Supplementary Material

Metabolomics and Diabetes: An updated Systematic Review and Meta-Analysis of prospective cohort studies

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Content:

Supplementary Table 1. Changes adopted to the protocol for the updated systematic review.

Adopted change	Explanation and justification
Search strategy	The pilot update search revealed that search terms used in the primary version of this systematic review did not identify all relevant reports. We extended the search strategy with additional terms for exposure (metabolomics, lipidomics) and study design (prospective observational studies). Additionally, we excluded terms related to prediabetes (i.e., glycemia and insulin resistance markers).
Eligibility criteria	The primary systematic review identified 27 cross-sectional studies and 19 prospective cohort studies, reporting associations between metabolomics and prediabetes/type 2 diabetes. At the time of publication, the availability of prospective observational studies (with the overlapping list of metabolomic measures, allowing for meta-analysis) was low. Therefore, it seemed reasonable to include studies with a cross-sectional setting as a vital part of the available body of evidence at that time. Since the publication, the number of available prospective metabolomic studies has greatly increased. During the planning of the update, we assumed that also a number of metabolites eligible for meta-analysis will be much extended. Previous studies reported key differences between results of metabolomic assessments in prevalent and incident disease states. Considering that prospective studies provide higher certainty of evidence and better insight into the temporality of associations between metabolites and health outcome, we decided to reduce the focus of the current update to prospective studies. We also narrowed our endpoints only to incident type 2 diabetes, as prediabetes is rarely reported in prospective studies and has no homogeneous definition (e.g., risk of impaired fasting glucose or continuous changes in glycated hemoglobin), limiting use for meta-analysis. Moreover, as the primary focus of this systematic review was a quantitative summary of the evidence, we planned to exclude studies reporting only multivariable analyses (e.g., principal component analysis, network analysis). This was due to the inability to use these results in meta-analyses.
Primary analysis	The previous version of this review assumed conducting random-effects meta-analysis for metabolites with at least three studies per comparison. In such case, risk estimates with 95% CIs (for one study-specific standard deviation increase in metabolite levels) were pooled with a random-effects model (with DerSimonian-Laird estimator). Secondarily, those results were re-assessed with fixed-effects model. For the present update, we 1) conducted meta-analysis in case of 2 studies per comparison, 2) used restricted maximum-likelihood estimator (currently its use is recommended over method by DerSimonian-Laird), 3) did not use fixed-effects model as secondary analysis as high inconsistency between studies was expected. As included studies had used multiple testing correction to P-values (not estimates extracted for this review), and we had expected a large number of metabolites, we adjusted all analyses for false-discovery rate.
Subgroup analysis	In the current version of this review, we extended subgroup analyses by stratifying them for: 1) fasting status (fasted/mixed), 2) fasting glucose adjustment (yes/no), and 3) study location. Additionally, we conducted comprehensive meta-regression analyses to explore the effects of fatty acyl length and degree of unsaturation on associations between lipid classes and incident type 2 diabetes. We did not conduct meta-regression of men proportion (majority of included studies were set in community-based cohorts with a similar representation of men and women; only few were conducted solely in men or women) and subgroup analysis stratified for study design.

Supplementary Table 2. Search strategies adopted for PubMed and Embase electronic databases.

PubMed
((metabolomics[MeSH Terms] OR metabolome[MeSH Terms] OR metabolite*[Title/abstract] OR metabolo*[Title/abstract] OR metabonom*[Title/abstract] OR metabolite network*[Title/abstract] OR metabolite profile*[Title/abstract] OR lipidom*[Title/abstract]) AND (diabetes mellitus[MeSH Terms] OR diabetes[Title/abstract]) AND (study[Title/abstract] OR prospective[Title/abstract] OR follow-up[Title/abstract] OR cohort[Title/abstract] OR longitudinal[Title/abstract] OR case-cohort[Title/abstract] OR nested case-control[Title/abstract])) NOT (animals[MeSH Terms] NOT humans[MeSH Terms]) **Dates covered: 01.08.2015-06.03.2021**
Embase
('metabolomics'/de OR 'metabolome'/de OR metabolite*:ti,ab OR 'metabolo*':ti,ab OR 'metabonom*':ti,ab OR 'metabolite network*':ti,ab OR 'metabolite profile':ti,ab OR 'lipidomics'/de OR 'lipidome'/de OR 'lipidom*':ti,ab OR 'proteomics'/de OR 'proteome'/de OR 'proteom*':ti,ab) AND ('diabetes mellitus'/exp OR 'diabetes':ti,ab) AND ('study':ti,ab OR 'prospective':ti,ab OR 'follow-up':ti,ab OR 'cohort':ti,ab OR 'longitudinal':ti,ab OR 'case-cohort':ti,ab OR 'nested case-control':ti,ab) AND [humans]/lim **Dates covered: 01.08.2015-06.03.2021**

Supplementary Table 3. Additional data received after contact with authors of included studies.

Author (Reference)	**Description**
Rhee et al. 2011	Risk estimates and 95% CIs for all analyzed metabolites. The original publication reported only those significantly (P<0.05) associated with incident type 2 diabetes.
Fall et al. 2018	
Gängler et al. 2019	
Peddinti et al. 2017	
Ottosson et al. 2018	Multivariable adjusted risk estimates for all analyzed metabolites. The original article reported fully-adjusted estimates only for those metabolites which were found as significantly associated in crude model.

Supplementary Table 4. Assumptions for grouping of metabolites in the present meta-analysis.

Metabolite group	**Description**
Glycerolipids	Depending on the applied protocol of metabolomics profiling, different precision of metabolomics data was provided. Glycerolipids were rather identified and reported at the **lipid species level (total N of carbons and double bonds in the particle),** e.g., TG 52:2 rather than **fatty acid level** (content of fatty acids) and **fatty acid position** (content and specific position). Therefore, for analysis of glycerolipids, we generalized the information to lipid species level, e.g., TG 16:0_18:1_18:1 was converted to TG 52:1. In case that several particles had the same sum of N of carbons and double bonds, we pooled those estimates with a fixed-effects model. For glycerolipids, we ignored the type of bond: acyl or alkyl (as frequently not reported) and regarded all particles as having acyl bonds (mono-, di- and triacyl). Following subclasses were considered: 1) monoacylglycerols (MG), 2) diacylglycerols (DG), and 3) triacylglycerols (TG).

Glycerophospholipids and their lyso-forms	Similarly to glycerolipids, glycerophospholipids were predominately reported at **lipid species level** e.g., rather than **fatty acid level** or **fatty acid position** (content and specific position). We generalized the information to lipid species level (sum of carbons and double bonds in both, e.g., PE 16:0_18:2 was converted to PE 34:2. In case that several particles had the same sum of N of carbons and double bonds, we pooled those estimates with a fixed-effects model. For glycerophospholipids, we ignored type of bond: acyl, alkyl or plasmalogens and regarded all particles as having acyl bonds. Following subclasses were considered: 1) phosphatidylcholines (PC), 2) phosphatidylethanolamines (PE), 3) phosphatidylinositols (PI), 4) phosphatidylcholines (LPC), 5) lysophosphatidylethanolamines (LPE), and 6) lysophosphatidylinositols (LPI).
Sphingomyelins	Sphingomyelins like the rest of lipid classes were primarily reported at lipid species level. Similarly, we generalized the information to **lipid species level**. For sphingomyelins, this meant ignoring the type of sphingoid base as its N of carbons and double bonds were accounted in total N of carbons and double bonds (eg. SM 34:0). In case that several particles had the same sum of N of carbons and double bonds, we pooled those estimates with a fixed-effects model. All compounds were considered as a single class: 1) sphingomyelins (SM)
Ceramides	Ceramides, unlike other lipid classes, were almost consistently reported at **fatty acyl level** (Cer d18:0/16:0), which allowed for meta-analysis of particular metabolites rather than group of metabolites with similar composition. Here we ignored estimates for ceramides reported at the lipid species level (e.g., Cer 36:0) Among extracted ceramides, a few studies also reported cerebrosides (ceramides with linked hexose), but we regarded them as a single class: 1) ceramides (Cer)

Supplementary Table 5. Reasons for exclusion of studies during the examination of full-text articles.

Reference	Reason
(1)	Adolescent population
(2-14)	Cross-sectional or retrospective case-control study design
(15-37)	Conference abstract
(38-46)	Duplicated report
(47-53)	Metabolomics assessment not performed
(54-60)	Multivariable analysis results only
(61-82)	Not relevant outcome for extraction
(83)	Review

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Supplementary Table 6. Summary characteristics of prospective observational studies evaluating metabolomics and risk of incident type 2 diabetes.

Reference	Study name, Location	Study design	Participants (Cases)	Follow-up	Platform, technique and metabolite targets	Biological sample (Fasting status)	Covariate adjustment set	Main findings	Study quality
Ahola-Olli et al. 2019	DILGOM, FINRISK-1997, NFBC, YFS, (Finland)	Prospective cohort	11,896 (392 incident type 2 diabetes cases)	8.0-15.0 years	**Platform: Nightingale Health** NMR; targeted (229 metabolic measures including amino acids, glycolysis-related metabolites, fatty acids and lipoprotein lipid profile)	Serum (Mixed)	Age, sex, BMI, plasma FG	(↑) **BCAA** (isoleucine, leucine, valine), **AAA** (phenylalanine, tyrosine), glycerol, glycoprotein acetyls, **FA** (total circulating FA, relative MUFA), **VLDL** (particle size, cholesterol and TG by size classes), **LDL** (cholesterol by size classes), **IDL** (cholesterol),**HDL** (cholesterol in S/M particles), ApoB, ApoB/A1 (↓) **FA** (relative PUFA, n-6 and linoleic acid), **HDL** (cholesterol in L/XL particles, particle size)	5
Chen et al. 2016	SHDS (China)	Prospective cohort	213 (51 incident type 2 diabetes cases)	10.0 years	**Platform: In-house** UPLC-MS/MS; targeted (5 metabolites including BCAA and AA)	Serum (Fasting)	Age, gender, BMI, fasting and postprandial glucose, fasting and postprandial insulin, TC, TG, HDL-C, LDL-C, SBP, DBP, and HOMA-IR	(↑) **BCAA** (isoleucine, leucine, valine), **AAA** (phenylalanine, tyrosine)	3.5
Chen et al. 2019	DPP (US)	Combined nested case-control studies from a RCT	2,015 (18.5% cases developed type 2 diabetes)	3.2 years	**Platform: Broad Institute** LC-MS/MS; targeted (331 metabolites including amino acids, amides, lipids, organic acids)	Plasma (Fasting)	Age, sex, race/ethnicity, hypertension status, baseline FG, and baseline BMI	(↑) **Acylcarnitines** (C5, C5-DC), cotinine, DG (32:0, 34:2, 38:4, 36:1, 32:1, 34:3, 30:0, 38:5, 36:2, 32:2), **carbohydrates** (glucose, fructose, galactose), isoleucine, **PE** (36:2, 34:2, 38:4, 36:4, 36:4, 40:6, 46:1, 36:3, 38:6), **TG** (50:1, 50:2, 48:1, 48:0, 46:1, 52:1, 46:2, 50:0, 44:0, 48:2) (↓)1,5-Anhydroglucitol, **AA** (asparagine, glutamine, glycine, serine), betaine, bilirubin, **CE** (16:0, 18:2), **PCP** (24:1, 36:1, 34:1, 34:2, 26:1, 36:4), **SM** (22:1, 16:0, 18:1, 16:1, 18:2)	4.5
Chen et al. 2020	HCHS/SOL (US)	Prospective cohort	2,010 (224 incident type 2 diabetes cases)	6.0 years	**Platform: Metabolon Inc.** UPLC-MS/MS; non-targeted (43 metabolites from lipid classes: ceramides, glucosylceramides, lactosylceramides, sphingomyelins)	Serum (Fasting)	Age, sex, Hispanic/ Latino background, US native, education, annual household income, AHEI-2010 score, total energy intake, smoking status, drinking status, physical activity, use of hypertensive or lipid-lowering drugs, fasting time for blood drawn, and family history of diabetes	(↑) **Cer** (d18:1/16:0, d18:1/18:0), **GlcCer** d18:1/24:1(2OH), **SM** (36:0, 38:0, d18:0/22:0 [0 db], d18:1/22:0 [1db], D18:1/24:0)	4.5
Chew et al. 2019	SMEC (Singapore)	Prospective cohort	2,302 (170 incident type 2 diabetes cases)	10.0 years	**Platform: In-house** UPLC-MS/MS; targeted (331 metabolites from lipid classes: including ceramides, cerebrosides, globosides,	Plasma (Fasting)	Age, sex, LDL-C, HDL-C, triglycerides, BMI, HbA1c	(↑) **SM** (d16:1/18:0, d18:1/18:0)	5.5

					gangliosides, sphingomyelins, sphingosines)				
de Mello et al. 2017	FDPS (Finland)	Prospective cohort	200 (96 incident type 2 diabetes cases)	15.0 years	**Platform: In-house** UHPLC-MS/MS; non-targeted (>8600 metabolic features including amino acids, phospholipids and bile acids)	Serum (Fasting)	Study group	(↑) **AA** (phenylalanine, alanine, tyrosine, proline, isoleucine, leucine), **Bile acids**: (glycocholic, taurochenodeoxycholic, glycochenodeoxycholic, glycodeoxycholic, deoxycholic, cholic), Phe-Phe dipeptide, LPE (18:0) (↓) betaine, indoleproprionic acid, **LPC** (17:0, 19:0, 20:1, 15:1, LPC 18:1, 15:0, 18:2), **LPE** (16:0, 18:0), **PC** (22:6/18:2, 18:1, 22:6, 20:4/17:0, 22:6/17:0. 15:1/18:2, 18:2/15:0, 18:2/17:0, 22:6/16:0. 20:3/18:0, 14:0/18:1)	3.5
	METSIM	Prospective cohort	110 (55 incident type 2 diabetes cases)	5.9 years					
	BioDIVA	Nested case-control	1,006 (503 incident type 2 diabetes cases)	7.0 years					
Fall et al. 2016	ULSAM (Sweden)	Prospective cohort	1,138 (78 incident type 2 diabetes cases)	NA	**Platform: In-house** UPLC-MS/MS; non-targeted (>7000 metabolic features including phospholipids, fatty acids, amino acids, bile acids)	Serum (Fasting)	Age, sex, WC, BMI, FG	(↑) 2-methylbutyroylcarnitine, barogenin, γ-glutamyl-leucine, tyrosine, deoxycholic acid, MG(18:2) (↓) cortisol, **LPC** (O-16:1/0:0, 20:2), **SM** (33:1, d18:2/18:1, 34:2), PC 42:7, CerPE 38:2	4
	PIVUS (Sweden)	Prospective cohort	970 (70 incident type 2 diabetes cases)	NA					
	TwinGene (Sweden)	Case-cohort	Subcohort: 1,549 Case-cohort: 81 (122 incident type 2 diabetes cases)	NA					
	KORA (Germany)	Prospective cohort	855 (88 cases incident type 2 diabetes)	7.0 years	**Platform: Metabolon Inc.** GC-MS; UPLC-MS; non-targeted (validation)				
Fernandez et al. 2020	MDC (Sweden)	Prospective cohort	3,668 (506 incident type 2 diabetes cases)	21.2 years	**Platform: Lipotype** MS; targeted (178 metabolites from lipid classes: cholesteryl esters, glycerolipids, glycerophospholipids, sphingomyelins)	Plasma (Fasting)	Age, sex	(↑) **DG** (16:0/18:1, 16:0/18:2, 16:1/18:1, 18:1/18:1). **PC** (16:0/20:3, 18:0/20:3), **TG** (46:1, 46:2, 48:0, 48:1, 48:2, 48:3, 49:1, 49:2, 50:1, 50:2, 50:3, 50:4, 51:1, 51:2, 51:3, 52:2, 52:3, 52:5, 53:2, 54:3, 54:6, 54:7, 56:3, 56:5, 56:6, 56:7, 58:7), SM 40:1 (↓) **CE** (20:2), **DG** (18:1/18:3), LPC 18:2, **LPE** (18:1, 18:2, 20:4), **PC** (15:0/18:2, 18:2/18:2, O-16:0/16:0, O-16:0/18:1, O-16:0/18:2, O-16:1/16:0, O-16:1/18:0, O-16:1/18:1, O-16:1/18:2, O-16:2/18:0, O-18:0/20:4, O-18:1/18:2, O-18:2/16:0, O-18:2/18:1), **PE** (O-18:1/18:1, O-18:2/18:2)	5
Friedrich et al. 2015	SHIP (Germany)	Prospective cohort	2,709 (137 incident type 2 diabetes cases)	5.0 years	**Platform: In-house** NMR; targeted (43 metabolites including amino acids, amines, organic acids)	Urine	Age, WC	(↑) **Women:** actetate, alanine, carnitine, ethanol, formate, glucose, glycine, glycolate, lactate, dimethylglycine, TMAO, trigonelline, urea, 3-hydroxyisovalerate; **Men**: glucose (↓) **Women:** Creatinine	4.5

