Effects of polyphenol intake on cardiovascular risk markers

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Polyphenols

- Most abundant antioxidants in daily diet.
- Widely spread around plant-derived foods such as **fruits, vegetables, cereals, legumes, and beverages.**





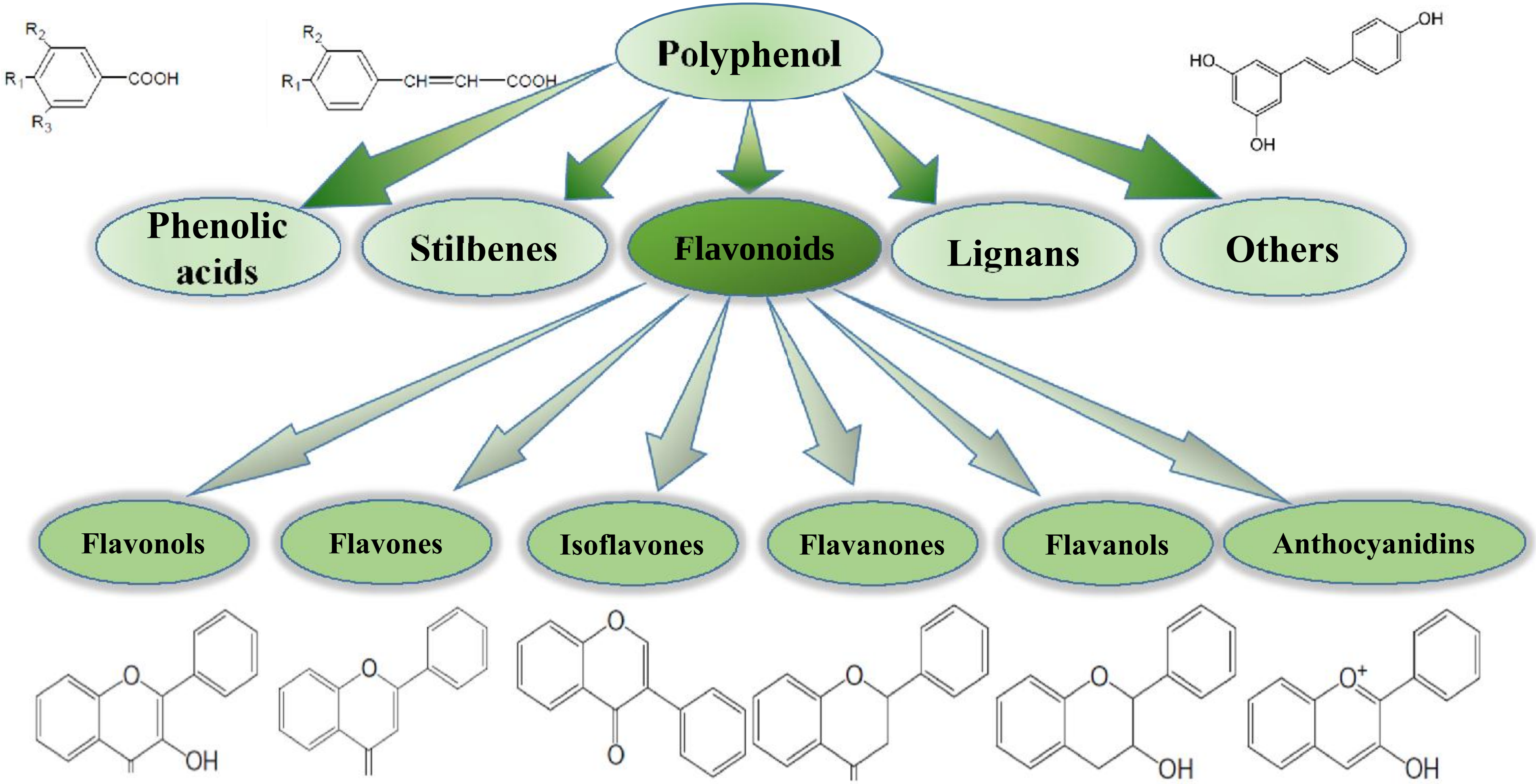


Daily intakes

Daily polyphenol intakes in different countries/regions (mg/day)

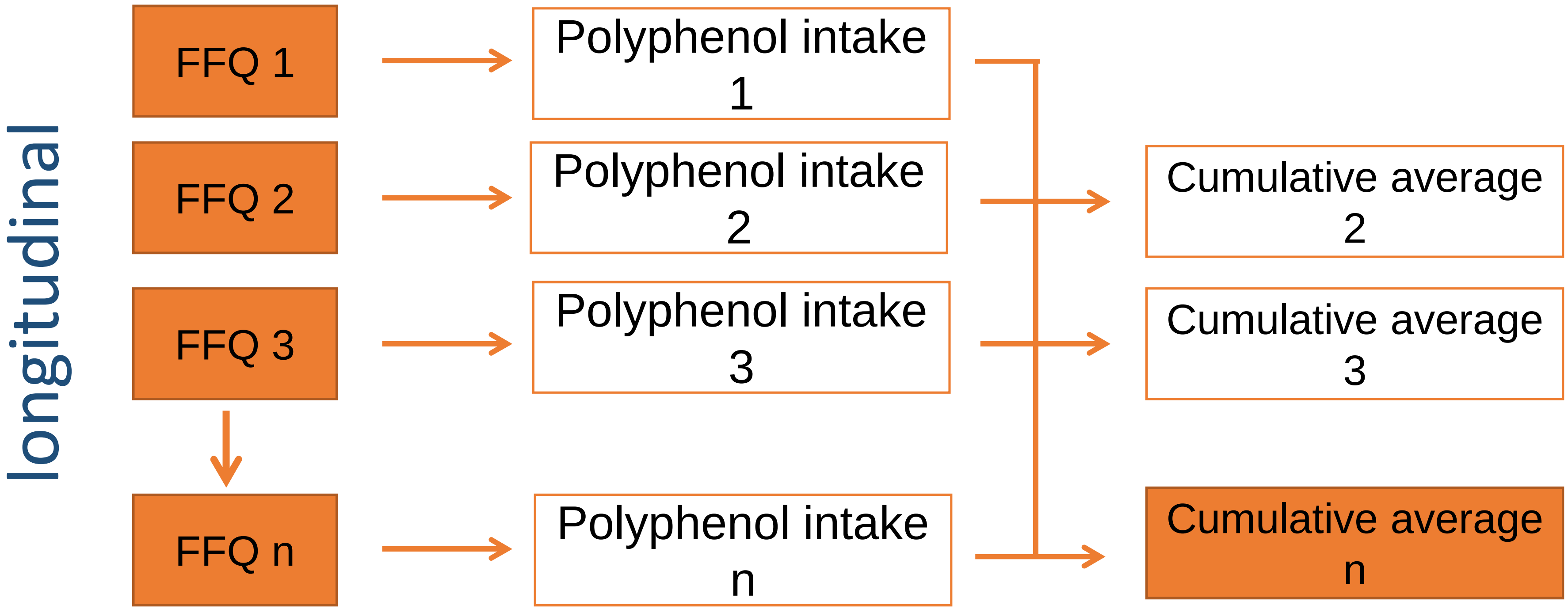
Country/Region	Population	Number	Database	Daily polyphenol intakes	Study
European	Adults	36,037	Phenol-Explorer	1,186	EPIC
Mediterranean	Elderly	304	Phenol-Explorer	312	-
Italy	Elderly	811	Own database	594	InCHIANTI
Polish	Adults	10,728	Phenol-Explorer	1,756	HAPIEE
Finland	Adults	2007	USDA	863	FINDIET2002
Brazil	Adults	1,103	Phenol-Explorer	377.5	Health Survey-São Paulo
Spain	Elderly	7,200	Phenol-Explorer	820	PREDIMED

Classification (Phenol Explorer)



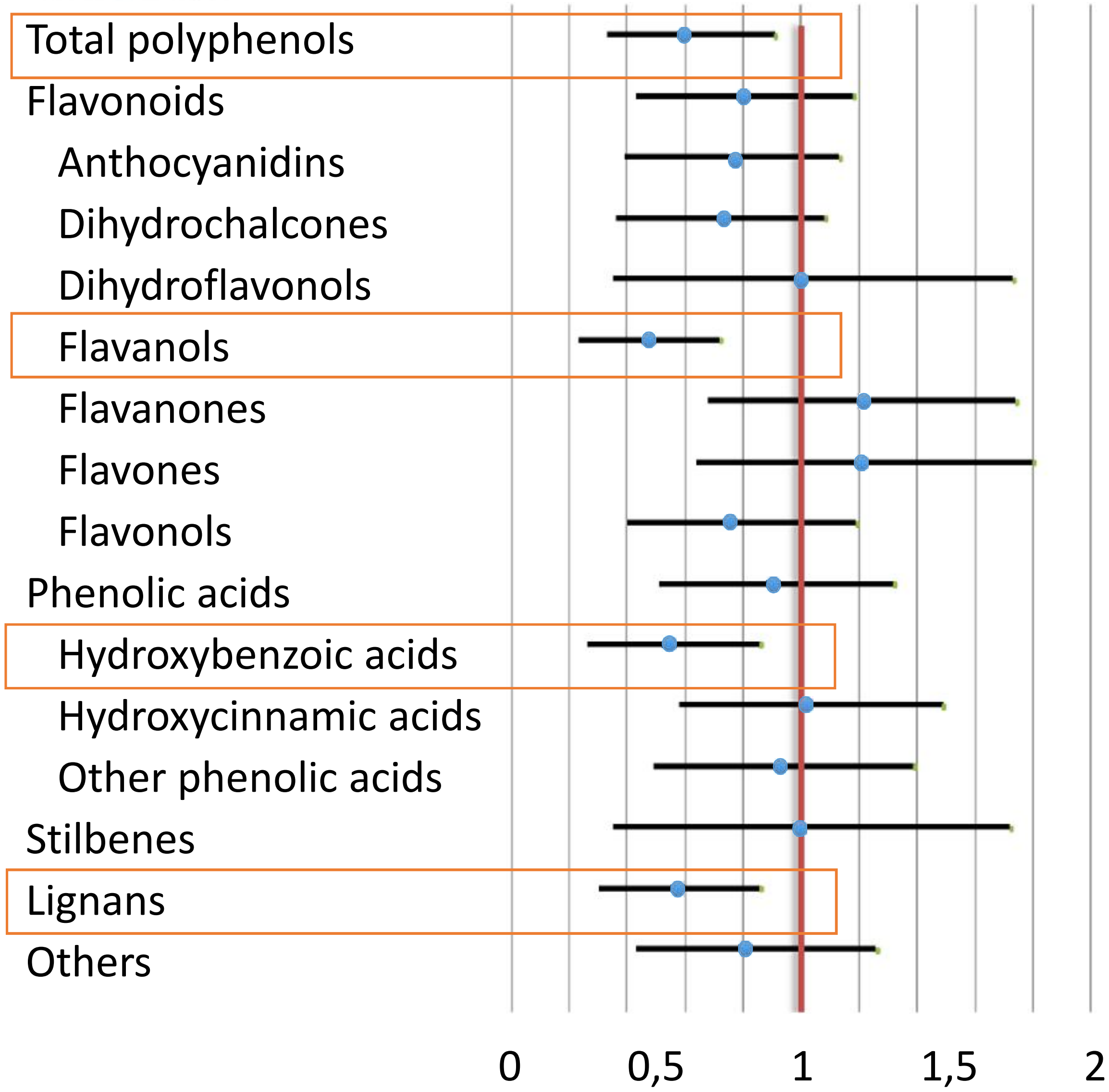
Polyphenol Intake and Cardiovascular Health

Intakes of polyphenols were adjusted for total energy intake (residual method) and cumulative averages were calculated for each participant.



