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Differential relationship between dietary fat and cholesterol on total mortality in Korean population cohorts

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Background. Associations among dietary fat, cholesterol intake and total mortality remain controversial, and most available data cover Western populations. The aim of this study was to assess associations for dietary fat and cholesterol in relation to total mortality in Koreans.

Methods. This study used data from three prospective Korean Genome and Epidemiology studies (conducted between June 2001 and December 2013). A total of 194,295 middle-aged and older Korean adults were included. Dietary fat intake was classified into quintiles. Dietary cholesterol intake was categorized into three groups based on cholesterol intake as follows: <200 mg, 200–299 mg and ≥300 mg. A multivariable Cox frailty model with random effects was applied to calculate hazard ratios (HR) and 95% confidence intervals (CIs) after adjusting for confounders.

Results. We documented 3866 deaths across a mean (min–max) follow-up period of 8.15 years (3–13 years). Higher fat intake was associated with lower total mortality (Q5 vs. Q1, HR 0.82 [95% CI 0.69, 0.98]; p trend < 0.01) after adjusting for age, sex, body mass index, alcohol, smoking, exercise and total calorie and protein (%) intake. Higher dietary cholesterol intake (≥300 mg/day) was associated with a higher risk of total mortality (HR 1.19 [95% CI 1.04, 1.37]) than lower cholesterol intake (<200 mg/day) in the multivariate model.

Conclusions. In Koreans, high dietary fat intake is associated with a lower risk of total mortality, while dietary cholesterol intake above 300 mg/day is associated with a higher risk of total mortality.

Keywords: dietary cholesterol, dietary fat, dyslipidaemia, KoGES, total mortality.

Abbreviations: CVD, cardiovascular disease; FFQ, food frequency questionnaire; KoGES, Korean Genome and Epidemiology Study; BMI, body mass index; WC, waist circumference.

Introduction

Dietary fats are essential nutrients that support cell growth, protect the internal organs and carry fat-soluble vitamins [1]. Dietary cholesterol is a sterol found only in animal products [2] and is an important precursor for bile acids, sex hormones and vitamin D [1]. However, excess fat and cholesterol intake are associated with unhealthy metabolic status [3,4]. For decades, dietary guidelines have emphasized reduced consumption of dietary saturated fats and cholesterol based on the assumption that higher intake of saturated fats and cholesterol increases the risk for cardiovascular diseases (CVD) due to increased levels of low-density lipoprotein cholesterol (LDL) [5]. Associations among dietary fat, cholesterol, cardiovascular mortality and total mortality, however, remain controversial despite decades of research [6,7]. The observational Prospective Urban and Rural Epidemiology (PURE) study across 18 countries concluded that total fat is related to a lower risk of total mortality and is not related to CVD mortality [7]. A recent large prospective cohort of 521,120 participants from

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the United States showed that replacing saturated fats with unsaturated fat is associated with lower total and CVD mortality [6].

Several advisory committees have published guidelines to promote lower cholesterol intake. The 2015 National Lipid Association's patient-centred dyslipidaemia management recommends limiting dietary cholesterol intake to <200 mg/day to reduce serum cholesterol levels in individuals with hypercholesterolaemia [8]. The 2019 American College of Cardiology/American Heart Association guidelines indicate that 'a diet containing reduced amounts of cholesterol and sodium can be beneficial to decrease CVD risk' without specifying the recommended dietary cholesterol intake [9]. Meanwhile, the Dietary Guidelines Advisory Committee removed the previously recommended dietary cholesterol level of <300 mg/day [10].

Dietary habits differ across countries, races and cultures. However, studies investigating the role of dietary fat and cholesterol on public health are mostly limited to Western countries. With rapid economic and nutrition transition [11], South Korea has recorded decreases in carbohydrate intake and gradual increases in fat intake [11]. In 2015, the Korean Nutrition Society elevated the acceptable macronutrient distribution range of fat from 15%–25% to 15%–30% [12]. Meanwhile, although changes in eating patterns can affect lifespan [13], studies assessing fat intake and total mortality in Asians are lacking. The primary aim of this study was to assess associations for dietary fat and cholesterol in relation to total mortality in Koreans. The secondary aim was to examine associations for dietary fat and cholesterol with total mortality in participants with comorbidities (hypertension, diabetes, or dyslipidaemia).

Methods

Study population

The data used in this prospective cohort study were from the Korean Genome and Epidemiology Study (KoGES), a large cohort study project designed to identify risk factors for common chronic diseases, such as type 2 diabetes, hypertension, metabolic syndrome, obesity and cardiovascular disease, in Korea with government funding (National Research Institute of Health, Centers for Disease Control and Prevention and the Ministry of Health and Welfare).

The population-based cohorts in the KoGES included 211,714 individuals from the KoGES_Ansan and Ansung, the KoGES_Health Examinee (HEXA) and the KoGES_ Cardiovascular Disease Association Study (CAVAS) studies. The KoGES_Ansan and Ansung study is a community-based cohort study involving participants aged 40–69 years recruited from an industrialized community (Ansan) and a rural area (Ansung) starting from 2001. The KoGES_HEXA study consists of participants aged 40 years and older recruited from the national health examinee registry starting from 2004. The KoGES_ CAVAS study is a community-based cohort of individuals aged 40 years and older from rural counties starting from 2005. Detailed information about the KoGES has been described in a previous study [14]. This research covered a study period beginning in June 2001 and ending in December 2013.

