SUPPLEMENTARY DATA

Search strategy and selection criteria. Metabolomics biomarkers of prediabetes and type 2 diabetes

References for this systematic review and meta-analysis were identified through searches of PubMed and EMBASE for articles published in any language from the earliest available online indexing year through August 2015, by use of the following approach:

(("metabolomics"[MeSH Terms] OR "metabolomics"[All Fields] OR "metabolome"[MeSH Terms] OR "metabolome"[All Fields]) AND ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "type 2 diabetes"[All Fields] OR "metabolic diseases"[MeSH Terms] OR "insulin resistance"[All Fields] OR "insulin sensitivity"[All fields] OR "metabolic syndrome x"[MeSH Terms] OR "metabolic syndrome"[All Fields] OR "HOMA-IR"[All Fields] OR "HOMA- β "[All Fields] OR “impaired glucose” [All Fields] OR “impaired fasting insulin” [All Fields]) AND "humans"[MeSH Terms]).
Articles resulting from these searches and relevant references cited in those articles were reviewed.

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Supplementary Table 1. Case-Control and Non-Prospective Population-Based Metabolomics Studies in Type 2 Diabetes.

Author –year – journal	Study – population	Study design	N, follow-up	Technique and metabolite targets	Biological sample	Outcome	Significant findings
Messana *et al*. 1988– *Clin Chem*	Universita Cattolica del Sacro Cuore – Italy	Case-control	53 (20 nondiabetic/33 T2D)	H NMR Targeted (17 amino acids)	Urine	T2D	**Amino acids** (↑) lactate, alanine, citrate, DMA (dimethylamine), TMAO (trimethylamine-N-oxide), hippurate, glycine, creatine, acetate, betaine, acetone, acetoacetate, β-hydroxybutyrate
Wang *et al*. 2005– *Anal Chem*	Second Affiliated Hospital of Dalian Medical University (Dalian, China) – China	Case-control	69 (35 nondiabetic/34 T2D)	LC/MS Targeted (83 phospholipids)	Plasma	T2D	**Lipids** (↑) phosphoethanolamines (PE), lysophosphocholine (LPC)
Yuan *et al*. 2007– *J Chromatog*	Second Affiliated Hospital of Dalian Medical University (Dalian, China) – China	Case-control	79 (26 nondiabetic/28 T2D)	GC-MS Targeted (195 organic acids)	Urine	T2D	**Organic acids** 5 organic acids associated with T2D: (↑) 4-Aminobenzoic acid (↓) Maleic acid, dimethyl ester, acetic acid, 2,5-bisoxy-benzeneacetic acid
Li *et al*. 2008– *Anal Chem Acta*	Zhejiang Affiliated Hospital of Zhejing TCM University – China	Case-control	79 (31 nondiabetic/48 T2D)	GC X GC – TOFMS Targeted (73 sugar and lipid metabolites)	Plasma	T2D	**Lipids and sugar metabolites** 5 associated with T2D (↑) glucose, 2-hydroxybutyric acid, linoleic acid, palmitic acid, phosphate
Haus *et al*. 2009– *Diabetes*	San Antonio Area – USA	Case-control	27 (14 lean healthy controls/13 obese T2D)	GC-MS/MS Targeted (at least 7 ceramides)	Plasma	Prediabetes (insulin sensitivity by hyper-insulinemic-euglycemic clamp)	**Ceramides** (↓) ceramides C18:0 (N-stearoylsphingosine), C20:0 (N-eicosanoylsphingosine), C24:1, and total ceramides (inversely associated with insulin sensitivity)
						T2D	(↑) ceramides C18:0, C20:0, C24:1 and total ceramides (↑) TNF-α

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Adams *et al.* 2009– *J Nutr*	SUGAR-Project, African-American women – USA	Case-control	56 (12 obese non diabetic With or without UCP3 g/a polymorphism/44 obese T2D)	HPLC-MS Targeted (42 acylcarnitines)	Plasma	T2D	**Acylcarnitines** 11 acylcarnitines associated with T2D (↑) total-free acylcarnitines, C6 (hexanoyl carnitine), C8 (octanoyl carnitine), cis-3,4-methylene-nonanoyl carnitine, C14 (myristoyl carnitine), C18:1 (oleoyl carnitine), (C8-dicarb (suberoyl carnitine), summed C10-C14, total acylcarnitines (↓) C3 (propionyl carnitine)
Zhang *et al.* 2009– *J Proteome Res*	Xiamen Hospital – China	Case-control	231 (80 nondiabetic, 74 T2D, 77 IFG)	H NMR Targeted (at least 30 metabolites, amino acids, lipids, sugar metabolites)	Serum	Prediabetes (OGTT, HOMA-IR)	**BCAA, amino acids and sugar metabolites** (↑) glucose (↓) lactate, alanine, tyrosine, phenylalanine, histidine, glutamine
						T2D	(↑) glucose (↓) BCAAs (isoleucine, leucine, valine), alanine, methionine, glutamine, citrate, lysine, choline, HDL-c, lactate, tyrosine, phenylalanine, histidine
Zhang *et al.* 2009– *Anal Chem Acta*	Xiamen Hospital – China	Case-control	58 (25 nondiabetic/33 T2D)	UPLC-oaTOF-MS Untargeted (>15000 metabolite features)	Serum	T2D	**Lipids and amino acids** (↓) Sphingolipids (phytosphingosine, dihydrosphingosine), leucine
Newgard *et al.* 2009– *Cell Metab*	Weight Loss Maintenance Study (WLM) (n=112); Duke University Bariatric Surgery Program (n= 13); Duke Diet and Fitness Center (n= 9); low-carbohydrate, ketogenic diet program (n= 4); and Structure House (n= 3) in African	Case-control	141 (74 obese/67 lean healthy controls)	GC-MS/MS Targeted (98 metabolites, amino acids, lipids, acylcarnitines)	Serum and plasma	Prediabetes (intravenous glucose tolerance testing, HOMA)	**BCAA** (↑) BCAA (↑) C16:1 (palmitoleate)

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	Americans – USA						
Tai *et al.* 2010– *Diabetologia*	Cross-sectional survey Asian-Indian and Chinese men – Singapore	Cohort, population-based study	263 men (97 Chinese low HOMA/83 Chinese high HOMA 30 Asian-Indian low HOMA/53 Asian-Indian high HOMA)	MS/MS (plasma amino acids) and GC/MS (urine organic acids) Targeted (at least ten amino acids, 45 acylcarnitines, 20 organic acids)	Plasma amino acids and urine organic acids	Prediabetes (HOMA-IR)	**BCAA, acylcarnitines, organic acids** (↑) BCAAs (valine, leucine/isoleucine), alanine, proline, phenylalanine, tyrosine, glutamate/glutamine, ornithine (↑) C10:1 and C8:1 acylcarnitines Also combination of these metabolites using principal component analysis
Lucio *et al.* 2010– *Plos One*	University Clinic in Tubingen – Germany	Cohort, population-based study	46 nondiabetic	Infusion ion cyclotron resonance Fourier transform – MS Untargeted (>15000 metabolite features)	Plasma	Prediabetes (OGTT, $ISI_{Matsuda)}$	**Lipids and sugar metabolites** Metabolites altered in subjects with reduced insulin sensitivity: arachidonic acid, steroid hormone biosynthesis, bile acid biosynthesis metabolites, linoleic and α-linoleic acid, biosynthesis of unsaturated fatty acids, retinol metabolism, sphingolipid metabolism, galactose metabolism, fructose and mannose metabolism, phenylalanine metabolism, fatty acid biosynthesis metabolites
Mihalik *et al.* 2010– *Obesity*	University of Pittsburg –USA	Case-control	36 (12 nondiabetic/14 obese nondiabetic/ 10 T2D)	HPLC-ESI-MS/MS Targeted (46 acylcarnitines)	Plasma	Prediabetes (OGTT, euglycemic-hyperinsulinemic clamp with variable intravenous glucose infusion)	**Acylcarnitines** In response to insulin infusion, a significant decrease in every acylcarnitine species detected between carbon lengths of 2 and 18
						T2D	(↑) C3 (propionyl carnitine), C5 (isovaleryl carnitine), C8 (octanoyl carnitine), C4-OH (3-hydroxy-butyryl carnitine), C4-DC (C4-dicarboxylcarnitine), C5-OH (3-hydroxy-isovaleryl carnitine), C6-OH (hydroxyhexanoycarnitine), free carnitine
Fiehn *et al.* 2010– *Plos One*	SUGAR-Project, African-American women	Case-control	56 women (12 obese nondiabetic/44 obese diabetic)	GC-TOF-MS Untargeted (>350 metabolite	Plasma	Prediabetes (HbA1c)	**Amino acids, acylcarnitines, sugar metabolites** (↑) BCAAs, acylcarnitines