Treserra-Rimbau BMC Med. 2014 May 13;12:77. doi: 10.1186/1741-7015-12-77.

Polyphenol Intake and Cardiovascular Health



Total polyphenol, flavanols, hydroxybenzoic acids and lignans intake were significantly and linearly associated with CV events after adjusting for confounders.

Total polyphenols

HR 0.54; CI 0.33 to 0.91; P-trend=0.04

Flavanols

HR 0.40; CI 0.23 to 0.72; P-trend=0.003

Hydroxybenzoic acids

HR 0.47; CI 0.26 to 0.86; P-trend=0.02

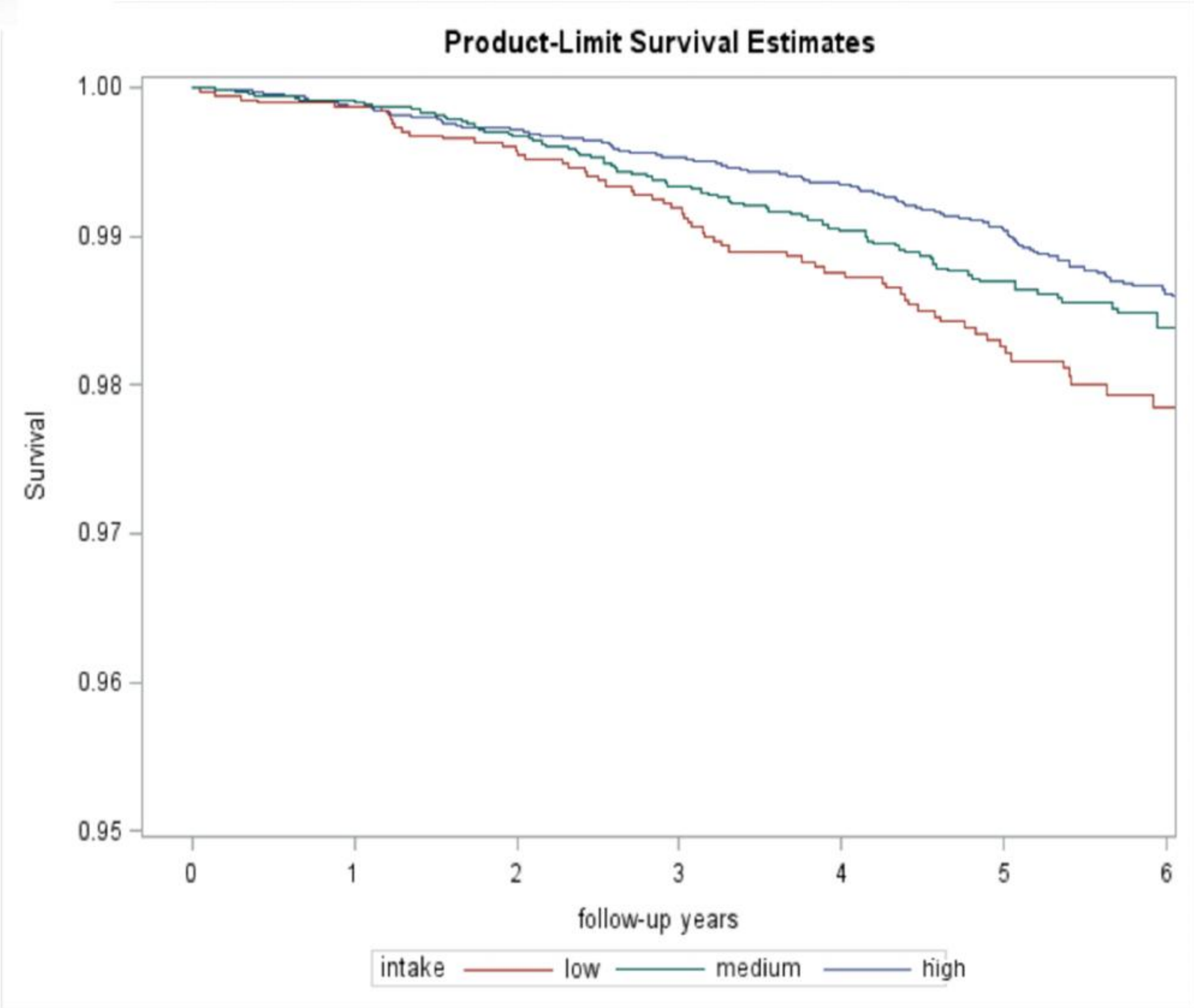
Lignans

HR 0.51; CI 0.30 to 0.86; P-trend=0.007

273 cases

Treserra-Rimbau Nutr Metab Cardiovasc Dis. 2014 Jun;24(6):639-47. doi: 10.1016/j.numecd.2013.12.014. Epub 2014 Jan 22.

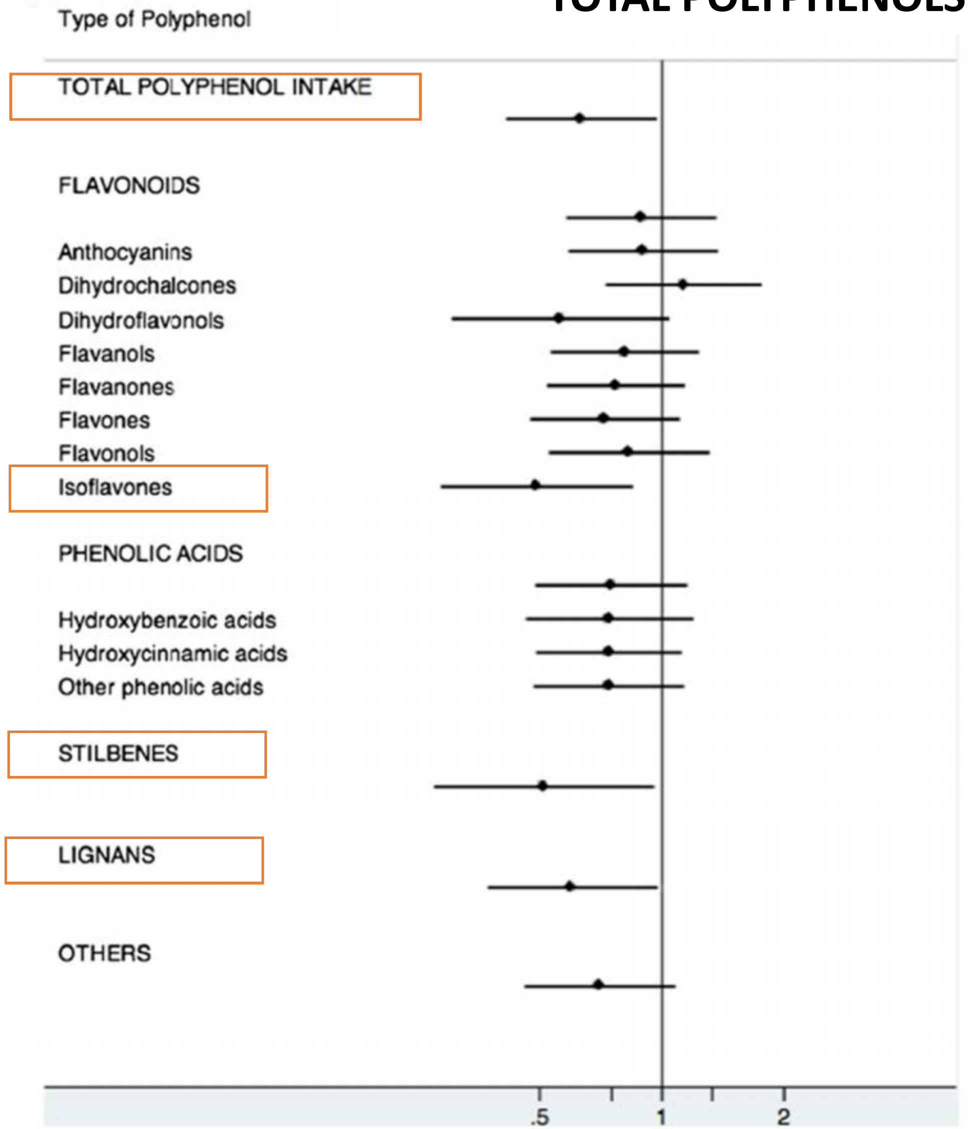
Polyphenol Intake and Mortality Risk



Treserra-Rimbau BMC Med. 2014 May 13;12:77. doi: 10.1186/1741-7015-12-77.

Polyphenol Intake and Mortality Risk

TOTAL POLYPHENOLS AND SUBGROUPS



Hazard ratios (95% CI) of total mortality for the highest vs. lowest quintiles of polyphenol intake.

Total polyphenols

HR 0.63; CI 0.41 to 0.97; P-trend=0.12

Isoflavones

HR 0.49; CI 0.28 to 0.84; P-trend=0.009

Stilbenes

HR 0.48; CI 0.25 to 0.91; P-trend=0.04

Lignans

HR 0.60; CI 0.37 to 0.95; P-trend=0.03

327 deaths

Predimed
Prevención con Dieta Mediterránea

Treserra-Rimbau BMC Med. 2014 May 13;12:77.
doi: 10.1186/1741-7015-12-77.

