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Why is body fatness important in cancer prevention? Lessons from Mendelian Randomisation

Satellite meeting for the European Congress on Obesity, Dundee

27 April 2019

Richard Martin

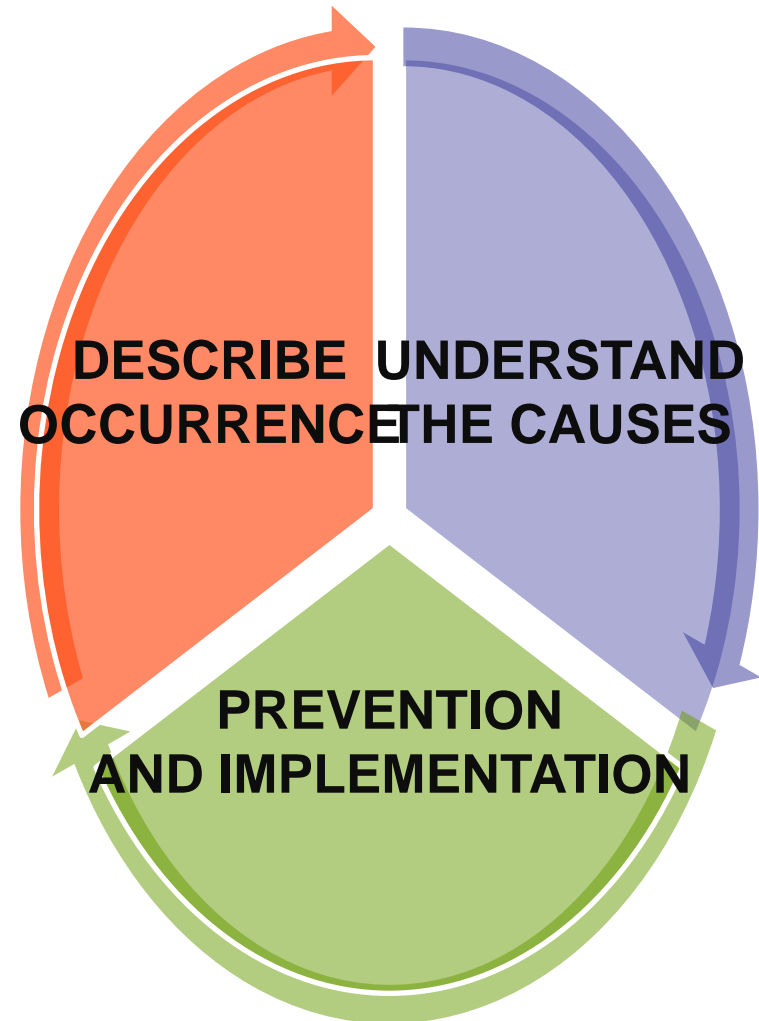
Cancer research for cancer prevention

Global burden of cancer

- 18.1 million new cancers in 2018
- 29.5 million by 2040

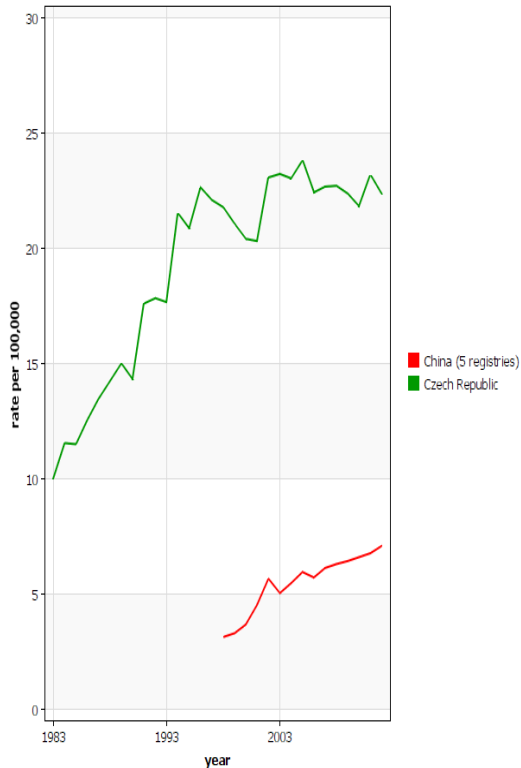
