Supplemental Table 1: Definitions and coding forms of potential effect modification factors evaluated in this study.

Variable	Definition
Gender	Participants were asked to specify gender. Males were coded as 0 and females as 1.
Age	Age at enrollment was calculated as Round ([Interview Date−Birthday Date]/365.25). Age grouping used a 65-year-old cutoff. Participants less than 65 were coded as 0 and participants over 65 were coded as 1.
Body mass index (BMI)	BMI was calculated as body weight in kilograms divided by the square of body height in meters (kg/m^2). Subjects were categorized into two groups as BMI ≤ 22 (coded as 0), BMI>22 (coded as 1).
Smoking	Participants were asked whether they smoked in the questionnaire. Subjects who did not smoke were coded as 0; subjects who smoked were coded as 1.
Alcohol consumption	Participants were asked whether they consumed alcohol in the questionnaire. Subjects who did not drink were coded as 0; subjects with alcohol consumption were coded as 1.
Family history of esophageal cancer	Participants were asked whether they had family members with esophageal cancer in the questionnaire. Subjects with at least 1 family member with esophageal cancer were coded as 1; subjects with no family member with esophageal cancer were coded as 0.

Supplemental Table 2: The interaction *P* values for factors evaluated in effect modification analysis in this study *.

Interaction factor	TC	TG	LDL-C	HDL-C
Family history of EC	0.016	0.478	0.013	0.204
Smoke	0.312	0.649	0.421	0.395
Alcohol consumption	0.172	0.357	0.272	0.130
Age[†]	0.162	0.736	0.907	0.172
Gender	0.511	0.767	0.954	0.627
BMI[‡]	0.653	0.803	0.426	0.916

*Effect modification in this study was evaluated by adding an interaction term of the factor assessed (age, gender, family history of EC, BMI, smoking and alcohol consumption) and serum lipid indicators one at a time in the adjusted multivariate model. Age, gender, family history of EC, body mass index, coal stove for heating, fume exposure in kitchen, fast eating speed and ingestion of leftovers were adjusted in multivariate models. BMI: Body mass index ; EC: Esophageal cancer;HDL-C: High-density lipoprotein cholesterol; LDL-C: Ligh-density lipoprotein cholesterol;TC: Total cholesterol; TG: Triglycerides.

[†]Age was defined as a dichotomized variable with cutoff of 65-year-old.

[‡]BMI was defined as a dichotomized variable with cutoff of $22kg/m^2$.

Supplemental Table 3: Sensitivity analysis excluding prevalent cancer cases at the time of blood lipid measurement.

Variables	Participants without family history of EC (*n*=583)			Participants with family history of EC (*n*=142)			*P* value for interaction
	Case(*n*)/ Control (*n*)	Crude OR (95% CI)	Adjusted OR* (95% CI)	Case(*n*)/ Control (*n*)	Crude OR (95% CI)	Adjusted OR* (95% CI)	
TC (mg/dL)							0.221
Low (<200)	35/328	Ref	Ref	6/75	Ref	Ref	
High (≥200)	18/202	0.83 (0.45−1.52)	0.85 (0.46−1.58)	7/48	1.82 (0.57‑5.79)	1.73 (0.53-5.63)	
TG (mg/dL)							−
Low (<230)	41/473	Ref	Ref	13/113	Ref	Ref	
High (≥230)	12/57	2.49 (1.22−5.10)	3.02 (1.40−6.51)	0/10	−	−	
LDL-C (mg/dL)							0.054
Low (<110)	43/375	Ref	Ref	7/84	Ref	Ref	
High (≥110)	10/155	0.57 (0.28−1.15)	0.59 (0.28−1.21)	6/39	1.80 (0.57−5.62)	2.03 (0.60−6.85)	
HDL-C (mg/dL)							0.728
Low (<70)	3/34	Ref	Ref	1/7	Ref	Ref	
High (≥70)	50/496	1.14 (0.34−3.86)	1.05 (0.30−3.62)	12/116	0.68 (0.07−6.19)	0.81 (0.08−7.85)	

* In multivariate models, adjustments were made for risk factors for ESCC previously identified in this population including age, gender, family history of EC, body mass index, coal stove for heating, fume exposure in kitchen, fast eating speed and ingestion of leftovers.CI: Confidence interval; EC: Esophageal cancer;HDL-C: High-density lipoprotein cholesterol; LDL-C: Ligh-density lipoprotein cholesterol;TC: Total cholesterol; TG: Triglycerides; OR: odds ratio.

