar alcohols (polyols) such as sorbitol, xylitol, mannitol, and lactitol, are usually not included in “sugars”.

Sugars naturally present in fruits and sucrose added to processed products yield chemically identical molecules in the blood stream, yet consumption of fruits and of products containing refined sugars, such as cookies, ice-creams, etc., have divergent association with health outcomes, and hence need to be evaluated separately. Several definitions have been proposed to specifically differentiate sugars in fruits from refined sugars added during food preparation:

- **Added sugars** initially proposed by U.S. Department of Agriculture (USDA), are defined as sugars and syrups that are added to foods during processing or preparation

(https://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/UCM535372.pdf). The definition covers all sugars not present initially, i.e. not only refined sucrose, glucose, fructose, or glucose-fructose syrups, but also honey and maple or agave syrups [104].

- **Added sugars (Definition EFSA):** the term "added sugars" refers to sucrose, fructose, glucose, starch hydrolysates (glucose syrup, high-fructose syrup) and other isolated sugar preparations used as such or added during food preparation and manufacturing. It includes sugars present in honey, syrups, and fruit juices and fruit juice concentrates." (High Level Group on Nutrition and Physical Activity https://ec.europa.eu/health//sites/health/files/nutrition_physical_activity/docs/added_sugars_en.pdf)

- **Free sugars** as proposed by WHO 2015 are defined as monosaccharides and disaccharides added to foods and beverages by the manufacturer, cook or consumer, and sugars naturally present in honey, syrups, fruit juices and fruit juice concentrates (http://apps.who.int/iris/bitstream/10665/149782/1/9789241549028_eng.pdf?ua=1). With this definition, lactose naturally present in milk and milk products is not considered as free sugar, nor are sugars contained in intact fruit and vegetables.

- **Extrinsic sugars**: The UK Scientific Advisory Committee on Nutrition (SACN) reports prior to 2015, and the initial 2015 draft report on carbohydrates, used the following definitions: Intrinsic (non-milk) sugars are those sugars naturally incorporated into the cellular structure of foods – mainly fruits and vegetables. Extrinsic (non-milk) sugars are those sugars not contained within the cellular structure of a food – mainly added refined sugars and fruit juices [105]. Note that lactose and other natural milk sugars are not included in this definition of extrinsic sugars. The final report of SACN however adopted the WHO free sugars definition.

The absence of one single, universal definition for sugars added during food processing is an important confounding issue [104]. In addition, sugars added during food processing are chemically similar to those naturally present in foods, and therefore no analytical procedure allows to selectively measure their presence in industrial foods.

Sugar-sweetened beverages (SSBs)

SSBs are defined here as liquids that are sweetened with various forms of added sugars like brown sugar, corn sweetener, corn syrup, dextrose, fructose, glucose, high-fructose corn syrup, honey, lactose, malt syrup, maltose, molasses, raw sugar, and sucrose [106], as well as beverages containing free sugars according to the WHO definition, examples are:

- Sodas and soft drinks
- Energy drinks and sport drinks
- Pure fruit juices and derivatives, e.g. nectars, smoothies, beverages containing juices as well as other ingredients (e.g. teas, infusions)
- Vegetable juices, in particular when based on the sugar-richer types of vegetables (e.g. carrots, beetroot)
- Milk-based drinks containing free sugars (as chocolate-flavored milk drinks for example)
- Tea and coffee with sugar, or sweetened beverages based on tea and coffee.

Fruit juices contain roughly the same amount of sugars as industrial sodas. Sugars from pure fruit juices are considered as "free sugars" according to the WHO definition, but not as "added sugars" according to the USDA definition.

One serving SSBs in the literature usually corresponds a 12 oz can, or 360 ml. Portion size is not defined for all SSBs in Switzerland, but portion size is 200 ml for fruit juices and 250 ml for milk. The free sugar content of usual SSBs ranges from 6 to 11 g/100 ml.

3.3.3 Present position and recommendations in the Swiss Food Pyramid and intake data

SSBs are presently not specifically included in the Swiss food pyramid at the beverage level. Present recommendations mention that consumption of the food group “beverages” should provide 1-2 l/day, preferably in the form of unsweetened beverages, and that one 2dl unsweetened fruit or vegetable juice can replace one daily portion of fruit or vegetable.

Similarly, SSBs are not represented in most North-American and European food pyramids, and no specific recommendation is given. However WHO [107] and USDA [106] specifically recommend that added or free sugar intake be less than 10% total energy intake, and the Scientific Advisory Committee on Nutrition (SACN) in UK [108] even recommend that free sugar intake be less than 5% total energy.

The first national Swiss nutrition survey (“menuCH”) reported that the average daily intake of the adult population was 9% and 11% of total energy for added and free sugars respectively, and hence exceeded the WHO recommendation in 56% of females and 55% of males. SSBs consumption averaged 2.4 dl/day and accounted for 29% of total free sugars (fruit and vegetable juices 13%, sodas and soft drinks 12%, dairy products (including yoghurt) 9%) [109].

3.3.4 Potential mechanisms linking SSBs to health outcomes

Several distinct mechanisms have been proposed to account for adverse health effects of sugars and SSB:

- Free sugars can be fermented by oral bacteria, leading to a decrease in dental plaque pH, and hence closely associated with the risk of dental caries [110].
- Sugar in SSB contains 50% fructose, some studies suggest this reduces satiating responses. SSBs containing fructose may therefore be associated with an impaired suppression of food intake [111, 112].
- It has also been hypothesized that sugar consumption in form of SSBs, i.e. in liquid foods may elicit less satiety as solid foods [113].
- The fructose component of sucrose or HFCS is highly lipogenic and hence may be associated with net fat synthesis, ectopic lipid deposition in the liver and muscle, abdominal obesity, and alterations of lipoprotein metabolism even at neutral energy balance levels [114].
- Most sodas, sport drinks and energy drinks contain sugars and artificial aromas, but are devoid of other nutritional factors (micronutrients, dietary fibers, unless these are added). As a consequence, a large proportion of total energy intake from these beverages may lower dietary micronutrient density and lead to micronutrient deficiencies (“nutrient dilution”) [115, 116].

3.3.5 Review of literature

3.3.5.1 Association with NCD

Cardiovascular diseases

One meta-analysis of prospective cohort studies (PCSs) reported a pooled relative risk (RR) of hypertension of 1.12 (1.03-1.23) in subjects consuming sugar-sweetened soda vs non consumers. This increased relative risk was observed for both males and females [117]. Two other meta-analysis of PCS observed a dose- response increase in incidence of hypertension of 8.2% and 8.0% for each daily 360 ml SSB consumed [118, 119]. Three meta-analyses of PCSs observed an association between SSB intake and risk of coronary heart disease [119–121]. One meta-analysis [120] reported an association between the risk of stroke and consumption of SSBs, but another one did not [119].

Type 2 diabetes

Two meta-analysis of PCS reported that the relative risk of diabetes increased by 1.20% and 1.18% for each 330 ml serving SSB/day [122, 123]. In one of them, there was no association for fruit juices [123].

Obesity and obesity risk factors

One meta-analysis reported a dose-response effect of SSBs consumption on body weight gain in PCSs of children and adults. For adults, a 0.22 kg/year body weight gain was attributed to each daily 360 ml SSB servings. For children, the increase in BMI /year was 0.06 kg/m2 for each daily 360 ml serving SSB. This meta-analysis also included a separate analysis of randomized controlled trials (RCTs); Interventions targeted to reduce SSBs intake in children were associated with significant weight loss, while interventions involving an increased SSBs intake in adults were associated with body weight gain [124]. A critical review of thirteen PCS, RCTs and cross-sectional studies performed in children, adolescents, and adults however concluded that the association between SSB and body weight became inconsistent when SSB intake was adjusted for total energy intake [125].

Another meta-analysis reported a positive relationship between SSB intake and total food energy intake in both children and adult, consistent with the hypothesis that SSB may favor weight gain by driving total energy intake [126].

Regarding the hypothesis that SSBs may be particularly harmful because liquid calories would fail to elicit satiety signals to the brain, we did not find any experimental study which specifically compared the effects of sugars ingested with solid vs liquid foods. However, several studies documented that the ingestion of excess energy as drinks led to a partial compensation of calories intake (reviewed in [127]).

Cancer

Some early studies had proposed that SSBs consumption may be associated with the development of colon cancer [128] or pancreatic cancer [129, 130]. These associations have however not been confirmed in other studies [131–133]. In a more general perspective, there has been (and is still) considerable debate regarding associations between dietary sugar intake and risk of cancer. Added sugar intake has been associated with the risk of colorectal, breast and ovarian cancers in some studies, but the association may be due to other covariates, such as obesity [134].

3.3.5.2 Micronutrients deficiency

One meta-analysis addressed the association between SSBs and dietary micronutrients' intakes. It reported that SSB intake was associated with lower calcium (and lower milk) intake, and mentioned also lower riboflavin, vitamin A and vitamin B12 intakes (although detailed

data were not displayed) [126]. Similar observations were reported in a recent cross-sectional evaluation of the UK National Diet and Nutrition Survey data [135].

Although not restricted to SSB, some studies reported significant micronutrient dilution with increasing added sugar intake in Australian children [115] and Australian elderly subjects (24). These reports however did not document cases of clinical micronutrient deficiency. Another study did not find evidence for micronutrient dilution in response to high added sugar intakes in elderly normal British subjects [136]. A systematic review (which did not assess specifically SSBs, but sugars intake) published in 2007 concluded that the mean intakes of most micronutrients were above reference nutrient intake irrespective of added sugar consumption, except for very high consumers of sugars [137].

3.3.5.3 Are fruit juices different from other SSBs?

There is some controversy regarding whether the consumption of fruit juices has different effects on health than that of other SSBs. We therefore performed an additional search of the literature to retrieve meta-analyses and large PCSs having specifically addressed associations between fruit juice consumption and the risk of NCDs (including obesity).

Consumption of beverages, and the relative contribution of sodas, fruit juices and milk vary widely across age groups and between countries. On average, intake of sodas worldwide amounts to 0.58 servings per day, of milk to 0.57 servings per day, and of fruit juices to 0.16 servings per day. Consumption of fruit juices represents a relatively minor fraction of total SSBs in most countries [98]. One critical review assessed the impact of fruit juices on body weight of children [138]: it did not find evidence for an association between fruit juice consumption and body weight gain. This analysis however adjusted fruit juice consumption to total energy. (Note: The meta-analysis by Malik et al [124] on SSBs and body weight did not adjust for energy intake, arguing that the effects of SSBs on body weight were linked to an increased, total energy intake. For SSBs also, the association with body weight gain becomes non-significant when intake is adjusted for energy intake [125].

One nested study from the PREDIMED study, performed on 1868 subjects [139], reported that incidence of the metabolic syndrome over a 3.3 year period was higher in participants consuming < 1 fruit juice per week than in those consuming > 5 fruit juices per week (OR 1.30, CI 1.00-1.69). One pooled analysis of 3 large PCSs (Nurse Health studies I and II, and Health Professional Follow-up Study) reported that body weight increased by 0.36 kg (0.24-0.48) and 0.22kg (0.15-0.28) for each serving per day increment of SSBs and fruit juice respectively. It did not made a distinction between 100% fruit juices and fruit juices with added sugar [140].

One meta-analysis specifically assessed the association between fruit juice consumption and risk of type 2 diabetes. It reported that consumption of 100% fruit juice, was not associated with an increased risk of type 2 diabetes [141]. In contrast, another meta-analysis [142] concluded that risk of type 2 diabetes was moderately increased by 7% (1%-14%) for each serving of fruit juice.

One meta-analysis of 26 intervention studies addressed the effects of juice consumption on plasma antioxidant status. It included both natural fruit and natural vegetable juices. Juice consumption was associated with higher vitamin C concentration and lower malondialdehyde concentration, but had no effect on superoxide dismutase and catalase levels, nor on total plasma antioxidant capacity, although the amount of juice consumed in some studies was very high (up to 1000 ml/day) [143]. The critical review by Crow on 100% fruit juice and obesity also found limited evidence that fruit juices consumption was associated with higher intake of dietary fibers, Vitamin C, Mg and K [138].

Finally, one meta-analysis reported that the consumption of carbonated beverages, sugar-containing snacks, and acid fruit juices increased the occurrence of tooth erosion in children

and adolescents [144]. Interestingly, consumption of milk and yoghurt was associated with reduced erosion occurrence.

3.3.5.4 Is the consumption of artificially sweetened beverages (ASBs) associated with risk of NCDs?

A detailed analysis of the effects of ASBs on health was beyond the scope of this review. The safety of artificial sweeteners has been recently reviewed by the French agency ANSES, and their experts' conclusions did not raise specific concern about these products. Nonetheless, it was felt important to address whether ASBs would be a suitable alternative to SSBs. We therefore made a non-exhaustive search of the meta-analyses addressing ASBs consumption and risks of NCDs.

Two meta-analysis of PCSs reported that consumption of ASBs was significantly associated with an increased risk of type 2 diabetes (pooled relative risks 1.13 (1.02-1.25) per 330 ml /d and 1.25 (1.18-1.33) per 250 ml/d [122, 123]. One meta-analysis [120] reported an association between the risk of stroke and consumption of ASBs. One nested study from the PREDIMED study [139] reported that incidence of the metabolic syndrome over a 3.3 year period was higher in participants consuming < 1 ASB per week than in those consuming > 5 ASBs per week (1.74 (1.26-2.41)). One publication from the EPIC study reported that consumption ASB consumption increased the risk of hepatocarcinoma by 6% for each one serving/day increment [145].

3.3.6 Discussion and research gaps

PCSs report a strong association between SSB intake and obesity in adults and children. This association is markedly weakened when SSB intake is adjusted for total energy intake. This suggests that SSBs consumption promotes weight gain mainly by increasing total dietary energy intake. In support of this hypothesis, there is indeed an association between SSB intake and total energy intake [126]. A relationship between SSBs and NCDs has further been by two large American PCSs showing increased total mortality with high SSBs intake [146, 147].

The mechanisms by which SSBs increase total energy intake remain controversial. It is often proposed that ingestion of "liquid calories" would not be sensed adequately (compared to solid foods) by the homeostatic brain systems regulating food intake [113]. Direct evidence supporting this hypothesis is lacking however. It has also been proposed that dietary sugars, and hence SSBs, may inhibit less food intake due to the fructose component of sugar, which does not stimulate the secretion of insulin or of gut satietogenic peptides and does not suppress gastric ghrelin secretion [111]. A recent study however documented that increased fructose intake markedly reduced the daily intake of other macronutrients [148, 149]. It appears therefore likely that other factors (thirst-triggered energy intake, hedonic tone of SSB, socio-cultural factors, etc.) account for a SSB-induced increase in energy intake and body weight gain.

Although the association between SSB intake (not adjusted for total energy intake) and weight gain is strong, how much SSBs actually contribute to the present epidemic of obesity remains unknown. The meta-analysis by Malik et al observed a 0.22 kg body weight gain/serving SSB/year, suggesting a relatively modest effect on body weight even with long exposure. One analysis of several US prospective cohort studies reported that SSB were one out of several foods groups associated with body weight gain over time, and that other foods (potatoes, cured meat, red meat) were also important contributors to overall weight gain [150]. In addition, RCTs assessing the effects of a reduction of SSB intake in overweight subjects failed to observe major reductions in body weight [151, 152].The amount of weight lost was indeed smaller than may have been expected from the reduction in SSBs calories.

PCSs show strong associations between SSB intake and cardiovascular diseases, and type 2 diabetes. For cardiovascular diseases, the association is robust with CHD and high blood

pressure, but inconsistent for stroke. Here again, the effect may be dependent on total dietary energy intake or on SSB-induced body weight gain.

There are presently few studies having assessed whether soft drinks and fruit juices have different effects on health outcomes. There is limited evidence that fruit juices containing added sugars have similar effects as other SSBs; few studies evaluated the effects of 100% fruit juices, and report no effect of 100% fruit juice [138] no study observed that 100% fruit juice consumption was associated with a lower risk for NCDs. This contrasts with the observation (chapter 4) that consumption of one fruit per day is already associated with a decreased risk for several NCDs. This strongly argues against including fruit juices among fruit and vegetables in the Swiss food pyramid.

Many studies and some meta-analyses have reported that not only SSBs, but also ASB consumption was associated with an increased risk of cardiovascular diseases. The reason for this association is unknown. It is possible that it may be due to reverse causation, i.e. ASB consumption being more likely to be consumed by obese subjects at increased risk of cardiometabolic diseases. It is also possible that not SSBs per se, but some associated dietary /like style patterns are actually responsible for the development of NCDs. Based on these observations, and on pathophysiological hypotheses raising concerns about adverse effects of artificial sweeteners on body weight [153], one may however question whether ASBs are adequate, safe alternatives to SSBs.

The concern that of SSBs consumption may be a cause of micronutrient deficiency is based on the observation that high SSB consumption is associated with lower intake of other food groups such as fruit and vegetable and whole grain, and with a lower micronutrient density of the diet (in weight micronutrient per kcal, eg a low Ca/ kcal or Vit B6/kcal content of the overall diet). There is however no evidence that this leads to inadequate micronutrients intakes (ie with a daily intake of a specific micronutrient inferior to the defined lower level of intake) or with actual micronutrients deficiency.

Another point to note is that the hypothesis of SSB-induced nutrient dilution (ie SSBs replacing foods with higher nutritional quality in the diet) is in contradiction with the hypothesis that liquid calories are not compensated by a reduction of other foods intake.

3.3.7 Recommendations

Sugar-sweetened beverages provide substantial energy under the form of glucose and fructose, which are non-essential nutritional elements. They may be instrumental in stimulating excess energy intake because of their hedonic properties, and because their intake is not specifically regulated by homeostatic neural circuits involved in body energy regulation, but also by neural and endocrine circuits involved in hydration and fluid balance. Furthermore, sodas and soft drinks provide energy but no vitamins, fibers, or micronutrients, while fruit juices, compared to whole fruits, contain little amounts of fibers.

Consumption of sugar-sweetened beverages is robustly associated with risk of NCD An association between 100% fruit juices and NCD is inconsistently observed. However, no study demonstrates that the consumption of one fruit juice per day decreases NCD risk to the same extent as consumption of one fruit does. The possible replacement of one serving of fruit or vegetable by a fruit juice is not supported by studies showing that fruit juices and whole fruits have comparable health benefits, and should be withdrawn.

Sugar-sweetened beverages, including 100% fruit juices, should be represented at the top level of the Swiss food pyramid together with sweets, salty snacks and alcoholic beverages, with the current recommendation of a moderate consumption.

There is presently no evidence that the consumption of artificially sweetened beverages is associated with a lower risk of NCDs. At the opposite, there is emerging concern that it may

have adverse health effects, through mechanisms which remain however hypothetical. Alterations of food intake control by the brain [154] and changes in gut microbiota [155] may possibly be involved. Artificially sweetened beverages should not be recommended as substitutes for sugar-sweetened beverages, and water should be the main source of fluid intake.

4 Fruit and vegetables intake and their impact on chronic diseases

Author: Murielle Bochud

Introduction

Fruits and vegetables are generally low in energy density and are sources of several vitamins, minerals, starches, and various phytochemicals considered to be beneficial for health. In the 2010 Global Burden of Disease study, diets low in fruits belonged to the most prominent dietary risk factors for death and disability-adjusted life years (DALYs) worldwide [156]. The combination of dietary risk factors and physical inactivity was estimated to account for 10.0% (95% uncertainly interval: 9.2–10.8) of global DALYs in 2010 [156]. In the 2013 Global Burden of Disease study, dietary risks (including low fruit intake, ranking 10th, and low vegetables intake, ranking 20th) accounted for 11.3 million deaths and 241.4 million DALYs worldwide and were the most important burden of all clusters of risk assessed [157] . Diet low in fruit had the highest burden (very close to the one of high sodium intake) of all dietary risk factors assessed, whereas diets low in whole grains and vegetables were ranking third and fourth, respectively [157]. In the 2015 Global Burden of Disease study, suboptimal diet remains, by far, the strongest contributor to DALYs worldwide, for both men and women [158]. For diets low in fruits and/or vegetables, most of the impact is on cardiovascular disease, in particular ischaemic heart disease, ischaemic and hemorrhagic strokes [158].

4.1 Definitions

In the Swiss legislation, fruits and vegetable are described in the food legislation: fruit is defined as an unprocessed plant product. A distinction is made between the following types of fruit: pome fruit, stone fruit, berries, citrus fruits, exotic fruits such as pineapples, bananas, dates, figs and avocados; hard nuts or nuts. In the following “fruit” will be narrowed down to sugar-containing products (in the frequent range of 8 to 18 % sugar / edible part). Nuts will be treated separately (chapter 7.2), due to their higher fat content.

Vegetables are plants, or parts of plants that serve human nutrition. A distinction is made between the following vegetable species: tuber and root vegetables, stem vegetables, leafy vegetables, fruit vegetables, fresh legumes and pulses (unripe, the ripe and drier seeds of legumes or pulses are described in chapter 6.3), allium plants, chicory plants, flower vegetables, algae, edible germinated seeds (seedlings). This description includes potatoes as a tuber food. From a dietary point of view, potatoes are considered as a starchy food, and will therefore not be included in the following considerations.

4.2 Current recommendations and intake data

The Swiss society of nutrition (www.sge-ssn.ch) currently recommends consuming 3 portions of vegetables and 2 portions of fruit of varying color each day. One portion corresponds to 120 g. This amounts to 600 g of fruits and vegetables per day, and, as already mentioned in chapter 3.3. It is suggested that one portion per day could be replaced by 2 dl of 100% pure vegetable juice resp. fruit juice (without added sugar). Frozen fruits and vegetables are a suitable replacement for fresh ones.

In 1990, WHO suggested consuming more than 400 g of fruits and vegetables per day to improve overall health and reduce the risk of certain non-communicable diseases (NCDs). This led to the launch of 5-a-day campaigns in several countries (e.g. UK, France, Germany, Switzerland). In the USA, the 5-a-day message was dropped in 2007 and replaced by “Fruit and veggies-more matters”. In Australia, the “Go for 2+5” campaign was launched in 2005, recommending two portions of fruit (150 g per portion) and 5 portions of vegetables (75 g per portion) daily (total of 675 g of combined fruits and vegetables per day). The differences in health policies across countries reflect, in part, the fact that, for selected relationships, the level of evidence is not very strong. The evidence for a protective effect of fruits and vegetables on cardiovascular disease (CVD) appears to be quite robust. More uncertainty exists for the relation with cancer.

The World Cancer Research Fund has the following public health recommendation [159]: population average consumption of non-starchy vegetables and of fruits should be at least 600 g (21 oz) daily, with varying colors including red, green, yellow, white, purple and orange, including tomato-based products and allium vegetables such as garlic. The WCRF has the following recommendation: eat at least five portions/servings (at least 400 g) of a variety of non-starchy vegetables and fruits every day.

Summary box recommendations and intake

Fruit and Vegetables	Description and recommendations
Current daily recommendations current Swiss Food Pyramid [2]	5 portions per day of different colours, at least 3 portions should be vegetables and 2 fruit. 1 portion = 120 g. One daily portion of fruit or vegetables can be replaced by 2 dl of vegetable or fruit juice (with no added sugar)
Daily Intake in Switzerland [3] Total	See below

Current intake data for Switzerland

The first national nutrition survey (menuCH [3]) conducted in 2014-2015 included 2000 participants across the three main linguistic regions of Switzerland and provides population-based information on fruit and vegetables consumption in adults aged 18 to 75 years [3]. Data are based on two standardized non-consecutive 24-hour recalls. Only 3.3% (3.0% of men and 3.6% of women) follow current national nutritional recommendations and report at least 2 portions of fruit and 3 portions of vegetables per day. A substantial proportion of Swiss adults consume less than one portion per day (15.8% of men and 10.3% of women). The mean intakes of vegetables and fruit were 203 and 171 g per day, respectively [3].

4.3 Putative mechanisms

The association of NCDs with fruit and vegetable intakes has been studied at different levels, including from a dietary pattern perspective: diets including a high intake of fruit and vegetables often also include whole cereals, and might be low in meat, sugary food items [160]. A higher intake of fruit and vegetables can be correlated with a higher intake of fiber, specific vitamins, minerals and phytochemicals, low energy density and high nutrient density. Most studies (RCTs and / or observational studies) address some of these elements.

The molecular mechanisms linking fruit and vegetables intakes with health outcomes are unclear and current evidence is somewhat conflicting. Among the hypotheses, antioxidants and polyphenols in fruit and vegetables (e.g. vitamin C, vitamin E, carotenoids and/or flavonoids) might reduce cardiovascular risk via blood pressure reduction [161], decreased lipid oxidation in arteries [162] and decreased endothelial dysfunction [163]. Also, fruit and vegetables are rich in magnesium and potassium and may thereby reduce blood pressure [164, 165]. Fruit

and vegetables are also good sources of dietary fiber, which may reduce insulin resistance [166]. Yet, a few examples exist for which the results of observational studies conflicted with those of experimental studies: (a) relation between vitamin C and coronary heart disease [167]; (b) vitamin and antioxidant supplements and prevention of cardiovascular disease [168]. For fruit and vegetables intakes, there is limited experimental evidence and most findings come from large-scale population-based cohorts. There is no randomized controlled trial (RCT) exploring the impact of an intervention modifying fruit and vegetables intake on the risk of chronic diseases. Of note, the consumption of fruit and vegetables tends to be positively correlated with other protective dietary risk factors, such as consumption of whole grains, and negatively correlated with the consumption of harmful foods, such as processed meat [156]. This implies that the protective effect of fruit and vegetables may be under- or over-estimated depending on the type of adjusted analyses conducted [156].

4.4 Review of literature

No randomized controlled trial exploring the impact of an intervention modifying fruit and/or vegetables intake on the risk of chronic diseases (cardiovascular disease [CVD], cancer or other types of common non-communicable diseases) was found [158]. In a Cochrane systematic review [169] including 10 interventions aiming at increasing fruit and vegetables intake among adults with at least 3-month follow-up (randomized controlled trials, cluster-randomized trials and cross-over trials), with a total of 1730 participants, the advice lead to an increase in fruit and vegetables consumption (with differing advices between trials) was associated with reduced systolic blood pressure (-3.0 mmHg, 95% CI [-4.92 to -1.09], p=0.002; 2 studies/891 participants) but not with blood lipid levels. No clinical events were recorded in the latter study [169].

A systematic review and meta-analysis of 8 trials, including 1026 participants, that assessed the effect of increasing fruit and vegetables consumption on body weight, found a small, but significant reduction in body weight of 540 g (95%CI: 40 g – 1050 g) at the end of the intervention (duration ranging from 4 to 52 weeks) in the high fruit and vegetables arm, compared to the low arm [170, 171].

4.4.1 All-cause mortality

In the most recent meta-analysis of prospective studies that used the NutriGrade scoring system to grade study quality, high compared to low intakes were associated with reduced all-cause mortality: 7% (95%CI: 5% − 10%) for vegetables (37 studies, 121’067 deaths) and 9% (95%CI: 6% − 11%) for fruit (24 studies, 120’033 deaths)9. Each 100g/d increase in vegetables and fruit intake were associated with 4% (95%CI: 2% − 5%) and 6% (95%CI: 3% − 8%) reductions in all-cause mortality, respectively, with significant heterogeneity across studies, even after stratifying by sex and geographic location [172]. For both vegetables and fruit, the dose-response relation was non-linear, with a significant mortality reduction with 200 g per day of vegetables or fruits with no additional benefit at higher intakes.

In a systematic review and meta-analysis including data from 7 prospective cohort studies (553’698 participants and 42’219 deaths), an increment of one serving of fruit and vegetables per day was associated with 5% (95%CI: 2%-8%) lower relative risk of all-cause mortality; in the latter study, a significant heterogeneity was observed across studies with evidence for a non-linear dose-response relation including a ceiling effect at 5 servings per day (i.e. no additional benefit observed beyond 5 servings per day 10; the relative risk for one serving per day was 6% (95%CI: 1%-8%) for fruit and 5% (95%CI: 1%-8%) for vegetables (data from 7 cohorts including 660’186 participants and 40’192 deaths) [173]. There was evidence for a non-linear dose-response relation both for vegetables and fruits, with further benefit for intakes above approx. 200g of vegetables or fruits [173].

The largest cohort, considered in this meta-analysis was EPIC, including 451,151 participants aged 25 to 70 years from 10 European countries with a median follow-up of 12.8 years and 25'682 deaths. This study found that an upward shift of one quartile in the consumption of fruit and vegetables (i.e. an increase of about 200 g/day/quartile) would prevent 2.68% of all deaths [174]. The highest quartile of fruit and vegetables consumption (>569 g/day) was associated with a 11% reduced risk of death compared with the lowest quartile (<249 g/day) [174]. In the EPIC cohort, a stronger negative association was observed for raw than for cooked vegetables, this more in southern European countries than in northern ones and adjustment for total energy intake did not change the results [174]. In the EPIC cohort, the median daily intake of fruit, vegetables and combined were 194 g/day, 173 d/day and 388 g/day, respectively, with large variations across countries (from 102 g/day in Sweden to 422 g/day in Greece for vegetables; from 137 g/day in Norway to 335 g/day in Greece for fruit) [174]. In EPIC, the benefit of combined fruit and vegetables consumption against all-cause mortality showed a threshold at 400 g/day, with no additional benefit at higher consumption levels [174]. A limitation of population-based cohorts such as EPIC is that participants are likely to be more health conscious than randomly chosen people from the general population [175]. The amount and types of fruit and vegetables eaten by the health conscious people may differ from those eaten by other people [175].

In the Health Survey for England (HSE) including 65'226 participants aged 35 years and over (2001-2008, median follow-up of 7.7. years), representative of the non-institutionalised population of England, combined fruit and vegetables consumption of at least 7 portions was associated with 33% (95%CI: 22%-42%) decreased all-cause mortality compared to consuming less than 1 portion (about 80 g or a handful), with a dose-response relation [175]. Eating 2, or 3, portions of fruit in the previous day was associated with 10% (95%CI: 2%-18%), or 16% (95%CI: 7%-24%), decreased all-cause mortality compared to eating less than 1 portion [175]. Eating 3 or more portions of vegetables in the previous day was associated with 32% (95%CI: 21%-42%) decreased all-cause mortality compared to eating less than 1 portion) [175]. All-cause mortality was reduced by 16% (95%CI: 12%-19%) for each portion of vegetables, by 13% (95%CI: 8%-18%) for each portion of salad, by 4% (95%CI: 2%-5%) for each portion of fresh fruit [175]. By contrast, all-cause mortality was increased by 17% (95%CI: 7%-28%) for each portion of frozen or canned fruit [175].

In an Australian population-based prospective cohort study including 150'969 adults aged over 45 years (mean age 60 years at baseline, 55.2% women), with a mean follow-up of 6.2 years (6038 recorded deaths), baseline consumption of fruit and vegetables was associated with reduced all-cause mortality, when comparing the highest with the lowest quartiles of intake: 10% (95%CI: 3% − 16%) for fruit and vegetables, 16% (95%CI: 7% − 24%) for fruit, 7% (95%CI: 0% − 13%) for vegetables [176]. For fruit and vegetables combined, the lowest and highest quartiles reported a mean of 2.44 and 10.27 servings per day, respectively; for fruit, the corresponding means were 0.001 and 3.73 servings, respectively; for vegetables, 1.65 and 7.83 servings, respectively [176]. In this cohort, diet was assessed using a short validated self-administered questionnaire, with servings defined as one medium piece or two small pieces of fresh fruit, or one cup of diced or canned fruit pieces as well as half a cup of cooked vegetables (including potatoes) or one cup of raw vegetables [176]. The protective effect of self-reported fruit and vegetables intake appeared to be higher in women than in men, in younger people than in the elderly [176].

In the Kadoorie prospective cohort, including 500'000 Chinese adults aged 30-79 years followed-up for 7 years (17'894 deaths recorded), all-cause mortality was 27% (95%CI : 24%-30%) lower per daily portion of fresh fruit, with a clear dose-response relation and similar effects in men and women [177]; this effect was driven, in large part, by reductions in mortality from cardiovascular disease, chronic obstructive pulmonary disease and cancer of the digestive tract [177].

4.4.2 Cardiovascular disease mortality and incidence

Although recent data confirm the protective role of fruit and vegetables against cardiovascular mortality, there is substantial heterogeneity in effect sizes across studies.

In a systematic review and meta-analysis of prospective cohort studies, an increment of one serving of combined fruit and vegetables per day was associated with 4% (95%CI: 1%-8%) lower cardiovascular mortality, without significant heterogeneity across studies (data from 4 studies including 469'551 participants and 6893 cardiovascular deaths) [173]; the risk reduction per daily serving (defined as 77g for vegetables and 80g for fruit) was 5% (95%CI: 0%-9%) for fruit consumption and 4% (95%CI: 1%-7%) for vegetables consumption, with significant heterogeneity across studies (data from 6 studies including 677'674 participants and 9744 cardiovascular deaths) [173].

In the Kadoorie prospective cohort, including 500'000 Chinese adults aged 30-79 years followed-up for 7 years (6'166 cardiovascular disease deaths recorded), one additional portion of fresh fruit per day was associated with 39% (95%CI: 30%-47%) lower relative risk of cardiovascular disease mortality, with a clear dose-response relation [177].

Among 451'665 participants to the Kadoorie cohort without a history of CVD at baseline, 5'173 cardiovascular deaths and 2'551 major coronary events (fatal and non-fatal) have been recorded after 5-6 year follow-up [178]. Each additional portion of fresh fruit per day was associated with 37% (95%CI: 28%-44%) lower **cardiovascular mortality** and 30% (95%CI: 17%-40%) lower risk of **major coronary events [178]**. Similar associations were observed in men and women, across age groups, education levels, smoking status and BMI categories [178]. In this study, assuming that the association is causal, low consumption of fresh fruit could be responsible for 16% (95%CI: 10%-23%) of cardiovascular deaths [178].

In the Health Survey for England (HSE) including 65'226 participants aged 35 years and over (2001-2008, median follow-up of 7.7. years), representative of the non-institutionalised population of England, combined fruit and vegetables consumption of at least 7 portions was associated with 31% (95%CI: 12%-47%) decreased **cardiovascular mortality** compared to consuming less than 1 portion (about 80 g or a handful), with a dose-response relation [175].

In a meta-analysis including 937,665 participants and 18,047 patients with coronary heart disease (CHD) from 23 prospective studies, low versus high intakes were associated with reduced risk of CHD, as follows: 16% (95% CI: 10% − 21%) for fruit and vegetables, 14% (95% CI: 9% − 18%) for fruit, 13% (95% CI, 7% − 19%) for vegetables [179]. The significant inverse association was found in Western populations, but not in Asian populations [179]. The dose-response relation tended to be non-linear, with some data showing a levelling-off at approx. 600g fruits + vegetables [179].

In the Spanish SUN prospective open cohort (1999 – ongoing) including 17'007 University graduates with mean age 38 years and 61% women, 112 cases of CVD (56 myocardial infarction, 33 strokes, 33 cardiovascular deaths) occurred during the median follow-up of 10.3 years [180]. Compared to participants in the lowest quintile of fruit consumption (median intake of 90 g/d), risk of CVD was reduced in those in the upper quintiles: 50% (95%CI: 2%-74%) for the third quintile (median intake of 280 g/d), 46% (95%CI: 0%-71%) for the fourth quintile (median intake of 398 g/d), 49% (95%CI: 5%-73%) for the fifth quintile (median intake of 653 g/d) [180]. This latter study includes highly educated young people, thereby limiting the external validity of the findings. Intake of vegetables was not associated with risk of CVD in this study [180].

In the PREDIMED multicentric randomized controlled trial aiming at assessing the protective effects of a Mediterranean diet on CVD, 7216 men (55-80 years) and women (60-80 years) at high cardiovascular risk (either type 2 diabetes or three cardiovascular risk factors) developed 342 composite CVD events (cardiovascular death, myocardial infarction and stroke)

during a 7-year follow-up [181]. Eating 9 or more servings per day of fruit and vegetables (≥ 720 g/d) was associated with 40% (95%CI: 4% − 60%) reduced risk of CVD [181]. Results for fruit and vegetables, when assessed separately, were not significant although a tendency toward a negative association was observed. An interesting feature of this study was the yearly dietary assessment using validated food-frequency questionnaires that allowed accounting for changes in diet during follow-up [181].

4.4.3 Stroke mortality and incidence

In a meta-analysis including 20 prospective cohort studies with 16'981 strokes among 760'629 participants with mean follow-up durations ranging from 3 to 37 years, the highest category of fruit and vegetables consumption was associated with a 21% (95%CI: 16% − 25%) reduction in the risk of stroke compared to the lowest category, with a linear dose-response relation and similar results for ischaemic and haemorrhagic strokes [182]. Each 200 g/day increase in fruit and vegetables consumption was associated with a 32% (95%CI: 18% − 44%) and 11% (95%CI: 2% − 19%) reduced risk of stroke, respectively [182].

In the Kadoorie prospective cohort, including 500'000 Chinese adults aged 30-79 years followed-up for 7 years (2'351 haemorrhagic stroke and 585 ischaemic stroke deaths recorded), one additional daily portion of fresh fruit was associated with 38% (95%CI : 21% − 51%) lower relative risk of haemorrhagic stroke mortality and with a non-significant 32% (95%CI : (-7%) − 57%) lower relative risk of ischaemic stroke mortality, with a clear dose-response relation [177]. Among 451'665 participants to the Kadoorie cohort without a history of CVD at baseline, 14'579 ischaemic strokes and 3'523 intracerebral hemorrhages have been recorded after 5-6 years of follow-up [178]. Compared to non-consumers, those who reported to consume fresh fruit daily (18% of the cohort, whereas 95% were daily vegetable consumers) had 25% (95%CI: 21% − 28%) lower risk of ischaemic stroke and 36% (95%CI: 26% − 44%) lower risk of haemorrhagic stroke [178]. Each additional daily portion of fresh fruit was associated with 20% (95%CI: 15% − 25%) lower risk of ischaemic stroke and 31% (95%CI: 19% − 41%) lower risk of haemorrhagic stroke [178]. For ischaemic stroke, the association appeared to be stronger in men, in highly educated people, in participants from urban areas and in those drinking alcohol regularly [178].

4.4.4 Overweight, obesity and weight gain

In a meta-analysis including 17 prospective cohort studies including 563,277 participants, fruit and vegetables intakes were inversely associated with risk of adiposity and weight improvement. Yet the quality of the evidence was considered as low [183].

4.4.5 Type 2 diabetes

In a meta-analysis of prospective studies, high versus low intakes of fruit or vegetables were associated with non-significant reduced risk of type 2 diabetes: 5% (95%CI: (-1% −11%) for vegetables (13 studies with 63'299 type 2 diabetes cases) and 4% (95%CI: 0% − 7%) for fruit (15 studies with 70'968 type 2 diabetes cases). For each 100 g/day increase in vegetables or fruit intakes, the risk of type 2 diabetes was (non-significantly) reduced by 2% (95%CI: 0% − 4%) and 2% (95%CI: 0% − 3%), respectively [184]. There was evidence of a non-linear relation between vegetables or fruits and risk of type 2 diabetes [184], with lowest risks at approx. 200 g fruits resp. vegetables.

In the Kadoorie prospective cohort, including 500'000 Chinese adults aged 30-79 years followed-up for 7 years, risk of incident type 2 diabetes was 12% (95% CI: 5%-19%) lower per daily portion of fresh fruit consumption [185].

4.4.6 Cardiovascular risk factors

Among 451'665 participants to the Kadoorie cohort without a history of CVD at baseline [178], after 5-6 years of follow-up, fresh fruit consumption was inversely associated, in both men

and women, with systolic blood pressure and blood glucose with a dose-response relation, whereas the association with body mass index and waist circumference was positive.

4.4.7 Cancers

In 2007, the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) comprehensively reviewed the relationship between diet and cancer risk [186]. High intake of fruit and vegetables probably decreases the risk of cancers of the digestive tract (mouth, larynx, pharynx, oesophagus, and stomach). The following conclusions have been reached: (1) non-starchy vegetables probably decrease the risk of mouth, pharynx, larynx, oesophagus and stomach cancer; (2) fruit probably decrease the risk of mouth, pharynx, larynx, oesophagus, stomach and lung cancer; (3) allium vegetables probably decrease the risk of stomach cancer and garlic the risk of colorectal cancer. The likely beneficial effect of fruit and vegetables could come from the fact that they are sources of beneficial molecules and the following links have been made: foods containing folate likely protect against pancreas cancer, carotenoids against mouth, pharynx, larynx and lung cancers, beta-carotene and vitamin C against oesophagus cancer, lycopene and selenium against prostate cancer.

The 2007 WCRF/AICR second expert report is now being continuously updated (Continuous Update Project [CUP]) (http://www.wcrf.org/int/research-we-fund/continuous-update-project-cup). The CUP, with more data available, has confirmed the conclusion of the WCRF/AICR second expert report that there is currently no convincing evidence that fruit and vegetables play a role on cancer etiology [186]. The association of fruit and vegetables intake and the risk of colorectal [187], breast [188], pancreatic [189], bladder [190] and lung [191] cancer was re-examined in the Continuous Update Project (CUP) and the results were quantitatively summarised in meta-analyses (see below).

