Annual review: year2

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Title

What lies behind the causal impact of body mass index (BMI) level and change on human health? Added value from complementary study design and deep metabolomic phenotyping

Start date: 01/10/2017

End date: 01/04/2021

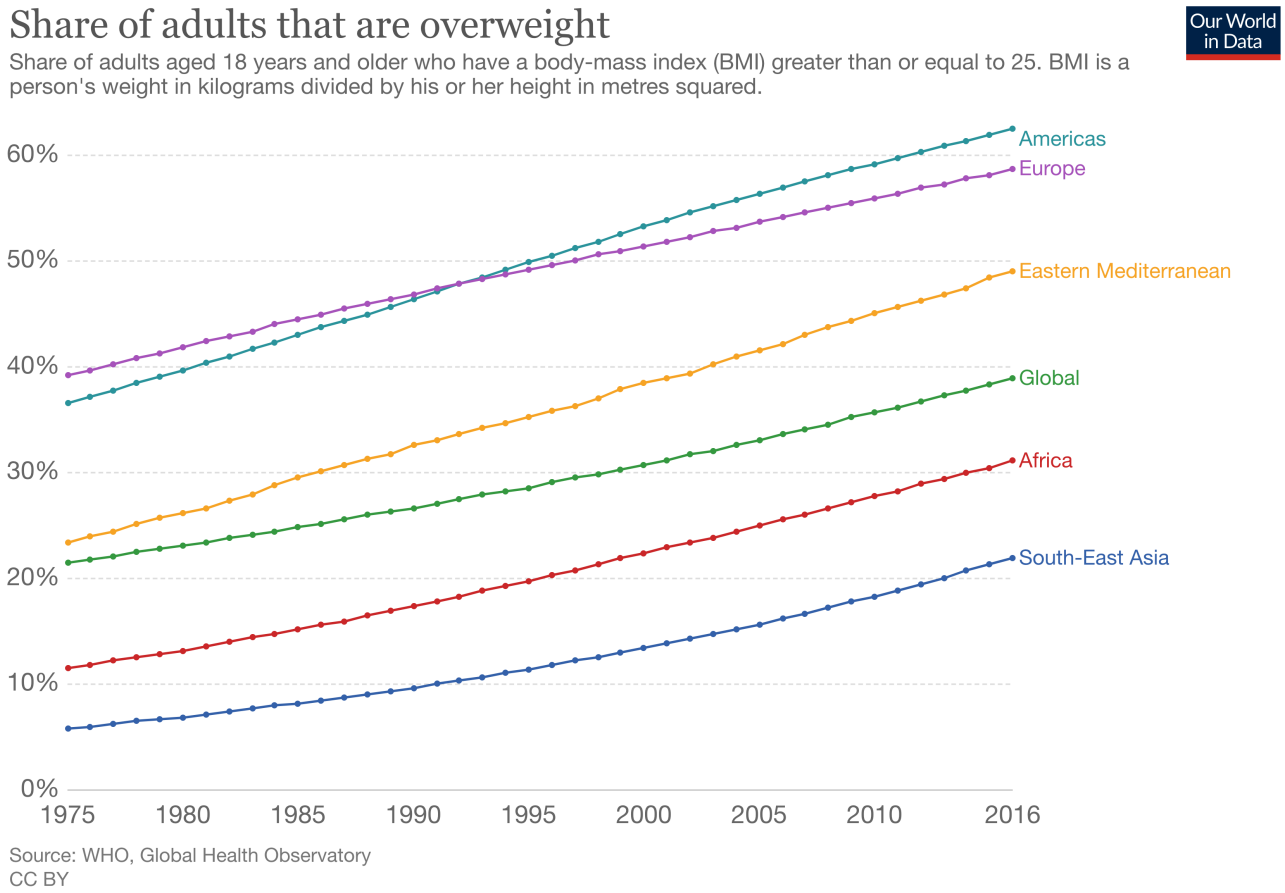
Aim

Identify metabolites that sit on the causal pathway from increased adiposity to disease