In Summary in the PREDIMED

CVD

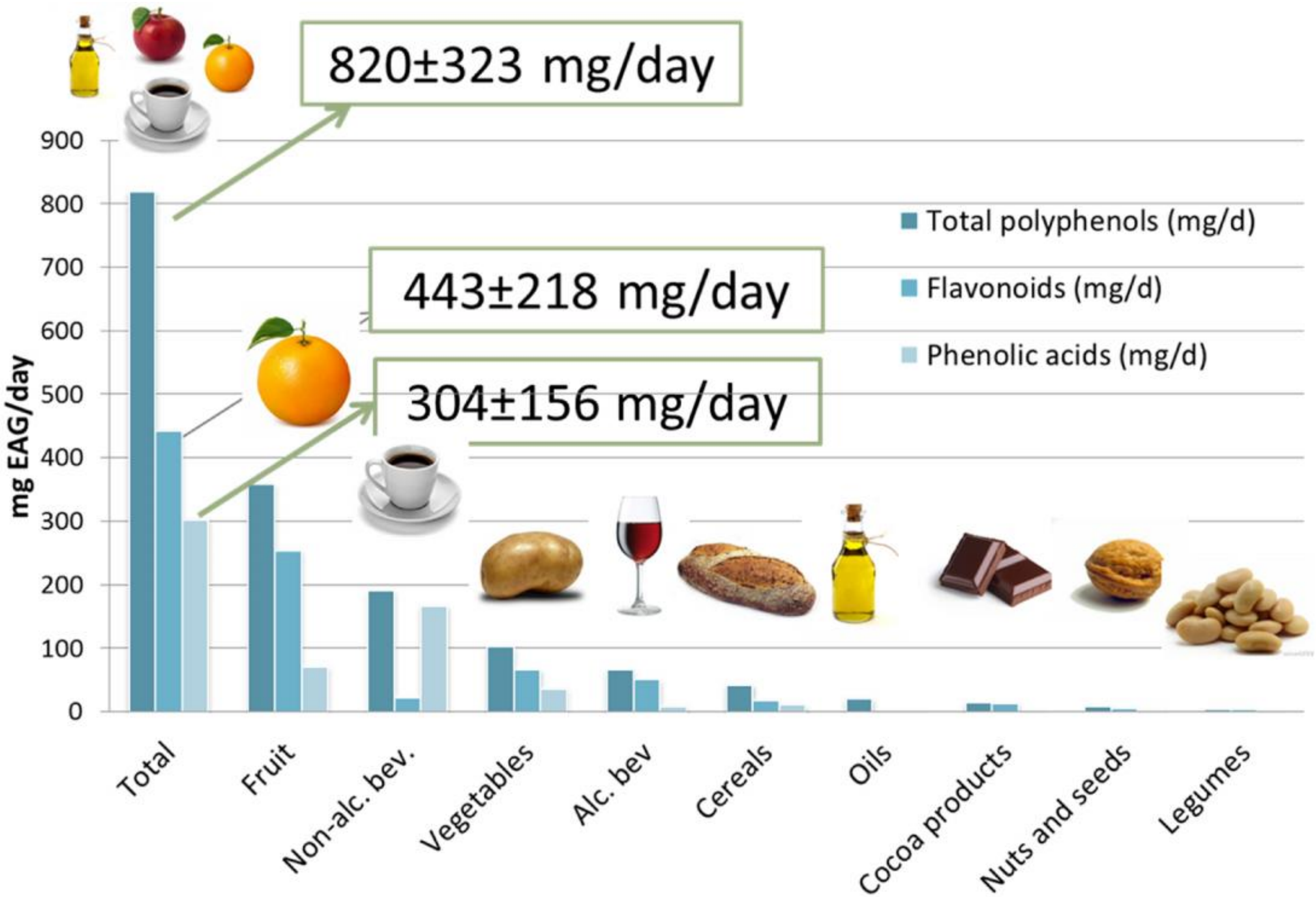
- Total Polyphenols
- Lignans
- Flavanols
- Hydroxybenzoics
- Isoflavones

Mortality

- Total Polyphenols
- Lignans
- Stilbenes
- Isoflavones

Sources of polyphenols

Total polyphenols - PREDIMED cohort - baseline



Total polyphenol intakes :
820±323 mg/day
Flavonoids intakes:
443±218 mg/day
Phenolic acids intakes:
304±156 mg/day

Treserra-Rimbau Nutr Metab Cardiovasc Dis. 2013 Oct;23(10):953-9. doi: 10.1016/j.numecd.2012.10.008. Epub 2013 Jan 17.

Polyphenols and Diabetes

Objective

To study the association between polyphenol intake (total and by groups) and type 2 diabetes within the PREDIMED cohort.

Observational and longitudinal study within the PREDIMED

7447 participants

Free of diabetes at baseline →

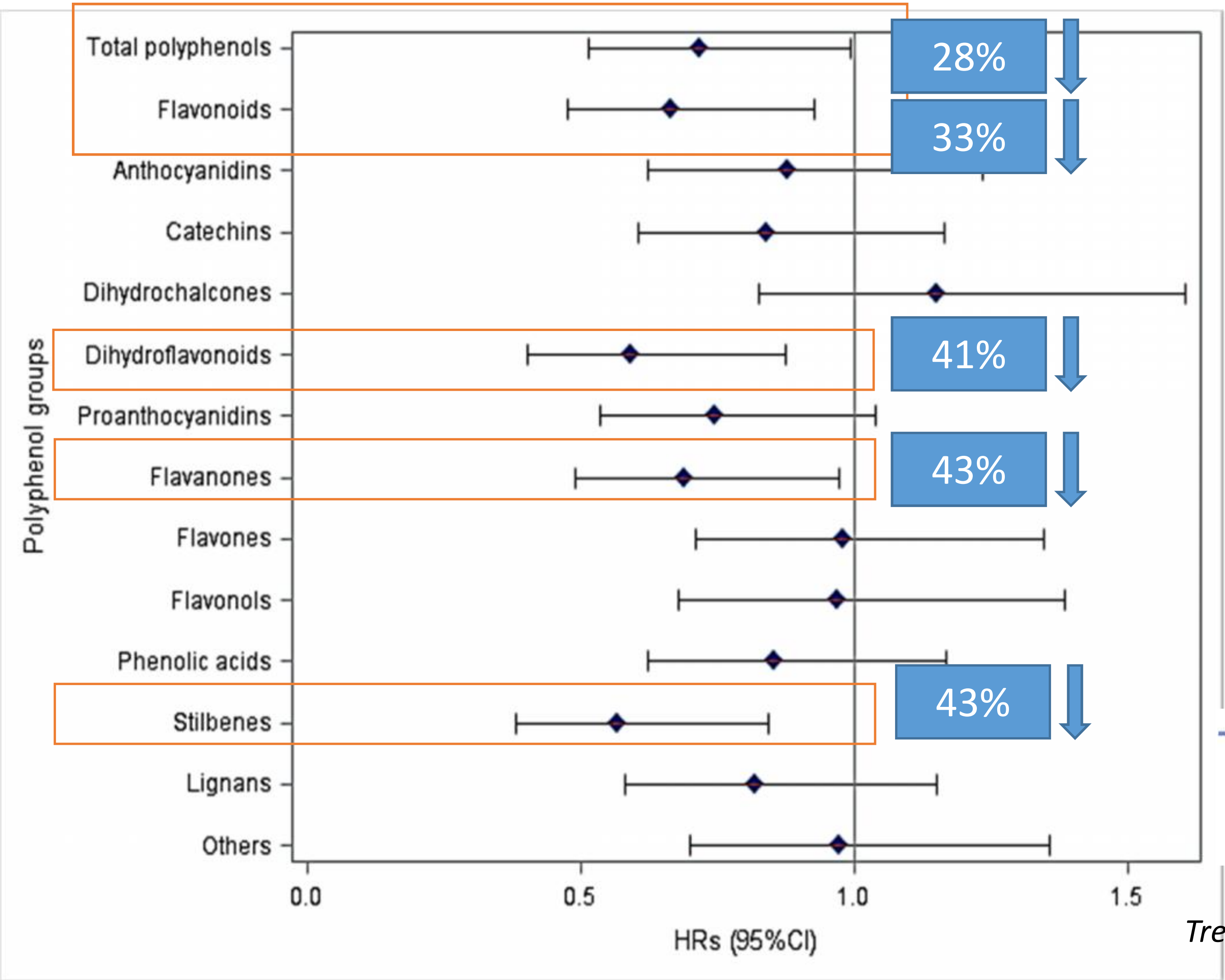
3430 participants

5.5±2.0 years of follow-up

314 new cases of diabetes

Treserra-Rimbau J Nutr. 2016 Mar 9. pii: jn223610.

Results Polyphenol Intake and Diabetes

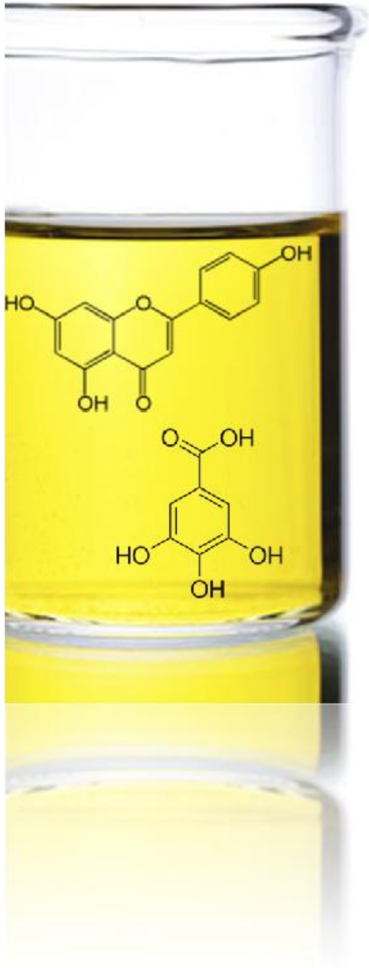


HRs (95% CI) of type 2 diabetes incidence for the highest vs. the lowest tertiles of polyphenol intake (fully adjusted model).

Predimed
Prevención con Dieta Mediterránea

Treserra-Rimbau J Nutr. 2016 Mar 9. pii: jn223610.

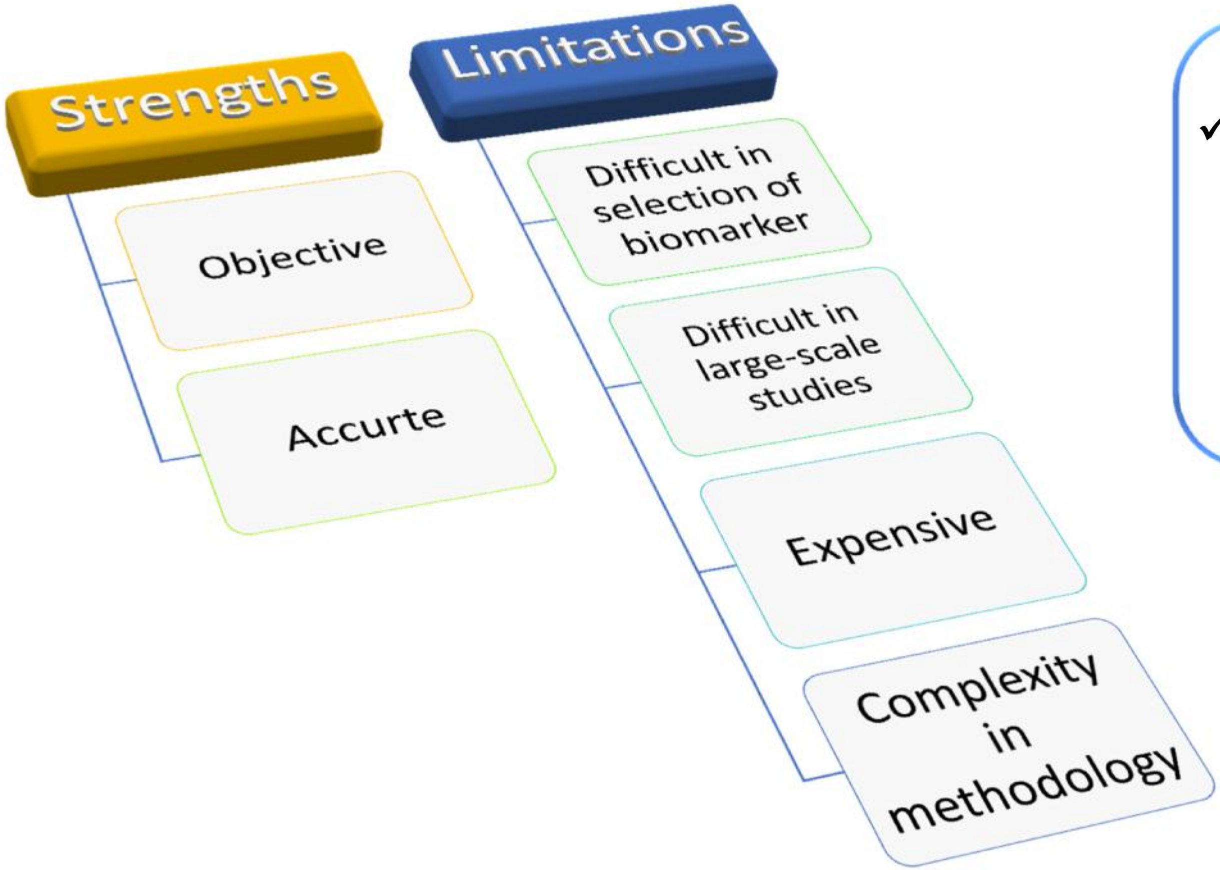
Biomarker of Polyphenol Intake



Needs for biomarkers

- Diversity of polyphenols
- Difficult in evaluation of habitual food intake
- Diversity of bioavailability
- Diversity of metabolism

