Novel findings in metabolomics in the PREDIMED study

www.predimed.es

Miguel A. Martinez-Gonzalez
University of Navarra, Dpt. Preventive Medicine
Dpt. Nutrition Harvard TH Chan School of P. Health

PREDIMED
Prevención con Dieta Mediterránea

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Instituto de Salud Carlos III

1. Clinic (Barcelona)- Ramón Estruch 
2. URV (Reus)- Jordi Salas 
3. IMIM (Barcelona)- Montse Fitó 
4. U. Valencia- Dolores Corella 
5. Hosp. Univ. Álava (Vitoria)- Fernando Arós 
6. U. Málaga- Enrique Gómez-Gracia 
7. CS S. Pablo (Sevilla)- José Lapetra 
8. Son Espases (Mallorca)- Miquel Fiol / D. Romaguera  
9. U. Las Palmas- Lluis Serra-Majem 
10. H. Belvitge (Barcelona)- Xavier Pintó 
11. U. Navarra / Osasunbidea – Miguel A. Martínez-González 

Clinic Lipids- Emilio Ros 

U. Barcelona- Rosa Lamuela 

Maribel Covas

G03/140: 2003-2005 (Clinic)

RD 06/0045: 2006-2013 (Univ. Navarra)

CIBERobn: 2013–

ciberobn
Centro de Investigación Biomédica en Red
Fisiopatología de la Obesidad y Nutrición

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Prevención con Dieta Mediterránea

Ros et al.
Adv Nutr.
2014;5:330S-6S

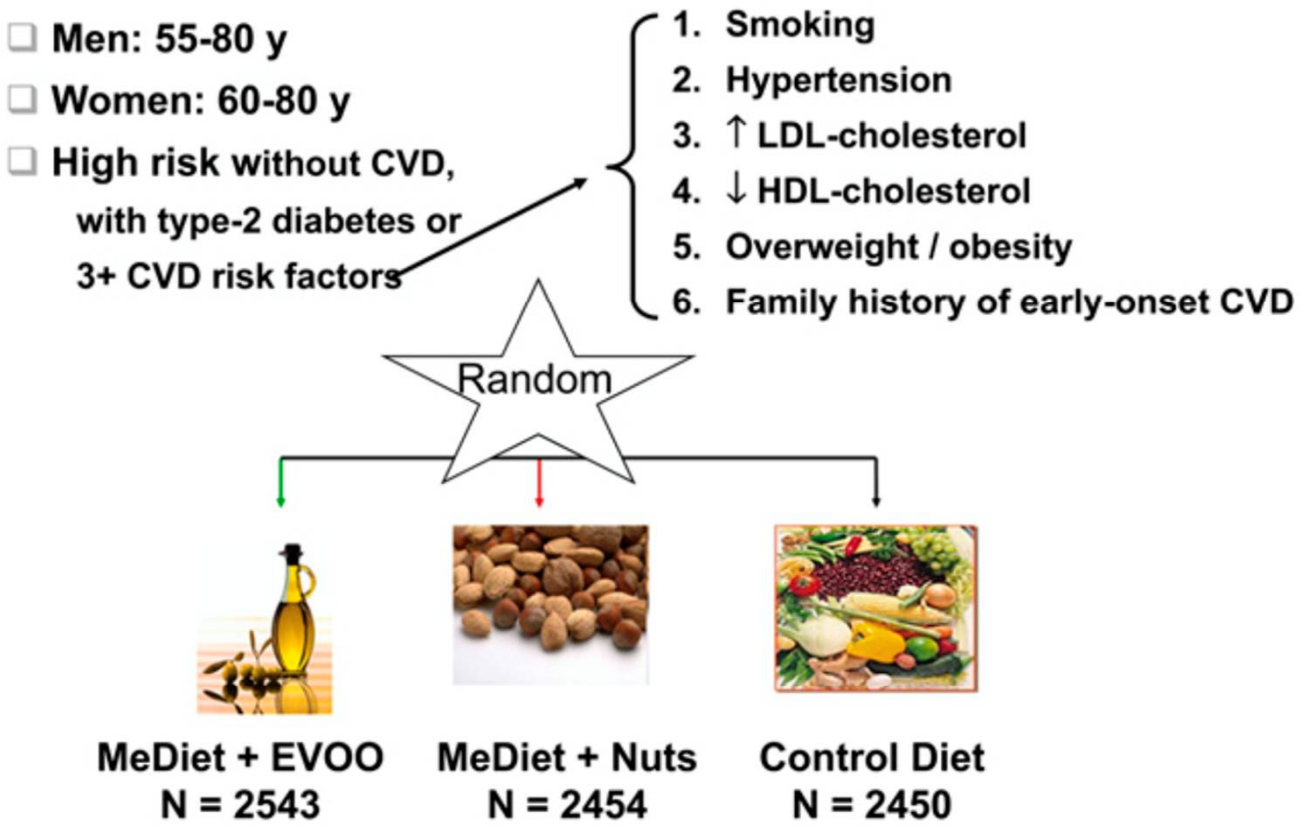


FIGURE 1 Design of the PREDIMED (Prevención con Dieta Mediterránea) study. CVD, cardiovascular disease; EVOO, extra-virgin olive oil; MeDiet, Mediterranean diet.

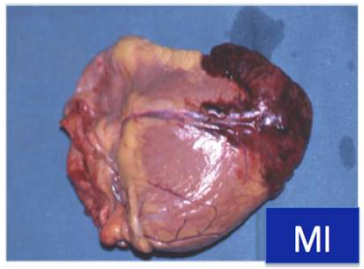
The NEW ENGLAND JOURNAL of MEDICINE

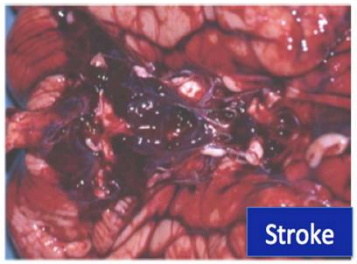
ESTABLISHED IN 1812 APRIL 4, 2013 VOL. 368 NO. 14

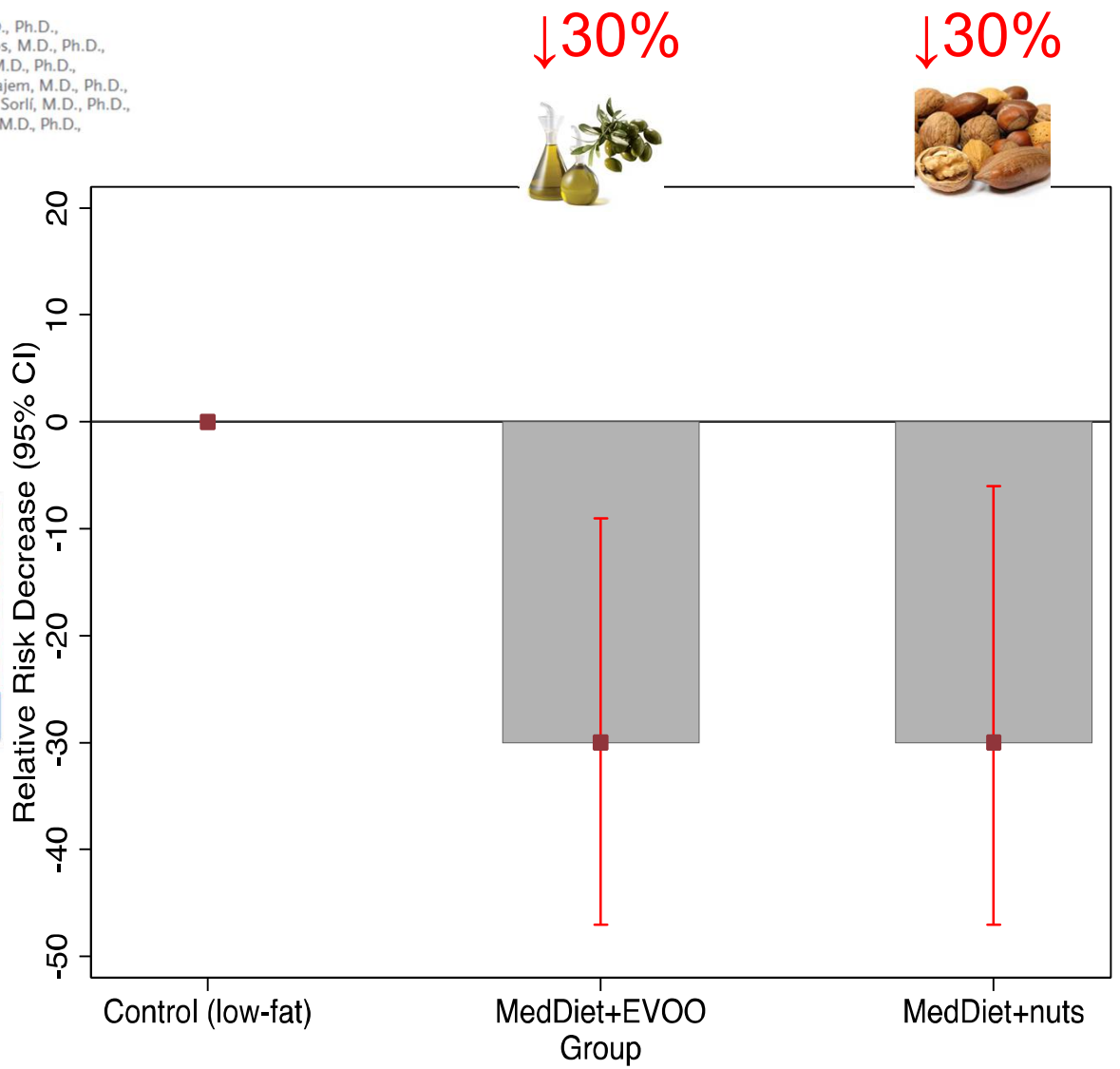
Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

Ramón Estruch, M.D., Ph.D., Emilio Ros, M.D., Ph.D., Jordi Salas-Salvadó, M.D., Ph.D., Maria-Isabel Covas, D.Pharm., Ph.D., Dolores Corella, D.Pharm., Ph.D., Fernando Arós, M.D., Ph.D., Enrique Gómez-Gracia, M.D., Ph.D., Valentina Ruiz-Gutiérrez, Ph.D., Miquel Fiol, M.D., Ph.D., José Lapetra, M.D., Ph.D., Rosa Maria Lamuela-Raventos, D.Pharm., Ph.D., Lluís Serra-Majem, M.D., Ph.D., Xavier Pintó, M.D., Ph.D., Josep Basora, M.D., Ph.D., Miguel Angel Muñoz, M.D., Ph.D., José V. Sorlí, M.D., Ph.D., José Alfredo Martínez, D.Pharm, M.D., Ph.D., and Miguel Angel Martínez-González, M.D., Ph.D., for the PREDIMED Study Investigators*

Myocardial Infarction– Heart Attack
Cerebrovascular disease– Stroke
Cardiovascular deaths







PREDIMED RCT– Primary end-point (MI, stroke or CV death)

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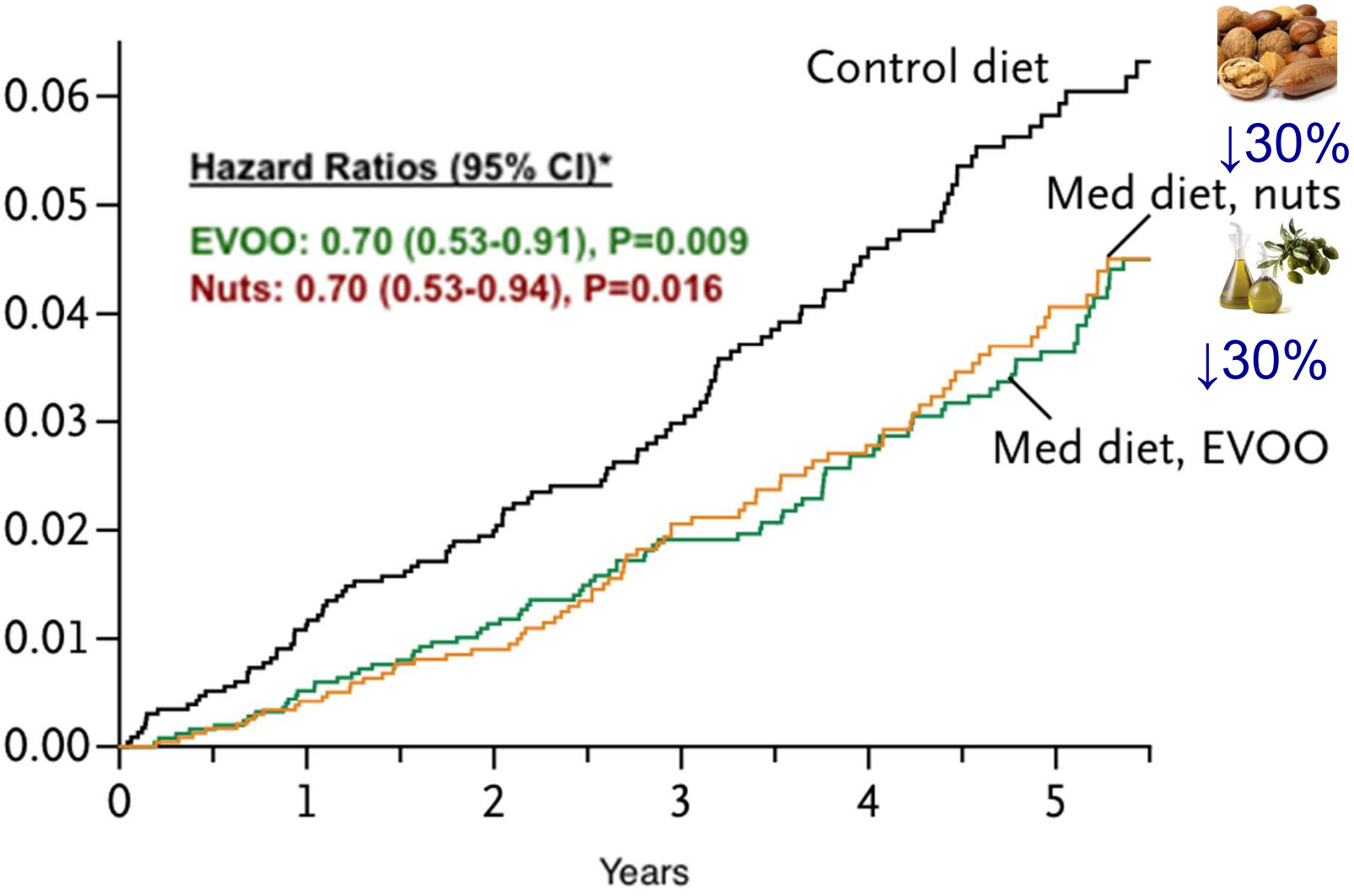
Prevención con Dieta Mediterránea



Number at risk

Control group	2450	2268	2020	1583	1268	946
MeDiet+EVOO	2543	2486	2320	1987	1687	1310
MeDiet+Nuts	2454	2343	2093	1657	1389	1031

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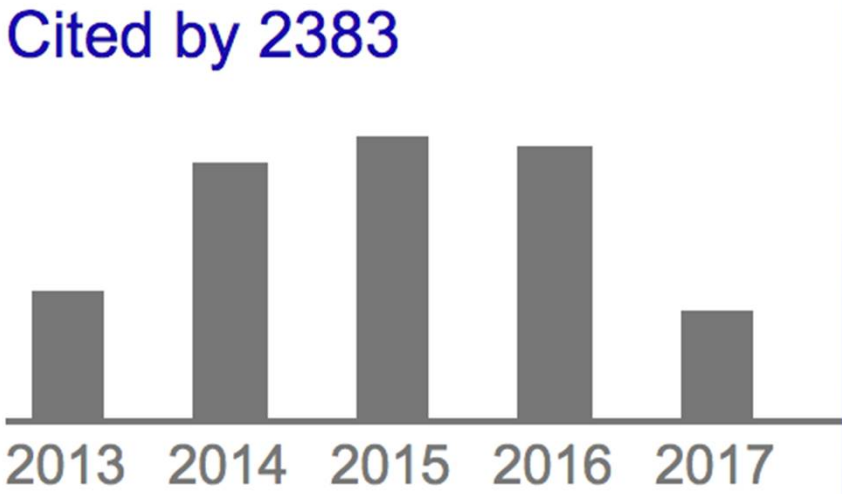

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Title	Primary Prevention of Cardiovascular Disease with a Mediterranean Diet.
Published in	New England Journal of Medicine, February 2013
DOI	10.1056/nejmoa1200303
Pubmed ID	23432189
Authors	Ramón Estruch, Emilio Ros, Jordi Salas-Salvadó, Maria-Isabel Covas, D.Pharm., Dolores Corella... [show]
Abstract	Observational cohort studies and a secondary prevention trial have shown an inverse association... [show]

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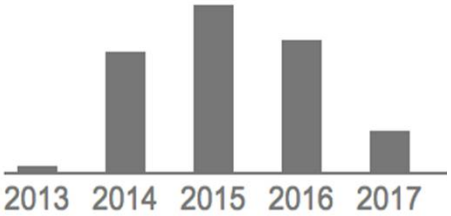


Prevention of Diabetes With Mediterranean Diets

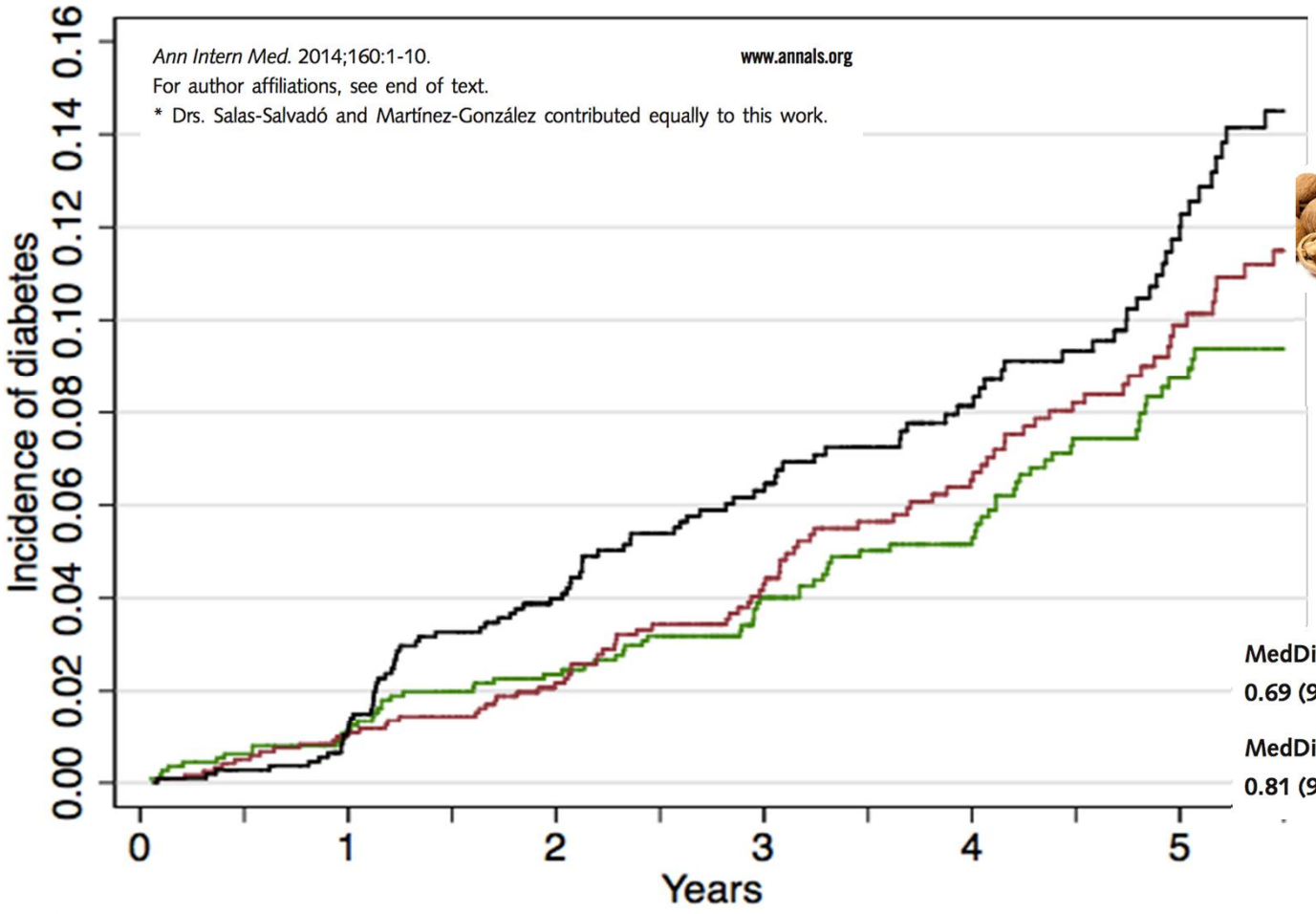
A Subgroup Analysis of a Randomized Trial

Jordi Salas-Salvadó, MD, PhD*; Mònica Bulló, PhD; Ramón Estruch, MD, PhD; Emilio Ros, MD, PhD; Maria-Isabel Covas, DPharm; Núria Ibarrola-Jurado, RD, PhD; Dolores Corella, DPharm, PhD; Fernando Arós, MD, PhD; Enrique Gómez-Gracia, MD, PhD; Valentina Ruiz-Gutiérrez, PhD; Dora Romaguera, MD, PhD; José Lapetra, MD, PhD; Rosa Maria Lamuela-Raventós, DPharm, PhD; Lluís Serra-Majem, MD, PhD; Xavier Pintó, MD, PhD; Josep Basora, MD, PhD; Miguel Angel Muñoz, MD, PhD; José V. Sorlí, MD, PhD; and Miguel A. Martínez-González, MD, PhD*

Ann Intern Med. 2014;160:1-10. www.annals.org

For author affiliations, see end of text.

