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# Mediterranean diet adherence and dietary fat intake in relation to lung cancer outcomes: a prospective cohort study

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*Background*: Lung cancer continues to be the most frequently diagnosed malignancy globally and a major contributor to cancer-related deaths. Although dietary factors have been increasingly implicated in its development, evidence for the Mediterranean diet (MED) and specific fat subtypes remains limited. *Objectives*: To examine the associations between MED adherence and dietary fat intakes with lung cancer incidence, mortality, and survival. *Methods*: We included 191 139 cancer-free participants from the UK Biobank. The validated Oxford WebQ 24-hour dietary questionnaire was used to measure dietary intake. The adherence of MED was assessed by the Alternate Mediterranean diet (AMED) score. Total dietary fat and fat subtype intakes were calculated as a proportion of total energy intake. Associations between dietary factors and lung cancer outcomes were analyzed using adjusted Cox regression. *Results*: After full adjustment, greater adherence to the MED was associated with a lower lung cancer risk ($HR_{Q4\ vs.\ Q1}$: 0.66; 95% CI: 0.58–0.77), and lower lung cancer-specific mortality ($HR_{Q4\ vs.\ Q1}$: 0.61; 95% CI: 0.50–0.74). Higher polyunsaturated fatty acids (PUFAs) intake was linked to lower lung cancer risk ($HR_{Q4\ vs.\ Q1}$: 0.82; 95% CI: 0.71–0.95) and mortality ($HR_{Q4\ vs.\ Q1}$: 0.77; 95% CI: 0.63–0.94), whereas higher saturated fatty acids (SFAs) intake was associated with increased lung cancer risk ($HR_{Q4\ vs.\ Q1}$: 1.25; 95% CI: 1.09–1.45) and mortality ($HR_{Q4\ vs.\ Q1}$: 1.23; 95% CI: 1.01–1.49). In isocaloric substitution analyses, replacing 1% of energy from SFAs with PUFAs was associated with a 9% and 10% lower risk of lung cancer incidence and mortality. Among participants who developed lung cancer, individuals with high pre-diagnosis AMED scores and PUFAs intake had better post-diagnosis survival than those with low AMED scores and low PUFAs intake (HR = 0.77; 95% CI: 0.61–0.96). *Conclusions*: Adherence to the MED and higher PUFAs intake were independently related to lower risk of lung cancer and reduced lung cancer-specific mortality. The combination of greater MED adherence and higher PUFAs intake may provide additional benefits for lung cancer post-diagnosis survival. These findings imply that dietary modifications might have a role in both the onset and progression of lung cancer. Further studies are warranted to clarify the mechanistic pathways and inform the development of dietary recommendations.

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## Introduction

Lung cancer ranks as the most commonly diagnosed malignancy globally, accounting for approximately 2.5 million new cases documented in 2022.[1] Despite substantial advances in treatment and care, the five-year survival rates remain under 20% in most regions.[2] Although tobacco smoking is the primary risk factor, growing evidence indicates that modifiable lifestyle factors, particularly diet, could contribute to lung cancer incidence, mortality, and post-diagnosis survival.[3,4] Therefore, understanding the significance of dietary patterns and nutrient composition for lung cancer outcomes is important for the development of effective prevention and management strategies.

The Mediterranean diet (MED) is defined by high consumption of vegetables, legumes, fruits, whole grains, nuts, and fish; moderate intake of dairy and wine; and reduced consumption of red and processed meat and saturated fats.[5] Adherence to the MED is linked to reduced risks of metabolic

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disorders, cardiovascular diseases, and several types of cancer.[6–8] Its protective effects are attributed to anti-inflammatory and antioxidant activities, favorable modulation of lipid metabolism, and potential influence on the tumor microenvironment. Nevertheless, evidence regarding the relationship between MED adherence and lung cancer outcomes, including incidence, mortality, and post-diagnosis survival, remains limited.[9]

High-quality fats are a key component of the MED and may contribute to its beneficial health effects. Dietary fat, a major macronutrient in human diets, has also been implicated in cancer development through mechanisms including systemic inflammation, metabolic regulation, membrane structure alteration, and intracellular signaling.[10] Beyond total fat intake, qualitative differences in fat intake may influence cancer risk and progression.[11,12] Notably, polyunsaturated fatty acids (PUFAs) have been involved in immune function, redox balance, and the maintenance of body weight and muscle mass.[13,14] Preclinical studies further suggest that high-quality fats may inhibit lung cancer-related signaling pathways.[15,16] However, population-based evidence linking fat subtypes with lung cancer incidence, mortality, and survival is limited.

In the present study, we investigated the associations of MED adherence and fat intake with lung cancer risk, mortality, and post-diagnosis survival in a large longitudinal cohort. We further explored whether the combination of greater MED adherence and higher intake of PUFAs provides additional benefits for lung cancer outcomes.

# Methods

### Study population

The UK Biobank study enrolled more than 500 000 adults aged 37–73 years at baseline during 2006–2010. A detailed description of UK Biobank has been provided in the previous publication.[17] Among the 502 356 participants, we excluded those who had been diagnosed with cancer before baseline, except for non-melanoma skin cancer ($n$ = 42 571) and those who withdrew consent ($n$ = 141). Participants who did not complete the dietary assessment or had implausible energy intakes (women: >3500 kcal or <600 kcal; men: >4200 kcal or <800 kcal (ref. 18)) were also excluded ($n$ = 268 505). In total, the analysis of lung cancer risk and mortality included 191 139 participants (SI Fig. S1). During follow-up, 1520 individuals developed lung cancer and were further included in the analyses of post-diagnosis survival outcomes. Ethical approval for the project was obtained from the NHS North West Multicenter Research Ethics Committee (Ref. 11/NW/0382), and written informed consent was secured from every UK Biobank participant at the time of recruitment.

