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Health Aspects of Nutritional Fats and Oils. A Review of Recent Findings

Ulrich Keller*

University of Basel, and Endocrine Practice, Missionsstr. 24 CH-4055 Basel, Switzerland

***Corresponding Author:** Ulrich Keller, University of Basel, and Endocrine Practice, Missionsstr. 24, Switzerland.

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Abstract

Current guidelines of professional organizations and governmental health authorities recommend to limit the consumption of saturated fats for the prevention of chronic diseases such as cardiovascular disease, and to propose upper limits for the intake of mono- and polyunsaturated fatty acids.

The present review of meta-analyses of prospective cohort studies and of randomized controlled trials published during the past 5 years indicates that these recommendations may need certain revisions. Regarding cardiovascular disease, current data suggest that intake of total and saturated fat (in % of energy intake) is not clearly associated with cardiovascular morbidity and mortality. A small benefit regarding cardiovascular risk results from reduction of saturated fat when it is replaced by polyunsaturated fat. This benefit was not observed in patients with established CVD.

According to recent data consumption of n-6 PUFA acid has been associated with diminished (and not with increased) cardiovascular morbidity and mortality, and there is insufficient evidence to prioritize a specific type of unsaturated fats replacing other macronutrients such as saturated fats or starchy or sugary foods.

Concerning risk of diabetes type 2, recent data show that total fat or saturated fat intake are not clearly associated with increased risk. In contrast, increased consumption of MUFA, olive oil and in some instances of PUFA have been associated with diminished diabetes risk and with improved metabolic control in patients with established diabetes when carbohydrates were replaced by MUFA.

Regarding overweight and obesity, lowering the proportion of fat in the diet resulted in a small decrease of body weight. Therefore, these new epidemiological trial data suggest that there is insufficient evidence to recommend limited consumption of the various types of fats and oils to improve health outcomes.

Keywords: *Dietary fats and oils; Cardiovascular disease; Diabetes type 2; Cancer risk; Public health recommendations*

Abbreviations: CHD: Coronary Heart Disease; CVD: Cardiovascular Disease; EPA: Eisosapentaenoic Acid; DHA: Docosahexaenoic Acid; DM: diabetes mellitus; PC: Prospective cohorts; RCTs: Randomised Controlled Trials; RR: Relative Risk; MUFA: Monounsaturated Fatty Acids; PUFA: Polyunsaturated Fatty Acids; SFA: Saturated Fatty Acids

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Introduction

Dietary fats and oils cover approximately one third of total energy requirements and are the most energy-dense nutrients. As nutrition-related diseases such as obesity, cardiovascular diseases and diabetes type 2 are becoming more and more prevalent; the role of fats and oils in their development and prevention is of particular interest. Not only the quantity but particularly the quality of fats and their fatty acid content is of great interest, specifically in relation to atherosclerotic diseases.

Guidelines such as the AHA/American College of Cardiology Guideline on Lifestyle Management to Reduce Cardiovascular Risk (2013) [1], the WHO and the 2010 Dietary Guidelines for Americans [2] recommend to limit consumption of saturated fats to less than 10% of energy consumption.

In addition, several governmental health recommendations such as the WHO/FAO Expert Consultation stated that a maximum of 10% of energy should be consumed as n–6 PUFA for CHD risk reduction. The Swiss Federal Commission on Nutrition has issued recommendations on the consumption of fats and oils for the public in 1992, 2006 [3] and 2012 [4]. These recommendations proposed a limitation of fat intake, both of the saturated and the unsaturated varieties.

In the meantime, results of several large epidemiological studies reporting associations between fat consumption and health outcomes have been published. The present article reviews and summarizes meta-analyses of epidemiological studies published in international journals related to the subject during the last decade, with the goal to propose possible revisions of the current recommendations.

