Current status of CVD & T2D metabolomics projects in the PREDIMED

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Dpt. Nutrition Harvard TH Chan School of P. Health


Good
News

Clinical Chemistry 62:4
582-592 (2016)

Lipids, Lipoproteins, and Cardiovascular Risk Factors

Clin Chem. 2016;62:582-92

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*]

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]**

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

J Nutr. 2016 [epub ahead of

The Journal of Nutrition
Supplement—Frontiers in Personalized and Community Nutrition:
9th Meeting on Nutrition Updates at UNAV

Protective Effects of the Mediterranean Diet on Type 2 Diabetes and Metabolic Syndrome[1–3]

Jordi Salas-Salvadó,[4,5]* Marta Guasch-Ferré,[4,5] Chih-Hao Lee,[6] Ramón Estruch,[5,7] Clary B Clish,[8] and Emilio Ros[5,9]

The Journal of Nutrition. First published ahead of print March 9, 2016 as doi: 10.3945/jn.115.219147.
The Journal of Nutrition
Supplement—Frontiers in Personalized and Community Nutrition:
9th Meeting on Nutrition Updates at UNAV

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,[5] Liming Liang,[7] Antonia Trichopoulou,[8] and Frank B Hu[6,7]

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

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]*

J Nutr. Mar 2017;147(3):314-22

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

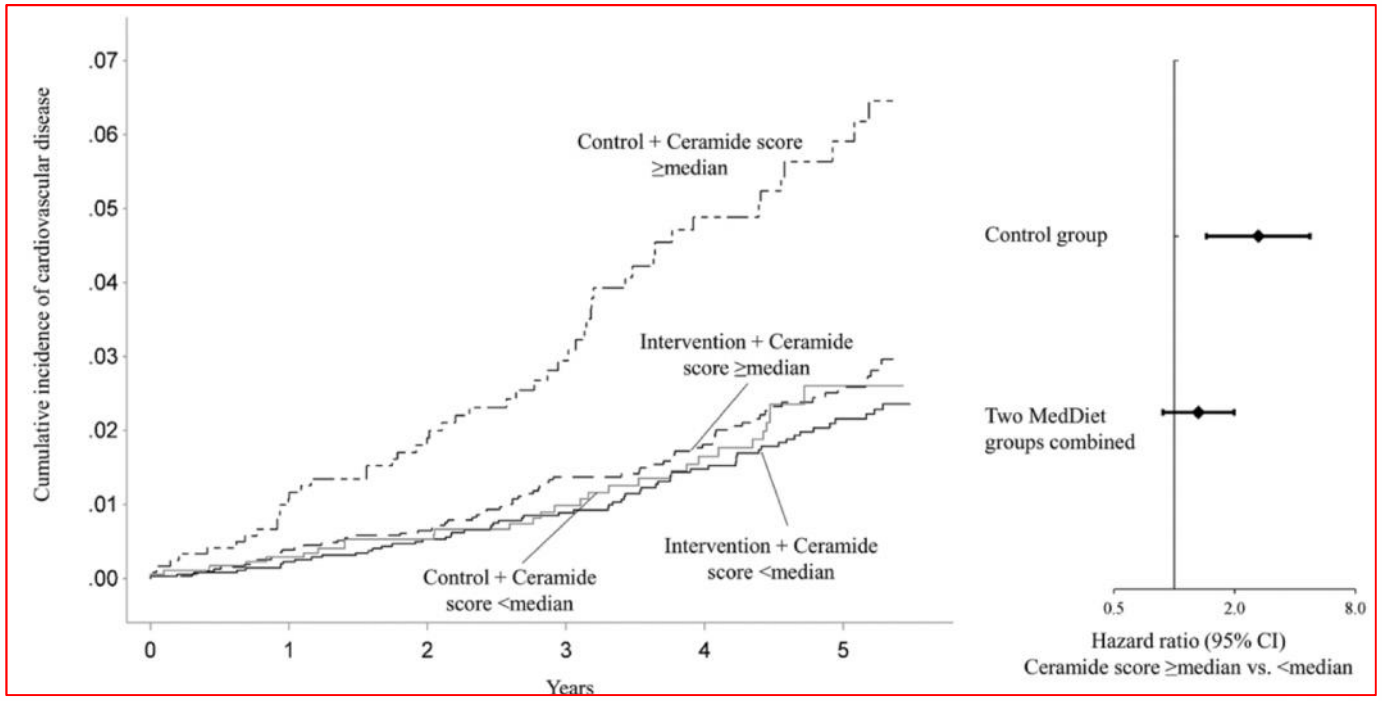
Edward Yu,[1] Miguel Ruiz-Canela,[2,3] Frank B. Hu,[1,4,5] Clary B. Clish,[6] Dolores Corella,[3,7] Jordi Salas-Salvadó,[3,8] Adela Hruby,[9] Montserrat Fitó,[3,10] Liming Liang,[11] Estefania Toledo,[2,3] Emilio Ros,[3,12] Ramón Estruch,[3,13] Enrique Gómez-Gracia,[3,14] Jose Lapetra,[3,15] Fernando 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
[epub ahead of print]

ORIGINAL RESEARCH ARTICLE

Plasma Ceramides, Mediterranean Diet, and Incident Cardiovascular Disease in the PREDIMED Trial (Prevención con Dieta Mediterránea)

Circulation. 2017;135:2028–2040.



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Correspondence to: Frank B. Hu, MD, PhD, 665 Huntington Avenue, Boston, MA 02115. E-mail nhbfh@channing.harvard.edu

Good NEWS!

Miguel Ruiz-Canela

Marta Guasch-Ferré

Monica Bulló

Estefania Toledo

Edward Yu

Daniel Wang

Yan Zheng

Liming Liang

Cristina Razquin

C. Papandreou

Monthly conference calls

Starting on March 28, 2014

PREDIMED Metabolomics Conference Call

Date	Friday, 28 March 2014
Time	9:30 ET US, 14:30 Spain (call duration approximately 1 hr 15 minutes)
Attendees	Frank Hu, Co-PI Clary Clish, Director of Metabolite Profiling Miguel Angel Martinez-Gonzalez, Co-PI Miguel Ruiz-Canela, Project Coordinator Estefania Toledo, Project Coordinator Cristina Razquin Marta Guasch Adela Hruby, Project Coordinator

