International Agency for Research on Cancer

World Health Organization

Maastricht University

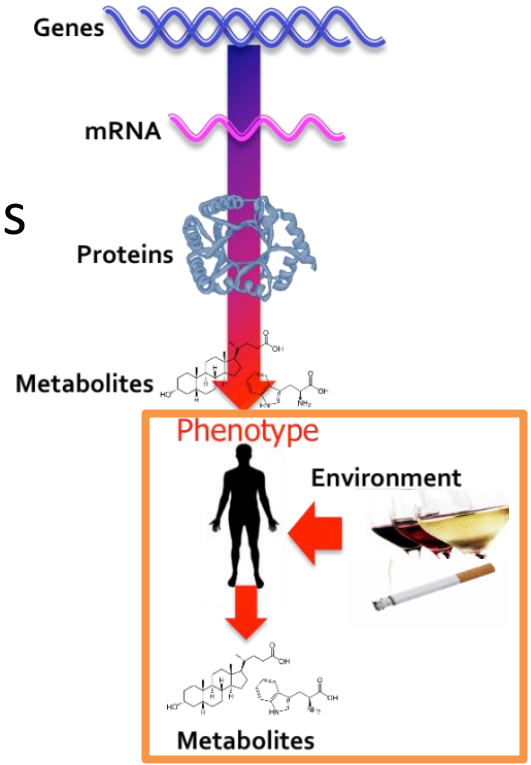
A metabolome-wide association study of alcohol consumption and smoking in the EPIC cohort

Eline van Roekel

IARC 50th Anniversary Conference – 10 June 2016

Background

- Alcohol and smoking → cancer
- Novel insight needed on biological mechanisms
- Metabolomics:
  - Environmental influences on metabolome
  - Understanding of biological mechanisms



Aim

To study associations of alcohol consumption and smoking habits with concentrations of 130 metabolites in blood

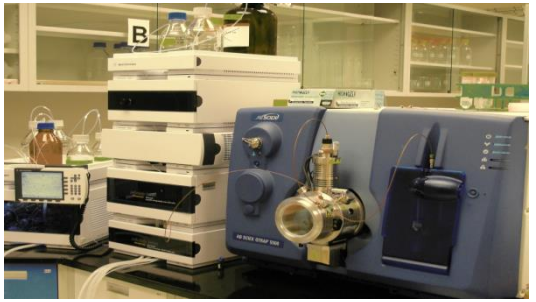
Methods

- Study population:
  - 327 controls of nested case-control study on hepatobiliary cancer within EPIC
  - 183 men and 144 women (mean age: 60 years)

- Alcohol consumption in g/day:
  - Moderate-to-heavy (>15 g/day in women, >30 g/day in men)
  - Light (0.1-15 g/day in women, 0.1-30 g/day in men)
  - Non-consumers (<0.1 g/day)