IARC Director

- “...no country can treat its way

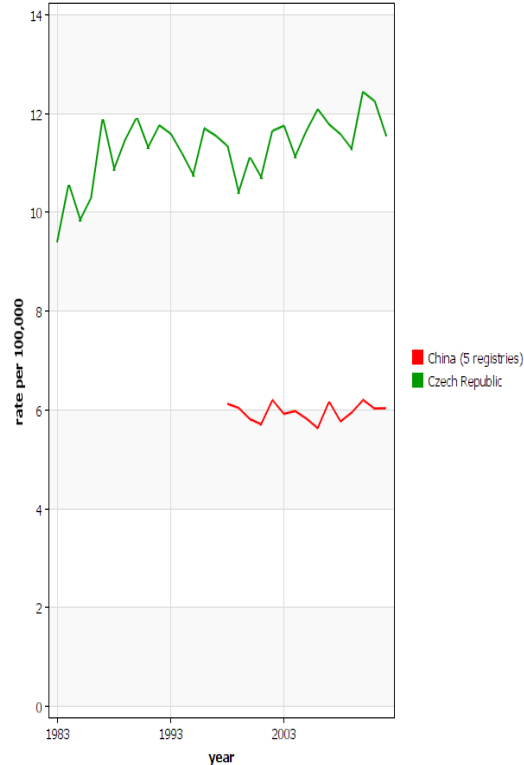


Age-standardised incidence of renal, pancreatic & colorectal cancer 2-4 X higher in central Europe than many parts of Asia

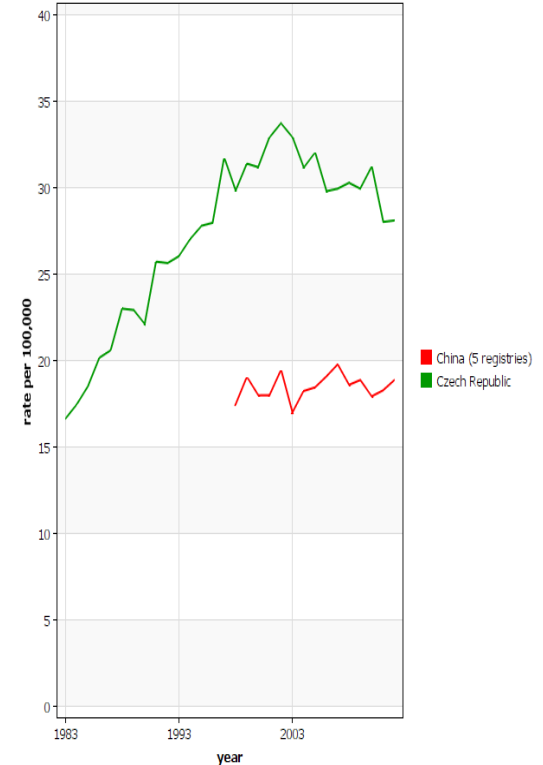
Kidney and renal pelvis
Age Standardised Incidence Rate (World), Male age [0-85+]



Pancreas
Age Standardised Incidence Rate (World), Male age [0-85+]