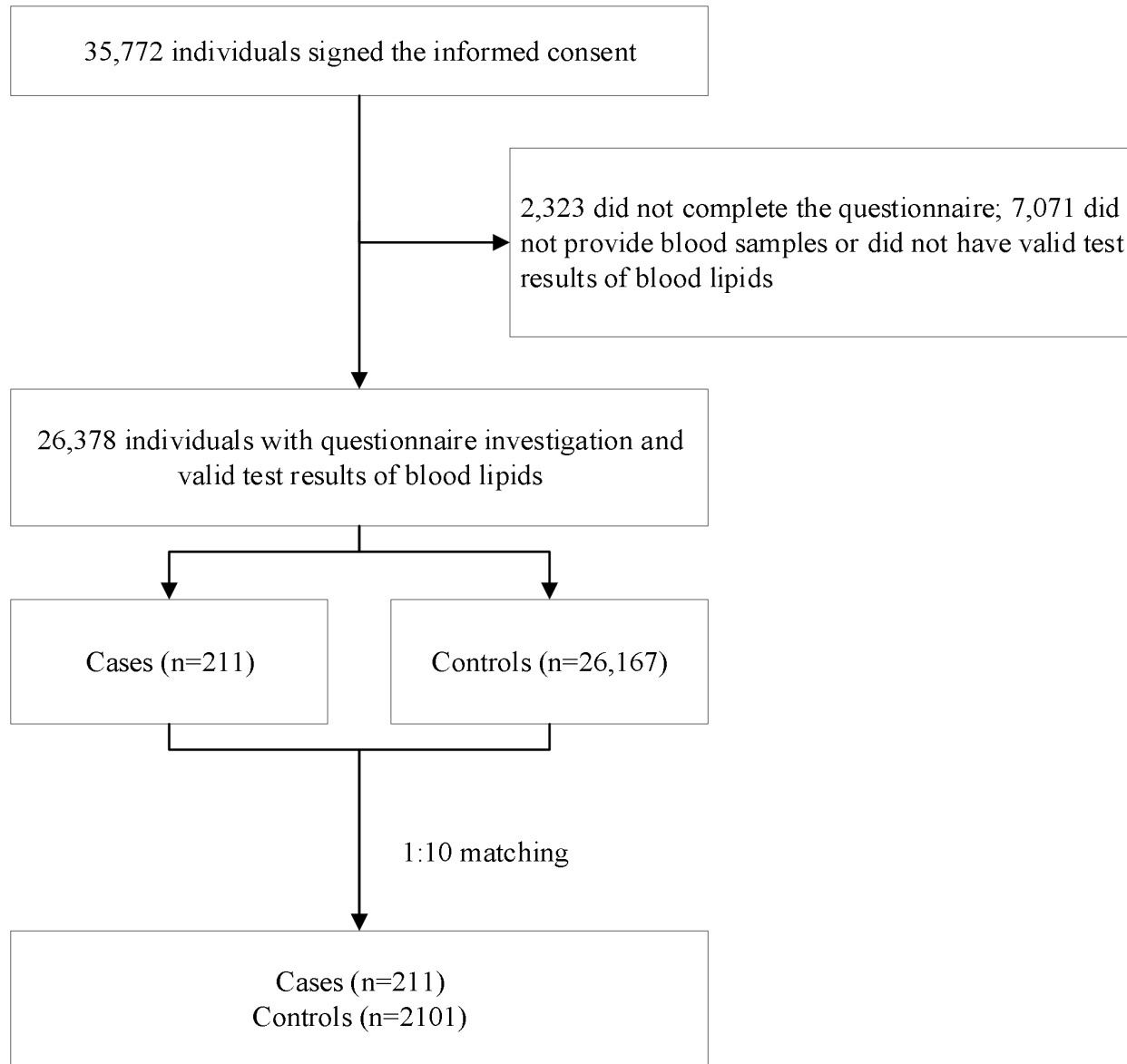**Supplemental Table 4: Sensitivity analysis excluding subjects with self-reported CVD or history of diabetes.**