- Smoking status:
  - Current, former or never

Methods

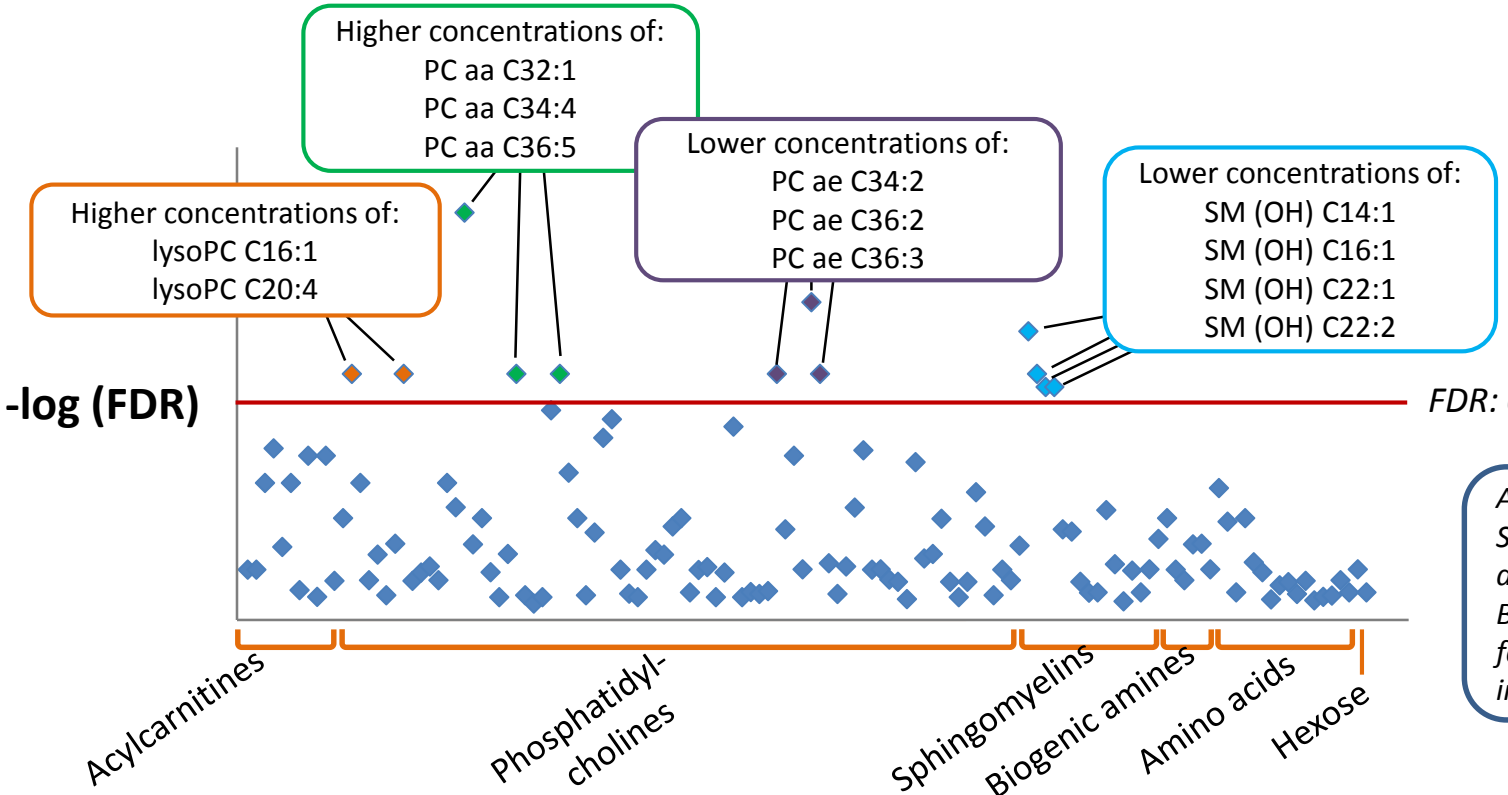


- Metabolomics:
  - Serum samples
  - 130 metabolites by tandem mass spectrometry (Biocrates AbsoluteIDQ™ p180 kit)
    11 acylcarnitines, 20 amino acids, 79 phosphatidylcholines, hexose (mainly glucose), 14 sphingomyelins, 5 biogenic amines

- Multivariable linear regression models
  - Adjusted for potential confounders
  - FDR method to correct for multiple testing

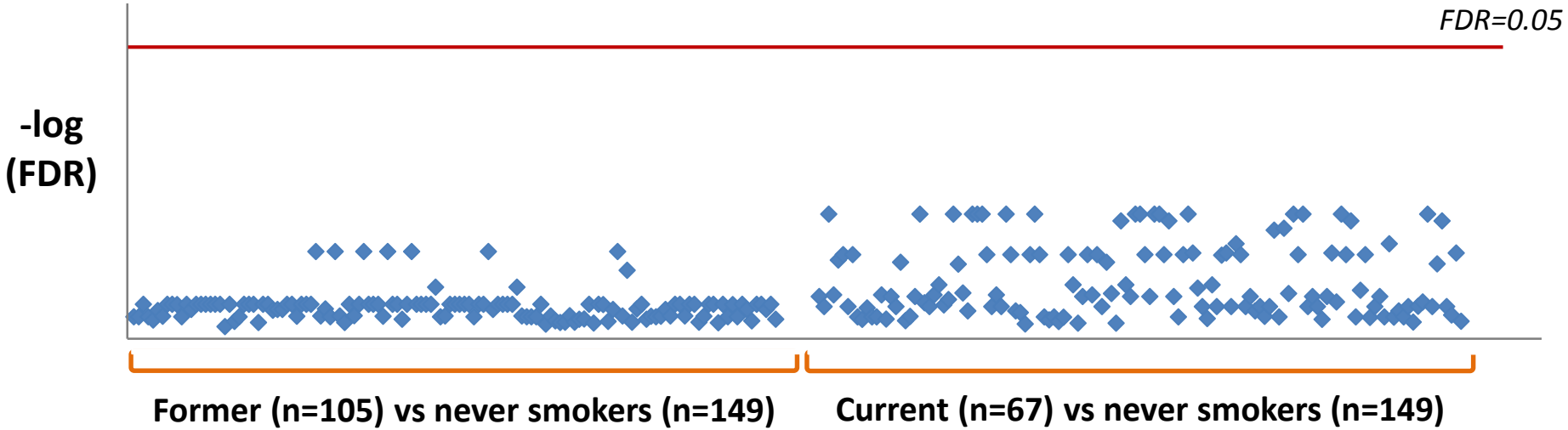
Results: Alcohol

Moderate-to-heavy (n=58) vs light consumption (n=220)