Gängler et al. 2019	HUNT (Norway)	Nested case-control	430 (215 incident type 2 diabetes cases)	3.6 years	**Platform: Metabolon Inc.** UHPLC-MS/MS; non-targeted (735 metabolites including amino acids, carbohydrates, lipids, nucleotides, peptides, xenobiotics)	Serum (Mixed, adjusted)	Age, sex, BMI	(↑) 2-pyrrolidinone, 3-methyl-2-oxobutyrate, 4-methyl-2-oxopentanoate, 5-bromotryptophan, 5-methylthioadenosine, α-ketoglutarate, **AA** (glutamate, isoleucine, phenylalanine, thioproline, tryptophan, tyrosine, valine) **Carbohydrates** (glucose, mannose), **Dipeptides** (γ-glutamylisoleucine, γ-glutamylphenylalanine, γ-glutamyltyrosine, γ-glutamylvaline), PC 16:0/18:1, PE 16:0:18:1 (↓) 1,5-AG, carotene diol, docosahexaenoylcholine, GlcCer 18:2/24:1, imidazole lactate, N-acetylglycine, **SM** (16:1/22:2, 18:1/20:1, 18:1/20:2, 18:1/24:1, 18:2/20:0, 18:2/20:1, 18:2/24:1, 18:2/24:2), **PC** (16:0/16:0, 16:0/16:1, 16:0/18:1, 16:0/18:2)	4
Guasch-Ferre et al. 2019	PREDIMED (Spain)	Case-cohort	892 (251 incident type 2 diabetes cases)	3.8 years	**Platform: Broad Institute** LC-MS/MS; targeted (28 metabolites; acylcarnitines and carnitine)	Plasma (Fasting)	Age, sex, center, smoking, BMI, hypertension, dyslipidemia, physical activity, baseline FG	(↑) **Acylcarnitines** (C2, C3, C4OH, C5, C6) (↓) **Acylcarnitines** (C5DC, C18, C18:1, C20)	5
Guasch-Ferre et al. 2020	PREDIMED (Spain)	Case-cohort	889 (251 incident type 2 diabetes cases)	3.8 years	**Platform: Broad Institute** LC-MS/MS; targeted (14 metabolites including organic acids, sugar phosphates, purines, pyrimidines, bile acids)	Plasma (Fasting)	Age, sex, intervention group, BMI, smoking, leisure-time physical activity, dyslipidemia, hypertension, baseline FG, recruitment center	(↑) Alanine, glycerol 3-phosphate, hexose monophosphate, isocitrate, lactate	5
Gunther et al. 2020	SP2 (Singapore)	Prospective cohort	3,313 (314 incident type 2 diabetes cases)	8.4 years	**Platform: In-house** LC-MS/MS; targeted (59 metabolites including acylcarnitines and amino acids)	Serum (Fasting)	Age, sex, ethnicity, height, parental history of diabetes	(↑) **Acylcarnitines** (C4, C16-OH), alanine, **AA** (phenylalanine, tyrosine), **BCAA** (isoleucine/ leucine, valine) glutamate/glutamine, ornithine, proline (↓) Acylcarnitine C8-DC, glycine, serine	4.5
Hang et al. 2020	NHS, NHSII (US)	Nested case-control	1,828 (457 incident type 2 diabetes cases)	19.0 years	**Platform: Broad Institute** LC-MS/MS; targeted (30 metabolites associated with coffee intake)	Plasma (Fasting)	Age at blood draw, race, BMI, physical activity, alcohol consumption, smoking status, whole grain, fruit, vegetable, PUFA-to-SFA ratio, fish, red meat, SSB, total energy intake, multivitamin use, aspirin/NSAID use, family history of diabetes, menopausal status, menopausal hormone therapy	(↑) **DG** (34:1, 34:2, 34:3. 36:2, 36:3), TG (50:2, 50:3, 50:5, 50,6 52:2, 52:3) (↓) **CE** (18:1, 18:2, 20:4)	5.5

Liu et al. 2017	ERF (Netherlands)	Prospective cohort	2,564 (137 incident type 2 diabetes cases)	11.3 years	**Platform: Netherland Metabolomics Center, Leiden; Center for Proteomics and Metabolomics, Leiden University Medical Center** LC-MS, NMR; targeted (261 metabolites including amino acids, triglycerides, glycerophospholipids, sphingolipids, ceramides, lipoprotein subfractions and components)	Plasma (Fasting)	Age, sex, lipid-lowering medication	(↑) 2-hydroxybutyrate, 1,5-AG, 2-oxoglutaric acid, glycine betaine, glycerol, lactate, isoleucine, methionine, tyrosine, pyruvate, **TG** (48:0, 48:1, 50:5), **VLDL** (TG, FC in XXL particles), **LDL** (ApoB in XS particles) (↓) **LDL** (phospholipids, TG in XXL particle), **HDL** (FC in L particles)	4.5
Liu et al. 2019	PREDIMED (Spain)	Case-cohort	892 (251 incident type 2 diabetes cases)	3.8 years	**Platform: Broad Institute** LC-MS/MS; targeted (2 metabolites: glutamate and glutamine)	Plasma (Fasting)	Age, sex, BMI, smoking, leisure-time physical activity, dyslipidemia, hypertension, recruitment center baseline FG	(↑) Glutamate (↓) Glutamine-to-glutamate ratio	5
Lotta et al. 2016	EPIC-Norfolk (UK)	Case-cohort	1503 (673 incident type 2 diabetes cases)	NA	**Platform: Metabolon Inc.** UPLC-MS/MS; non-targeted (18 metabolites related to BCAA metabolism)	Plasma (Fasting)	Age at baseline, sex, BMI, WC, ethnicity, educational attainment, family history of type 2 diabetes, smoking status, alcohol consumption, level of self-reported physical activity	(↑) 3-methyl-2-oxovalerate, 3-methyl-2-oxobutyrate, 3-hydroxy-2-ethylpropionate, 2-hydroxy-3-methylvalreate, 3-hydroxyisobutyrate α-hydroxyisovalerate, α-hydroxyisocaprocate, isoleucine, leucine, valine, (↓) Isobutrylcarnitine	4
Lu et al. 2016	SCHS (Singapore)	Nested case-control	394 (197 incident type 2 diabetes cases)	6.0 years	**Platform: In-house** UPLC-MS/MS, GC-MS/MS; non-targeted (>7000 metabolic features including amino acids, carbohydrates fatty acids, phospholipids and organic acids)	Serum (Mixed)	BMI, smoking status, history of hypertension	(↑) 1,3-propanediol, **AA** (aminomalonic acid, glycine, isoleucine, leucine, threonine, valine), **carbohydrates** (CDP glucose, galactose, gluconate), **FA** (palmitic, stearic, oleic, linoleic, lactic acid), pyruvate, urea, LPG 12:0, **LPI** (16:1, 18:1, 18:2, 20:3, 20:4, 22:6) (↓) **AA** (2-aminooctanoic acid, ornithine, phosphoserine, proline, serine), glycerol, 9-decenoylcarnitine, CMPF, **LPE** (20:3, 20:5)	5
Lu et al. 2018	SCHS (Singapore)	Nested case-control	320 (160 incident type 2 diabetes cases)	6.0 years	**Platform: In-house** HPLC-MS/MS; targeted (61 metabolites including LPI, fatty acids and acylcarnitines)	Serum (Mixed)	BMI, history of hypertension, smoking, physical activity, fasting status, TG, HDL-C	(↑) **FA** (mystric, palmitic, palmitoleic, stearic, eicosadienoic, dihomo-gamma-linolenic, mead, arachidonic, adrenic), **LPI** (16:1, 18:0)	5
Lu et al. 2019	SCHS (Singapore)	Nested case-control	320 (160 incident type 2 diabetes cases)	6.0 years	**Platform: In-house** HPLC-MS/MS; targeted (19 metabolites; amino acids)	Serum (Mixed)	BMI, history of hypertension, smoking status, HDL-C, and TG	(↑) **AA** (valine, leucine, leucine, tryptophan, glutamic acid, tyrosine)	5
Lu et al. 2019	Jiading Study (China)	Nested case-control	200 (100 incident type 2 diabetes cases)	4.4 years	**Platform: In-house** HPLC-MS/MS; targeted	Serum (Fasting)	Age, sex, BMI, smoking status, drinking status, education, physical	(↑) **TG** (48:1, 48:2, 48:3, 50:0, 50:1, 50:2, 50:3, 51:0, 51:2, 51:3, 53:2, 53:3, 54:3, 54:4, 54:5,	4

	REACTION (China)	Nested case-control	724 (362 incident type 2 diabetes cases)	3.8 years	(>800 metabolites including various lipid subclasses)		activity, family history of diabetes, FPG, and SBP	54:6, 54:7, 55:6. 56:5, 56:6), CE 14:0, LPI 15:1, PC 34:3 (↓) PE plasmalogen 38:4	
Mamtani et al. 2016	SAFHS (US)	Prospective cohort	771 (122 incident type 2 diabetes cases)	5.0 years	**Platform: Metabolomics Laboratory, Baker IDI Heart and Diabetes Institute** LC-MS/MS; targeted (319 metabolites including various lipid subclasses)	Plasma (Fasting)	Age, sex, SBP, DBP, WC, BMI, total serum cholesterol, HDL-C, serum triglycerides, use of anti-lipid and anti-hypertensive drugs	(↑) **Cer** (d18:0/18:0, d18:0/22:0, d18:1/18:0), **TG** (48:0, 50:0, 50:1, 50:2, 52:1) (↓) PE (36:1)	5
Merino et al. 2018	FHS Offspring (US)	Prospective cohort	1,150 (91 incident type 2 diabetes cases)	20.0 years	**Platform: Broad Institute** LC-MS/MS; targeted (220 metabolites including amino acids, carbohydrates, lipids and organic acids)	Plasma (Fasting)	Age, sex, BMI, FG, fasting TG at baseline	(↑) 2-aminodipate, isocitrate, D-glucose, CE 20:3, DG 36:1, **TG** (48:1, 48:1, 52:1, 54:8, 58:11)	6
Muilwijk et al. 2020	HELIUS (Netherlands)	Case-cohort	763 (95 incident type 2 diabetes cases)	4.0 years	**Platform: In-house** LC-MS/MS; targeted (58 metabolites including acylcarnitines amino acids and ceramides)	Plasma (Fasting)	Age, sex, smoking, physical activity, BMI, WC	(↑) **AA** (alanine, glutamate, leucine, lysine, isoleucine, phenylalanine, proline), **Cer** (d17:1, d18:0, d18:1, d18:2, d20:1) (↓) **AA** (glutamine, glycine), **acylcarnitine** (C2, C3DC, C4, C5DC, C6, C6DC, C12, C12OH, C12:1, C18, C18:1), **LacCer** (d18:1, d18:2)	4.5
Noerman et al. 2019	KIHD (Finland)	Prospective cohort	2,682 (432 incident type 2 diabetes cases)	19.3 years	**Platform: In-house** LC-MS/MS; non-targeted (>5300 metabolic features)	Serum (Fasting)	Unadjusted	(↑) 1,3-dimethyluratate, caffeine, creatinine, piperine, **PC** (16:1/18:1, 14:0/16:1, 14:0/16:0, 16:0/22:2, 14:0/18:2), tyrosine (↓) **Acylcarnitine** (16:2, 20:4), choline, DHA, glycerophosphocholine, lactic acid, linoleic acid, **LPC** (22:6, 20:1, 22:5, 20:4, 18:1, 17:1, 18:0, 20:2, 17:0, 16:1, 16:0, 20:5, 18:2, 19:1, O-18:1, O-18:0), **PC** (18:0/23:5, 16:0/24:4, 16:0/25:5)	3.5
Ottosson et al. 2018	MPP (Sweden)	Case-cohort	1,049 (204 incident type 2 diabetes cases)	6.3 years	**Platform: In-house** UPLC-MS/MS; non-targeted (1025 metabolic features)	Plasma (Fasting)	Age, sex, analysis batch, FG, BMI, LDL-C, HDL-C, TG, SBP, antihypertensive treatment, smoking status	(↑) **AA** (glutamate, isoleucine, ornithine, leucine, lysine) (↓) glutamine, asparagine	5.5
Ottosson et al. 2019	MPP (Sweden)	Case-cohort	698 (202 incident type 2 diabetes cases)	6.3 years	**Platform: In-house** UPLC-MS/MS; targeted (78 metabolites including phospholipids, peptides, purine metabolism, carnitine biosynthesis, urea cycle, and tryptophan metabolism)	Plasma (Fasting)	Age, sex, FG, BMI, SBP, fasting TG, HDL-C, LDL-C	(↑)7-methylguanine, creatinine, N_2,N_2-dimethylguanosine, 3-hydroxytrimethyllysine, hypoxanthine, kynureate, N-acetylcarnosine, pantothenate, trimethyllysine, urea (↓) β-carotene	5.5
	MDC (Sweden)	Prospective cohort	3,423 (402 incident type 2 diabetes cases)	18.2 years					
Papandreou et al. 2018	PREDIMED (Spain)	Case-cohort	892 (251 incident type 2 diabetes cases)	3.8 years	**Platform: Broad Institute** LC-MS/MS; targeted (16 metabolites related to TMAO metabolism)	Plasma (Fasting)	Age, sex, BMI, intervention group, baseline FG, smoking, leisure-time physical activity, dyslipidemia, hypertension	(↓) α-glycerophosphocholine, betaine, choline, L-carnitine, **LPC** (16:0, 18:1, 18:0, 20:4, 22:6, 18:1), LPE 16:0, phosphocholine	5

Peddinti et al. 2017	BPS (Finland)	Case-cohort	543 (146 incident type 2 diabetes cases)	7.7 years	**Platform: Metabolon Inc.** UHPLC-MS, GC-MS; non-targeted (542 metabolites) UHPLC-MS/MS; targeted (26 metabolites)	Serum (Fasting)	Age, sex, BMI, fasting insulin level and family history at baseline.	(↑) α-hydroxybutyric, **AA** (isoleucine, valine, glutamate), **carbohydrates** (glucose, mannose, trehasole) (↓) α-tocopherol, bilirubin, glutamine, histamine	5
Qiu et al. 2016	DFTJ (China)	Nested case-control	2078 (1039 incident type 2 diabetes cases)	4.6 years	**Platform: School of Public Health, Tongji Medical College, Huazhong University of Science and Technology** HPLC-MS/MS; targeted (52 metabolites including amino acids, amines, acylcarnitines, cholines, indole and purine derivatives)	Plasma (Fasting)	Age, BMI, education level, smoking status, drinking status, physical activity, SBP, serum HDL-C and TG, FG, family history of diabetes, metabolomics batch	(↑) **AA** (alanine, glutamate, leucine/isoleucine, ornithine, phenylalanine, proline, tyrosine, valine), palmitoylcarnitine, TMAO, inosine (↓) α-glycerophosphocholine, acetylcholine, betaine, creatinine, indoleacetate	4.5
	JSNCD (China)	Nested case-control	1040 (520 incident type 2 diabetes cases)	7.6 years					
Razquin et al. 2019	PREDIMED (Spain)	Case-cohort	853 (243 incident type 2 diabetes cases)	3.8 years	**Platform: Broad Institute** LC-MS/MS; targeted (3 metabolites including 2-aminoadipic, lysine and pipecolic acid)	Plasma (Fasting)	Age, sex and intervention, BMI, smoking, dyslipidemia, hypertension, baseline FPG	(↑) 2-aminoadipic acid, lysine	5
Reboholz et al. 2018	ARIC (US)	Prospective cohort	2939 (1126 incident type 2 diabetes cases)	20.0 years	**Platform: Metabolon Inc.** UPLC-MS/MS; non-targeted (245 metabolites including amino acids, carbohydrates, lipids, nucleotides, peptides and xenobiotics)	Serum (Fasting)	Age, sex, race, centre, batch, education level, SBP, DBP, BMI, HDL-C, LDL-C, smoking status, physical activity level, history of cardiovascular disease, eGFR and FG	(↑) isoleucine, leucine, valine, 3-(4-hydroxyphenyl)lactate, trehasole, erythritol (↓) asparagine	5
Salvaloinen et al. 2017	GS (Sweden)	Nested case-control	391 (69 incident type 2 diabetes cases)	5.5 years	**Platform: In-house** GC-MS/MS; non-targeted (10 metabolites including alkylresorcinols, fatty acids and tocopherols)	Plasma (Fasting)	Unadjusted	(↓) α-tocopherol, CMPF	3
Shi et al. 2018	VIP (Sweden)	Nested case-control	842 (421 incident type 2 diabetes cases)	7.0 years	**Platform: In-house** LC-MS/MS; non-targeted (>29,000 metabolic features)	Plasma (Fasting)	Smoking status, education, physical activity at diet assessment, daily energy intake, FPG, BMI, TC, TG, SBP, DBP	No significant associations	5
Shi et al. 2018	VIP (Sweden)	Nested case-control	1006 (503 incident type 2 diabetes cases)	7.0 years	**Platform: In-house** LC-MS/MS; non-targeted (>29,000 metabolic features)	Plasma (Fasting)	FPG, BMI, physical activity, education, smoking, consumption of alcohol intake, dietary fiber, red and processed meat intake, TC, TG, SBP, DBP	(↑) 3-methyl-2-oxovaleric acid, 3-hydroxyisovalerylcarnitine, **AA** (alanine, citrulline, isoleucine, leucine, tryptophan, tyrosine) (↓) 2-Hydroxyethanesulfonate, N-acetylglycine, **LPC** (19:1, 17:0, 20:1, p-16:0, 16:0, 18:2, 18:1), **PC** (17:0/18:2)	5
Shi et al. 2019	VIP (Sweden)	Nested case-control	842 (421 incident type 2 diabetes cases)	7.0 years	**Platform: In-house** LC-MS/MS; non-targeted (>29,000 metabolic features)	Plasma (Fasting)	BMI, smoking status, education, physical activity, and daily energy intake	(↑) Eicosapentaenoic acid (↓) LPE 18:2	5