All cancers

In a systematic review and meta-analysis including data from 7 prospective cohort studies (640'852 participants and 16'468 cancer deaths recorded), an increment of one serving of fruit (defined as 80 g) per day was associated with 1% (95%CI: 0%-3%) lower cancer mortality, without significant heterogeneity across studies (-) [173]; an increment of one serving of vegetables (defined as 77 g) per day was associated with 1% (95%CI: (-1%)− (+3%)) lower cancer mortality, without significant heterogeneity across studies (data from 8 prospective cohorts including 16'510 cancer deaths from 642'123 participants) () [173]. An increment of one serving of combined fruit and vegetables per day was associated with 3% (95%CI: (-3%)− (+10%)) lower cancer mortality for each additional serving per day, without significant heterogeneity across studies (data from 2 prospective cohorts including 10'745 cancer deaths from 457'302 participants) [173].

In the Kadoorie prospective cohort, including 500'000 Chinese adults aged 30-79 years followed-up for 7 years (6'796 cancer deaths recorded), one additional portion of fresh fruit per day was associated with 16%(95%CI: 4%-26%) lower relative risk of cancer mortality, with a dose-response relation [177].

In the Health Survey for England (HSE) including 65'226 participants aged 35 years and over (2001-2008, median follow-up of 7.7 years), representative of the non-institutionalized population of England, combined fruit and vegetable consumption of at least 7 portions was associated with 25% (95%CI: 4%-41%) decreased cancer mortality compared to consuming less 1 portion (about 80 g or a handful) [175].

Bladder cancer

In two meta-analyses, fruit and vegetables consumption was not associated with the risk of bladder cancer [190, 192].

Breast cancer

In a systematic review and meta-analysis including data from 15 prospective studies, the reduction in breast cancer risk for the highest versus lowest intake was: 11% (95%CI: 1% − 20%) for fruit and vegetables combined, 8% (95%CI: 2% − 14%) for fruit and 0% (95%CI: (-6%) − 5%) for vegetables [188]. Hence, high intake of fruit, and fruit and vegetables combined, but not vegetables alone, appears to be weakly associated with reduced risk of breast cancer [188].

Colorectal cancer

In a meta-analysis including 19 prospective studies including over 1.5 million participants, the following reduced risk of colorectal cancer for the highest versus lowest intakes were: 8% (95%CI: 1%-14%) for fruit and vegetables combined, 10% (95%CI: 2%-17%) for fruit, 9% (95%CI: 4%-14%) for vegetables, with little heterogeneity across studies [187]. The possible protective effect of fruit and vegetables intake appeared to be restricted to colon cancer [187]. Colorectal cancer risk decreased non-linearly with increasing intakes of fruit and vegetables [187].

In the EPIC study (521'448 followed-up for 13 years, 3'370 colorectal cancer cases), a high consumption of fruits and vegetables at baseline was weakly associated with lower risk of colorectal cancer, with no consistent association for separate fruit and vegetables consumptions and no association with the risk of rectal cancer [193]. No clear association was found beyond a follow-up of 10 years [193].

A recent publication of the WCRF Continuous Update Project concluded that current evidence for a protective effect of vegetables on colorectal cancer risk was present, although weak, and that no significant protective effect of fruit was observed: the reduced colorectal cancer risks per 100 g/day increase in consumption were: 2% (95%CI: 1%-3%) for fruit and vegetables, 4% (95%CI: 0%-7%) for fruit and 2% (95%CI: 1%-4%) for vegetables [194]. The authors describe a significant non-linear relationship with higher risk of colorectal cancer for low intakes (< 300 g/day) of fruit and vegetables and no further reductions with intakes above 700 g/day [194].

In the Kadoorie prospective cohort, including 500'000 Chinese adults aged 30-79 years followed-up for 7 years (474 colorectal cancer deaths recorded), one additional daily portion of fresh fruit was associated with a statistically non-significant 35% (95%CI : (-4%)−(+59%)) lower relative risk of colorectal cancer mortality [177].

Lung cancer

In a meta-analysis including 37 studies with more than 20'000 lung cancer cases, vegetable intake (high vs low category) was associated with lower risk of lung cancer in both case-control (39% [95%CI: 30%-46%]) and cohort studies (12% [95%CI: 3%-19%]) [195]. Fruit intake (high vs low category) was associated with lower risk of lung cancer in both case-control (23% [95%CI: 12%-33%]) and cohort studies (16% [95%CI: 6%-25%]) [195]. Results were heterogeneous across studies, independent of smoking status and associations tended to be stronger in women [195]. In a recent meta-analysis including a slightly different set of studies, there was evidence of a non-linear relationship for both fruit and vegetables with a plateau reached at around 200 g/day [191]. In the large EPIC cohort (included in the meta-analyses), a 100 g/day increase in fruit and vegetables intake was associated with a 6% (95%CI: 1%-11%) reduction in lung cancer risk (521,468 participants aged 25–70 years, 1,830 incident cases, 8.7 years of follow-up) [196]. In EPIC, there was some evidence of effect modification by smoking (with a negative association in smokers and no association in never smokers) and possibly residual confounding.

Oesophageal cancer

A meta-analysis of prospective studies (1'160'130 participants and 1057 cases from 6 studies) concluded that citrus fruits may decrease the risk of esophageal and gastric cardia cancers, but further studies are needed [197].

In the Kadoorie prospective cohort, including 500'000 Chinese adults aged 30-79 years followed-up for 7 years (801 oesophageal cancer deaths recorded), one additional daily portion of fresh fruit was associated with 38%(95%CI : 5%-60%) lower relative risk of oesophageal cancer mortality, with a clear dose-response relation [177].

Pancreatic cancer

In a pooled analysis of data from 14 cohort studies (North America), including 319'673 men and 542'911 women with 2'212 pancreatic cases during a follow-up ranging from 7 to 20 years, intakes of fruit and vegetables, fruit alone or vegetables alone were not associated with risk of pancreatic cancer, without evidence for heterogeneity across studies [189].

Stomach cancer

A meta-analysis including 24 studies (2.4 million participants, 6632 gastric cancer cases, median follow-up of 10 years) found the following risk reductions for high versus low consumption: 10% (95%CI: 2% − 17%) for fruit and 4% (95%CI: (-6%) − 12%) for vegetables [198]. These results suggest a protective effect of fruit, but not vegetables.

In the Kadoorie prospective cohort, including 500'000 Chinese adults aged 30-79 years followed-up for 7 years (990 stomach cancer deaths recorded), one additional daily portion of fresh fruit was associated with a non-significant 20%(95%CI : (-10%)−(+42%) lower relative risk of stomach cancer mortality, with a clear dose-response relation [177].

A meta-analysis including 5 prospective cohorts (follow-up between 4.5 years and 11 years), found a 13% (95%CI: 1% − 24%) reduced risk of gastric cancer for high intake of citrus fruit with a dose-response relation [199]. The gastric cancer risk reduction per 100 g/day intake of citrus fruit provided in this study is surprisingly large (40% [95%CI: 27%-56%]) and the results should therefore be interpreted with caution [199].

4.4.8 Chronic obstructive pulmonary disease (COPD)

In the Swedish Kaluza cohort including 44 335 men, aged 45-79 years (1918 incident COPD cases during the mean follow-up of 13.2 years), each additional serving in combined fruit and vegetables intake decreased risk of COPD significantly by 8% (95% CI 4% to 11%) in current smokers and by 4% (95% CI 0% to 7%) in ex-smokers, whereas no such effect was observed in never-smokers [200].

In the Kadoorie prospective cohort, including 500'000 Chinese adults aged 30-79 years followed-up for 7 years, mortality from COPD (n=1119 deaths) was 49% (95%CI : 27%-65%) lower per additional portion of fresh fruit per day [177].

4.5 Final conclusions and recommendations

A majority of studies show a beneficial association between fruit and vegetables intake and selected NCDs, as well as overall mortality. Putative causal mechanisms are unclear at this stage. The studies do not all show a linear increase in benefits with an increase in intake, with most studies showing maximal associations at intakes of approx. 200-300 g of vegetables per day and 200-300 g of fruit per day. Beneficial effects of consumption up to two servings of whole fruits and up to ≥ three servings of vegetables/day are well supported by the current literature, and the existing recommendations should be more specific. Available studies were performed mainly with fresh products without specific details on the degree of processing. At the time being, there is no clear evidence for recommending canned products.

These studies did not include fruit juices. Specific studies on this topic are reviewed in chapter 3.3.

5 Cereals and starchy foods

Author: Luc Tappy

5.1 Introduction

The macronutrient composition of the diet has long been a major area of interest in public health nutrition. More specifically, the relationship between dietary carbohydrate and health outcomes has been the subject of many controversies in the past, and have recently become an area of intense area of intense questioning and re-assessment. Dietary recommendations in the 1980es mainly aimed at increasing total carbohydrate in order to reduce saturated fat and cholesterol intake. However, several new health-related effects of carbohydrates have been identified since then. First, dietary sugars intake has increased markedly, to represent presently between 15 to 20% of total energy instead of the 10% recommended by most national and international agencies. Second, it has been recognized that health outcomes were not only associated with the amount of sugars and starch intake, but also with the food classes from which they were obtained. This led to some paradoxical observations, for instance that total fructose intake was associated with adverse effects [201, 202], yet that consumption of fruits (see chapter 6), which is a major source of dietary fructose, was associated with protective effects against non-communicable diseases (NCD). Along the same line, evidence has steadily built to demonstrate that the intake of starchy foods from different food groups have different health effects.

5.2 Definition of "cereals and starchy foods" and present level of intake

Starch represents the most important part of total dietary carbohydrate, and as such makes a major contribution to overall energy intake. It is mainly consumed in form of foods presently grouped as "grain, potatoes and pulses" in the Swiss food pyramid.

Cereals provide metabolizable energy as starch, but also contain variable amounts of proteins. In addition, unrefined cereals contain soluble and insoluble dietary fibers and micronutrients. Whole wheat flour contains 72 g starch, 13 g protein, and 10g dietary fibers/100g (protein:starch ratio = 0.18, fiber:starch ratio= 0.14. Fiber and micronutrients' content however decreases with refining. Tuberous legumes are starch-storing roots which contain little protein, and less fibers and micronutrients than cereals. Potatoes, which are by far the most widely consumed tuberous legume in Switzerland, contains about 17g starch, 2 g protein (protein:starch ratio = 0.12), and 2 g fibers (fiber:starch ratio = 0.12) / 100 g. Pulses provide metabolizable energy as starch, but are also a major source of vegetable protein, and contain important amounts of dietary fibers. This subclass of starchy foods is discussed in chapter 6 with other protein-rich foods.

Summary box current recommendations and intake

Grains, potatoes, pulses	Description and recommendations
Current daily recommendations current Swiss Food Pyramid [2]	3 portions per day. Cereals should preferably be whole grain. 1 portion = 75–125 g bread/pastry or 60–100 g pulses (dry weight) or 180–300 g potatoes, or 45–75 g crisp bread/whole-grain crackers/ flakes/flour/pasta/rice/corn/other grains (dry weight).
Daily Intake in Switzerland [203].	The recent Swiss nutrition survey "menuCH" reports that the average consumption of grains, potatoes and pulses is 2.4 servings per day, with minor differences according to age, gender and geographical location. Bread, pasta, ice and potatoes represent the main source of intake, while average daily pulse intake account for 4.1 g (Italian-speaking part of Switzerland) to 11.9 g (German-speaking part of Switzerland)

5.3 Potential mechanisms linking cereals and starchy food intake to health outcomes

Postprandial hyperglycemia and hyperinsulinemia have been proposed to contribute to the development of insulin resistance, pancreatic beta cell exhaustion, and the development of type 2 diabetes. Hyperinsulinemia has also been proposed to play a pathogenic role in the development of hypertension and of atherosclerosis. In addition, high carbohydrate diets are also associated with high plasma triglyceride, low HDL cholesterol concentrations, and an increase in small, dense LDL particles, compared to high fat diet, and these alterations of blood lipids may be important factors in the development of atherosclerosis. It is also increasingly recognized that postprandial hyperglycemia and hyperinsulinemia are frequently associated with postprandial hypertriglyceridemia, mainly due to accumulation of low-density, TG-rich chylomicrons- and VLDL- remnants, and that this may constitute a powerful atherogenic factor [204–206].

The ingestion of isocaloric amounts of starch exert variable postprandial glucose, insulin and blood lipid responses according to the food source and pre-ingestion food processing. For example: the same starch load will elicit a lower blood glucose response when eaten as brown rice than as refined white rice, or as “al dente” than overcooked pasta [207]. Several mechanisms may account for such between-foods variability:

- Starch digestibility and biovailability
- Rate of starch digestion and of subsequent intestinal glucose absorption
- Dietary fiber:starch ratio, with dietary fibers (mainly soluble fibers) delaying intestinal transit time.

Several criteria have been proposed to predict the postprandial metabolic responses and long term health effects of carbohydrate-containing foods.

1. Glycemic index (GI) of foods and glycemic load (GL) of the diet: The GI of carbohydrate containing foods is defined as the ratio of its postprandial incremental glycemic response to that of isocaloric amounts of pure glucose [204]. GIs of a large range of foods can be retrieved from online database, such as http://www.glycemicindex.com/foodSearch.php?num=2659&ak=detail.

   GI varies according to the food’s fiber content (legumes and unrefined cereals have a high fiber content and a low GI), to the degree of cooking (longer cooking time increase GI), and to the ripeness of fruits.

   The effects of foods on postprandial blood glucose depends on both their GI and the amount of food consumed, which implies that some studies calculate a GL, ie the amount of carbohydrate consumed from a carbohydrate-containing food multiplied by its GI; these parameters provide a better estimate on glycemic responses, but is not independent of total energy. In addition, the presence of fructose in a food decreases its GI, but there is concern that fructose may exert adverse effects of its own [114].

2. Degree of grain refining. Much literature has documented that consumption of unrefined cereals are associated with low levels of blood glucose and lipids and with beneficial health outcomes. Since unrefined cereals include products ranging from partially refined flour to completely unprocessed grains, and since beneficial effects are mostly observed with unrefined products, authors have proposed that “whole grain products” may be the healthiest source of dietary carbohydrate. Whole grains are generally defined as the intact, ground, cracked or flaked kernel of cereals after the removal of inedible parts such as the hull and husk. Whole grain can be processed as long as the grain components (endosperm, germ and bran) are present in the same relative proportions as they exist in the intact grain [208]. There is presently no unanimously accepted definition for whole grain, however [209].

3. Food's fiber content. Since postprandial metabolic responses are largely conditioned by the dietary fiber component of foods, dietary fiber intake may be used as a "proxy" index for carbohydrate quality. Dietary fiber intake however reflects consumption of starchy, fiber rich foods (unrefined cereals, some starchy vegetables (some tuberous vegetables, legumes,) and of sugar-rich fruits and vegetables. It does not take into account the specific effects of soluble vs insoluble fibers, nor the effects of food processing or meal preparation.

5.4 Review of literature

Methods

Documentation of the associations between types of cereals and other starchy foods and health outcomes covers a broad range of clinical outcomes, which have been addressed by a very large number of studies. The Scientific Advisory Committee on Nutrition, U.K. (SACN) has recently carried out an extensive analysis of the literature available, and the present analysis is largely based on its report [108]. In addition, we extracted meta-analysis published between 2012 and 2017, and which assessed the association between either whole grains intake or diet GI/GL on one hand and total mortality, obesity, type 2 diabetes mellitus, cardiovascular diseases (total, coronary heart disease, stroke, hypertension), or cancer on the other hand. We also included meta-analyses assessing the health outcomes associated with total dietary fiber intake if they also provided a sub-analysis by food classes. The extracted meta-analysis and their main conclusions are summarized in tables 5.1-5.4.

5.5 Results

5.5.1 Total dietary starch intake

We first took into consideration that both the total amount of dietary carbohydrate and the type of carbohydrate consumed might be relevant for human health. Current recommended dietary intake is set at 50-55% by the European Food Safety Agency (EFSA) [210] and by many national food agencies. It has however been observed that high carbohydrate diets were associated with high blood triglyceride and low HDL cholesterol concentration, and that these effects may increase cardiovascular and metabolic risk [211]. We therefore searched for evidence linking total dietary starch intake and health outcomes. This question has been addressed in the SACN report on carbohydrate, [108]. The SACN expert panel systematically assessed the associations between total dietary starch content and health related outcomes. Of 7 cohort studies that presented evidence on total starch intake and incidence of coronary heart disease [212–218],only one of them one [217] observed that total starch intake was associated with greater incidence of coronary events in men, but not in women. Based on the analysis of 4 cohort studies [219–222], the SACN also found no association between starch intake and the incidence of type 2 diabetes. Their report also concluded that the consumption of refined grains was not associated with cardiovascular and type 2 diabetes incidence [108], but that the consumption of white rice was positively associated with adverse cardiometabolic health outcomes (RR 1.11, 95% CI 1.08, 1.14 for each 158g serving/day increase). Average daily rice intake in Switzerland is 62.5-73.9 g, ie much lower than daily intakes associated with possible adverse health effects [108].

5.5.2 Association according to specific foods (whole grain vs refined cereals; low GI vs high GI; dietary fiber content)

We next searched for evidence linking specific starchy foods and health outcomes. For this purpose, we relied on critical reviews and meta-analyses having directly or indirectly assessed the associations between whole grain vs refined cereals consumption, low vs high GI foods

consumption, or between low vs high total dietary fiber intake on one hand, and the risk of cardiovascular and metabolic diseases, of cancers, and total mortality on the other hand. The main observations are summarized in supplementary tables S5.1-S5.4. As a further source of summary information, the SACN report on carbohydrate includes an exhaustive compilation of prospective cohort studies and detailed meta-analyses pertaining to a large list of health-related issues [108].

Cardiovascular risk

- **by whole grain intake:** the meta-analysis by Aune et al [223] reported a dose-dependent association between whole grain consumption and a reduced incidence of coronary heart disease (5 studies; RR 0.84 (0.77-0.92) per 90g intake/day) and cardiovascular diseases (2 studies; RR =0. 87 (0.78-0.97)); there was no significant association with stroke incidence however. The meta-analysis by Mellen et al, [224] compared health outcomes in individuals with highest (> or= 2.5 serving/day) vs lowest (< 0.2 serving/day) quantiles of whole grain consumption. They reported lower incidences of cardiovascular disease in the highest quantiles in general adult populations (7 studies), in males only (2 studies), and in females only (2 studies) cohorts. The difference between high and low consumers regarding the incidence of stroke was much less pronounced and of borderline significance. Interestingly, these authors also compared low vs highly refined grain consumption, and did not observe any effect on cardiovascular incidence.
- **by diet GI/GL:** the meta-analysis by Mirrahimi et al. [225] reported a lower incidence of cardiovascular diseases in subjects consuming a low GI vs high GI foods(GI: RR=1.11 (95% confidence interval [CI] 0.99 to 1.24) ; GL: RR=1.27 (95% CI 1.09 to 1.49). One meta-analysis by Evens et al, reported a dose-response reduction in systolic and diastolic blood pressure with decreasing GI.
- **by dietary fiber intake**: one meta-analysis by Threapleton et al, [226]reported a dose-dependent reduction association between total daily fiber intake and the risk of coronary heart diseases (RR 0.91 (0.87-0.94) per 7 g fiber intake per day). Sub-analysis by food groups indicated that fiber from cereals, fruits, and vegetables, were inversely associated with cardiovascular risk. Another meta-analysis by the same authors reported also a dose-dependent reduction in the risk of stroke [227].

Type 2 diabetes risk

- **by whole grain intake:** the meta-analysis by Aune et al, [223] reported a dose-dependent reduction in the risk of type 2 diabetes with increasing whole grain consumption (RR 0.68 (0.58-0.81) per 3 servings/day); a sub-analysis confirmed this association for whole grain consumed as bread, breakfast cereals, wheat bran and brown rice. The same meta-analysis reported an increased risk with consumption of white rice.
- **by diet GI/GL:** the meta-analysis of Greenwood et al, [228] reported an increase risk of developing type 2 diabetes with each 5-unit increase in the total dietary GI (RR 1.08 (1.03-1.15). In contrast, the SACN meta-analysis of five prospective cohort studies observed no significant association between GI and incidence of cardiovascular disease events. A meta-analysis of prospective studies by Mirrahimi et al, [225]reported that a high dietary GI or GL was significantly associated with coronary heart disease risk in women, but not in men.

Obesity

Effects of starchy foods on food intake

Several studies have addressed potential relationships between starchy food intake and body weight.

c1) relationship of dietary GI/GL with total energy intake:

Several mechanistic studies tested the hypothesis that ingestion of foods with high GI would elicit a lower satiety and be associated with higher energy intake at subsequent meals. These studies, performed on small number of subjects, and hence with little statistical power, did not observe significant impact of diet GI on subsequent food intake [229–231].

c2) effects of dietary GI/GL intervention studies on body weight:

Two RCTs compared the effects of a high vs low GI diet on body weight over periods of 6 months and 18 months and did not observe any significant difference [232, 233]. Finally, a large multicentric European study (DIOGENES) compared the effects on body weight of five different dietary conditions: a low-protein and low-GI diet; a low-protein and high-GI diet; a high-protein and low-GI diet; a high-protein and high-GI diet; a control diet. Each dietary condition was applied at the end of a weight loss program, and the primary outcome of the study was the weight loss maintenance after 26 weeks. The analysis performed on the 938 subjects having entered the study showed that 0.95 kg (95% CI, 0.33 - 1.57) less weight was re-gained with the low GI diets than with the high GI diets. [234, 235].

c3) PCS studies with association between whole grain intake and body weight changes:

One meta-analysis of three prospective cohort studies documented that whole grain consumption was associated with less body weight gain over time (+1.64 kg over 8-13 y in those consuming 48-80 g 3-5 serving/d vs 1+1.27 kg in non-consumers, $p<0.001$). [236].

The literature addressing effects of starchy foods on body weight is by nature complex and possibly affected by important bias. The SACN report concludes that the relationships between starchy foods intake (type of starch, fibers, GI) is presently insufficient [108].

Gastro-intestinal and breast cancers

- **by diet GI/GL:** One meta-analysis by Mullie et al, [237] reported an increase in breast cancer risk with increasing diet GI (RR 1.05 (1.00-1.10).

- **by total dietary fiber intake:** a meta-analysis by Aune et al, [238] reported a dose-dependent reduction in the risk of colon cancer with increasing dietary fiber intake (RR 0.90 (0.86-0.94) per 10 g daily dietary fiber intake ; a sub-analysis indicated that risk reduction was mainly associated with whole grain and cereal fibers consumption. The SACN meta-analysis [108] reported strong associations between dietary fiber intake and risk of colorectal cancers. A meta-analysis by Zhang et al, [239] reported a strong association between dietary fiber intake and gastric cancer (RR 056 (0.45-0.71) per 10g daily dietary fiber intake). The meta-analysis of Aune et al, [238] reported a significant association between dietary fiber intake and risk of breast cancer (RR 0.95 (0.91-0.98) per 10 g daily dietary fiber intake. Another meta-analysis by Schlesinger et al, [240] further concluded that this association was particularly valid for estrogen-receptor negative breast cancer in postmenopausal women.

Mortality

- **by whole grain intake:** the meta-analysis by Aune et al, [223] reported a dose-dependent reduction in all causes mortality and in mortality associated with coronary heart diseases, cardiovascular diseases, cancer, and non-cardiovascular, non-cancer causes with increasing whole grain consumption (RR per 90g whole grain intake/day: 0.83 (0.77-0.90). A meta-analysis by Chen et al [241] reported a dose dependent reduction in total mortality (RR/50g intake per day: 0.78 (0.67-0.91), mortality from cancer (RR:0.82 (0.69-0.96)), and mortality from cardiovascular diseases (RR: 0.70 (0.61-0.79)) with increasing intake of

whole grain products. For cardiovascular diseases, the reduction was significant for coronary heart disease, but not for stroke. Two large prospective cohort studies also reported that whole grain consumption was associated with lower total and CVD mortality in U.S. men and women [242].

- **by dietary fiber intake:** a meta-analysis by Kim et al [243] reported a reduced all-causes mortality (RR: 0.89 (0.85-0.92)) per 10 g. daily dietary fiber intake); this association was mainly due to cereal and vegetable fiber intake.

5.5.3 Discussion and research gaps

The assessment of cereals and starchy foods' health effects is presently incomplete, and at best partially conclusive for several reasons. First there are large variations in overall macronutrient composition and in physical-chemical structure (starch structure, swelling characteristics, interaction with digestive enzymes), both between food groups and between individual foods within the same food group [244, 245]. Second, many of the mechanisms by which starchy foods modulate risk factors for NCD remain poorly understood. Over recent years, there has been growing interest in gut microbiota-host interaction, and the research of how microbial metabolites may modulate human metabolism is presently very active. Many observations point to a role of gut microbiota in the pathogenesis of NCD [246], and further research is needed to assess the effects of various types of starchy foods on gut microbiota. There is also increasing awareness that nutrient' and metabolite receptors (bitter and sweet taste receptors, receptors of bile acids) are expressed throughout the small and large intestine [247], and even on some cells located outside the digestive tract (pancreatic beta cells, some neurons etc.. These receptors modulate important metabolic processes such as glucose absorption, insulin secretion or gastric emptying. How dietary fiber content and starch digestibility of starchy foods impact on the activity of these receptors may be key to some of their health effects.

5.5.4 Conclusions and recommendations

Cereals and starchy foods are important constituents of our diet, and provide digestible carbohydrate energy, dietary fibers, and micronutrients. The recommendation to consume three serving of this class of food per day appears valid given that recommended total carbohydrate intake is of approximately 50% (45-60%) total daily energy [108], and consumption of free sugar should be as low as possible [107, 108].

There is strong evidence that consumption of whole grains, minimally processed or processed in a way that the components (endosperm, germ and bran) are present in the same relative proportions as they exist in the intact grain [208] is associated with decreased risk of cardiovascular diseases and type 2 diabetes. There is also strong evidence that consumption of whole grains is associated with decreased mortality from cardiovascular diseases, from cancer, and from non-cardiovascular, non-cancer cause.

Assessing health effects of cereals and starchy foods from whole dietary fiber content equally indicate that a high dietary fiber intake is associated with lower risk for cardiovascular diseases, type 2 diabetes, gastro-intestinal and breast cancer, and with lower mortality from all causes, cardiovascular diseases and cancer; some of these studies further show specific associations between cereal fibers and health outcomes.

Assessing health effects of the diet from GI/GL showed inconsistent associations with health outcomes.

There is insufficient information to provide a specific recommendation regarding the number of whole grain serving to be consumed on a daily basis. We therefore propose to recommend that three daily serving of cereal and starchy foods be consumed daily, and that as many as possible should be from whole grain.

Pulses are an important source of carbohydrate and as such are presently represented at the same level as cereals and other starchy foods. It is however a major source of dietary protein as well, and replacing part of animal protein intake with pulses may have beneficial health effects (see chapter 6.2). It is therefore recommended that pulses be replaced with meat, fish and eggs in the Swiss food pyramid.

6 Protein sources

6.1 Meat, fish and eggs

Author: Clara Benzi Schmid

6.1.1 Introduction

An adequate intake of high quality protein is an absolute nutritional requirement in order to ensure sufficient provision of essential amino acids. Although protein is present in small quantities in most foods, the fourth level of the Swiss food pyramid regroups dairy products, meat, fish, eggs, and tofu and foods, which are our main sources of dietary protein intake. The relationship between milk and dairy product intakes and NCD has been specifically re-assessed, and results are presented in chapter 6-2. The other foods present in this food group are currently meat, fish, eggs, and tofu as a representative of proteins of plant origin.

Pulses (including tofu), which represent a major source of vegetable protein, are presently included at the third level together with grains and potatoes. The scientific evidence specifically linking vegetable protein intake and risk of NCD has been assessed and reported in chapter 6-3.

The scientific evidence linking meat consumption and risk of NCDs has been recently reviewed in an FCN report [248], and those regarding fish consumption have been revised by several national food agencies and scientific bodies. It has therefore been estimated that re-assessment of the scientific literature regarding these foods was not warranted at the present moment. Finally, the literature specifically addressing eggs is currently too scarce to run a specific analysis. In this chapter, we only briefly recall the recent guidelines from the World Cancer Research Fund International (WCRF), the American Institute for Cancer Research (AICR), and the French ANSES regarding meat and fish.

6.1.2 Definitions

From a nutritional point of view, evidence shows that it might be important to distinguish between:

- red meat from mammals such as beef (including calf), goat, pork, mutton (including lamb) or horse,
- white meat from poultry and domesticated rabbits,
- processed meat (smoked, salted and / or and containing other additives, in particular preservatives) [249],
- fatty fishes, often deep sea fish (e.g. salmon, tuna, herring, swordfish) with high long-chain n-3 fatty acid (EPA and DHA) and vitamin D content
- and low-fat fishes, often lake fish in Switzerland (e.g. trout, perch, pike) sea food.

6.1.3 Current recommendations and intake data

The current Swiss food recommends one serving of an additional portion of another high-protein food item per day, without differentiating between the various protein sources.

Summary box current recommendations and intake

Meat, Fish, Eggs & Tofu	Description and recommendations
Current daily recommendations current Swiss Food Pyramid [2]	In addition [to 3 portions of dairy products] 1 daily portion of another protein-rich food (e.g. meat, poultry, fish, eggs, tofu, quorn, seitan, cheese or fresh cheese [quark]). Alternate between these sources of protein. 1 portion = 100–120 g meat /poultry/ fish/ tofu/quorn/seitan (fresh weight) or 2–3 eggs or 30 g semi/hard cheese or 60 g soft cheese or 150–200 g fresh cheese (quark) /cottage cheese.
Daily Intake in Switzerland [3]	See below

The average consumption of meat in the adult Swiss population is estimated at 111 g/day, of which 67 g/d unprocessed meat (including 27 g/day poultry) and 44 g/day processed meat. It tends to decrease with age (129 g/day for people 18-34 y, 110 g/day for people 35-49 y, 103 g/d for people 50-64 y and 88 g/d for people 65-75 y) [250].

The weighted mean daily intakes for fish and seafood were of 21g but varied between the linguistic areas: 18 g (German-speaking), 29 g (French-speaking), 34 g (Italian-speaking) [251].

6.1.4 Potential mechanisms linking meat, fish and eggs consumption and NCDs

Red meat contains heme-iron that contributes to the production of carcinogenic N-nitroso compounds by colonic bacteria. Heme-iron also contributes to the production of pro-inflammatory cytokines, free radicals and other carcinogen substances [252]. Furthermore, an oversupply of heme-iron is be considered as a potentially atherogenic and diabetogenic [248] factor due to the oxidative stress that it generates. Red meat also contains choline and phosphatidylcholine as well as creatinine, which may be involved in the formation of the atherogenic compound Trimethyl-amin-N-Oxide (TMAO) in the colon [248]. Finally, high-temperature cooking of red meat causes the formation of heterocyclic amines and polycyclic aromatic hydrocarbons. These substances may promote colon carcinogenesis, in particular in genetically prone subjects (e.g. subjects with Cytochrome p450 1A2 and N-acetyltransferase 2[5]isoforms) [248].

Although few studies have specifically assessed the associations between white meat consumption and NCDs, the present consensus is that this type of meat has a neutral effect on the NCDs risk [42].

Additional potential mechanisms for processed meat could be found in its content in preservatives used for the processing such as salt, nitrite and nitrate. Nitrate and nitrite may be directly involved in carcinogenesis [253]. Furthermore, nitrate and nitrite can react with amino acid products and/or heme iron to form N-nitroso compounds. Furthermore, depending on the fuel used to produce the smoke, smoked meat may contain carcinogenic and mutagenic substances [253].

In contrast, there is an inverse relationship between fish consumption and NCDs, and more specifically with cardiovascular diseases. This may be related to the high content of n-3-long chain polyunsaturated fatty acids (LC-PUFA) -in fatty fish [254]. Dietary LC-PUFAs exert favorable cardiovascular effects, have antiarythmic properties, decreased blood triglyceride

concentration, and have also anti-inflammatory and anti-hypertensive effects [252]. The beneficial effects of fish consumption may however be counterbalanced by the fact that consuming a high amount of fish, and, in particular fatty fish, was associated with toxicological risks: fatty fish may contain a high level of contaminants such as PCBs (salmons) and methylmercury (tuna, swordfish). Considering these risks and benefits, the Dutch dietary guidelines 2015 and ANSES 2016 recommended respectively one serving size (100 g) of fish per week, preferably oily fish and 1-2 servings per week (from which one oily fish) [42, 255].

6.1.5 Review of recent recommendations for meat, fish and eggs

Red meat / processed meat

The FCN report [248] concluded that consumption of red meat and processed meat was associated with an increased all-causes mortality, an increased risk of cardiovascular diseases, and a moderate risk of weight gain (the latter without any plausible biological mechanisms, however).

The French ANSES concluded that there is a positive association between red meat consumption and the risk of cardiovascular diseases incidence [248, 252]. The risks of IHD and/or stroke significantly increased by 10-15 % for an increment of 100 g daily intake of either red meat alone or red meat and processed meat together. For an increment of 50g/d of processed meat the risk increased by 40% [252]. The French ANSES therefore concluded that there is a probable association between CVD and mortality and consumption of red meat and/or processed meat [252].

Considering type 2 diabetes, the FCN report concluded to a positive association between red meat and processed meat consumption and risk of developing the disease. Although there remain uncertainties regarding the threshold for such effect, 100 g/day red meat and 50 g/day processed meat were considered to be associated with a significantly increased risk (+ 20% and 50% respectively) [248]. The ANSES report also concluded to a probable association between red and processed meat consumption and risk of type 2 diabetes [252].

The WCRF/AICR updated scientific evidence linking meat consumption and cancer in 2018 [256].They reported that the consumption of red meat was associated with the risk of colorectal cancer [249]. They also reported an association between processed meat and the onset of colorectal cancer [249]. A daily consumption of 100 g of red meat significantly increased the risk of colorectal cancer by about 12% [249]. A daily consumption of 50 g of processed meat increases the risk of colorectal from 15-20% [249]. The ANSES found convincing evidence for such an association but noticed a certain inconstancy among studies [252]. It also observed that the relative risk found in individual studies decreased markedly over the past decade (from +29% to 14%) [252]. Concerning increased risks for other cancers, the WCRF/AICR experts concluded to an association for red meat consumption (100 g/d) and lung and pancreas cancers but evidence suggesting this is limited [256]. Processed meat consumption (50 g/d) was also associated with risk of esophageal and gastric cancers, but evidence suggesting this is limited [256]. There is an association suggesting an increased risk for nasopharyngeal cancer at a consumption of 100 and 30 g/week for red meat and processed meat respectively [256].

White meat

Although there are few studies specifically assessing health effects/associations with white meat, the consensus is nonetheless that this type of meat has a neutral effect on the NCDs.

Fish

There are insufficient studies to establish a positive, neutral or negative association relating the weight gain with fish consumption [252].

The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice concluded that eating fish at least once a week results in a 16% and a 6% reduction in the risk of IHD and stroke respectively by comparison with eating less fish, resp. less than once per week [257]. The ANSES experts concluded that a consumption of fish (once a week) probably decreased the risk of stroke [252]

Regarding associations between fish consumption and colorectal cancer, the evidence that consumption of fish decreases the risk of colorectal cancer is limited, according the WCRF and AIRC [258]. An inverse association is observable for men, but not for women [259]. The French ANSES did not conclude to an association [252].

WCRF and AIRC experts concluded that a consumption of at least 20 g/d fish was associated with decreased risk of liver cancer [260].

Considering Trimethylamin-N-Oxide, studies reported geographical disparities. While consuming fish shows a positive association in the Western countries with risk of type 2 diabetes, in the U.S.A, fish consumption has a protective effect against the type 2 diabetes [252]. In Europe, the situation is not so clear because data are limited and highly heterogeneous [252]. The cooking method (frying) could have an influence on the peroxidation of this LC-PUFA producing a pro-inflammatory process [252].

6.1.6 Conclusions and recommendations

A well-balanced diet must include a variety of protein sources, meat, fish, eggs are some of the possible options, alongside milk and dairy (chapter 6.2) and proteins of plant origin (chapter 6.3).

The 2014 FCN report on meat concluded that consumption of unprocessed red meat and processed was associated with an increased risk of NCDs, and more specifically of cardiovascular diseases, type 2 diabetes and cancer. This conclusion remains supported by the recent scientific literature, and several nutritional agencies recently made specific recommendations.

For unprocessed red meat, WCRF and AICR recommend a maximal consumption of three portions of red meat per week. Three portions is equivalent to about 350 to 500 grams cooked weight in total [261]. Other valuable protein sources may be consumed to meet to nutritional requirements and to substitute the consumption of red meat (e.g. egg, poultry and fish (1-2 x/week) [261].

For processed meat, WCRF/AICR recommend consuming very little, if any, processed meat [261]. ANSES recommend a maximal consumption of 25g/d of processed meat [255]. For fish: ANSES recommends consuming fish one to two times per week (1 portion = 100 g). It further specifies that consumption of fatty, deep sea fish should be limited to one serving per week to avoid excessive exposure to toxicological compounds present in these type of fishes, and that the second weekly fish serving should be from another type of fish [262].

WCRF/AICR do not make any recommendation for fish regarding cancer prevention. However, it mentions recommendations for the prevention of other NCDs (one to two times per week, one of which should be a fatty fish) [261].

These recommendations correspond to the current Swiss recommendations, however more attention should be paid to a diversification of protein sources, including proteins of plant origin etc. This pyramid level should be revised as soon as more data is available for proteins from alternative sources (e.g. insects, bio-engineered meat, other novel food items derived from cellular agriculture).

6.2 Milk and dairy products

Authors: Barbara Walther, with contributions of Alexandra Schmid, Doreen Gille, Guy Vergères

6.2.1 Definition

Swiss law („Verordnung des EDI über Lebensmittel tierischer Herkunft“ [VLtH] of 16 December 2016 [263]) defines several food items as **dairy products**. Besides milk, there is yoghurt, cheese, kefir, buttermilk, cream, butter and milk powder.

Milk

According to Swiss law (Art. 32 Abs. 2 VLtH) milk is the product of the milking of one or more mammals that are milked regularly. Only the following mammals may provide milk for human consumption: domesticated bovids (*Bovidae*), deer (*Cervidae*), camelids (*Camelidae*), pigs (*Suidae*) and horses (*Equidae*) (Art. 2a VLtH). “Milk” without further specification has to come from cows. Otherwise, the animal species has to be indicated (e.g. sheep milk, goat milk) (Art.36 VLtH).

In Switzerland whole or full-fat milk (“Vollmilch”) contains at least 3.5% fat (Art. 33 VLtH). In semi-skimmed milk (“halbentrahmte Milch”) the fat content is between 1.5 and 1.8%, in reduced fat milk (“teilentrahmte Milch”) the fat content is between 0.5 and 3.5% and skimmed milk (“Magermilch”) contains less than 0.5%.

Yoghurt

According to Art. 45 VLtH yoghurt is produced by fermenting milk with the microorganisms *Lactobacillus delbrueckii ssp. bulgaricus* und *Streptococcus thermophilus.* There have to be at least 10^6 cfu/g of the microorganisms in the end product. Regarding fat content, the same levels as in milk are used: (regular yoghurt: ≥3.5% fat, reduced fat yoghurt: >0.5 and <3.5% fat, low-fat/skim yoghurt: <0.5% fat).

Cheese

Cheese is a food derived from milk that is produced by separating the solid curds from liquid whey with the help of rennet or other coagulating substances or processes. Depending on the product, it can be further processed or ripened (Art. 50 VLtH). Cheese can be classified by firmness and by fat content. According to Art. 52 Abs. 2 VLtH there are four firmness types based on the moisture content of fat free cheese: soft, semi-hard, hard and extra hard. Art. 52 Abs. 1 VLtH categorizes cheese based on the fat content in dry matter in double cream cheese (>650 g/kg), cream cheese (550-649 g/kg), full-fat cheese (450-549 g/kg), three-quarter fat cheese (350-449 g/kg), semi-fat cheese (250-349 g/kg), quarter-fat cheese (150-249 g/kg) and low-fat cheese (<150 g/kg).

Nutritional characteristics of milk and dairy products

Milk and dairy products provide macronutrients (protein, fat, carbohydrates) as well as many vitamins and minerals. The macronutrient composition varies according to the product. Depending on type, cheese contains less water, no or only small amounts of lactose, but more protein and fat compared with milk or yoghurt on a weight/weight basis. Milk fat contains predominantly saturated but also mono- and polyunsaturated fatty acids including essential linoleic and α-linolenic acid. Additionally, milk fat provides *trans* fatty acids (mainly vaccenic acid) and conjugated linoleic acid (CLA). There is a large seasonal variation in the fatty acid composition of milk fat with higher amounts of unsaturated and trans fatty acids as well as CLA during summer [264, 265]. Milk and dairy products contain high-quality protein providing all essential amino acids in an optimal composition.

The mineral fraction of milk and dairy products encompasses the macroelements Ca, Mg, Na, K, P, Cl and the microelements Fe, Cu, I, Zn, Se and Mn. The predominant mineral in milk is Ca (about 1200 mg/l in cow's milk) [264, 266]. The vitamin fraction of milk and dairy products is composed of the lipophilic vitamins A, D, E and K as well as the hydrophilic vitamins B_1, B_2, B_6, B_{12}, C, niacin, pantothenic acid, biotin and folate [266].

