Supplementary materials for

Effects of Diet on Risk of cancer and the Mediating role of Metabolites

Yi Fan^{1,2†}, Chanchan Hu^{1†}, Xiaoxu Xie^{1†}, Yanfeng Weng^{1†}, Chen Chen¹, Zhaokun

Wang², Xueqiong He², Dongxia Jiang², Shaodan Huang^{2,3*}, Zhijian Hu^{1*}, Fengqiong

 Liu^{1*}

¹ Department of Epidemiology and Health Statistics, Fujian Provincial Key Laboratory

of Environment Factors and Cancer, School of Public Health, Fujian Medical

University, Fuzhou 350122, China;

² Department of Occupational and Environmental Health Sciences, School of Public

Health, Peking University, Beijing 100191, China;

³ Key Laboratory of Epidemiology of Major Diseases (Peking University), Ministry of

Education, School of Public Health, Peking University, Beijing 100191, China;

†These authors contributed equally to this work.

* Corresponding author.

Fengqiong Liu. E-mail address: <u>lfq@fjmu.edu.cn</u>

Zhijian Hu. E-mail address: huzhijian@fjmu.edu.cn

Shaodan Huang. E-mail address: shhuang@bjmu.edu.cn

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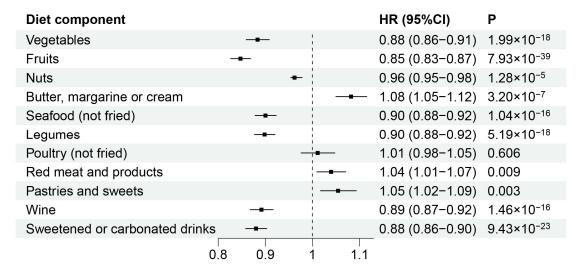
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Figure S5. Associations between the MEDAS and MIND scores, metabolites, and overall cancer risk (N=85,669).

Figure S6. Flowchart of the study

| Diet component | | | | HR (95%CI) | Р |
|---------------------------|-----|-----|---------------|------------------|------------------------|
| Green Leafy Vegetables | | | 1 | 0.88 (0.85-0.90) | 4.13×10 ⁻²⁰ |
| Other Vegetables | _ | - | 1 | 0.86 (0.84-0.89) | 2.06×10 ⁻²¹ |
| Berries | | | 1 | 0.87 (0.85-0.89) | 4.21×10 ⁻²³ |
| Nuts | | - | | 0.96 (0.93-0.99) | 0.006 |
| Butter, margarine or crea | m | | - | 1.12 (1.01-1.33) | 3.20×10 ⁻⁷ |
| Cheese | | | · | 1.04 (1.01-1.07) | 0.005 |
| Whole grains | | | 1 | 0.89 (0.85-0.93) | 8.90×10 ⁻⁷ |
| Seafood (not fried) | | | | 0.90 (0.88-0.92) | 8.99×10 ⁻¹⁷ |
| Legumes | | | 1 | 0.90 (0.87-0.92) | 2.44×10 ⁻¹⁸ |
| Poultry (not fried) | | | - | 1.02 (0.99-1.04) | 0.231 |
| Red meat and products | | | - | 1.04 (1.01-1.07) | 0.005 |
| Fast/fried foods | | | - | 1.05 (1.04-1.07) | 2.24×10 ⁻¹¹ |
| Pastries and sweets | | | · — | 1.07 (1.04-1.11) | 3.56×10 ⁻⁵ |
| Wine | | - | 1 | 0.87 (0.85-0.89) | 2.40×10 ⁻²³ |
| | 0.8 | 0.9 | 1 1.1 | | |

(a) Associations between diet components of MEDAS and overall cancer risk



(b) Associations between diet components of MIND and overall cancer risk

Figure S1. Associations between diet components of MEDAS and MIND and overall cancer risk (N=187,485)

HR: hazard ratio; CI: confidence interval. The HR and 95%CI were estimated using Cox regression with adjustment for covariates in model 3 (two-sided Wald test). The gray dashed line represents the null (HR = 1). Each point shows the point estimate of HR from cox regression. Bars show 95%CI. Diet components of these two scores were treated as continuous in the model. Source data are provided with this publication as a Source Data file.

