Genetics, Epigenetics and Obesity

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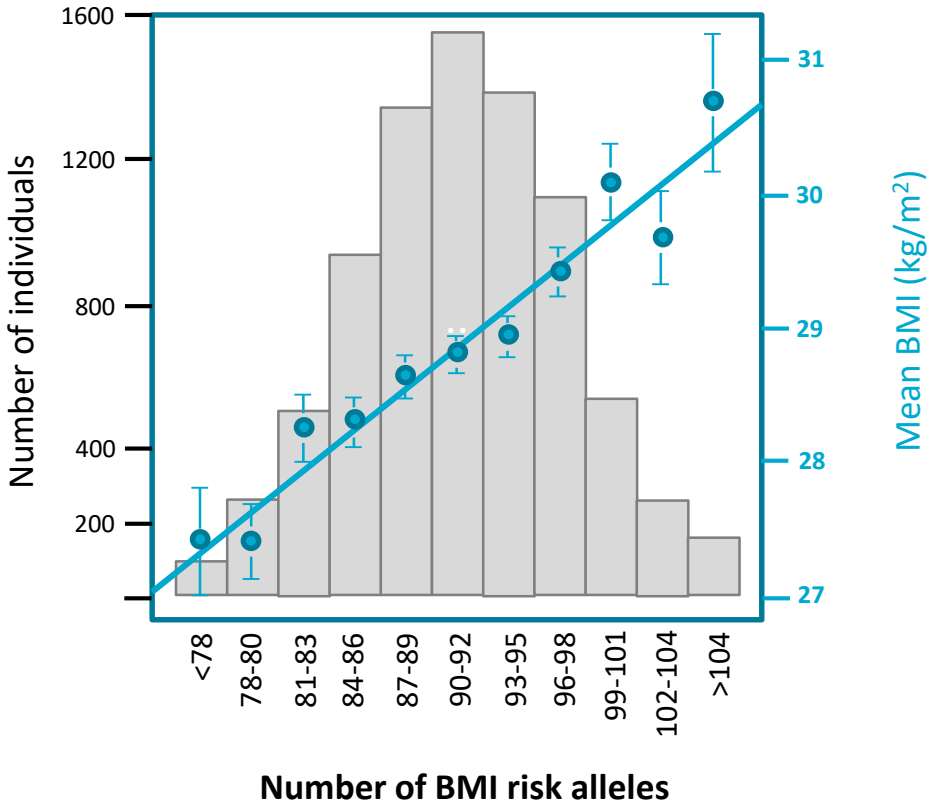
Genetics and Obesity Risk

- Mutations in a small number of genes are associated with severe forms of obesity - rare
- More generally – based on twin, family and population studies:
  - inherited contribution to Body Mass Index (risk of developing obesity) is estimated at 40-70%
  - large genetic studies have identified common variants (alleles) in more than 100 genes that contribute to a person's risk of high BMI (similar for diabetes/cardiovcascular)
  - Effects of individual genetic variants are small
  - Top 100 genes only contribute about 4% to BMI-risk
  - Summed variants across the genome:
    - up to 20% of risk explained

1. Locke AE et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature* **518**: 197-206 (2015)
2. Loos RJF. The genetics of adiposity. Curr Opinin in Genetics and Development 50:86–95 (2018)

Genetics and Obesity Risk (2)

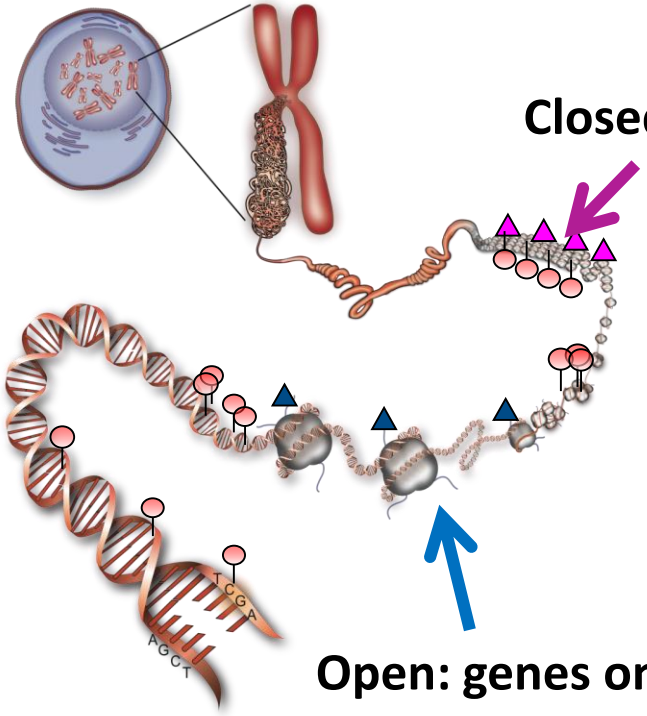
- Top 97 BMI risk alleles derived from meta-analysis of ~340,000 individuals
- In separate group of 8,164 individuals, mean BMI determined for groups of individuals carrying different numbers of risk alleles (right)
- 3.3 kg/m2 difference between those carrying the least and most risk alleles