Variables	Participants without family history of EC (n=1702)			Participants with family history of EC (n=394)			*P* value for interaction
	Case(n)/Control (n)	Crude OR (95% CI)	Adjusted OR (95% CI) *	Case(n)/Control (n)	Crude OR (95% CI)	Adjusted OR (95% CI) *	
TC (mg/dL)							0.003
Low (<200)	111/968	Ref	Ref	13/215	Ref	Ref	
High (≥200)	48/575	0.70 (0.49−1.00)	0.71 (0.50−1.02)	22/144	2.36 (1.13−4.91)	2.43 (1.14−5.18)	
TG (mg/dL)							0.439
Low (<230)	137/1407	Ref	Ref	31/317	Ref	Ref	
High (≥230)	22/136	1.69 (1.03−2.76)	1.83 (1.11−3.02)	4/42	1.15 (0.38−3.45)	1.10 (0.36−3.36)	
LDL-C (mg/dL)							<0.001
Low (<110)	129/1065	Ref	Ref	18/251	Ref	Ref	
High (≥110)	30/478	0.51 (0.34−0.78)	0.52 (0.34−0.79)	17/108	2.18 (1.09−4.37)	2.10 (1.04−4.26)	
HDL-C (mg/dL)							0.775
Low (<70)	17/129	Ref	Ref	3/34	Ref	Ref	
High (≥70)	142/1414	0.71 (0.42−1.23)	0.68 (0.39−1.18)	32/325	0.85 (0.24−3.02)	0.89 (0.24−3.29)	

*In multivariate models, adjustments were made for risk factors for ESCC previously identified in this population including age, gender, family history of EC, body mass index, coal stove for heating, fume exposure in kitchen, fast eating speed and ingestion of leftovers.CI: Confidence interval; EC: Esophageal cancer;HDL-C: High-density lipoprotein cholesterol; LDL-C: Ligh-density lipoprotein cholesterol;TC: Total cholesterol; TG: Triglycerides; OR: odds ratio.

Supplemental Table 5: Independent associations of serum lipids with esophageal cancer risk in stratification of family history of EC, under the cut-off derived from the CVD prevention guideline.

Variables	Participants without family history of EC (n=1859)			Participants with family history of EC (n=453)			P value for interaction
	Case(n)/ Control (n)	Crude OR (95% CI)	Adjusted OR (95% CI)*	Case(n)/ Control (n)	Crude OR (95% CI)	Adjusted OR (95% CI)*	
TC (mg/dL)							0.002
Normal (<200)	120/1058	Ref	Ref	17/243	Ref	Ref	
Borderline high and above (≥200)	49/632	0.67 (0.47–0.96)	0.69 (0.48–0.98)	25/168	2.2 (1.14–4.26)	2.22 (1.14–4.35)	
TG (mg/dL)							0.650
Normal (<150)	122/1173	Ref	Ref	30/266	Ref	Ref	
Borderline high and above (≥150)	47/517	0.87 (0.61–1.24)	0.93 (0.65–1.34)	12/145	0.73 (0.36–1.47)	0.73 (0.35–1.48)	
LDL-C (mg/dL)							0.002
Normal (<130)	157/1490	Ref	Ref	31/360	Ref	Ref	
Borderline high and above (≥130)	12/200	0.57 (0.31–1.04)	0.58 (0.31–1.06)	11/51	2.43 (1.16–5.09)	2.78 (1.29–5.97)	
HDL-C (mg/dL)							0.968
Low (<40)	19/144	Ref	Ref	5/38	Ref	Ref	
Normal (≥40)	150/1546	0.74 (0.44–1.22)	0.69 (0.41–1.15)	37/373	0.72 (0.26–2.03)	0.73 (0.26–2.07)	

