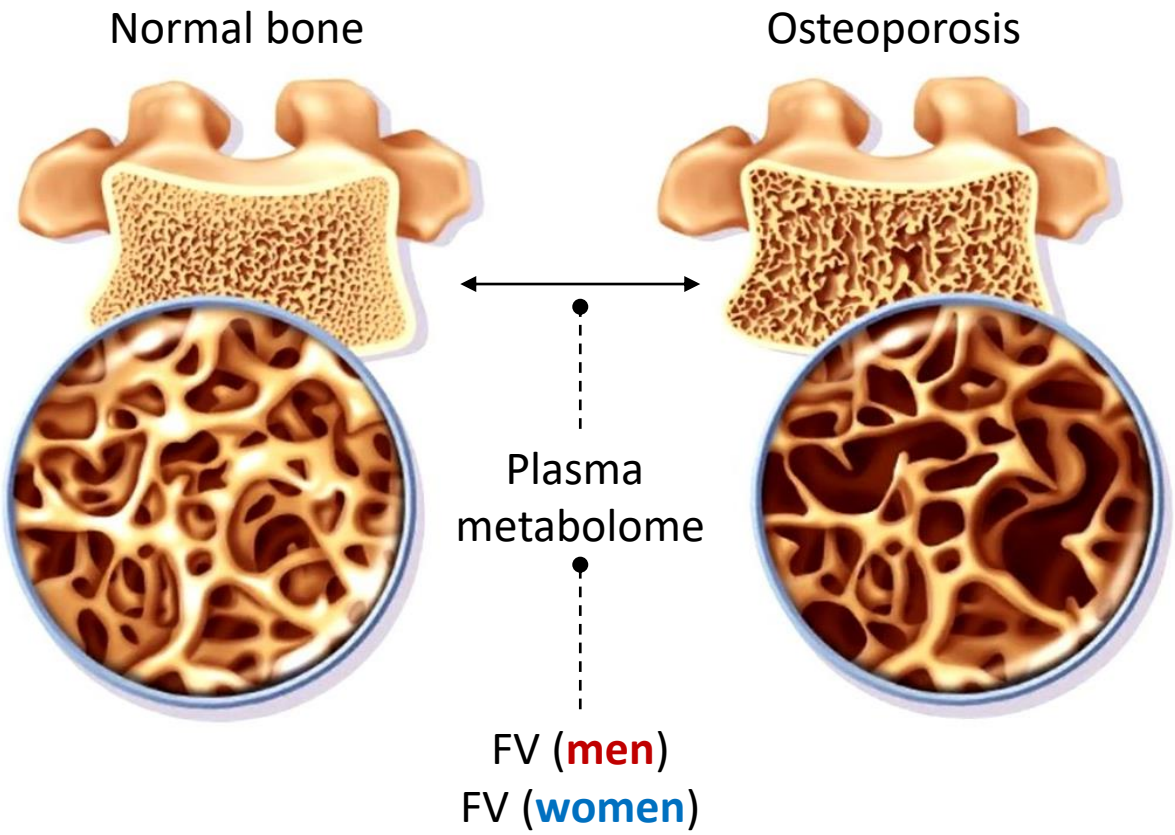
Diet-derived fruit and vegetable metabolites suggest sex-specific mechanisms conferring protection against osteoporosis in humans

Jacob J Christensen
Clinical dietitian, PhD

National Advisory Unit on FH, OUH
Department of Nutrition, UiO



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[Mangano KM et al, in review]

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Dept of Biomedical and Nutritional Sciences
University of Massachusetts Lowell, Lowell, MA

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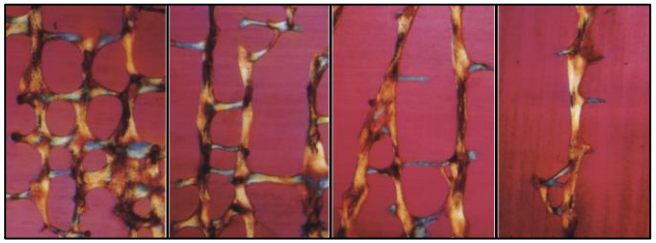
Jean Mayer U.S. Department of Agriculture
Human Nutrition Research Center on Aging
Tufts University, Boston, MA

In this talk, I will present sex-specific associations between FV intake, metabolite profile and OS in Puerto Rican adults

Background

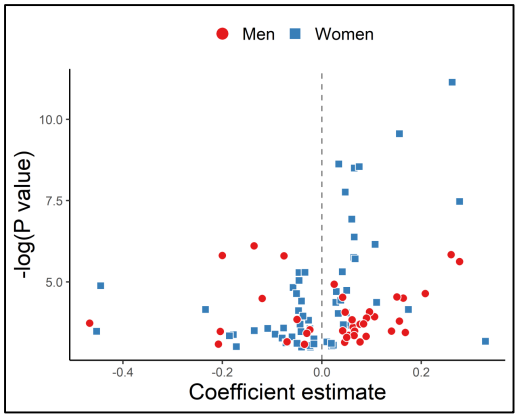


2004 → 2009

Baseline interview (n = 1504)

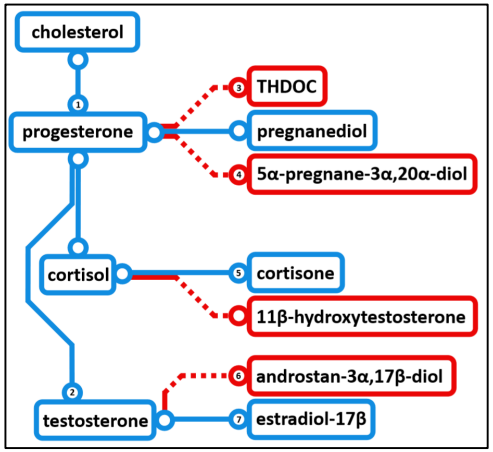
Recruitment (year 2000 Census):
- Puerto Ricans
- 45-75 years
- Greater Boston
- Door-to-door enumeration
- Community-engaged activities

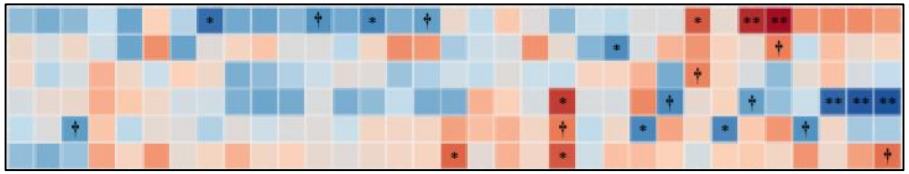
Population



Gender-specific effects of FV and OS

FV intake in women:
effects on steroid synthesis pathway?