* Drs. Salas-Salvadó and Martínez-González contributed equally to this work.



22%n.s.

↓34%

MedDiet + EVOO: unadjusted HR, 0.69 (95% CI, 0.51–0.93)

MedDiet + nuts: unadjusted HR, 0.81 (95% CI, 0.61–1.08)

Number at risk

Group = MeDiet+EVOO	1135	1109	996	830	681	488
Group = MeDiet+nuts	1201	1172	1000	774	629	427
Group = Control	1092	1052	901	678	522	367

2017

238: De la Torre R, Corella D, Castañer O, et al.
Protective effect of homovanillyl alcohol on cardiovascular disease and total mortality: virgin olive oil, wine, and catechol-methylathion.
Am J Clin Nutr. 2017 doi: 10.3945/ajcn.116.145813.

237: Guo X, Tresserra-Rimbau A, Estruch R, et al.
Polyphenol Levels Are Inversely Correlated with Body Weight and Obesity in an Elderly Population after 5 Years of Follow Up (The Randomised PREDIMED Study).
Nutrients. 2017 doi: 10.3390/nu9050452.

236: García-Layana A, Ciufo G, Toledo E, et al.
The Effect of a Mediterranean Diet on the Incidence of Cataract Surgery.
Nutrients. 2017 doi: 10.3390/nu9050453.

235: Henríquez-Hernández LA, Luzardo OP, Zumbado M, et al.
Determinants of increasing serum POPs in a population at high risk for cardiovascular disease. Results from the PREDIMED-CANARIAS study.
Environ Res. 2017 doi: 10.1016/j.envres.2017.03.053

234: Gutiérrez-Bedmar M, Martínez-González, MA, Muñoz-Bravo C, et al.
Chromium Exposure and Risk of Cardiovascular Disease in High Cardiovascular Risk Subjects— Nested Case-Control Study in the Prevention With Mediterranean Diet (PREDIMED) Study.
Circ J. 2017. doi:10.1253/circj.CJ-17-0032

233: Becerra-Tomás N, Díaz-López A, Rosique-Esteban N , et al.
Legume consumption is inversely associated with type 2 diabetes incidence in adults: A prospective assessment from the PREDIMED study.

Intervention Trials with the Mediterranean Diet in Cardiovascular Prevention: Understanding Potential Mechanisms through Metabolomic Profiling[1–3]

Miguel Á Martínez-González,[4,5]* Miguel Ruiz-Canela,[4,5] Adela Hruby,[6] Liming Liang,[7] Antonia Trichopoulou,[8] and Frank B Hu[6,7]

J Nutr 2016 Mar 9
[Epub ahead of print]

- Known mechanisms:
  - Inflammation
  - Adiponectin
  - Coagulation
  - Endothelial function
  - Oxidative stress & ox-LDL
  - Improved function of HDL
  - Apolipoproteins
- Metabolic pathways:
  - Largely unknown
- Candidates (small molecules):
  - BCAA & aromatic AA
  - Acylcarnitines
  - Glutamine : Glutamate ratio
  - Gut flora-related metabolites
  - Urea cycle metabolites
  - Lipid subclasses

Metabolomics

Prediimed
Prevención con Dieta Mediterránea

CVD
(2013-2017)

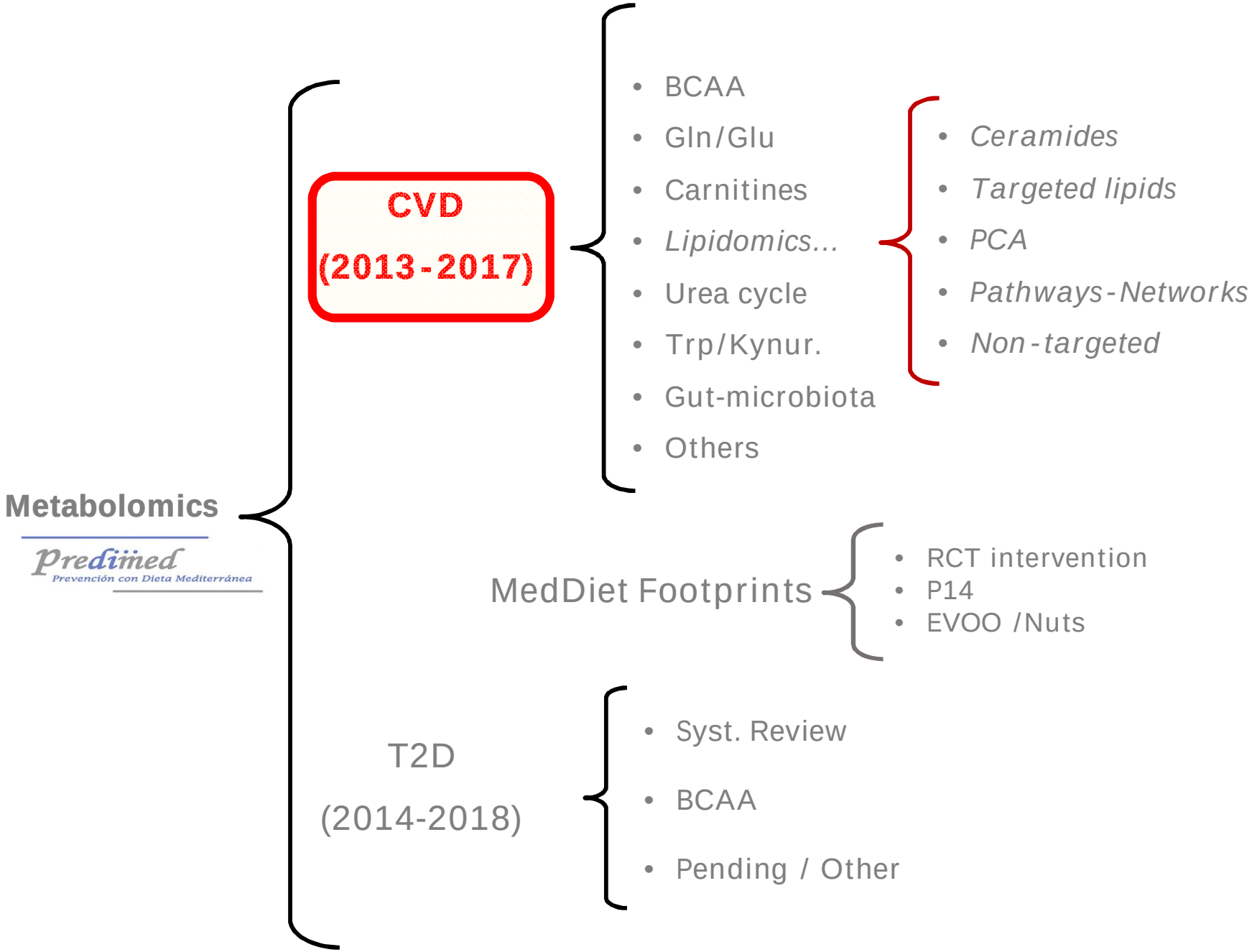
- BCAA
- Gln/Glu
- Carnitines
- *Lipidomics…*
  - *Ceramides*
  - *Targeted lipids*
  - *PCA*
  - *Pathways-Networks*
  - *Non-targeted*
- Urea cycle
- Trp/Kynur.
- Gut-microbiota
- Others

MedDiet Footprints

- RCT intervention
- P14
- EVOO /Nuts

T2D
(2014-2018)

- Syst. Review
- BCAA
- Pending / Other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BCAA
Pending / Other

Mediterranean diet, Metabolites, and Cardiovascular Disease

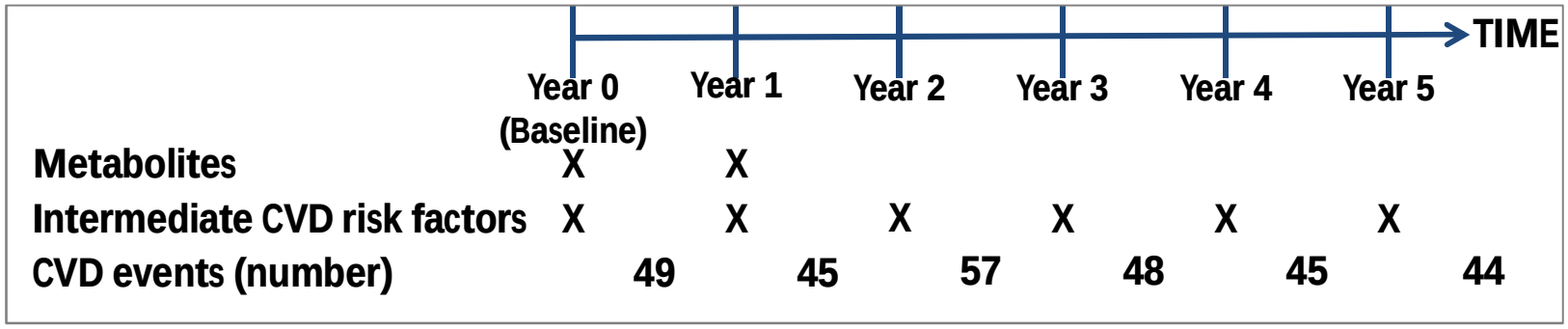
5R01HL118264-02: Jul 15, 2013 – Jun 30, 2017

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH
Powerful ideas for a healthier world

Universidad de Navarra

Case-cohort study

- Baseline metabolites & metabolite 1-y change → CVD
- MeDiet → Changes in metabolites → ↓CVD



CVD grant: Specific aims

- Effects of the **interventions** on changes in plasma levels of **metabolites** from baseline to year 1.
- Whether **1-year change** in metabolites **mediate** the effect of the **interventions** on CVD from years 2 to 5.
- Whether baseline metabolite levels **modify** the effect of the **interventions** on CVD risk.

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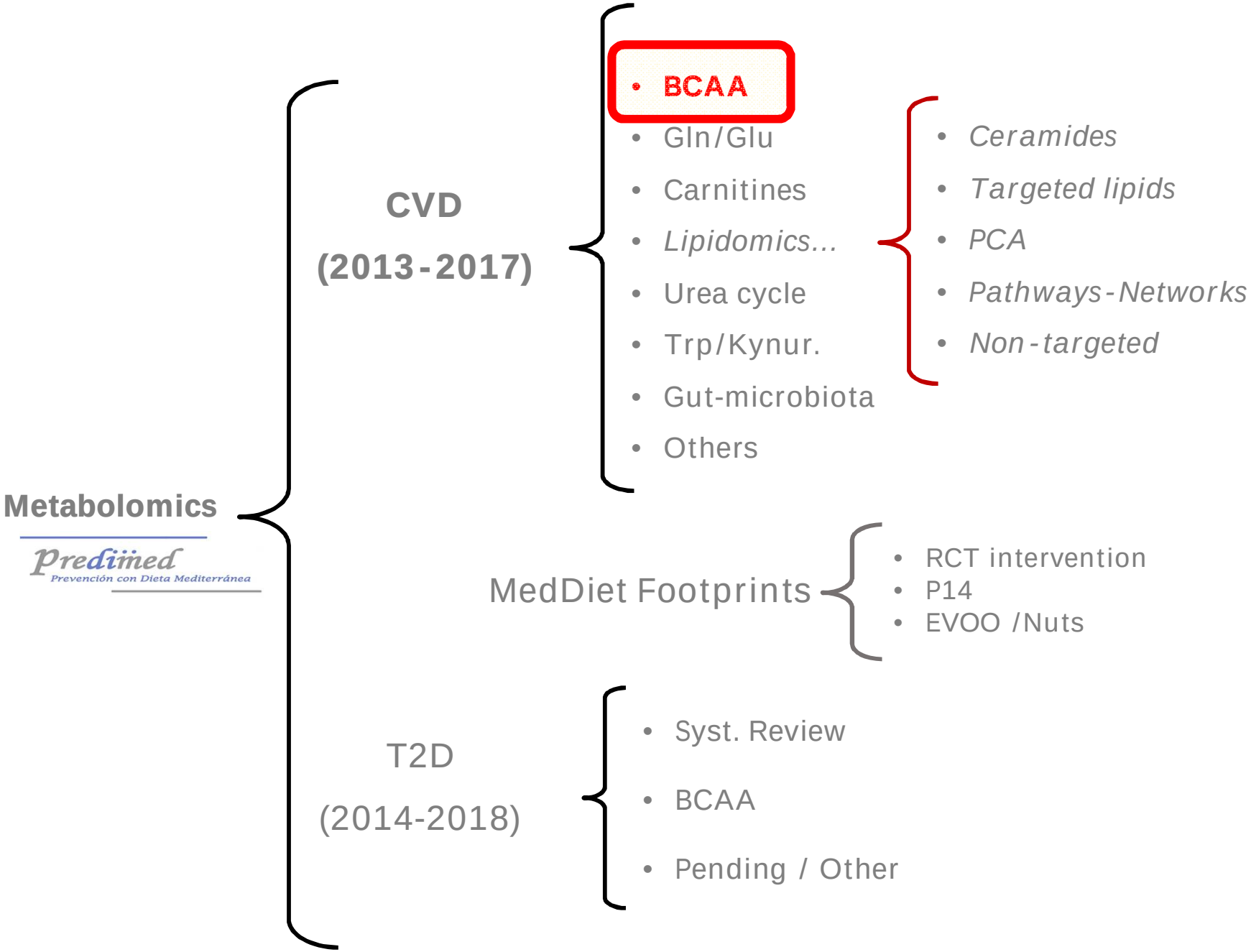
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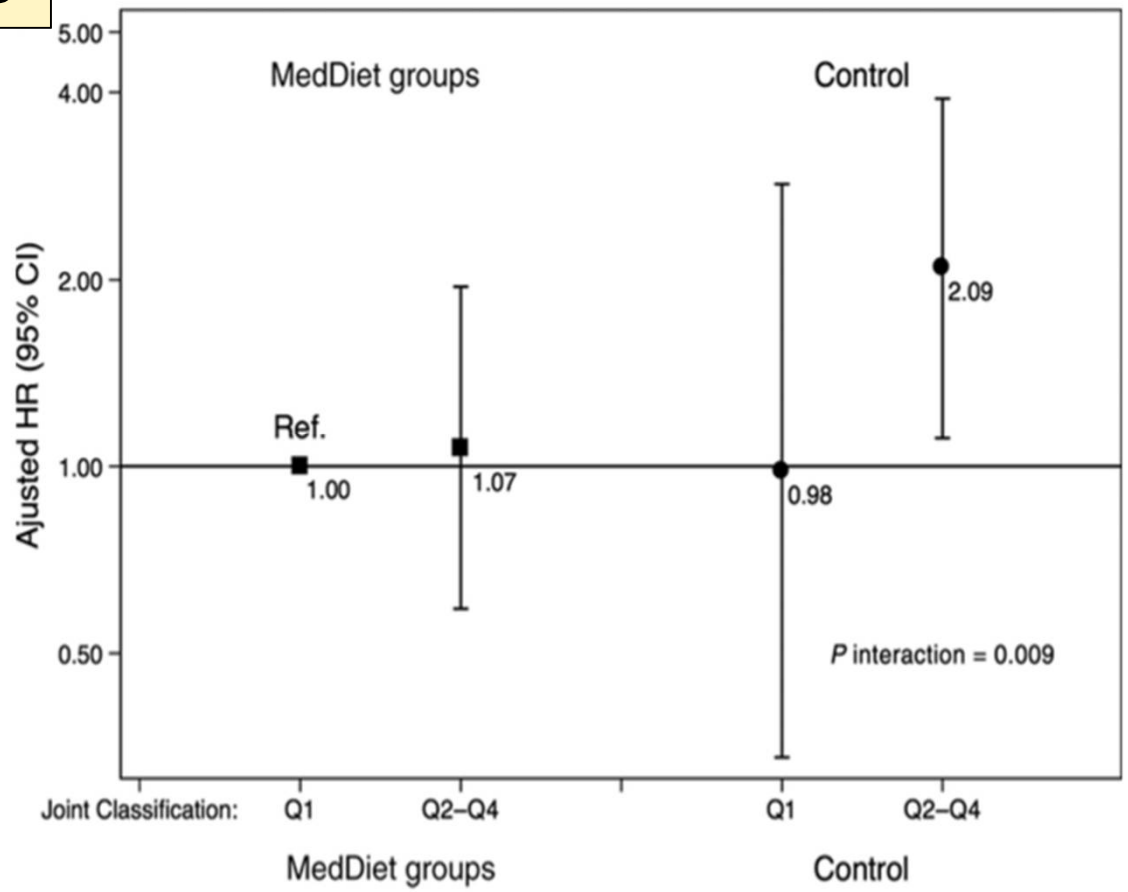
Clinical Chemistry 62:4
582–592 (2016)

Plasma Branched-Chain Amino Acids and Incident Cardiovascular Disease in the PREDIMED Trial

Miguel Ruiz-Canela,[1,2,3] Estefania Toledo,[1,2,3] Clary B. Clish,[4] Adela Hruby,[5] Liming Liang,[6,7] Jordi Salas-Salvadó,[3,8] Cristina Razquin,[1,2,3] Dolores Corella,[3,9] Ramón Estruch,[3,10] Emilio Ros,[3,11] Montserrat Fitó,[3,12] Enrique Gómez-Gracia,[3,13] Fernando Arós,[3,14] Miquel Fiol,[3,15] José Lapetra,[3,16] Lluis Serra-Majem,[3,17,18] Miguel A. Martínez-González,[1,2,3] and Frank B. Hu[5,7,19*]

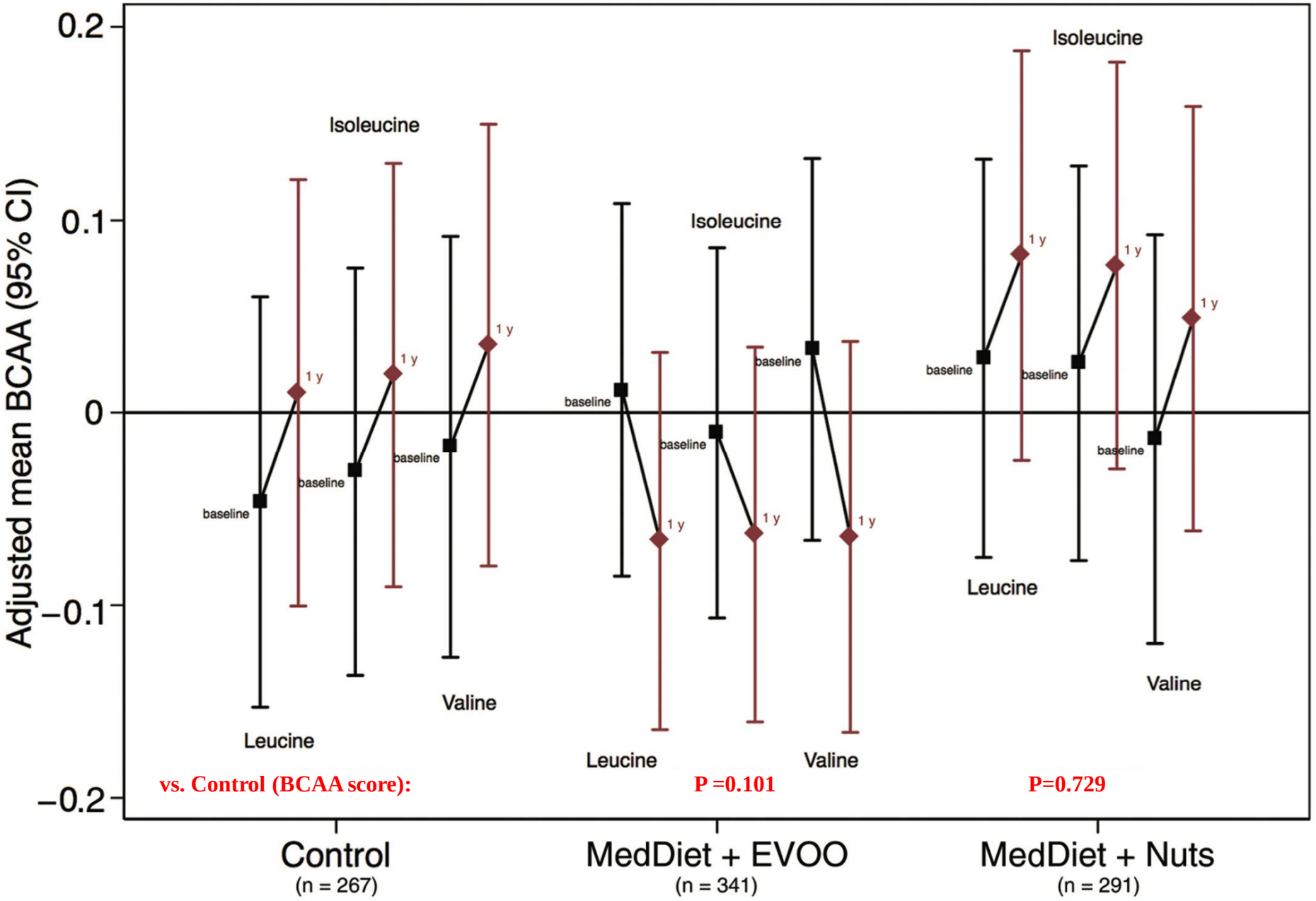
Stroke



Adjusted for age, sex, intervention group, BMI, smoking (never, current, former), leisure-time physical activity (METs min/day), and family history of premature coronary heart disease.