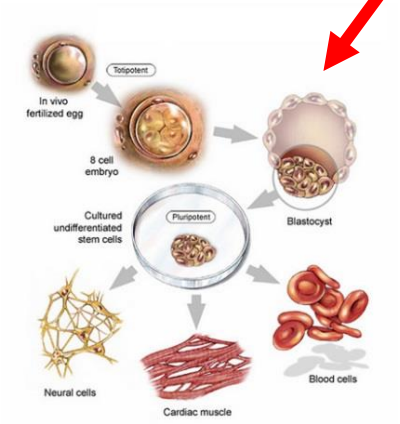


❖ Measurable contribution,
but currently impractical to apply clinically

Adapted from Nature: Extended data Fig2. Locke AE et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature* **518**: 197-206 © 2015.

“Epi”genome

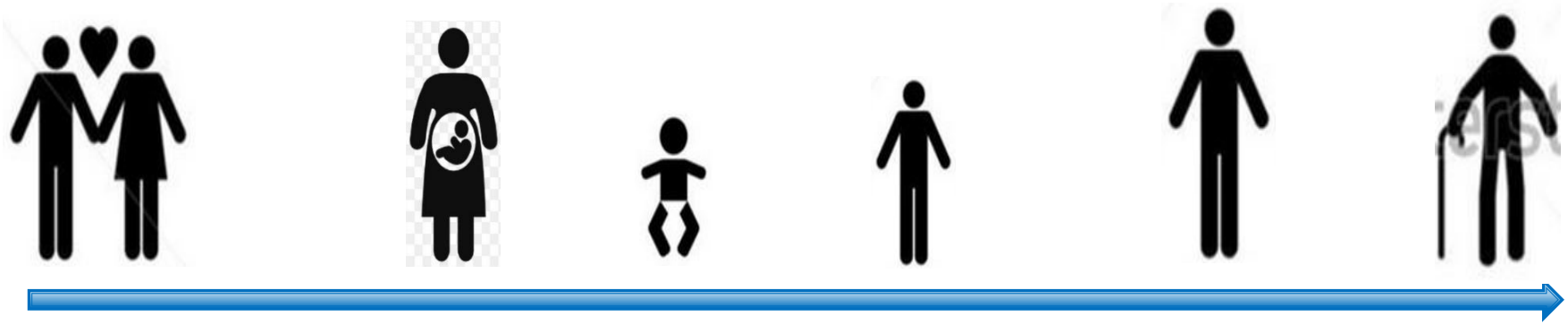




- *Set of marks that are added to DNA or associated proteins*
- *Marks allow or prevent genes being switched on*
- *Allows expression of specific genes in each cell type*
- *Epigenome is “re-set’ in the early embryo and during formation of sperm and eggs*
- *Inherited through cell division*
- *Effected by environment and modulated in disease*

- The epigenome is the interface between the environment and the genome

Epigenome in health and disease throughout life



Peri-conception

In utero, neonatal

Childhood/ adolescence

Adult development

Aging

Preconception and early developmental environment/metabolism contributes to epigenomic factors that predispose to disease