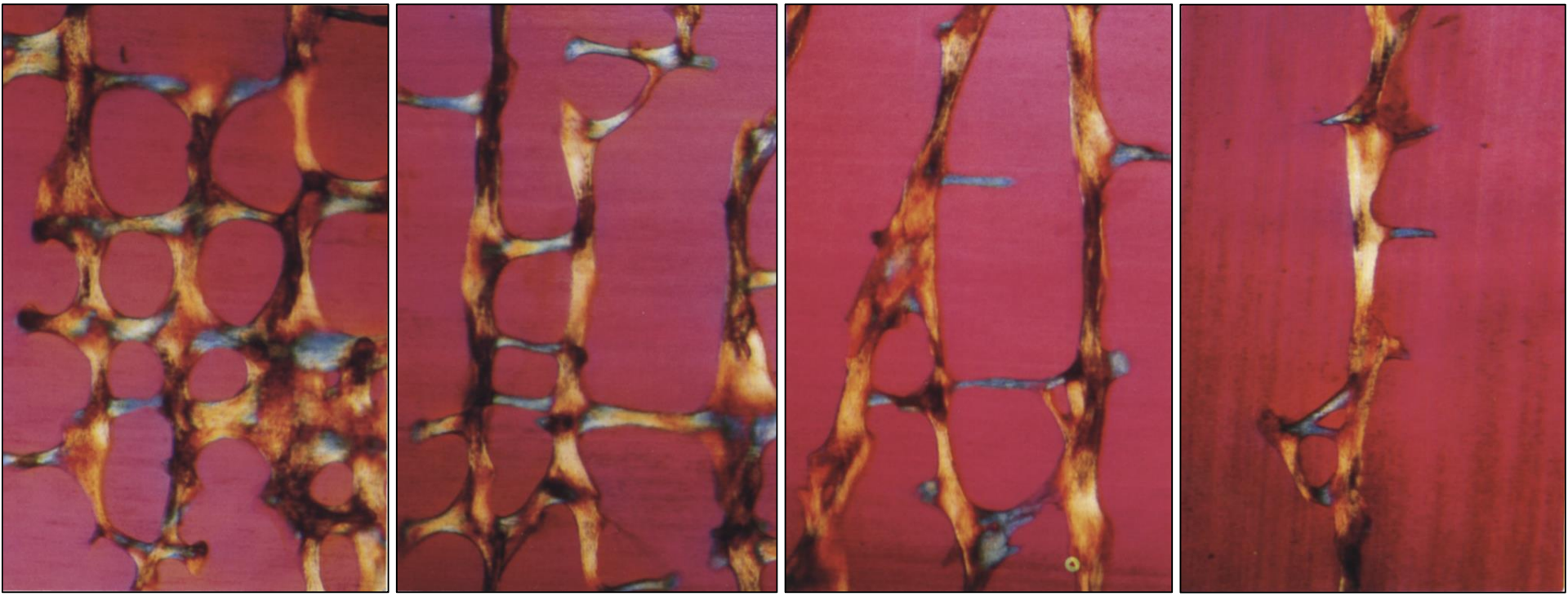




Normalization of OS metabolome by FV?

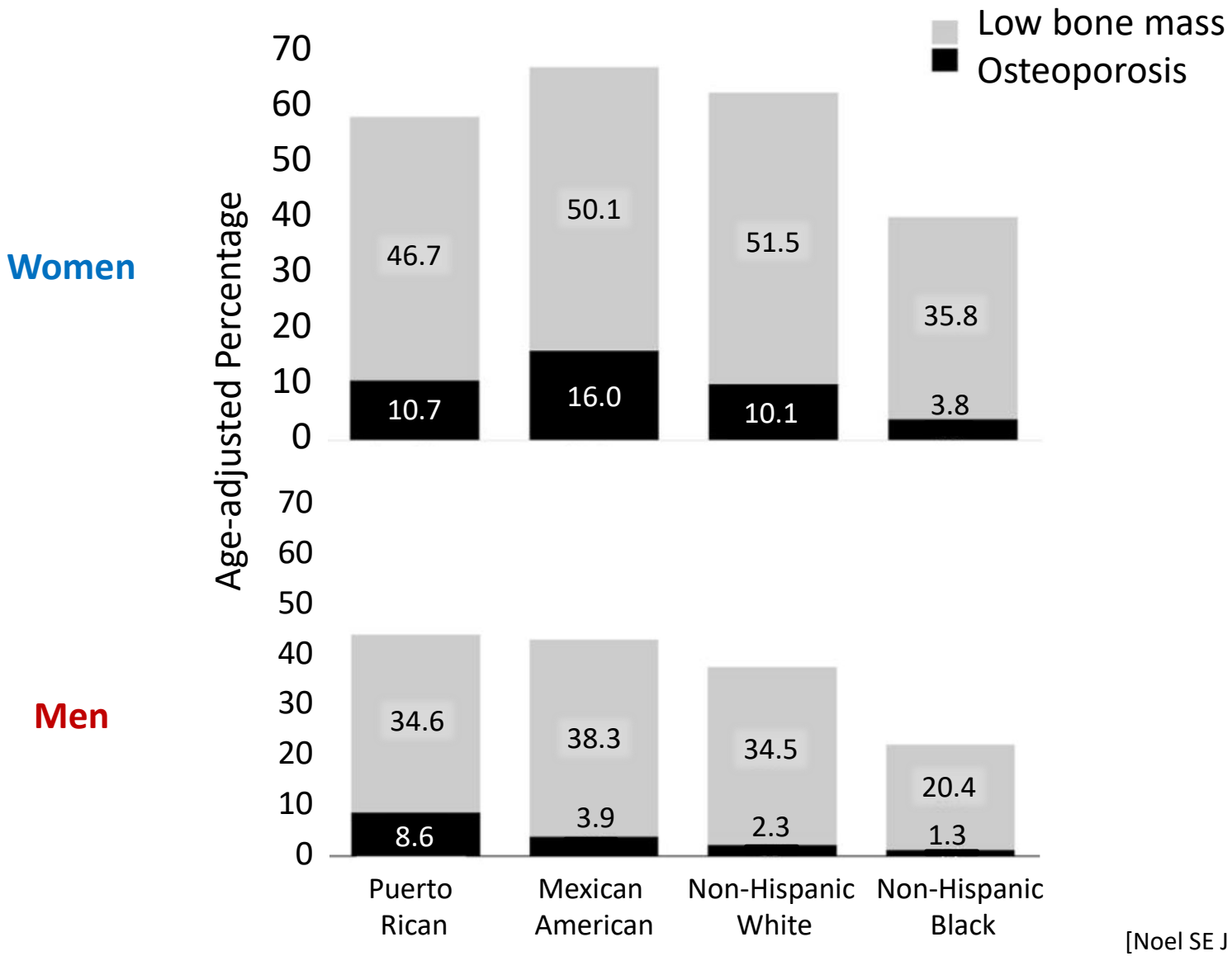
OS is characterized by thinning and breakdown of the trabecular network

50-y (man) 58-y (man) 76-y (man) 87-y (woman)



