Supplemental Methods

Detection and quantification of metabolites by high performance liquid chromatography (HPLC)-tandem mass spectrometry.

P-cresyl sulfate (PCS), hippuric acid, indole-3-propionic acid (I3P), tryptophan (trp), kynurenine (kyn), indoxyl sulfate (IS), and serotonin. Fifty microliters of plasma and internal standards (n-methyl serotonin and p-toluene sulfonic acid) were prepared as described previously[1] with the following modifications. After extraction with 200 µL methanol and clarification by centrifugation, the supernatant was dried in a water bath (50°C) under nitrogen gas, resuspended in water:acetonitrile (98:2 volume:volume), and filtered. One microliter of eluent was separated by reverse-phase HPLC on a Zorbax Eclipse XDB-C18 Rapid Resolution High-Throughput, 2.1x50 mm, particle size 1.8 µ column (Agilent Technologies, Santa Clara, CA) with an Eclipse XDB-C8, 2.1 x 12.5 mm, 5 µ guard (Agilent Technologies), and the metabolites of interest were measured by tandem mass spectrometry on a triple quadrupole instrument (Agilent 6410) operating in multiple reaction monitoring mode. For positive ion analysis, solvents were (A) .1% formic acid and (B) acetonitrile at a flow rate on .3 mL/min. The gradient began with 98% solvent A and 2% solvent B and changed to 90% solvent A and 10% solvent B (0 → 4 min) followed by 50% solvent A and 50% solvent B (4 → 6 min), where it remained until 10 minutes, followed by a 3-minute re-equilibration at 98% A/2% B. For negative ion analysis, 5 mM ammonium acetate was used in place of formic acid, and solvent B was methanol instead of acetonitrile. The gradient began with 88% solvent A and 12% solvent B and changed to 86% solvent A and 14% solvent B (0 → 3 min), followed by 65% solvent A and 35% solvent B (3 → 4 min) where it remained until 8 min, followed by a 4-min re-equilibration to 88% A/12% B. The mass-to-charge ratios of the

precursor-to-product ion reactions monitored were 209 → 192 for kyn, 205 → 188 for trp, 190 → 130 for I3P, 180 → 105 for hippuric acid, 177 →160 for serotonin, 191 → 160 for n-methyl serotonin, 212 → 80 for IS, 187 → 107 for PCS, and 171 → 80 for p-toluenesulfonic acid. Retention times for serotonin, kyn, n-methyl serotonin, trp, hippuric acid, I3P, IS, p-toluenesulfonic acid, and PCS were 3.3, 3.5, 3.8, 5.8, 6.9, 8.2, 2.9, 2.9, and 5.8 min, respectively. The linear range for plasma kyn, trp, I3P, hippuric acid, serotonin, IS, and PCS standard curves were .006 to .60 nmol/L, 1.22 to 122.4 nmol/L, .0017 to .17 nmol/L, .18 to 17.86 mmol/L, .0028 to 11.8 nmol/L, .23 to 23.5 nmol/L, and .025 to 25.3 nmol/L, respectively.

Indole, indole-3-aldehyde (I3A), and 3-hydroxyanthranilic acid. Samples were prepared by solid-phase extraction. In brief, 50 μL of plasma sample, methanolic internal standard (bupivacaine) solution and 20% phosphoric acid solution were vortexed and clarified by centrifugation. The sorbent of the wells of a 96-well Strata-X Polymeric Reversed Phase 96-well plate (Phenomenex, Torrance, CA), 2 mg/well, were conditioned sequentially with methanol and formic acid solution under vacuum. The sample was applied to the conditioned sorbent and drawn through gently by vacuum. The sorbent was washed with 1% formic acid solution under vacuum. Samples were then eluted into a 96-well plate by 1% ammonium hydroxide in methanol. Two microliters of the eluent were then analyzed by an API 3000 HPLC–tandem mass spectrometry system (Applied Biosystems, Foster City, CA) equipped with an Agilent 1100 series HPLC system (Agilent Technologies) operating in positive ion mode. Samples were eluted by gradient from a Poroshell 120, EC-C18, 2.1 x 100 mm, 2.7 μ column (Agilent) with a UHPLC EC-C18 2.1 x 5 mm ID, 2.7 μ guard cartridge (Agilent) using a mobile phase consisting of .1% formic acid in water (solvent A) and .1% formic acid in methanol (solvent B) at a flow rate of .20 mL/min. The gradient began with 70% solvent A and 30% solvent B for one-half min before changing to 35% solvent A and 65%

