Genome-wide association study of birth weight in a population indigenous to the Southwestern United States

Cambridge Diabetes Seminar

Lauren Wedekind, MSc

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UNIVERSITY OF OXFORD

NIH National Institute of Diabetes and Digestive and Kidney Diseases

- Epidemiologic studies in multiple populations have shown **birth weight** to be **associated** with **type 2 diabetes (T2D)** in adulthood.

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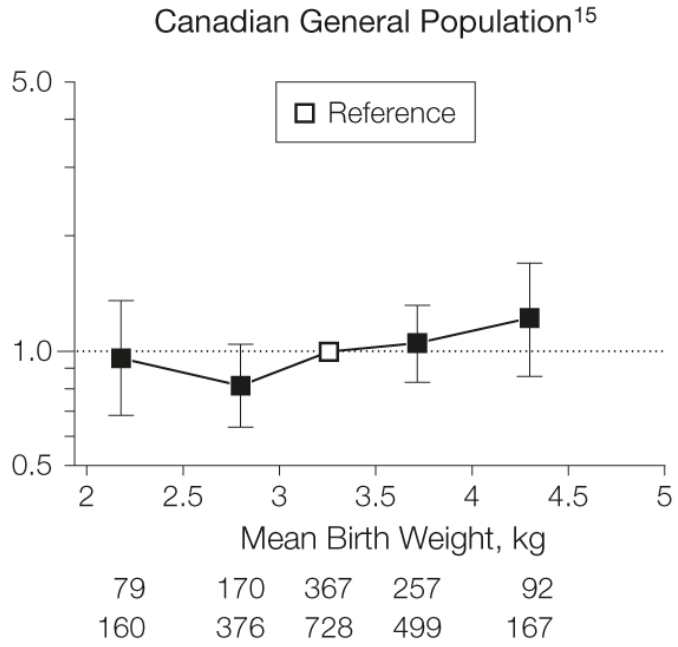

Whincup, *JAMA* (2008)

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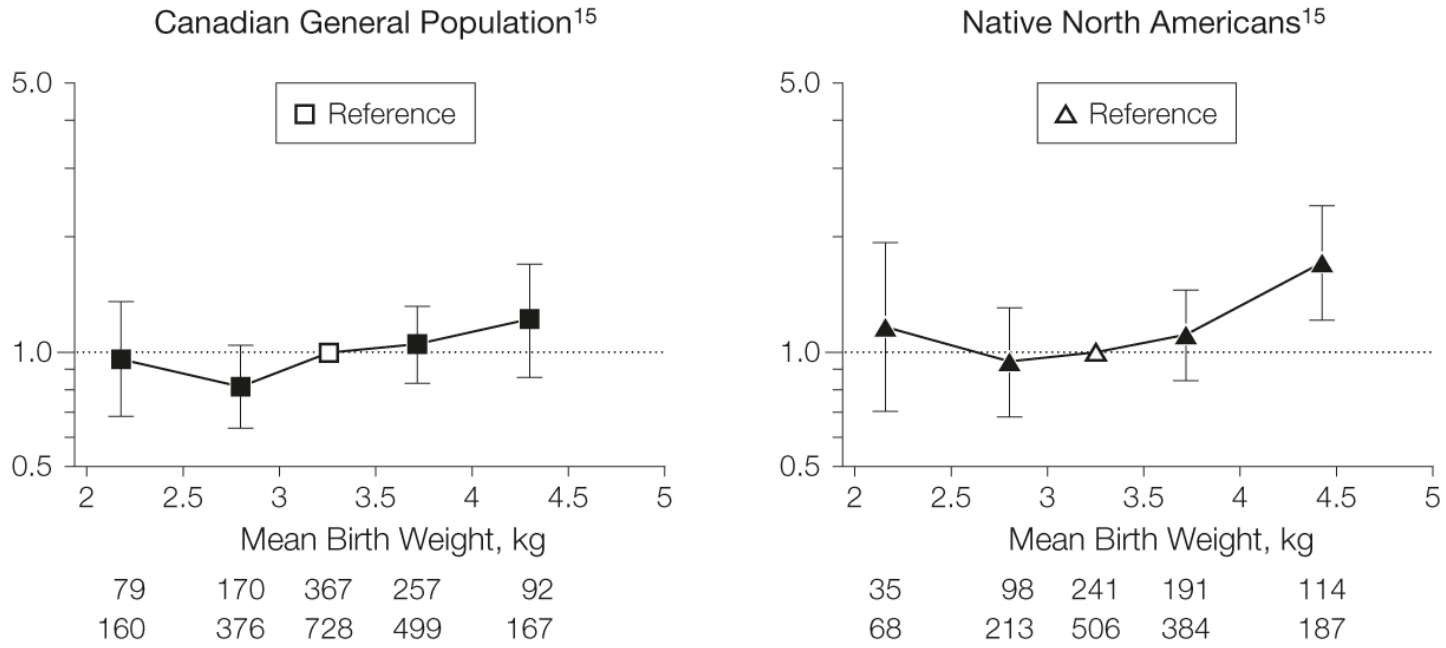