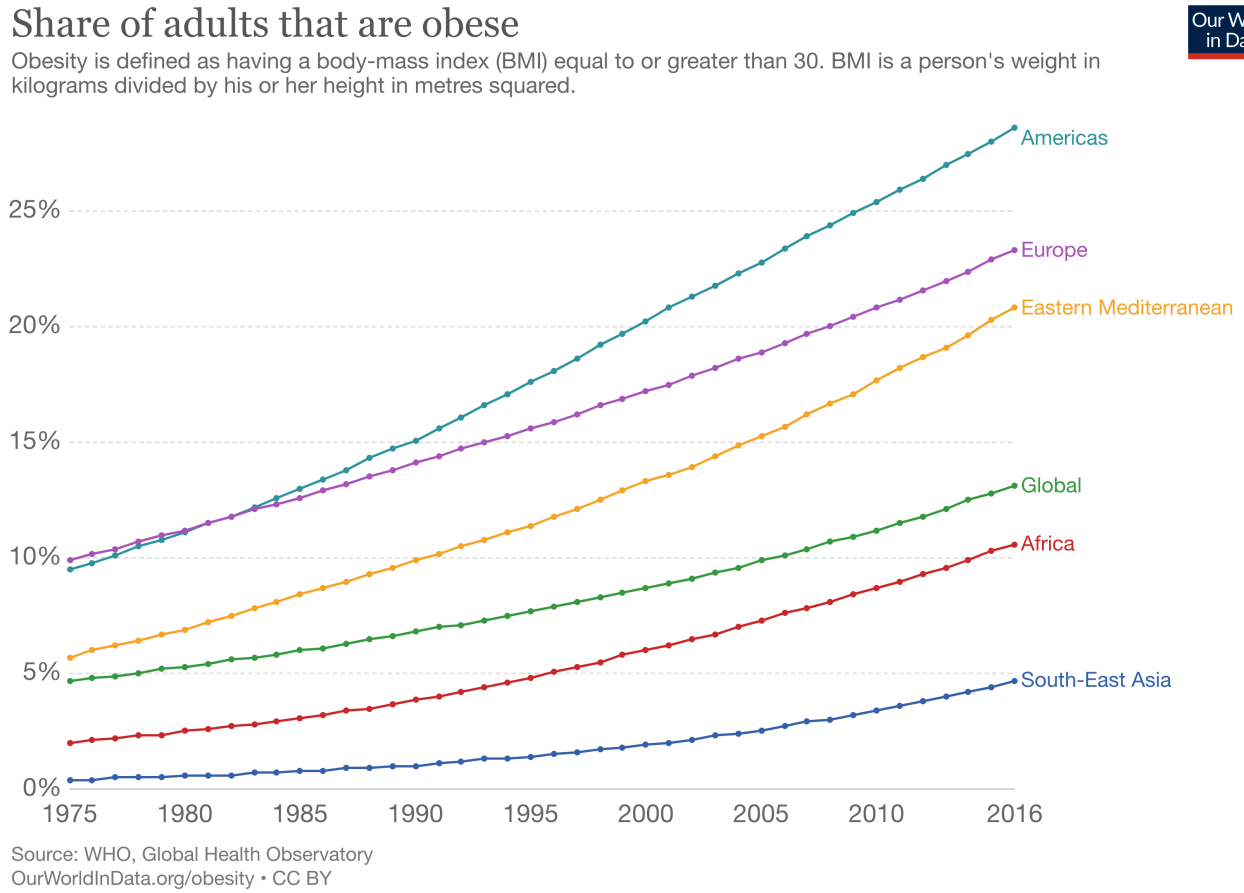
Objectives

1. Identify diseases causally associated with increased adiposity
2. Identify and describe appropriate instrumentation of increased adiposity
3. Identify metabolites causally associated with increased adiposity
4. Design and implement methods and rules to cluster metabolites
5. Identify diseases causally associated with metabolites

