

Supplemental Material

Gut microbiota-bile acid axis mediated the beneficial associations between dietary lignans and hyperuricemia: a prospective study

Lai-Bao Zhuo ^{1,#}, Yingdi Yang ^{1,#}, Congmei Xiao ^{2,3,#}, Fanqin Li ¹, Lishan Lin ¹,
Yue Xi ¹, Yuanqing Fu ^{2,3}, Ju-Sheng Zheng ^{2,*}, Yu-ming Chen ^{1,*}

¹ Department of Epidemiology, Guangdong Provincial Key Laboratory of Food,
Nutrition and Health, School of Public Health, Sun Yat-sen University, Guangzhou
510080, China;

² Zhejiang Key Laboratory of Multi-Omics in Infection and Immunity, School of
Medicine and School of Life Sciences, Westlake University, Hangzhou 310030,
China.

³ Shenzhen Bao'an Center for Chronic Diseases Control, Shenzhen, China

L.B. Z., Y. Y., and C. X. contributed equally to the work

Corresponding authors:

Yu-ming Chen, PhD, MD

Department of Epidemiology, School of Public Health, Sun Yat-sen University,
Guangzhou 510080, China. Tel: +8620 87330605. Email: chenyum@mail.sysu.edu.cn.

AND

Prof Ju-Sheng Zheng, PhD

Key Laboratory of Growth Regulation and Translational Research of Zhejiang
Province, School of Life Sciences, Westlake University, 18 Shilongshan Rd, Cloud

Town, Hangzhou, China. Tel: +86 (0)57186915303. Email:

23 zhengjusheng@westlake.edu.cn.

24 **CONTENTS**

25 **Part 1 Supplemental Methods**

26 **Part 2 Figures S1-S10:**

27 Fig. S1 Additional analysis of the relationship between dietary lignans intake and the
28 incidence of hyperuricemia

29 Fig. S2 Gut microbiota alpha-diversity by dietary lignans intake groups (high vs. low
30 intake)

31 Fig. S3 Gut microbiota beta-diversity by dietary lignans intake groups (high vs. low
32 intake)

33 Fig. S4 Differences in fecal metabolome composition

34 Fig. S5 Microbe risk score mediated the association of dietary lignans with uric acid

35 Fig. S6 Gut microbiota mediated the association of dietary matairesinol with uric acid

36 Fig. S7 Gut microbiota mediated the association of dietary pinoresinol with uric acid

37 Fig. S8 Gut microbiota mediated the association of dietary secoisolariciresinol with
38 uric acid

39 Fig. S9 Fecal bile acid mediated the association of dietary lignans with uric acid

40 Fig. S10 Gut microbiota-fecal bile acid axis mediated the association of dietary
41 lignans with uric acid

42 **Part 3 Tables S1-S8:**

43 Table S1 Characteristics of study participant

44 Table S2 The association of dietary lignans intake with hyperuricemia incidence

- 45 Table S3 MaAsLin identified gut microbes associated with hyperuricemia
- 46 Table S4 The association of microbe risk score with hyperuricemia
- 47 Table S5 The association of dietary lignans intake with gut microbes
- 48 Table S6 OPLS-DA identified fecal metabolites associated with hyperuricemia
- 49 Table S7 The association of bile acid risk score with hyperuricemia
- 50 Table S8 The association of dietary lignans intake with bile acids
- 51

52

Part 1 Supplemental Methods

53 **Quality control for metagenomic**

54 The microbial DNA extraction and shotgun metagenome sequencing were performed
55 at Novogene Company (Beijing, China). Post-sequencing, we obtained an average of
56 41.9 million paired-end raw reads per sample, with a range from 22.1 million to 65.2
57 million. We utilized PRINSEQ (version 0.20.447) to filter out low-quality reads
58 according to the following criteria: (1) trimming reads by quality score from the 5' and
59 3' ends with a quality threshold of 20; (2) removing read pairs if either read was less
60 than 60 bp, contained 'N' bases, or had an average quality score below 30; and (3)
61 deduplicating the reads. Additionally, reads that aligned to the human genome (H.
62 sapiens, UCSC hg19) were excluded using Bowtie2 (version 2.2.5) with the settings –
63 reorder –no-contain –dovetail. Batch effects were controlled by randomizing sample
64 processing between batches and using internal standards.

65 **Quality control for metabolomic**

66 Quality control samples, consisting of pooled samples, were analyzed every 14 samples
67 to maintain consistent analytical standards. Raw data generated by ultra-performance
68 liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) were processed
69 using QuanMET software (version 2.0, Metabo-Profile, Shanghai, China). This
70 software facilitated peak integration, calibration, and quantification of each metabolite.
71 Metabolomic features were annotated with a MSI level 1 confidence by comparing
72 them to the standards of targeted metabolites, ensuring high accuracy and reliability in
73 metabolite identification. Principal component analysis was used to assess batch effects

74 and outliers in metabolomic data. Data were normalized using the total peak area to
75 mitigate the impact of sample concentration variations.

76 **Risk scores construction:**

77 We calculated the MRS and BRS of each individual according to the following
78 formulas:

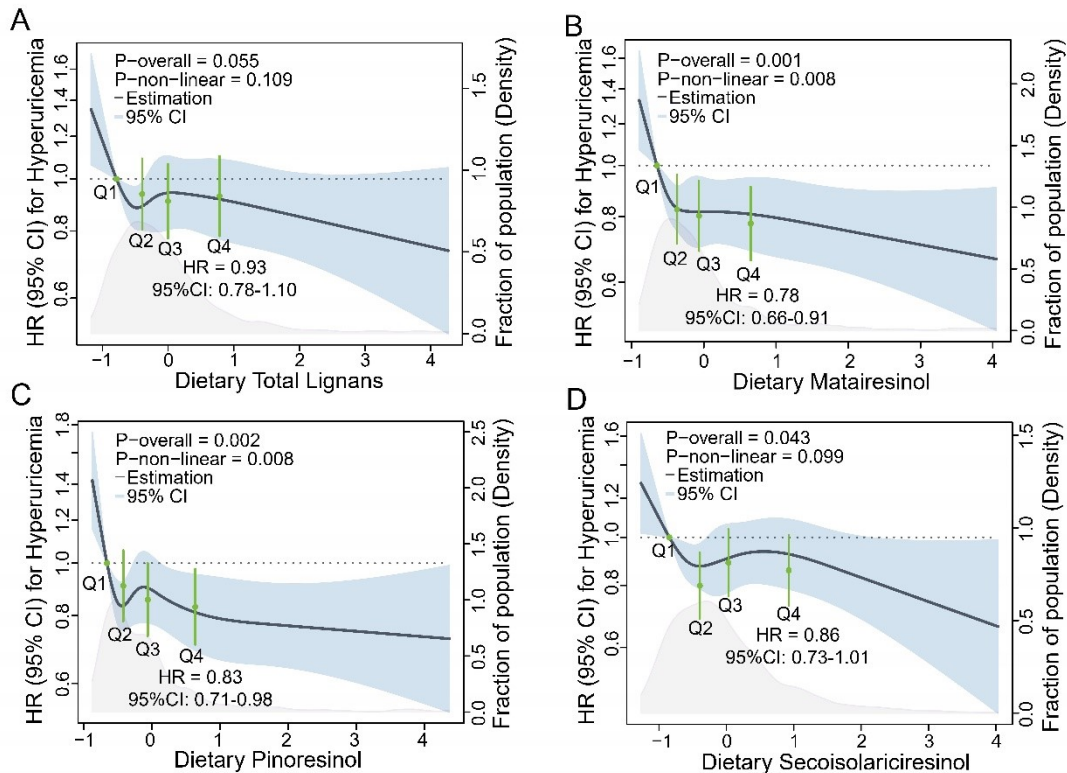
$$79 \quad MRS_i = \sum_{j=0}^m Microbe_{ij} direction_j$$

$$80 \quad BRS_i = \sum_{j=0}^n Fmet_{ij} direction_j$$

81 The individual is represented by i . The letters m and n represent the total numbers of
82 gut microbes and fecal bile acids, respectively. $Microbe_{ij}$ represents the relative
83 abundance of the j th gut microbiota for the i th individual. $Fmet_{ij}$ represents the
84 concentration of the j th fecal bile acid for the i th individual. $direction_j$ represents the
85 direction of association between the j th biomarker and hyperuricemia.