### Dietary intake assessment

Dietary information was obtained *via* the Oxford WebQ, an online 24-hour questionnaire validated by comparison with traditional interviewer-based dietary recall.[19] Participants reported the intakes of 206 foods and 32 beverages in standard portions during the preceding 24 hours at each assessment.[20] Participants could complete up to five dietary assessments, and to minimize within-person variation, we computed mean dietary intake across multiple assessments for those completing more than one assessment.[21]

### Mediterranean diet adherence

The Alternate Mediterranean Diet (AMED) score is an adapted scoring system for quantifying adherence to the Mediterranean diet in non-Mediterranean populations and has been widely applied in the UK Biobank study.[22–26] The AMED consists of nine components, each representing a distinct food group. For each component, participants were assigned 0 or 1 point based on whether their intake was below or equal to/above the sex-specific population median. Participants who consumed amounts above the sex-specific median of vegetables, fruits, legumes, fish, whole grains, nuts, or had a higher MUFA/SFA ratio received 1 point; others were assigned 0 points. Participants who consumed amounts below the sex-specific median of red and processed meats received 1 point; others received 0 points. Participants who consumed 5–15 g day$^{-1}$ of alcohol for women or 10–25 g day$^{-1}$ for men received 1 point, while others were assigned 0 points. A higher AMED score indicated greater adherence to MED, and the total score varies between 0 and 9. Details of the AMED scoring criteria are provided in SI Table S1.

### Dietary fat assessment

Total energy and fat intake were derived by multiplying the recorded intake of individual food items by their nutrient composition in the UK Nutrient Databank, then summing across all foods.[27] Total dietary fat and fatty acid subtypes, including saturated fatty acids (SFAs), polyunsaturated fatty acids (PUFAs), monounsaturated fatty acids (MUFAs), and *trans*-fatty acids (TFAs), were presented as percentages of total energy intake. One gram of dietary fat provides approximately nine kilocalories (kcal) of energy.

### Outcome ascertainment

The study outcomes included lung cancer risk, lung cancer mortality, and post-diagnosis survival. Participants remained under observation until death or the last follow-up on December 19, 2022. For lung cancer risk analysis, incident cases were determined through hospital inpatient records and cancer registries.[17] The date of diagnosis was determined based on the earliest record from these sources. Lung cancer cases were identified using the 10th Revision of the International Classification of Diseases (ICD-10), code C34. Follow-up time in person-years was accrued from recruitment until lung cancer onset, mortality, or the last follow-up. For lung cancer mortality analysis, death information was obtained from the NHS Central Register (Scotland) and the NHS Information Center (England and Wales).[17] with participants followed from baseline until death or the last day of follow-up. For lung cancer survival analysis, follow-up duration

was calculated from diagnosis until the first occurrence of all-cause mortality or the last follow-up.

### Statistical analysis

Participant baseline characteristics were compiled through descriptive statistics. Analysis of variance (ANOVA) was performed on numeric variables, and values are summarized as mean ± standard deviation (SD). Chi-square testing was applied to categorical variables, and results are shown as counts (percentages). Relationships between dietary exposures and lung cancer outcomes (incidence, mortality, and post-diagnosis survival) were evaluated by Cox proportional hazards models, and hazard ratios (HRs) with 95% confidence intervals (CIs) were derived. Dietary exposures in this study included adherence to MED and different types of fats: total fat, SFAs, MUFAs, PUFAs, and TFAs. Participants were categorized into quartiles for each dietary exposure, taking the lowest quartile as reference. To test linear trends, the quartile medians were treated as continuous variables. To account for multiple comparisons among total fat and its subtypes, *P* values for trend were adjusted using the Benjamini-Hochberg false discovery rate (FDR) procedure separately for each outcome. Restricted cubic splines (RCS) were incorporated in Cox models to examine potential non-linear relationships between MED adherence and lung cancer outcomes. The RCS models were specified with three knots located at the 10th, 50th, and 90th percentiles of the exposure distribution, setting the median as the reference. Likelihood ratio tests were used to evaluate non-linear associations by comparing models containing only linear terms with those including both linear and cubic spline terms. Stratified analyses by smoking status (never *vs.* ever) were conducted to assess whether associations between MED adherence and lung cancer outcomes differed across smoking subgroups. Additionally, isocaloric substitution models were employed to assess the impact of replacing SFAs with PUFAs or MUFAs on lung cancer outcomes.

To assess the combined relationships of MED adherence and PUFAs intake with lung cancer outcomes, participants were classified into high and low groups for each exposure. High adherence to the MED was defined as AMED scores in the highest quartile (≥6), and low adherence as scores in the lowest quartile (≤3) to maximize contrast in overall dietary adherence patterns and reduce within-group heterogeneity. PUFAs intake was grouped into low and high levels according to the median value to ensure balanced exposure groups and stable estimates for the cross-classification analysis. Participants were then cross-classified into four combined groups: "low AMED-low PUFAs", "low AMED-high PUFAs", "high AMED-low PUFAs", and "high AMED-high PUFAs". This cross-classification was used to examine whether the associations of Mediterranean diet adherence with lung cancer incidence, mortality, and post-diagnosis survival varied according to PUFAs intake. Considering that AMED adherence and PUFAs intake are often highly correlated, we evaluated potential effect modification by including a cross-product term in the fully adjusted Cox proportional hazards models to test for multiplicative interactions. Supplementary analyses further included the moderate AMED adherence group (quartiles 2 and 3), cross-classifying the three AMED categories with low and high PUFAs intake.

Covariates were accounted for using two multivariable models. Model 1 (minimally adjusted) included age (years, continuous), sex (female/male), and total energy intake (kcal $day^{-1}$, continuous) as covariates. Model 2 (fully adjusted) additionally included adjustments for ethnicity (white/non-white), Townsend Deprivation Index (continuous), education level (less than high school/high school or equivalent/college or above), smoking status (never smokers/ever smokers), alcohol consumption (never or moderate/excessive), physical activity level (insufficiently active/sufficiently active), body mass index (kg $m^{-2}$, continuous), and family history of lung cancer (no/yes). For lung cancer survival analysis, the age variable was defined as age at diagnosis (years, continuous), and model 2 included additional adjustment for histological type (non-small cell lung cancer/small cell lung cancer). These variables were selected as potential confounders or factors related to exposures or outcomes. Detailed definitions and classifications of covariates are provided in SI Table S2. No severe multicollinearity was observed among the explanatory variables (SI Table S3), and Schoenfeld residuals indicated no violation of the proportional hazards assumption (SI Table S4). Missing covariate data were addressed using random-forest based multiple imputation, generating five imputed datasets, and the resulting multivariable estimates were pooled according to Rubin's rules.