Shi et al. 2019	VIP (Sweden)	Nested case-control	842 (421 incident type 2 diabetes cases)	7.0 years	**Platform: In-house** LC-MS/MS; non-targeted (>29,000 metabolic features)	Plasma (Fasting)	BMI, FPG, smoking status, education, physical activity, total daily energy, Baltic Sea Diet Score	(↑) Caffeine, Cyclo(leucylprolyl) peptide, ethyl 3-mercaptopropanoic acid, PE 20:4/16:0 (↓) 7-hydroxy-4-(methoxymethyl)coumarin	5
Strand et al. 2018	WENBIT+ (Norway)	Prospective cohort	2,519 (173 incident type 2 diabetes cases)	7.7 years	**Platform: In-house** LC-MS/MS; targeted (8 metabolites related to carnitine metabolism)	Serum (Mixed)	Age, sex, fasting status, BMI, eGFR, HbA1c, TG, HDL-C, study center	(↑) trimethyllysine, γ-butyrobetaine, acylcarnitine C16	4
Sun et al. 2016	NHAPC (China)	Prospective cohort	2,103 (507 incident type 2 diabetes cases)	6.0 years	**Platform: In-house** LC-MS/MS; targeted (34 metabolites; acylcarnitines)	Plasma (Fasting)	Age, sex, geographical region, residence, current smoking, drinking, physical activity, family history of diabetes, BMI, SBP, FG, HbA1c	(↑) Carnitine, **acylcarnitines** (C3DC, C8:1, C16:2, C18, C18:OH, C18:1, C18:2, C20, C20:4) (↓) **Carnitine precursors** (3-dehydroxycarnitine, 3-dehydrocarnitine) **acylcarnitines** (C10DC, C12DC, C12, C12OH, C12:1)	5.5
Svingen et al. 2016	WENBIT+ (Norway)	Prospective cohort	3,621 (233 incident type 2 diabetes cases)	7.5 years	**Platform: In-house** LC-MS/MS, GC-MS/MS; targeted (5 metabolites related to choline metabolism)	Plasma/ serum (Mixed), Urine	Age, sex, fasting status, BMI, HbA1c, eGFR, HDL-C, albumin-to-creatinine ratio, use of loop diuretics, thiazides, b-blockers, statins, ACE inhibitors, angiotensin receptor blockers	(↑) **Urine** (betaine, dimethylglycine, sarcosine) (↓) Plasma betaine	4.5
Vangipurapu et al. 2019	METSIM (Finland)	Prospective cohort	4,851 (522 incident type 2 diabetes cases)	7.4 years	**Platform: Metabolon Inc.** UPLC-MS/MS; non-targeted (20 metabolites: amino acids)	Plasma (Fasting)	Batch	(↑) **AA** (tyrosine, alanine, isoleucine, aspartate, glutamate)	3.5
Vangipurapu et al. 2020	METSIM (Finland)	Prospective cohort	4,851 (522 incident type 2 diabetes cases)	7.4 years	**Platform: Metabolon Inc.** UHPLC-MS/MS; non-targeted (86 metabolites related to gut microbiota)	Plasma (Fasting)	Batch	(↑) creatine, dimethylglycine, kynurenate, urate, xanthine, xanthurenate, 3-(4-hydroxyphenyl) propionate, 2-hydroxyhippurate, 2-hydroxybutyrate, **MG** (14:0, 18:1, 16:1) (↓) LPC 18:2	3.5
Yang et al. 2018	KoGES (South Korea)	Prospective cohort	1,939 (282 incident type 2 diabetes cases)	8.0 years	**Platform: Biocrates** FIA-MS/MS, LC-MS/MS; targeted (135 metabolites: acylcarnitines, amino acids, biogenic amines, hexose, glycerophospholipids, sphingolipids)	Serum (Fasting)	Age, sex, BMI, educational level, household income, smoking status, drinking status, METs, total energy, consumptions of coffee, red meat and whole grain, and history of hypertension	(↑) **AA** (alanine, arginine, isoleucine, proline, tyrosine, valine, hexose), **PC** (32:1, 34:1, 36:1, 40:5, 42:5) (↓) Spermine, **LPC** (17:0, 18:2), **PC** (38:0, 40:1, 42:1, O-34:3, O-36:3), **SM** (16:1, OH-22:2)	4.5
Yu et al. 2016	SWHS, SMHS (China)	Prospective cohort	976 (73 incident type 2 diabetes cases)	NA	**Platform: Metabolon Inc.** LC-MS/MS, GC-MS/MS; non-targeted (>1300 metabolic features: carbohydrates, amino acids, other organic acids, lipids, nucleotides, peptides)	Plasma (Mixed)	Age, sex, smoking, waist circumference, history of hypertension, time of blood draw, time interval since last meal, and assay batch	(↑) **Carbohydrates** (1,5-AG, glucose, fructose, mannose), 2-hydroxybutyrate, 2-amimobutyrate, 2-ketobutyrate, glycine, 3-methoxythyrosine	3.5

Yu et al. 2018	PREDIMED (Spain)	Case-cohort	892 (251 incident type 2 diabetes cases)	3.8 years	**Platform: Broad Institute** LC-MS/MS; targeted (5 metabolites including tryptophan–kynurenine metabolites)	Plasma (Fasting)	Age, sex, intervention group, BMI, smoking, leisure-time physical activity, dyslipidemia, hypertension baseline FG	(↑) Quinolinic acid (1-year change)	5
Yu et al. 2019	PREDIMED (Spain)	Case-cohort	892 (251 incident type 2 diabetes cases)	3.8 years	**Platform: Broad Institute** LC-MS/MS; targeted (6 metabolites including urea cycle and methylarginines)	Plasma (Fasting)	Age, sex, intervention group, BMI, smoking, leisure-time physical activity, dyslipidaemia, hypertension, baseline FG, plasma creatinine	(↓) Arginine (1-year change)	5
Yun et al. 2020	NHAPC (China)	Prospective cohort	1,974 (529 incident type 2 diabetes cases)	6.0 years	**Platform: In-house** LC-MS/MS; targeted (76 metabolites from lipid classes: ceramides, sphingomyelins and their derivates	Plasma (Fasting)	Age, sex, region, residence, educational attainment, current smoking, alcohol drinking, physical activity, family history of diabetes, BMI	(↑) **Cer** (d18:1/18:1, d18:1/20:0, d18:1/20:1, d18:1/22:1), **HexCer** d18:1/20:1, **SM** (34:0, 34:1, (2OH) 34:1, 36:0, 36:1, 38:0, (OH) 38:3, 40:0. 42:3)	5

(↑) – positive association (i.e. higher metabolite, higher risk), (↓) – negative association (i.e. lower metabolite, lower risk), ACE – angiotensin-converting enzyme, AHEI – Alternate Healthy Eating Index BMI – body mass index, (S/D)BP – Systolic/diastolic blood pressure, F(P)G – fasting (plasma) glucose, HbA1c – glycated hemoglobin, eGFR – estimated glomerular filtration rate, HDL-C – high-density lipoprotein cholesterol, HOMA-IR – homeostatic model assessment for insulin resistance, LDL-C – low density lipoprotein cholesterol, NSAID – non-steroidal anti-inflammatory drugs, PUFA – polyunsaturated fatty acids, SFA – saturated fatty acids, SSB – sugar-sweetened beverages, TC – total cholesterol, WC – waist circumference.

Metabolite abbreviations: 1,5-AG – 1,5-Anhydroglucitol, (BC/A)AA – (branched-chain/aromatic) amino acids, CE – cholesteryl esters, Cer – ceramides, CMPF - 3-Carboxy-4-methyl-5-propyl-2-furanpropanoic acid, DG – diglycerides, (H/I/L/VL)DL – (high/intermediate/low/very low) density lipoprotein, FA – fatty acids, LPI – lysophosphatidylinositol, (L)PC(P) – (lyso)phosphatidylcholine (plasmalogen), (L)PE – (lyso)phosphatidylethanolamine, SM – sphingomyelin, TG – triglycerides, TMAO – trimethylamine N-oxide.

Methods abbreviations: GC – gas chromatography, FIA – flow injection analysis, (HP/UP/UHP)LC – high/ultra/ultra-high performance liquid chromatography, MS – mass spectrometry, MS/MS – tandem mass spectrometry.

Study abbreviations: ARIC - Atherosclerosis Risk in Communities, BioDIVA – Biomarker Discovery Project in High Grade Serous Ovarian Cancer, BPS - Botnia Prospective Study, DFTJ - Dongfeng-Tongji Cohort, DILGOM - Dietary, Lifestyle, and Genetic Determinants of Obesity and Metabolic Syndrome, DPP - Diabetes Prevention Program, EPIC - European Prospective Investigation into Cancer and Nutrition, FHS – Framingham Heart Study, ERF - Erasmus Rucphen Family Study, FDPS - Finnish Diabetes Prevention Study, GS - Gothenburg Study, HCHS/SOL – Hispanic Community Health Study / Study of Latinos, HELIUS – Healthy Life in an Urban Setting, HUNT - Nord-Trøndelag Health Study, JSNCD - Jiangsu Noncommunicable Disease Cohort , KIHD – Kuopio Ischaemic Heart Disease Risk Factor Study, KoGES - Korean Genome and Epidemiology Study, KORA - Cooperative Health Research in the Region of Augsburg, MDC - Malmö Diet and Cancer, MPP – Malmö Preventive Project, METSIM – Metabolic Syndrome in Men, NFBC - Northern Finland Birth Cohort, NHAPC - Nutrition and Health of Aging Population in China, NHS – Nurses' Health Study, PIVUS - Prospective Investigation of the Vasculature in Uppsala Seniors, PREDIMED - Prevención con Dieta Mediterránea, REACTION - Risk Evaluation of Cancers in Chinese Diabetic Individuals, SAFHS – San Antonio Family Heart Study, SCHS – Singapore Chinese Health Study, SHDS – Shanghai Diabetes Study, SHIP - Study of Health in Pomerania, SMHS – Shanghai Men's Health Study, SMEC – Singapore Multi-Ethnic Cohort, SP2 – Singapore Prospective Study, SWHS – Shanghai Women's Health Study, ULSAM - Uppsala Longitudinal Study of Adult Men, VIP – Västerbotten Intervention Programme, YFS - Cardiovascular Risk in Young Finns Study, WENBIT – Western Norway Vitamin B Trial.

Study quality assessment: Study quality was assessed using 6 criteria (up to 1 point per criterion), including participation (1 point if characteristics of the study population were described and inclusion and exclusion criteria reported and if there was a record of sampling, period, and location of recruitment), attrition (1 point if completeness of follow-up described and adequate), exposure characteristics (1 point if description of metabolomics method and metabolites analyzed), validated outcome (1 point if criteria for diabetes/prediabetes were defined), control of confounding (1 point if the models were adjusted at least for age, sex, BMI, and fasting glucose), and analysis (1 point if risk estimate determination and statistical approaches were appropriate for study design and multiple comparison testing was applied). Scores were summed; studies with scores <3 and ≥3 were considered to be of lower and higher quality, respectively.

Supplementary Table 7. Pooled relative risk for the association between study specific 1-SD increase in metabolite level and risk of incident type 2 diabetes.

No.	Compound	HMDB/ChEBI ID	N	SRR (95% CI)	P	P-FDR	I^2	τ^2
BCAA metabolism								
1	2-hydroxy-3-methylbutyrate	HMDB00407	3	1.18 (1.04; 1.34)	**0.008**	**0.029**	0	0.000
2	2-hydroxyisocaproate	HMDB00746	3	1.22 (1.06; 1.39)	**0.004**	**0.017**	0	0.000
3	3-hydroxy-2-ethylpropionate	HMDB00396	2	1.36 (1.20; 1.55)	**<0.001**	**<0.001**	0	0.000
4	3-hydroxyisobutyrate	HMDB00023	5	1.36 (1.18; 1.56)	**<0.001**	**<0.001**	69	0.016
5	3-hydroxyisovalerate	HMDB00754	2	1.19 (1.04; 1.37)	**0.011**	**0.037**	0	0.000
6	3-methyl-2-oxobutyrate	HMDB00019	6	1.49 (1.05; 2.11)	**0.024**	0.072	93	0.167
7	3-methyl-2-oxovalerate	HMDB00491	6	1.53 (1.06; 2.20)	**0.022**	0.067	94	0.186
8	4-methyl-2-oxopentanoate	HMDB00695	4	1.48 (0.98; 2.24)	0.065	0.153	90	0.157
9	Isoleucine	HMDB00172	19	1.54 (1.36; 1.74)	**<0.001**	**<0.001**	88	0.058
10	Leucine	HMDB00687	23	1.40 (1.29; 1.52)	**<0.001**	**<0.001**	74	0.027
11	Valine	HMDB00883	19	1.40 (1.25; 1.57)	**<0.001**	**<0.001**	86	0.047
AAA metabolism								
12	3-(4-hydroxyphenyl)lactate	HMDB00755	2	1.35 (1.01; 1.81)	**0.046**	0.119	67	0.030
13	3-methoxytyrosine	HMDB01434	3	0.81 (0.61; 1.07)	0.134	0.258	68	0.042
14	4-hydroxyphenylpyruvate	HMDB00707	2	1.17 (0.82; 1.66)	0.396	0.538	79	0.053
15	Benzoate	HMDB01870	3	0.97 (0.88; 1.07)	0.569	0.687	8	0.001
16	Hippurate	HMDB00714	9	0.97 (0.89; 1.06)	0.466	0.601	64	0.010
17	Hydrocinnamate	HMDB00764	3	0.86 (0.80; 0.93)	**<0.001**	**<0.001**	0	0.000
18	Phenylalanine	HMDB00159	18	1.30 (1.16; 1.45)	**<0.001**	**<0.001**	87	0.044
19	Tyrosine	HMDB00158	18	1.35 (1.22; 1.49)	**<0.001**	**<0.001**	81	0.031
Alanine, aspartate, and glutamate metabolism								
20	Alanine	HMDB00161	21	1.32 (1.20; 1.44)	**<0.001**	**<0.001**	79	0.030
21	Asparagine	HMDB00168	8	1.03 (0.82; 1.29)	0.817	0.885	95	0.099
22	Aspartic acid	HMDB00191	6	1.13 (1.00; 1.28)	0.060	0.146	78	0.016
23	Glutamate	HMDB00148	13	1.38 (1.20; 1.60)	**<0.001**	**<0.001**	91	0.058
24	Glutamine	HMDB00641	19	0.84 (0.75; 0.94)	**0.002**	**0.011**	89	0.051
Arginine and proline metabolism, Urea cycle								
25	Arginine	HMDB00517	13	1.00 (0.91; 1.11)	0.965	0.988	81	0.024
26	Citrulline	HMDB00904	12	1.00 (0.94; 1.06)	0.997	0.998	31	0.003
27	Creatinine	HMDB00562	13	0.98 (0.89; 1.09)	0.736	0.835	72	0.022
28	Hydrooxyproline	HMDB00725	3	1.04 (0.96; 1.12)	0.324	0.469	0	0.000
29	NMMA	HMDB29416	4	1.01 (0.88; 1.16)	0.851	0.906	67	0.012
30	Ornithine	HMDB00214	13	1.06 (0.97; 1.17)	0.212	0.358	72	0.018
31	Proline	HMDB00162	2	1.65 (0.84; 3.23)	0.148	0.278	95	0.226
32	SDMA+ADMA	HMDB03334/ HMDB01539	10	0.97 (0.92; 1.02)	0.206	0.353	0	0.000
33	Urea	HMDB00294	5	1.18 (0.97; 1.44)	0.102	0.213	86	0.041
34	Xanthine	HMDB00292	3	1.11 (0.92; 1.34)	0.295	0.438	87	0.023

Beta-alanine metabolism								
35	Beta-alanine	HMDB00056	2	0.92 (0.83; 1.01)	0.089	0.192	0	0.000
36	Pantothenate	HMDB00210	6	1.06 (0.92; 1.23)	0.404	0.548	79	0.025
Glycine, serine, and threonine metabolism								
37	2-hydroxybutyrate	HMDB00008	8	1.45 (1.24; 1.70)	**<0.001**	**<0.001**	85	0.040
38	2-ketobutyrate	HMDB00005	2	1.28 (0.65; 2.53)	0.483	0.614	91	0.221
39	3-hydroxypyruvate	HMDB01352	2	1.29 (0.80; 2.08)	0.287	0.430	83	0.098
40	Creatine	HMDB00064	5	1.08 (0.91; 1.28)	0.381	0.528	87	0.031
41	Glycine	HMDB00123	18	0.79 (0.68; 0.90)	**0.001**	**0.003**	89	0.071
42	N-acetylglycine	HMDB00532	4	0.82 (0.67; 1.00)	**0.045**	0.119	72	0.028
43	Sarcosine	HMDB00271	4	1.01 (0.94; 1.08)	0.832	0.895	0	0.000
44	Serine	HMDB00187	12	0.92 (0.83; 1.02)	0.130	0.256	80	0.023
45	Threonine	HMDB00167	9	1.01 (0.96; 1.05)	0.796	0.872	0	0.000
Histidine metabolism								
46	Histamine	HMDB00870	3	1.06 (0.94; 1.18)	0.332	0.473	56	0.006
47	Histidine	HMDB00177	17	0.95 (0.90; 1.01)	0.111	0.227	55	0.008
Lysine metabolism								
48	2-aminoadipate	HMDB00510	3	1.33 (1.18; 1.51)	**<0.001**	**<0.001**	0	0.000
49	Lysine	HMDB00182	11	1.10 (1.05; 1.15)	**<0.001**	**<0.001**	0	0.000
Methionine metabolism								
50	2-aminobutyrate	HMDB00452	2	1.53 (1.04; 2.27)	**0.032**	0.092	77	0.062
51	Methionine	HMDB00696	12	1.10 (1.04; 1.17)	**0.001**	**0.006**	46	0.005
52	Putrescine	HMDB01414	2	0.95 (0.87; 1.04)	0.250	0.403	0	0.000
53	Spermidine	HMDB01257	3	0.90 (0.84; 0.96)	**0.002**	**0.007**	0	0.000
Taurine and hypotaurine metabolism								
54	Taurine	HMDB00251	6	0.96 (0.83; 1.12)	0.638	0.741	89	0.031
Tryptophan Metabolism								
55	Indoleacetate	HMDB00197	4	0.92 (0.79; 1.07)	0.268	0.411	70	0.014
56	Indolelactate	HMDB00671	3	1.13 (1.06; 1.21)	**<0.001**	**0.001**	0	0.000
57	Indolepropionate	HMDB02302	8	0.82 (0.74; 0.92)	**<0.001**	**<0.001**	67	0.014
58	Kynurenate	HMDB00715	4	1.25 (0.90; 1.74)	0.188	0.333	95	0.104
59	Kynurenine	HMDB00684	6	1.00 (0.88; 1.13)	0.998	0.998	76	0.017
60	Quinolinate	HMDB00232	2	0.98 (0.89; 1.08)	0.642	0.741	0	0.000
61	Serotonin	HMDB00259	4	1.04 (0.89; 1.21)	0.642	0.741	90	0.023
62	Tryptophan	HMDB00929	14	1.14 (0.99; 1.30)	0.065	0.153	88	0.054
Glycolysis/gluconeogenesis and TCA cycle								
63	2-hydroxyglutarate	HMDB59655	2	1.06 (0.97; 1.16)	0.223	0.369	17	0.002
64	Citrate	HMDB00193	6	0.95 (0.87; 1.04)	0.244	0.399	0	0.000
65	Fumarate	HMDB00134	3	0.94 (0.84; 1.05)	0.266	0.411	21	0.002
66	Glycerol	HMDB00131	9	1.11 (0.88; 1.40)	0.365	0.510	91	0.091
67	Isocitrate	HMDB00193	2	1.35 (1.00; 1.84)	0.052	0.130	82	0.040
68	Lactate	HMDB00190	12	1.16 (1.01; 1.34)	**0.034**	0.096	86	0.047