The fermentation of milk can lead to an enrichment of new compounds in the food product such as some B vitamins including folate, riboflavin and B12 or vitamin K2 (menachinone), which are synthesized from various non-vitamin precursors by certain bacteria in fermented dairy food [267]. Fermented dairy products are also ideal vehicles for the delivery of microbes/probiotics to the human GIT. Fermentation-associated microorganisms might alter the intestinal composition or function of the autochthonous microbiota in the GIT. However, the magnitude of these changes and importance to probiotic efficacy is currently a point of contention [268]. Furthermore, live microorganisms in fermented dairy foods such as yoghurt help lactose-intolerant persons to digest lactose [269]. Finally, fermentation improves digestibility, in particular for proteins [270].

6.2.2 General comments on the studies analysed

In this report, we concentrate on the dairy products indicated in the fourth level of the Swiss food pyramid. That means that we do not specifically look at the evidence for butter (see chapter fat and oils), cream or ice cream consumption. However, depending on the study these products may be included in the total dairy group. Some studies include butter, ice cream, sherbet, milkshakes, smoothies or/and custard or even porridge in total dairy group, others do not. These variations may influence study findings.

Randomized controlled trials usually concentrate on a specific, well-defined product or a combination of products. Observational studies (prospective cohort, case-control or cross-sectional studies) generally include several dairy foods. The exact fat content of the included low-fat dairy foods is not specified. Low-fat dairy groups often encompass all products with a reduced fat content (reduced fat, semi-skimmed and skimmed products). Besides plain milk, studies of observational nature may also have included flavoured and sweetened milk products. Consumption amount is normally assessed in servings per time unit (day, week, month etc). Depending on the study, one serving corresponds to between 125 and 250 ml milk. It is also the same with yoghurt. Observational studies usually do not differentiate between plain and fruit/sweetened yoghurt or between regular and reduced-fat products. Yoghurt consumption is usually assessed in servings. Depending on the location (country) of the study serving size varies between 100 g and 230 g yoghurt.

Cheese intake in observational studies mostly consists of regular (full-fat) cheese. Portion size in the studies depends on type of cheese. One serving of ripened cheese normally corresponds to 20 - 50 g depending on study and country.

When available, we present findings for subgroups like whole-fat, low-fat or fermented dairy products or dairy categories such as milk, yoghurt and cheese. We did not evaluate the evidence regarding health effects of probiotic products as this is beyond the scope of this report.

6.2.3 Recommendations and intake data

In Switzerland, milk and most dairy products (yoghurt, kefir, buttermilk and all sorts of cheese [curd, cottage, soft, semi-soft and hard cheese]) are located on the fourth level of the Swiss food pyramid together with other protein rich foods [2].

Summary box: current recommendations and estimated levels of intake in the Swiss population

	Definition	Quantity
Daily recommendations current Swiss Food Pyramid [2]	Food level: Milk and dairy products	3 portions per day, 1 portion =200ml milk, or =150-200g yoghurt/curd/cottage cheese other fermented dairy product, or =30g hard or semi-hard cheese, or =60g soft cheese
Other recommendations [271] Optimal level of intake (optimal range of intake)	Milk (not further classified)	435 g (350–520) per day
Daily Intake in Switzerland [3]* Total / male / female	Milk / milk drinks Yoghurt Hard / semi-hard cheese Soft cheese Cream and spread cheese	1.1 dl / 1.1 dl / 1.1 dl 52.6 g / 50.4 g / 54.8 g 26.7 g / 30.2 g / 23.3 g 13.1 g / 15.6 g / 10.5 g 10.6 g / 9.3 g / 11.8 g

[1]An extra portion of curd or cheese may be consumed as additional protein source in alternation with meat, poultry, fish, eggs or alternative plant protein sources
*Data are mean values of two 24-hour recalls protocols, weighted and corrected for seasonality and weekdays.
Comparable recommendations are found worldwide: most countries recommend between 1 and 3 servings per day [272].

6.2.4 Results

6.2.4.1 Dairy and cardiovascular diseases - Review of meta-analyses and prospective cohort studies

Dairy intake and risk of cardio-vascular diseases (CVD)

Eight meta-analyses of prospective cohort studies investigated the associations of total dairy, cheese, yoghurt, milk, high-fat and low-fat dairy as well as fermented dairy products on CVD risk in the last 5 years [273–280]. Four of them reported a significant inverse association between total dairy intake or milk intake and CVD risk, while three reported no significant association. One meta-analysis found an inverse association between cheese intake and CVD risk (maximal risk reduction with 40 g/d cheese [279] and five reported no association. There was no association between yoghurt intake and CVD risk (three meta-analyses). When associations with dairy products were assessed according to their fat content, there was no association between high fat dairy products intake and CVD risk (four meta-analysis), while two meta-analyses showed an inverse association and two meta-analysis no association between low-fat dairy intake and CVD risk. Drouin-Chartier et al. [281] summarized the results of all relevant meta-analyses published so far, and came to the conclusion that there is no association of total dairy, cheese and yoghurt with CVD risk with scientific evidence of moderate to high-quality. They considered that the quality of evidence for high-fat dairy, low-fat dairy, milk and fermented dairy products was not sufficient to draw relevant conclusions.

Dairy intake and risk of coronary heart disease (CHD)/coronary artery disease (CAD)

Five meta-analyses of prospective cohort studies investigating the associations between total dairy, cheese, yoghurt, milk, high-fat and low-fat dairy/cheeses, and fermented dairy products intake and CHD risk were published during the last 5 years [273, 275, 278–280]. For total dairy, yoghurt, milk, high-fat and low-fat dairy no or not significant associations were found in terms of CHD risk. Interestingly, three of four meta-analysis reported that cheese intake was inversely associated with CHD risk (risk reduction 2-18%). Dose-response analyses of milk consumption revealed no significant association with CHD risk [273]. Drouin-Chartier et al. [281] reported that total dairy, high-fat dairy and low-fat dairy intake were not associated with CAD risk (high evidence). No associations were found between CAD and intakes of milk,

cheese, and yoghurt with moderate evidence. Also, trans-fatty acids from ruminant sources were not associated with CAD risk [282]. In their view, it is not possible to make a statement of associations between CAD and fermented dairy products, as evidence is very limited [281].

Dairy intake and risk of stroke

Seven meta-analyses of prospective cohort studies investigated the associations of total dairy, cheese, yoghurt, milk, high-fat and low-fat dairy/milk as well as fermented dairy products on CHD risk in the last 5 years [275, 278, 279, 281, 283–285]. An inverse association with stroke risk was found for total dairy (five of six meta-analyses), low-fat dairy (five of six meta-analyses) and cheese (three of four meta-analyses) whereas milk, fermented dairy and yoghurt showed no associations. For high-fat dairy associations were inconsistent: two meta-analyses identified an inverse association and three meta-analyses no association. Four dose-response analyses of milk, cheese and total dairy revealed that the highest stroke risk reduction was associated with >1.5 servings dairy products/day (-9%), 0.5-1.5 servings cheese/day (-14%) and 200 mL milk per day (-18%) [273]. One study found no associations with increasing milk intake [284]. The intake of total dairy, low-fat dairy, cheese, and fermented dairy products may be associated with a reduced stroke risk. The consumption of regular and high-fat dairy, yoghurt and milk showed mostly no association with stroke risk. The evidence of all findings is moderate [281].

Dairy intake and risk of myocardial infarction

There was no meta-analysis published in the last 5 years that specifically investigated the association of dairy intake and the risk of myocardial infarction. However, a prospective cohort study in 98’529 Danish adults found no association between milk intake and risk of ischaemic heart disease and myocardial infarction [286].

Dairy intake and risk of hypertension

Two meta-analyses of prospective cohort studies investigated the association between dairy products and hypertension risk in the last 5 years [276, 277]. Both meta-analyses identified a small but significant inverse association between total dairy, low-fat dairy and milk and the risk of hypertension. Full-fat dairy, yoghurt and cheese were not associated with the risk of hypertension.

Dose-dependent dairy intake and risks of CVD, coronary heart diseases (CHD) and stroke

Some meta-analyses of prospective cohort studies investigated the associations of increased or decreased dairy intake on CVD, CHD and stroke. The highest reduction of stroke risk was found for an intake of 125 g milk (14% risk reduction) and above 25 g cheese per day [283]. Another meta-analysis found a non-linear dose-response relationship for milk consumption with stroke risk (100-700 mL milk/d, no information about fat content) with a maximal risk reduction of 18% at about 200 mL/d [284]. Dairy intake (per 200 g/d) as well as milk intake (per 244 g/d) showed no association with CVD and CHD risk. For total fermented dairy products (per 20 g/d) and cheese (per 10 g/d) there was also no association with risk of CHD but the risk of CVD was marginally reduced [287].

An overview of the associations between dairy product consumption and risk of CVD, CHD and stroke based on the evaluated meta-analyses of prospective cohort studies is given in table 1.

6.2.4.2 Review of randomized controlled trials (RCTs)

An increase of low-fat and high-fat dairy consumption was not associated with risk factors of CVD in RCTs [288]. Fermented dairy products showed inverse associations with blood pressure [289–291], serum triglycerides and low-density lipoproteins (LDL) [292, 293] – the effects

are small but significant. An amelioration of these parameters may contribute to the prevention of CVD.

6.2.4.3 Dairy and metabolic disease

Eleven meta-analyses and 22 individual studies (9 clinical trials and 13 studies of observational nature) published in the last 5 years were included in the evaluation of the effect of milk and dairy products in regard to overweight/obesity, type 2 diabetes and metabolic syndrome. The meta-analyses included between 883 and 579'832 male and female subjects at the age ≥18 years with a follow-up duration from 9 months to 30 years in the prospective cohort studies. The characteristics of the included studies are presented in Table S2 in supplementary material.

Metabolic syndrome (MetS)

Two meta-analyses [294, 295], both compiling data of prospective cohort studies and also of cross-sectional studies (separately evaluated), investigated the association of milk and dairy products consumption and MetS in male and female adults. Both found a significantly decreased (about 14%) relative risk of MetS incidence for the highest category of milk and dairy consumption compared to the lowest category based on the prospective cohort studies. There was no heterogeneity between studies and no evidence of publication bias. The inverse association between total dairy consumption and MetS was more pronounced in the separately compiled cross-sectional studies but those are of lower quality than prospective cohort studies [294, 295]. Also, evidence from cross-sectional studies suggests that milk and cheese, but not yoghurt, may decrease the incidence of metabolic MetS [294].

An additional small prospective cohort study in male and female adults reported a similar but non-significant inverse association between total dairy and MetS [296]. Two additional cross-sectional studies in Korea and Brazil also showed an inverse association between dairy and calcium intake, respectively, and MetS [297, 298].

Overall, the available studies suggest an inverse association between dairy intake and MetS but data is limited and the quality of the evidence is moderate [281].

Obesity

One meta-analysis [299] compiled data of prospective cohort studies in male and female adults that investigated the association of dairy products consumption with obesity and body weight changes. There was no significant association between servings of full-fat or low-fat dairy and annual body weight changes. However, an inverse association was observed between changes of body weight and each serving's increase of yoghurt and a positive association for each serving's increase of cheese. Additionally, the highest category of total dairy intake was significantly associated with a reduced risk of abdominal obesity and risk of overweight compared to the lowest intake [299]. Four meta-analyses [288, 300–302] compiled data of randomized controlled trials concerning the impact of dairy intake on body weight and body composition. Three of them suggest that an increased dairy intake may have a modest beneficial effect on body weight, fat mass and lean body mass when combined with an energy-reduced diet. No effect of dairy products intake was found when diet was not energy reduced [300–302]. The fourth meta-analysis reported a modest weight gain with increased intake of either whole or low-fat dairy food [288].

Several other randomized controlled trials [303–307] and one non-randomized controlled trial [308] showed no beneficial effect on body weight with an increased amount of dairy products in (energy restricted and energy non-restricted) diets. A cross sectional study in Ireland reported significantly lower BMI and body fat mass associated with higher total dairy consumption [309]. Another cross sectional study in Luxembourg indicated a significantly decreased risk of obesity associated with total dairy intake [310]. On the other hand, an Australian cross

sectional study found no association between total dairy intake and the risk of being overweight [311].

Overall, there is some evidence that increased dairy consumption has a modest beneficial effect on weight loss when combined with energy-restricted diets but results are not consistent. Epidemiologic studies suggest that total dairy intake is inversely associated with the risk of overweight (moderate evidence).

Type 2 diabetes (T2D)

Four meta-analyses [312–315] were published in the last 5 years that compiled data of prospective cohort studies with the aim to investigate the association of milk and dairy products consumption with incidence of T2D. Two of the meta-analyses [312, 314] found an inverse association between total dairy intake and the risk of T2D (about 11% risk reduction comparing highest vs. lowest intake), the other two [313, 315] reported no association although all were more or less based on the same studies. The meta-analyses indicate heterogeneity between the studies but no publication-bias. However, there is evidence that different dairy products may differ in their effect on T2D. Three of the meta-analyses [312, 314, 315] individually evaluated high-fat dairy, low-fat dairy, milk and cheese and all four meta-analyses separately evaluated yoghurt. No association with T2D risk was reported for high-fat dairy and milk intake. Two of the three meta-analyses found a significantly decreased risk associated with low-fat dairy products and with cheese intake (comparing highest vs. lowest consumption and also per serving) but not the third meta-analysis [315]. Yoghurt was inversely associated with T2D risk in all 4 meta-analyses (highest vs. lowest intake [312, 314], per serving of 244 g [313] or 80 g [315].

In one prospective cohort study, milk intake was not associated with the risk of T2D [316]. Three further prospective cohort studies investigated whether circulating blood biomarkers of dairy fat (15:0, 17:0, t16:1n-7) were associated with T2D incidence [317–319]. All studies reported significant inverse associations. Two cross-sectional studies comparing high with low dairy products intake reported a significantly inverse association for T2D risk [320, 321]and a third one associated plasma biomarkers for dairy fat intake with greater oral glucose tolerance and insulin sensitivity [322]. Finally, 3 randomized crossover studies are not consistent in their results regarding dairy intake and insulin sensitivity [323–325].

Overall, the available studies suggest with high to moderate quality that there is no association between high-fat dairy as well as milk and T2D. There is moderate evidence for an inverse association of total dairy, low-fat dairy and cheese with T2D and high-quality evidence that yoghurt is inversely associated with T2D risk [281]. Thus, a preventive effect on T2D depends on the dairy subtype with yoghurt showing a more consistent benefit than other types of dairy [326].

The following table summarizes the associations between dairy product intake and risk of disease based on the evaluated meta-analyses of prospective cohort studies and individual prospective cohort studies of the last 5 years.

Table 1 Summary of the association between dairy product intake and risk of cardiovascular and metabolic diseases based on meta-analyses of prospective cohort studies (adjusted from [281])

	CVD	CAD/ CHD	Stroke	MetS	T2D	Obesity
Total dairy	–	oo	–	–	–	–
Regular / high-fat dairy	o	oo	o	?	o	o
Low-fat dairy	–	oo	–	?	–	o
Milk	?	o	o	–	o	?
Cheese	oo	o	–	?	–	–
Yoghurt	o	o	o	?	– –	–
Fermented dairy	?	?	o	?	o	?

– / – –= decreased risk with increased dairy intake (moderate / high quality of evidence)
o / oo= no association with dairy intake (moderate / high quality of evidence)
+ / ++= increased risk with increased dairy intake (moderate / high quality of evidence)
?= uncertain association (very low quality of evidence or no evidence, inconsistent evidence)
The quality of evidence is based on the GRADE grading system [327].

6.2.4.4 Dairy and cancer

Twenty-three meta-analyses, observational studies or systematic and non-systematic reviews published in the last 5 years were included in the evaluation of the influence of milk and dairy products on cancer risk and cancer mortality. In absence of clinical trials, we had to concentrate on the meta-analysis combining the results of prospective cohort and case-control studies to assess the association of dairy and cancer. Colorectal, prostate, pancreatic, gastric, breast, lung, and ovarian cancer as well as total cancer mortality was the subject of one or more meta-analyses, whereas reviews also considered cancer of other organs like bladder, thyroid or kidney. The meta-analyses included over 200'000 up to over 2 Mio subjects at the age of 0 to > 100 years with a follow up duration from 1 to 68 years (for study characteristics see Table S3 in supplementary material). The risk was calculated for high vs. low dairy intake and/or a dose response evaluation. Obviously prostate cancer was only analysed in men and ovarian and breast cancer respectively only in women. The other cancer types always included both genders.

Colorectal cancer

Three meta-analyses and one systematic review summarized the evidence for colorectal cancer risk [328–331]. (Non-fermented) Milk and total dairy products were associated with a significant reduction in colon cancer risk (RR 0.83 (95% CI: 0.74–0.93)) resp. RR 0.81 (95% CI: 0.74–0.90)) whereas cheese (RR 0.96 (CI 0.83–1.12)) and other dairy products were not associated. No association was found for rectal cancer risk independent on the dairy product [328]. The results remain the same for high vs. low consumption and for dose response analysis. Ralston et al. [329] confirmed the finding of Aune et al. [328]and found no association for fermented dairy products and colorectal cancer and a significant inverse association between the intake of non-fermented dairy products and the risk of colorectal cancer. The influence of fat content is inconclusive. A separate gender analysis showed no association in women and an inverse association in men [329]. The review of Thorning et al. [330] concludes in the same direction as the meta-analysis concerning the inverse association of milk and dairy intake and colorectal cancer risk, but opposite to Ralston et al. [329] they found a more robust result in women but men. The results of Fardet and Boire [331] showed no association of regular/high consumption of milk and dairy products with colorectal cancer risk when all studies were included and an inverse association when only meta-analyses were included. The WCRF concluded 2017 in the continuous update project (CUP) report on colorectal cancer that an increased dairy product intake probably decreases colorectal cancer risk and that the evidence is consistent for total dairy, milk and cheese [258].

The quality of the included studies is moderate to good and the heterogeneity was low to moderate.

Prostate cancer

Two meta-analyses and one review evaluated dairy consumption and the risk of prostate cancer [331–333]). High intake of dairy products, total milk, low-fat milk, yoghurt and cheese may increase total prostate cancer risk. Whole milk was not associated [331, 332]. Diverging results for types of dairy products and sources of calcium suggest that other components of dairy rather than fat and calcium may increase prostate cancer risk. The CUP prostate cancer report of WHO published in 2014 concluded, that the evidence that a higher consumption of dairy products increases the risk of prostate cancer is limited [333]. The 2007 Second Expert Report of WHO rated the evidence that diets high in calcium increase risk of prostate cancer to be strong but this rating has been downgraded to limited evidence in the CUP prostate cancer report of 2014.

The quality of the included studies is moderate to good.

Pancreatic cancer

One meta- analysis and a review of meta-analyses conclude that there was no association between total milk intake and pancreatic cancer risk comparing high vs. low consumption. Similarly, intakes of low-fat milk, whole milk, cheese, cottage cheese and yoghurt were not associated with pancreatic cancer risk [330, 334].

The quality of the included studies is moderate to good.

Gastric cancer

Three meta-analyses and a review of meta-analyses conclude that milk consumption was not associated with gastric cancer risk independent of main or subgroup analysis [280, 331, 335, 336]. The results of prospective cohort studies, but not case-control studies, suggest that total dairy might be associated with a reduction of gastric cancer risk [280] but not strongly protective [331, 335]. Sun et al. [336] reported a non-significant increased risk of gastric cancer when high consumption of dairy products was compared to low consumption, but suggested to verify these results in future well-designed prospective studies, because significant heterogeneity of the case-control studies with a rather low quality score could bias the results. Further investigations should also verify, whether the effect of dairy product consumption varies by gastric cancer type.

Ovarian cancer

There is only one meta-analysis summarizing the results of 19 case-control studies suggesting that low-fat/skim milk, whole milk, yoghurt and lactose intake is not associated with increased risk of ovarian cancer [337]. A recent case-control study suggests that frequent intake of most types of dairy products and increasing intake of lactose is associated with a modest increased risk of ovarian cancer [338]. However, this is only one case-control study with 2100 subjects compared to 19 studies summarized in the meta-analysis of Liu et al. [337]. Also Thorning et al. [330] reported in their review no association between milk and dairy intake and ovarian cancer risk.

Breast cancer

High-level dairy consumption was associated with a significantly lower risk of breast cancer [339]. Modest dairy consumption (400–600 g/d) was associated with a mildly lower risk of breast cancer. A dose-response analysis revealed evidence of a linear relationship between dairy consumption and risk of breast cancer, especially for yoghurt. High milk consumption was not found to have a preventive effect on breast cancer compared to low milk consumption [339]. These results were confirmed by the reviews of Thorning et al. [330] and Fardet and

Boirie [331]. The WCRF concluded 2017 in the CUP report on breast cancer that there is limited evidence that dairy products intake decreases premenopausal breast cancer risk [340].

Lung cancer

The meta-analyses of Yang et al. and Yu et al. and the review of Thorning et al. [330, 341, 342] conclude that dairy product or calcium intake is not significantly associated with lung cancer risk. The quality of these studies was moderate to good.

Other cancers (bladder, kidney)

Meta-analyses reported either no or an inverse effect between milk and dairy consumption and risk of bladder cancer [330, 331] and no association with the risk of kidney cancer [331]. Because of the inconsistent results of the studies regarding bladder cancer, the evidence is inconclusive.

The following table summarizes the associations between dairy product consumption and risk of cancer based on the evaluated meta-analyses of prospective cohort studies and individual prospective cohort studies from the last five years.

Table 2 Summary of the association between dairy product consumption and risk of cancer

	Total dairy	Milk	Yoghurt	Cheese
Colorectal cancer	– –	– –	o	–
Prostate cancer	+	+	+	+
Lung cancer	o	o	o	o
Breast cancer	–	o	–	?
Pancreatic cancer	o	o	o	o
Gastric cancer	?	o	?	?
Ovarian cancer	o	o	o	o
Bladder cancer	?	?	?	?
Kidney cancer	o	o	?	?

– / – –= decreased risk with increased dairy intake (moderate / high quality of evidence)
o / oo= no association with dairy intake (moderate / high quality of evidence)
+ / ++= increased risk with increased dairy intake (moderate / high quality of evidence)
?= uncertain association (very low quality of evidence, no evidence, inconsistent evidence)
The quality of evidence is based on the GRADE grading system [327].

6.2.4.5 Mortality

Recently, a Swedish cohort study reported higher all-cause mortality associated with intakes of non-fermented milk and butter but lower all-cause mortality associated with fermented milk and cheese intake [343]. However, previous meta-analyses were not able to show a consistent association between non-fermented or fermented milk consumption and mortality (cancer, CVD and all causes) [274, 344]. Larsson et al. [344] pointed out that there is substantial heterogeneity among the studies probably due to large variations in the range of milk consumption and types of milk/ dairy included as well as differences in the incorporated potential confounders. The most recent meta-analyses observed no association for high compared to low intake and for each additional serving of 200 g of dairy products with all-cause mortality but also reported significant heterogeneity between the 27 included studies [172]. Subgroup analysis showed no difference between low-fat and high-fat dairy products.

6.2.5 Discussion

Overall, there is no evidence that increased intake of milk and dairy products is detrimental to health. The only exception is a positive association between dairy products and risk of prostate cancer but with limited evidence. The assembled studies indicate no association between total dairy consumption and risk of CVD, CHD and most cancer and inverse associations between total dairy intake and risk of stroke, MetS, T2D, overweight and colorectal and breast cancer. For the main dairy product categories, there is moderate evidence that a high milk consumption is inversely associated with the risk of hypertension, MetS, colorectal cancer and T2D. An increased cheese intake is inversely associated with the risk of stroke and T2D, and there is moderate to high evidence that yoghurt consumption is inversely associated with the risk of T2D and breast cancer.

The French ANSES also states in a scientific report published end of 2016 [252] that dairy products probably decrease the risk of T2D (especially yoghurt, cheese and low-fat dairy products) and of colon cancer and may as well reduce the risk of CVD. Limited evidence suggests they may be associated with an increased risk of prostate cancer [252].

The committee for the Dutch dietary guidelines 2015 [42] also concludes that the consumption of milk and dairy products is associated with a lower risk of colorectal cancer and yoghurt intake with a lower risk of type 2 diabetes. They did not find enough evidence to differentiate between low-fat and high-fat dairy products [42].

The German Max Rubner-Institut, Federal Research Institute of Nutrition and Food, further assessed the available evidence regarding milk and dairy products consumption and health and came to similar results: epidemiologic studies suggest that the usual intake of milk and dairy products is either not associated with disease risk, or is associated with decrease risk (e.g. CVD, hypertension, type 2 diabetes), with the exception of prostate cancer [345].

Finally, in 2016, Mozaffarian published dietary priorities for cardiometabolic health based on an extensive literature review [346]. Among other things he recommends to consume more dairy products (2-3 servings/d), especially yoghurt and possibly cheese [346]. He states that dairy products are a diverse class of foods with complex effects that vary between specific product types. Long-term studies do not indicate any harmful effects in regard to cardiovascular disease, type 2 diabetes and obesity but suggest potential benefits of dairy fat or high-fat dairy foods such as cheese [346].

Dietary recommendations in some countries limit dairy consumption to low-fat or fat-reduced dairy products because regular-fat dairy products are rich in cholesterol-raising saturated fatty acids and provide more energy than low-fat products. However, evidence for this statement is rather low as RCTs have reported mixed effects of reduced- and regular-fat dairy intake on blood lipids [347]. The studies evaluated in this report indicated no association between regular- or high-fat dairy intake and the investigated NCD. Specifically, meta-analyses were not able to show associations between increased CVD risk and the consumption of dairy products with regular-/high-fat content. Furthermore, whole-fat dairy intake is not associated with overweight/obesity, studies suggest rather the inverse. However, there is moderate evidence that low-fat dairy products are inversely associated with the risk of stroke, hypertension and type 2 diabetes. On the other hand, a subgroup analysis suggests an increased prostate cancer risk for low-fat milk but not whole milk [332]. In regard to all-cause mortality, no difference between low-fat and high-fat dairy products was observed [172]. Neither the committee Dutch dietary guidelines [42] nor Mozaffarian [346] found evidence to support recommendations to emphasize low-fat dairy. The latter recommends to leave the choice between low-fat vs. whole-fat to personal preference. However, this should be considered in the context of total fat resp. energy consumption.

Most of the available information is based on prospective cohort studies. Although epidemiological studies are valuable, they mainly indicate associations but cannot prove causality. The quality of the presented epidemiologic studies varies. Risk associations are usually multivariable-adjusted. However, it is not impossible that the rather weak associations found may be due to residual confounding. Meta-analyses of prospective cohort studies provide more precision but do not increase the validity of a finding as this stands and falls with the quality of the included studies [348]. Furthermore, as mentioned in the introduction, observational studies in particular must be critically assessed, as they often do not distinguish between sweetened / unsweetened or processed /unprocessed milk products.

A large amount of literature is available on fermented foods in health and disease prevention, in particular in regard to dairy products [349]. This literature is characterized by a wealth of data on bioactive components of fermented foods, including metabolites and bacteria, which might beneficially contribute to a large range of physiological properties. However, this data is not mirrored by the results of the meta-analyses presented in this report. This discrepancy can be explained by a range of factors, including the complexity of the investigated food-health interactions, the quality of the studies, and the real magnitude of the health benefits offered by these products. Further research should specifically integrate the impact of fermentation on risk factors in their study design, including the statistical approach. Such an approach may provide better indication of the impact of fermented foods on health.

The assessed meta-analyses often document rather large heterogeneity. This is probably due to diverging and over the years changing consumption patterns in regard to dairy products as there is an extensive choice (various types of milk, cheese and yoghurt and other dairy products such as e.g. butter milk, kefir, curd, ice cream). Large-scale intervention studies and randomized clinical trials are required to determine beneficial effects of the various types of dairy products.

6.2.6 Conclusion and recommendations

The current Swiss recommendations regarding dairy products, i.e. the consumption of three portions each day, are reasonable based on currently available information and scientific evidence. Recommendations should not emphasize reduced-fat dairy products since there is no evidence indicating that whole-fat products are detrimental to health. We suggest to add a recommendation to diversify the consumption of dairy products, keeping in mind the overall energy, fat and sugar intakes, with emphasis on smaller portions for high-fat resp. sugar-sweetened dairy products.

6.3 Plant protein and legumes (pulses)

Author: Sabine Rohrmann

6.3.1 Definitions

Legumes can be considered a subcategory of vegetables. This group belongs to the fabaceae family and encompasses beans, lentils, peas, chickpeas, soybeans, and peanuts, but also alfalfa, clover and lupin beans. From a nutritional point of view, several distinctions are important.

The term “pulses” refers to crops harvested for the ripe dry seed. Pulses are rich in protein, dietary fiber, and carbohydrates (e.g. “resistant starch”), and they are also important sources of certain minerals (e.g. iron, zinc, and potassium) and vitamins, in particular B-vitamins such as folate [350]. Ripe peanuts are however often studied together with nuts, and are discussed in chapter 7.2. Unripe legumes such as green peas and green beans do not belong into this group, but are rather considered vegetables, due to a nutritional composition more consistent with vegetables, however due to their more elevated content of anti-nutritive components (e.g. protease inhibitors, lectins), they should be cooked before consumption.

Legumes are abundant in the essential amino acids lysine and threonine, which are typically low in other plant-based protein sources, but low in other amino acids, including methionine, tryptophan, and cysteine (see [351]). Because of the latter, legumes are often considered to be of lower protein quality. However, if consumed in conjunction with other plant-based and/or animal protein sources that contain the limiting essential amino acids they contribute to a diet containing a high-quality protein mixture.

Soy and soy products such as tofu are traditionally consumed in many Asian societies but are more and more frequently used and consumed in Western societies, because of increasing vegetarian or vegan eating habits.

As for legumes mentioned above, plant protein in general has a lower concentration of some essential amino acids. However, the combination of different food groups increases the protein quality. For example, the combination of cereals with legumes, milk with potatoes, or egg with cereal products leads to a good protein quality.

Recommendations and intake data

Plant proteins do not form a specific food group, but can be found in numerous foods, some of which are also described in other chapters. Based on an NHANES analysis of 2007-2010, overall protein intake of US adults (mean ± SE) was 82.3 ± 0.8 g/day (98.6 ± 1.1 g/day for men and 67.0 ± 0.7 g/day for women). Plant protein accounted for 30% of total protein intake (28% in men, 32% in women) [352]. Thirty-one food categories contributed at least 1% plant protein intake and together provided almost 73% of plant protein in the diet. Yeast breads and rolls/buns were the top two plant protein food categories, providing nearly 18% of total plant protein intake, 6% total protein and total energy intake; bean, peas and legumes were fifth most important food group for plant proteins providing 2.9% of plant protein and 1.3% of total protein intake. In an analysis of a non-representative US cohort study, major food contributors to plant protein included bread, cereals, pasta, nuts, beans, and legumes [353].

In the Swiss food pyramid, legumes are categorized into the "Cereals" group, and it is recommended to consume 3 portions of this group per day: 75–125 g bread/pastry (preferably whole grain products), or 60–100 g legumes/pulses (dry weight), or 180–300 g potatoes, or 45–75 g crisp bread/whole-grain crackers/flakes/flour/pasta/rice/corn/other grains (dry weight).

With respect to protein intake, SGE currently recommends 1 serving of a protein-rich food per day (meat, poultry, fish, eggs, tofu, *quorn*, *seitan*, cheese or cottage cheese; in addition to three portions of dairy foods per day). No specific recommendations with respect to consumption of plant protein is given besides the recommendation that consumers should switch between different protein sources, which are, with the exception of *tofu, quorn and seitan* solely animal foods.

Summary box: current recommendations and estimated levels of intake in the Swiss population

	Definition	Quantity
Daily recommendations current Swiss Food Pyramid [2]	Food level: Cereals, potatoes **legumes** Milk products, meat, fish, egg, **tofu, seitan, quorn**	3 portions of this group per day (e.g. 1 portion corresponds to 60-100 g legumes) 1 portion (100-120 g) of protein rich food source per day
Other recommendations [271] Optimal level of intake (optimal range of intake)	Legumes	60 g per day (50-70 g)
Daily Intake in Switzerland [3]* Total / male / female	Legumes	5 g / 4.1 g / 5.9 g

*Data are mean values of two 24-hour recalls protocols, weighted and corrected for seasonality and weekdays.

6.3.2 Review of the literature -legumes

Cardiovascular diseases (CVD)

Fourteen studies conducted on eleven cohorts and accounting for a total of 367'000 individuals and 18'475 cases of CVD (7451 CHD and 6336 stroke cases) were considered in a large meta-analysis [354]. Compared with lower legume consumption, the highest intake was associated with a decreased risk of 10% in both CVD and CHD (relative risk [RR]: 0.90; 95% confidence interval [CI] 0.84-0.97) with no or little evidence of heterogeneity and no publication bias. Null results were observed regarding legume consumption and stroke risk. No substantial confounding factors were evident in stratified analyses. This confirms results of a meta-analysis by Afshin et al. [355].

Cancer

A recent WCRF/AICR systematic review concluded that the intake of legumes was not associated with colorectal cancer risk [194]. A meta-analysis by Zhu et al. observed an inverse association between legumes consumption and risk of total colorectal cancer, but not for colon or rectal cancer separately [356]. In addition, the inverse association was only observed in Asian, but not European or US studies.

In a review, DGE concluded that there was no association between soy consumption and risk of breast cancer, colorectal cancer, stomach cancer, or cancers of the gastrointestinal tract [357]. Two meta-analyses on bladder cancer revealed conflicting results (one inverse, one null), and two of three meta-analysis on the association of soy consumption with lung cancer observed inverse associations whereas one reported no association. There is, however, some indication that effect on cancer risk might differ between Asian and Western populations: Dong et al. [358] reported in their meta-analysis that protective effect of soy was only observed among studies conducted in Asian (RR: 0.76, 95% CI: 0.65-0.86) but not in Western populations (RR: 0.97, 95% CI 0.87-1.06). This finding may be due to (a) different amount of soy consumption between Asian and Western populations, (b) lifelong or early life exposure to soy in Asian populations, and (c) the higher ability of Asian populations to produce equol, which has a higher antioxidant activity than other isoflavones, from daizdzein than Western populations [358].

Body weight

In a meta-analysis that included 21 trials with 940 participants observed that diets containing dietary pulses (median intake of 132 g/d or ~1 serving/d) were associated with a significant weight reduction of -0.34 kg (95% CI: -0.63, -0.04 kg; P = 0.03) compared with diets without a dietary pulse intervention over a median duration of 6 wk. Interestingly, a statistically significant weight loss was observed in matched negative-energy-balance (weight loss) diets (P = 0.02) as well as in neutral-energy-balance (weight-maintaining) diets (P = 0.03). Heterogeneity between the studies was rather small, which allows for the conclusion that including dietary pulses in a diet may be a beneficial weight-loss strategy [359].

Type 2 Diabetes

A meta-analysis that included two studies did not observe a statistically significant association between legumes consumption and risk of type 2 diabetes [355]. A more recent one, by Schwingshackl et al. [184] included 12 studies with 26,778 type-2 diabetes cases , but came to the same conclusion: There was no statistically significant association for the highest versus lowest legume intake category (RR: 0.96; 95% CI 0.87–1.05, I2 = 85%) and for each additional daily 50 g (RR: 1.00; 95% CI 0.92–1.09, I2 = 87%, n = 12 studies).

Mortality

A recent meta-analysis that included seventeen studies with 53,085 deaths compared high with low intake of legumes (overall intake range: 6-166 g/d) [172]. An inverse association was

observed for the highest compared with lowest legume intake categories (RR: 0.96; 95% CI 0.93-1.00; I2 = 48%; P-heterogeneity = 0.01), but not for each additional daily 50 g (RR: 0.96; 95% CI 0.90-1.01; I2 = 48%; P-heterogeneity = 0.09; n = 6). Interestingly, they observed an inverse association for studies conducted in Asia and Australia, and studies with long-term follow-up.

6.3.3 Review of the literature - Plant protein

Plant protein in general has less frequently been studied than consumption of legumes with respect to the risk of chronic diseases.

Body weight

Protein quality has long been thought to be particularly important for children and adolescents, and animal protein has been favored because of its higher nutritional value. In the HELENA study, a cross-sectional study of 1804 randomly selected adolescents aged 12.5-17.5 years, absolute plant protein intake was inversely associated with BMI z-scores and percent body fat such that the authors concluded that plant protein intakes may play a role in preventing obesity among European adolescents [360].

Type 2 diabetes

In the EPIC-Interact study, which included more than 12,000 type 2 diabetes cases, the incidence of type 2 diabetes was higher in participants with high intake of total protein (Hazard Ratio [HR]: 1.06 per 10 g; 95% CI 1.02-1.09, P(trend) < 0.001) and animal protein (HR: 1.05 per 10 g; 95% CI 1.02-1.08, P(trend) = 0.001) [361]. Plant protein intake was not associated with type 2 diabetes (HR: 1.04 per 10 g; 95% CI 0.93-1.16, P(trend) = 0.098). In a meta-analysis of 11 prospective studies, pooled RRs for the comparison of the highest with lowest categories of total, animal, and plant protein intakes were 1.09 (95% CI 1.06-1.13), 1.19 (95% CI 1.11-1.28), and 0.95 (95% CI 0.89-1.02), respectively [362]. Associations between animal protein intake and type 2 diabetes were similar across sex, geographic region, length of follow-up, study quality, and method of expressing protein intake. An inverse association between plant protein intake and type 2 diabetes was observed in women (RR: 0.93; 95% CI 0.85, 1.00) and in US populations (RR: 0.91; 95% CI 0.84-0.97).

In a meta-analysis of randomized clinical trials conducted among patients with type 2 diabetes, diets emphasizing a replacement of animal with plant protein at a median level of about 35% of total protein per day lowered HbA1c (mean difference = -0.15%; 95%-CI -0.26, -0.05%; 9 trials), fasting glucose (mean difference = -0.53 mmol/L; 95%-CI -0.92, -0.13 mmol/L; 10 trials) and fasting insulin concentrations (mean difference = -10.09 pmol/L; 95%-CI -17.31, -2.86 pmol/L; 5 trials) compared with control arms [363]. Overall, the results indicate that replacing sources of animal with plant protein leads to modest improvements in glycemic control in individuals with type 2 diabetes.

All-cause mortality

In an analysis of the Nurses' Health Study and the Health Professionals Follow-up Study, consumption of plant protein by participants with at least 1 unhealthy lifestyle factor (smoking, heavy alcohol intake, overweight or obesity, and physical inactivity) was associated with lower all-cause mortality (HR: 0.90 per 3% energy increment; 95%CI 0.86-0.95) and cardiovascular mortality (HR: 0.88 per 3% energy increment; 95% CI 0.80-0.97) [353]. No statistically significant associations were seen in participants without unhealthy lifestyle factors. Replacing animal protein of various origins with plant protein was associated with lower mortality. In particular, the HRs for all-cause mortality were 0.66 (95% CI 0.59-0.75) when 3%of energy from plant protein was substituted for an equivalent amount of protein from processed red meat, 0.88 (95% CI 0.84-0.92) from unprocessed red meat, and 0.81 (95% CI 0.75-0.88) from egg.

In an analysis of an observational study among diabetics, substitution of carbohydrates with plant protein was associated with lower all-cause mortality risk (HR: 0.79 [95% CI 0.64-0.97]),

whereas substitution with total or animal protein was not associated with (CVD) mortality risk [364].

6.3.4 Discussion and research gap

Legumes are an important source of plant protein, in particular in combination with other foods. Based on current evidence, there is some indication that consumption of legumes decreases the risk of some chronic diseases (coronary heart disease, lung cancer [soy products]), but results are sometimes inconsistent. For example, the inverse association between soy consumption and breast cancer risk appears to be confined to Asian women.

An emerging research gap is the effect of Western-type soybean processing technologies and the subsequent isoflavone content, which could be higher than the traditional Eastern soaking processes [365]. Isoflavones at high intakes could have an endocrine disruptive effect.

With respect to consumption of plant protein, intervention studies point towards a protective effect via glycemic control. Substituting animal with plant protein has shown some benefit with respect to mortality. However, the number of studies so far is limited.

Although most epidemiological studies looking at health effects of legume consumption or plant protein intake make an effort to control for confounding and try to elucidate the mechanisms of their health effects, it currently appears to be unclear whether the effects of legumes (and partly also plant protein) are due to specific components such as isoflavones, protein, resistant starch, or fibers.

6.3.5 Recommendation

Based on the results, legumes should be given more weight in the pyramid. The positioning of legumes in starchy foods is very questionable also due to their main ingredients. Pulses (ripe dry seed) should be a component of protein-rich foods in the Swiss food pyramid, where currently only tofu is mentioned. This should be modified, listing pulses and then possible pulse-derived products such as tofu, tempeh, etc.). Unripe products such as green peas and green beans should be clearly listed in the food group “fruit and vegetables”.

Other plant-protein based products, in particular some ready-to-cook meat analogues, which are sometimes rich in salt and saturated fatty acids, are highly processed, and as will be mentioned in chapter 8, this type of products has not yet been sufficiently investigated, currently there is no evidence which supports their recommendation.

Furthermore, "quorn", which is a trade name for a specific commercial product, should not be mentioned in the recommendations, especially as there are no specific studies on this subject and many similar products are currently being sold.

