Surrogates or biomarkers to monitor the efficacy or effect of an intervention

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Compliance – difficult to measure and hard to maintain

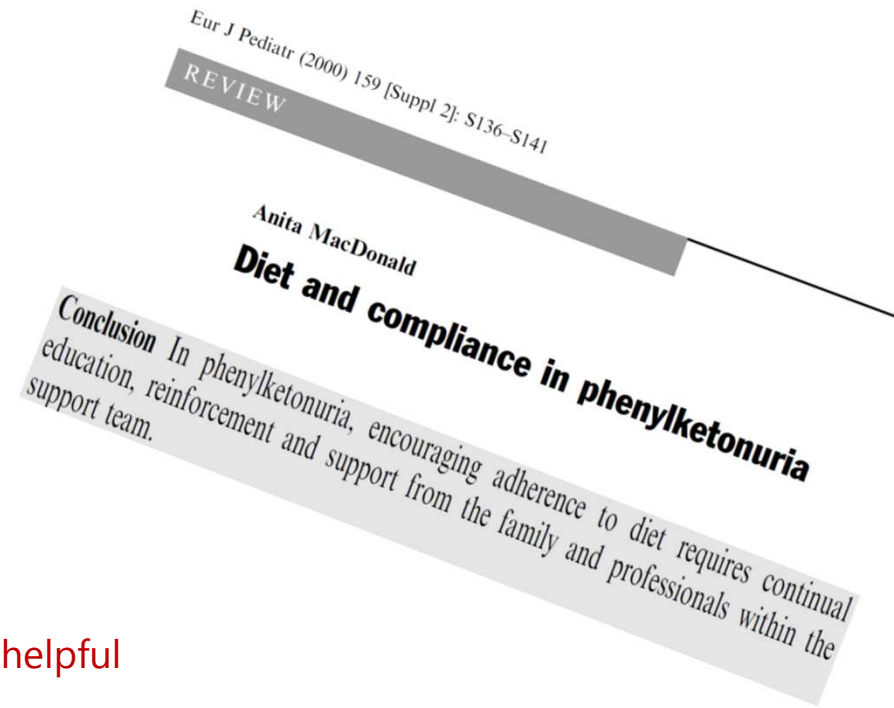
- There is no concensus method for measuring compliance to a diet or intervention
- Typically, studies and reviews conclude that nutritional compliance is suboptimal, even in patients at risk


Compliance with the Dietary Approaches to Stop Hypertension (DASH) Diet: A Systematic Review

Mandy Wing-Man Kwan[1], Martin Chi-Sang Wong[1]*, Harry Hao-Xiang Wang[1,2], Kirin Qi-Lin Liu[1], Catherine Lok-Sze Lee[1], Bryan Ping-Yen Yan[3], Cheuk-Man Yu[3], Sian Meryl Griffiths[1]

Conclusions: To conclude, although no consensus existed regarding the best approach to assess DASH compliance, its suboptimal compliance warrants attention. This study implied a need to investigate effective approaches to sustain the DASH dietary pattern beyond counselling alone.

PLoS ONE 8(10): e78412. doi:10.1371/journal.pone.0078412


Eur J Pediatr (2000) 159 [Suppl 2]: S136–S141

REVIEW

Anita MacDonald

Diet and compliance in phenylketonuria

Conclusion In phenylketonuria, encouraging adherence to diet requires continual education, reinforcement and support from the family and professionals within the support team.

Biomarkers could be helpful

Biomarkers and their overall classes

Biomarkers in general are objective measures used to characterize the current condition of a biological system.

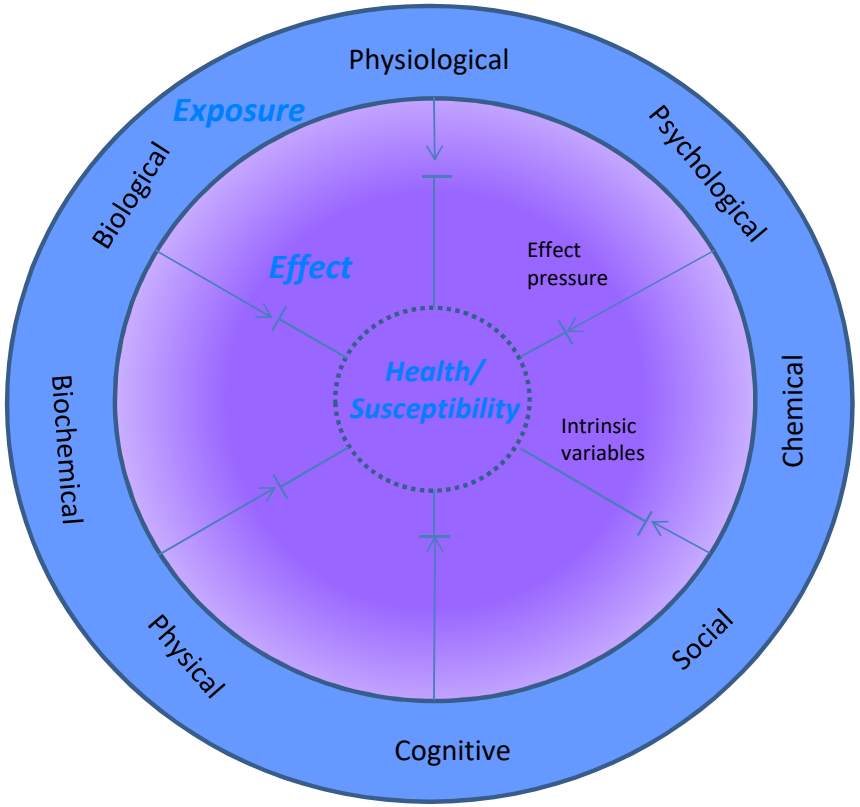
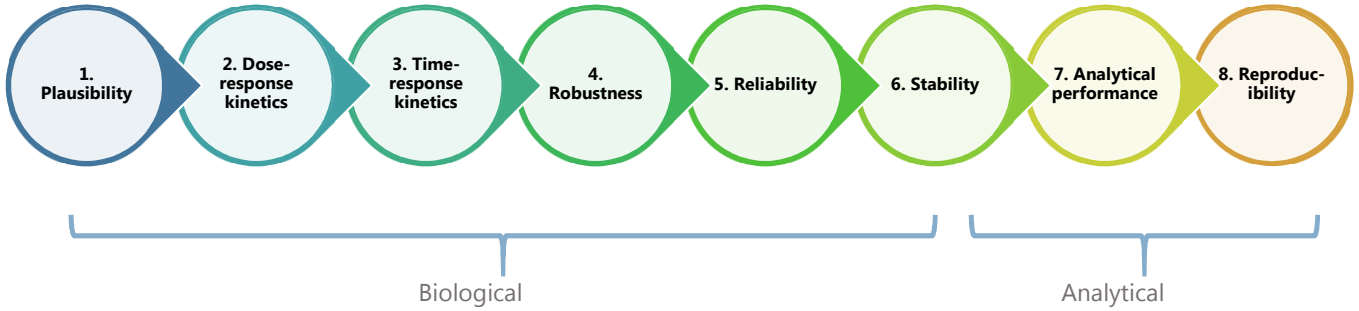


Figure. Diversity of interaction between the biological system with intrinsic system variables and the surrounding environmental variables.

