Clinical Nutrition 40 (2021) 1060–1070

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Association between dietary fat intake and mortality from all-causes, cardiovascular disease, and cancer: A systematic review and meta-analysis of prospective cohort studies

Youngyo Kim [a], Youjin Je [b, *], Edward L. Giovannucci [c]

[a] Department of Food and Nutrition/Institute of Agriculture and Life Science, Gyeongsang National University, Jinju, South Korea
[b] Department of Food and Nutrition, Kyung Hee University, Seoul, South Korea
[c] Departments of Nutrition and Epidemiology, Harvard TH Chan School of Public Health, Boston, MA, USA

ARTICLE INFO

Article history:
Received 2 May 2020
Accepted 3 July 2020

Keywords:
Dietary fat
Mortality
Meta-analysis
Prospective cohort studies

SUMMARY

Background & aims: The association between dietary fat and mortality remains inconsistent, and recent results for the association between dietary saturated fat and chronic disease are controversial. To quantitatively assess this association, we conducted a meta-analysis of prospective cohort studies.
Methods: The PubMed and Web of Science were searched up to February 2020. A random effects model was used.
Results: Nineteen studies including 1,013,273participants and 195,515deaths were identified. Significant inverse associations between all-cause mortality and a 5% energy increment in intakes of total (RR = 0.99; 95% CI:0.98−1.00), monounsaturated (RR = 0.98; 95% CI:0.97−0.99), and polyunsaturated fat (RR = 0.93; 95% CI:0.89−0.97) were found. A 5% increase in energy from polyunsaturated fat was associated with 5% (RR = 0.95; 95% CI:0.91−0.98) and 4% (RR = 0.96; 95% CI:0.94−0.99) lower mortality from CVD and cancer, respectively. A 1% energy increment in dietary *trans*-fat was associated with 6% higher risk of mortality from all-causes (RR = 1.06; 95% CI:1.01−1.10) and CVD (RR = 1.06; 95% CI:1.02−1.11). We found a non-linear association between dietary saturated fat and all-cause mortality showing a significant increased risk up to 11% of energy from saturated fat intake. The risk of cancer mortality increased by 4% for every 5% increase in energy from saturated fat (RR = 1.04; 95% CI:1.02−1.06).
Conclusions: Diets high in saturated fat were associated with higher mortality from all-causes, CVD, and cancer, whereas diets high in polyunsaturated fat were associated with lower mortality from all-causes, CVD, and cancer. Diets high in *trans*-fat were associated with higher mortality from all-causes and CVD. Diets high in monounsaturated fat were associated with lower all-cause mortality.

1. Introduction

Dietary fats are mostly made up of triacylglycerols comprising a glycerol backbone linked to three independent fatty acids by an ester bond [1,2]. There are various kinds of fatty acids depending on the number and position of the double bonds they have, and this diversity of structure may indicate different biological effects on human health [2]. Traditionally, high dietary fat consumption has been considered detrimental to the health, and the current dietary guidelines generally recommend avoiding a high fat diet and encourage low intake of saturated fat in particular [3–5]. However, recently, several meta-analyses from prospective cohort studies and randomized controlled trials found no significant association between intakes of saturated fat and health outcomes including cardiovascular disease (CVD) [6–8], diabetes [7], and cancer [9].

Many prospective cohort studies have examined the association between dietary fat intake and mortality from all-causes, CVD, and cancer [10–27]. Among the studies, one study for population in 18 countries from 5 continents found lower all-cause mortality in people with high intake of total fat, monounsaturated fat, polyunsaturated fat, and saturated fat [19], and another study reported a positive association between *trans*-fat intake and all-cause mortality [15]. The other studies observed different associations by type

* Corresponding author. Department of Food and Nutrition, Kyung Hee University, 26 Kyunghee-daero, Dongdaemun-gu, Seoul 02447, South Korea. Fax: +82 2 961 0538.
E-mail address: youjinje@khu.ac.kr (Y. Je).

https://doi.org/10.1016/j.clnu.2020.07.007
0261-5614/

of fatty acids [10,14,16–18,20,26,27] or found no significant association between dietary fat intake and mortality [11–13,21–25]. There is a discrepancy between current dietary guidelines and recent findings indicating no association between dietary saturated fat and risk of chronic diseases. Furthermore, to our knowledge, the association between dietary fat intake and mortality has not been comprehensively reviewed despite the inconsistency among previous results.

Therefore, to further understand the association of dietary fat intake on risk of mortality and quantitatively assess the association by various types of fatty acids intake, we performed a systematic review and meta-analysis of the association between intakes of total fat, saturated fat, monounsaturated fat, polyunsaturated fat, and *trans*-fat and mortality from all-causes, CVD, and cancers.

2. Methods

2.1. Data sources and searches

Studies published from inception to February 2020 as full-length articles and written in English were searched through electronic databases PubMed and ISI Web of Science. The computer-based search included combinations of following keywords: "(fat intake OR dietary fatty acids) AND (mortality OR death OR survival OR fatal)." The search was supplemented by hand-searching of reference lists of all retrieved articles and reviews to identify additional eligible studies.

2.2. Study selection

Observational studies were included in this meta-analysis if they: 1) were prospective in design; 2) reported the exposure of interest as intake of dietary fat and fatty acids; 3) reported the outcome of interest as mortality from all-causes, CVD, or cancer; 4) provided relative risks (RR) and the corresponding confidence intervals (CI) or sufficient data to calculate them. We did not include the studies which reported exposure as omega-3 polyunsaturated fatty acids only, because two recent meta-analyses completely examined the association between consumption of omega-3 polyunsaturated fatty acids and all-cause mortality [28,29]. Studies that evaluated risk of mortality in participants with pre-existing disease at baseline were excluded. If more than one study was from the same cohort, we included the study with more subjects or longer follow-up times.

2.3. Data extraction and quality assessment

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [30], two authors (Y.K. and Y.J.) independently extracted data on study characteristics. Any disagreements were addressed by checking the original reports and discussion. We extracted the following information from each study: study name, number of patients and deaths, country name or geographical region, the last name of first author, publication year, study period or follow-up time, baseline age, categories of fat intake, RRs and 95% CIs for the association between each fat intake category and mortality, and adjustment factors. For studies reporting several RRs, the RR maximally adjusted for confounding variables was included in the meta-analysis. We considered one publication as two prospective cohort studies, if it reported pooled RRs from two different cohorts [18,21]. When two individual articles [21,25] provided the results for polyunsaturated fatty acids and saturated fatty acids from the same cohort, respectively, we counted these as one study and the results were separately included in the relevant analyses.

We used the Newcastle–Ottawa quality assessment scale [31] to assess the quality of the studies included in meta-analysis. The quality of each study was independently assessed by two authors (Y.K. and Y.J.) for the three domains: selection of subjects, comparability of cohorts, and ascertainment of outcomes of interest. Studies that scored 10 or higher (out of 13) were considered high-quality. We considered a study with scores of 7–9 and a score of 6 or less as possessing good and low quality, respectively.

2.4. Data synthesis and analysis

We calculated pooled RRs of mortality from all-causes, CVD, and cancer for the highest *versus* the lowest level of total, saturated, monounsaturated, polyunsaturated, and *trans*-fat intake using the DerSimonian and Laird random effects models [32], which takes into account both within- and between-study variations. Linear dose–response analyses using the method by Greenland and Longnecker [33–35] were conducted to compute study specific slopes across categories of fat intake. We used the median value reported in the original article for each category of fat intake. When a study used units of fat intake not as % of total energy intake but as grams per day, we converted the units into % of energy considering that fat provides nine calories per gram [11,12,21,27]. We also assessed a potential non-linear dose–response association between fat intake and mortality using restricted cubic splines with 3 knots at fixed percentiles (10%, 50%, and 90%) of the aggregated exposure [36]. The *P* value for non-linearity was obtained by testing the null hypothesis in which the regression coefficient of the second spline is equal to zero. To examine whether the association between dietary fat and all-cause mortality varied by sex, geographical region (US/Europe/Asia), type of dietary assessment (food frequency questionnaire or food record/24-h recall) and adjustment for other types of fat intake or serum lipids (yes/no), we conducted a subgroup analysis when data were available.