7 Fat-containing food

7.1 Oils and fats

Author: Ulrich Keller

7.1.1 Definition and scope

In an average diet, fats and oils cover approximately one third of total energy requirements and are the most energy-dense nutrients. Due to the increase in prevalence of nutrition-related chronic diseases such as obesity, cardiovascular diseases and type 2 diabetes, the role of fats and oils in the etiology, prevention and therapy of such diseases is of particular interest. Not only the total intake but also the fatty acid composition is of great interest specifically in relation to atherosclerotic diseases.

Dietary fats and oils are present in visible form or they are contained in composite, processed food products (“hidden fat”). Solid fats at room temperature are mostly of animal origin (exceptions are e.g. cocoa and coconut fat), and liquid oils at room temperature are usually of plant origin (exceptions are e.g. fish oils). Dietary fats and oils contain fatty acids of various chain lengths and degrees of saturation which exert different effects on the risk of non-communicable diseases.

The main focus of this review is to summarize epidemiological evidence on the association between consumption of certain fats and oils (defined by their fatty acid composition) and health outcomes. Earlier studies reported on the relationship between fat and oil consumption and biomarkers such as serum lipids (see e.g. meta-analysis be Mensink et al [366]. This led to the “Diet Heart” hypothesis, which placed a major emphasis on the relationship between dietary fats, particularly saturated fats, serum lipids and cardiovascular disease. However, due to the complexity of the relationship between lipoproteins and coronary disease and the increasingly recognized role of non-lipid factors, recent studies focus on hard end-points such as cardiovascular morbidity and mortality, rather than blood lipid profiles [367].

Furthermore, current dietary guidelines are shifting towards food group recommendations, rather than indicating recommended intakes for specific nutrients, i.e. specific fatty acids intakes [42, 106, 346]. The reason for this is that health effects of certain nutrients depend on the type of food in which they are contained, due to the texture of the food and to other food components [172, 368, 369]. Examples: Identical quantities of saturated fatty acids in butter or cheese may have slightly different effects on serum lipids [370]. In addition, fermented dairy products have different health effects compared to unfermented products [371] even with an identical content of macronutrients. Nevertheless, the present survey focusses on fats and oils as they are defined by their biochemical composition. The reason for this is the fact that the currently available epidemiological literature was largely based on this aspect. Frequently consumed fats and oils in Switzerland are discussed, if possible.

7.1.2 Recommendations and intake data

The Swiss Federal Commission on Nutrition has issued recommendations on the consumption of fats and oils in 1992 and in 2006 [372]. In 2012 the latter recommendations have been updated and revised [373].

Summary box: present recommendations and estimated levels of intake in the Swiss population

FAT		
Daily recommendations according to the current Swiss Food Guide Pyramid[2]	2-3 tablespoons (20-30 g) of vegetable oil per day, at least half in form of rapeseed oil. In addition, butter, margarine, cream etc. can be used sparingly (approx. 1 tbsp = 10 g per day).	
Other recommendations [271] Federal commission on nutrition (2012)[373] , is based on Percentage of daily energy requirement / Amount with energy intake of 2000 kcal	Total fat Saturated fatty acid Monounsaturated fatty acid Polyunsaturated fatty acid n-6 fatty acids n-3 fatty acids EPA + DHA DHA during pregnancy & lactation Trans fatty acids	20-35% (max 40%) / 45-80 g** <10% / <20 g 10-15% (max 20%) / 20-35 g 2.5-9% / 5.5-20 g 0.5-2% / 1-4.4 g 500 mg min. 200 mg as small quantities as possible
Daily Intake in Switzerland* [3] Total / male / female	Vegetable oils Fat**	13.6 g / 14 g / 13.3 g 39 g / 44.4 g / 34.6 g

* Data are mean values of two 24-hour recalls protocols, weighted and corrected for seasonality and weekdays.

**For example: butter, margarine, cream, coconut fat, animal fats, mayonnaise

An analysis of the per capita fat consumption in Switzerland 2016 shows that the major fat sources are in decreasing order of per capita consumption): 1. sunflower oil; 2. butter; 3. rapeseed (canola) oil; 4. palm oil; 5. other and undefined plant fats and oils; 6. olive oil; and 7. other animal fats [374].

7.1.3 Mechanisms

Dietary fats are more energy-dense than other energy-providing foods. The different fatty acids in fats and oils determine their physical properties (melting point or fluidity of cell membranes), chemical behaviour (e.g. process of chemical reactions) and their biological functions. They exert different effects on plasma lipoprotein concentrations and are precursors of eicosanoids (metabolites of n-3 and n-6 fatty acids). Dietary fats are also sources of fat-soluble vitamins and of flavouring agents. Vegetable oils such as extra virgin olive oil also contain phenolic compounds which may have anti-inflammatory properties [375].

7.1.4 Review of the literature

In this paragraph, results of major meta-analysis are described. Further review papers and articles are mentioned in the annexes, as well as in the graph below.

Review of meta-analyses of the relationship between dietary fats and oils and coronary heart disease, stroke, and type 2 diabetes published between 2006 and 2014 (publication by Mozaffarian et al. in 2016 [346])

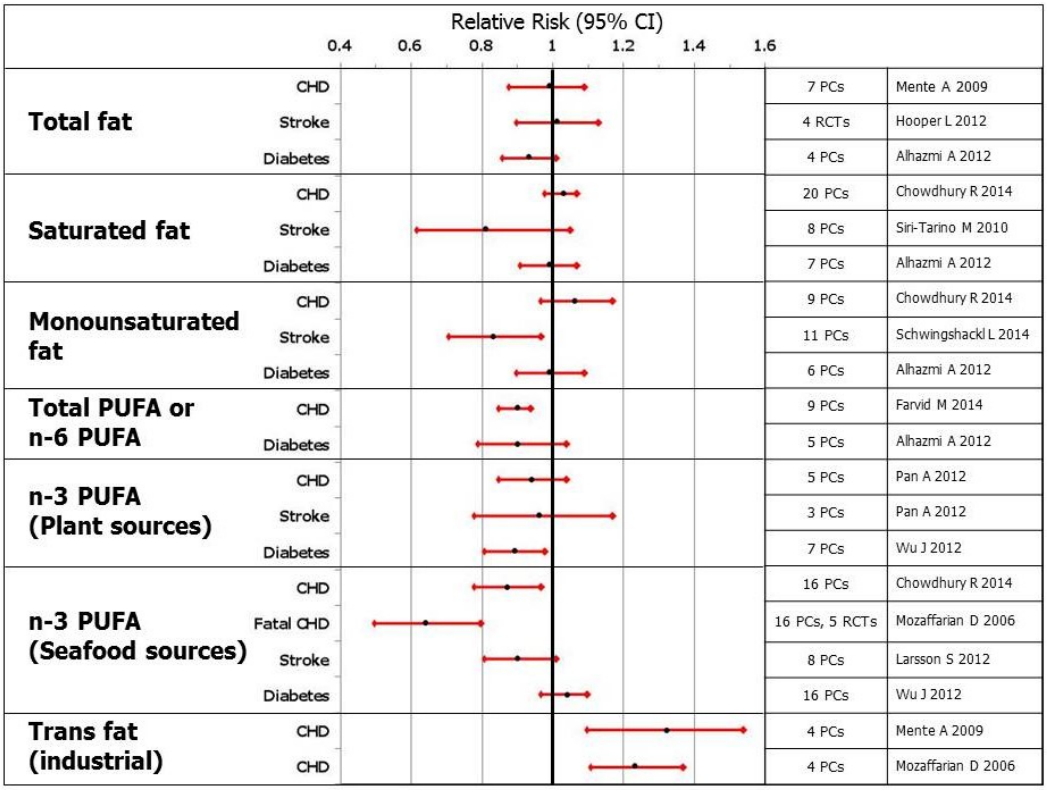

Figure 2 shows the relative risks with 95% confidence intervals for major health outcomes during high versus low consumption of specific fats (redrawn from Fig. 7 in [172]).

The citations in the figure are: Mente A 2009 [376], Hooper L 2012 [377], Alhazmi A 2012 [378], Chowdhury R 2014 [379], Siri-Tarino M 2010 [380], Schwingshackl L 2014 [381], Farvid M 2014 [382], Pan A 2012 [383], Wu J 2012 [384], Mozaffarian D 2006 (1) [385], Larsson S 2012 [386], Mozaffarian D 2006 (2) [387].

Conclusions from this review of meta-analyses: Total fat and saturated fat is not clearly associated with CHD, stroke and type 2 diabetes, Monounsaturated fats appear to be protective for stroke. Total or n-6 PUFA are associated with diminished CHD events. Plant-based n-3 PUFA are shown to be protective for type 2 diabetes, however, inspection of reference Wu J et al. [384] shows that the decrease of type 2 diabetes risk was not statistically significant. Seafood-derived n-3 PUFA are associated with a reduction of CHD risk, and they reduce the risk of CHD death. The most –statistically significant association is that of industrial trans-fats with an increase of CHD risk.

Dietary fat or fatty acid intake in relation to cardiovascular disease (CVD) and stroke. Results of meta-analyses published between 2012 and 2017 (see Annex Table S1) [377, 379, 381, 382, 388–405]

Consumption of total fat and saturated fat (in % of energy intake) is not clearly associated with cardiovascular morbidity and mortality. A small but potentially important benefit regarding cardiovascular risk results from the (total/partial) replacement of saturated fat with polyunsaturated fat. This benefit has however not been observed in patients with diagnosed CVD. Consumption of the PUFA linoleic acid has been associated with reduced cardiovascular morbidity and mortality; however, there is insufficient evidence to prioritize a specific type of unsaturated fat when replacing saturated fats. Seafood-derived PUFA (n-3) supplements have been shown to diminish cardiovascular and total mortality in cardiovascular high-risk patients. Consumption of industrial trans-fatty acids has been associated with increased cardiovascular morbidity and mortality and total mortality. Regarding stroke risk, higher consumption of MUFA (particularly olive oil) has been associated with diminished risk. There is evidence from cohort studies that consumption of long-chain n-3 PUFAs is associated with diminished stroke risk, however, RCTs with long-chain n-3 PUFAs are inconclusive.

Dietary fat or fatty acid intake in relation to type 2 diabetes and obesity. Results of meta-analyses published between 2012 and 2017 (see Annex Table S2) [282, 378, 384, 392, 406–421]

Consumption of total fat or saturated fat intake has not been clearly associated with type 2 diabetes risk. Increased consumption of MUFA, olive oil and in some instances of n-6 PUFA have been associated with diminished type 2 diabetes risk, and with improved metabolic control in patients with established type 2 diabetes when carbohydrates were replaced by MUFA. Regarding high versus low consumption of plant-derived n-3 PUFA, some studies suggested a diminished risk of developing type 2 diabetes and decreased insulin resistance but the findings were not consistent. Seafood-derived n-3- PUFA have not been shown to reduce type 2 diabetes risk (in Western populations). Regarding overweight and obesity, lowering the proportion of fat in the diet resulted in a small but noticeable decrease of body weight. When fat reduction was compared to carbohydrate reduction in weight loss trials, the latter was somewhat more efficacious to reduce weight than the former.

Dietary fat or fatty acid intake in relation to certain types of cancer. Results of meta-analyses published between 2012 and 2017 (see Annex Table S3) [422–426]

High intake of total fat and of SFA was associated with increased risk of cancer of breast, endometrium and stomach in some but not all observational studies.

Dietary fat or fatty acid intake in relation to other endpoints (neurologic, psychiatric). Results of meta-analyses published between 2012 and 2017 (see Annex Table S4) [427–430]

Observational studies suggest that long-chain n-3 fatty acids are associated with diminished incidence of cognitive impairment in elderly subjects, decreased risk of dementia and decreased risk of severe depression. Randomised controlled trials confirmed an improvement of cognition only in subjects, which were n-3 PUFA deficient.

Recent important publications

Authors	Conclusions of the authors	Comments
Dehghan M et al 2017 [431]	This study showed that across 18 countries from 5 continents increased fats are not associated with higher cardiovascular disease or mortality.	There was a large socio-demographic and economic heterogeneity between these 18 countries with widely discrepant rates of total mortality. Therefore, there is a high likelihood of residual confounders.
May-Wilson S, Sud A, Law PJ, Palin K, Tuupanen S, Gylfe A, et al. 2017 [432]	Colorectal cancer (CRC) risk reduction was observed in association with serum MUFAs und with PUFA (linoleic) concentrations; increased risk was observed with serum PUFA (arachidonic acid) and SFA (stearic acid). Thus, a proinflammatory serum fatty acid profile was associated with increased colon cancer risk.	
Guasch-Ferre M et al. 2015 [433]	Intakes of MUFAs and PUFAs in this study (PREDIMED) were associated with a lower risk of CVD and death, whereas SFA and trans-fat intakes were associated with a higher risk of CVD. The replacement of SFAs with MUFAs and PUFAs or of trans fat with MUFAs was inversely associated with CVD.	
Ramsden CE et al. 2016[434]	Available evidence from randomized controlled trials shows that replacement of saturated fat in the diet with linoleic acid effectively lowers serum cholesterol but does not support the hypothesis that this translates to a lower risk of death from coronary heart disease or all causes. Findings from the Minnesota Coronary Experiment add to growing evidence that incomplete publication has contributed to overestimation of the benefits of replacing saturated fat with vegetable oils rich in linoleic acid.	
Wang DD et al. 2016 [435]	Different types of dietary fats have divergent associations with total and cause-specific mortality. These findings support current dietary recommendations to replace saturated fat and trans-fat with unsaturated fats.	
Wu JH et al. 2014 [436]	The findings suggest that circulating levels of LA, the major dietary n-6 PUFA, is related to lower total mortality and especially subtypes of CVD mortality in older adults. Other circulating n-6 PUFA, including AA, were not significantly associated with total or CVD mortality.	

7.1.5 Conclusion

7.1.5.1 Discussion and research gap about fatty acids

Cardiovascular disease: Total fat and saturated fat (in % of energy intake) are not clearly associated with cardiovascular morbidity and mortality. A small but potentially important benefit regarding cardiovascular risk results from the replacement of saturated fat with polyunsaturated fat. This benefit is not observed in patients with established CVD. Consumption of

n-6 PUFAs is associated with reduced cardiovascular morbidity and mortality. There is insufficient evidence to prioritize a specific type of unsaturated fats replacing other macronutrients such as saturated fats or starchy or sugary foods. Seafood-derived n-3 PUFA supplements have been shown to diminish cardiovascular and total mortality in cardiovascular high-risk patients. Industrial trans fatty acids have been associated with increased cardiovascular morbidity and mortality and total mortality.

Type 2 diabetes: Total fat or saturated fat intake have not been clearly associated with increased risk. Increased consumption of MUFA, olive oil and in some instances of PUFA have been associated with diminished type 2 diabetes risk, and with improved metabolic control in patients with established type 2 diabetes when carbohydrates were replaced by MUFA.

Overweight and obesity: Lowering the proportion of fat in the diet resulted in a small but noticeable decrease of body weight. When fat reduction was compared to carbohydrate reduction in weight loss diets, the latter was somewhat more efficacious to reduce weight than the former.

Cancer: High intake of total fat and of SFA has been associated with increased risk of cancer of breast, endometrium and stomach in some but not all observational studies.

Cognitive impairment, dementia and depression: Observational studies suggest that long-chain n-3 fatty acids are associated with diminished incidence of cognitive impairment in elderly subjects, decreased risk of dementia and decreased risk of severe depression.

7.1.5.2 Transfer of results to fats and oils

Fats and oils which are consumed with the daily diet consist of a mixture of different fatty acids. For example: Animal fats consist predominantly of saturated fatty acids, but they also contain different quantities of MUFAs. On the other hand, vegetable fats/oil may vary considerably in their composition of MUFA, n-3 and n-6 fatty acids, and some of them like palm oil or coconut oil have also high proportions of SFA. In addition, there are other ingredients like polyphenols or antioxidants that can occur in different quantities and can also have an influence on the diseases discussed. This makes it almost impossible to transfer or quantify the results to specific fats/oils. Studies on fats and oils with endpoints such as CV morbidity and mortality are rarely available.

On the basis of the results, however, the following recommendations can be derived concerning cardiovascular health: The quantity of fat intake is probably less important than quality. The quality of fat consumption can be improved by replacing a high proportion of SFA (e.g. butter, lard) by fats with a high proportion of unsaturated fatty acids like plant oils. According to current evidence, it is not necessary to give preference to certain plant oils and fats.

The evidence for recommending specific tropical oils, in particular coconut oil, is still vary scarce. On the contrary, a meta-analysis studying the association of coconut oil and blood lipids in interventional studies showed a slight increase of LDLs [437]. In order to be able to derive more specific recommendations, long-term studies, including a better distinction between refined and unrefined coconut oils and fats are needed.

7.1.6 Recommendation

Specific issues of the *yellow level (fats, oils and nuts*) incl. the explanatory text („Oils, fats and nuts: Daily 2-3 large spoons (20-30 g) vegetable oil; thereof at least half as canola (rapeseed) oil. In addition, use sparingly butter, margarine and cream (approx... 1 spoon= 10 g per day)) *of the current Swiss Food Pyramid* require discussion and revision according to the present literature survey:

- It is not appropriate to display vegetable oils and butter as equivalents, since recommendations for their intake differ. It is recommended to emphasize that the consumption of vegetable oils should be increased.
- The literature search failed to provide a scientific basis to recommend specifically canola (rapeseed) oil, rather than other vegetable oils, such as sunflower, safflower or olive oil. This conclusion is supported also by the evidence derived from Mediterranean diets (PREDIMED study [160].
- The canola oil recommendation has historic origins. Nowadays a variety of fats and oils are available on the market and the recommendations should place more emphasis on a selection of oils to cover all fatty acid needs. Equivalent oils (regarding fatty acid composition) should be treated equally regarding potential health benefits.
- The specific role of nuts in the recommendations is considered separately (chapter 7.2).

7.2 Nuts

Author: David Faeh

7.2.1 Definition of nuts

A nut is a fruit composed of a shell and a seed. However, nuts in the culinary sense are botanically very heterogeneous. For example, almonds, pecans, pistachios, walnuts, and Brazil nuts, are not nuts in a botanical sense. Also, peanuts belong botanically to the legumes. In this report, "nuts" are defined according to their culinary definition. In Switzerland, the following nuts are the most frequently consumed: peanuts, walnuts, almonds, hazelnuts, chestnut, pistachio, pine seeds, brazil nut, cashew, macadamia, pecan. In most studies, a serving size of nuts is 30g. If not otherwise mentioned this serving size is used in this report.

The food group "nuts" in the swiss food pyramid also includes seeds. Due to the low frequency of consumption, resp. missing consumption data, seeds are neglected in this evaluation.

In contrast to most other fruits, nuts are energy dense, mainly due to their high fat content. Unlike fruits, they also contain considerable amounts of protein. However, due to the botanical heterogeneity of nuts, the content of micro and macro nutrients as well as fibers varies substantially between nuts (and oily seeds) [438]. Nuts are also a good source of minerals and vitamin E, and have a favourable fatty acid composition [439].

7.2.2 Recommendations and intake data

To date, in the Swiss Food Pyramid, nuts are in the category below the top category: "Oils, fats and nuts: to consume daily in small amounts". More precisely, the Swiss Society for Nutrition (SSN) recommends the daily consumption of 20-30 g of unsalted nuts. The daily intake of Swiss adults is less than half of the swiss recommendation [3], as shown in the table below.

Summary box: present recommendations and estimated levels of intake in the Swiss population

NUTS / SEEDS	Definition	Quantity
Daily recommendations current Swiss Food Pyramid[2]	Unsalted nuts, seeds	1 portion =20-30 g
Other recommendations [271]	Nuts, seeds	21 g (16-25) per day
Daily Intake in Switzerland* [3] Total / male / female	Nuts, seeds, olives, avocados	10.5 g / 9.3 g / 11.7 g

*Data are mean values of two 24-hour recalls protocols, weighted and corrected for seasonality and weekdays.

The German DGE recommends daily consumption of nuts and counts one serving size (30g) towards a "5-a-day" serving. The USDA currently recommends the consumption 2.5 ounces of nuts seeds (71 g) per week for a person with a daily energy requirement of 2000 kcal [440]. In the Harvard Food Pyramid, nuts are situated in the healthy protein group immediately above the fruit and vegetable group [441]. In the Mediterranean diet pyramid, nuts are in the same group as fruits and vegetables [442].

7.2.3 Putative mechanisms linking nuts intake and NCDs

The nutrients present in nuts may offer anti-carcinogenic, anti-inflammatory and antioxidant properties. One major effect of regular nuts consumption is a reduction of the risk of developing cardio-vascular/-metabolic disease, most likely via improvement of glycemic, lipid and inflammatory (CRP, TNF-alpha) parameters, blood pressure, vascular stiffness and endothelial function [443–453]. Studies also suggest that the effects are independent of the type of nuts consumed and rather depend on nuts dose [451]. Recent research focuses on the prebiotics properties in humans of the non-bioaccessible material of nuts (polymerized polyphenols and polysaccharides), which provides substrates for the human gut microbiota and on the formation of new bioactive metabolites, potentially providing additional health benefit [453].

7.2.4 Literature review

Cardiovascular disease (CVD) & type 2 diabetes mellitus

In the PREDIMED nutrition intervention trial, a Mediterranean diet enriched with nuts decreased CVD incidence and mortality and decreased cancer mortality, compared to an isocaloric control diet [454]. However, after the recent reanalysis of the PREDIMED-data, survival of participants with the nuts-enriched diet was virtually the same as that of participants following the control diet [160]. Because CVD mortality was still lower in the nuts group, this suggests that non-CVD-mortality must have been higher in participants following the nuts enriched diet compared to the control group. This is at odds with most of the literature showing that nuts consumption is associated with lower cancer and non-cancer-non-CVD-mortality (see below). Based on meta-analyses of PCS , nut intake is associated with reduced risk of CVD, including stroke, total cancer and all-cause mortality, and mortality from respiratory disease, type 2 diabetes, and infections [355, 455–458]. However, observational studies are prone to substantial (residual) confounding and their results should be interpreted cautiously.

Obesity

Nut consumption may positively impact on body weight by stabilizing [443, 444] or even lowering the BMI [443, 445]. One explanation for the alleged contradiction between the high energy density of nuts and their favourable properties for body weight control could be explained by the fact that only a part of the energy content in nuts assessed in laboratory (physical calorific value) is indeed absorbed by the human body (physiological calorific value) [459]. Other explanations include the high satiating power of nuts and an increase in energy expenditure associated with nut consumption, the latter accounting for 10-15% of the beneficial body weigh properties of nuts [460].

Cancer

Consumption of nuts is inversely associated with cancer (from all causes) [456–458]. There is limited evidence on a possible protective effect of nuts consumption on lung cancer [461] but the mechanisms are unclear. The potentially preventive effect of walnut consumption on colon cancer development may be due to walnut-induced changes to the gut microbiome [462].

7.2.5 Discussion and research gap

To date, there is some evidence that nuts decrease the risk of NCDs. However, two systematic reviews and meta-analyses concluded that there is much inconsistency and insufficient high quality evidence substantiating the effect of nut consumption on CVD in primary prevention [449] and in metabolic syndrome patients respectively [452]. Therefore, more data from high quality RCTs is needed in order to determine the specific impact of different types and amounts of nuts on risk factors and disease outcomes [449, 452]. Nevertheless, evidence speaking in favour of regularly consuming nuts is still way better than that for most other foods where mostly no RCT evidence is available at all. Furthermore, there is sufficient evidence that consuming unsalted nuts does not entail health risks, in particular that it does not lead to weight gain, but could even help managing body weight [463].

The current version of the Swiss Food Pyramid groups foods according to their physical energy density with those having the highest density being at the top. Placing nuts among energy-dense foods may be wrong in the sense that only a part of the calories contained in nuts contributes to the energy balance. In fact, the physiological energy content of nuts is substantially lower than their physical content. As consequence, there is no scientific rational for the current position (almost on the top) of nuts in the pyramid.

There is only little evidence on the “ideal” amount of nuts daily consumed that provides the maximum health benefits. Available evidence suggests a beneficial effect already at amounts below 30g. Whether larger amounts (>30g) provide additional or less benefit cannot be determined based on the current literature [172].

7.2.6 Conclusion and recommendation

Nuts are energy and fat-dense foods, but contains also many valuable nutrients, such as essential fatty acids, protein, dietary fibers, calcium, iron, and many others.

The present literature provides evidence, mainly based on PCSs, that the consumption of unprocessed nuts is not associated with an increased risk of NCDs, and more specifically with an increased risk of obesity. This suggests that their energy density is not associated with a risk of excess energy/fat intake and accumulation in the body.

There is some evidence, mainly based on PCSs, that consumption of unsalted nuts is associated with decreased incidence of NCD and decreased total mortality. This conclusion is supported by a fairly large number of RCTs showing that nut supplementation has short-term beneficial effects on cardiovascular risk factors, body weight, glucose homeostasis, and blood markers of inflammation.

The evidence for beneficial health effects is supported for consumption of one serving unsalted nuts per day; the available dose-response data suggests a beneficial effect already with a third of a serving (10g) but there is no evidence available for larger amounts (>30g) [172].

The present recommendation to consume small amounts of nuts and oils daily appears valid, but nonetheless may underemphasize the nutritional value of nuts. Based on their probable positive effects on health, nuts, like vegetable fats, should not be placed at the same level with animal fat sources in the Swiss food pyramid; based on their high fiber, protein and micronutrient content, nuts may possibly be located at other/lower levels of the pyramid than oils and fats.

Nuts location together with vegetables and fruits, or protein –rich foods, may allow to provide a more positive, quantitative message regarding this food group, i.e.: consume 1 serving (30g) minimally processed nuts daily, i.e. maybe slightly roasted, but not salted, or coated with sugar or fats.

8 Packaged foods and snacks

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8.1 General discussion

It was initially planned to include recommendations regarding packaged foods and snacks (sweet and “salted”/savoury) in the Swiss dietary guidelines and/or the Swiss food pyramid. Searching the literature for studies related to consumption of snacks and packaged food, it was however quickly observed that very few studies, whether prospective cohort studies or randomized controlled trials, allowed to obtain information about consumption of specific snacks or packaged foods. This is likely linked to the large variety of products included in these categories, each being consumed at a low frequency, and the absence of well-defined classifications.

Packaged food products can roughly be classified into two main categories:

- Products from major food groups (e.g. canned vegetables or fruits, tinned fish, processed meat such as ham, bacon, cheese, breakfast cereals).
- Mixed products (usually ready to eat (RTE) or ready to heat (RTH)): usually made of a combination of multiple ingredients (e.g. frozen meals, pizzas, cake mixes, instant packaged soups and noodles).

Products from the first group are already covered in the Swiss pyramid, regardless of their format (packaged vs raw vs home-made). Regarding the second group, the main challenge rests in the fact that RTE/RTH products are widely heterogeneous in all aspects (composition, eating occasion, serving size) to classify them into one group as a whole.

To overcome this challenge, one approach would be to strictly consider the degree of processing, and several food processing classification systems have been proposed [464, 465]. There are however important limitations to this approach, since industrial RTE/RTH products are collectively viewed as highly-processed, without an objective assessment of the ingredient listing and processing modalities applied. As the food industry is moving more and more towards ‘clean label’ products made of simple, recognizable ingredients, their recipe and nutritional compositions can be expected to be closer to those of home-made equivalents. In addition, packaged RTE food products are categorized based on the end product, while home-prepared meals are categorized based on the individual ingredients, even if they are made with exactly the same ingredients.

Given these limitations, it is difficult to delineate scientifically sound criteria that would allow to group all “packaged food” into one single category. What is usually understood as “non-packaged foods” are unprocessed single ingredients that include fresh fruits and vegetables, nuts, seeds, fresh meats, seafood, eggs. However, in each of these food categories, “packaged, industrial” versions exist, and many criteria need to be taken into account. For instance, a decision needs to be made about culinary *versus* industry ingredients and whether the presence of even one industrial ingredient (*e.g.,* citric acid, sodium benzoate, caramel colour, or ascorbic acid) would result in the classification of the food as an industrial/packaged food, and whether it would alter its nutritional quality and impact on health.

An additional challenge that prevent a specific recommendation on “packaged food” as one group is the fact that no health impact data is available on “home-made/non-packaged” versions of mixed meals, such as lasagna, pizzas, soups, etc., which, when directly bought in the stores, are considered as highly processed foods. It is therefore unknown whether the nutritional composition and associations with health outcomes of these homemade products may differ from their industrial versions.

Similary, regarding snacks, the major issue may be the definition of what constitutes a snack: In the Collins dictionary, a snack is defined the as “a light quick meal eaten between or in place of main meals”. According to this definition, foods from any group (cereals, fruits, vegetables, nuts, dairy, etc) and processed home-made or industrial foods (cookies, ice-creams, chocolate bars, etc) can be consumed as snacks. Some national guidelines define snacks as foods consumed in-between main meals, or foods containing up to 150 kcal, consumed in one single eating occasion. The Macmillan dictionary provide a non-exhaustive list of foods items considered as snacks (http://www.macmillandictionary.com/thesaurus-category/british/sweet-food-and-desserts), which gives an idea of the large range of products which are covered in this category.

Many national dietary guidelines provide recommendations for snacks [466]. Most propose consumption of up to two snacks per day, and specify that the amount of energy consumed as snacks should be balanced by reduced energy intake at meals. Snacks should contain enough energy to ensure satiety until the next main meal, but not too much to avoid energy overconsumption. Furthermore, snacks should also provide non-caloric nutrients (including dietary fibers) to contribute to overall daily nutritional requirements.

Based on the present knowledge in the field, there is neither obvious advantage nor obvious adverse effects of snacking for the general population, provided that total daily energy intake remains within energy requirements. The dietary guidelines may therefore mention the possibility to rely on snacking as part of a healthy diet, and may include recommendations about frequency, size, and composition for healthy snacking. Key criteria can include the following:

- Amount of energy (50-150 kcal)
- Nutrients content (fiber, fiber:energy ratio, content in specific micronutrients with inadequate intake)
- Low saturated fat; no trans-fat
- Low sodium
- Low “free sugar”

Until such criteria are developed, it can be proposed that the food-group based dietary guidelines may include a more extensive list or description of snacks to be consumed sparingly only, and which should remain at the top of the food pyramid. It may also inform about the fact that fruits health benefits are limited to whole fruits, and that there is no evidence that processed fruit products (e.g. fruit juices, fruit pastes, fruits concentrates, products containing “fruit sugar”) share the same effects.

In conclusion there is no clear scientific basis to classify neither packaged food, nor snacks, as a whole group, given their highly heterogeneous nature. However, within these two groups, large differences in nutritional values exist, and it is critical to help provide the population with accurate and transparent nutrition information. Adoption of a unified front-of-pack labelling system could help differentiate products based on their nutritional profile.

Various nutrient profiling systems have been proposed with the general purpose of preventing disease and promoting health [467]. There is a substantial amount of heterogeneity in the way these profiling systems are designed depending on their application, which can range from the regulation of nutrition and health claims, marketing to children, product promotion at point of sale, front-of-package labeling, to product innovation/ renovation by food companies [467]. These methods would still need validation and research is needed in assessing their efficacy in promoting healthier choices.

9 Final discussion and conclusions

This evaluation was performed with the specific aim of assessing whether, based on the present scientific evidence, changes in the Swiss food pyramid are warranted to reduce the risk of NCD in the general population. In order to address this question, experts were asked to review the relevant literature starting from 2012 (date of the previous similar assessment by the SSN + EEK) to 2017. Since making our own complete critical review of the literature was not possible within the timeframe and with the budget allowed, it was decided to rely primarily on published critical reviews and meta-analyses, either released by other nutrition- or health-agencies (expert working groups), or published in peer-reviewed journals by independent researchers. Experts also included in their analysis the original reports of recent studies not yet included in meta-analyses if felt relevant, and original reports of studies 2012-2017 for outcomes for which no meta-analyses were available.

NCD represent a very large group of diseases, and a literature search for all NCDs-related terms was obviously not possible. This work was specifically targeted to NCDs with high incidence in the Swiss population and with known links to nutrition, i.e. obesity, type 2 diabetes, cardiovascular diseases, and cancer. The analysis was also targeted to total mortality. One should keep in mind that several important NCDs (degenerative neurological diseases, osteoporosis, lung diseases, and many others) were however not included in this assessment.

The aim of this work was not to review the scientific evidence underlying the present Swiss food-based dietary guidelines, which were mainly developed to insure a balanced overall diet with adequate intake of total energy and of all essential micronutrients. It was rather aimed at identifying whether adaptation to present guidelines would possibly provide additional benefit for NCD prevention while at the same time ensuring adequate overall nutrition

Our evaluation therefore included not only a qualitative but also a quantitative dimension. For each food group, both the experts and the working group assessed a) whether habitual intake of food groups were associated with NCDs and whether a causal relationship was likely, b) whether beneficial or adverse effects could be related to well defined intake data (dose-dependent effect, or threshold dose for health-related effects, and c) whether optimal intake data determined in b) were different from present guidelines and expected effect size would be sufficient to support a change. For each food group assessed, the following conclusions were attained.

9.1 Fluids and beverages

9.1.1 Fluids

Fluid intake adequacy is poorly defined, and prevalence of disorders linked to inadequate hydration is unknown. Current recommendations for total water intake are based on adequate intakes (AI) in temperate climates at moderate physical activity levels and not on estimated average requirement (EAR) nor on Recommended Dietary Allowance (RDA). To date, recommendations for water intakes have been established from population intake data and not from studies having linked long-term water intake with health outcome. Given the limited amount of current evidence linking total water intake to health outcomes, we need further data to guide evidence-based recommendations on water intake. In particular, scientific evidence on the levels of long-term water intake needed to reduce the risk of common chronic diseases is currently limited. No change to present guidelines is presently warranted.

9.1.2 Coffee

The evaluation addressed exclusively coffee consumption (the effects of sugar-sweetened caffeinated beverages was addressed with SSBs, but did not include assessment of the effects of their caffeine content).

The present evaluation indicates that coffee consumption (including decaffeinated coffee) up to 4 cups/day (400 mg caffeine/day) has no identified deleterious effects on health, and may even be associated with reduced NCD risk. These conclusions are restricted to healthy adult male and non-pregnant females, and does not extend to women during pregnancy and children. Coffee does not contain essential nutrients, however, and level of evidence is not sufficient to recommend its daily intake. Unsweetened coffee up to 4 cups/d may however be specifically mentioned as a possible non-caloric fluid source.

9.1.3 Sugar sweetened beverages

Sugar-sweetened beverages (SSBs) include sugar-sweetened sodas, energy drinks, sport drinks, artificially sweetened fruit juices, 100% fruit juices and sugar-sweetened milk-based drinks. They contain mainly water and sugar, but generally do not provide other essential nutrients (with the exception of fruit juices and sweetened milk-based drinks), and therefore have no or minimal potential benefits to health.

There is robust evidence that consumption of SSBs is dose-dependently associated with body weight gain in children and adults. SSBs intake is also significantly associated with increased risk for type 2 diabetes and most cardiovascular diseases. There is however only weak evidence for an association with cancer. The present conclusions, together with those communicated recently by several health agencies (UK-SACN, WHO, FR-ANSES) support the proposal that they should not be represented in the Swiss food pyramid, or mentioned only at the top level of the pyramid.

The scientific evidence linking fruit juices consumption and NCD has not been comprehensively addressed. Commercial fruit juices may contain added refined sugar, but home-made fruit juices and some commercial preparations (pure fruit juice, 100% fruit juice) may contain only the sugar naturally present in fruits. Many studies indicate that consumption of fruit juices at large (i.e. without distinguishing between fruit juice with added sugar and 100% fruit juices) is associated with increased risk of NCD. Few studies specifically assessed the effect of 100% fruit juices, and yielded discrepant results. Of importance, in contrast to whole fruits, no study show a beneficial effect of fruit juice intake on NCD risk. The equivalence of a 100% fruit juice to one fruit serving is also quite problematic: a 2 dl 100% fruit juice, compared to one serving of the same fresh fruit, contains about twice as much sugars and almost no fibers. It is therefore proposed not to consider fruit juices as possible substitutes for fresh fruits in the Swiss food pyramid.

The scientific literature reports possible associations between the consumption of artificially sweetened beverages and NCD risk. Although such association may not be causal, and mechanisms accounting for adverse effects of artificial sweeteners have not been demonstrated, it may be cautious not to advocate this type of beverages as a substitute for SSBs.

9.2 Fruits and vegetables

There is strong evidence that the consumption of fruits and vegetables is associated with reduced risk of type 2 diabetes, cardiovascular diseases, and some type of cancers. There is however only weak evidence that is associated with a reduced risk of overweight and adiposity. When fruits and vegetables are considered together, there is a dose-dependent risk reduction for most NCDs. When assessed individually, there is a strong effect of consuming 1

or 2 fruits servings per day compared to no fruit, but consumption of more than 2 fruit servings/day does not further reduce the risk. In contrast, consumption of vegetables is associated with a continuous risk decrease up to 4 servings/day.

These observations confirm that current guidelines (ie 2 fruit serving and 3 vegetable serving per day) are well supported by the present literature, and that no change is presently warranted.

9.3 Cereals and starchy foods

The present dietary recommended intake for total carbohydrate is 50-60% total energy. Several international and national nutrition agencies and medical associations have recently revised it to lower values, i.e. 40-55%. Cereals and starchy foods should make up 80% of total carbohydrate intake, i.e. about 32-44% total energy intake.

There is strong evidence that starchy foods differ in the way they alter NCD risk. Consumption of unrefined cereals is associated with reduced risk of cardiovascular diseases, type 2 diabetes and some cancer and with lower overall mortality, while consumption of refined cereals appears to have a neutral effect.

The mechanisms underlying these differences remain poorly understood. Effects of unrefined cereals may be mediated by their fiber content, by their slow rate of digestion and absorption, and by the way they alter postprandial glycemia and insulinemia. When assessing the relationship between intake data and health outcome, consumption of whole grains (defined as cereals minimally processed or processed in a way that the cereal's components (endosperm, germ and bran) are present in the same relative proportions as they exist in the intact grain) is consistently associated with beneficial effects on cardiovascular and type 2 diabetes risk and on total mortality. Consumption of cereal fiber is also consistently associated with reduced risk of cancers. Evaluation of dietary carbohydrate intake based on glycemic index is however not, or inconsistently associated with reduced risk for NCDs

There is strong evidence that consumption of 30 g whole grain and beyond (up to 90-100g/day, i.e. 3 servings/d) reduces NCDs risk. Compared to present recommendations, it would be advisable to provide an adequate description of whole grains and fiber-rich starchy foods, and to specifically recommend that 1-3 portions are to be consumed daily.

9.4 Dietary proteins

9.4.1 Meat, fish and eggs

No systematic search of the literature was performed for these food groups, and conclusions were mainly based on recent Swiss and foreign reports. The recent literature was nonetheless scanned and results of recent studies was taken into consideration when felt appropriate.

As recently concluded from the Swiss report on meats, there is a positive association between processed meat and red meat consumption and risk of NCDs. Based on recent meta-analyses and reappraisals by other expert groups, adverse effects are observed with intake above 50 g/day for processed meat and 100 g/day for red meats.

As concluded from previous Swiss and foreign reports, there is an inverse relationship between fish consumption and overall mortality. There is however no significant effect on risk of overweight or type 2 diabetes. Recently, there has also been increasing concern regarding intake of contaminants (heavy metals) associated with fish consumption. This regards mainly carnivorous fish (at the end of the fish food chain), and deep-sea fishes. The risk appears also more important with aged vs young fishes due to bioaccumulation of contaminants. This has led several agencies to revise their guidelines and advise the consumption of 1 one deep sea

fish and one other fish per week. Finally, there is presently insufficient information regarding eggs consumption and health.

9.4.2 Dairy products

The literature does not support strong links between dairy products consumption and risk of NCDs. It however does not demonstrate any adverse effects of dairy products on mortality, incidence of cardiovascular diseases, type 2 diabetes, obesity or cancer. There is instead some evidence that consumption of fermented dairy products may offer some protection against obesity. Effects on bone health were not included in this evaluation.

The current Swiss recommendations regarding dairy products, that postulate the consumption of three portions each day, are reasonable on the basis of currently available information and scientific evidence. Also, the defined portion sizes can be considered as reasonable. Recommendations should not emphasize reduced-fat dairy products since there is no evidence indicating that whole-fat products are detrimental to health. The present recommendation to consume 3 portion/day dairy products remains adequate. We suggest to add a recommendation to diversify the consumption of dairy products, to take total energy into consideration, and to restrict consumption of sugar-sweetened dairy products.

9.4.3 Pulses and vegetable proteins

Pulses are an important source of plant protein, in particular in combination with other foods. Based on current evidence, there is evidence that consumption of pulses decreases the risk of some chronic diseases (coronary heart disease, lung cancer).

With respect to consumption of plant protein, intervention studies point towards a protective effect against NCDs. Substituting animal with plant protein has shown some benefit with respect to mortality. However, the number of studies so far is limited.

Although most epidemiological studies looking at health effects of pulses or plant protein intake make an effort to control for confounding factors and try to elucidate the mechanisms of their health effects, it currently remains unclear whether they are due to other nutritional components such as isoflavones, protein, resistant starch, or fibers.