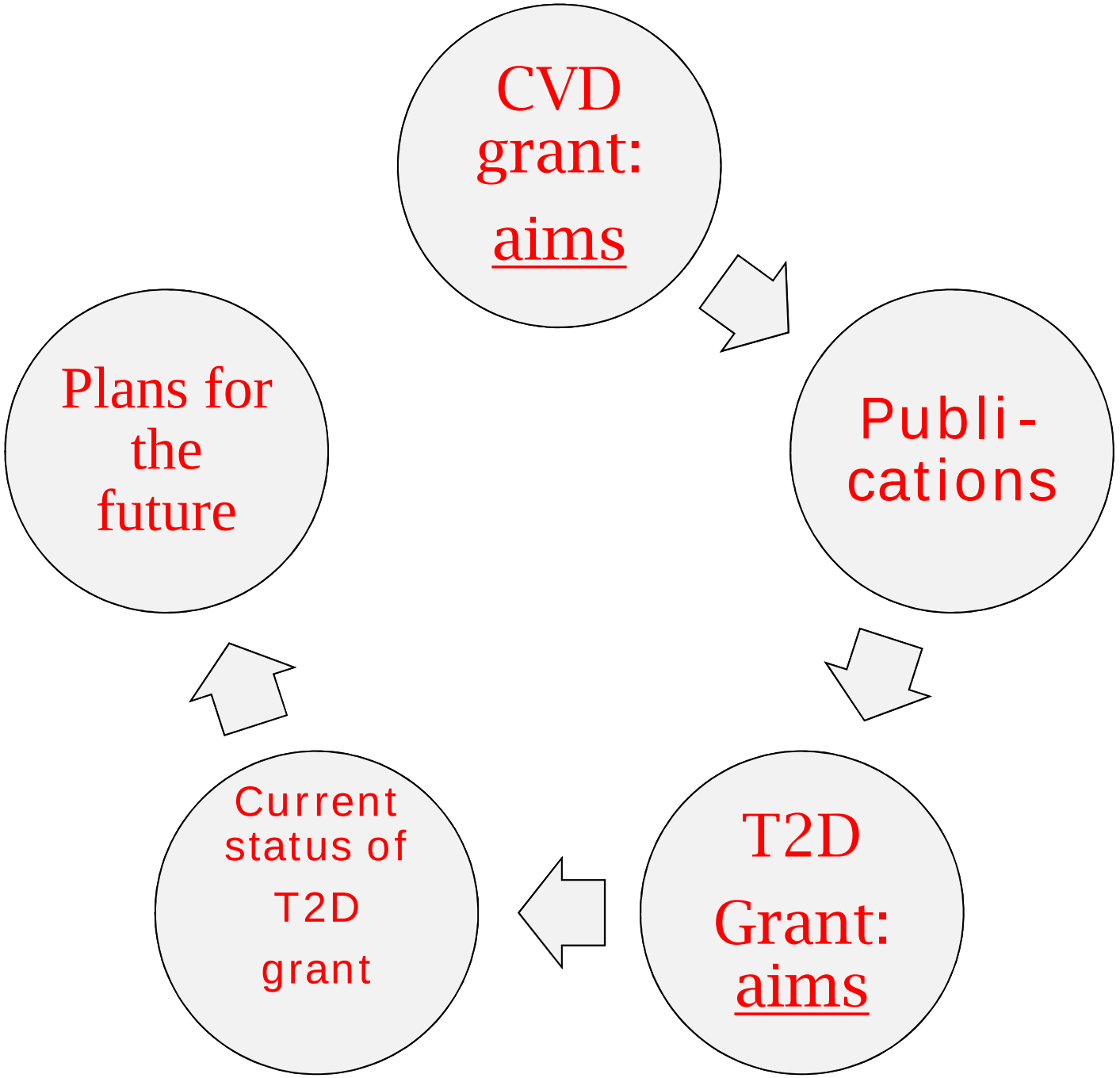
Ensuing conference calls

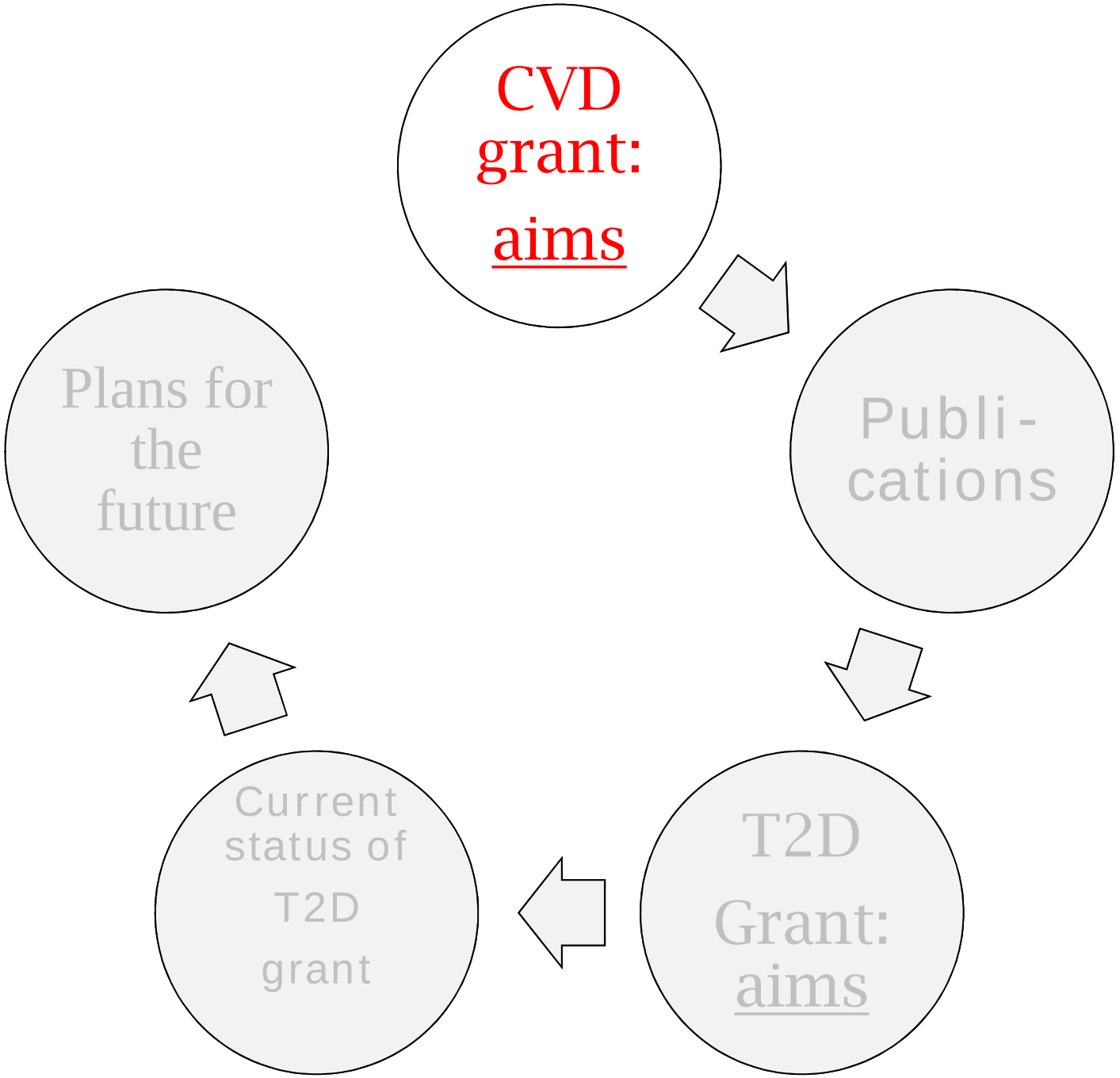
2.	Date: 2 May 2014	Time: 9:30 ET US, 15:30 Spain
3.	Date: 13 June 2014	Time: 9:30 ET US, 15:30 Spain
4.	Date: 2 September 2014	Time: 9:30 ET US, 15:30 Spain
5.	Date: 13 October 2014	Time: 9:30 ET US, 15:30 Spain
6.	Date: 1 December 2014	Time: 9:30 ET US, 15:30 Spain
7.	Tuesday, 13 January 2015	11:00 ET US, 17:00 Spain
8.	Tuesday, 10 February 2015	11:00AM Boston / 17:00 Spain
9.	Tuesday, 17 March 2015	11:00AM Boston / 16:00 Spain
10.	**16:00 due to earlier “spring ahead” time change in US	
11.	Tuesday, 14 April 2015	Time: 11:00AM Boston / 17:00 Spain
12.	Tuesday, 12 May 2015	Time: 11:00AM Boston / 17:00 Spain
13.	Tuesday, 30 June 2015	Time: 11:00AM Boston / 17:00 Spain
14.	Wednesday, 15 July 2015	Time: 11:00AM Boston / 17:00 Spain
15.	Monday, 17 August 2015	11:00AM Boston / 17:00 Spain
16.	**Acknowledging that many of us will be on holiday	
17.	Tuesday, 15 September 2015	11:00AM Boston / 17:00 Spain
18.	Tuesday, 13 October 2015	11:00AM Boston / 17:00 Spain
19.	Tuesday, 10 November 2015	11:00AM Boston / 17:00 Spain
20.	Tuesday, 15 December 2015	11:00AM Boston / 17:00 Spain
21.	January 26, 2016	9:00AM Boston / 15:00 Spain
22.	February 23, 2016	9:00AM Boston / 15:00 Spain
23.	March 15, 2016	9:00AM Boston / 14:00 Spain**
24.	April 19, 2016	9:00AM Boston / 17:00 Spain
25.	May 24, 2016	9:00AM Boston / 17:00 Spain
26.	June 21, 2016	9:00AM Boston / 17:00 Spain
27.	July 26, 2016	9:00AM Boston / 17:00 Spain
28.	August 23, 2016	9:00AM Boston / 17:00 Spain
29.	September 27, 2016	9:00AM Boston / 17:00 Spain
30.	October 25, 2016	9:00AM Boston / 17:00 Spain
31.	November 22, 2016	9:00AM Boston / 17:00 Spain
32.	December 20, 2016	9:00AM Boston / 17:00 Spain

33.	January 24, 2017	9:00AM Boston / 15:00 Spain
34.	February 21, 2017	9:00AM Boston / 15:00 Spain
35.	March 21, 2017	9:00AM Boston / 14:00 Spain
36.	April 25, 2017	9:00AM Boston / 15:00 Spain

SYMPOSIUM

June 20, 2017	9:00AM Boston / 15:00 Spain
July 25, 2017	9:00AM Boston / 15:00 Spain
August 22, 2017	9:00AM Boston / 15:00 Spain
Sept. 26, 2017	9:00AM Boston / 15:00 Spain
October 24, 2017	9:00AM Boston / 15:00 Spain
Nov. 21, 2017	9:00AM Boston / 15:00 Spain
Dec. 19, 2017	9:00AM Boston / 15:00 Spain


CVD grant: aims
Publi-cations
T2D Grant: aims
Current status of T2D grant
Plans for the future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Plans for the future

Mediterranean diet, Metabolites, and Cardiovascular Disease

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

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Powerful ideas for a healthier world

Universidad de Navarra

Case-cohort study

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

	Year 0 (Baseline)	Year 1	Year 2	Year 3	Year 4	Year 5
Metabolites	X	X				
Intermediate CVD risk factors	X	X	X	X	X	X
CVD events (number)	49	45	57	48	45	44

TIME

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DOG

CVD grant: Specific aims

1. To examine the effects of the randomized dietary interventions on changes in plasma levels of metabolites from baseline to year 1 in 745 randomly selected trial participants

CVD grant: Specific aims

2. To examine whether 1-year changes in plasma levels of metabolites mediate the effect of the randomized dietary interventions on subsequent clinical CVD outcomes from years 2 to 5, using the efficient case-cohort design

CVD grant: Specific aims

3. To examine whether baseline metabolite levels modify the effects of the randomized dietary interventions on CVD risk, using a case-cohort design.

CVD grant: Specific aims

As a secondary aim, we will examine whether 1-year changes in metabolites mediate the benefits of dietary interventions on subsequent occurrence of the metabolic syndrome, among 745 randomly selected trial participants