Gao et al., Genes & nutrition. 2017

Validation of food intake biomarkers



Dragsted et al. Genes & Nutrition (2018) 13:14
https://doi.org/10.1186/s12263-018-0603-9

Genes & Nutrition

REVIEW Open Access

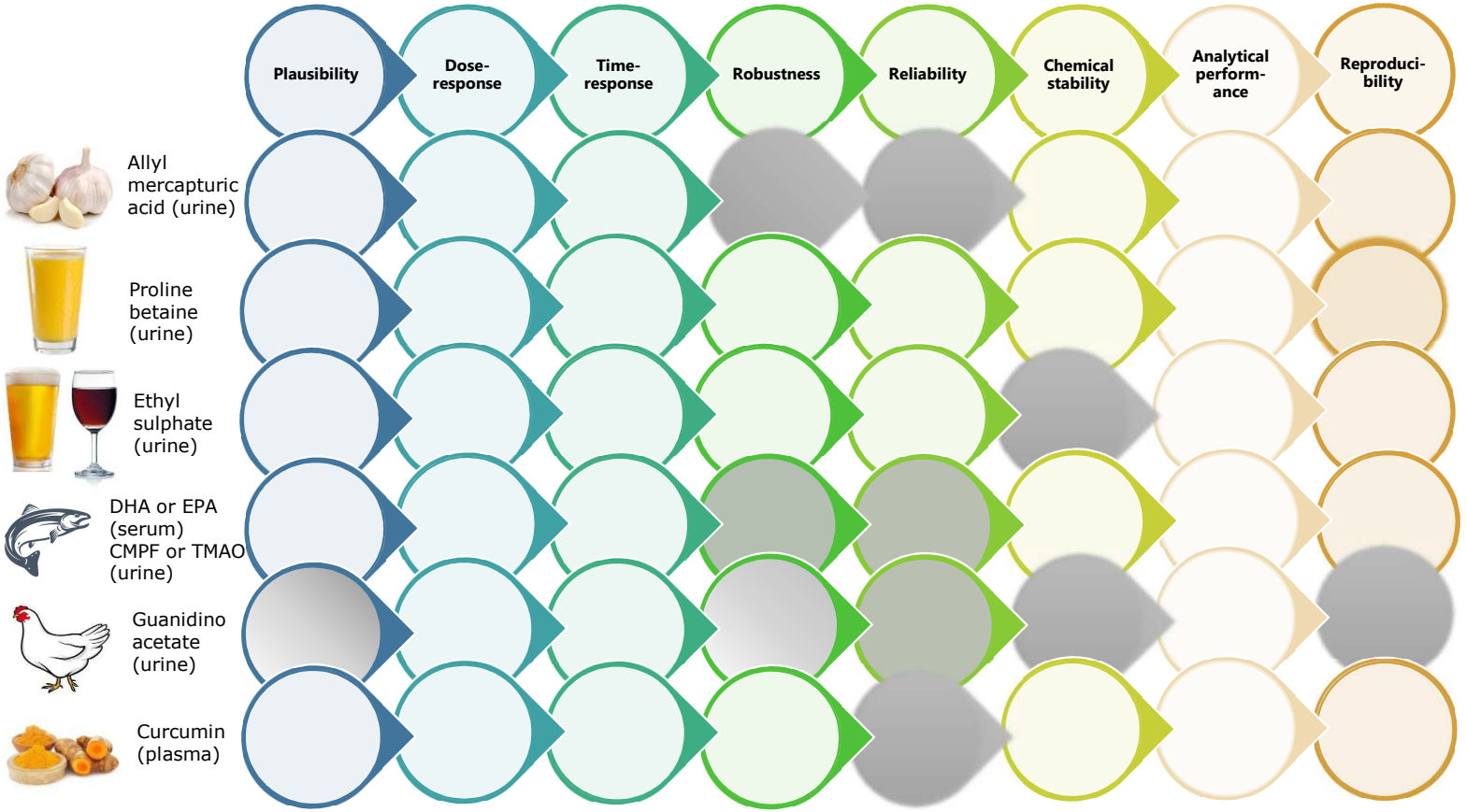
Validation of biomarkers of food intake—critical assessment of candidate biomarkers

L. O. Dragsted[1*], Q. Gao[1], A. Scalbert[3], G. Vergères[4], M. Kolehmainen[5], C. Manach[6], L. Brennan[7], L. A. Afman[8], D. S. Wishart[9], C. Andres Lacueva[10,11], M. Garcia-Aloy[10,11], H. Verhagen[12,13], E. J. M. Feskens[8] and G. Praticò[1,2]