Statistical heterogeneity between studies was evaluated with the *Q* statistic [37] and inconsistency was quantified by I^2 statistic [38]. Sensitivity analyses in which we eliminated one study at a time from each analysis were performed to assess the robustness of the findings. Publication bias was examined through Begg's [39] and Egger's [40] tests. A two-tailed *P* value of <0.05 was considered statistically significant. Stata version 14.2 software (StataCorp, TX, USA) was used for all statistical analyses.

3. Results

3.1. Study characteristics

A total of 19 prospective cohort studies [10–27] including 1,013,273 participants and 195,515 deaths were included in the current meta-analysis. The detailed process used to select prospective cohort studies for a meta-analysis of the association between dietary fat intake and mortality is shown in Supplementary Fig. 1. Table 1 presents the general characteristics of the included studies for the current meta-analysis. By geographic region, 9 studies were from the US [12,15,18,20–23,26], 5 were from Europe [10,11,13,17,24] 4 were from Asia [14,16,21,25], and one study from multi-continent including 18 countries [19]. The follow-up durations of studies ranged from 6 years to 32 years, and a median follow-up time was 13.2 years. The study populations were all adults aged >20 years at baseline. To measure dietary fat intake, 11 studies used food frequency questionnaire [11,13–19,26,27] 5 studies used 24-h recall [20–23,25], 2 studies used food record [12,24], and 1 study used both questionnaire and food record [10]. All studies except one [11], which targeted for elderly population (65–84 years), adjusted for age. Most of the studies controlled for

Table 1
Characteristics of studies included in the meta-analysis on dietary fat intake and mortality from all-causes, CVD, and cancer.

First author, year	Country	Cohort name	Follow-up period	Age at baseline	Study size		Dietary fat	Cause of death	Adjustment for covariates
					Participants	No. of death			
Leosdottir, 2005	Sweden	The Malmö Diet and Cancer Study	6.6 years	47-78 y	28,098	1250	Total fat Saturated fat Monounsaturated fat Polyunsaturated fat	All-causes CVD Cancer	Age, alcohol consumption, smoking, social class, marital status, physical activity, BMI, fibre intake. Fat intake were mutually adjusted for intake of remaining fat. Adjustments were made for total fat intake for the ratio between unsaturated and saturated fats.
Solfrizzi, 2005	Italy	Italian Longitudinal Study on Aging	8.5 years	65−84 y	278	91	Total fat Saturated fat Monounsaturated fat Polyunsaturated fat	All-causes	−
Tucker, 2005	US	Baltimore Longitudinal Study of Aging	18 years	34-80 y	501	71	Saturated fat	All-causes CVD	Age, total energy intake, BMI, smoking, alcohol use, physical activity score, supplement use, fruit and vegetables intake, secular trend (year of first visit before vs. after 1980)
Akbaraly, 2011	UK	Whitehall II cohort	17.7 years	39−63 y	7319	534	*trans*-fat	All-causes CVD	Age, sex, ethnicity, occupational grade, marital status, smoking status, total energy intake, physical activity, BMI categories, prevalent CVD, type 2 diabetes, hypertension, dyslipidemia, metabolic syndrome, and inflammatory markers
Nagata, 2012	Japan	The Takayama Study	16 years	≥35 y	28,356	4616	Total fat Saturated fat Monounsaturated fat Polyunsaturated fat	All-causes CVD Cancer	Age, nonalcohol energy, and protein expressed as percentage of nonalcohol energy, height, BMI, physical activity, smoking status, alcohol intake, education, marital status, histories of diabetes and hypertension, and intakes of fruits, vegetables, and dietary fiber, percent energy from carbohydrate in foods remaining than rice. Fat intake were mutually adjusted for intake of remaining fat.
Kiage, 2013	US	Reasons for Geographic and Racial Differences in Stroke study	7 years	≥45 y	18,513	1572	*trans*-fat	All-causes	Age, sex, smoking status, race, region, alcohol use, education, waist circumference, level of physical activity, diabetes, coronary heart disease, hypertension, stroke, heart failure, chronic kidney disease, statin use, total energy intake, and energy-adjusted intakes of saturated, monounsaturated, and polyunsaturated fat, proteins, and carbohydrates.
Wakai, 2014	Japan	Japan Collaborative Cohort	19.3 years	40-79 y	58,672	11,656	Total fat Saturated fat Monounsaturated fat Polyunsaturated fat	All-causes CVD Cancer	Age, area, education, smoking, alcohol consumption, BMI, sleep duration, walking, consumption of vegetables and fruit, and total energy intake.
Guasch-Ferré, 2015	Spain	PREvención con DIeta MEDiterránea (PREDIMED) study	6 years	55-80 y	7038	414	Total fat Saturated fat Monounsaturated fat Polyunsaturated fat *trans*-fat	All-causes	Age, sex, intervention group, total energy intake (kcal/d), alcohol intake, updated quintiles of fiber, protein intake, dietary cholesterol for the total fat analysis, BMI, smoking status, educational level, leisure-time physical activity, baseline diabetes, hypertension, hypercholesterolemia, family history of coronary heart disease, use of antihypertensive medication, use of oral antidiabetic agents, use of lipid-lowering drugs. Fat intake were mutually adjusted for intake of remaining fat.
Wang, 2016	US	Nurses' Health Study Health Professionals Follow-up Study	32 years 26 years	30-55 y 40-75 y	83,349 42,884	33,304	Total fat Saturated fat Monounsaturated fat Polyunsaturated fat *trans*-fat	All-causes CVD Cancer	Age, white race, marital status, BMI, physical activity, smoking status, alcohol consumption, multivitamin use, vitamin E supplement use, current aspirin use, family history of myocardial infarction, family history of diabetes and cancer, history of hypertension and hypercholesterolemia, intakes of total energy and dietary cholesterol, percentage of energy intake from dietary protein, and menopausal status and hormone use in women. All models, except total fat intake, also included percentages of energy intake from remaining fatty acids