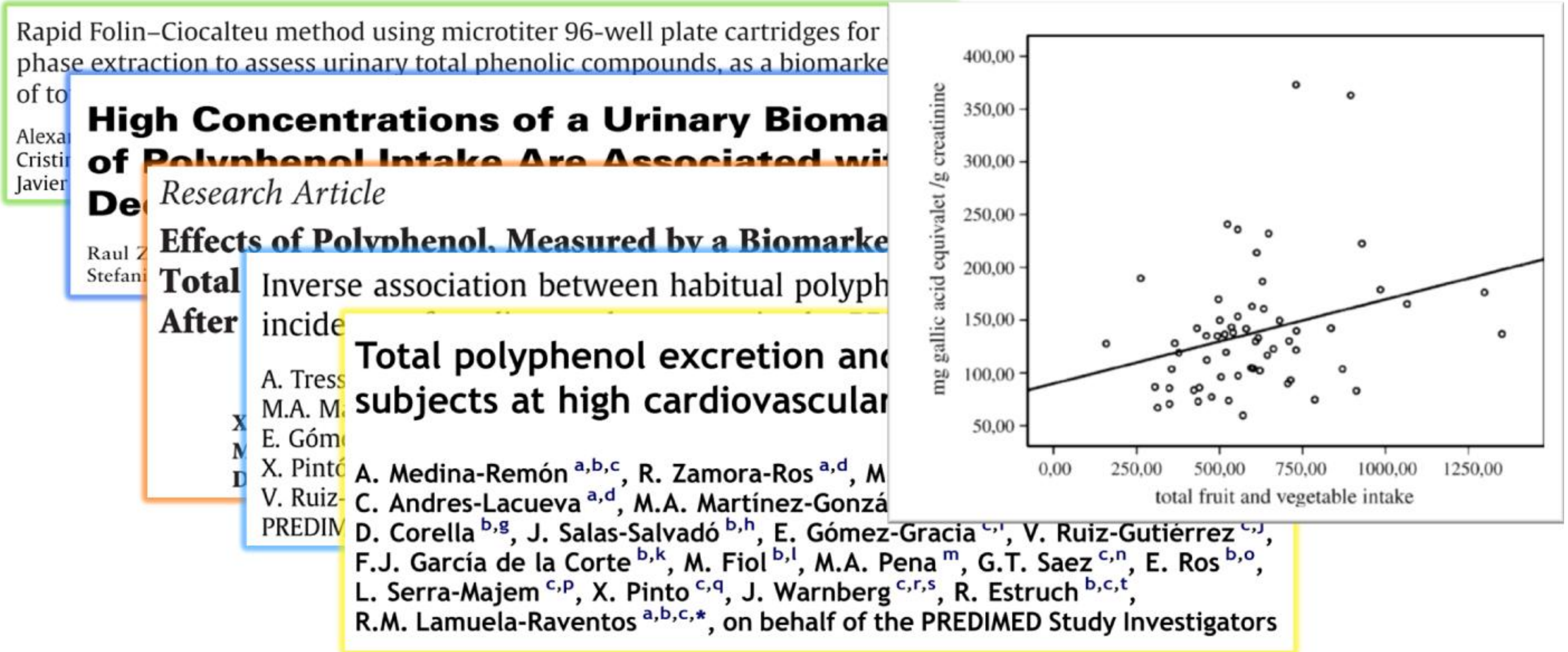
Strengths and Limitations



- ✓ Biomarkers can improve the information acquired by FFQ

Urinary Total Polyphenol Excretion

- Urinary total polyphenol excretion, after a solid phase extraction (SPE) clean-up, analyzed by a Folin-Ciocalteu (F–C) assay, could be considered as an accurate biomarker of polyphenol-rich food intake



Hypothesis and Aims

hypothesis

- We hypothesized that a high dietary polyphenol intake, recorded by urinary polyphenol excretion (TPE), could be associated to low CVD risk in an elderly population with high cardiovascular risk.

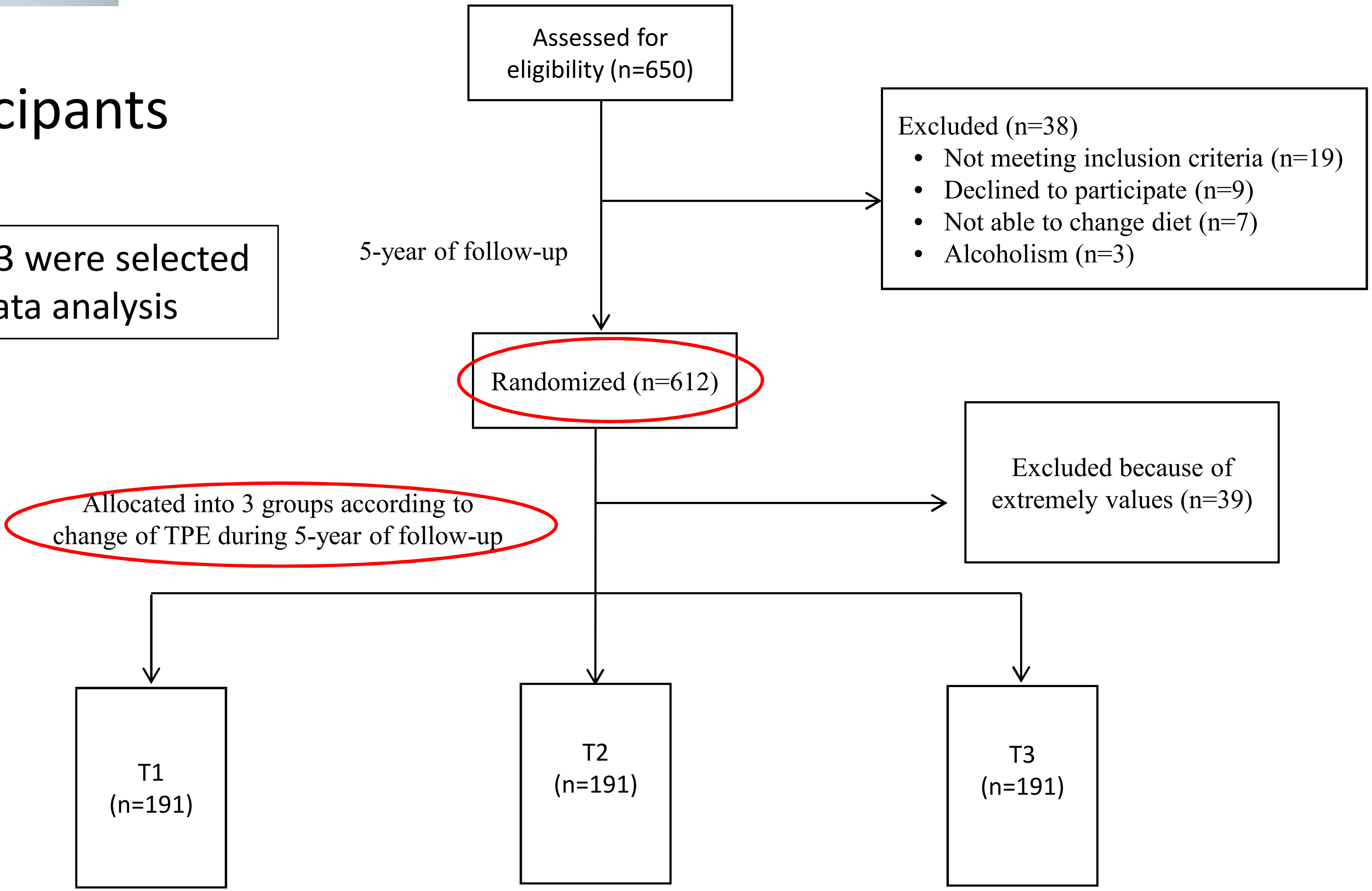
- Evaluate the cardiovascular protective role of dietary polyphenols, total polyphenol excretion (TPE) in urine as a reliable biomarker in the PREDIMED population.

Predimed
Prevención con Dieta Mediterránea

Polyphenol and CVD Risk Factors

Participants

Finally, 573 were selected for data analysis



Guo, X et al . Nutrients. 2017 May 3;9(5). pii: E452. doi: 10.3390/nu9050452.

Polyphenol and CVD Risk Factors

573 participants were randomly selected

Urinary samples were collected both at baseline and 5-year of intervention. TPE were measured with Folin-Ciocalteu method after solid phase extraction.