| Subgroup | Diet Adherence | N | Incidence | P for interactio | on | HR (95%CI) |
|--------------------------------|----------------|--------|-----------|------------------|---------------------|---------------------|
| Sex | | | | | 1 | |
| Female | MEDAS score | 101709 | 12437 | 0.480 | - | 0.900 (0.878-0.923) |
| Male | MEDAS score | 85776 | 13954 | | | 0.884 (0.862-0.906) |
| Female | MIND score | 101709 | 12437 | 0.018 | - | 0.918 (0.898-0.938) |
| Male | MIND score | 85776 | 13954 | | - | 0.880 (0.862-0.897) |
| Completion of full-time educat | ion | | | | | |
| No | MEDAS score | 80992 | 10825 | 0.976 | | 0.894 (0.870-0.919) |
| Yes | MEDAS score | 106493 | 15566 | | - | 0.895 (0.874-0.916) |
| No | MIND score | 80992 | 10825 | 0.512 | - | 0.903 (0.882-0.924) |
| Yes | MIND score | 106493 | 15566 | | - | 0.896 (0.879-0.914) |
| Family history of cancer | | | | | | |
| No | MEDAS score | 138612 | 18667 | 0.451 | | 0.898 (0.879-0.917) |
| Yes | MEDAS score | 48873 | 7724 | | | 0.885 (0.856-0.914) |
| No | MIND score | 138612 | 18667 | 0.573 | - | 0.901 (0.886-0.918) |
| Yes | MIND score | 48873 | 7724 | | | 0.892 (0.868-0.917) |
| Smoking status | | | | | | |
| No | MEDAS score | 106872 | 13582 | 0.101 | | 0.877 (0.856-0.899) |
| Yes | MEDAS score | 80613 | 12809 | | | 0.902 (0.880-0.926) |
| No | MIND score | 106872 | 13582 | 0.489 | - | 0.890 (0.871-0.908) |
| Yes | MIND score | 80613 | 12809 | | - | 0.899 (0.880-0.918) |
| Alcohol drinking | | | | | | |
| No | MEDAS score | 11695 | 1511 | 0.165 | | 0.873 (0.806-0.946) |
| Yes | MEDAS score | 175790 | 24880 | | - | 0.897 (0.881-0.913) |
| No | MIND score | 11695 | 1511 | 0.861 | | 0.917 (0.859-0.979) |
| Yes | MIND score | 175790 | 24880 | | - | 0.899 (0.885-0.913) |
| ВМІ | | | | | | |
| <25 | MEDAS score | 69907 | 9092 | 0.200 | | 0.902 (0.875-0.929) |
| ≥25 | MEDAS score | 117578 | 17299 | | - | 0.885 (0.866-0.905) |
| <25 | MIND score | 69907 | 9092 | 0.131 | | 0.908 (0.886-0.932) |
| ≥25 | MIND score | 117578 | 17299 | | 0.8 0.85 0.9 0.95 1 | 0.889 (0.873-0.906) |

Figure S2. Associations between MEDAS and MIND scores and overall cancer risk stratified by basic characteristics (N=187,485)

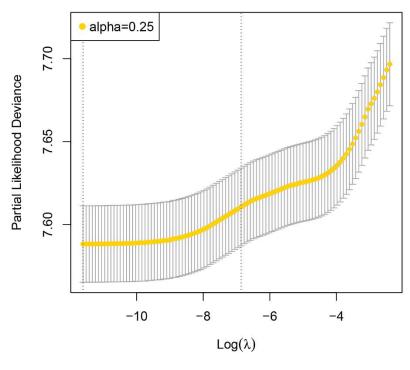
BMI body mass index; HR: hazard ratio; CI: confidence interval; MEDAS: mediterranean diet adherence screener; MIND: Mediterranean-DASH Diet Intervention for Neurodegenerative Delay. The HR and 95%CI were estimated using Cox regression, adjusting for covariates in model 3, and including the cross-product term of MEDAS (or MIND) and the basic characteristics in multivariable regressions (two-sided Wald test). The gray dashed line represents the null (HR = 1). Each blue point shows the point estimate of HR from cox regression. Bars show 95%CI. Source data are provided with this publication as a Source Data file