86

Part 2 Figures S1-S10



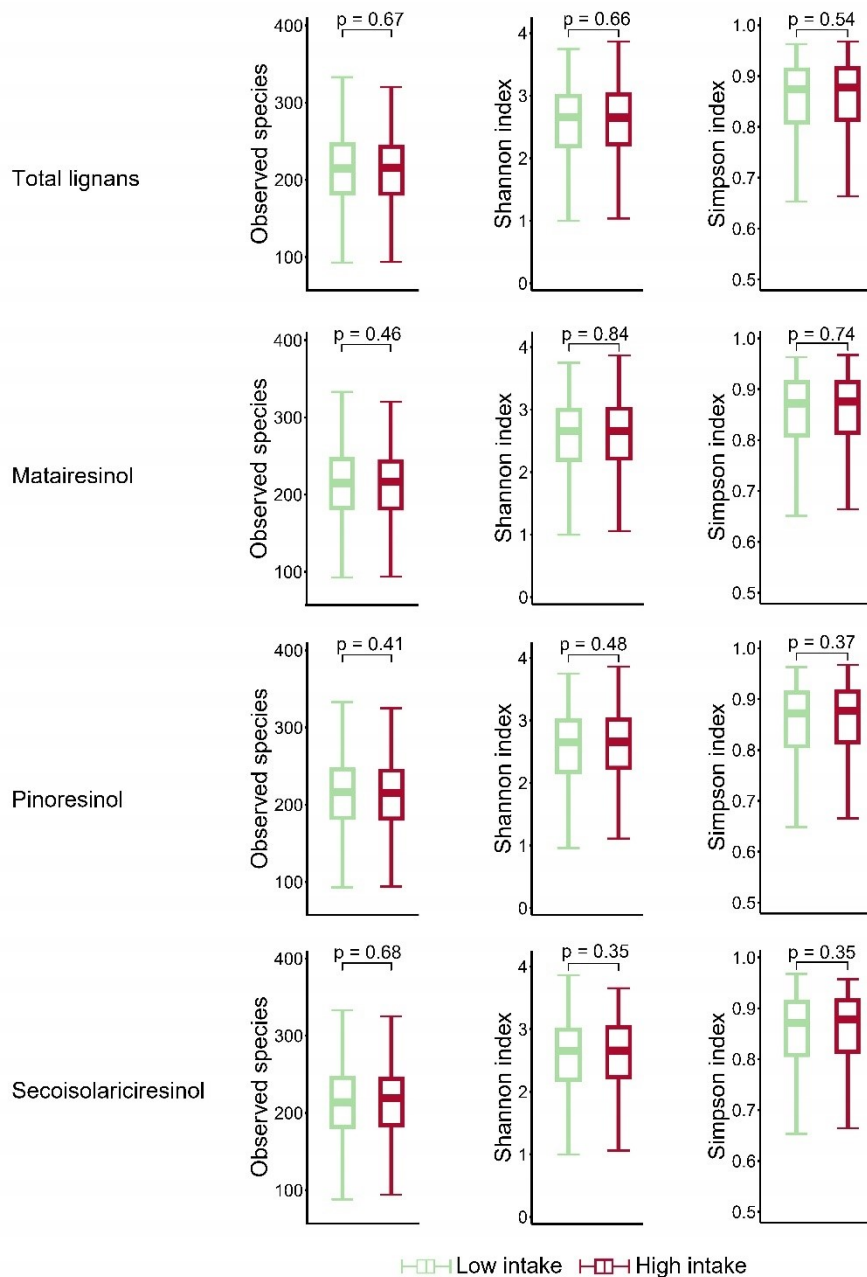
88

89 **Fig. S1 Additional analysis of the relationship between dietary lignans intake and**
 90 **the incidence of hyperuricemia** A-D, Hazard ratios (HRs) and 95% confidence
 91 intervals (CIs) for hyperuricemia by the dietary total lignans (A), matairesinol (B),
 92 pinoresinol (C), and secoisolariciresinol (D), respectively, based on Cox proportional
 93 hazards regression. Covariate adjustments: age, sex, BMI, education level, household
 94 average income, marital status, smoking status, drinking status, tea intake, physical
 95 activity, dietary energy intake, fruit intake, vegetable intake, fish intake, red meat
 96 intake, hypertension, type 2 diabetes, chronic kidney disease, and the use of
 97 antihypertensive and antidiabetic drugs. Blue lines and shaded blue areas represent HRs
 98 and 95% CIs. Gray shaded areas show dietary lignans intake density. Forest plots

99 indicate HRs and 95% CIs for the quartiles (Q) of dietary lignans intake using adjusted

100 Cox proportional hazards regression. HRs: Hazard ratios; CIs: confidence intervals.

101



102

103 **Fig. S2 Gut microbiota alpha-diversity by dietary lignans intake groups (high vs.**

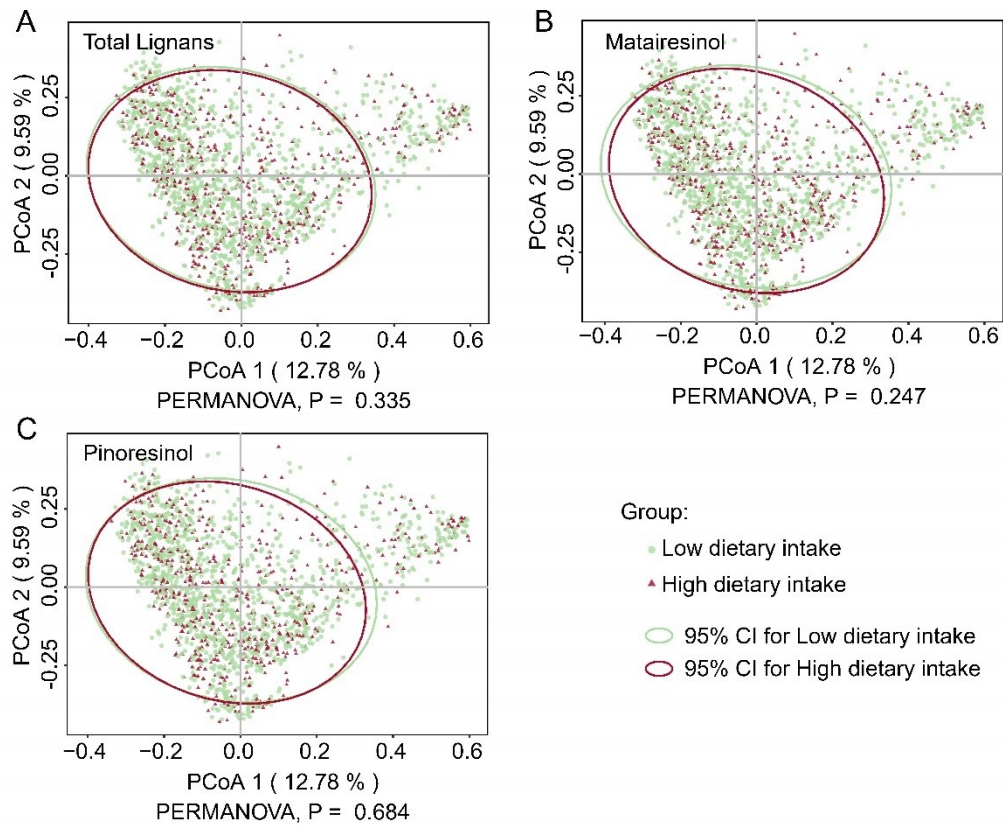
104 **low intake)** Boxplots of alpha diversity (Richness, Shannon, and Simpon index)

105 comparisons between high intake group and low intake group. The Wilcoxon rank-sum

106 test was conducted to compare differences in alpha diversity indices between two

107 groups. Participants were divided into two groups based on the upper tertile of dietary

108 lignan intake, distinguishing between high and low intake groups.



109

110 **Fig. S3 Gut microbiota beta-diversity by dietary lignans intake groups (high vs.**

111 **low intake) A-C, β -diversity by the dietary total lignans groups (A), matairesinol**

112 **groups (B), pinoresinol groups (C). β -diversity was evaluated using a principal**

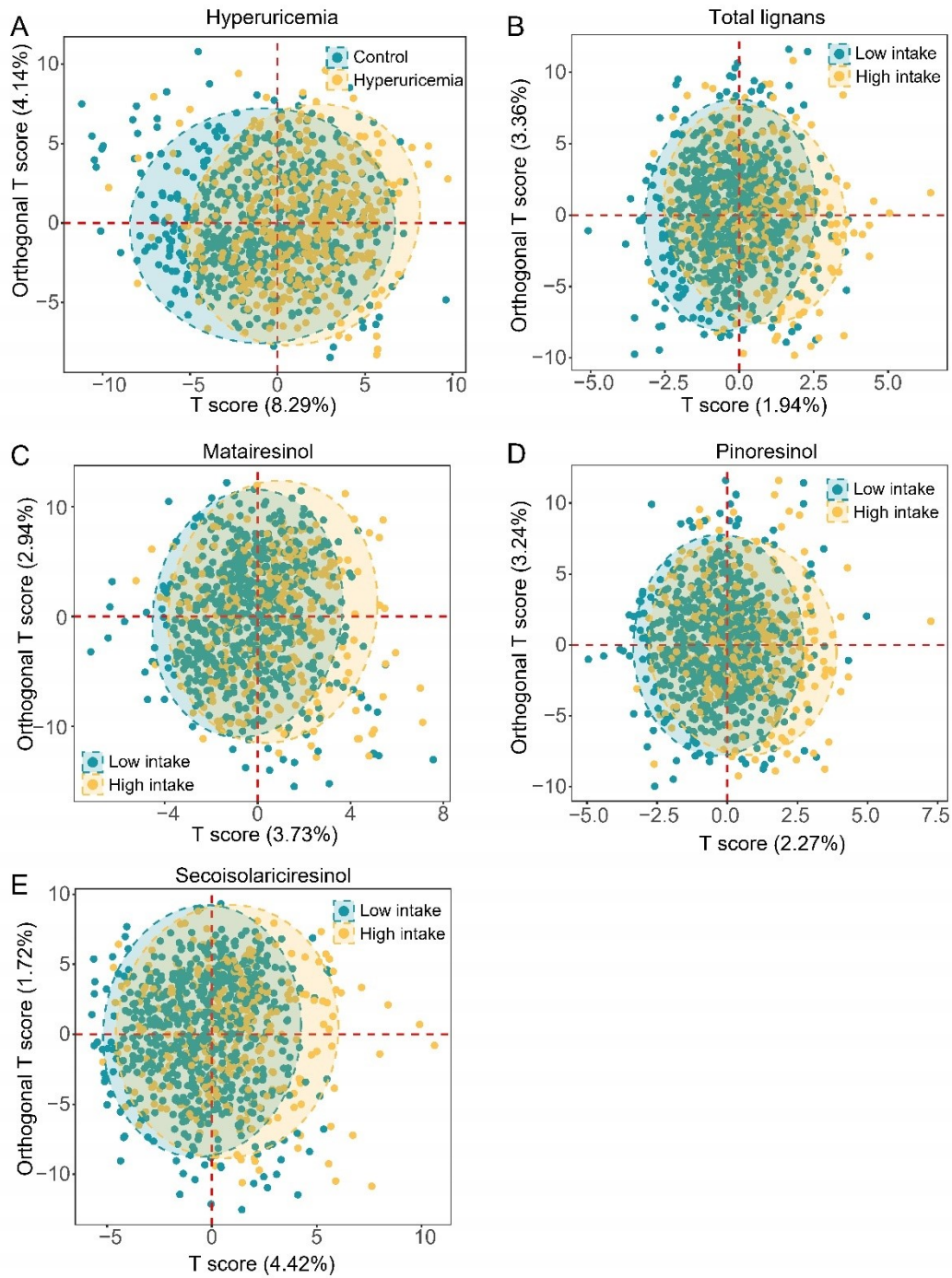
113 **coordinate analysis plot based on Bray-Cutis distance at the species level.**