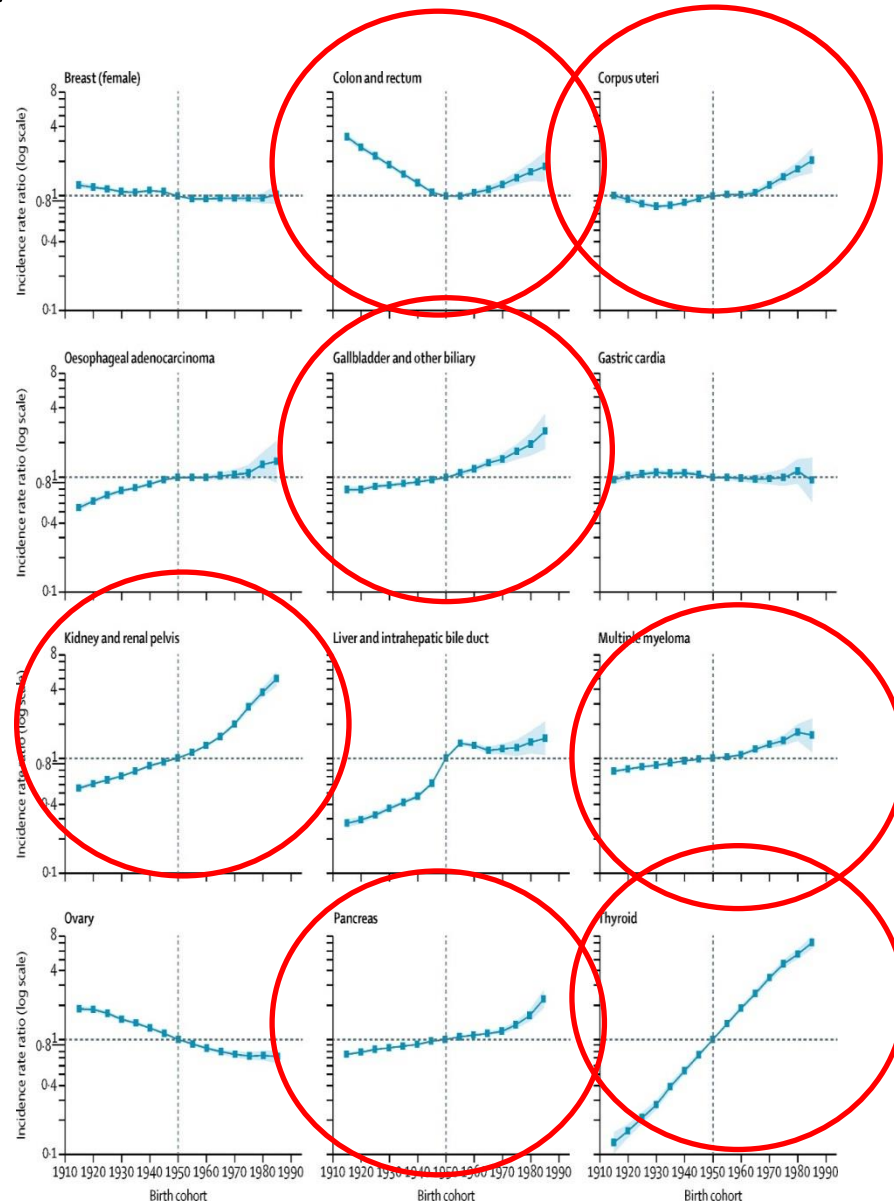
Colon
Age Standardised Incidence Rate (World), Male age [0-85+]



Several cancers rising in successively younger birth cohorts, USA

cohorts, USA

Incidence rate ratio by birth cohort from 1910-19 to 1980-89 for 12 cancers, 1995-2014



SPECIAL REPORT

Body Fatness and Cancer — Viewpoint of the IARC Working Group

Kyrgiou M et al. *BMJ*. 2017

Lauby-Secretan B. et al. *NEJM*. 2016

- Sufficient evidence to conclude obesity/overweight causes cancer on 13 sites
- IARC Working Group:
 - “absence of excess body fatness lower risk of most cancers”
- Why?
 - Conclusive mechanistic evidence largely lacking

Cancer Site or Type	Strength of the Evidence in Humans [†]	Relative Risk of the Highest BMI Category Evaluated versus Normal BMI (95% CI) [‡]
Esophagus: adenocarcinoma	Sufficient	4.8 (3.0–7.7)
Gastric cardia	Sufficient	1.8 (1.3–2.5)
Colon and rectum	Sufficient	1.3 (1.3–1.4)
Liver	Sufficient	1.8 (1.6–2.1)
Gallbladder	Sufficient	1.3 (1.2–1.4)
Pancreas	Sufficient	1.5 (1.2–1.8)
Breast: postmenopausal	Sufficient	1.1 (1.1–1.2) [§]
Corpus uteri	Sufficient	7.1 (6.3–8.1)
Ovary	Sufficient	1.1 (1.1–1.2)
Kidney: renal-cell	Sufficient	1.8 (1.7–1.9)
Meningioma	Sufficient	1.5 (1.3–1.8)
Thyroid	Sufficient	1.1 (1.0–1.1) [§]
Multiple myeloma	Sufficient	1.5 (1.2–2.0)

Obesity thought to cause 1/20 cancers (2nd only to tobacco smoke)

% of UK cancers accounted for by smoking & overweight/obesity:

- 2015, overweight & obesity: 6% of all UK cancers; smoking: 15%
- 2035, overweight & obesity: 8% of all UK cancers; smoking: 11%
- 2043, overweight & obesity > smoking in women

Brown et al, BJC 2018;118:1130–1141

<https://www.cancerresearchuk.org/about-us/cancer-news/press-release/2018-09-24-obesity-could-overtake-smoking-as-biggest-preventable-cause-of-cancer-in-women-0>

**ADDRESSING THE PREVENTION OF CANCERS
ATTRIBUTED TO EXCESS ADIPOSITY IS A
GROWING & GLOBALLY IMPORTANT HEALTH
PROBLEM**

How can genetic approaches help improve the evidence-base for interventions?