Among the 211,714 individuals, we excluded those missing data on smoking, alcohol intake, age, hypertension, diabetes mellitus or dyslipidaemia (n = 3286). We also excluded individuals who had a daily calorie intake <500 kcal/day or >6000 kcal/day and those who were missing data on carbohydrate, fat or protein intake (n = 12,708). We further excluded individuals who died within 3 years of participating in the KoGES (n = 1425). A final total of 194,295 individuals were included in this study. Figure 1 shows a flow chart of the study population. This study was approved by the Institute Review Board of Gangnam Severance Hospital (IRB No; 3-2020-0093).

Assessment of dietary fat and cholesterol intake

Diet history was collected at baseline using a validated 103-item food frequency questionnaire (FFQ) developed by the Korea Centers for Disease Control and Prevention and the Ministry of Health and Welfare [15]. The FFQ used in this study is a well-validated tool, as described in a previous study [16]. Dietary data were obtained from the three study cohorts following the same standardized protocol. Participants were asked how often, on average, they consumed a standard portion size of each food in the past year. Carbohydrate and protein intake were calculated as follows: carbohydrate intake (g/day) × 4 kcal/total energy intake (kcal/day) × 100 and protein intake (g/day) × 4 kcal/total energy intake (kcal/day) × 100. Fat intake was calculated as follows: fat intake (g/day) × 9 kcal/total energy intake (kcal/day) × 100. Cholesterol intake was recorded as mg/day.

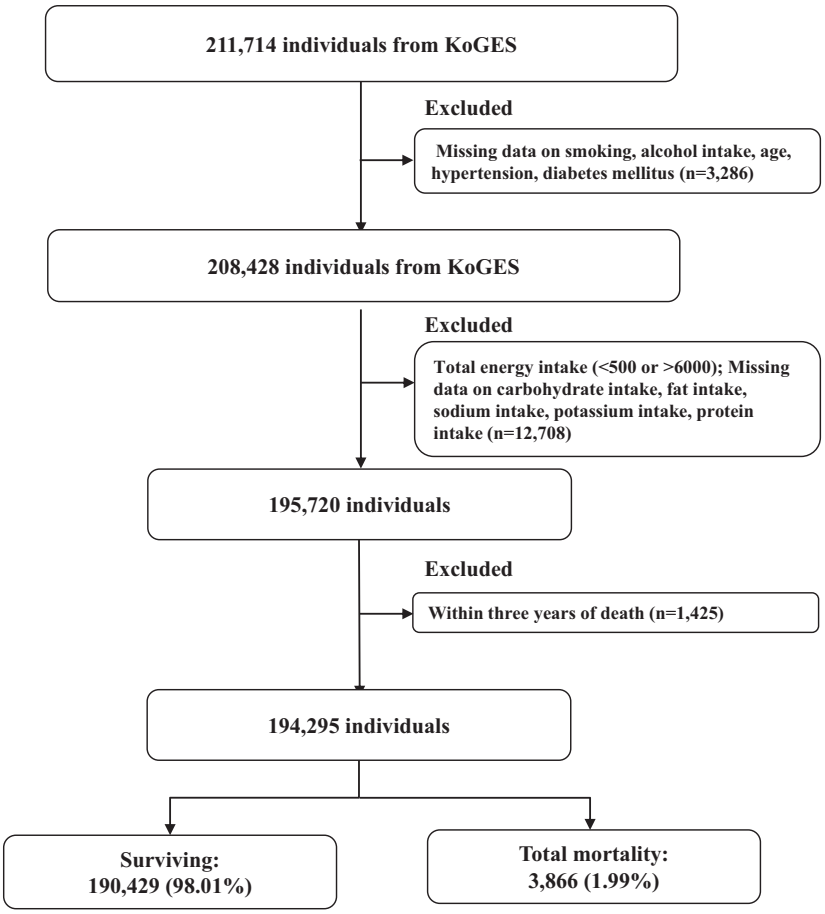

Fig. 1 *Flow chart of study population.*

Assessment of total mortality

Mortality status and causes of death were determined using publicly accessible files in the KoGES-linked National Death Index as a reference. Participant deaths were tracked from October 2001 to December 2017. Similarly, the follow-up period for each study participant was calculated as the time from their KoGES initial assessment to either a mortality event or the censoring date. The underlying causes of death were based on Korean Standard Classification of Diseases (KCD) codes listed in the National Death Index. Total mortality included all deaths of specified and unknown causes.

Covariates

The cohort studies shared core questionnaire and examination items. Age, smoking, alcohol intake and exercise status were assessed in the questionnaires. Height, weight and waist circumference (WC) were checked by trained staff. Body mass index (BMI) was calculated as a person's weight in kilograms divided by their height in meters squared. Smoking status was categorized as non-smoker, ex-smoker and current smoker. Alcohol intake was classified as non-drinker, ex-drinker and current drinker. Regular exercise was defined as a person who answered that he/she exercised regularly enough to induce sweat. Blood tests were conducted after midnight fasting. Hypertension was defined as a blood pressure at or above 140/90 mm Hg, a diagnosis of hypertension by a physician or use of anti-hypertensive drugs. Diabetes was defined as having a fasting glucose at or above 125 mg/dl, a diagnosis of diabetes by a physician or use of anti-diabetes drugs. Dyslipidaemia was defined as having one of the following: hypercholesterolaemia (serum total cholesterol ≥240 mg/dl), hypertriglyceridaemia (serum triglyceride ≥200 mg/dl), hyper-LDL