* In multivariate models, adjustments were made for risk factors for ESCC previously identified in this population including age, gender, family history of EC, body mass index, coal stove for heating, fume exposure in kitchen, fast eating speed and ingestion of leftovers.CI: Confidence interval; EC: Esophageal cancer;HDL-C: High-density lipoprotein cholesterol; LDL-C: Ligh-density lipoprotein cholesterol;TC: Total cholesterol; TG: Triglycerides; OR: odds ratio.

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│   35,772 individuals signed the informed consent      │
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                          │        ┌──────────────────────────────────────────┐
                          │        │ 2,323 did not complete the questionnaire; │
                          ├───────▶│ 7,071 did not provide blood samples or     │
                          │        │ did not have valid test results of blood   │
                          │        │ lipids                                     │
                          │        └──────────────────────────────────────────┘
                          ▼
┌─────────────────────────────────────────────────────┐
│ 26,378 individuals with questionnaire investigation   │
│        and valid test results of blood lipids         │
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            │                              │
            ▼                              ▼
┌──────────────────┐          ┌──────────────────────┐
│ Cases (n=211)    │          │ Controls (n=26,167)   │
└──────────────────┘          └──────────────────────┘
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┌─────────────────────────────────────────────────────┐
│                 Cases (n=211)                         │
│                 Controls (n=2101)                     │
└─────────────────────────────────────────────────────┘
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Supplemental Figure 1: Flowchart of participant enrollment in this study.

Variables	Case(*n*)/ Control (*n*)	Crude OR (95% CI)	Adjusted OR (95% CI)[*]
TC (mg/dL)			
Q1	45/410	Ref	Ref
Q2	43/419	0.93 (0.60 – 1.45)	0.96 (0.62 – 1.50)
Q3	43/406	0.96 (0.62 – 1.50)	0.98 (0.63 – 1.53)
Q4	37/433	0.78 (0.49 – 1.23)	0.80 (0.51 – 1.27)
Q5	43/433	0.90 (0.58 – 1.41)	0.92 (0.59 – 1.45)
P for trend		0.452	0.525
TG (mg/dL)			
Q1	48/416	Ref	Ref
Q2	48/423	0.97 (0.64 – 1.49)	1.03 (0.67 – 1.58)
Q3	39/418	0.80 (0.51 – 1.26)	0.86 (0.54 – 1.35)
Q4	36/415	0.74 (0.47 – 1.17)	0.82 (0.51 – 1.30)
Q5	40/429	0.79 (0.5 – 1.24)	0.87 (0.55 – 1.38)
P for trend		0.153	0.334
LDL-C (mg/dL)			
Q1	51/417	Ref	Ref
Q2	35/375	0.77 (0.49 – 1.20)	0.75 (0.48 – 1.19)
Q3	55/452	1.00 (0.66 – 1.50)	1.00 (0.66 – 1.50)
Q4	35/433	0.66 (0.42 – 1.04)	0.66 (0.42 – 1.04)
Q5	35/424	0.68 (0.43 – 1.06)	0.70 (0.44 – 1.10)
P for trend		0.067	0.093
HDL-C (mg/dL)			
Q1	47/390	Ref	Ref
Q2	37/381	0.80 (0.50 – 1.26)	0.77 (0.48 – 1.21)
Q3	41/430	0.78 (0.50 – 1.22)	0.77 (0.49 – 1.20)
Q4	42/441	0.78 (0.50 – 1.22)	0.74 (0.47 – 1.16)
Q5	44/459	0.78 (0.50 – 1.22)	0.71 (0.45 – 1.13)
P for trend		0.325	0.171