114 **Permutational ANOVA (999 permutations) was used to identify the variation in β -**

115 **diversity in the human gut microbiota structure by dietary lignans intake groups (high**

116 **vs. low intake).**

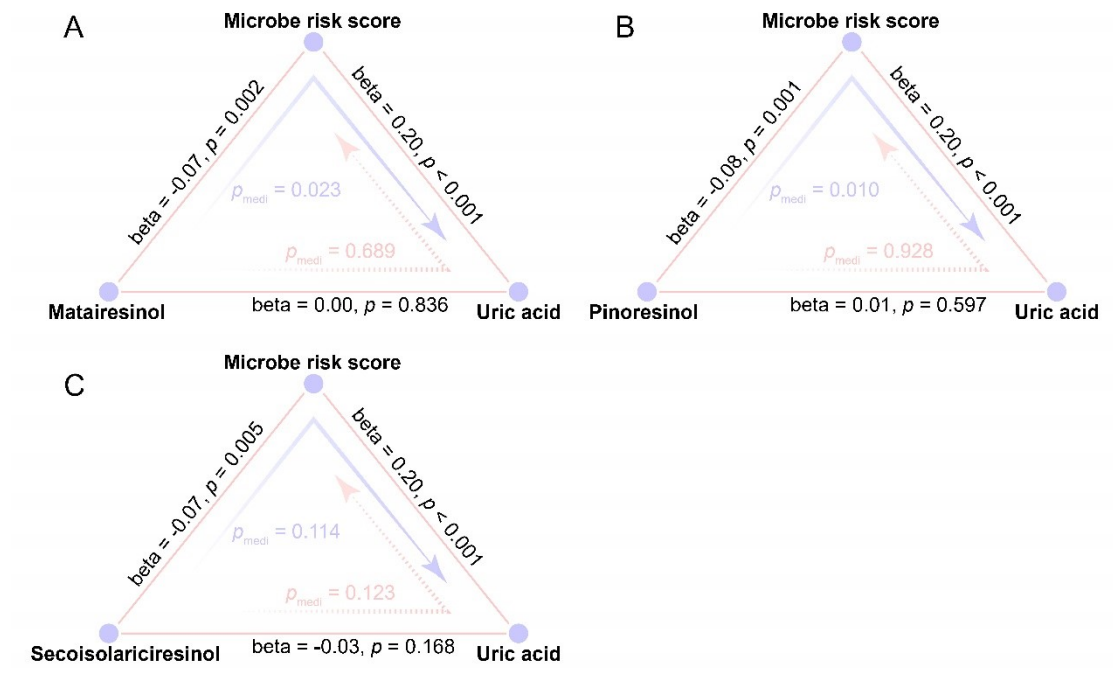
117



118

119 **Fig. S4 Differences in fecal metabolome composition A-E**, Differences in fecal
 120 metabolome composition by hyperuricemia groups (hyperuricemia vs. control, **A**),
 121 dietary total lignans groups (high vs. low intake, **B**), matairesinol groups (**C**),
 122 pinoresinol groups (**D**), and secoisolariciresinol groups (**E**).

123

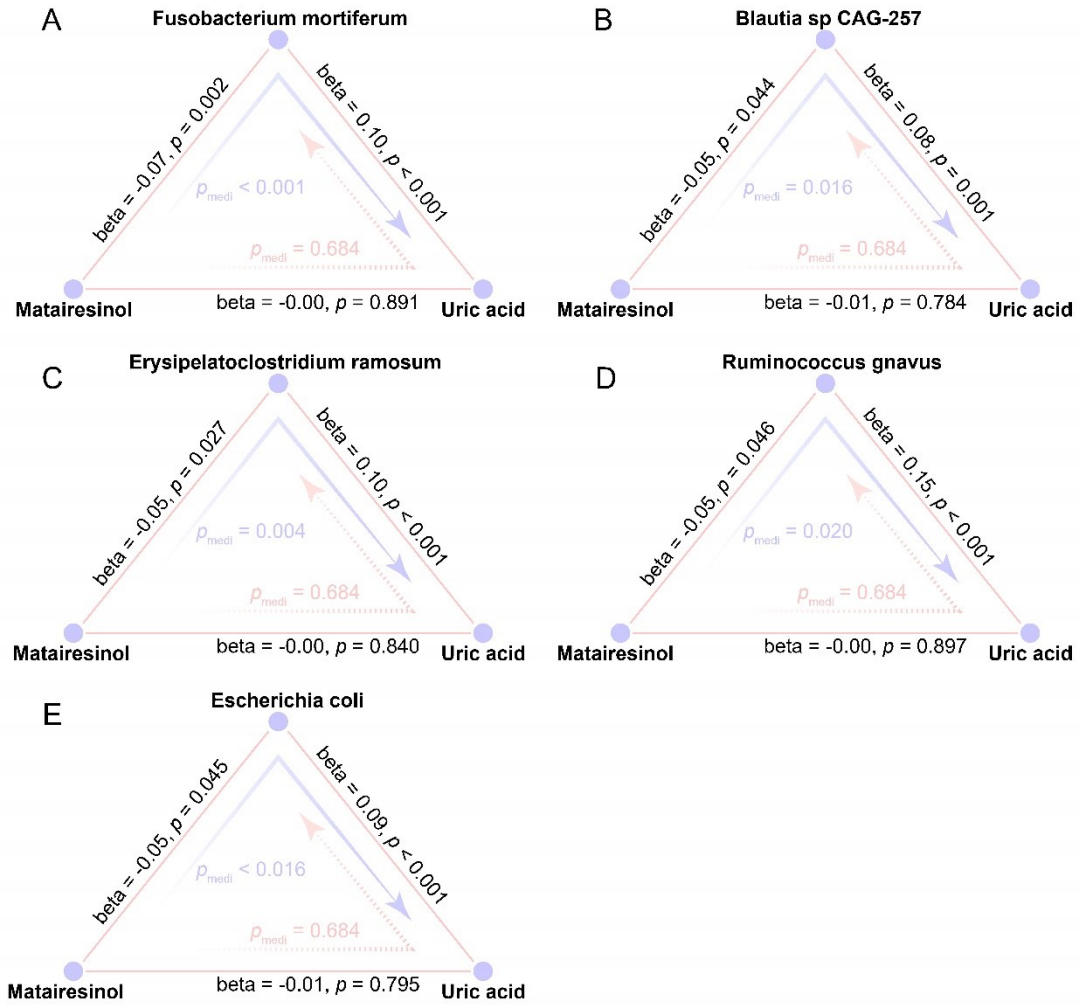


124

125 **Fig. S5 Microbe risk score mediated the association of dietary lignans with uric**

126 **acid.** Diagrams display standardized regression weights.