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	– USA			features)		T2D	36 metabolites higher and 59 lower in T2D (↑) long-chain fatty acids and carbohydrate derivatives: oleic acid, gluconic acid, fructose, palmitoleic acid, 3,6-anhydrogalactose, glucuronic acid, glucose, heptadecanoic acid ,inulobiose, 2-deoxyerythritol, palmitic acid, uridine, cysteine, xylose, stearic acid (↑) amino acids and derivatives: leucine, 2-ketoisocaproate, valine, cysteine, histidine (↓) benzylalcohol, benzoic acid, lysine, ethanolamine, arachidonic acid, glycine, glycerol-3-phosphate
Gall *et al.* 2010– *Plos One*	EGIR-RISC – Europe	Case-control	399 nondiabetic (256 normal glucose tolerance, 82 impaired glucose tolerance, 61 IFG)	GC/MS UHPLC/MS/MS Untargeted (485 metabolite features)	Plasma	Prediabetes (OGTT)	**BCAA and lipids** (↑) α-hydroxybutyrate, 3-methyl-2-oxobutyrate, cysteine, creatinine, isoleucine, adrenate, stearate, palmitate (16:0) (↓) glycine, serine
Suhre *et al.* 2010– *Plos One*	Cooperative Health Research in the Region of Ausgburg (KORA men) – Germany	Case-control	100 men (60 nondiabetic/40 T2D)	UHPLC/MS/MS/ GC-MS NMR Untargeted (420 metabolite features)	Serum and Plasma	T2D	**Sugar metabolites, ketone bodies, BCAAs** (↑) desoxyhexose, glucose, glicolipids (H3-HNAc2-NANA, HNAC, HNAc-H2-dH) uronic acid, dihexose, mannose, creatinine, glutamylvaline, gamma-glutamylisoleucine, β-hydroxybutyrate, PAGN, phenylalanine, 3-indoxyl sulfate, kynurenine, homocitrulline, myristate, palmitate, 2-hydroxypalmitate, margarate, 10-heptadecenoate, stearate, 2-hydroxystearate, oleate, linoleate, linoleamide, linolenate, eicosenoate, dihomo-alpha-linolenate, adrenate, isoleucine, leucine, gamma-glutamylleucine, valine (↓) 1,5-anhydroglucitol, caproate, heptanoate, pelargonate, glycerophosphorylcholine, PC a C20:4, PC aa (OH, COOH) C28:4, PC aa C34:4, SM C14:0, SM C22:2, 10-undecenoate, arachidonate
Han *et al.* 2011– *Anal Chem Acta*	China-Japan Friendship	Case-control	60 (30 nondiabetic/ 30 T2D)	GC-MS Targeted (25 fatty	Plasma	T2D	**Lipids**

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	Hospital – China			acids)			21 significantly associated (↑) non-esterified fatty acids (C16:0, C18:2, C18:1, 18:0, C20:4, C20:3, C20:2, C20:0, C20:6) (↓) esterified fatty acids (C10:0, C14:0, C16, C16:1n-9, C18:2, C18:1n-9, C18:0, C20:4, C20:5, C20:3, C20:2, C22:6)
Ha *et al.* 2012– *Clin Endocrinol*	National Health Insurance Corporation Ilsan hospital – Korea (men)	Case-control	53 men (27 nondiabetic/26 T2D)	UPLC/Q-TOF MS Untargeted (382 metabolite features)	Plasma	T2D	**Lipids** (↑) dodecanoic acid, myristic acid, leucine, lysine, phenylalanine, propionyl carnitine, octanoyl carnitine, decanoyl carnitine, dodecanoyl carnitine, palmityl carnitine, heptadecanoyl carnitine, linoleyl carnitine, vaccenyl carnitine, lysoPC (14:0, 16:0, 16:1, 18:1, 18:2, 18:3, 20:5, 22:6), lysoPE (18:2, 22:6) (↓) serine, LPC (18:0), LPE (18:1)
Würtz et al. 2012– *Diabetes*	Northern Finland Birth Cohort (NFBC) and Cardiovascular Risk in Young Finns Study (YFS) – Finland	Cohort, population-based	7098 nondiabetic	NMR Targeted (39 amino acids, lipid)	Serum	Prediabetes (HOMA-IR)	**Amino acids and lipid** 20 metabolites were associated with HOMA-IR (↑) BCAAs, phenylalanine, tyrosine, glycolysis and gluconeogenesis intermediates, total fatty acids, n-3, n-6 and n-7, phosphocholines, phosphoglycerides, (↓) glutamine, acetoacetate, 3-hydroxybutyrate,
Zhou *et al.* 2013– *Clin Bioc*	Dahua Hospital and Xuhui District Central Hospital – China	Case-control	226 [100 nondiabetic (80 obese/20 lean)/126 T2D (31 obese/95 lean)]	LC-MS/MS Targeted (42 amino acids)	Plasma	Prediabetes (fasting glucose, HbA1c, fasting insulin)	**BCAAs and amino acids** Related to fasting glucose: (↑) proline (↓) cystathionine, citrulline Related to HbA1c: (↑) proline (↓) glycine, sarcosine Related to fasting insulin: (↑) alanine, 3-methylhistidine (↓) aminobutryic acid, aspargine, cystathionine

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						T2D	16 amino acid lower and 11 higher in T2D (↑) hydroxyproline, glutamine, ethanolamine, citrulline, sarcosine, β-alanine, glutamate, 3-methyl histidine, 4-aminobutyric acid, 3-aminoisobutyric acid, proline (↓) phosphoserine, phosphoric acid ethanolamine, taurine, serine, aspartate, histidine, 1-methylhistidine, arginosuccinic acid, carnosine, anserine, aminoadipic acid, δ-hydroxylysine, lysine, homocysteine, leucine, tryptophan
Menni *et al.* 2013– *Diabetes*	Twins UK women – UK	Case-control	2204 (1897 nondiabetic/192 individuals IFG/115 T2D)	UPLC-MS/MS Untargeted (447 metabolite features)	Plasma	Prediabetes (IFG)	**BCAAs, lipids and sugar metabolites** 14 metabolites associated with IFG (1 unknown) (↑) BCKAs (3-methyl-2-oxovalerate, derivative of isoleucine) (↑) 2-hydroxybutyrate, 3-methyl-2-butyrate, 4-methyl-2-oxo-pentanoate (↑) leucine, isoleucine, arachidonate, adrenate, urate, glucose, mannose, fructose, and erythritol
						T2D	42 metabolites associated with T2D (14 unknown) (↑) BCKAs (3-methyl-2-oxovalerate (derivative of isoleucine) (↑) sugar metabolites (glucose, mannose, malate, arabinose, fructose, lactate,) (↓) 5-dodecenoat, heptanoat, pelargonate, 1,5-anhydroglucitol (shorter chain) (↑) medium and long-chain free fatty acids (adrenate, arachidonate) (↑) BCAAs or derivatives (valine, isoleucine, leucine, proline)
	Replication: Cooperative Health Research in the Region of Ausgburg	Case-control	720 (184 healthy controls/536 IFG)	LC-MS/MS Targeted (3-methyl-2-oxovalerate)	Plasma	Prediabetes (IFG)	(↑) BCKAs (3-methyl-2-oxovalerate (derivative of isoleucine)

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	(KORA) – Germany						
Xu *et al.* 2013– *JCEM*	School of Public Health – Singapore	Case-control	111 (60 healthy controls/24 IFG/ 27 T2D)	LC-MS and GC-MS Targeted (238 metabolites, amino acid, lipid and sugar metabolites)	Plasma	Prediabetes (HOMA-IR)	**BCAAs, lipids, sugar metabolites** (↑) fructose, α-hydroxybutyrate, (↑) alanine, proline, phenylalanine, glutamine (↑) BCAAs (isoleucine, valine, leucine) (↑) low carbon number lipids (myristic, palmitic, stearic acid) (↓) pyroglutamic acid, glycerophospholipids, and sphingomyelins
						T2D	(↑) fructose, α-hydroxybutyrate, (↑) alanine, proline, phenylalanine, glutamine (↑) BCAAs (isoleucine, valine, leucine) (↑) low carbon number lipids (myristic, palmitic, stearic acid) (↓) pyroglutamic acid, glycerophospholipids, sphingomyelins
Kaur *et al.* 2013– *Mol Bio Syst*	Hamad Medical Hospital – Qatar	Case-control	182 (77 nondiabetic/105 T2D)	UPLC-ESI-QTOF-MS Untargeted (>1500 metabolite features) and targeted (nine amino acid, lipid and sugar metabolites)	Plasma and Urine	T2D	**Amino acids, TCA cycle** Plasma: (↑) itaconic acid, leucine, 3-hydroxymethylglutaric acid, PC (18:0/0:0), sphingosine-1-phosphate, PG (18:0/18:1) (↓) inosine, uric acid, succinic acid, taurine, PE (P16:0/22:6) Urine: (↑) N-acetyl-D-phenylalalanine, serotonin (↓) 2-ketobutyric acid, 2-ketoglytaric acid, 1-methylhistidine, kynurenic acid, xanthurenic acid, pyruvic acid
Ho *et al.* 2013– *Diabetes*	Framingham Heart Study Offspring – USA	Cohort, population-based study	377 nondiabetic	LC/MS-MS Targeted (110 metabolites, amino acids, purine	Plasma	Prediabetes (OGTT)	**Amino acids, urea cycle, purines/pyrimidines, sugar metabolites** 73 metabolites decreased after OGTT: (↓) amino acids, β-hydroxybutyrate,

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				nucleotides, sugar metabolites, organic acids)			tricarboxylic acid cycle intermediates, serotonin derivatives, urea cycle metabolites (citrulline, ornithine and arginine) and B vitamins, unconjugated bile acids, nitrogenous bases (purines and pyrimidines) 18 increased after OGTT: (↑) glycolysis products, conjugated bile acids
Meikle *et al.* 2013– *Plos One*	Australian Diabetes, Obesity and Lifestyle Study (AusDiab) – Australia	Case-control	351 (170 normoglycemics, 64 prediabetic and 117 T2D)	LC/MS-MS Targeted (65 diacylglycerol and triacylglycerol species and 194 other lipid species)	Plasma	Prediabetes (OGTT)	**Lipids** Significant associations with 134 individual lipids (↑) dihydroceramide, ceramide, phosphatidylethanolamine, phosphatidylinositol, phosphatidylglycerol, free cholesterol, cholesterol ester, diacylglycerol, triacylglycerol (↓) Trihexosylceramide, alkylphosphatidylcholine
						T2D	**Lipids** Significant associations with 135 individual lipids (↑) dihydroceramide, ceramide, phosphatidylethanolamine, phosphatidylinositol, phosphatidylglycerol, free cholesterol, cholesterol ester, diacylglycerol, triacylglycerol (↓) Trihexosylceramide, alkylphosphatidylcholine
	Replication: San Antonio Family Heart Study (SAFHS) – USA	Cohort, population-based study	1076 (808 normoglycemics, 126 prediabetic and 142 T2D)	LC/MS-MS Targeted (65 diacylglycerol and triacylglycerol species and 194 other lipid species)	Plasma	Prediabetes (OGTT)	**Lipids** Significant associations with 104 individual lipids (↑) dihydroceramide, ceramide, phosphatidylethanolamine, phosphatidylinositol, phosphatidylglycerol, cholesterol ester, diacylglycerol, triacylglycerol (↓) Trihexosylceramide