Table 1 *Baseline characteristics of the cohort according to fat intake proportion (%) quintiles*

Fat intake (%)	Q1 (<8.82)	Q2 (8.82–11.58)	Q3 (11.58–14.28)	Q4 (14.28–17.77)	Q5 (17.77<)
N	38,775 (20.0%)	38,982 (20.1%)	38,983 (20.1%)	39,027 (20.1%)	38,528 (19.8%)
Gender (men)	10,545 (27.0%)	13,043 (33.5%)	14,182 (36.4%)	14,903 (38.2%)	14,720 (38.2%)
Age (years)	57.6 ± 8.6	54.9 ± 8.5	53.5 ± 8.5	52.2 ± 8.3	51.0 ± 8.2
Body mass index (kg/m^2)	24.2 ± 3.0	24.1 ± 2.9	24.0 ± 2.9	24.0 ± 2.9	23.9 ± 3.0
Waist circumference (cm)	82.1 ± 8.6	81.7 ± 8.6	81.4 ± 8.6	81.3 ± 8.8	81.1 ± 9.0
Systolic blood pressure (mmHg)	125.3 ± 16.7	123.9 ± 15.9	123.0 ± 15.7	122.2 ± 15.4	121.5 ± 15.4
Diastolic blood pressure (mmHg)	77.4 ± 10.3	76.9 ± 10.2	76.6 ± 10.2	76.3 ± 10.2	76.1 ± 10.2
Heart rate (bpm)	69.2 ± 9.9	69.0 ± 9.6	68.9 ± 9.5	68.9 ± 9.4	68.9 ± 9.4
Glucose (mg/dl)	97.0 ± 23.5	96.0 ± 22.0	95.6 ± 21.9	95.1 ± 21.0	94.8 ± 21.0
Total cholesterol (mg/dl)	196.7 ± 36.8	197.5 ± 36.0	197.4 ± 35.5	198.3 ± 35.6	199.1 ± 35.1
HDL-C (mg/dl)	50.1 ± 12.3	52.0 ± 12.7	53.0 ± 12.9	53.8 ± 13.2	54.9 ± 13.5
LDL-C (mg/dl)	119.9 ± 32.8	119.9 ± 32.5	119.6 ± 32.0	119.9 ± 31.9	120.1 ± 31.7
Triglyceride (mg/dl)	138.4 ± 95.8	131.8 ± 89.7	128.2 ± 87.9	127.2 ± 92.0	125.3 ± 93.1
Smoking status					
Never smoker	30,864 (79.6%)	29,085 (74.6%)	28,004 (71.8%)	27,169 (69.6%)	26,067 (67.7%)
Former smoker	4745 (12.2%)	5702 (14.6%)	6037 (15.5%)	6105 (15.6%)	5888 (15.3%)
Current smoker	3166 (8.2%)	4195 (10.8%)	4942 (12.7%)	5753 (14.7%)	6573 (17.1%)
Alcohol intake					
Never drinker	24,331 (62.8%)	21,229 (54.5%)	19,339 (49.6%)	17,784 (45.6%)	16,261 (42.2%)
Former drinker	2011 (5.2%)	1662 (4.3%)	1634 (4.2%)	1528 (3.9%)	1546 (4.0%)
Current drinker	12,433 (32.1%)	16,091 (41.3%)	18,010 (46.2%)	19,715 (50.5%)	20,721 (53.8%)
Regular exercise (yes)	16,383 (42.3%)	19,183 (49.3%)	20,089 (51.7%)	20,299 (52.1%)	20,231 (52.6%)
Hypertension (yes)	15,208 (39.2%)	13,309 (34.1%)	12,142 (31.2%)	11,104 (28.5%)	10,155 (26.4%)
Diabetes mellitus (yes)	5268 (13.6%)	4578 (11.7%)	4330 (11.1%)	3989 (10.2%)	36,48 (9.5%)
Dyslipidaemia (yes)	18,606 (48.0%)	16,981 (43.6%)	16,088 (41.3%)	15,549 (39.8%)	14,913 (38.7%)
Residential area					
Urban	28,868 (74.5%)	32,994 (84.6%)	34,446 (88.4%)	35,301 (90.5%)	35,396 (91.9%)
Rural	9907 (25.6%)	5988 (15.4%)	4537 (11.6%)	3726 (9.6%)	3132 (8.1%)
House income (10,000 Korean won)					
<150	11,952 (42.2%)	9088 (29.2%)	7415 (23.3%)	6195 (19.0%)	5279 (16.3%)
150–300	8729 (30.8%)	10,364 (33.3%)	10,700 (33.6%)	10,805 (33.1%)	10,420 (32.2%)
300–600	6408 (22.6%)	9682 (31.1%)	11,282 (35.4%)	12,628 (38.7%)	13,331 (41.2%)
600≤	1221 (4.3%)	1996 (6.4%)	2494 (7.8%)	2972 (9.1%)	3328 (10.3%)
Total energy intake (kcal/day)	1485.0 ± 382.0	1644.4 ± 419.7	1741.3 ± 468.7	1843.0 ± 546.0	2001.5 ± 748.3
Carbohydrate intake (g/day)	298.8 ± 77.4	313.3 ± 81.3	317.4 ± 86.6	318.9 ± 95.6	308.3 ± 114.2
Carbohydrate (%)	80.5 ± 2.3	76.2 ± 1.8	72.9 ± 1.9	69.2 ± 2.2	61.8 ± 5.7
Fat intake (g/day)	11.2 ± 4.2	18.7 ± 5.1	25.0 ± 7.0	32.6 ± 10.0	48.8 ± 23.0