Abstract

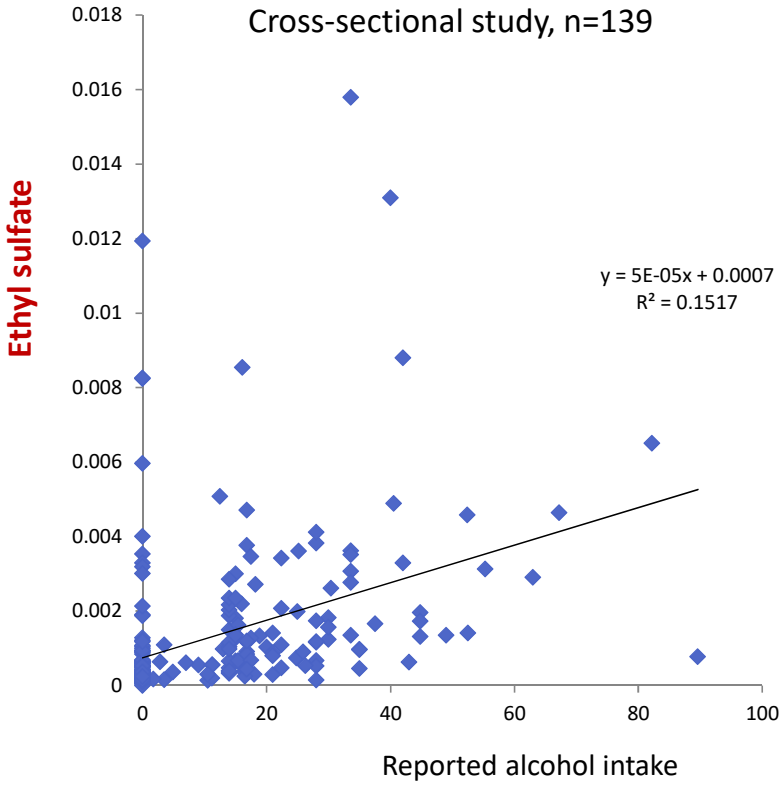
Biomarkers of food intake (BFIs) are a promising tool for limiting misclassification in nutrition research where more subjective dietary assessment instruments are used. They may also be used to assess compliance to dietary guidelines or to a dietary intervention. Biomarkers therefore hold promise for direct and objective measurement of

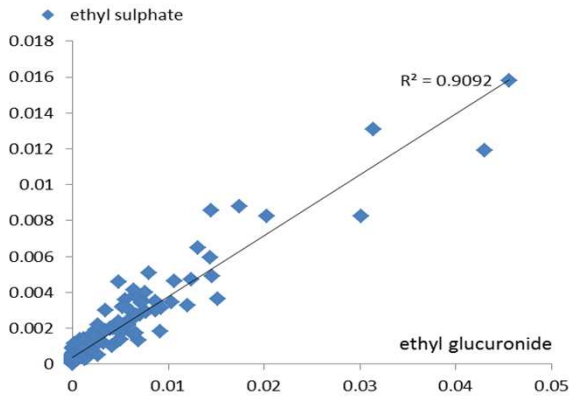
Some of the better validated food intake biomarkers



Others include markers of WG rye and wheat, some legumes, oils, and smoked meat

How do single intake biomarkers perform?





Alcohol - Comparing ethyl glucuronide and - sulphate

With more than one biomarker, you can strengthen the compliance assessment

LO Dragsted et al. (unpubl.)

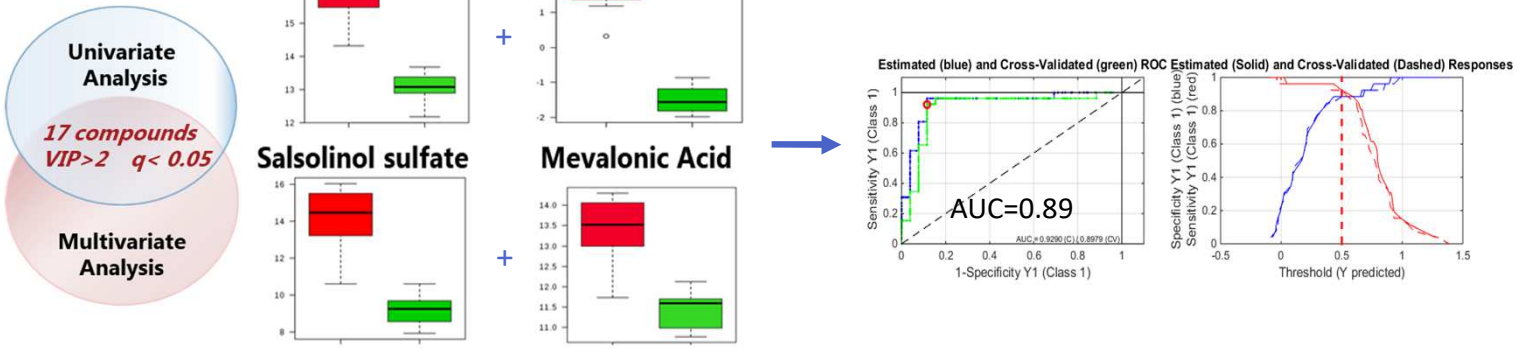
Combined Biomarker for banana intake (from metabolic profile)