0.25
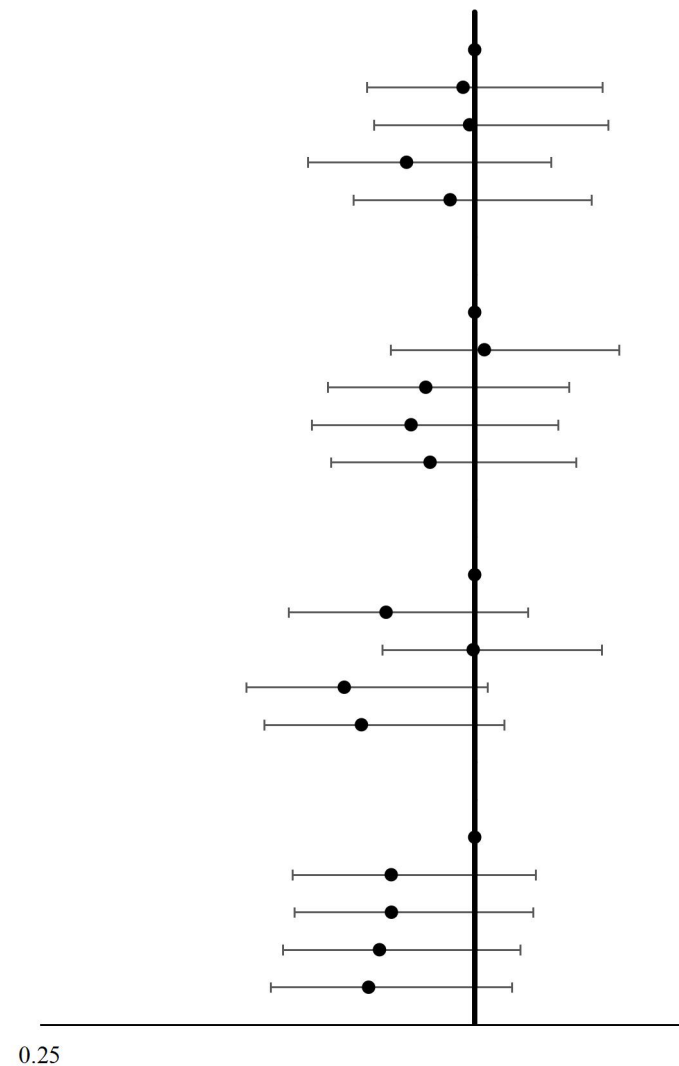
Supplemental Figure 2: ORs and 95% CIs for risk of malignant esophageal lesions by lipids components in quintiles (compared to the lowest quintile).CI: Confidence interval; HDL-C: High-density lipoprotein cholesterol; LDL-C: Ligh-density lipoprotein cholesterol;TC: Total cholesterol; TG: Triglycerides; OR: odds ratio.

[*] In multivariate models, adjustments were made for risk factors for ESCC previously identified in this population including age, gender, family history of EC, body mass index, coal stove for heating, fume exposure in kitchen, fast eating speed and ingestion of leftovers.

| Variables | Adjusted OR (95% CI) | | P value for interaction |
	Participants without family history of EC (*n*=1859)	Participants with family history of EC (*n*=461)	
TC (mg/dL)			0.016
Q1	Ref	Ref	
Q2	1.13 (0.7 – 1.81)	0.43 (0.12 – 1.56)	
Q3	1.10 (0.68 – 1.77)	0.49 (0.14 – 1.74)	
Q4	0.62 (0.36 – 1.06)	1.83 (0.66 – 5.07)	
Q5	0.81 (0.48 – 1.36)	1.45 (0.55 – 3.85)	
P for trend	0.094	0.061	
TG (mg/dL)			0.478
Q1	Ref	Ref	
Q2	1.06 (0.66 – 1.71)	0.85 (0.32 – 2.29)	
Q3	0.94 (0.57 – 1.55)	0.51 (0.16 – 1.59)	
Q4	0.80 (0.47 – 1.36)	0.76 (0.27 – 2.11)	
Q5	1.02 (0.61 – 1.70)	0.49 (0.17 – 1.42)	
P for trend	0.682	0.195	
LDL-C (mg/dL)			0.013
Q1	Ref	Ref	
Q2	0.82 (0.50 – 1.34)	0.53 (0.17 – 1.62)	
Q3	1.08 (0.69 – 1.68)	0.53 (0.17 – 1.66)	
Q4	0.68 (0.41 – 1.12)	0.59 (0.20 – 1.69)	
Q5	0.47 (0.26 – 0.82)	1.65 (0.70 – 3.89)	
P for trend	0.010	0.178	
HDL-C (mg/dL)			0.204
Q1	Ref	Ref	
Q2	0.72 (0.43 – 1.20)	1.01 (0.33 – 3.07)	
Q3	0.71 (0.43 – 1.17)	1.02 (0.34 – 3.05)	
Q4	0.75 (0.46 – 1.21)	0.70 (0.20 – 2.46)	
Q5	0.56 (0.33 – 0.95)	1.51 (0.55 – 4.15)	
P for trend	0.063	0.496	