Table 1 (*Continued*)

Fat intake (%)	Q1 (<8.82)	Q2 (8.82–11.58)	Q3 (11.58–14.28)	Q4 (14.28–17.77)	Q5 (17.77<)
Fat (%)	6.7 ± 1.6	10.2 ± 0.8	12.9 ± 0.8	15.9 ± 1.0	21.8 ± 4.0
Protein intake (g/day)	40.1 ± 11.6	50.1 ± 14.1	57.2 ± 16.9	65.1 ± 21.2	80.9 ± 35.3
Protein (%)	10.8 ± 1.4	12.2 ± 1.5	13.2 ± 1.7	14.2 ± 1.9	16.2 ± 2.8
Cholesterol intake (mg/day)	64.3 ± 46.1	113.0 ± 62.7	152.5 ± 79.8	195.6 ± 100.2	281.6 ± 166.0

HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; Multivariable Cox frailty model with random effect were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

cholesterolaemia (serum low-density lipoprotein cholesterol ≥160 mg/dl), hypo-HDL cholesterolaemia (serum high-density lipoprotein cholesterol <40 mg/dl), taking medication for dyslipidaemia or being previously diagnosed with dyslipidaemia [17].

Statistical analysis

General characteristics of the study population at baseline were compared using an independent *t*-test for continuous variables or chi-squared test for categorical variables. Dietary fat was divided into quintiles, and dietary cholesterol was divided into three groups. A multivariable Cox frailty model with random effects in a multilevel cohort study was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) by defining the follow-up period as the time metric and the first quintiles or tertiles of fat or cholesterol intakes as references. Tests for trends were performed. We adjusted for baseline covariates. To build a theoretical model, we developed four multivariate models: we aimed to design an isocaloric model in model 2, a substitutional model in model 3 and medication by possible diet quality and underlying diseases in model 4. Model 1 was adjusted for age and sex. In model 2, we additionally adjusted for alcohol, exercise, smoking and total energy intake for an isocaloric model. Model 3 was further adjusted for protein (%) intake for a substitutional model. The final multivariable model (Model 4) was adjusted for fibre intake and a history of hypertension, diabetes, or dyslipidaemia. In analyses of dietary cholesterol, model 3 was further adjusted for fat (%) and protein (%) intake in the substitutional model. We also conducted a test for interactions between dietary fats or cholesterol and dyslipidaemia, hypertension or diabetes. All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA). Two-sided p values < 0.05 were considered statistically significant.

Results

Baseline characteristics

A total of 194,295 participants were included in this study. We documented 3866 deaths across a mean (min-max) follow-up period of 8.15 years (3–13 years). Baseline characteristics of the study population according to quintiles of percentage energy from carbohydrate intake are shown in Table 1. Participants who consumed a relatively high percentage of total energy from fats (i.e. participants in the highest quintile of fat intake, Q5) were more likely to be male, young, have low body mass index, low waist circumference, smoke cigarettes more, exercise more, drink alcohol drinking more, live in urban area, have high income and have less hypertension, diabetes and dyslipidaemia. Participants in the highest fat quintile had lower average consumption of carbohydrates and higher average consumption of protein.

Table 2 shows the baseline characteristics of participants according to cholesterol groups. Overall, 72.9%, 16.1% and 11.0% of the participants consumed <200 mg/day, 200–299 mg/day, ≥300 mg/day of dietary cholesterol, respectively. Participants who consumed a relatively low amount of dietary cholesterol (<200 mg) were more likely to be female, old, smoke less, drink less, exercise less, live in a rural area, have low income and have more hypertension, diabetes and dyslipidaemia. Participants who consumed <200 mg/day of dietary cholesterol had higher average consumption of carbohydrates and lower average consumption of protein.

Table 2 *Baseline characteristics of the cohort according to cholesterol intake (mg/day)*