69	Malate	HMDB00156	4	1.04 (0.97; 1.13)	0.270	0.411	0	0.000
70	Oxoglutarate	HMDB00208	4	1.30 (0.85; 1.97)	0.223	0.369	93	0.165
71	Pyruvate	HMDB00243	11	1.24 (1.10; 1.40)	**<0.001**	**0.003**	74	0.027
72	Succinate	HMDB00254	4	1.02 (0.98; 1.07)	0.352	0.495	0	0.000
Ketone body metabolism								
73	3-hydroxybutyrate	HMDB00011	9	1.17 (0.98; 1.39)	0.074	0.169	83	0.054
74	Acetoacetate	HMDB00060	7	1.12 (0.99; 1.26)	0.071	0.163	56	0.013
Mono-, di- and oligosaccharides								
75	1,5-anhydrosorbitol	HMDB02712	5	0.81 (0.54; 1.21)	0.311	0.458	96	0.195
76	Fructose	HMDB00660	3	1.33 (0.89; 1.98)	0.169	0.311	84	0.105
77	Gluconate	HMDB00625	5	1.27 (1.04; 1.56)	**0.020**	0.064	66	0.030
78	Glucose	HMDB00122	4	2.53 (1.09; 5.87)	**0.031**	0.089	97	0.699
79	Mannitol	HMDB00765	2	0.65 (0.29; 1.46)	0.295	0.438	84	0.290
80	Mannose	HMDB00169	3	2.58 (1.59; 4.20)	**<0.001**	**0.001**	87	0.157
81	Trehalose	HMDB00975	2	1.17 (1.09; 1.25)	**<0.001**	**<0.001**	0	0.000
Ascorbate and aldarate metabolism								
82	Threonate	HMDB00943	2	0.86 (0.65; 1.15)	0.312	0.458	60	0.025
Choline metabolism								
83	Betaine	HMDB00043	10	0.82 (0.76; 0.89)	**<0.001**	**<0.001**	49	0.007
84	Choline	HMDB00097	9	0.94 (0.85; 1.04)	0.234	0.384	72	0.016
85	Dimethylglycine	HMDB00092	7	1.04 (0.92; 1.17)	0.549	0.669	90	0.020
86	Trimethylamine N-oxide	HMDB00925	8	1.07 (1.00; 1.14)	0.065	0.153	48	0.004
Inositol metabolism								
87	Myo-inositol	HMDB00211	2	0.85 (0.68; 1.07)	0.177	0.317	14	0.004
Methylxanthine metabolism								
88	1-methylurate	HMDB03099	2	0.95 (0.81; 1.11)	0.491	0.619	0	0.000
89	1,3-dimethylurate	HMDB01857	2	1.25 (0.97; 1.59)	0.079	0.178	45	0.014
90	Caffeine	HMDB01847	4	1.17 (0.95; 1.44)	0.132	0.257	63	0.028
91	Hypoxanthine	HMDB00725	6	1.11 (0.95; 1.29)	0.198	0.343	83	0.029
92	Paraxanthine	HMDB01860	2	0.99 (0.85; 1.15)	0.870	0.921	0	0.000
93	Theobromine	HMDB02825	2	0.98 (0.68; 1.41)	0.896	0.935	78	0.055
94	Theophylline	HMDB01889	2	1.14 (0.97; 1.35)	0.122	0.242	0	0.000
Nicotinate and nicotinamide metabolism								
95	1-methylnicotinamide	HMDB00699	2	1.00 (0.90; 1.11)	0.973	0.988	30	0.002
96	Cotinine	HMDB01046	3	1.11 (0.98; 1.25)	0.117	0.231	52	0.007
97	Niacinamide	HMDB01406	5	1.04 (0.89; 1.21)	0.640	0.739	81	0.025
98	Trigonelline	HMDB00875	2	0.98 (0.83; 1.16)	0.803	0.882	0	0.000
Purine metabolism								
99	Inosine	HMDB00195	3	1.12 (1.00; 1.26)	**0.049**	0.124	21	0.002
100	Urate	HMDB00289	3	1.19 (0.99; 1.43)	0.062	0.148	81	0.020
Pyrimidine metabolism								
101	3-aminoisobutanate	HMDB03911	3	0.95 (0.88; 1.03)	0.210	0.357	7	0.000

102	Pseudouridine	HMDB00767	3	0.89 (0.66; 1.19)	0.421	0.564	82	0.053
103	Uridine	HMDB00296	5	0.97 (0.75; 1.24)	0.788	0.869	91	0.071
Ubiquinone and other terpenoid-quinone biosynthesis								
104	γ-tocopherol	HMDB01492	2	0.87 (0.73; 1.04)	0.139	0.267	0	0.000
Xenobiotics, food components								
105	2-hydroxyhippurate	HMDB00840	2	1.08 (0.89; 1.30)	0.433	0.571	44	0.009
106	2-hydroxyisobutyrate	HMDB00729	3	1.33 (1.22; 1.45)	**<0.001**	**<0.001**	0	0.000
107	Erythirol	HMDB02994	2	1.12 (0.92; 1.35)	0.254	0.408	0	0.000
108	Piperine	HMDB29377	3	0.98 (0.74; 1.30)	0.884	0.927	76	0.048
Acylcarnitine metabolism								
109	3-dehydrocarnitine	HMDB12154	2	0.72 (0.50; 1.02)	0.066	0.154	84	0.056
110	Deoxycarnitine	HMDB01161	3	0.66 (0.46; 0.94)	**0.022**	0.067	90	0.088
111	Trimethyllysine	HMDB01325	4	1.25 (1.15; 1.35)	**<0.001**	**<0.001**	0	0.000
112	Carnitine	HMDB00062	14	1.04 (0.96; 1.14)	0.330	0.473	74	0.018
113	Acylcarnitine C2	HMDB00201	16	1.00 (0.94; 1.07)	0.993	0.998	56	0.008
114	Acylcarnitine C3	HMDB00824	16	1.06 (0.98; 1.14)	0.131	0.256	73	0.015
115	Acylcarnitine C3DC	HMDB02095	5	1.07 (0.81; 1.40)	0.632	0.741	94	0.083
116	Acylcarnitine C4	HMDB02013	14	0.97 (0.88; 1.06)	0.473	0.606	76	0.020
117	Acylcarnitine C4DC	HMDB62785	4	1.10 (1.02; 1.18)	**0.013**	**0.046**	0	0.000
118	Acylcarnitine C4OH	HMDB0013127	6	1.09 (1.02; 1.16)	**0.011**	**0.037**	0	0.000
119	Acylcarnitine C5	HMDB13128	14	1.13 (1.08; 1.18)	**<0.001**	**<0.001**	18	0.001
120	Acylcarnitine C5DC	HMDB13130	7	0.97 (0.81; 1.16)	0.722	0.821	88	0.046
121	Acylcarnitine C5OH	CHEBI:86467	6	1.14 (1.03; 1.26)	**0.011**	**0.037**	58	0.008
122	Acylcarnitine C5:1	HMDB02366	6	0.96 (0.86; 1.08)	0.483	0.614	72	0.013
123	Acylcarnitine C6	HMDB00756	10	0.94 (0.82; 1.07)	0.327	0.471	84	0.036
124	Acylcarnitine C6DC	NA	5	0.85 (0.73; 1.00)	**0.048**	0.123	69	0.020
125	Acylcarnitine C6OH	CHEBI:88772	2	0.97 (0.76; 1.25)	0.832	0.895	68	0.023
126	Acylcarnitine C7	CHEBI:74303	2	1.00 (0.91; 1.11)	0.960	0.988	0	0.000
127	Acylcarnitine C7DC	NA	5	0.92 (0.84; 1.01)	0.080	0.179	55	0.006
128	Acylcarnitine C8	HMDB00791	13	0.97 (0.92; 1.02)	0.221	0.368	22	0.002
129	Acylcarnitine C8OH	CHEBI:84100	2	1.01 (0.72; 1.41)	0.957	0.988	80	0.048
130	Acylcarnitine C8:1	CHEBI:86052	5	1.16 (1.07; 1.25)	**<0.001**	**0.002**	39	0.003
131	Acylcarnitine C9	HMDB13288	3	1.03 (0.94; 1.13)	0.557	0.677	35	0.002
132	Acylcarnitine C10	HMDB00651	11	1.01 (0.93; 1.10)	0.779	0.865	64	0.011
133	Acylcarnitine C10:1	CHEBI:86063	2	0.88 (0.78; 0.98)	**0.021**	0.066	0	0.000
134	Acylcarnitine C12	HMDB02250	11	0.93 (0.84; 1.03)	0.175	0.315	71	0.018
135	Acylcarnitine C12DC	CHEBI:74121	2	0.93 (0.74; 1.18)	0.564	0.684	89	0.025
136	Acylcarnitine C12OH	CHEBI:73056	4	0.78 (0.47; 1.30)	0.344	0.487	93	0.248
137	Acylcarnitine C12:1	CHEBI:86065	8	0.89 (0.72; 1.10)	0.284	0.427	91	0.078
138	Acylcarnitine C13	CHEBI:137646	3	0.87 (0.75; 1.02)	0.085	0.188	0	0.000
139	Acylcarnitine C14	HMDB05066	10	0.99 (0.92; 1.06)	0.746	0.844	44	0.005
140	Acylcarnitine C14OH	CHEBI:137647	4	1.31 (0.94; 1.85)	0.114	0.230	93	0.104

141	Acylcarnitine C14:1	CHEBI:86066	9	0.94 (0.89; 0.99)	**0.020**	0.065	0	0.000
142	Acylcarnitine C14:1OH	CHEBI:86067	4	1.16 (0.75; 1.80)	0.492	0.619	96	0.180
143	Acylcarnitine C14:2	CHEBI:86069	7	0.97 (0.91; 1.02)	0.249	0.403	10	0.001
144	Acylcarnitine C16	HMDB00222	15	1.06 (0.99; 1.12)	**0.083**	0.184	52	0.007
145	Acylcarnitine C16OH	CHEBI:73070	4	1.07 (0.93; 1.23)	0.358	0.501	62	0.011
146	Acylcarnitine C16:1	CHEBI:86032	6	1.11 (0.81; 1.52)	0.517	0.640	94	0.142
147	Acylcarnitine C16:1OH	CHEBI:86033	3	1.02 (0.93; 1.13)	0.646	0.744	0	0.000
148	Acylcarnitine C16:2	CHEBI:86035	6	1.13 (0.82; 1.55)	0.466	0.601	96	0.143
149	Acylcarnitine C18	HMDB00848	14	0.97 (0.81; 1.17)	0.759	0.854	94	0.108
150	Acylcarnitine C18OH	CHEBI:73077	3	1.17 (0.93; 1.47)	0.175	0.315	58	0.024
151	Acylcarnitine C18:1	CHEBI:86475	11	0.98 (0.84; 1.15)	0.835	0.895	90	0.058
152	Acylcarnitine C18:1OH	CHEBI:86039	4	1.00 (0.83; 1.21)	0.979	0.989	58	0.020
153	Acylcarnitine C18:2	CHEBI:86480	10	1.08 (0.88; 1.31)	0.471	0.605	94	0.092
154	Acylcarnitine C18:2OH	CHEBI:73075	3	1.09 (0.87; 1.36)	0.441	0.578	53	0.020
155	Acylcarnitine C20	HMDB06460	6	1.08 (0.78; 1.49)	0.651	0.747	95	0.147
156	Acylcarnitine C20:4	HMDB06455	5	1.18 (0.78; 1.78)	0.434	0.571	96	0.203
157	Acylcarnitine C26	NA	2	1.02 (0.91; 1.15)	0.761	0.854	0	0.000
Triacylglycerols								
158	TG 46:1	CHEBI:85869	3	1.33 (1.23; 1.44)	**<0.001**	**<0.001**	22	0.001
159	TG 46:2	CHEBI:77447	3	1.29 (1.22; 1.37)	**<0.001**	**<0.001**	0	0.000
160	TG 48:0	CHEBI:85870	5	1.55 (1.37; 1.76)	**<0.001**	**<0.001**	79	0.014
161	TG 48:1	CHEBI:85726	7	1.46 (1.32; 1.61)	**<0.001**	**<0.001**	73	0.012
162	TG 48:2	CHEBI:85725	6	1.31 (1.21; 1.43)	**<0.001**	**<0.001**	63	0.006
163	TG 48:3	CHEBI:85871	6	1.26 (1.09; 1.47)	**0.002**	**0.010**	83	0.025
164	TG 48:4	CHEBI:85825	2	1.24 (1.13; 1.36)	**<0.001**	**<0.001**	0	0.000
165	TG 49:2	CHEBI:85727	2	1.38 (1.30; 1.47)	**<0.001**	**<0.001**	0	0.000
166	TG 50:0	CHEBI:85874	6	1.51 (1.30; 1.75)	**<0.001**	**<0.001**	75	0.023
167	TG 50:1	CHEBI:84665	6	1.55 (1.38; 1.73)	**<0.001**	**<0.001**	80	0.015
168	TG 50:2	CHEBI:84662	8	1.52 (1.36; 1.70)	**<0.001**	**<0.001**	82	0.018
169	TG 50:3	CHEBI:85729	7	1.37 (1.14; 1.66)	**0.001**	**0.005**	93	0.055
170	TG 50:4	CHEBI:85832	5	1.15 (0.99; 1.34)	0.061	0.148	79	0.020
171	TG 50:5	CHEBI:90301	5	1.26 (1.13; 1.39)	**<0.001**	**<0.001**	55	0.007
172	TG 50:6	CHEBI:141285	2	1.25 (1.13; 1.37)	**<0.001**	**<0.001**	0	0.000
173	TG 51:0	CHEBI:140862	3	1.38 (1.25; 1.53)	**<0.001**	**<0.001**	0	0.000
174	TG 51:1	CHEBI:85733	2	1.54 (1.36; 1.74)	**<0.001**	**<0.001**	51	0.004
175	TG 51:2	CHEBI:85732	4	1.33 (1.21; 1.46)	**<0.001**	**<0.001**	51	0.004
176	TG 51:3	CHEBI:85731	3	1.31 (1.22; 1.42)	**<0.001**	**<0.001**	0	0.000
177	TG 52:1	CHEBI:90302	4	1.78 (1.35; 2.35)	**<0.001**	**<0.001**	89	0.068
178	TG 52:2	CHEBI:85736	5	1.57 (1.37; 1.80)	**<0.001**	**<0.001**	57	0.012
179	TG 52:3	CHEBI:84661	6	1.24 (1.08; 1.43)	**0.002**	**0.009**	80	0.021
180	TG 52:4	CHEBI:84660	4	1.06 (0.90; 1.23)	0.484	0.614	85	0.020
181	TG 52:5	CHEBI:85734	3	1.09 (0.88; 1.35)	0.445	0.582	85	0.028

182	TG 52:6	CHEBI:85875	5	1.21 (1.03; 1.42)	**0.022**	0.067	81	0.025
183	TG 52:7	CHEBI:136390	2	1.12 (1.02; 1.24)	**0.019**	0.062	0	0.000
184	TG 53:2	CHEBI:85739	3	1.33 (1.24; 1.44)	**<0.001**	**<0.001**	0	0.000
185	TG 53:3	CHEBI:85738	4	1.24 (0.99; 1.53)	0.056	0.138	87	0.039
186	TG 54:1	CHEBI:90305	4	1.28 (1.03; 1.59)	**0.027**	0.080	88	0.041
187	TG 54:2	CHEBI:85743	4	1.42 (1.15; 1.74)	**0.001**	**0.005**	78	0.030
188	TG 54:3	CHEBI:84659	6	1.21 (1.12; 1.31)	**<0.001**	**<0.001**	35	0.003
189	TG 54:4	CHEBI:85742	6	1.16 (0.95; 1.41)	0.154	0.287	93	0.055
190	TG 54:5	CHEBI:85741	6	1.18 (0.96; 1.45)	0.110	0.224	92	0.056
191	TG 54:6	CHEBI:85876	6	1.16 (0.98; 1.37)	0.094	0.199	88	0.036
192	TG 54:7	CHEBI:85740	6	1.30 (1.08; 1.56)	**0.005**	**0.018**	89	0.043
193	TG 54:8	CHEBI:85837	3	1.17 (0.89; 1.55)	0.267	0.411	86	0.051
194	TG 54:9	CHEBI:138346	3	1.00 (0.89; 1.12)	0.967	0.988	16	0.002
195	TG 55:6	CHEBI:85744	2	1.53 (1.08; 2.19)	**0.018**	0.059	65	0.045
196	TG 56:3	CHEBI:85843	3	1.22 (1.08; 1.39)	**0.002**	**0.008**	64	0.007
197	TG 56:4	CHEBI:85842	3	1.13 (0.95; 1.36)	0.174	0.315	80	0.018
198	TG 56:5	CHEBI:85751	5	1.24 (1.02; 1.51)	**0.029**	0.083	90	0.042
199	TG 56:6	CHEBI:85750	5	1.25 (1.07; 1.47)	**0.005**	**0.018**	76	0.022
200	TG 56:7	CHEBI:85749	4	1.21 (0.94; 1.55)	0.141	0.269	91	0.057
201	TG 56:8	CHEBI:85748	5	1.10 (0.88; 1.39)	0.407	0.550	94	0.063
202	TG 56:9	CHEBI:85747	3	0.89 (0.72; 1.11)	0.312	0.458	72	0.026
203	TG 56:10	CHEBI:85877	3	0.94 (0.81; 1.10)	0.453	0.588	46	0.008
204	TG 58:7	CHEBI:85755	2	1.18 (1.02; 1.37)	**0.026**	0.078	76	0.009
205	TG 58:8	CHEBI:85754	3	1.07 (0.90; 1.27)	0.434	0.571	77	0.016
206	TG 58:9	CHEBI:85753	3	1.02 (0.88; 1.18)	0.779	0.865	59	0.009
207	TG 58:10	CHEBI:85732	3	1.01 (0.67; 1.52)	0.974	0.988	93	0.121
208	TG 58:11	CHEBI:132733	2	1.30 (0.82; 2.07)	0.265	0.411	92	0.103
209	TG 60:12	CHEBI:134112	2	0.89 (0.65; 1.21)	0.451	0.588	79	0.039
Diacylglycerols								
210	DG 30:0	CHEBI:85683	3	1.17 (1.10; 1.25)	**<0.001**	**<0.001**	0	0.000
211	DG 32:0	CHEBI:85688	2	1.36 (1.06; 1.74)	**0.015**	**0.049**	88	0.028
212	DG 32:1	CHEBI:85687	3	1.17 (1.10; 1.25)	**<0.001**	**<0.001**	0	0.000
213	DG 32:2	CHEBI:85686	3	1.10 (0.99; 1.23)	0.089	0.192	48	0.005
214	DG 34:0	CHEBI:86974	2	1.36 (0.92; 2.01)	0.125	0.249	95	0.076
215	DG 34:1	CHEBI:85694	5	1.47 (1.22; 1.77)	**<0.001**	**<0.001**	66	0.027
216	DG 34:2	CHEBI:85693	6	1.34 (1.19; 1.52)	**<0.001**	**<0.001**	71	0.013
217	DG 34:3	CHEBI:85692	2	1.44 (0.94; 2.21)	0.094	0.199	89	0.085
218	DG 36:1	CHEBI:86980	3	1.74 (1.01; 3.01)	**0.046**	0.119	97	0.222
219	DG 36:2	CHEBI:85701	5	1.30 (1.09; 1.55)	**0.003**	**0.014**	87	0.030
220	DG 36:3	CHEBI:85700	5	1.22 (1.14; 1.31)	**<0.001**	**<0.001**	13	0.001
221	DG 36:4	CHEBI:85699	3	0.98 (0.77; 1.24)	0.875	0.929	90	0.038
222	DG 38:4	CHEBI:85705	2	1.25 (1.14; 1.36)	**<0.001**	**<0.001**	39	0.002