0.0625 0.125 0.25 0.5 1 2 4 8 16
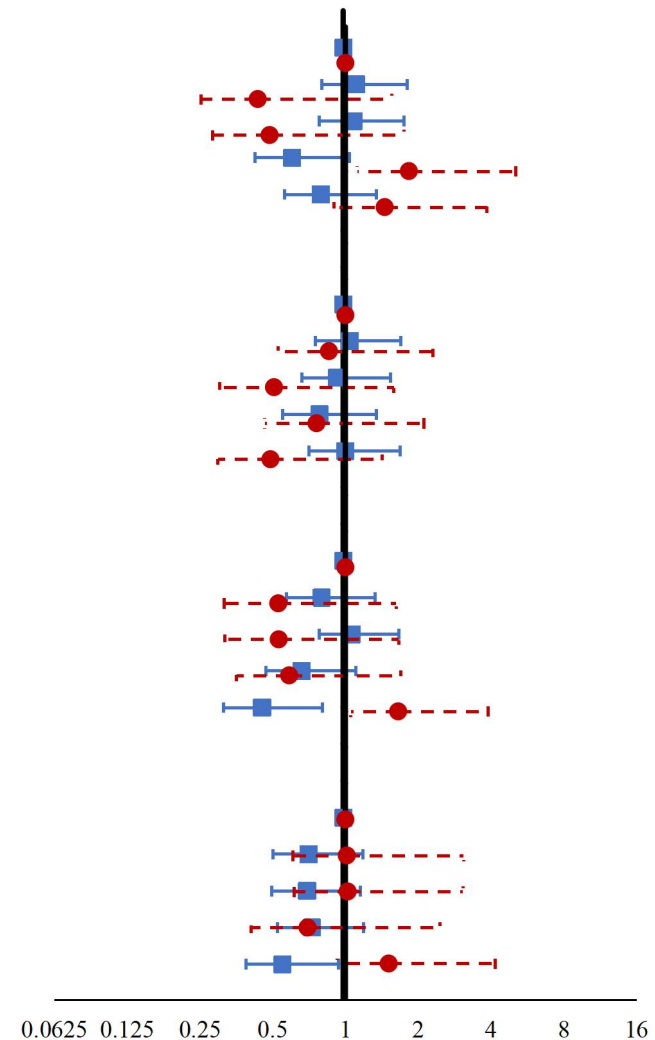
Supplemental Figure 3: ORs and 95% CIs for risk of esophageal malignant lesions by lipids components in quintiles (compared to the lowest quintile), stratified by status of family history of EC. CI: Confidence interval; HDL-C: High-density lipoprotein cholesterol; LDL-C: Ligh-density lipoprotein cholesterol;TC: Total cholesterol; TG: Triglycerides; OR: odds ratio.In multivariate models, adjustments were made for risk factors for ESCC previously identified in this population including age, gender, family history of EC, body mass index, coal stove for heating, fume exposure in kitchen, fast eating speed and ingestion of leftovers. Solid blue line represents participants without family history of EC, and dotted red line represents participants with family history of EC.