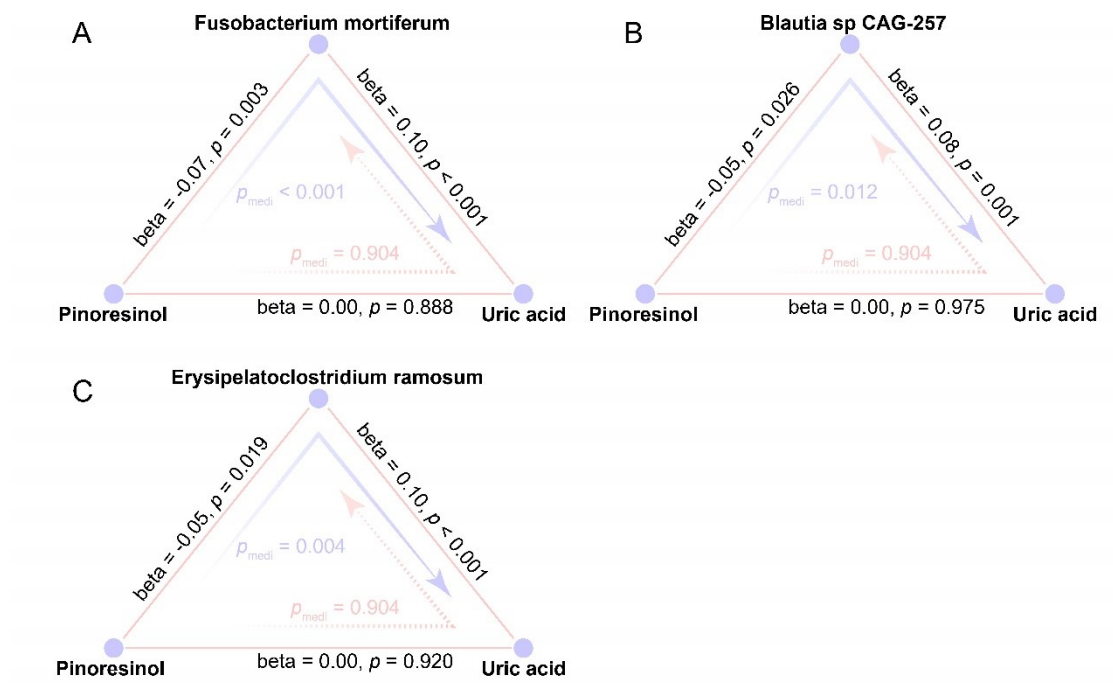
127



128

129 **Fig. S6 Gut microbiota mediated the association of dietary matairesinol with uric**
 130 **acid.** Diagrams display standardized regression weights.

131

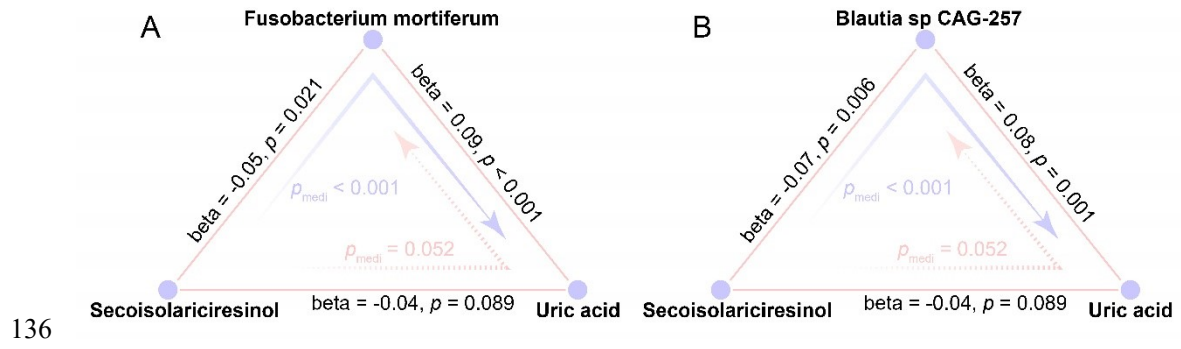


132

133 **Fig. S7 Gut microbiota mediated the association of dietary pinoreosinol with uric**

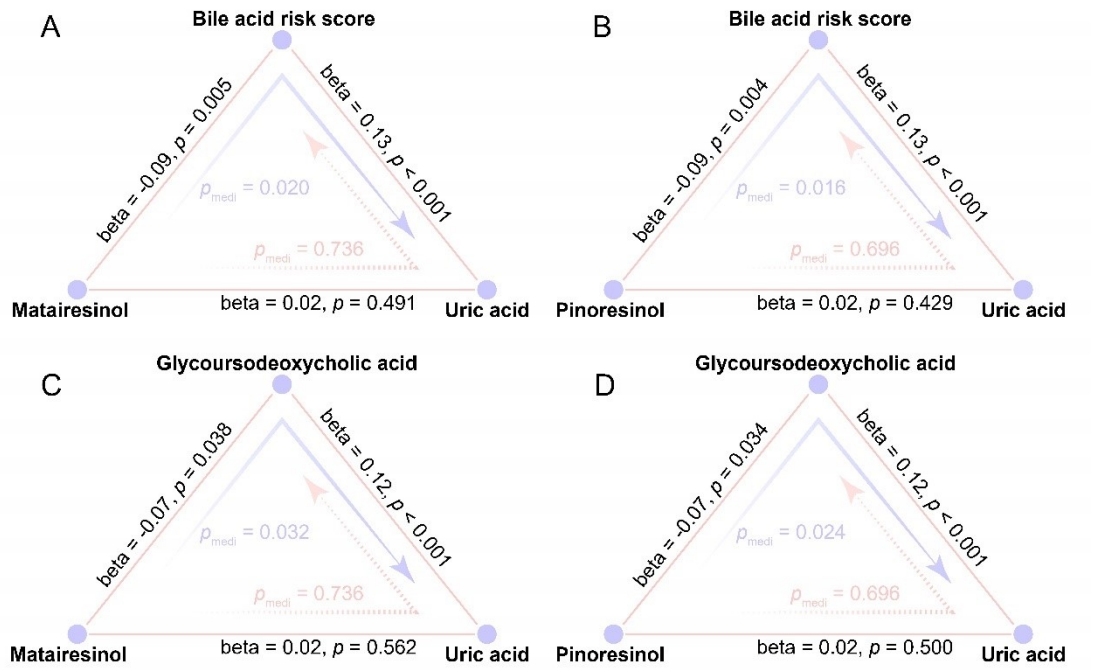
134 **acid.** Diagrams display standardized regression weights.

135



136
 137 **Fig. S8 Gut microbiota mediated the association of dietary secoisolariciresinol**
 138 **with uric acid.** Diagrams display standardized regression weights.

139

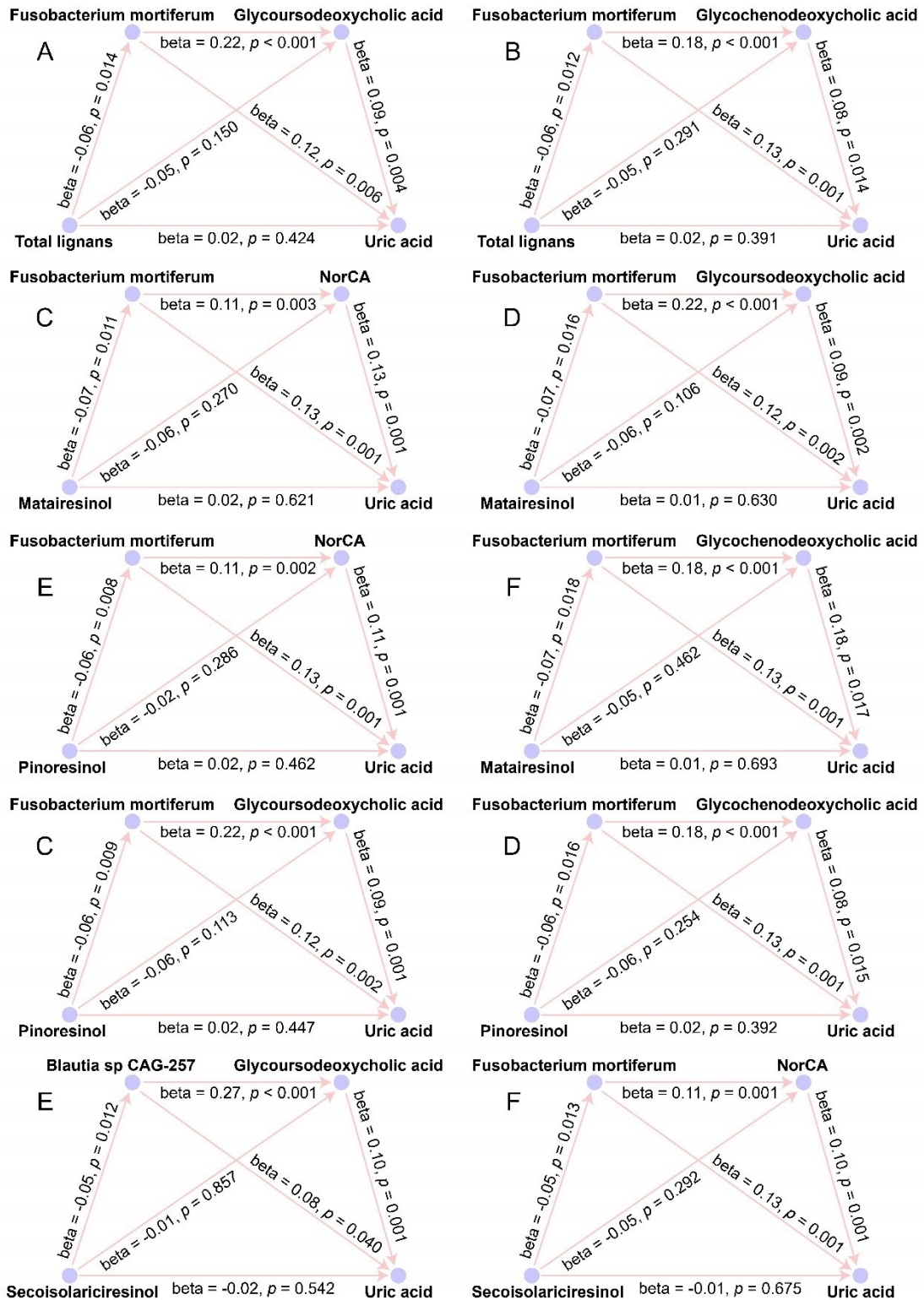


140

141 **Fig. S9 Fecal bile acid mediated the association of dietary lignans with uric acid.**

142 Diagrams display standardized regression weights.

143



144

145 **Fig. S10** Gut microbiota-fecal bile acid axis mediated the association of dietary
 146 lignans with uric acid. Diagrams display standardized regression weights.