Diseases may manifest later in life due to early developmental exposure

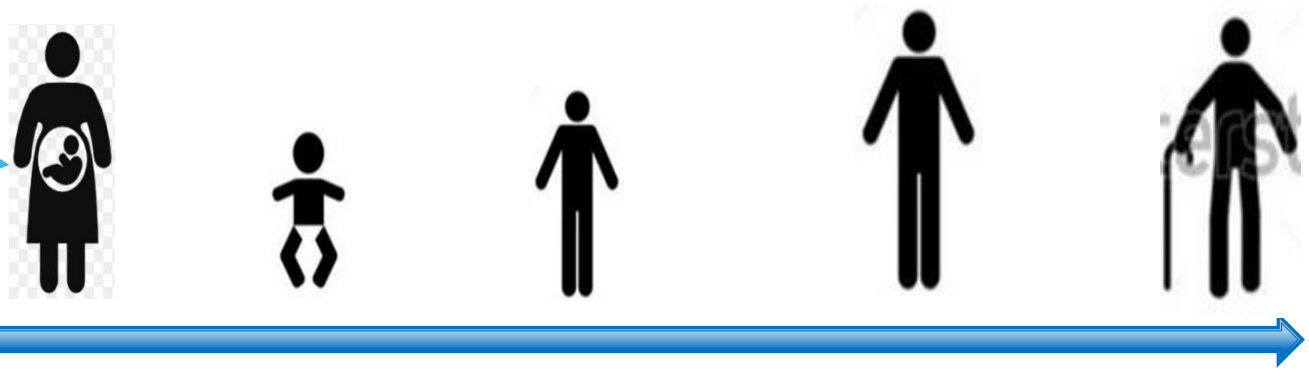
In utero and early life environment

effects on health
role of epigenetics

Smoking, alcohol

Hormones
steroids
VitD etc.
Signalling pathways

Nutrition
Macronutrients
Micronutrients



In utero, neonatal

Childhood/ adolescence

Adult development

Aging

Early developmental environment/metabolism contributes to epigenome changes and “Tuning”of epigenetic programs

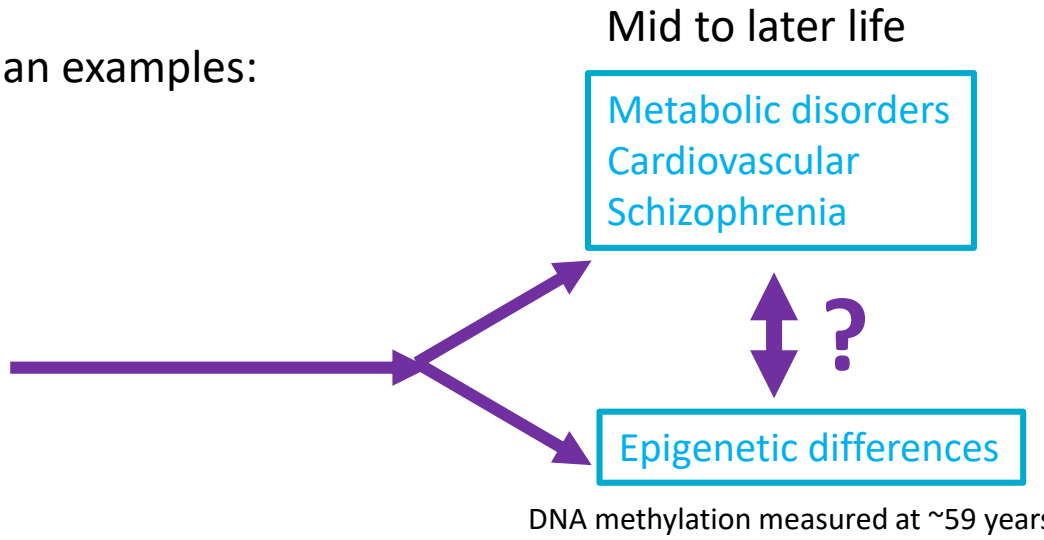
Diseases may manifest later in life due to early developmental exposure

Early life (in utero) impacts on the health outcomes and the epigenome

Spurred by animal studies and human examples:

Dutch “Hunger Winter” (1944/45)

Population northern Netherlands subjected to starvation conditions near the end of World War 2