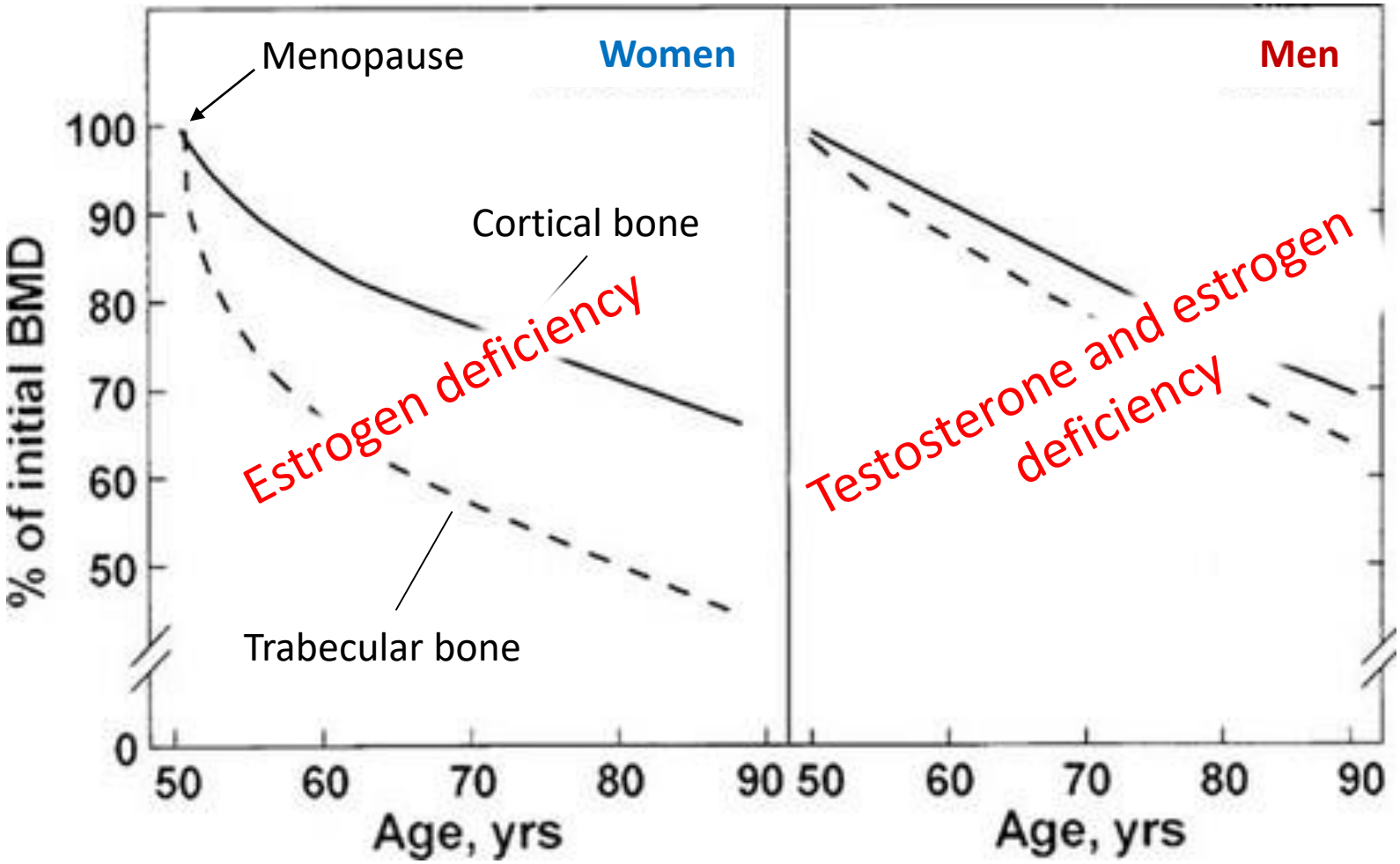
[Mosekilde L Bone 1988]

OS has emerged as a chief public health problem among aging Puerto Rican adults



[Noel SE J Bone Miner Res 2018]

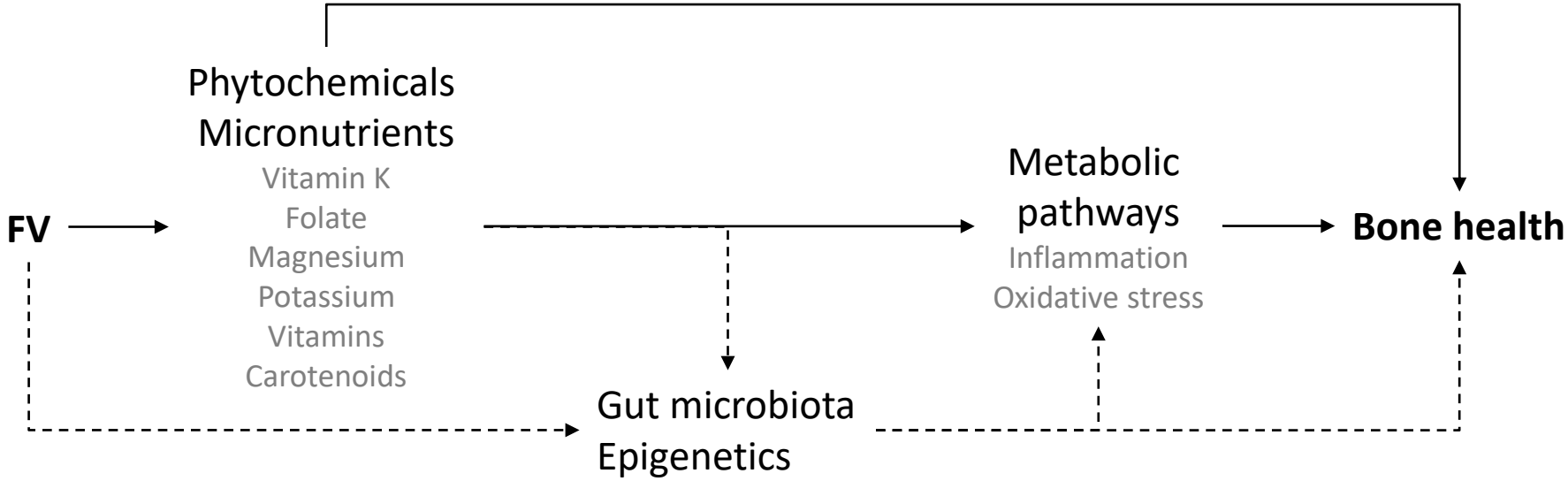
Variation in PBM and bone loss can explain a large proportion of the variation in prevalence of OS



[Riggs BL J Bone Miner Res 1998]

FV intake may protect against low BMD, OS and fractures

Design	Exposure	Outcome	Result	Reference
Cross-sectional	Higher FV intake	BMD	Greater BMD	Chen YM Br J Nutr 2006 Tucker KL AJCN 1999 Prynne CJ AJCN 2006
Cross-sectional	Higher FV intake	BMD OS	Greater BMD Lower risk	Qiu R PLoS One 2017
Cohort	FV < 1 serving/d	OS fracture	39 % increased risk	Benetou V J Bone Miner Res 2016
Cohort	FV < 5 servings/d	Hip fracture	Increased risk	Byberg L J Bone Miner Res 2015
MA (cohorts)	Higher V intake	Fracture	Lower incidence	Luo S Sci Rep 2016



[Sahni S Curr Osteoporos Rep 2015, Klinder A Food Funct 2016, Trost K Food Res Int 2018]

BPROS is an extension of the BPRHS, a prospective cohort of Puerto Ricans living in the Greater Boston area

2004 → 2009

Baseline interview (n = 1504)

Recruitment (year 2000 Census):
- Puerto Ricans
- 45-75 years
- Greater Boston
- Door-to-door enumeration
- Community-engaged activities

2-y follow up (n = 1267)

Invited to join BPROS

Declined participation (n = 205)
Moved (n = 13)
Difficult to schedule interview (n = 47)
Lost to follow up (n = 11)
Other reasons (n = 2)
Died since 2-y interview (n = 20)

Did not complete 2-y interview, but re-consented to BPROS (n = 4)

Re-consented to BPROS (n = 973)

	Declined	Re-consented	P
Age	60.9 yr	58.7 yr	<0.001
T2DM	47.8 %	40.4 %	0.03

No difference in gender (P=0.91), smoking status (P=0.16), PA score (P=0.42) or activities of daily living (P=0.34)

[BPROS, Boston Puerto Rican Osteoporosis Study; BPRHS, Boston Puerto Rican Health Study]

The present study includes 600 subjects with data on body composition, dietary intake and plasma metabolomics

Re-consented for BPROS (n = 973)

Bone Metabolism Laboratory (HNRCA):
- In-person interview
- Bone health

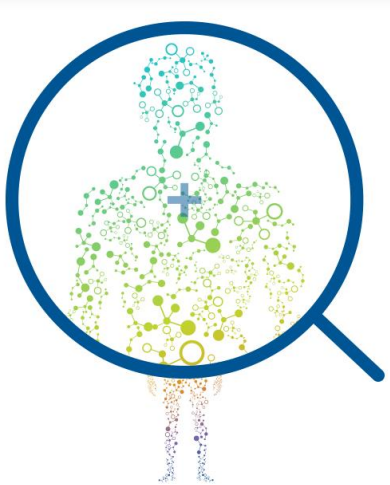
Invalid BMD measurement (n = 21)