									(saturated, polyunsaturated, and monounsaturated and trans-fatty acids, all in quintiles).
Dehghan, 2017	Multicontinent	The Prospective Urban Rural Epidemiology (PURE) study	7.4 years	35−70 y	135,335	5796	Total fat Saturated fat Monounsaturated fat Polyunsaturated fat	All-causes CVD	Age, sex, education, waist-to-hip ratio, smoking, physical activity, diabetes, urban or rural location, and energy intake.
Ricci, 2018	US	American National Health and Nutrition Examination Survey	6.1 years	≥30 y	18,372	1118	Saturated fat Monounsaturated fat Polyunsaturated fat	All-causes CVD Cancer	Age, sex, ethnicity, BMI, alcohol intake, smoking status, education, sedentariness, fibre intake, blood pressure
Zhuang, 2018	China	China Health and Nutrition Survey	14 years	38.8 y	14,117	1007	Polyunsaturated fat	All-causes	Age, sex, BMI, education, marital status, residence, physical activity, smoking, alcohol drinking status, history of hypertension, history of diabetes, intake of total energy, vegetables, fruits, red meat and saturated fat.
	US	National Health and Nutrition Examination Survey	9.1 years	43.8 y	36,032	4826	Polyunsaturated fat	All-causes	Age, sex, race-ethnicity, BMI, education, marital status, physical activity, smoking, alcohol drinking status, history of hypertension, history of diabetes, family history of cardiovascular disease, intake of total energy, vegetables, fruits, red meat and saturated fat.
Zhuang, 2019, a	China	China Health and Nutrition Survey	14 years	>20 y	14,383	1011	Saturated fat	All-causes	Age, quartiles of income, educational level, marital status, residence, location, physical activity, smoking status, alcohol intake, intake of total energy, percentage of energy from dietary protein, monounsaturated fat polyunsaturated fat, and remaining unmeasured or unknown fatty acids, BMI
Zhuang, 2019, b	US	National Institutes of Health −American Association of Retired Persons Diet and Health Study	16 years	50-71 y	521,120	129,328	Saturated fat Monounsaturated fat Polyunsaturated fat *trans*-fat	All-causes CVD Cancer	Age, sex, BMI, race, education, marital status, household income, smoking, alcohol, physical activity, history of hypertension and hypercholesterolemia, perceived health condition, history of heart disease, stroke, diabetes mellitus, and cancer at baseline, multi-vitamin use, aspirin use, hormones use for women. intake of total energy, percentages of energy intake from protein, Fat intake were mutually adjusted for intake of remaining fat.
Esrey, 1996	US	Lipid Research Clinics Prevalence Follow-Up Study	12.4 years	30-79 y	4546	90	Total fat Saturated fat Monounsaturated fat Polyunsaturated fat	CVD	Age, sex, energy intake, serum lipids, systolic blood pressure, cigarette smoking status, BMI, glucose intolerance.
Pietinen, 1997	Finland	The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	6.1 years	50-69 y	21,930	635	Total fat Saturated fat Monounsaturated fat Polyunsaturated fat *trans*-fat	CVD	Age, smoking, BMI, blood pressure, intakes of energy, alcohol, and fiber (quintiles), education, physical activity
Xu, 2006	US	Strong Heart Study	7.2 years	47−79 y	2938	138	Total fat Saturated fat Monounsaturated fat Polyunsaturated fat *trans*-fat	CVD	Age, sex, study center, diabetes status, BMI, HDL, LDL, triacylglycerol (log-transformed), smoking, alcohol consumption, hypertension, percentage of energy from protein, and total energy intake.
Virtanen, 2014	Finland	The Kuopio Ischemic Heart Disease Risk Factor Study	21.4 years	42-60 y	1981	183	Total fat Saturated fat Monounsaturated fat Polyunsaturated fat *trans*-fat	CVD	Age, examination year, energy intake, BMI, diabetes mellitus, hypertension, family history of coronary heart disease, pack-years of smoking, education, leisure-time physical activity, intakes of alcohol and fiber, percentage of energy from protein, Fat intake were mutually adjusted for intake of remaining fat.

CVD, cardiovascular disease; BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein.

potential confounders including smoking (n = 17) [10,12–27], BMI (n = 15) [10,12–14,16–18,20–27], alcohol consumption (n = 14) [10,12,14–18,20,21,23–27], and physical activity (n = 15) [10,12–19,21,24–27]. The results of the quality assessment showed a mean quality assessment score of 10.3, ranging from 7 to 12.

3.2. Total fat

Eight prospective cohort studies including 57,127 deaths and 384,010 subjects examined the association between dietary total fat and all-cause mortality [10,11,14,16–19]. The pooled RR for highest *versus* lowest levels of total fat intake was 0.89 (95% CI: 0.81–0.99, $I^2 = 82.3\%$, $P_{heterogeneity}<0.001$) (Table 2, Supplementary Fig. 2A). The heterogeneity was slightly decreased when two studies from Japan [14,16] were excluded ($P = 0.006$, $I^2 = 69.3\%$). A 5% increase in energy from total fat intake was associated with a 1% lower risk of all-cause mortality (RR = 0.99; 95% CI: 0.98–1.00) (Table 2, Supplementary Fig. 2B). We found no significant non-linear association between total fat intake and all-cause mortality (P for non-linearity = 0.39) (Fig. 1). Regarding dietary total fat and CVD mortality, we did not find a significant association (Table 2, Supplementary Fig. 3). Although a significant non-linear association between dietary total fat and cancer mortality was observed (P for non-linearity = 0.03) (Fig. 1), there was no evidence of an association between total fat intake and cancer mortality as all confidence intervals included 1.0 (Table 2, Supplementary Fig. 4).

3.3. Saturated fat

Twelve prospective cohort studies including 188,655 deaths and 938,386 subjects investigated the association between dietary saturated fat and all-cause mortality [10–12,14,16–20,25,26]. The pooled RR for highest *versus* lowest levels of saturated fat intake was 1.03 (95% CI: 0.94–1.13, $I^2 = 90.4\%$, $P_{heterogeneity}<0.001$) (Table 2, Supplementary Fig. 5A). The heterogeneity was slightly reduced when studies from Japan [14,16] and multi-continent [19] were excluded ($P < 0.001$, $I^2 = 85.7\%$). A significant non-linear association between saturated fat intake and all-cause mortality was found (P for non-linearity = 0.001) (Fig. 2). The risk of all-cause mortality was significantly increased up to 11% of the energy from saturated fat intake, with a tendency to plateau at higher percentage. For CVD mortality, 5% energy increments in saturated fat intake were associated with 3% (RR = 1.03; 95% CI: 1.00–1.07) higher risk of CVD mortality (Table 2, Supplementary Fig. 6B). In the non-linearity test, a significant non-linear association between dietary saturated fat and CVD mortality was observed (P for non-linearity <0.001) (Fig. 2). A significant increased risk of CVD mortality was observed from 3 to 12% of the energy from saturated fat intake. We found a positive association between dietary saturated fat and cancer mortality (RR = 1.09; 95% CI: 1.00–1.18) in the comparison of highest *versus* lowest intake (Table 2, Supplementary Fig. 7A).

3.4. Monounsaturated fat

Ten prospective cohort studies including 187,573 deaths and 923,502 subjects examined the association between dietary monounsaturated fat and all-cause mortality [10,11,14,16–20,26]. The pooled RR for highest *versus* lowest levels of monounsaturated fat intake was 0.94 (95% CI: 0.89–0.99, $I^2 = 61.2\%$, $P_{heterogeneity} = 0.003$) (Table 2, Supplementary Fig. 8A). The heterogeneity was slightly reduced when studies with long follow-up durations [18] were excluded ($P = 0.02$, $I^2 = 53.6\%$). A 5% increase in energy from monounsaturated fat intake was associated with 2% lower risk of all-cause mortality (RR = 0.98; 95% CI: 0.97–0.99) (Table 2, Supplementary Fig. 8B). There was no evidence of a non-linear association between dietary monounsaturated fat and all-cause mortality (P for non-linearity = 0.30) (Fig. 3). We did not find any significant association between dietary monounsaturated fat and CVD mortality (Table 2, Supplementary Fig. 9) and cancer mortality (Table 2, Supplementary Fig. 10).

3.5. Polyunsaturated fat

Eleven prospective cohort studies including 192,288 deaths and 955,279 subjects examined the association between dietary polyunsaturated fat and all-cause mortality [10,11,14,16–19,21,26]. The pooled RR for highest *versus* lowest levels of polyunsaturated fat intake was 0.88 (95% CI: 0.81–0.94, $I^2 = 84.7\%$, $P_{heterogeneity}<0.001$) (Table 2, Supplementary Fig. 11A). The heterogeneity was a little decreased when studies with long follow-up durations [18] were

Table 2
Summary of pooled relative risks (RR) of mortality from all-causes, CVD, and cancer for total and specific types of fat intake.

