Metabolic features of colorectal cancer liability: life course study integrating genetic risk with repeated metabolomics

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Motivation & Aim

- In most cases, colorectal cancers develop slowly over a period of several years and little is known about the very beginnings of disease – i.e. its early metabolic features. A better understanding of these features would inform the targeting of key pathways to halt cancer development.
- We aimed to investigate how being more genetically susceptible to colorectal cancer might be reflected in the circulating metabolome at four stages of life – in childhood, adolescence, young-adulthood and adulthood.

Methods

- Up to 4,760 offspring from the Avon Longitudinal Study of Parents and Children (ALSPAC) were studied.
- Linear models were used to examine effects of a genetic risk score – 72 variants associated with colorectal cancer at a genome wide level of significance ($p < 5 \times 10^{-8}$)[1] on 229 metabolomic traits[2] (lipoprotein-subclass-specific cholesterol and triglycerides, amino acids, glycoprotein acetyls, others) measured at age 8y, 16y, 18y, and 25y by nuclear magnetic resonance (NMR) spectroscopy.
- Two-sample Mendelian randomization (MR) was conducted using genome-wide association study data on metabolomic traits in an independent sample of 118,466 adults (UK Biobank). Three statistical methods were used to generate MR estimates using the TwoSampleMR package: random-effects inverse variance weighted (IVW), MR-Egger and weighted-median, heterogeneity was assessed using Cochran's *Q* statistic[3].