Adjusted for: Smoking, gender, age at blood collection, BMI, physical activity, fasting status, meat intake, batch, country

Results: Smoking



Adjusted for:
Alcohol, gender, age at blood collection, BMI, physical activity, fasting status, meat intake, batch, country

Discussion

- Alcohol results consistent with results KORA study[1]
- Insight into potential biological mechanisms:
  - Higher concentrations of LysoPCs: which may be cytotoxic and associated with atherosclerosis and ischaemia
  - Lower concentrations of PC ae's: which may be associated with reduced platelet aggregation

- Smoking results not consistent with results KORA[2]:
  none of the metabolites found in our study
  → Sample size too small?
  → Differences in population?
  → Different confounding adjustment?

[1] Jaremek *et al*., Transl Psychiatry (2013)

[2] Xu *et al*., BMC Medicine (2013)

Conclusion

Our results indicate that alcohol consumption may affect sphingo- and phospholipid metabolism.

Prospective studies and research aiming to elucidate underlying biological mechanisms are necessary.

Acknowledgements

International Agency for Research on Cancer

Biomarkers Group
Augustin Scalbert
Sabina Rinaldi
David Achaintre

Nutritional Epidemiology Group
Pietro Ferrari
Marion Carayol
Nada Assi
Magdalena Stepien
Mazda Jenab

Maastricht University

Department of Epidemiology
Matty Weijenberg

Questions?

Additional slides not for presentation

Results: Population characteristics

Characteristic	N=327 (56% men)
Age (years), mean (SD)	59.6 (7.4)
Alcohol consumption, n (%)	
Moderate-to-heavy drinkers	58 (18%)
Light drinkers	220 (69%)
Non-consumers	43 (13%)
Smoking, n (%)[1]	
Current	67 (21%)
Former	105 (32%)
Never	149 (46%)

[1] 6 cases with missing data on smoking

Correlations between significant metabolites

	z_log_..	z_l~20_4	z_log_..	z_l~34_4	z_log_..	z_log_..	z_log_..	z_log_..	z_log_..	z_log_..	z_l~22_1
z_log_g~16_1	1.0000										
z_log_g~20_4	0.4740	1.0000									
z_lo~a_c32_1	0.5611	0.0432	1.0000								
z_log_g~34_4	0.4730	0.3118	0.7269	1.0000							
z_lo~a_c36_5	0.3245	0.0976	0.4356	0.3833	1.0000						
z_lo~e_c34_2	0.0235	0.0188	0.1701	0.3251	0.0806	1.0000					
z_lo~e_c36_2	0.1136	0.0627	0.1421	0.3465	0.1397	0.7749	1.0000				
z_lo~e_c36_3	0.1411	0.0638	0.2062	0.3542	0.0797	0.9309	0.7683	1.0000			
z_log_s~14_1	0.1754	0.0524	0.2068	0.2930	0.2389	0.5808	0.6692	0.5005	1.0000		
z_lo~m_c16_1	0.2204	0.1293	0.1697	0.2996	0.1588	0.5009	0.4902	0.5243	0.6963	1.0000	
z_log_sp~2_1	0.0420	0.1282	0.1013	0.2800	0.0971	0.4529	0.5519	0.4892	0.6114	0.6006	1.0000
z_log_sp~2_2	0.1100	0.0655	0.1461	0.2514	0.2604	0.5085	0.6125	0.5107	0.7863	0.7384	0.8424

Confounders adjusted for

Smoking, alcohol, gender, age at blood collection, BMI, physical activity, fasting status, meat intakes, batch, country

Controls were selected by incidence density sampling from all cohort members alive and free of cancer (except non-melanoma skin cancer), and matched by age at blood collection (+/- 1 year), gender, study center, time of the day (+/- 3 hours) and fasting status at blood collection (<3, 3-6 and >6 hours).