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						T2D	**Lipids** Significant associations with 121 individual lipids (↑) dihydroceramide, ceramide, phosphatidylethanolamine, phosphatidylinositol, phosphatidylglycerol, cholesterol ester, diacylglycerol, triacylglycerol
Zhang *et al.* 2014– *J Physiol Biochem*	Hospital of Heilongjiang – China	Case-control	123 (42 nondiabetic/81 T2D)	UPLC-QTOF-HDMS Untargeted (>9000 metabolite features)	Urine	T2D	**Acylcarnitines, sugar metabolites, amino acids** (↑) Acylcarnitines, 3-indoxylsulfate, glucose, glycine (↓) citric acid, kynurenic acid, ureic acid, glucuronolactone, lysine, phosphate
Thalacker-Mercer *et al.* 2014– *Diabetes*	University of Alabama – USA	Case-control	124 (61 insulin sensitives/32 insulin resistants/31 T2D)	Flow injection MS Targeted (16 amino acids)	Serum	Prediabetes (HOMA-IR)	**Amino acids, BCAAs** (↓) glycine, serine, and citrulline (↑) glutamine/glutamate
						T2D	(↑) leucine/isoleucine, valine, glutamine/glutamate, aspartate/aspargine (↓) glycine, histidine
Geidenstam *et al.* 2014– *Obesity*	Endocrinology Deparment, Skane University Hospital – Sweden	Case-control	20 (14 nondiabetic obese/6 lean controls)	GC/MS Targeted (59 metabolites, amino acids, lipids, sugar metabolites)	Serum	Prediabetes (OGTT)	**Lipids, BCAAs, sugar metabolites** (↑) BCAAs, asparagine, glutamate, tyrosine, taurine, pyrophosphate, threonic acid, phenyalalanine, serine, glyceric acid, aspartate (↓) palmitic acid, lauric acid, oleic acid, pentadecanoic acid, stearic acid

(↑) positive association, or (↓) inverse association with prediabetes traits or type 2 diabetes. Abbreviations: BCAA, branched-chain amino acid; BCKA, branched-chain keto acid; EFA, esterified fatty acid; GC, gas chromatography; GC-SIM-MS, gas chromatography with single ion monitoring mass spectrometry; GC x GC-TOFMS, two-dimensional gas chromatography/time-of-flight mass spectrometry; IFG, impaired fasting glucose; ISI,insulin sensitivity index; HOMA, homeostasis model assessment; HPLC-ESI-MS, high-performance liquid chromatography-electrospray ionization-mass spectromety; LC, liquid cromatography; LPC, lysophosphatidylcholine; MS, mass spectometry; MUFA, monounsaturated fatty acids; N, number; NEFA, non-sterified fatty acids; NMR, nuclear magnetic resonance; OGTT, oral glucose tolerance test; PC, phosphatidylchline; PE, phosphethanolamine; SFA, saturated fatty acids; SM, sphingomyelin; T2D, type 2 diabetes; UHPLC, ultra-high performance liquid chromatography; UPLC-MS, ultra-performance liquid chromatography coupled with mass spectometry.

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SUPPLEMENTARY DATA

Supplementary Table 2. Description of data included in the meta-analysis.

Metabolite	Author - year– journal	Study	Participants	Covariates	Amino acid concentration	HR/RR/OR (CI) per SD
Isoleucine						
1	Wang *et al*. 2011– *Nat Med*	Framingham Heart Study (FHS) – discovery sample	189 cases/189 controls	Age, sex, BMI, fasting glucose	145.1 (123.4, 165.8) µm [median (IQ)]	1.70 (1.27-2.28)
2	Wang *et al*. 2011– *Nat Med*	Malmö Diet and Cancer Study (MDC) – replication sample	163 cases/163 controls	Age, sex, BMI, fasting glucose	NR	1.37 (0.95-1.96)
3	Wang-Sattler *et al*. 2012– *Mol Sys Biol*	KORA S4	91 cases/91 controls	Age, sex, BMI, physical activity, alcohol intake, smoking, systolic BP, HDL cholesterol, HbA1c and fasting glucose and insulin	72.65 (19.67) µm [mean (SD)]	1.73 (1.15-2.60)
4	Floegel *et al.* 2013– *Diabetes*	EPIC-Potsdam	800 cases/ 2282 nondiabetic	Age, sex, alcohol intake, smoking, physical activity, coffee intake, red meat intake, whole-grain bread intake, prevalent hypertension, BMI, waist circumference	211 (63.3) µm [mean (SD)]	1.30 (1.17-1.43)
5	Tillin *et al*. 2015– *Diabetes*	Southall And Brent Revisited Study (SABRE) – European men	113 cases/688 nondiabetic	Age, sex, BMI, fasting glucose	0.058 (0.050, 0.066) µm [median (IQ)]	1.21 (0.97-1.51)
	Tillin *et al.* 2015– *Diabetes*	Southall And Brent Revisited Study (SABRE) – South Asian men	227 cases/780 nondiabetic	Age, sex, BMI, fasting glucose	0.060 (0.052, 0.068) µm [median (IQ)]	1.42 (1.16-1.75)
7	Stancáková *et al*. 2012– *Diabetes*	Metabolic Syndrome in Men (METSIM)	151 cases/375 nondiabetic	Unadjusted, adjusted means NR	Cases: 17.95 (4.42); Non-cases: 17.25 (4.1) µm [means(SD)]	1.34 (1.18-1.53)*
8	Ferrannini *et al.* 2013– *Diabetes*	Botnia Prospective Study	130 cases/ 412 nondiabetic	Unadjusted, adjusted means NR	Cases: 72 (23); Non-cases: 69 (20), µm median [IQR]	1.29 (1.08-1.56)*
Leucine						

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1	Wang *et al*. 2011– *Nat Med*	FHS – discovery sample	189 cases/189 controls	Age, sex, BMI, fasting glucose	85.1 (72.3, 102.5) µm [median (IQ)]	1.62 (1.20-2.17)
2	Wang *et al*. 2011– *Nat Med*	MDC – replication sample	163 cases/163 controls	Age, sex, BMI, fasting glucose	NR	1.60 (1.13-2.27)
3	Wang-Sattler *et al*. 2012– *Mol Sys Biol*	KORA S4	91 cases/91 controls	Age, sex, BMI, physical activity, alcohol intake, smoking, systolic BP, HDL cholesterol, HbA1c and fasting glucose and insulin	160.26 (43.19) µm [mean (SD)]	1.43 (0.98-2.08)
4	Tillin *et al.* 2015– *Diabetes*	SABRE – European men	113 cases/688 nondiabetic	Age, sex, BMI, fasting glucose	0.092 (0.081,0.11) µm [median (IQ)]	1.11 (0.92-1.35)
5	Tillin *et al.* 2015– *Diabetes*	SABRE – South Asian men	780 nondiabetics/227 TD2	Age, sex, BMI, fasting glucose	0.092 (0.083, 0.10) µm [median (IQ)]	1.36 (1.11-1.68)
6	Stancáková *et al*. 2012– *Diabetes*	METSIM	151 cases/375 nondiabetics	Unadjusted, adjusted means NR	Cases: 29.57 (6.86); Non-cases: 28.54 (6.04), [means(SD)]	1.33 (1.17-1.51)*
7	Ferrannini *et al.* 2013– *Diabetes*	Botnia Prospective Study	412 nondiabetic/130 T2D	Unadjusted, adjusted means NR	Cases: 145 (51); Non-cases: 134 (39), µm [median (IQ)]	1.60 (1.33-1.93)*
Valine						
1	Wang *et al*. 2011– *Nat Med*	FHS – discovery sample	189 cases/189 controls	Age, sex, BMI, fasting glucose	191.4 (172.2, 213.0) µm [median (IQ)]	1.57 (1.17-2.09)
2	Wang *et al*. 2011– *Nat Med*	MDC – replication sample	163 cases/163 controls	Age, sex, BMI, fasting glucose	NR	2.01 (1.18-3.42)
3	Wang-Sattler *et al*. 2012– *Mol Sys Biol*	KORA S4	91 cases/91 controls	Age, sex, BMI, physical activity, alcohol intake, smoking, systolic BP, HDL cholesterol, HbA1c and fasting glucose and insulin	228.02 (51.89) µm [mean (SD)]	1.48 (1.03-2.13)
4	Floegel *et al.* 201 – *Diabete*s	EPIC-Potsdam	800 cases/ 2282 nondiabetic	Age, sex, alcohol intake, smoking, physical activity, coffee intake, red meat intake, whole-grain bread intake, prevalent hypertension, BMI, waist circumference	294 (74.5) µm [mean (SD)]	1.27 (1.16-1.40)