- **Our aim was to assess the association between urinary total polyphenols excretion (TPE) and clinical cardiovascular risk factors (glucose, cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, body weight) in a population at high cardiovascular risk.**

Evaluate dietary polyphenol intake expressed by TPE

Evaluate cardio-protective effects of polyphenol intake

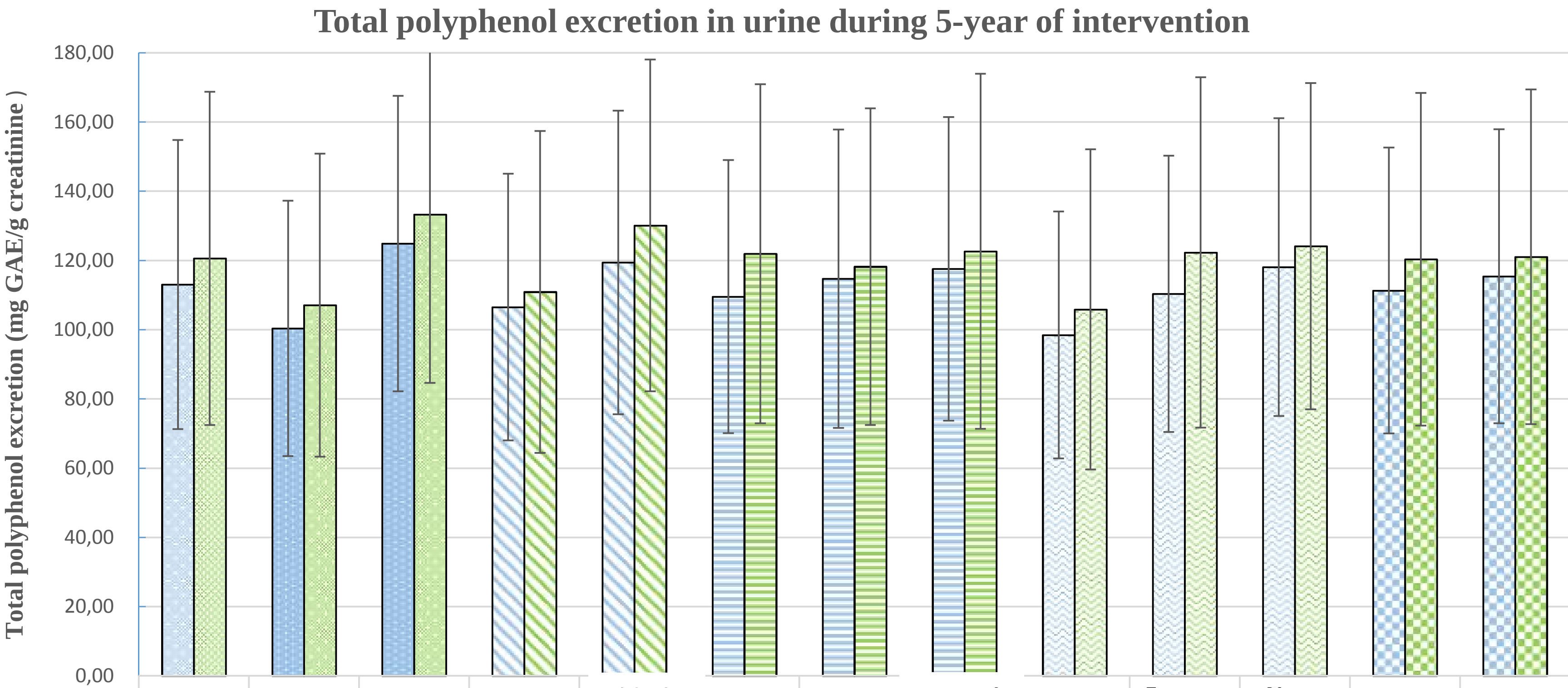
Evaluate effects of polyphenol intake on body weight

Guo, X et al . Nutrients. 2017 May 3;9(5). pii: E452. doi: 10.3390/nu9050452.

Clinical Measurements

- Measurements
  - Blood Pressure
  - Cholesterol
    - Total cholesterol
    - HDL-cholesterol
    - LDL-cholesterol
  - Glucose
  - Triglyceride
  - Anthropometic
    - Body weight
    - BMI
    - Waist circumference
    - Weight to height ratio

Total polyphenol extraction in urine

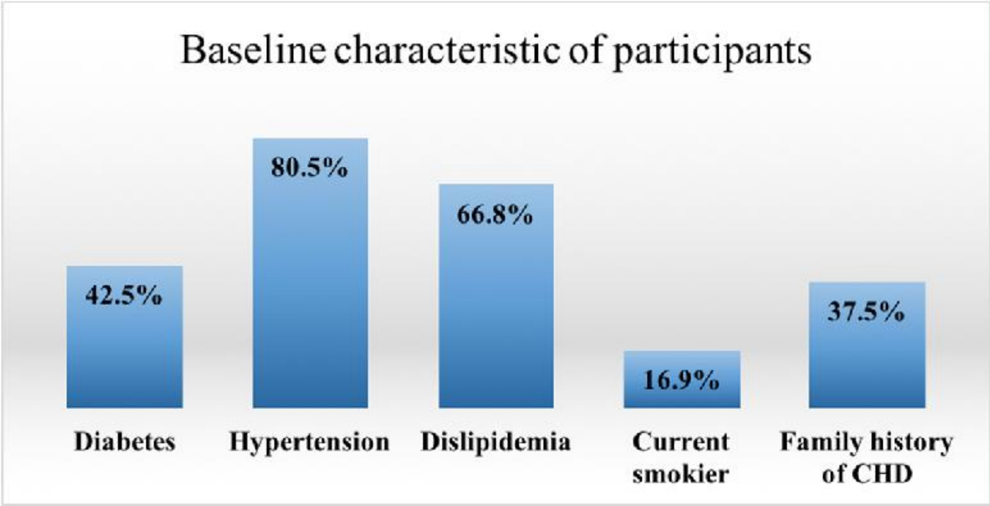


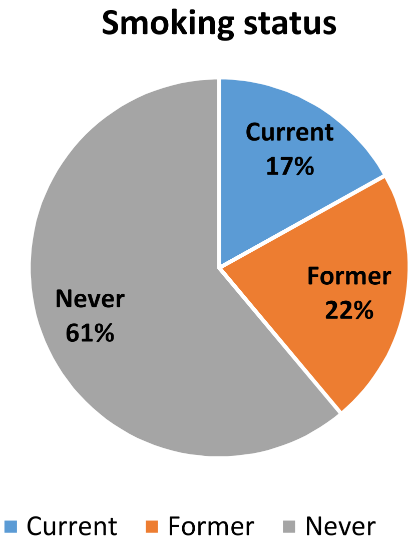
	Total	Male	Female	Younger	Elderly	Olive oil	Nuts	Control	Smoker	Former Somker	None smoker	P<9	P>9
Baseline	113,06	100,38	124,92	106,54	119,42	109,54	114,75	117,58	98,46	110,36	118,08	111,33	115,45
5-year	120,64	107,11	133,30	110,94	130,10	121,95	118,22	122,66	105,88	122,32	124,12	120,35	121,03

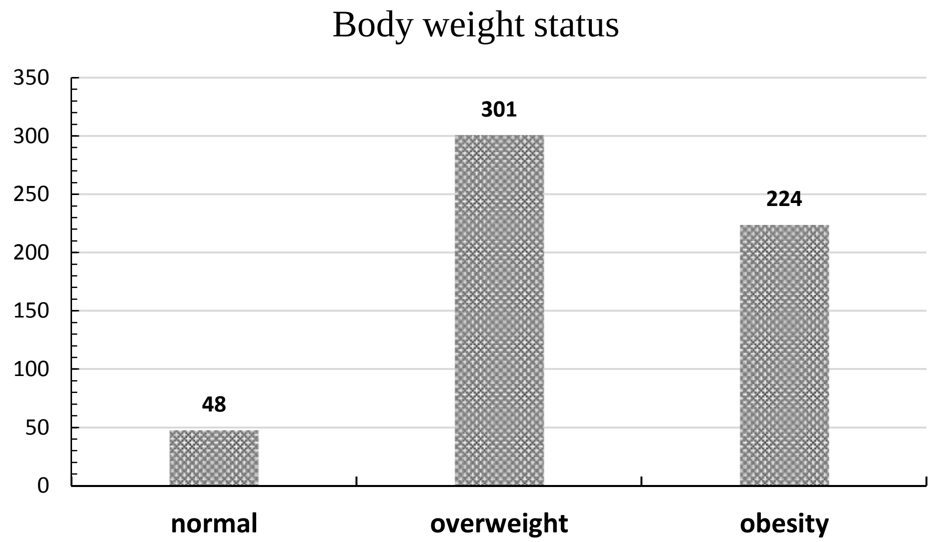
Baseline 5-year

Guo, X et al . Nutrients. 2017 May 3;9(5). pii: E452. doi: 10.3390/nu9050452.

Baseline characteristic of participants







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Changes in food and nutrients

Nutrients	Changes
Total Carbohydrate	→
Protein	→
Fat	↑
MUFA	↑
SFA	→
PUFA	↑
Fiber	↑
Alcohol	↓
Cholesterol	→

TPE and CVD risk factors

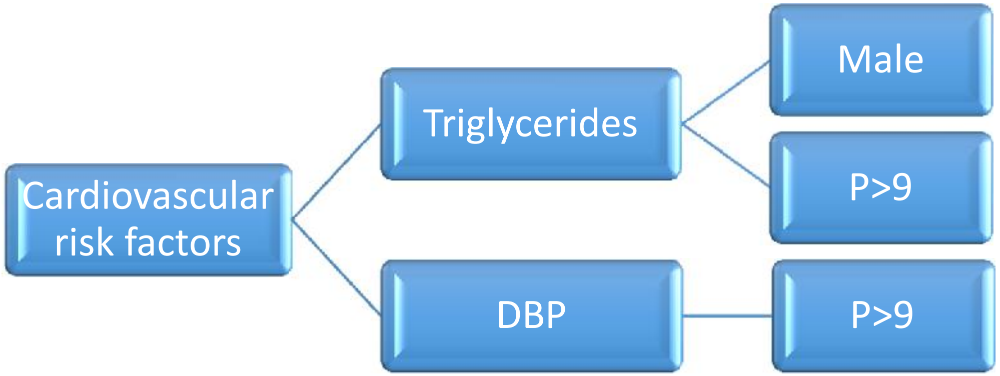
Association between TPE and cardiovascular risk factors

		β	SE	Beta	sig.	95% CI	
Change in Glucose (mg/dL)	Model 1	-4.164	1.979	-0.095	0.036	-8.053	-0.275
	Model 2	-4.316	1.981	-0.098	0.030	-8.208	-0.424
	Model 3	-4.355	1.949	-0.099	0.026	-8.186	-0.525
	Model 4	-4.372	1.953	-0.099	0.026	-8.209	-0.534
Change in Triglycerides (mg/dL)	Model 1	-8.356	3.06	-0.123	0.007	-14.369	-2.344
	Model 2	-8.563	3.058	-0.126	0.005	-14.572	-2.554
	Model 3	-8.627	3.094	-0.127	0.006	-14.708	-2.546
	Model 4	-8.572	3.099	-0.126	0.006	-14.662	-2.483
Change in Diastolic Blood Pressure (mm Hg)	Model 1	-1.316	0.531	-0.104	0.013	-2.359	-0.273
	Model 2	-1.254	0.532	-0.099	0.019	-2.298	-0.209
	Model 3	-1.153	0.532	-0.091	0.031	-2.198	-0.108
	Model 4	-1.156	0.533	-0.091	0.031	-2.203	-0.109

Significant inverse associations were found between tertiles of changes in TPE and glucose (β=-4.372; P=0.026), triglycerides (β=-8.572; P=0.006) and DBP (β=-1.156; P=0.031) after adjustment for potential confounders.

Guo, X et al . Nutrients. 2017 May 3;9(5). pii: E452. doi: 10.3390/nu9050452.