223	DG 38:5	CHEBI:85704	2	1.19 (1.11; 1.27)	**<0.001**	**<0.001**	0	0.000
Monoacylglycerols								
224	MG 16:1	CHEBI:87251	3	1.39 (1.27; 1.52)	**<0.001**	**<0.001**	0	0.000
225	MG 18:1	CHEBI:87256	4	1.16 (1.04; 1.29)	**0.007**	**0.026**	72	0.008
226	MG 18:2	CHEBI:87257	2	1.09 (0.88; 1.35)	0.432	0.571	79	0.019
Phosphatidylcholines								
227	Glycerophosphocholine	HMDB00086	7	0.85 (0.71; 1.01)	0.060	0.146	83	0.040
228	PC 28:1	CHEBI:65293	2	0.99 (0.89; 1.10)	0.814	0.885	45	0.003
229	PC 30:0	CHEBI:65303	5	1.07 (1.03; 1.12)	**0.001**	**0.005**	0	0.000
230	PC 30:1	CHEBI:65302	4	1.02 (0.85; 1.22)	0.836	0.895	82	0.026
231	PC 32:0	CHEBI:66850	7	1.06 (0.95; 1.19)	0.270	0.411	87	0.016
232	PC 32:1	CHEBI:66849	9	1.09 (0.99; 1.21)	0.093	0.199	88	0.018
233	PC 32:2	CHEBI:66848	7	1.04 (0.95; 1.14)	0.384	0.528	76	0.010
234	PC 32:3	CHEBI:66847	3	0.89 (0.83; 0.95)	**0.001**	**0.005**	0	0.000
235	PC 33:1	CHEBI:86472	3	1.09 (0.85; 1.38)	0.504	0.627	92	0.039
236	PC 33:2	CHEBI:85853	4	0.83 (0.64; 1.07)	0.142	0.270	91	0.056
237	PC 33:3	CHEBI:134587	3	0.79 (0.58; 1.09)	0.149	0.280	85	0.063
238	PC 34:0	CHEBI:66855	6	1.03 (0.98; 1.09)	0.218	0.365	27	0.001
239	PC 34:1	CHEBI:64517	7	0.97 (0.85; 1.1.)	0.633	0.741	93	0.027
240	PC 34:2	CHEBI:64516	9	1.01 (0.89; 1.15)	0.866	0.920	92	0.028
241	PC 34:3	CHEBI:64424	9	0.97 (0.83; 1.14)	0.702	0.801	94	0.050
242	PC 34:4	CHEBI:64423	5	1.06 (0.97; 1.17)	0.203	0.351	64	0.007
243	PC 35:2	CHEBI:85766	4	0.81 (0.67; 0.97)	**0.025**	0.075	84	0.028
244	PC 36:0	CHEBI:66858	4	0.95 (0.86; 1.04)	0.262	0.411	77	0.007
245	PC 36:1	CHEBI:66857	6	1.05 (1.00; 1.11)	**0.044**	0.116	48	0.002
246	PC 36:2	CHEBI:64433	9	0.99 (0.96; 1.02)	0.433	0.571	0	0.000
247	PC 36:3	CHEBI:64523	6	1.00 (0.92; 1.08)	0.943	0.978	80	0.006
248	PC 36:4	CHEBI:64520	7	0.93 (0.82; 1.06)	0.261	0.411	94	0.025
249	PC 36:5	CHEBI:64504	5	0.98 (0.91; 1.05)	0.505	0.627	66	0.004
250	PC 36:6	CHEBI:66856	3	0.99 (0.9.; 1.08)	0.786	0.868	49	0.003
251	PC 37:4	CHEBI:72427	3	0.81 (0.58; 1.13)	0.212	0.358	95	0.076
252	PC 38:0	CHEBI:66861	2	0.88 (0.83; 0.93)	**<0.001**	**<0.001**	0	0.000
253	PC 38:1	CHEBI:66860	2	0.91 (0.82; 1.02)	0.093	0.199	74	0.005
254	PC 38:2	CHEBI:66859	7	1.02 (0.97; 1.08)	0.394	0.538	21	0.001
255	PC 38:3	CHEBI:64446	7	1.19 (1.09; 1.29)	**<0.001**	**<0.001**	75	0.008
256	PC 38:4	CHEBI:64526	6	0.98 (0.95; 1.01)	0.206	0.353	0	0.000
257	PC 38:5	CHEBI:64525	5	0.95 (0.90; 1.01)	0.089	0.192	63	0.002
258	PC 38:6	CHEBI:64519	9	0.94 (0.88; 0.99)	**0.032**	0.091	59	0.004
259	PC 39:6	CHEBI:131430	2	0.73 (0.46; 1.15)	0.178	0.317	86	0.096
260	PC 40:1	CHEBI:66865	2	0.83 (0.77; 0.90)	**<0.001**	**<0.001**	28	0.001
261	PC 40:2	CHEBI:66864	2	0.92 (0.84; 1.00)	0.052	0.130	56	0.002
262	PC 40:3	CHEBI:66863	2	0.88 (0.83; 0.93)	**<0.001**	**<0.001**	0	0.000

263	PC 40:4	CHEBI:66862	3	0.93 (0.79; 1.08)	0.331	0.473	82	0.014
264	PC 40:5	CHEBI:64524	4	1.05 (0.98; 1.12)	0.191	0.335	53	0.002
265	PC 40:6	CHEBI:64431	7	1.05 (0.97; 1.13)	0.266	0.411	70	0.007
266	PC 40:7	CHEBI:64521	2	0.68 (0.39; 1.20)	0.188	0.333	91	0.152
267	PC 40:9	CHEBI:85850	2	0.89 (0.80; 1.00)	0.053	0.131	0	0.000
268	PC 42:0	CHEBI:66971	2	0.78 (0.63; 0.95)	**0.015**	**0.049**	87	0.019
269	PC 42:1	CHEBI:66970	2	0.83 (0.78; 0.89)	**<0.001**	**<0.001**	19	0.000
270	PC 42:2	CHEBI:66969	2	0.88 (0.83; 0.93)	**<0.001**	**<0.001**	0	0.000
271	PC 42:3	CHEBI:66968	2	0.82 (0.75; 0.89)	**<0.001**	**<0.001**	0	0.000
272	PC 42:4	CHEBI:66967	2	0.88 (0.83; 0.93)	**<0.001**	**<0.001**	0	0.000
273	PC 42:5	CHEBI:66966	2	0.98 (0.88; 1.10)	0.751	0.848	73	0.005
274	PC 42:6	CHEBI:66965	2	1.05 (0.98; 1.13)	0.193	0.338	0	0.000
275	PC 44:3	CHEBI:66976	2	0.92 (0.86; 1.00)	**0.038**	0.104	0	0.000
276	PC 44:4	CHEBI:66975	2	0.81 (0.70; 0.94)	**0.007**	**0.024**	68	0.008
277	PC 44:5	CHEBI:66974	3	0.86 (0.70; 1.05)	0.133	0.258	86	0.026
278	PC 44:6	CHEBI:66973	2	0.76 (0.60; 0.96)	**0.020**	0.064	87	0.025
279	Phosphorylcholine	HMDB01565	3	0.91 (0.75; 1.11)	0.351	0.495	75	0.022
Lysophosphatidylcholines								
280	LPC 14:0	CHEBI:64483	7	1.09 (1.04; 1.14)	**<0.001**	**0.003**	0	0.000
281	LPC 15:0	CHEBI:72736	3	0.83 (0.64; 1.08)	0.170	0.311	77	0.039
282	LPC 16:0	CHEBI:64563	11	0.96 (0.89; 1.03)	0.228	0.375	70	0.009
283	LPC 16:1	CHEBI:64560	11	0.98 (0.93; 1.04)	0.574	0.691	46	0.004
284	LPC 17:0	CHEBI:72737	8	0.80 (0.74; 0.85)	**<0.001**	**<0.001**	18	0.002
285	LPC 17:1	CHEBI:73853	2	0.79 (0.72; 0.87)	**<0.001**	**<0.001**	0	0.000
286	LPC 18:0	CHEBI:64561	13	0.89 (0.82; 0.96)	**0.003**	**0.013**	76	0.013
287	LPC 18:1	CHEBI:64566	13	0.79 (0.75; 0.83)	**<0.001**	**<0.001**	24	0.002
288	LPC 18:2	CHEBI:64549	13	0.74 (0.69; 0.79)	**<0.001**	**<0.001**	58	0.008
289	LPC 18:3	CHEBI:64565	3	0.85 (0.79; 0.92)	**<0.001**	**0.001**	16	0.001
290	LPC 19:1	NA	2	0.69 (0.58; 0.82)	**<0.001**	**<0.001**	0	0.000
291	LPC 20:0	CHEBI:67058	3	0.81 (0.69; 0.94)	**0.008**	**0.028**	71	0.013
292	LPC 20:1	CHEBI:67057	4	0.70 (0.60; 0.81)	**<0.001**	**<0.001**	50	0.012
293	LPC 20:2	CHEBI:67056	4	0.84 (0.78; 0.90)	**<0.001**	**<0.001**	0	0.000
294	LPC 20:3	CHEBI:64481	7	1.02 (0.98; 1.07)	0.316	0.461	8	0.000
295	LPC 20:4	CHEBI:64568	9	0.87 (0.81; 0.94)	**0.001**	**0.004**	61	0.008
296	LPC 20:5	CHEBI:64559	5	0.92 (0.85; 0.99)	**0.025**	0.074	3	0.000
297	LPC 22:5	CHEBI:74349	2	0.76 (0.53; 1.10)	0.143	0.271	74	0.051
298	LPC 22:6	CHEBI:64567	7	0.84 (0.75; 0.94)	**0.002**	**0.008**	73	0.015
299	LPC 24:0	CHEBI:74470	3	0.81 (0.71; 0.93)	**0.003**	**0.012**	73	0.009
Phosphatidylethanolamines								
300	PE 34:1	CHEBI:155834	2	1.36 (1.08; 1.72)	**0.009**	**0.032**	59	0.019
301	PE 34:2	CHEBI:155835	2	1.19 (1.1; 1.29)	**<0.001**	**<0.001**	45	0.001
302	PE 34:3	NA	2	1.04 (0.79; 1.36)	0.786	0.868	93	0.035

303	PE 36:1	CHEBI:134451	3	1.41 (1.15; 1.74)	**0.001**	**0.005**	83	0.026
304	PE 36:2	CHEBI:141588	4	1.18 (1.07; 1.30)	**0.001**	**0.006**	75	0.007
305	PE 36:3	CHEBI:141589	3	1.03 (0.81; 1.30)	0.825	0.892	96	0.041
306	PE 36:4	CHEBI:134271	5	1.18 (0.98; 1.41)	0.075	0.171	93	0.036
307	PE 36:5	NA	2	1.02 (0.93; 1.12)	0.696	0.796	62	0.003
308	PE 38:4	CHEBI:134270	4	1.17 (1.07; 1.28)	**<0.001**	**0.002**	57	0.004
309	PE 38:5	CHEBI:134239	4	1.09 (0.89; 1.34)	0.395	0.538	93	0.038
310	PE 38:6	CHEBI:134428	3	1.08 (0.86; 1.35)	0.498	0.624	95	0.036
311	PE 40:6	CHEBI:134241	2	1.21 (1.13; 1.29)	**<0.001**	**<0.001**	0	0.000
Lysophosphatidylethanolamines								
312	LPE 16:0	CHEBI:90452	8	0.90 (0.78; 1.03)	0.133	0.258	89	0.032
313	LPE 18:0	CHEBI:64576	8	0.95 (0.88; 1.04)	0.250	0.403	72	0.009
314	LPE 18:1	CHEBI:64575	7	0.94 (0.83; 1.05)	0.268	0.411	82	0.019
315	LPE 18:2	CHEBI:91296	7	0.93 (0.81; 1.06)	0.264	0.411	85	0.025
316	LPE 20:4	CHEBI:64569	6	0.96 (0.84; 1.10)	0.520	0.642	86	0.022
317	LPE 22:6	CHEBI:72734	4	0.99 (0.92; 1.07)	0.844	0.901	12	0.001
Phosphatidylinositols								
318	PI 34:0	CHEBI:74232	2	1.12 (0.90; 1.39)	0.325	0.469	87	0.022
319	PI 34:1	CHEBI:74237	3	1.11 (0.92; 1.34)	0.281	0.426	91	0.026
320	PI 36:1	CHEBI:74371	3	1.04 (0.93; 1.17)	0.504	0.627	54	0.005
321	PI 36:2	CHEBI:74372	2	1.00 (0.93; 1.08)	0.936	0.974	28	0.001
322	PI 36:3	CHEBI:91036	2	0.95 (0.78; 1.15)	0.575	0.691	86	0.017
323	PI 36:4	CHEBI:75194	2	1.06 (0.92; 1.21)	0.424	0.568	72	0.007
324	PI 38:3	CHEBI:91039	2	1.13 (1.05; 1.21)	**0.001**	**0.005**	0	0.000
325	PI 38:4	CHEBI:74240	3	1.04 (0.90; 1.19)	0.615	0.728	80	0.012
326	PI 38:5	CHEBI:74241	2	0.85 (0.80; 0.92)	**<0.001**	**<0.001**	0	0.000
Lysophosphatidylinositols								
327	LPI 16:1	CHEBI:74464	3	1.57 (1.16; 2.12)	**0.003**	**0.013**	68	0.047
Sphingomyelins								
328	SM 32:1	CHEBI:64586	8	1.05 (0.95; 1.16)	0.318	0.462	79	0.013
329	SM 32:2	CHEBI:72510	4	0.91 (0.74; 1.12)	0.385	0.528	84	0.032
330	SM 33:1	CHEBI:64585	2	1.04 (0.80; 1.36)	0.771	0.861	92	0.034
331	SM 34:0	CHEBI:72513	3	1.15 (1.10; 1.21)	**<0.001**	**<0.001**	0	0.000
332	SM 34:1	CHEBI:72514	11	0.97 (0.88; 1.08)	0.699	0.728	85	0.022
333	SM 34:2	CHEBI:64587	10	0.95 (0.86; 1.06)	0.374	0.557	85	0.025
334	SM 35:1	CHEBI:133629	2	1.02 (0.90; 1.16)	0.770	0.861	65	0.005
335	SM 36:0	CHEBI:72517	2	1.45 (0.95; 2.19)	0.082	0.183	98	0.088
336	SM 36:1	CHEBI:72518	11	1.11 (1.01; 1.21)	**0.028**	0.081	81	0.017
337	SM 36:2	CHEBI:72519	10	1.00 (0.90; 1.11)	0.991	0.998	85	0.022
338	SM 36:3	CHEBI:72520	6	0.86 (0.79; 0.93)	**<0.001**	**0.001**	44	0.004
339	SM 38:0	CHEBI:72522	2	1.37 (1.02; 1.83)	**0.034**	0.096	97	0.042
340	SM 38:1	CHEBI:72523	6	1.13 (1.01; 1.26)	**0.034**	0.095	87	0.016

341	SM 38:2	CHEBI:72524	5	0.94 (0.83; 1.05)	0.261	0.411	72	0.011
342	SM 38:3	CHEBI:72525	2	0.92 (0.85; 1.00)	**0.039**	0.104	0	0.000
343	SM 39:1	CHEBI:85761	2	1.11 (1.03; 1.19)	**0.005**	**0.018**	0	0.000
344	SM 40:0	CHEBI:72527	2	1.43 (0.92; 2.22)	0.114	0.230	99	0.100
345	SM 40:1	CHEBI:72528	7	1.16 (1.00; 1.34)	**0.047**	0.119	89	0.028
346	SM 40:2	CHEBI:72529	5	0.99 (0.88; 1.12)	0.881	0.926	74	0.013
347	SM 41:1	CHEBI:83893	4	1.23 (1.14; 1.33)	**<0.001**	**<0.001**	0	0.000
348	SM 41:2	CHEBI:85762	4	0.98 (0.92; 1.05)	0.538	0.662	0	0.000
349	SM 41:3	CHEBI:137914	2	0.74 (0.40; 1.37)	0.334	0.475	84	0.172
350	SM 42:1	CHEBI:72533	9	0.97 (0.79; 1.19)	0.792	0.870	96	0.086
351	SM 42:2	CHEBI:72534	8	0.99 (0.89; 1.11)	0.896	0.935	83	0.019
352	SM 42:3	CHEBI:72535	4	0.99 (0.86; 1.13)	0.871	0.921	78	0.013
353	SM 42:4	CHEBI:72536	2	0.59 (0.31; 1.11)	0.102	0.213	86	0.182
354	SM 44:1	CHEBI:72538	2	1.00 (0.84; 1.20)	0.974	0.988	86	0.015
355	SM 44:2	CHEBI:72539	2	0.88 (0.81; 0.96)	**0.004**	**0.014**	23	0.001
356	Sphinganine	HMDB00269	2	1.30 (0.88; 1.93)	0.191	0.335	56	0.045
357	Sphingosine	HMDB00252	3	0.95 (0.82; 1.10)	0.467	0.602	0	0.000
Ceramides								
358	Cer d18:0/16:0	HMDB11760	2	1.19 (0.96; 1.49)	0.117	0.234	91	0.023
359	Cer d18:0/18:0	HMDB11761	2	1.37 (0.93; 2.02)	0.108	0.222	96	0.074
360	Cer d18:0/20:0	HMDB11764	2	1.24 (1.04; 1.48)	**0.017**	0.057	84	0.014
361	Cer d18:0/22:0	HMDB11765	2	1.33 (0.96; 1.86)	0.087	0.190	95	0.054
362	Cer d18:0/24:0	HMDB11768	2	1.29 (1.01; 1.64)	**0.041**	0.109	90	0.028
363	Cer d18:0/24:1	HMDB11769	2	1.27 (0.95; 1.70)	0.105	0.218	94	0.042
364	Cer d18:1/16:0	HMDB04949	4	1.16 (1.01; 1.35)	**0.039**	0.104	89	0.019
365	Cer d18:1/18:0	HMDB04950	3	1.36 (1.06; 1.74)	**0.017**	0.055	95	0.046
366	Cer d18:1/18:1	HMDB04948	2	1.15 (1.07; 1.23)	**<0.001**	**<0.001**	0	0.000
367	Cer d18:1/20:0	HMDB04951	2	1.27 (1.02; 1.58)	**0.036**	0.098	89	0.023
368	Cer d18:1/20:1	HMDB04951	2	1.18 (1.10; 1.26)	**<0.001**	**<0.001**	0	0.000
369	Cer d18:1/22:0	HMDB04952	3	1.22 (1.00; 1.47)	**0.047**	0.119	90	0.026
370	Cer d18:1/22:1	HMDB04951	2	1.17 (1.08; 1.27)	**<0.001**	**<0.001**	0	0.000
371	Cer d18:1/24:0	HMDB04956	4	1.11 (1.04; 1.20)	**0.003**	**0.014**	15	0.001
372	Cer d18:1/24:1	HMDB04953	4	1.15 (1.05; 1.26)	**0.003**	**0.013**	51	0.004
373	Cer d18:1/26:0	HMDB04955	2	1.09 (1.01; 1.17)	**0.036**	0.098	0	0.000
374	Cer d18:1/26:1	NA	2	1.00 (0.93; 1.07)	0.973	0.988	0	0.000
375	Hex2Cer d18:1/24:0	NA	2	1.18 (0.88; 1.58)	0.267	0.411	62	0.030
376	Hex2Cer d18:1/24:1	NA	2	1.03 (0.92; 1.15)	0.584	0.698	0	0.000
377	HexCer d18:1/16:0	CHEBI:77462	2	1.21 (1.01; 1.44)	**0.035**	0.096	85	0.014
378	HexCer d18:1/18:0	NA	3	1.11 (1.05; 1.18)	**0.001**	**0.004**	0	0.000
379	HexCer d18:1/20:0	NA	2	1.08 (0.98; 1.18)	0.101	0.213	50	0.002
380	HexCer d18:1/22:0	NA	3	1.10 (1.03; 1.17)	**0.004**	**0.017**	0	0.000
381	HexCer d18:1/24:0	NA	3	1.11 (1.03; 1.19)	**0.004**	**0.015**	0	0.000