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- **3700 Native individuals** indigenous to the Southwestern US (2037 female; 1663 male)

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- **Birth weight (grams)** recorded from medical record or Arizona state birth certificate

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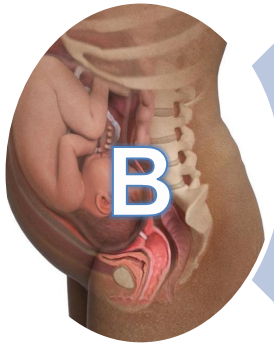
- **Blood samples, phenotypic data collected** from consenting members in longitudinal study

- **Genome-wide association study** using 2 models:

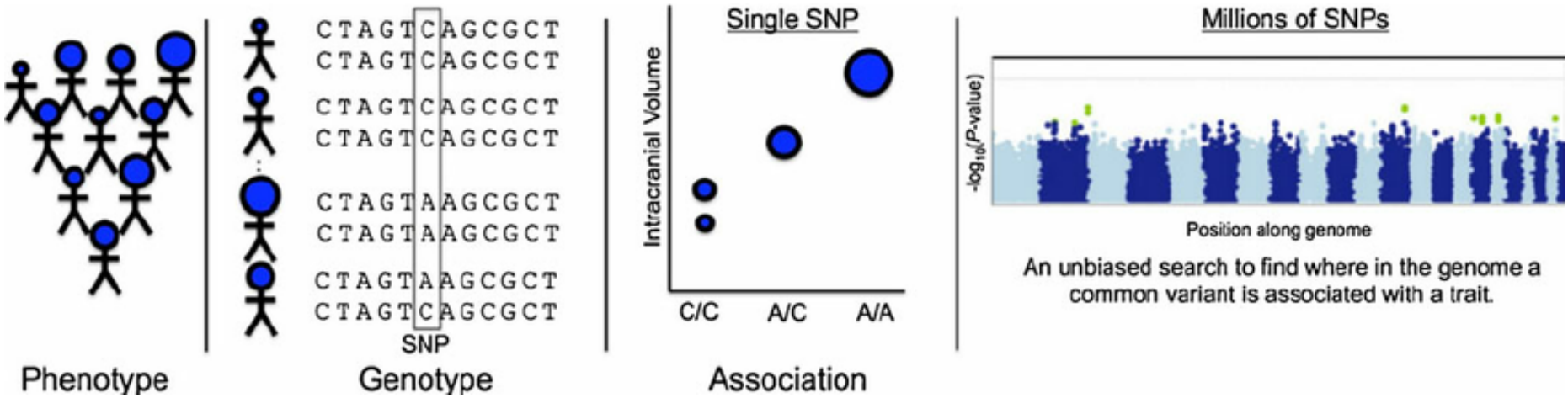
A

•Adjusted for birth year and cryptic relatedness



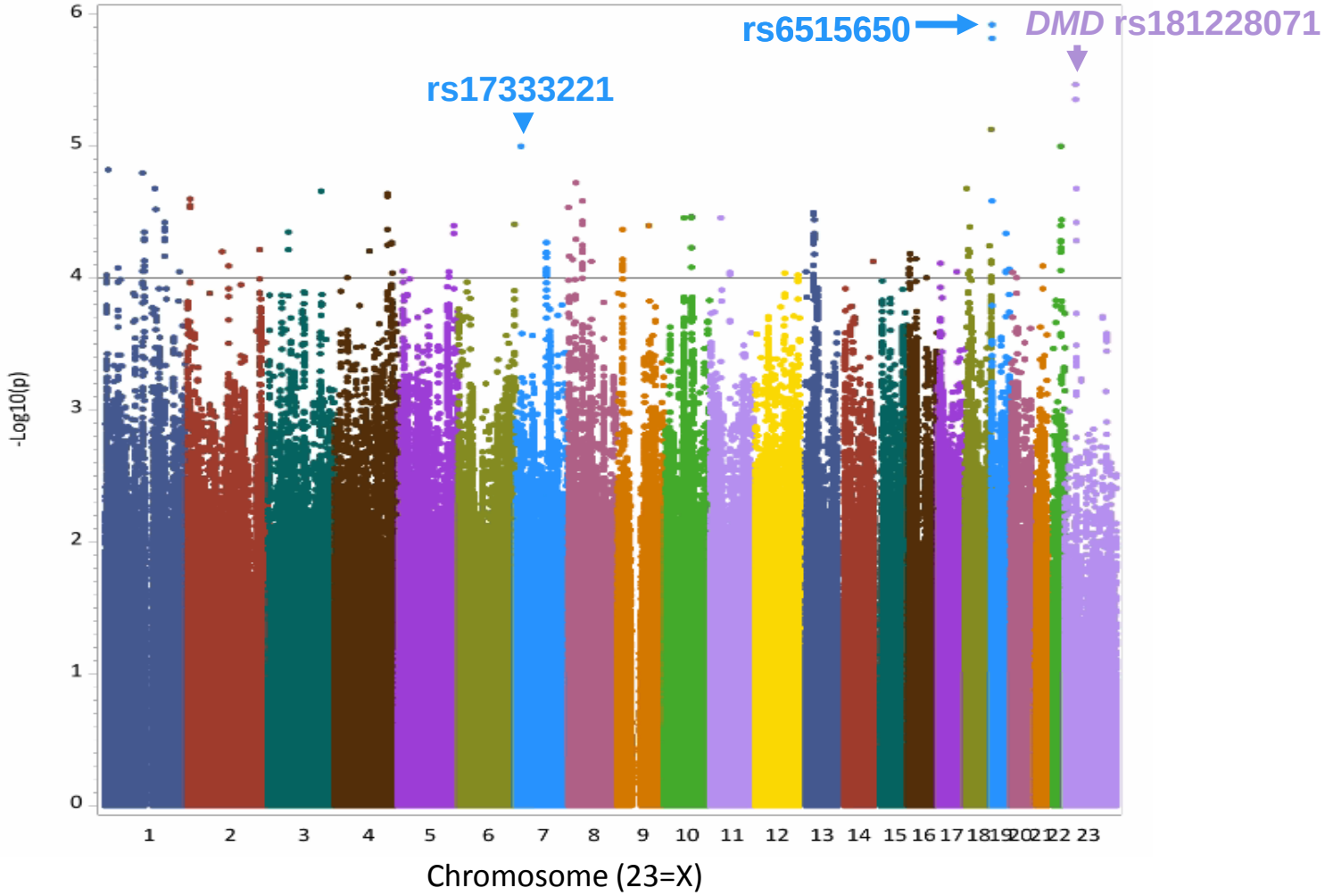
•Adjusted for birth year, cryptic relatedness, **and exposure to maternal diabetes *in utero***