Final data merge (n = 635)

Current analysis (n = 600)

Invalid dietary data (n = 35)

BPRHS samples (n = 817)



Metabolon, Inc (Morrisville):
- Metabolomic analysis

[metabolon.com]

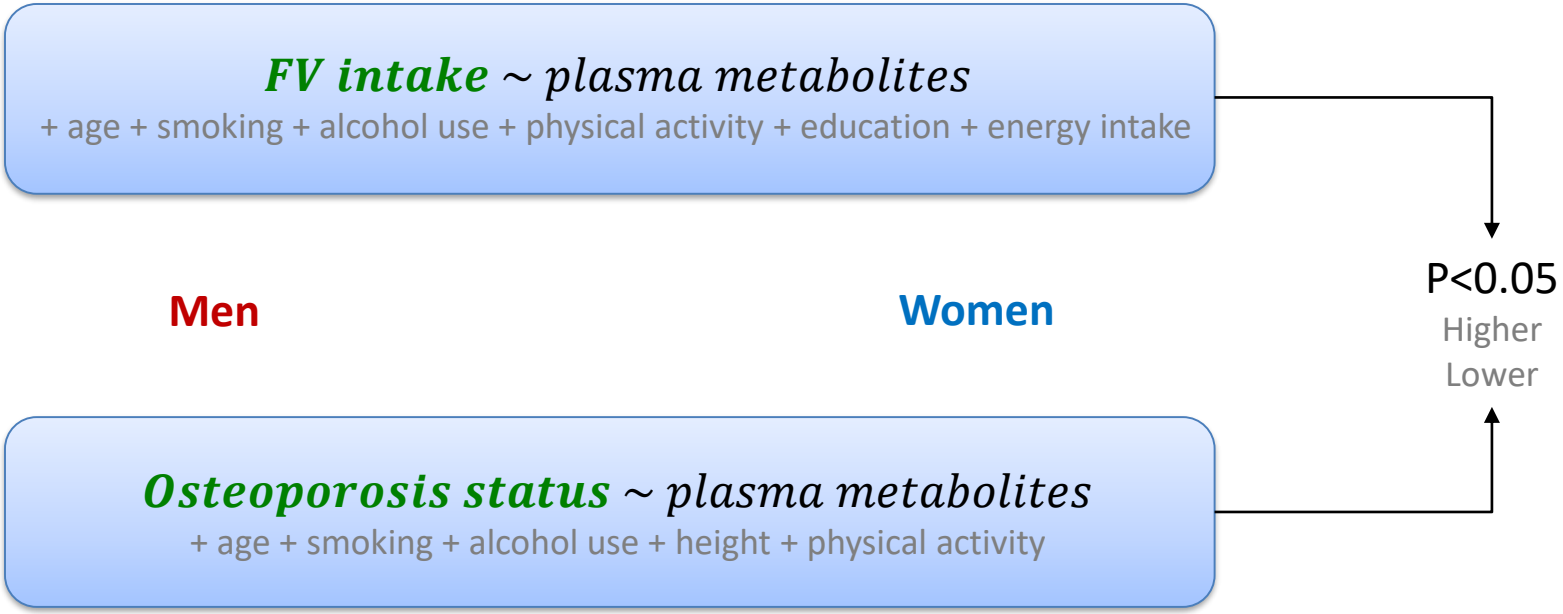
Men and subjects with OS consumed less FV compared to women and subjects without OS

Characteristic	Men (n = 174)	Women (n = 426)
	Mean (SD) or n (%)	Mean (SD) or n (%)
Age (y) (range: 46-79)	59.8 (7.8)	60.3 (7.3)
BMI (kg/m2)	30.1 (5.1)	33.1 (7.0)
Serum 25(OH) D (nmol/L)	18.2 (7.0)	19.8 (7.5)
Physical activity score	33.1 (6.5)	30.9 (3.6)
Current smoker (yes)	56 (32)	82 (19)
Heavy alcohol consumption (yes)	22 (13)	20 (5)
Education		
≤8th grade	73 (42)	214 (50)
>8th grade – high school diploma	79 (46)	143 (34)
Some college	21 (12)	69 (16)
	2375 (828)	2017 (851)
	1.218 (0.189)	1.133 (0.171)
Femoral Neck	1.007 (0.147)	0.916 (0.136)

Servings of FV	No OS	OS
	Mean (SD)	Mean (SD)
Both women and men	3.1 (1.8)	2.3 (1.4)
Women	3.2 (1.8)	2.4 (1.4)
Men	2.8 (1.8)	2.0 (1.2)

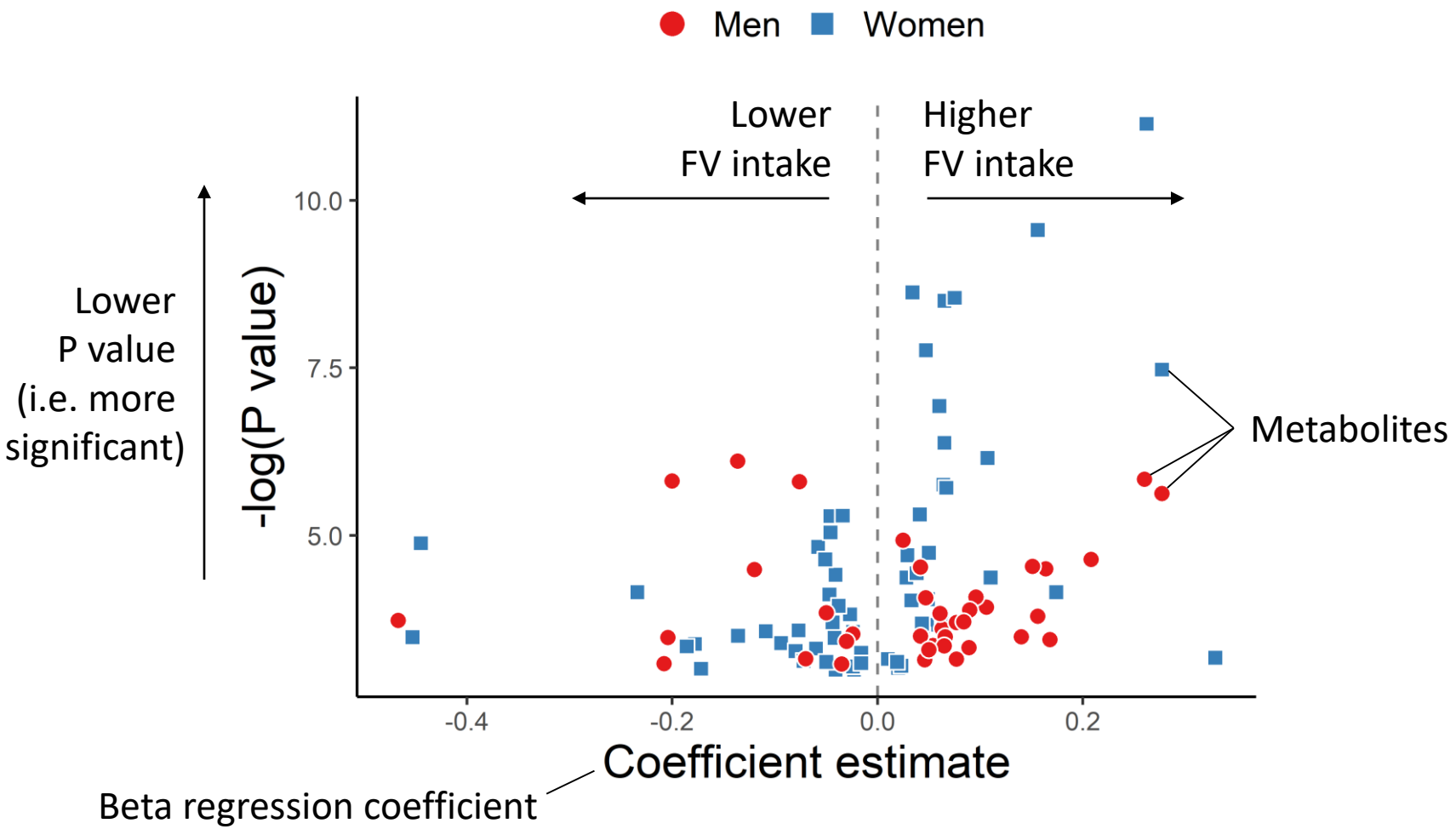
	OR (95 % CI)	*P*
Crude	0.73 (0.57-0.94)	0.013
+ FV variety	0.72 (0.56-0.93)	0.012