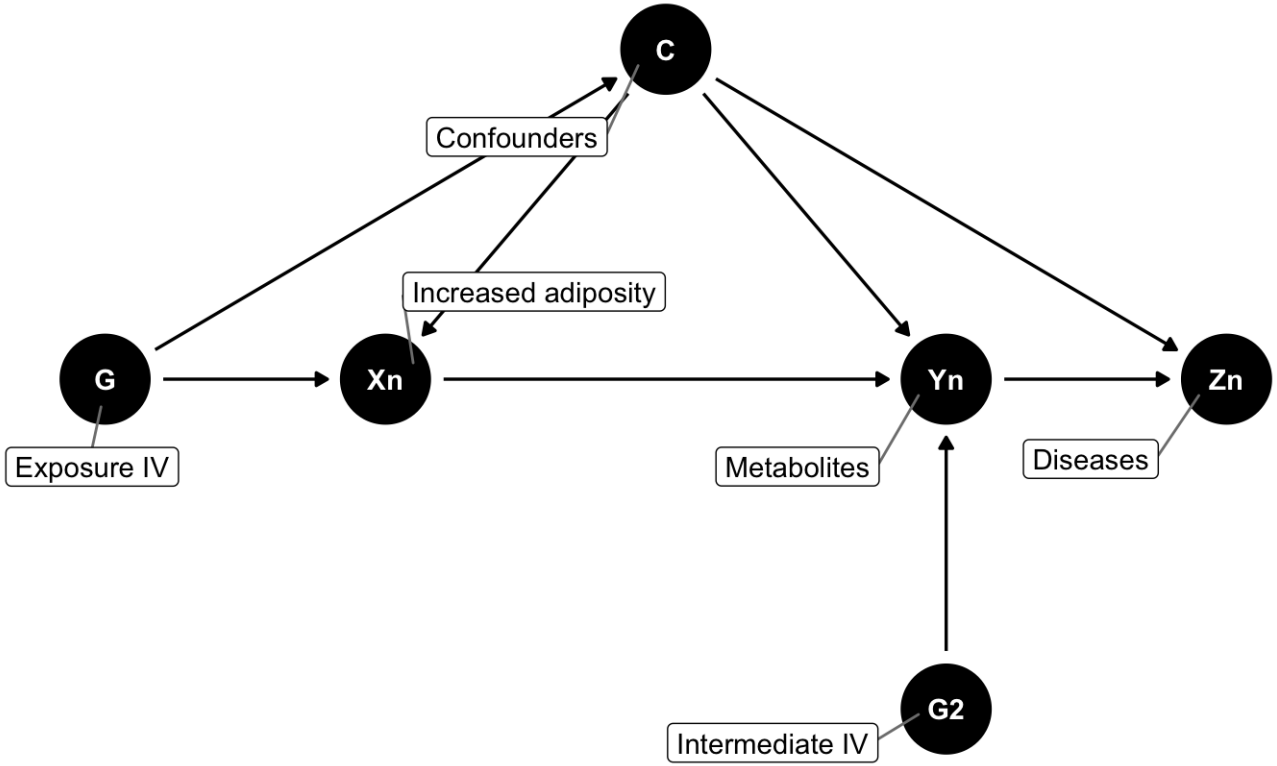
Overview



Proportion of overweight individuals



Proportion of obese individuals

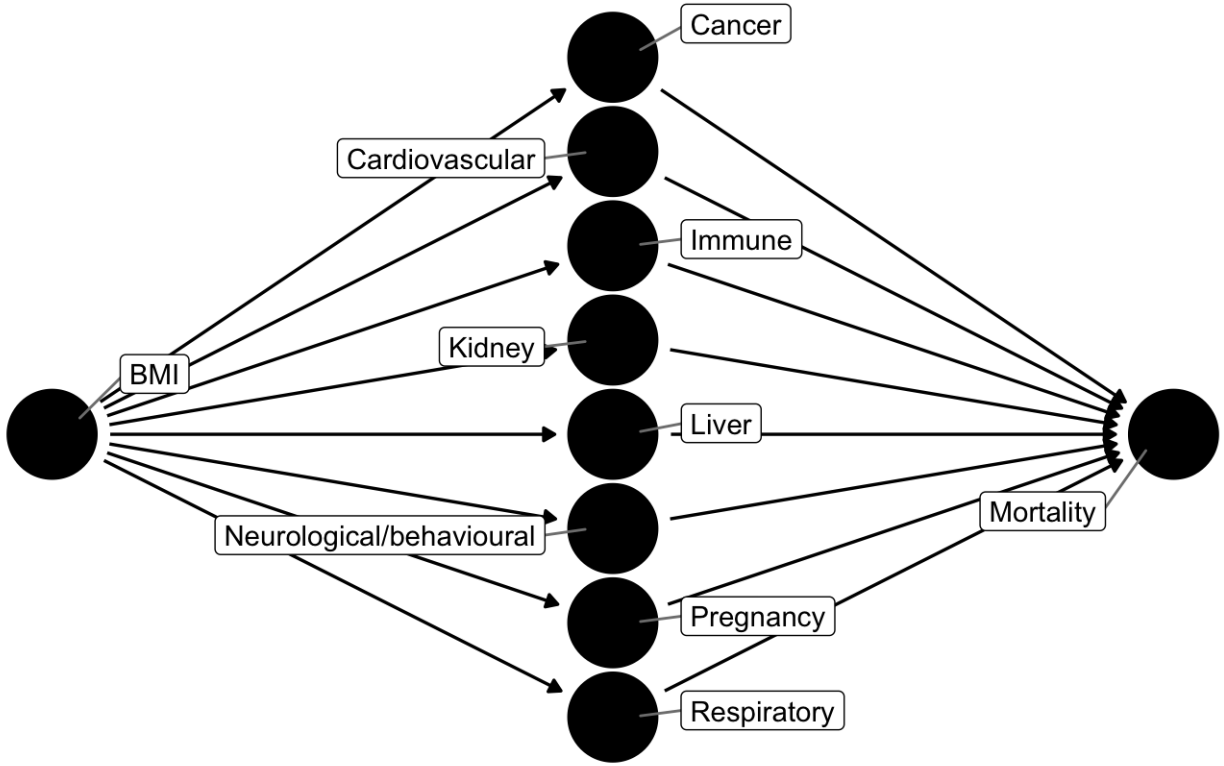


Can we build a flowchart of decisions to achieve this?

Chapter 1

Intro/overview

- What is the problem (100%)
- What is adiposity (100%)
    - inc. adipose cells - idea of genetics and metabolites introduced
    - inc. different measures
- Broad overview of diseases (90%)
- Application of metabolites and MR (0%)



MELODI analysis: 975,402 articles; 10,828 enriched terms, filtering left 77 terms, 8 categories plus ‘Other’

Intermediates identified between BMI and all targets using MELODI

Cancer	Cardiovascular	Immune	Kidney	Liver	Neuro_behav	Pregnancy	Respiratory	Other
Primary carcinoma of the liver cells	Heart failure	Pancreatitis	End stage renal failure	Liver diseases	Depressive disorder	Pre-Eclampsia	Tuberculosis	Metabolic syndrome
Malignant neoplasm of stomach	Anemia	Inflammatory disorder	Kidney Failure, Chronic	Non-alcoholic fatty liver	Dementia	Pregnancy	Sleep Apnea, Obstructive	Cessation of life
Malignant neoplasm of prostate	Dyslipidemias	Immunocompromised Host	Glomerular Filtration Rate	Liver and Intrahepatic Biliary Tract Carcinoma		Hypertension induced by pregnancy	Pneumonia	Malnutrition