***P* for interaction** (2 df) between each MedDiet intervention group (EVOO and nuts) (binary, yes/no) and the BCAA score (continuous), with 2 cross-product terms (EVOO × BCAA and nuts × BCAA).

Ruiz-Canela et al. Clin Chem. 2016;62:582-92



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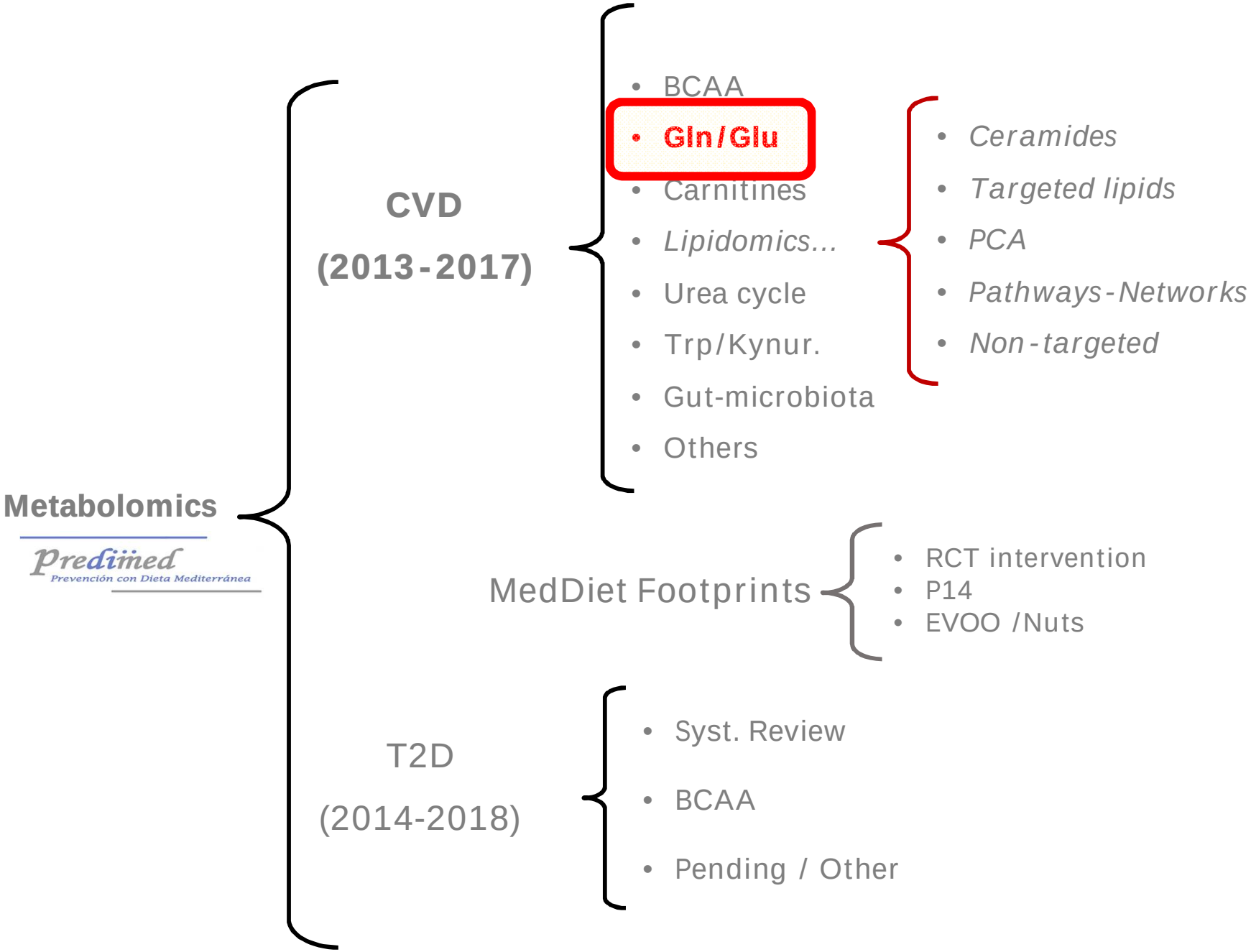
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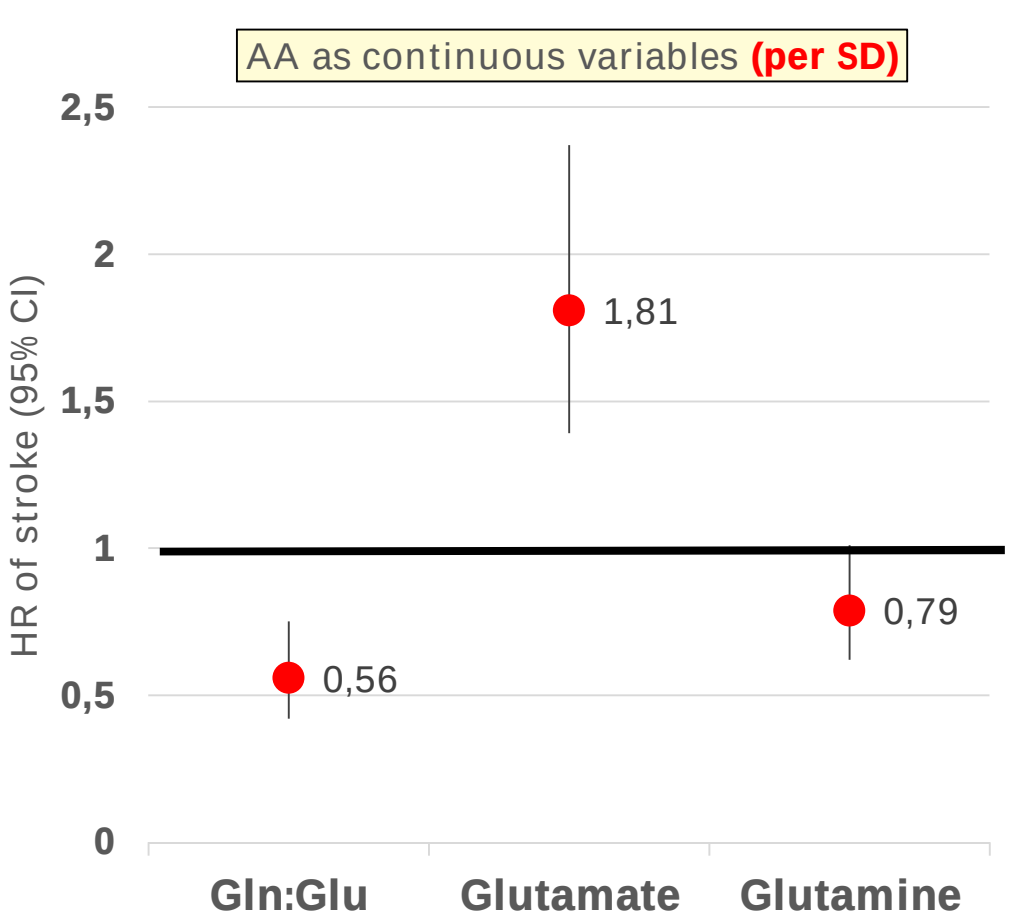
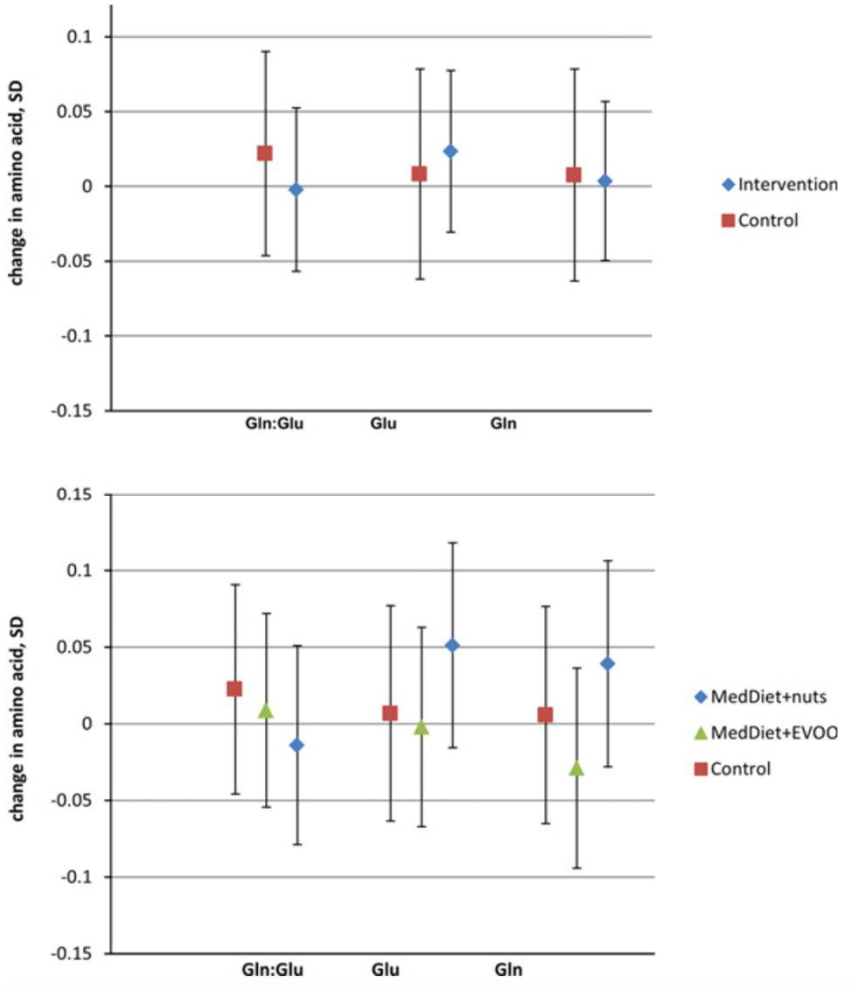
Metabolites of Glutamate Metabolism Are Associated With Incident Cardiovascular Events in the PREDIMED PREvención con DIeta MEDiterránea (PREDIMED) Trial

J Am Heart Assoc. 2016;5:

Yan Zheng, MD, PhD; Frank B. Hu, MD, PhD; Miguel Ruiz-Canela, PhD; Clary B. Clish, PhD; Courtney Dennis, BS; Jordi Salas-Salvado, MD, PhD; Adela Hruby, PhD, MPH; Liming Liang, PhD; Estefania Toledo, MD, PhD; Dolores Corella, DPharm, PhD; Emilio Ros, MD, PhD; Montserrat Fitó, MD, PhD; Enrique Gómez-Gracia, MD, PhD; Fernando Arós, MD, PhD; Miquel Fiol, MD, PhD; José Lapetra, MD, PhD; Lluis Serra-Majem, MD, PhD; Ramón Estruch, MD, PhD; Miguel A. Martínez-González, MD, PhD





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J Am Heart Assoc. 2016;5:

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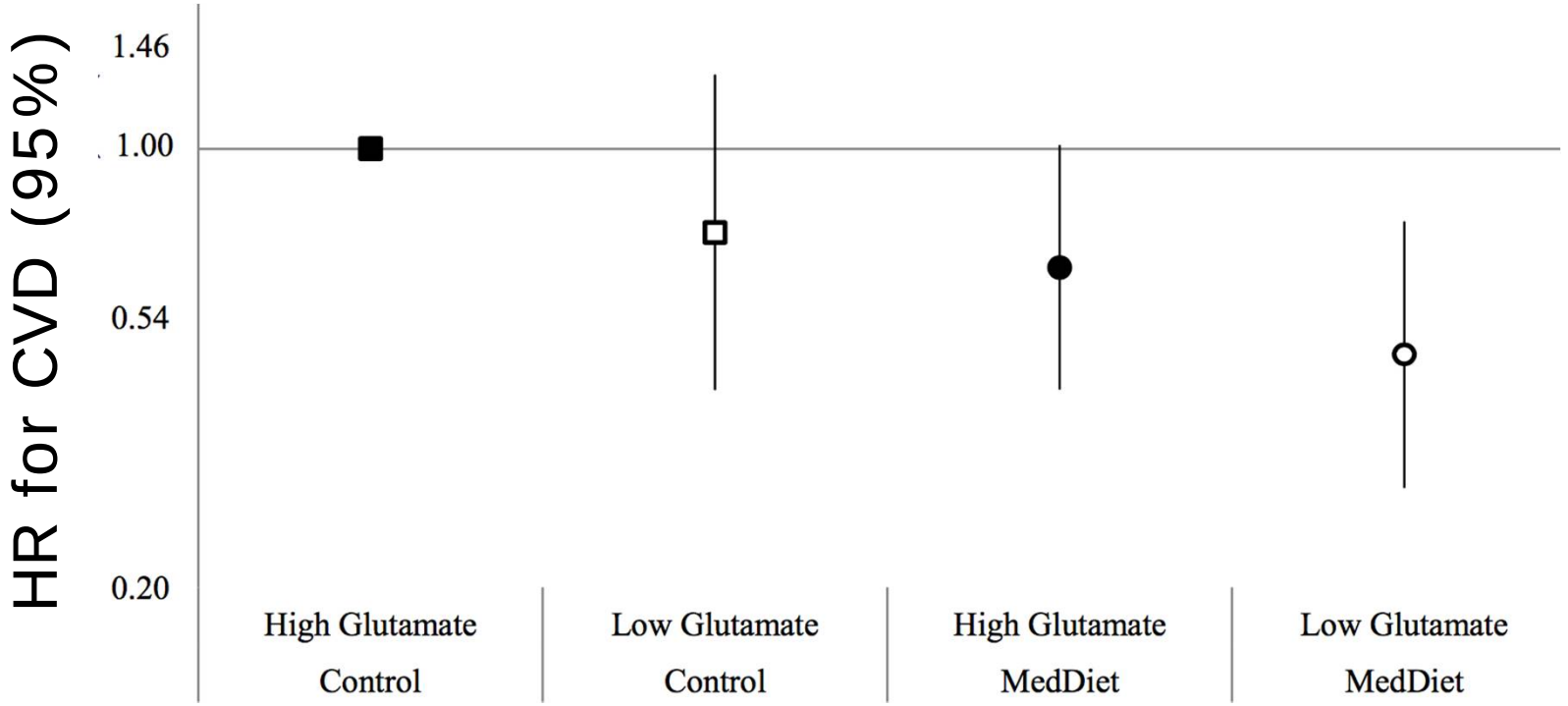
- Among participants with high baseline glutamate, the interventions lowered CVD risk by 37% compared to the control diet;
- the intervention effects were n.s. when baseline glutamate was low (Pinteract.=0.02).



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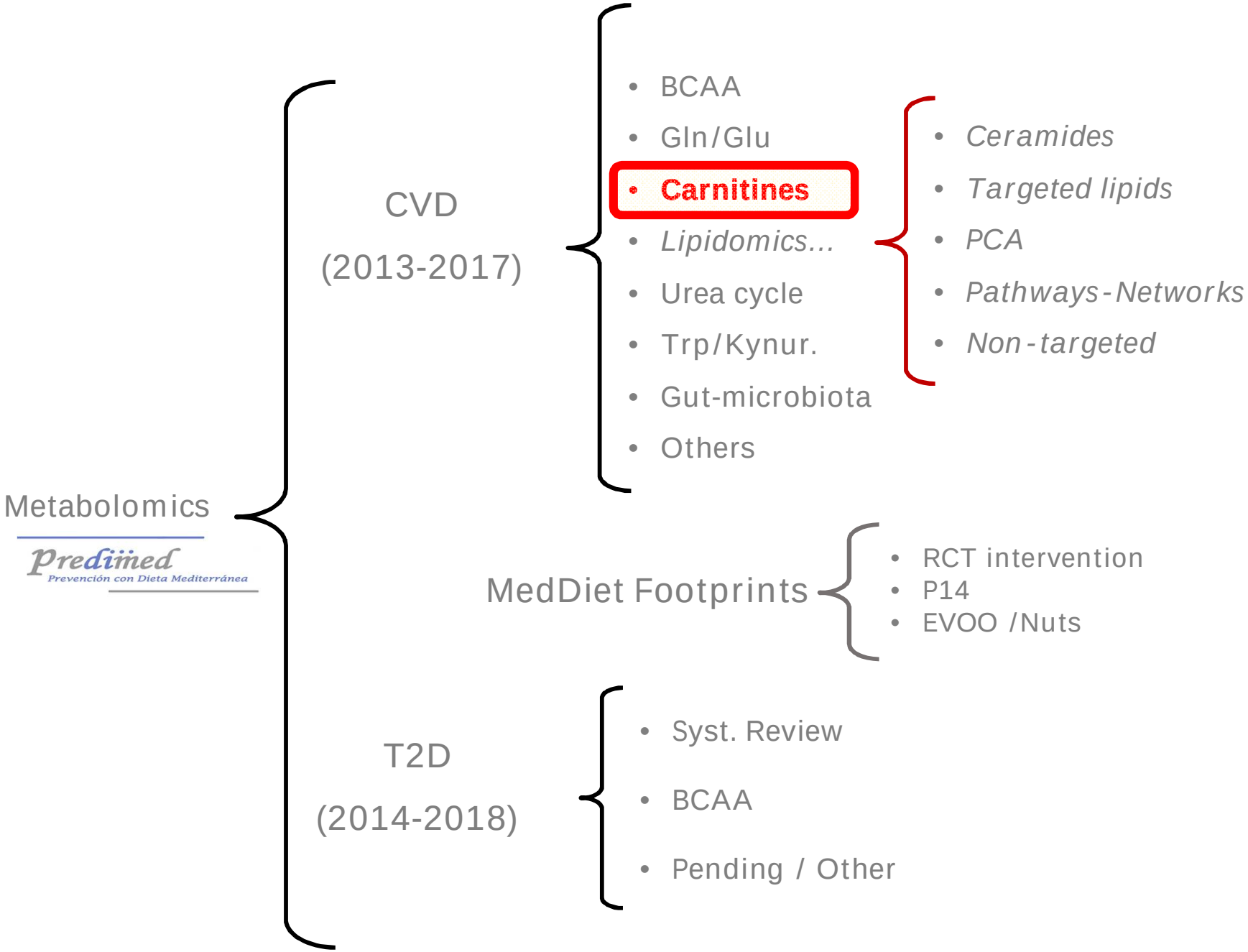
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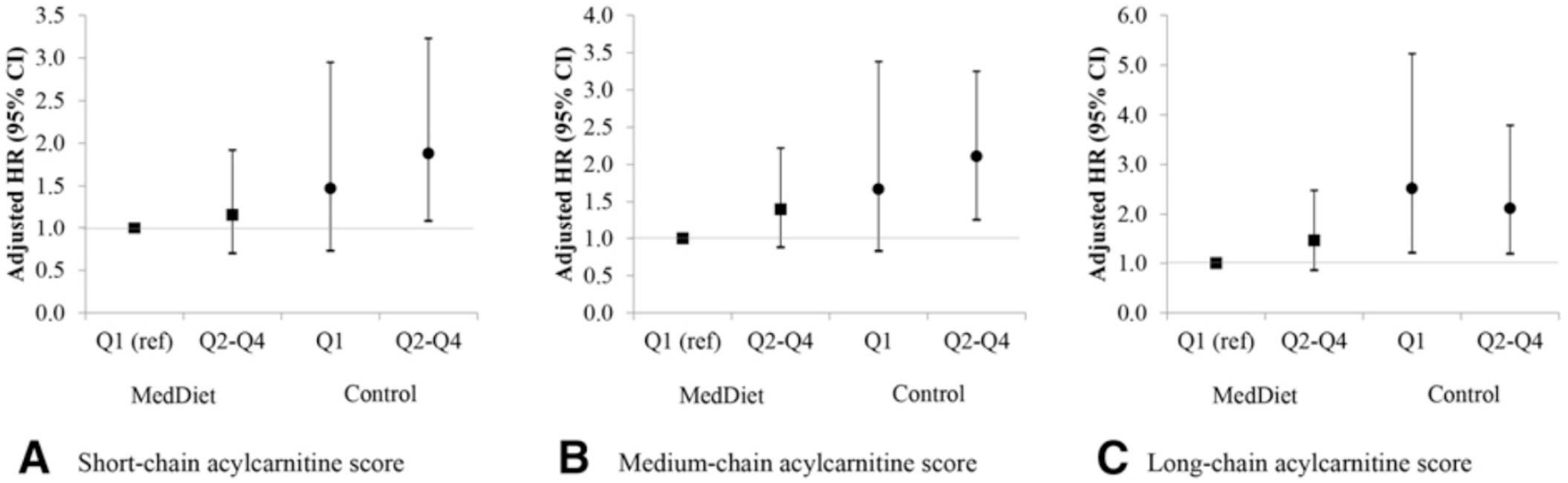
Plasma acylcarnitines and risk of cardiovascular disease: effect of Mediterranean diet interventions[1–3]

Am J Clin Nutr 2016;103:1408-16

*Marta Guasch-Ferré,[4,6,7] Yan Zheng,[4] Miguel Ruiz-Canela,[7,8] Adela Hruby,[4] Miguel A Martínez-González,[7,8] Clary B Clish,[9] Dolores Corella,[7,10] Ramon Estruch,[7,11] Emilio Ros,[7,12] Montserrat Fitó,[7,13] Courtney Dennis,[9] Isabel M Morales-Gil,[14] Fernando Arós,[15] Miquel Fiol,[16] José Lapetra,[7,17] Lluís Serra-Majem,[7,18] Frank B Hu,[4,5,19] and Jordi Salas-Salvadó[6,7]**



P values for interaction:

0.04 0.09 0.48

Metabolomics

Prediimed
Prevención con Dieta Mediterránea

CVD
(2013-2017)