	Highest *versus* lowest				% of energy increment from fat				
	No. of studies	RR (95% CI)	I^2 (%)	*P* value	% of energy	No. of studies	RR (95% CI)	I^2 (%)	*P* value
All-cause mortality									
Total fat	8	0.89 (0.81–0.99)	82.3	<0.001	5	6	0.99 (0.98–1.00)	67.5	0.002
Saturated fat	11	1.03 (0.94–1.13)	90.4	<0.001	5	10	1.02 (1.00–1.05)	83.1	<0.001
Monounsaturated fat	10	0.94 (0.89–0.99)	61.2	0.003	5	8	0.98 (0.97–0.99)	36.8	0.11
Polyunsaturated fat	11	0.88 (0.81–0.94)	84.7	<0.001	5	9	0.93 (0.89–0.97)	83.7	<0.001
Trans-fat	5	1.11 (1.02–1.21)	80.8	0.001	1	6	1.06 (1.01–1.10)	89.5	<0.001
CVD mortality									
Total fat	9	0.95 (0.85–1.07)	51.3	0.02	5	7	1.00 (0.99–1.01)	48.3	0.04
Saturated fat	11	1.02 (0.92–1.12)	78.2	<0.001	5	10	1.03 (1.00–1.07)	76.1	<0.001
Monounsaturated fat	11	0.94 (0.88–1.01)	47.1	0.03	5	9	0.99 (0.96–1.01)	53.1	0.01
Polyunsaturated fat	11	0.95 (0.89–1.02)	64.2	0.001	5	9	0.95 (0.91–0.98)	59.1	0.004
Trans-fat	6	1.14 (1.02–1.26)	46.6	0.1	1	7	1.06 (1.02–1.11)	50.8	0.05
Cancer mortality									
Total fat	5	1.00 (0.88–1.14)	69.2	0.003	5	4	1.00 (0.99–1.01)	50.9	0.07
Saturated fat	7	1.09 (1.00–1.18)	73.2	<0.001	5	6	1.04 (1.02–1.06)	58.8	0.02
Monounsaturated fat	7	0.98 (0.93–1.03)	35.8	0.13	5	6	0.99 (0.98–1.00)	11.8	0.34
Polyunsaturated fat	7	0.92 (0.89–0.95)	13.0	0.33	5	6	0.96 (0.94–0.99)	41.9	0.10
Trans-fat	3	0.97 (0.91–1.03)	46.1	0.17	1	3	0.99 (0.98–1.00)	0.0	0.37

CVD, cardiovascular disease.

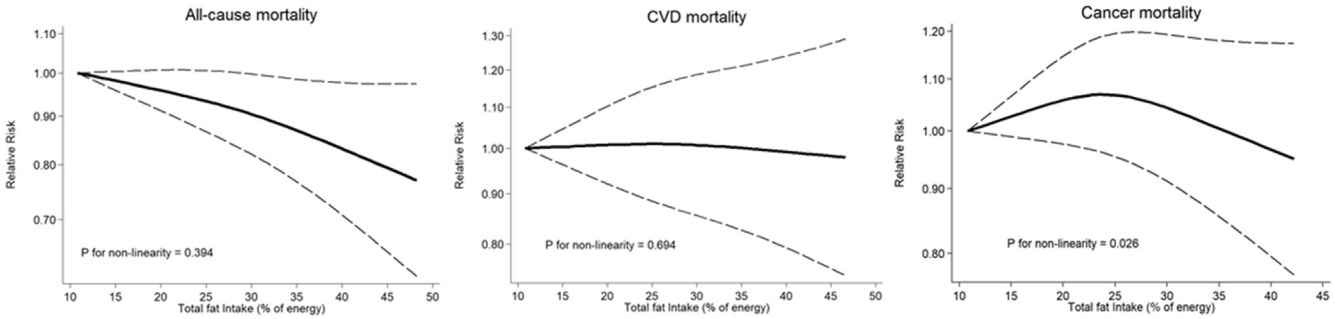

Fig. 1. Pooled dose–response association between dietary total fat and mortality from all-causes, CVD, and cancer. Solid lines represent relative risk (RR), dashed lines represent 95% confidence intervals.

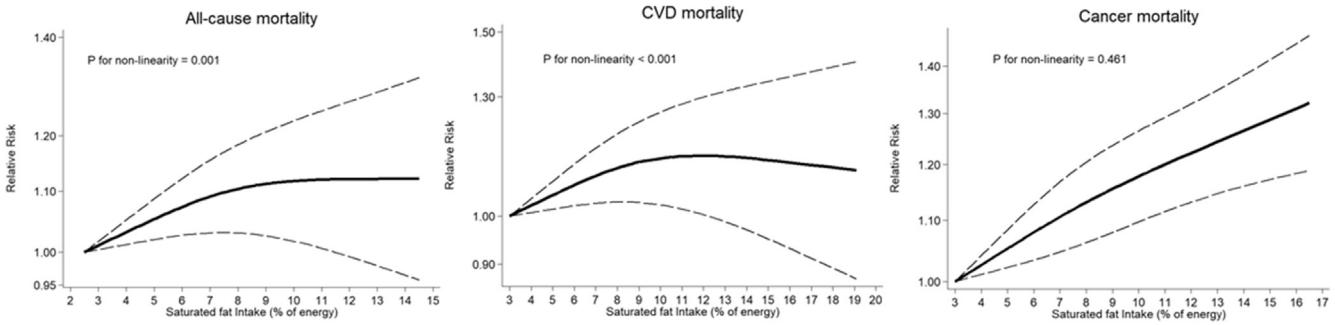

Fig. 2. Pooled dose–response association between dietary saturated fat and mortality from all-causes, CVD, and cancer. Solid lines represent relative risk (RR), dashed lines represent 95% confidence intervals.

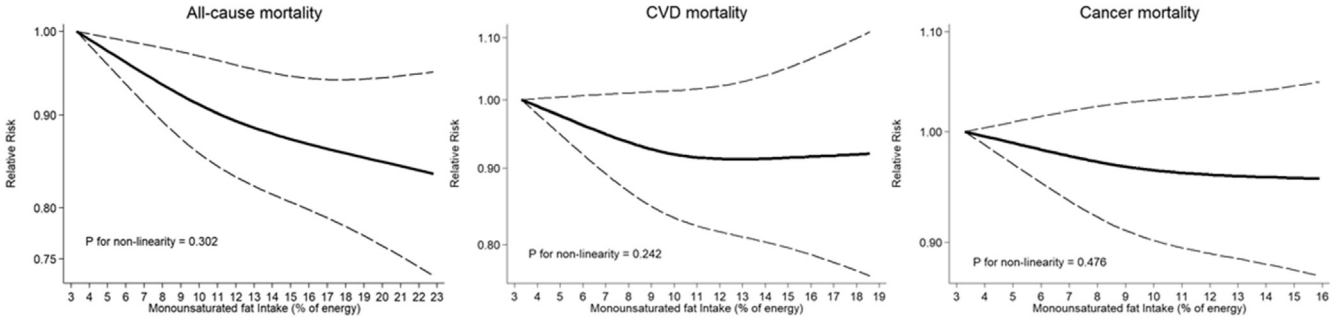

Fig. 3. Pooled dose–response association between dietary monounsaturated fat and mortality from all-causes, CVD, and cancer. Solid lines represent relative risk (RR), dashed lines represent 95% confidence intervals.

