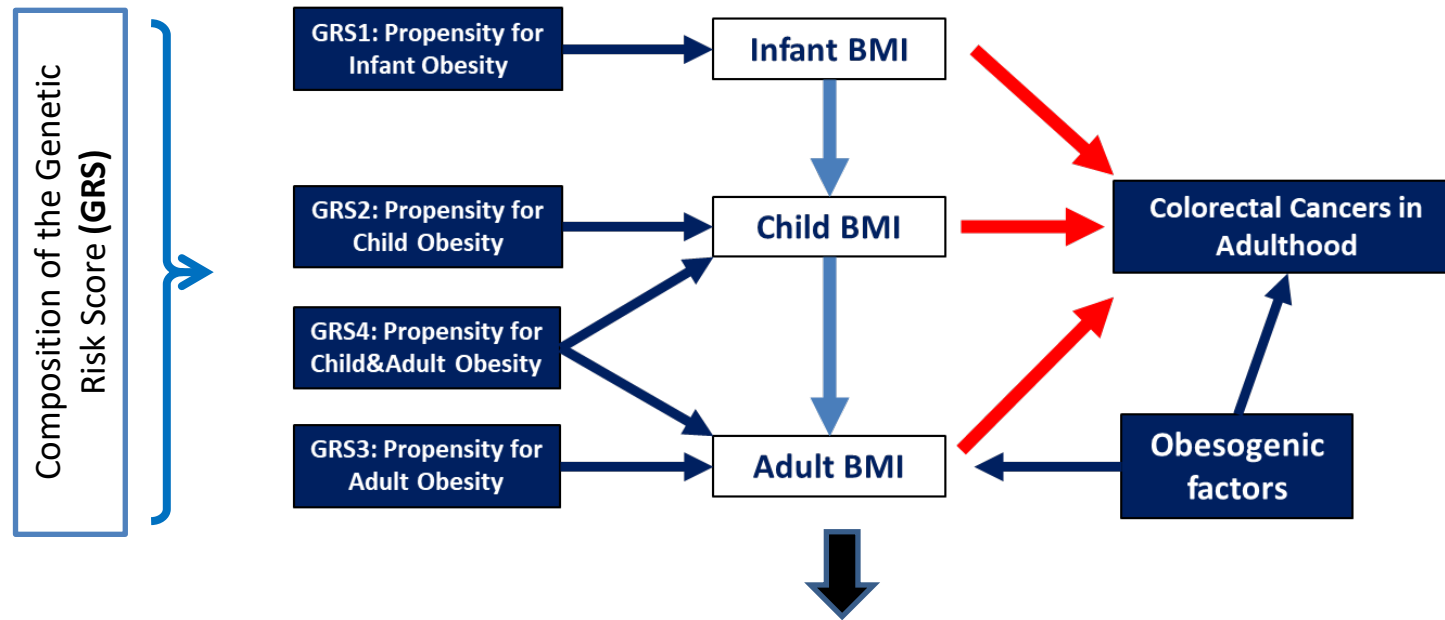November 3rd & 4th, 2021

Exploring the role of genetically determined BMI in infancy, childhood and early adulthood on colorectal cancer development in later life

'LIfeGene Obesity'

David Hughes, University College Dublin, Ireland

Project Analytical Strategy

Composition of the Genetic Risk Score (**GRS**)

- **GRS1: Propensity for Infant Obesity** → Infant BMI
- **GRS2: Propensity for Child Obesity** → Child BMI
- **GRS4: Propensity for Child&Adult Obesity**
- **GRS3: Propensity for Adult Obesity** → Adult BMI

Infant BMI → Child BMI → Adult BMI

Infant BMI → Colorectal Cancers in Adulthood
Child BMI → Colorectal Cancers in Adulthood
Adult BMI → Colorectal Cancers in Adulthood

Obesogenic factors → Adult BMI
Obesogenic factors → Colorectal Cancers in Adulthood

- The GRS will be calculated from the sum of risk alleles corresponding to obesity phenotypes - weighted by the effect size estimate of the corresponding GWAS on the phenotype

- Cause specific risks for the GRS-cancer associations will be estimated using logistic regression models or Cox proportional hazard, as appropriate

Obesity Variables for Stratified Analyses / Adjustment:
- Early life obesity assessed by birth weight (UKBB only)
- Adult obesity assessed by: (1) WHO BMI categories, (2) duration of obesity during adult life, (3) Cross categorization of weight/waist-circumference (UKBB, GECCO, EPIC)