solvent B between 0.5 and 1.3 min and again changing to 20% solvent A and 80% solvent B between 1.3 and 3 min. The mobile phase remained at 20% solvent A and 80% solvent B until it was returned to 70% solvent A and 30% solvent B between 9 and 9.1 min for reequilibration until 15 min. The mass-to-charge ratios of the precursor-to-product ion reactions monitored were 154.2 → 135.9 for 3-hydroxyanthranilic acid, 146.3 → 91.2 for I3A, 118.0 → 91.1 for indole, and 289.3 → 140.1 for the internal standard. The retention times of 3-hydroxyanthranilic acid, I3A, and indole were approximately 2.1, 6.9, and 8.2 min, respectively, while that of the internal standard was approximately 7.4 min. The linear range for plasma 3-hydroxyanthranilic acid, I3A, and indole standard curves were .00017 to .033 nmol/L, .0069 to .69 nmol/L, and .017 to 1.11 nmol/L, respectively.

Supplemental Table I. Compounds under study in current targeted metabolomics screen and known links to atherosclerosis or vascular cell biology

Metabolite	Relationship to gut microbiome	Known links to atherosclerosis or vascular cell biology	References (Supplemental)
Indole and indole derivatives			
Indole	Metabolite was observed only in conventionally-raised mice compared to germ-free mice. (Wikoff 2009)[1]	Aryl hydrocarbon receptor activation in ApoE knockout mice promotes atherosclerosis	Wu 2011,[2] Shimada 2013,[3] and Lee 2010[4]
Tryptophan (trp)	Plasma concentration was	Negatively correlates with all-cause and	Zuo 2016[5]

	1.7-fold higher in germ-free mice compared to conventionally-raised mice. (Wikoff 2009)[1]	cardiovascular mortality in population-based study	
		Decreased trp and increased kyn/trp ratio in patients with CAD	Wirleitner 2003[6]
		IDO1-dependent inhibition of IL-10 leads to worse atherosclerosis in mice; kynureninic acid and trp correlate	Metgahalchi 2015[7]

		with death or recurrent MI in human study	
Kynurenine (kyn)[a]	Germ-free mice have decreased kyn concentration, which is reversed after colonization by microbes. (El Aidy 2012)[9]	Associated with all-cause mortality in population-based study	Zuo 2016,[5] Clarke 2013[10]
		Urinary kyn/trp ratio associated with major coronary events and mortality after coronary angiography	Pedersen 2013[11]

		Plasma kynurenine associated with risk of acute MI in patients with stable angina	Pedersen 2015[12]
		IDO1 deficiency in ApoE knockout mice decreased atherosclerosis lesion size	Cole 2015[13]
		Decreased trp and increased kyn/trp ratio in patients with CAD	Wirleitner 2003[6]
		Kyn/trp ratio correlates with	Niinisalo 2008[15]

		carotid intima-media thickness in elderly patients	
		Kyn/trp ratio correlates with carotid intima-media thickness and LDL and inversely with HDL in young adults	Pertovaara 2007[16]
		IDO1 gene and protein expression in atherosclerotic plaques	Niinisalo 2010[17]
3-Hydroxyanthranilic acid (HAA)		Reduced atherosclerotic plaque in LDL	Zhang 2012[18]

		receptor knockout mice and reduced oxidized LDL uptake in macrophages	
		Plasma HAA associated with risk of acute MI in patients with stable angina	Pedersen 2015[13]
Serotonin	Plasma concentration was 2.8-fold higher in conventionally-raised mice compared to germ-free mice. (Wikoff	Serum serotonin is higher in patients with CAD	Sugiura 2016[18]

	2009)[1]		
Indole-3-propionic acid (I3P)	Metabolite was observed only in conventionally-raised mice. (Wikoff 2009)[1]	Aryl hydrocarbon receptor activation in ApoE knockout mice promotes atherosclerosis	Wu 2011[2]
Indole-3-aldehyde (I3A)	Metabolite was observed only in conventionally-raised mice. (Wikoff 2009)[1]	Aryl hydrocarbon receptor activation in ApoE knockout mice promotes atherosclerosis	Wu 2011,[2] Shimada 2013,[3] and Lee 2010[4]
Indoxyl sulfate (IS)	Metabolite was observed only in conventionally-raised mice. (Wikoff 2009)[1]	Stimulates reactive oxygen species production in endothelial cells	Dou 2007[19]