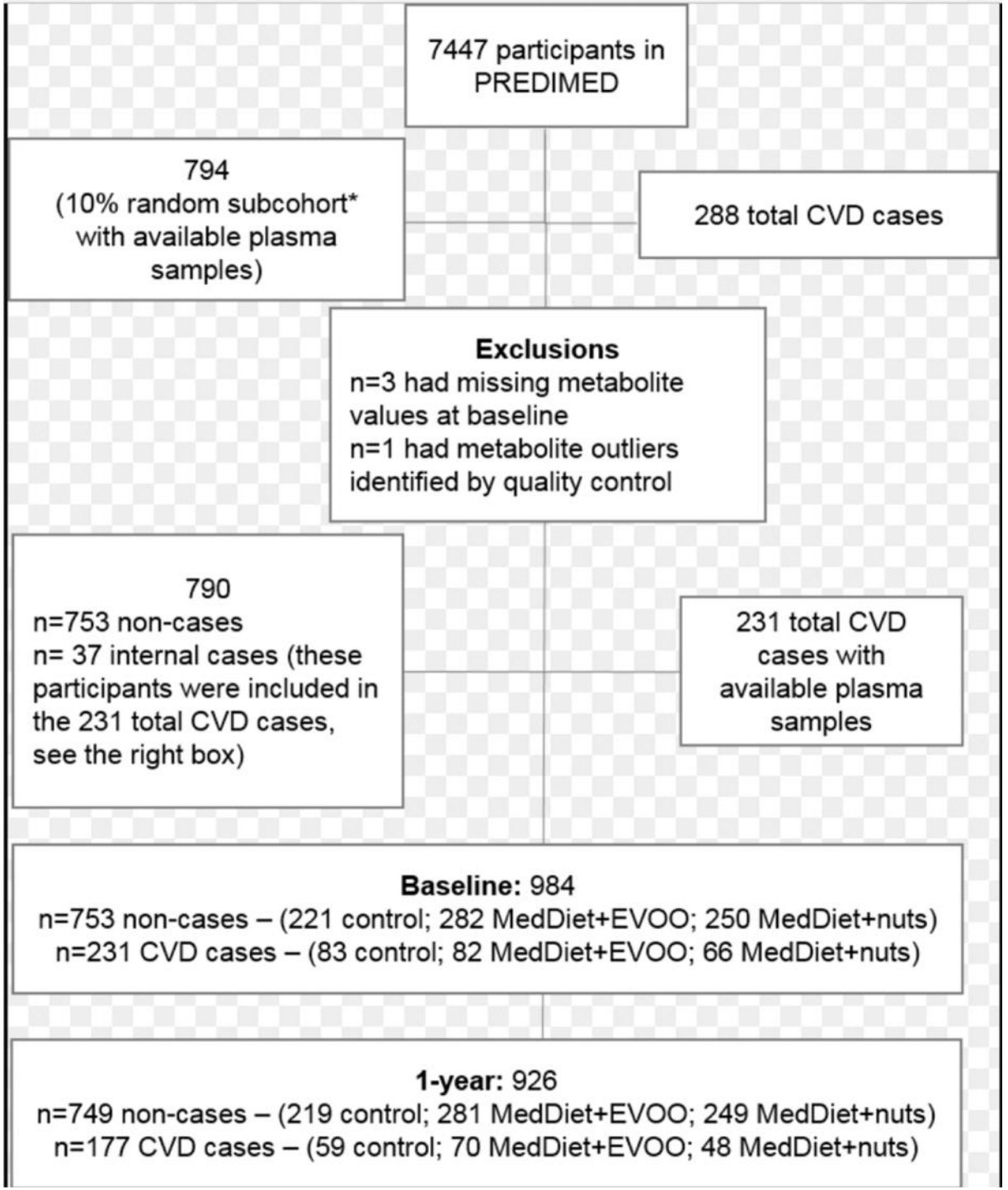
CVD grant: Specific aims

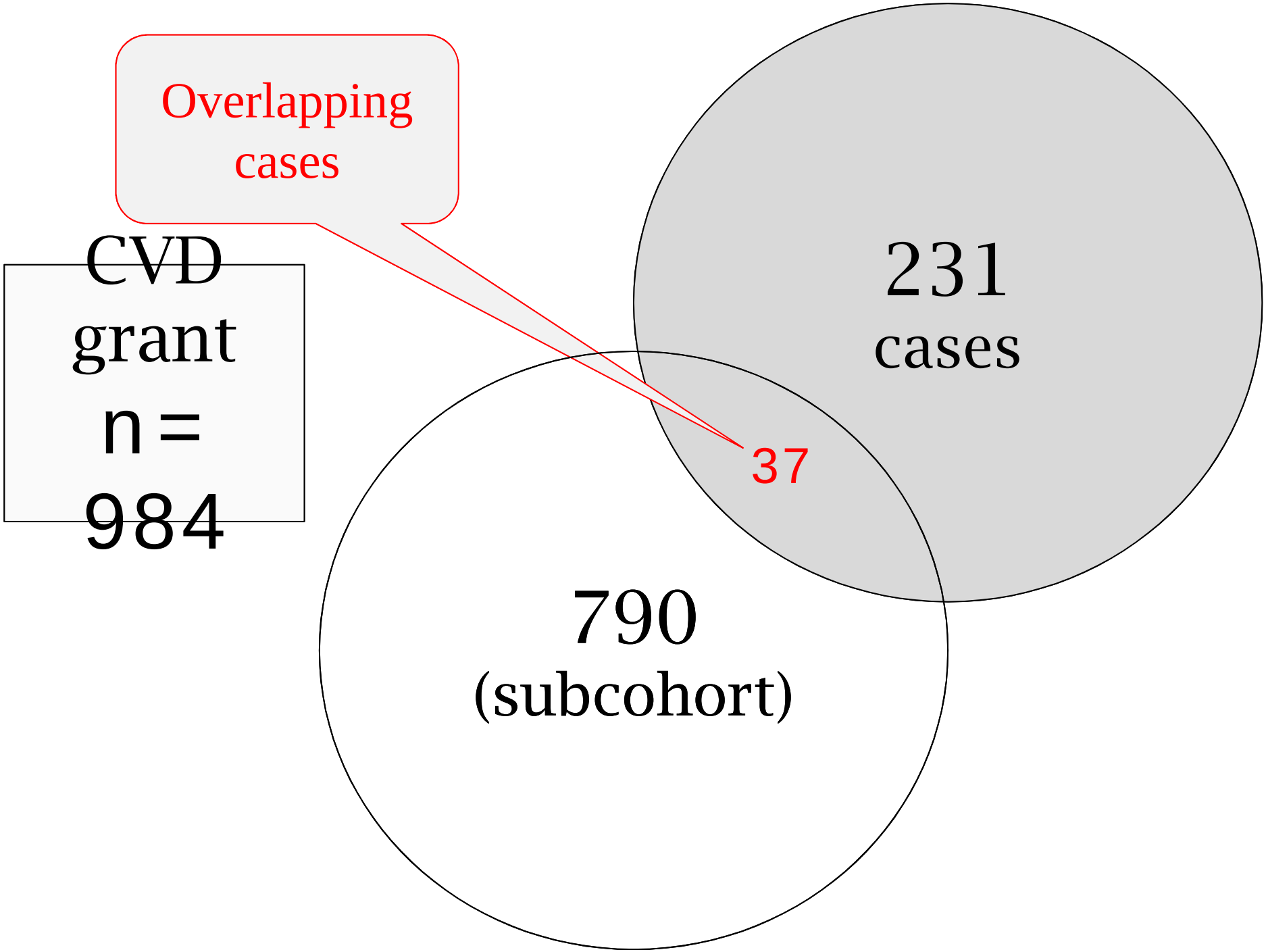
1. To examine the effects of the randomized dietary interventions on changes in plasma levels of metabolites from baseline to year 1 in 745 randomly selected trial participants;
2. To examine whether 1-year changes in plasma levels of metabolites mediate the effect of the randomized dietary interventions on subsequent clinical CVD outcomes from years 2 to 5, using the efficient case-cohort design
3. To examine whether baseline metabolite levels modify the effects of the randomized dietary interventions on CVD risk, using a case-cohort design.

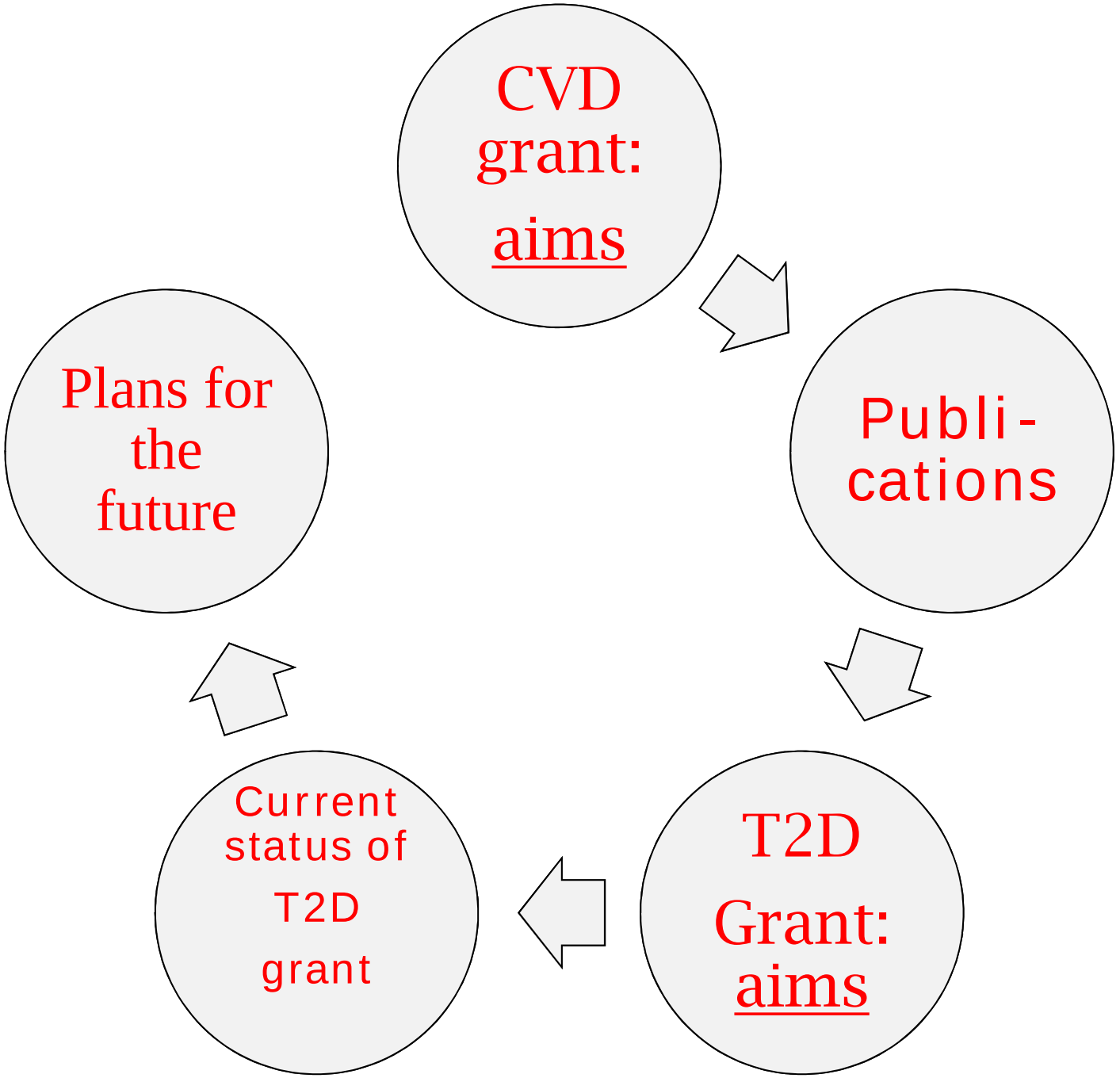
As a secondary aim, we will examine whether 1-year changes in metabolites mediate the benefits of dietary interventions on subsequent occurrence of the metabolic syndrome, among 745 randomly selected trial participants

Routine analyses

1. Baseline metabolites → CVD, Stroke
   - Stratified by intervention
   - Stratified by baseline metabolite cut point
2. Interaction between baseline and intervention → CVD, Stroke
3. 1-y changes in metabolites, adjusting for baseline level→ CVD, Stroke (occurring in years 2 to 5)
4. Interaction between change and intervention → CVD, Stroke
5. Intervention → changes in metabolites


7447 participants in PREDIMED
794 (10% random subcohort* with available plasma samples)
288 total CVD cases
Exclusions
n=3 had missing metabolite values at baseline
n=1 had metabolite outliers identified by quality control
790
n=753 non-cases
n= 37 internal cases (these participants were included in the 231 total CVD cases, see the right box)
231 total CVD cases with available plasma samples
Baseline: 984
n=753 non-cases – (221 control; 282 MedDiet+EVOO; 250 MedDiet+nuts)
n=231 CVD cases – (83 control; 82 MedDiet+EVOO; 66 MedDiet+nuts)
1-year: 926
n=749 non-cases – (219 control; 281 MedDiet+EVOO; 249 MedDiet+nuts)
n=177 CVD cases – (59 control; 70 MedDiet+EVOO; 48 MedDiet+nuts)