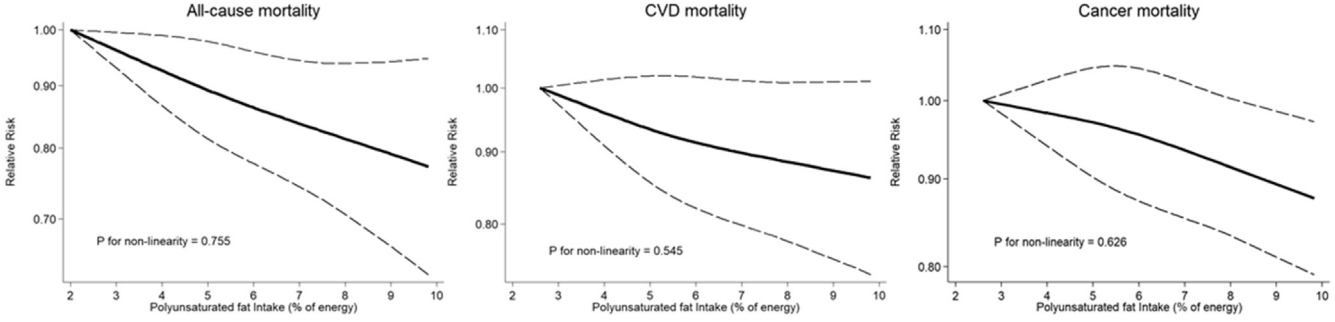

Fig. 4. Pooled dose–response association between dietary polyunsaturated fat and mortality from all-causes, CVD, and cancer. Solid lines represent relative risk (RR), dashed lines represent 95% confidence intervals.

excluded ($P < 0.001$, $I^2 = 71.7\%$). A 5% increase in energy from polyunsaturated fat was associated with 7% lower risk of all-cause mortality (RR = 0.93; 95% CI: 0.89–0.97) (Table 2, Supplementary Fig. 11B). We found no evidence of a non-linear association between dietary polyunsaturated fat and all-cause mortality (P for non-linearity = 0.76) (Fig. 4). A 5% energy increment in polyunsaturated fat intake was associated with 5% lower risk of CVD mortality (RR = 0.95; 95% CI: 0.91–0.98) (Table 2, Supplementary Fig. 12B). For risk of cancer mortality, we found an inverse association with dietary polyunsaturated fat (RR = 0.92; 95% CI: 0.89–0.95) in the comparison of highest *versus* lowest intake (Table 2, Supplementary Fig. 13A).

3.6. Trans-fat

Six prospective cohort studies including 165,152 deaths and 680,223 subjects investigated the association between dietary *trans*-fat and all-cause mortality [13,15,17,18,26]. The pooled RR for highest *versus* lowest levels of *trans*-fat intake was 1.11 (95% CI: 1.02–1.21, $I^2 = 80.8\%$, $P_{heterogeneity} = 0.001$) (Table 2, Supplementary Fig. 14A). The heterogeneity disappeared when the study which showed a weak positive association [26] was excluded ($P = 0.49$, $I^2 = 0.0\%$). A 1% increase in energy from *trans*-fat was associated with 6% higher risk of all-cause mortality (RR = 1.06; 95% CI: 1.01–1.10) (Table 2, Supplementary Fig. 14B). We found no evidence of a non-linear association between dietary *trans*-fat and all-cause mortality (P for non-linearity = 0.28) (Fig. 5). In the highest *versus* lowest meta-analysis, we found a positive association between dietary *trans*-fat and CVD mortality (RR = 1.14; 95% CI: 1.02–1.26) (Table 2, Supplementary Fig. 15A). A 1% energy increment in *trans*-fat intake was associated with 6% (RR = 1.06; 95% CI: 1.02–1.11) higher risk of CVD mortality (Table 2, Supplementary Fig. 15B). We did not find any significant association between intakes of dietary *trans*-fat and risk of cancer mortality (Table 2, Supplementary Fig. 16).

3.7. Subgroup analyses of all-cause mortality for dietary fat

In the subgroup analysis by sex, geographical region, type of dietary assessment and adjustment for other types of fat intake or serum lipids, no significant difference was observed in the comparison of highest *versus* lowest dietary fat categories (P for difference>0.06 in all comparisons) (Table 3). We found some evidence of difference by geographical region in the analysis for a 5% energy increment in polyunsaturated fat intake. A strong inverse association was found in studies conducted in Europe (RR = 0.69; 95% CI: 0.59–0.82) than Asia (RR = 0.96; 95% CI: 0.88–1.05) and the US (RR = 0.93; 95% CI: 0.88–0.97) (P for Asia or the US *versus* Europe = 0.02 and 0.03, respectively).

3.8. Publication bias

There was no evidence of publication bias with Begg's ($P > 0.2$) and Egger's test ($P > 0.05$) of all-cause mortality for dietary total, saturated, monounsaturated, polyunsaturated, and *trans*-fat. We found no indication of publication bias of mortality from CVD and cancer for total and subtypes of fat intake either (Begg's $P > 0.4$ and Egger's $P > 0.07$ for the all analyses).

4. Discussion

In the present meta-analysis of 19 prospective cohort studies, we found inverse associations between dietary total, monounsaturated, and polyunsaturated fat intake and all-cause mortality. A 5% energy increment in total, monounsaturated, and polyunsaturated fat intake was associated with 1%, 2%, and 7% lower all-cause mortality, respectively. A 5% increase in energy from polyunsaturated fat was also associated with 5% and 4% lower risks of mortality from CVD and cancer, respectively. In contrast, we found a positive association between dietary *trans*-fat and all-cause mortality. A 1% energy increment in *trans*-fat intake was associated with 6% higher all-cause-mortality and CVD-specific mortality, respectively. We found a non-linear positive association between dietary saturated fat intake and mortality from all-causes and CVD. The risk of death was increased with increasing intake of saturated fat, but no further increased risk was observed above the 11% of energy from dietary saturated fat. A linear positive association was observed between dietary saturated fat and risk of cancer death.

Recent meta-analyses reporting non-significant positive associations between dietary saturated fat and risk of CVD [6] and breast cancer [9] questioned current diet guidelines that recommend people to decrease saturated fat intake. One study included in our meta-analysis showed a possibility that the effect of dietary saturated fat on risk of mortality differs by structure of saturated fat [25]. This study reported an unusual strong inverse association between odd-chain saturated fat intake and all-cause mortality. Another study included in the current meta-analysis also provided the results by food source of saturated fat, and showed that only dietary saturated fat from fish was associated with lower risk of all-cause mortality [17]. Other food sources of saturated fat mostly indicated non-significant positive associations in relation to all-cause mortality. Fish is a minor source of saturated fat so other aspects of fish may have accounted for the lower risk. Among foods high in saturated fat, red and processed meat have been associated with higher all-cause mortality [41], whereas intake of dairy products which are primary source of odd-chain saturated fat was associated with lower all-cause mortality [42]. Given the results of previous studies and our meta-analysis, total saturated fat intake is associated with higher risk of death, but the specific dietary source

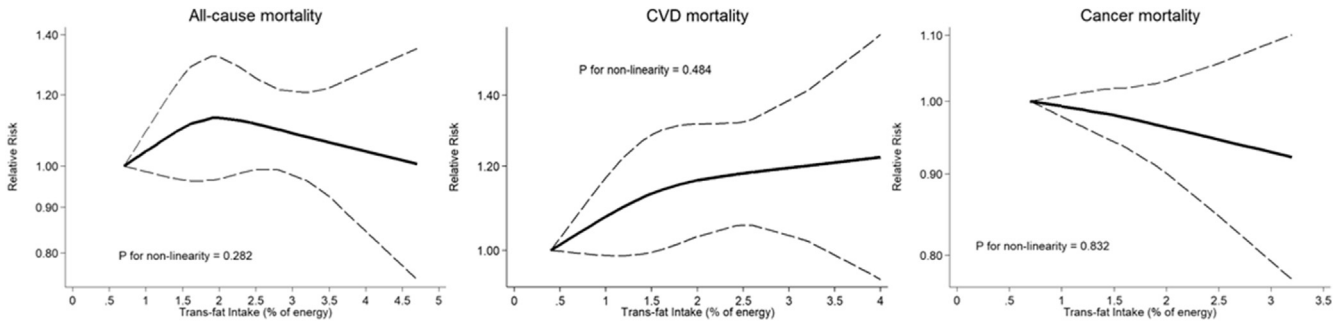

Fig. 5. Pooled dose–response association between dietary *trans*-fat and mortality from all-causes, CVD, and cancer. Solid lines represent relative risk (RR), dashed lines represent 95% confidence interval.