Given that it is recommended to limit consumption of red meat and processed meat on one hand, that there is increasing interest for reducing consumption of meat for ecological and sustainability issues on the other hand, it appears appropriate to stress that consumption of plant protein should be increased at the expense of animal protein. Given that pulses are an important source of plant protein in our diet, it is proposed that this class of food be relocated with other protein-rich foods (meat, fish and eggs) at the third level of the Swiss food pyramid.

9.5 Fats and oils

The review of meta-analyses of prospective cohort studies and of randomized controlled trials published during the past 5 years indicates that the recommendations dietary fats and oils of the EEK/FCN published in 2012 need some revisions.

Total fat and saturated fat intakes (in % of energy intake) are not clearly associated with cardiovascular morbidity and mortality. Consumption of the n-6 PUFA acid is associated with diminished cardiovascular morbidity and mortality. A small but potentially important benefit regarding cardiovascular risk results from reduction of saturated fat when it is replaced by polyunsaturated fat. This benefit is not observed in patients with established cardiovascular diseases, however. Seafood-derived n-3 PUFA supplements have also been shown to diminish cardiovascular and total mortality in subjects at high risk for cardiovascular diseases.

Based on these findings, it appears that replacing animal fat with vegetable oils have overall protective effects on cardiovascular risk, and hence that vegetable oils and butter should not be located at the same level of the pyramid. There is no scientific basis to recommend specifically canola oil, and it is therefore recommended that as other vegetable oils, such as olive oil or sunflower oil should be treated equally.

9.6 Nuts and seeds

Nuts are energy and fat-dense foods, but contains also many valuable nutrients, such as essential fatty acids, protein, dietary fibers, calcium, and iron.

The present literature provides strong evidence, mainly based on prospective cohort studies, that minimally processed nut consumption is not associated with increased risk of NCDs, and more specifically with increased risk of obesity. This suggests that their energy density is not associated with a risk of excess energy/fat intake.

There is also strong evidence that consumption of minimally processed nuts (unsalted and without sugar/fat containing coatings) is associated with decreased incidence of NCD and decreased total mortality. This conclusion is supported by prospective cohort studies and by a large number of randomized clinical trial showing that nut supplementation has short-term beneficial effects on cardiovascular risk factors, body weight, glucose homeostasis, and blood markers of inflammation.

The evidence for beneficial health effects is well supported for consumption of one serving unprocessed nuts per day; the available dose-response data suggests a beneficial effect already with a third of a serving (10g) but there is no evidence available for larger amounts (>30g).

The present recommendation to consume small amounts of nuts and oils daily appears valid, but nonetheless may underemphasize the nutritional value of nuts. Based on their probable positive effects on health, nuts, like vegetable fats, should not be placed level with animal fat in the Swiss food pyramid; based on their high fiber, protein and micronutrient content, nuts may possibly be located at other levels of the pyramid than oils and fats.

9.7 General conclusions

Compliance to the current guidelines from the Swiss Food Pyramid is generally associated with a low nutrition-related NCD risk, and specific recommendations for many food groups do not need to be modified.

There is evidence that fruit and vegetable, and dietary fibers intake in the population is below current recommendations, and that recommendations should be to eat MORE of these. There is limited, but concerning evidence that consumption of fruit juices do not share the beneficial effects of whole fruits, and that fruits juices should not be proposed as a substitute for a fruit portion.

There is also evidence that a regular consumption of pulses, nuts and whole grain products is likely to decrease NCD risk, and that recommendations to increase their consumption (to include daily intake of x portion/day or week) should be issued.

10 References

10.1 References Chapter 3.1

1. Armstrong LE, Johnson EC (2018) Water Intake, Water Balance, and the Elusive Daily Water Requirement. Nutrients 10(12). doi: 10.3390/nu10121928
2. Schweizerische Gesellschaft für Ernährung (2016) Schweizer Lebensmittelpyramide. http://www.sge-ssn.ch/ich-und-du/essen-und-trinken/ausgewogen/schweizer-lebensmittelpyramide/. Accessed 09 Oct 2019
3. Bundesamt für Lebensmittelsicherheit und Veterinärwesen, L (2019) Ergebnisse zum Lebensmittelkonsum. https://www.blv.admin.ch/blv/de/home/lebensmittel-und-ernaehrung/ernaehrung/menuch/menu-ch-ergebnisse-ernaehrung.html. Accessed 09 Oct 2019
4. EFSA Panel on Dietetic Products, Nutrition, and Allergies (2010) Scientific Opinion on Dietary Reference Values for water. EFSA Journal 8(3): 1459. doi: 10.2903/j.efsa.2010.1459
5. Gandy J (2015) Water intake: validity of population assessment and recommendations. Eur J Nutr 54 Suppl 2: 11–16. doi: 10.1007/s00394-015-0944-8
6. Nissensohn M, Sánchez-Villegas A, Galan P et al. (2017) Beverage Consumption Habits among the European Population: Association with Total Water and Energy Intakes. Nutrients 9(4). doi: 10.3390/nu9040383
7. O'Connor L, Walton J, Flynn A (2014) Water intakes and dietary sources of a nationally representative sample of Irish adults. J Hum Nutr Diet 27(6): 550–556. doi: 10.1111/jhn.12189
8. Gibson S, Shirreffs SM (2013) Beverage consumption habits "24/7" among British adults: association with total water intake and energy intake. Nutr J 12: 9. doi: 10.1186/1475-2891-12-9
9. Dhayat NA, Ackermann D, Pruijm M et al. (2016) Fibroblast growth factor 23 and markers of mineral metabolism in individuals with preserved renal function. Kidney Int 90(3): 648–657. doi: 10.1016/j.kint.2016.04.024
10. Forni Ogna V, Ogna A, Vuistiner P et al. (2015) New anthropometry-based age- and sex-specific reference values for urinary 24-hour creatinine excretion based on the adult Swiss population. BMC Med 13: 40. doi: 10.1186/s12916-015-0275-x
11. Moulin F, Ponte B, Pruijm M et al. (2017) A population-based approach to assess the heritability and distribution of renal handling of electrolytes. Kidney Int 92(6): 1536–1543. doi: 10.1016/j.kint.2017.06.020
12. Petrovic D, Estoppey Younes S, Pruijm M et al. (2016) Relation of 24-hour urinary caffeine and caffeine metabolite excretions with self-reported consumption of coffee and other caffeinated beverages in the general population. Nutr Metab (Lond) 13: 81. doi: 10.1186/s12986-016-0144-4
13. Ponte B, Pruijm M, Ackermann D et al. (2015) Copeptin is associated with kidney length, renal function, and prevalence of simple cysts in a population-based study. J Am Soc Nephrol 26(6): 1415–1425. doi: 10.1681/ASN.2014030260
14. Pruijm M, Ponte B, Ackermann D et al. (2016) Associations of Urinary Uromodulin with Clinical Characteristics and Markers of Tubular Function in the General Population. Clin J Am Soc Nephrol 11(1): 70–80. doi: 10.2215/CJN.04230415
15. Schoen T, Blum J, Paccaud F et al. (2013) Factors associated with 24-hour urinary volume: the Swiss salt survey. BMC Nephrol 14: 246. doi: 10.1186/1471-2369-14-246
16. Popkin BM, D'Anci KE, Rosenberg IH (2010) Water, hydration, and health. Nutr Rev 68(8): 439–458. doi: 10.1111/j.1753-4887.2010.00304.x

17. Guelinckx I, Tavoularis G, König J et al. (2016) Contribution of Water from Food and Fluids to Total Water Intake: Analysis of a French and UK Population Surveys. Nutrients 8(10). doi: 10.3390/nu8100630
18. Manz F, Wentz A (2003) 24-h hydration status: parameters, epidemiology and recommendations. Eur J Clin Nutr 57 Suppl 2: S10-8. doi: 10.1038/sj.ejcn.1601896
19. Armstrong LE (2007) Assessing hydration status: the elusive gold standard. J Am Coll Nutr 26(5 Suppl): 575S-584S. doi: 10.1080/07315724.2007.10719661
20. Manz F, Wentz A, Sichert-Hellert W (2002) The most essential nutrient: defining the adequate intake of water. J Pediatr 141(4): 587–592. doi: 10.1067/mpd.2002.128031
21. Adan A (2012) Cognitive performance and dehydration. J Am Coll Nutr 31(2): 71–78. doi: 10.1080/07315724.2012.10720011
22. Lieberman HR (2007) Hydration and cognition: a critical review and recommendations for future research. J Am Coll Nutr 26(5 Suppl): 555S-561S. doi: 10.1080/07315724.2007.10719658
23. KLEINER SM (1999) Water. J Am Diet Assoc 99(2): 200–206. doi: 10.1016/S0002-8223(99)00048-6
24. McCartney D, Desbrow B, Irwin C (2017) The Effect of Fluid Intake Following Dehydration on Subsequent Athletic and Cognitive Performance: a Systematic Review and Meta-analysis. Sports Med Open 3(1): 13. doi: 10.1186/s40798-017-0079-y
25. Littlejohns TJ, Neal NL, Bradbury KE et al. (2019) Fluid Intake and Dietary Factors and the Risk of Incident Kidney Stones in UK Biobank: A Population-based Prospective Cohort Study. Eur Urol Focus. doi: 10.1016/j.euf.2019.05.002
26. Xu C, Zhang C, Wang X-L et al. (2015) Self-Fluid Management in Prevention of Kidney Stones: A PRISMA-Compliant Systematic Review and Dose-Response Meta-Analysis of Observational Studies. Medicine (Baltimore) 94(27): e1042. doi: 10.1097/MD.0000000000001042
27. Fink HA, Akornor JW, Garimella PS et al. (2009) Diet, fluid, or supplements for secondary prevention of nephrolithiasis: a systematic review and meta-analysis of randomized trials. Eur Urol 56(1): 72–80. doi: 10.1016/j.eururo.2009.03.031
28. Gazan R, Sondey J, Maillot M et al. (2016) Drinking Water Intake Is Associated with Higher Diet Quality among French Adults. Nutrients 8(11). doi: 10.3390/nu8110689
29. Clark WF, Sontrop JM, Huang S-H et al. (2016) Hydration and Chronic Kidney Disease Progression: A Critical Review of the Evidence. Am J Nephrol 43(4): 281–292. doi: 10.1159/000445959
30. Sontrop JM, Huang S-H, Garg AX et al. (2015) Effect of increased water intake on plasma copeptin in patients with chronic kidney disease: results from a pilot randomised controlled trial. BMJ Open 5(11): e008634. doi: 10.1136/bmjopen-2015-008634
31. Chan J, Knutsen SF, Blix GG et al. (2002) Water, other fluids, and fatal coronary heart disease: the Adventist Health Study. Am J Epidemiol 155(9): 827–833. doi: 10.1093/aje/155.9.827
32. Muckelbauer R, Sarganas G, Grüneis A et al. (2013) Association between water consumption and body weight outcomes: a systematic review. Am J Clin Nutr 98(2): 282–299. doi: 10.3945/ajcn.112.055061
33. Muckelbauer R, Barbosa CL, Mittag T et al. (2014) Association between water consumption and body weight outcomes in children and adolescents: a systematic review. Obesity (Silver Spring) 22(12): 2462–2475. doi: 10.1002/oby.20911
34. Melander O (2016) Vasopressin, from Regulator to Disease Predictor for Diabetes and Cardiometabolic Risk. Ann Nutr Metab 68 Suppl 2: 24–28. doi: 10.1159/000446201
35. Lim WH, Wong G, Lewis JR et al. (2017) Total volume and composition of fluid intake and mortality in older women: a cohort study. BMJ Open 7(3): e011720. doi: 10.1136/bmjopen-2016-011720

36. Kant AK, Graubard BI (2017) A prospective study of water intake and subsequent risk of all-cause mortality in a national cohort. Am J Clin Nutr 105(1): 212–220. doi: 10.3945/ajcn.116.143826
37. Perrier ET, Bottin JH, Vecchio M et al. (2017) Criterion values for urine-specific gravity and urine color representing adequate water intake in healthy adults. Eur J Clin Nutr 71(4): 561–563. doi: 10.1038/ejcn.2016.269
38. Gandy J, Le Bellego L, König J et al. (2016) Recording of fluid, beverage and water intakes at the population level in Europe. Br J Nutr 116(4): 677–682. doi: 10.1017/S0007114516002336
271. Afshin A, Sur PJ, Fay KA et al. (2019) Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet 393(10184): 1958–1972. doi: 10.1016/S0140-6736(19)30041-8

10.2 References chapter 3.2

39. EFSA Panel on Dietetic Products, Nutrition, and Allergies (2015) Scientific Opinion on the safety of caffeine. EFS2 13(5): 425. doi: 10.2903/j.efsa.2015.4102
40. Superior Health Council (2012) The use of caffeine in foodstuffs. Advisory Report of the Superior Health Council No. 8689, Brussels
41. Goverment of Canada (2012) Caffeine in Food. https://www.canada.ca/en/health-canada/services/food-nutrition/food-safety/food-additives/caffeine-foods/foods.html. Accessed 11 Oct 2019
42. Kromhout D, Spaaij CJK, Goede J de et al. (2016) The 2015 Dutch food-based dietary guidelines. Eur J Clin Nutr 70(8): 869–878. doi: 10.1038/ejcn.2016.52
43. Frary CD, Johnson RK, Wang MQ (2005) Food sources and intakes of caffeine in the diets of persons in the United States. J Am Diet Assoc 105(1): 110–113. doi: 10.1016/j.jada.2004.10.027
44. Bøhn SK, Ward NC, Hodgson JM et al. (2012) Effects of tea and coffee on cardiovascular disease risk. Food Funct 3(6): 575–591. doi: 10.1039/c2fo10288a
45. Tunnicliffe JM, Eller LK, Reimer RA et al. (2011) Chlorogenic acid differentially affects postprandial glucose and glucose-dependent insulinotropic polypeptide response in rats. Appl Physiol Nutr Metab 36(5): 650–659. doi: 10.1139/h11-072
46. Bonita JS, Mandarano M, Shuta D et al. (2007) Coffee and cardiovascular disease: in vitro, cellular, animal, and human studies. Pharmacol Res 55(3): 187–198. doi: 10.1016/j.phrs.2007.01.006
47. Guessous I, Eap CB, Bochud M (2014) Blood pressure in relation to coffee and caffeine consumption. Curr Hypertens Rep 16(9): 468. doi: 10.1007/s11906-014-0468-2
48. Freedman ND, Park Y, Abnet CC et al. (2012) Association of coffee drinking with total and cause-specific mortality. N Engl J Med 366(20): 1891–1904. doi: 10.1056/NEJMoa1112010
49. Crippa A, Discacciati A, Larsson SC et al. (2014) Coffee consumption and mortality from all causes, cardiovascular disease, and cancer: a dose-response meta-analysis. Am J Epidemiol 180(8): 763–775. doi: 10.1093/aje/kwu194
50. Je Y, Giovannucci E (2014) Coffee consumption and total mortality: a meta-analysis of twenty prospective cohort studies. Br J Nutr 111(7): 1162–1173. doi: 10.1017/S0007114513003814
51. Herber-Gast G-CM, van Essen H, Verschuren WM et al. (2016) Coffee and tea consumption in relation to estimated glomerular filtration rate: results from the population-based longitudinal Doetinchem Cohort Study. Am J Clin Nutr 103(5): 1370–1377. doi: 10.3945/ajcn.115.112755
52. Kim K, Kim K, Park SM (2016) Association between the Prevalence of Metabolic Syndrome and the Level of Coffee Consumption among Korean Women. PLoS One 11(12). doi: 10.1371/journal.pone.0167007

53. Larsson SC, Giovannucci EL, Wolk A (2017) Coffee Consumption and Risk of Gallbladder Cancer in a Prospective Study. J Natl Cancer Inst 109(3): 1–3. doi: 10.1093/jnci/djw237
54. Miller PE, Di Zhao, Frazier-Wood AC et al. (2017) Associations of Coffee, Tea, and Caffeine Intake with Coronary Artery Calcification and Cardiovascular Events. Am J Med 130(2): 188-197.e5. doi: 10.1016/j.amjmed.2016.08.038
55. Ogilvie RP, Lutsey PL, Heiss G et al. (2017) Dietary intake and peripheral arterial disease incidence in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Clin Nutr 105(3): 651–659. doi: 10.3945/ajcn.116.137497
56. Shang F, Li X, Jiang X (2016) Coffee consumption and risk of the metabolic syndrome: A meta-analysis. Diabetes Metab 42(2): 80–87. doi: 10.1016/j.diabet.2015.09.001
57. Zuchinali P, Ribeiro PAB, Pimentel M et al. (2016) Effect of caffeine on ventricular arrhythmia: a systematic review and meta-analysis of experimental and clinical studies. Europace 18(2): 257–266. doi: 10.1093/europace/euv261
58. Ding M, Bhupathiraju SN, Satija A et al. (2014) Long-term coffee consumption and risk of cardiovascular disease: a systematic review and a dose-response meta-analysis of prospective cohort studies. Circulation 129(6): 643–659. doi: 10.1161/CIRCULATIONAHA.113.005925
59. Grioni S, Agnoli C, Sieri S et al. (2015) Espresso coffee consumption and risk of coronary heart disease in a large Italian cohort. PLoS One 10(5): e0126550. doi: 10.1371/journal.pone.0126550
60. Grosso G, Stepaniak U, Polak M et al. (2016) Coffee consumption and risk of hypertension in the Polish arm of the HAPIEE cohort study. Eur J Clin Nutr 70(1): 109–115. doi: 10.1038/ejcn.2015.119
61. Guessous I, Pruijm M, Ponte B et al. (2015) Associations of ambulatory blood pressure with urinary caffeine and caffeine metabolite excretions. Hypertension 65(3): 691–696. doi: 10.1161/HYPERTENSIONAHA.114.04512
62. Liebeskind DS, Sanossian N, Fu KA et al. (2016) The coffee paradox in stroke: Increased consumption linked with fewer strokes. Nutr Neurosci 19(9): 406–413. doi: 10.1179/1476830515Y.0000000035
63. Nordestgaard AT, Thomsen M, Nordestgaard BG (2015) Coffee intake and risk of obesity, metabolic syndrome and type 2 diabetes: a Mendelian randomization study. Int J Epidemiol 44(2): 551–565. doi: 10.1093/ije/dyv083
64. Larsson SC, Drca N, Jensen-Urstad M et al. (2015) Coffee consumption is not associated with increased risk of atrial fibrillation: results from two prospective cohorts and a meta-analysis. BMC Med 13: 207. doi: 10.1186/s12916-015-0447-8
65. Akter S, Kashino I, Mizoue T et al. (2016) Coffee drinking and colorectal cancer risk: an evaluation based on a systematic review and meta-analysis among the Japanese population. Jpn J Clin Oncol 46(8): 781–787. doi: 10.1093/jjco/hyw059
66. Caini S, Cattaruzza MS, Bendinelli B et al. (2017) Coffee, tea and caffeine intake and the risk of non-melanoma skin cancer: a review of the literature and meta-analysis. Eur J Nutr 56(1): 1–12. doi: 10.1007/s00394-016-1253-6
67. Deng W, Yang H, Wang J et al. (2016) Coffee consumption and the risk of incident gastric cancer--A meta-analysis of prospective cohort studies. Nutr Cancer 68(1): 40–47. doi: 10.1080/01635581.2016.1115093
68. Han MA, Kim JH (2017) Coffee Consumption and the Risk of Thyroid Cancer: A Systematic Review and Meta-Analysis. Int J Environ Res Public Health 14(2). doi: 10.3390/ijerph14020129
69. Li Y-M, Peng J, Li L-Z (2016) Coffee consumption associated with reduced risk of oral cancer: a meta-analysis. Oral Surg Oral Med Oral Pathol Oral Radiol 121(4): 381-389.e1. doi: 10.1016/j.oooo.2015.12.006

70. Xie Y, Huang S, He T et al. (2016) Coffee consumption and risk of gastric cancer: an updated meta-analysis. Asia Pac J Clin Nutr 25(3): 578–588. doi: 10.6133/apjcn.092015.07
71. Zhou Q, Luo M-L, Li H et al. (2015) Coffee consumption and risk of endometrial cancer: a dose-response meta-analysis of prospective cohort studies. Sci Rep 5: 13410. doi: 10.1038/srep13410
72. Lu Y, Zhai L, Zeng J et al. (2014) Coffee consumption and prostate cancer risk: an updated meta-analysis. Cancer Causes Control 25(5): 591–604. doi: 10.1007/s10552-014-0364-8
73. Nie K, Xing Z, Huang W et al. (2016) Coffee intake and risk of pancreatic cancer: an updated meta-analysis of prospective studies. Minerva Med 107(4): 270–278
74. Xie Y, Qin J, Nan G et al. (2016) Coffee consumption and the risk of lung cancer: an updated meta-analysis of epidemiological studies. Eur J Clin Nutr 70(2): 199–206. doi: 10.1038/ejcn.2015.96
75. Caini S, Masala G, Saieva C et al. (2017) Coffee, tea and melanoma risk: findings from the European Prospective Investigation into Cancer and Nutrition. Int J Cancer 140(10): 2246–2255. doi: 10.1002/ijc.30659
76. Ogawa T, Sawada N, Iwasaki M et al. (2016) Coffee and green tea consumption in relation to brain tumor risk in a Japanese population. Int J Cancer 139(12): 2714–2721. doi: 10.1002/ijc.30405
77. Budhathoki S, Iwasaki M, Yamaji T et al. (2015) Coffee intake and the risk of colorectal adenoma: The colorectal adenoma study in Tokyo. Int J Cancer 137(2): 463–470. doi: 10.1002/ijc.29390
78. Schmit SL, Rennert HS, Rennert G et al. (2016) Coffee Consumption and the Risk of Colorectal Cancer. Cancer Epidemiol Biomarkers Prev 25(4): 634–639. doi: 10.1158/1055-9965.EPI-15-0924
79. Oh J-K, Sandin S, Ström P et al. (2015) Prospective study of breast cancer in relation to coffee, tea and caffeine in Sweden. Int J Cancer 137(8): 1979–1989. doi: 10.1002/ijc.29569
80. Petrick JL, Freedman ND, Graubard BI et al. (2015) Coffee Consumption and Risk of Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma by Sex: The Liver Cancer Pooling Project. Cancer Epidemiol Biomarkers Prev 24(9): 1398–1406. doi: 10.1158/1055-9965.EPI-15-0137
81. Gosvig CF, Kjaer SK, Blaakær J et al. (2015) Coffee, tea, and caffeine consumption and risk of epithelial ovarian cancer and borderline ovarian tumors: Results from a Danish case-control study. Acta Oncol 54(8): 1144–1151. doi: 10.3109/0284186X.2014.1001035
82. Parodi S, Merlo DF, Stagnaro E (2017) Coffee and tea consumption and risk of leukaemia in an adult population: A reanalysis of the Italian multicentre case-control study. Cancer Epidemiol 47: 81–87. doi: 10.1016/j.canep.2017.01.005
83. Hashibe M, Galeone C, Buys SS et al. (2015) Coffee, tea, caffeine intake, and the risk of cancer in the PLCO cohort. Br J Cancer 113(5): 809–816. doi: 10.1038/bjc.2015.276
84. Turati F, Bosetti C, Polesel J et al. (2015) Coffee, Tea, Cola, and Bladder Cancer Risk: Dose and Time Relationships. Urology 86(6): 1179–1184. doi: 10.1016/j.urology.2015.09.017
85. Guertin KA, Freedman ND, Loftfield E et al. (2015) A prospective study of coffee intake and pancreatic cancer: results from the NIH-AARP Diet and Health Study. Br J Cancer 113(7): 1081–1085. doi: 10.1038/bjc.2015.235
86. Bhoo-Pathy N, Peeters PHM, Uiterwaal CSPM et al. (2015) Coffee and tea consumption and risk of pre- and postmenopausal breast cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. Breast Cancer Res 17: 15. doi: 10.1186/s13058-015-0521-3

87. Ding M, Bhupathiraju SN, Chen M et al. (2014) Caffeinated and decaffeinated coffee consumption and risk of type 2 diabetes: a systematic review and a dose-response meta-analysis. Diabetes Care 37(2): 569–586. doi: 10.2337/dc13-1203
88. Bhupathiraju SN, Pan A, Manson JE et al. (2014) Changes in coffee intake and subsequent risk of type 2 diabetes: three large cohorts of US men and women. Diabetologia 57(7): 1346–1354. doi: 10.1007/s00125-014-3235-7
89. Grosso G, Micek A, Castellano S et al. (2016) Coffee, tea, caffeine and risk of depression: A systematic review and dose-response meta-analysis of observational studies. Mol Nutr Food Res 60(1): 223–234. doi: 10.1002/mnfr.201500620
90. Sugiyama K, Tomata Y, Kaiho Y et al. (2016) Association between Coffee Consumption and Incident Risk of Disabling Dementia in Elderly Japanese: The Ohsaki Cohort 2006 Study. J Alzheimers Dis 50(2): 491–500. doi: 10.3233/JAD-150693
91. Liu Q-P, Wu Y-F, Cheng H-Y et al. (2016) Habitual coffee consumption and risk of cognitive decline/dementia: A systematic review and meta-analysis of prospective cohort studies. Nutrition 32(6): 628–636. doi: 10.1016/j.nut.2015.11.015
92. Kim Y-S, Kwak SM, Myung S-K (2015) Caffeine intake from coffee or tea and cognitive disorders: a meta-analysis of observational studies. Neuroepidemiology 44(1): 51–63. doi: 10.1159/000371710

10.3 References Chapter 3.3

93. Chun OK, Chung CE, Wang Y et al. (2010) Changes in intakes of total and added sugar and their contribution to energy intake in the U.S. Nutrients 2(8): 834–854. doi: 10.3390/nu2080834
94. Lei L, Rangan A, Flood VM et al. (2016) Dietary intake and food sources of added sugar in the Australian population. Br J Nutr 115(5): 868–877. doi: 10.1017/S0007114515005255
95. Moshtaghian H, Louie JCY, Charlton KE et al. (2017) Trends in added sugar intake and food sources in a cohort of older Australians: 15 years of follow-up from the Blue Mountains Eye Study. J Hum Nutr Diet 30(3): 339–348. doi: 10.1111/jhn.12425
96. Vorster HH, Kruger A, Wentzel-Viljoen E et al. (2014) Added sugar intake in South Africa: findings from the Adult Prospective Urban and Rural Epidemiology cohort study. Am J Clin Nutr 99(6): 1479–1486. doi: 10.3945/ajcn.113.069005
97. Sánchez-Pimienta TG, Batis C, Lutter CK et al. (2016) Sugar-Sweetened Beverages Are the Main Sources of Added Sugar Intake in the Mexican Population. J Nutr 146(9): 1888S-96S. doi: 10.3945/jn.115.220301
98. Singh GM, Micha R, Khatibzadeh S et al. (2015) Global, Regional, and National Consumption of Sugar-Sweetened Beverages, Fruit Juices, and Milk: A Systematic Assessment of Beverage Intake in 187 Countries. PLoS One 10(8): e0124845. doi: 10.1371/journal.pone.0124845
99. Kit BK, Fakhouri THI, Park S et al. (2013) Trends in sugar-sweetened beverage consumption among youth and adults in the United States: 1999-2010. Am J Clin Nutr 98(1): 180–188. doi: 10.3945/ajcn.112.057943
100. Ruff RR, Akhund A, Adjoian T et al. (2014) Calorie intake, sugar-sweetened beverage consumption, and obesity among New York City adults: findings from a 2013 population study using dietary recalls. J Community Health 39(6): 1117–1123. doi: 10.1007/s10900-014-9865-3
101. Sonestedt E, Hellstrand S, Schulz C-A et al. (2015) The association between carbohydrate-rich foods and risk of cardiovascular disease is not modified by genetic susceptibility to dyslipidemia as determined by 80 validated variants. PLoS One 10(4): e0126104. doi: 10.1371/journal.pone.0126104
102. Musunuru K (2010) Atherogenic dyslipidemia: cardiovascular risk and dietary intervention. Lipids 45(10): 907–914. doi: 10.1007/s11745-010-3408-1

103. Stanhope KL, Havel PJ (2008) Fructose consumption: potential mechanisms for its effects to increase visceral adiposity and induce dyslipidemia and insulin resistance. Curr Opin Lipidol 19(1): 16–24. doi: 10.1097/MOL.0b013e3282f2b24a
104. Erickson J, Slavin J (2015) Total, added, and free sugars: are restrictive guidelines science-based or achievable? Nutrients 7(4): 2866–2878. doi: 10.3390/nu7042866
105. Edgar WM (1993) Extrinsic and intrinsic sugars: a review of recent UK recommendations on diet and caries. Caries Res 27 Suppl 1: 64–67. doi: 10.1159/000261605
106. U.S. Department of Health and Human Services and U.S. Department of Agriculture (2015) 2015–2020 Dietary Guidelines for Americans. 8th Edition… https://health.gov/dietaryguidelines/2015/guidelines/.
107. World Health Organization (2015) Guideline - Sugars intake for adults and children. https://apps.who.int/iris/bitstream/handle/10665/149782/9789241549028_eng.pdf;jsessionid=DC965DE360BE777DDBE870E473B01A48?sequence=1
108. Scientific Advisory Committee on Nutrition (2015) Carbohydrates and health. https://www.gov.uk/government/publications/sacn-carbohydrates-and-health-report. Accessed 19 Nov 2019
109. Chatelan A, Gaillard P, Kruseman M et al. (2019) Total, Added, and Free Sugar Consumption and Adherence to Guidelines in Switzerland: Results from the First National Nutrition Survey menuCH. Nutrients 11(5). doi: 10.3390/nu11051117
110. Gupta P, Gupta N, Pawar AP et al. (2013) Role of sugar and sugar substitutes in dental caries: a review. ISRN Dent 2013: 519421. doi: 10.1155/2013/519421
111. Teff KL, Elliott SS, Tschöp M et al. (2004) Dietary fructose reduces circulating insulin and leptin, attenuates postprandial suppression of ghrelin, and increases triglycerides in women. J Clin Endocrinol Metab 89(6): 2963–2972. doi: 10.1210/jc.2003-031855
112. Teff KL, Grudziak J, Townsend RR et al. (2009) Endocrine and metabolic effects of consuming fructose- and glucose-sweetened beverages with meals in obese men and women: influence of insulin resistance on plasma triglyceride responses. J Clin Endocrinol Metab 94(5): 1562–1569. doi: 10.1210/jc.2008-2192
113. Hu FB (2013) Resolved: there is sufficient scientific evidence that decreasing sugar-sweetened beverage consumption will reduce the prevalence of obesity and obesity-related diseases. Obes Rev 14(8): 606–619. doi: 10.1111/obr.12040
114. Tappy L, Lê K-A (2010) Metabolic effects of fructose and the worldwide increase in obesity. Physiol Rev 90(1): 23–46. doi: 10.1152/physrev.00019.2009
115. Louie JCY, Tapsell LC (2015) Intake of total and added sugars and nutrient dilution in Australian children and adolescents. Br J Nutr 114(11): 1875–1886. doi: 10.1017/S0007114515003542
116. Moshtaghian H, Louie JCY, Charlton KE et al. (2016) Added sugar intake that exceeds current recommendations is associated with nutrient dilution in older Australians. Nutrition 32(9): 937–942. doi: 10.1016/j.nut.2016.02.004
117. Cheungpasitporn W, Thongprayoon C, Edmonds PJ et al. (2015) Sugar and artificially sweetened soda consumption linked to hypertension: a systematic review and meta-analysis. Clin Exp Hypertens 37(7): 587–593. doi: 10.3109/10641963.2015.1026044
118. Jayalath VH, Souza RJ de, Ha V et al. (2015) Sugar-sweetened beverage consumption and incident hypertension: a systematic review and meta-analysis of prospective cohorts. Am J Clin Nutr 102(4): 914–921. doi: 10.3945/ajcn.115.107243
119. Xi B, Huang Y, Reilly KH et al. (2015) Sugar-sweetened beverages and risk of hypertension and CVD: a dose-response meta-analysis. Br J Nutr 113(5): 709–717. doi: 10.1017/S0007114514004383
120. Narain A, Kwok CS, Mamas MA (2016) Soft drinks and sweetened beverages and the risk of cardiovascular disease and mortality: a systematic review and meta-analysis. Int J Clin Pract 70(10): 791–805. doi: 10.1111/ijcp.12841

121. Huang C, Huang J, Tian Y et al. (2014) Sugar sweetened beverages consumption and risk of coronary heart disease: a meta-analysis of prospective studies. Atherosclerosis 234(1): 11–16. doi: 10.1016/j.atherosclerosis.2014.01.037
122. Greenwood DC, Threapleton DE, Evans CEL et al. (2014) Association between sugar-sweetened and artificially sweetened soft drinks and type 2 diabetes: systematic review and dose-response meta-analysis of prospective studies. Br J Nutr 112(5): 725–734. doi: 10.1017/S0007114514001329
123. Imamura F, O'Connor L, Ye Z et al. (2015) Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic review, meta-analysis, and estimation of population attributable fraction. BMJ 351: h3576. doi: 10.1136/bmj.h3576
124. Malik VS, Pan A, Willett WC et al. (2013) Sugar-sweetened beverages and weight gain in children and adults: a systematic review and meta-analysis. Am J Clin Nutr 98(4): 1084–1102. doi: 10.3945/ajcn.113.058362
125. Trumbo PR, Rivers CR (2014) Systematic review of the evidence for an association between sugar-sweetened beverage consumption and risk of obesity. Nutr Rev 72(9): 566–574. doi: 10.1111/nure.12128
126. Vartanian LR, Schwartz MB, Brownell KD (2007) Effects of soft drink consumption on nutrition and health: a systematic review and meta-analysis. Am J Public Health 97(4): 667–675. doi: 10.2105/AJPH.2005.083782
127. Drewnowski A, Bellisle F (2007) Liquid calories, sugar, and body weight. Am J Clin Nutr 85(3): 651–661. doi: 10.1093/ajcn/85.3.651
128. Bostick RM, Potter JD, Kushi LH et al. (1994) Sugar, meat, and fat intake, and non-dietary risk factors for colon cancer incidence in Iowa women (United States). Cancer Causes Control 5(1): 38–52. doi: 10.1007/bf01830725
129. Schernhammer ES, Hu FB, Giovannucci E et al. (2005) Sugar-sweetened soft drink consumption and risk of pancreatic cancer in two prospective cohorts. Cancer Epidemiol Biomarkers Prev 14(9): 2098–2105. doi: 10.1158/1055-9965.EPI-05-0059
130. Larsson SC, Bergkvist L, Wolk A (2006) Consumption of sugar and sugar-sweetened foods and the risk of pancreatic cancer in a prospective study. Am J Clin Nutr 84(5): 1171–1176. doi: 10.1093/ajcn/84.5.1171
131. Bao Y, Stolzenberg-Solomon R, Jiao L et al. (2008) Added sugar and sugar-sweetened foods and beverages and the risk of pancreatic cancer in the National Institutes of Health-AARP Diet and Health Study. Am J Clin Nutr 88(2): 431–440. doi: 10.1093/ajcn/88.2.431
132. Zhang X, Albanes D, Beeson WL et al. (2010) Risk of colon cancer and coffee, tea, and sugar-sweetened soft drink intake: pooled analysis of prospective cohort studies. J Natl Cancer Inst 102(11): 771–783. doi: 10.1093/jnci/djq107
133. Navarrete-Muñoz EM, Wark PA, Romaguera D et al. (2016) Sweet-beverage consumption and risk of pancreatic cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). Am J Clin Nutr 104(3): 760–768. doi: 10.3945/ajcn.116.130963
134. Calle EE, Rodriguez C, Walker-Thurmond K et al. (2003) Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 348(17): 1625–1638. doi: 10.1056/NEJMoa021423
135. Gibson SA, Horgan GW, Francis LE et al. (2016) Low Calorie Beverage Consumption Is Associated with Energy and Nutrient Intakes and Diet Quality in British Adults. Nutrients 8(1). doi: 10.3390/nu8010009
136. Gibson S (2001) Dietary sugars and micronutrient dilution in normal adults aged 65 years and over. Public Health Nutr. 4(6): 1235–1244. doi: 10.1079/PHN2001173
137. Gibson SA (2007) Dietary sugars intake and micronutrient adequacy: a systematic review of the evidence. Nutr Res Rev 20(2): 121–131. doi: 10.1017/S0954422407797846

138. Crowe-White K, O'Neil CE, Parrott JS et al. (2016) Impact of 100% Fruit Juice Consumption on Diet and Weight Status of Children: An Evidence-based Review. Crit Rev Food Sci Nutr 56(5): 871–884. doi: 10.1080/10408398.2015.1061475
139. Ferreira-Pêgo C, Babio N, Bes-Rastrollo M et al. (2016) Frequent Consumption of Sugar- and Artificially Sweetened Beverages and Natural and Bottled Fruit Juices Is Associated with an Increased Risk of Metabolic Syndrome in a Mediterranean Population at High Cardiovascular Disease Risk. J Nutr 146(8): 1528–1536. doi: 10.3945/jn.116.230367
140. Pan A, Malik VS, Hao T et al. (2013) Changes in water and beverage intake and long-term weight changes: results from three prospective cohort studies. Int J Obes (Lond) 37(10): 1378–1385. doi: 10.1038/ijo.2012.225
141. Xi B, Li S, Liu Z et al. (2014) Intake of fruit juice and incidence of type 2 diabetes: a systematic review and meta-analysis. PLoS One 9(3): e93471. doi: 10.1371/journal.pone.0093471
142. Imamura F, O'Connor L, Ye Z et al. (2016) Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic review, meta-analysis, and estimation of population attributable fraction. Br J Sports Med 50(8): 496–504. doi: 10.1136/bjsports-2016-h3576rep
143. Tonin FS, Steimbach LM, Wiens A et al. (2015) Impact of Natural Juice Consumption on Plasma Antioxidant Status: A Systematic Review and Meta-Analysis. Molecules 20(12): 22146–22156. doi: 10.3390/molecules201219834
144. Salas MMS, Nascimento GG, Vargas-Ferreira F et al. (2015) Diet influenced tooth erosion prevalence in children and adolescents: Results of a meta-analysis and meta-regression. J Dent 43(8): 865–875. doi: 10.1016/j.jdent.2015.05.012
145. Stepien M, Duarte-Salles T, Fedirko V et al. (2016) Consumption of soft drinks and juices and risk of liver and biliary tract cancers in a European cohort. Eur J Nutr 55(1): 7–20. doi: 10.1007/s00394-014-0818-5
146. Collin LJ, Judd S, Safford M et al. (2019) Association of Sugary Beverage Consumption With Mortality Risk in US Adults: A Secondary Analysis of Data From the REGARDS Study. JAMA Netw Open 2(5): e193121. doi: 10.1001/jamanetworkopen.2019.3121
147. Malik VS, Li Y, Pan A et al. (2019) Long-Term Consumption of Sugar-Sweetened and Artificially Sweetened Beverages and Risk of Mortality in US Adults. Circulation 139(18): 2113–2125. doi: 10.1161/CIRCULATIONAHA.118.037401
148. Taskinen M-R, Söderlund S, Bogl LH et al. (2017) Adverse effects of fructose on cardiometabolic risk factors and hepatic lipid metabolism in subjects with abdominal obesity. J Intern Med 282(2): 187–201. doi: 10.1111/joim.12632
149. Matikainen N, Söderlund S, Björnson E et al. (2017) Fructose intervention for 12 weeks does not impair glycemic control or incretin hormone responses during oral glucose or mixed meal tests in obese men. Nutr Metab Cardiovasc Dis 27(6): 534–542. doi: 10.1016/j.numecd.2017.03.003
150. Mozaffarian D, Hao T, Rimm EB et al. (2011) Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med 364(25): 2392–2404. doi: 10.1056/NEJMoa1014296
151. Ebbeling CB, Feldman HA, Chomitz VR et al. (2012) A randomized trial of sugar-sweetened beverages and adolescent body weight. N Engl J Med 367(15): 1407–1416. doi: 10.1056/NEJMoa1203388
152. Ruyter JC de, Olthof MR, Seidell JC et al. (2012) A trial of sugar-free or sugar-sweetened beverages and body weight in children. N Engl J Med 367(15): 1397–1406. doi: 10.1056/NEJMoa1203034
153. Swithers SE (2016) Not-so-healthy sugar substitutes? Curr Opin Behav Sci 9: 106–110. doi: 10.1016/j.cobeha.2016.03.003

154. Swithers SE (2013) Artificial sweeteners produce the counterintuitive effect of inducing metabolic derangements. Trends Endocrinol Metab 24(9): 431–441. doi: 10.1016/j.tem.2013.05.005
155. Suez J, Korem T, Zeevi D et al. (2014) Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature 514(7521): 181–186. doi: 10.1038/nature13793