Discovery in 12 subjects, controlled meal study

Validation in 78 subjects, cross-sectional study 24hr recall

MRI Max Rubner-Institut

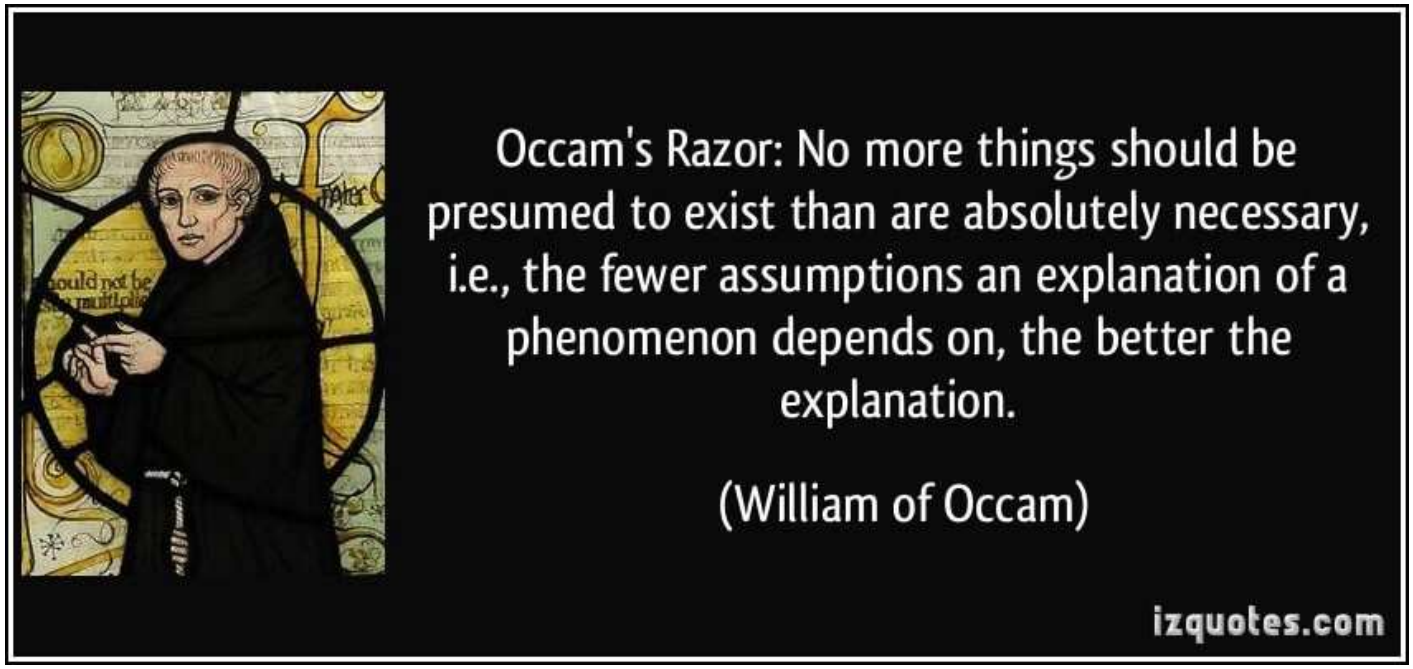
The KarMen Study



Note: The combined markers answer a qualitative question, a classification

FOODBALL The Food Biomarker Alliance

Vazquez-Manjarrez et al., 2019; *J. Nutr.* (**149**, 10) 1701-1713

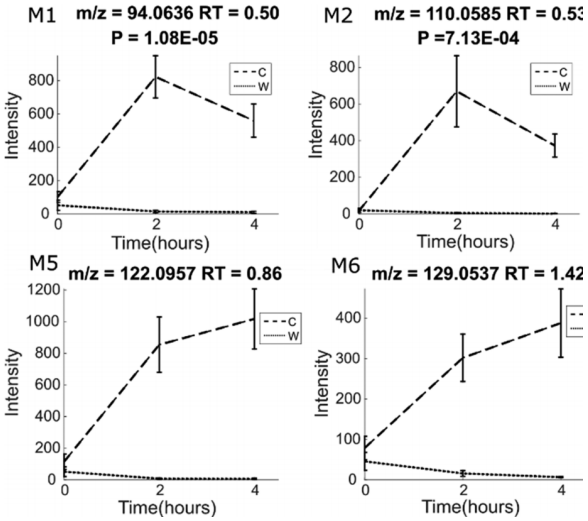


We use this principle for finding the combined biomarker with the fewest compounds.
If several non-overlapping combined markers exist they may be used for mutual validation.

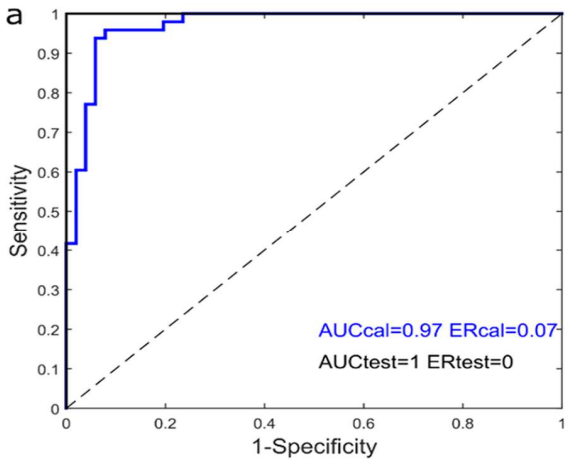
(Recent) coffee intake biomarkers

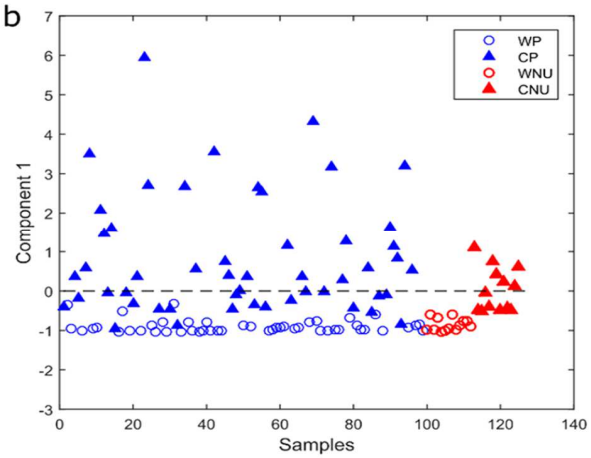
Using Occam's razor

no. of candidate biomarkers	type of consumer	AUC_test	ER_Test	NMP	1H-pyrrole-2-carboxaldehyde sulfate	3′,4′-DHAP sulfate	ferulic acid sulfate	4-ethylcatechol GlcA
2	AC	1	0		X	X		
3	AC	1	0	X			X	X
4	AC	1	0		X	X	X	X
5	AC	1	0	X	X	X	X	X



Kinetics for four of the 23 markers





Xi et al., J. Agric. Food Chem. 2021, 69, 7230−7242

Predicting (reported) coffee intake in an observational study

– predicting from multiple datasets

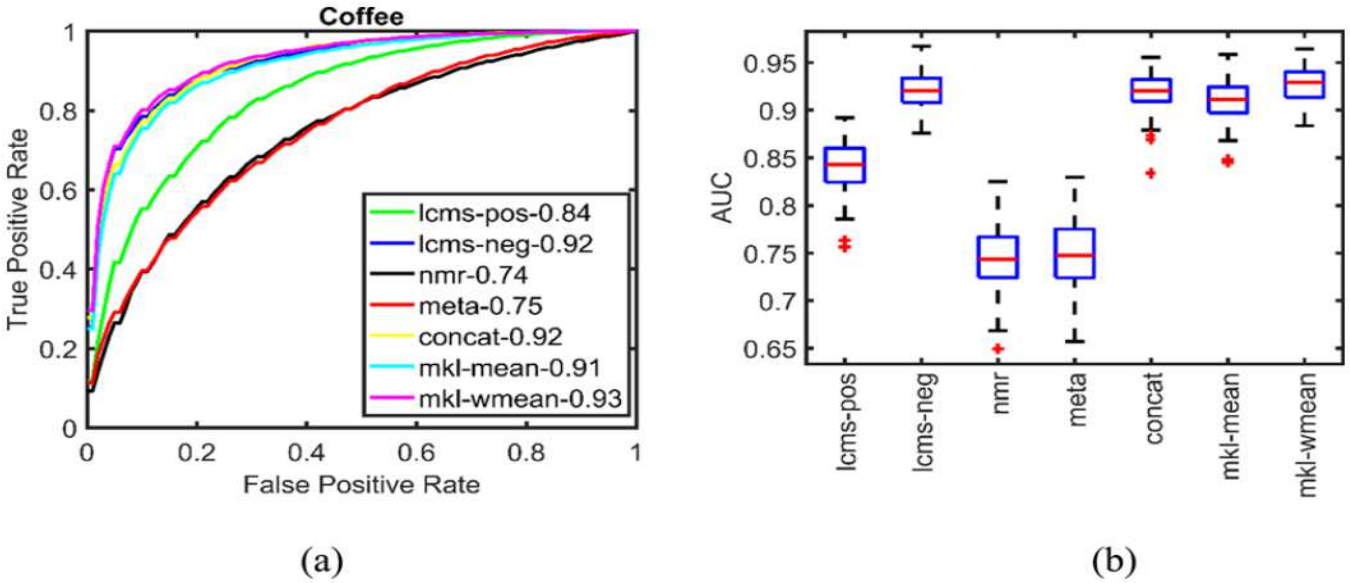
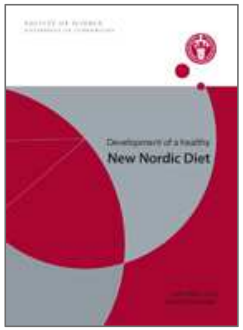