Dietary, Lifestyle Variables Stratified Analyses / Adjustment (UKBB, GECCO, EPIC):
- Healthy Lifestyle (HLI) and Mediterranean Diet (MDS) Scores
- Physical activity, alcohol intake, alcohol drinking pattern, smoking patterns
- By Sex (men/women), by age group at study enrolment and at diagnosis (<40, 40 to <60, ≥60 years old)

Additional exploratory analyses:
- By levels of pre-diagnostic circulating CRP, C-peptide, and by calculated metabolic syndrome (MetS) score (EPIC, UKBB where possible)

Polygenic Risk Score
a weighted sum of the number of risk alleles

$$PRS = \beta_1 SNP_1 + \ldots + \beta_m SNP_m$$

➤ β, the effect size estimated by different approaches
➤ m, the number of SNPs included in the polygenic risk score

Project Timelines (1st May 2021- 31st October 2022)

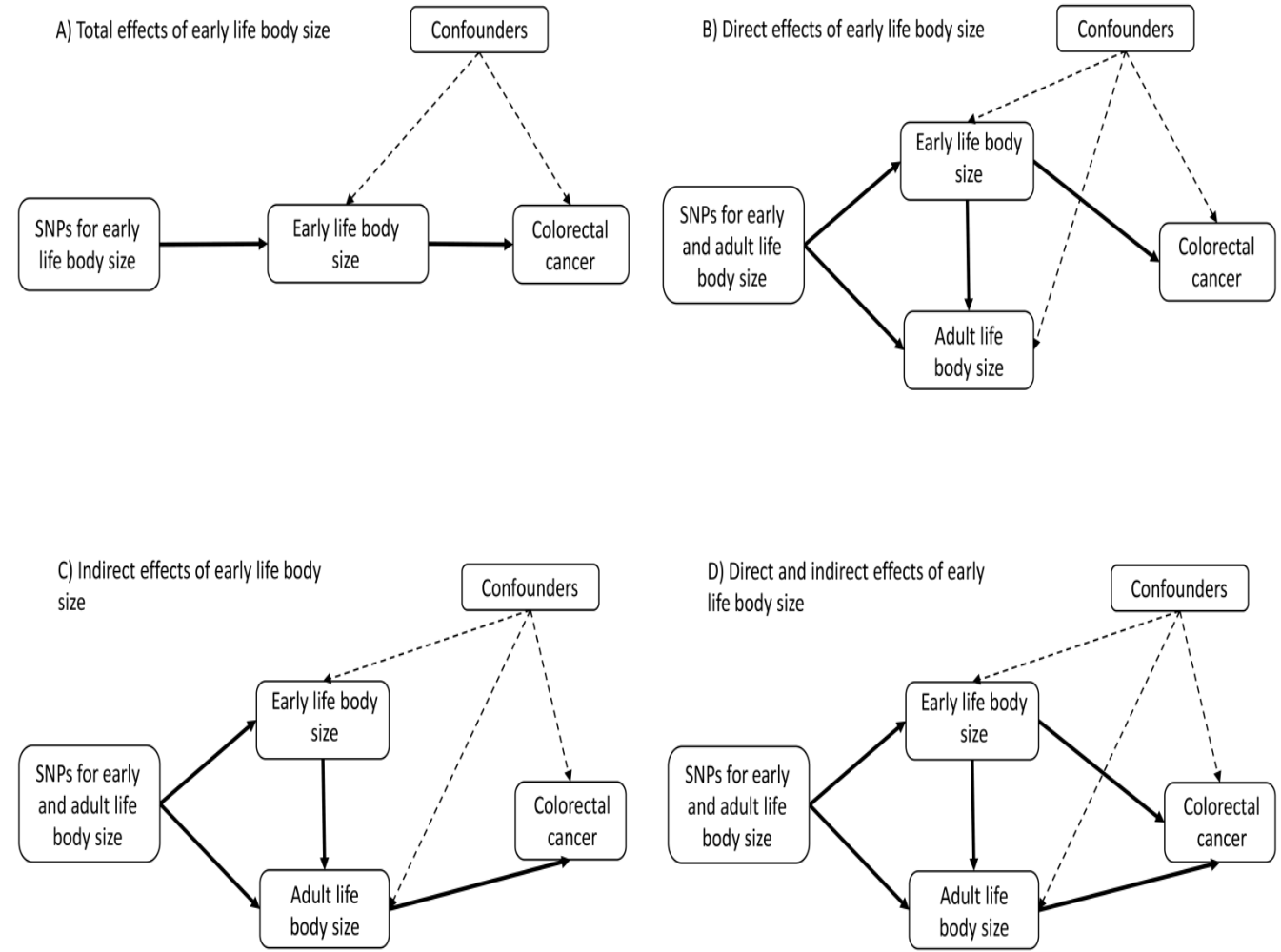| Time	Month 1-6	Month 7-12	Month 13-18
Objectives			
1. Construct different life stage Genetic Risk Scores to associate with colorectal cancer development [all cohorts]:			
Approval from UKBB, EPIC, and GECCO datasets for extraction of existing relevant data *(for objectives 1, 2)*	✓		
Additional: MR analysis of early and later life adiposity on CRC risk	✓*		
Construction of life-course 'obesity predisposition' SNP-based Genetic Risk Scores (GRS 1 to 4 from infant to adulthood obesity)	✓		
Assessment of GRS values for BMI and CRC development risk (all cohorts)			
2. Determine whether the assessed CRC risks are modified by body size at different life stages, exposure to obesogenic factors in adult life, or by sex [all cohorts] *(exploratory analyses)*			
3. Assess association of the GRSs with BMI-trajectories and age categories of CRC onset			
4. Assess association between the GRSs and important mechanisms of obesity-mediated CRC development, i.e., metabolic dysfunction and inflammation, using existing biomarker measures [EPIC & UKBB] *(exploratory analyses)*			
Review and update of work plans / Project meetings	✓		
Write up & Publish a high-impact manuscript & other dissemination activities	✓*		