10.4 References Chapter 4

2. Schweizerische Gesellschaft für Ernährung (2016) Schweizer Lebensmittelpyramide. http://www.sge-ssn.ch/ich-und-du/essen-und-trinken/ausgewogen/schweizer-lebensmittelpyramide/. Accessed 09 Oct 2019
156. Lim SS, Vos T, Flaxman AD et al. (2012) A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet 380(9859): 2224–2260. doi: 10.1016/S0140-6736(12)61766-8
157. Forouzanfar MH, Alexander L, Anderson HR et al. (2015) Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet 386(10010): 2287–2323. doi: 10.1016/S0140-6736(15)00128-2
158. Forouzanfar MH, Afshin A, Alexander LT et al. (2016) Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet 388(10053): 1659–1724. doi: 10.1016/S0140-6736(16)31679-8
159. AICR/WCRF Recommendations and public health and policy implications. https://www.wcrf.org/sites/default/files/Recommendations.pdf. Accessed 30 Oct 2019
160. Estruch R, Ros E, Salas-Salvadó J et al. (2018) Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. N Engl J Med 378(25): e34. doi: 10.1056/NEJMoa1800389
161. John JH, Ziebland S, Yudkin P et al. (2002) Effects of fruit and vegetable consumption on plasma antioxidant concentrations and blood pressure: a randomised controlled trial. The Lancet 359(9322): 1969–1974. doi: 10.1016/S0140-6736(02)98858-6
162. Asplund K (2002) Antioxidant vitamins in the prevention of cardiovascular disease: a systematic review. J Intern Med 251(5): 372–392. doi: 10.1046/j.1365-2796.2002.00973.x
163. Yamagata K (2019) Polyphenols Regulate Endothelial Functions and Reduce the Risk of Cardiovascular Disease. Curr Pharm Des 25(22): 2443–2458. doi: 10.2174/1381612825666190722100504.
164. Whelton PK, He J, Cutler JA et al. (1997) Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. JAMA 277(20): 1624–1632. doi: 10.1001/jama.1997.03540440058033
165. Jee SH, Miller ER, Guallar E et al. (2002) The effect of magnesium supplementation on blood pressure: a meta-analysis of randomized clinical trials. American Journal of Hypertension 15(8): 691–696. doi: 10.1016/S0895-7061(02)02964-3
166. Anderson JW, O'Neal DS, Riddell-Mason S et al. (1995) Postprandial serum glucose, insulin, and lipoprotein responses to high- and low-fiber diets. Metabolism 44(7): 848–854. doi: 10.1016/0026-0495(95)90236-8
167. Ebrahim S, Davey Smith G (2013) Commentary: Should we always deliberately be non-representative? Int J Epidemiol 42(4): 1022–1026. doi: 10.1093/ije/dyt105
168. Myung S-K, Ju W, Cho B et al. (2013) Efficacy of vitamin and antioxidant supplements in prevention of cardiovascular disease: systematic review and meta-analysis of randomised controlled trials. BMJ 346: f10. doi: 10.1136/bmj.f10

169. Hartley L, Igbinedion E, Holmes J et al. (2013) Increased consumption of fruit and vegetables for the primary prevention of cardiovascular diseases. Cochrane Database Syst Rev(6): CD009874. doi: 10.1002/14651858.CD009874.pub2
170. Mytton OT, Nnoaham K, Eyles H et al. (2017) Erratum to: systematic review and meta-analysis of the effect of increased vegetable and fruit consumption on body weight and energy intake. BMC Public Health 17(1): 662. doi: 10.1186/s12889-017-4664-2
171. Mytton OT, Nnoaham K, Eyles H et al. (2014) Systematic review and meta-analysis of the effect of increased vegetable and fruit consumption on body weight and energy intake. BMC Public Health 14: 886. doi: 10.1186/1471-2458-14-886
172. Schwingshackl L, Schwedhelm C, Hoffmann G et al. (2017) Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr 105(6): 1462–1473. doi: 10.3945/ajcn.117.153148
173. Wang X, Ouyang Y, Liu J et al. (2014) Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies. BMJ 349: g4490. doi: 10.1136/bmj.g4490
174. Leenders M, Sluijs I, Ros MM et al. (2013) Fruit and vegetable consumption and mortality: European prospective investigation into cancer and nutrition. Am J Epidemiol 178(4): 590–602. doi: 10.1093/aje/kwt006
175. Oyebode O, Gordon-Dseagu V, Walker A et al. (2014) Fruit and vegetable consumption and all-cause, cancer and CVD mortality: analysis of Health Survey for England data. J Epidemiol Community Health 68(9): 856–862. doi: 10.1136/jech-2013-203500
176. Nguyen B, Bauman A, Gale J et al. (2016) Fruit and vegetable consumption and all-cause mortality: evidence from a large Australian cohort study. Int J Behav Nutr Phys Act 13: 9. doi: 10.1186/s12966-016-0334-5
177. Du H, Li L, Bennett D et al. (2017) Fresh fruit consumption and all-cause and cause-specific mortality: findings from the China Kadoorie Biobank. Int J Epidemiol 46(5): 1444–1455. doi: 10.1093/ije/dyx042
178. Du H, Li L, Bennett D et al. (2016) Fresh Fruit Consumption and Major Cardiovascular Disease in China. N Engl J Med 374(14): 1332–1343. doi: 10.1056/NEJMoa1501451
179. Gan Y, Tong X, Li L et al. (2015) Consumption of fruit and vegetable and risk of coronary heart disease: a meta-analysis of prospective cohort studies. Int J Cardiol 183: 129–137. doi: 10.1016/j.ijcard.2015.01.077
180. Buil-Cosiales P, Martinez-Gonzalez MA, Ruiz-Canela M et al. (2017) Consumption of Fruit or Fiber-Fruit Decreases the Risk of Cardiovascular Disease in a Mediterranean Young Cohort. Nutrients 9(3). doi: 10.3390/nu9030295
181. Buil-Cosiales P, Toledo E, Salas-Salvadó J et al. (2016) Association between dietary fibre intake and fruit, vegetable or whole-grain consumption and the risk of CVD: results from the PREvención con DIeta MEDiterránea (PREDIMED) trial. Br J Nutr 116(3): 534–546. doi: 10.1017/S0007114516002099
182. Hu D, Huang J, Wang Y et al. (2014) Fruits and vegetables consumption and risk of stroke: a meta-analysis of prospective cohort studies. Stroke 45(6): 1613–1619. doi: 10.1161/STROKEAHA.114.004836
183. Schwingshackl L, Hoffmann G, Kalle-Uhlmann T et al. (2015) Fruit and Vegetable Consumption and Changes in Anthropometric Variables in Adult Populations: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. PLoS One 10(10): e0140846. doi: 10.1371/journal.pone.0140846
184. Schwingshackl L, Hoffmann G, Lampousi A-M et al. (2017) Food groups and risk of type 2 diabetes mellitus: a systematic review and meta-analysis of prospective studies. Eur J Epidemiol 32(5): 363–375. doi: 10.1007/s10654-017-0246-y
185. Du H, Li L, Bennett D et al. (2017) Fresh fruit consumption in relation to incident diabetes and diabetic vascular complications: A 7-y prospective study of 0.5 million Chinese adults. PLoS Med 14(4): e1002279. doi: 10.1371/journal.pmed.1002279

186. Norat T, Aune D, Chan D et al. (2014) Fruits and vegetables: updating the epidemiologic evidence for the WCRF/AICR lifestyle recommendations for cancer prevention. Cancer Treat Res 159: 35–50. doi: 10.1007/978-3-642-38007-5_3
187. Aune D, Lau R, Chan DSM et al. (2011) Nonlinear reduction in risk for colorectal cancer by fruit and vegetable intake based on meta-analysis of prospective studies. Gastroenterology 141(1): 106–118. doi: 10.1053/j.gastro.2011.04.013
188. Aune D, Chan DSM, Vieira AR et al. (2012) Fruits, vegetables and breast cancer risk: a systematic review and meta-analysis of prospective studies. Breast Cancer Res Treat 134(2): 479–493. doi: 10.1007/s10549-012-2118-1
189. Koushik A, Spiegelman D, Albanes D et al. (2012) Intake of fruits and vegetables and risk of pancreatic cancer in a pooled analysis of 14 cohort studies. Am J Epidemiol 176(5): 373–386. doi: 10.1093/aje/kws027
190. Vieira AR, Vingeliene S, Chan DSM et al. (2015) Fruits, vegetables, and bladder cancer risk: a systematic review and meta-analysis. Cancer Med 4(1): 136–146. doi: 10.1002/cam4.327
191. Vieira AR, Abar L, Vingeliene S et al. (2016) Fruits, vegetables and lung cancer risk: a systematic review and meta-analysis. Ann Oncol 27(1): 81–96. doi: 10.1093/annonc/mdv381
192. Xu C, Zeng X-T, Liu T-Z et al. (2015) Fruits and vegetables intake and risk of bladder cancer: a PRISMA-compliant systematic review and dose-response meta-analysis of prospective cohort studies. Medicine (Baltimore) 94(17): e759. doi: 10.1097/MD.0000000000000759
193. Leenders M, Siersema PD, Overvad K et al. (2015) Subtypes of fruit and vegetables, variety in consumption and risk of colon and rectal cancer in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer 137(11): 2705–2714. doi: 10.1002/ijc.29640
194. Vieira AR, Abar L, Chan DSM et al. (2017) Foods and beverages and colorectal cancer risk: a systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project. Ann Oncol 28(8): 1788–1802. doi: 10.1093/annonc/mdx171
195. Wang M, Qin S, Zhang T et al. (2015) The effect of fruit and vegetable intake on the development of lung cancer: a meta-analysis of 32 publications and 20,414 cases. Eur J Clin Nutr 69(11): 1184–1192. doi: 10.1038/ejcn.2015.64
196. Büchner FL, Bueno-de-Mesquita HB, Linseisen J et al. (2010) Fruits and vegetables consumption and the risk of histological subtypes of lung cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). Cancer Causes Control 21(3): 357–371. doi: 10.1007/s10552-009-9468-y
197. Vingeliene S, Chan DSM, Aune D et al. (2016) An update of the WCRF/AICR systematic literature review on esophageal and gastric cancers and citrus fruits intake. Cancer Causes Control 27(7): 837–851. doi: 10.1007/s10552-016-0755-0
198. Wang Q, Chen Y, Wang X et al. (2014) Consumption of fruit, but not vegetables, may reduce risk of gastric cancer: results from a meta-analysis of cohort studies. Eur J Cancer 50(8): 1498–1509. doi: 10.1016/j.ejca.2014.02.009
199. Bae J-M, Kim EH (2016) Dietary intakes of citrus fruit and risk of gastric cancer incidence: an adaptive meta-analysis of cohort studies. Epidemiol Health 38: e2016034. doi: 10.4178/epih.e2016034
200. Kaluza J, Larsson SC, Orsini N et al. (2017) Fruit and vegetable consumption and risk of COPD: a prospective cohort study of men. Thorax 72(6): 500–509. doi: 10.1136/thoraxjnl-2015-207851
251. Chatelan A, Beer-Borst S, Randriamiharisoa A et al. (2017) Major Differences in Diet across Three Linguistic Regions of Switzerland: Results from the First National Nutrition Survey menuCH. Nutrients 9(11). doi: 10.3390/nu9111163

10.5 References Chapter 5

2. Schweizerische Gesellschaft für Ernährung (2016) Schweizer Lebensmittelpyramide. http://www.sge-ssn.ch/ich-und-du/essen-und-trinken/ausgewogen/schweizer-lebensmittelpyramide/. Accessed 09 Oct 2019
107. World Health Organization (2015) Guideline - Sugars intake for adults and children. https://apps.who.int/iris/bitstream/handle/10665/149782/9789241549028_eng.pdf;jsessionid=DC965DE360BE777DDBE870E473B01A48?sequence=1
108. Scientific Advisory Committee on Nutrition (2015) Carbohydrates and health. https://www.gov.uk/government/publications/sacn-carbohydrates-and-health-report. Accessed 19 Nov 2019
114. Tappy L, Lê K-A (2010) Metabolic effects of fructose and the worldwide increase in obesity. Physiol Rev 90(1): 23–46. doi: 10.1152/physrev.00019.2009
201. Bray GA (2010) Fructose: pure, white, and deadly? Fructose, by any other name, is a health hazard. J Diabetes Sci Technol 4(4): 1003–1007. doi: 10.1177/193229681000400432
202. Bray GA (2012) Fructose and risk of cardiometabolic disease. Curr Atheroscler Rep 14(6): 570–578. doi: 10.1007/s11883-012-0276-6
203. Bundesamt für lebensmittelsicherheit und Veterinärwesen (2017) Getreideprodukte-, Kartoffel- und Hülsenfrüchtekonsum in der Schweiz 2014/15. www.blv.admin.ch%2Fdam%2Fblv%2Ffr%2Fdokumente%2Flebensmittel-und-ernaehrung%2Fernaehrung%2Ffi-menuch-getreide.pdf.download.pdf%2Ffi-menuch-getreide.pdf&usg=AOvVaw3apcb3VdeI-CBPcg28HOhs
204. Augustin LSA, Kendall CWC, Jenkins DJA et al. (2015) Glycemic index, glycemic load and glycemic response: An International Scientific Consensus Summit from the International Carbohydrate Quality Consortium (ICQC). Nutr Metab Cardiovasc Dis 25(9): 795–815. doi: 10.1016/j.numecd.2015.05.005
205. Blackburn P, Lemieux I, Lamarche B et al. (2012) Hypertriglyceridemic waist: a simple clinical phenotype associated with coronary artery disease in women. Metab Clin Exp 61(1): 56–64. doi: 10.1016/j.metabol.2011.05.017
206. Lemieux I, Poirier P, Bergeron J et al. (2007) Hypertriglyceridemic waist: A useful screening phenotype in preventive cardiology? Canadian Journal of Cardiology 23: 23B-31B. doi: 10.1016/S0828-282X(07)71007-3
207. Jenkins DJ, Wolever TM, Taylor RH et al. (1981) Glycemic index of foods: a physiological basis for carbohydrate exchange. Am J Clin Nutr 34(3): 362–366. doi: 10.1093/ajcn/34.3.362
208. Ferruzzi MG, Jonnalagadda SS, Liu S et al. (2014) Developing a standard definition of whole-grain foods for dietary recommendations: summary report of a multidisciplinary expert roundtable discussion. Adv Nutr 5(2): 164–176. doi: 10.3945/an.113.005223
209. Mozaffarian RS, Lee RM, Kennedy MA et al. (2013) Identifying whole grain foods: a comparison of different approaches for selecting more healthful whole grain products. Public Health Nutr 16(12): 2255–2264. doi: 10.1017/S1368980012005447
210. (2010) Scientific Opinion on Dietary Reference Values for carbohydrates and dietary fibre. EFS2 8(3): 605. doi: 10.2903/j.efsa.2010.1462
211. Parks EJ, Hellerstein MK (2000) Carbohydrate-induced hypertriacylglycerolemia: historical perspective and review of biological mechanisms. Am J Clin Nutr 71(2): 412–433. doi: 10.1093/ajcn/71.2.412
212. Fehily AM, Yarnell JW, Sweetnam PM et al. (1993) Diet and incident ischaemic heart disease: the Caerphilly Study. Br J Nutr 69(2): 303–314. doi: 10.1079/bjn19930035
213. Pietinen P, Rimm EB, Korhonen P et al. (1996) Intake of dietary fiber and risk of coronary heart disease in a cohort of Finnish men. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Circulation 94(11): 2720–2727. doi: 10.1161/01.cir.94.11.2720

214. Liu S, Willett WC, Stampfer MJ et al. (2000) A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. Am J Clin Nutr 71(6): 1455–1461. doi: 10.1093/ajcn/71.6.1455
215. Beulens JWJ, Bruijne LM de, Stolk RP et al. (2007) High dietary glycemic load and glycemic index increase risk of cardiovascular disease among middle-aged women: a population-based follow-up study. J Am Coll Cardiol 50(1): 14–21. doi: 10.1016/j.jacc.2007.02.068
216. Sieri S, Krogh V, Berrino F et al. (2010) Dietary glycemic load and index and risk of coronary heart disease in a large italian cohort: the EPICOR study. Arch Intern Med 170(7): 640–647. doi: 10.1001/archinternmed.2010.15
217. Burger KNJ, Beulens JWJ, Boer JMA et al. (2011) Dietary glycemic load and glycemic index and risk of coronary heart disease and stroke in Dutch men and women: the EPIC-MORGEN study. PLoS One 6(10): e25955. doi: 10.1371/journal.pone.0025955
218. Wallström P, Sonestedt E, Hlebowicz J et al. (2012) Dietary fiber and saturated fat intake associations with cardiovascular disease differ by sex in the Malmö Diet and Cancer Cohort: a prospective study. PLoS One 7(2): e31637. doi: 10.1371/journal.pone.0031637
219. Meyer KA, Kushi LH, Jacobs DR et al. (2000) Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. Am J Clin Nutr 71(4): 921–930. doi: 10.1093/ajcn/71.4.921
220. Hodge AM, English DR, O'Dea K et al. (2004) Glycemic index and dietary fiber and the risk of type 2 diabetes. Diabetes Care 27(11): 2701–2706. doi: 10.2337/diacare.27.11.2701
221. Barclay AW, Flood VM, Rochtchina E et al. (2007) Glycemic index, dietary fiber, and risk of type 2 diabetes in a cohort of older Australians. Diabetes Care 30(11): 2811–2813. doi: 10.2337/dc07-0784
222. Schulze MB, Schulz M, Heidemann C et al. (2008) Carbohydrate intake and incidence of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. Br J Nutr 99(5): 1107–1116. doi: 10.1017/S0007114507853360
223. Aune D, Keum N, Giovannucci E et al. (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: i2716. doi: 10.1136/bmj.i2716
224. Mellen PB, Walsh TF, Herrington DM (2008) Whole grain intake and cardiovascular disease: a meta-analysis. Nutr Metab Cardiovasc Dis 18(4): 283–290. doi: 10.1016/j.numecd.2006.12.008
225. Mirrahimi A, Souza RJ de, Chiavaroli L et al. (2012) Associations of glycemic index and load with coronary heart disease events: a systematic review and meta-analysis of prospective cohorts. J Am Heart Assoc 1(5): e000752. doi: 10.1161/JAHA.112.000752
226. Threapleton DE, Greenwood DC, Evans CEL et al. (2013) Dietary fibre intake and risk of cardiovascular disease: systematic review and meta-analysis. BMJ 347: f6879. doi: 10.1136/bmj.f6879
227. Threapleton DE, Greenwood DC, Evans CEL et al. (2013) Dietary fiber intake and risk of first stroke: a systematic review and meta-analysis. Stroke 44(5): 1360–1368. doi: 10.1161/STROKEAHA.111.000151
228. Greenwood DC, Threapleton DE, Evans CEL et al. (2013) Glycemic index, glycemic load, carbohydrates, and type 2 diabetes: systematic review and dose-response meta-analysis of prospective studies. Diabetes Care 36(12): 4166–4171. doi: 10.2337/dc13-0325

229. Kristensen M, Jensen MG, Riboldi G et al. (2010) Wholegrain vs. refined wheat bread and pasta. Effect on postprandial glycemia, appetite, and subsequent ad libitum energy intake in young healthy adults. Appetite 54(1): 163–169. doi: 10.1016/j.appet.2009.10.003
230. Geliebter A, Lee MI-C, Abdillahi M et al. (2013) Satiety following intake of potatoes and other carbohydrate test meals. Ann Nutr Metab 62(1): 37–43. doi: 10.1159/000342638
231. Wu M-Y, Bowtell JL, Williams CA (2014) Glycaemic index of meals affects appetite sensation but not energy balance in active males. Eur J Nutr 53(1): 309–319. doi: 10.1007/s00394-013-0529-3
232. Sichieri R, Moura AS, Genelhu V et al. (2007) An 18-mo randomized trial of a low-glycemic-index diet and weight change in Brazilian women. Am J Clin Nutr 86(3): 707–713. doi: 10.1093/ajcn/86.3.707
233. Juanola-Falgarona M, Salas-Salvadó J, Ibarrola-Jurado N et al. (2014) Effect of the glycemic index of the diet on weight loss, modulation of satiety, inflammation, and other metabolic risk factors: a randomized controlled trial. Am J Clin Nutr 100(1): 27–35. doi: 10.3945/ajcn.113.081216
234. Larsen TM, Dalskov S-M, van Baak M et al. (2010) Diets with high or low protein content and glycemic index for weight-loss maintenance. N Engl J Med 363(22): 2102–2113. doi: 10.1056/NEJMoa1007137
235. Aller EEJG, Larsen TM, Claus H et al. (2014) Weight loss maintenance in overweight subjects on ad libitum diets with high or low protein content and glycemic index: the DIOGENES trial 12-month results. Int J Obes (Lond) 38(12): 1511–1517. doi: 10.1038/ijo.2014.52
236. Ye EQ, Chacko SA, Chou EL et al. (2012) Greater whole-grain intake is associated with lower risk of type 2 diabetes, cardiovascular disease, and weight gain. J Nutr 142(7): 1304–1313. doi: 10.3945/jn.111.155325
237. Mullie P, Koechlin A, Boniol M et al. (2016) Relation between Breast Cancer and High Glycemic Index or Glycemic Load: A Meta-analysis of Prospective Cohort Studies. Crit Rev Food Sci Nutr 56(1): 152–159. doi: 10.1080/10408398.2012.718723
238. Aune D, Chan DSM, Lau R et al. (2011) Dietary fibre, whole grains, and risk of colorectal cancer: systematic review and dose-response meta-analysis of prospective studies. BMJ 343: d6617. doi: 10.1136/bmj.d6617
239. Zhang Z, Xu G, Ma M et al. (2013) Dietary fiber intake reduces risk for gastric cancer: a meta-analysis. Gastroenterology 145(1): 113-120.e3. doi: 10.1053/j.gastro.2013.04.001
240. Schlesinger S, Chan DSM, Vingeliene S et al. (2017) Carbohydrates, glycemic index, glycemic load, and breast cancer risk: a systematic review and dose-response meta-analysis of prospective studies. Nutr Rev 75(6): 420–441. doi: 10.1093/nutrit/nux010
241. Chen G-C, Tong X, Xu J-Y et al. (2016) Whole-grain intake and total, cardiovascular, and cancer mortality: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr 104(1): 164–172. doi: 10.3945/ajcn.115.122432
242. Wu H, Flint AJ, Qi Q et al. (2015) Association between dietary whole grain intake and risk of mortality: two large prospective studies in US men and women. JAMA Intern Med 175(3): 373–384. doi: 10.1001/jamainternmed.2014.6283
243. Kim Y, Je Y (2016) Dietary fibre intake and mortality from cardiovascular disease and all cancers: A meta-analysis of prospective cohort studies. Arch Cardiovasc Dis 109(1): 39–54. doi: 10.1016/j.acvd.2015.09.005
244. Bertoft E, Annor GA, Shen X et al. (2016) Small differences in amylopectin fine structure may explain large functional differences of starch. Carbohydr Polym 140: 113–121. doi: 10.1016/j.carbpol.2015.12.025
245. Dhital S, Dabit L, Zhang B et al. (2015) In vitro digestibility and physicochemical properties of milled rice. Food Chem 172: 757–765. doi: 10.1016/j.foodchem.2014.09.138

246. Heianza Y, Ma W, Manson JE et al. (2017) Gut Microbiota Metabolites and Risk of Major Adverse Cardiovascular Disease Events and Death: A Systematic Review and Meta-Analysis of Prospective Studies. J Am Heart Assoc 6(7). doi: 10.1161/JAHA.116.004947
247. Depoortere I (2014) Taste receptors of the gut: emerging roles in health and disease. Gut 63(1): 179–190. doi: 10.1136/gutjnl-2013-305112

10.6 References Chapter 6.1

2. Schweizerische Gesellschaft für Ernährung (2016) Schweizer Lebensmittelpyramide. http://www.sge-ssn.ch/ich-und-du/essen-und-trinken/ausgewogen/schweizer-lebensmittelpyramide/. Accessed 09 Oct 2019
42. Kromhout D, Spaaij CJK, Goede J de et al. (2016) The 2015 Dutch food-based dietary guidelines. Eur J Clin Nutr 70(8): 869–878. doi: 10.1038/ejcn.2016.52
248. Eidgenössische Ernährungskommission (2014) Gesundheitliche Aspekte des Fleischkonsums – Stellungnahme der Eidgenössischen Ernährungskommission zur aktuellen epidemiologischen Datenlage.: Expertenbericht der EEK. . https://www.blv.admin.ch/blv/de/home/das-blv/organisation/kommissionen/eek/gesundheitliche-aspekte-des-fleischkonsums.html. Accessed 12 Jan 2018
249. World Cancer Research Fund International and American Institute for Cancer Research (2018) Continuous Update Project Expert Report 2018. Meat, fish and dairy products and the risk of cancer.: 2018. www.dietandcancerreport.org
251. Chatelan A, Beer-Borst S, Randriamiharisoa A et al. (2017) Major Differences in Diet across Three Linguistic Regions of Switzerland: Results from the First National Nutrition Survey menuCH. Nutrients 9(11). doi: 10.3390/nu9111163
252. Agence nationale de sécurité sanitaire de l'alimentation de l'environnement et du travail (2016) Etude des relations entre consommation de groupes d'aliments et risque de maladies chroniques non transmissibles. https://www.anses.fr/fr/system/files/NUT2012SA0103Ra-3.pdf. Accessed 12 Jan 2018
253. World Cancer Research Fund International and American Institute for Cancer Research (2016) Continuous Update Project Report: Diet Nutrition, Physical Activity and Stomach Cancer. http://www.wcrf.org/stomach-cancer-2016. Accessed 23 Jan 2018
254. Bechthold A, Boeing H, Schwedhelm C et al. (2019) Food groups and risk of coronary heart disease, stroke and heart failure: A systematic review and dose-response meta-analysis of prospective studies. Crit Rev Food Sci Nutr 59(7): 1071–1090. doi: 10.1080/10408398.2017.1392288
255. Agence nationale de sécurité sanitaire de l'alimentation de l'environnement et du travail. (2016) Actualisation des repères du PNNS: révision des repères de consommaitons alimentaires. https://www.anses.fr/fr/system/files/NUT2012SA0103Ra-1.pdf. Accessed 14 Aug 2018
256. World Cancer Research Fund International and American Institute for Cancer Research (2018) Diet, Nutrition, Physical Activity and Cancer: a Global Perspective.: Continuous Update Project Expert Report. www.dietandcancerreport.org.
257. Piepoli MF, Hoes AW, Agewall S et al. (2016) 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 37(29): 2315–2381. doi: 10.1093/eurheartj/ehw106
258. World Cancer Research Fund International and American Institute for Cancer Research (2017) Continuous Update Project Report: Diet Nutrition, Physical Activity and Colorectal Cancer. http://www.wcrf.org/colorectal-cancer-2017. Accessed 23 Aug 2018

259. Schwingshackl L, Schwedhelm C, Hoffmann G et al. (2018) Food groups and risk of colorectal cancer. Int J Cancer 142(9): 1748–1758. doi: 10.1002/ijc.31198
260. World Cancer Research Fund International and American Institute for Cancer Research (2018) Continuous Update Project Report: Diet Nutrition, Physical Activity and Liver cancer. https://www.wcrf.org/sites/default/files/Liver-cancer-report.pdf. Accessed 13 Aug 2018
261. World Cancer Research Fund International and American Institute for Cancer Research. (2018) Continuous Update Project Report 2018. Recommendations and public health and policy impli-cations. www.dietandcancerreport.org
262. Agence nationale de sécurité sanitaire de l'alimentation de l'environnement et du travail (2013) avis de l'ANSES relatif aux recommandations sur les bénéfices et les risques liés à la consommation de produits de la pêche dans le cadre de l'actualisation des repères nutritionnels du PNNS: Avis du 3 juin 2013. https://www.anses.fr/fr/system/files/NUT2012sa0202.pdf

10.7 References Chapter 6.2

2. Schweizerische Gesellschaft für Ernährung (2016) Schweizer Lebensmittelpyramide. http://www.sge-ssn.ch/ich-und-du/essen-und-trinken/ausgewogen/schweizer-lebensmittelpyramide/. Accessed 09 Oct 2019
42. Kromhout D, Spaaij CJK, Goede J de et al. (2016) The 2015 Dutch food-based dietary guidelines. Eur J Clin Nutr 70(8): 869–878. doi: 10.1038/ejcn.2016.52
172. Schwingshackl L, Schwedhelm C, Hoffmann G et al. (2017) Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr 105(6): 1462–1473. doi: 10.3945/ajcn.117.153148
250. Bundesamt für lebensmittelsicherheit und Veterinärwesen (2017) Fleischkonsum in der Schweiz 2014/15. https://www.blv.admin.ch/dam/blv/fr/dokumente/lebensmittel-und-ernaehrung/ernaehrung/fi-menuch-fleisch.pdf.download.pdf/fi-menuch-fleisch.pdf
252. Agence nationale de sécurité sanitaire de l'alimentation de l'environnement et du travail (2016) Etude des relations entre consommation de groupes d'aliments et risque de maladies chroniques non transmissibles. https://www.anses.fr/fr/system/files/NUT2012SA0103Ra-3.pdf. Accessed 12 Jan 2018
258. World Cancer Research Fund International and American Institute for Cancer Research (2017) Continuous Update Project Report: Diet Nutrition, Physical Activity and Colorectal Cancer. http://www.wcrf.org/colorectal-cancer-2017. Accessed 23 Aug 2018
263. (2016) Verordnung des EDI über Lebensmittel tierischer Herkunft: 817.022.108
264. Sieber R (2011) Milch und Milchprodukte schweizerischer Herkunft. ALP-science, vol 538. Eidgenössische Forschungsanstalt f. Milchwirtschaft, Bern
265. German JB, Dillard CJ (2006) Composition, structure and absorption of milk lipids: a source of energy, fat-soluble nutrients and bioactive molecules. Crit Rev Food Sci Nutr 46(1): 57–92. doi: 10.1080/10408690590957098
266. Gaucheron F (2011) Milk and dairy products: a unique micronutrient combination. J Am Coll Nutr 30(5 Suppl 1): 400S-9S. doi: 10.1080/07315724.2011.10719983
267. Walther B, Schmid A (2017) Effect of Fermentation on Vitamin Content in Food. In: Frias J, Martinez-Villaluenga C, Penas E (ed) Fermented Foods in Health and Disease Prevention. Elsevier, pp 131–157
268. Kato-Kataoka A, Nishida K, Takada M et al. (2016) Fermented Milk Containing Lactobacillus casei Strain Shirota Preserves the Diversity of the Gut Microbiota and Relieves Abdominal Dysfunction in Healthy Medical Students Exposed to Academic Stress. Appl Environ Microbiol 82(12): 3649–3658. doi: 10.1128/aem.04134-15.
269. (2010) Scientific Opinion on the substantiation of health claims related to live yoghurt cultures and improved lactose digestion (ID 1143, 2976) pursuant to Article 13(1) of

Regulation (EC) No 1924/2006. EFSA Journal 8(10): 131. doi: 10.2903/j.efsa.2010.1763
270. Dallas DC, Sanctuary MR, Qu Y et al. (2017) Personalizing protein nourishment. Crit Rev Food Sci Nutr 57(15): 3313–3331. doi: 10.1080/10408398.2015.1117412
271. Afshin A, Sur PJ, Fay KA et al. (2019) Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet 393(10184): 1958–1972. doi: 10.1016/S0140-6736(19)30041-8
272. Muehlhoff E, Bennett A, MacMahon D (eds) (2013) Milk and dairy products in human nutrition. Food and Agriculture Organization of the United Nations, Rome
273. Alexander DD, Bylsma LC, Vargas AJ et al. (2016) Dairy consumption and CVD: a systematic review and meta-analysis. Br J Nutr 115(4): 737–750. doi: 10.1017/S0007114515005000
274. O'Sullivan TA, Hafekost K, Mitrou F et al. (2013) Food sources of saturated fat and the association with mortality: a meta-analysis. Am J Public Health 103(9): e31-42. doi: 10.2105/ajph.2013.301492.
275. Qin L-Q, Xu J-Y, Han S-F et al. (2015) Dairy consumption and risk of cardiovascular disease: an updated meta-analysis of prospective cohort studies. Asia Pac J Clin Nutr 24(1): 90–100. doi: 10.6133/apjcn.2015.24.1.09
276. Ralston RA, Lee JH, Truby H et al. (2012) A systematic review and meta-analysis of elevated blood pressure and consumption of dairy foods. J Hum Hypertens 26(1): 3–13. doi: 10.1038/jhh.2011.3.
277. Soedamah-Muthu SS, Verberne LDM, Ding EL et al. (2012) Dairy consumption and incidence of hypertension: a dose-response meta-analysis of prospective cohort studies. Hypertension 60(5): 1131–1137. doi: 10.1161/hypertensionaha.112.195206.
278. Gholami F, Khoramdad M, Esmailnasab N et al. (2017) The effect of dairy consumption on the prevention of cardiovascular diseases: A meta-analysis of prospective studies. J Cardiovasc Thorac Res 9(1): 1–11. doi: 10.15171/jcvtr.2017.01.
279. Chen M, Li Y, Sun Q et al. (2016) Dairy fat and risk of cardiovascular disease in 3 cohorts of US adults. Am J Clin Nutr 104(5): 1209–1217. doi: 10.3945/ajcn.116.134460.
280. Guo Y, Shan Z, Ren H et al. (2015) Dairy consumption and gastric cancer risk: a meta-analysis of epidemiological studies. Nutr Cancer 67(4): 555–568. doi: 10.1080/01635581.2015.1019634.
281. Drouin-Chartier J-P, Brassard D, Tessier-Grenier M et al. (2016) Systematic Review of the Association between Dairy Product Consumption and Risk of Cardiovascular-Related Clinical Outcomes. Adv Nutr 7(6): 1026–1040. doi: 10.3945/an.115.011403.
282. Souza RJ de, Mente A, Maroleanu A et al. (2015) Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. BMJ 351: h3978. doi: 10.1136/bmj.h3978.
283. Goede J de, Soedamah-Muthu SS, Pan A et al. (2016) Dairy Consumption and Risk of Stroke: A Systematic Review and Updated Dose-Response Meta-Analysis of Prospective Cohort Studies. J Am Heart Assoc 5(5). doi: 10.1161/jaha.115.002787
284. Hu D, Huang J, Wang Y et al. (2014) Dairy foods and risk of stroke: a meta-analysis of prospective cohort studies. Nutr Metab Cardiovasc Dis 24(5): 460–469. doi: 10.1016/j.numecd.2013.12.006
285. Tian D-y, Tian J, Shi C-h et al. (2015) Calcium intake and the risk of stroke: an updated meta-analysis of prospective studies. Asia Pac J Clin Nutr 24(2): 245–252. doi: 10.6133/apjcn.2015.24.2.22.
286. Bergholdt HKM, Nordestgaard BG, Varbo A et al. (2015) Milk intake is not associated with ischaemic heart disease in observational or Mendelian randomization analyses in 98,529 Danish adults. Int J Epidemiol 44(2): 587–603. doi: 10.1093/ije/dyv109.

287. Guo J, Astrup A, Lovegrove JA et al. (2017) Milk and dairy consumption and risk of cardiovascular diseases and all-cause mortality: dose-response meta-analysis of prospective cohort studies. Eur J Epidemiol 32(4): 269–287. doi: 10.1007/s10654-017-0243-1.
288. Benatar JR, Sidhu K, Stewart RAH (2013) Effects of high and low fat dairy food on cardio-metabolic risk factors: a meta-analysis of randomized studies. PLoS One 8(10): e76480. doi: 10.1371/journal.pone.0076480.
289. Dong J-Y, Szeto IMY, Makinen K et al. (2013) Effect of probiotic fermented milk on blood pressure: a meta-analysis of randomised controlled trials. Br J Nutr 110(7): 1188–1194. doi: 10.1017/s0007114513001712.
290. Khalesi S, Sun J, Buys N et al. (2014) Effect of probiotics on blood pressure: a systematic review and meta-analysis of randomized, controlled trials. Hypertension 64(4): 897–903. doi: 10.1161/hypertensionaha.114.03469.
291. Usinger L, Reimer C, Ibsen H (2012) Fermented milk for hypertension. Cochrane Database Syst Rev(4): CD008118. doi: 10.1002/14651858.CD008118.pub2.
292. Shimizu M, Hashiguchi M, Shiga T et al. (2015) Meta-Analysis: Effects of Probiotic Supplementation on Lipid Profiles in Normal to Mildly Hypercholesterolemic Individuals. PLoS One 10(10): e0139795. doi: 10.1371/journal.pone.0139795.
293. Sun J, Buys N (2015) Effects of probiotics consumption on lowering lipids and CVD risk factors: a systematic review and meta-analysis of randomized controlled trials. Ann Med 47(6): 430–440. doi: 10.3109/07853890.2015.1071872.
294. Kim Y, Je Y (2016) Dairy consumption and risk of metabolic syndrome: a meta-analysis. Diabet Med 33(4): 428–440. doi: 10.1111/dme.12970.
295. Chen G-C, Szeto IMY, Chen L-H et al. (2015) Dairy products consumption and metabolic syndrome in adults: systematic review and meta-analysis of observational studies. Sci Rep 5: 14606. doi: 10.1038/srep14606.
296. Babio N, Becerra-Tomás N, Martínez-González MÁ et al. (2015) Consumption of Yogurt, Low-Fat Milk, and Other Low-Fat Dairy Products Is Associated with Lower Risk of Metabolic Syndrome Incidence in an Elderly Mediterranean Population. J Nutr 145(10): 2308–2316. doi: 10.3945/jn.115.214593.
297. Shin B-R, Choi Y-K, Kim H-N et al. (2016) High dietary calcium intake and a lack of dairy consumption are associated with metabolic syndrome in obese males: the Korean National Health and Nutrition Examination Survey 2010 to 2012. Nutr Res 36(6): 518–525. doi: 10.1016/j.nutres.2016.01.002.
298. Drehmer M, Pereira MA, Schmidt MI et al. (2016) Total and Full-Fat, but Not Low-Fat, Dairy Product Intakes are Inversely Associated with Metabolic Syndrome in Adults. J Nutr 146(1): 81–89. doi: 10.3945/jn.115.220699.
299. Schwingshackl L, Hoffmann G, Schwedhelm C et al. (2016) Consumption of Dairy Products in Relation to Changes in Anthropometric Variables in Adult Populations: A Systematic Review and Meta-Analysis of Cohort Studies. PLoS One 11(6): e0157461. doi: 10.1371/journal.pone.0157461
300. Stonehouse W, Wycherley T, Luscombe-Marsh N et al. (2016) Dairy Intake Enhances Body Weight and Composition Changes during Energy Restriction in 18-50-Year-Old Adults-A Meta-Analysis of Randomized Controlled Trials. Nutrients 8(7). doi: 10.3390/nu8070394.
301. Abargouei AS, Janghorbani M, Salehi-Marzijarani M et al. (2012) Effect of dairy consumption on weight and body composition in adults: a systematic review and meta-analysis of randomized controlled clinical trials. Int J Obes (Lond) 36(12): 1485–1493. doi: 10.1038/ijo.2011.269.
302. Chen M, Pan A, Malik VS et al. (2012) Effects of dairy intake on body weight and fat: a meta-analysis of randomized controlled trials. Am J Clin Nutr 96(4): 735–747. doi: 10.3945/ajcn.112.037119.