Overlapping cases
CVD grant n= 984
231 cases
37
790 (subcohort)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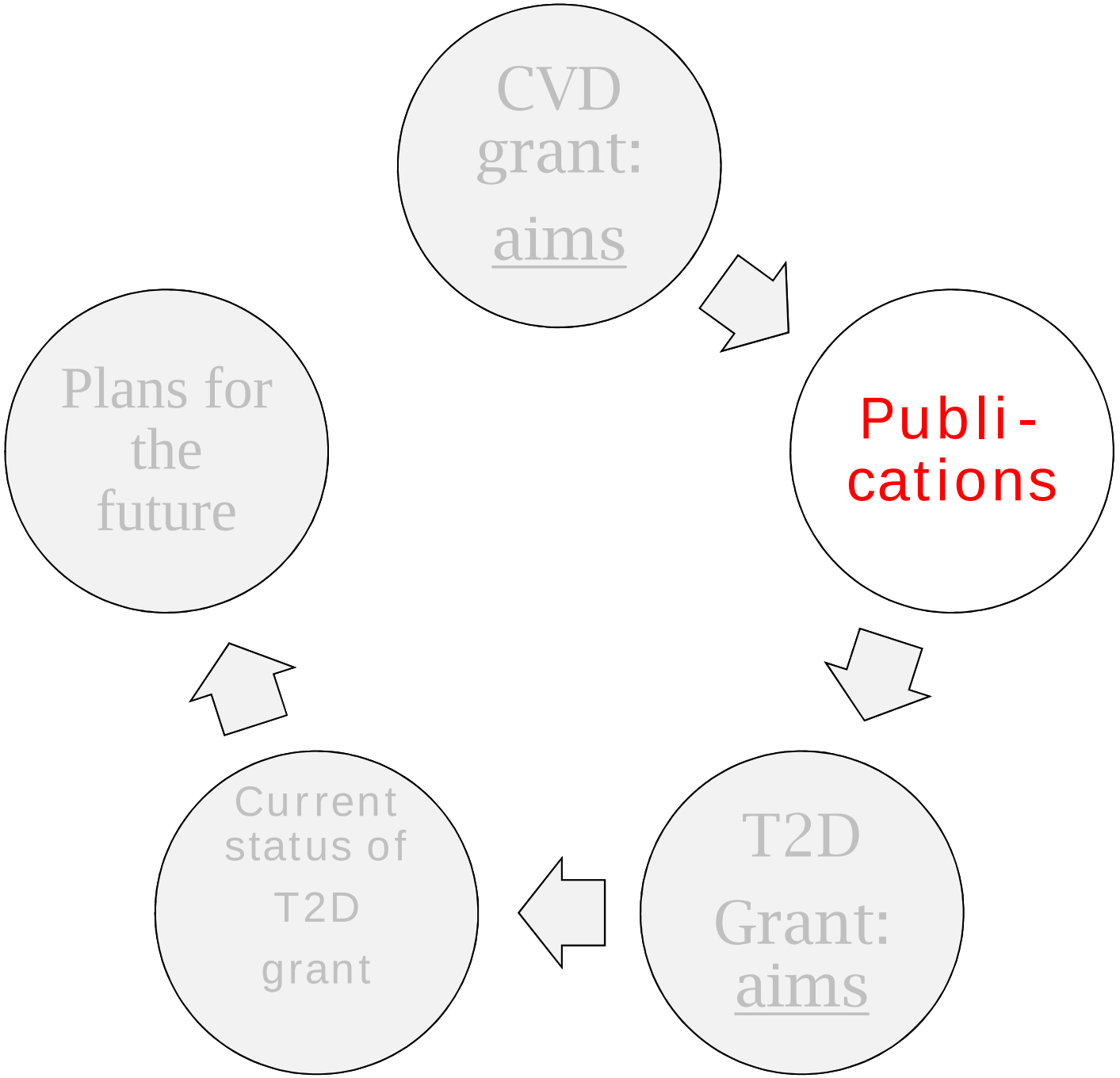
CVD grant: aims
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Hypotheses in the grant

A5.i. Branched-chain and aromatic amino acids

A5.ii. Glutamine-cycling pathway

A5.iii. Small and medium-chain acylcarnitines

A5.iv. Gut flora metabolites

A5.v. Urea cycle metabolites

A5.vi. Lipid Classes (TAG,CEs,LPCs,PC,LPE,DAGS,SMs)

Published papers

- Reviews
  - Guasch-Ferré et al. SR metabolomics-T2D.
    Diabetes Care 2016;39:833
  - Martínez-González et al. Understanding...
    J Nutr 2016 pii: jn219147.
  - Salas-Salvado et al. MedDiet & T2D-MetSyndr.
    J Nutr 2016 pii: jn218487.

Published papers (2)

- Original articles
  - Ruiz-Canela et al. BCAA-CVD.
    Clin Chem 2016 Apr;62(4):582-92
  - Guasch-Ferré et al. Acylcarnitines-CVD.
    Am J Clin Nutr 2016 Jun;103(6):1408-16
  - Zheng et al. Glutamine/Glutamates-CVD.
    J Am Heart Assoc 2016 Sep 15;5(9).
  - Yu et al. Tryptophan, kynurenines & CVD.
    J Nutr 2017 Mar;147(3):314-322..
  - Yu et al. Urea cycle-Arginine/ADMA ratio & CVD.
    J Clin Endocrinol Metab 2017 Mar 2. [Epub ahead print]
  - Wang et al. Ceramides & CVD.
    Circulation 2017 2017 May 23;135(21):2028-2040.

Submitted papers

- Second/Third reviews
  - Ruiz-Canela et al. Systematic Review- metabolomics CVD.

    J Am Heart Assoc (resubmitted May'17)
  - Guasch-Ferré et al. Gut-microbiota Betaine/choline-CVD.

    J Am Heart Assoc (preparing resubmission)
  - Toledo et al. Intervention & changes in lipidome-CVD.

    Am J Clin Nutr (3rd review resubmitted May'17).

Recent/next submissions

- Submitted
  - Razquin et al. Lipidome-PCA analyses CVD.
    J Lipid Res (submitted May'17)
  - Papandreou et al. Gut-microbiota, TMAO & T2D.
    Lancet Diab Endocrinol (submitted May'17)

- Next-immediate submissions
  - Liang et al. Metproc for QC
    J Proteome Res
  - Wang et al. Network-Pathway analyses-CVD
    J Am Coll Cardiol
  - Ruiz-Canela et al. BCAA, AA & T2D.
    Target journal?

T2D grant

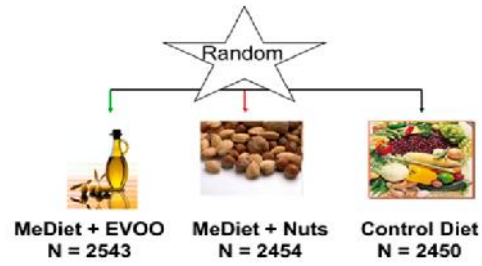
In the pipeline

- Tables done (some of them will circulate soon)
  - Wang et al. Bile acids - CVD.
    Target journal?
  - Wang et al. Uridine - CVD.
    Target journal?
  - Santos JL, Ruiz-Canela et al. Lactate-glycolysis- CVD.
    Target journal?
  - Razquin et al. 2-aminoadipic acid (AA)- CVD.
    Target journal?
- Others
  - Zheng et al. Non-targeted lipids
    Target journal?
  - Zheng et al. BAIBA (beta-amino-isobutiric acid) CVD/T2D
    Target journal?
  - Liu, Liang, et al. Artifact detection without PPP
    Target journal?

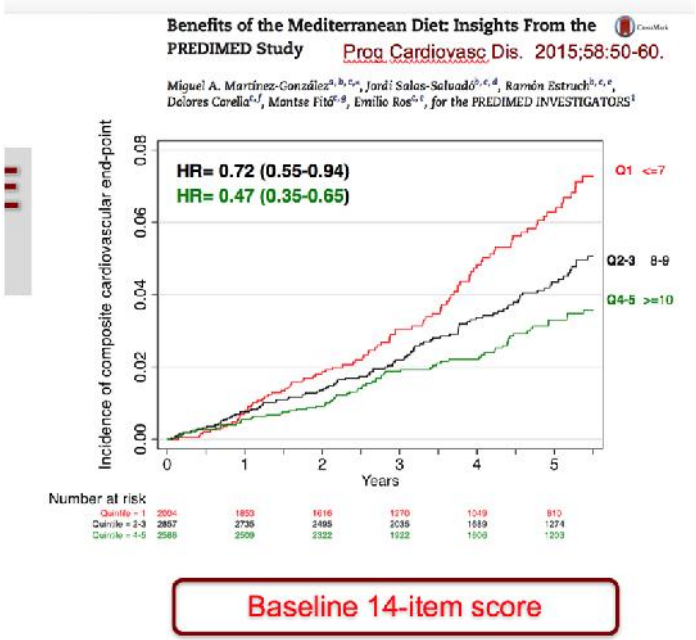
Metabolites (date accepted /submitted)	Baseline -CVD	1 yr-CVD	Effect Modification	Interv.– 1 y chg
BCAA (8Jan16)	+	–	+	–
Acylcarn. (28Mar16)	+	+	+	–
Gln/Glu (12Aug16)	+	–	+	–
Trp/Kyn (9Jan17)	±	+ (Trp)	+	+
Ceramides (20Feb17)	+	–	+	–
Lipidome (11May17-AJCN*)	+	–	–	±
Gut-microb. (May17-JAHA*)	+	–	–	–
PCA (13May17 JLR-1st)	+	±	–	–

Metabolomic footprints MedDiet

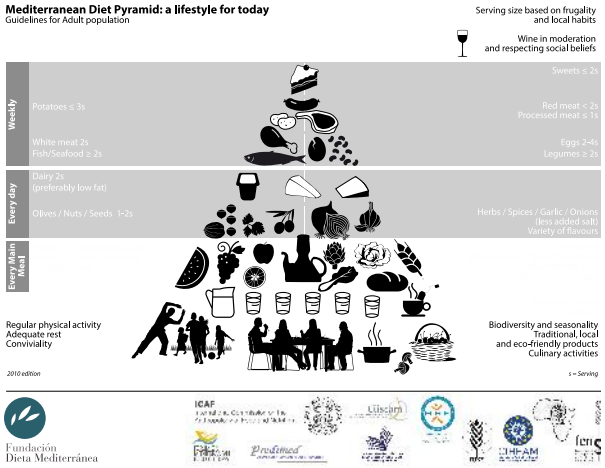
- RCT:
  - **MeDiet+EVOO** vs. Control: discrimination
  - **MeDiet+nuts** vs. Control: discrimination