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5	Palmer *et al.* 2014– *JCEM*	Insulin Resistance in Atherosclerosis Study (IRAS)	76 cases/ 70 nondiabetic	Age, sex, BMI, ethnicity, insulin sensitivity	Cases: 232 (36); Non-cases: 201 (36) µm [mean (SD)]	1.77 (1.15-2.74)
6	Tillin *et al.* 2015– *Diabetes*	SABRE – European men	113 cases/688 nondiabetic	Age, sex, BMI, fasting glucose	0.180 (0.158, 0.504) µm [median (IQ)]	1.04 (0.84-1.29)
7	Tillin *et al.* 2015– *Diabetes*	SABRE – South Asian men	227 cases/780 nondiabetics	Age, sex, BMI, fasting glucose	0.176 (0.155, 0.198) µm [median (IQ)]	1.32 (1.08-1.62)
8	Stancáková *et al*. 2012– *Diabetes*	METSIM	151 cases/375 nondiabetic	Unadjusted, adjusted means NR	Cases: 67.16 (11.06); Non-cases: 65.61 (11.49) µm [means(SD)]	1.28 (1.13-1.46)*
9	Ferrannini *et al.* 2013– *Diabetes*	Botnia Prospective Study	130 cases/412 nondiabetic	Unadjusted, adjusted means NR	Cases: 217 (69); Non-cases: 209 (50), µm [median (IQ)]	1.30 (1.08-1.56)*
Tyrosine						
1	Wang *et al*. 2011– *Nat Med*	FHS – discovery sample	189 cases/189 controls	Age, sex, BMI, fasting glucose	NR	1.85 (1.35-2.55)
2	Wang *et al*. 2011– *Nat Med*	MDC – replication sample	163 cases/163 controls	Age, sex, BMI, fasting glucose	NR	1.41 (1.05-1.91)
3	Wang-Sattler *et al*. 2012– *Mol Sys Biol*	KORA S4	91 cases/91 controls	Age, sex, BMI, physical activity, alcohol intake, smoking, systolic BP, HDL cholesterol, HbA1c and fasting glucose and insulin	72.51 (20.2) µm [mean (SD)]	1.52 (1.03-2.24)
4	Floegel *et al.* 2013– *Diabetes*	EPIC-Potsdam	800 cases/2282 nondiabetic	Age, sex, alcohol intake, smoking, physical activity, coffee intake, red meat intake, whole-grain bread intake, prevalent hypertension, BMI, waist circumference	81.5 (22.7) [mean (SD)]	1.31 (1.18-1.45)
5	Palmer *et al.* 2014– *JCEM*	IRAS	76 cases/70 nondiabetic	Age, sex, BMI, ethnicity, insulin sensitivity	Cases: 78 (17); Non-cases: 72 (17) µm [median (IQ)]	0.93 (0.61-1.41)
6	Tillin *et al.* 2015– *Diabetes*	SABRE – European men	113 cases/688 nondiabetic	Age, sex, BMI, fasting glucose	0.054 (0.048, 0.061) µm [median (IQ)]	1.11 (0.90-1.39)

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7	Tillin *et al.* 2015– *Diabetes*	SABRE – South Asian men	227cases/780 nondiabetic	Age, sex, BMI, fasting glucose	0.059 (0.052, 0.067) µm [median (IQ)]	1.56 (1.26-1.93)
8	Stancáková *et al*. 2012– *Diabetes*	METSIM	151 cases/375 nondiabetic	Unadjusted, adjusted means NR	Cases: 17.4 (3.04); Non-cases: 17.11 (2.94), µm [means(SD)]	1.19 (1.05-1.35)*
9	Ferrannini *et al.* 2013– *Diabetes*	Botnia Prospective Study	130 cases/412 nondiabetic	Unadjusted, adjusted means NR	Cases: 61 (12); Non-cases: 57 (15), µm [median (IQ)]	1.65 (1.37-1.99)*
Phenylalanine						
1	Wang *et al*. 2011– *Nat Med*	FHS – discovery sample	189 cases/189 controls	Age, sex, BMI, fasting glucose	62.0 (57.0, 67.9) µm [median (IQ)]	2.02 (1.40-2.92)
2	Wang *et al*. 2011– *Nat Med*	MDC – replication sample	163 cases/163 controls	Age, sex, BMI, fasting glucose	NR	1.37 (1.01-1.84)
3	Wang-Sattler *et al*. 2012– *Mol Sys Biol*	KORA S4	91 cases/91 controls	Age, sex, BMI, physical activity, alcohol intake, smoking, systolic BP, HDL cholesterol, HbA1c and fasting glucose and insulin	77.51 (17.62) µm [means(SD)]	1.21 (0.88-1.67)
4	Floegel *et al.* 2013– *Diabetes*	EPIC-Potsdam	800 cases/2282 nondiabetic	Age, sex, alcohol intake, smoking, physical activity, coffee intake, red meat intake, whole-grain bread intake, prevalent hypertension, BMI, waist circumference, glucose, HbA_{1c}, HDL cholesterol, triglycerides	56.4 (12.0) µm [means(SD)]	1.25 (1.12-1.39)
5	Palmer *et al.* 2014– *JCEM*	IRAS	76 cases/70 nondiabetic	Age, sex, BMI, ethnicity, insulin sensitivity	Cases: 72 (12); Non-cases: 67 (13) µm [means(SD)]	1.14 (0.71-1.85)
6	Tillin *et al.* 2015– *Diabetes*	SABRE – European men	113 cases/688 nondiabetic	Age, sex, BMI, fasting glucose	0.092 (0.084, 0.10) µm [median (IQ)]	0.97 (0.80-1.18)
7	Tillin *et al.* 201 – *Diabetes*	SABRE – South Asian men	227 cases/780 nondiabetic	Age, sex, BMI, fasting glucose	0.094 (0.085,0.10) µm [median (IQ)]	1.29 (1.06-1.57)
8	Stancáková *et al*. 2012– *Diabetes*	METSIM	151 cases/375 nondiabetic	Unadjusted, adjusted means NR	Cases: 23.32 (3.05); Non-cases: 23.18 (3.33) µm [means(SD)]	1.08 (0.95-1.23)*
9	Ferrannini *et al.* 2013– *Diabetes*	Botnia Prospective Study	130 cases/412 nondiabetic	Unadjusted, adjusted means NR	Cases: 55 (15); Non-cases: 55 (11) µm [median (IQ)]	1.00 (0.83-1.19)*

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Isoleucine, phenylalanine, tyrosine						
1	Wang *et al*. 2011– *Nat Med*	FHS – discovery sample	189 cases/189 controls	Age, sex, BMI, fasting glucose	NR	2.42 (1.66-3.54)
2	Wang *et al*. 2011– *Nat Med*	MDC – replication sample	163 cases/163 controls	Age, sex, BMI, fasting glucose	NR	1.52 (1.10-2.11)
3	Wang *et al*. 2011– *Nat Med*	FHS – random subcohort	201 cases /400 controls	Age, sex, BMI, fasting glucose	NR	1.33 (1.08-1.63)
4	Tillin *et al.* 2015– *Diabetes*	SABRE – European men	113 cases/688 nondiabetic	Age, sex, BMI, fasting glucose	0.205 (0.186, 0.228) μm [median (IQ)]	1.02 (0.81-1.27)
5	Tillin *et al.* 2015– *Diabetes*	SABRE – South Asian men	227 cases/780 nondiabetic	Age, sex, BMI, fasting glucose	0.213 (0.197, 0.233) μm [median (IQ)]	1.39 (1.10-1.75)
Glycine						
1	Wang-Sattler *et al*. 2012– *Mol Sys Biol*	KORA S4	91 cases/91 controls	Age, sex, BMI, physical activity, alcohol intake, smoking, systolic BP, HDL cholesterol, HbA1c and fasting glucose and insulin	263.02 (74.35) μm [means (SD)]	1.03 (0.74-1.44)
2	Wang-Sattler *et al*. 2012– *Mol Sys Biol*	KORA	91 cases/876 nondiabetic	Age, sex, BMI, physical activity, alcohol intake, smoking, systolic BP, HDL cholesterol, HbA1c and fasting glucose and fasting insulin	NR	0.85 (0.62-1.14)
3	Floegel *et al.* 2013– *Diabetes*	EPIC-Potsdam	800 cases/2282 nondiabetic	Age, sex, alcohol intake, smoking, physical activity, coffee intake, red meat intake, whole-grain bread intake, prevalent hypertension, BMI, waist circumference, glucose, HbA_{1c},HDL cholesterol, triglycerides	256 (77.2) μm [means (SD)]	0.89 (0.78-1.01)
4	Palmer *et al.* 2014– *JCEM*	IRAS	76 cases/70 nondiabetic	Age, sex, BMI, ethnicity, insulin sensitivity	Cases: 204 (45); Non-cases: 238 (71) μm [means (SD)]	0.80 (0.52-1.25)
5	Tillin *et al.* 2015– *Diabetes*	SABRE – European men	113 cases/688 nondiabetic	Age, sex, BMI, fasting glucose	0.287 (0.262, 0.316) μm [median (IQ)]	0.78 (0.64-0.96)
6	Tillin *et al.* 2015 –	SABRE – South	227 cases/780	Age, sex, BMI, fasting glucose	0.282 (0.257, 0.312) μm	0.96 (0.80-1.15)

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	Diabetes	Asian men	nondiabetic		[median (IQ)]	
7	Ferrannini *et al.* 2013– *Diabetes*	Botnia Prospective Study	130 cases/412 nondiabetic	Unadjusted, adjusted means NR	Cases: 174 (60); Non-cases: 184 (61) µm [median (IQ)]	0.74 (0.62-0.89)*
Glutamine						
1	Cheng *et al.* 2012– *Circulation*	FHS	601 non diabetic/T2D NR	Age, sex, BMI, fasting glucose	NR	0.83 (0.68-1.02)
2	Cheng *et al.* 2012– *Circulation*	MDC	409 non diabetic/T2D NR	Age, sex, BMI, fasting glucose	NR	0.81 (0.67-0.99)
3	Tillin *et al.* 2015– *Diabetes*	SABRE – European men	113 cases/688 nondiabetic	Age, sex, BMI, fasting glucose	0.385 (0.262, 0.450) µm [median (IQ)]	0.94 (0.77-1.15)
4	Tillin *et al.* 2015– *Diabetes*	SABRE – South Asian men	227 cases/780 nondiabetic	Age, sex, BMI, fasting glucose	0.415 (0.317, 0.473) µm [median (IQ)]	0.88 (0.73-1.05)
5	Floegel *et al.* 2013– *Diabetes*	EPIC-Potsdam	800 cases/2282 nondiabetic	Age, sex, alcohol intake, smoking, physical activity, education, coffee intake, red meat intake, whole grain bread intake. prevalent hypertension, BMI, and waist circumference	584 (94.5) µm [means (SD)]	0.85 (0.81-0.89)**
6	Stancáková *et al*. 2012– *Diabetes*	METSIM	151 cases/375 nondiabetic	Unadjusted, adjusted means NR	Cases: 155.55 (18.07); Non-cases 159.6 (20.77) µm [means (SD)]	0.68 (0.60-0.77)*
7	Ferrannini *et al.* 2013– *Diabetes*	Botnia Prospective Study	130 cases/412 nondiabetic	Unadjusted, adjusted means NR	Cases: 11 (11); Non-cases: 15 (20), µm [median (IQ)]	0.67 (0.56-0.80)*
Alanine						
1	Palmer *et al.* 2014– *JCEM*	IRAS	76 cases/70 nondiabetic	Age, sex, BMI, ethnicity, insulin sensitivity	Cases: 405 (91); Non-cases: 359 (78) µm [means (SD)]	1.49 (0.97-2.30)
2	Tillin *et al.* 2015– *Diabetes*	SABRE – European men	113 cases/688 nondiabetic	Age, sex, BMI, fasting glucose	0.328 (0.290, 0.367) µm [median (IQ)]	1.03 (0.84-1.28)
3	Tillin *et al.* 201 –	SABRE – South	227 cases/ 780	Age, sex, BMI, fasting glucose	0.335 (0.302, 0.374) µm	1.25 (1.03-1.51)