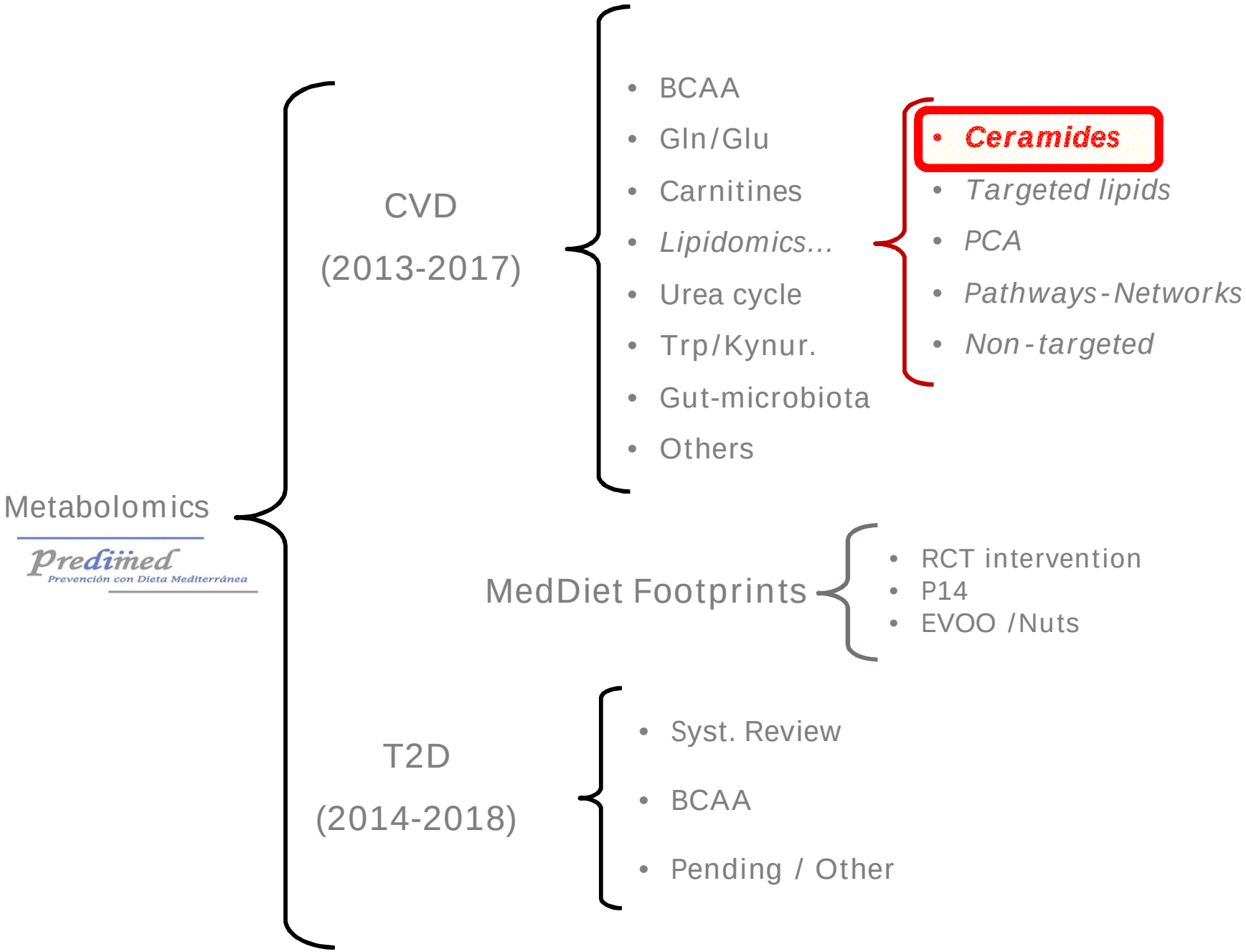
- BCAA
- Gln/Glu
- Carnitines
- *Lipidomics…*
  - *Ceramides*
  - *Targeted lipids*
  - *PCA*
  - *Pathways-Networks*
  - *Non-targeted*
- Urea cycle
- Trp/Kynur.
- Gut-microbiota
- Others

MedDiet Footprints

- RCT intervention
- P14
- EVOO /Nuts

T2D
(2014-2018)

- Syst. Review
- BCAA
- Pending / Other


Metabolomics
PREDIMED
Prevención con Dieta Mediterránea
CVD
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Gln/Glu
Carnitines
Lipidomics...
Urea cycle
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Targeted lipids
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Non-targeted
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RCT intervention
P14
EVOO /Nuts
T2D
(2014-2018)
Syst. Review
BCAA
Pending / Other

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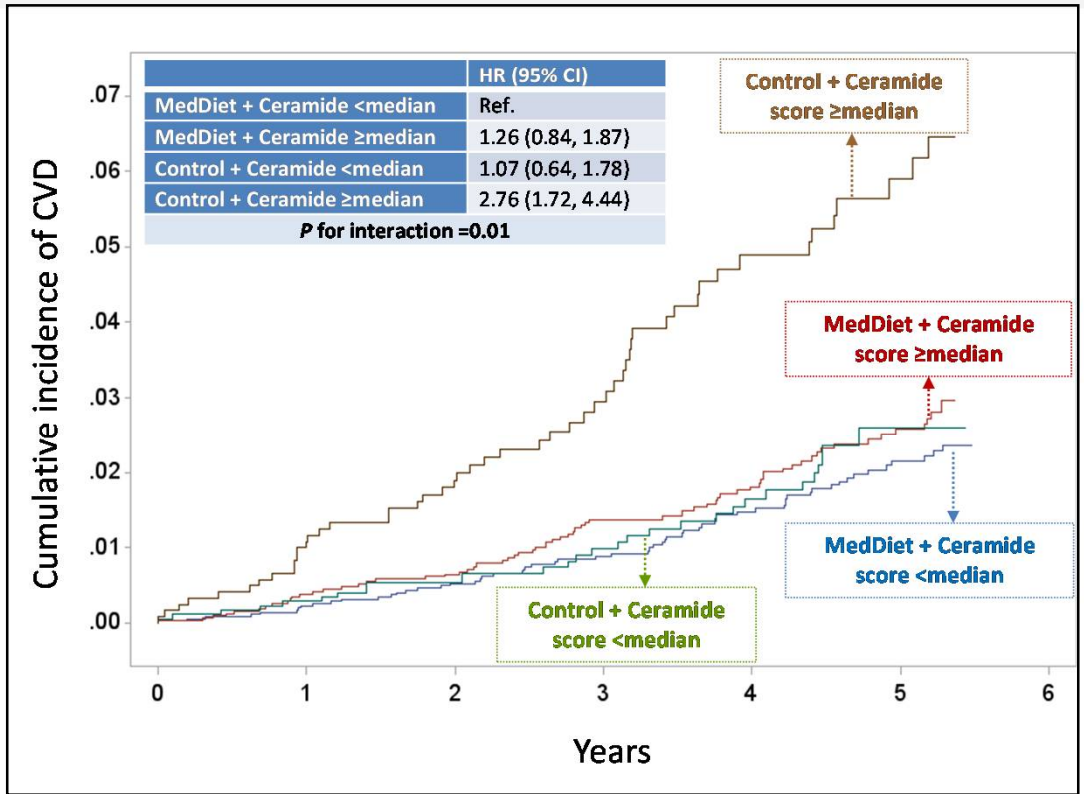
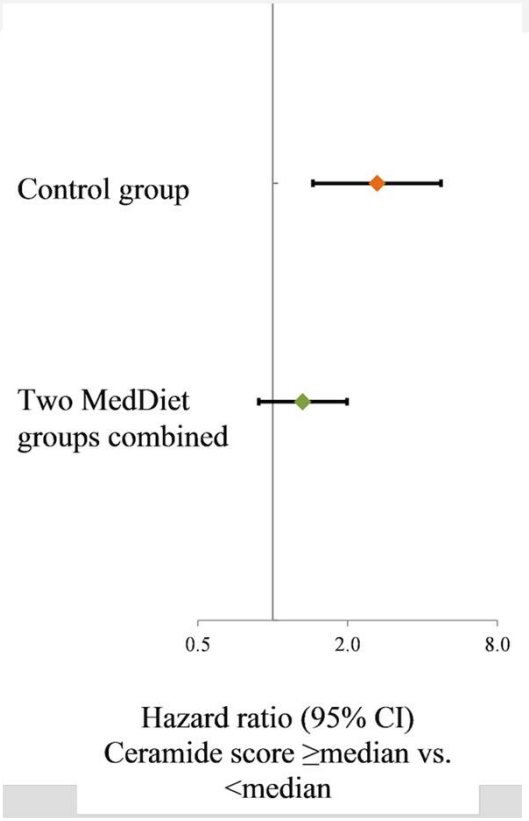
Circulation. 2017;135:2028–2040.

ORIGINAL RESEARCH ARTICLE

Plasma Ceramides, Mediterranean Diet, and Incident Cardiovascular Disease in the PREDIMED Trial

Dong D. Wang, Estefanía Toledo, Adela Hruby, Bernard A. Rosner, Walter C. Willett, Qi Sun, Cristina Razquin, Yan Zheng, Miguel Ruiz-Canela, Marta Guasch-Ferré, Dolores Corella, Enrique Gómez-Gracia, Miquel Fiol, Ramón Estruch, Emilio Ros, José Lapetra, Montserrat Fitó, Fernando Aros, Luis Serra-Majem, Chih-Hao Lee, Clary B. Clish, Liming Liang, Jordi Salas-Salvadó, Miguel A. Martínez-González, Frank B. Hu





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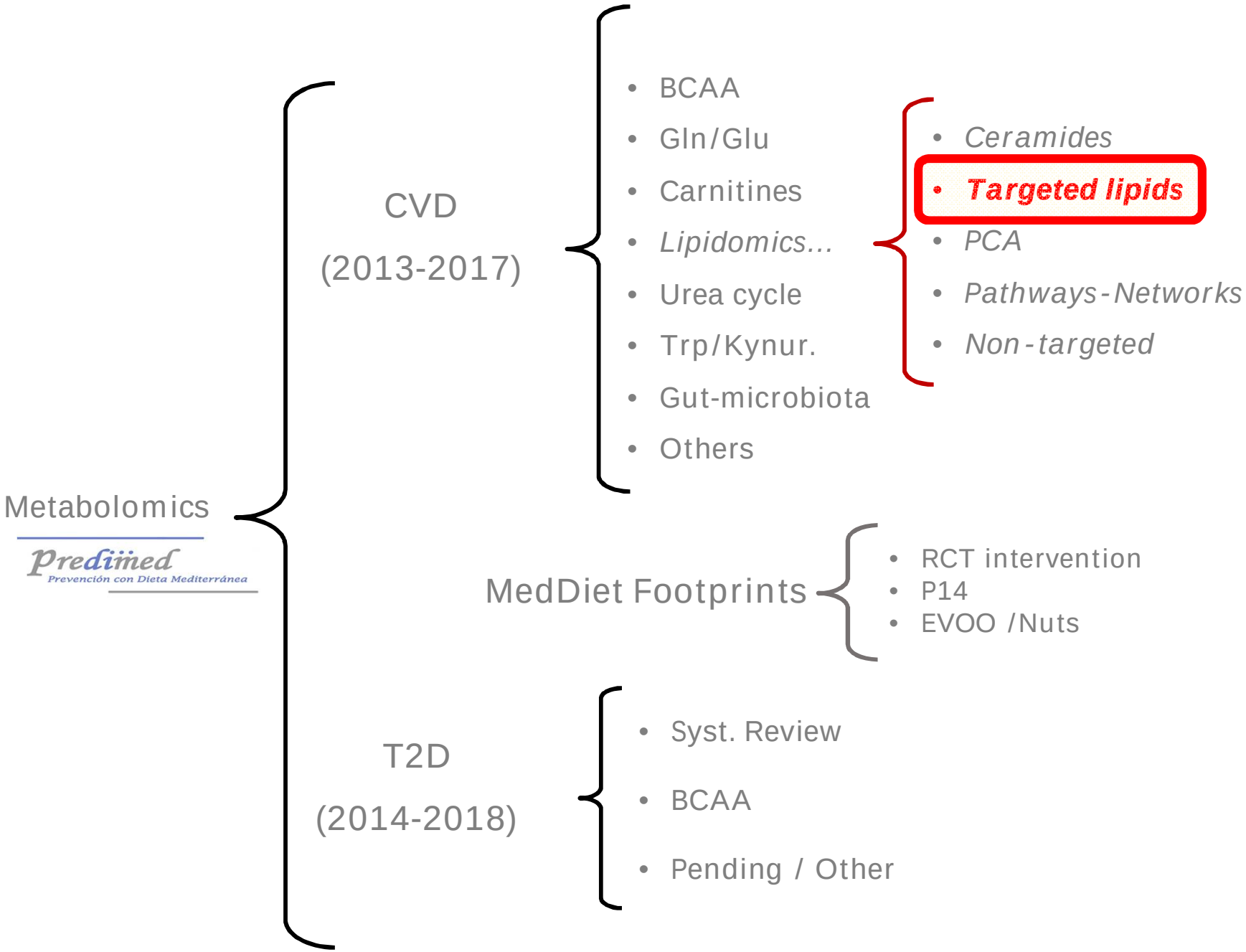
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Syst. Review
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PLASMA LIPIDOMIC PROFILES AND CARDIOVASCULAR EVENTS IN A RANDOMISED

INTERVENTION TRIAL WITH MEDITERRANEAN DIET

Author names

Am J Clin Nutr (3rd review)

Estefanía Toledo, MD, PhD, Dong D. Wang, MD, ScD, Miguel Ruiz-Canela López,

ta

rique

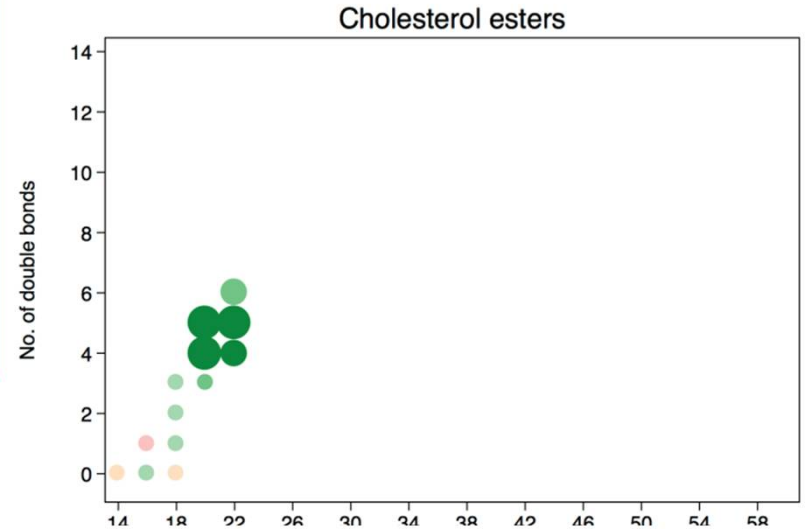
Emilio

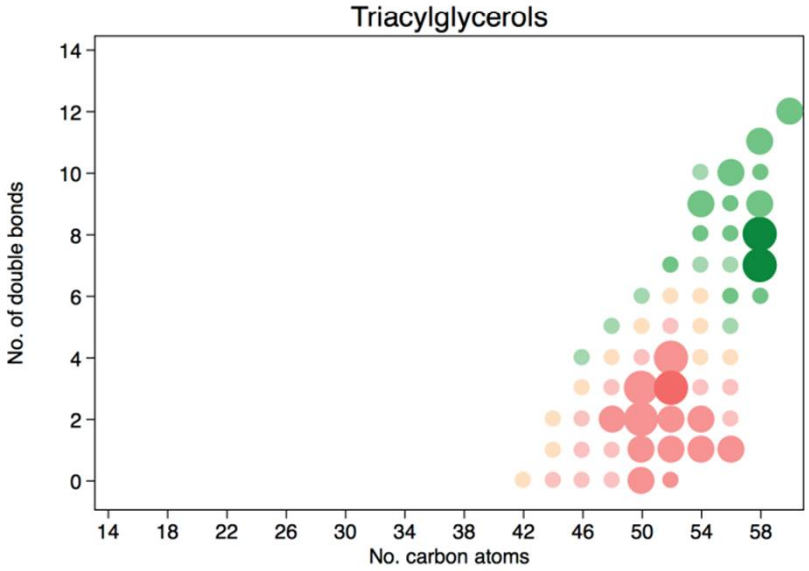
Aros,

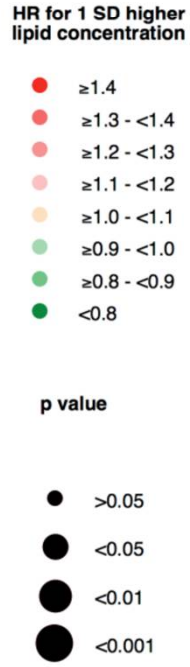
adó, MD,

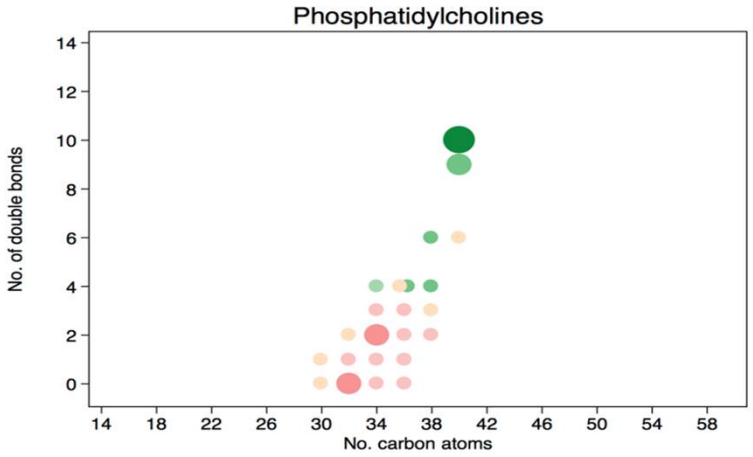
or

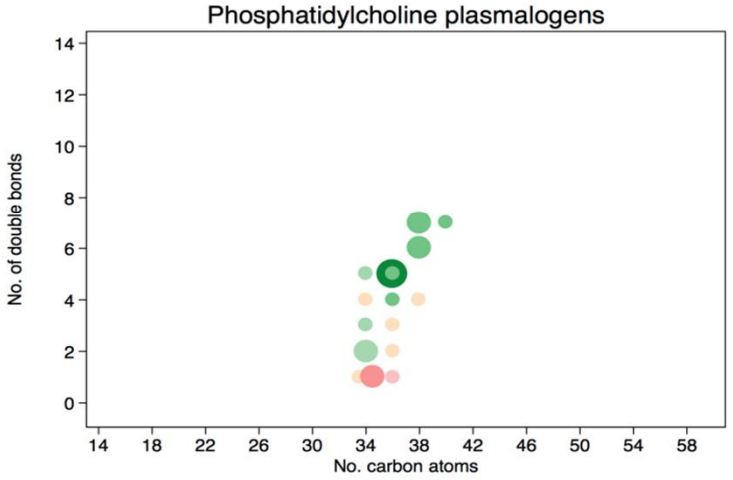
D

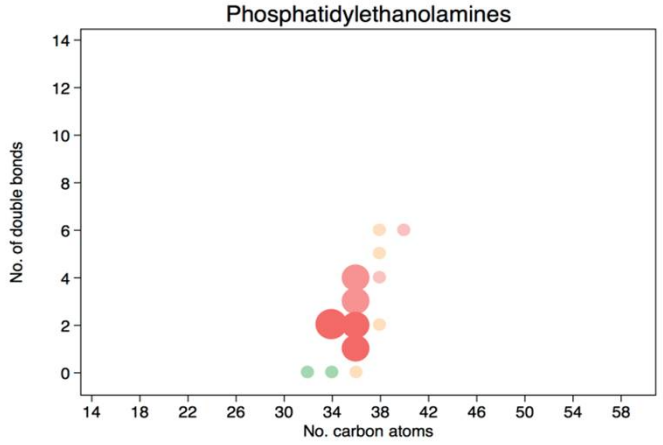












Direct associations with CVD remaining after correction for multiple testing

- Three Phosphatidylethanolamines
  - PE(34:2), PE(36:2) and PE(36:1)
- Three Lysophophatidylethanolamines
  - LPE(16:0), LPE(18:2), and LPE(18:0),
- Phosphatidylethanolamine plasmalogen PEP(36:3)
- Phosphatidylserine PS(38:4)
- Two Ceramides
  - C(16:0) and C(22:0)
- Three *Hydroxy*-phosphatidylcholines
  - [M+Na]+ OHPCMA(34:2), OHPCMA(36:4) and OHPC(36:4)
- Four Diacylglycerols
  - DAG(34:2), DAG(34:1), DAG(36:1), and DAG(36:0)
- Three Triacylglycerols
  - TAG(50:3), TAG(50:2) and TAG(52:3)