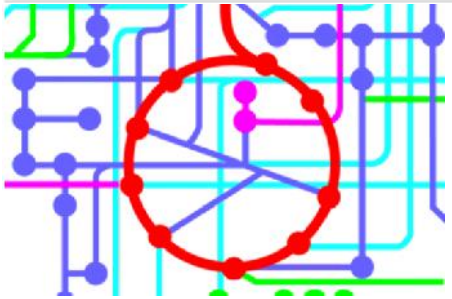


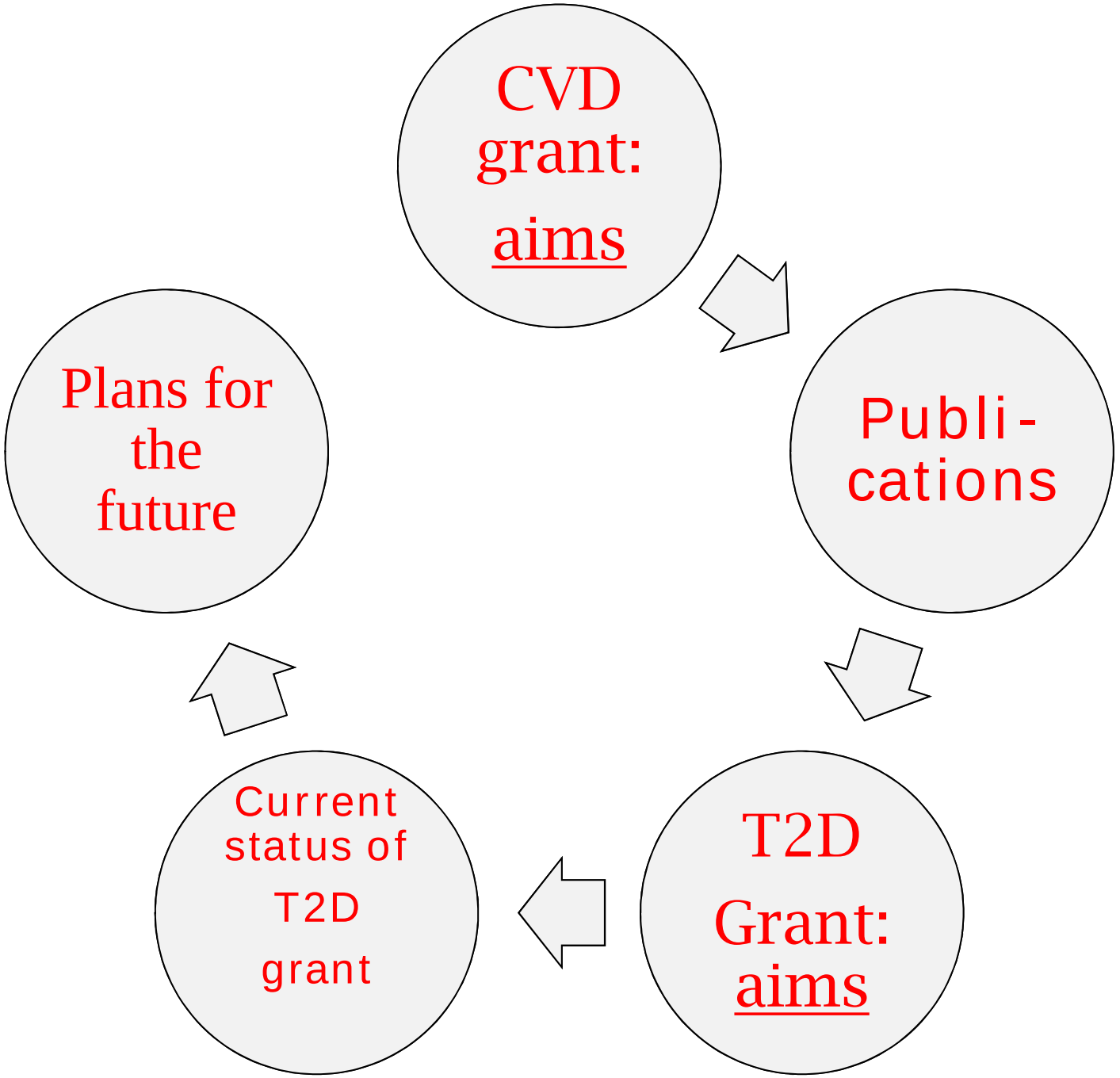
- 14-item screener assessing adherence
  - Baseline
  - Repeated measurements 1-y



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



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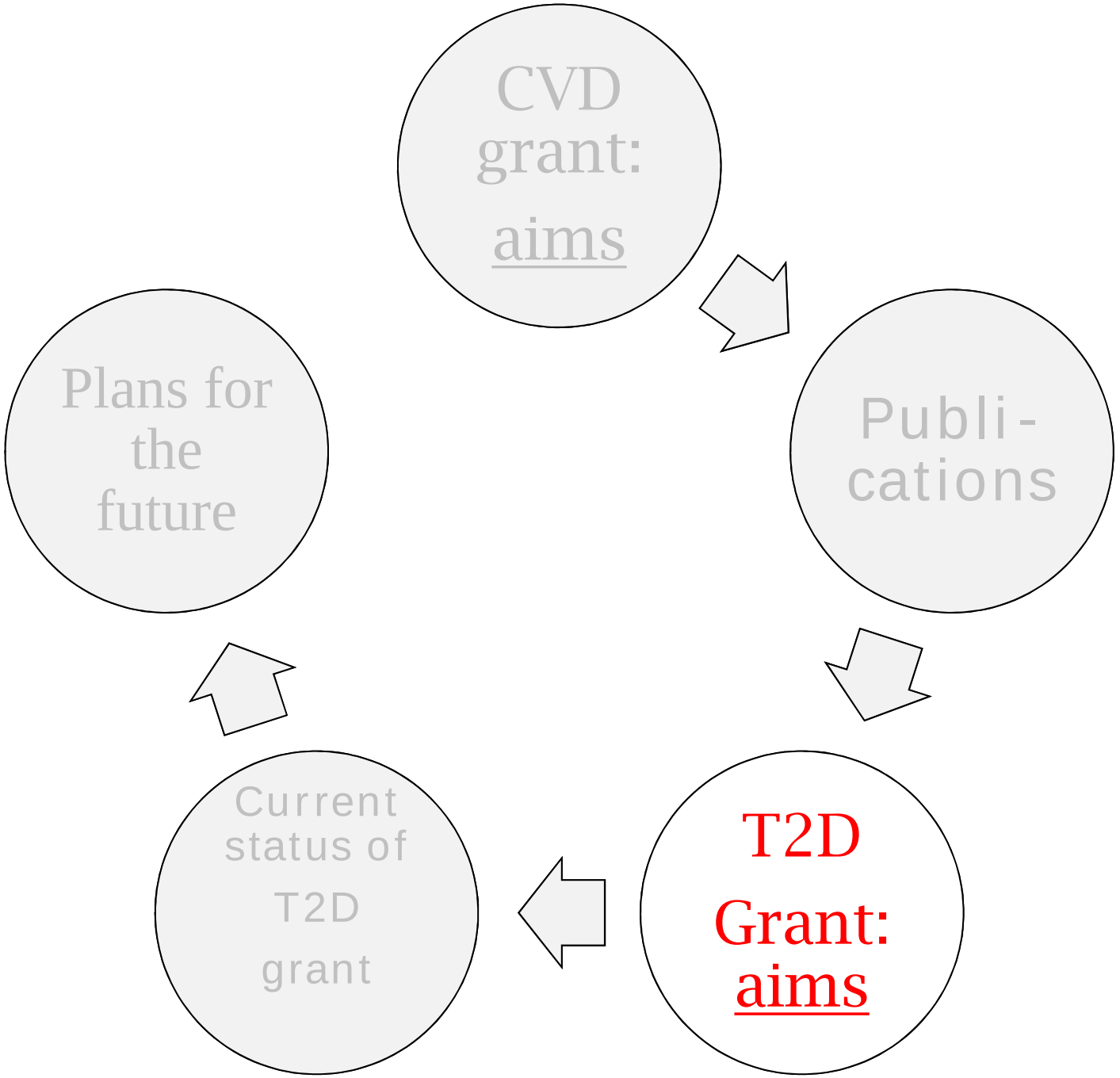
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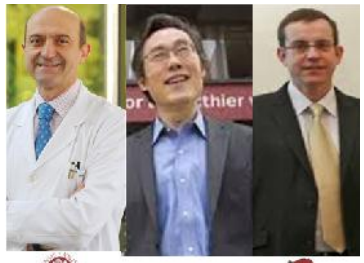
Dietary interventions, metabolites and risk of T2D

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



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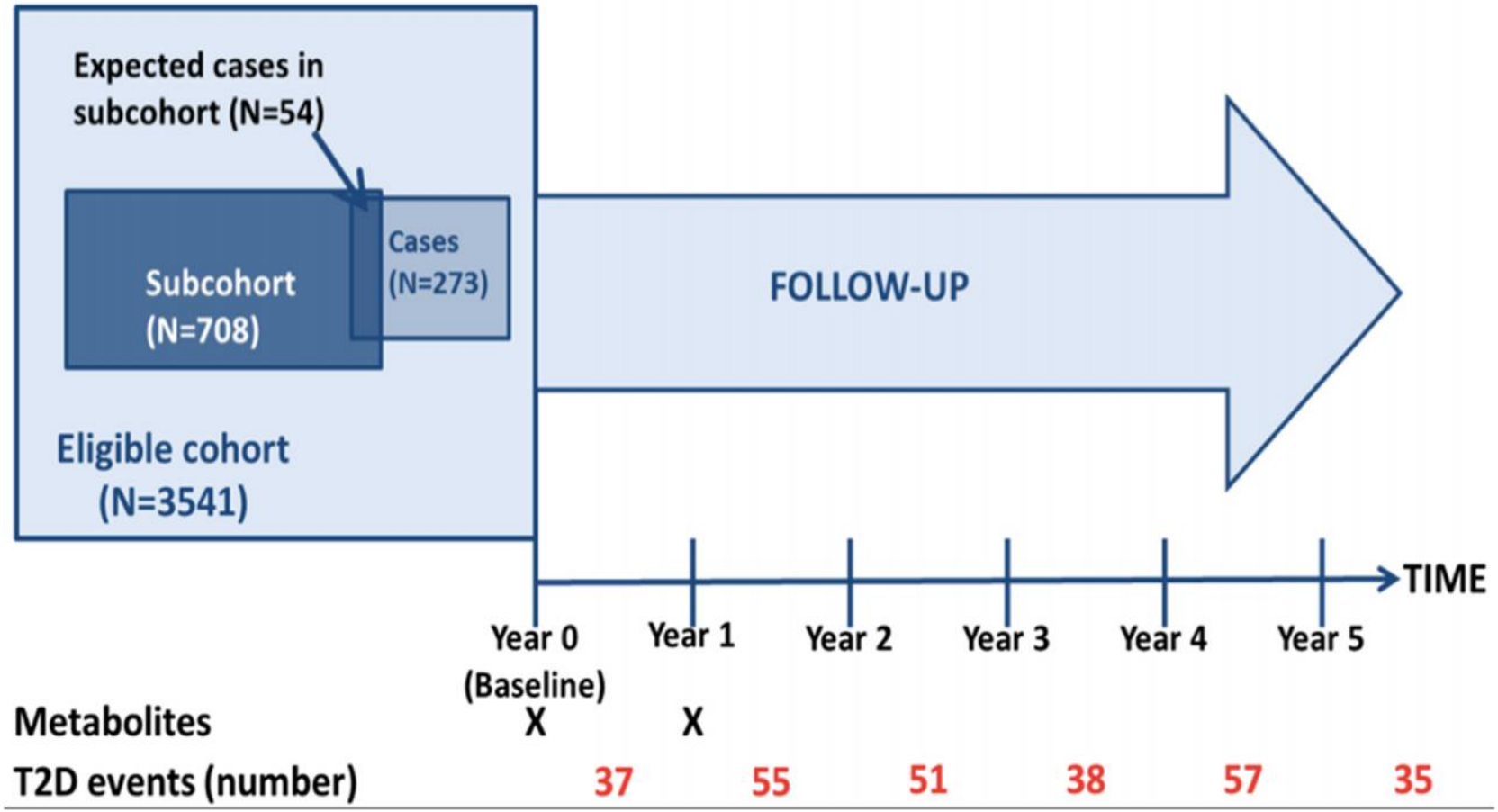
Case-cohort study