Multiple sensitivity analyses were performed to confirm the reliability of the primary results. First, to achieve a more accurate estimate of dietary habits, we restricted the sample to individuals who provided two or more 24-hour dietary assessments.[19] Second, to evaluate the influence of missing data in sociodemographic and lifestyle confounders, we excluded individuals with missing values in key covariates. Third, participants with follow-up less than one year were excluded to reduce potential bias arising from reverse causation. Fourth, we calculated standardized mean differences (SMDs) to assess baseline imbalances between the included and excluded participants, and employed inverse probability weighting (IPW) Cox models to account for potential selection bias resulting from data exclusion. Fifth, we used the Fine-Gray subdistribution hazard models to account for competing risk bias, defining death prior to lung cancer diagnosis and non-lung cancer death as competing events for lung cancer incidence and lung cancer mortality, respectively. Sixth, to account for potential confounding by other dietary components in the associations between dietary fats and lung cancer outcomes, we further adjusted for the intakes of fruits, vegetables, and red and processed meats.[28,29] Furthermore, subgroup analyses were conducted by stratifying participants according to age, sex, ethnicity, educational level, Townsend Deprivation Index, alcohol consumption, physical activity, and body mass index. R (version 4.4.0) was used to perform all statistical analyses, and a two-sided *P*-value below 0.05 was deemed statistically significant.

 

# Results

### Participant characteristics

In total, 191 139 individuals were included in the study, with 1520 lung cancer cases identified during follow-up. Baseline characteristics for the overall population stratified by quartiles of the Alternate Mediterranean Diet (AMED) score are presented in Table 1. A total of 54.20% were women, with the mean age at baseline being 55.82 years (±7.95). The majority of participants were white (93.35%) and had completed high school or higher education (91.18%). Nearly half of the participants were ever-smokers (42.08%), and 26.58% reported excessive alcohol consumption. Additionally, 22 252 participants (11.64%) had a family history of lung cancer. Individuals who scored higher on AMED tended to have a lower Townsend Deprivation Index, higher education level, be never-smokers, consume no or moderate alcohol, and engage in sufficient physical activity. Baseline characteristics of incident lung cancer cases are summarized in SI Table S5.

### Mediterranean diet adherence and lung cancer outcomes

Based on the quartile distribution of AMED scores, individuals were divided into four categories. Fully adjusted HRs indicated a reduction in risk of lung cancer at higher AMED scores ($HR_{Q4\ vs.\ Q1}$: 0.66; 95% CI: 0.58–0.77; *P*-trend < 0.001) (Table 2). Similarly, a reduced risk of lung cancer mortality was observed at higher AMED scores ($HR_{Q4\ vs.\ Q1}$: 0.61; 95% CI: 0.50–0.74; *P*-trend < 0.001). In contrast, after adjustment for all covariates, no significant linear association was observed between pre-diagnosis MED adherence and post-diagnosis survival among lung cancer patients (*P*-trend = 0.544).

In restricted cubic spline analyses, no indication of non-linear relationships was found between AMED scores and lung cancer incidence or mortality (Fig. 1). However, a non-linear association was identified for lung cancer survival, whereby AMED scores above 4 were associated with better survival outcomes (*P* for non-linear = 0.038). In stratified analyses by smoking status, higher AMED scores were significantly related to lower risk of lung cancer incidence and mortality, and better post-diagnosis survival among ever smokers. By contrast, no significant correlations were observed among never smokers.

### Dietary fat and lung cancer outcomes

Higher polyunsaturated fatty acids (PUFAs) consumption was significantly linked to lower lung cancer risk ($HR_{Q4\ vs.\ Q1}$: 0.82; 95% CI: 0.71–0.95; $P_{adj}$ for trend = 0.006), and lung cancer-specific mortality ($HR_{Q4\ vs.\ Q1}$: 0.77; 95% CI: 0.63–0.94; $P_{adj}$ for

**Table 1** Baseline characteristics according to quartiles of Alternate Mediterranean Diet (AMED) score

| Variable/subgroups | Overall *n* = 191 139 | Q1 *n* = 68 396 | Q2 *n* = 40 977 | Q3 *n* = 36 816 | Q4 *n* = 44 950 | *P* value |
|---|---|---|---|---|---|---|
| **Age, years** | 55.82 (7.95) | 55.13 (8.07) | 55.78 (7.97) | 56.14 (7.88) | 56.63 (7.71) | <0.001 |
| **Sex** | | | | | | <0.001 |
| Male | 87 536 (45.80) | 31 166 (45.57) | 18 542 (45.25) | 16 791 (45.61) | 21 037 (46.80) | |
| Female | 103 603 (54.20) | 37 230 (54.43) | 22 435 (54.75) | 20 025 (54.39) | 23 913 (53.20) | |
| **Ethnicity** | | | | | | <0.001 |
| White | 182 251 (95.35) | 65 549 (95.84) | 38 994 (95.16) | 35 035 (95.16) | 42 673 (94.93) | |
| Non-white | 8188 (4.28) | 2593 (3.79) | 1819 (4.44) | 1666 (4.53) | 2110 (4.69) | |
| Unknown | 700 (0.37) | 254 (0.37) | 164 (0.40) | 115 (0.31) | 167 (0.37) | |
| **Townsend Deprivation index** | −1.58 (2.87) | −1.47 (2.91) | −1.60 (2.86) | −1.65 (2.84) | −1.66 (2.84) | <0.001 |
| **Education level** | | | | | | <0.001 |
| Less than high school | 15 925 (8.33) | 7004 (10.24) | 3528 (8.61) | 2775 (7.54) | 2618 (5.82) | |
| High school or equivalent | 92 534 (48.41) | 36 339 (53.13) | 20 054 (48.94) | 17 117 (46.49) | 19 024 (42.32) | |
| College or above | 81 755 (42.77) | 24 666 (36.06) | 17 200 (41.97) | 16 754 (45.51) | 23 135 (51.47) | |
| Unknown | 925 (0.48) | 387 (0.57) | 195 (0.48) | 170 (0.46) | 173 (0.38) | |
| **Smoking status** | | | | | | <0.001 |
| Never smokers | 108 058 (56.53) | 37 126 (54.28) | 23 324 (56.92) | 21 271 (57.78) | 26 337 (58.59) | |
| Ever smokers | 80 434 (42.08) | 30 354 (44.38) | 17 101 (41.73) | 15 032 (40.83) | 17 947 (39.93) | |
| Unknown | 2647 (1.38) | 916 (1.34) | 552 (1.35) | 513 (1.39) | 666 (1.48) | |
| **Alcohol consumption** | | | | | | <0.001 |
| Never or moderate | 120 249 (62.91) | 40 333 (58.97) | 25 531 (62.31) | 23 757 (64.53) | 30 628 (68.14) | |
| Excessive | 50 807 (26.58) | 20 342 (29.74) | 11 092 (27.07) | 9189 (24.96) | 10 184 (22.66) | |
| Unknown | 20 083 (10.51) | 7721 (11.29) | 4354 (10.63) | 3870 (10.51) | 4138 (9.21) | |
| **Physical activity level** | | | | | | <0.001 |
| Insufficiently active | 28 434 (14.88) | 11 546 (16.88) | 6251 (15.25) | 5216 (14.17) | 5421 (12.06) | |
| Sufficiently active | 129 513 (67.76) | 43 639 (63.80) | 27 525 (67.17) | 25 433 (69.08) | 32 916 (73.23) | |
| Unknown | 33 192 (17.37) | 13 211 (19.32) | 7201 (17.57) | 6167 (16.75) | 6613 (14.71) | |
| **Body mass index, kg m$^{-2}$** | 26.95 (4.64) | 27.51 (4.86) | 27.05 (4.62) | 26.75 (4.53) | 26.16 (4.26) | <0.001 |
| **Family history of lung cancer** | | | | | | <0.001 |
| No | 144 544 (75.62) | 51 367 (75.10) | 30 924 (75.47) | 28 002 (76.06) | 34 251 (76.20) | |
| Yes | 22 252 (11.64) | 8262 (12.08) | 4838 (11.81) | 4157 (11.29) | 4995 (11.11) | |
| Unknown | 24 343 (12.74) | 8767 (12.82) | 5215 (12.73) | 4657 (12.65) | 5704 (12.69) | |
| **Energy intake, kcal day$^{-1}$** | 2044.29 (539.22) | 2141.12 (534.63) | 2026.35 (537.15) | 1980.63 (532.95) | 1965.45 (530.78) | <0.001 |