Cholesterol intake (mg/day)	<200	200–299	≥300
N	141,541 (72.9%)	31,316 (16.1%)	21,438 (11.0%)
Gender (men)	47,789 (33.8%)	11,607 (37.1%)	7997 (37.3%)
Age (years)	54.5 ± 8.7	52.2 ± 8.4	51.9 ± 8.4
BMI (kg/m^2)	24.0 ± 2.9	24.0±	24.0 ± 3.0
Waist circumference (cm)	81.6 ± 8.7	81.3 ± 8.9	81.3 ± 9.0
Systolic BP (mmHg)	123.6 ± 16.0	122.1 ± 15.4	121.9 ± 15.4
Diastolic BP (mmHg)	76.8 ± 10.3	76.2 ± 10.2	76.3 ± 10.2
Heart rate (bpm)	69.0 ± 9.7	69.0 ± 9.3	68.8 ± 9.3
Laboratory			
Glucose (mg/dl)	95.9 ± 22.2	95.0 ± 21.3	95.0 ± 20.7
Total cholesterol (mg/dl)	197.6 ± 36.0	198.4 ± 35.5	198.6 ± 35.4
HDL-C (mg/dl)	52.3 ± 12.9	53.8 ± 13.2	54.3 ± 13.3
LDL-C (mg/dl)	119.8 ± 32.3	120.0 ± 31.9	119.9 ± 31.8
Triglycerides (mg/dl)	131.4 ± 91.5	127.3 ± 92.3	126.5 ± 93.3
Smoking status			
Never smoker	104,334 (73.7%)	21,969 (70.2%)	14,886 (69.4%)
Former smoker	20,399 (14.4%)	4764 (15.2%)	3314 (15.5%)
Current smoker	16,808 (11.9%)	4583 (14.6%)	3238 (15.1%)
Alcohol intake			
Never drinker	74,317 (52.5%)	14,689 (46.9%)	9938 (46.4%)
Former drinker	6267 (4.4%)	1228 (3.9%)	886 (4.1%)
Current drinker	60,957 (43.1%)	15,399 (49.2%)	10,614 (49.5%)
Regular exercise (yes)	67,690 (47.9%)	16,580 (53.0%)	11,915 (55.7%)
Hypertension (yes)	47,204 (33.4%)	8845 (28.2%)	5869 (27.4%)
Diabetes mellitus (yes)	16,727 (11.8%)	3040 (9.7%)	2046 (9.5%)
Dyslipidaemia (yes)	61,099 (43.2%)	12,558 (40.1%)	8480 (39.6%)
Residential area			
Urban	119,122 (84.2%)	28,483 (91.0%)	19,400 (90.5%)
Rural	22,419 (15.8%)	2833 (9.1%)	2038 (9.5%)
House income (10,000 Korean won)			
<150	31,937 (28.5%)	4802 (18.2%)	3190 (17.8%)
150–300	36,305 (32.4%)	8881 (33.6%)	5832 (32.6%)
300–600	35,834 (32.0%)	10,355 (39.1%)	7142 (39.9%)
600≤	7841 (7.0%)	2420 (9.2%)	1750 (9.8%)
Total energy intake (kcal/day)	1579.1 ± 417.0	2005.6 ± 482.3	2439.4 ± 747.1
Carbohydrate intake (g/day)	293.9 ± 79.9	340.8 ± 91.4	383.8 ± 119.0
Carbohydrate (%)	74.5 ± 5.6	67.7 ± 5.8	63.2 ± 7.5
Fat intake (g/day)	20.8 ± 9.9	37.3 ± 12.9	54.9 ± 26.8
Fat (%)	11.8 ± 4.5	16.8 ± 4.6	19.9 ± 5.6
Protein intake (g/day)	49.1 ± 14.6	73.4 ± 17.2	100.4 ± 37.4
Protein (%)	12.5 ± 2.1	14.8 ± 2.3	16.5 ± 3.1

Table 3 *Risk of all-cause mortality according fat intake (%) quintile*

Fat intake (%)	Person-years	Number of events	Mortality rate (10,000 person-year)	Multivariate HR (95% CI)			
Quintiles				Model 1	Model 2	Model 3	Model 4
Q1 (8.82%>)	328,421.92	1205	36.69	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Q2 (8.82%–11.58%)	320,692.00	828	25.82	0.87 (0.79, 0.95)	0.91 (0.83, 0.99)	0.89 (0.80, 0.97)	0.91 (0.81, 0.99)
Q3 (11.58%–14.28%)	316,233.92	706	22.33	0.79 (0.72, 0.87)	0.85 (0.76, 0.94)	0.81 (0.72, 0.91)	0.84 (0.75, 0.94)
Q4 (14.28%–17.77%)	312,353.58	579	18.54	0.79 (0.71, 0.87)	0.85 (0.76, 0.96)	0.81 (0.71, 0.92)	0.85 (0.74, 0.97)
Q5 (17.77%≤)	305,099.00	548	17.96	0.80 (0.72, 0.89)	0.90 (0.78, 1.04)	0.82 (0.69, 0.98)	0.89 (0.74, 1.05)
p for trend				<0.01	0.02	<0.01	0.02

Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95 per cent confidence intervals (95% CIs).
Model 1: adjustment for age and gender.
Model 2: adjustment for age, gender, BMI, alcohol, exercise, smoking, and total energy intake.
Model 3 adjustment for age, gender, BMI, alcohol, exercise, smoking, and total energy and protein (%) intake.
Model 4: adjustment for age, gender, BMI, alcohol, exercise, smoking, total energy and protein (%) intake, fibre (g/day), hypertension, diabetes and dyslipidaemia.

Associations among fat intake, cholesterol intake and all-cause mortality

Table 3 shows the HRs and 95% CIs according to fat intake quintiles. Higher fat intake was associated with lower total mortality (Q5 vs. Q1, HR 0.82 [95% CI 0.69, 0.98]; *p* trend<0.01 in model 3 and HR 0.89 [95% CI 0.74, 1.05]; *p* trend = 0.02 in model 4). Table 4 shows the HRs and 95% CIs according to cholesterol intake three groups. In comparison of dietary cholesterol consumption <200 mg/day and ≥300 mg/day, higher dietary cholesterol intake was associated with a higher risk of total mortality (HR 1.19 [95% CI 1.04, 1.37]; *p* trend=0.06 in model 3 and HR 1.21 [95% CI 1.05, 1.39]; *p* trend = 0.03 in model 4). After additionally adjusting for waist circumference and household income, there were similar results in all analyses (data not shown).