We associated each of the 525 metabolites with OS status or FV intake separately for women and men



Metabolites significantly related to *FV intake* differ by sex

Women (*P*<0.05): **66** / 525 (12.6 %) metabolites
Men (*P*<0.05): **38** / 525 (7.2 %) metabolites



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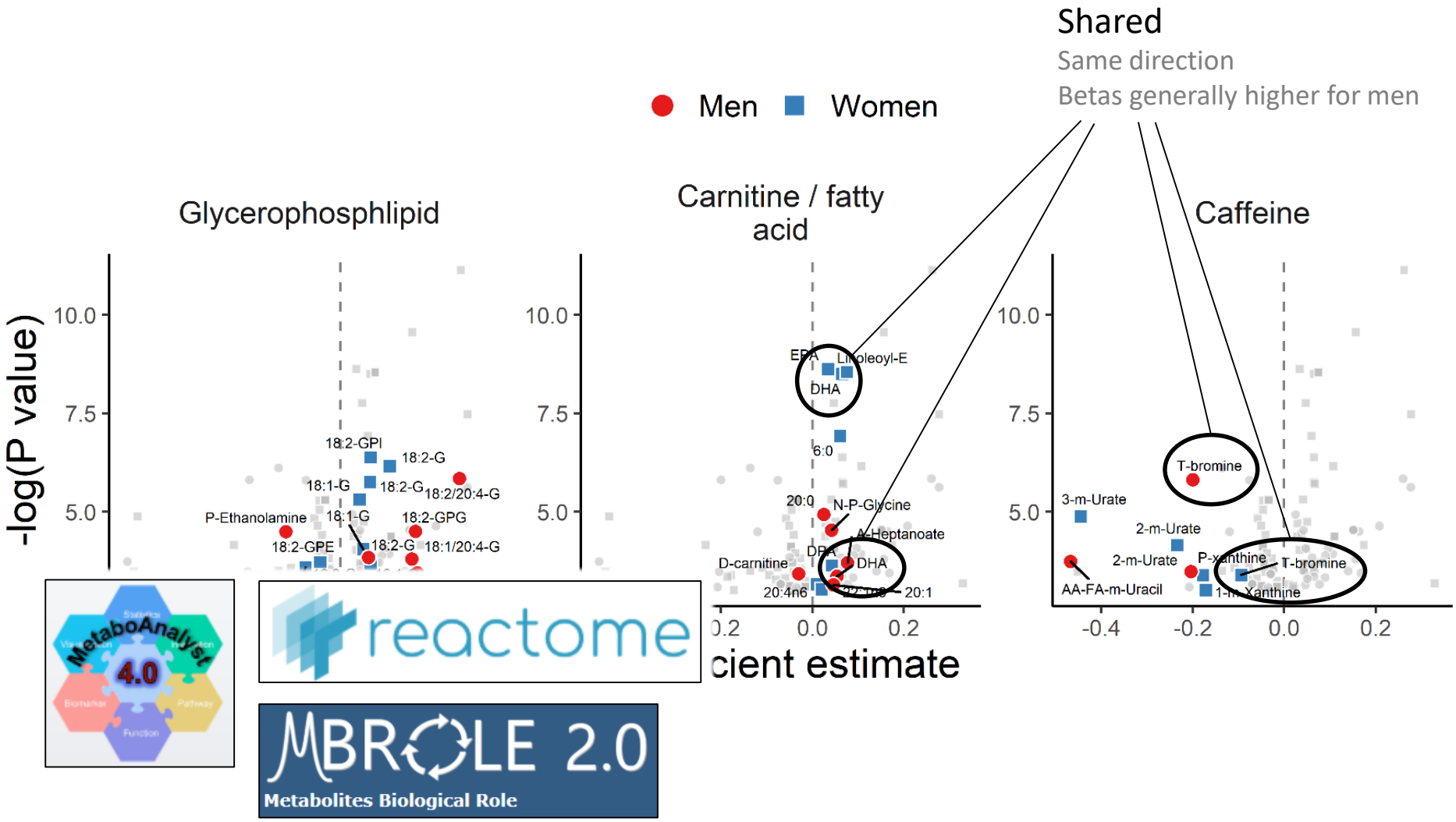

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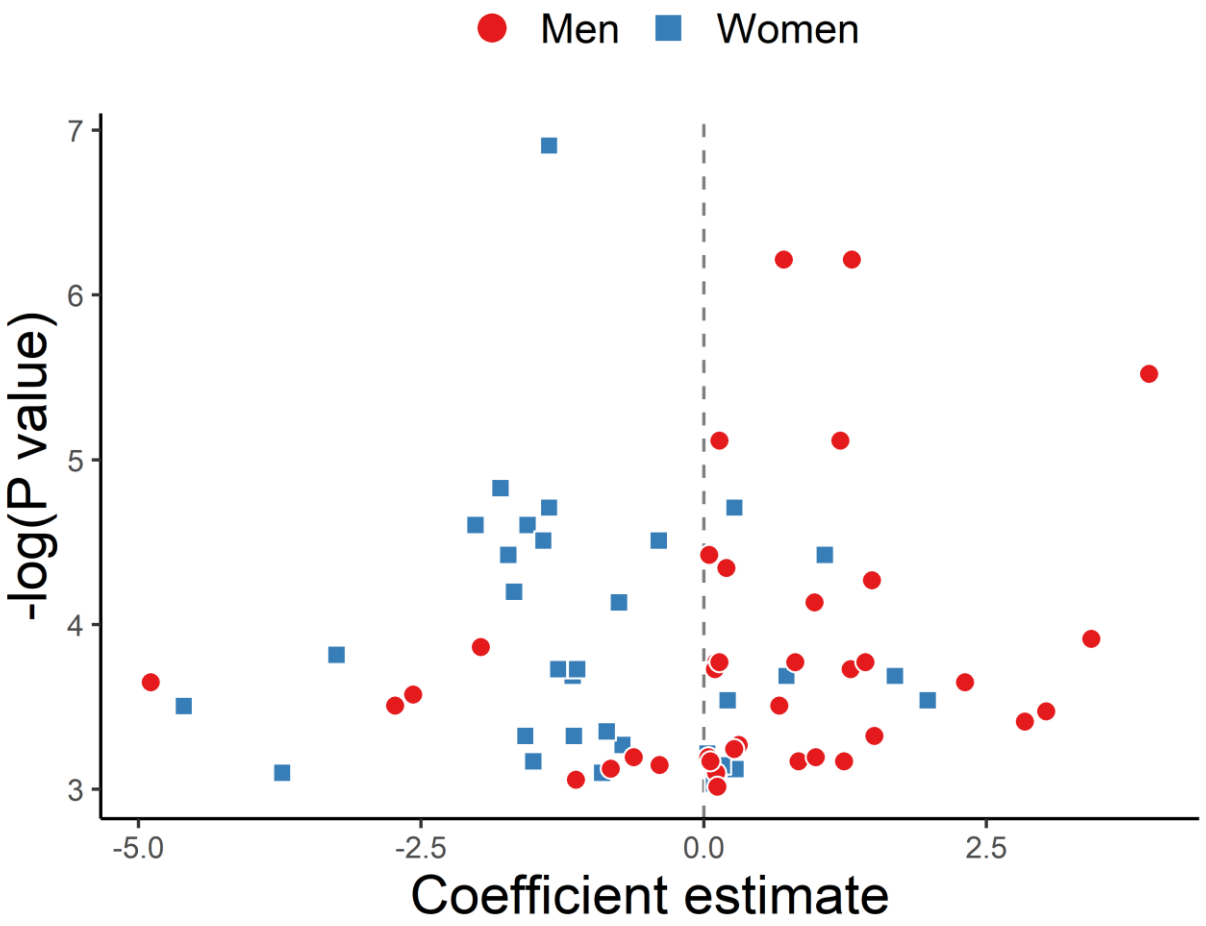