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	Diabetes	Asian men	nondiabetic		[median (IQ)]	
4	Stancáková *et al*. 2012– *Diabetes*	METSIM	151 cases/375 nondiabetic	Unadjusted, adjusted means NR	Cases: 127.87 (18.1); Non-cases: 125.09 (15.96) μm [means (SD)]	1.34 (1.18-1.52)*
5	Ferrannini *et al.* 2013– *Diabetes*	Botnia Prospective Study	130 cases/412 nondiabetic	Unadjusted, adjusted means NR	Cases: 371 (128); Non-cases: 350 (123) μm [median (IQ)]	1.35 (1.13-1.63)*
Histidine						
1	Palmer *et al.* 2014– *JCEM*	IRAS	76 cases/ 70 nondiabetic	Age, sex, BMI, ethnicity, insulin sensitivity	Cases: 73 (14) ; Non-cases: 77 (13) μm [means (SD)]	0.81 (0.56-1.18)
2	Tillin *et al.* 2015– *Diabetes*	SABRE – European men	113 cases/ 688 nondiabetics	Age, sex, BMI, fasting glucose	0.077 (0.068, 0.088) μM [median (IQ)]	0.92 (0.75-1.12)
3	Tillin *et al.* 2015 – *Diabetes*	SABRE – South Asian men	227 cases/780 nondiabetic	Age, sex, BMI, fasting glucose	0.078 (0.070, 0.090) μM [median (IQ)]	1.13 (0.93-1.38)
4	Floegel *et al.* 2013– *Diabetes*	EPIC-Potsdam	800 cases/2282 nondiabetic	Age, sex, alcohol intake, smoking, physical activity, education, coffee intake, red meat intake, whole grain bread intake. prevalent hypertension, BMI, and waist circumference	93.4 (16.6) μm [means (SD)]	0.98 (0.92-1.04)**
5	Stancáková *et al*. 2012– *Diabetes*	METSIM	151 cases/375 nondiabetic	Unadjusted, adjusted means NR	Cases: 19.66 (2.48); Non-cases: 19.70 (2.65) μm [means (SD)]	0.97 (0.85-1.10)*
6	Ferrannini *et al.* 2013– *Diabetes*	Botnia Prospective Study	130 cases/412 nondiabetic	Unadjusted, adjusted means NR	Cases: 41 (13); Non-cases: 43 (10) [median (IQR)]	0.71 (0.59-0.85)*
Arginine						
1	Palmer *et al.* 2014– *JCEM*	IRAS	76 cases/ nondiabetic	Age, sex, BMI, ethnicity, insulin sensitivity	Cases: 86 (18); Non-cases: 80 (17) μm [means (SD)]	1.33 (0.90-1.98)
2	Ferrannini *et al.* 2013– *Diabetes*	Botnia Prospective Study	130 cases/412 nondiabetic	Unadjusted, adjusted means NR	Cases: 71 (23); Non-cases: 67 (24), μm [median (IQR)]	1.35 (1.13-1.63)*

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3	Floegel et al. 2013– *Diabetes*	EPIC-Potsdam	800 cases/2282 nondiabetic	Age, sex, alcohol intake, smoking, physical activity, education, coffee intake, red meat intake, whole grain bread intake. prevalent hypertension, BMI, and waist circumference	106 (23) μm [means (SD)]	1.18 (1.12-1.24)**
Ornithine						
1	Palmer *et al*. 2014– *JCEM*	IRAS	76 cases/ nondiabetic	Age, sex, BMI, ethnicity, insulin sensitivity	Cases: 58 (15); Non-cases: 54 (14) μm [means (SD)]	1.19 (0.83-1.74)
2	Ferrannini *et al.* 2013– *Diabetes*	Botnia Prospective Study	130 cases/412 nondiabetic	Unadjusted, adjusted means NR	Cases: 59 (23); Non-cases: 61 (14) μm [median (IQR)]	0.80 (0.67-0.96)*
3	Floegel *et al.* 2013– *Diabetes*	EPIC-Potsdam	800 cases/2282 nondiabetic	Age, sex, alcohol intake, smoking, physical activity, education, coffee intake, red meat intake, whole grain bread intake. prevalent hypertension, BMI, and waist circumference	100 (27.2) μm [means (SD)]	1.12 (1.07-1.18)**
Serine						
1	Palmer *et al.* 2014– *JCEM*	IRAS	76 cases/ nondiabetic	Age, sex, BMI, ethnicity, insulin sensitivity	Cases: 92 (20); Non-cases: 98 (20) μm [means (SD)]	0.91 (0.58-1.44)*
2	Ferrannini *et al.* 2013– *Diabetes*	Botnia Prospective Study	130 cases/412 nondiabetic	Unadjusted, adjusted means NR	Cases: 99 (14); Non-cases: 100 (14) μm [median (IQR)]	0.88 (0.73-1.05)*
3	Floegel *et al.* 2013– *Diabetes*	EPIC-Potsdam	800 cases/2282 nondiabetic	Age, sex, alcohol intake, smoking, physical activity, education, coffee intake, red meat intake, whole grain bread intake. prevalent hypertension, BMI, and waist circumference	115 (28.4) μm [means (SD)]	0.98 (0.92-1.04)**
Methionine						
1	Palmer *et al.* 2014– *JCEM*	IRAS	76 cases/ nondiabetic	Age, sex, BMI, ethnicity, insulin sensitivity	Cases: 18 (5); Non-cases: 19 (6) μm [means (SD)	0.65 (0.39-1.06)
2	Ferrannini *et al.* 2013– *Diabetes*	Botnia Prospective Study	130 cases/412 nondiabetic	Unadjusted, adjusted means NR	Cases: 1.3 (1.6); Non-cases: 1.3 (1.0), μm [median (IQR)]	1.00 (0.83-1.20)*

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3	Floegel *et al.* 2013–*Diabetes*	EPIC-Potsdam	800 cases/2282 nondiabetic	Age, sex, alcohol intake, smoking, physical activity, education, coffee intake, red meat intake, whole grain bread intake. prevalent hypertension, BMI, and waist circumference	29.1 (7.90) μm [means (SD)]	1.50 (1.43-1.58)**
*Converted from means (SD) using standardized mean difference and Hasselblad and Hedge's method. **Converted using exponential of the B-coefficient. NR, not reported.						

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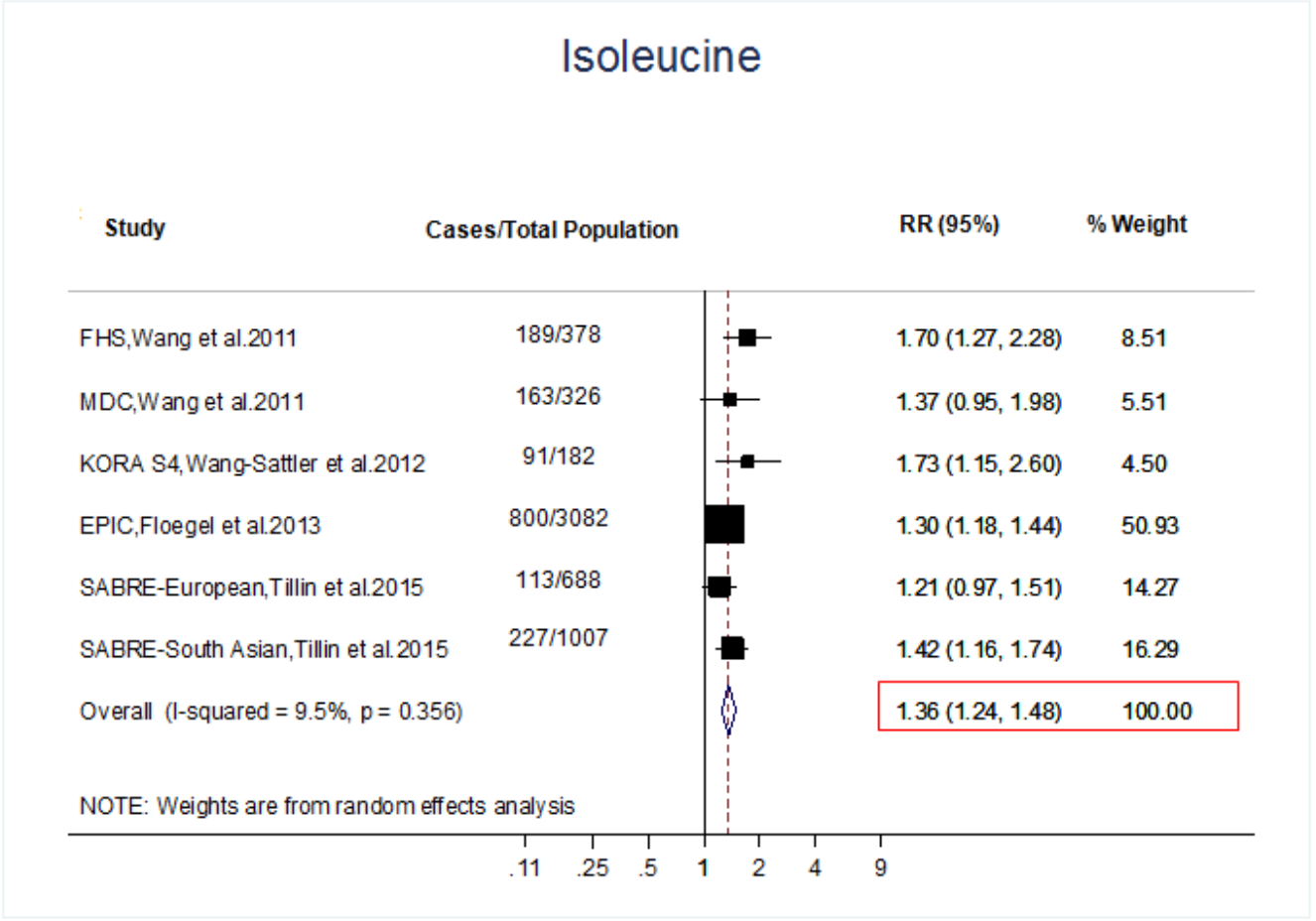
Supplementary Figure 1. Forest plots and random effects meta-analyses of studies evaluating branched-chain amino acids (BCAAs), amino acids and incidence of type 2 diabetes. The BCAAs are (A) Isoleucine; (B) Leucine; (C) Valine; the aromatic amino acids are (D) Tyrosine and (E) Phenylalanine; (F) Glycine; (G) Glutamine; (H) Alanine; (I) Histidine. Estimates were derived from the most fully adjusted model in each included analysis. Closed circles and horizontal bars represent the point estimates and 95% confidence intervals, respectively, from each study. The meta-analyzed estimate and confidence interval is represented by the open diamond.