Data are presented as means (standard deviations) for continuous variables and numbers (percentages) for categorical variables.

Table 2 Association between Mediterranean diet and lung cancer outcomes (risk, mortality, and survival)

| | AMED score | | | | |
|---|---|---|---|---|---|
| | Q1 (0–3) | Q2 (4) | Q3 (5) | Q4 (6–9) | *P* trend |
| **Lung cancer risk** | | | | | |
| Cases/total | 669/68 396 | 307/40 977 | 256/36 816 | 288/44 950 | |
| Model 1 (HR 95%CI) | Reference | **0.71 (0.62, 0.81)** | **0.64 (0.55, 0.74)** | **0.56 (0.49, 0.65)** | **<0.001** |
| Model 2 (HR 95%CI) | Reference | **0.77 (0.67, 0.88)** | **0.71 (0.62, 0.83)** | **0.66 (0.58, 0.77)** | **<0.001** |
| **Lung cancer mortality** | | | | | |
| Cases/total | 379/68 396 | 168/40 977 | 144/36 816 | 144/44 950 | |
| Model 1 (HR 95%CI) | Reference | **0.69 (0.57, 0.83)** | **0.63 (0.52, 0.77)** | **0.50 (0.41, 0.60)** | **<0.001** |
| Model 2 (HR 95%CI) | Reference | **0.76 (0.63, 0.91)** | **0.73 (0.60, 0.89)** | **0.61 (0.50, 0.74)** | **<0.001** |
| **Lung cancer survival** | | | | | |
| Cases/total | 442/669 | 194/307 | 159/256 | 164/288 | |
| Model 1 (HR 95%CI) | Reference | 1.01 (0.86, 1.20) | 0.99 (0.83, 1.19) | **0.82 (0.69, 0.99)** | 0.107 |
| Model 2 (HR 95%CI) | Reference | 1.07 (0.90, 1.27) | 1.08 (0.90, 1.31) | 0.88 (0.73, 1.06) | 0.544 |

Abbreviations: AMED – alternate Mediterranean diet; HR – hazard ratio; CI – confidence interval. Model 1 (minimally adjusted) was adjusted for age, sex, and total energy intake; model 2 (fully adjusted) was additionally adjusted for ethnicity, Townsend Deprivation Index, education level, smoking status, physical activity level, body mass index, and family history of lung cancer. For the lung cancer survival analysis, age was defined as age at diagnosis, and model 2 was additionally adjusted for histological type. Data with *P* values below 0.05 are shown in bold type.

trend = 0.031) (Fig. 2). For post-diagnosis survival, neither the hazard ratios across quartiles nor the overall linear trend reached statistical significance ($P_{adj}$ for trend = 0.205). In contrast, higher consumption of saturated fatty acids (SFAs) and *trans* fatty acids (TFAs) was related to elevated risks of lung cancer incidence (for SFAs, $HR_{Q4\ vs.\ Q1}$: 1.25, 95% CI: 1.09–1.45, $P_{adj}$ for trend = 0.006; for TFAs, $HR_{Q4\ vs.\ Q1}$: 1.17, 95% CI: 1.01–1.35, $P_{adj}$ for trend = 0.037), and SFAs intake in the highest quartile was linked to increased lung cancer mortality ($HR_{Q4\ vs.\ Q1}$: 1.23; 95% CI: 1.01–1.49), although no significant linear trend was observed ($P_{adj}$ for trend = 0.077). No significant correlation was identified between total fat or monounsaturated fatty acids (MUFAs) and any lung cancer outcomes.

Isocaloric substitution analyses found that replacing 1% and 5% of energy from SFAs with PUFAs was related to 9% (HR: 0.91; 95% CI: 0.87–0.94) and 39% (HR: 0.61; 95% CI: 0.50–0.75) decreased risk of lung cancer incidence, and 10% (HR: 0.90; 95% CI: 0.85–0.96) and 40% (HR: 0.60; 95% CI: 0.46–0.80) reduction in lung cancer-specific mortality, respectively (Table 3). In contrast, substituting SFAs with MUFAs was not significantly linked to lung cancer incidence or mortality. Similarly, isocaloric substitution of SFAs for either PUFAs or MUFAs showed no relationship to post-diagnosis survival.