		Impairs endothelial cell repair	Dou 2004[20]
		Induces vascular smooth muscle cell proliferation	Yamamoto 2011[21]
		Promotes platelet reactivity and carotid thrombosis in mouse model	Yang 2017[22]
		Induces leukocyte-endothelial interactions	Ito 2010[23]
		Associated with CAD severity in humans	Hsu 2013[24]
		Promotes aortic	Adijiang 2008[25]

		calcification and aortic wall thickening in rats	
Phenyl derivatives			
Hippuric acid	Plasma concentration was 17.4-fold higher in conventionally-raised mice compared to germ-free mice. (Wikoff 2009)[1]	Urine hippuric acid levels are elevated in atherosclerotic rats	Zhang 2009[26]
p-Cresyl sulfate (PCS)	Metabolite was observed only in conventionally-raised mice. (Wikoff	Higher plasma levels in humans are associated with cardiovascular	Liabeuf 2010[27]

	2009)[1]	mortality	
		ApoE knockout mice that underwent 5/6 nephrectomy and treated with PCS had more pronounced atherosclerotic plaque areas compared to vehicle-treated mice	Han 2016[28]
		Serum PCS is associated with carotid plaques in patients on hemodialysis	Jing 2016[29]
		Correlates with free	Schepers 2007[30]

		radical production *in vitro*	
		Correlates with vascular calcification in hemodialysis patients	Meijers 2008[31]

[a]The kynurenine/tryptophan ratio is an estimate of the activity of indoleamine 2,3-dioxygenase (IDO1).[8]

IDO1 (indole-2,3-deoxygenase 1); CAD, coronary artery disease; LDL, low density lipoprotein; HDL, high density lipoprotein; ApoE, apolipoprotein E

Supplemental References

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Supplemental Table IIA. Baseline characteristics of control cohort and severe carotid stenosis subgroup.

Covariate	**Control cohort (n = 22)**	**Carotid endarterectomy (n = 48)**	**P value**
Median age (years)	70 (68, 76)	68.5 (63.5, 74)	.19
Female sex	9 (40.9%)	18 (37.5%)	.79
Non-Caucasian race	1 (4.6%)	1 (2.1%)	.53
Body mass index (kg/m^2)	26.8 (24.8, 28.4)	28.2 (26.1, 32.2)	.41
Past medical history			
Diabetes mellitus	2 (9.1%)	2 (9.1%)	.20
Hypertension	15 (78.2%)	46 (95.8%)	**.003**
Prior MI	0	7 (14.6%)	.09
CHF	0	6 (12.5%)	.17
Stroke	0	12 (25%)	.05
Current or former smoker	10 (45.5%)	35 (72.9%)	**.03**
Statin use	9 (40.9%)	47 (97.9%)	**<.001**

Lowest ABI	1.12 (1.1, 1.2)	.66 (.62, .78)	**<.001**
LDL cholesterol (mg/dL)	115.4 (95.2, 125.8)	81.5 (51, 112)	**.04**
HDL cholesterol (mg/dL)	57.7 (41.9, 68.0)	42.5 (33.5, 49.5)	**.009**
eGFR (mL/min/1.73mm^2)	72.4 (59.0, 96.1)	63.9 (51.1, 81.2)	.09
hs-CRP (mg/mL)	2.1 (.78-3.42)	2.9 (1.2, 48.5)	.46
Indole derivatives			
Indole (nmol)	72.6 (0, 170.7)	0 (0, 0)	**.008**
Tryptophan (μmol)	101.6 (97.4, 110.4)	82.3 (75.0, 87.7)	**<.001**
Kynurenine (nmol)	10048.97 (9275.3, 11888.19)	9080 (7924.5, 10670.1)	**.02**
Kynurenine/tryptophan ratio	98.0 (86.1, 108.3)	108.65 (95.42, 131.65)	**.01**
3-Hydroxyanthranilic acid (nmol)	238.3 (98.0, 333.0)	339.57 (261.20, 483.23)	**.006**
Indole-3-propionic acid (μmol)	.41 (.27, .90)	.24 (.20, .43)	**.001**

Indole-3-aldehyde (μmol)	124.0 (103.3, 158.4)	89.56 (58.56, 113.67)	**<.001**
Indoxyl sulfate (μmol)	7.76 (6.6, 9.1)	7.6 (6.1, 9.6)	.82
Phenyl derivatives			
Hippuric acid (μmol)	9.03 (7.87, 10.42)	8.12 (7.33, 12.21)	.51
p-Cresyl sulfate (μmol)	94.0 (67.7, 130.3)	116.3 (65.7, 157.5)	.34

All values shown are median (interquartile range) or n (%). MI indicates myocardial infarction. CHF, congestive heart failure. ABI, ankle-brachial index. LDL, low density lipoprotein. HDL, high density lipoprotein. eGFR, estimated glomerular filtration rate. hs-CRP, high-sensitivity C-reactive protein. CEA, carotid endarterectomy.