Figure S3. Associations between MEDAS and MIND scores and 22 specific types of cancer risk stratified by basic characteristics

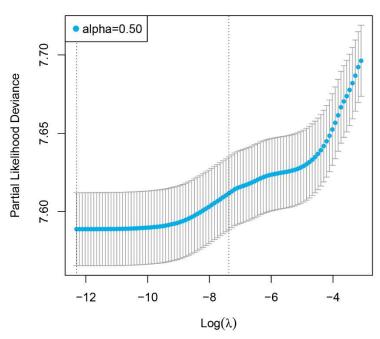
BMI: body mass index; HR: hazard ratio; CI: confidence interval; MEDAS: mediterranean diet adherence screener; MIND: Mediterranean-DASH Diet Intervention for Neurodegenerative Delay. The HR and 95%CI were estimated using Cox regression, adjusting for covariates in model 3, and including the cross-product term of MEDAS (or MIND) and the basic characteristics in multivariable regressions (two-sided Wald test). The green color indicates MEDAS score, while the orange color indicates MIND score. The green blue represents MEDAS score, and the orange blue represents MIND score. The red box represents statistically significant interactions between MEDAS (or MIND) and basic characteristics and the details results were shown in Table S9. The sample size of study populations for each specific types of cancer risk are as follows: Nhead and neck cancer=161440; Nesophagus cancer=161401; Nstomach cancer=; N_{colorectal cancer}=162960; N_{liver cancer}=161286; N_{gallbaldder cancer}=161196; N_{pancreas} cancer=161529; N_{lung cancer}=161094; N_{malignant melanoma}=162154; N_{breast cancer}=161094; N_{uterus} and cervix cancer=161417; Novary cancer=161424; Nprostate cancer=165267; Ntestis cancer=161137; N_{kidney cancer}=161596; N_{bladder cancer}=161466; N_{brain cancer}=161382; N_{thyroid cancer}=161230; Nhodgkin lymphoma=161135; Nnon-Hodgkin lymphoma=161879; Nmultiple myeloma=161457; $N_{leukemia}$ =161513. Source data are provided with this publication as a Source Data file.