382	HexCer d18:1/24:1	NA	3	1.09 (0.83; 1.17)	**0.006**	**0.024**	0	0.000
Fatty acids								
383	3-carboxy-4-methyl-5-propyl-2-furanpropionate	HMDB61112	4	0.80 (0.70; 0.92)	**0.001**	**0.005**	0	0.000
384	3-hydroxydecanoate	HMDB02203	2	1.13 (0.93; 1.38)	0.206	0.353	0	0.000
385	3-hydroxyoctanoate	HMDB10722	2	1.22 (0.93; 1.61)	0.159	0.294	51	0.021
386	Adrenate	HMDB02226	2	1.36 (1.11; 1.66)	**0.003**	**0.012**	0	0.000
387	Arachidonate	HMDB01043	7	1.15 (1.02; 1.29)	**0.023**	0.070	49	0.011
388	Dihomo-gamma-linolenate	HMDB02925	2	1.48 (0.98; 2.25)	0.064	0.153	75	0.068
389	Docosahexaenoate	HMDB02183	10	1.04 (0.93; 1.16)	0.498	0.624	62	0.018
390	Docosapentaenoate	HMDB01976	2	1.29 (0.83; 2.01)	0.256	0.409	83	0.085
391	Dodecanoate	HMDB00638	4	1.07 (0.94; 1.22)	0.282	0.426	23	0.004
392	Eicosapentaenoate	HMDB01999	4	1.06 (0.93; 1.20)	0.374	0.520	0	0.000
393	Hexadecanedioate	HMDB00672	2	1.19 (0.99; 1.44)	0.060	0.146	0	0.000
394	Linoleate	HMDB00673	11	0.96 (0.90; 1.03)	0.249	0.403	29	0.003
395	Linolenate	HMDB01388	4	1.05 (0.90; 1.21)	0.540	0.662	49	0.011
396	Mystrate	HMDB00806	4	1.11 (0.87; 1.42)	0.383	0.528	77	0.046
397	Octadecanedioate	HMDB00782	2	1.05 (0.86; 1.29)	0.612	0.727	0	0.000
398	Oleate	HMDB00207	5	1.10 (0.81; 1.48)	0.542	0.664	87	0.100
399	Palmitate	HMDB00220	3	1.19 (0.94; 1.51)	0.157	0.287	58	0.026
400	Palmitoleate	HMDB03229	2	1.12 (0.69; 1.82)	0.636	0.739	83	0.101
401	Pelargonate	HMDB00847	2	0.99 (0.83; 1.19)	0.948	0.984	0	0.000
402	Pentadecanate	HMDB00826	2	0.98 (0.85; 1.13)	0.798	0.879	19	0.002
403	Stearate	HMDB00827	3	1.32 (0.85; 2.06)	0.218	0.362	91	0.138
404	Stearidonate	HMDB06547	2	1.00 (0.86; 1.16)	0.979	0.986	0	0.000
405	Tetradecanedioate	HMDB00872	2	1.13 (0.95; 1.34)	0.175	0.312	0	0.000
Bile acids								
406	Cholate	HMDB00619	2	1.15 (0.63; 2.11)	0.642	0.741	81	0.154
407	Deoxycholate	HMDB00626	4	1.08 (0.83; 1.40)	0.583	0.698	86	0.055
408	Glycochenodeoxycholate	CHEBI:36274	4	1.11 (0.91; 1.34)	0.311	0.458	75	0.027
409	Glycocholate	HMDB00138	5	1.17 (1.05; 1.29)	**0.004**	**0.017**	63	0.008
410	Taurochenodeoxycholate	HMDB00951	4	1.16 (0.99; 1.37)	0.067	0.156	81	0.018
411	Taurocholate	HMDB00036	2	1.06 (0.99; 1.13)	0.074	0.169	0	0.000
412	Taurodeoxycholate	HMDB00896	2	1.02 (0.94; 1.11)	0.607	0.723	0	0.000

Summary relative risk (SRR) with 95% confidence intervals (95% CI) were derived from random-effects meta-analysis model with restricted maximum likelihood estimator.

N – number of studies per comparison, P – P-value for SRR, P-FDR – false discovery rate adjusted P-value for SRR, τ^2 – between-study variability, I^2 – variability attributable to between-study heterogeneity.

HMDB – Human Metabolome Database, ChEBI - Chemical Entities of Biological Interest.

Supplementary Table 8. Meta-regression analysis exploring the influence of number of carbons and double bonds on the association between lipid classes metabolites and incident type 2 diabetes risk.

Moderator	Estimate coefficient	Standard error	P	τ^2 statistic
Triacylglycerols				
N of carbons	-0.182	0.003	**<0.001**	0.040
N of double bonds	-0.030	0.003	**<0.001**	0.033
Diacylglycerols				
N of carbons	0.000	0.011	0.988	0.053
N of double bonds	-0.036	0.014	**0.008**	0.045
Phosphatidylcholines				
N of carbons	-0.013	0.002	**<0.001**	0.036
N of double bonds	-0.015	0.004	**<0.001**	0.036
Lysophosphatidylcholines				
N of carbons	-0.010	0.004	**0.006**	0.035
N of double bonds	-0.007	0.006	0.270	0.030
Phosphatidylethanolamines				
N of carbons	0.005	0.007	0.495	0.040
N of double bonds	-0.004	0.009	0.693	0.040
Lysophosphatidylethanolamines				
N of carbons	0.001	0.008	0.895	0.025
N of double bonds	0.001	0.007	0.911	0.025
Phosphatidylinositols				
N of carbons	-0.019	0.010	0.060	0.014
N of double bonds	-0.025	0.012	**0.034**	0.014
Sphingomyelins				
N of carbons	0.002	0.004	0.683	0.058
N of double bonds	-0.101	0.013	**<0.001**	0.057
Acylcarnitines				
Short chain	0.056	0.017	**0.049**	0.012
Medium chain	-0.031	0.018	0.863	0.016
Long chain	0.069	0.029	**0.016**	0.071

Estimates coefficients (and respective standard errors) were derived from mixed-effect meta-analysis model with moderator as fixed effect (*number of carbons* or *number of double bonds*) and *metabolite* and *study* as random effects (assuming that metabolite is a variable nested in study).

P – P-value for coefficient, τ^2 – between study variability.

Supplementary Table 9. Subgroup analysis for metabolites and risk of incident type 2 diabetes stratified for biospecimen: plasma samples and serum samples.

Metabolite	Plasma samples			Serum samples			P_{sub}
	N	SRR (95% CI)	I^2	N	SRR (95% CI)	I^2	
Acylcarnitine C10	6	1.03 (0.92: 1.16)	64	5	0.99 (0.87: 1.12)	61	0.640
Acylcarnitine C12	7	0.91 (0.79: 1.06)	81	4	0.97 (0.83: 1.13)	48	0.575
Acylcarnitine C14	8	0.97 (0.90: 1.05)	44	2	1.12 (0.82: 1.53)	77	0.403
Acylcarnitine C16	8	1.03 (0.92: 1.15)	70	7	1.07 (1.00: 1.16)	34	0.531
Acylcarnitine C18	7	1.01 (0.71: 1.43)	97	7	0.97 (0.91: 1.03)	0	0.846
Acylcarnitine C18:1	5	0.97 (0.70: 1.35)	94	6	1.03 (0.97: 1.09)	0	0.743
Acylcarnitine C18:2	5	1.16 (0.79: 1.73)	95	5	0.98 (0.93: 1.05)	0	0.406
Acylcarnitine C2	8	1.01 (0.89: 1.13)	76	8	1.00 (0.94: 1.05)	0	0.914
Acylcarnitine C3	10	1.05 (0.95: 1.17)	75	6	1.07 (0.95: 1.20)	69	0.857
Acylcarnitine C4	9	0.92 (0.79: 1.06)	85	5	1.04 (0.94: 1.16)	39	0.151
Acylcarnitine C5	9	1.15 (1.09: 1.21)	12	5	1.07 (0.96: 1.18)	43	0.200
Acylcarnitine C6	7	0.88 (0.71: 1.10)	92	3	1.02 (0.89: 1.16)	31	0.290
Acylcarnitine C8	8	1.00 (0.95: 1.06)	0	5	0.92 (0.83: 1.01)	37	0.129
Alanine	10	1.38 (1.18: 1.61)	89	11	1.25 (1.14: 1.38)	49	0.281
Arginine	8	0.96 (0.86: 1.08)	72	5	1.07 (0.88: 1.29)	87	0.366
Betaine	7	0.84 (0.77: 0.91)	56	3	0.72 (0.59: 0.88)	0	0.179
Carnitine	8	1.02 (0.90: 1.15)	80	6	1.08 (0.95: 1.22)	66	0.508
Citrulline	8	1.02 (0.93: 1.11)	46	4	0.97 (0.88: 1.07)	23	0.473
Creatinine	5	1.01 (0.84: 1.21)	88	8	0.95 (0.84: 1.08)	42	0.611
Docosahexaenoate	1	1.18 (0.94: 1.49)	-	9	1.02 (0.91: 1.15)	64	0.283
Glutamate	8	1.34 (1.12: 1.61)	92	5	1.48 (1.13: 1.94)	90	0.545
Glutamine	9	0.79 (0.67: 0.92)	90	10	0.90 (0.77: 1.05)	87	0.257
Glycine	6	0.65 (0.53: 0.80)	86	12	0.87 (0.74: 1.02)	86	**0.030**
Histidine	6	0.91 (0.82: 1.02)	71	11	0.99 (0.93: 1.05)	19	0.241
Isoleucine	8	1.54 (1.26: 1.88)	92	11	1.55 (1.31: 1.83)	83	0.960
Lactate	4	1.22 (1.09: 1.36)	69	8	1.13 (0.90: 1.42)	84	0.574
Leucine	8	1.45 (1.23: 1.72)	86	15	1.38 (1.25: 1.51)	61	0.589
Linoleate	1	0.79 (0.58: 1.08)	0	10	0.97 (0.91: 1.04)	35	0.200
LPC 16:0	6	0.93 (0.84: 1.03)	79	5	1.00 (0.91: 1.11)	41	0.288
LPC 16:1	6	0.97 (0.91: 1.04)	49	5	0.99 (0.85: 1.16)	70	0.782
LPC 18:0	6	0.91 (0.80: 1.03)	84	7	0.87 (0.78: 0.97)	69	0.636
LPC 18:1	7	0.78 (0.73: 0.84)	50	6	0.81 (0.75: 0.87)	0	0.530
LPC 18:2	6	0.74 (0.65: 0.83)	82	7	0.74 (0.68: 0.80)	0	0.994
Lysine	8	1.11 (1.05: 1.16)	0	3	1.07 (0.91: 1.25)	43	0.664
Methionine	8	1.10 (0.96: 1.26)	81	4	1.14 (1.07: 1.21)	0	0.629
Ornithine	7	1.09 (0.99: 1.21)	48	6	1.02 (0.82: 1.28)	90	0.595
Phenylalanine	10	1.31 (1.16: 1.49)	81	8	1.30 (1.01: 1.69)	94	0.970
Pyruvate	4	1.32 (1.06: 1.65)	86	7	1.16 (1.02: 1.32)	47	0.317
Serine	7	0.96 (0.80: 1.15)	89	5	0.90 (0.82: 1.00)	46	0.588
SM 34:1	6	1.07 (0.94: 1.21)	84	5	0.89 (0.82: 0.96)	32	**0.015**
SM 34:2	6	0.98 (0.86: 1.13)	80	4	0.92 (0.75: 1.13)	93	0.595
SM 36:1	6	1.14 (0.99: 1.31)	86	5	1.08 (0.96: 1.20)	66	0.560
SM 36:2	6	1.01 (0.89: 1.15)	79	4	0.98 (0.81: 1.20)	91	0.828
Tryptophan	8	1.07 (0.89: 1.30)	91	6	1.22 (1.03: 1.45)	73	0.326
Tyrosine	9	1.31 (1.14: 1.51)	80	9	1.39 (1.20: 1.62)	84	0.569
Valine	11	1.32 (1.15: 1.52)	85	8	1.54 (1.26: 1.88)	86	0.218

CI – confidence interval, I^2 – variability attributable to the between-study heterogeneity, LPC – lysophosphatidylcholines, N – number of studies, SM – sphingomyelins, SRR – summary relative risk, P_{sub} – P-value for the difference in coefficient between subgroups.

Supplementary Table 10. Subgroup analysis for metabolites and risk of incident type 2 diabetes stratified for study location: United States, Europe, and Asia.

Metabolite	United States			Europe			Asia			P_{sub}
	N	SRR (95% CI)	I^2	N	SRR (95% CI)	I^2	N	SRR (95% CI)	I^2	
Acylcarnitine C10	1	1.12 (0.79: 1.58)	-	5	1.01 (0.93: 1.11)	20	5	1.02 (0.88: 1.19)	81	0.860
Acylcarnitine C12	2	1.08 (0.80: 1.46)	57	4	0.83 (0.67: 1.02)	66	5	0.96 (0.84: 1.10)	78	0.310
Acylcarnitine C14	2	0.97 (0.87: 1.08)	0	3	0.91 (0.81: 1.02)	0	5	1.06 (0.92: 1.21)	76	0.243
Acylcarnitine C16	2	0.87 (0.69: 1.10)	48	7	1.05 (0.97: 1.15)	36	6	1.11 (1.01: 1.20)	55	0.170
Acylcarnitine C18	2	0.97 (0.85: 1.09)	0	6	0.85 (0.72: 1.00)	69	6	1.14 (0.80: 1.61)	97	0.251
Acylcarnitine C18:1	2	0.84 (0.74: 0.94)	0	5	0.88 (0.75: 1.04)	68	4	1.21 (0.93: 1.58)	94	**0.042**
Acylcarnitine C18:2	2	0.88 (0.78: 1.01)	0	4	0.98 (0.91: 1.06)	0	4	1.27 (0.81: 1.98)	98	0.197
Acylcarnitine C2	2	1.02 (0.92: 1.13)	0	8	0.98 (0.92: 1.05)	0	6	1.02 (0.91: 1.15)	77	0.727
Acylcarnitine C3	2	1.06 (1.00: 1.13)	0	8	1.06 (0.93: 1.19)	68	6	1.05 (0.92: 1.20)	81	0.983
Acylcarnitine C4	2	0.81 (0.40: 1.64)	74	6	0.88 (0.74: 1.04)	68	6	1.04 (0.93: 1.15)	72	0.222
Acylcarnitine C5	1	1.13 (1.04: 1.23)	-	8	1.15 (1.07: 1.23)	19	5	1.06 (0.93: 1.22)	73	0.612
Acylcarnitine C6	2	0.95 (0.78: 1.15)	48	3	0.71 (0.37: 1.34)	94	5	1.01 (0.95: 1.07)	2	0.475
Acylcarnitine C8	2	0.98 (0.84: 1.14)	0	5	0.98 (0.89: 1.09)	15	6	0.95 (0.88: 1.03)	46	0.889
Alanine	2	1.31 (0.78: 2.20)	82	14	1.33 (1.17: 1.51)	81	5	1.34 (1.19: 1.51)	57	0.996
Arginine	2	1.01 (0.92: 1.12)	0	6	1.04 (0.89: 1.22)	81	5	0.94 (0.78: 1.12)	85	0.659
Betaine	1	0.81 (0.71: 0.92)	-	7	0.80 (0.72: 0.89)	50	2	0.86 (0.70: 1.05)	71	0.856
Carnitine	2	1.11 (0.95: 1.31)	43	7	1.03 (0.90: 1.17)	71	5	1.03 (0.88: 1.22)	84	0.731
Citrulline	2	0.98 (0.90: 1.07)	0	5	1.03 (0.85: 1.24)	63	5	0.99 (0.92: 1.07)	22	0.912
Creatinine	-	-	-	10	1.05 (0.94: 1.16)	56	3	0.86 (0.73: 1.01)	64	**0.041**
Docosahexaenoate	-	-	-	9	1.02 (0.91: 1.15)	64	1	1.22 (0.91: 1.63)	0	0.270
Glutamate	1	1.08 (0.98: 1.20)	0	7	1.60 (1.26: 2.03)	91	5	1.23 (1.11: 1.36)	60	**0.008**
Glutamine	2	0.84 (0.76: 0.94)	0	12	0.77 (0.68: 0.87)	82	5	1.06 (0.89: 1.28)	86	**0.013**
Glycine	3	0.71 (0.57: 0.87)	64	11	0.79 (0.70: 0.89)	73	4	0.95 (0.50: 1.80)	98	0.542
Histidine	2	0.91 (0.75: 1.09)	28	10	0.94 (0.87: 1.02)	52	5	0.98 (0.87: 1.11)	66	0.726
Isoleucine	3	1.63 (0.93: 2.87)	92	12	1.54 (1.31: 1.82)	87	4	1.49 (1.37: 1.63)	0	0.901
Lactate	1	1.09 (0.99: 1.20)	-	10	1.16 (0.97: 1.37)	87	1	1.42 (1.05: 1.92)	0	0.242
Leucine	3	1.56 (0.99: 2.44)	88	16	1.38 (1.25: 1.52)	69	4	1.43 (1.24: 1.64)	59	0.836
Linoleate	-	-	-	10	0.94 (0.89: 0.99)	13	1	1.44 (1.00: 2.07)	0	**0.023**
LPC 16:0	3	1.01 (0.93: 1.09)	9	7	0.92 (0.81: 1.04)	83	1	1.01 (0.89: 1.14)	0	0.426
LPC 16:1	3	0.91 (0.84: 0.98)	0	7	1.03 (0.98: 1.08)	0	1	1.04 (0.92: 1.17)	0	**0.021**
LPC 18:0	3	0.97 (0.89: 1.06)	22	8	0.87 (0.78: 0.97)	83	2	0.81 (0.59: 1.10)	77	0.201
LPC 18:1	3	0.82 (0.70: 0.95)	72	9	0.78 (0.74: 0.81)	0	1	0.81 (0.71: 0.93)	0	0.721