Malignant neoplasm of lung	Cerebrovascular accident	Bacteremia	Kidney Diseases	Chronic liver disease			Chronic Obstructive Airway Disease	Diabetic
Common Neoplasm	Cardiovascular Diseases	Septicemia	Kidney Failure				Respiration Disorders	Multiple Organ Failure
Liver neoplasms	Atherosclerosis	Lupus Erythematosus, Systemic	Renal function				Respiratory Distress Syndrome, Adult	Fibrosis
Malignant disease	Myocardial Infarction	Sepsis Syndrome					Respiratory Tract Infections	Deglutition Disorders
Carcinoma of the Large Intestine	Ischemic stroke						Respiratory Failure	Vitamin D Deficiency
Pancreatic carcinoma	Acute coronary syndrome						Acute respiratory failure	
	Atrial Fibrillation							
	Coronary heart disease							
	Systemic arterial pressure							
	Thrombosis							
	Cerebrovascular Disorders							
	Acute myocardial infarction							
	Sinus rhythm							
	Cardiomyopathies							
	Myocardial Ischemia							
	Peripheral Vascular Diseases							
	Vascular calcification							

Chapter 2

Systematic review

All MR studies using a measure of increased adiposity as the exposure; ~150 articles included

- Literature search (100%)
- Screening (100%)
- Data extraction (30%)
- Writing (40%)

Chapter 3

Instrumentation

- Current instrumentation practices (will get from SR)
- GWAS descriptions (80%)
- Selecting instruments (0%)
- Writing (30%)