8 countries: Denmark, Germany, Greece, Italy, Spain, Sweden, the Netherlands and United Kingdom

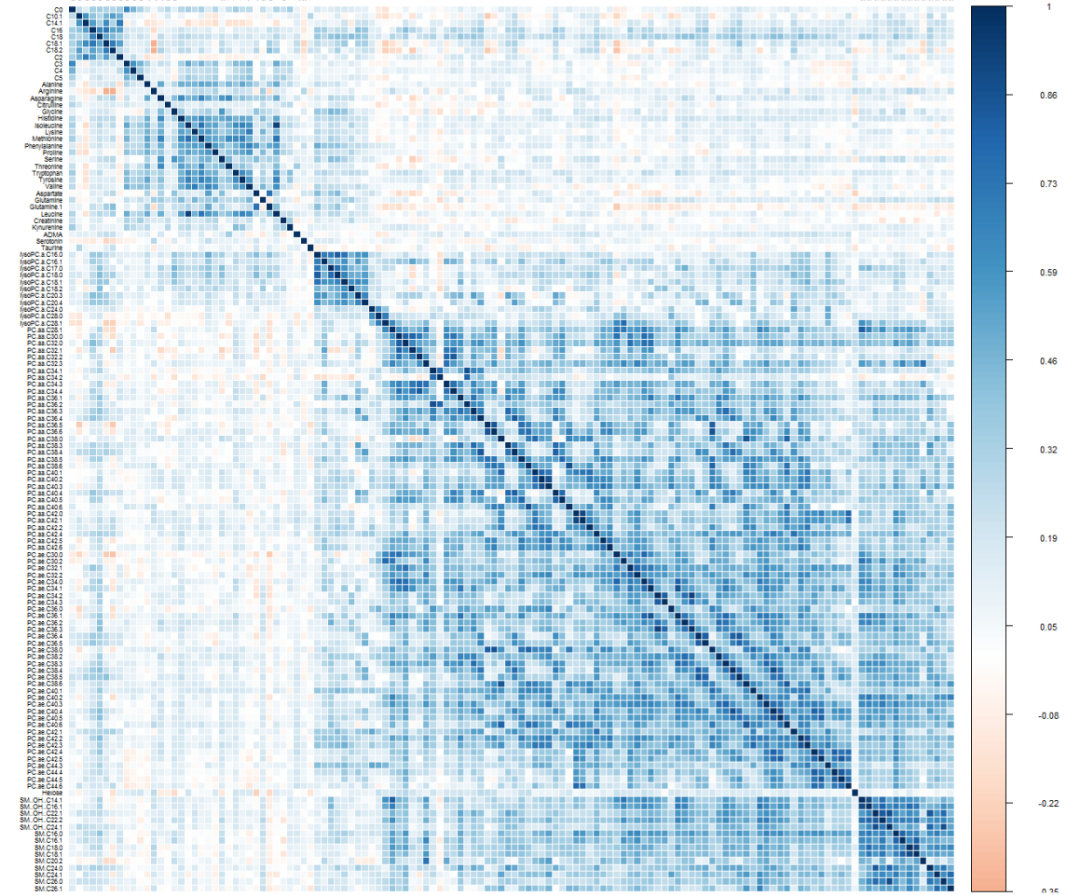
Metabolomics additional info (1)

- Samples had gone to 2 or 3 freeze-thaw cycles
- Amino acids and biogenic amines: LC-MS
- Acylcarnitines, PCs, hexose and sphingolipids: FIA
- Previous reliability study:
  - Median ICC fasting samples: 0,70
  - Median ICC non-fasting samples: 0,54
- Metabolites with CVs > 20%, >30% outside measurable range and with missing information for >30% of participants
  → excluded
- When outside measurable range:
  - Below LOD → set to half LOD
  - Below LOQ → set to half LOQ