LPC 18:2	3	0.80 (0.65: 0.98)	83	8	0.69 (0.65: 0.72)	0	2	0.75 (0.65: 0.87)	0	0.246
Lysine	1	1.05 (0.95: 1.16)	-	6	1.14 (1.06: 1.24)	15	4	1.09 (1.01: 1.17)	0	0.410
Methionine	2	0.88 (0.63: 1.23)	50	5	1.22 (1.04: 1.43)	82	5	1.08 (1.01: 1.15)	3	0.163
Ornithine	2	1.03 (0.93: 1.15)	0	6	1.05 (0.88: 1.27)	73	5	1.06 (0.88: 1.27)	87	0.973
Phenylalanine	3	1.25 (0.97: 1.62)	75	9	1.34 (1.05: 1.71)	94	6	1.29 (1.14: 1.45)	67	0.934
Pyruvate	1	1.00 (0.90: 1.11)	-	8	1.23 (1.08: 1.40)	67	2	1.56 (1.27: 1.91)	0	**<0.001**
Serine	2	0.85 (0.76: 0.95)	0	5	1.02 (0.80: 1.31)	91	5	0.89 (0.81: 0.99)	57	0.420
SM 34:1	4	0.98 (0.85: 1.13)	79	4	0.87 (0.71: 1.07)	84	3	1.08 (0.84: 1.39)	91	0.422
SM 34:2	4	0.97 (0.80: 1.18)	85	3	0.93 (0.78: 1.11)	90	3	0.96 (0.73: 1.28)	88	0.948
SM 36:1	4	1.08 (0.89: 1.31)	89	4	1.08 (0.91: 1.30)	79	3	1.15 (1.02: 1.29)	62	0.804
SM 36:2	4	1.00 (0.81: 1.23)	88	3	0.99 (0.85: 1.15)	81	3	1.02 (0.81: 1.28)	84	0.968
Tryptophan	1	0.99 (0.88: 1.11)	-	9	1.22 (1.10: 1.35)	59	4	0.99 (0.68: 1.43)	94	**0.026**
Tyrosine	2	1.13 (0.84: 1.51)	54	10	1.38 (1.18: 1.62)	88	6	1.35 (1.26: 1.44)	0	0.466
Valine	2	1.47 (0.80: 2.70)	87	10	1.36 (1.16: 1.60)	87	7	1.47 (1.23: 1.75)	82	0.806

CI – confidence interval, I^2 – variability attributable to the between-study heterogeneity, LPC – lysophosphatidylcholines, N – number of studies, SM – sphingomyelins, SRR – summary relative risk, P_{sub} – P-value for the difference in coefficient between subgroups

Supplementary Table 11. Subgroup analysis for metabolites and risk of incident type 2 diabetes stratified for fasting status: fasting and non-fasting or mixed.

Metabolite	Fasting			Non-fasting or mixed			P_{sub}
	N	SRR (95% CI)	I^2	N	SRR (95% CI)	I^2	
Acylcarnitine C10	9	0.99 (0.90: 1.09)	63	2	1.08 (1.00: 1.16)	0	0.178
Acylcarnitine C12	10	0.91 (0.83: 1.00)	64	1	1.27 (0.96: 1.68)	0	**0.028**
Acylcarnitine C14	9	0.97 (0.92: 1.03)	26	1	1.35 (1.01: 1.80)	0	**0.029**
Acylcarnitine C16	12	1.03 (0.96: 1.10)	54	3	1.15 (1.06: 1.25)	0	**0.046**
Acylcarnitine C18	11	0.99 (0.79: 1.24)	95	3	0.93 (0.76: 1.14)	51	0.714
Acylcarnitine C18:1	9	0.97 (0.80: 1.17)	92	2	1.03 (0.94: 1.13)	0	0.544
Acylcarnitine C18:2	8	1.10 (0.86: 1.40)	94	2	0.97 (0.88: 1.06)	0	0.350
Acylcarnitine C2	12	0.98 (0.90: 1.07)	71	4	1.02 (0.94: 1.10)	0	0.541
Acylcarnitine C3	13	1.04 (0.96: 1.13)	73	3	1.16 (0.99: 1.36)	54	0.236
Acylcarnitine C4	13	0.96 (0.87: 1.06)	78	1	1.13 (0.81: 1.57)	0	0.349
Acylcarnitine C5	12	1.14 (1.09: 1.19)	9	2	0.92 (0.61: 1.37)	80	0.286
Acylcarnitine C6	9	0.91 (0.79: 1.06)	87	1	1.17 (0.89: 1.54)	0	0.118
Acylcarnitine C8	11	0.96 (0.91: 1.02)	18	2	0.95 (0.69: 1.31)	74	0.931
Alanine	15	1.36 (1.21: 1.53)	86	6	1.15 (1.04: 1.27)	0	**0.027**
Arginine	11	1.00 (0.90: 1.11)	79	2	0.97 (0.63: 1.50)	87	0.893
Betaine	8	0.84 (0.78: 0.91)	46	2	0.72 (0.62: 0.85)	0	0.090
Carnitine	11	1.02 (0.93: 1.13)	74	3	1.12 (0.93: 1.34)	72	0.413
Citrulline	10	1.00 (0.93: 1.07)	42	2	0.99 (0.80: 1.24)	0	0.955
Creatinine	8	1.01 (0.88: 1.17)	84	5	0.92 (0.81: 1.05)	0	0.323
Docosahexaenoate	5	0.93 (0.80: 1.07)	58	5	1.18 (1.08: 1.29)	0	**0.006**
Glutamate	11	1.33 (1.16: 1.53)	90	2	1.97 (0.86: 4.56)	89	0.364
Glutamine	13	0.84 (0.72: 0.99)	93	6	0.84 (0.78: 0.91)	0	0.978
Glycine	10	0.74 (0.66: 0.83)	75	8	0.89 (0.66: 1.21)	92	0.269
Histidine	11	0.93 (0.86: 1.01)	68	6	1.00 (0.93: 1.09)	0	0.182
Isoleucine	16	1.54 (1.34: 1.77)	89	3	1.54 (1.13: 2.11)	75	0.991
Lactate	6	1.06 (0.85: 1.31)	92	6	1.29 (1.07: 1.54)	65	0.181
Leucine	17	1.41 (1.26: 1.57)	82	6	1.36 (1.24: 1.50)	2	0.673
Linoleate	5	0.92 (0.89: 0.95)	0	6	1.06 (0.95: 1.18)	14	**0.012**
LPC 16:0	9	0.94 (0.87: 1.01)	70	2	1.08 (0.98: 1.19)	0	**0.022**
LPC 16:1	9	0.96 (0.90: 1.03)	47	2	1.16 (0.88: 1.52)	53	0.187
LPC 18:0	10	0.89 (0.82: 0.97)	76	3	0.85 (0.64: 1.12)	73	0.719
LPC 18:1	11	0.78 (0.74: 0.83)	33	2	0.84 (0.75: 0.94)	0	0.302
LPC 18:2	10	0.74 (0.68: 0.80)	66	3	0.74 (0.67: 0.82)	0	0.934
Lysine	10	1.10 (1.05: 1.15)	0	1	1.20 (0.91: 1.58)	0	0.536
Methionine	10	1.10 (1.01: 1.19)	63	2	1.16 (1.06: 1.27)	0	0.389
Ornithine	10	1.08 (0.99: 1.17)	57	3	1.05 (0.61: 1.80)	90	0.931
Phenylalanine	15	1.26 (1.13: 1.41)	85	3	1.77 (0.88: 3.55)	95	0.349
Pyruvate	4	1.20 (0.99: 1.47)	83	7	1.27 (1.08: 1.50)	69	0.673
Serine	10	0.94 (0.83: 1.05)	82	2	0.85 (0.60: 1.20)	75	0.592
SM 34:1	9	1.01 (0.92: 1.12)	82	2	0.66 (0.36: 1.22)	81	0.177
SM 34:2	9	0.98 (0.87: 1.10)	85	1	0.79 (0.72: 0.88)	0	0**.007**
SM 36:1	9	1.14 (1.03: 1.25)	81	2	0.89 (0.60: 1.31)	63	0.225
SM 36:2	9	1.02 (0.91: 1.14)	85	1	0.88 (0.78: 0.99)	0	0.080
Tryptophan	11	1.06 (0.93: 1.22)	86	3	1.55 (1.11: 2.16)	68	**0.040**
Tyrosine	15	1.33 (1.19: 1.48)	82	3	1.50 (1.12: 2.00)	71	0.442
Valine	15	1.34 (1.19: 1.50)	83	4	1.75 (1.26: 2.43)	84	0.131

CI – confidence interval, I^2 – variability attributable to the between-study heterogeneity, LPC – lysophosphatidylcholines, N – number of studies, SM – sphingomyelins, SRR – summary relative risk, P_{sub} – P-value for the difference in coefficient between subgroups.

Supplementary Table 12. Subgroup analysis for metabolites and risk of incident type 2 diabetes stratified for metabolomic platform: mass spectrometry and nuclear magnetic resonance.

Metabolite	Mass spectrometry			Nuclear magnetic resonance			P_{sub}
	N	SRR (95% CI)	I^2	N	SRR (95% CI)	I^2	
Acylcarnitine C10	11	1.01 (0.93: 1.10)	64	-	-	-	-
Acylcarnitine C12	11	0.93 (0.84: 1.03)	71	-	-	-	-
Acylcarnitine C14	10	0.99 (0.92: 1.06)	44	-	-	-	-
Acylcarnitine C16	15	1.06 (0.99: 1.12)	52	-	-	-	-
Acylcarnitine C18	14	0.97 (0.81: 1.17)	94	-	-	-	-
Acylcarnitine C18:1	11	0.98 (0.84: 1.15)	90	-	-	-	-
Acylcarnitine C18:2	10	1.08 (0.88: 1.31)	94	-	-	-	-
Acylcarnitine C2	16	1.00 (0.94: 1.07)	56	-	-	-	-
Acylcarnitine C3	16	1.06 (0.98: 1.14)	73	-	-	-	-
Acylcarnitine C4	14	0.97 (0.88: 1.06)	76	-	-	-	-
Acylcarnitine C5	14	1.13 (1.08: 1.18)	18	-	-	-	-
Acylcarnitine C6	10	0.94 (0.82: 1.07)	84	-	-	-	-
Acylcarnitine C8	13	0.97 (0.92: 1.02)	22	-	-	-	-
Alanine	16	1.38 (1.23: 1.54)	83	5	1.13 (1.04: 1.23)	0	**0.007**
Arginine	13	1.00 (0.91: 1.11)	81	-	-	-	-
Betaine	10	0.82 (0.76: 0.89)	49	-	-	-	-
Carnitine	14	1.04 (0.96: 1.14)	74	-	-	-	-
Citrulline	12	1.00 (0.94: 1.06)	31	-	-	-	
Creatinine	9	1.00 (0.88: 1.15)	82	4	0.93 (0.81: 1.06)	0	-
Docosahexaenoate	5	0.99 (0.83: 1.18)	67	5	1.09 (0.95: 1.25)	54	0.418
Glutamate	13	1.38 (1.20: 1.60)	91	-	-	-	-
Glutamine	14	0.83 (0.71: 0.96)	93	5	0.87 (0.79: 0.97)	20	0.584
Glycine	13	0.75 (0.61: 0.91)	93	5	0.90 (0.82: 0.99)	0	0.087
Histidine	12	0.92 (0.86: 1.00)	64	5	1.04 (0.96: 1.14)	0	**0.039**
Isoleucine	19	1.54 (1.36: 1.74)	88	-	-	-	-
Lactate	8	1.15 (0.94: 1.40)	91	4	1.19 (0.98: 1.45)	65	0.794
Leucine	18	1.44 (1.30: 1.60)	79	5	1.28 (1.16: 1.41)	21	0.110
Linoleate	6	0.93 (0.81: 1.07)	46	5	1.00 (0.90: 1.11)	50	0.415
LPC 16:0	11	0.96 (0.89: 1.03)	70	-	-	-	-
LPC 16:1	11	0.98 (0.93: 1.04)	46	-	-	-	-
LPC 18:0	13	0.89 (0.82: 0.96)	76	-	-	-	-
LPC 18:1	13	0.79 (0.75: 0.83)	24	-	-	-	-
LPC 18:2	13	0.74 (0.69: 0.79)	58	-	-	-	-
Lysine	11	1.10 (1.05: 1.15)	0	-	-	-	-
Methionine	12	1.10 (1.04: 1.17)	46	-	-	-	
Ornithine	13	1.06 (0.97: 1.17)	72	-	-	-	-
Phenylalanine	18	1.30 (1.16: 1.45)	87	-	-	-	-
Pyruvate	7	1.31 (1.12: 1.54)	76	4	1.10 (0.96: 1.26)	40	0.097
Serine	12	0.92 (0.83: 1.02)	80	-	-	-	-
SM 34:1	11	0.97 (0.88: 1.08)	85	-	-	-	-
SM 34:2	10	0.96 (0.86: 1.07)	87	-	-	-	-
SM 36:1	11	1.11 (1.01: 1.21)	81	-	-	-	-
SM 36:2	10	1.00 (0.90: 1.11)	85	-	-	-	-
Tryptophan	14	1.14 (0.99: 1.30)	88	-	-	-	-
Tyrosine	18	1.35 (1.22: 1.49)	81	-	-	-	-
Valine	19	1.40 (1.25: 1.57)	86	-	-	-	-

CI – confidence interval, I^2 – variability attributable to the between-study heterogeneity, LPC – lysophosphatidylcholines, N – number of studies, SM – sphingomyelins, SRR – summary relative risk, P_{sub} – P-value for the difference in coefficient between subgroups.

Supplementary Table 13. Subgroup analysis for metabolites and risk of incident type 2 diabetes stratified for fasting glucose adjustment: adjusted and non-adjusted.