Figure 7. (a) Average ROC curves showing the classification performance for coffee drinking. (b) Boxplots summarize the performance of different data sets/classifiers across 100 training/test sets.

More information does not improve classification – as Occam indicated

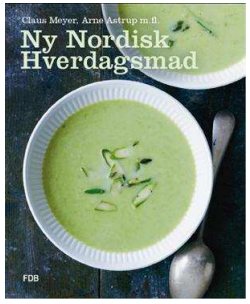
Acar et al. 2017 J Proteome Res 16 2435-44

New Nordic Diet paradigm



PhD thesis by Mithril 2013

Mithril et al. Public Health Nutr. 2012
Mithril et al. Public Health Nutr. 2013

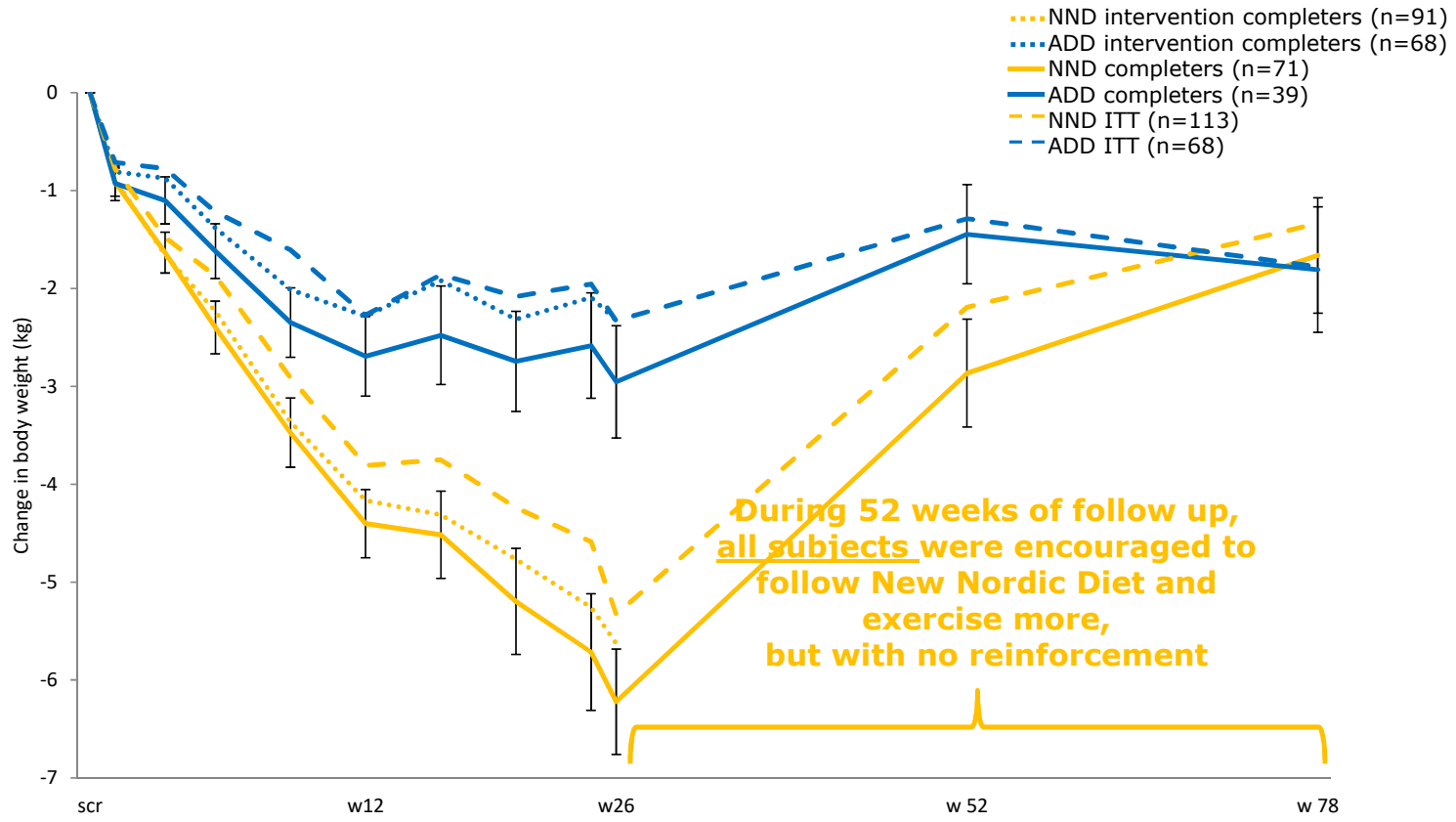


New Nordic Cookbook
- Book of the year 2013

1. **More fruit and vegetables – much more berries, cabbage, root crops, legumes, potatoes and fresh herbs**
2. **More whole grain – especially oat, rye and barley**
3. **More food from the sea – fish, seafood and sea weed**
4. **Meat of high quality – but in small quantities**
5. **More food from the wild landscapes**
6. **Organic whenever possible**
7. **Avoid additives**
8. **More meals closer to nature**
9. **More homemade food**
10. **Less waste**

NORDEA FONDEN

Change in body weight with New Nordic or average Danish diets (SHOPUS)