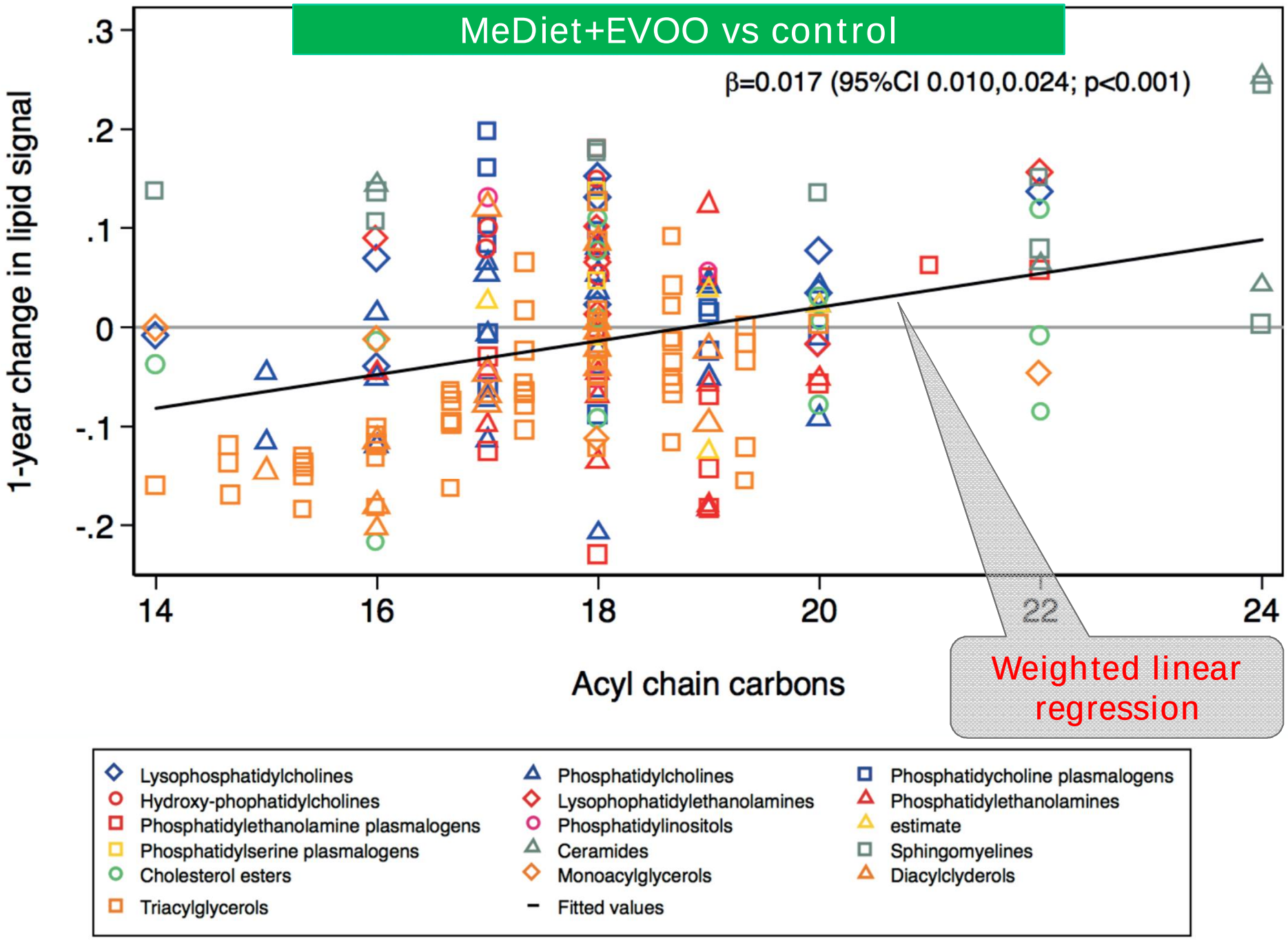
Inverse associations with CVD remaining after correction for multiple testing

- **Three Cholesterol esters**
  - CE(20:5), CE(20:4) and CE(22:5),
- **Phosphatidylcholine** PC(40:10)
- **Phosphatidylcholine plasmalogen** PCP(36:5)
- **Triacylglycerol** TAG(58:8)

Families of lipids weighted by # double bonds & carbon atoms & risk of CVD

score= lipid level * # carbon atoms * (# double bonds + 1)

	HR 95% CI for Q5 vs. Q1	P for trend
Lysophosphatidylethanolamines	**2.47 (1.44-4.25)**	**.004**
Phosphatidylethanolamines	**1.60 (0.97-2.63**	.039
Diacylglycerols	**1.58 (0.95-2.63)**	.010
Cholesterol esters	***0.40 (0.23-0.70***	***.002***


MeDiet+EVOO vs control
β=0.017 (95%CI 0.010,0.024; p<0.001)
1-year change in lipid signal
.3
.2
.1
0
-.1
-.2
14
16
18
20
22
24
Acyl chain carbons
Weighted linear regression
Lysophosphatidylcholines
Hydroxy-phophatidylcholines
Phosphatidylethanolamine plasmalogens
Phosphatidylserine plasmalogens
Cholesterol esters
Triacylglycerols
Phosphatidylcholines
Lysophophatidylethanolamines
Phosphatidylinositols
Ceramides
Monoacylglycerols
Fitted values
Phosphatidycholine plasmalogens
Phosphatidylethanolamines
estimate
Sphingomyelines
Diacylclyderols

Changes in total lipidome by dietary intervention

- A positive association between average length of acyl chain and diff. In 1-y changes vs control with MedDiet+EVOO
- Lipids with longer mean acyl chains exhibited greater increases with MedDiet+EVOO (vs. control) than those with shorter chains

	Average length of acyl chain	# double bonds per acyl chain
MedDiet + EVOO vs. control	+	ns
MedDiet + nuts vs. control	ns	ns

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T2D
(2014-2018)

- Syst. Review
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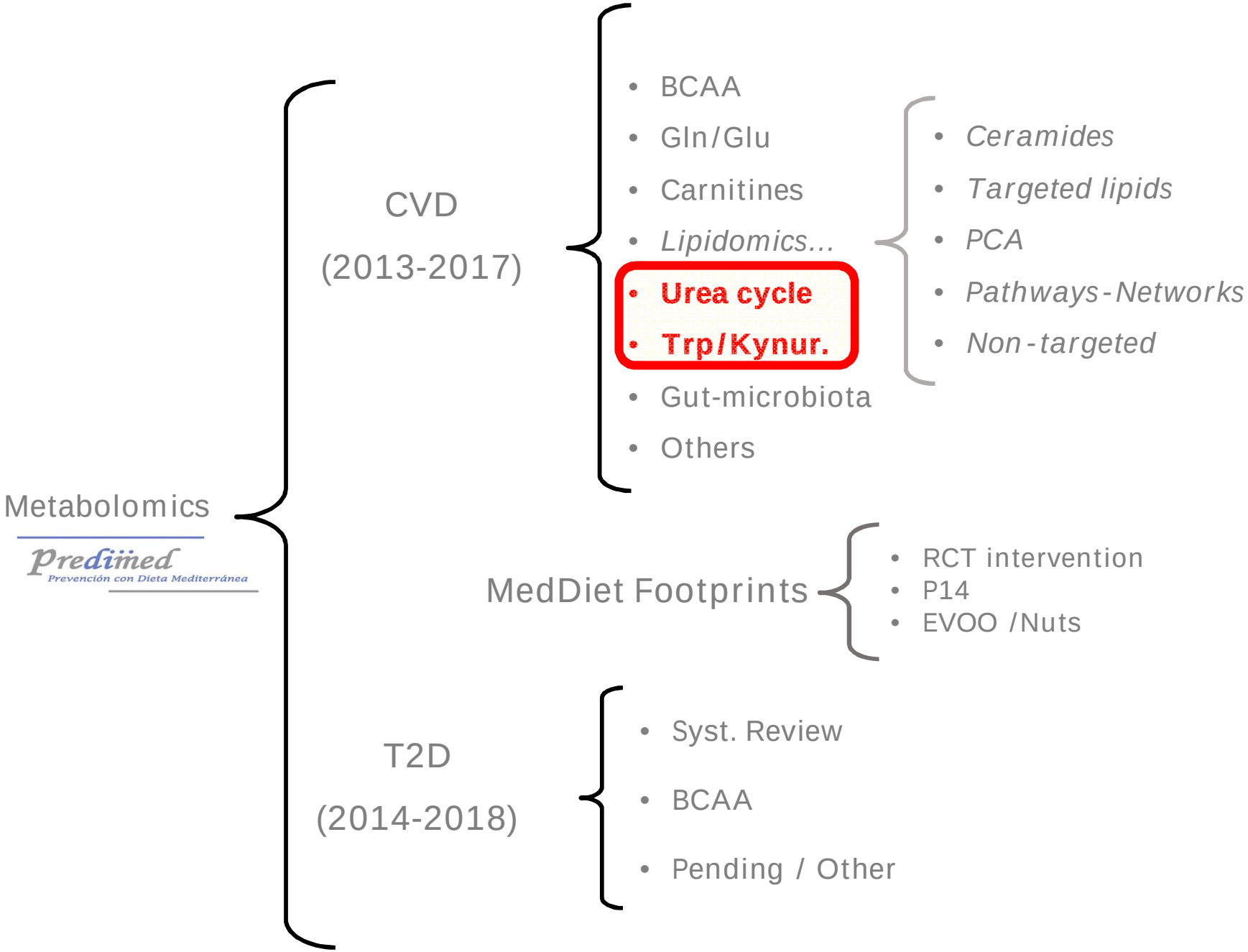
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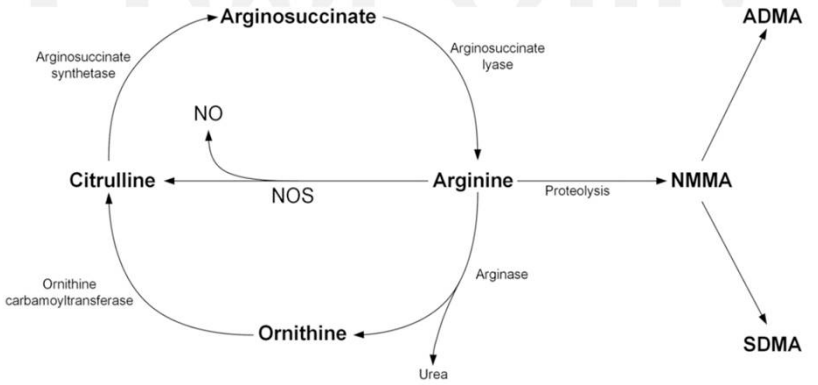
T2D
(2014-2018)
Syst. Review
BCAA
Pending / Other

Plasma Arginine/Asymmetric Dimethylarginine Ratio and Incidence of Cardiovascular Events: A Case-Cohort Study

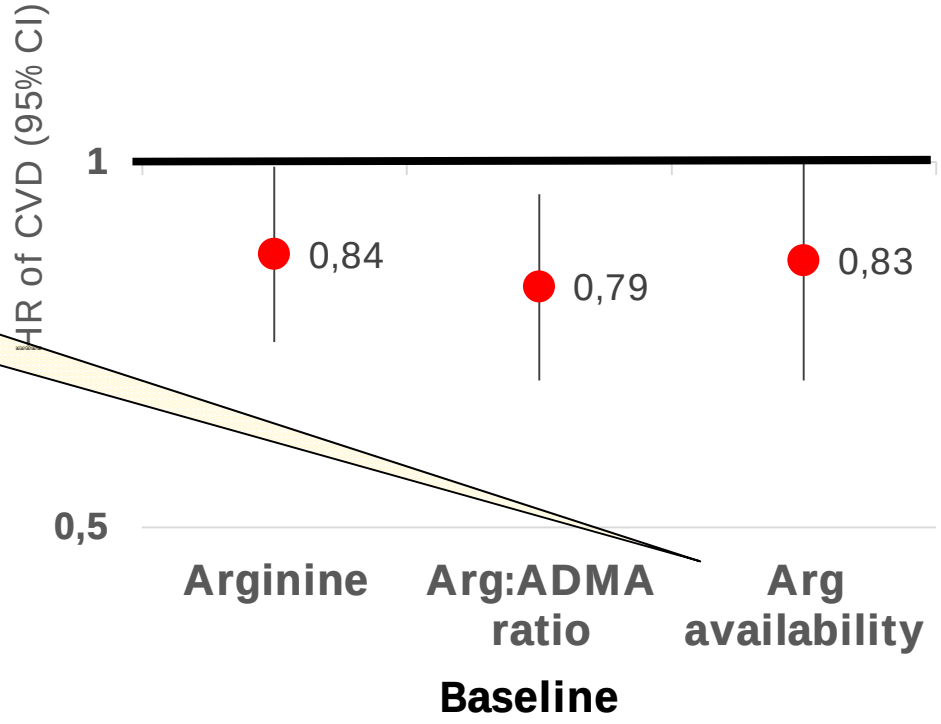
Edward Yu,[1] Miguel Ruiz-Canela,[2,3] Frank B. Hu,[1,4,5] Clary B. Clish,[6] Dolores Corella,[3,7] Jordi Salas-Salvadó,[3,8] Adela Hruby,[9] Montserrat Fitó,[3,10] Liming Liang,[11] Estefania Toledo,[2,3] Emilio Ros,[3,12] Ramón Estruch,[3,13] Enrique Gómez-Gracia,[3,14] Jose Lapetra,[3,15] Fernando Arós,[3,16] Dora Romaguera,[3,17,18] Lluís Serra-Majem,[3,19] Marta Guasch-Ferré,[1] Dong D. Wang,[1] and Miguel A. Martínez-González[2,3]

J Clin Endocrinol Metab. 2017 Mar 2. doi: 10.1210/jc.2016-3569. [Epub ahead of print]
PMID: 28323949



Exposures as continuous variables **(per SD)**

Arginine availability score = arginine/ (citrulline + ornithine).



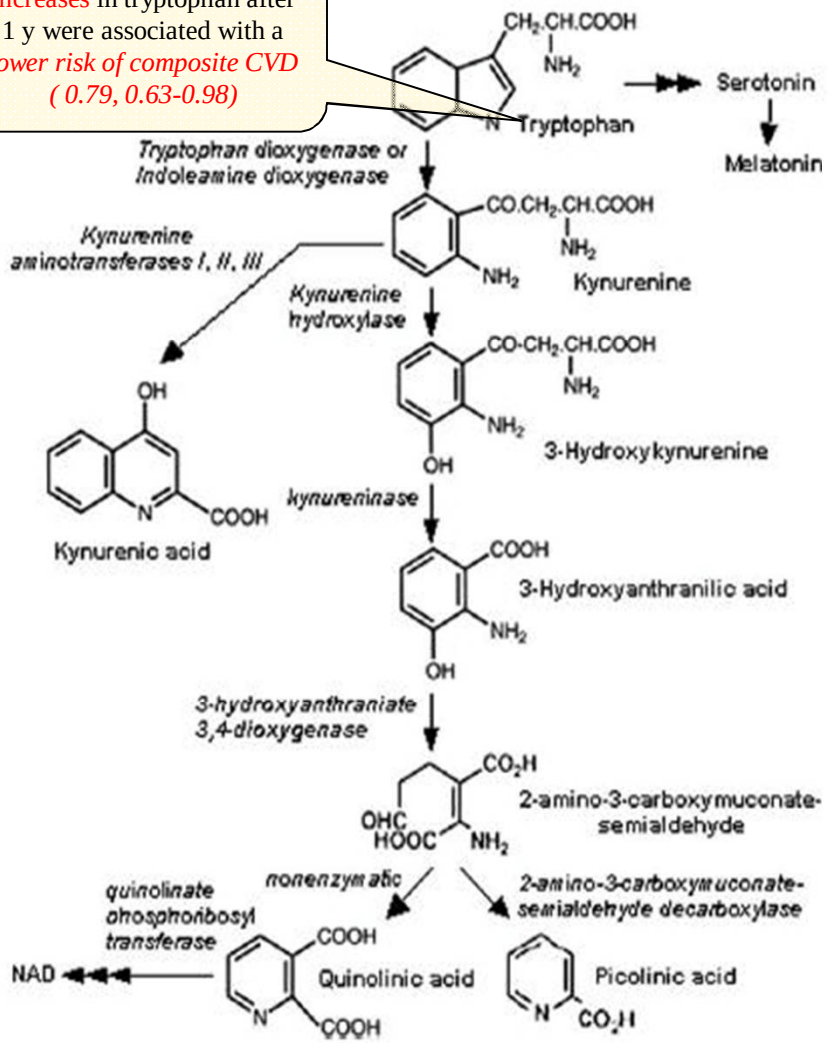
Emerging TRP-KYN pathway

- Chronic inflammation → cardiometabolic disorders
- A potential mechanism is the transcriptional induction of indoleamine 2,3-dioxygenase (IDO), rate-limiting enzyme of **tryptophan** (TRP)-**kynurenine** (KYN) pathway, by pro-inflammatory cytokines.
- Activation of IDO shifts TRP metabolism from *serotonin* synthesis to formation of kynurenines.
- ⇓serotonin →depression
- ⇑kynurenines → MetS & cardiometabol. conditions by:
  - Apoptotic effects
  - Neurotoxic effects
  - Pro-oxidative effects
  - upregulation of inducible NO synthase, phospholipase A2, arachidonic acid, prostaglandin, 5-lipoxygenase, and leukotriene cascade.

Increases in Plasma Tryptophan Are Inversely Associated with Incident Cardiovascular Disease in the Prevención con Dieta Mediterránea (PREDIMED) Study[1–3]

Edward Yu,[4] Miguel Ruiz-Canela,[7–9] Marta Guasch-Ferré,[4,8,9] Yan Zheng,[4] Estefania Toledo,[7–9] Clary B Clish,[11] Jordi Salas-Salvadó,[9,10] Liming Liang,[5] Dong D Wang,[4] Dolores Corella,[9,12] Montse Fitó,[9,13] Enrique Gómez-Gracia,[14] José Lapetra,[9,15] Ramón Estruch,[9,16] Emilio Ros,[9,17] Montserrat Cofán,[9,17] Fernando Arós,[9,18] Dora Romaguera,[9,19] Lluis Serra-Majem,[9,20] Jose V Sorlí,[9,13] Frank B Hu,[4,6,21] and Miguel A Martinez-Gonzalez[4,7–9]*

Increases in tryptophan after 1 y were associated with a *lower risk of composite CVD (0.79, 0.63-0.98)*



KYNURINE RISK SCORE (KRS):
Normalized individual metabolites weighted by their b coefficient (from a fully adjusted model with that metabolite alone)

The weights were:
–0.13 for tryptophan
+0.06 for kynurenine
+0.20 for kynurenic acid,
–0.20 for 3-hydroxyanthranilic acid
+0.14 for quinolinic acid.

A higher KRS was more strongly associated with CVD in the control group than in the 2 intervention groups (*P*-interaction = 0.003)

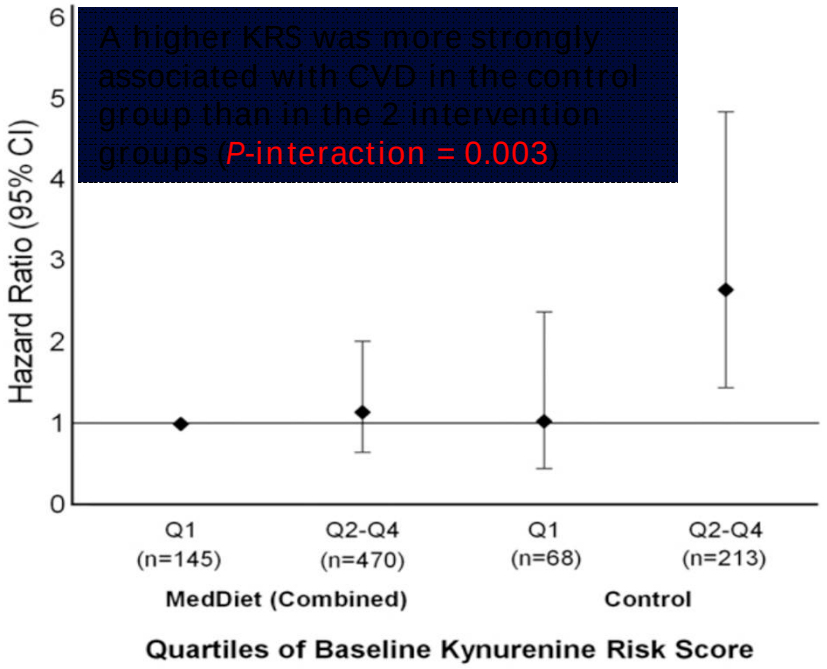


FIGURE 1 Multivariate adjusted HRs (95% CIs) of composite CVD by Qs of baseline kynurenine risk score stratified by intervention group (Mediterranean interventions combined compared with the control group) among participants with available data for all 5 metabolites under study (n = 896). MedDiet, Mediterranean diet; Q, quartile.