Stratified analysis for CVD risk factors



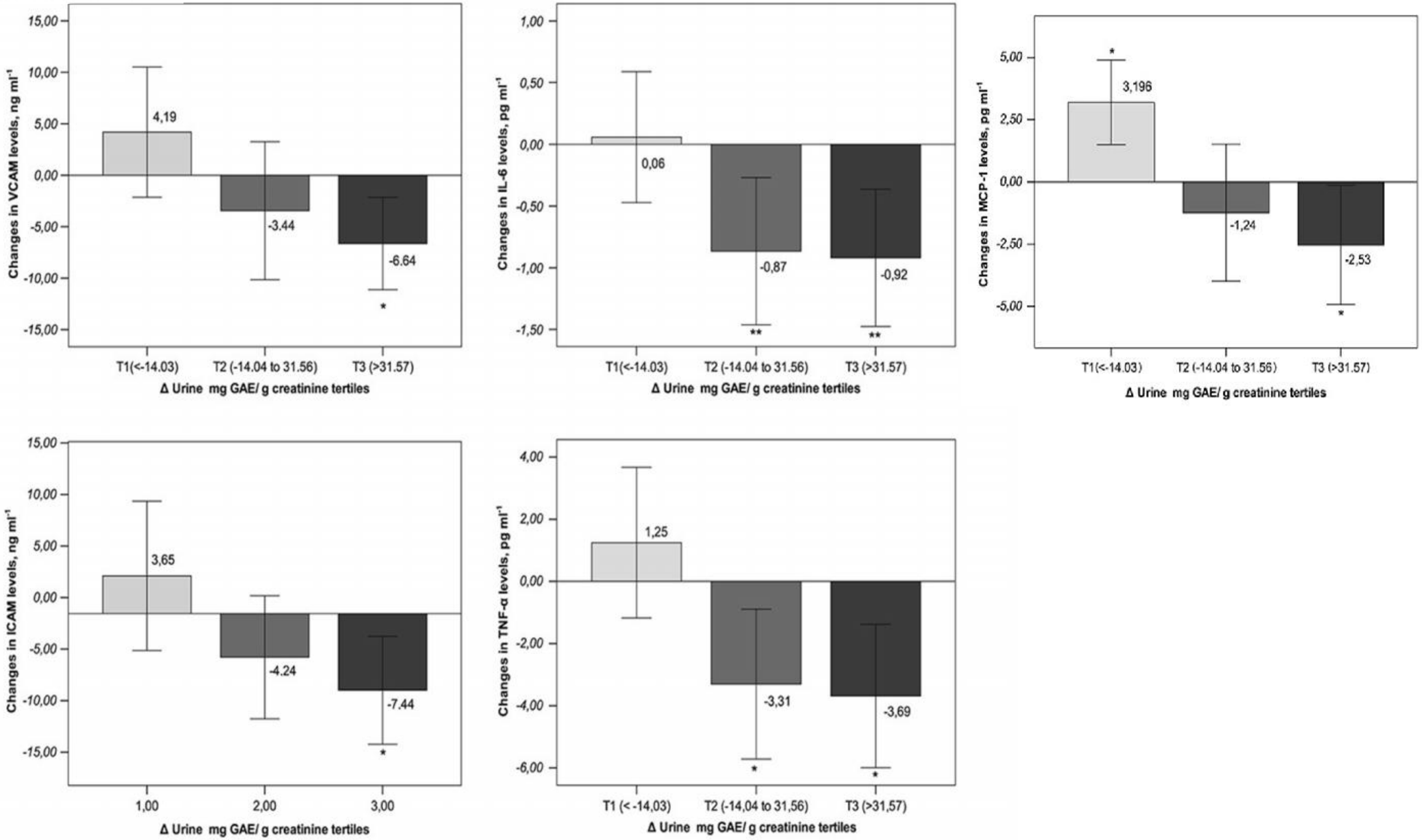
		N	Change in TG (mg/dL) Q1 mean	Q1 SD	Q2 mean	Q2 SD	Q3 mean	Q3 SD	P[a]
Gender	Male	236	6.41	43.58	-17.86	62.54	-14.80	44.68	0.007

		N	Change in TG (mg/dL) Q1 mean	Q1 SD	Q2 mean	Q2 SD	Q3 mean	Q3 SD	P[a]
P-14	<9	274	-0.89	57.27	-5.27	58.57	-10.63	67.61	0.676
	≥9	211	12.07	35.90	-6.49	61.19	-8.33	53.71	0.007

		N	Change in DBP (mg/dL) Q1 mean	Q1 SD	Q2 mean	Q2 SD	Q3 mean	Q3 SD	P[a]
P-14	<9	274	-1.24	10.04	-2.43	9.73	-2.14	11.67	0.714
	≥9	211	-1.46	10.24	-3.67	10.75	-5.29	9.84	0.026

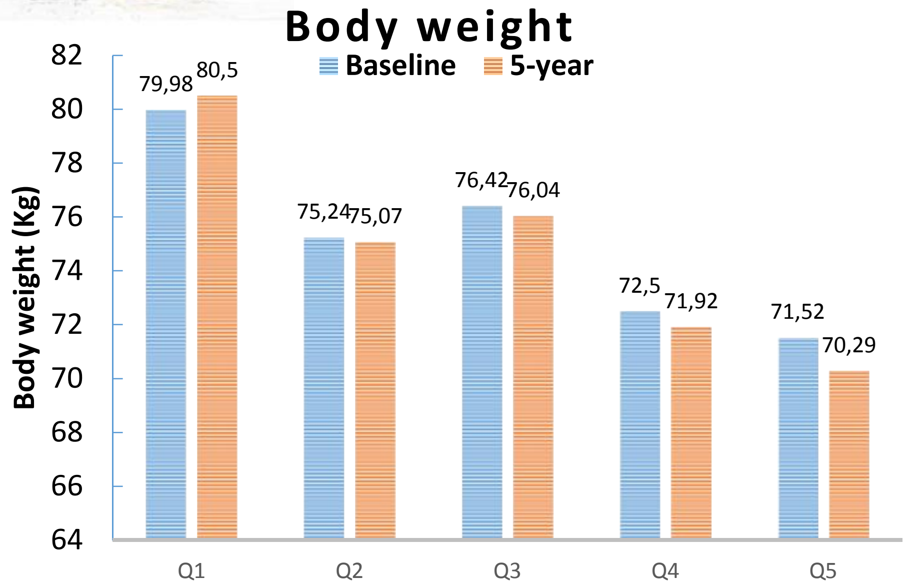
Guo, X et al . Nutrients. 2017 May 3;9(5). pii: E452. doi: 10.3390/nu9050452.

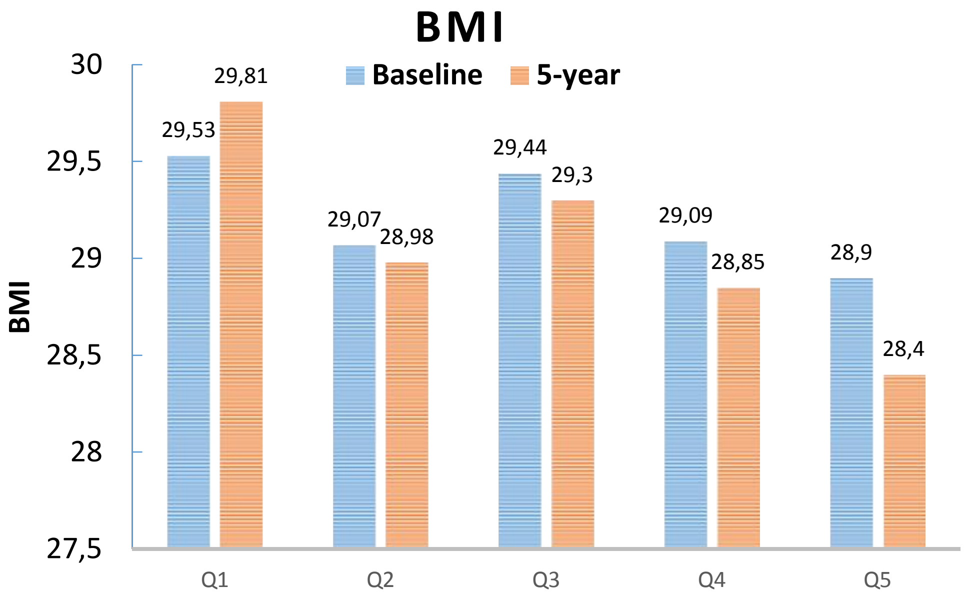
Polyphenols and Inflammatory Biomarkers

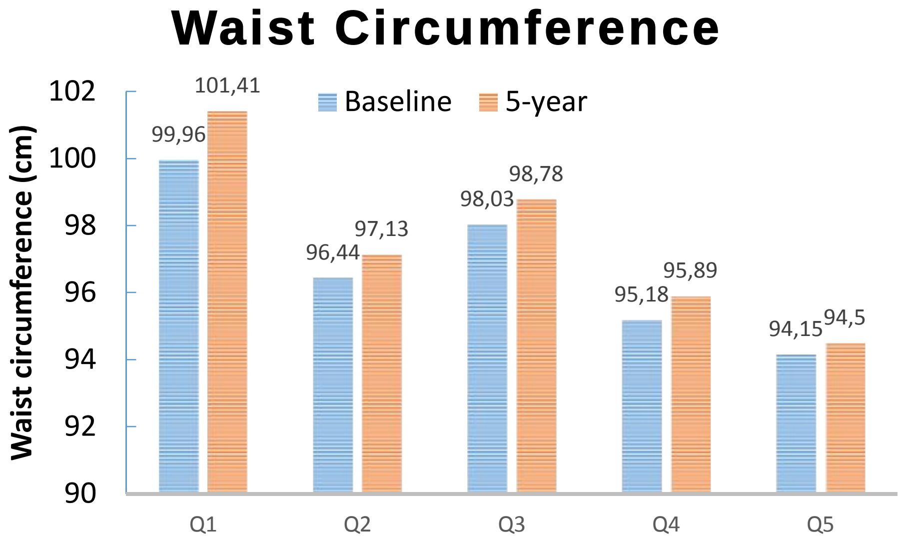


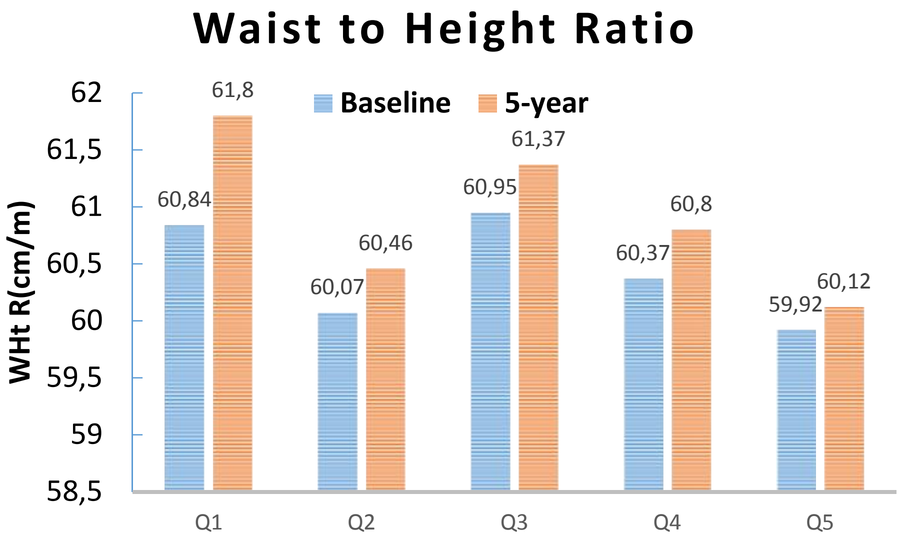
Medina-Remón A. et al . Br J Clin Pharmacol. 2017 Jan;83(1):114-128. doi: 10.1111/bcp.12986