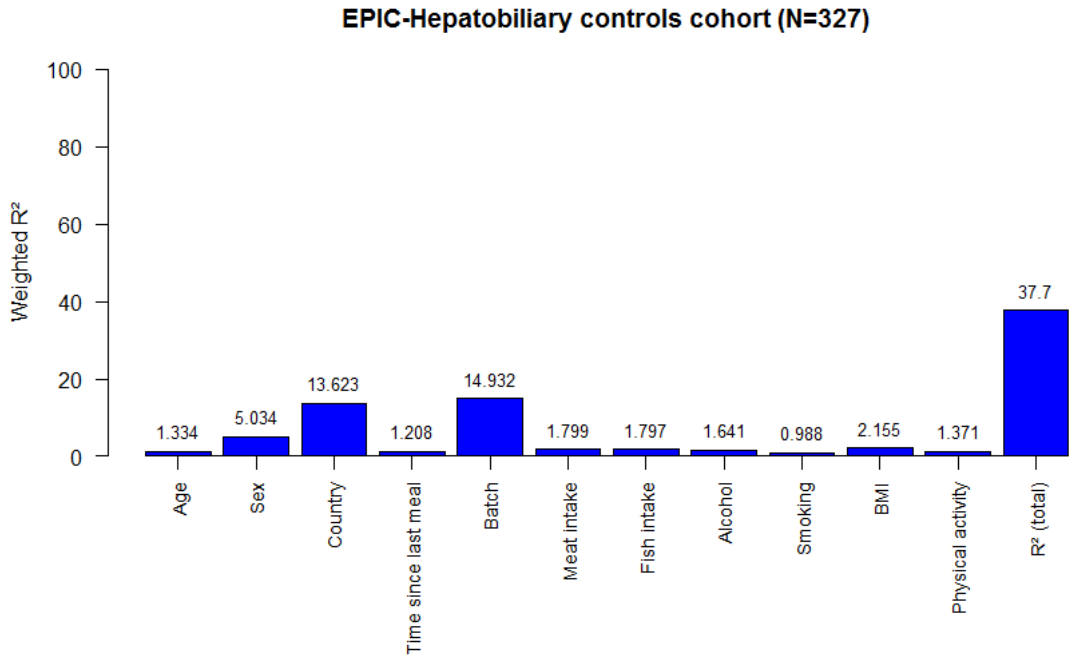
Metabolomics additional info (2)

- Centers randomly distributed in analytical batches and two QC samples included in duplicate in each batch
- Median CVs:
  - Acylcarnitines: 3,3%
  - Amino acids: 7,2%
  - Biogenic amines: 6,6%
  - PCs: 4,1%
  - Hexose: 2,6%
  - Spingolipids: 5,4%

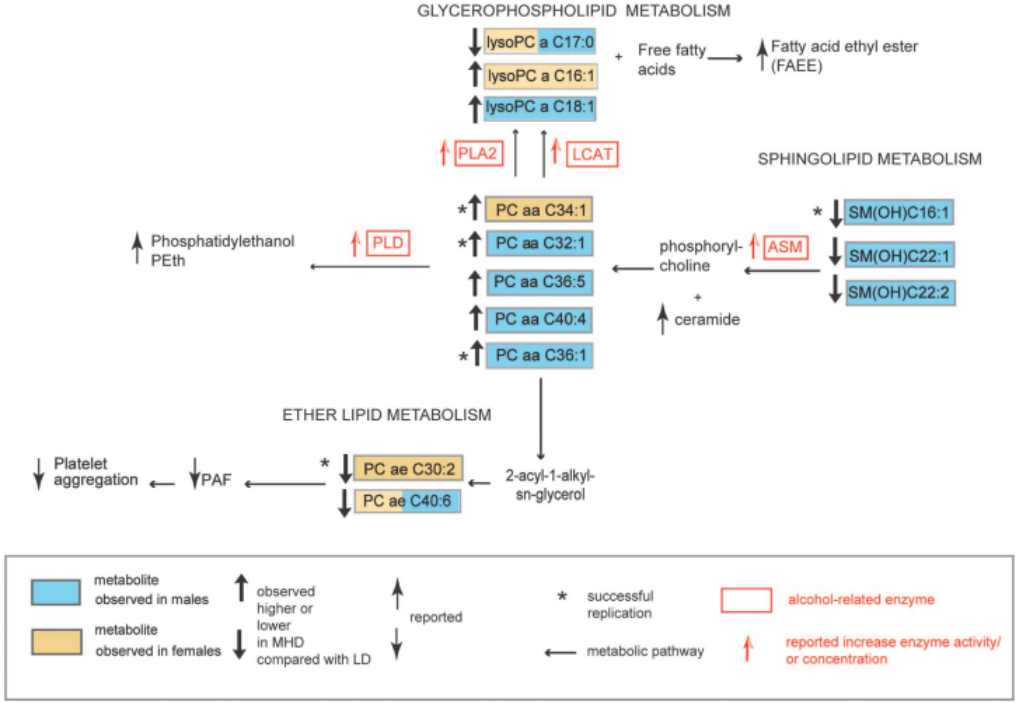
Heat map



PC-PR2 results graph



Alcohol mechanisms[1]



[1] Jaremek *et al.*, Transl Psychiatry (2013)