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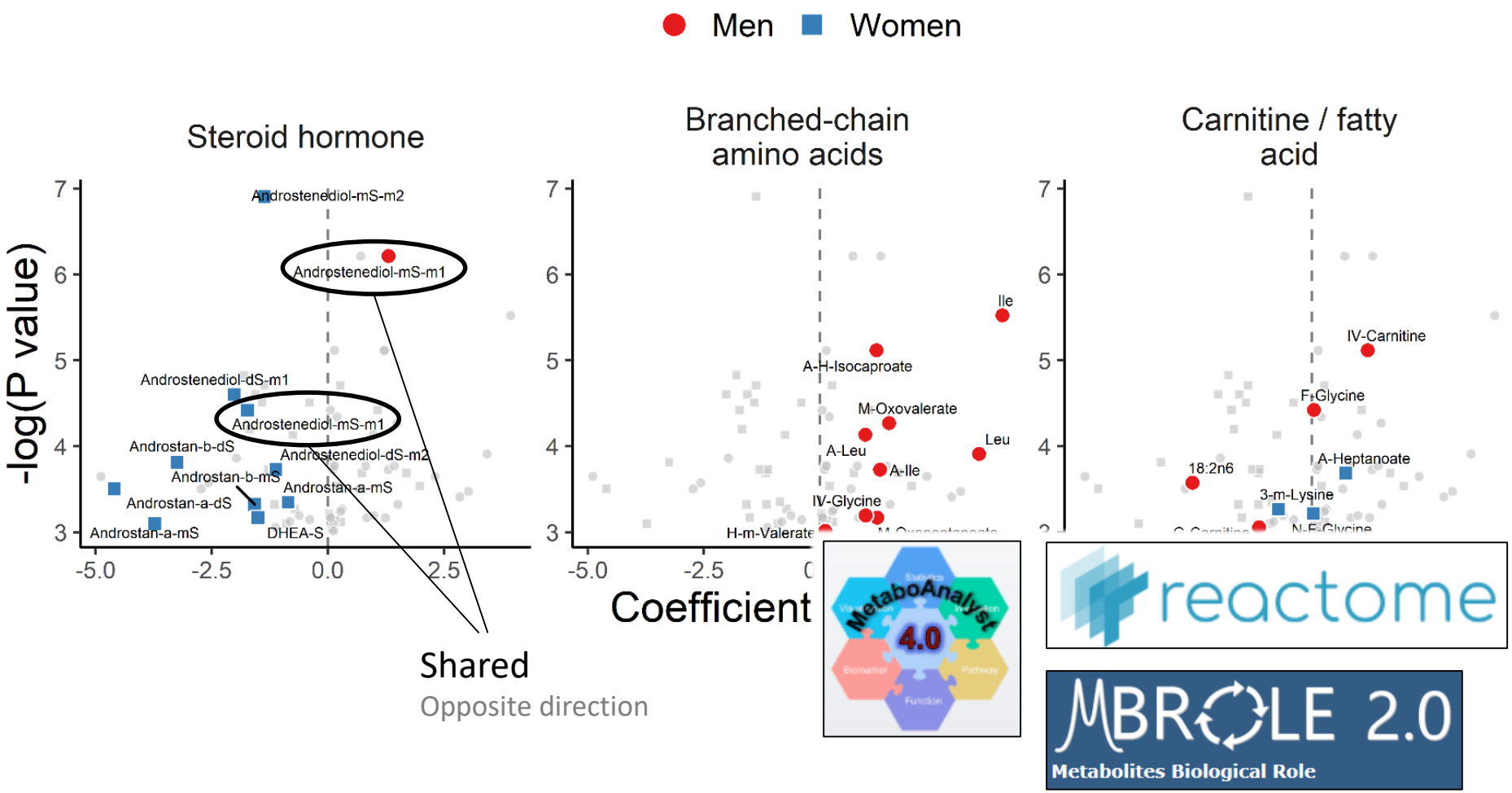
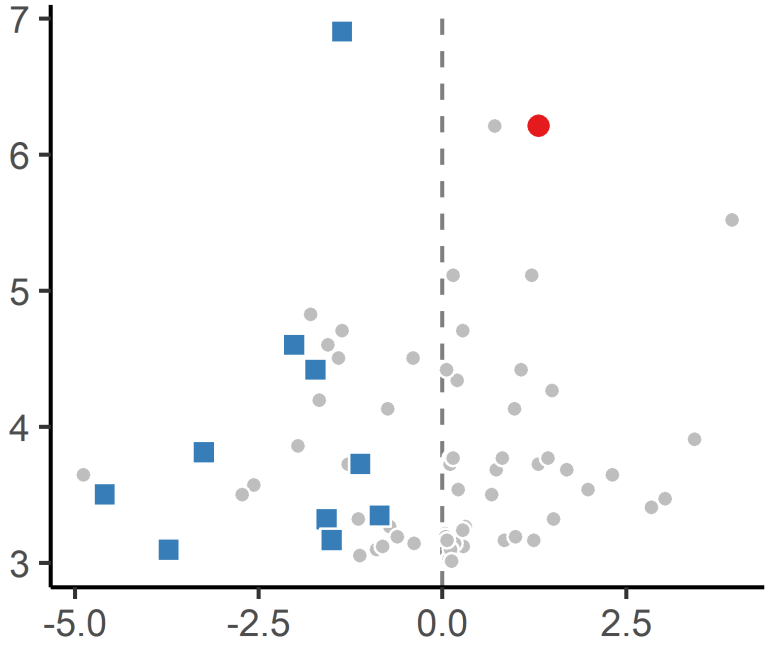


Can FV-associated metabolites affect steroid hormone biosynthesis?