147

Part 3 Tables S1-S8

Table S1 Characteristics of study participants

	Low intake N = 2509	High intake N = 1292	<i>p</i> value
Matairesinol ($\mu\text{g/d}$) *	3.60 (2.54, 4.82)	8.20 (6.19, 11.1)	<0.001
Pinoresinol ($\mu\text{g/d}$) *	154 (103, 222)	412 (312, 577)	<0.001
Secoisolariciresinol ($\mu\text{g/d}$) *	49.3 (37.0, 63.6)	92.2 (74.6, 120)	<0.001
Total lignans ($\mu\text{g/d}$) *	414 (314, 513)	826 (709, 1063)	<0.001
Uric acid ($\mu\text{mol/L}$)	307 (102)	291 (95.0)	<0.001
Sex			0.121
Female	1690 (67.4%)	903 (69.9%)	
Male	819 (32.6%)	389 (30.1%)	
Age (years)	58.7 (6.33)	58.3 (6.10)	0.051
Marital status			0.677
Having a partner	2261 (90.1%)	1158 (89.6%)	
Living alone	248 (9.88%)	134 (10.4%)	
Education			<0.001
Low	826 (32.9%)	345 (26.7%)	
Medium	1103 (44.0%)	599 (46.4%)	
High	580 (23.1%)	348 (26.9%)	
Income			0.068
Low	1255 (50.0%)	604 (46.7%)	
Medium	622 (24.8%)	320 (24.8%)	
High	632 (25.2%)	368 (28.5%)	
Smoking			0.781
No	2096 (83.5%)	1074 (83.1%)	
Yes	413 (16.5%)	218 (16.9%)	
Drinking			0.499
No	2337 (93.1%)	1195 (92.5%)	
Yes	172 (6.86%)	97 (7.51%)	
Tea intake			0.646
No	1177 (46.9%)	617 (47.8%)	
Yes	1332 (53.1%)	675 (52.2%)	
BMI (kg/m^2)	23.3 (3.12)	23.5 (3.19)	0.124
Physical activity (MET-h/d)	40.5 (14.5)	41.8 (14.9)	0.008
Total energy intake (kcal/d)	1606 (455)	2139 (699)	<0.001
Red meat intake (g/d) *	65.0 (43.1, 104)	81.2 (53.4, 122)	<0.001
Fish intake (g/d) *	37.0 (21.1, 60.2)	50.9 (30.0, 83.6)	<0.001
Vegetable intake (g/d) *	292 (218, 378)	489 (374, 606)	<0.001
Fruit intake (g/d) *	105 (58.7, 167)	165 (102, 246)	<0.001

150 Participants were divided into two groups based on the upper tertile of dietary lignan
151 intake, distinguishing between high and low intake groups. Continuous variables with
152 normal distribution were presented as means (standard deviations), and statistical

153 differences between groups were assessed using t-tests. Conversely, continuous
154 variables with non-normal distribution (marked with *) were expressed as medians
155 (interquartile ranges), with statistical differences between groups evaluated using
156 Wilcoxon rank-sum test. Differences in population characteristics between two groups
157 were examined by chi-square test for categorical variables. BMI: body mass index.
158

159 Table S2 the association of dietary lignans intake with hyperuricemia incidence

Dietary lignans	HRs	Lower CI	Upper CI
Total lignans			
Q1	1		
Q2	0.94	0.80	1.09
Q3	0.91	0.77	1.07
Q4	0.93	0.78	1.10
Matairesinol			
Q1	1		
Q2	0.82	0.71	0.96
Q3	0.80	0.69	0.93
Q4	0.77	0.66	0.90
Pinoresinol			
Q1	1		
Q2	0.91	0.78	1.06
Q3	0.85	0.73	1.00
Q4	0.83	0.70	0.97
Secoisolariciresinol			
Q1	1		
Q2	0.80	0.69	0.94
Q3	0.89	0.76	1.04
Q4	0.85	0.73	1.00
Lariciresinol			
Q1	1		
Q2	1.05	0.89	1.22
Q3	1.11	0.94	1.31
Q4	1.17	0.96	1.42

160 Hazard ratios (HRs) and 95% confidence intervals (CIs) for hyperuricemia incidence
 161 by the quartiles of the dietary total lignans, matairesinol, pinoresinol,
 162 secoisolariciresinol, and lariciresinol, respectively, based on Cox proportional hazards
 163 regression. Covariate adjustments: age, sex, BMI, education level, household average
 164 income, marital status, smoking status, drinking status, tea intake, physical activity,
 165 dietary energy intake, fruit intake, vegetable intake, fish intake, and red meat intake.
 166 HRs: Hazard ratios; CIs: confidence intervals.

167

Table S3 MaAsLin identified gut microbes associated with hyperuricemia

Gut microbes	coef	pval	qval
s__Oscillibacter_sp_57_20	-0.013	< 0.001	< 0.001
s__Ruminococcus_gnavus	0.028	< 0.001	< 0.001
s__Eubacterium_siraeum	-0.019	< 0.001	< 0.001
s__Odoribacter_splanchnicus	-0.007	< 0.001	< 0.001
s__Oscillibacter_sp_CAG_241	-0.006	< 0.001	< 0.001
s__Firmicutes_bacterium_CAG_83	-0.012	< 0.001	< 0.001
s__Butyricimonas_virosa	-0.005	< 0.001	< 0.001
s__Alistipes_shahii	-0.009	< 0.001	< 0.001
s__Ruminococcus_bicirculans	-0.010	< 0.001	0.001
s__Catabacter_hongkongensis	-0.002	< 0.001	0.003
s__Roseburia_hominis	-0.014	< 0.001	0.003
s__Christensenella_minuta	-0.002	< 0.001	0.003
s__Alistipes_indistinctus	-0.006	< 0.001	0.003
s__Faecalibacterium_prausnitzii	-0.021	< 0.001	0.003
s__Firmicutes_bacterium_CAG_110	-0.005	< 0.001	0.003
s__Prevotella_copri	-0.038	0.001	0.010
s__Alistipes_finegoldii	-0.010	0.001	0.010
s__Anaerotruncus_colihominis	-0.003	0.001	0.011
s__Escherichia_coli	0.043	0.001	0.011
s__Alistipes_putredinis	-0.023	0.002	0.012
s__Firmicutes_bacterium_CAG_95	-0.002	0.002	0.012
s__Megamonas_hypermegale	0.006	0.002	0.013
s__Actinomyces_sp_ICM47	0.002	0.002	0.014
s__Fusicatenibacter_saccharivorans	-0.011	0.002	0.014
s__Butyricimonas_synergistica	-0.001	0.003	0.020
s__Intestinimonas_butyriciproducens	-0.003	0.003	0.020
s__Lawsonibacter_asaccharolyticus	-0.002	0.003	0.020
s__Desulfovibrio_piger	-0.006	0.003	0.020
s__Clostridium_clostridioforme	0.004	0.004	0.022
s__Bifidobacterium_adolescentis	-0.014	0.005	0.024
s__Barnesiella_intestinihominis	-0.006	0.005	0.024
s__Blautia_hansenii	0.004	0.005	0.024
s__Clostridium_bolteae	0.005	0.005	0.024
s__Clostridium_sp_CAG_299	0.005	0.006	0.030
s__Fusobacterium_mortiferum	0.003	0.008	0.038
s__Eubacterium_eligens	-0.009	0.008	0.038
s__Parabacteroides_goldsteinii	-0.002	0.012	0.053
s__Ruminococcus_callidus	-0.001	0.013	0.055
s__Collinsella_stercoris	0.003	0.013	0.056
s__Bacteroides_cellulosilyticus	-0.004	0.013	0.056
s__Anaeromassilibacillus_sp_An250	-0.001	0.015	0.059
s__Phascolarctobacterium_sp_CAG_266	-0.004	0.015	0.059