Separating the Effects of early and later life adiposity on CRC risk: A Mendelian randomization (MR) study*

MR analysis of possible causal relationships between body size at 10 years old and adulthood with CRC risk

Combination of GWAS body size data from UK Biobank (n = 453,169)

Plus, CRC data from meta-analysis of 3 genetic consortia, CORECT, CCFR, & GECCO, of up to 125,478 participants (58,131 cases and 67,347 controls)

MR instruments for early life body size (305 SNPs) and adult body size (557 SNPs) explained an estimated 4.5% and 6.4% of variability in early life and adult body size traits, respectively

A) Total effects of early life body size

B) Direct effects of early life body size

C) Indirect effects of early life body size

D) Direct and indirect effects of early life body size

*Currently under review in *Cancer Research*: ***Childhood adiposity putatively influences colorectal cancer risk due to a long-term effect of remaining overweight throughout the life course*** (Papadimitriou et al 2021).
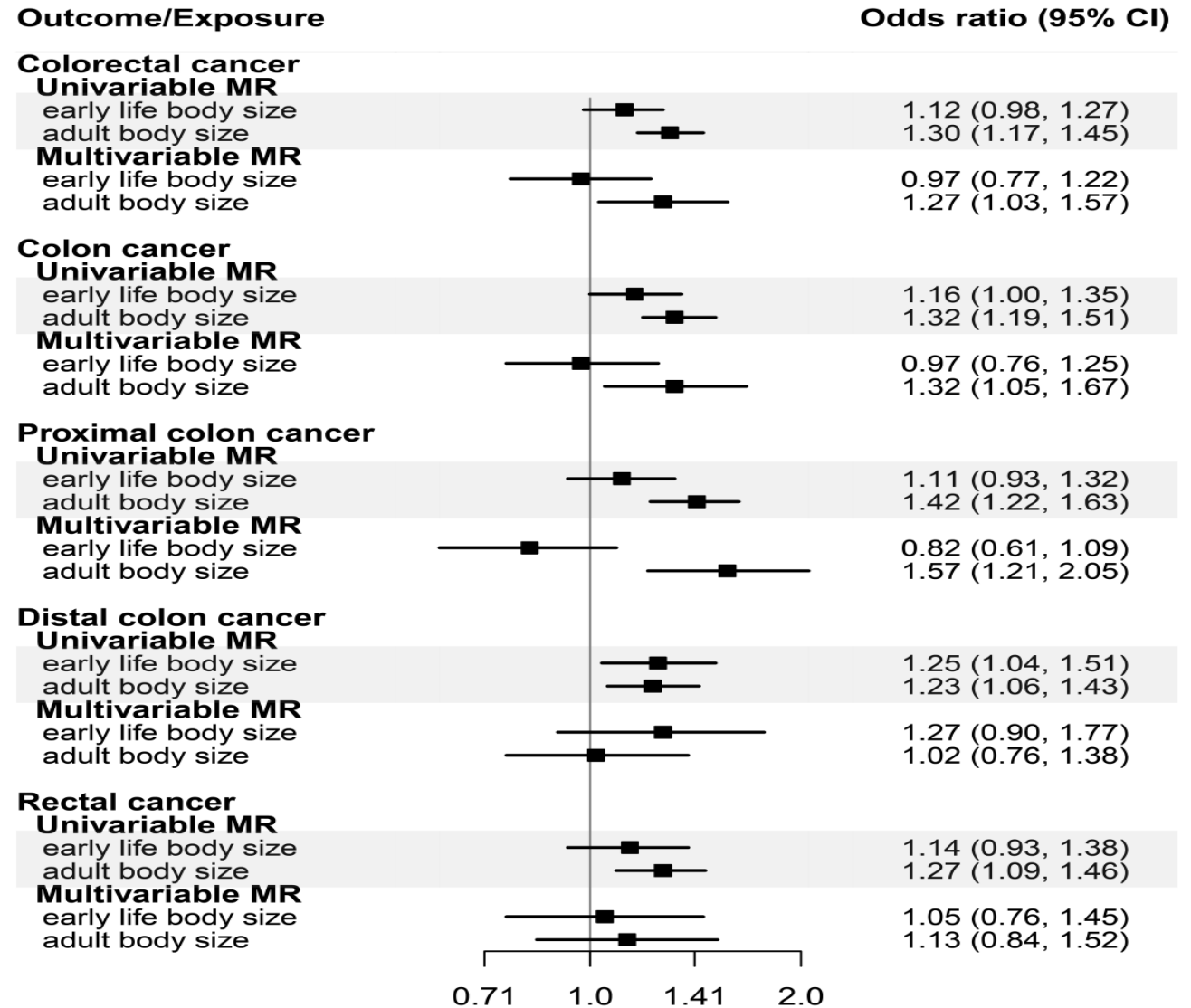
Summary Results

Some positive genetically predicted effects prior to adjustments (univariable MR) between early body size and CRC risk, strongest for colon cancer and distal cancers

After accounting for adult body size, the direct effect estimates - towards the null for CRC and colon cancer while similar magnitude, but more imprecise estimate, was observed for distal colon cancer

Adult body size was estimated to increase colorectal, colon, and proximal colon cancer risk

Overall: Effect of early life body size are more likely linked to the retaining of that weight during adulthood, which in turn increases CRC risk