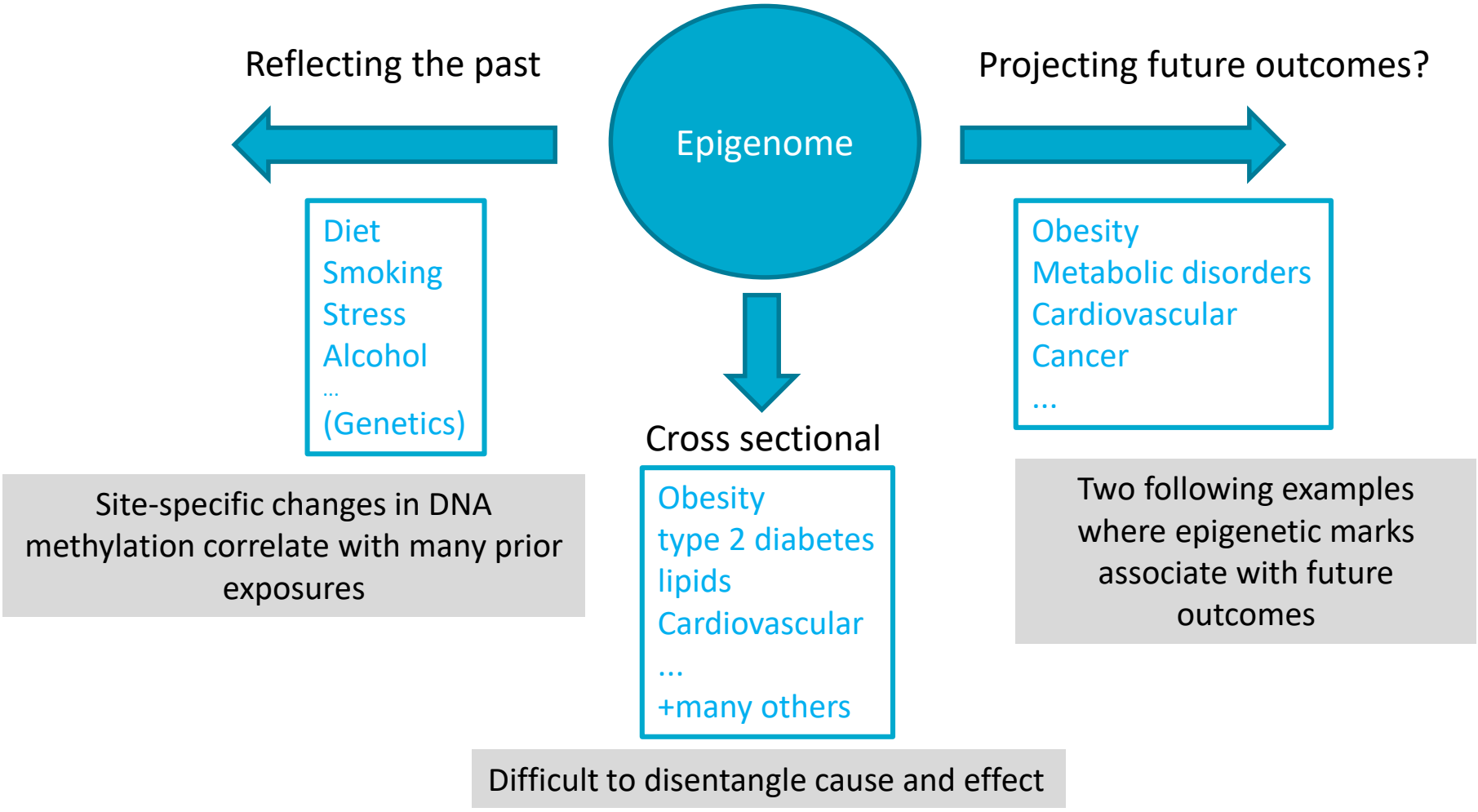


- Health impacts and epigenetic differences seen in those in first trimester during famine.
- Challenging to determine if epigenetic changes cause or effect

Tobi E et al. (2014) DNA methylation signatures link prenatal famine exposure to growth and metabolism. Nature Communications 5: 5592

Epigenome data and its application

quantifying patterns of DNA methylation

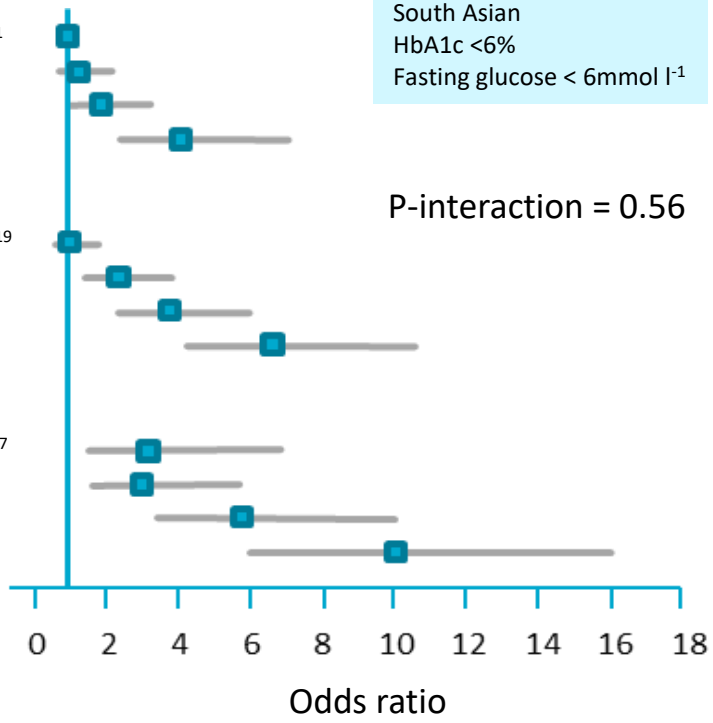


Risk of newly incident type 2 diabetes within five years
(adults, 62 gene signature)