- **Genome-wide association study**

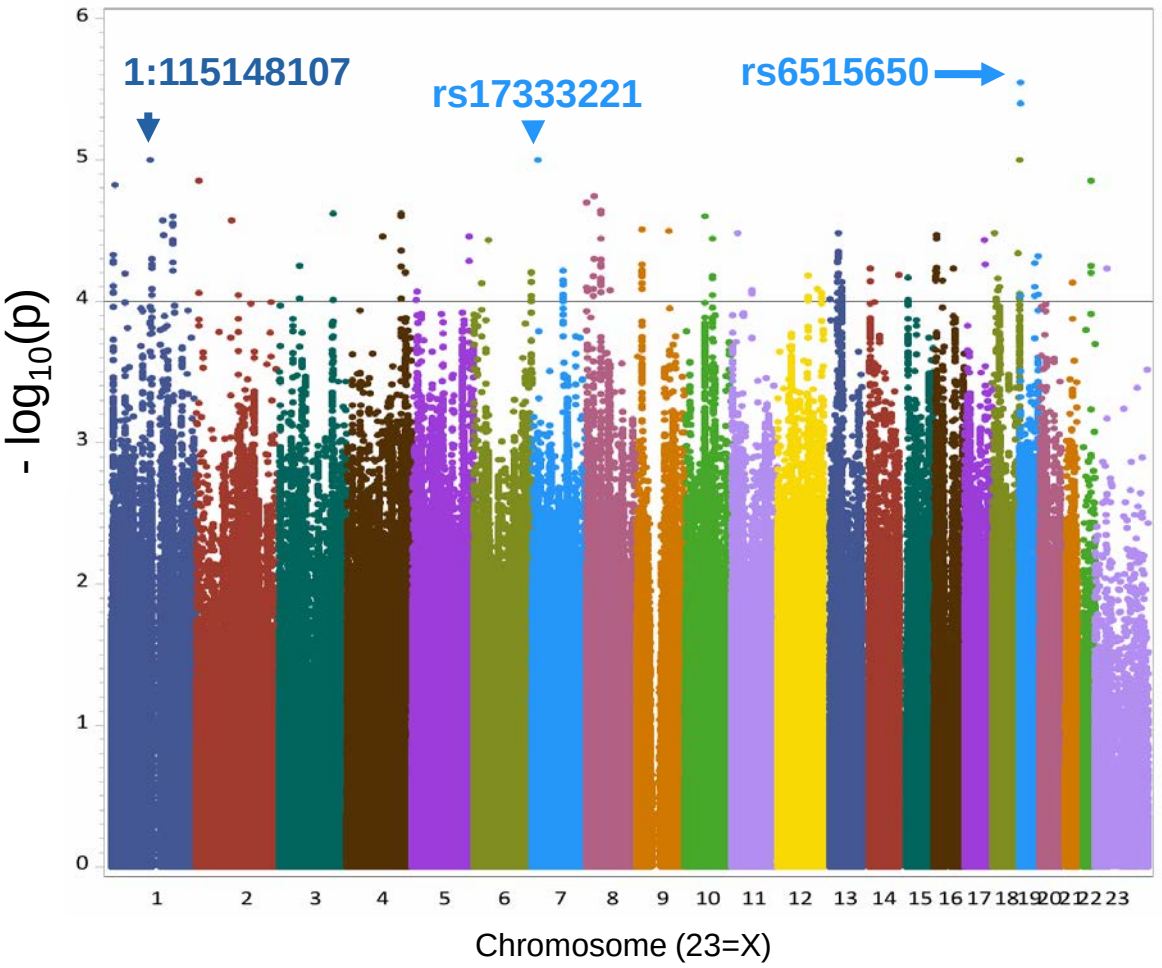


Adapted from Thompson P *et al*, *Brain Imag Behav* (2014)