303. Jones KW, Eller LK, Parnell JA et al. (2013) Effect of a dairy- and calcium-rich diet on weight loss and appetite during energy restriction in overweight and obese adults: a randomized trial. Eur J Clin Nutr 67(4): 371–376. doi: 10.1038/ejcn.2013.52.
304. Madjd A, Taylor MA, Mousavi N et al. (2016) Comparison of the effect of daily consumption of probiotic compared with low-fat conventional yogurt on weight loss in healthy obese women following an energy-restricted diet: a randomized controlled trial. Am J Clin Nutr 103(2): 323–329. doi: 10.3945/ajcn.115.120170.
305. Larnkjaer A, Arnberg K, Michaelsen KF et al. (2015) Effect of increased intake of skimmed milk, casein, whey or water on body composition and leptin in overweight adolescents: a randomized trial. Pediatr Obes 10(6): 461–467. doi: 10.1111/ijpo.12007.
306. Fathi Y, Faghih S, Zibaeenezhad MJ et al. (2016) Kefir drink leads to a similar weight loss, compared with milk, in a dairy-rich non-energy-restricted diet in overweight or obese premenopausal women: a randomized controlled trial. Eur J Nutr 55(1): 295–304. doi: 10.1007/s00394-015-0846-9.
307. Lappe JM, McMahon DJ, Laughlin A et al. (2017) The effect of increasing dairy calcium intake of adolescent girls on changes in body fat and weight. Am J Clin Nutr 105(5): 1046–1053. doi: 10.3945/ajcn.116.138941.
308. Celik N, Inanc N (2016) Effects of dairy products consumption on weight loss and blood chemistry in premenopausal obese women. J Pak Med Assoc 66(1): 76–82
309. Feeney EL, O'Sullivan A, Nugent AP et al. (2017) Patterns of dairy food intake, body composition and markers of metabolic health in Ireland: results from the National Adult Nutrition Survey. Nutr Diabetes 7(2): e243. doi: 10.1038/nutd.2016.54.
310. Crichton GE, Alkerwi A'a (2014) Whole-fat dairy food intake is inversely associated with obesity prevalence: findings from the Observation of Cardiovascular Risk Factors in Luxembourg study. Nutr Res 34(11): 936–943. doi: 10.1016/j.nutres.2014.07.014.
311. O'Sullivan TA, Bremner AP, Bremer HK et al. (2015) Dairy product consumption, dietary nutrient and energy density and associations with obesity in Australian adolescents. J Hum Nutr Diet 28(5): 452–464. doi: 10.1111/jhn.12264.
312. Aune D, Norat T, Romundstad P et al. (2013) Dairy products and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of cohort studies. Am J Clin Nutr 98(4): 1066–1083. doi: 10.3945/ajcn.113.059030.
313. Chen M, Sun Q, Giovannucci E et al. (2014) Dairy consumption and risk of type 2 diabetes: 3 cohorts of US adults and an updated meta-analysis. BMC Med 12: 215. doi: 10.1186/s12916-014-0215-1.
314. Gao D, Ning N, Wang C et al. (2013) Dairy products consumption and risk of type 2 diabetes: systematic review and dose-response meta-analysis. PLoS One 8(9): e73965. doi: 10.1371/journal.pone.0073965
315. Gijsbers L, Ding EL, Malik VS et al. (2016) Consumption of dairy foods and diabetes incidence: a dose-response meta-analysis of observational studies. Am J Clin Nutr 103(4): 1111–1124. doi: 10.3945/ajcn.115.123216.
316. Bergholdt HKM, Nordestgaard BG, Ellervik C (2015) Milk intake is not associated with low risk of diabetes or overweight-obesity: a Mendelian randomization study in 97,811 Danish individuals. Am J Clin Nutr 102(2): 487–496. doi: 10.3945/ajcn.114.105049.
317. Yakoob MY, Shi P, Willett WC et al. (2016) Circulating Biomarkers of Dairy Fat and Risk of Incident Diabetes Mellitus Among Men and Women in the United States in Two Large Prospective Cohorts. Circulation 133(17): 1645–1654. doi: 10.1161/circulationaha.115.018410.
318. Mozaffarian D, Oliveira Otto MC de, Lemaitre RN et al. (2013) trans-Palmitoleic acid, other dairy fat biomarkers, and incident diabetes: the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Clin Nutr 97(4): 854–861. doi: 10.3945/ajcn.112.045468.
319. Forouhi NG, Koulman A, Sharp SJ et al. (2014) Differences in the prospective association between individual plasma phospholipid saturated fatty acids and incident type 2

diabetes: the EPIC-InterAct case-cohort study. The Lancet Diabetes & Endocrinology 2(10): 810–818. doi: 10.1016/S2213-8587(14)70146-9
320. Drehmer M, Pereira MA, Schmidt MI et al. (2015) Associations of dairy intake with glycemia and insulinemia, independent of obesity, in Brazilian adults: the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Am J Clin Nutr 101(4): 775–782. doi: 10.3945/ajcn.114.102152
321. Eussen SJPM, van Dongen MCJM, Wijckmans N et al. (2016) Consumption of dairy foods in relation to impaired glucose metabolism and type 2 diabetes mellitus: the Maastricht Study. Br J Nutr 115(8): 1453–1461. doi: 10.1017/S0007114516000313.
322. Kratz M, Marcovina S, Nelson JE et al. (2014) Dairy fat intake is associated with glucose tolerance, hepatic and systemic insulin sensitivity, and liver fat but not β-cell function in humans. Am J Clin Nutr 99(6): 1385–1396. doi: 10.3945/ajcn.113.075457.
323. Rideout TC, Marinangeli CPF, Martin H et al. (2013) Consumption of low-fat dairy foods for 6 months improves insulin resistance without adversely affecting lipids or bodyweight in healthy adults: a randomized free-living cross-over study. Nutr J 12: 56. doi: 10.1186/1475-2891-12-56
324. Turner KM, Keogh JB, Clifton PM (2015) Red meat, dairy, and insulin sensitivity: a randomized crossover intervention study. Am J Clin Nutr 101(6): 1173–1179. doi: 10.3945/ajcn.114.104976.
325. Turner KM, Keogh JB, Clifton PM (2016) Acute effect of red meat and dairy on glucose and insulin: a randomized crossover study. Am J Clin Nutr 103(1): 71–76. doi: 10.3945/ajcn.115.123505.
326. Salas-Salvadó J, Guasch-Ferré M, Díaz-López A et al. (2017) Yogurt and Diabetes: Overview of Recent Observational Studies. J Nutr 147(7): 1452S-1461S. doi: 10.3945/jn.117.248229.
327. Kunz R, Burnand B, Schünemann HJ (2008) Das GRADE-System. Ein internationaler Ansatz zur Vereinheitlichung der Graduierung von Evidenz und Empfehlungen in Leitlinien (The GRADE System. An international approach to standardize the graduation of evidence and recommendations in guidelines). Internist (Berl) 49(6): 673–680. doi: 10.1007/s00108-008-2141-9.
328. Aune D, Lau R, Chan DSM et al. (2012) Dairy products and colorectal cancer risk: a systematic review and meta-analysis of cohort studies. Ann Oncol 23(1): 37–45. doi: 10.1093/annonc/mdr269.
329. Ralston RA, Truby H, Palermo CE et al. (2014) Colorectal cancer and nonfermented milk, solid cheese, and fermented milk consumption: a systematic review and meta-analysis of prospective studies. Crit Rev Food Sci Nutr 54(9): 1167–1179. doi: 10.1080/10408398.2011.629353.
330. Thorning TK, Raben A, Tholstrup T et al. (2016) Milk and dairy products: good or bad for human health? An assessment of the totality of scientific evidence. Food Nutr Res 60: 32527. doi: 10.3402/fnr.v60.32527.
331. Fardet A, Boirie Y (2014) Associations between food and beverage groups and major diet-related chronic diseases: an exhaustive review of pooled/meta-analyses and systematic reviews. Nutr Rev 72(12): 741–762. doi: 10.1111/nure.12153.
332. Aune D, Navarro Rosenblatt DA, Chan DSM et al. (2015) Dairy products, calcium, and prostate cancer risk: a systematic review and meta-analysis of cohort studies. Am J Clin Nutr 101(1): 87–117. doi: 10.3945/ajcn.113.067157.
333. World Cancer Research Fund International/American Institute for Cancer Research (2014) Diet, Nutrition, Physical Activity, and Prostate Cancer. https://www.wcrf.org/sites/default/files/Prostate-Cancer-2014-Report.pdf
334. Genkinger JM, Wang M, Li R et al. (2014) Dairy products and pancreatic cancer risk: a pooled analysis of 14 cohort studies. Ann Oncol 25(6): 1106–1115. doi: 10.1093/annonc/mdu019.

335. Tian S-b, Yu J-c, Kang W-m et al. (2014) Association between dairy intake and gastric cancer: a meta-analysis of observational studies. PLoS One 9(7): e101728. doi: 10.1371/journal.pone.0101728.
336. Sun Y, Lin L-J, Sang L-X et al. (2014) Dairy product consumption and gastric cancer risk: a meta-analysis. World J Gastroenterol 20(42): 15879–15898. doi: 10.3748/wjg.v20.i42.15879.
337. Liu J, Tang W, Sang L et al. (2015) Milk, yogurt, and lactose intake and ovarian cancer risk: a meta-analysis. Nutr Cancer 67(1): 68–72. doi: 10.1080/01635581.2014.956247.
338. Faber MT, Jensen A, Søgaard M et al. (2012) Use of dairy products, lactose, and calcium and risk of ovarian cancer - results from a Danish case-control study. Acta Oncol 51(4): 454–464. doi: 10.3109/0284186x.2011.636754.
339. Zang J, Shen M, Du S et al. (2015) The Association between Dairy Intake and Breast Cancer in Western and Asian Populations: A Systematic Review and Meta-Analysis. J Breast Cancer 18(4): 313–322. doi: 10.4048/jbc.2015.18.4.313.
340. World Cancer Research Fund International AIfCR. Diet, Nurition, Physical Activity, and Breast Cancer. Continuous Update Project Report. London, UK, 2017:120. (2017) Continuous Update Project Report: Diet, Nurition, Physical Activity, and Breast Cancer. https://www.wcrf.org/sites/default/files/Breast-Cancer-2017-Report.pdf
341. Yang Y, Wang X, Yao Q et al. (2016) Dairy Product, Calcium Intake and Lung Cancer Risk: A Systematic Review with Meta-Analysis. Sci Rep 6: 20624. doi: 10.1038/srep20624.
342. Yu Y, Li H, Xu K et al. (2016) Dairy consumption and lung cancer risk: a meta-analysis of prospective cohort studies. Onco Targets Ther 9: 111–116. doi: 10.2147/OTT.S95714.
343. Tognon G, Nilsson LM, Shungin D et al. (2017) Nonfermented milk and other dairy products: associations with all-cause mortality. Am J Clin Nutr 105(6): 1502–1511. doi: 10.3945/ajcn.116.140798.
344. Larsson SC, Crippa A, Orsini N et al. (2015) Milk Consumption and Mortality from All Causes, Cardiovascular Disease, and Cancer: A Systematic Review and Meta-Analysis. Nutrients 7(9): 7749–7763. doi: 10.3390/nu7095363.
345. Max Rubner- Institut (2014) Ernährungsphysiologische Bewertung von Milch und Milchprodukten und ihren Inhaltsstoffen. https://www.bmel.de/SharedDocs/Downloads/Ernaehrung/Gesundheit/Milch-und-Milchprodukte.pdf?__blob=publicationFile
346. Mozaffarian D (2016) Dietary and Policy Priorities for Cardiovascular Disease, Diabetes, and Obesity: A Comprehensive Review. Circulation 133(2): 187–225. doi: 10.1161/circulationaha.115.018585
347. Drouin-Chartier J-P, Côté JA, Labonté M-È et al. (2016) Comprehensive Review of the Impact of Dairy Foods and Dairy Fat on Cardiometabolic Risk. Adv Nutr 7(6): 1041–1051. doi: 10.3945/an.115.011619.
348. Grimes DA, Schulz KF (2012) False alarms and pseudo-epidemics: the limitations of observational epidemiology. Obstet Gynecol 120(4): 920–927. doi: 10.1097/AOG.0b013e31826af61a.
349. Frias J, Martinez-Villaluenga C, Penas E (ed) (2017) Fermented Foods in Health and Disease Prevention. Elsevier

10.8 References Chapter 6.3

2. Schweizerische Gesellschaft für Ernährung (2016) Schweizer Lebensmittelpyramide. http://www.sge-ssn.ch/ich-und-du/essen-und-trinken/ausgewogen/schweizer-lebensmittelpyramide/. Accessed 09 Oct 2019
172. Schwingshackl L, Schwedhelm C, Hoffmann G et al. (2017) Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr 105(6): 1462–1473. doi: 10.3945/ajcn.117.153148

184. Schwingshackl L, Hoffmann G, Lampousi A-M et al. (2017) Food groups and risk of type 2 diabetes mellitus: a systematic review and meta-analysis of prospective studies. Eur J Epidemiol 32(5): 363–375. doi: 10.1007/s10654-017-0246-y
194. Vieira AR, Abar L, Chan DSM et al. (2017) Foods and beverages and colorectal cancer risk: a systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project. Ann Oncol 28(8): 1788–1802. doi: 10.1093/annonc/mdx171
271. Afshin A, Sur PJ, Fay KA et al. (2019) Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet 393(10184): 1958–1972. doi: 10.1016/S0140-6736(19)30041-8
350. Campos-Vega R, Loarca-Piña G, Oomah BD (2010) Minor components of pulses and their potential impact on human health. Food Research International 43(2): 461–482. doi: 10.1016/j.foodres.2009.09.004
351. Havemeier S, Erickson J, Slavin J (2017) Dietary guidance for pulses: the challenge and opportunity to be part of both the vegetable and protein food groups. Ann N Y Acad Sci 1392(1): 58–66. doi: 10.1111/nyas.13308
352. Pasiakos SM, Agarwal S, Lieberman HR et al. (2015) Sources and Amounts of Animal, Dairy, and Plant Protein Intake of US Adults in 2007-2010. Nutrients 7(8): 7058–7069. doi: 10.3390/nu7085322
353. Song M, Fung TT, Hu FB et al. (2016) Association of Animal and Plant Protein Intake With All-Cause and Cause-Specific Mortality. JAMA Intern Med 176(10): 1453–1463. doi: 10.1001/jamainternmed.2016.4182
354. Marventano S, Izquierdo Pulido M, Sánchez-González C et al. (2017) Legume consumption and CVD risk: a systematic review and meta-analysis. Public Health Nutr 20(2): 245–254. doi: 10.1017/S1368980016002299
355. Afshin A, Micha R, Khatibzadeh S et al. (2014) Consumption of nuts and legumes and risk of incident ischemic heart disease, stroke, and diabetes: a systematic review and meta-analysis. Am J Clin Nutr 100(1): 278–288. doi: 10.3945/ajcn.113.076901
356. Zhu B, Sun Y, Qi L et al. (2015) Dietary legume consumption reduces risk of colorectal cancer: evidence from a meta-analysis of cohort studies. Sci Rep 5: 8797. doi: 10.1038/srep08797
357. (2017) 13. DGE-Ernährungsbericht, 1. Auflage. Deutsche Ges. f. Ernährung, Bonn
358. Dong J-Y, Qin L-Q (2011) Soy isoflavones consumption and risk of breast cancer incidence or recurrence: a meta-analysis of prospective studies. Breast Cancer Res Treat 125(2): 315–323. doi: 10.1007/s10549-010-1270-8
359. Kim SJ, Souza RJ de, Choo VL et al. (2016) Effects of dietary pulse consumption on body weight: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr 103(5): 1213–1223. doi: 10.3945/ajcn.115.124677
360. Lin Y, Mouratidou T, Vereecken C et al. (2015) Dietary animal and plant protein intakes and their associations with obesity and cardio-metabolic indicators in European adolescents: the HELENA cross-sectional study. Nutr J 14: 10. doi: 10.1186/1475-2891-14-10
361. van Nielen M, Feskens EJM, Mensink M et al. (2014) Dietary protein intake and incidence of type 2 diabetes in Europe: the EPIC-InterAct Case-Cohort Study. Diabetes Care 37(7): 1854–1862. doi: 10.2337/dc13-2627
362. Shang X, Scott D, Hodge AM et al. (2016) Dietary protein intake and risk of type 2 diabetes: results from the Melbourne Collaborative Cohort Study and a meta-analysis of prospective studies. Am J Clin Nutr 104(5): 1352–1365. doi: 10.3945/ajcn.116.140954
363. Viguiliouk E, Stewart SE, Jayalath VH et al. (2015) Effect of Replacing Animal Protein with Plant Protein on Glycemic Control in Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients 7(12): 9804–9824. doi: 10.3390/nu7125509

364. Campmans-Kuijpers MJ, Sluijs I, Nöthlings U et al. (2015) Isocaloric substitution of carbohydrates with protein: the association with weight change and mortality among patients with type 2 diabetes. Cardiovasc Diabetol 14: 39. doi: 10.1186/s12933-015-0202-7
365. Fernandez-Lopez A, Lamothe V, Delample M et al. (2016) Removing isoflavones from modern soyfood: Why and how? Food Chem 210: 286–294. doi: 10.1016/j.foodchem.2016.04.126

10.9 References Chapter 7.1

2. Schweizerische Gesellschaft für Ernährung (2016) Schweizer Lebensmittelpyramide. http://www.sge-ssn.ch/ich-und-du/essen-und-trinken/ausgewogen/schweizer-lebensmittelpyramide/. Accessed 09 Oct 2019
3. Bundesamt für Lebensmittelsicherheit und Veterinärwesen, L (2019) Ergebnisse zum Lebensmittelkonsum. https://www.blv.admin.ch/blv/de/home/lebensmittel-und-ernaehrung/ernaehrung/menuch/menu-ch-ergebnisse-ernaehrung.html. Accessed 09 Oct 2019
42. Kromhout D, Spaaij CJK, Goede J de et al. (2016) The 2015 Dutch food-based dietary guidelines. Eur J Clin Nutr 70(8): 869–878. doi: 10.1038/ejcn.2016.52
106. U.S. Department of Health and Human Services and U.S. Department of Agriculture (2015) 2015–2020 Dietary Guidelines for Americans. 8th Edition… https://health.gov/dietaryguidelines/2015/guidelines/.
160. Estruch R, Ros E, Salas-Salvadó J et al. (2018) Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. N Engl J Med 378(25): e34. doi: 10.1056/NEJMoa1800389
172. Schwingshackl L, Schwedhelm C, Hoffmann G et al. (2017) Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr 105(6): 1462–1473. doi: 10.3945/ajcn.117.153148
271. Afshin A, Sur PJ, Fay KA et al. (2019) Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet 393(10184): 1958–1972. doi: 10.1016/S0140-6736(19)30041-8
346. Mozaffarian D (2016) Dietary and Policy Priorities for Cardiovascular Disease, Diabetes, and Obesity: A Comprehensive Review. Circulation 133(2): 187–225. doi: 10.1161/circulationaha.115.018585
366. Mensink RP, Zock PL, Kester ADM et al. (2003) Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. Am J Clin Nutr 77(5): 1146–1155. doi: 10.1093/ajcn/77.5.1146
367. Forouhi NG, Krauss RM, Taubes G et al. (2018) Dietary fat and cardiometabolic health: evidence, controversies, and consensus for guidance. BMJ 361: k2139. doi: 10.1136/bmj.k2139
368. Michas G, Micha R, Zampelas A (2014) Dietary fats and cardiovascular disease: putting together the pieces of a complicated puzzle. Atherosclerosis 234(2): 320–328. doi: 10.1016/j.atherosclerosis.2014.03.013
369. O'Sullivan TA, Hafekost K, Mitrou F et al. (2013) Food sources of saturated fat and the association with mortality: a meta-analysis. Am J Public Health 103(9): e31-42. doi: 10.2105/AJPH.2013.301492
370. Brassard D, Tessier-Grenier M, Allaire J et al. (2017) Comparison of the impact of SFAs from cheese and butter on cardiometabolic risk factors: a randomized controlled trial. Am J Clin Nutr 105(4): 800–809. doi: 10.3945/ajcn.116.150300
371. Thorning TK, Bertram HC, Bonjour J-P et al. (2017) Whole dairy matrix or single nutrients in assessment of health effects: current evidence and knowledge gaps. Am J Clin Nutr 105(5): 1033–1045. doi: 10.3945/ajcn.116.151548

372. Colombani P, Keller U, Moser U, Müller M. (2006) Fette in der Ernährung- Expertenbericht der Eidgenössischen Ernährungskommission. https://www.blv.admin.ch/blv/de/home/das-blv/organisation/kommissionen/eek/fette-in-der-ernaehrung1.html
373. Keller U, Moser U, Darioli R. (2012) Fette in der Ernährung–Aktualisierte Empfehlungen der Eidgenössischen Ernährungskommission. https://www.blv.admin.ch/dam/eek/de/dokumente/publikation-und-dokumentation/empfehlung-fette-ernaehrung.pdf.download.pdf/3_EEK_Revision%20Fettempfehlungen%202012_FINAL_D.pdf
374. Obrist L, Walther B, Schmid A (2018) Trendanalysen zum Nahrungsmittelverbrauch in der Schweiz. Schweizer Ernährungsbulletin: 5–22
375. Visioli F, Bellomo G, Galli C (1998) Free radical-scavenging properties of olive oil polyphenols. Biochem Biophys Res Commun 247(1): 60–64. doi: 10.1006/bbrc.1998.8735
376. Mente A, Koning L de, Shannon HS et al. (2009) A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. Arch Intern Med 169(7): 659–669. doi: 10.1001/archinternmed.2009.38
377. Hooper L, Summerbell CD, Thompson R et al. (2012) Reduced or modified dietary fat for preventing cardiovascular disease. Cochrane Database Syst Rev(5): CD002137. doi: 10.1002/14651858.CD002137.pub3
378. Alhazmi A, Stojanovski E, McEvoy M et al. (2012) Macronutrient intakes and development of type 2 diabetes: a systematic review and meta-analysis of cohort studies. J Am Coll Nutr 31(4): 243–258. doi: 10.1080/07315724.2012.10720425
379. Chowdhury R, Warnakula S, Kunutsor S et al. (2014) Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. Ann Intern Med 160(6): 398–406. doi: 10.7326/M13-1788
380. Siri-Tarino PW, Sun Q, Hu FB et al. (2010) Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease12345. Am J Clin Nutr 91(3): 535–546. doi: 10.3945/ajcn.2009.27725
381. Schwingshackl L, Hoffmann G (2014) Monounsaturated fatty acids, olive oil and health status: a systematic review and meta-analysis of cohort studies. Lipids Health Dis 13: 154. doi: 10.1186/1476-511X-13-154
382. Farvid MS, Ding M, Pan A et al. (2014) Dietary linoleic acid and risk of coronary heart disease: a systematic review and meta-analysis of prospective cohort studies. Circulation 130(18): 1568–1578. doi: 10.1161/CIRCULATIONAHA.114.010236
383. Pan A, Sun Q, Bernstein AM et al. (2012) Red Meat Consumption and Mortality: Results from Two Prospective Cohort Studies. Arch Intern Med 172(7): 555–563. doi: 10.1001/archinternmed.2011.2287
384. Wu JHY, Micha R, Imamura F et al. (2012) Omega-3 fatty acids and incident type 2 diabetes: a systematic review and meta-analysis. Br J Nutr 107 Suppl 2: S214-27. doi: 10.1017/S0007114512001602
385. Mozaffarian D, Rimm EB (2006) Fish intake, contaminants, and human health: evaluating the risks and the benefits. JAMA 296(15): 1885–1899. doi: 10.1001/jama.296.15.1885
386. Larsson SC, Virtamo J, Wolk A (2012) Dietary fats and dietary cholesterol and risk of stroke in women. Atherosclerosis 221(1): 282–286. doi: 10.1016/j.atherosclerosis.2011.12.043
387. Mozaffarian D, Katan MB, Ascherio A et al. (2006) Trans fatty acids and cardiovascular disease. N Engl J Med 354(15): 1601–1613. doi: 10.1056/NEJMra054035
388. Harcombe Z, Baker JS, Davies B (2017) Evidence from prospective cohort studies does not support current dietary fat guidelines: a systematic review and meta-analysis. Br J Sports Med 51(24): 1743–1749. doi: 10.1136/bjsports-2016-096550

389. Micha R, Shulkin ML, Peñalvo JL et al. (2017) Etiologic effects and optimal intakes of foods and nutrients for risk of cardiovascular diseases and diabetes: Systematic reviews and meta-analyses from the Nutrition and Chronic Diseases Expert Group (NutriCoDE). PLoS One 12(4): e0175149. doi: 10.1371/journal.pone.0175149
390. Micha R, Peñalvo JL, Cudhea F et al. (2017) Association Between Dietary Factors and Mortality From Heart Disease, Stroke, and Type 2 Diabetes in the United States. JAMA 317(9): 912–924. doi: 10.1001/jama.2017.0947
391. Alexander DD, Miller PE, van Elswyk ME et al. (2017) A Meta-Analysis of Randomized Controlled Trials and Prospective Cohort Studies of Eicosapentaenoic and Docosahexaenoic Long-Chain Omega-3 Fatty Acids and Coronary Heart Disease Risk. Mayo Clin Proc 92(1): 15–29. doi: 10.1016/j.mayocp.2016.10.018
392. Pimpin L, Wu JHY, Haskelberg H et al. (2016) Is Butter Back? A Systematic Review and Meta-Analysis of Butter Consumption and Risk of Cardiovascular Disease, Diabetes, and Total Mortality. PLoS One 11(6): e0158118. doi: 10.1371/journal.pone.0158118
393. Souza RJ de, Mente A, Maroleanu A et al. (2015) Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. BMJ 351: h3978. doi: 10.1136/bmj.h3978
394. Hooper L, Martin N, Abdelhamid A et al. (2015) Reduction in saturated fat intake for cardiovascular disease. Cochrane Database Syst Rev(6): CD011737. doi: 10.1002/14651858.CD011737
395. Wen YT, Dai JH, Gao Q (2014) Effects of Omega-3 fatty acid on major cardiovascular events and mortality in patients with coronary heart disease: a meta-analysis of randomized controlled trials. Nutr Metab Cardiovasc Dis 24(5): 470–475. doi: 10.1016/j.numecd.2013.12.004
396. Schwingshackl L, Hoffmann G (2014) Dietary fatty acids in the secondary prevention of coronary heart disease: a systematic review, meta-analysis and meta-regression. BMJ Open 4(4): e004487. doi: 10.1136/bmjopen-2013-004487
397. Goede J de, Verschuren WMM, Boer JMA et al. (2013) N-6 and N-3 fatty acid cholesteryl esters in relation to fatal CHD in a Dutch adult population: a nested case-control study and meta-analysis. PLoS One 8(5): e59408. doi: 10.1371/journal.pone.0059408
398. Ramsden CE, Zamora D, Leelarthaepin B et al. (2013) Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis. BMJ 346: e8707. doi: 10.1136/bmj.e8707
399. Pan A, Chen M, Chowdhury R et al. (2012) α-Linolenic acid and risk of cardiovascular disease: a systematic review and meta-analysis. Am J Clin Nutr 96(6): 1262–1273. doi: 10.3945/ajcn.112.044040
400. Kotwal S, Jun M, Sullivan D et al. (2012) Omega 3 Fatty acids and cardiovascular outcomes: systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes 5(6): 808–818. doi: 10.1161/CIRCOUTCOMES.112.966168
401. Cheng P, Wang J, Shao W et al. (2016) Can dietary saturated fat be beneficial in prevention of stroke risk? A meta-analysis. Neurol Sci 37(7): 1089–1098. doi: 10.1007/s10072-016-2548-3
402. Cheng P, Huang W, Bai S et al. (2015) BMI Affects the Relationship between Long Chain N-3 Polyunsaturated Fatty Acid Intake and Stroke Risk: a Meta-Analysis. Sci Rep 5: 14161. doi: 10.1038/srep14161
403. Martínez-González MA, Dominguez LJ, Delgado-Rodríguez M (2014) Olive oil consumption and risk of CHD and/or stroke: a meta-analysis of case-control, cohort and intervention studies. Br J Nutr 112(2): 248–259. doi: 10.1017/S0007114514000713

404. Larsson SC, Orsini N, Wolk A (2012) Long-chain omega-3 polyunsaturated fatty acids and risk of stroke: a meta-analysis. Eur J Epidemiol 27(12): 895–901. doi: 10.1007/s10654-012-9748-9
405. Chowdhury R, Stevens S, Gorman D et al. (2012) Association between fish consumption, long chain omega 3 fatty acids, and risk of cerebrovascular disease: systematic review and meta-analysis. BMJ 345: e6698. doi: 10.1136/bmj.e6698
406. Jovanovski E, Li D, Thanh Ho HV et al. (2017) The effect of alpha-linolenic acid on glycemic control in individuals with type 2 diabetes: A systematic review and meta-analysis of randomized controlled clinical trials. Medicine (Baltimore) 96(21): e6531. doi: 10.1097/MD.0000000000006531
407. Wu JHY, Marklund M, Imamura F et al. (2017) Omega-6 fatty acid biomarkers and incident type 2 diabetes: pooled analysis of individual-level data for 39 740 adults from 20 prospective cohort studies. The Lancet Diabetes & Endocrinology 5(12): 965–974. doi: 10.1016/S2213-8587(17)30307-8
408. Schwingshackl L, Lampousi A-M, Portillo MP et al. (2017) Olive oil in the prevention and management of type 2 diabetes mellitus: a systematic review and meta-analysis of cohort studies and intervention trials. Nutr Diabetes 7(4): e262. doi: 10.1038/nutd.2017.12
409. Lin N, Shi J-J, Li Y-M et al. (2016) What is the impact of n-3 PUFAs on inflammation markers in Type 2 diabetic mellitus populations?: a systematic review and meta-analysis of randomized controlled trials. Lipids Health Dis 15: 133. doi: 10.1186/s12944-016-0303-7
410. Qian F, Korat AA, Malik V et al. (2016) Metabolic Effects of Monounsaturated Fatty Acid-Enriched Diets Compared With Carbohydrate or Polyunsaturated Fatty Acid-Enriched Diets in Patients With Type 2 Diabetes: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Diabetes Care 39(8): 1448–1457. doi: 10.2337/dc16-0513
411. Imamura F, Micha R, Wu JHY et al. (2016) Effects of Saturated Fat, Polyunsaturated Fat, Monounsaturated Fat, and Carbohydrate on Glucose-Insulin Homeostasis: A Systematic Review and Meta-analysis of Randomised Controlled Feeding Trials. PLoS Med 13(7): e1002087. doi: 10.1371/journal.pmed.1002087
412. Abbott KA, Burrows TL, Thota RN et al. (2016) Do ω-3 PUFAs affect insulin resistance in a sex-specific manner? A systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr 104(5): 1470–1484. doi: 10.3945/ajcn.116.138172
413. Chen C, Yu X, Shao S (2015) Effects of Omega-3 Fatty Acid Supplementation on Glucose Control and Lipid Levels in Type 2 Diabetes: A Meta-Analysis. PLoS One 10(10): e0139565. doi: 10.1371/journal.pone.0139565
414. Aronis KN, Khan SM, Mantzoros CS (2012) Effects of trans fatty acids on glucose homeostasis: a meta-analysis of randomized, placebo-controlled clinical trials. Am J Clin Nutr 96(5): 1093–1099. doi: 10.3945/ajcn.112.040576
415. Zheng J-S, Huang T, Yang J et al. (2012) Marine N-3 polyunsaturated fatty acids are inversely associated with risk of type 2 diabetes in Asians: a systematic review and meta-analysis. PLoS One 7(9): e44525. doi: 10.1371/journal.pone.0044525
416. Zhou Y, Tian C, Jia C (2012) Association of fish and n-3 fatty acid intake with the risk of type 2 diabetes: a meta-analysis of prospective studies. Br J Nutr 108(3): 408–417. doi: 10.1017/S0007114512002036
417. Wallin A, Di Giuseppe D, Orsini N et al. (2012) Fish consumption, dietary long-chain n-3 fatty acids, and risk of type 2 diabetes: systematic review and meta-analysis of prospective studies. Diabetes Care 35(4): 918–929. doi: 10.2337/dc11-1631
418. Mansoor N, Vinknes KJ, Veierød MB et al. (2016) Effects of low-carbohydrate diets v. low-fat diets on body weight and cardiovascular risk factors: a meta-analysis of randomised controlled trials. Br J Nutr 115(3): 466–479. doi: 10.1017/S0007114515004699

419. Tobias DK, Chen M, Manson JE et al. (2015) Effect of low-fat diet interventions versus other diet interventions on long-term weight change in adults: a systematic review and meta-analysis. The Lancet Diabetes & Endocrinology 3(12): 968–979. doi: 10.1016/S2213-8587(15)00367-8
420. Sackner-Bernstein J, Kanter D, Kaul S (2015) Dietary Intervention for Overweight and Obese Adults: Comparison of Low-Carbohydrate and Low-Fat Diets. A Meta-Analysis. PLoS One 10(10): e0139817. doi: 10.1371/journal.pone.0139817
421. Hooper L, Abdelhamid A, Bunn D et al. (2015) Effects of total fat intake on body weight. Cochrane Database Syst Rev(8): CD011834. doi: 10.1002/14651858.CD011834
422. Brennan SF, Woodside JV, Lunny PM et al. (2017) Dietary fat and breast cancer mortality: A systematic review and meta-analysis. Crit Rev Food Sci Nutr 57(10): 1999–2008. doi: 10.1080/10408398.2012.724481
423. Zhao J, Lyu C, Gao J et al. (2016) Dietary fat intake and endometrial cancer risk: A dose response meta-analysis. Medicine (Baltimore) 95(27): e4121. doi: 10.1097/MD.0000000000004121
424. Cao Y, Hou L, Wang W (2016) Dietary total fat and fatty acids intake, serum fatty acids and risk of breast cancer: A meta-analysis of prospective cohort studies. Int J Cancer 138(8): 1894–1904. doi: 10.1002/ijc.29938
425. Xia H, Ma S, Wang S et al. (2015) Meta-Analysis of Saturated Fatty Acid Intake and Breast Cancer Risk. Medicine (Baltimore) 94(52): e2391. doi: 10.1097/MD.0000000000002391
426. Han J, Jiang Y, Liu X et al. (2015) Dietary Fat Intake and Risk of Gastric Cancer: A Meta-Analysis of Observational Studies. PLoS One 10(9): e0138580. doi: 10.1371/journal.pone.0138580
427. Grosso G, Micek A, Marventano S et al. (2016) Dietary n-3 PUFA, fish consumption and depression: A systematic review and meta-analysis of observational studies. J Affect Disord 205: 269–281. doi: 10.1016/j.jad.2016.08.011
428. Zhang Y, Chen J, Qiu J et al. (2016) Intakes of fish and polyunsaturated fatty acids and mild-to-severe cognitive impairment risks: a dose-response meta-analysis of 21 cohort studies. Am J Clin Nutr 103(2): 330–340. doi: 10.3945/ajcn.115.124081
429. Appleton KM, Sallis HM, Perry R et al. (2015) Omega-3 fatty acids for depression in adults. Cochrane Database Syst Rev(11): CD004692. doi: 10.1002/14651858.CD004692.pub4
430. Cooper RE, Tye C, Kuntsi J et al. (2015) Omega-3 polyunsaturated fatty acid supplementation and cognition: A systematic review and meta-analysis. J Psychopharmacol (Oxford) 29(7): 753–763. doi: 10.1177/0269881115587958
431. Dehghan M, Mente A, Zhang X et al. (2017) Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. The Lancet 390(10107): 2050–2062. doi: 10.1016/S0140-6736(17)32252-3
432. May-Wilson S, Sud A, Law PJ et al. (2017) Pro-inflammatory fatty acid profile and colorectal cancer risk: A Mendelian randomisation analysis. Eur J Cancer 84: 228–238. doi: 10.1016/j.ejca.2017.07.034
433. Guasch-Ferré M, Babio N, Martínez-González MA et al. (2015) Dietary fat intake and risk of cardiovascular disease and all-cause mortality in a population at high risk of cardiovascular disease. Am J Clin Nutr 102(6): 1563–1573. doi: 10.3945/ajcn.115.116046
434. Ramsden CE, Zamora D, Majchrzak-Hong S et al. (2016) Re-evaluation of the traditional diet-heart hypothesis: analysis of recovered data from Minnesota Coronary Experiment (1968-73). BMJ 353: i1246. doi: 10.1136/bmj.i1246
435. Wang DD, Li Y, Chiuve SE et al. (2016) Association of Specific Dietary Fats With Total and Cause-Specific Mortality. JAMA Intern Med 176(8): 1134–1145. doi: 10.1001/jamainternmed.2016.2417

436. Wu JHY, Lemaitre RN, King IB et al. (2014) Circulating omega-6 polyunsaturated fatty acids and total and cause-specific mortality: the Cardiovascular Health Study. Circulation 130(15): 1245–1253. doi: 10.1161/CIRCULATIONAHA.114.011590
437. Eyres L, Eyres MF, Chisholm A et al. (2016) Coconut oil consumption and cardiovascular risk factors in humans. Nutr Rev 74(4): 267–280. doi: 10.1093/nutrit/nuw002

10.10 References Chapter 7.2

2. Schweizerische Gesellschaft für Ernährung (2016) Schweizer Lebensmittelpyramide. http://www.sge-ssn.ch/ich-und-du/essen-und-trinken/ausgewogen/schweizer-lebensmittelpyramide/. Accessed 09 Oct 2019
3. Bundesamt für Lebensmittelsicherheit und Veterinärwesen, L (2019) Ergebnisse zum Lebensmittelkonsum. https://www.blv.admin.ch/blv/de/home/lebensmittel-und-ernaehrung/ernaehrung/menuch/menu-ch-ergebnisse-ernaehrung.html. Accessed 09 Oct 2019
160. Estruch R, Ros E, Salas-Salvadó J et al. (2018) Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. N Engl J Med 378(25): e34. doi: 10.1056/NEJMoa1800389
172. Schwingshackl L, Schwedhelm C, Hoffmann G et al. (2017) Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr 105(6): 1462–1473. doi: 10.3945/ajcn.117.153148
271. Afshin A, Sur PJ, Fay KA et al. (2019) Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet 393(10184): 1958–1972. doi: 10.1016/S0140-6736(19)30041-8
355. Afshin A, Micha R, Khatibzadeh S et al. (2014) Consumption of nuts and legumes and risk of incident ischemic heart disease, stroke, and diabetes: a systematic review and meta-analysis. Am J Clin Nutr 100(1): 278–288. doi: 10.3945/ajcn.113.076901
438. Brufau G, Boatella J, Rafecas M (2006) Nuts: source of energy and macronutrients. Br J Nutr 96 Suppl 2: S24-8. doi: 10.1017/bjn20061860
439. Chung KH, Shin KO, Hwang HJ et al. (2013) Chemical composition of nuts and seeds sold in Korea. Nutr Res Pract 7(2): 82–88. doi: 10.4162/nrp.2013.7.2.82
440. Committee DGA, HHS OoDPaHP, USDA CfNPP et al. (2016) Dietary Guidelines for Americans 2015-2020. Office of Disease Prevention and Health Promotion, Washington
441. Harvard University Healthy Eating Plate. https://www.hsph.harvard.edu/nutritionsource/healthy-eating-plate/. Accessed 29 May 2017
442. PREDIMED Pyramids. http://www.predimed.es/pyramids.html. Accessed 29 May 2017
443. Flores-Mateo G, Rojas-Rueda D, Basora J et al. (2013) Nut intake and adiposity: meta-analysis of clinical trials. Am J Clin Nutr 97(6): 1346–1355. doi: 10.3945/ajcn.111.031484
444. Perna S, Giacosa A, Bonitta G et al. (2016) Effects of Hazelnut Consumption on Blood Lipids and Body Weight: A Systematic Review and Bayesian Meta-Analysis. Nutrients 8(12). doi: 10.3390/nu8120747
445. Abazarfard Z, Salehi M, Keshavarzi S (2014) The effect of almonds on anthropometric measurements and lipid profile in overweight and obese females in a weight reduction program: A randomized controlled clinical trial. J Res Med Sci 19(5): 457–464
446. Gulati S, Misra A, Pandey RM et al. (2014) Effects of pistachio nuts on body composition, metabolic, inflammatory and oxidative stress parameters in Asian Indians with metabolic syndrome: a 24-wk, randomized control trial. Nutrition 30(2): 192–197. doi: 10.1016/j.nut.2013.08.005
447. Kasliwal RR, Bansal M, Mehrotra R et al. (2015) Effect of pistachio nut consumption on endothelial function and arterial stiffness. Nutrition 31(5): 678–685. doi: 10.1016/j.nut.2014.10.019

448. Sauder KA, McCrea CE, Ulbrecht JS et al. (2015) Effects of pistachios on the lipid/lipoprotein profile, glycemic control, inflammation, and endothelial function in type 2 diabetes: A randomized trial. Metab Clin Exp 64(11): 1521–1529. doi: 10.1016/j.metabol.2015.07.021
449. Martin N, Germanò R, Hartley L et al. (2015) Nut consumption for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev(9): CD011583. doi: 10.1002/14651858.CD011583.pub2
450. Wu L, Piotrowski K, Rau T et al. (2014) Walnut-enriched diet reduces fasting non-HDL-cholesterol and apolipoprotein B in healthy Caucasian subjects: a randomized controlled cross-over clinical trial. Metab Clin Exp 63(3): 382–391. doi: 10.1016/j.metabol.2013.11.005
451. Del Gobbo LC, Falk MC, Feldman R et al. (2015) Effects of tree nuts on blood lipids, apolipoproteins, and blood pressure: systematic review, meta-analysis, and dose-response of 61 controlled intervention trials. Am J Clin Nutr 102(6): 1347–1356. doi: 10.3945/ajcn.115.110965
452. Blanco Mejia S, Kendall CWC, Viguiliouk E et al. (2014) Effect of tree nuts on metabolic syndrome criteria: a systematic review and meta-analysis of randomised controlled trials. BMJ Open 4(7): e004660. doi: 10.1136/bmjopen-2013-004660
453. Lamuel-Raventos RM, Onge M-PS (2017) Prebiotic nut compounds and human microbiota. Crit Rev Food Sci Nutr 57(14): 3154–3163. doi: 10.1080/10408398.2015.1096763
454. Guasch-Ferré M, Bulló M, Martínez-González MÁ et al. (2013) Frequency of nut consumption and mortality risk in the PREDIMED nutrition intervention trial. BMC Med 11: 164. doi: 10.1186/1741-7015-11-164
455. Shao C, Tang H, Zhao W et al. (2016) Nut intake and stroke risk: A dose-response meta-analysis of prospective cohort studies. Sci Rep 6: 30394. doi: 10.1038/srep30394
456. Grosso G, Yang J, Marventano S et al. (2015) Nut consumption on all-cause, cardiovascular, and cancer mortality risk: a systematic review and meta-analysis of epidemiologic studies. Am J Clin Nutr 101(4): 783–793. doi: 10.3945/ajcn.114.099515
457. Aune D, Keum N, Giovannucci E et al. (2016) Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: a systematic review and dose-response meta-analysis of prospective studies. BMC Med 14(1): 207. doi: 10.1186/s12916-016-0730-3
458. Bao Y, Han J, Hu FB et al. (2013) Association of nut consumption with total and cause-specific mortality. N Engl J Med 369(21): 2001–2011. doi: 10.1056/NEJMoa1307352
459. Baer DJ, Gebauer SK, Novotny JA (2016) Walnuts Consumed by Healthy Adults Provide Less Available Energy than Predicted by the Atwater Factors. J Nutr 146(1): 9–13. doi: 10.3945/jn.115.217372
460. Mattes RD, Dreher ML (2010) Nuts and healthy body weight maintenance mechanisms. Asia Pac J Clin Nutr 19(1): 137–141
461. Lee JT, Lai GY, Liao LM et al. (2017) Nut Consumption and Lung Cancer Risk: Results from Two Large Observational Studies. Cancer Epidemiol Biomarkers Prev 26(6): 826–836. doi: 10.1158/1055-9965.EPI-16-0806
462. Nakanishi M, Chen Y, Qendro V et al. (2016) Effects of Walnut Consumption on Colon Carcinogenesis and Microbial Community Structure. Cancer Prev Res (Phila) 9(8): 692–703. doi: 10.1158/1940-6207.CAPR-16-0026
463. Du Toit G, Roberts G, Sayre PH et al. (2015) Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med 372(9): 803–813. doi: 10.1056/NEJMoa1414850