Enzymes involved in steroid hormone biosynthesis

Metabolites associated with higher FV intake

Estrogens and androgens slow the rate of bone remodeling and protect against bone loss

BRENDA
1987 2019
The Comprehensive Enzyme Information System

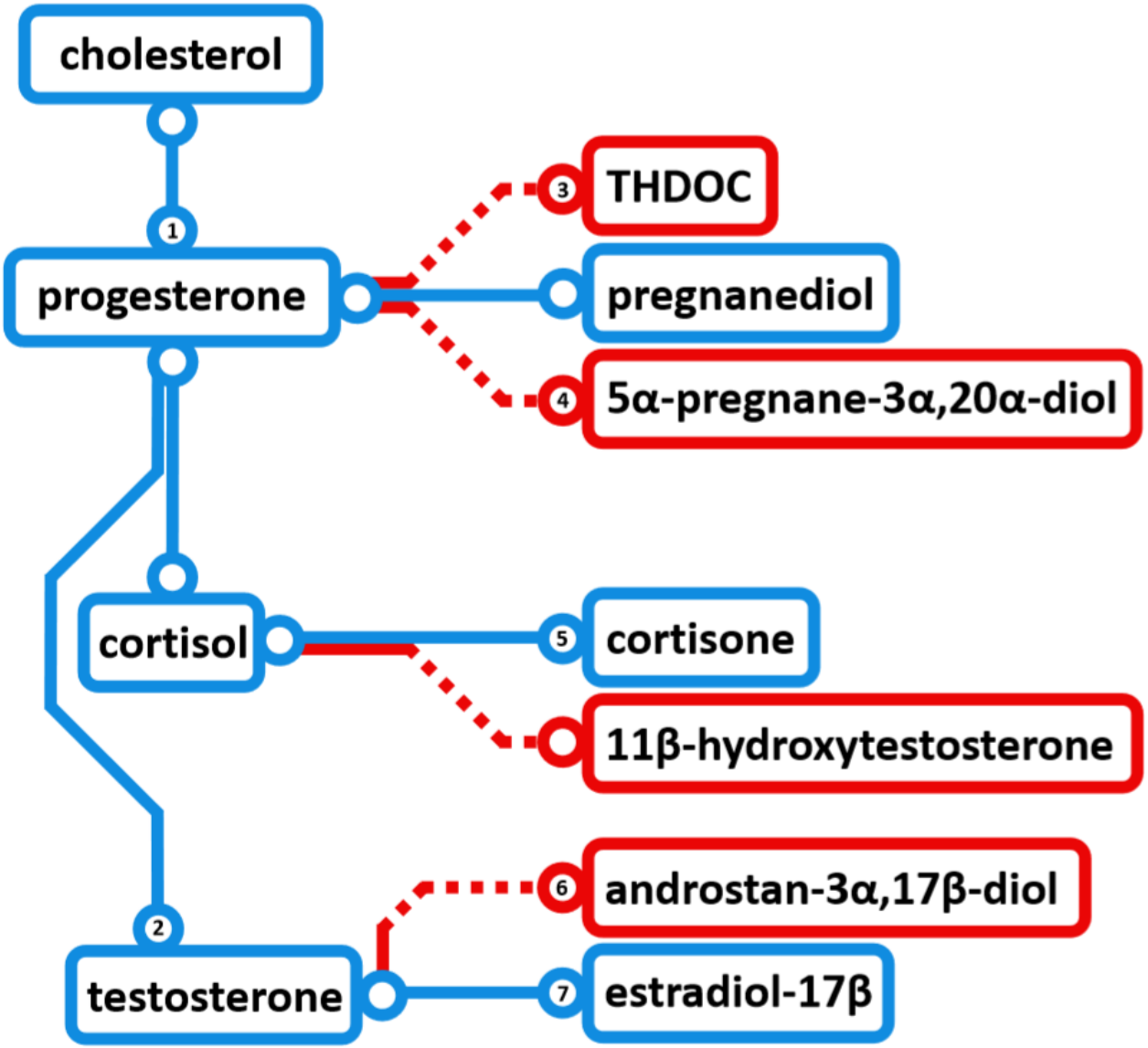
KEGG
Kyoto Encyclopedia of Genes and Genomes

FV-associated metabolites may interfere with the steroid hormone biosynthesis pathway in women

Metabolite	Direction	Biosynthesis module
linoleate (18:2n6)	Higher	progesterone → THDOC testosterone → androstan-3α,17β-diol
oleate/vaccenate (18:1)	Higher	
palmitate (16:0)	Higher	
piperine	Higher	
stearate (18:0)	Higher	
1-methylnicotinamide	Higher	progesterone → 5α-pregnane-3α,20α-diol
arachidonate (20:4n6)	Higher	cortisol → cortisone testosterone → estradiol-17β
linoleate (18:2n6)	Higher	
oleate/vaccenate (18:1)	Higher	
deoxycholate	Lower	cholesterol → progesterone cholesterol → testosterone
ursodeoxycholate	Lower	testosterone → androstan-3α,17β-diol
naproxen	Lower	testosterone → estradiol-17β

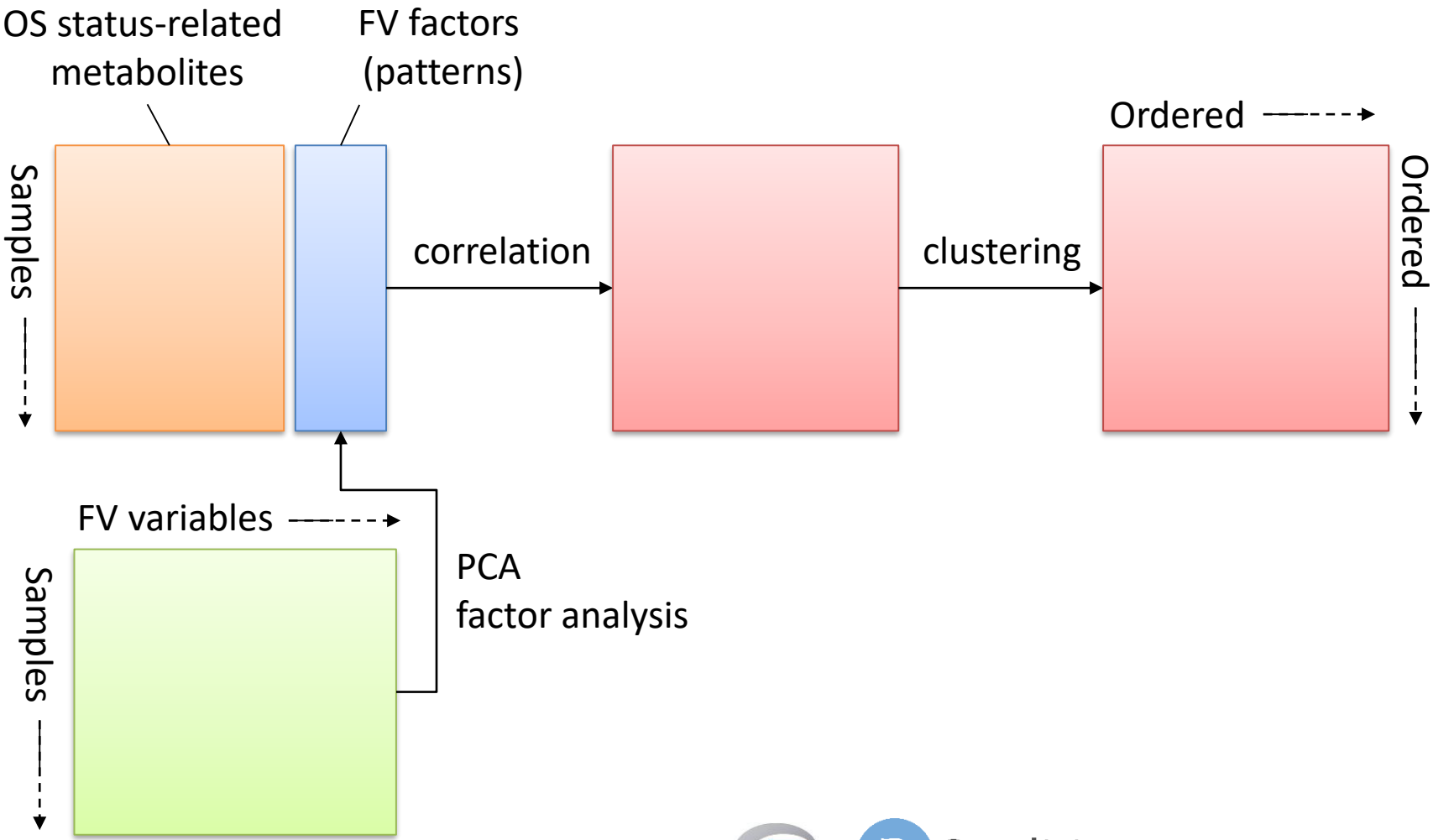
[BRENDA, KEGG]