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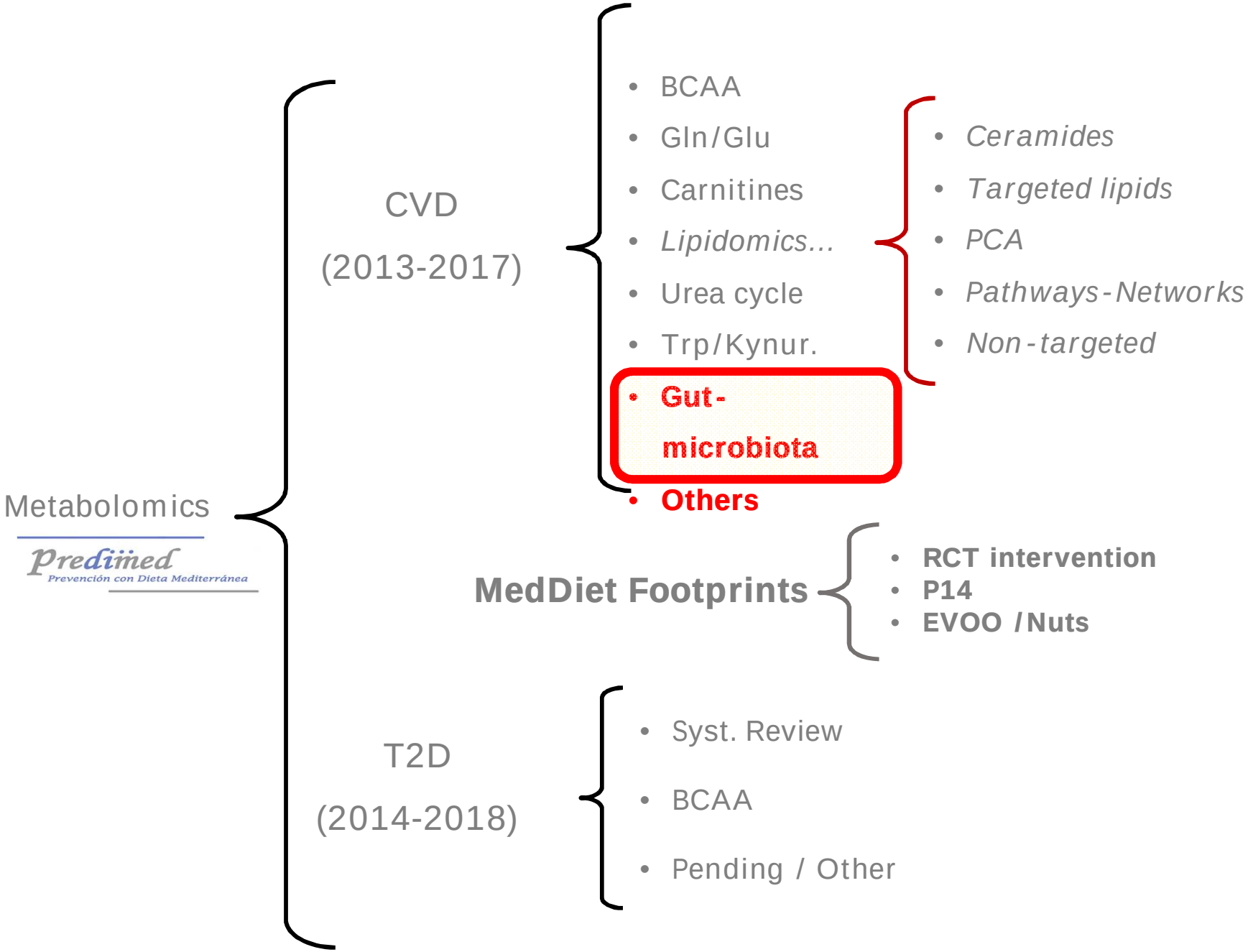
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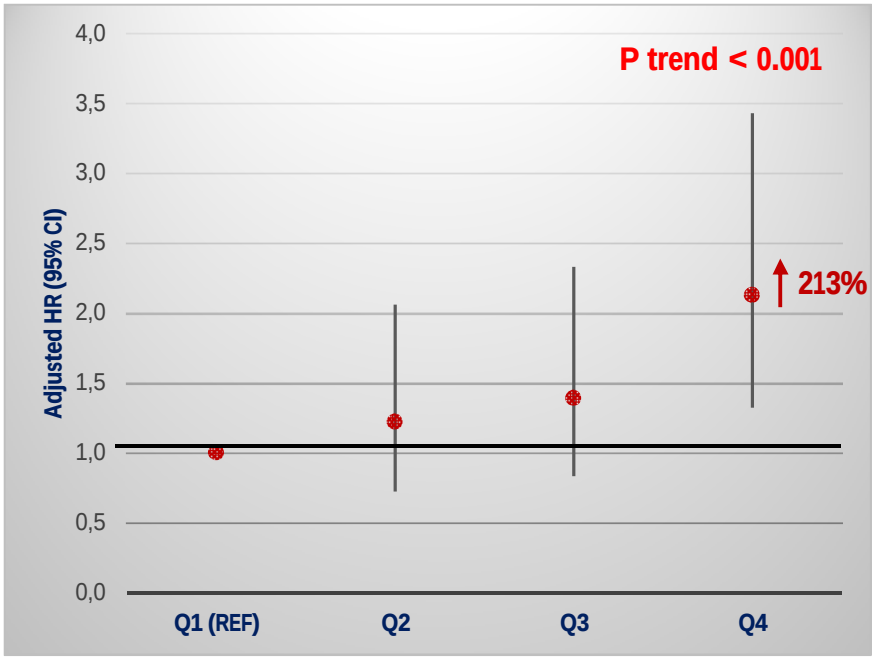
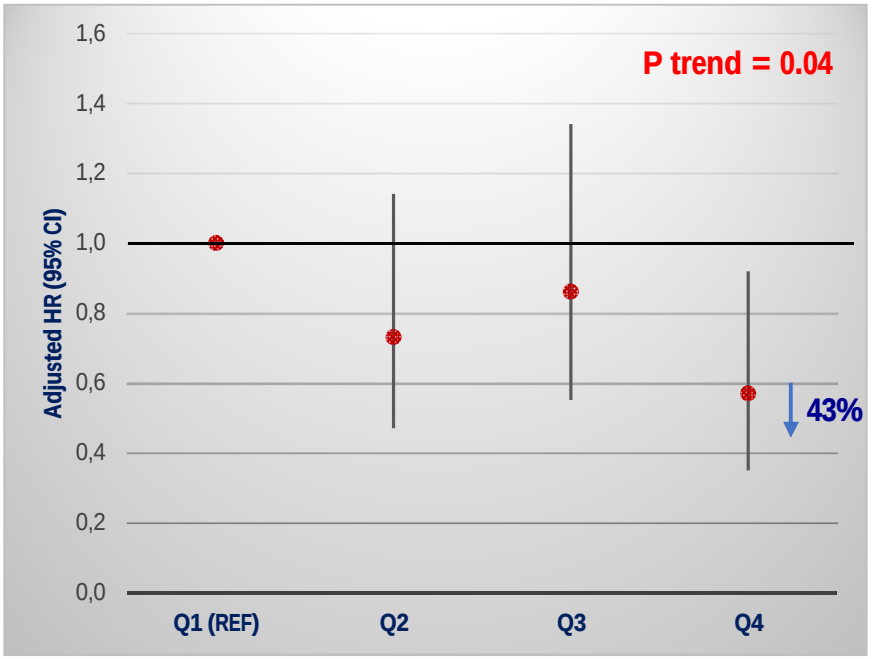
Guasch-Ferre, et al. Gut microbiota related plasma metabolites and risk of cardiovascular disease in the PREDIMED Study (**submitted**)

TMAO, betaine, choline, phosphocholine, alphaglycerophosphocholine, proline, hydroxyproline, and allantoin

a) Metabolite score



b) Betaine / choline ratio



Adjusted for age, sex, body mass index, family history of premature heart disease, smoking, physical activity, hypertension, dyslipidemia, and diabetes, and stratified by intervention group

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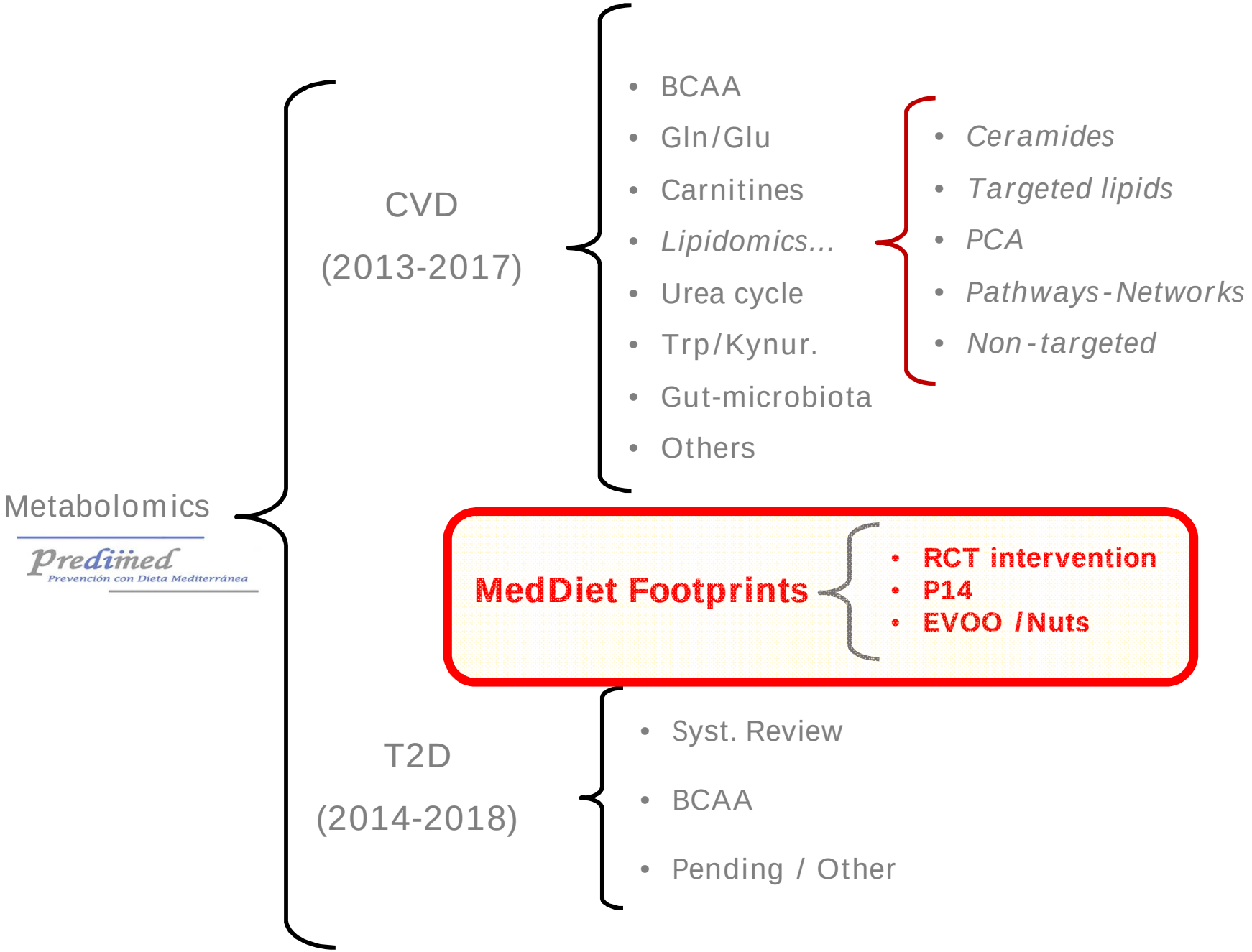
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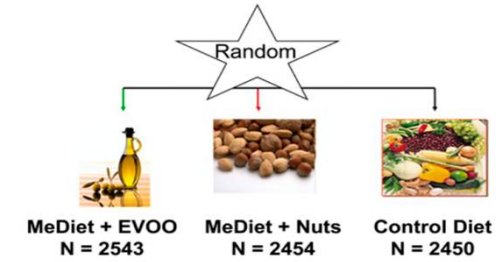
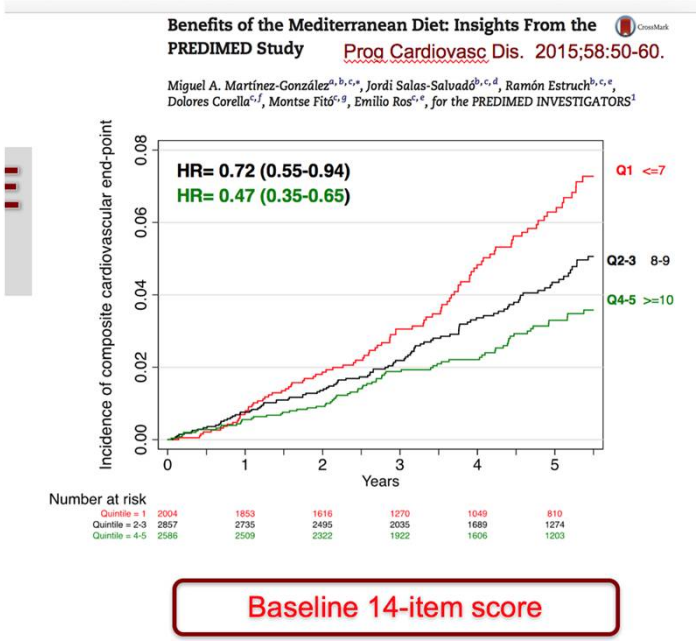
Metabolomic footprints MedDiet

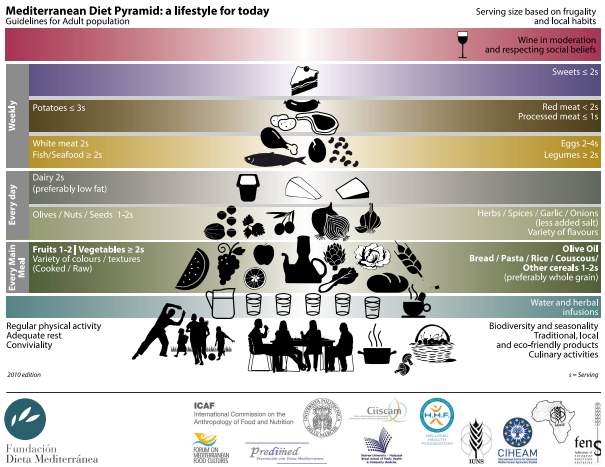
- RCT:
  - **MeDiet+EVOO** vs. Control: discrimination
  - **MeDiet+nuts** vs. Control: discrimination

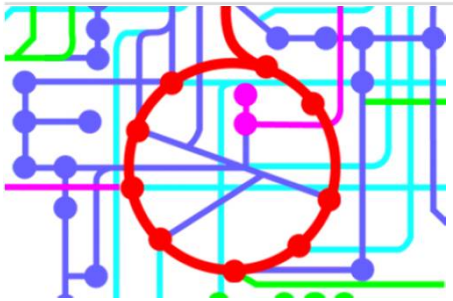


- 14-item screener assessing adherence
  - Baseline
  - Repeated measurements 1-y



- **Food** Frequency questionnaires (0, 1-y)
  - EVOO
  - Nuts





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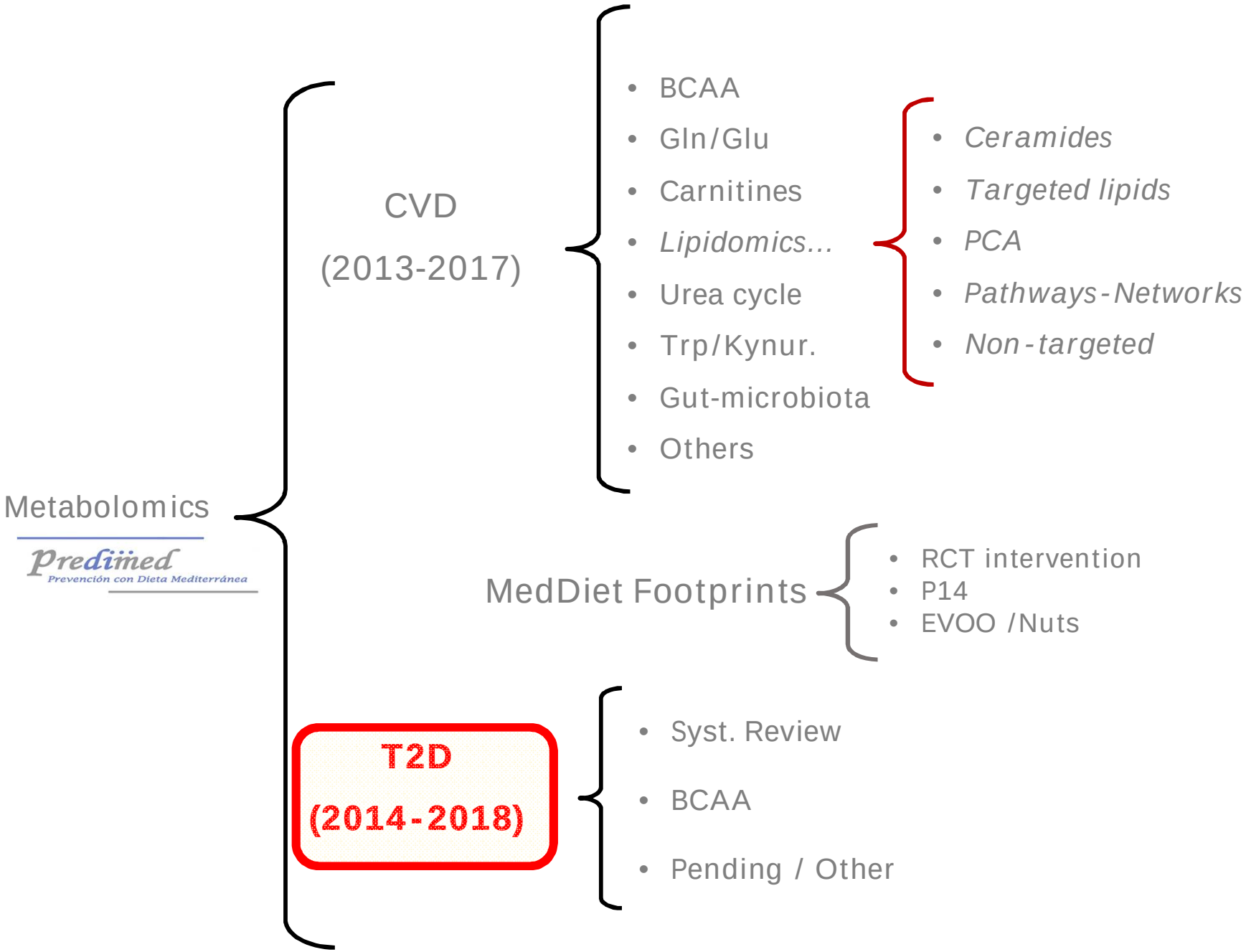
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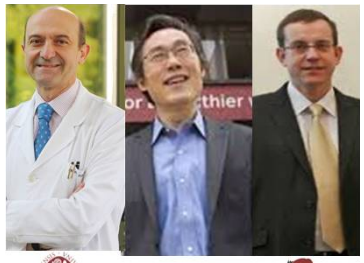
Pathways-Networks
Non-targeted
MedDiet Footprints
RCT intervention
P14
EVOO /Nuts
T2D
(2014-2018)
Syst. Review
BCAA
Pending / Other

Dietary interventions, metabolites and risk of T2D

NIH/NIDDK-R01DK 102896 Sep 1, 2014 – Ago 31, 2018



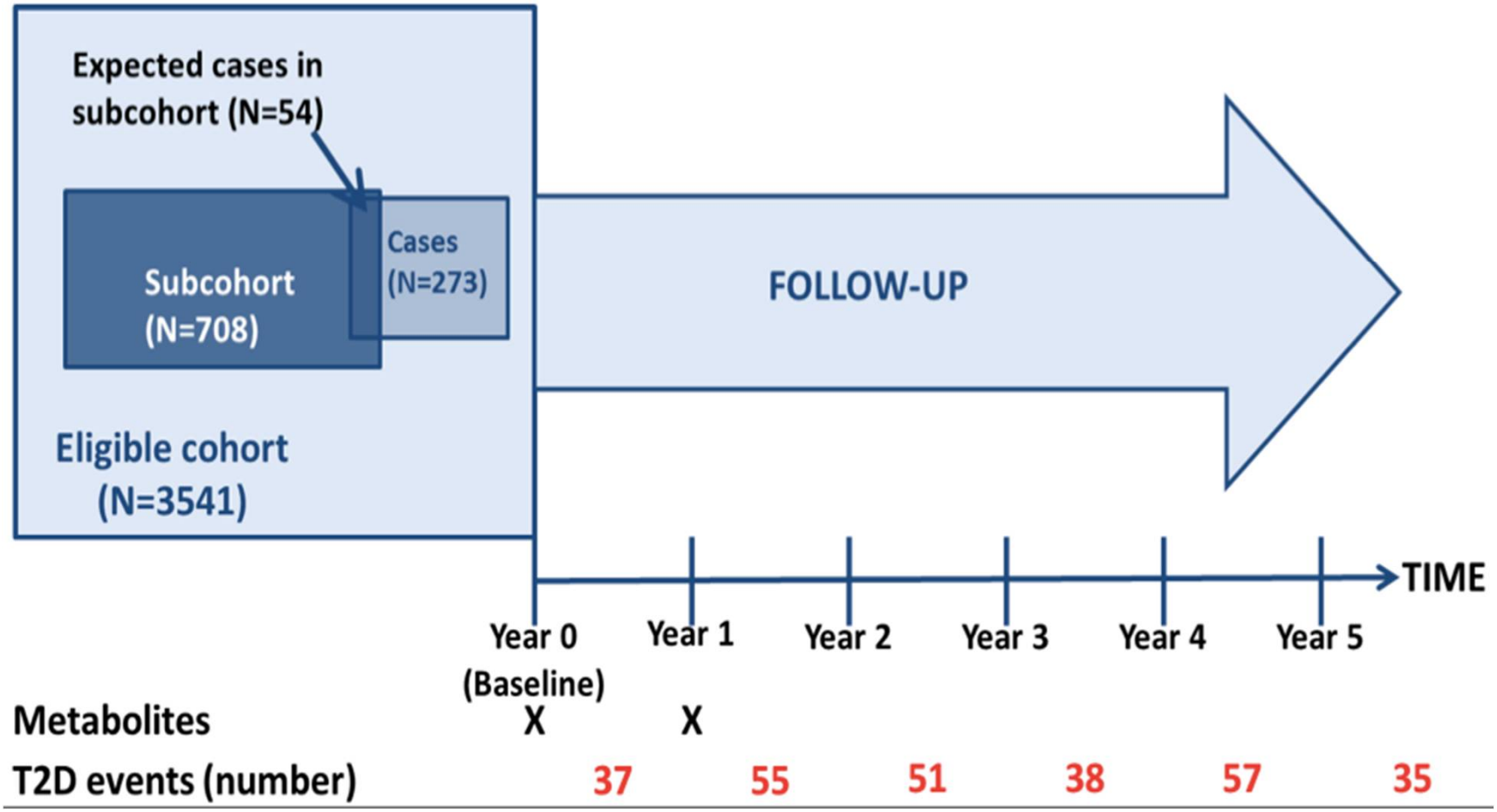
Universidad de Navarra

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH
Powerful ideas for a healthier world