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



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T2D grant: Specific aims

1. To examine the association between the baseline metabolite concentrations and the risk of T2D using a case-cohort design;

T2D grant: Specific aims

2. To examine whether the dietary interventions modify the relationships between baseline levels of metabolites and subsequent T2D risk using a case- cohort design;

T2D grant: Specific aims

3. To examine whether 1-year changes in metabolites mediate the effect of the dietary interventions on subsequent T2D outcomes from years 2 to 5 using a case-cohort design

T2D grant: Specific aims

4. To examine whether 1-year changes in metabolites influence insulin resistance and β-cell function from years 2 to 5 among 708 randomly selected participants free of diabetes at baseline

T2D grant: Specific aims

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

Hypotheses in the grant

A5.i. Gut microbiota metabolites

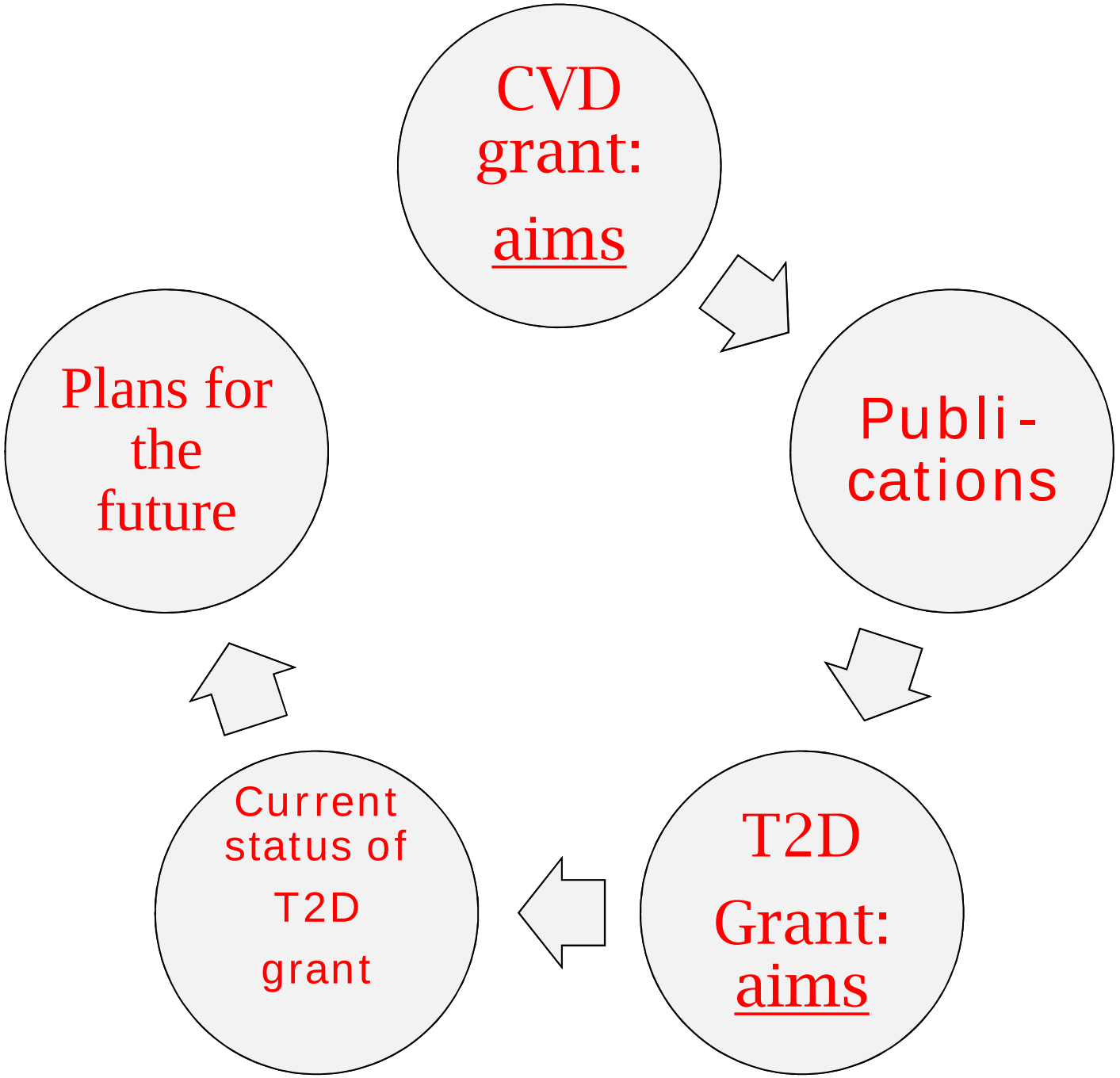
A5.ii. Lipid classes

A5.iii. Branched-chain & aromatic amino acids

A5.iv. Glutamine-cycling pathway

A5.v. Short- and medium-chain acylcarnitines

A5.vi. Urea cycle metabolites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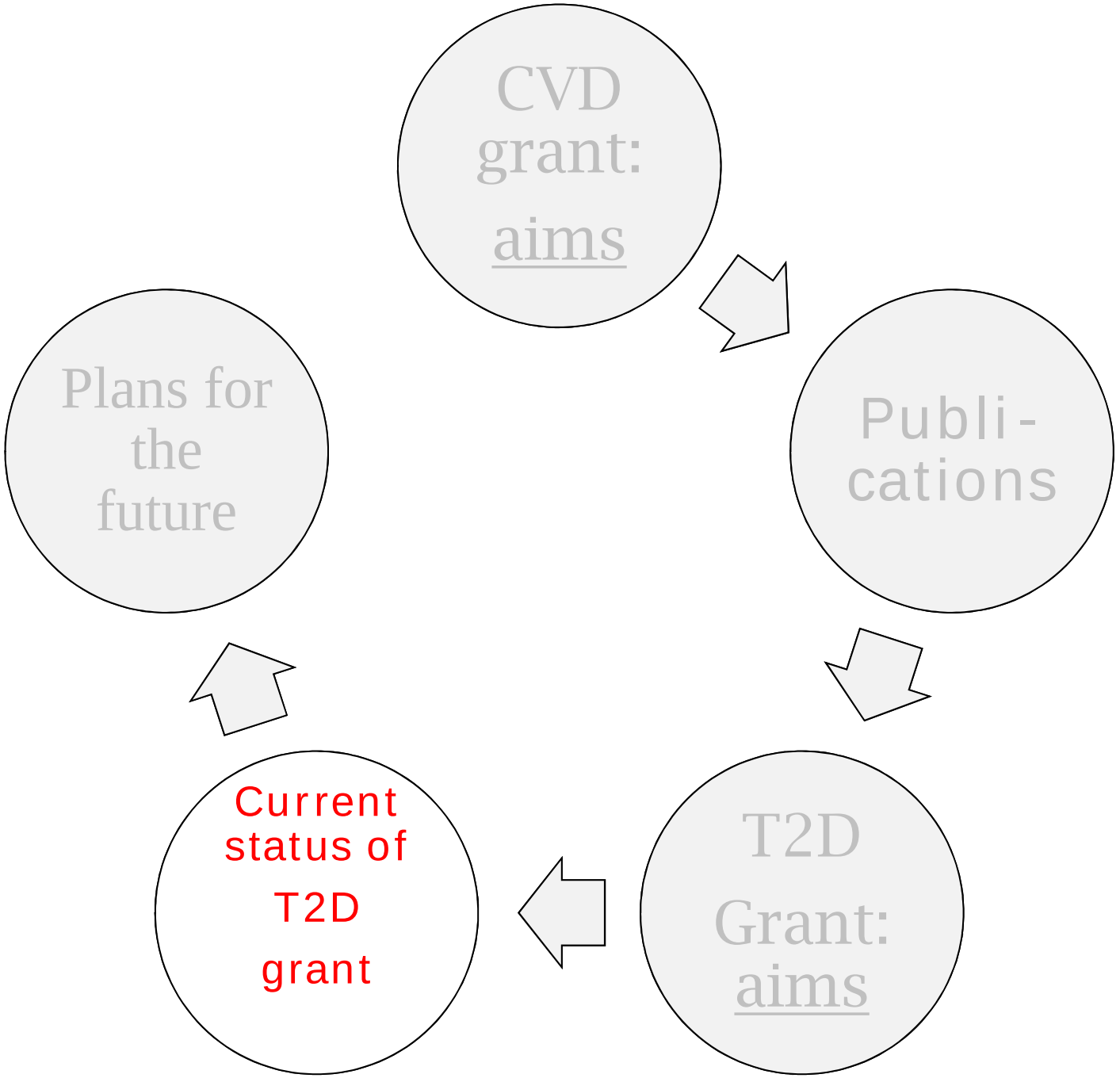
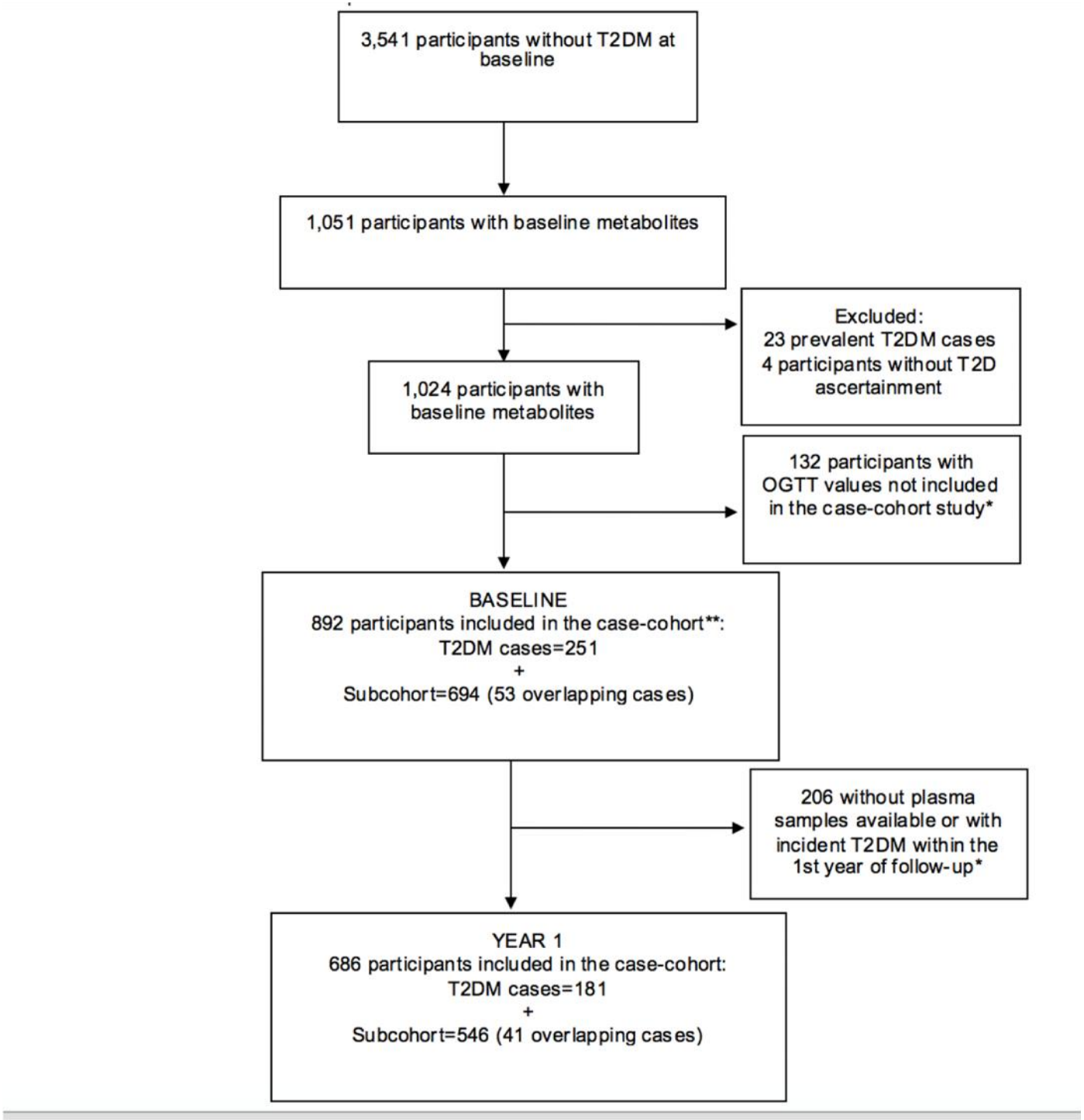
Current status of T2D grant
Plans for the future