A.



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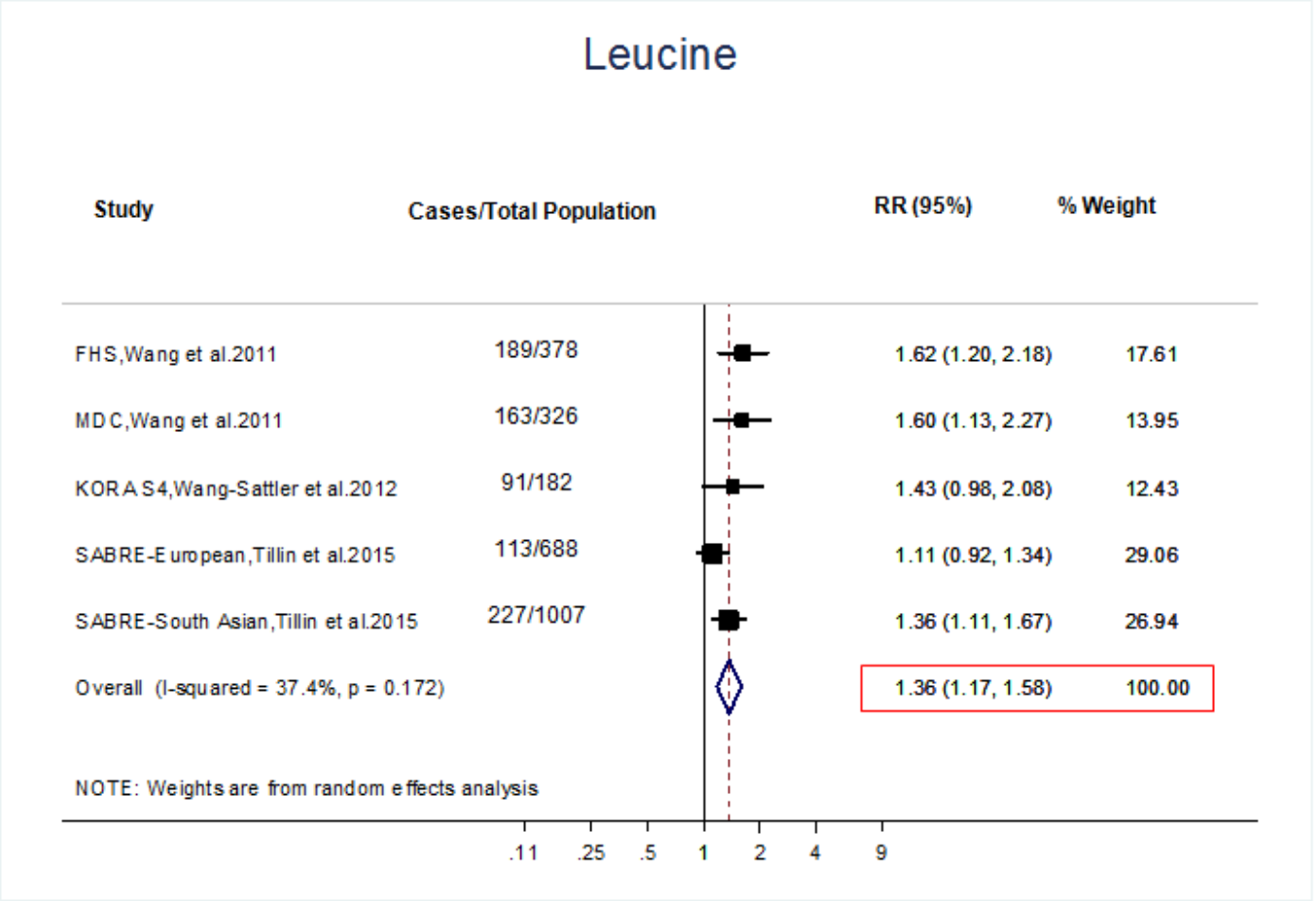
B.



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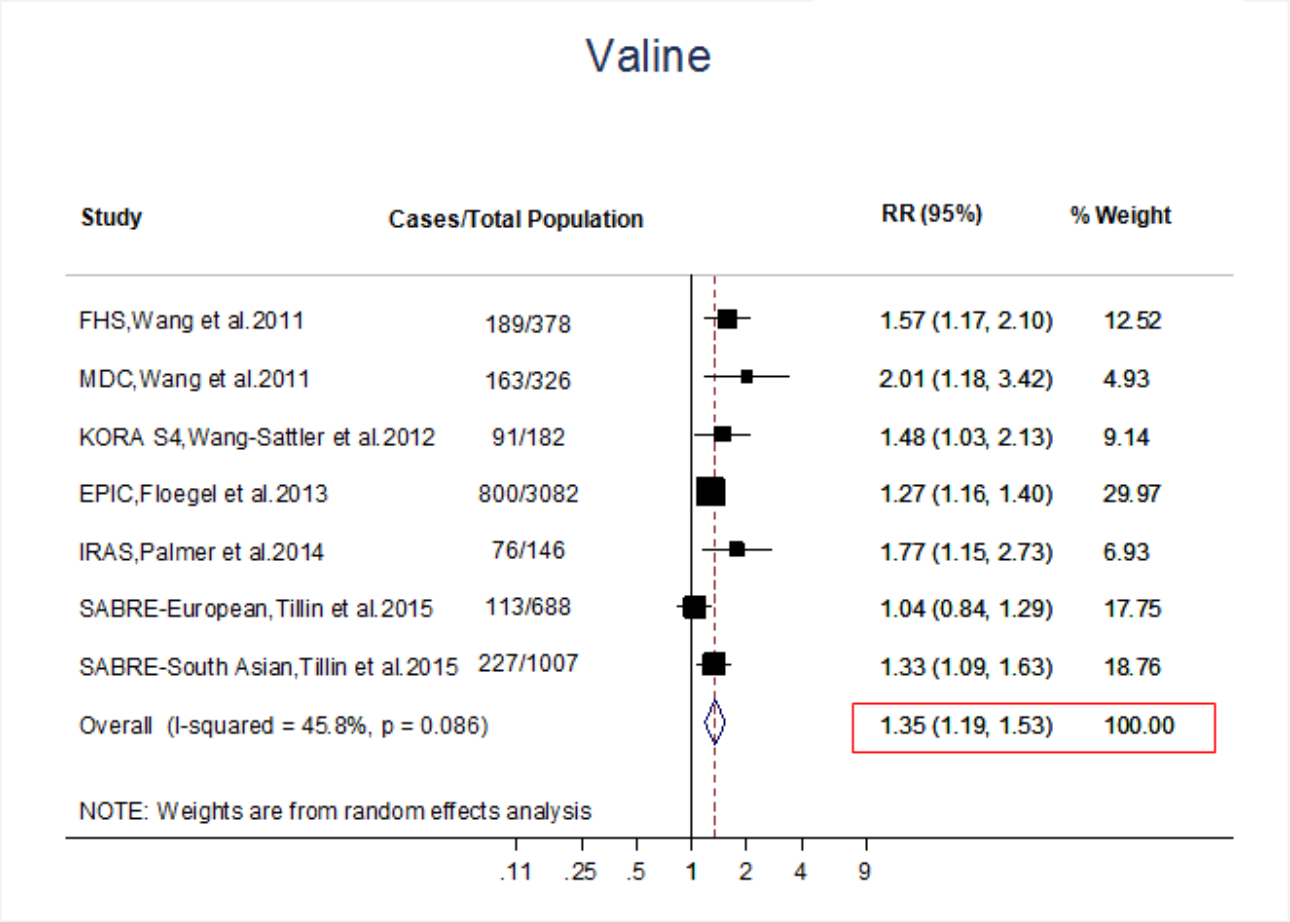
C.