Table 3
Summary of pooled relative risks (RR) of all-cause mortality for total and specific types of fat intake by sex, geographical region, and adjustment for other types of fat intake.

	No. of studies	RR	95% CI	*P* for difference	No. of studies	RR	95% CI	*P* for difference
	Highest *versus* lowest				5% of energy increment from fat			
Total fat								
Sex								
Males	4	0.91	0.80–1.04	0.59	3	0.99	0.96–1.01	0.37
Females	4	0.97	0.82–1.15		3	1.00	0.98–1.02	
Geographical region								
Europe	3	0.83	0.59–1.17		2	0.99	0.96–1.01	
Asia	2	0.97	0.85–1.10	0.50[a]	2	0.99	0.97–1.01	0.75[a]
US	2	0.84	0.81–0.88	0.98[b]	2	0.99	0.98–0.99	0.96[b]
Multi-continent	1	0.77	0.68–0.88	0.75[c]	–	–	–	–
Adjustment for other types of fat intake								
Yes	5	0.88	0.76–1.03	0.85	5	0.99	0.98–1.00	0.56
No	3	0.91	0.78–1.07		1	1.00	0.98–1.02	
Adjustment for serum lipids								
Yes	3	0.69	0.44–1.08	0.14	3	0.99	0.98–0.99	0.41
No	5	0.94	0.84–1.05		5	0.99	0.98–1.01	
Saturated fat								
Sex								
Males	5	0.99	0.90–1.08	0.44	5	1.00	0.96–1.04	0.53
Females	5	1.06	0.92–1.22		4	1.02	0.96–1.09	
Geographical region								
Europe	3	0.95	0.80–1.13		2	1.03	0.92–1.17	
Asia	3	1.00	0.89–1.12	0.72[a]	3	0.98	0.94–1.03	0.46[a]
US	4	1.16	1.03–1.31	0.13[b]	5	1.05	1.02–1.07	0.86[b]
Multi-continent	1	0.86	0.75–0.98	0.55[c]	–	–	–	–
Adjustment for other types of fat intake								
Yes	7	1.08	0.96–1.22	0.23	6	1.04	1.00–1.07	0.26
No	4	0.97	0.86–1.09		4	1.00	0.95–1.06	
Adjustment for serum lipids								
Yes	4	1.17	1.00–1.37	0.08	4	1.05	1.01–1.08	0.13
No	7	0.99	0.90–1.08		6	1.00	0.96–1.05	
Type of dietary assessment								
FFQ or food record	9	1.01	0.90–1.13	0.28	8	1.02	0.98–1.05	0.51
24-h recall	2	1.16	0.94–1.42		2	1.05	0.97–1.14	
Monounsaturated fat								
Sex								
Males	4	0.97	0.91–1.03	0.38	3	0.98	0.96–1.00	0.27
Females	4	0.94	0.83–1.06		3	0.97	0.95–0.98	
Geographical region								
Europe	3	0.88	0.61–1.27		2	0.94	0.89–0.99	
Asia	2	0.97	0.91–1.02	0.64[a]	2	0.96	0.93–0.99	0.45[a]
US	4	0.95	0.90–1.01	0.72[b]	4	0.98	0.97–1.00	0.15[b]
Multi-continent	1	0.81	0.71–0.92	0.53[c]	–	–	–	–
Adjustment for other types of fat intake								
Yes	6	0.95	0.87–1.03	0.81	5	0.98	0.96–0.99	0.55
No	4	0.93	0.86–1.01		3	0.98	0.96–1.01	
Adjustment for serum lipids								
Yes	4	0.91	0.82–1.01	0.62	4	0.98	0.96–0.99	0.71
No	6	0.95	0.89–1.02		4	0.99	0.97–1.00	
Type of dietary assessment								
FFQ or food record	9	0.93	0.87–0.99	0.59	7	0.98	0.97–0.99	0.17
24-h recall	1	0.98	0.93–1.03		1	1.00	0.98–1.01	
Polyunsaturated fat								
Sex								
Males	4	0.88	0.72–1.06	0.84	3	0.93	0.81–1.07	0.98
Females	4	0.84	0.80–0.87		3	0.92	0.89–0.94	
Geographical region								
Europe	3	0.71	0.55–0.93		2	0.69	0.59–0.82	
Asia	3	0.96	0.84–1.10	0.06[a]	3	0.96	0.88–1.05	0.02[a]
US	4	0.87	0.77–0.97	0.24[b]	4	0.93	0.88–0.97	0.03[b]
Multi-continent	1	0.80	0.71–0.90	0.62[c]	–	–	–	–
Adjustment for other types of fat intake								
Yes	8	0.86	0.79–0.94	0.72	7	0.91	0.87–0.96	0.35
No	3	0.89	0.75–1.06		2	0.97	0.83–1.14	
Adjustment for serum lipids								
Yes	4	0.82	0.71–0.94	0.33	4	0.89	0.84–0.95	0.23
No	7	0.90	0.81–0.99		5	0.96	0.90–1.03	
Type of dietary assessment								
FFQ or food record	9	0.86	0.80–0.93	0.30	7	0.92	0.88–0.96	0.37
24-h recall	2	1.00	0.73–1.38		2	0.98	0.91–1.04	

FFQ, food frequency questionnaire.
[a] *P* value difference in RR for studies conducted in Asia *versus* Europe.
[b] *P* value difference in RR for studies conducted in the US *versus* Europe.
[c] *P* value difference in RR for studies conducted in multi-continent *versus* Europe.

and type of saturated fat may be a key determinant of the association. We could not perform the analysis by subtype of saturated fat due to limited number of studies. Unlike our results indicating a higher risk of total mortality among people with a high saturated fat intake, one large prospective study [19] reported an inverse association between dietary saturated fat intake and risk of total mortality. This study did not adjust for alcohol consumption in the analysis of dietary saturated fat and risk of total mortality. Previous studies on the association between fat intake and risk of mortality showed that people with a high saturated fat intake tended to have a lower alcohol consumption [17,26]. Although it is difficult to identify the reason for different results between our study and previous cohort study [19], the potential confounding by alcohol consumption may explain, in part, the discrepancy.

Our observed inverse association between polyunsaturated fat intake and mortality are mostly concordant with previous evidence. Recent two meta-analyses both found a lower risk of all-cause mortality among people with high intake of long-chain n-3 polyunsaturated fatty acids [28,29]. Long-chain n-3 polyunsaturated fat has anti-inflammatory properties through inhibiting activation of pro-inflammatory factors such as nuclear factor kappa B (NFkB) and activating of peroxisome proliferator-activated receptor-γ (PPARγ), which has anti-inflammatory properties [43,44]. These anti-inflammatory actions may have contributed to lowering the risk of death by reducing the risk of inflammation-related diseases including CVD and cancer. Previous evidence for the effect of dietary polyunsaturated fat on mortality was focused on n-3 polyunsaturated fat. Several studies examined the association between dietary n-6 polyunsaturated fat and mortality, but the results were inconsistent showing null [16,21] or inverse [18,26] associations. Although some have recommended to reduce n-6 polyunsaturated fat intake [45,46], accumulating evidence indicates that the intake of 5–10% of energy from n-6 polyunsaturated fat decreases the risk of coronary heart disease [47]. Replacing dietary saturated or *trans*-fat with n-6 polyunsaturated fat has been associated with lower levels of LDL cholesterol, which are important in the incidence of CVD [48–50]. Also increasing literature reported that n-6 polyunsaturated fat may have anti-cancer effects [51]. Studies which reported the results by n-6/n-3 ratio showed null association [18] or lower all-cause mortality with an increased ratio of the n-6/n-3 [26]. More studies are needed to identify the difference by the subtype of dietary polyunsaturated fat. In the subgroup analysis by geographical region, we found stronger inverse association between dietary polyunsaturated fat and risk of all-cause mortality in Europe than in Asia. The reasons of regional differences may be due to lower intake of polyunsaturated fat in Asia than in Europe [16,17]. However, the number of studies included in subgroup analysis was small and thus, the results should be interpreted with caution.