Gut microbes	coef	pval	qval
s__Clostridium_lavalense	0.001	0.018	0.066
s__Oxalobacter_formigenes	-0.002	0.018	0.066
s__Gemmiger_formicilis	-0.005	0.020	0.075
s__Blautia_obeum	-0.004	0.023	0.082
s__Blautia_sp_CAG_257	0.004	0.023	0.082
s__Bacteroides_fragilis	0.010	0.024	0.082
s__Actinomyces_sp_oral_taxon_181	0.001	0.026	0.089
s__Ruthenibacterium_lactatiformans	-0.006	0.029	0.095
s__Ruminococcus_lactaris	-0.004	0.030	0.098
s__Veillonella_parvula	0.005	0.031	0.098
s__Bacteroides_finegoldii	-0.003	0.034	0.106
s__Citrobacter_youngae	-0.002	0.037	0.113
s__Bacteroides_caccae	-0.006	0.038	0.114
s__Bacteroides_uniformis	-0.017	0.041	0.117
s__Parabacteroides_merdae	-0.006	0.040	0.117
s__Gemella_sanguinis	0.001	0.041	0.117
s__Eisenbergiella_tayi	-0.001	0.043	0.121
s__Clostridium_leptum	-0.002	0.048	0.133
s__Holdemania_filiformis	-0.002	0.049	0.133
s__Clostridium_bolteae_CAG_59	0.001	0.051	0.135
s__Streptococcus_gordonii	0.001	0.054	0.141
s__Clostridium_aldenense	0.001	0.057	0.148
s__Asaccharobacter_celatus	-0.001	0.059	0.149
s__Coproccoccus_catus	-0.002	0.060	0.149
s__Megamonas_funiformis	0.006	0.063	0.156
s__Bacteroides_sp_OM05_12	-0.002	0.064	0.156
s__Ruminococcus_bromii	0.013	0.066	0.156
s__Veillonella_atypica	0.002	0.066	0.156
s__Klebsiella_quasipneumoniae	0.005	0.067	0.156
s__Bacteroides_intestinalis	-0.004	0.069	0.156
s__Veillonella_sp_T11011_6	0.001	0.069	0.156
s__Streptococcus_mitis	0.002	0.070	0.156
s__Adlercreutzia_equolifaciens	-0.002	0.079	0.173
s__Collinsella_intestinalis	0.004	0.080	0.174
s__Veillonella_dispar	0.001	0.082	0.176
s__Eubacterium_rectale	-0.011	0.088	0.186
s__Clostridium_sp_CAG_242	-0.002	0.093	0.195
s__Erysipelatoclostridium_ramosum	0.004	0.097	0.199
s__Parasutterella_excrementihominis	-0.003	0.100	0.203
s__Intestinibacter_bartlettii	0.001	0.114	0.229
s__Bacteroides_coprocola	-0.005	0.120	0.239
s__Akkermansia_muciniphila	-0.007	0.122	0.240
s__Coproccoccus_eutactus	-0.004	0.128	0.248

Gut microbes	coef	pval	qval
s_Klebsiella_pneumoniae	0.010	0.147	0.282
s_Bacteroides_coprophilus	-0.002	0.157	0.290
s_Bacteroides_stercoris	-0.009	0.153	0.290
s_Parabacteroides_distasonis	0.005	0.156	0.290
s_Bacteroides_clarus	0.002	0.164	0.296
s_Tyzzarella_nexilis	0.002	0.162	0.296
s_Coprococcus_comes	-0.004	0.170	0.301
s_Klebsiella_variicola	0.005	0.169	0.301
s_Streptococcus_salivarius	-0.005	0.180	0.317
s_Eggerthella_lenta	0.003	0.192	0.326
s_Bacteroides_dorei	-0.008	0.191	0.326
s_Streptococcus_cristatus	0.001	0.189	0.326
s_Roseburia_faecis	-0.006	0.205	0.345
s_Bacteroides_massiliensis	-0.003	0.225	0.362
s_Streptococcus_sanguinis	0.001	0.220	0.362
s_Streptococcus_thermophilus	-0.002	0.218	0.362
s_Dorea_formicigenerans	-0.003	0.226	0.362
s_Veillonella_infantium	0.001	0.226	0.362
s_Bacteroides_ovatus	-0.005	0.237	0.376
s_Eubacterium_sp_CAG_274	0.002	0.244	0.383
s_Gordonibacter_pamelaeae	-0.001	0.263	0.410
s_Hungatella_hathewayi	0.001	0.275	0.424
s_Roseburia_inulinivorans	0.005	0.279	0.426
s_Bifidobacterium_longum	0.006	0.290	0.437
s_Clostridium_innocuum	0.001	0.291	0.437
s_Eubacterium_sp_CAG_251	-0.003	0.302	0.444
s_Anaerostipes_hadrus	-0.004	0.300	0.444
s_Proteobacteria_bacterium_CAG_139	-0.001	0.326	0.476
s_Eubacterium_ventriosum	-0.001	0.329	0.477
s_Lachnospira_pectinoschiza	0.002	0.338	0.481
s_Roseburia_intestinalis	0.003	0.337	0.481
s_Bifidobacterium_dentium	0.001	0.372	0.511
s_Enorma_massiliensis	-0.001	0.371	0.511
s_Paraprevotella_xylaniphila	-0.001	0.365	0.511
s_Eubacterium_sp_CAG_38	0.003	0.370	0.511
s_Olsenella_scatoligenes	-0.002	0.386	0.526
s_Agathobaculum_butyriciproducens	0.002	0.391	0.529
s_Cloacibacillus_porcorum	0.000	0.395	0.530
s_Collinsella_aerofaciens	-0.005	0.402	0.535
s_Streptococcus_oralis	0.001	0.417	0.550
s_Holdemanella_biformis	-0.001	0.420	0.550
s_Bacteroides_thetaiotaomicron	-0.003	0.425	0.552
s_Clostridium_sp_CAG_58	-0.001	0.429	0.552

Gut microbes	coef	pval	qval
s__Sutterella_parvirubra	-0.001	0.435	0.557
s__Allisonella_histaminiformans	0.000	0.448	0.568
s__Bacteroides_plebeius	0.006	0.464	0.581
s__Streptococcus_vestibularis	0.000	0.464	0.581
s__Haemophilus_parainfluenzae	0.001	0.477	0.591
s__Bifidobacterium_bifidum	-0.002	0.483	0.592
s__Clostridium_citroniae	0.001	0.484	0.592
s__Actinomyces_sp_S6_Spd3	0.000	0.555	0.673
s__Streptococcus_australis	0.000	0.573	0.677
s__Streptococcus_parasanguinis	0.001	0.575	0.677
s__Flavonifractor_plautii	-0.002	0.574	0.677
s__Phascolarctobacterium_faecium	-0.002	0.571	0.677
s__Clostridium_symbiosum	0.001	0.587	0.686
s__Clostridium_saccharolyticum	0.000	0.626	0.727
s__Rothia_mucilaginosa	-0.001	0.635	0.733
s__Dialister_sp_CAG_357	-0.003	0.648	0.742
s__Eisenbergiella_massiliensis	0.000	0.654	0.744
s__Bifidobacterium_pseudocatenulatum	0.003	0.669	0.756
s__Sellimonas_intestinalis	0.000	0.674	0.757
s__Megasphaera_elsdenii	0.001	0.686	0.765
s__Eubacterium_ramulus	-0.001	0.704	0.780
s__Blautia_wexlerae	-0.001	0.721	0.794
s__Bilophila_wadsworthia	0.000	0.727	0.794
s__Streptococcus_anginosus_group	0.000	0.750	0.811
s__Eubacterium_limosum	0.000	0.752	0.811
s__Actinomyces_odontolyticus	0.000	0.810	0.868
s__Bacteroides_salyersiae	0.000	0.856	0.906
s__Bacteroides_xylanisolvans	-0.001	0.853	0.906
s__Dorea_longicatena	0.000	0.876	0.921
s__Bacteroides_eggerthii	0.000	0.909	0.948
s__Clostridium_asparagiforme	0.000	0.913	0.948
s__Ruminococcus_torques	0.000	0.921	0.950
s__Bacteroides_vulgatus	-0.001	0.950	0.963
s__Streptococcus_infantis	0.000	0.947	0.963
s__Eubacterium_sp_CAG_180	0.000	0.952	0.963
s__Eubacterium_hallii	0.000	0.991	0.994
s__Enterobacter_cloacae_complex	0.000	0.994	0.994

169 MaAsLin identified gut microbes associated with hyperuricemia. Threshold was set as

170 $q < 0.25$.

171

172

Table S4 The association of microbe risk score with hyperuricemia

	ORs	Lower CI	Upper CI
Microbe risk score			
Q1	1		
Q2	1.295	0.974	1.721
Q3	1.448	1.091	1.922
Q4	2.623	1.976	3.482

173 Odds ratios (ORs) and 95% confidence intervals (CIs) for hyperuricemia by the
 174 quartiles of the microbe risk score, based on Cox proportional hazards regression.
 175 Covariate adjustments: age, sex, BMI, education level, household average income,
 176 marital status, smoking status, drinking status, tea intake, physical activity, dietary
 177 energy intake, fruit intake, vegetable intake, fish intake, and red meat intake. ORs: Odds
 178 ratios; CIs: confidence intervals.