Manhattan Plot: GWAS of Birth Weight (Model A)



Manhattan Plot: GWAS of Birth Weight (Model B: adjusted for Exposure to Maternal Diabetes *in utero*)



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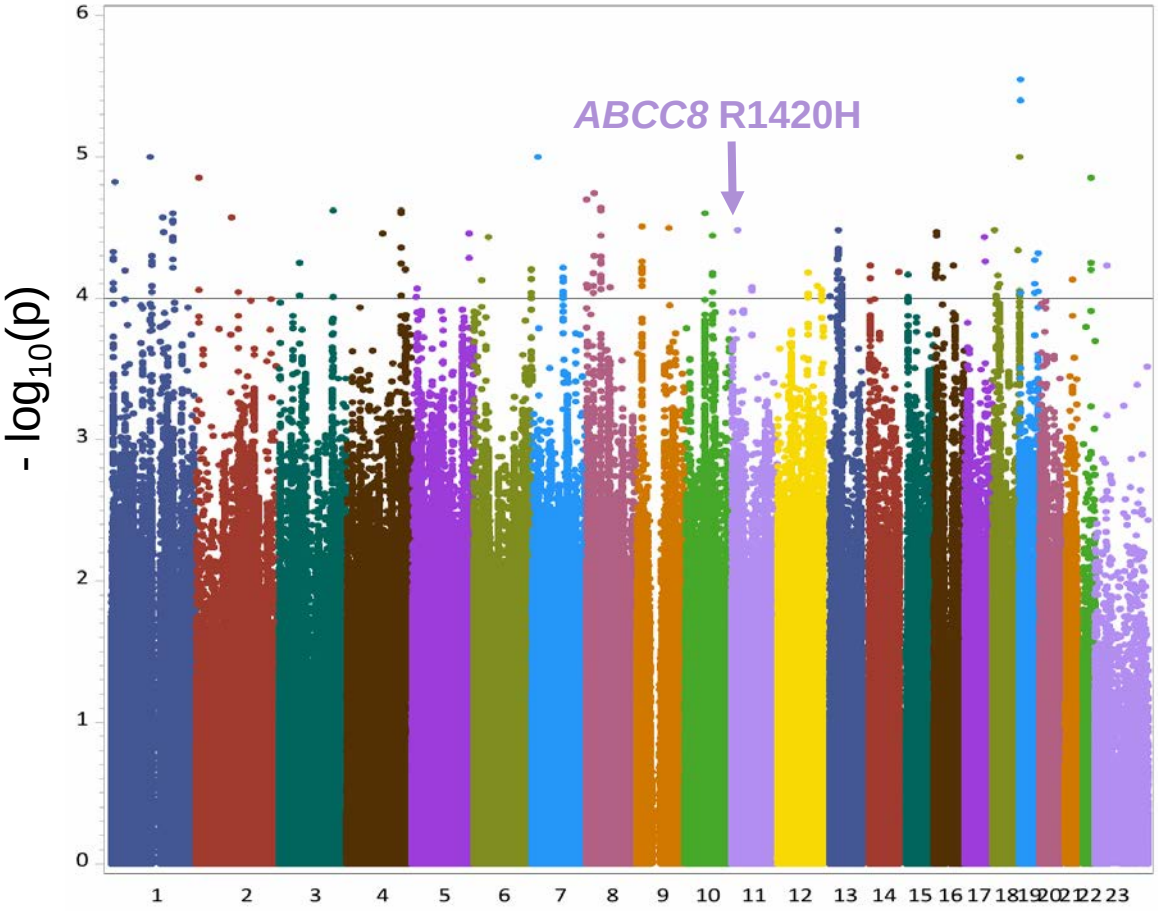