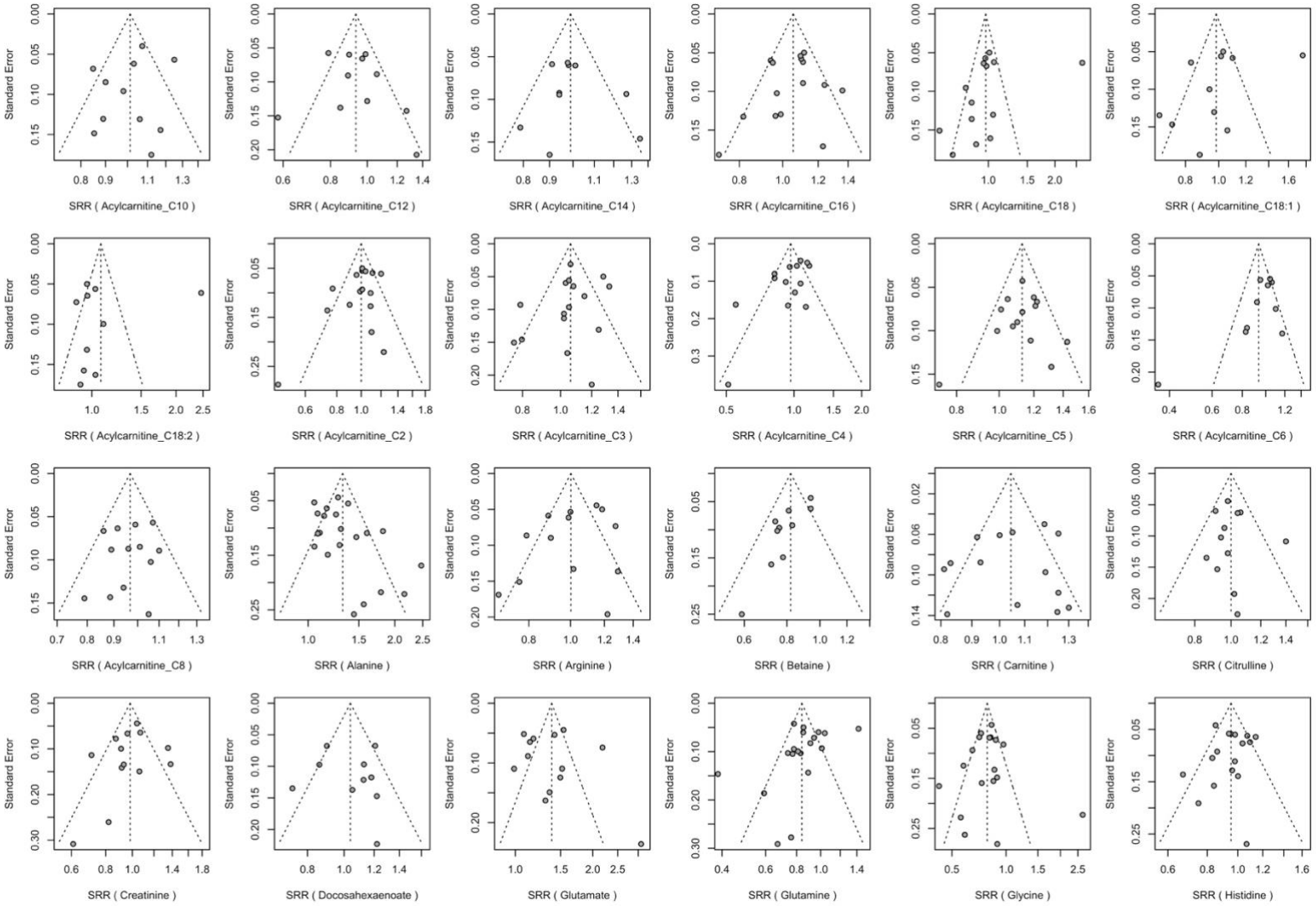
Metabolite	Adjusted			Non-adjusted			P_{sub}
	N	SRR (95% CI)	I^2	N	SRR (95% CI)	I^2	
Acylcarnitine C10	4	1.04 (0.90: 1.02)	75	7	0.99 (0.89: 1.10)	50	0.536
Acylcarnitine C12	5	0.93 (0.84: 1.03)	65	6	0.94 (0.75: 1.18)	80	0.913
Acylcarnitine C14	6	0.99 (0.92: 1.08)	48	4	0.98 (0.80: 1.20)	67	0.912
Acylcarnitine C16	7	1.10 (1.01: 1.20)	59	8	1.01 (0.92: 1.10)	48	0.171
Acylcarnitine C18	5	1.13 (0.73: 1.75)	98	9	0.92 (0.83: 1.01)	52	0.349
Acylcarnitine C18:1	3	1.11 (0.70: 1.77)	97	8	0.95 (0.85: 1.07)	69	0.509
Acylcarnitine C18:2	3	1.34 (0.72: 2.48)	98	7	0.98 (0.92: 1.04)	0	0.323
Acylcarnitine C2	7	1.03 (0.93: 1.14)	69	9	0.99 (0.93: 1.05)	0	0.524
Acylcarnitine C3	8	1.06 (0.95: 1.18)	76	8	1.06 (0.94: 1.19)	71	0.988
Acylcarnitine C4	6	1.02 (0.93: 1.12)	64	8	0.90 (0.76: 1.07)	81	0.214
Acylcarnitine C5	9	1.15 (1.10: 1.21)	8	5	1.07 (0.99: 1.16)	0	0.121
Acylcarnitine C6	5	1.00 (0.94: 1.07)	0	5	0.81 (0.56: 1.17)	92	0.261
Acylcarnitine C8	7	1.01 (0.96: 1.07)	0	6	0.89 (0.83: 0.96)	0	**0.009**
Alanine	12	1.23 (1.12: 1.36)	72	9	1.48 (1.24: 1.76)	82	0.071
Arginine	5	0.90 (0.80: 1.01)	61	8	1.09 (0.96: 1.23)	78	**0.027**
Betaine	6	0.81 (0.75: 0.88)	38	4	0.81 (0.67: 0.98)	53	0.937
Carnitine	7	1.00 (0.89: 1.13)	79	7	1.09 (0.97: 1.24)	66	0.327
Citrulline	6	1.02 (0.91: 1.14)	65	6	0.97 (0.89: 1.06)	9	0.479
Creatinine	8	0.97 (0.84: 1.12)	74	5	1.00 (0.85: 1.18)	69	0.734
Docosahexaenoate	6	1.10 (0.98: 1.24)	53	4	0.94 (0.76: 1.16)	64	0.197
Glutamate	6	1.29 (1.01: 1.63)	93	7	1.46 (1.26: 1.68)	79	0.382
Glutamine	11	0.88 (0.82: 0.93)	31	8	0.79 (0.60: 1.03)	96	0.454
Glycine	7	0.84 (0.75: 0.93)	51	11	0.75 (0.59: 0.96)	95	0.431
Histidine	9	0.99 (0.92: 1.07)	41	8	0.91 (0.83: 1.00)	62	0.136
Isoleucine	7	1.65 (1.32: 2.07)	86	12	1.48 (1.27: 1.71)	87	0.408
Lactate	7	1.21 (1.08: 1.37)	68	5	1.09 (0.77: 1.53)	90	0.553
Leucine	12	1.44 (1.27: 1.64)	76	11	1.36 (1.21: 1.52)	69	0.463
Linoleate	5	1.03 (0.94: 1.12)	0	6	0.92 (0.89: 0.95)	0	**0.016**
LPC 16:0	3	0.90 (0.69: 1.17)	83	8	0.97 (0.91: 1.03)	58	0.594
LPC 16:1	3	0.94 (0.85: 1.03)	0	8	1.00 (0.92: 1.07)	59	0.297
LPC 18:0	4	0.90 (0.75: 1.08)	83	9	0.88 (0.81: 0.97)	75	0.878
LPC 18:1	4	0.77 (0.65: 0.90)	69	9	0.79 (0.76: 0.82)	0	0.711
LPC 18:2	3	0.76 (0.61: 0.93)	74	10	0.73 (0.67: 0.78)	52	0.740
Lysine	6	1.09 (1.02: 1.17)	11	5	1.12 (1.05: 1.19)	0	0.672
Methionine	5	1.04 (0.96: 1.14)	30	7	1.14 (1.08: 1.20)	0	0.088
Ornithine	5	1.13 (1.02: 1.25)	46	8	1.01 (0.85: 1.19)	83	0.261
Phenylalanine	8	1.29 (1.12: 1.50)	80	10	1.32 (1.08: 1.61)	93	0.871
Pyruvate	7	1.18 (1.03: 1.35)	77	4	1.39 (1.11: 1.74)	56	0.225
Serine	4	0.89 (0.80: 0.98)	44	8	0.95 (0.80: 1.13)	89	0.521
SM 34:1	4	1.08 (0.88: 1.34)	88	7	0.93 (0.85: 1.02)	68	0.193
SM 34:2	5	0.96 (0.83: 1.13)	82	5	0.95 (0.80: 1.13)	91	0.882
SM 36:1	4	1.06 (0.88: 1.29)	85	7	1.14 (1.04: 1.25)	73	0.511
SM 36:2	5	0.98 (0.85: 1.13)	76	5	1.01 (0.86: 1.19)	90	0.749
Tryptophan	6	1.03 (0.81: 1.31)	92	8	1.18 (1.09: 1.27)	30	0.297
Tyrosine	8	1.36 (1.15: 1.60)	83	10	1.33 (1.27: 1.39)	0	0.802
Valine	7	1.37 (1.10: 1.72)	91	12	1.41 (1.26: 1.58)	77	0.837

CI – confidence interval, I^2 – variability attributable to the between-study heterogeneity, LPC – lysophosphatidylcholines, N – number of studies, SM – sphingomyelins, SRR – summary relative risk, P_{sub} – P-value for the difference in coefficient between subgroups.

Supplementary Table 14. Subgroup analysis for metabolites and risk of incident type 2 diabetes stratified for length of follow-up: ≤7 years and >7 years.

Metabolite	≤7 years			>7 years			P_{sub}
	N	SRR (95% CI)	I^2	N	SRR (95% CI)	I^2	
Acylcarnitine C10	7	1.08 (0.99: 1.17)	48	4	0.89 (0.81: 0.97)	0	**0.002**
Acylcarnitine C12	7	0.93 (0.78: 1.11)	86	4	0.95 (0.85: 1.05)	19	0.876
Acylcarnitine C14	8	0.96 (0.91: 1.02)	0	2	1.10 (0.85: 1.42)	83	0.311
Acylcarnitine C16	9	1.04 (0.96: 1.11)	44	6	1.09 (0.97: 1.23)	64	0.443
Acylcarnitine C18	9	1.00 (0.75: 1.32)	96	5	0.93 (0.86: 1.00)	6	0.636
Acylcarnitine C18:1	7	0.99 (0.79: 1.26)	93	4	0.99 (0.86: 1.13)	61	0.950
Acylcarnitine C18:2	7	1.12 (0.84: 1.48)	95	3	1.00 (0.92: 1.08)	0	0.452
Acylcarnitine C2	11	1.04 (0.98: 1.11)	35	5	0.90 (0.77: 1.05)	74	0.082
Acylcarnitine C3	10	1.11 (1.01: 1.21)	69	5	0.96 (0.84: 1.10)	71	0.085
Acylcarnitine C4	8	0.97 (0.82: 1.13)	85	5	0.98 (0.86: 1.12)	65	0.868
Acylcarnitine C5	8	1.15 (1.05: 1.26)	59	4	1.05 (0.97: 1.14)	0	0.152
Acylcarnitine C6	7	0.91 (0.71: 1.16)	93	3	0.96 (0.85: 1.09)	39	0.666
Acylcarnitine C8	8	0.99 (0.93: 1.05)	4	5	0.95 (0.86: 1.04)	36	0.419
Alanine	9	1.32 (1.12: 1.55)	83	12	1.33 (1.19: 1.48)	76	0.925
Arginine	8	0.98 (0.87: 1.09)	69	5	1.05 (0.87: 1.27)	89	0.512
Betaine	5	0.83 (0.75: 0.92)	37	5	0.81 (0.71: 0.92)	57	0.733
Carnitine	8	1.07 (0.95: 1.20)	79	6	1.00 (0.88: 1.14)	64	0.470
Citrulline	7	1.03 (0.93: 1.15)	57	4	0.96 (0.88: 1.05)	17	0.297
Creatinine	3	1.06 (0.81: 1.41)	78	10	0.96 (0.86: 1.07)	67	0.495
Docosahexaenoate	3	1.06 (0.84: 1.33)	66	6	1.07 (0.92: 1.24)	59	0.940
Glutamate	8	1.45 (1.14: 1.85)	93	5	1.32 (1.17: 1.50)	78	0.506
Glutamine	7	0.75 (0.60: 0.93)	92	12	0.90 (0.79: 1.02)	85	0.157
Glycine	7	0.79 (0.52: 1.19)	95	10	0.81 (0.75: 0.88)	52	0.885
Histidine	6	0.96 (0.86: 1.06)	55	11	0.95 (0.88: 1.03)	57	0.901
Isoleucine	8	1.61 (1.29: 2.01)	91	10	1.52 (1.29: 1.81)	86	0.694
Lactate	4	1.27 (1.07: 1.51)	65	8	1.10 (0.91: 1.33)	87	0.274
Leucine	7	1.49 (1.23: 1.81)	72	15	1.39 (1.26: 1.53)	75	0.520
Linoleate	4	0.96 (0.80: 1.14)	60	6	0.99 (0.87: 1.12)	38	0.764
LPC 16:0	5	0.96 (0.82: 1.13)	84	6	0.94 (0.88: 1.01)	46	0.815
LPC 16:1	5	0.98 (0.89: 1.08)	55	6	1.02 (0.96: 1.07)	0	0.493
LPC 18:0	6	0.86 (0.73: 1.02)	85	6	0.88 (0.80: 0.98)	72	0.816
LPC 18:1	6	0.81 (0.73: 0.89)	54	7	0.77 (0.74: 0.81)	0	0.482
LPC 18:2	7	0.80 (0.73: 0.87)	32	6	0.67 (0.64: 0.71)	0	**0.001**
Lysine	6	1.15 (1.06: 1.24)	25	5	1.07 (0.99: 1.15)	27	0.205
Methionine	7	1.11 (0.95: 1.30)	82	5	1.11 (1.05: 1.18)	0	0.964
Ornithine	9	1.06 (0.92: 1.22)	79	4	1.06 (0.92: 1.21)	68	0.973
Phenylalanine	9	1.34 (1.10: 1.62)	89	9	1.28 (1.10: 1.49)	88	0.719
Pyruvate	4	1.26 (1.02: 1.55)	76	6	1.18 (1.01: 1.37)	70	0.636
Serine	7	0.95 (0.77: 1.17)	89	5	0.91 (0.84: 0.97)	27	0.694
SM 34:1	6	0.92 (0.78: 1.09)	92	5	1.02 (0.89: 1.18)	71	0.367
SM 34:2	5	0.96 (0.80: 1.16)	92	4	0.95 (0.79: 1.13)	72	0.884
SM 36:1	6	1.07 (0.93: 1.24)	89	5	1.15 (1.01: 1.30)	63	0.493
SM 36:2	5	1.01 (0.85: 1.20)	92	4	1.00 (0.84: 1.17)	71	0.909
Tryptophan	9	1.24 (1.07: 1.45)	82	5	0.96 (0.77: 1.20)	89	0.056
Tyrosine	9	1.25 (1.12: 1.41)	61	8	1.46 (1.24: 1.72)	87	0.130
Valine	9	1.34 (1.12: 1.61)	88	8	1.45 (1.22: 1.73)	87	0.549

CI – confidence interval, I^2 – variability attributable to the between-study heterogeneity, LPC – lysophosphatidylcholines, N – number of studies, SM – sphingomyelins, SRR – summary relative risk, P_{sub} – P-value for the difference in coefficient between subgroups.


Standard Error
SRR (Acylcarnitine_C10)
SRR (Acylcarnitine_C12)
SRR (Acylcarnitine_C14)
SRR (Acylcarnitine_C16)
SRR (Acylcarnitine_C18)
SRR (Acylcarnitine_C18:1)
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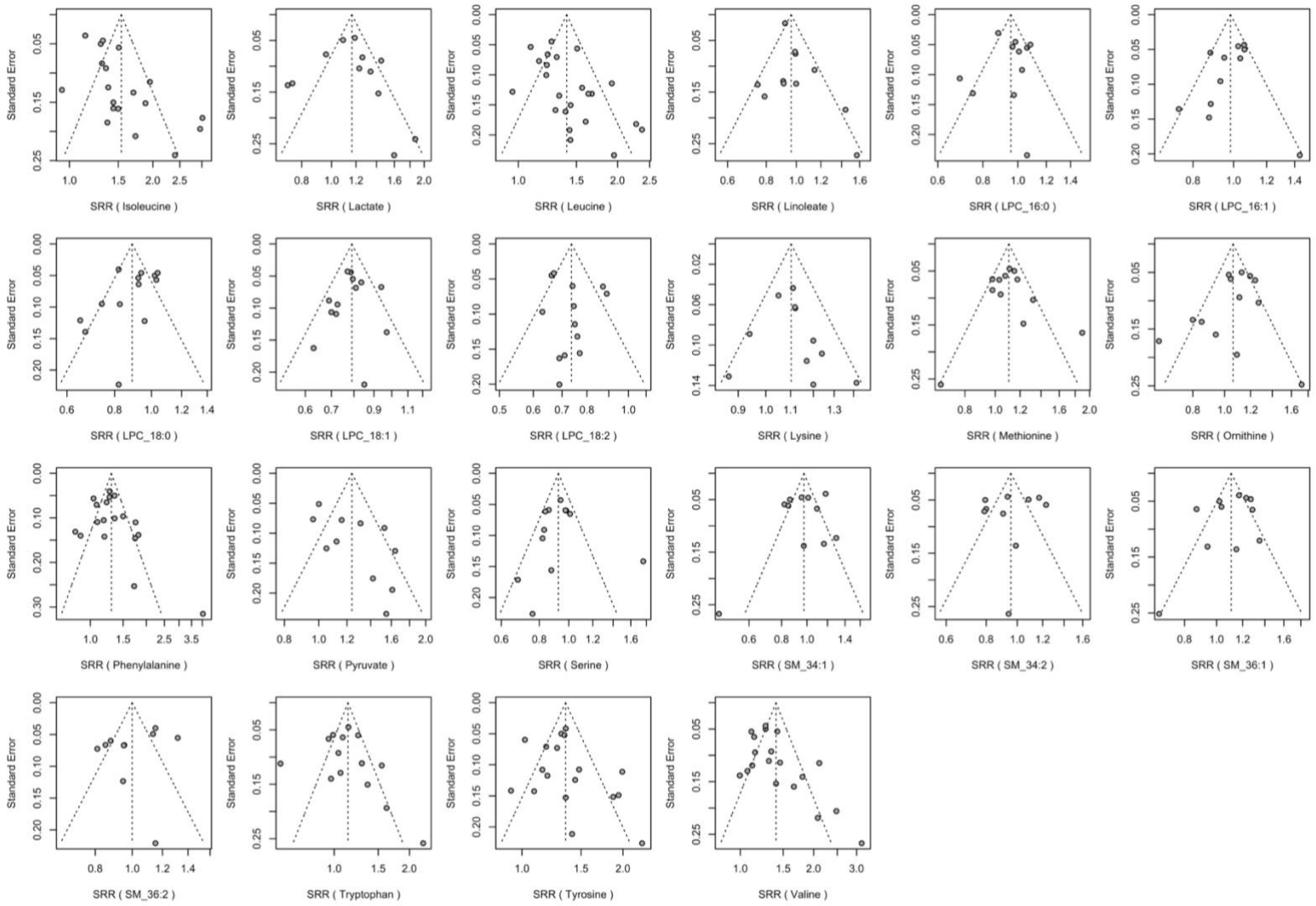
SRR (Acylcarnitine_C2)
SRR (Acylcarnitine_C3)
SRR (Acylcarnitine_C4)
SRR (Acylcarnitine_C5)
SRR (Acylcarnitine_C6)
SRR (Acylcarnitine_C8)
SRR (Alanine)
SRR (Arginine)
SRR (Betaine)
SRR (Carnitine)
SRR (Citrulline)
SRR (Creatinine)
SRR (Docosahexaenoate)
SRR (Glutamate)
SRR (Glutamine)
SRR (Glycine)
SRR (Histidine)



Supplementary Figure 1. Funnel plots showing study precision against the relative risk with 95% confidence intervals for incident type 2 diabetes. LPC – lysophosphatidylcholines, SM – sphingomyelins, SRR – summary relative risk.

Supplementary Table 15. Results of Egger's linear regression test for funnel plot asymmetry.

Metabolite	P_{Egger}
Acylcarnitine C10	0.642
Acylcarnitine C12	0.510
Acylcarnitine C14	0.699
Acylcarnitine C16	0.271
Acylcarnitine C18	0.067
Acylcarnitine C18:1	0.095
Acylcarnitine C18:2	0.394
Acylcarnitine C2	0.064
Acylcarnitine C3	0.175
Acylcarnitine C4	**0.008**
Acylcarnitine C5	0.499
Acylcarnitine C6	**0.002**
Acylcarnitine C8	0.588
Alanine	**0.006**
Arginine	0.369
Betaine	**0.001**
Carnitine	0.905
Citrulline	0.903
Creatinine	0.248
Docosahexaenoate	0.677
Glutamate	0.109
Glutamine	**0.014**
Glycine	0.779
Histidine	0.233
Isoleucine	**0.001**
Lactate	0.301
Leucine	**0.002**
Linoleate	0.064
LPC 16:0	0.399
LPC 16:1	0.327
LPC 18:0	**0.015**
LPC 18:1	0.507
LPC 18:2	0.961
Lysine	0.435
Methionine	0.543
Ornithine	0.253
Phenylalanine	**0.013**
Pyruvate	**0.027**
Serine	0.777
SM 34:1	0.271
SM 34:2	0.803
SM 36:1	0.160
SM 36:2	0.829
Tryptophan	**0.043**
Tyrosine	0.081
Valine	**<0.001**

LPC – lysophosphatidylcholines, SM – sphingomyelins,
P_{Egger} – P-value for Egger's linear regression test.