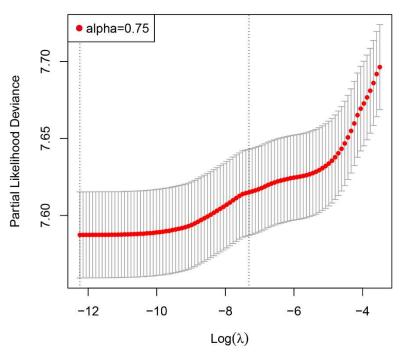


(a) Test α of 0.25 in ENM

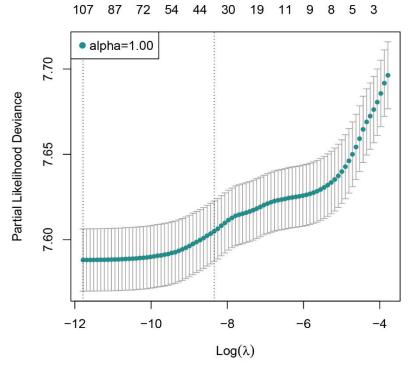




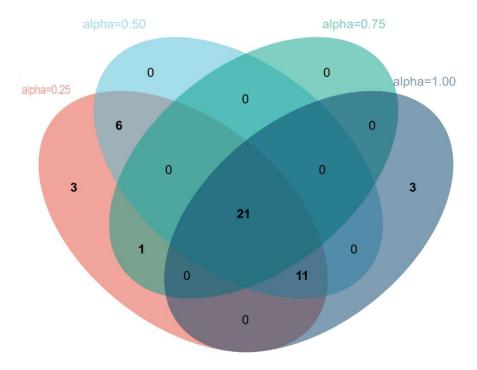
(b) Test α of 0.50 in ENM



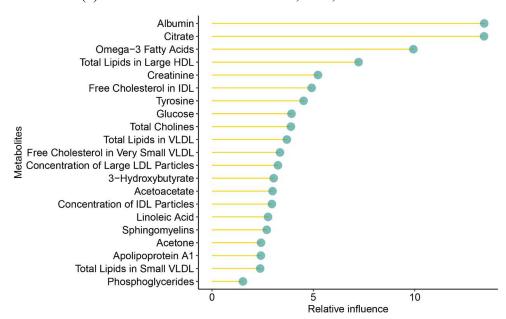
(c) Test α of 0.75 in ENM



(d) Test α of 1.00 in ENM



(e) Shared metabolites of α of 0.5, 0.75, and 1 in ENM

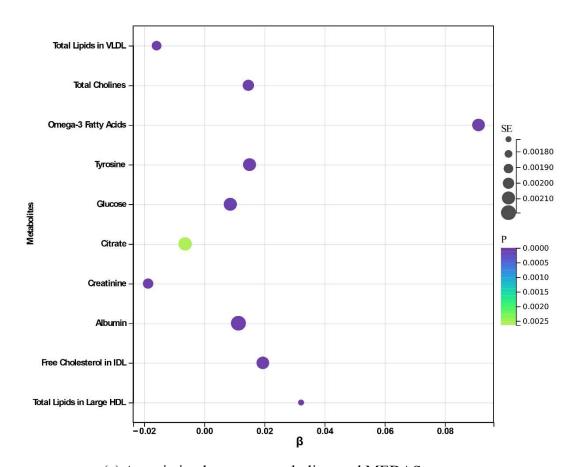


(f) The top 10 shared metabolites selected by gradient boosting trees

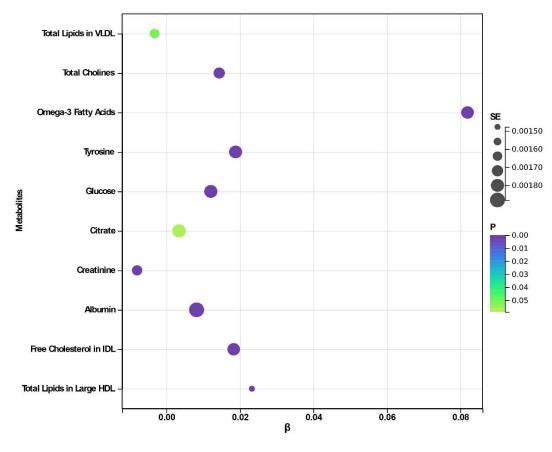
Figure S4. Selection of metabolites in in training set (N=121,382).

ENM: elastic net model. (a-d) 10-fold cross-validation ENM Cox regression models with α value of 0.25, 0.50, 0.75, and 1.00 were used to select metabolites. Metabolites with coefficients not equal to zero were selected. (e) Venn plot was used to visually display the shared metabolites with α values of 0.5, 0.75, and 1 in ENM (f) The Y-axis represents the shared metabolites with α values of 0.5, 0.75, and 1 in ENM, while the

X-axis represents the relative influence of 10-fold cross-validation gradient boosting trees using the Cox regression model as the underlying model. Source data are provided with this publication as a Source Data file.



(a) Association between metabolites and MEDAS score



(b) Association between metabolites and MIND score

| Diet Adherence | N | Inicidence | | | HR (95%CI) |
|-------------------------|-------|------------|-------------|---------|---------------------|
| MEDAS score | | | | 1 | |
| Tertile 1 (0 [<4]) | 32919 | 4167 | | • | |
| Tertile 2 (4 [<6]) | 25234 | 3328 | | 1 | 0.836 (0.802-0.871) |
| Tertile 3 (6 [≤11]) | 27516 | 3630 | | 1 | 0.818 (0.774-0.866) |
| Continuous | 85669 | 11125 | + | 1 | 0.944 (0.934-0.953) |
| MIND score | | | | 1 | |
| Tertile 1 (0 [<5.5]) | 14040 | 1430 | | ÷ | |
| Tertile 2 (5.5 [<7.0]) | 10698 | 1113 | | ; | 0.892 (0.852-0.934) |
| Tertile 3 (7.0 [≤13.5]) | 11163 | 1131 | | | 0.798 (0.763-0.836) |
| Continuous | 35901 | 3674 | 0.7 0.8 0.9 | 1.0 1.1 | 0.945 (0.934-0.956) |