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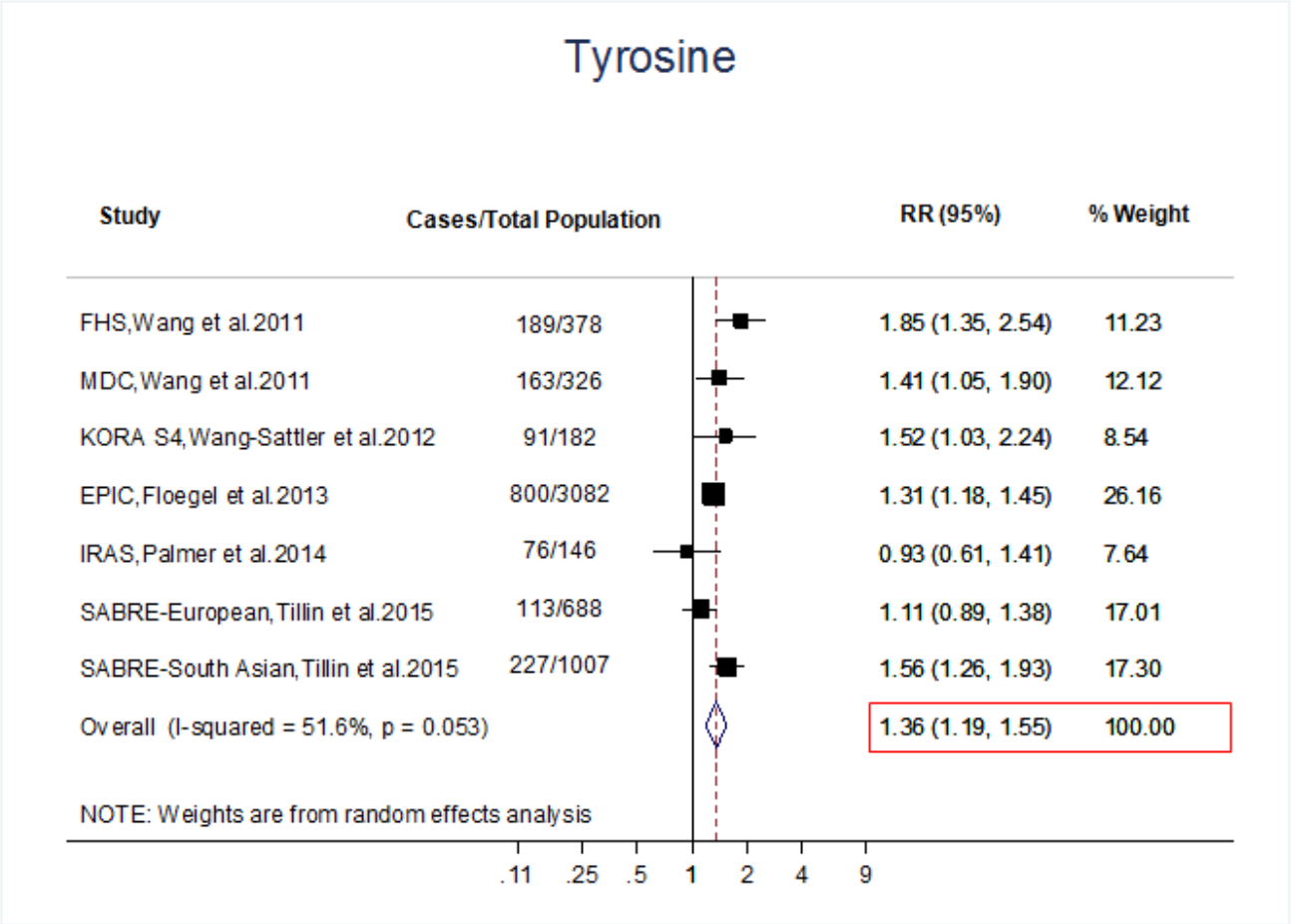
D.



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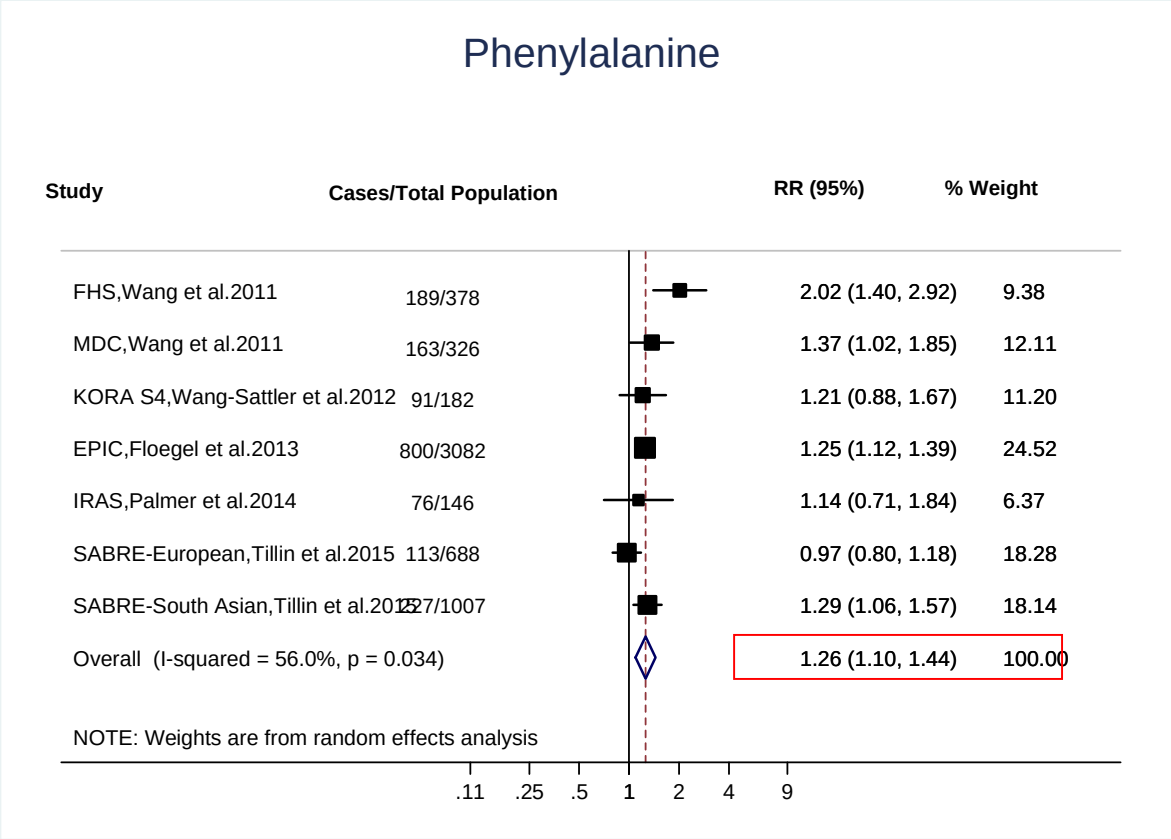
E.



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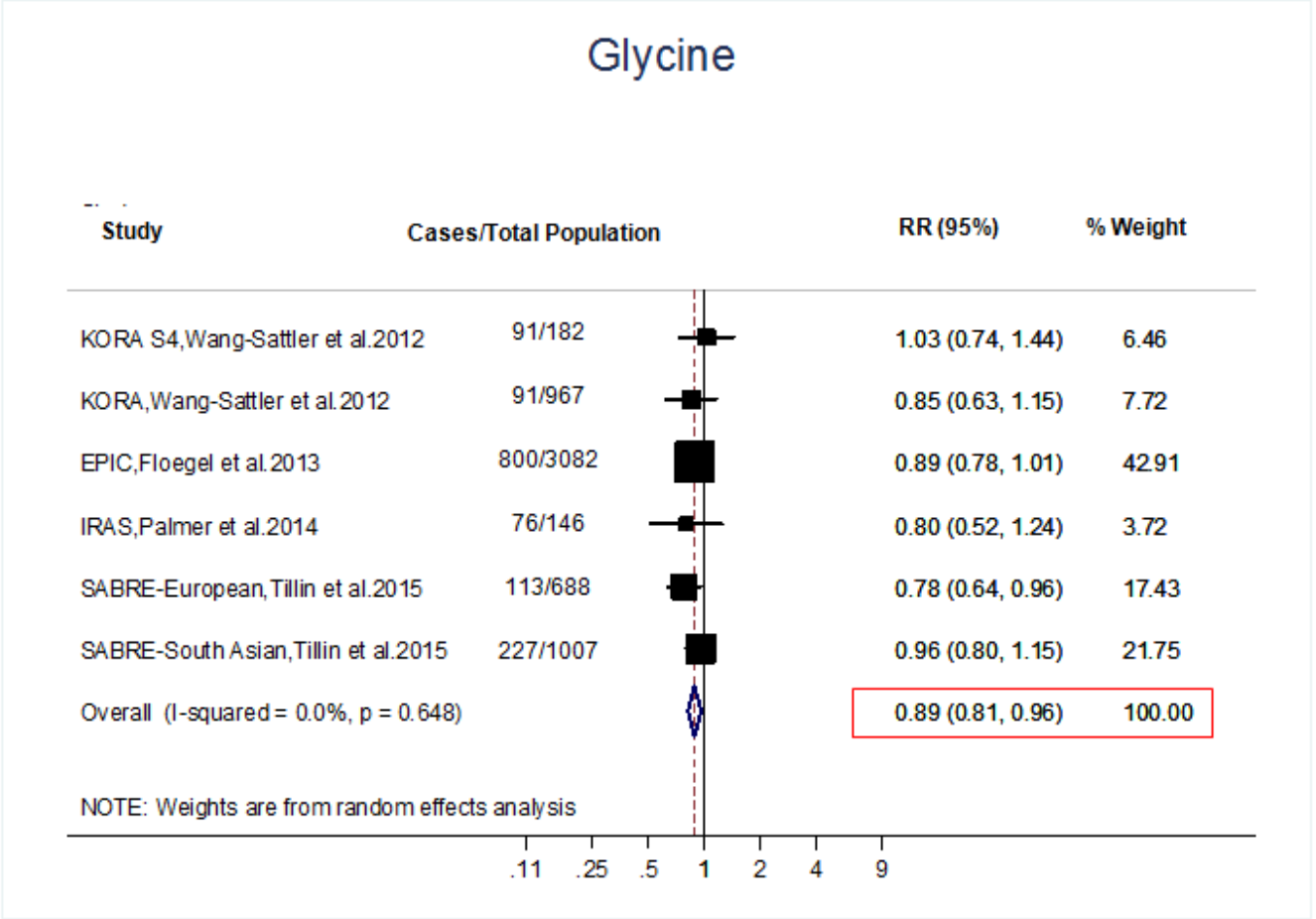
F.



