Online Supplement

Original Research
Isoflavone Intake is Associated With Decreased Chronic Obstructive Pulmonary Disease Morbidity

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Table S1. Association between Person-Average Total Isoflavones and Repeated Measures of COPD Morbidity by Continuous Person-Average EPA+DHA

	Low EPA+DHA†		High EPA+DHA‡		Interaction
	Mean Difference	P-value	Mean Difference	P-value	P-value
Respiratory Symptoms [a]					
CAT	**-3.7 (-5.7, -1.6)**	**<0.001**	**-1.2 (-2.2, -0.1)**	**0.026**	**0.025**
MMRC	-0.3 (-0.7, 0.03)	0.076	0.01 (-0.1, 0.1)	0.787	0.052
SGRQ	**-6.9 (-11.7, -2.2)**	**0.004**	-1.3 (-3.6, 1.0)	0.263	**0.046**
CCQ	**-0.3 (-0.6, -0.02)**	**0.034**	-0.1 (-0.2, 0.02)	0.097	0.252
ECSC	**-1.0 (-1.6, -0.4)**	**0.001**	**-0.6 (-0.9, -0.3)**	**<0.001**	0.204
FEV1 % Predicted	-2.9 (-8.9, 3.1)	0.339	-0.6 (-2.9, 1.6)	0.592	0.402
Exacerbations [b]	IRR	P-value	IRR		P-value
Moderate or Severe	1.4 (0.7, 2.7)	0.311	0.8 (0.4, 1.5)	0.457	0.272
Biomarkers [c]	Mean Difference	P-value	Mean Difference	P-value	P-value
11-dehydro-thromboxane B2	**-14.1% (-25.7%, -0.6%)**	**0.041**	-0.4% (-7.6%, 7.3%)	0.913	0.079

† Low EPA+DHA represents 5th percentile level of the person-average EPA+DHA.
‡ High EPA+DHA represents 95th percentile level of the person-average EPA+DHA.
[a] Generalized estimating equation (GEE) regression with gaussian probability distribution and identity link and exchangeable correlation was run in regressing the repeated measures of the continuous respiratory outcome on the person-average total isoflavone intake, person-average EPA+DHA, and their interactions, adjusted by the baseline covariates. The table shows the point estimate and the 95% confidence interval of the predicted mean difference in the outcome level for one standard deviation difference in the person-average total isoflavone (SD=2.3mg) while holding constant the person-average EPA+DHA level at either low (5th percentile) or high (95th percentile) level, adjusted by the covariates. CAT ranges from 0-40, MMRC from 0-5, and SGRQ from 0-100, CCQ from 0-6, and ECSC from 0-25, with higher score indicating worse impact of COPD. The minimal clinically important difference (MCID) for CAT is 2, SGRQ 4, and CCQ 0.4.
[b] Cross-sectional negative binomial regression of the total frequency of exacerbation (for the entire study period) was run on the person-average total isoflavone intake, person-average EPA+DHA, and their interactions, with total follow-up days included as an offset, and adjusted by covariates—sequentially as specified below. The table shows the point estimate and the 95% confidence interval of the predicted incidence rate ratio (IRR) of the exacerbation for one standard deviation difference in the person-average total isoflavone (SD=2.3mg) while holding constant the person-average EPA+DHA level at either low (5th percentile) or high (95th percentile) level, adjusted by the covariates.
[c] Generalized estimating equation (GEE) regression with gaussian probability distribution and identity link and exchangeable correlation was run in regressing the repeated measures of the continuous log-transformed biomarkers on the person-average total isoflavone intake, dichotomous person-average EPA+DHA, and their interactions, adjusted by the baseline covariates. The table shows the point estimate and the 95% confidence interval of the predicted percentage difference in the geometric mean level of the biomarker for one standard deviation difference in the person-average total isoflavone (SD=2.3mg) while holding constant the person-average EPA+DHA level at either low (5th percentile) or high (95th percentile) level, adjusted by the covariates.
All analyses were adjusted by person-average total energy and baseline covariates: age, gender, race, educational attainment, household income, smoking pack-years, obesity, comorbidity, and FEV1 % predicted (except when FEV1 % predicted was the outcome).