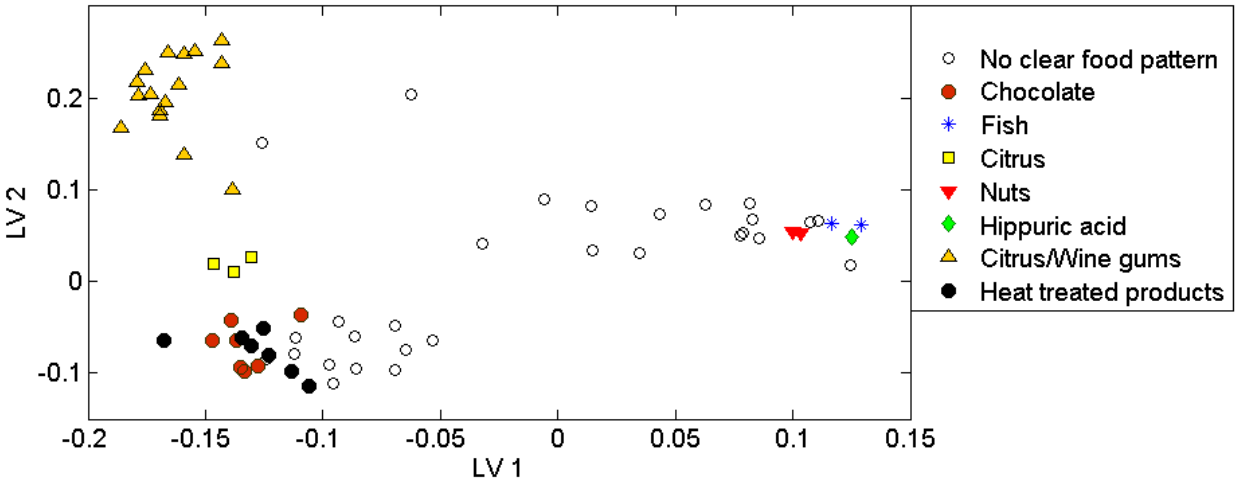
Poulsen et al. 2014 Amer J Clin Nutr 99:1 35-45

Main factors affecting metabolite patterns in SHOPUS

NORDEA FONDEN

1. Dietary contrasts,
   e.g. biomarkers of berry, fruit, nuts and fish intake for Nordic diets
   Biomarkers of sweets, citrus, fried/grilled food and chocolate in controls

Average diet ⟷ New Nordic diet



Pictures from Wikimedia by creative commons

Andersen et al. 2014, J. Proteome Res. 13:3 1405-.18

Diet level classification SYSDIET NORDIC CENTRE OF EXCELLENCE healthy Nordic diet vs. average

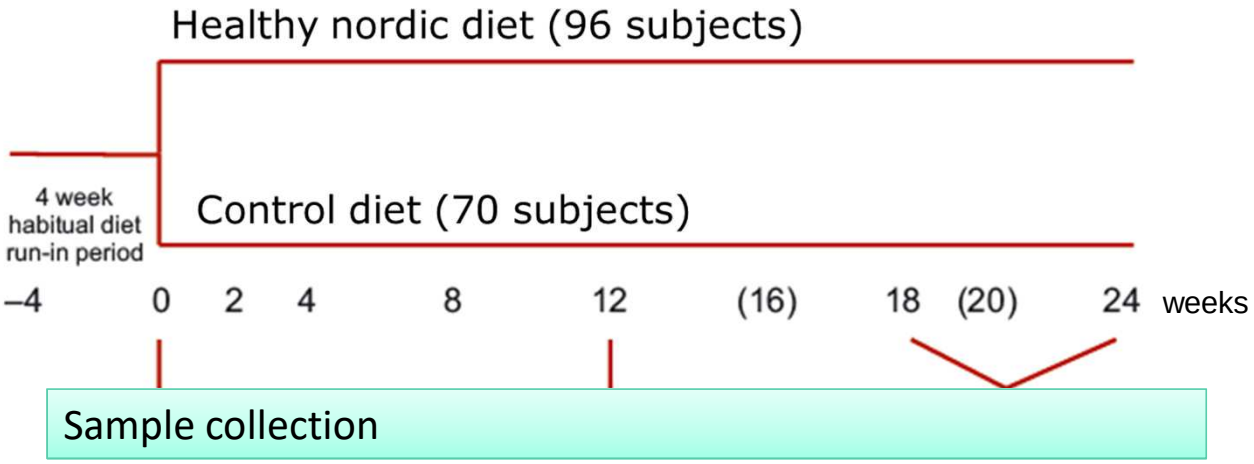
Study design and subjects

A randomized controlled multi-centre intervention

- Finland (*Kuopio* and *Oulu*)
- Iceland (*Reykjavik*)
- Sweden (*Lund* and *Uppsala*)
- Denmark (*Aarhus*)