Anthropometric parameters at baseline and after 5 years according to quintiles of TPE (mg GAE/g creatinine)









Association between TPE and Anthropometrics

Multivariate linear regression analyses with obesity indexes and quintiles of TPE (mg GAE/g creatinine) at 5-year

		β	SE	Beta	P	95%CI	
BW (kg)	Model 1	-2.350	0.331	-0.285	<0.001	-3.000	-1.700
	Model 2	-1.070	0.315	-0.130	0.001	-1.689	-0.451
	Model 3	-1.148	0.323	-0.139	<0.001	-1.783	-0.513
	Model 4	-1.004	0.320	-0.124	0.002	-1.634	-0.375
BMI	Model 1	-0.295	0.104	-0.118	0.005	-0.499	-0.090
	Model 2	-0.328	0.110	-0.131	0.003	-0.544	-0.111
	Model 3	-0.358	0.113	-0.143	0.002	-0.580	-0.136
	Model 4	-0.320	0.113	-0.129	0.005	-0.541	-0.098
WC (cm)	Model 1	-1.500	0.296	-0.208	<0.001	-2.082	-0.918
	Model 2	-0.721	0.293	-0.100	0.014	-1.296	-0.147
	Model 3	-0.877	0.302	-0.122	0.004	-1.471	-0.283
	Model 4	-0.742	0.297	-0.104	0.013	-1.326	-0.158
WHtR (cm/m)	Model 1	-0.298	0.178	-0.070	0.094	-0.648	0.051
	Model 2	-0.367	0.189	-0.087	0.052	-0.739	0.004
	Model 3	-0.474	0.195	-0.112	0.016	-0.857	-0.090
	Model 4	-0.408	0.194	-0.097	0.036	-0.788	-0.028

Significant inverse associations were found between quintiles of TPE at 5 years and BW (β=-1.004; P=0.002), BMI (β=-0.320; P=0.005), WC (β=-0.742; P=0.013) and WHtR (β=-0.408; P=0.036) after adjustment for potential confounders.

TPE and Prevalence of Obesity

Multivariate adjusted odds ratios (95% CI) for obesity (n=213)

	Q1	Q2	95% CI		Q3	95% CI		Q4	95% CI		Q5	95% CI		*P-trend*
Model 1	1 (ref.)	0.639	(0.375	1.089)	0.769	(0.454	1.302)	0.664	(0.390	1.129)	0.450	(0.259	0.782)	0.073
Model 2	1 (ref.)	0.597	(0.344	1.035)	0.691	(0.400	1.192)	0.618	(0.350	1.091)	0.383	(0.211	0.694)	0.036
Model 3	1 (ref.)	0.559	(0.314	0.995)	0.649	(0.367	1.147)	0.543	(0.296	0.996)	0.318	(0.166	0.606)	0.015
Model 4	1 (ref.)	0.604	(0.332	1.100)	0.720	(0.399	1.300)	0.560	(0.298	1.054)	0.346	(0.176	0.678)	0.039

In fully-adjusted models, participants in the category of highest TPE had a lower prevalence of obesity (odds ratio (OR) = 0.346, 95% confidence interval (CI) 0.176 to 0.678; P-trend, 0.039) than those in the lowest category.

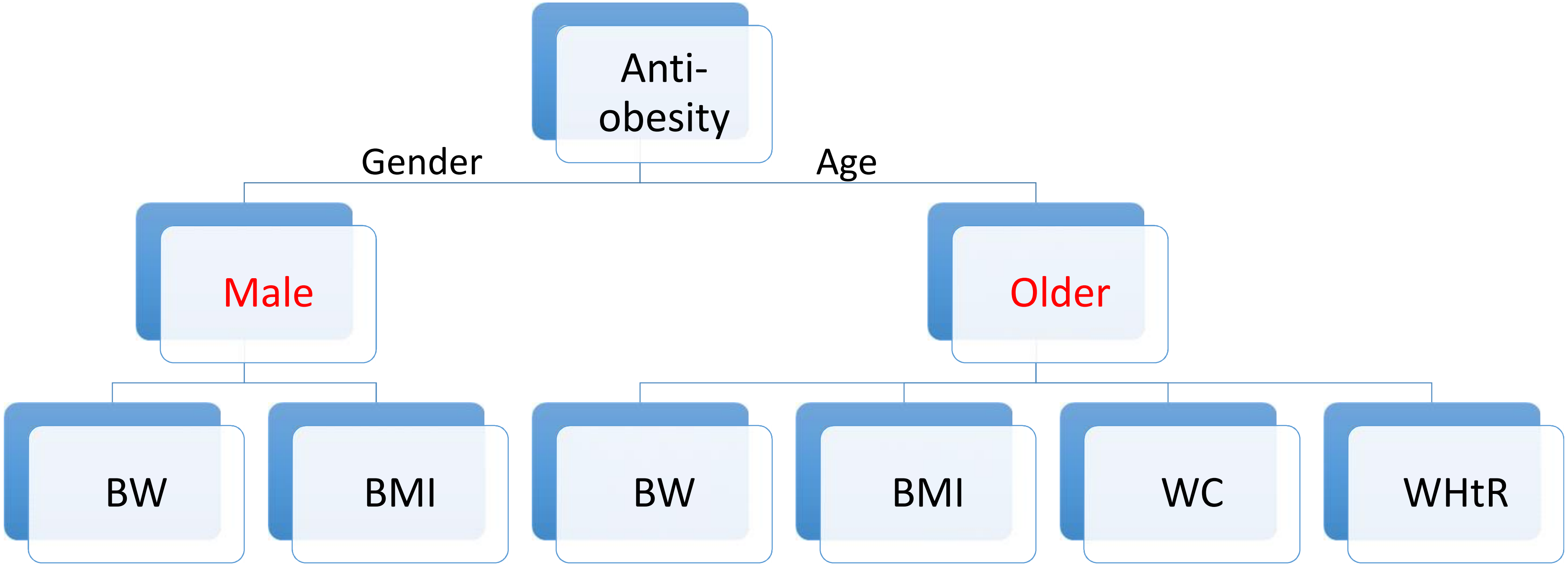
TPE and Incidence of Obesity

Multivariate adjusted odds ratios (95% CI) for obesity (n=213)

	Q1	Q2	95% CI		Q3	95% CI		Q4	95% CI		Q5	95% CI		P
Model 1	1 (ref.)	0.912	(0.337	2.468)	0.676	(0.253	1.810)	0.351	(0.142	0.866)	0.406	(0.164	1.005)	0.054
Model 2	1 (ref.)	0.454	(0.185	1.115)	0.235	(0.072	0.767)	0.285	(0.093	0.868)	0.145	(0.037	0.558)	0.014
Model 3	1 (ref.)	0.382	(0.146	1.001)	0.193	(0.055	0.676)	0.272	(0.084	0.885)	0.119	(0.028	0.505)	0.014
Model 4	1 (ref.)	0.366	(0.126	1.062)	0.156	(0.040	0.612)	0.218	(0.054	0.881)	0.095	(0.018	0.498)	0.018

In fully-adjusted models, participants in the category of highest TPE had a lower incidence of obesity (odds ratio (OR) = 0.095, 95% confidence interval (CI) 0.018 to 0.498; P-trend, 0.018) than those in the lowest category.

Stratified Analysis



Males showed significant inverse associations with BW (β=-1.004; P=0.031) and BMI (β=-0.298; P=0.036). All adiposity parameters [BW (β=-1.358; P=0.002), BMI (β=-0.466; P=0.003), WC (β=-1.061; P=0.012), and WHtR (β=-0.623; P=0.023))] were lower in the older group (age ≥ 67).

Strengths

- The prospective design, relatively long-term follow-up and comprehensive data on risk factors and confounders.
- The evaluation of overall effects of polyphenol intakes on specific cardiovascular risk factors, which provide clinical evidence of the protective role of polyphenol intake against CVD.
- The use of a reliable biomarker of total polyphenol intakes.
- The Folin-Ciocalteu assay is a rapid, cheap, and environmentally friendly measurement that can be applied in large intervention studies.

Limitations

- Our sub-study was conducted only among elderly subjects at high cardiovascular risk; therefore, the results should not be extrapolated to the general population.

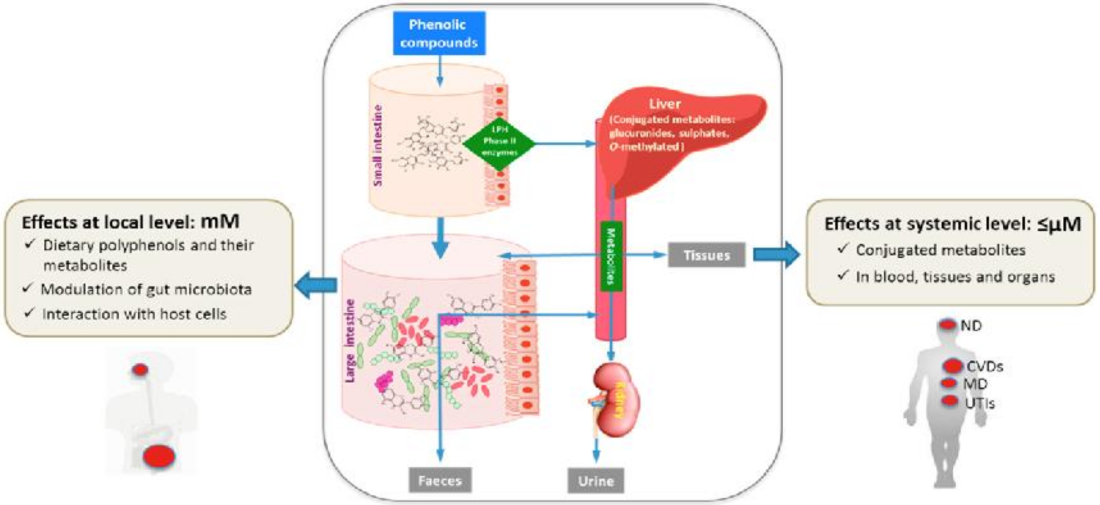
- Residual confounding could still exist even though we adjusted for potential confounders related to lifestyles, profiles of participants, family history of CVD, and eating habits.

- Possible synergistic effects between different types of polyphenols and other dietary components have not been measured.

- Intrinsic limitations of biomarkers: measurement error from the analysis and variability between individuals.