179

Table S5 The association of dietary lignans intake with gut microbes

	beta	2.5%	97.5%	p value
Total lignans				
s__Fusobacterium_mortiferum	-0.08	-0.13	-0.03	0.001
s__Blautia_sp_CAG_257	-0.07	-0.11	-0.02	0.004
s__Erysipelatoclostridium_amosum	-0.07	-0.11	-0.02	0.006
s__Blautia_hansenii	-0.05	-0.09	0.00	0.045
s__Ruminococcus_gnavus	-0.04	-0.09	0.00	0.077
s__Escherichia_coli	-0.04	-0.08	0.01	0.135
s__Akkermansia_muciniphila	0.02	-0.03	0.07	0.375
s__Alistipes_finegoldii	0.05	0.00	0.09	0.049
s__Barnesiella_intestinihominis	0.05	0.00	0.09	0.046
s__Eubacterium_siraeum	0.05	0.00	0.10	0.033
Microbe risk score	-0.09	-0.14	-0.05	< 0.001
Matairesinol				
s__Fusobacterium_mortiferum	-0.08	-0.13	-0.03	0.001
s__Blautia_sp_CAG_257	-0.05	-0.10	-0.01	0.024
s__Erysipelatoclostridium_amosum	-0.06	-0.10	-0.01	0.017
s__Blautia_hansenii	-0.04	-0.09	0.00	0.067
s__Ruminococcus_gnavus	-0.05	-0.10	-0.01	0.027
s__Escherichia_coli	-0.05	-0.10	-0.01	0.029
s__Akkermansia_muciniphila	0.01	-0.04	0.06	0.696
s__Alistipes_finegoldii	0.03	-0.02	0.07	0.287
s__Barnesiella_intestinihominis	0.03	-0.01	0.08	0.141
s__Eubacterium_siraeum	0.04	-0.01	0.09	0.090
Microbe risk score	-0.08	-0.13	-0.04	< 0.001
Pinoresinol				
s__Fusobacterium_mortiferum	-0.08	-0.12	-0.03	0.001
s__Blautia_sp_CAG_257	-0.06	-0.10	-0.01	0.015
s__Erysipelatoclostridium_amosum	-0.06	-0.10	-0.01	0.018
s__Blautia_hansenii	-0.04	-0.08	0.01	0.117
s__Ruminococcus_gnavus	-0.04	-0.09	0.00	0.063
s__Escherichia_coli	-0.04	-0.09	0.01	0.097
s__Akkermansia_muciniphila	0.02	-0.03	0.06	0.493
s__Alistipes_finegoldii	0.04	-0.01	0.08	0.131
s__Barnesiella_intestinihominis	0.04	0.00	0.09	0.078
s__Eubacterium_siraeum	0.05	0.00	0.09	0.041
Microbe risk score	-0.08	-0.13	-0.04	< 0.001
Secoisolariciresinol				
s__Fusobacterium_mortiferum	-0.06	-0.11	-0.02	0.007
s__Blautia_sp_CAG_257	-0.07	-0.12	-0.02	0.003
s__Erysipelatoclostridium_amosum	-0.04	-0.09	0.00	0.067
s__Blautia_hansenii	-0.03	-0.08	0.02	0.209
s__Ruminococcus_gnavus	-0.02	-0.06	0.03	0.466

	beta	2.5%	97.5%	p value
s__Escherichia_coli	0.01	-0.04	0.05	0.802
s__Akkermansia_muciniphila	0.06	0.01	0.10	0.019
s__Alistipes_finegoldii	0.03	-0.02	0.08	0.204
s__Barnesiella_intestinihominis	0.05	0.00	0.10	0.032
s__Eubacterium_siraeum	0.04	-0.01	0.09	0.096
Microbe risk score	-0.07	-0.12	-0.03	0.002

181 Beta coefficients of gut microbes for each SD of dietary total lignans, matairesinol,
182 pinoreesinol, and secoisolariciresinol.

183

Table S6 OPLS-DA identified fecal metabolites associated with hyperuricemia

Fecal metabolites	VIP	coef	p value
L_Lysine	0.35	-0.001	0.574
L_Histidine	1.00	-0.001	0.935
L_Arginine	0.45	-0.001	0.918
Ornithine	0.36	-0.004	0.217
L_Glutamine	0.77	-0.002	0.578
L_Glutamic.acid	1.49	-0.006	0.023
L_Cystine	0.80	-0.002	0.786
Anserine	0.20	0.000	0.941
Carnosine	0.50	0.005	< 0.001
Sarcosine	0.60	-0.006	0.013
Beta_Alanine	0.70	0.005	0.011
L_Alanine	0.49	-0.001	0.770
Dimethylglycine	1.18	-0.004	0.142
Gamma_Aminobutyric.acid	0.53	0.004	0.147
L_Serine	0.33	-0.004	0.279
L_threonine	0.21	-0.002	0.523
Creatine	1.03	0.006	0.032
Threonic.acid	0.07	-0.001	0.464
Hydroxypropionic.acid	0.63	-0.001	0.609
Glycylproline	0.75	-0.002	0.765
L_Homocitrulline	0.10	-0.004	0.067
Adenosine.monophosphate	0.72	-0.004	0.044
L_Lactic.acid	0.18	0.001	0.384
Nicotinic.acid	1.41	-0.005	0.119
Methylcysteine	0.20	0.001	0.905
X2_Phenylglycine	0.20	0.000	0.946
Gallic.acid	1.11	0.007	0.008
L_Tyrosine	0.73	-0.002	0.566
X3.4_Dihydroxyhydrocinnamic.acid	0.82	0.009	< 0.001
L_Asparagine	0.65	0.001	0.550
Protocatechuic.acid	1.02	0.002	0.088
Hydroxyphenyllactic.acid	0.62	0.004	0.082
L_Aspartic.acid	0.03	-0.005	0.028
Glucaric.acid	0.34	0.001	0.924
But_2_enoic.acid	0.70	-0.005	0.027
Pyrrole_2_carboxylic.acid	0.60	-0.003	0.222
X2_Hydroxy_3_methylbutyric.acid	0.96	0.009	0.002
Picolinic.acid	0.60	-0.002	0.354
X4_Hydroxybenzoic.acid	0.65	0.004	0.075
Ortho_Hydroxyphenylacetic.acid	0.25	0.002	0.756
Hippuric.acid	0.18	0.001	0.976
L_Malic.acid	0.67	-0.001	0.934

Fecal metabolites	VIP	coef	p value
N_Acetyl_L_aspartic.acid	0.86	-0.003	0.306
Indole_3_methyl.acetate	0.30	-0.001	0.110
Ethylmethylacetic.acid	1.19	-0.009	0.001
X2_Methyl_4_pentenoic.acid	0.68	-0.001	0.718
Benzoic.acid	0.54	-0.004	0.034
Phenylacetic.acid	0.94	-0.009	0.001
Coumaric.acid.and.4_Hydroxycinnamic.acid	1.22	0.008	0.005
Indoleacetic.acid	0.72	-0.005	0.031
Fumaric.acid	0.28	0.000	0.919
Glutaric.acid	1.37	-0.007	0.013
trans_Aconitic.acid	0.13	0.001	0.574
X2_Pherylpropionate	1.65	-0.010	< 0.001
Hydrocinnamic.acid	1.71	-0.011	< 0.001
X3_Indolepropionic.acid	0.92	-0.006	0.009
X4_Hydroxyphenylpyruvic.acid	0.18	-0.002	0.279
Azelaic.acid	2.04	-0.014	< 0.001
Sebacic.acid	1.82	-0.016	< 0.001
Alpha_ketoisovaleric.acid	0.09	-0.006	0.049
Ketoleucine	0.09	-0.005	0.068
X3_Methyl_2_oxovaleric.acid	0.02	-0.005	0.042
Phenylpyruvic.acid	0.21	-0.004	0.158
Methylmalonic.acid	0.45	0.001	0.792
D_2_Hydroxyglutaric.acid	0.61	-0.002	0.146
Glycine	0.63	-0.003	0.270
Guanidoacetic.acid	0.48	0.004	0.089
Citrulline	0.26	-0.006	0.059
D_Gluconolactone	0.23	0.001	0.167
Glycolic.acid	0.96	0.002	0.140
L_Alpha_aminobutyric.acid	0.57	0.004	0.060
Glyceric.acid	0.05	0.003	0.191
L_Proline	0.42	-0.005	0.075
Acetylglycine	0.46	0.005	0.041
L_Pipecolic.acid	0.37	0.000	0.410
Erythronic.acid	0.17	0.004	0.217
N_Acetylserine	0.13	0.004	0.160
Shikimic.acid	0.39	0.005	0.018
N_Acetylglutamine	0.24	0.004	0.098
N_Acetylneuraminic.acid	0.01	0.003	0.207
L_Valine	0.50	-0.001	0.417
Pyroglutamic.acid	1.43	-0.005	0.034
X5_Aminolevulinic.acid	0.31	0.003	0.139
D_Glucose	0.78	0.005	0.034
D_Maltose.and.Alpha_Lactose	0.67	0.006	0.043