	Controls/cases	*P*	*P trend*
Normal (BMI 18.5 - 24.9)			
Q1	144/29		3.85 x 10^{-1}
Q2	141/32	4.97 X10^{-1}	
Q3	130/43	2.61 X10^{-2}	
Q4	106/69	1.89 X10^{-7}	
Overweight (BMI 25 – 29.9)			
Q1	129/27	9.50 X10^{-1}	5.66 x 10^{-19}
Q2	185/78	7.70 X10^{-4}	
Q3	169/115	9.00 X10^{-8}	
Q4	301/321	4.00 X10^{-16}	
Obese (BMI >30)			
Q1	27/17	2.50 X10^{-3}	4.19 x 10^{-7}
Q2	50/28	5.20 X10^{-4}	
Q3	59/61	5.10 X10^{-10}	
Q4	149/255	7.90 X10^{-22}	

Subjects at baseline:
South Asian
HbA1c <6%
Fasting glucose < 6mmol l^{-1}

P-interaction = 0.56

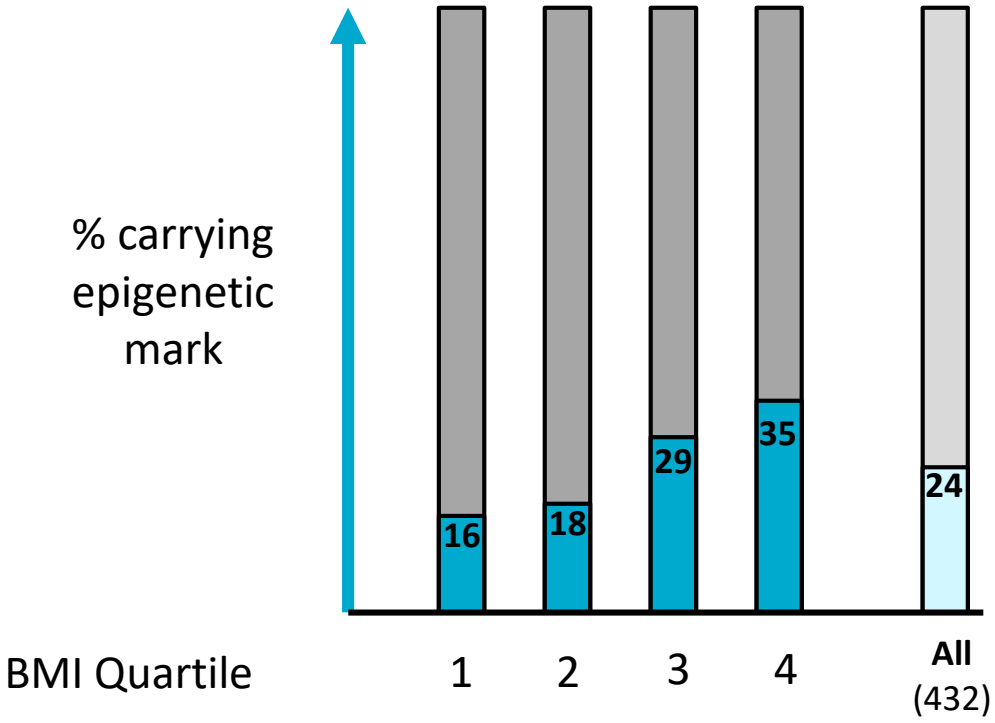


P significance relative to Normal BMI, Q1 epigenetic signature
P trend significance of trend within each BMI group
Interaction P value
-interaction between adiposity and DNA methylation score in risk of T2D

- 62 gene epigenetic signature can predict risk of developing T2D
- Both on European and Indian cohorts
- Strong association with risk even after correcting for adiposity & glycaemic measures
- Applicable across weight range

Adapted from Nature: Fig 4, Wahl S et al. Epigenome-wide association study of body mass index, and the adverse outcomes of adiposity. Nature 541:81-86 © 2017.