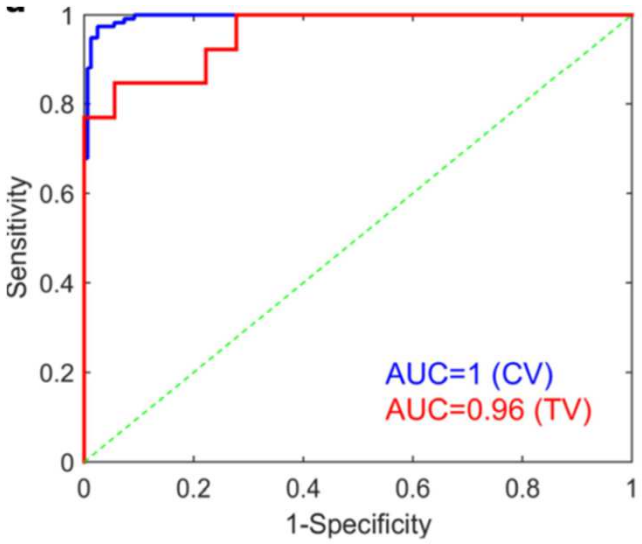
Inclusion criteria

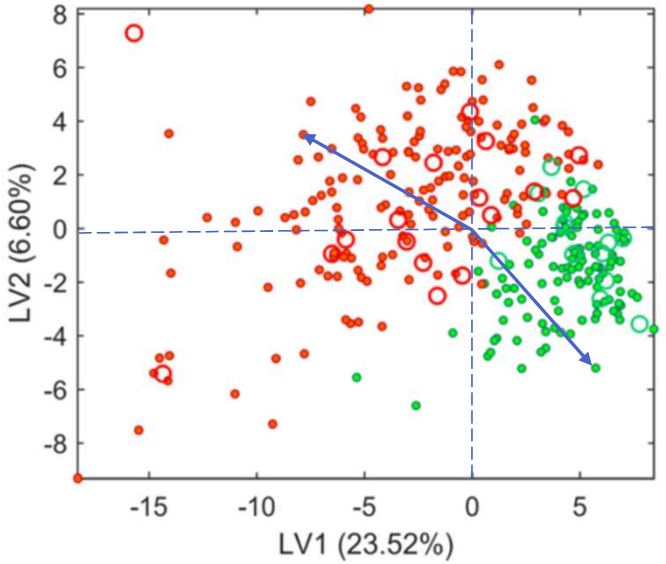
Age 30–65 years, BMI 27–38 kgm^{-2}



Uusitupa M et al. *J Intern Med* 2013;274: 52–66

Classification performance – urine metabolome after feature selection





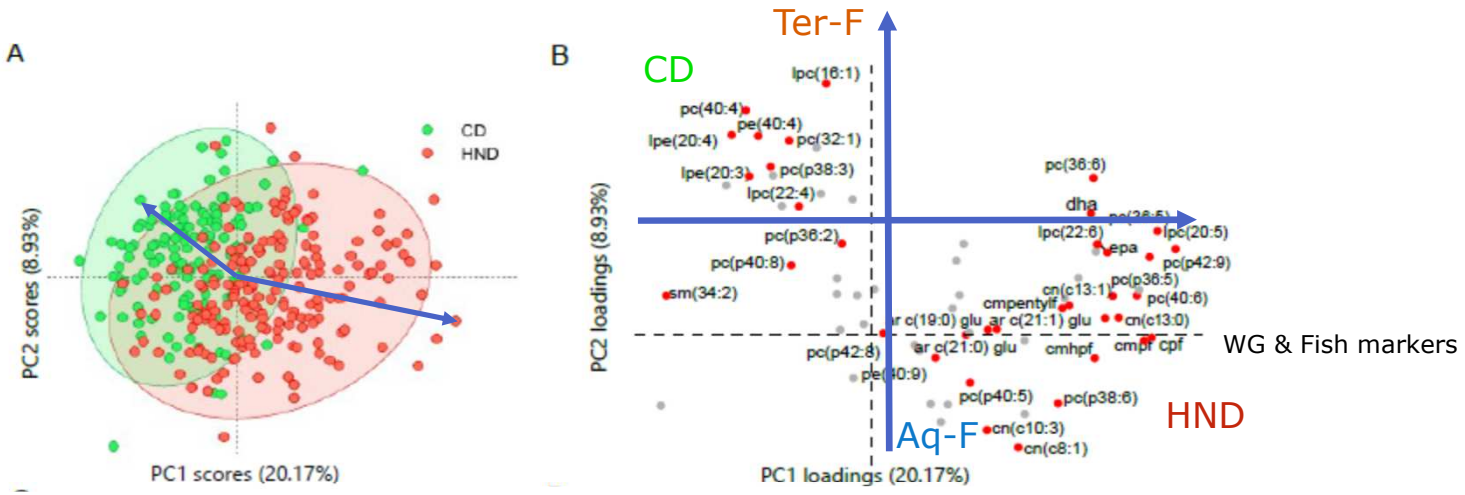
→ Every subject has X and Y coordinates

(Good classification also for plasma features)

SYSDIET
NORDIC CENTRE OF EXCELLENCE

Gürdeniz et al. 2021 (submitted)

Classifying serum metabolites – Nordic diets



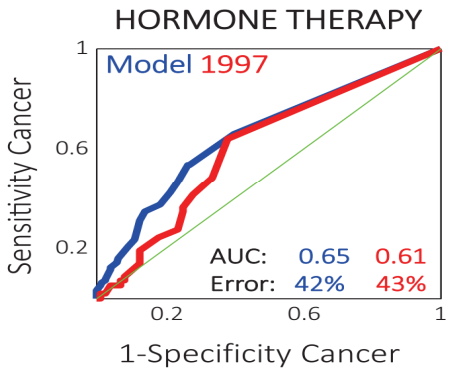
SYSDIET
NORDIC CENTRE OF EXCELLENCE

Gürdeniz et al. 2021 (submitted)

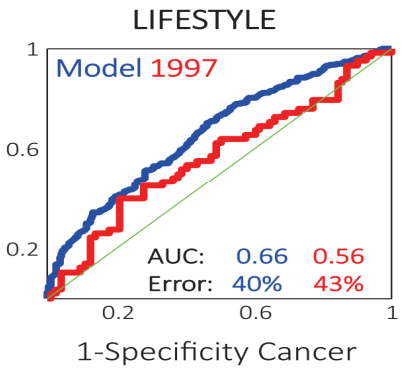
Combined markers used for evaluating effect

Breast cancer in a nested study of 838 women of whom 412 contracted breast cancer 2-5 years later. The subset enrolled 1992-1994 was used for building the model and a subset of 30% enrolled 1995-1997 were used for validation

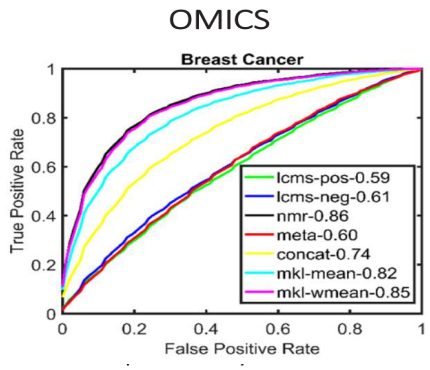
HRT as a single marker



Combining 47 life style features



Validating several data sets and their concatenation



More data = more noise; combined omics reduces predictability.
The best model used only 27 combined features

Bro R et al. 2015 Metabolomics 11:5 1376-80.