Outcome/Exposure	Odds ratio (95% CI)
Colorectal cancer	
Univariable MR	
early life body size	1.12 (0.98, 1.27)
adult body size	1.30 (1.17, 1.45)
Multivariable MR	
early life body size	0.97 (0.77, 1.22)
adult body size	1.27 (1.03, 1.57)
Colon cancer	
Univariable MR	
early life body size	1.16 (1.00, 1.35)
adult body size	1.32 (1.19, 1.51)
Multivariable MR	
early life body size	0.97 (0.76, 1.25)
adult body size	1.32 (1.05, 1.67)
Proximal colon cancer	
Univariable MR	
early life body size	1.11 (0.93, 1.32)
adult body size	1.42 (1.22, 1.63)
Multivariable MR	
early life body size	0.82 (0.61, 1.09)
adult body size	1.57 (1.21, 2.05)
Distal colon cancer	
Univariable MR	
early life body size	1.25 (1.04, 1.51)
adult body size	1.23 (1.06, 1.43)
Multivariable MR	
early life body size	1.27 (0.90, 1.77)
adult body size	1.02 (0.76, 1.38)
Rectal cancer	
Univariable MR	
early life body size	1.14 (0.93, 1.38)
adult body size	1.27 (1.09, 1.46)
Multivariable MR	
early life body size	1.05 (0.76, 1.45)
adult body size	1.13 (0.84, 1.52)

0.71   1.0   1.41   2.0

Currently under review in *Cancer Research*: ***Childhood adiposity putatively influences colorectal cancer risk due to a long-term effect of remaining overweight throughout the life course*** (Papadimitriou et al 2021).

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https://www.ukbiobank.ac.uk/researchers/

UKBB, GECCO, CORECT, & CCFR cohorts

Rory Collins (UKBB); Ulrike Peters (GECCO)
& all associated colleagues
& all subjects participating in these studies

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