Associations among fat intake, cholesterol intake and total mortality according to the presence of comorbidities

We further examined associations among dietary fat intake, cholesterol intake and total mortality according to the presence of dyslipidaemia, hypertension or diabetes (Figure 2a–l). Although there were no significant interactions among dietary fats, cholesterol intake and each comorbidity (dyslipidaemia, hypertension or diabetes), we conducted subgroup analysis to investigate the effect of dietary fat and cholesterol intake on total mortality based on comorbidities. Higher fat intake was associated with lower total mortality in participants without dyslipidaemia, hypertension or diabetes. Meanwhile, higher fat intake was not associated with total mortality in participants with dyslipidaemia, hypertension or diabetes.

Associations between dietary cholesterol intake and total mortality varied depending on the comorbidities. For participants without dyslipidaemia, higher cholesterol intake was not associated with total mortality (≥300 mg/day vs. <200 mg/day; HR 1.17 [95% CI 0.96, 1.42]) after adjusting for age, sex, BMI, alcohol, exercise, smoking and total energy, fat (%) and protein (%) intake. For participants with dyslipidaemia, higher cholesterol intake was associated with total mortality (≥300 mg/day vs. <200 mg/day; HR 1.21 [95% CI 1.00, 1.48]) after adjusting for the same confounders. For participants without hypertension, higher cholesterol intake was associated with total mortality (≥300 mg/day vs. <200 mg/day; HR 1.26 [95% CI 1.03, 1.53]) after adjusting for age, sex, BMI, alcohol, exercise, smoking and total energy,