10.11 References Chapter 8

464. Moubarac J-C, Parra DC, Cannon G et al. (2014) Food Classification Systems Based on Food Processing: Significance and Implications for Policies and Actions: A Systematic Literature Review and Assessment. Curr Obes Rep 3(2): 256–272. doi: 10.1007/s13679-014-0092-0
465. Monteiro CA, Cannon G, Moubarac J-C et al. (2018) The UN Decade of Nutrition, the NOVA food classification and the trouble with ultra-processing. Public Health Nutr 21(1): 5–17. doi: 10.1017/S1368980017000234
466. Potter M, Vlassopoulos A, Lehmann U (2018) Snacking Recommendations Worldwide: A Scoping Review. Adv Nutr 9(2): 86–98. doi: 10.1093/advances/nmx003
467. Drewnowski A (2017) Uses of nutrient profiling to address public health needs: from regulation to reformulation. Proc Nutr Soc 76(3): 220–229. doi: 10.1017/S0029665117000416

Table S1. Meta-analyses on dietary fat or fatty acid intake in relation to cardiovascular disease (CVD) and stroke

Source	Study category	Disease	End point	Main nutritional theme	No. of included studies	No. of subjects	Subject group	Duration	RR (95%CI)	Limitations	Conclusions	LOE[1] [26]
Harcombe Z, 2017	Meta-analysis of PCs	**CHD**	Mortality	Total fat and SFA intake	6 PCs	89'801	Adults without CHD	6-20 yrs	The RR 1.04 (0.98-1.1) for total fat, and 1.08 (0.94-1.25) for SFA	Lack of generalisability, dietary recalls are unreliable	Epidemiological evidence to date found no significant association between CHD mortality and total fat or saturated fat intake	II a
Micha R 2017 (PLoS1)	Meta-analysis and systematic review of meta-analyses of PCs & RCTs	CVD & diabetes	Disease risk	10 foods & 7 nutrients (including PUFA & trans)	23 meta-analyses	140'000-820'000	Adults		Refers to individual meta-analyses	Possible bias by clustering of dietary patterns which could still cause unmeasured confounding, e.g., from clustering of healthful factors.	There was evidence for protective cardiometabolic effects of seafood omega-3s, polyunsaturated fats, and adverse effects of trans-fats. Optimal mean population intake of PUFA replacing SAFA or CHO: 11% E [of 2000 kcal]	I a & II a
Micha R 2017 (JAMA)	Data from NHANES & meta-analyses of PCs & RCTs	CVD & diabetes	Mortality	10 dietary factors (including PUFA & seafood omega-3 fats)	not stated	not stated	Adults	years	CHD: PUFAs,%energy replacing carbohydrates or saturated fats per 5% energy/d (age 50): RR 0.88 (0.83-0.94); Seafood omega 3 per 100 mg/d: RR0.82 (0.075-0.90)	Dietary habits were based on self-reported 24-hour recalls, which have known measure-ment errors for individual people	Most cardiometabolic deaths in USA were estimated to be related to excess sodium intake, insufficient intake of nuts/seeds, high intake of processed meats, and low intake of seafood omega-3 fats	I a & II a
Alexander D. et al. 2017	Meta-analysis of PCs & RCTs	CHD	Risk & mortality	EPA &DHA from foods or supplements	18 RCTs & 16 PCs	93,000 (RCT trials) & 732,000 in PC studies	Adults with and without CHD	5-40 yrs	Among RCTs, risk reduction (CHD) with EPA&DHA (SRRE=0.94; 95% CI, 0.85-1.05) was n.s. Subgroup analyses indicated a significant CHD risk reduction with EPA&DHA in higher-risk populations (e.g. with elevated TG levels (SRRE=0.84; 95% CI, 0.72-0.98) and elevated LDL-c (SRRE=0.86; 95% CI, 0.76-0.98). Meta-analysis of PCs resulted in a significant SRRE of 0.82 (95% CI, 0.74-0.92) for higher intakes of EPA&DHA	Large heterogeneity of studies	EPA&DHA may be associated with reducing CHD risk, with a greater benefit observed among higher-risk populations in RCTs	I a & II a
Pimpin 2016	Meta-analysis of PCs	CVD, Mortality	Risk & Mortality	Butter	15 PCs	636'151	Adults	10-22 yrs	Butter consumption (14 g/d) was weakly associated with mortality; RR = 1.01, 95%CI = 1.00, 1.03, P =0.045) but not with any CVD(RR = 1.00,95%CI = 0.98, 1.02; P = 0.704), CHD (RR = 0.99, 95%CI = 0.96,1.03; P = 0.537), or stroke (N = 3; RR = 1.01, 95%CI = 0.98, 1.03; P = 0.737)	No evidence for heterogeneity nor publication bias	There were relatively small or neutral overall associations of butter with mortality & CVD	II a

[1] LOE= Level Of Evidence

de Souza RJ, 2015	Meta-analysis of PCs	CVD, stroke, diabetes	Risk & mortality	SFA & trans fats (industrial & ruminant)	12 PCs	90'500-339'000	Adults	Not stated	RR SFA 0.99 (0.91-1.09) for total mortality, 0.95 (0.88-1.03) for CVD mortality, 1.02 (0.9-1.15) for stroke, 0.95 (0.88-1.03) for DM. Industrial, but not ruminant, trans fats were associated with CHD mortality (1.18 (1.04 to 1.33) v 1.01 (0.71 to 1.43)) and CHD (1.42 (1.05 to 1.92) v 0.93 (0.73 to 1.18))	Evidence is heterogeneous; methodological limitations	SFA are not associated with all cause mortality, CVD, CHD, ischemic stroke, or type 2 diabetes, but the evidence is heterogeneous with methodological limitations. Trans fats are associated with all cause mortality, total CHD, and CHD mortality, probably because of higher levels of intake of industrial than ruminant trans fat	II a
Hooper L. 2015 (Cochrane)	Meta-analysis of RCTs	CVD	Morbidity, mortality	Replacing SFA with CHO, PUFA or other nutrients	15 RCTs	59'000	Adults	>2 yrs	Reducing dietary saturated fat reduced the risk of cardiovascular events by 17% (risk ratio (RR) 0.83; 95% confidence interval (CI) 0.72 to 0.96, mainly when saturated fat calories replaced polyunsaturated fat	The studies provide mode-rate-quality evi-dence that redu-cing SFA and replacing it with PUFA reduces our risk of CVD	A small but potentially important reduction in cardiovascular risk on reduction of saturated fat intake is observed when replacing SFA with PUFA	I a
Farvid M.S. 2014	Meta-analysis of PCs	CHD	Risk & death	Dietary linoleic acid	13 PCs	310'602	Adults	5.3-30 yrs	Highest vs lowest category of LA intake resulted in a 15% lower risk of CHD events (pooled RR, 0.85; 95% CI 0.78–0.92; /2=35.5%), and a 21% lower risk of CHD deaths (pooled RR, 0.79; 95% CI 0.71–0.89; /2=0.0%). A 5% of energy increment in LA intake replacing SFA was associated with a 9% lower risk of CHD events (RR, 0.91; 95% CI, 0.87–0.96) and a 13% lower risk of CHD deaths (RR, 0.87; 95% CI, 0.82–0.94)	No evidence of publication bias for either CHD events or death.	In prospective observational studies, dietary LA intake is inversely associated with CHD risk in a dose– response manner. These data provide support for current recommendations to replace saturated fat with polyunsaturated fat for primary prevention of CHD	II a
Wen YT, 2014	Meta-analysis of RCTs	CV events & mortality	CV events & mortality	Omega 3 PUFA supplements	14 RCTs	16'338	Patients with CHD	3 mo.- 4.6 yrs	Omega-3 PUFAs did not demonstrate satisfactory improvements of major cardiovascular events (OR, 0.93; 95% CI, 0.86 to 1.01; P Z 0.08; I2 Z 46%). By contrast, omega3 PUFAs reduced risks of death from cardiac causes and death from all causes (OR, 0.88; 95% CI, 0.80 to 0.96; P= 0.003; OR, 0.86; 95% CI, 0.76 to 0.98; P= 0.03; and OR, 0.92; 95% CI, 0.85 to 0.99; P= 0.02)	No evidence of publication bias for either CHD events or death	Supplement of Omega-3 PUFAs in patients with CHD does not prevent major cardiovascular events, but reduces death from cardiac causes and death from all causes. Whether dietary supplementation with Omega-3 PUFAs should be still considered in patients with CHD is currently debated	I a

Schwings-hackl L, 2014 [BMJ open]	Meta-analysis of RCTs	CHD	Risk & death	Fat reduction; replacing SFA with PUFA or other nutrients	12 RCTs	7'150	Patients with CHD	1-6 yrs	When comparing modified fat diets versus control diets no significant risk reduction could be observed considering all-cause mortality (RR 0.92, p=0.60; I2=59%) and cardiovascular mortality (RR 0.96, p=0.84; I2=69%), combined cardiovascular events (RR 0.85, p=0.30; I2=75%) and myocardial infarction (RR 0.76, p=0.13; I2=55%). Sensitivity analyses did not reveal a significant risk reduction for any outcome parameter when polyunsaturated fat was increased in exchange for saturated fat	Some studies were >50 yrs old. Substantial heterogeneity for several outcomes	Recommending higher intakes of PUFA in replacement of SFA was not associated with risk reduction in patients with CHD	I a
Chowdhury R, 2014	Systematic review & meta-analysis of observational studies & of RCTs	CHD	Risk	Dietary & circulating fatty acids	32 observational studies, 27 RCTs	up to 512'000	Adults, with and without CHD	5-23 yrs in PCs, 1-8 yrs in RCTs	In observational studies, relative risks for CHD were 1.03 (95% CI, 0.98 to 1.07) for SFA, 1.00 (CI, 0.91 to 1.10) for MUFA, 0.87 (CI, 0.78 to 0.97) for LC n-3 PUFA, 0.98 (CI, 0.90 to 1.06) for n-6 PUFA, and 1.16 (CI, 1.06 to 1.27) for trans fatty acids when the top and bottom thirds of baseline dietary fatty acid intake were compared. In RCTs, relative risks for CHD were 0.97 (CI, 0.69 to 1.36) for ALA, 0.94 (CI, 0.86 to 1.03) for LC n-3 PUFA, and 0.86 (CI, 0.69 to 1.07) for n-6 PUFA supplementations	Potential biases from preferential publication and selective reporting	Current evidence from RCTs does not clearly support cardiovascular guidelines that encourage high consumption of polyunsaturated fatty acids and low consumption of total saturated fats	I a & II a
de Goede J, 2013	Meta-Analysis of 2 cohort studies	CHD	Mortality	Associations with plasma fatty acid cholesteryl esters	2 observational cohorts	558	Dutch adults	8-19 yrs	After adjustment for confounders, the OR (95%CI) for fatal CHD per SD increase in plasma linoleic acid was 0.89 (0.74–1.06). The ORs (95%CI) for fatal CHD for an SD increase in n-3 PUFA were 0.92 (0.74–1.15) for alpha-linolenic acid and 1.06 (0.88–1.27) for EPA-DHA. In the meta-analysis, a 5% higher linoleic acid level was associated with a 9% lower risk (relative risk: 0.91; 95% CI: 0.84–0.98) of CHD	Blood samples were stored >10 yrs. Data of plasma n-3 FA esters were possibly unreliable	Linoleic acid in plasma cholesteryl is inversely associated with CHD. There was no such relation with n-3 PUFA cholesteryl esters	II a

Ramsden CE, 2013	RCT (Sydney Diet Heart Study) & meta-Analysis of RCTs	CHD	Mortality	Dietary linoleic acid (LA)	1 (+2+4) RCTs	458	Men with recent CHD		Replacement of dietary SFA with omega 6 LA (intervention) had higher rates of death than controls (all cause 17.6% v 11.8%, HR 1.62 (95% CI 1.00 to 2.64), P=0.05; CVD 17.2% v 11.0%, 1.70 (1.03 to 2.80), P=0.04; CHD 6.3% v 10.1%, 1.74 (1.04 to 2.92), P=0.04)	Results of borderline significance. Small trial	□-Linoleic acid intervention trials showed no evidence of cardiovascular benefit	I a
Pan A, 2012	Meta-analysis of cohorts	CVD	Risk	Dietary □-linolenic acid (ALA)	27 cohorts (pro-& retrospecti ve)	251'049	Adults	5- 33.7 yrs	The overall pooled RR was 0.86 (95% CI: 0.77, 0.97; I2 = 71.3%). The association was n.s. with biomarkers of ALA	High unexplained heterogeneity	Higher ALA exposure is associated with a moderately lower risk of CVD. The results were generally consistent for dietary studies but were not statistically significant for biomarker studies	II a
Kotwal S, 2012	Meta-analysis of RCTs	CVD	Risk & death	Omega 3 PUFA supplements (fish oil) or intervention	20 RCTs	>60'000	Mostly patients with CHD	0.6-7 yrs	There was no overall effect of ω-3 FA on composite cardiovascular events (RR=0.96; 95% CI, 0.90–1.03; *P*=0.24) or on total mortality (RR=0.95; 95% CI, 0.86–1.04; *P*=0.28). ω-3 FA did protect against vascular death (RR=0.86; 95% CI, 0.75–0.99; *P*=0.03) but not coronary events (RR=0.86; 95% CI, 0.67–1.11; *P*=0.24)	Significant heterogeneity between the trials	Omega 3 fatty acids did not protect against composite cardiovascular events but showed some protection against CV death. There is no clear effect on total mortality, sudden death, stroke, or arrhythmia. The beneficial effects of omega 3 fatty acids are not as large as previously implied	I a
Hooper L. 2012 (Cochrane)	Meta-analysis of RCTs	CVD	Risk & death	Fat intake, replacement of fat with other macronutrients	48 RCTs	>80'000	Adults, with and without CHD	>6 mo	Reducing SFA by reducing and/or modifying dietary fat reduced the risk of CV events by 14% (RR 0.86, 95%CI 0.77 to 0.96, 24 comparisons, 65'508 participants of whom 7% had a cardiovascular event).Subgrouping suggested that this reduction was observed only in studies of at least two years duration and in men (not of women). Dietary fat reduction/modification had no effect on total and on CV mortality	Uncertainty over allocation concealment, lack of blinding and presence of systematic differences- but scale and consistency of evidence makes findings relatively robust	Modifying fat in our food (replacing some SFA with plant oils and unsaturated spreads) may reduce risk of heart and vascular disease, but it is not clear whether MUFA or PUFA are more beneficial. There were no clear effects of dietary fat changes on total and cardiovascular mortality	I a

Schwings-hackl L, 2014 [Lipids Health Dis]	Meta-analysis of PCs	CVD & **stroke**	CV events & mortality, stroke risk	Monounsaturated fatty acids, olive oil	32 PCs	841'211	Adults, most of them without CVD at baseline	4.6- 30 yrs	The comparison of the top versus bottom third of the distribution of a combination of MUFA (of both plant and animal origin) showed reduced all-cause mortality (RR: 0.89, 95% CI 0.83, 0.96, p = 0.001; I2 = 64%), CV mortality (RR: 0.88, 95% CI 0.80,0.96, p = 0.004; I2 = 50%), CV events (RR: 0.91, 95% CI 0.86, 0.96, p = 0.001; I2 = 58%), and stroke (RR: 0.83,95% CI 0.71, 0.97, p = 0.02).	Potential public-cation bias for combined CV events (p = 0.018) & total mortality (p = 0.041). No evidence of publication bias for risk of CHD (p = 0.28) and stroke (p = 0.28)	There was an overall risk reduction of stroke (17%) when comparing the top versus bottom third of MUFA, olive oil, oleic acid, and MUFA:SFA ratio. Only olive oil seems to be associated with reduced risk	II a
Cheng P, 2016	Meta-analysis of cohorts	Stroke	Risk & death	SFA	15 PCs	476'569	Adults	7.6- 18 yrs	Higher SFA intake was associated with reduced stroke risks for East-Asians [RR = 0.79 (95 % CI 0.69–0.90)], for dose <25 g/day [RR = 0.81 (95 % CI 0.71–0.92)], for males [RR = 0.85 (95 % CI 0.75–0.96)], and for individuals with body mass index (BMI) <24 [RR = 0.75 (95 % CI 0.65–0.87)], but not for non-East- Asians, females, and individuals with dose >25 g/day and BMI >24	Possible threshold effect of SFA consumption	Higher consumption of SFA was associated with decreased stroke risk (morbidity, mortality) in certain groups of subjects (not in Non-East-Asians)	II a
Cheng P 2015	Meta-analysis of cohorts	Stroke	Risk & death	Long-chain n-3 PUFA	14 PCs	514'483	Adults	4-21.2 yrs	Higher long chain n-3 PUFA intake was associated with reduced overall stroke risk [relative risk (RR) = 0.87; 95% confidence interval (CI), 0.79–0.95	Significant heterogeneity between the trials	Higher long chain n-3 PUFA intake is inversely associated with risk of stroke morbidity and mortality	II a
Martínez-González MA 2014	Meta-analysis of cohorts; 1 RCT	Stroke	Risk	Olive Oil consumption	2 PCs, 1 RCT	Ca. 40'000	Adults	years	The combined RR of stroke for an increment of 25 g olive oil consumed per d was 0·76 (95% CI 0·67, 0·86; P,0·001), with a negligible change after including the PREDIMED trial	Relatively few trials	Higher olive oil intake is inversely associated with risk of stroke incidence	I a & II b
Larssen SC 2012	Meta-analysis of PCs	Stroke	Risk	Long-chain n-3 PUFA	8 PCs	242'076	Adults	4-28 yrs	The combined RR of total stroke was 0.90 (95 % CI, 0.81–1.01) for the highest versus lowest category of long-chain omega-3 PUFA intake, without heterogeneity among studies (P = 0.32)		No association between stroke risk & n-3 PUFA intake	II a

Chowdhury R, 2012	Meta-analysis of PC & RCTs	Stroke (cerebro-vascular disease)	Risk & mortality	Long-chain n-3 PUFA	26 PC2 & 12 RCTs	794'000	Adult with & without CVD	3- 15.1 yrs	The RR for cerebrovascular disease comparing the top thirds of baseline LC omega 3 fatty acids with the bottom thirds for circulating biomarkers was 1.04 (0.90 to 1.20) and for dietary exposures was 0.90 (0.80 to 1.01). In the RCTs the RR for cerebrovascular disease in the LC omega 3 supplement compared with the control group in primary prevention trials was 0.98 (0.89 to 1.08) and in secondary prevention trials 1.17 (0.99 to 1.38)		There were moderate, inverse associations of fish consump-tion and LC omega 3 fatty acids with cerebrovascular risk. LC omega 3 fatty acids in RCTs with supplements had no significant effect	I a & II a

Table S2. Meta-analyses on dietary fat or fatty acid intake in relation to diabetes type 2 and obesity

Source	Study category	Disease	End point	Main nutritional theme	No. of included studies	No. of subjects	Subject group	Duration	RR (95%CI)	Limitations	Conclusions	LOE
Jovanovski E 2017	Systematic review & meta-analysis of RCTs	**Diabetes T2**	Glycemic control, insulin sensitivity	□-linolenic acid	8 RCTs	212	Adults with DM T2	3 months	n.s. for: HbA1c, IR (HOMA), FBG	Considerable unexplained heterogeneity	□-linolenic acid-enriched diets did not affect HbA1c, FBG, or FBI.	I a
Wu J.H.Y 2017	Systematic review & meta-analysis of PCs	Diabetes T2	New diabetes risk	Omega-6 fatty acid biomarkers	20 PCs	39'740	Adults	mean 8 yrs	Higher proportions of linoleic acid biomarkers as % of total fatty acid were associated with a lower risk of type 2 diabetes [RR per interquintile range 0·65, 95% CI 0·60–0·72, p<0.0001). Levels of arachidonic acid were n.s.	Linoleic acid biomarkers reflect dietary intake but are not identical to dietary intake	Linoleic acid has long-term benefits for the prevention of type 2 DM and that arachidonic acid is not harmful	II a
Schwingshackl L 2017	Systematic review & meta-analysis of PCs	Diabetes T2	Diabetes T2 risk & glycemic control	Olive oil	4 PCs, 29 RCTs	15'784 DM T2	Adults with and without DM T2	5- 22 yrs for PCs, 2 wks-4 yrs for RCTs	The highest olive oil intake category showed a 16% reduced risk of T2D (RR: 0.84; 95% CI: 0.77, 0.92) compared with the lowest. In T2D patients olive oil supplementation resulted in a significantly more pronounced reduction in HbA1c (MD: − 0.27%; 95% CI: − 0.37, − 0.17) and fasting plasma glucose (MD: − 0.44 mmol/; 95% CI − 0.66, − 0.22) as compared with the control groups	There was evidence for a nonlinear relationship	Olive oil could be beneficial for the prevention and management of T2D	II a
Lin N 2016	Systematic review & meta-analysis of RCTs	Diabetes T2	CRP, other markers of inflammation	n-3 PUFA, mostly fish oil	8 RCTs	955	Adults with DM T2	6- 12 weeks	N-3 PUFAs significantly reduced CRP concentration compared with control [SMD 95 % CI, 1.90 (0.64, 3.16), Z = 2.96, P = 0.003, random effect model	Small trials, short duration	N-3 PUFAs decrease CRP concentration in type-2 DM mellitus	I a
Pimpin 2016	Meta-analysis of PCs	Diabetes	Risk	Butter	11 PCs	23'954 incident DM	Adults	10- 22 yrs	Butter consumption (14 g/d) was inversely associated with incidence of diabetes (N = 11; RR = 0.96, 95%CI = 0.93, 0.99;P = 0.021)	No evidence for heterogeneity nor publication bias	There was a relatively small association of butter with diminished risk of DM	II a
Qian F 2016	Systematic review & meta-analysis of RCTs	Diabetes T2 (T2D)	Glycemic control, blood pressure lipids	MUFA compared to CHO & PUFA	24 RCTs comparing with CHO, 4 RCTs with PUFA	1'504	Adults with DM T2	2- 48 weeks	High-MUFA compared to high-CHO diets reduced fasting plasma glucose (WMD -0.57mmol/L [95%CI -0.76,-0.39]), triglycerides (-0.31 mmol/L [-0.44, -0.18]), body weight (-1.56 kg [-2.89,-0.23]), and systolic blood pressure (-2.31 mm Hg), &-increased HDL cholesterol (0.06 mmol/L [0.02, 0.10]). High-MUFA diets compared with high-PUFA diets reduced fasting plasma glucose (-0.87 mmol/L [-1.67, -0.07])	Low to medium levels of heterogeneity	Evidence that consuming diets high in MUFA can improve metabolic risk factors among patients with T2D	I a

Imamura F 2016	Systematic review & meta-analysis of RCTs	Diabetes T2, metabolic syndrome	Glucose-insulin homeostasis (HOMA model)	SFA, PUFA, MUFA, and carbohydrate	102 RCTs	4'220	Adults with and without DM T2	3- 168 days	Replacing 5% energy from carbohydrate with SFA had no significant effect on fasting glucose; replacing carbohydrate with MUFA lowered HbA1c (-0.09%; -0.12, -0.05; n = 23), 2 h post-challenge insulin (-20.3 pmol/L; -32.2, -8.4; n = 11), and HOMA-IR (-2.4%; -4.6, -0.3; n = 30). Replacing carbohydrate with PUFA significantly lowered HbA1c (-0.11%; -0.17, -0.05) and fasting insulin (-1.6 pmol/L; -2.8, -0.4). Replacing SFA with PUFA significantly lowered glucose, HbA1c, C-peptide, and HOMA	Small number of trials for some out-comes and potential issues of blinding, compliance, generalisability, heterogeneity due to unmea-sured factors, and public-cation bias	In comparison to carbohydrate, SFA, or MUFA, most consistent favourable effects were seen with PUFA, which were linked to improved glycaemia, diminished insulin resistance, and improved insulin secretion capacity	I a
Abbott KA 2016	Systematic review & meta-analysis of RCTs	Diabetes T2, metabolic syndrome	Insulin resistance (IR), in men and women	n-3 PUFA, mostly fish oil	26 RCTs	1'848	Adults with and without DM T2	1-6 months	With all studies pooled, there was no effect of n–3 PUFA on IR at the group level (SMD: 0.089; 95% CI: 20.105,0.283; P = 0.367). In trials of >6 wks, a significant improvement in IR was seen in women (SMD: 20.266; 95% CI: 20.524, 20.007; P =0.045) but not in men (SMD: 0.619; 95% CI: 20.583, 1.820; P = 0.313	There was significant heterogeneity between groups and a limited number of trials in men and women separately	Improvement of insulin resistance with LC-n-3-PUFA in women but not in men	I a
Chen C 2015	Meta-analysis of RCTs	Diabetes T2	Glucose control, lipids, BMI	n-3 PUFA, mostly fish oil	20 RCTs	1'209	Adults with DM T2	mostly <12 weeks	Triglyceride (TG) levels were significantly decreased by 0.24 mmol/L by n-3 PUFAs. No significant change of total cholesterol (TC), HbA1c, fasting plasma glucose, postprandial plasma glucose, BMI or body weight was observed. High ratio of EPA/DHA contributed to a greater decreasing tendency in plasma insulin, HbAc1, TC, TG, and BMI measures, although no statistical significance was identified (except TG).	Relatively small studies	Suggestion that a high EPA/DHA ratio affects glucose control favourably	I a
Souza RJ 2015	Systematic review & meta-analysis of PCs & RCTs	Diabetes T2	Diabetes T2 risk	SFA & trans fats (industrial & ruminant)	12 PCs	90000-339000	Adults	1- 32 yrs	SFA intake was not associated with type 2 diabetes (0.95, 0.88 to 1.03). Ruminant *trans*-palmitoleic acid was inversely associated with type 2 diabetes (0.58, 0.46 to 0.74)	The evidence is heterogeneous with method-logical limitations	SFA are not associated with risk of type 2 DM; ruminant trans fats appear to be associated with protection	I a & II a
Aronis KN 2012	Meta-analysis of RCTs	Diabetes T2	Glucose, insulin & lipids	Trans fats (TFA)	7 RCTs	208	Adults, non-diabetic	4-16 wks	Increased TFA intake did not result in significant changes in glucose or insulin concentrations. Increased TFA intake led to a significant increase in total and LDL-cholesterol [ES (95% CI): 0.28 (0.04, 0.51) and 0.36 (0.13, 0.60), respectively] and a significant decrease in HDL-cholesterol	No publication bias	TFA affect LDL-C & HDL-C but not glucose-insulin homeostasis	I a

									concentrations [ES (95% CI): 20.25 (20.48, 20.01)			
Zheng J-S, 2012	Systematic review & meta-analysis of PCs	Diabetes T2	Relative Risk of diabetes T2	n-3 PUFA, mostly fish oil, and fish	24 PCs	>500'000	Adults	4-18 yrs	The RR of T2D for the highest vs lowest categories of total fish, marine n-3 PUFA and alpha-linolenic acid intake was 1.07 (95% CI: 0.91, 1.25), 1.07 (95% CI: 0.95, 1.20) and 0.93 (95% CI: 0.81, 1.07), respectively. For Asian populations the RR (highest vs lowest category) of T2D for fish and marine n-3 PUFA intake was 0.89 (95% CI: 0.81, 0.98) and 0.87 (95% CI: 0.79, 0.96) ; for Western populations the RR was 1.20 (95% CI: 1.01, 1.44) and 1.16 (95% CI: 1.04, 1.28)	Classifications of fish and n-3 PUFA intake amounts were inconsistent;; observational studies could not avoid residual confounders	Marine n-3 PUFA have beneficial effects on the prevention of T2DM in Asian populations	II a
Zhou Y, 2012	Systematic review & meta-analysis of PCs	Diabetes T2	Relative Risk of diabetes T2	n-3 PUFA, mostly fish oil, and fish	13 PCs (mostly Western)	>100'000	Adults	6- 15 yrs	Comparing the highest v. lowest categories, the pooled RR of T2DM for intake of fish and n-3 fatty acid was 1·146 (95% CI 0·975, 1·346) and 1·076 (95% CI 0·955, 1·213), respectively. In the linear dose–response relationship, the pooled RR for an increment of one time (about 105 g)/week of fish intake (four times/month) and of 0·1 g/d of n-3 fatty acid intake was 1·042 (95% CI 1·026, 1·058) and 1·057 (95% CI 1·042, 1·073), respectively	Potential biases and confounders could not be ruled out completely	Both fish oil and other n-3 fatty acids might be weakly positively associated with the T2DM risk (mostly Western populations)	II a
Wu J.H.Y 2012	Systematic review & meta-analysis of PCs	Diabetes T2	Diabetes T2 incidence	n-3 PUFA, ALA & mostly fish oil	18 PCs	540'184	Adults	4-17 yrs	Consumption of fish and/or seafood was not significantly associated with DM (n=13 studies; RR per 100 g/d = 1·12, 95% CI = 0·94, 1·34); nor were consumption of EPA &DHA (n= 16 cohorts; RR per 250 mg/d= 1·04, 95% CI= 0·97, 1·10) nor circulating levels of EPA &DHA biomarkers (n=5 cohorts; RR per 3% of total fatty acids = 0·94, 95% CI= 0·75, 1·17). Both dietary ALA (n=7 studies; RR per 0·5 g/d = 0·93, 95% CI = 0·83, 1·04) and circulating ALA biomarker levels (n=6 studies; RR per 0·1% of total fatty acid = 0·90, 95% CI = 0·80, 1·00, P=0·06) were associated with non-significant trend towards lower risk of DM	No publication bias, but substantial heterogeneity between fish oil studies	The findings do not support either major harms or benefits of fish/seafood or EPA&DHA on development of DM. ALA consumption showed a n.s. trend towards diminished risk.	II a

Wallin A 2012	Systematic review & meta-analysis of PCs	Diabetes T2	Diabetes T2 incidence	n-3 PUFA, mostly fish oil, and fish	16 PCs	527'441	Adults	6- 19 yrs	For each serving per week increment in fish consumption, the RRs (95% CIs) of type 2 diabetes were 1.05 (1.02–1.09), 1.03 (0.96–1.11), and 0.98 (0.97– 1.00) combining U.S., European, and Asian/Australian studies, respectively	Heterogeneous results due to geographical differences	There was a differences of risk of DM between geographical regions with observed associations of fish consumption and dietary intake of long-chain n-3 fatty acids	II a
Alhazmi A 2012	Systematic review & meta-analysis of PCs	Diabetes T2	Relative Risk of diabetes T2	Macronutrient intake	22 PCs	>500'000	Adults	4.6- 20 yrs	High intake of dietary carbohydrate was associated with an increased type 2 diabetes risk (RR= 1.11, 95% CI: 1.01 to 1.22, p=0.035); however, this effect was not observed in an analysis stratified by gender. Intake of total fat, SFA, MUFA & PUFA was not associated with diabetes risk	No studies fulfilled all requirements for a high-quality study free of bias	Fat and individual fatty acid intake was not associated with DM T2 risk	II a
Mansoor N 2016	Meta-analysis of RCTs	**Obesity** & CV risk factors	Weight loss, lipids	Low fat versus low carb	11 RCTs	1'369	Adults, overweight-obese	6 months	Participants on LoFat diets compared to LoCarb diets lost more weight (WMD –2·17 kg; 95% CI –3·36, –0·99) and triglycerides (WMD –0·26 mmol/l; 95% CI –0·37, –0·15), but had a greater increase in HDL-cholesterol (WMD 0·14 mmol/l; 95% CI 0·09, 0·19) and LDL-cholesterol (WMD 0·16mmol/l; 95% CI 0·003, 0·33)	Heterogeneity was moderate to high for all variables	The beneficial changes of LoCarb diets must be weighed against the possible detrimental effects of increased LDL-cholesterol	I a
Tobias DK 2015	Meta-analysis of RCTs	Obesity	Weight loss, serum triglycerides	Low fat versus other dietary interventions	53 RCTs	68128	Adults, overweight-obese, formerly obese	>1 yr	In weight loss trials, low-carbohydrate interventions led to significantly greater weight loss than did low-fat interventions (18 comparisons; WMD 1.15 kg [95% CI 0.52 to 1.79	Incomplete outcome data was a high potential source of bias for 39 trials because of drop-out and loss-to-follow-up rates exceeding 5%	Higher-fat, low-carbohydrate dietary interventions led to a slight but significant, greater long-term weight loss than did low-fat interventions	I a
Sackner-Bernstein J, 2015	Meta-analysis of RCTs	Obesity	Weight loss, CV risk factors	Low fat versus low carb	17 RCTs	1'797	Adults, overweight-obese	8 wks- 2 yrs	Compared with low fat diet, low carbohydrate was associated with significantly greater reduction in weight (Δ = -2.0 kg, 95% CI: -3.1, -0.9) and significantly lower predicted risk of atherosclerotic cardiovascular disease events (p<0.03)	No patient-level data; frequent loss of follow-up	LoCarb diet appears to achieve greater weight loss and reduction in predicted risk of ASCVD events compared with LoFat diet	I a

Hooper L 2015 (Cochrane)	Meta-analysis of RCTs & of PCs	Weight gain	Change of body weight, Lipids	Total fat intake	32 RCTs, 25 PCs	54'000 (RCTs)	Adults, not aiming to lose weight	Median: 5 yrs	Eating less fat (compared with usual diet) resulted in a mean weight reduction of 1.5 kg (95% CI -2.0 to -1.1 kg), but greater weight loss results from greater fat reductions. The size of the effect on weight does not alter over time and is mirrored by reductions in body mass index (BMI) (-0.5 kg/m2, 95% CI -0.7 to -0.3) and waist circumference (-0.3 cm, 95% CI -0.6 to -0.02)	There was a high risk of performance bias due to lack of blinding; most RCTs were at unclear risk of reporting bias; some trials had high attrition rates	Lowering the proportion of fat in food leads to a small but noticeable decrease in body weight, body mass index and waist circumference in both, adults and children. The effect did not change over time	I a & II a

Table S3. Meta-analyses on dietary fat or fatty acid intake in relation to certain types of cancer

Source	Study category	Disease	End point	Main nutritional theme	No. of included studies	No. of subjects	Subject group	Duration	RR (95%CI)	Limitations	Conclusions	LOE
Brennan SF 2017	Systematic review & meta-analysis of PCs	Breast cancer	Survival from breast cancer	Dietary fat, SFA	15 PCs	29241	Women with breast cancer	16 yrs	There was no difference in risk of breast-cancer-specific death or all-cause death in the highest versus lowest category of total fat intake. Breast-cancer-specific death (n=4; HR=1.51; 95% CI: 1.09, 2.09; p < 0.01) was higher for women in the highest versus lowest category of saturated fat intake	Heterogeneity between studies; small sample size	Saturated fat intake was negatively associated with breast cancer survival	II a
Zhao J 2016	Systematic review & meta-analysis of PCs or case control studies	Endometrial cancer	Risk of new cancer	Dietary fat, SFA, MUFA, PUFA	7 PCs & 14 case controls	approx. 15'000	Women	1 mo.- 10 yrs.	Endometrial cancer risk was significantly increased by 5% per 10% kilocalories from total fat intake (P=0.02) and by 17% per 10g/1000 kcal of saturated fat intake (P<0.001). 3 cohort studies showed significant inverse association between MUFA & cancer risk (odds ratio=0.84, 95% confidence interval= 0.73–0.98). No significant associations were found for PUFAs	Measurement error linked to the nature of food frequen-cy question-naire	High intake of total fat and SFA was associated with increased endometrial cancer risk. In addition, dietary MUFA was associated with decreased risk in cohort studies	II a
Cao Y 2016	Systematic review & meta-analysis of PCs	Breast cancer	Risk of new cancer	Dietary fat, SFA, PUFA, MUFA	24 PCs	38262 & 1.4 Mio controls	Women	2- 25 yrs.	No association was observed between animal fat, vegetable fat, SAFA, MUFA, PUFA, n-3 PUFA, n-6 PUFA and risk of breast cancer	No subgroups of cancer types. FFQ are subject to error.	Dietary total fat and fatty acids might be not associated with risk of breast cancer	II a
Xia H, 2015	Systematic review & meta-analysis of PCs or case control studies	Breast cancer	Risk of new cancer	Dietary SFA	24 PCs & 28 case controls	35651 BC, 1.8 Mio controls	Women	Not stated	The associations between dietary SFA intake and risk of BC were 1.18 for case–control studies (high vs low intake, 95% confidence interval [CI]=.03–1.34) and 1.04 for cohort studies (95% CI=0.97–1.11)	Possible bias in case control studies (selection & recall)	A relationship was found between SFA intake and incidence of BC in case–control studies, and of postmenopausal BC risk in case–control but not in cohort studies	II a
Han J 2015	Meta-analysis of observational studies	Gastric cancer	Risk of new cancer	Dietary fat	22 studies	approx. 8500 cases & 500'000 controls	Adults		The S-RR was 1.18 with highest intake versus lowest intake of total fat (95% CI: 0.999–1.39; n = 28; P< 0.001). There were positive associations between SAFA intake (SRR = 1.31; 95%CI: 1.09–1.58;n = 18;P<0.001), and inverse association between PUFA intake (SRR = 0.77; 95%CI: 0.65–0.92; n = 16; P = 0.003)	Case control studies may introduce recall and selection bias, FFQ, measurement errors etc.	Intake of total fat is potentially positively associated with gastric cancer risk, and specific subtypes of fats account for different effects	II a

Table S4. Meta-analyses on dietary fat or fatty acid intake in relation to other endpoints (neurologic, psychiatric)

Source	Study category	Disease	End point	Main nutritional theme	No. of included studies	No. of subjects	Subject group	Duration	RR (95%CI)	Limitations	Conclusion	LOE
Grosso G 2016	Review & meta-analysis of observational studies	Depression	Risk of new disease	n-3 PUFA & fish	31 observational studies	255'076 sub-jects, 20'000 cases with depression	Adults	Not stated	Pooled risk estimates of depression for extreme categories of both total n-3 PUFA and fish-derived n-3 PUFA [EPA&DHA] resulted in decreased risk for the highest compared with the lowest intake (RR=0.78, 95% CI:0.67, 0.92and RR=0.82, 95% CI:0.73, 0.92, respectively.	Design of the studies included and confound-ding due to lack adjustment for certain variables	Dietary n-3 PUFA intake is associated with lower risk of depression	II a
Zhang y, 2016	Meta-analysis of PCs	Dementia, Parkinson disease	Risk of new disease	n-3 PUFA & fish	21 PCs	18'1580 subjects, 4438 with cognitive impairment	Elderly adults, mostly >65 yrs.	2.1-21 yrs.	A 1-serving/wk increment of dietary fish was associated with lower risks of dementia (RR: 0.95; 95% CI: 0.90, 0.99; P = 0.042, I2 = 63.4%) and Alzheimer D. (RR: 0.93; 95% CI: 0.90, 0.95; P = 0.003, I2 = 74.8%). Pooled RRs of Mild Cognitive Impairment and Parkinson Disease were 0.71 (95% CI: 0.59, 0.82; P = 0.733, I2 = 0%) and 0.90 (95% CI: 0.80, 0.99; P = 0.221), respectively, for an 8-g/d increment of PUFA intake. A 0.1-g/d increment of dietary DHA intake was associated with lower risks of dementia (RR: 0.86; 95% CI: 0.76, 0.96; P=0.001).	Vitamin E intake appeared as the most-frequent confounding factor	Marine-derived DHA was associated with lower risk of dementia and Alzheimer disease but without a linear dose-response relation	II a
Appleton KM, 2015 (Cochrane)	Meta-analysis of RCTs	Depression	Risk of new disease	n-3 PUFA & fish	25 RCTs	1'438	Adults	wks.-months	For the placebo comparison, n-3 PUFA supplementation results in a small to modest benefit for depressive symptomology, compared to placebo: standardised mean difference (SMD) -0.30 (95% confidence interval (CI) -0.10 to -0.50	The quality of the evidence for all outcomes was judged as low to very low.	Possible benefit in severe depression (not in mild symptomatology)	I a
Cooper RE, 2015	Meta-analysis of RCTs	Cognitive Impairment	Symptoms	Omega-3 PUFA	24 RCTs		Adults & children (with ADHD & related disorders)		n-3 PUFA supplementation, in the whole sample and the TD and ADHD+RD subgroup, did not show improvements in any of the cognitive performance measures. In those with low *n*-3 PUFA status, supplementation improved short-term memory.		There is some evidence that *n*-3 PUFA supplementation improves cognition in those who are *n*-3 PUFA deficient, but not in those who were sufficient.	I a