Definition and scope

Fats are present in visible form or they are contained in food products with a mixture of nutrients ("hidden fat"). Solid fats are mostly of animal origin, and oils are usually of plant origin. 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. Since most fats and oils contain mixtures of fatty acids, and certain fatty acids are often present in both animal and plant-based sources, they are discussed as a whole group. The main focus of this review is to summarize associations between consumption of certain fats and oils (defined by their fatty acid composition) and health outcomes according to epidemiological studies. Specific foodstuff with mixtures of nutrients including fat (e.g. dairy, processed meat) is not discussed.

Research of the literature and grading of evidence

The literature search focused on meta-analyses quoted in PubMed during the past 5 years (2012-2017). Key words used were dietary fats, fatty acids, oils, and health outcomes, cardiovascular disease, coronary heart disease, obesity, diabetes type 2, mortality, blood lipids, cancer, depression, cognitive impairment. A total of 122 meta-analyses were retrieved. Only original publications dealing with adults, healthy individuals were considered; studies with focus on biomarkers were excluded. Tables of individual meta-analyses of cohort studies and randomized controlled studies including their main features and conclusions was prepared.

Classification of levels of evidence (LOE, according to WHO [5] was the following:
LOE I: Ia Meta-analyses of randomised controlled intervention studies;
Ib randomised controlled intervention studies
LOE II: IIa Meta-analyses of cohort studies;
IIb cohort studies

A few selected epidemiological studies which appeared to be of importance in relation to the subject of this publication were quoted.

Mechanisms

Dietary fats are more energy-dense than other energy providing foods. The different fatty acids in fats and oils determine their physical (melting point or fluidity of cell membranes) and chemical (e.g. process of chemical reactions) behaviour and their biological

functions. They exert different effects on plasma lipoprotein concentrations and are precursors of eicosanoids as 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 contain also phenolic compounds which may exert anti-inflammatory properties [6].

Survey of publications

Basic considerations

There has been a tendency during the past years in international nutritional recommendations [7,8] to recommend consumption of certain foods or food groups rather than quantities of specific nutrients such as fats or carbohydrates. Reason for this is that health effects of certain nutrients depend on the type of food in which they are consumed, due to the texture of the food and to other food components [9-11]. Examples: Identical quantities of SFA in the form of butter or cheese may have slightly different effects on serum lipids [12]. In addition, fermented dairy products have different health effects compared to unfermented products [13] even with 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.

Summary of a publication of meta-analyses of the relationship between dietary fats and oils and coronary heart disease, stroke, and diabetes mellitus published between 2006 and 2014 [14]