Inactivating mutations in ***ABCC8* R1420H** cause **hyperinsulimic hyperglycemia** of infancy

Associated with **T2D** (OR=2.2)

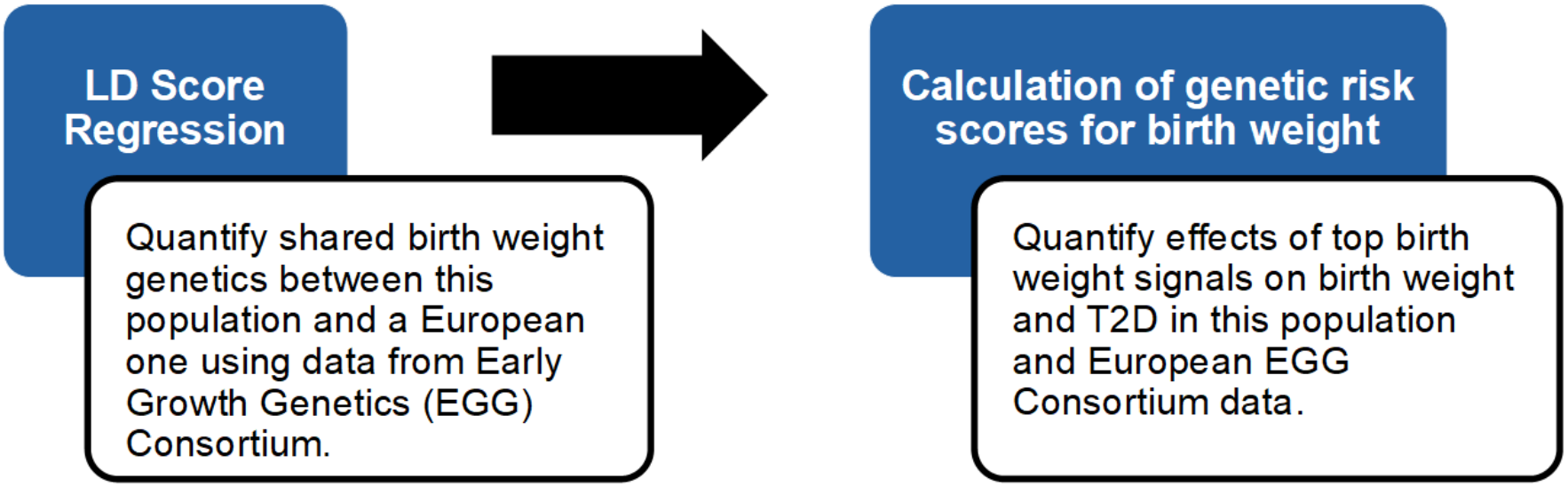
(Baier et al, *Diabetes* (2015))

Discussion: Next Steps

LD Score Regression

Quantify shared birth weight genetics between this population and a European one using data from Early Growth Genetics (EGG) Consortium.

Discussion: Next Steps



Many Thanks

Participants in the Gila River Indian Study

NIDDK Phoenix Epidemiology & Clinical Research Branch

Dr Robert L Hanson
Sayuko Kobes
Dr Muideen Olaiya
Dr Leslie J Baier
Dr Wen-Chi Hsueh
Dr William Knowler

McCarthy Group at Oxford Wellcome Centre for Human Genetics

Dr Anubha Mahajan
Professor Mark McCarthy

@WedekindLE

RESULTS: HERITABILITY ESTIMATES

Trait	h^2 Estimate	h^2 95% CI
Birth weight	0.49	0.29, 0.68
Birth weight (**adjusted for *in utero* exposure to maternal diabetes**)	0.53	0.50, 0.56

- **Heritability (h^2):** part of the total variation that is due to **additive genetic values** (V_A)
- V_G represents genetic variance in a population
- V_E represents environmental variance in a population

$$h^2 = \frac{V_A}{V_G + V_E}$$