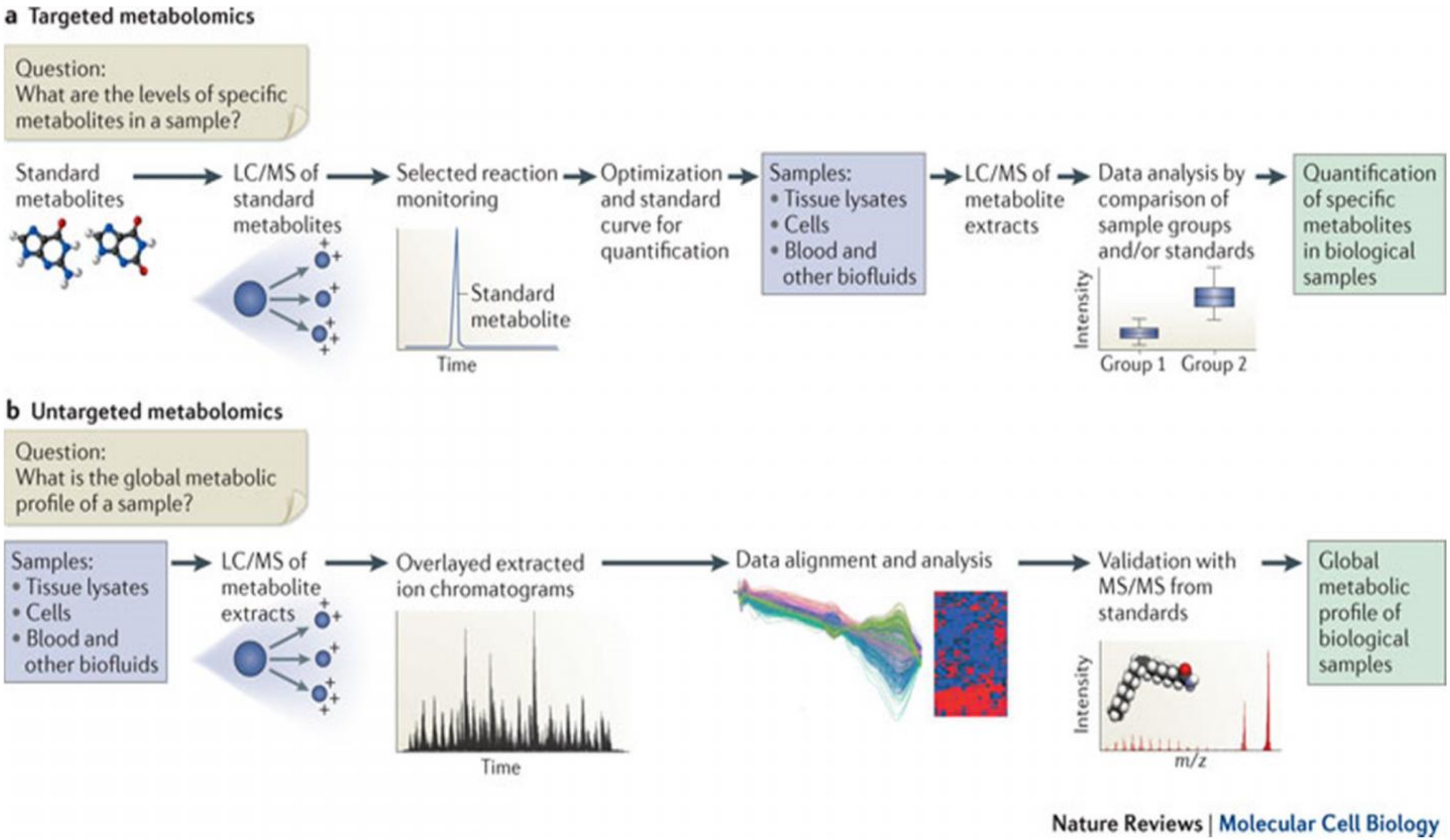
Future

Biomarkers analysis of these polyphenols (mainly from microbiota) in urines is necessary to corroborate our results and to evaluate the possible mechanism of action



Cueva et al. Molecules 2017, 22(1), 99; doi:10.3390/molecules22010099

Targeted and Untargeted Metabolomics



METHODOLOGY

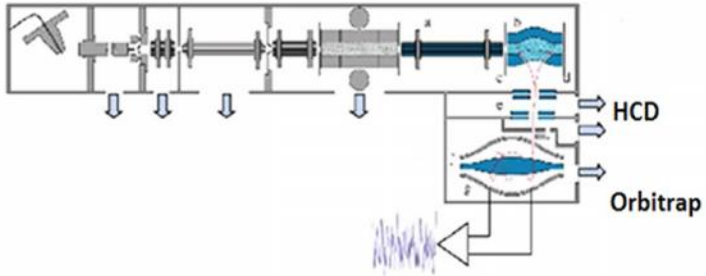
HPLC - LTQ - ORBITRAP - MS

EXACT MASS MEASUREMENTS AND ELUCIDATION OF THE STRUCTURES OF UNKNOWN COMPOUNDS.

SINGLE-STAGE MASS ANALYSIS, TWO-STAGE MASS ANALYSIS (MS/MS) AND MULTI-STAGE MASS ANALYSIS (MSN).

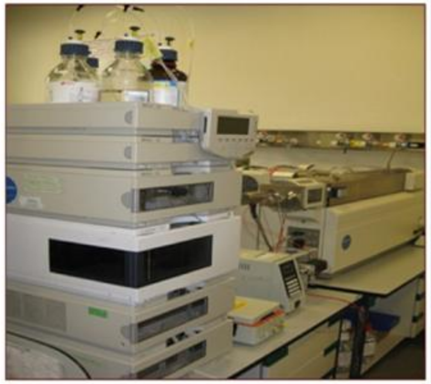
VERY GOOD MASS ACCURACIES BOTH IN MS AND MS/MS.

UNAMBIGUOUS ASSIGNMENT OF ALL FRAGMENT IONS WITH FEWER EXPERIMENTS AND EASIER INTERPRETATION THAN PREVIOUS METHODS.

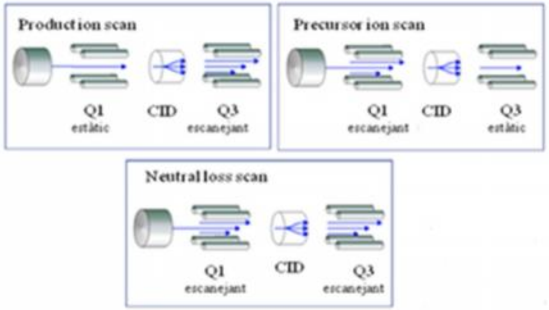


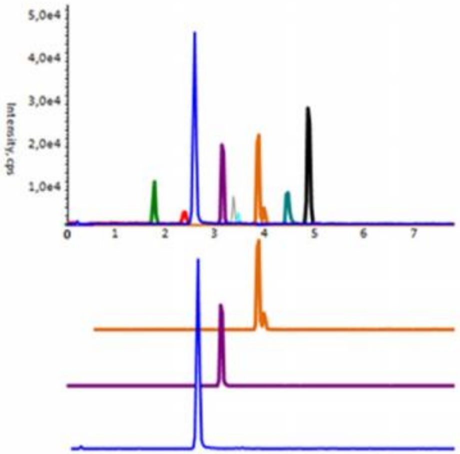
METHODOLOGY

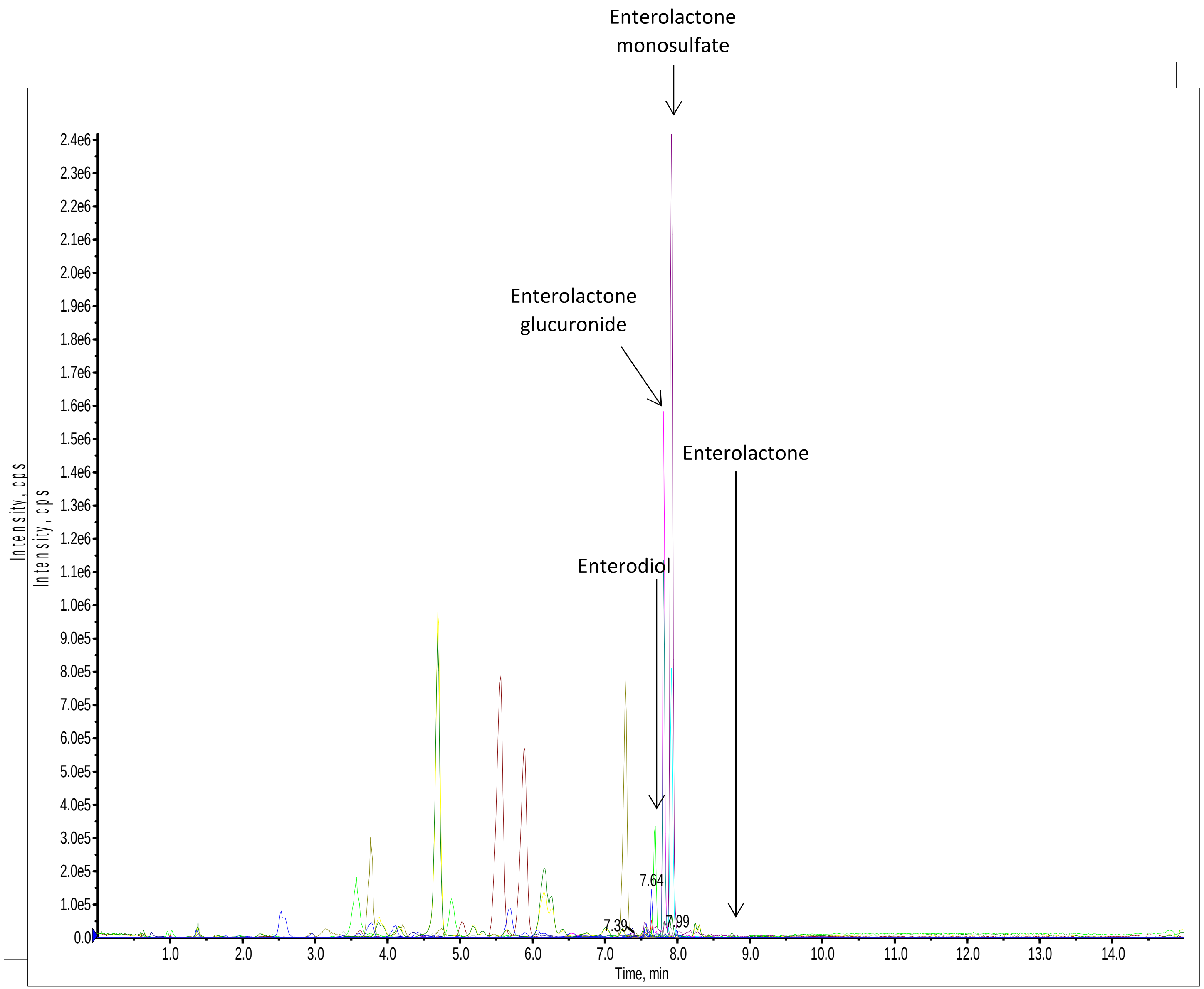
HPLC - MS/MS



ACCURATE QUANTIFICATION
BETTER SENSITIVITY







Enterolactone monosulfate
Enterolactone glucuronide
Enterolactone
Enterodiol
Intensity, cps
Time, min
7.64
7.39
7.99

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Thank you

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