### Mediterranean diet adherence, dietary fat and lung cancer outcome

In the cross-classified analysis, participants in the "low AMED-high PUFAs" group had a 19% (HR = 0.81; 95% CI: 0.68–0.95) lower lung cancer incidence and a 23% (HR = 0.77; 95% CI: 0.62–0.95) lower lung cancer mortality compared with the "low AMED-low PUFAs" reference group. For post-diagnosis survival, participants in the "high AMED-high PUFAs" group showed better survival than those in the "low AMED-low PUFAs" reference group (HR = 0.77; 95% CI: 0.61–0.96), whereas no significant association was found for those in the "low AMED-high PUFAs" group (HR = 0.83; 95% CI: 0.69–1.01) and "high AMED-low PUFAs" group (HR = 0.97; 95% CI: 0.71–1.32). Consistent associations were observed among ever smokers. More details are presented in Table 4. Interaction analyses revealed no statistically significant multiplicative interactions between AMED adherence and PUFAs intake across all lung cancer outcomes (all *P* for interaction > 0.05; SI Table S6). Furthermore, in the SI analyses including participants with moderate AMED adherence, while the cross-classified groups with moderate AMED adherence showed intermediate reductions in lung cancer risk and mortality, significant survival benefits remained restricted to the "high AMED-high PUFAs" group (SI Table S7).

### Sensitivity analyses

The main findings were consistent across multiple sensitivity studies. Comparable results were obtained after restricting the dataset to individuals who completed at least two dietary recalls (SI Tables S8–S10). The results remained consistent after excluding participants with missing covariate values (SI Tables S11–S13) or those with follow-up time less than one year (SI Tables S14–S16). Regarding potential selection bias, although excluded participants were generally older, more socioeconomically deprived, less educated, and had a higher BMI than those in the analytic cohort (SMDs > 0.1; SI Table S17), the primary findings remained materially unchanged in the IPW analyses (SI Tables S18–S20). Accounting for competing events using the Fine-Gray subdistribution hazard models did not substantially alter the results (SI Tables S21–S23). Furthermore, the associations between specific dietary fats and lung cancer outcomes remained robust after further adjustment for other major dietary components (SI Tables S24 and S25). Finally, subgroup analyses revealed no significant effect modification by the predefined stratification variables (all *P* for interaction > 0.05; SI Table S26).

 

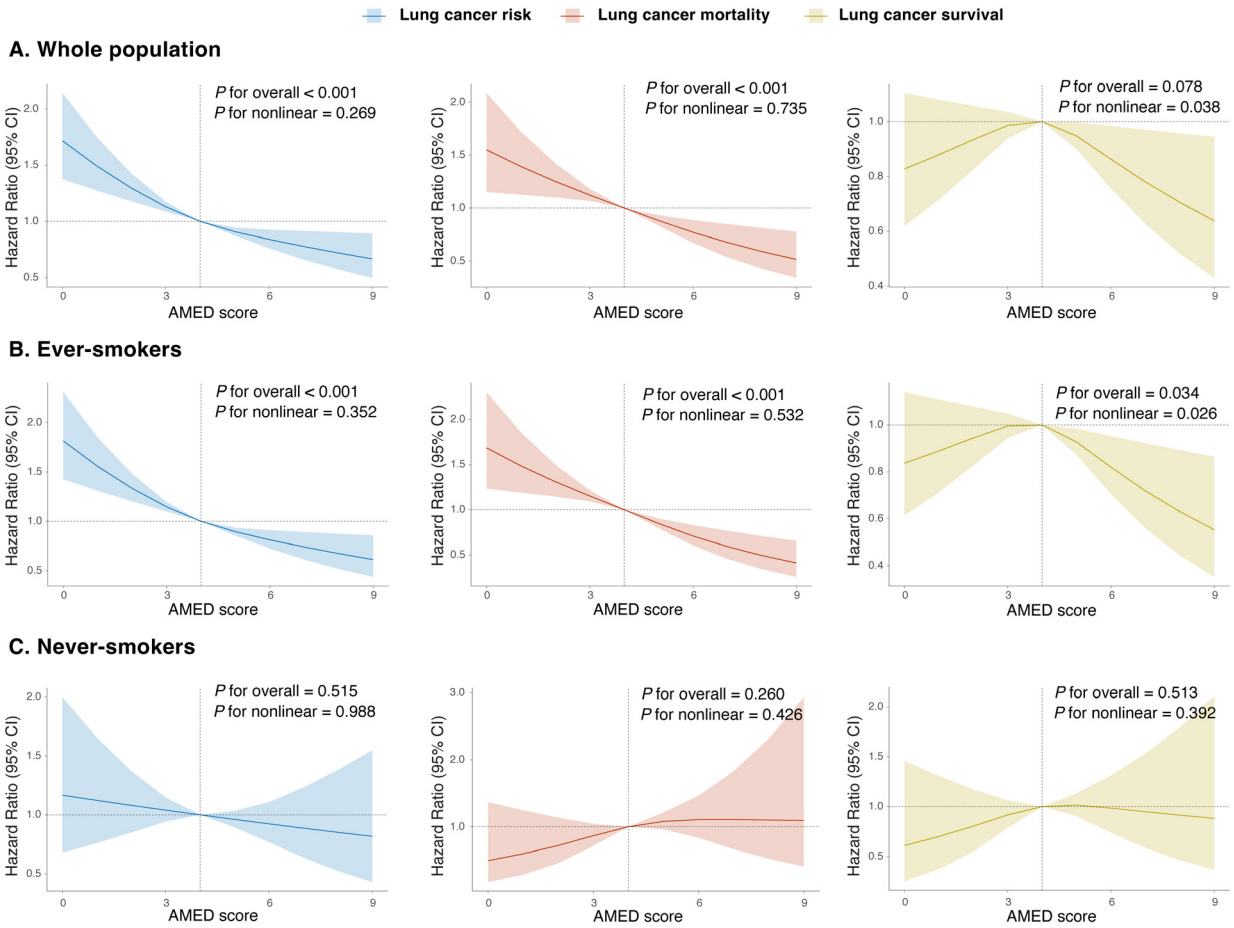


**Fig. 1** Cubic spline curves describing the associations between adherence to the Mediterranean diet and lung cancer outcomes (risk, mortality, and survival) in the overall population and in analyses stratified by smoking status. All models were adjusted for age, sex, total energy intake, ethnicity, Townsend Deprivation Index, education level, smoking status, physical activity level, body mass index, and family history of lung cancer. For the lung cancer survival analysis, age was defined as age at diagnosis, and the models were additionally adjusted for histological type. Abbreviations: AMED – Alternate Mediterranean Diet.