Fecal metabolites	VIP	coef	p value
X3_Hydroxybutyric.acid	0.43	0.004	0.068
L_Methionine	0.45	-0.003	0.373
alpha_Hydroxyisobutyric.acid	0.51	-0.003	0.500
X2_Hydroxybutyric.acid	0.59	0.006	0.020
X3_Hydroxyisovaleric.acid	0.51	0.000	0.580
Glutaconic.acid	0.74	-0.002	0.195
L_Isoleucine	0.50	-0.005	0.225
L_Leucine	0.60	-0.004	0.111
D_Xylose	0.11	-0.001	0.987
D_Xylulose	0.12	0.001	0.723
Rhamnose	1.14	0.005	0.073
D_Fructose	0.21	-0.001	0.548
N_Acetyl_D_glucosamine	0.58	0.005	0.041
Propanoic.acid	0.11	0.003	0.221
Homovanillic.acid	0.74	0.008	< 0.001
X3_3_Hydroxyphenyl_3_hydroxypropanoic.acid	0.83	0.009	< 0.001
p_Hydroxyphenylacetic.acid	0.27	0.002	0.339
X3_Aminosalicylic.acid	0.27	0.002	0.421
L_Tryptophan	1.07	-0.002	0.749
Butyric.acid	0.84	0.000	0.955
Isobutyric.acid	1.30	-0.008	0.004
Mandelic.acid	0.18	-0.002	0.972
Malonic.acid	0.31	0.006	0.015
Alpha_N_Phenylacetyl_L_glutamine	0.09	0.000	0.932
Tartaric.acid	0.31	0.000	0.803
Isovaleric.acid	1.16	-0.009	0.001
Valeric.acid	1.51	-0.008	0.003
N_Methylnicotinamide	1.02	-0.009	0.001
Phenyllactic.acid	0.00	0.002	0.444
Maleic.acid	0.21	-0.003	0.242
Citraconic.acid	0.35	-0.002	0.743
Methylsuccinic.acid	1.73	-0.006	0.030
Adipic.acid	2.14	-0.014	< 0.001
Methylglutaric.acid	1.60	-0.009	0.001
Phthalic.acid	1.71	-0.009	< 0.001
cis_Aconitic.acid	0.43	0.000	0.756
Pimelic.acid	1.57	-0.011	< 0.001
X3_Methyladipic.acid	2.11	-0.012	< 0.001
Isocaproic.acid	1.27	-0.007	0.017
Caproic.acid	1.71	-0.010	< 0.001
Tauroursodeoxycholic.acid	1.31	0.005	0.004
Taurocholic.acid	0.98	0.007	0.002
Citric.acid	0.50	-0.005	0.137

Fecal metabolites	VIP	coef	p value
Isocitric.acid	0.29	0.000	0.797
Heptanoic.acid	1.65	-0.011	< 0.001
Pyruvic.acid	0.31	-0.001	0.797
Taurodeoxycholic.acid	0.02	-0.001	0.707
Taurochenodeoxycholic.acid	1.20	0.007	0.014
X7_DHCA	1.97	0.011	< 0.001
X3_DHCA	1.16	0.008	0.004
a_muricholic.acid.and.b_muricholic.acid	1.91	0.011	< 0.001
Oxoglutaric.acid	0.80	-0.005	0.032
Glycoursodeoxycholic.acid	1.79	0.008	0.001
Octanoic.acid	0.88	-0.006	0.003
Taurolithocholic.acid	0.19	0.002	0.252
muro_cholic.acid	1.98	0.010	< 0.001
bHyodeoxycholic.acid	2.23	0.013	< 0.001
Ursodeoxycholic.acid	1.39	-0.011	< 0.001
Hyodeoxycholic.acid	0.86	-0.005	0.610
Hyochoolic.acid	1.33	0.003	0.426
Cholic.acid	1.97	0.012	< 0.001
Glycocholic.acid	1.51	0.009	< 0.001
Decanoic.acid	0.67	-0.004	0.017
isolithocholic.acid	0.97	-0.006	0.031
Glycochenodeoxycholic.acid	1.62	0.012	< 0.001
Glycodeoxycholic.acid	0.26	0.000	0.673
Tridecanoic.acid	0.49	-0.008	0.005
Ricinoleic.acid	0.29	-0.001	0.280
Lithocholic.acid	0.96	-0.007	0.061
Glycolithocholic.acid	0.43	-0.003	0.221
Myristic.acid	0.03	-0.002	0.397
X9_Pentadecenoic.acid	0.68	0.003	0.589
Pentadecanoic.acid	0.19	-0.004	0.095
Palmitoleic.acid	1.30	0.004	0.125
X10_Trans_Heptadecenoic.acid	0.27	0.002	0.352
Alpha_Linolenic.acid	0.43	0.001	0.639
Linoleic.acid	0.04	-0.001	0.461
Eicosapentaenoic.acid..EPA	1.26	0.005	0.030
Arachidonic.acid	1.72	0.008	0.005
X8.11.14_Eicosatrienoic.acid	2.22	0.012	< 0.001
Docosahexaenoic.acid.DHA	1.55	0.006	0.001
Docosapentaenoic.acid.DPA	2.30	0.012	< 0.001
Docosapentaenoic.acid.22n_6	1.58	0.011	< 0.001
Adrenic.acid	2.19	0.010	< 0.001
Succinic.acid	0.50	0.002	0.702
Citramalic.acid	0.49	0.007	0.014

Fecal metabolites	VIP	coef	p value
Oleic.acid	0.11	-0.002	0.284
Petroselinic.acid	0.13	0.003	0.082
Nonadeca_10Z_enoic.acid	0.88	0.001	0.446
Carnitine	1.08	0.005	0.018
Malonylcarnitine	0.64	0.005	0.011
Palmitoylcarnitine	2.33	0.015	< 0.001
Oleylcarnitine.C18.1	2.14	0.013	< 0.001
Linoleylcarnitine	1.53	0.008	< 0.001
Stearyl carnitine	2.01	0.011	< 0.001
Methionine.sulfoxide	0.00	-0.005	0.148
Methylmalonylcarnitine.C4DC	0.75	0.001	0.882
NorCA	1.21	0.008	0.003
NorDCA	0.83	-0.008	0.001
X2.2_dimethyladipic.acid	0.63	-0.002	0.086
X7ketoLCA	2.01	0.011	< 0.001
Chenodeoxycholic.acid	1.72	0.011	< 0.001
L_Phenylalanine	0.91	-0.001	0.607
N_acetyltryptophan	0.13	-0.001	0.819
Benzamide	0.29	-0.003	0.374
Oxalic.acid	0.60	-0.004	0.303
Fructose.1.6_bisphosphate	0.31	-0.005	0.015
Suberic.acid	2.19	-0.016	< 0.001
Nonanoic.acid	0.79	-0.008	0.004
Trehalose	0.80	-0.005	0.035
Palmitic.acid	0.11	-0.004	0.089
Stearic.acid	0.57	-0.004	0.124
Acetic.acid	0.61	0.002	0.583

185 OPLS-DA identified fecal metabolites associated with hyperuricemia. Threshold was
186 set as VIP > 1 and P < 0.05.

187

188

189

Table S7 The association of bile acid risk score with hyperuricemia

	ORs	Lower CI	Upper CI
Bile acid risk score			
Q1	1		
Q2	1.229	0.839	1.802
Q3	1.36	0.928	1.992
Q4	2.19	1.499	3.198

190 Odds ratios (ORs) and 95% confidence intervals (CIs) for hyperuricemia by the
 191 quartiles of the bile acid risk score, based on logistic regression. Covariate adjustments:
 192 age, sex, BMI, education level, household average income, marital status, smoking
 193 status, drinking status, tea intake, physical activity, dietary energy intake, fruit intake,
 194 vegetable intake, fish intake, and red meat intake. ORs: Odds ratios; CIs: confidence
 195 intervals.

196

Table S8 The association of dietary lignans intake with bile acids

	beta	2.5%	97.5%	p value
Total lignans				
NorCA	-0.08	-0.14	-0.01	0.016
Taurochenodeoxycholic acid	-0.07	-0.14	-0.01	0.021
Glycoursodeoxycholic acid	-0.06	-0.13	0.00	0.045
Glycochenodeoxycholic acid	-0.06	-0.12	0.00	0.060
Bile acid risk score	-0.09	-0.15	-0.03	0.004
Matairesinol				
NorCA	-0.07	-0.13	-0.01	0.027
Taurochenodeoxycholic acid	-0.08	-0.14	-0.02	0.010
Glycoursodeoxycholic acid	-0.07	-0.13	-0.01	0.030
Glycochenodeoxycholic acid	-0.06	-0.12	0.00	0.070
Bile acid risk score	-0.09	-0.15	-0.03	0.004
Pinoresinol				
NorCA	-0.06	-0.13	0.00	0.046
Taurochenodeoxycholic acid	-0.09	-0.15	-0.02	0.006
Glycoursodeoxycholic acid	-0.07	-0.13	-0.01	0.024
Glycochenodeoxycholic acid	-0.07	-0.13	-0.01	0.034
Bile acid risk score	-0.10	-0.16	-0.03	0.003
Secoisolariciresinol				
NorCA	-0.05	-0.12	0.01	0.096
Taurochenodeoxycholic acid	0.01	-0.06	0.07	0.868
Glycoursodeoxycholic acid	-0.02	-0.08	0.04	0.483
Glycochenodeoxycholic acid	-0.02	-0.09	0.04	0.470
Bile acid risk score	-0.03	-0.09	0.03	0.335

198 Beta coefficients of fecal bile acid for each SD of dietary total lignans, matairesinol,

199 pinoresinol, and secoisolariciresinol.