UNIVERSITAT ROVIRA I VIRGILI

Case-cohort study

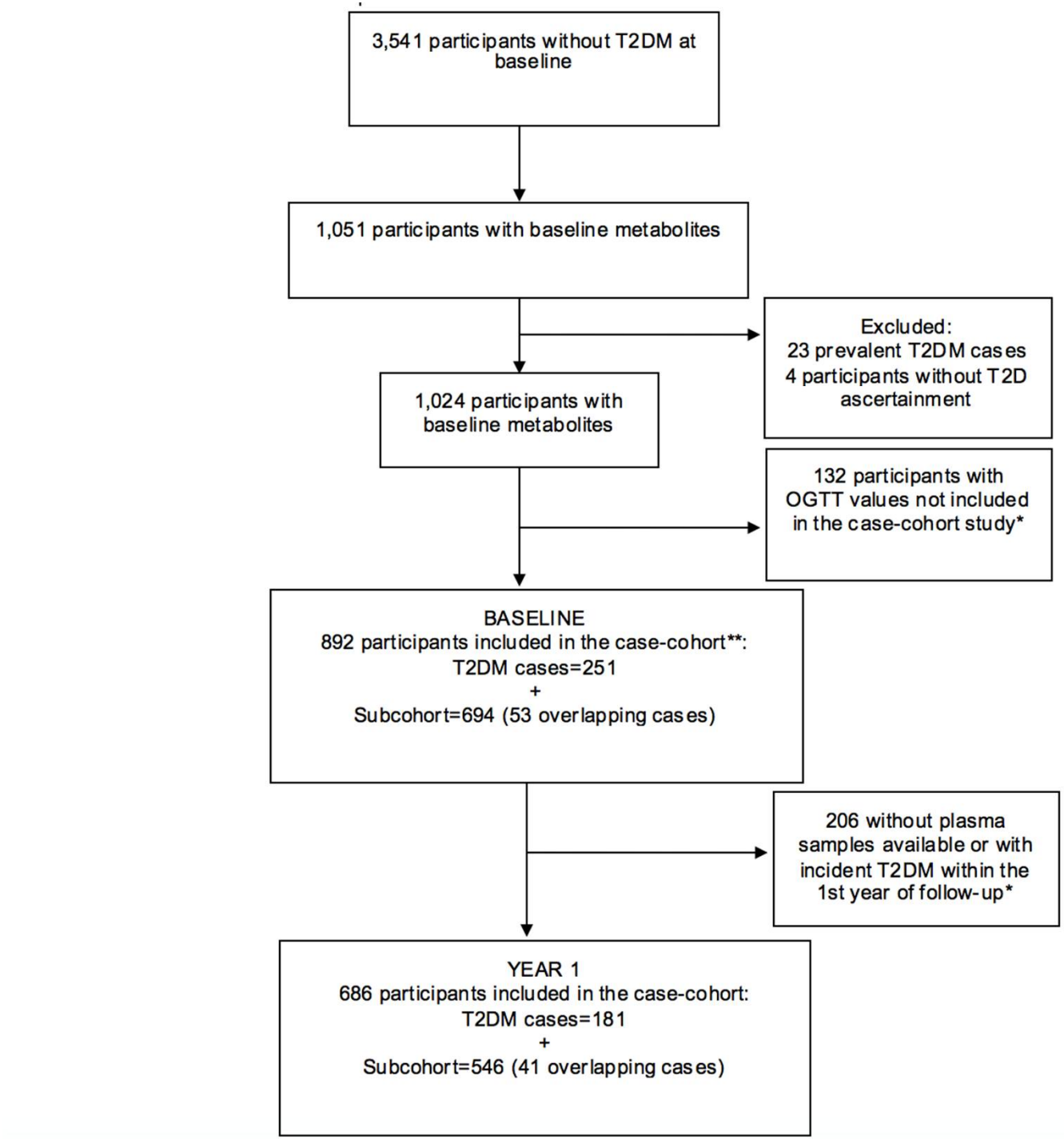
- Baseline metabolites & metabolite 1-y change → T2DM
- MeDiet → Changes in metabolites → ↓T2DM



T2D grant: Specific aims

- Association baseline metabolites & T2D
- Whether the **interventions modify** the effect of baseline metabolites and T2D risk.
- Whether **1-year change** in metabolites **mediate** the effect of the **interventions** on CVD from years 2 to 5.
- Whether **1-year change** in metabolites influence insulin resistance from years 2 to 5 in a subsample of 708 participantes free of T2D

T2D grant


3,541 participants without T2DM at baseline
1,051 participants with baseline metabolites
Excluded:
23 prevalent T2DM cases
4 participants without T2D ascertainment
1,024 participants with baseline metabolites
132 participants with OGTT values not included in the case-cohort study*
BASELINE
892 participants included in the case-cohort**:
T2DM cases=251
+
Subcohort=694 (53 overlapping cases)
206 without plasma samples available or with incident T2DM within the 1st year of follow-up*
YEAR 1
686 participants included in the case-cohort:
T2DM cases=181
+
Subcohort=546 (41 overlapping cases)

Metabolomics

Prediimed
Prevención con Dieta Mediterránea

CVD
(2013-2017)

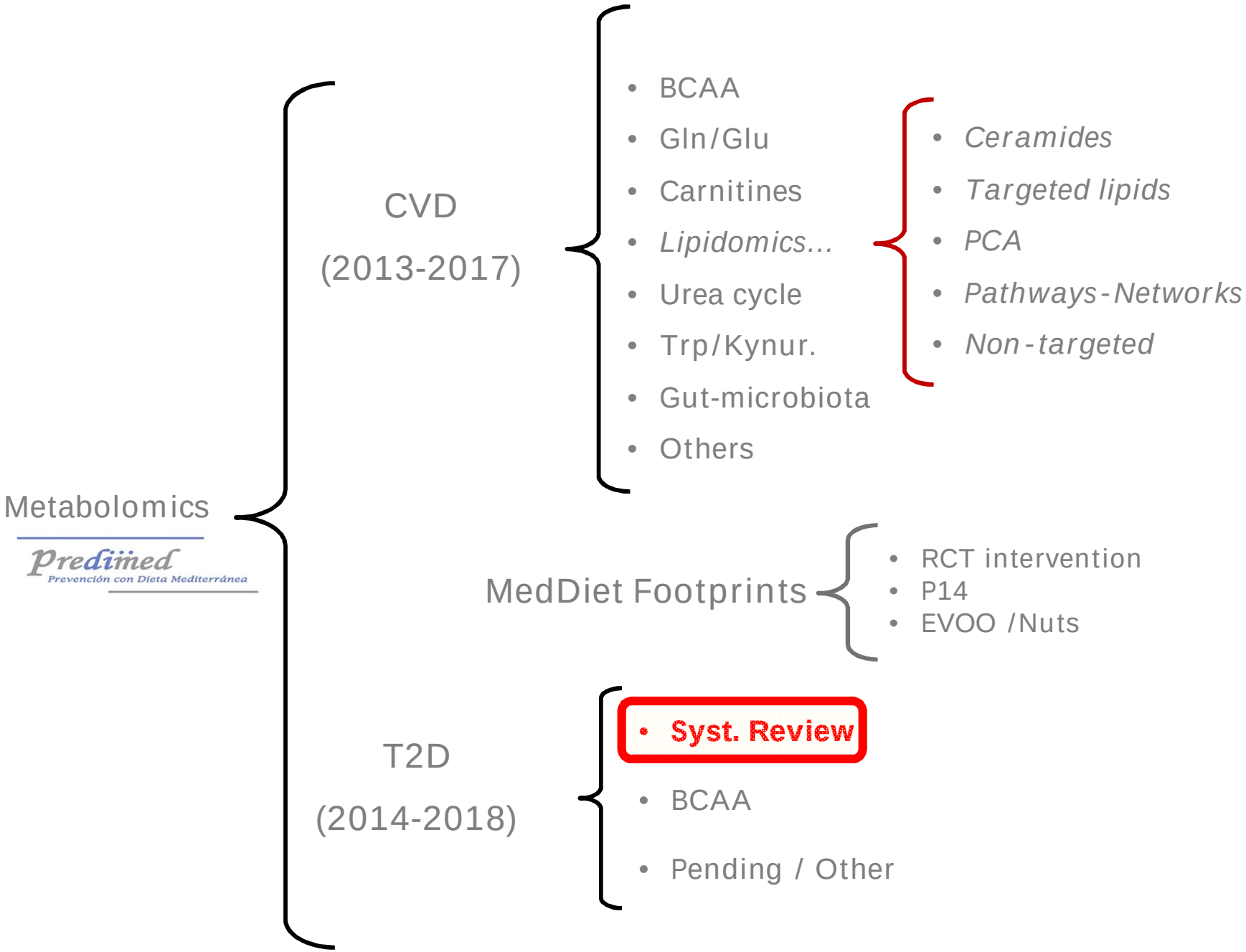
- BCAA
- Gln/Glu
- Carnitines
- *Lipidomics…*
  - *Ceramides*
  - *Targeted lipids*
  - *PCA*
  - *Pathways-Networks*
  - *Non-targeted*
- Urea cycle
- Trp/Kynur.
- Gut-microbiota
- Others

MedDiet Footprints

- RCT intervention
- P14
- EVOO /Nuts

T2D
(2014-2018)

- Syst. Review
- BCAA
- Pending / Other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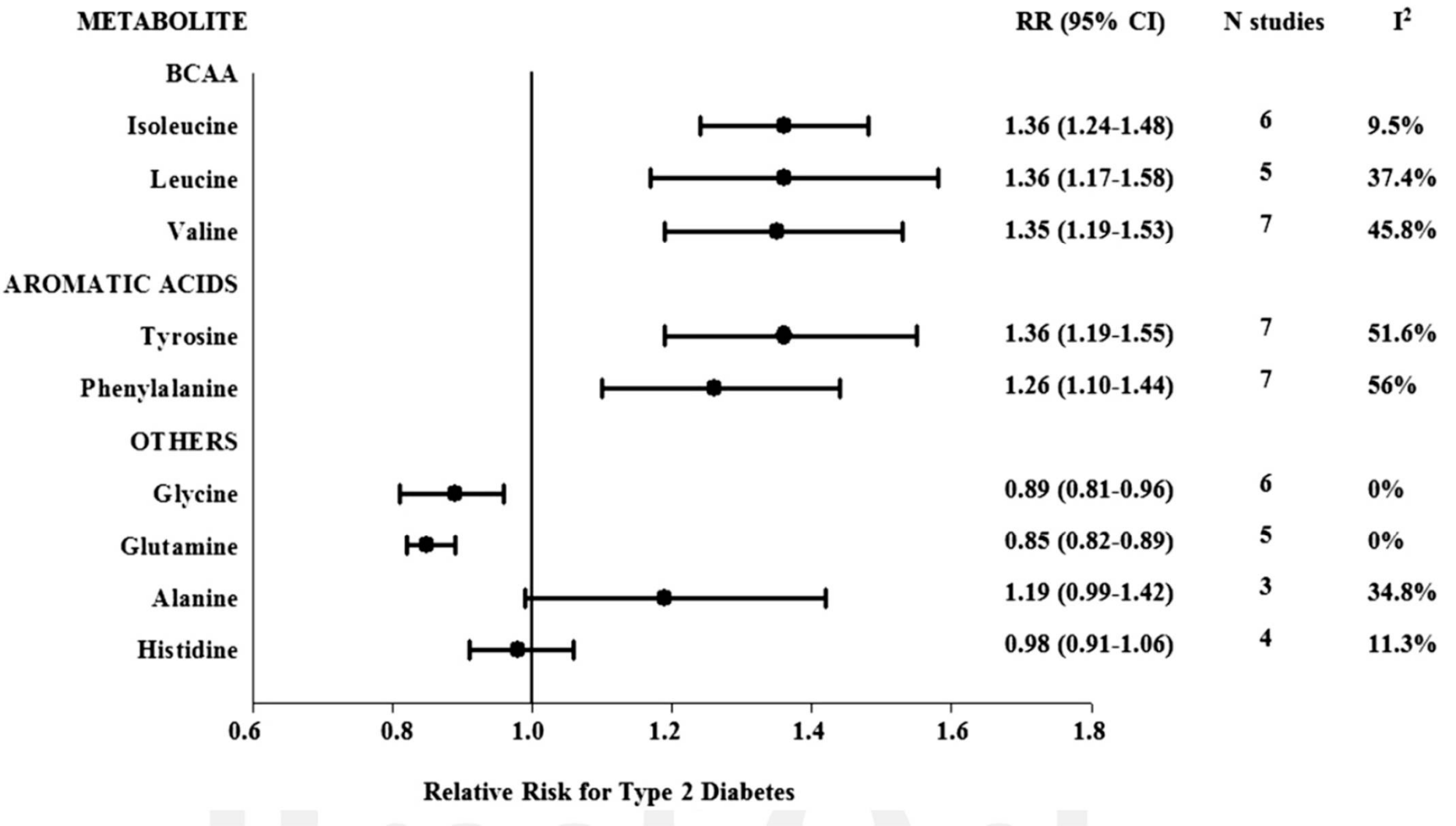
Metabolomics in Prediabetes and Diabetes: A Systematic Review and Meta-analysis

Marta Guasch-Ferré,[1,2,3] Adela Hruby,[1] Estefanía Toledo,[3,4] Clary B. Clish,[5] Miguel A. Martínez-González,[3,4] Jordi Salas-Salvadó,[2,3] and Frank B. Hu[1,6,7]

Diabetes Care 2016;39:833-46



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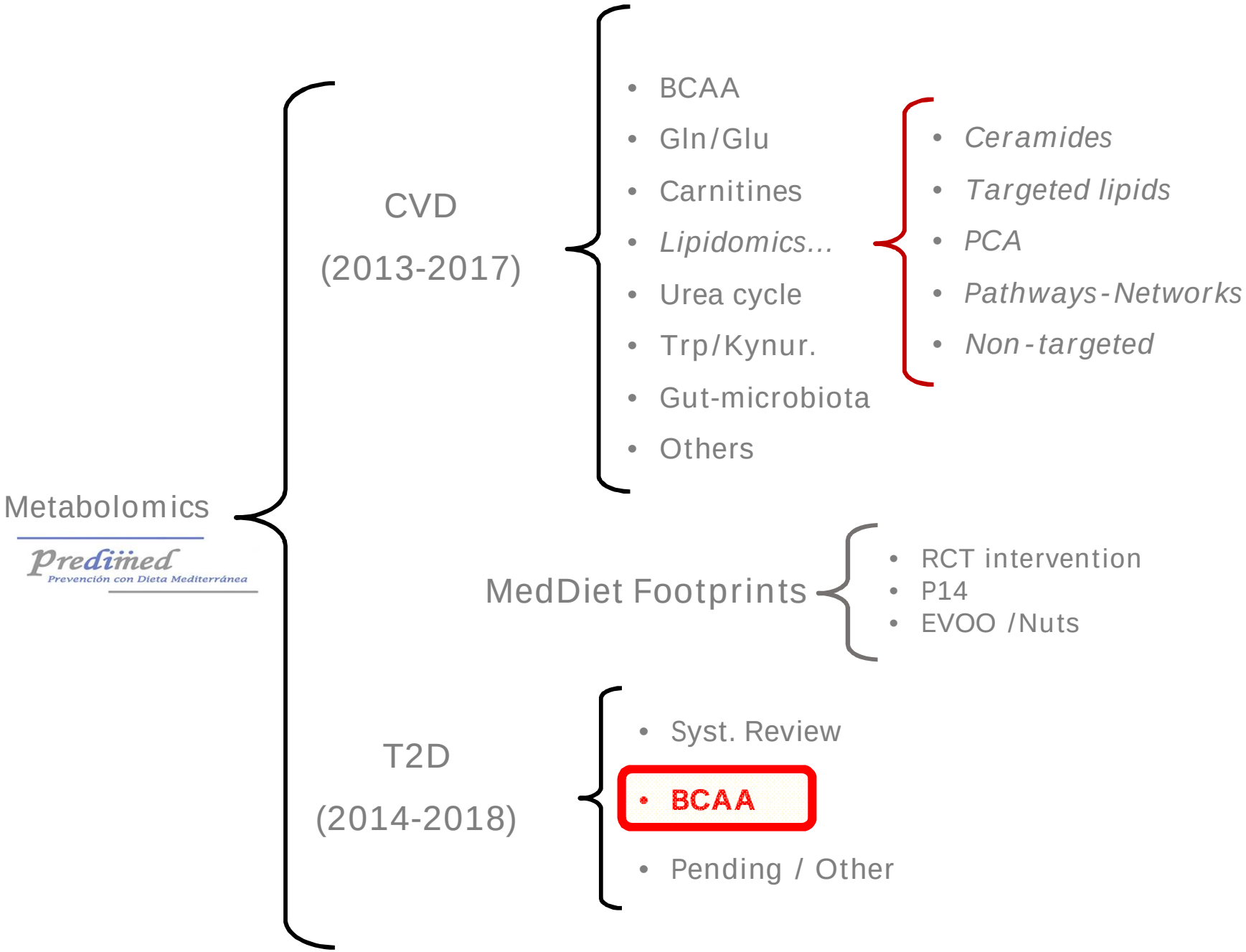
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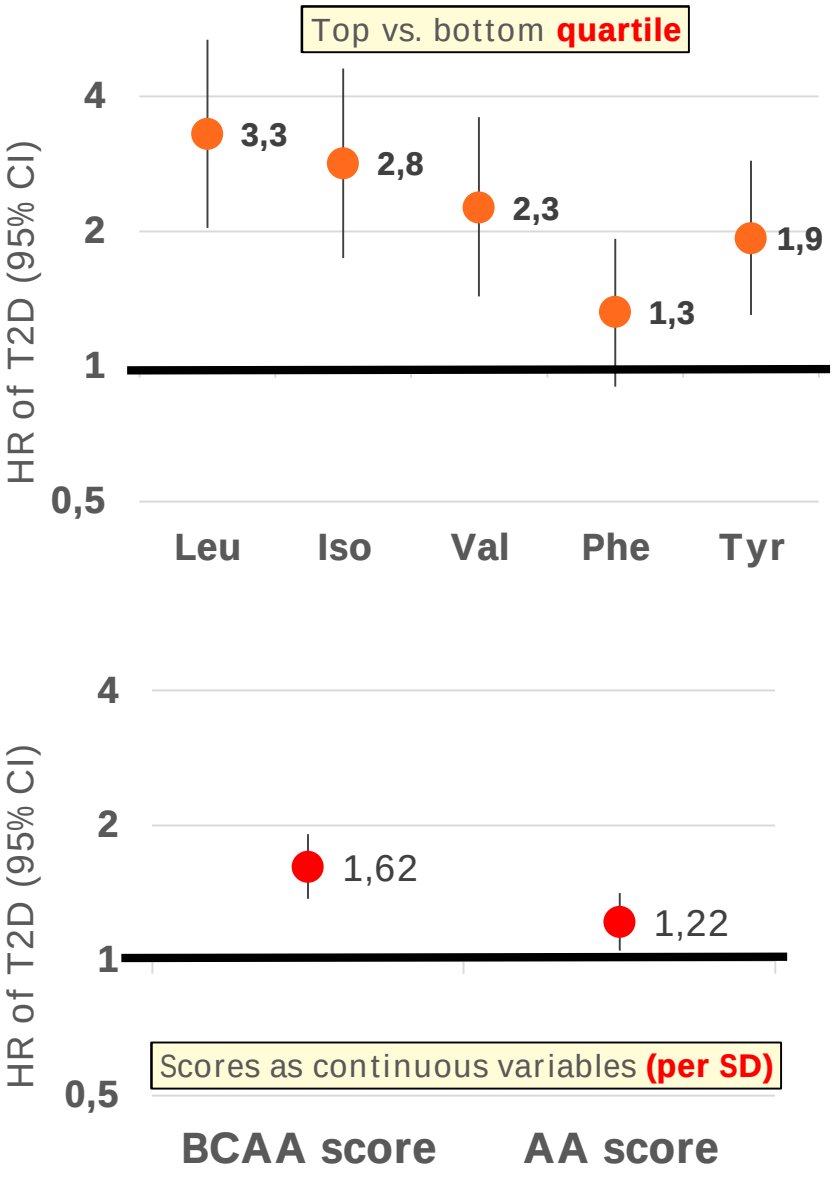
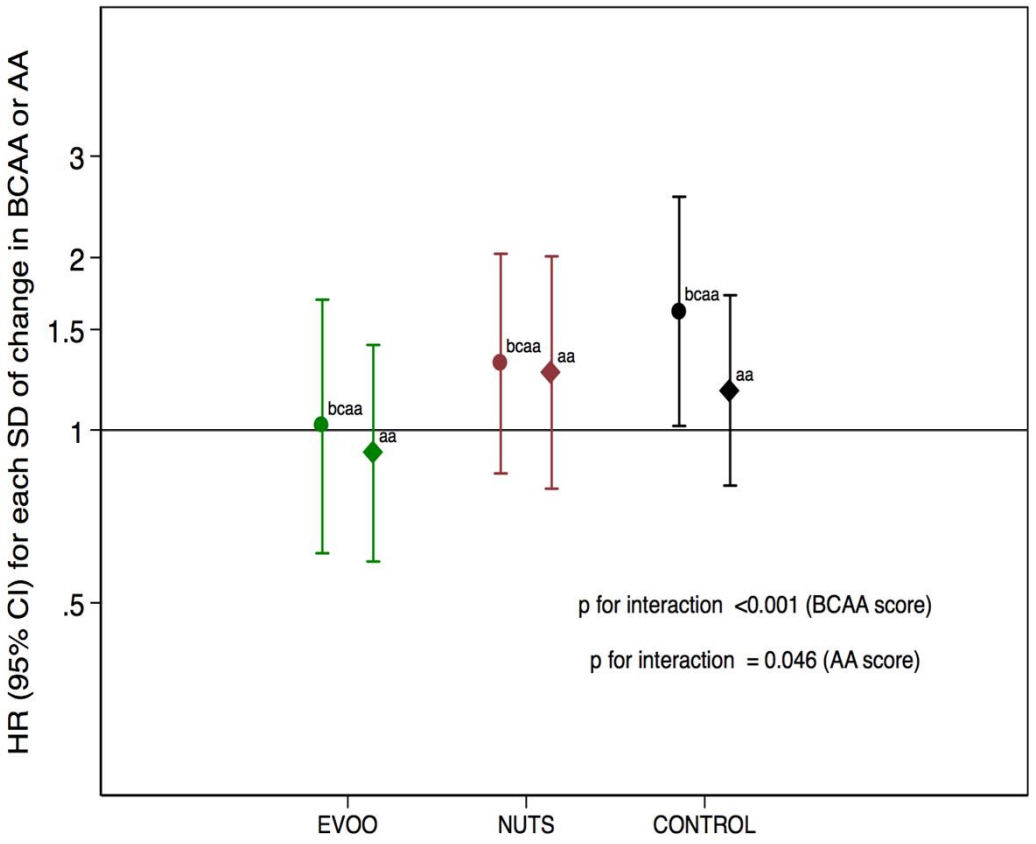
Plasma amino-acids, their changes after a Mediterranean diet intervention and risk of type 2 diabetes: The randomized PREDIMED Trial