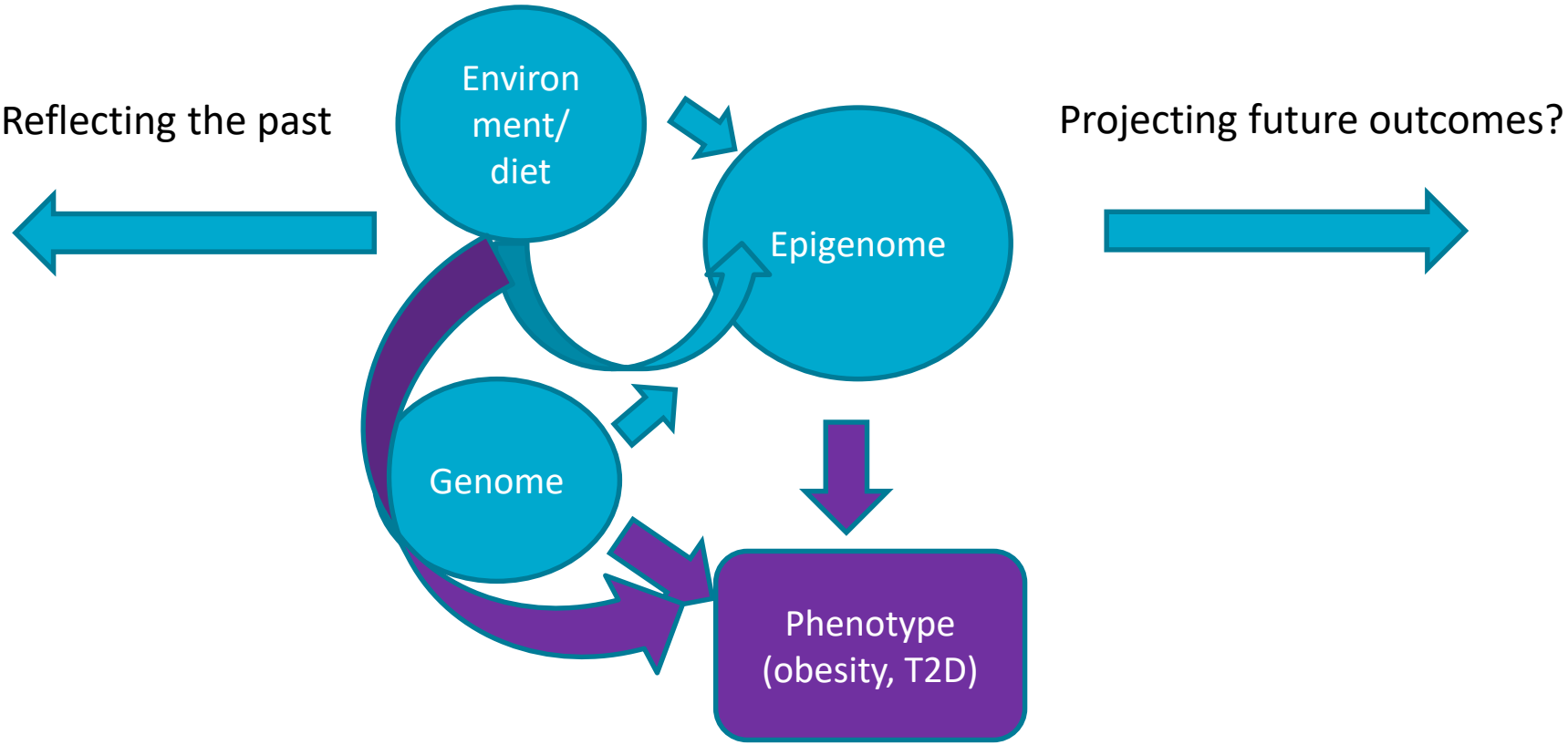
Epigenetic mark at birth associated with child BMI at 5 yrs



Newborns with epigenetic mark, twice as likely to be classified as overweight or obese at 5 years

van Dijk SJ et al. DNA methylation in blood from neonatal screening cards and the association with BMI and insulin sensitivity in early childhood. Int J Obes (Lond) 42:28-35 (2018).

Summary



- Clear genetic contribution to obesity and associated metabolic disorders – but difficult to use clinically at present
- Epigenetic data can integrate genetic and environmental inputs – early days, but showing some promise in predicting health outcomes
- Both data types are identifying targets for pharmacological intervention