## Discussion

In this prospective study, higher adherence to Mediterranean diet (MED) and higher consumption of polyunsaturated fatty acids (PUFAs) were independently linked to decreased risk of lung cancer incidence and lung cancer-specific mortality, whereas higher saturated fatty acids (SFAs) intake was linked to higher risk. Participants with both high MED adherence and high PUFAs intake exhibited improved post-diagnosis survival compared with those with low MED adherence and low PUFAs. Sensitivity analyses produced consistent results, supporting the robustness of these findings.

The MED is widely acknowledged as a healthy dietary pattern, but few observational research has focused on the relationship between lung cancer and MED adherence. One multiethnic cohort study reported that participants with higher AMED scores had decreased risks of lung cancer, with a hazard ratio of 0.83;[30] similarly, a large US cohort study observed an inverse relationship between the MED adherence and lung cancer incidence, with a hazard ratio of 0.85,[31] consistent with our findings. Additionally, similar associations have been observed in broader cancer populations. Two cohort studies of 6370 and 802 cancer patients reported that high Mediterranean diet scores were related to low mortality, with hazard ratios of 0.74 and 0.68, respectively.[32,33] Evidence specific to lung cancer survivors is particularly scarce. We identified only one prospective cohort study from a single center, involving 37 individuals. The study reported that adherence to the MED was associated with a significantly improved 6-month survival rate in comparison with non-adherence ($P$ = 0.019),[9] although socioeconomic factors were not controlled for. In our study, the minimal model only adjusted for total energy intake, sex, and age at diagnosis, suggesting that greater MED adherence was significantly correlated with better survival ($HR_{Q4\ vs.\ Q1}$: 0.82; 95% CI: 0.69–0.99). After further controlling for socioeconomic and lifestyle factors, this association was attenuated, likely reflecting the confounding effects of these covariates, as healthy dietary patterns frequently cluster with favorable socioeconomic status and lifestyle behaviors.[34–36] However, nonlinear and subgroup analyses

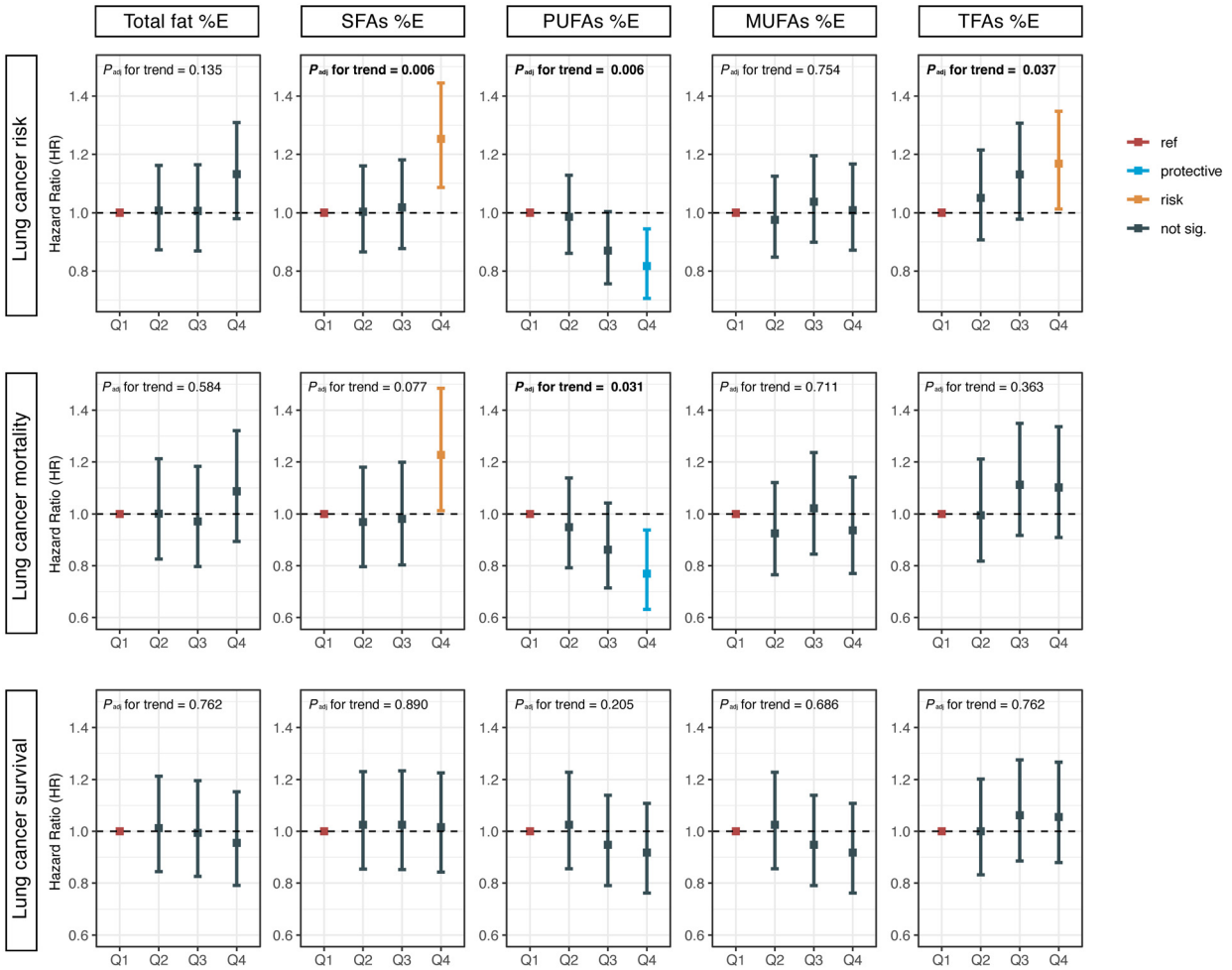


**Fig. 2** Association between intakes of total fat and fat subtypes and lung cancer outcomes (risk, mortality, and survival). Hazard ratios and 95% confidence intervals for quartiles of intake are shown, with the lowest quartile serving as the reference. All models were adjusted for age, sex, total energy intake, ethnicity, Townsend Deprivation Index, education level, smoking status, alcohol consumption, physical activity level, body mass index, and family history of lung cancer. For the lung cancer survival analysis, age was defined as age at diagnosis, and the models were additionally adjusted for histological type. $P_{adj}$ for trend: *P* values for trend across quartiles were adjusted for multiple comparisons using the Benjamini–Hochberg false discovery rate (FDR) procedure. Data with *P* values below 0.05 are shown in bold type. Abbreviations: SFA – saturated fatty acid; MUFA – monounsaturated fatty acid; PUFA – polyunsaturated fatty acid; TFA – *trans*-fatty acid; %E, percentage of total energy.