Baseline



Working report

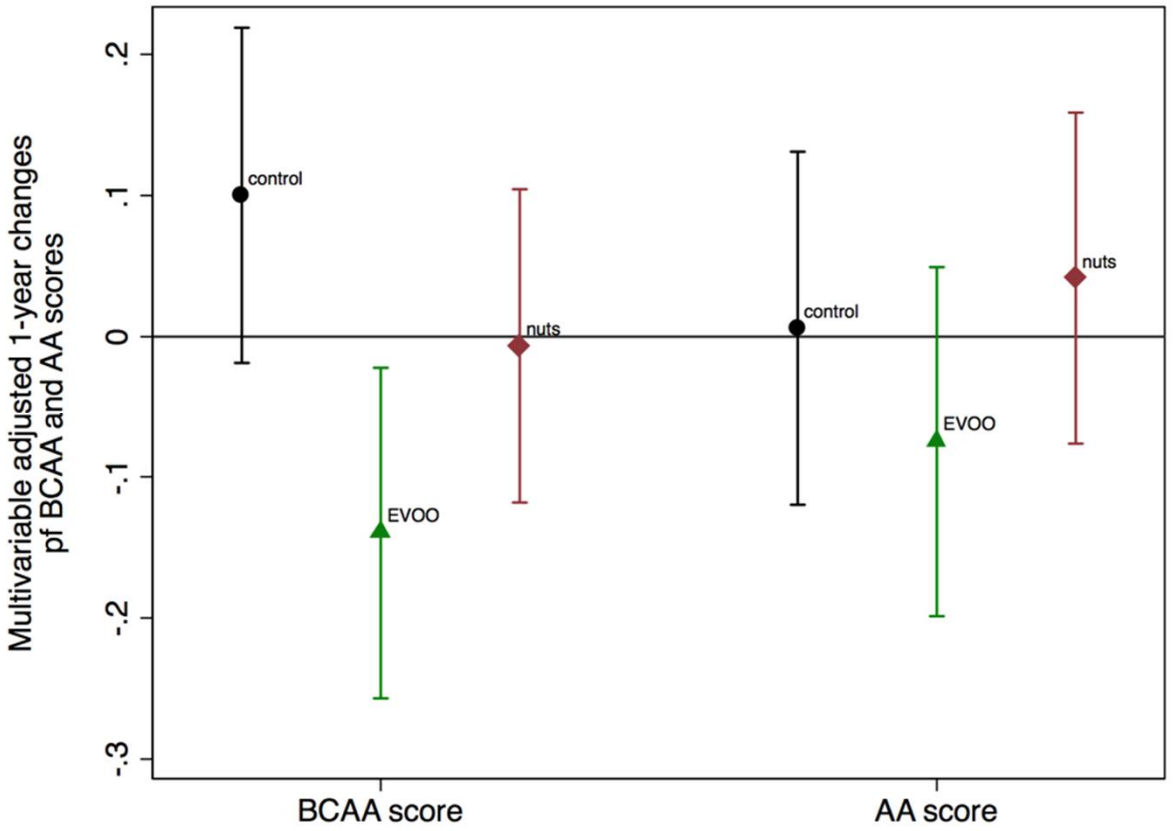


Changes in scores (per SD) and subsequent risk of T2D

Plasma amino-acids, their changes after a Mediterranean diet intervention and risk of type 2 diabetes: The randomized PREDIMED Trial

Changes in BCAA and AA scores after 1 Year of Intervention, by Intervention Group.

Working report



Changes are adjusted for age (years), sex (male, female), body mass index (kg/m2), smoking (never, current, former), leisure-time physical activity (metabolic equivalent tasks in minutes/day), dyslipidemia, hypertension, baseline fasting glucose and baseline BCAA levels.

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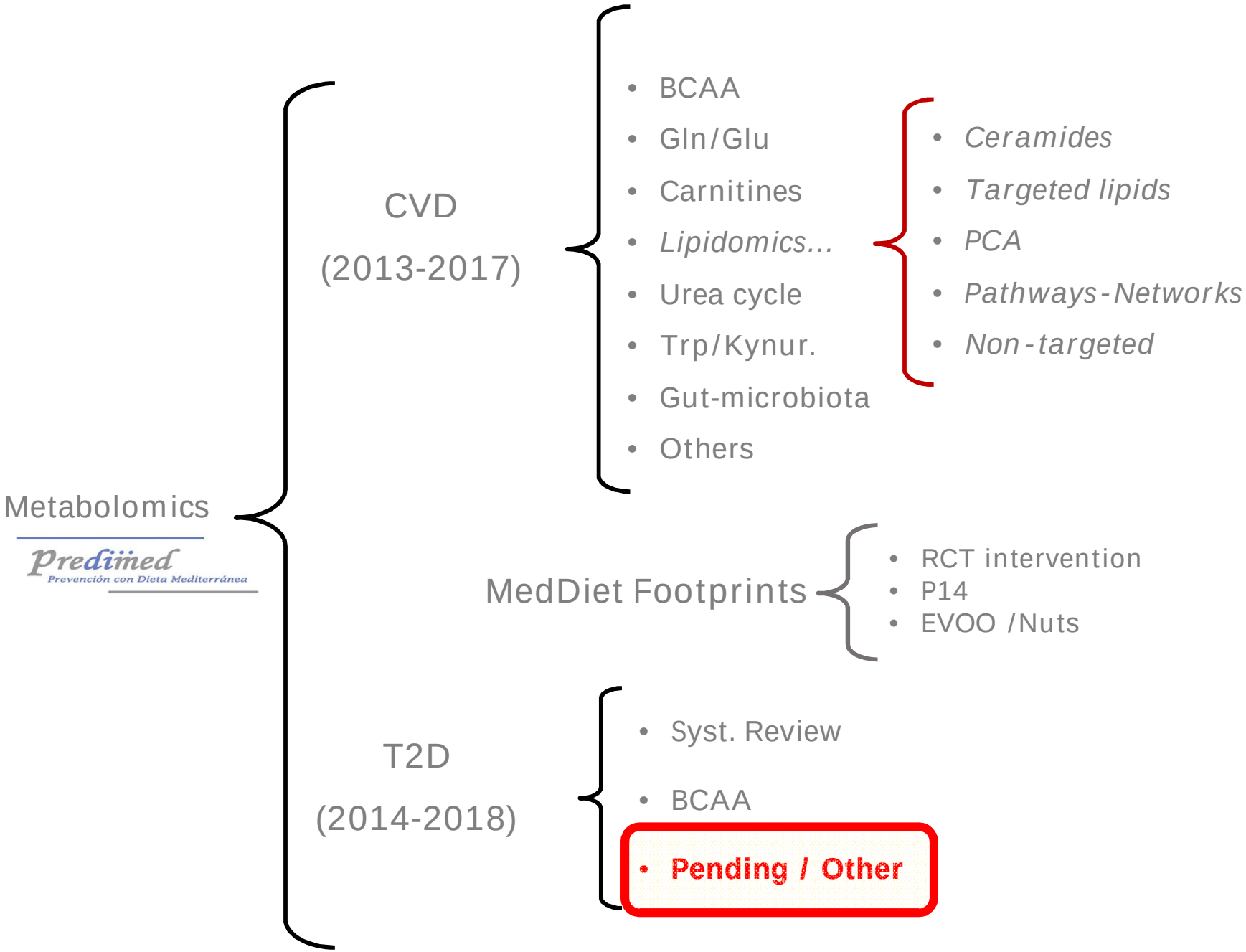
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T2D grant: pending

1. Gut microbiota-related metabolites
2. Acylcarnitines
3. Tryptophan, Kynurenines
4. Urea cycle metabolites
5. Lipidomics, 2-bonds, length
6. Lipids PCA
7. 2-Amino-adipic acid
8. Lactate-glycolysis-gluconeogenesis
9. Purine catabolism
10. Uridine
11. Network-Pathways
12. Glutamine cycling pathway
13. Non-targeted metabolites

To be presented tomorrow

Thank you!

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Miguel A. Martinez-Gonzalez
University of Navarra, Dpt. Preventive Medicine
Dpt. Nutrition Harvard TH Chan School of P. Health

Gln/Glu mechanisms

- Gln and Glu are transformed into each other as part of numerous physiological processes. Cycling between Gln and Glu is regulated by the activity of glutamine synthetase and glutaminase, enzymes that have wide tissue distribuion.
- The proposed mechanisms underlying the beneficial effects of Gln include a wide range of metabolic pathways, such as stimulation of insulin secretion via enhancing release of glucagon-like peptide 1 and improvement in insulin sensitivity.
- Furthermore, Gln has a regulatory capacity in immune cell modulation and has antiobesity and antidiabetic effects.

Acyl-carnitine mechanisms

- meat eaters tend to have increased concentrations of acylcarnitines and other metabolites
- Various short- and long-chain acylcarnitines possess a trimethylamine moiety, and consequently, they are likely to be involved in gut microbe–dependent pathways that contribute to the formation of trimethylamine and trimethylamine-N-oxide, which may increase risk of atherosclerosis and consequently of CVD
- acylcarnitine concentrations have been associated with increased risks of insulin resistance and type 2 diabetes

Acyl-carnitine mechanisms (2)

- The accumulation of acylcarnitines may be indicative of inefficient b oxidation and altered mitochondrial metabolism.
  - Acylcarnitines are derived from both fatty acid and amino acid betaoxidation.
  - The main function of L-carnitine is to transport fatty acids from the cytosol to the mitochondrial matrix where beta oxidation takes place; this process results in the esterification of L-carnitine to form acylcarnitine derivatives
- Advanced age leads to an impaired flux of carnitines through the mitochondrial pathway, thereby reflecting mitochondrial dysfunction.
  - an increased mitochondrial production of reactive oxygen species that enhances vascular inflammation and contributes to alterations in the composition of plaque and to its rupture

Ceramide mechanisms

- precursors of complex sphingolipids
- aberrant accumulation of ceramides may lead to the activation of several signaling and putative targets that impair normal cellular function, including insulin action
- excess de novo ceramide biosynthesis is linked to cellular stress stimuli, especially to the exposure to saturated free fatty acids (FFAs)
- Ceramides have been proposed as an intermediate link between overnutrition and certain underlying abnormalities driving cardiometabolic disease risk, including insulin resistance and low-grade inflammation

Ceramide mechanisms (2)

- Earlier studies using cultured cells and animal models suggested that endogenous ceramides antagonized insulin-stimulated glucose uptake and anabolism by blocking activation of Akt/PKB, a serine/ threonine kinase that is obligate for insulin and growth factor activation of anabolism and cell survival
- human studies have observed positive correlations between plasma ceramide concentrations and inflam-matory makers (eg, interleukin-6 and tumor necrosis factor-α), suggesting a relationship between excess ceramides and inflammation

Ceramide mechanisms (3)

- pharmacological inhibition of ceramide biosynthesis prevents atherogenesis
- Ceramides and other sphingolipids may contribute to plaque erosion and therefore induce thrombosis.
- These studies on plaque formation also found that inhibition of ceramide biosynthesis caused a reduction of circulating total cholesterol and LDL

Lipidome mechanisms

- The detrimental effect of saturation in triacylglycerols may be attributable to the higher atherogenic potential of saturated fats
- cholesterol esters, with longer and more unsaturated acyl chains associated with lower the risk of CVD is consistent with a lower diabetes risk observed by Rhee et al., although the association they observed disappeared after multivariable adjustment J Clin Invest. 2011;121:1402–1

Lipidome mechanisms (2)

- Phosphatidylcholines are membrane lipids that are the most abundant lipids in mammal plasma membranes. If phosphatidylcholines with shorter chains and more highly saturated acyl chains are available, this could confer less fluidity to the cell membranes
- long-chain fatty acids, with many carbon atoms and many double bonds (i.e. long-chain PUFA), mainly omega-3 PUFAs, are associated with reduced triglyceride levels, reduced myocardial oxygen demands and beneficial changes in endothelial function, together with reduced heart rate (and lower heart rate variability) and decreased blood pressure

Lipidome mechanisms (3)

- SFA with a lower number of carbon atoms (16:0) are known to exert more detrimental effects on lipids and cardiovascular disease than those with a higher number of carbon atoms (18.0) (Zong et al, BMJ 206;355:i5796).
- Long-chain PUFA are also precursors to bioactive lipid metabolites, including specialized pro-resolving mediators and cytochrome P450–generated monoepoxides (Arnold et al, Pharmacol Rep 2010;62:536; Serhan. Am J Pathol 2010;177:1576)
- hydroxy-phosphatidylcholines can be formed as adducts under conditions of oxidative stress and/or inflammation and may be components of oxidized LDL, thus increasing the risk of CVD

Urea cycle mechanisms

- The Framingham Offspring cohort reported a significantly lower risk of CVD associated with the arginine/ADMA ratio
- A meta-analysis of 22 prospective cohort studies with a mean follow-up time of 7.1 years reported a robust association between ADMA concentrations and higher risk of subsequent CVD events (Willeit et al, J Am Heart Assoc 2015;4:e001833)
- High ADMA in concert with low NO has been reported to propagate a variety of harmful detrimental processes biologically related to atherosclerosis:free radical generation, smooth cell proliferation, systemic inflammation, and endothelial dysfunction

Urea cycle mechanisms (2)

- Arginine (and only L-arginine) is the required substrate for all isoforms of the enzyme NOS to produce NO
- NO is acknowledged as a powerful short-life vasodilator with an important defensive role against ischemic disease through endothelial smooth muscle relaxation
- Inhibition of arginase, a competitive inhibitor of arginine, improves vascular integrity, and protects against ischemia-induced injury
-

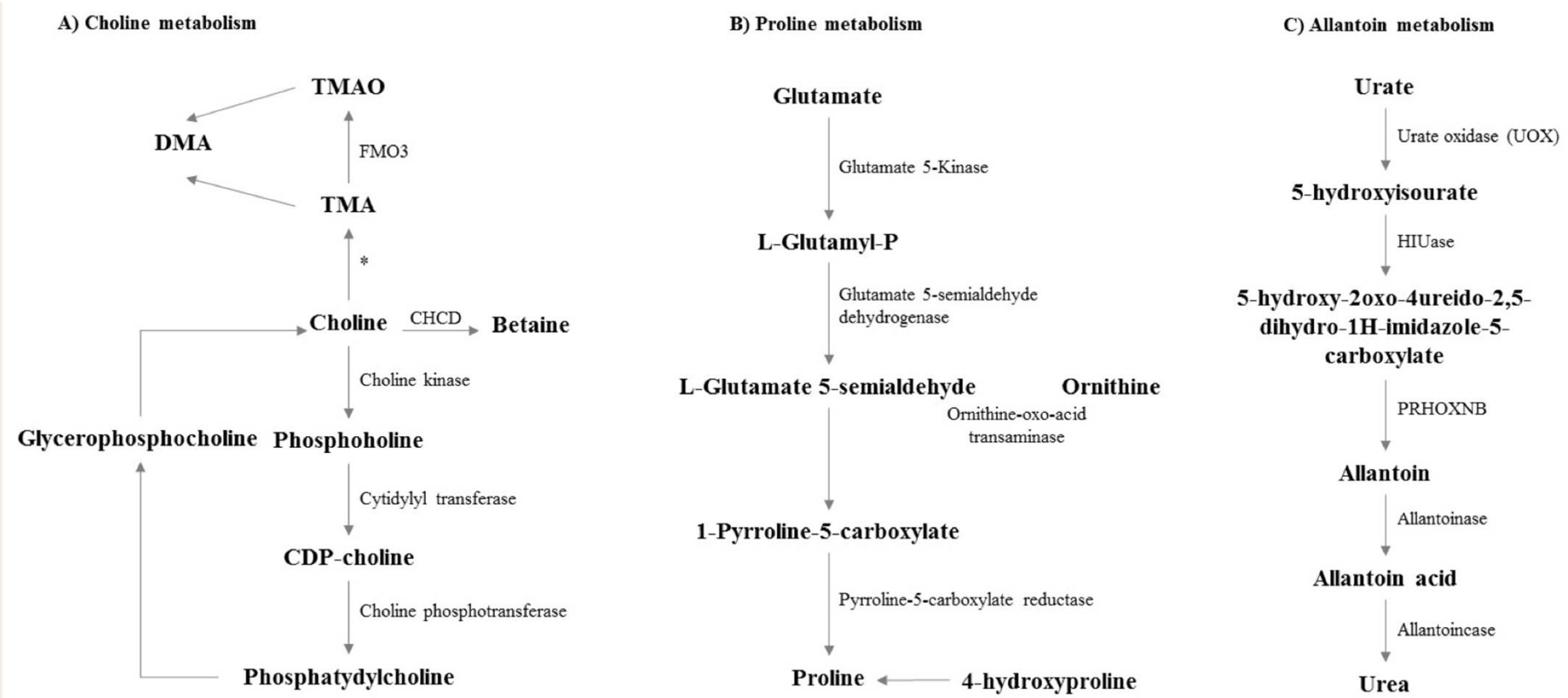
TRP/KYN mechanisms

- Indoleamine 2,3-dioxygenase (IDO), an enzyme catalyzing the rate-limiting step in the **kynurenine** pathway of **tryptophan** degradation, is strongly induced by inflammation in several tissues, including the artery wall
- IFN-gamma plays a central role in the activation of IDO and subsequent degradation of tryptophan
- however, activation of the kynurenine pathway has also been shown to have anti-inflammatory effects.
- activation of the tryptophan-kynurenine pathway may be a compensatory mechanism to, rather than a cause of, inflammation and cardiovascular dysfunction.

TRP/KYN mechanisms (2)

- Treatment of human peripheral blood mononuclear cells and monocyte-derived macrophages with IFN-g attenuated the extent of LDL oxidation, and tryptophan degradation in concert with 3-HAA formation was instrumental in this inhibitory effect.
- 3-HAA has also been independently identified as having antiatherogenic properties by regulating lipid me- tabolism and inflammation.
- Other experimental studies suggest a beneficial effect of IDO on the vasculature.
- IDO-deficient mice fed high-fat diets showed marked increases in F4/80 and TNF mRNA concentrations, as well as greater hepatic inflammation compared with control mice

Gut-microbiota related metabolites



The figure shows key metabolic pathways of choline, proline and allantoin. *Bacterial degration of choline by the gut microbiota. FMO3 indicates, Flavin-containing monoxygenase; CHCD, choline dehydrogenase; HIUase, 5-hydroxyisourate hydrolase; PRHOXNB, parahox neighbor B.

Gut-microbiota related metabolites (2)

- Alterations in the gut microbiome have been previously related to multifactorial diseases such as obesity, T2D and CVD, probably through several mechanisms including
    - modulation of host energy metabolism
    - gut epithelial permeability
    - gut peptide hormone secretion
    - and increasing metabolic endotoxemia and inflammatory status.
- However, the association between plasma gut microbiota related metabolites, identified using novel high-throughput metabolomics techniques, and the incidence of CVD in a population-based level have only recently been reported.

Gut-microbiota related metabolites (3)

- dietary phosphatidylcholine/choline can be converted by the intestinal microbiota into trimethylamine and subsequently converted into TMAO by hepatic flavin-containing monooxigenases and TMAO has been linked with CVD pathogenesis
- in vivo and in vitro studies suggestthat choline metabolites may increase the risk of atherosclerosis and coronary heart disease
- The ability of oral broad-spectrum antibiotics to temporarily suppress the production of TMAO suggests that intestinal microorganisms may play an important role in the production of TMAO from phosphatidylcholine in humans