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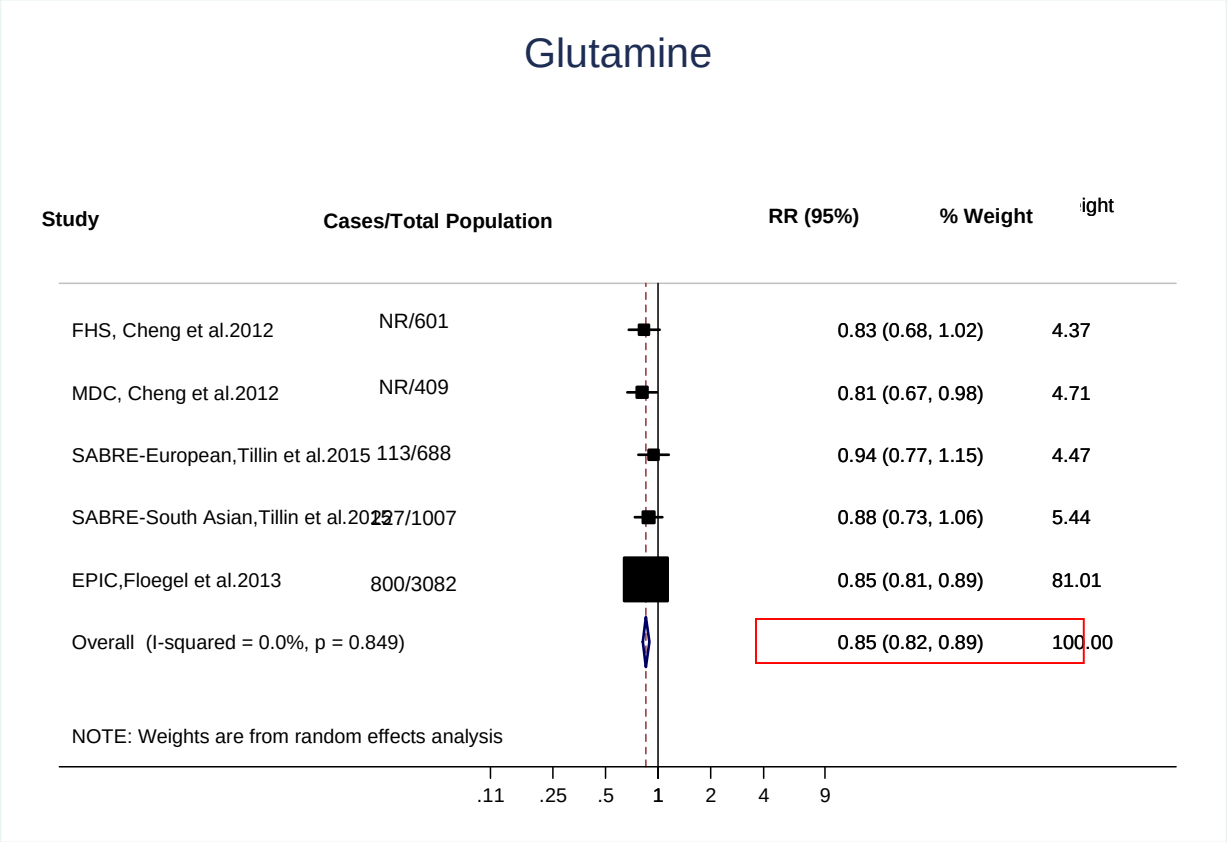
G.



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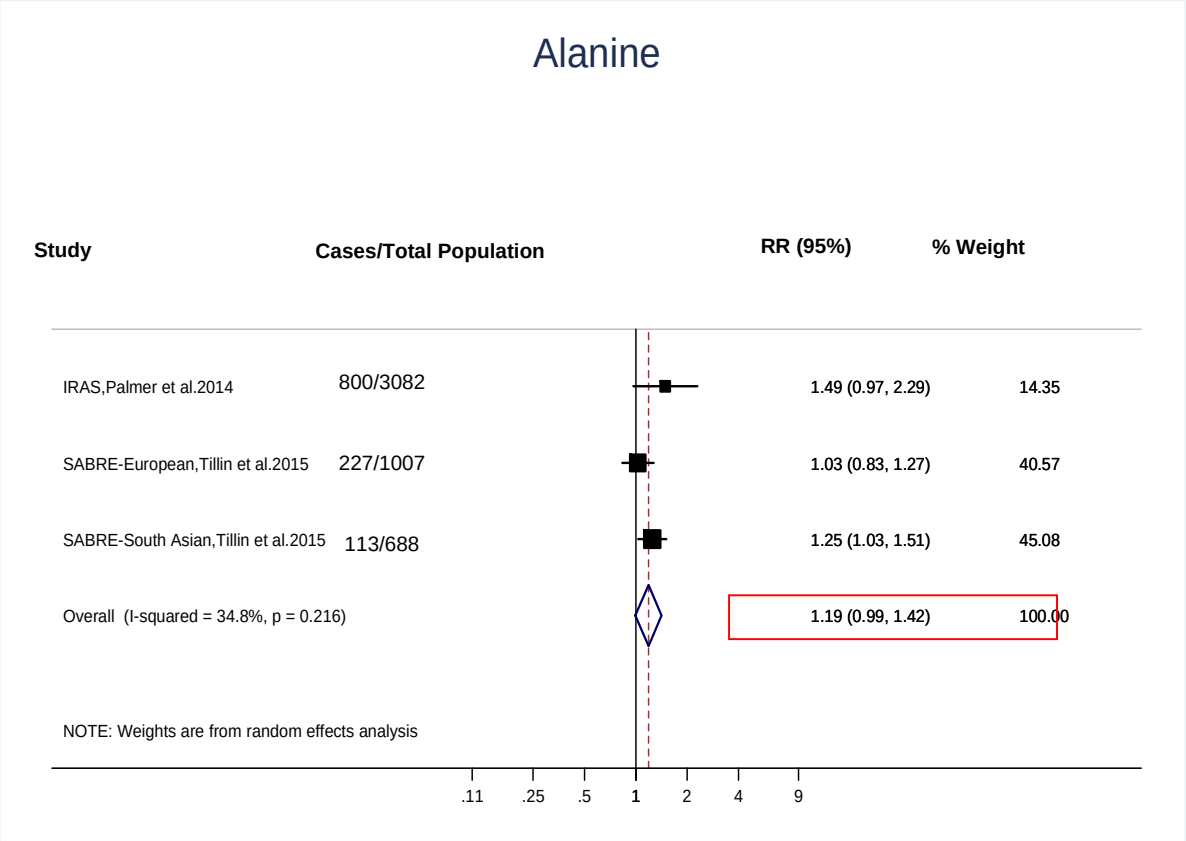
H.



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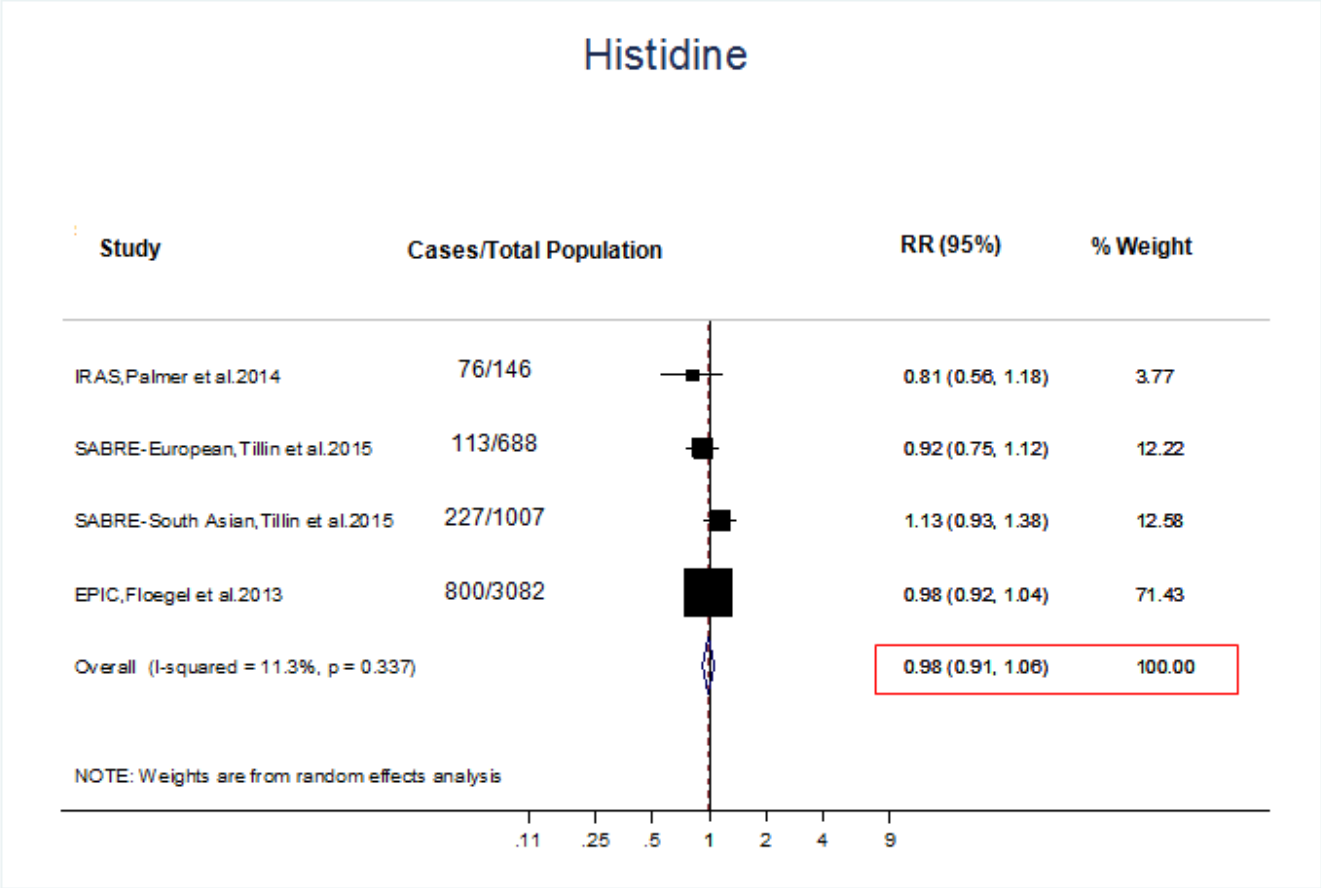
I.



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