FV-associated metabolites may interfere with the steroid hormone biosynthesis pathway in women



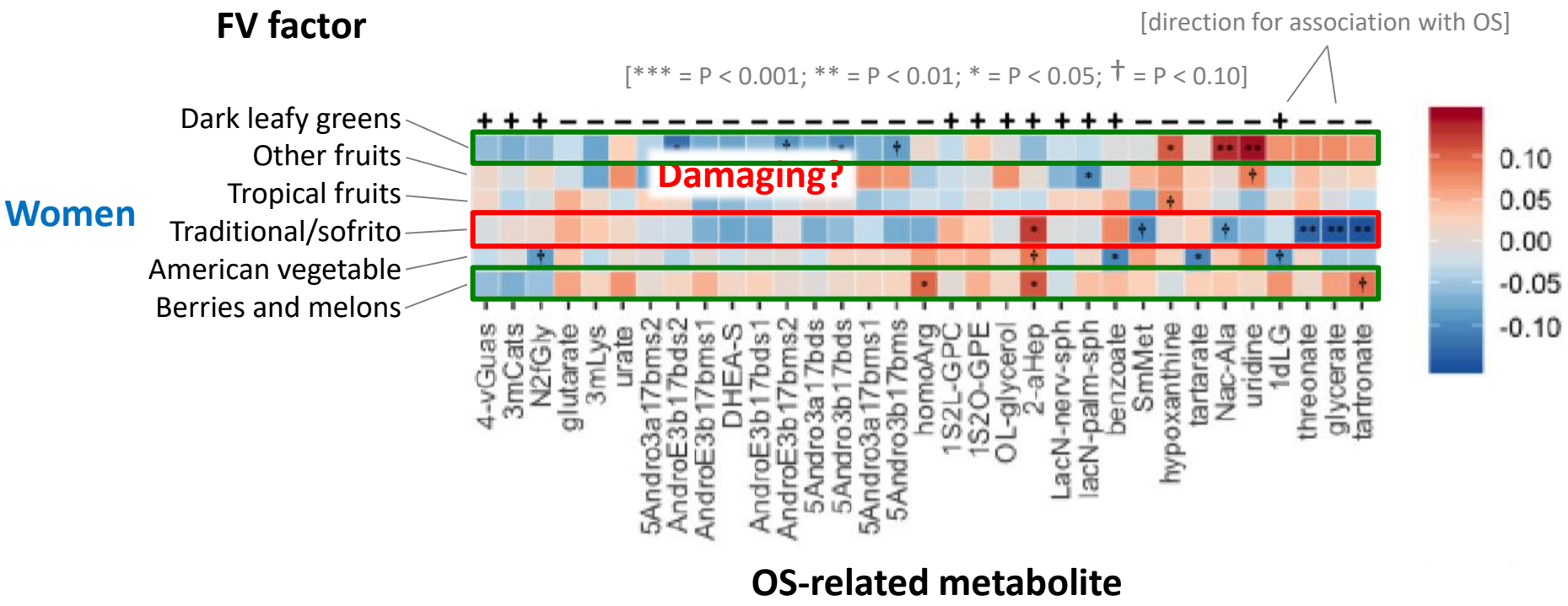
[BRENDA, KEGG]

We analyzed the co-variance between FV patterns and OS status-related metabolites



[tidyverse, factoextra, stats, Hmisc]

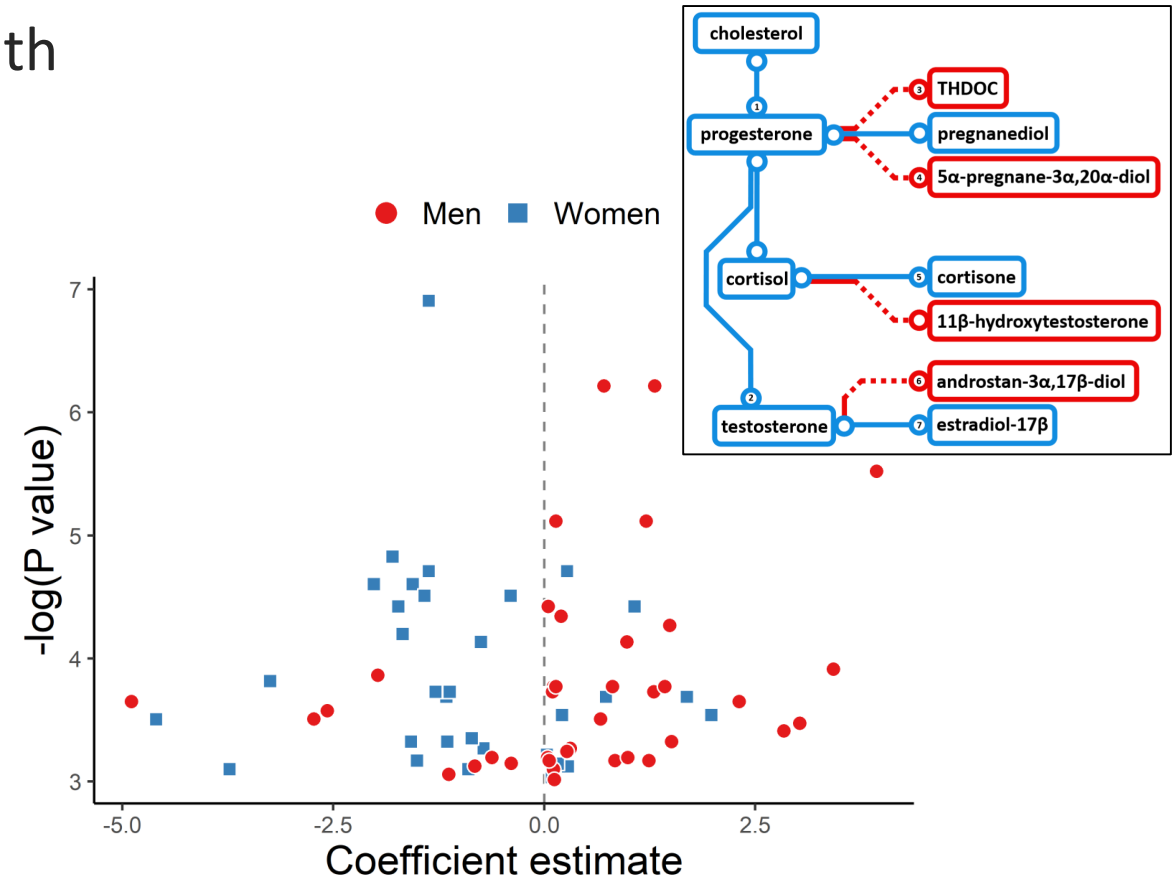
OS-associated metabolites correlated with FV factors



In summary, we found that plasma metabolite patterns relate to OS status and FV intake in a sex-specific manner

Diet may exert specific mechanisms on bone health

Potential for personalized nutrition advice?



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Questions?