Acar et al. 2017 J Proteome Res 16 2435-44

Comparing with colon cancer

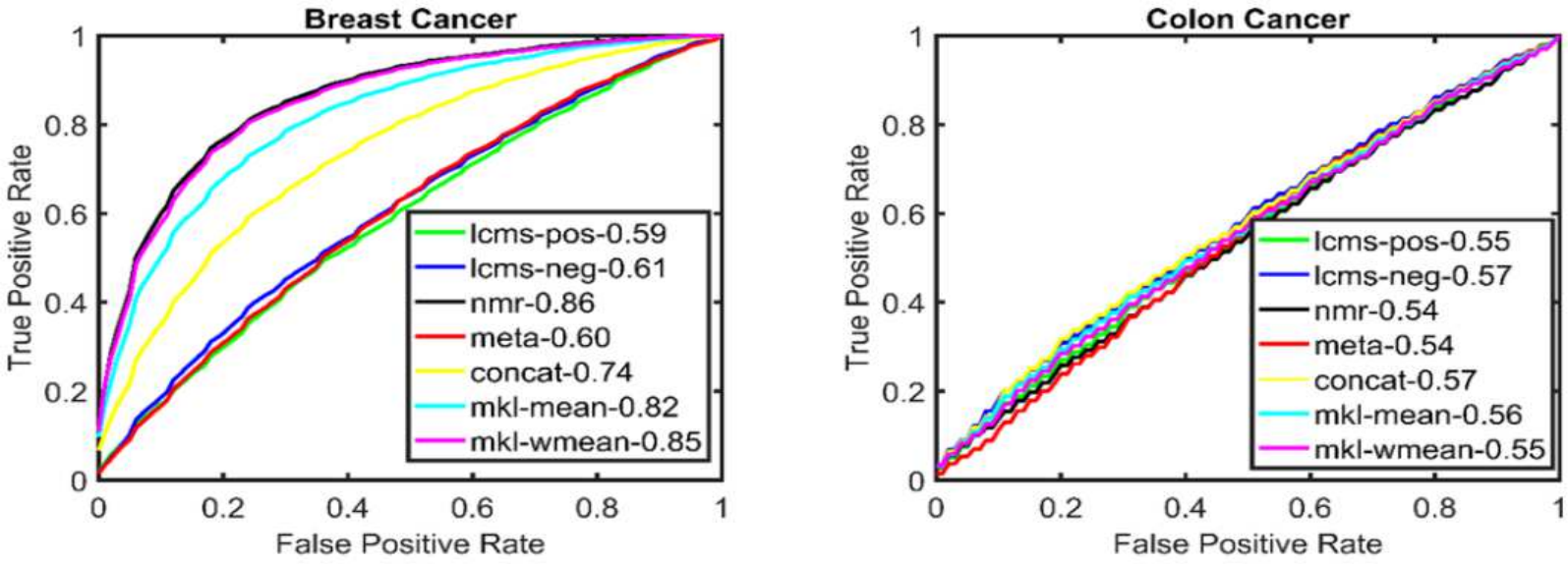


Figure 5. Average ROC curves illustrating the forecasting performance of (a) breast cancer and (b) colon cancer.

Acar et al. 2017 J Proteome Res 16 2435-44

Acute coronary syndrome

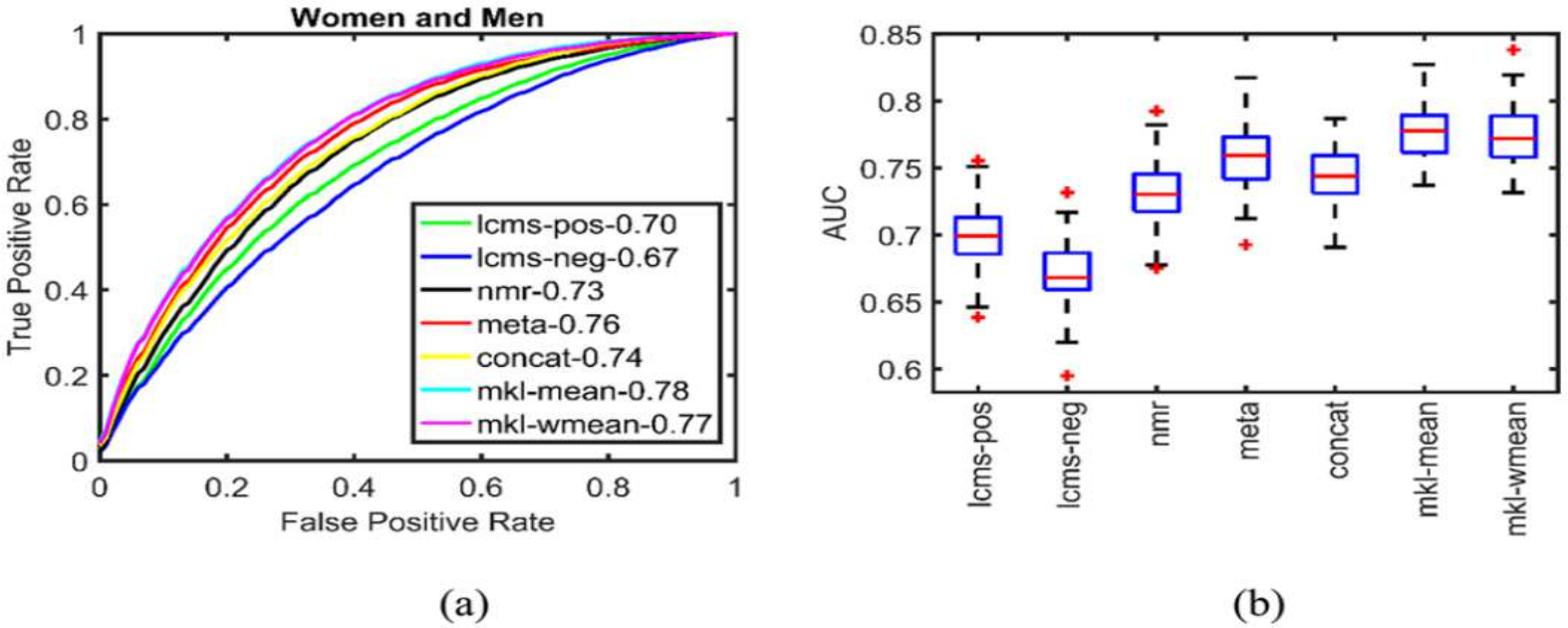


Figure 3. Acute coronary syndrome. (a) Average ROC curves showing the forecasting performance of individual data sets as well as fusion methods for women and men. (b) Boxplots summarize the performance of different approaches across 100 training/test sets.

Acar et al. 2017 J Proteome Res 16 2435-44

Conclusions and messages

Biomarkers can be classified by their use; the same mneasurement may serve several uses

Biomarkers need to be validated for each way they are used

There is often not a single biomarker for a specific use, combinations may be needed

Combined biomarkers can be used to classify e.g. exposures or disease risk

For complex dietary exposures coordinates within a biomarker pattern may be used to assess compliance to the dietary pattern

Few studies exist on forecasting disease based on multivariate metabolite patterns and none of the combined predictive biomarkers have been tested in different populations yet

Combined predictive biomarkers rely on association, no mediation analysis has been made yet

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