CVD grant: aims
Publi-cations
T2D Grant: aims
Current status of T2D grant
Plans for the future

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)

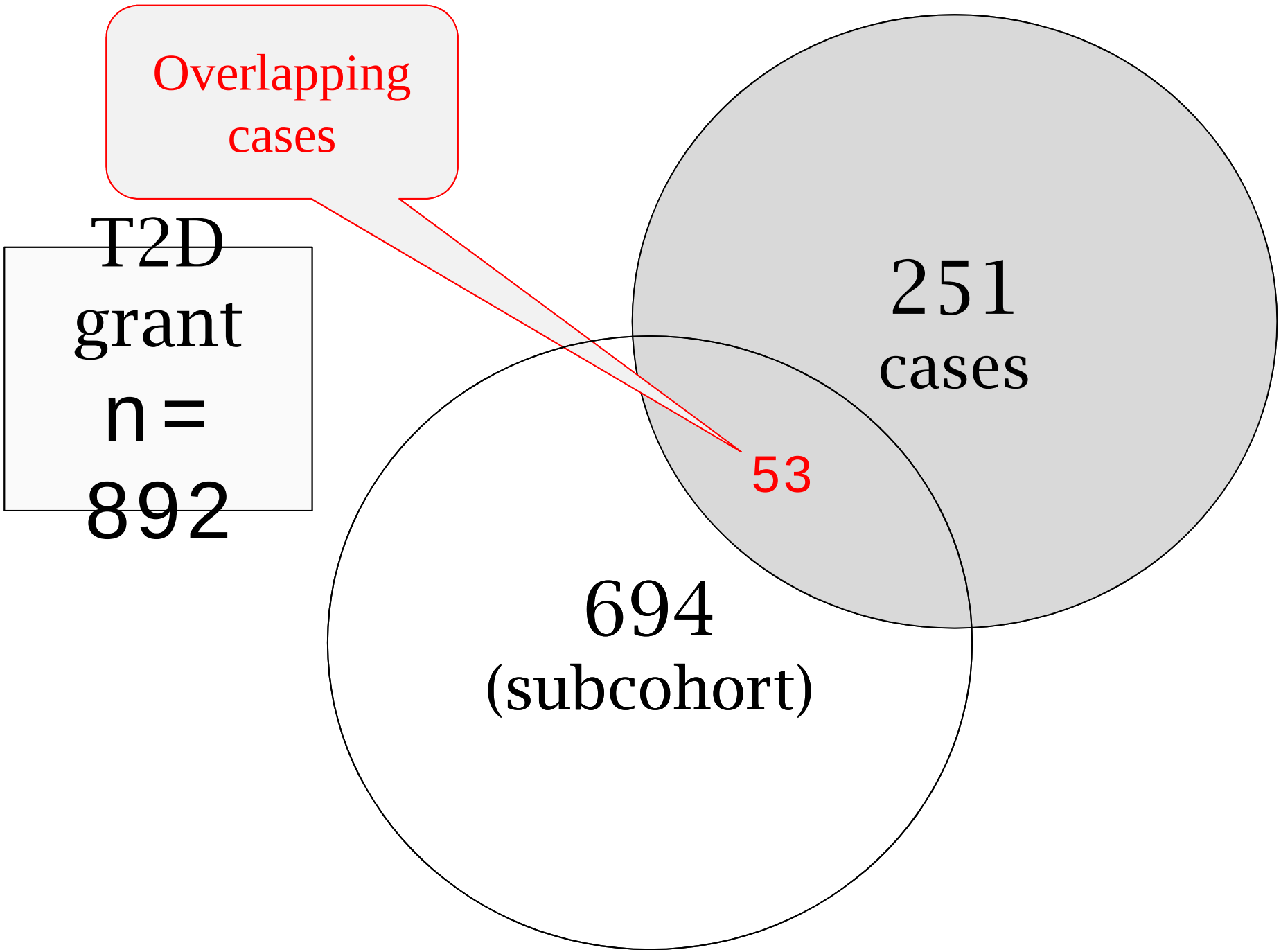

Overlapping cases
T2D grant n= 892
251 cases
53
694 (subcohort)

Table 1. Baseline participant characteristics in the random subcohort and of the cases

	Subcohort[a]	Cases
n	694	251
Age (years)	66.5 (5.7)	66.4 (5.7)
Sex (% women),	62.8	55.0
Intervention group, %		
MedDiet+EVOO	30.7	29.9
MedDiet+nuts	37.2	33.9
Control	32.1	36.3
Hypertension, %	90.8	96.0
Dyslipidemia, %	85.0	79.7
Smoking, %		
Never	61.0	52.6
Former	22.6	22.3
Current	16.4	25.1
Waist circumference, cm	99.5 (10.7)	103.4 (10.0)
Body mass index, kg/m^2	29.9 (3.6)	30.8 (3.3)
Physical activity, METs/d	238 (238)	249 (232)
Education, %		
Elementary or lower	75.4	76.5
Secondary or higher	24.6	23.5
Total energy intake, kcal/d	2277 (566)	2327 (622)
14-p score adherence MedDiet[b]	8.6 (2.0)	8.4 (2.0)

EVOO, Extra-virgin olive oil;
CHD, coronary heart disease;
MET, metabolic equivalent. V
alues are mean (SD) or percentage.

[b]This score is based on the 14-item dietary screener.

Methods - Broad	Content	CVD	T2D
1. Amino Acids (+ ion mode)	84 known AA + acylcarnitines	✓	✓
2. Lipids & Non-targeted	200 known lipids + >5000 unknown signals	✓	✓
3. Polar metabolites (– ion mode)	>100: purines, pyrimidines, bile acids, 2AA, etc.	✓	–

Methods - Reus	Content	CVD	T2D
1. HOMA (~3370 determinations)	Glucose, Insulin, HOMA	N/A	✓
2. OGTT (n~200)	in T2D subcohort	N/A	✓

Recent/next submissions

- Submitted
  - Razquin et al. Lipidome-PCA analyses CVD.
    J Lipid Res (submitted May'17)
  - Papandreou et al. Gut-microbiota, TMAO & T2D.
    Lancet Diab Endocrinol (submitted May'17)

- Next-immediate submissions
  - Liang et al. Metproc for QC
    J Proteome Res
  - Wang et al. Network-Pathway analyses-CVD
    J Am Coll Cardiol
  - Ruiz-Canela et al. BCAA, AA & T2D.
    Target journal?