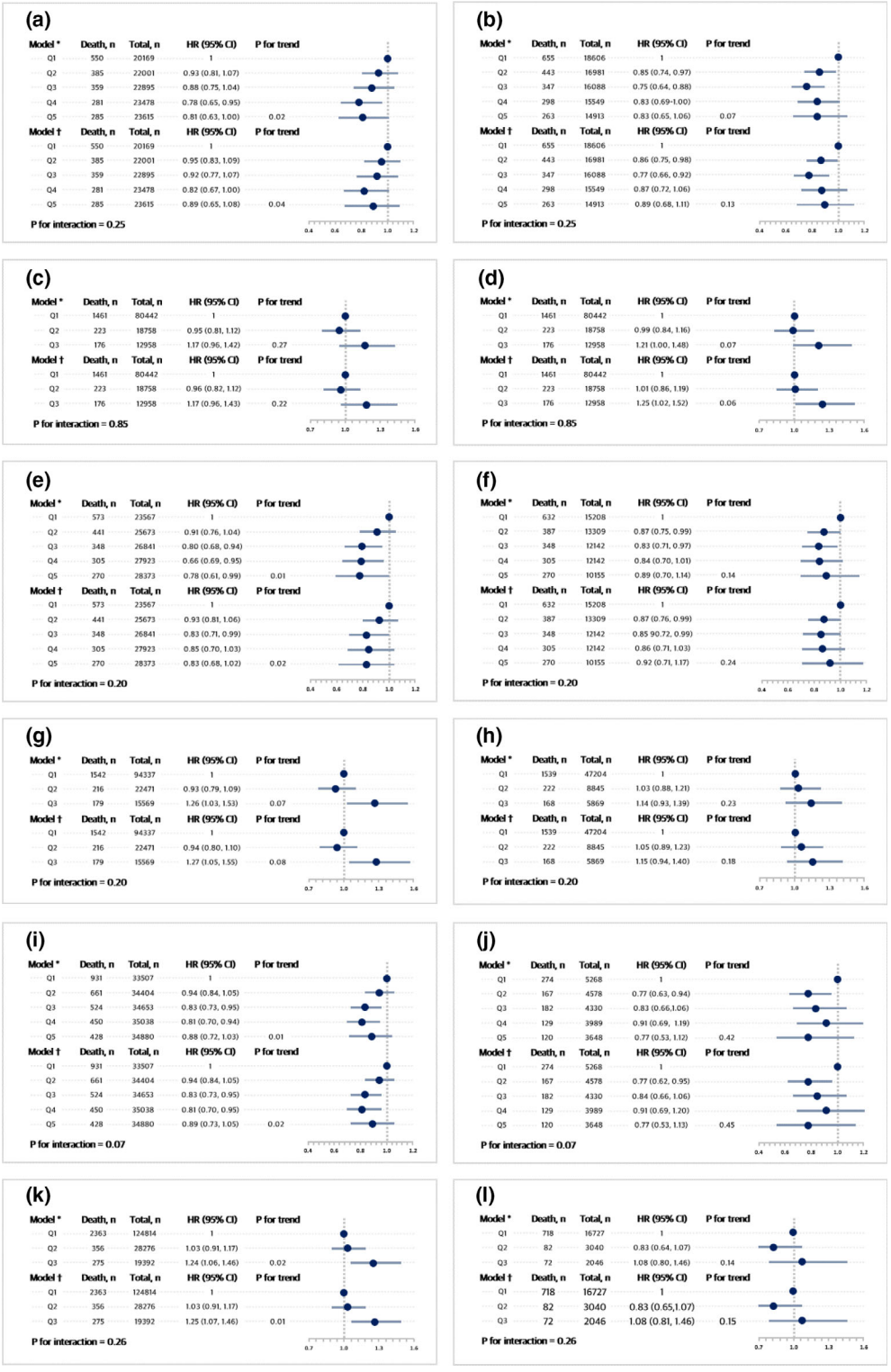

Fig. 2 *Adjusted hazard ratios and 95% confidence intervals for total mortality according to dietary fat quintiles and cholesterol intake three groups among the different subgroups. (a) The association between dietary fat intake and total mortality in participants without dyslipidaemia. (b) The association between dietary fat intake and total mortality in participants with dyslipidaemia. (a and b) *adjusted for age, sex, body mass index, alcohol, exercise, smoking, total energy intake, and protein (%), †adjusted for fibre (g/day), hypertension and diabetes. (c) The association between dietary cholesterol intake and total mortality in participants without dyslipidaemia. (d) The association between dietary cholesterol intake and total mortality in participants with dyslipidaemia. (c and d) *adjusted for age, sex, body mass index, alcohol, exercise, smoking, total energy intake, fat (%) and protein (%), †adjusted for fibre (g/day), additionally hypertension and diabetes. (e) The association between dietary fat intake and total mortality in participants without hypertension. (f) The association between dietary fat intake and total mortality in participants with hypertension. (e and f) *adjusted for age, sex, body mass index, alcohol, exercise, smoking, total energy intake and protein (%), †adjusted for additionally fibre (g/day), dyslipidaemia and diabetes. (g) The association between dietary cholesterol intake and total mortality in participants without hypertension. (h) The association between dietary cholesterol intake and total mortality in participants with hypertension. (g and h) *adjusted for age, sex, body mass index, alcohol, exercise, smoking, total energy intake, fat (%) and protein (%), †adjusted for additionally fibre (g/day), dyslipidaemia and diabetes. (i) The association between dietary fat intake and total mortality in participants without diabetes. (j) The association between dietary fat intake and total mortality in participants with diabetes. (i and j) *adjusted for age, sex, body mass index, alcohol, exercise, smoking, total energy intake, and protein (%), †adjusted for additionally fibre (g/day), dyslipidaemia and hypertension. (k) The association between dietary cholesterol intake and total mortality in participants without diabetes. (l) The association between dietary cholesterol intake and total mortality in participants with diabetes. (k and l) *adjusted for age, sex, body mass index, alcohol, exercise, smoking, total energy intake, fat (%) and protein (%), †adjusted for additionally fibre (g/day), dyslipidaemia and hypertension*

fat (%) and protein (%) intake. For participants with hypertension, higher cholesterol intake was not associated with total mortality (≥300 mg/day vs. <200 mg/day; HR 1.14 [95% CI 0.93, 1.39]) after adjusting for the same confounders. For participants without diabetes, higher cholesterol intake was associated with total mortality (≥300 mg/day vs. <200 mg/day; HR 1.24 [95% CI 1.06, 1.46]) after adjusting for the same confounders. For participants with diabetes, higher cholesterol intake was not associated with total mortality (≥300 mg/day vs. <200 mg/day; HR 1.08 [95% CI 0.80, 1.46]) after adjusting the same confounders.

Discussion

We explored the relationship between dietary fat and cholesterol intake on the total mortality of 194,295 adults from three prospective cohort studies in Korea with a mean follow-up period of 8.15 years. Higher dietary fat intake was significantly associated with a lower risk of total mortality. We found that replacement of carbohydrates with fats was also associated with lower total mortality. Meanwhile, dietary cholesterol intake above 300 mg/day was significantly associated with a higher risk of total mortality.

In subgroup analysis according to the presence of comorbidities, the inverse effect of dietary fat was seen in non-dyslipidaemic participants, but not in dyslipidaemic participants. There were similar results after stratifying for hypertension and diabetes. There were diverse associations between dietary cholesterol and total mortality according to the presence of dyslipidaemia, hypertension or diabetes.

Although many studies over the past few decades have tried to clarify the link between macronutrients and total mortality, evidence linking dietary fat intake with all-cause mortality and cardiovascular health remains controversial [7,18–20]. Furthermore, many of these studies were conducted in Western populations, with data on fat intake in relation to mortality lacking for Asian countries. The recent PURE study encompassing 18 countries established that dietary total, saturated, monounsaturated and polysaturated fat intake all decreased total mortality [7]. The PURE study included Asian countries (Bangladesh, China, India, Malaysia, and Pakistan) and non-Asian countries. In the results from Asian countries, higher total fat intake was significantly associated with lower total mortality, and this result was not different from the those of non-Asian countries. The PREvención con DIeta MEDiterránea (PREDIMED) study on 7038 participants with high CVD risk also found that total fat intake was associated with a reduced risk of all-cause mortality [20]. Our

Table 4 *Risk of all-cause mortality according cholesterol intake (mg)*

Cholesterol (mg)		Number of	Mortality rate	Multivariate HR (95% CI)			
Quartiles	Person-years	events	(10,000 person-year)	Model 1	Model 2	Model 3	Model 4
Q1 (<200 mg)	1,164,151.50	3081	26.47	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Q2 (200–299 mg)	247,442.33	438	17.70	0.88 (0.79, 0.97)	0.95 (0.85, 1.05)	0.97 (0.87, 1.08)	0.99 (0.88, 1.10)
Q3 (300 mg≤)	171,206.58	347	20.27	1.01 (0.90, 1.12)	1.16 (1.02, 1.31)	1.19 (1.04, 1.37)	1.21 (1.05, 1.39)
p for trend				0.32	0.13	0.06	0.03

Model 1: adjustment for age and gender.
Model 2: adjustment for age, gender, BMI, alcohol, exercise, smoking, and total energy intake.
Model 3: adjustment for age, gender, BMI, alcohol, exercise, smoking, total energy intake, fat (%) and protein (%).
Model 4: adjustment for age, gender, BMI, alcohol, exercise, smoking, total energy and protein (%) intake, fibre (g/day), hypertension, diabetes and dyslipidaemia.

study observed similar results in Korean adults: higher fat intake was associated with a lower risk of total mortality after adjusting for potential confounders.