Table S2. Association between Person-Average Total Isoflavones and Repeated Measures of COPD Morbidity, Additionally Adjusted by Person-Average EPA+ DHA

Respiratory Symptoms [a]	Mean Difference	P-val.
CAT	**-2.0 (-3.5, -0.4)**	**0.012**
MMRC	-0.1 (-0.3, 0.1)	0.352
SGRQ	-3.2 (-6.4, 0.05)	0.053
CCQ	**-0.2 (-0.3, -0.03)**	**0.018**
ECSC	**-0.7 (-1.1, -0.4)**	**<0.001**
FEV1 % Predicted	-1.3 (-4.4, 1.7)	0.385
Exacerbations [b]	IRR	P-val.
Moderate or Severe	1.0 (0.7, 1.4)	1.000
Biomarkers [c]	Mean Difference	P-val.
11-dehydro-thromboxane B2	-6.3% (-14.4%, 2.5%)	0.158

[a] Generalized estimating equation (GEE) regression with gaussian probability distribution and identity link and exchangeable correlation was run in regressing the repeated measures of the continuous respiratory outcome on the person-average total isoflavone intake, adjusted by the baseline covariates and additionally adjusted by person-average EPA+DHA intake. The table shows the point estimate and the 95% confidence interval of the predicted mean difference in the outcome level for one standard deviation difference in the person-average total isoflavone (SD=2.3mg), adjusted by the covariates. CAT ranges from 0-40, MMRC from 0-5, and SGRQ from 0-100, CCQ from 0-6, and ECSC from 0-25, with higher score indicating worse impact of COPD. The minimal clinically important difference (MCID) for CAT is 2, SGRQ 4, and CCQ 0.4.

[b] Cross-sectional negative binomial regression of the total frequency of exacerbation (for the entire study period) was run on the person-average total isoflavone intake, with total follow-up days included as an offset, and adjusted by covariates—sequentially as specified below. The table shows the point estimate and the 95% confidence interval of the predicted incidence rate ratio (IRR) of the exacerbation for one standard deviation difference in the person-average total isoflavone (SD=2.3mg), adjusted by the covariates.

[c] Generalized estimating equation (GEE) regression with gaussian probability distribution and identity link and exchangeable correlation was run in regressing the repeated measures of the continuous log-transformed biomarkers on the person-average total isoflavone intake, adjusted by the baseline covariates. The table shows the point estimate and the 95% confidence interval of the predicted percentage difference in the geometric mean level of the biomarker for one standard deviation difference in the person-average total isoflavone (SD=2.3mg), adjusted by the covariates. All analyses were adjusted by person-average total energy and baseline covariates: age, gender, race, educational attainment, household income, smoking pack-years, obesity, comorbidity, and FEV1 % predicted (except when FEV1 % predicted was the outcome).

Table S3. Association between Person-Average Total Isoflavones and Repeated Measures of COPD Morbidity, Additionally Adjusted by Aspirin/Plavix Use (Y/N)

Respiratory Symptoms [a]	Mean Difference	P-val.
CAT	**-1.9 (-3.3, -0.5)**	**0.007**
MMRC	-0.1 (-0.3, 0.1)	0.330
SGRQ	-2.9 (-5.8, 0.1)	0.056
CCQ	**-0.1 (-0.3, -0.02)**	**0.020**
ECSC	**-0.7 (-1.0, -0.4)**	**<0.001**
FEV1 % Predicted	-1.0 (-4.1, 2.2)	0.555
Exacerbations [b]	IRR	P-val.
Moderate or Severe	1.0 (0.7, 1.4)	0.931
Biomarkers [c]	Mean Difference	P-val.
11-dehydro-thromboxane B2	-4.2% (-9.8%, 1.8%)	0.166

[a] Generalized estimating equation (GEE) regression with gaussian probability distribution and identity link and exchangeable correlation was run in regressing the repeated measures of the continuous respiratory outcome on the person-average total isoflavone intake, adjusted by the baseline covariates and additionally adjusted the aspirin or Plavix use (yes/no) at baseline. The table shows the point estimate and the 95% confidence interval of the predicted mean difference in the outcome level for one standard deviation difference in the person-average total isoflavone (SD=2.3mg), adjusted by the covariates. CAT ranges from 0-40, MMRC from 0-5, and SGRQ from 0-100, CCQ from 0-6, and ECSC from 0-25, with higher score indicating worse impact of COPD. The minimal clinically important difference (MCID) for CAT is 2, SGRQ 4, and CCQ 0.4.

[b] Cross-sectional negative binomial regression of the total frequency of exacerbation (for the entire study period) was run on the person-average total isoflavone intake, with total follow-up days included as an offset, and adjusted by covariates—sequentially as specified below. The table shows the point estimate and the 95% confidence interval of the predicted incidence rate ratio (IRR) of the exacerbation for one standard deviation difference in the person-average total isoflavone (SD=2.3mg), adjusted by the covariates.

[c] Generalized estimating equation (GEE) regression with gaussian probability distribution and identity link and exchangeable correlation was run in regressing the repeated measures of the continuous log-transformed biomarkers on the person-average total isoflavone intake, adjusted by the baseline covariates. The table shows the point estimate and the 95% confidence interval of the predicted percentage difference in the geometric mean level of the biomarker for one standard deviation difference in the person-average total isoflavone (SD=2.3mg), adjusted by the covariates. All analyses were adjusted by person-average total energy and baseline covariates: age, gender, race, educational attainment, household income, smoking pack-years, obesity, comorbidity, and FEV1 % predicted (except when FEV1 % predicted was the outcome).