Chapter 4

Observational analysis

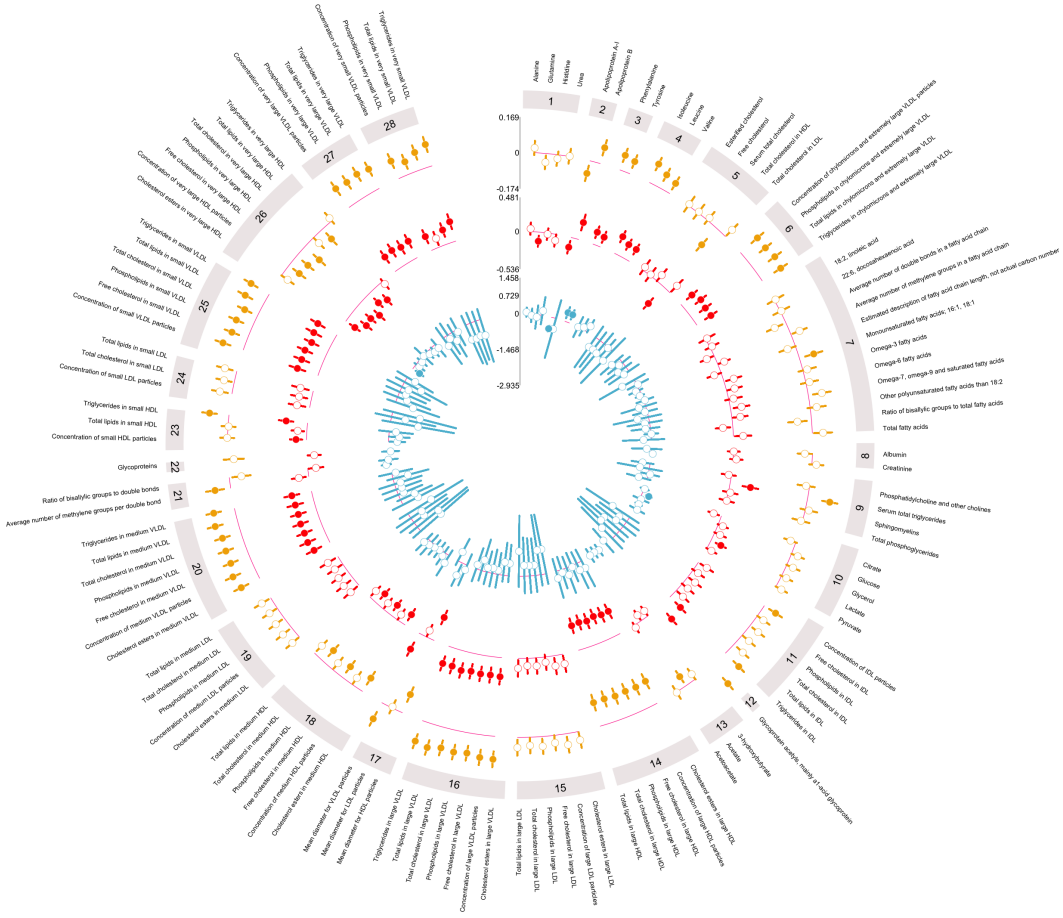
- BMI/WHR/BF% -> metabolites in ALSPAC/FGFP/Biobank (20%)
- Writing (0%)

