Cancer survivorship, excess body fatness and weight-loss intervention—where are we in 2020?

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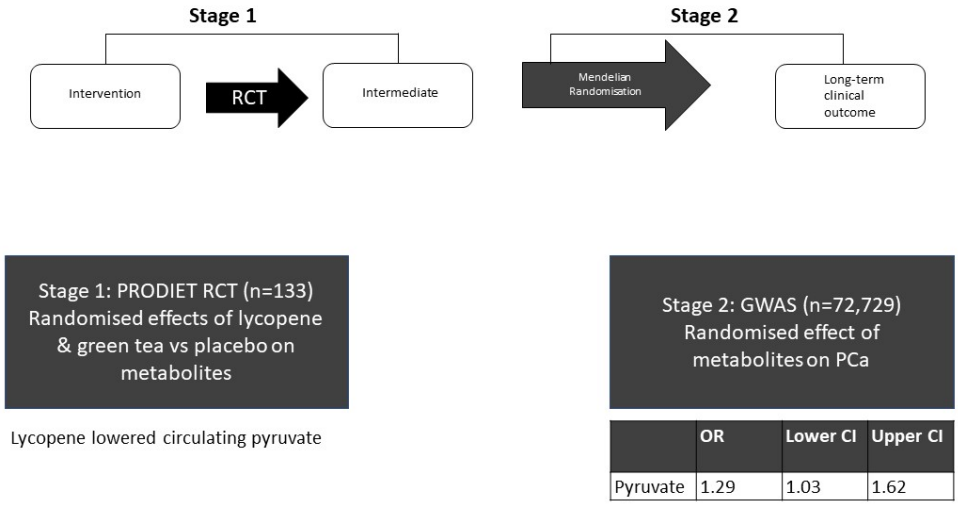
Figure 2. Two-step Mendelian Randomisation procedure: Integration of feasibility randomised controlled trial (RCT) results with MR to predict long-term effect of interventions



[1]

[1] Introduction to Mendelian randomisation: Mendelian randomisation is a form of instrumental variable analysis that uses genetic variants as instruments to examine the causal effects of modifiable exposures on outcomes of interest. This method depends on the existence of genetic variants that are robustly associated with metabolite levels.
In the example outlined here, the results of a feasibility RCT of dietary interventions for the prevention of prostate cancer were carried forward to a large-scale Mendelian randomisation analysis to infer the causal effect of the interventions on prostate cancer risk via intermediate metabolites.
Step 1 assessed the randomised effects of lycopene and green tea consumption for 6 months versus placebo on 159 serum metabolic traits, quantified by Nuclear Magnetic Resonance (NMR), amongst 133 men enrolled in the ProDiet randomised controlled trial
Step 2 used Mendelian randomisation to assess the effects of those metabolic traits altered by the intervention on prostate cancer risk, using genome-wide association studies (GWAS) summary statistics from the Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL) consortium. The lycopene intervention lowered circulating levels of pyruvate, a change that the Mendelian randomisation analysis suggested was associated with decreases in prostate cancer risk (a genetically instrumented SD increase in pyruvate increased the odds of prostate cancer by 1.29 (1.03, 1.62; p = 0.027)). Lycopene lowered levels of pyruvate, which our Mendelian randomisation analysis suggests may be causally related to reduced prostate cancer risk. By combining the results of a feasibility study with Mendelian randomisation, it has been possible to identify potential intermediate mechanisms through which interventions might be influencing cancer risk (see 767,68 (step 2).