(c) Associations between MEDAS and MIND score and overall cancer risk

| Metabolites | | | HR (95%CI) | P | FDR | |
|---------------------------|------------|--|---------------------|------------------------|------------------------|--|
| Total Lipids in VLDL | : | | 0.962 (0.941-0.982) | 3.40×10 ⁻⁴ | 3.78×10 ⁻⁴ | |
| Total Cholines | | | 0.922 (0.905-0.940) | 1.59×10 ⁻¹⁶ | 3.18×10 ⁻¹⁶ | |
| Omega-3 Fatty Acids | - ; | | 0.881 (0.864-0.898) | 5.35×10 ⁻³⁷ | 5.35×10 ⁻³⁶ | |
| Tyrosine | ; | | 0.925 (0.907-0.943) | 1.86×10 ⁻¹⁵ | 3.10×10 ⁻¹⁵ | |
| Glucose | ; | | 0.953 (0.935-0.970) | 3.06×10 ⁻⁷ | 3.83×10 ⁻⁷ | |
| Citrate | | | 0.906 (0.889-0.924) | 1.87×10 ⁻²³ | 6.43×10 ⁻²³ | |
| Creatinine | - i | | 0.971 (0.961-0.993) | 0.023 | 0.035 | |
| Albumin | i | | 1.060 (1.037-1.083) | 1.45×10 ⁻⁷ | 2.07×10 ⁻⁷ | |
| Free Cholesterol in IDL | - ; | | 0.904 (0.886-0.922) | 1.93×10 ⁻²³ | 6.43×10 ⁻²³ | |
| Total Lipids in Large HDL | | | 0.901 (0.880-0.922) | 2.86×10 ⁻¹⁸ | 7.15×10 ⁻¹⁸ | |
| 0.8 0.85 0.9 0.95 1 1.1 | | | | | | |

(d) Associations between metabolites and overall cancer risk

Figure S5. Associations between the MEDAS and MIND scores, metabolites, and overall cancer risk (N=85,669)

(a-b) SE: standard error. Multivariable linear regression was used to obtain the β coefficient and SE of the metabolites (two-sided Wald test). The Y-axis represents the metabolites, while the X-axis represents β coefficient of these metabolites. The point size represents the SE of these metabolites, the point color represents the p-value. (c) HR: hazard ratio; CI: confidence interval; MEDAS: mediterranean diet adherence screener; MIND: Mediterranean-DASH Diet Intervention for Neurodegenerative Delay. The HR and 95%CI were estimated using Cox regression with adjustment for covariates in model 3 (two-sided Wald test). Each point shows the point estimate of HR from cox regression. Bars show 95%CI. (d) FDR: false discovery rate. The HR and 95%CI of metabolites (treated as continuous in model) were estimated using Cox regression with

adjustment for covariates in model 3 . Each point shows the point estimate of HR from cox regression. Bars show 95%CI. FDR is an indicator used to adjust p-value and to control for false detective rate in multiple hypothesis testing. Associations were considered significant when FDR < 0.05 (two-sided Wald test). Source data are provided with this publication as a Source Data file.

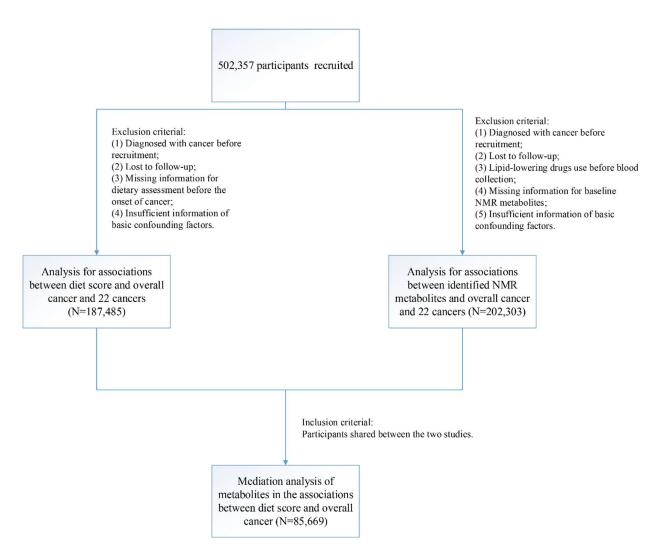


Figure S6. Flowchart of the study