Regarding dietary monounsaturated fat, a weak inverse association was found for all-cause mortality and no significant association was observed for mortality from CVD and cancer. A major source of monounsaturated fat is olive oil, which is one of the components of the Mediterranean diet, in populations with high intakes of olive oil. High olive oil intake has been found to be associated with lower all-cause mortality [52]. A large cohort study including 521,120 subjects reported the RRs for all-cause mortality by source of monounsaturated fat. In comparison of high *versus* low intake, animal-based monounsaturated fat was associated with higher mortality, while plant-based monounsaturated fat was associated with lower mortality [26]. Since most studies included in the current meta-analysis have evaluated total monounsaturated fat, the weak inverse or no association observed with total monounsaturated fat may be driven by animal-based monounsaturated fat.

Our findings that dietary *trans*-fat was associated with higher mortality from all-causes and CVD are in line with the current diet guidelines that recommend avoidance of *trans*-fat intake [3,4]. Dietary *trans*-fat has been reported to possess detrimental health effects through increasing LDL cholesterol and systematic inflammation [53]. Furthermore, *trans*-fat may affect the fluidity of the cell membranes by disordering the membrane phospholipids, and thus lead to damage on body systems and function [54]. No significant association between dietary trans-fat and cancer mortality was observed, though this result was based on only 3 studies. We found that high dietary total fat was associated with lower all-cause mortality. However, the composition of dietary fat seems to be more important than the total fat intake, because the association between dietary fat and mortality differed by the type of dietary fat.

To the best of our knowledge, this is the first comprehensive meta-analysis to examine the association between dietary total, saturated, monounsaturated, polyunsaturated, and *trans*-fat and mortality from all-causes, CVD, and cancer. The generalizability of our finding was enhanced by including a large number of cases (n = 195,515) and subjects (n = 1,013,273) from diverse regions such as Europe, the US, and Asia in the meta-analysis. In addition, all of the studies included in this meta-analysis were judged as good or high-quality, and there was no publication bias which could be of concern in meta-analysis. We also analyzed our data using fixed effects models, and the results were similar.

There were several limitations of note. First, the meta-analysis combined results from original studies with different highest and lowest categories of fat intake. However, we conducted a dose–response meta-analysis that showed RRs of mortality according to increment of dietary fat after testing the non-linearity between fat intake and risk of death. Second, although we conducted analyses for total, saturated, monounsaturated, polyunsaturated and *trans*-fat, there are more specific subtypes of fat (e.g. even-and odd-chain saturated fat, n-3 polyunsaturated fat, and linoleic acid, etc.) and the association between dietary fat and risk of mortality may vary accordingly. We could not perform an analysis by subtype of saturated or polyunsaturated fat due to the limited data. Third, most of the studies adjusted for potential confounders such as smoking, alcohol, BMI, and physical activity, but there is a possibility of residual confounding. As animal fats are common primary sources of saturated and monounsaturated fat in traditional Western diets, monounsaturated fat intake was strongly correlated with saturated fat intake [18,26]. This correlation could affect the association between mortality and monounsaturated and saturated fat intake. Among 19 studies, 11 studies provided the RRs which mutually adjusted for dietary fat subtypes [10,14,15,17,18,21,24–26]. We could not find any significant differences in RRs when we conducted subgroup analysis by mutual adjustment for subtype of dietary fat. In addition, we performed a subgroup analysis by adjustment for serum lipids (e.g., hypercholesterolemia), but significant differences were not observed. Although substitution analysis may be more ideal for dietary fats, only a few studies conducted this type of analysis [55].

In conclusion, diets high in total, monounsaturated, and polyunsaturated fat were associated with lower all-cause mortality, compared with diets low in fat, whereas diets high in saturated and *trans*-fat were associated with higher all-cause mortality. A diet high in saturated fat was positively associated with higher mortality from CVD and cancer, while a diet high in polyunsaturated fat was inversely associated with lower mortality from CVD and cancer. Our findings support current dietary guidelines to reduce saturated and *trans*-fat intake and emphasize mono-and polyunsaturated fat intake. In further large prospective cohort studies that examine the association between subtypes and sources of saturated, mono- and polyunsaturated fat and mortality,

substitution analysis could enhance understanding of the effect of dietary fat on health.

Statement of authorship

All authors have read and approved the final version submitted for publication. Y.K.,Y.J., and E.G. developed study concept and design and contributed to critical revision of the manuscript for important intellectual content; Y.K. wrote the manuscript; Y.K. and Y.J. researched data, conducted the statistical analysis; Y.K., Y.J., and E.G. contributed to discussion and reviewed/edited the manuscript.

Funding sources

This work was supported by the Basic Science Research Program through the National Research Foundation of Korea, funded by the Ministry of Science, ICT and Future Planning (NRF 2018R1D1A1B07045353). Funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2020.07.007.