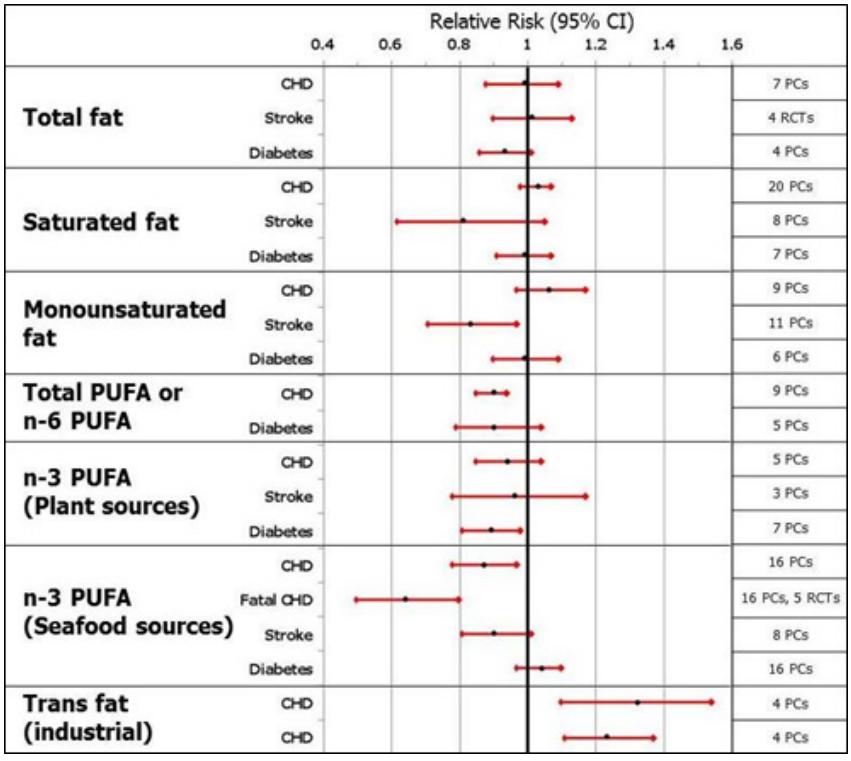

Figure 1: *shows the relative risks with 95% confidence intervals for major health outcomes during high versus low consumption of specific fats (redrawn from Figure 7 in [14].*

Conclusions from this review of meta-analyses: Total fat and saturated fat is not clearly associated with CHD, stroke and 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 diabetes type 2, however, inspection of reference Wu J., *et al*. (2012) [15] shows that the decrease of diabetes risk was not statistically significant. Seafood-derived n-3 PUFA are associated with diminished CHD risk, and they diminish CHD death. The most striking association is the association of industrial trans fats with CHD risk.

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
Harcombe Z, 2017 [20]	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) [21]	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	Not stated	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) [22]	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 measurement 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 [23]	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 [24]	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
de Souza RJ, 2015 [25]	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) [26]	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 moderate-quality evidence that reducing 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 [27]	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; I2=35.5%), and a 21% lower risk of CHD deaths (pooled RR, 0.79; 95% CI 0.71–0.89; I2=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 [28]	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

Schwingshackl L, 2014 [BMJ open] [29]	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 [30]	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 [31]	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 [32]	RCT (Sydney Diet Heart Study) & meta-Analysis of RCTs	CHD	Mortality	Dietary linoleic acid (LA)	1 (+2+4) RCTs	458	Men with recent CHD	12 mo.	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 [33]	Meta-analysis of cohorts	CVD	Risk	Dietary -linolenic acid (ALA)	27 cohorts (pro-& retrospective)	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 [34]	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) [35]	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

Schwingshackl L, 2014 [Lipids Health Dis] [36]	Meta-analysis of PCs	CVD & stroke	CV events & mortality, stroke risk	Mono-unsaturated 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 publication 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 [37]	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 [38]	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 [39]	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 [40]	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 [41]	Meta-analysis of PC & RCTs	Stroke (cerebrovascular 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 consumption 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 1: *Dietary fat or fatty acid intake in relation to cardiovascular disease (CVD) and stroke. List of meta-analyses published between 2012 and 2017.*

These studies demonstrate that 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 reduction of saturated fat when it is replaced by polyunsaturated fat. This benefit has not been observed in patients with established CVD. Consumption of the PUFA linoleic acid has been associated with diminished cardiovascular morbidity and mortality; however, there is insufficient evidence to prioritize a specific type of unsaturated fat 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.

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 [42]	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 [43]	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 [44]	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 [45]	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 [24]	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 [46]	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 [47]	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 outcomes and potential issues of blinding, compliance, generalisability, heterogeneity due to unmeasured factors, and publication 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 [48]	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 [49]	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 [25]	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 methodological 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 [50]	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 concentrations [ES (95% CI): 20.25 (20.48, 20.01)	No publication bias	TFA affect LDL-C & HDL-C but not glucose-insulin homeostasis	I a
Zheng J-S, 2012 [51]	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 [52]	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 [15]	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 [53]	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 were differences of risk of DM between geographical regions with observed associations of fish consumption and dietary intake of LC n-3 FA.	II a
Alhazmi A 2012 [54]	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 [55]	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 [56]	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 [57]	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) [58]	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 2: *Dietary fat or fatty acid intake in relation to diabetes type 2 and obesity.*

List of meta-analyses published between 2012 and 2017.