Waiting on Biobank data…

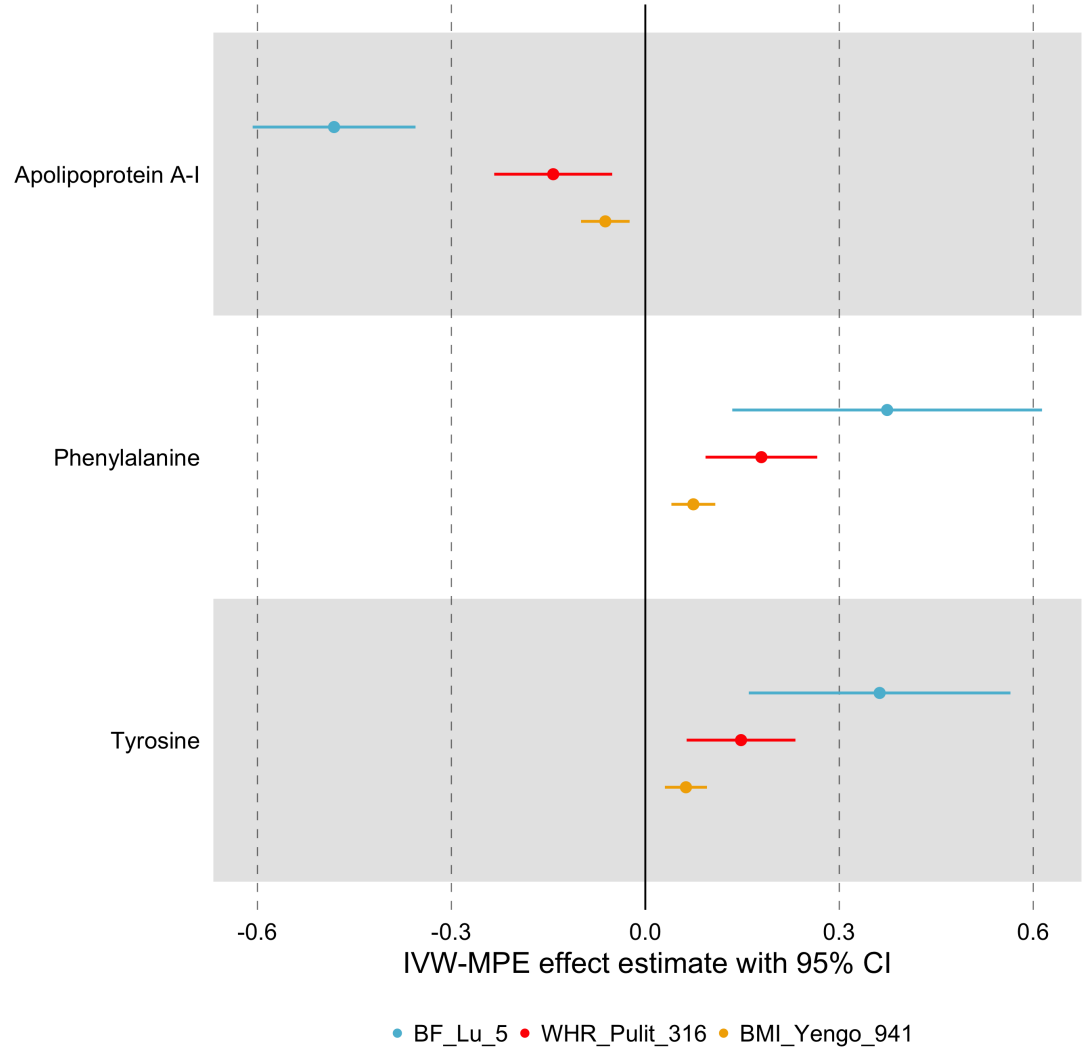
Chapter 5

MR step 1

- BMI/WHR/BF% -> metabolites analysis (100%)
- Wiriting/paper (60%)



BMI_Yengo_941	1. Amino acids	5. Cholesterol	9. Glycerides and phospholipids	13. Ketone bodies	17. Lipoprotein particle size	21. Metabolites ratio	25. Small VLDL
WHR_Pulit_316	2. Apolipoproteins	6. Extremely large VLDL	10. Glycolysis related metabolites	14. Large HDL	18. Medium HDL	22. Protein	26. Very large HDL
BF_Lu_7	3. Aromatic amino acids	7. Fatty acids	11. IDL	15. Large LDL	19. Medium LDL	23. Small HDL	27. Very large VLDL
P > 0.05/22	4. Branched-chain amino acids	8. Fluid balance	12. Inflammation	16. Large VLDL	20. Medium VLDL	24. Small LDL	28. Very Small VLDL