Supplemental Table IIB. Odds ratios for carotid stenosis obtained from logistic models, each involving individual metabolites separately, adjusted for diabetes mellitus, hypertension, smoking, and HDL cholesterol.

Metabolite	**Odds ratio**	**95% CI**	**P value**
ln indole (nmol)	.87	.77, .98	**.03**
ln tryptophan (μmol)	<.001	<.001, <.001	**.001**
ln kynurenine (nmol)	.02	<.001, 1.5	.07
ln kynurenine/tryptophan ratio	99.0	1.5, > 999	**.03**
ln 3-hydroxyanthranilic acid (nmol)	.92	.69, 1.2	.59
ln indole-3-propionic acid (μmol)	.30	.07, 1.3	.10
ln indole-3-aldehyde (nmol)	.10	.009, .959	.046

Supplemental Table III. Plasma concentrations of certain metabolites stratify by procedure type in the advanced atherosclerosis cohort.

Metabolite	**CEA (n=48)**	**Infrainguinal bypass (n=40)**	**Major amputation (n=12)**	**P value**
Indole (nmol)	0 (0, 0)	0 (0, 0)	0 (0, 128.0)	.53
Tryptophan (μmol)	82.4 (75.0, 87.7)	81.8 (73.3, 89.4)	71.2 (64.7, 79.5)	**.008**
Kynurenine (nmol)	9080.0 (7924.5, 10760.1)	9124.5 (8242.5, 10863.8)	9825.9 (7644.9, 12852.0)	.38
Kynurenine/tryptophan ratio	108.7 (95.4, 131.7)	111.9 (97.2, 135.9)	124.8 (101.5, 190.7)	**.02**
3-Hydroxyanthranilic acid (nmol)	339.6 (261.2,	313.4 (254.7,	346.1	.34

	483.2)	509.3)	(137.1, 417.9)	
Indole-3-propionic acid (μmol)	.25 (.20, .43)	.21 (.15, .32)	.08 (.08, .17)	**.005**
Indole-3-aldehyde (nmol)	89.6 (58.6, 113.7)	110.2 (82.7, 124.0)	0 (0, 96.4)	**.02**
Indoxyl sulfate (μmol)	7.6 (6.1, 9.6)	7.4 (6.5, 8.8)	5.3 (4.3, 8.1)	.40
Hippuric acid (μmol)	8.1 (7.3, 12.2)	7.8 (7.3, 10.5)	7.0 (6.9, 7.5)	.42
p-Cresyl sulfate (μmol)	116.3 (65.7, 157.5)	106.0 (60.7, 150.8)	23.6 (0, 75.1)	.30

Supplemental Table IV. Spearman correlation coefficients between metabolites using ln-transformed values.

Indole and indole derivatives

	ln indole	ln tryptophan	ln kynurenine	ln kynurenine /tryptophan ratio	ln 3-hydroxyanthranilic acid	ln indole-3-propionic acid	ln indole-3-aldehyde	ln indoxyl sulfate	ln CRP
ln indole									
ln tryptophan	.11 P = .23								
ln kynurenine	-.018 P = .85	**.24** **P = .007**							
ln kynurenine/tryptophan ratio	-.095 P = .31	**-.45** **P < .001**	**.68** **P = 0**						
ln 3-hydroxyanthranil	-.14 P = .13	**-.24** **P = .009**	-3.8×10^{-4} P = .99	**.21** **P = .02**					

ic acid									
ln indole-3-propionic acid	.13 P = .19	**.58** **P < .001**	**.26** **P = .004**	-.14 P = .13	-.16 P = .085				
ln indole-3-aldehyde	-.013 P = .89	**.54** **P < .001**	**.32** **P = .001**	-.11 P = .26	**-.36** **P < .001**	**.33** **P < .001**			
ln indoxyl sulfate	**.22** **P = .02**	.081 P = .38	**.25** **P = .005**	**.26** **P = .005**	.14 P = .14	**.22** **P = .013**	**.20** **P = .038**		
ln CRP	-.03 P = .87	**-.42** **P = .01**	-.038 P = .83	.27 P = .11	-.09 P = .64	**-.35** **P=.038**	-.22 P = .25	-.21 P = .23	

Phenyl derivatives

	ln hippuric acid	ln p-cresyl sulfate	ln CRP
ln hippuric acid			
ln p-cresyl sulfate	**.24**		

	P = .007		
ln CRP	-.11 P = .53	-.20 P = .25	

CRP, C-reactive protein