These findings show that consumption of total fat or saturated fat intake has not been clearly associated with diabetes type 2 risk. Increased consumption of MUFA, olive oil and in some instances of n-6 PUFA have been associated with diminished diabetes risk and with improved metabolic control in patients with established 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 diabetes type 2 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.

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 [59]	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 [60]	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 frequency questionnaire	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 [61]	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 [62]	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 [63]	Meta-analysis of observational studies	Gastric cancer	Risk of new cancer	Dietary fat	22 studies	approx. 8500 cases & 500'000 controls	Adults	Not stated	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 3: *Dietary fat or fatty acid intake in relation to certain types of cancer.*

List of meta-analyses published between 2012 and 2017.

These studies show that 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.

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 [64]	Review & meta-analysis of observational studies	Depression	Risk of new disease	n-3 PUFA & fish	31 observational studies	255'076 subjects, 20'000 cases with depression	Adults	Not stated	Pooled risk estimates of depres- sion for extreme categories of both total n-3 PUFA and fish-de-rived n-3 PUFA [EPA&DHA] resulted in decreased risk for the highest compared with the low-est 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 confounding due to lack adjustment for certain variables	Dietary n-3 PUFA intake is associated with lower risk of depression	II a
Zhang y, 2016 [65]	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 die-tary fish was associated with lower risks of dementia (RR: 0.95; 95% CI: 0.90, 0.99; P = 0.042, I2 = 63.4%) and Alzhei-mer 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) [66]	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 [67]	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

Table 4: *Dietary fat or fatty acid intake in relation to other endpoints (neurologic, psychiatric). List of meta-analyses published between 2012 and 2017.*

The main findings of observational studies suggest that intake of long-chain n-3 fatty acids is 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.show that 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.

The main findings of observational studies suggest that intake of long-chain n-3 fatty acids is 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 publications of large trials not reviewed in the meta-analyses of Tables 1-4

The PURE study showed that across 18 countries from 5 continents increased fat consumption was associated with lower total and cardiovascular disease mortality (Dehghan M., *et al*. [16]. The data showed there was a large socio-demographic and economic heterogeneity between these 18 countries with widely discrepant rates of total mortality. Countries with higher levels of income and education had both, higher rates of fat consumption and higher life expectancy. Therefore, there is a considerable likelihood of residual confounders- that other factors explained the higher life expectancy in countries with higher fat consumption.

The question whether high consumption of pro-inflammatory (n-6 polyunsaturated fatty acids) exert negative health effect is still debated. An new approach to this topic was taken by May-Wilson S., *et al*. [17]. These authors showed in a study using Mendelian

randomisation analysis that a pro-inflammatory fatty acid profile (due to genetic factors) affected colorectal cancer risk. In particular, decreased risk of colon cancer was associated with high serum MUFAs and PUFA (linoleic) concentrations, and increased risk with high serum PUFA (arachidonic acid) and SFA (stearic acid) concentrations.

In a re-evaluation of the traditional diet-heart hypothesis, Ramsden., *et al*. analysed data of the Minnesota Coronary Experiment (1968-73) [18]. The authors concluded that 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 translates 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.

In order to assess the relationship between consumption of n-6 PUFA and total and cause specific mortality, Wu JH., *et al*. measured circulating n-6 PUFA in the Cardiovascular Health Study [19]. The authors found that circulating levels of LA, the major dietary n-6 PUFA, was 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.

Propositions for specific changes of current nutritional guidelines such as those published in Switzerland [4] The recommendation that saturated fatty acids should be less than 10% of total energy consumption should be changed to that there is no convincing reason to limit the consumption to this range of consumption The consumption of vegetable oils should not be limited, and a detailed recommendation regarding the type of vegetable oil should not be given. The recommendation for long-chain n-3 PUFA should be limited to subjects with established cardiovascular disease [7].

Conflict of interest

The author declares to have not conflict of interest in the subject of this publication.

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