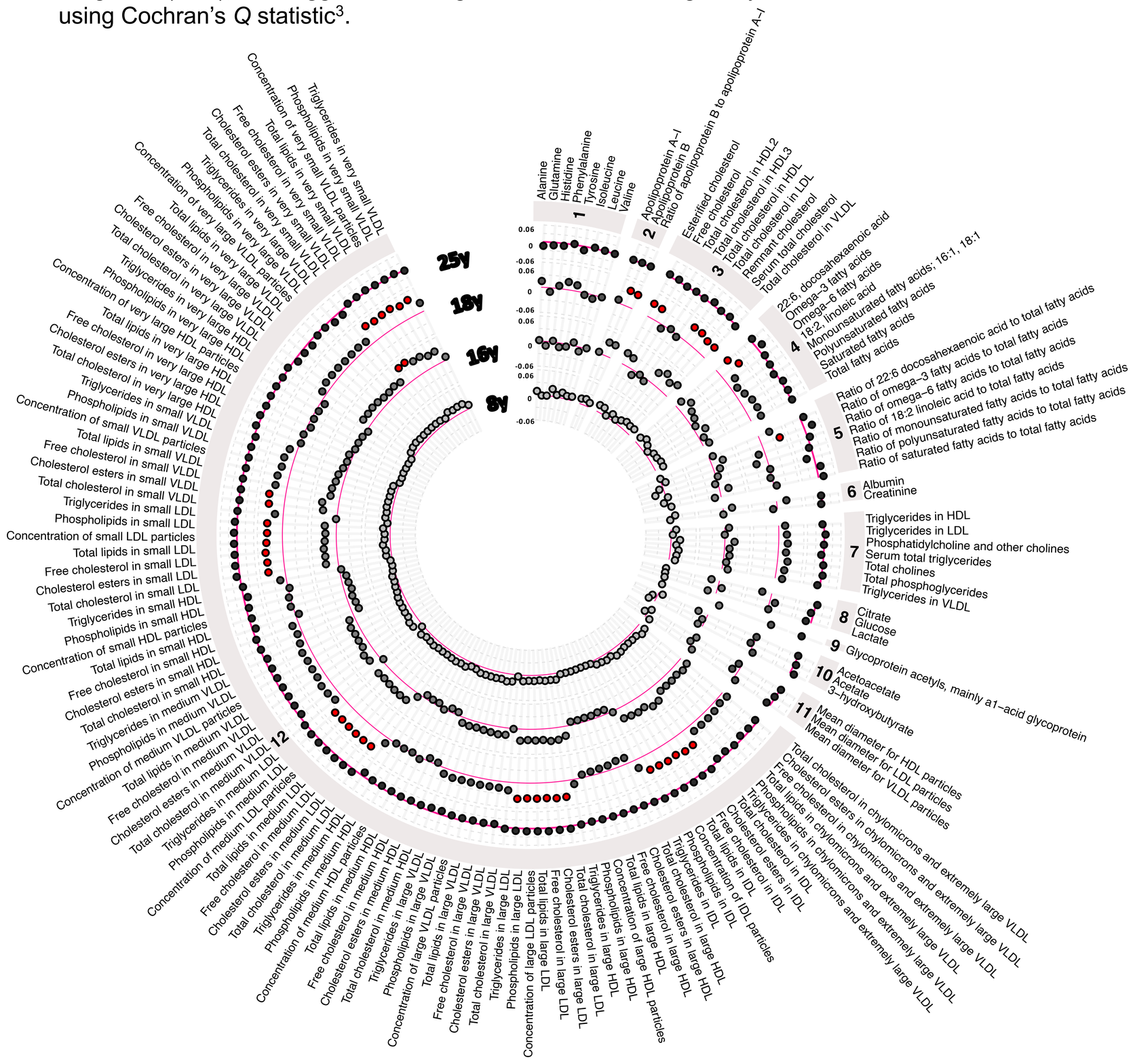

Figure 1: Associations of genetic liability to adult colorectal cancer with metabolic traits at different early life stages among ALSPAC offspring. Estimates shown are beta coefficients representing SD difference in metabolic trait per doubling odds of colorectal cancer, ordered concentrically (inner circle to outer circle) by increasing age at measurement. Estimates highlighted in red indicate where the FDR p-value< 0.05. Metabolite subclasses: 1. Amino acids; 2. Apolipoproteins; 3. Cholesterol; 4. Fatty acids; 5. Fatty acid ratios; 6. Fluid balance; 7. Triglycerides; 8. Glycolysis related metabolites; 9. Inflammation; 10. Ketone bodies; 11. Particle size; 12. Lipids

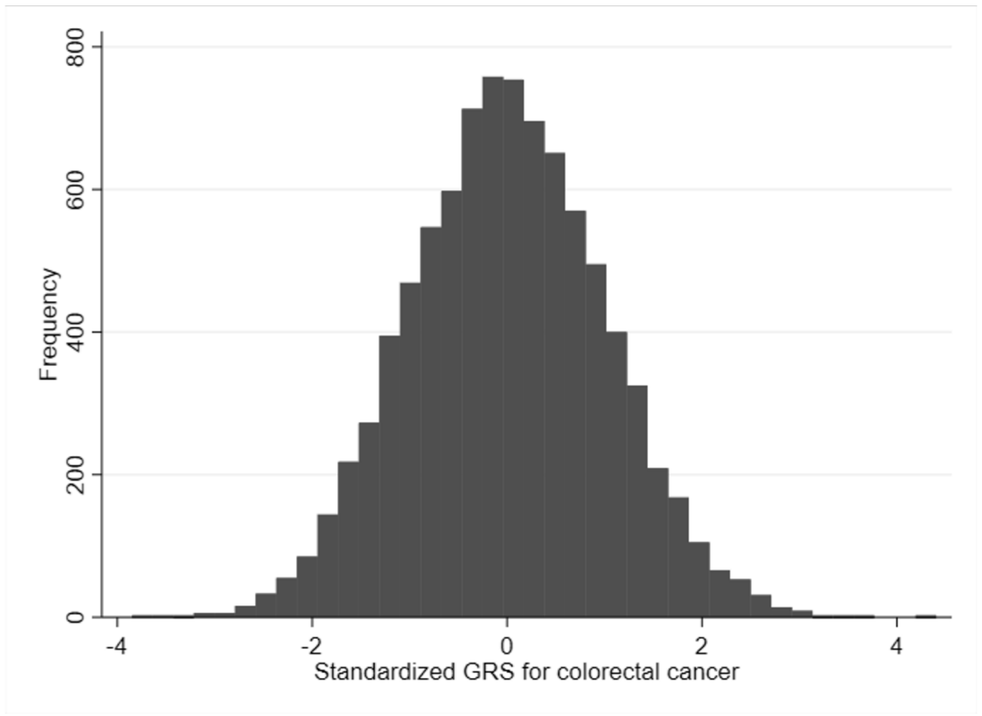

Figure 2: Genetic risk score for adult colorectal cancer representing the average per-SNP effect on colorectal cancer among ALSPAC offspring

Results

- The colorectal cancer genetic risk score was associated with up to 35% of the circulating metabolic traits (Benjamini-Hochberg adjusted P value ≤ 0.05) at a single time point, in particular the fatty acid, VLDL, LDL, and IDL subclasses.
- Colorectal cancer liability (per 2-fold increase) was most strongly associated with metabolic alterations at 18y e.g. 0.08 SD (95% CI=0.04, 0.12) for omega-3 fatty acids.
- At 8y, 16y and 25y, associations showed consistent directionality, but were smaller in magnitude.
- Two-sample MR estimates among adults indicated broadly persistent patterns of effect of disease liability, however, *Q* statistics indicted high heterogeneity.
- Associations were persistent, but slightly attenuated following the removal of a FADS variant (rs174533) from the colorectal cancer genetic risk score.

Conclusions

- Our results implicate perturbed fatty acid and non-HDL lipid metabolism as an early feature of colorectal cancer liability.
- Further investigations are required to understand the mechanisms behind the potential effects of genetic risk for colorectal cancer on metabolites.
- This analysis reveals subtle changes in metabolism over time which precede the onset of clinically detectable cancer by several decades.

References

1. Huyghe JR, Bien SA, Harrison TA, Kang HM, Chen S, Schmit SL, et al. Discovery of common and rare genetic risk variants for colorectal cancer. Nature Genet. 2019;51(1):76.
2. Würtz et al. Quantitative Serum NMR Metabolomics in Large-Scale Epidemiology: A Primer on-Omic Technology. Am J Epidemiol. 2017:kwx016.
3. Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, et al. The MR-Base platform supports systematic causal inference across the human phenome. eLife. 2018;7:e34408