among ever smokers demonstrated a survival benefit associated with high MED adherence, indicating that the protective effect is observed at higher adherence levels and in specific population subgroups. Subgroup analyses showed that MED adherence was linked to lower lung cancer risk in ever smokers, in line with a meta-analysis reporting that healthy dietary patterns are inversely related to lung cancer incidence in former and current smokers.[37] Overall, our study supplements current knowledge supporting the potential protective effect of the MED in lung cancer. Such protective effects may be explained by its anti-inflammatory and antioxidant properties, reduction of oxidative damage, and beneficial influence on insulin sensitivity and immune regulation.[38,39] Nevertheless, further well-designed prospective studies are warranted to validate these associations and clarify the underlying biological processes, particularly regarding lung cancer survival.

Dietary fat may influence lung cancer progression through multiple biological processes, including inflammation, immune modulation, oxidative stress, cell proliferation, angiogenesis, and energy metabolism. SFAs have been associated with pro-inflammatory and tumor-promoting effects, whereas PUFAs may confer protective effects by attenuating oxidative stress, inducing apoptosis, and supporting immune regulation.[40–42] The independent beneficial effects of PUFAs in this study may be partly explained by these biological mechanisms. For lung cancer incidence, a *meta*-analysis reported that participants with higher SFAs intake had an increased risk of lung cancer ($HR_{Q5\ vs.\ Q1}$: 1.14; 95% CI: 1.02–1.22, *P*-trend < 0.001), whereas higher consumption of PUFAs was

Table 3 Associations between isocaloric substitution of saturated fatty acid with unsaturated fatty acid and lung cancer outcomes (risk, mortality, and survival)

| | HR 95%CI | | |
|---|---|---|---|
| | Substitution of 1% energy | Substitution of 5% energy | *P* value |
| **Lung cancer risk** | | | |
| PUFAs for SFAs | **0.91 (0.87, 0.94)** | **0.61 (0.50, 0.75)** | **<0.001** |
| MUFAs for SFAs | 1.00 (0.95, 1.05) | 1.00 (0.78, 1.28) | 0.990 |
| **Lung cancer mortality** | | | |
| PUFAs for SFAs | **0.90 (0.85, 0.96)** | **0.60 (0.46, 0.80)** | **<0.001** |
| MUFAs for SFAs | 1.00 (0.93, 1.07) | 0.99 (0.70, 1.39) | 0.945 |
| **Lung cancer survival** | | | |
| PUFAs for SFAs | 0.99 (0.94, 1.05) | 0.97 (0.75, 1.25) | 0.795 |
| MUFAs for SFAs | 1.01 (0.95, 1.07) | 1.03 (0.76, 1.39) | 0.864 |

Abbreviations: AMED – Alternate Mediterranean Diet; MUFA – monounsaturated fatty acid; PUFA – polyunsaturated fatty acid; SFA – saturated fatty acid; HR – hazard ratio; CI – confidence interval. Models were adjusted for age, sex, total energy intake, ethnicity, Townsend Deprivation Index, education level, smoking status, alcohol consumption, physical activity level, body mass index, and family history of lung cancer. For the lung cancer survival analysis, age was defined as age at diagnosis, and the models were additionally adjusted for histological type. Data with *P* values below 0.05 are shown in bold type.

linked to a reduced risk ($HR_{Q5\ vs.\ Q1}$: 0.92; 95% CI: 0.87–0.98, *P*-trend < 0.001), and no significant association was found for MUFAs intake.[43] The findings are consistent with our results. Moreover, we extended the evidence by showing that dietary fat composition was also associated with lung cancer-specific mortality. Furthermore, our isocaloric substitution analyses indicated that replacing SFAs with PUFAs significantly reduced the risks of both lung cancer incidence and mortality, strengthening the robustness of our findings. Regarding survival, several randomized controlled trials have suggested that oral PUFA-enriched products with an isocaloric diet may improve treatment tolerance or nutritional status in lung cancer patients. However, evidence for survival benefits remains inconclusive, potentially due to differences in population characteristics, treatments, and follow-up periods.[44–47] Our analysis revealed an overall significant trend between higher PUFAs intake and improved survival, although individual intake categories did not reach statistical significance. This suggests a potential dose–response relationship that warrants further confirmation. While our findings highlight the potential benefits of PUFAs in lung cancer outcomes, additional prospective studies are required to establish optimal intake ranges and long-term safety.

Our study further suggests that participants with both high adherence to the MED and high PUFAs intake had better post-diagnosis survival compared with those with low MED adherence and low PUFAs intake. This observation may reflect the beneficial effects of PUFA-rich components within the MED, as well as PUFAs from other dietary sources beyond the MED. While no previous research directly compares to our results, studies on specific food groups provide supportive evidence. Foods contributing to PUFAs intake within the Mediterranean diet are primarily fish and nuts. A meta-analysis combining 12 studies across various cancer types reported that higher fish consumption was related to a significantly reduced mortality rate among cancer survivors (HR: 0.87; 95% CI: 0.81–0.94);[48] however, this analysis did not include lung cancer cases. Additionally, prior research has linked higher fish intake with better lung function,[49] suggesting potential pulmonary benefits of fish consumption. Studies focusing on specific cancers have indicated that higher nut intake is associated with improved overall survival among participants with breast and colorectal cancers, with hazard ratios of 0.72 and 0.43, respectively.[50,51] Those previous studies on PUFA-rich foods within the Mediterranean diet may help contextualize our findings, and future intervention trials or prospective cohort studies specifically designed to examine PUFAs intake and MED adherence are warranted. Subgroup analysis among ever smokers showed results consistent with those in the overall population. However, because of the limited sample size, we could not examine the association among never smokers.

This study has multiple strengths. Notably, our analysis assessed the independent relationships of MED adherence and fat intake with multiple lung cancer outcomes, including incidence, mortality, and post-diagnosis survival. By analyzing these three outcomes together, we were able to comprehensively examine the association of diet with lung cancer development and progression. Additionally, our study employed multiple complementary analytical approaches, including quartile-based analyses, restricted cubic spline (RCS) modeling, isocaloric substitution, and cross-classification of Mediterranean diet adherence and PUFAs intake, along with sensitivity analyses, providing a comprehensive and robust assessment of the associations with lung cancer outcomes. Moreover, lung cancer cases ascertainment relied on both hospital inpatient records and national cancer registries, ensuring the accuracy and completeness of case ascertainment. The analysis also utilized detailed dietary information and adjusted for multiple confounding factors.