References

[1] Mu H, Hoy CE. The digestion of dietary triacylglycerols. Prog Lipid Res 2004;43:105–33.
[2] Ratnayake WM, Galli C. Fat and fatty acid terminology, methods of analysis and fat digestion and metabolism: a background review paper. Ann Nutr Metab 2009;55:8–43.
[3] U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015–2020 dietary guidelines for Americans. 8th ed. 2015. http://health.gov/dietaryguidelines/2015/guidelines/.
[4] Food and Agriculture Organization of the United Nations. Summary of conclusions and dietary recommendations on total fat and fatty acids. In: Fats and fatty acids in human nutrition—report of an expert consultation; 2010. http://www.fao.org/ag/agn/nutrition/docs/Fats%20and%20Fatty%20Acids%20Summary.pdf.
[5] Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 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 2016;37:2315–81.
[6] Chowdhury R, Warnakula S, Kunutsor S, Crowe F, Ward HA, Johnson L, et al. Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. Ann Intern Med 2014;160:398–406.
[7] de Souza RJ, Mente A, Maroleanu A, Cozma AI, Ha V, Kishibe T, et al. 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 2015;351:h3978.
[8] Harcombe Z, Baker JS, Cooper SM, Davies B, Sculthorpe N, DiNicolantonio JJ, et al. Evidence from randomised controlled trials did not support the introduction of dietary fat guidelines in 1977 and 1983: a systematic review and meta-analysis. Open Heart 2015;2:e000196.
[9] Cao Y, Hou L, Wang W. Dietary total fat and fatty acids intake, serum fatty acids and risk of breast cancer: a meta-analysis of prospective cohort studies. Int J Canc 2016;138:1894–904.
[10] Leosdottir M, Nilsson PM, Nilsson JA, Mansson H, Berglund G. Dietary fat intake and early mortality patterns–data from the Malmo Diet and Cancer Study. J Intern Med 2005;258:153–65.
[11] Solfrizzi V, D'Introno A, Colacicco AM, Capurso C, Palasciano R, Capurso S, et al. Unsaturated fatty acids intake and all-causes mortality: a 8.5-year follow-up of the Italian Longitudinal Study on Aging. Exp Gerontol 2005;40:335–43.
[12] Tucker KL, Hallfrisch J, Qiao N, Muller D, Andres R, Fleg JL, et al. The combination of high fruit and vegetable and low saturated fat intakes is more protective against mortality in aging men than is either alone: the Baltimore Longitudinal Study of Aging. J Nutr 2005;135:556–61.
[13] Akbaraly TN, Ferrie JE, Berr C, Brunner EJ, Head J, Marmot MG, et al. Alternative Healthy Eating Index and mortality over 18 y of follow-up: results from the Whitehall II cohort. Am J Clin Nutr 2011;94:247–53.
[14] Nagata C, Nakamura K, Wada K, Oba S, Tsuji M, Tamai Y, et al. Total fat intake is associated with decreased mortality in Japanese men but not in women. J Nutr 2012;142:1713–9.
[15] Kiage JN, Merrill PD, Robinson CJ, Cao Y, Malik TA, Hundley BC, et al. Intake of trans fat and all-cause mortality in the reasons for geographical and racial differences in stroke (REGARDS) cohort. Am J Clin Nutr 2013;97:1121–8.
[16] Wakai K, Naito M, Date C, Iso H, Tamakoshi A, Group JS. Dietary intakes of fat and total mortality among Japanese populations with a low fat intake: the Japan Collaborative Cohort (JACC) Study. Nutr Metab (Lond) 2014;11:12.
[17] Guasch-Ferre M, Babio N, Martinez-Gonzalez MA, Corella D, Ros E, Martin-Pelaez S, et al. 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 2015;102:1563–73.
[18] Wang DD, Li Y, Chiuve SE, Stampfer MJ, Manson JE, Rimm EB, et al. Association of specific dietary fats with total and cause-specific mortality. JAMA Intern Med 2016;176:1134–45.
[19] Dehghan M, Mente A, Zhang X, Swaminathan S, Li W, Mohan V, et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. Lancet 2017;390:2050–62.
[20] Ricci C, Baumgartner J, Zec M, Kruger HS, Smuts CM. Type of dietary fat intakes in relation to all-cause and cause-specific mortality in US adults: an iso-energetic substitution analysis from the American National Health and Nutrition Examination Survey linked to the US mortality registry. Br J Nutr 2018;119:456–63.
[21] Zhuang P, Wang W, Wang J, Zhang Y, Jiao J. Polyunsaturated fatty acids intake, omega-6/omega-3 ratio and mortality: findings from two independent nationwide cohorts. Clin Nutr 2019;38(2):848–55.
[22] Esrey KL, Joseph L, Grover SA. Relationship between dietary intake and coronary heart disease mortality: lipid research clinics prevalence follow-up study. J Clin Epidemiol 1996;49:211–6.
[23] Xu J, Eilat-Adar S, Loria C, Goldbourt U, Howard BV, Fabsitz RR, et al. Dietary fat intake and risk of coronary heart disease: the Strong Heart Study. Am J Clin Nutr 2006;84:894–902.
[24] Virtanen JK, Mursu J, Tuomainen TP, Voutilainen S. Dietary fatty acids and the risk of fatal and non-fatal coronary heart disease in middle-aged or older men: the kuopio ischaemic heart disease risk factor study. Circulation 2013;127.
[25] Zhuang P, Cheng L, Wang J, Zhang Y, Jiao J. Saturated fatty acid intake is associated with total mortality in a nationwide cohort study. J Nutr 2019;149:68–77.
[26] Zhuang P, Zhang Y, He W, Chen X, Chen J, He L, et al. Dietary fats in relation to total and cause-specific mortality in a prospective cohort of 521 120 individuals with 16 Years of follow-up. Circ Res 2019;124:757–68.
[27] Pietinen P, Ascherio A, Korhonen P, Hartman AM, Willett WC, Albanes D, et al. Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Am J Epidemiol 1997;145:876–87.
[28] Wan Y, Zheng J, Wang F, Li D. Fish, long chain omega-3 polyunsaturated fatty acids consumption, and risk of all-cause mortality: a systematic review and dose-response meta-analysis from 23 independent prospective cohort studies. Asia Pac J Clin Nutr 2017;26:939–56.
[29] Chen GC, Yang J, Eggersdorfer M, Zhang W, Qin LQ. N-3 long-chain polyunsaturated fatty acids and risk of all-cause mortality among general populations: a meta-analysis. Sci Rep 2016;6:28165.
[30] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
[31] Wells GASB, O'Connell D. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
[32] DerSimonian R, Laird N. Meta-analysis in clinical trials. Contr Clin Trials 1986;7:177–88.
[33] Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 1992;135:1301–9.
[34] Berlin JA, Longnecker MP, Greenland S. Meta-analysis of epidemiologic dose-response data. Epidemiology 1993;4:218–28.
[35] Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. STATA J 2006;6:40–57.
[36] Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. Am J Epidemiol 2012;175:66–73.
[37] Cochran WG. The combination of estimates from different experiments. Biometrics 1954;10:101–29.
[38] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[39] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.

[40] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[41] Larsson SC, Orsini N. Red meat and processed meat consumption and all-cause mortality: a meta-analysis. Am J Epidemiol 2014;179:282–9.
[42] Mazidi M, Mikhailidis DP, Sattar N, Howard G, Graham I, Banach M, et al. Consumption of dairy product and its association with total and cause specific mortality - a population-based cohort study and meta-analysis. Clin Nutr 2019;38(6):2833–45.
[43] Wall R, Ross RP, Fitzgerald GF, Stanton C. Fatty acids from fish: the anti-inflammatory potential of long-chain omega-3 fatty acids. Nutr Rev 2010;68:280–9.
[44] Larsson SC, Kumlin M, Ingelman-Sundberg M, Wolk A. Dietary long-chain n-3 fatty acids for the prevention of cancer: a review of potential mechanisms. Am J Clin Nutr 2004;79:935–45.
[45] Simopoulos AP. The importance of the ratio of omega-6/omega-3 essential fatty acids. Biomed Pharmacother 2002;56:365–79.
[46] Simopoulos AP, Leaf A, Salem Jr N. Essentiality of and recommended dietary intakes for omega-6 and omega-3 fatty acids. Ann Nutr Metab 1999;43:127–30.
[47] Harris WS, Mozaffarian D, Rimm E, Kris-Etherton P, Rudel LL, Appel LJ, et al. Omega-6 fatty acids and risk for cardiovascular disease: a science advisory from the American heart association nutrition subcommittee of the council on nutrition, physical activity, and metabolism; council on cardiovascular nursing; and council on epidemiology and prevention. Circulation 2009;119:902–7.
[48] Mensink RP. Effects of saturated fatty acids on serum lipids and lipoproteins: a systematic review and regression analysis. World Health Organization; 2016.
[49] Vega-Lopez S, Matthan NR, Ausman LM, Ai M, Otokozawa S, Schaefer EJ, et al. Substitution of vegetable oil for a partially-hydrogenated fat favorably alters cardiovascular disease risk factors in moderately hypercholesterolemic post-menopausal women. Atherosclerosis 2009;207:208–12.
[50] Sacks FM, Lichtenstein AH, Wu JHY, Appel LJ, Creager MA, Kris-Etherton PM, et al. Dietary fats and cardiovascular disease: a presidential advisory from the American heart association. Circulation 2017;136:e1–23.
[51] Huerta-Yepez S, Tirado-Rodriguez AB, Hankinson O. Role of diets rich in omega-3 and omega-6 in the development of cancer. Bol Med Hosp Infant Mex 2016;73:446–56.
[52] Schwingshackl L, Hoffmann G. Monounsaturated fatty acids, olive oil and health status: a systematic review and meta-analysis of cohort studies. Lipids Health Dis 2014;13:154.
[53] Kummerow FA. The negative effects of hydrogenated trans fats and what to do about them. Atherosclerosis 2009;205:458–65.
[54] Ginter E, Simko V. New data on harmful effects of trans-fatty acids. Bratisl Lek Listy 2016;117:251–3.
[55] Song M, Giovannucci E. Substitution analysis in nutritional epidemiology: proceed with caution. Eur J Epidemiol 2018;33:137–40.