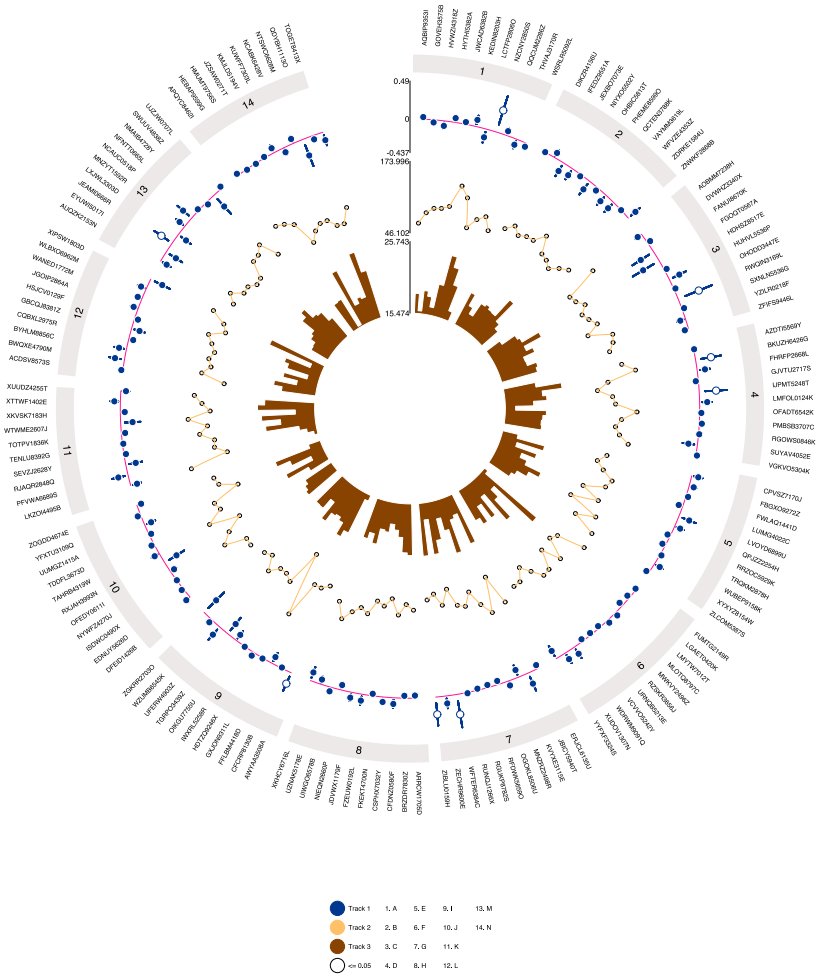

Apolipoprotein A-I
Phenylalanine
Tyrosine
-0.6
-0.3
0.0
0.3
0.6
IVW-MPE effect estimate with 95% CI
BF_Lu_5
WHR_Pulit_316
BMI_Yengo_941

Chapter 6

MR Viz

- web app (90%)
- R package (90%)
- Writing/paper (60%)
- App / R package

```
library(EpiCircos)
circos_plot(track_number = 3,
            track1_data = EpiCircos::EpiCircos_data,
            track2_data = EpiCircos::EpiCircos_data,
            track3_data = EpiCircos::EpiCircos_data,
            track1_type = "points", track2_type = "lines", track3_type = "bar",
            label_column = 1, section_column = 2,
            estimate_column = 4, pvalue_column = 5,
            pvalue_adjustment = 1,
            lower_ci = 7, upper_ci = 8,
            lines_column = 10, lines_type = "o",
            bar_column = 9,
            legend = TRUE,
            track1_label = "Track 1",
            track2_label = "Track 2",
            track3_label = "Track 3",
            pvalue_label = "<= 0.05",
            circle_size = 25)
```


0.49
0
-0.437
173.996
46.102
25.743
15.474
Track 1
Track 2
Track 3
<= 0.05
1, A
2, B
3, C
4, D
5, E
6, F
7, G
8, H
9, I
10, J
11, K
12, L
13, M
14, N

Chapter 7

Clustering metabolites

- not started
- Writing (0%)
- Priors
    - class
    - subclass
    - biological pathway
    - size
    - shared genetic variants
- No priors
    - PCA
    - factor analysis
    - Hierarchical clustering
    - density clustering
    - self organising map
    - LDSR
    - ontology
        - have discussed with Ben Elsworth (pipeline can be adpated)

Chapter 8

Rules for instrumenting clusters

- have ideas
- not started - in parallel with Chapter 7
- Writing (0%)

Chapter 9

MR step 2

- metabolites -> diseases analysis (20%) - will be scaled quickly
- Final figure for global overview (1%)
    - combining MR step 1 and MR step 2 results together
    - possible to incorporate multiple clustering methods
- Writing (0%)

Chapter 10

Discussion/limitations/conclusion

- Final flowchart figure of pipeline
- not started
- Writing (0%)