However, this study has several limitations. First, while the Oxford WebQ dietary assessment tool has demonstrated acceptable validity in comparison with biochemical markers,[19] and participants with implausible energy intakes were excluded, recall bias cannot be completely ruled out. Second, information on dietary and lifestyle was collected at a single assessment, and potential behavioral changes could lead to exposure misclassification. However, previous research has indicated that dietary habits in adults remain relatively stable over time, including before and after a cancer diagnosis.[52] To minimize the impact of short-term dietary changes triggered by the diagnosis, we excluded participants who developed lung cancer within one year after baseline in sensitivity analyses. Third, because relevant variables were not available in the UK Biobank, tumor stage and treatment were not considered in the survival analysis. Finally, due to the observational design, residual or unmeasured confounding cannot be entirely excluded, even after adjusting for multiple potential confounders in our study.

Table 4 Association of Mediterranean diet and PUFAs intake with lung cancer outcomes (risk, mortality, and survival)

| | Low AMED score and low PUFAs | Low AMED score and high PUFAs | High AMED score and low PUFAs | High AMED score and high PUFAs |
|---|---|---|---|---|
| **Whole population** | | | | |
| **Lung cancer risk** | | | | |
| Cases/total | 459/42 324 | 210/26 072 | 105/15 515 | 183/29 435 |
| Model 1 (HR 95%CI) | Reference | **0.80 (0.68, 0.94)** | **0.52 (0.42, 0.65)** | **0.53 (0.44, 0.62)** |
| Model 2 (HR 95%CI) | Reference | **0.81 (0.68, 0.95)** | **0.63 (0.50, 0.78)** | **0.64 (0.54, 0.76)** |
| **Lung cancer mortality** | | | | |
| Cases/total | 266/42 324 | 113/26 072 | 51/15 515 | 93/29 435 |
| Model 1 (HR 95%CI) | Reference | **0.76 (0.61, 0.95)** | **0.45 (0.33, 0.61)** | **0.46 (0.36, 0.58)** |
| Model 2 (HR 95%CI) | Reference | **0.77 (0.62, 0.95)** | **0.56 (0.41, 0.77)** | **0.59 (0.46, 0.74)** |
| **Lung cancer survival** | | | | |
| Cases/total | 287/422 | 155/247 | 53/85 | 111/203 |
| Model 1 (HR 95%CI) | Reference | 0.84 (0.69, 1.02) | 0.92 (0.68, 1.25) | **0.72 (0.58, 0.90)** |
| Model 2 (HR 95%CI) | Reference | 0.83 (0.69, 1.01) | 0.97 (0.71, 1.32) | **0.77 (0.61, 0.96)** |
| **Ever-smokers** | | | | |
| **Lung cancer risk** | | | | |
| Cases/total | 384/19 468 | 175/11 290 | 79/6494 | 140/11 706 |
| Model 1 (HR 95%CI) | Reference | **0.83 (0.70, 1.00)** | **0.52 (0.40, 0.66)** | **0.56 (0.46, 0.68)** |
| Model 2 (HR 95%CI) | Reference | **0.81 (0.68, 0.97)** | **0.59 (0.46, 0.76)** | **0.63 (0.51, 0.76)** |
| **Lung cancer mortality** | | | | |
| Cases/total | 242/19 468 | 103/11 290 | 42/6494 | 72/11 706 |
| Model 1 (HR 95%CI) | Reference | **0.78 (0.62, 0.98)** | **0.44 (0.32, 0.61)** | **0.46 (0.35, 0.60)** |
| Model 2 (HR 95%CI) | Reference | **0.76 (0.60, 0.96)** | **0.51 (0.37, 0.72)** | **0.52 (0.40, 0.69)** |
| **Lung cancer survival** | | | | |
| Cases/total | 253/356 | 136/204 | 45/64 | 82/154 |
| Model 1 (HR 95%CI) | Reference | 0.87 (0.70, 1.07) | 1.05 (0.76, 1.45) | **0.67 (0.52, 0.86)** |
| Model 2 (HR 95%CI) | Reference | 0.84 (0.68, 1.04) | 1.04 (0.75, 1.44) | **0.69 (0.53, 0.89)** |

Abbreviations: AMED – Alternate Mediterranean Diet; PUFA – polyunsaturated fatty acid; HR – hazard ratio; CI – confidence interval. Model 1 (minimally adjusted) was adjusted for age, sex, and total energy intake; model 2 (fully adjusted) was additionally adjusted for ethnicity, Townsend Deprivation Index, education level, smoking status, physical activity level, body mass index, and family history of lung cancer. For the lung cancer survival analysis, age was defined as age at diagnosis, and model 2 was additionally adjusted for histological type. Data with *P* values below 0.05 are shown in bold type.

## Conclusions

In this study, we found that greater adherence to the Mediterranean diet and higher intake of polyunsaturated fatty acids (PUFAs) were associated with decreased risk of adverse lung cancer outcomes. The findings underscore the potential influence of dietary modifications on lung cancer and suggest a possible protective role for both the Mediterranean diet and PUFAs. However, more well-designed prospective studies and mechanistic investigations are essential to confirm these relationships and elucidate underlying biological processes, thereby informing evidence-based dietary guidance for reducing lung cancer risk and mortality.

## Author contributions

Qiyun Xue: conceptualization, methodology, formal analysis, writing – original draft, writing – review and editing. Huakang Tu: methodology, writing – review and editing. Yan Liu: methodology, validation, writing – review and editing. Shiyu Jiang: writing – review and editing. Lizhi Zhang: formal analysis, writing – review and editing. Fang Hu: data curation, writing – review and editing. Qingfeng Hu: data curation, writing – review and editing. Min Yang: conceptualization, writing – review and editing. Xifeng Wu: conceptualization, supervision, project administration, writing – review and editing, funding acquisition.

## Conflicts of interest

All authors declare no conflict of interest.

## Data availability

Data from the UK Biobank are available subject to approval following an application to the UK Biobank (https://www.ukbiobank.ac.uk/).

Supplementary information (SI) is available. See DOI: https://doi.org/10.1039/d6fo00080k.

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