As different types of fats have differing effects on cardiovascular health and mortality [21], researchers have focussed not only on total amount of fat intake but also on the specific kind of dietary fat. Total and specific fats (saturated, monounsaturated and polyunsaturated) were not associated with CVD mortality in the PURE study, whereas saturated fat exhibited an inverse association with stroke [7]. Several meta-analyses also showed that reduction of saturated fat was not associated with reduced CVD risk [18,19]. On the contrary, a US Nurses' Health Study and Health Professionals Follow-up Study (HPFS) found that saturated fat intake was related to higher total mortality [22]. The National Institutes of Health-American Association of Retired Persons (NIHAA-AARP) Diet and Health Study found consistent associations for saturated fat, monounsaturated fat from animal sources and trans-fatty acid intake with higher mortality [6]. In contrast, participants with higher intake of plant monounsaturated fats, marine omega-3 polyunsaturated fats and linoleic acid had lower total mortality. Moreover, replacing saturated fat with monounsaturated and polyunsaturated fats or trans-fat with monounsaturated fat was inversely associated with CVD [6]. The discrepant results in these studies may have resulted from different food consumption patterns, food supply and processing, dietary assessment method, socioeconomic factors and genetic predisposition.

Interestingly, we found that the effects of dietary fat on total mortality were not significant in patients with dyslipidaemia, hypertension, or diabetes. This suggested that the effects of dietary fat can vary between subpopulations, depending on the risk factors present. Further work is needed to characterize the role of specific dietary fat intake after considering underlying diseases in individual study participants.

For cholesterol intake, >300 mg per day significantly increased total mortality regardless of dyslipidaemia. This contradicts the 2015 Dietary Guidelines Advisory Committee guidelines that removed the specific dietary cholesterol target recommendations and raised questions over its impact on CVD [10]. The National Lipid Association

still recommends heart-healthy eating patterns for managing dyslipidaemia (<7% of energy from saturated fat, <200 mg/day of dietary cholesterol) [8]. Additionally, a recent study of 29,615 adults in the US with a median follow-up period of 17.5 years reported that higher consumption of dietary cholesterol or eggs posed a significantly higher dose-dependent risk of CVD and all-cause mortality [23]. In this aforementioned study, dietary cholesterol intake (above 300 mg/day) was significantly associated with all-cause mortality with/without hypertension, diabetes, and hyperlipidaemia [23]. These findings differ from our results. Dietary cholesterol is often found together with major food sources of animal-based saturated fat [24], and different cholesterol intake between various racial/ethnics could be one possible explanation for the discrepant results. Further well-conducted cohort studies are needed to identify adequate amounts of dietary cholesterol for different ethnic populations/subpopulations.

Our study has some limitations. First, the FFQ used to evaluate dietary intake for each participant was not accurate for assessing intake amounts; however, FFQs are suitable for epidemiological studies [25]. Second, dietary intake was assessed only at baseline, and dietary habits could have changed during the follow-up period. Third, our nutrients data were assessed only for foods investigated in the FFQ, and we could not differentiate between various types of fats. Due to the lack of information on types of fats, we could not adjust for the effects of saturated fats in the dietary cholesterol analysis. Also, the FFQ did not cover all fat-rich foods. Fourth, we could not determine the exact role of dietary fat and cholesterol on CVD mortality due to limited CVD mortality cases. Further studies investigating the associations among dietary fat, cholesterol and cause-specific mortality are needed. Fifth, we did not conduct Bonferroni correction to interpret the results in an exploratory manner. If the current results are interpreted conservatively, they are amenable to Bonferroni correction. Further studies considering underlying conditions in each individual are needed to clarify the role of dietary fat and cholesterol on all-cause mortality. Lastly, observational studies are not able to determine causality. Also, selection bias and the presence of confounding variables are possible.

Despite these weaknesses, this study has several strengths. Our study comprised a prospective design, large population size and an extensive 8-year follow-up period. We also assessed associations for dietary fat and cholesterol intake and mortality according to the presence of dyslipidaemia, hypertension and diabetes.

In conclusion, we found that higher dietary fat intake was significantly associated with a lower risk of total mortality in Korean adults. Dietary cholesterol intake >300 mg per day significantly increased total mortality. Associations for dietary fat and cholesterol in relation to total mortality varied according to presence of dyslipidaemia, hypertension or diabetes. Future work is needed to characterize the mechanisms behind dietary fat and cholesterol intake in relation to individual health circumstances.

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Conflict of interest

All authors declare no conflicts of interest.

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Data availability statement

Data described in the manuscript, code book and analytic code will be made available upon request pending approval by the Korea Centers for Disease Control.

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