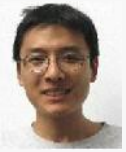
T2D grant

T2D grant: pending

1. Acylcarnitines- to be presented today (TBPT)

Marta Guasch-Ferré

2. Tryptophan, Kynurenines- TBPT (pending 3rd method)
3. Urea cycle metabolites- TBPT



Edward Yu

4. Lipidomics, 2-bonds, length-TBPT

Estefania Toledo

5. Lipids PCA-TBPT
6. 2-Amino-adipic acid

Cristina Razquin

7. Lactate-glycolysis-gluconeogenesis

Miguel Ruiz-Canela
Marta Guasch-Ferré

8. Purine catabolism

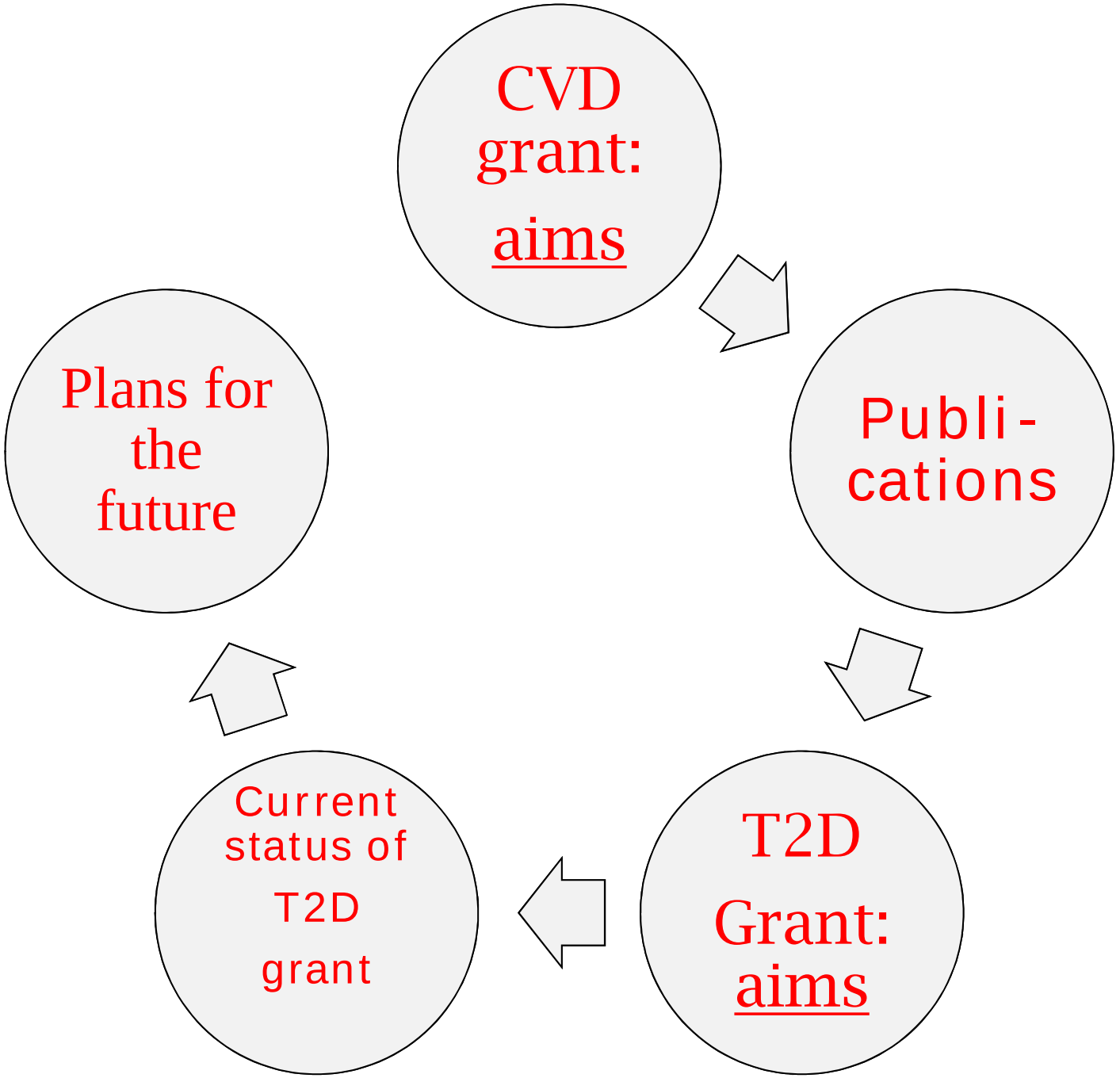
Christopher Papndreou

9. Uridine
10. Network-Pathways

Daniel Wang

11. Glutamine cycling pathway
12. Non-targeted metabolites

Yan Zheng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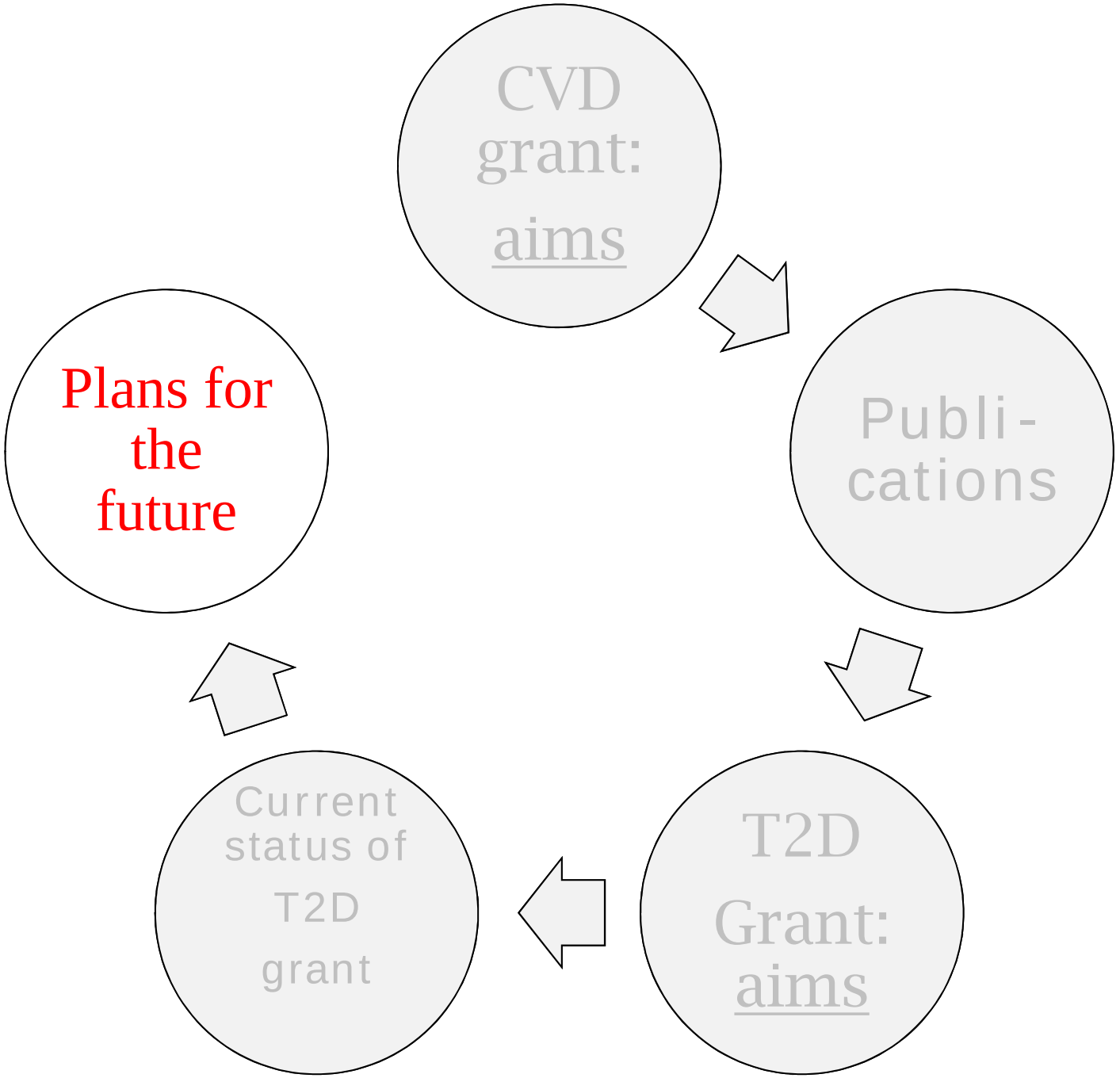
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Potential future research lines

- Pending
  - Metabolic syndrome in CVD grant
- Already proposed
  - Purine catabolism
  - Cross trait analyses: CVD/T2D/Obes/Lipids
  - Obesity & weight changes
- New potential analyses
  - Average of baseline & 1 year as exposure
  - Consistency: baseline vs 1-y levels (not the 1-y change)
  - Combination of metabolites in predictive scores
  - Proper mediation analysis
  - Cases of depression

Mediterranean dietary pattern and depression: the PREDIMED randomized trial

Almudena Sánchez-Villegas[1,2*], Miguel Angel Martínez-González[1,3], Ramón Estruch[1,4], Jordi Salas-Salvadó[1,5], Dolores Corella[1,6], Maria Isabel Covas[1,7], Fernando Arós[1,8], Dora Romaguera[1,9,10], Enrique Gómez-Gracia[1,11], José Lapetra[1,12], Xavier Pintó[1,13], Jose Alfredo Martínez[1,14], Rosa María Lamuela-Raventós[1,15], Emilio Ros[1,16,17], Alfredo Gea[1,3], Julia Wärnberg[1,11] and Lluis Serra-Majem[1,2]

Results: We identified 224 new cases of depression during follow-up. There was an inverse association with depression for participants assigned to a Mediterranean diet supplemented with nuts (multivariate hazard ratio (HR) 0.78; 95% confidence interval (CI) 0.55 to 1.10) compared with participants assigned to the control group, although this was not significant. However, when the analysis was restricted to participants with DM2, the magnitude of the effect of the intervention with the Mediterranean diet supplemented with nuts did reach statistical significance (multivariate HR = 0.59; 95% CI 0.36 to 0.98).

224 cases
after at least 3 years of intervention

Competing renewal

- CVD
  - Additional CVD outcomes
    - atrial fibrillation
    - heart failure
    - peripheral artery disease
  - Grant was scored at the 19th percentile and the payline was 15.
  - Resubmission:
    - MRC and Yan worked on it
    - Jordi Salas offered his knowledge and help to address the reviewer comments.
  - The deadline is early July.

Competing renewal

- T2D
  - 2018
  - Pending of decisions
    - Incident T2D in PREDIMED-PLUS?
    - Complications of T2D in PREDIMED?
    - Other ideas?
  - To be discussed today at the end of the sessions

In summary…

- A highly productive team in the CVD grant
  - 9 published papers
  - 4 under review (3 of them potentially acceptable)
  - Other 9 papers in preparation
  - Not far from the payline for competing renewal
  - Resubmission next July
- Many pending papers in T2D grant
  - 1 published systematic review
  - 1 submitted, another close to be submitted
  - 12 papers in preparation
  - Higher expertise obtained in the first grant
  - New possibilities with HOMA/OGTT
  - Decisions to be made for competing renewal

Thank you!

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Dpt. Nutrition Harvard TH Chan School of P. Health