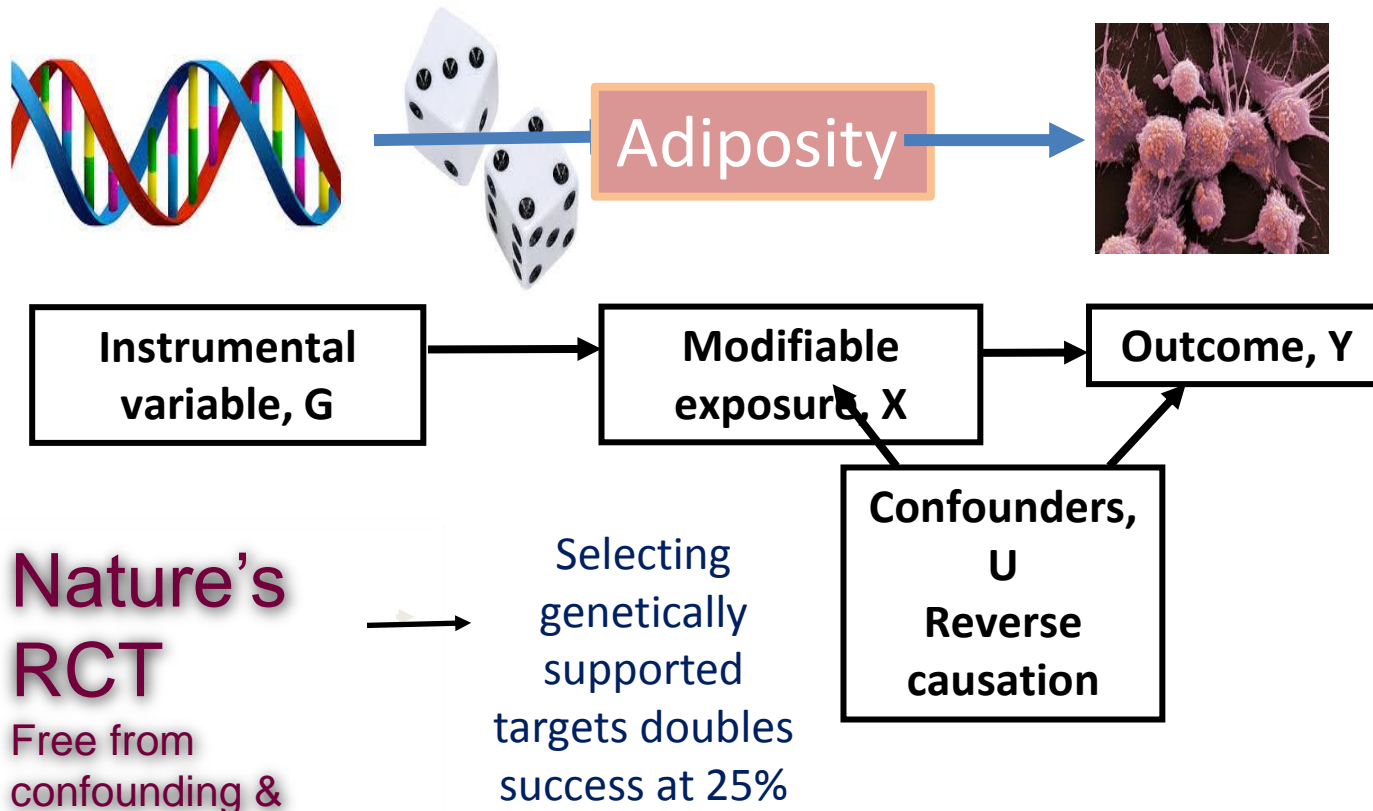
- Confirm causal relevance & generate more precise estimates of effect vs single exposure measure (i.e. predict the effect of intervening)
- Identify molecular mechanisms
- Inform targeted public health interventions
- Inform potential drug repurposing (e.g. statins)

Mendelian randomization:

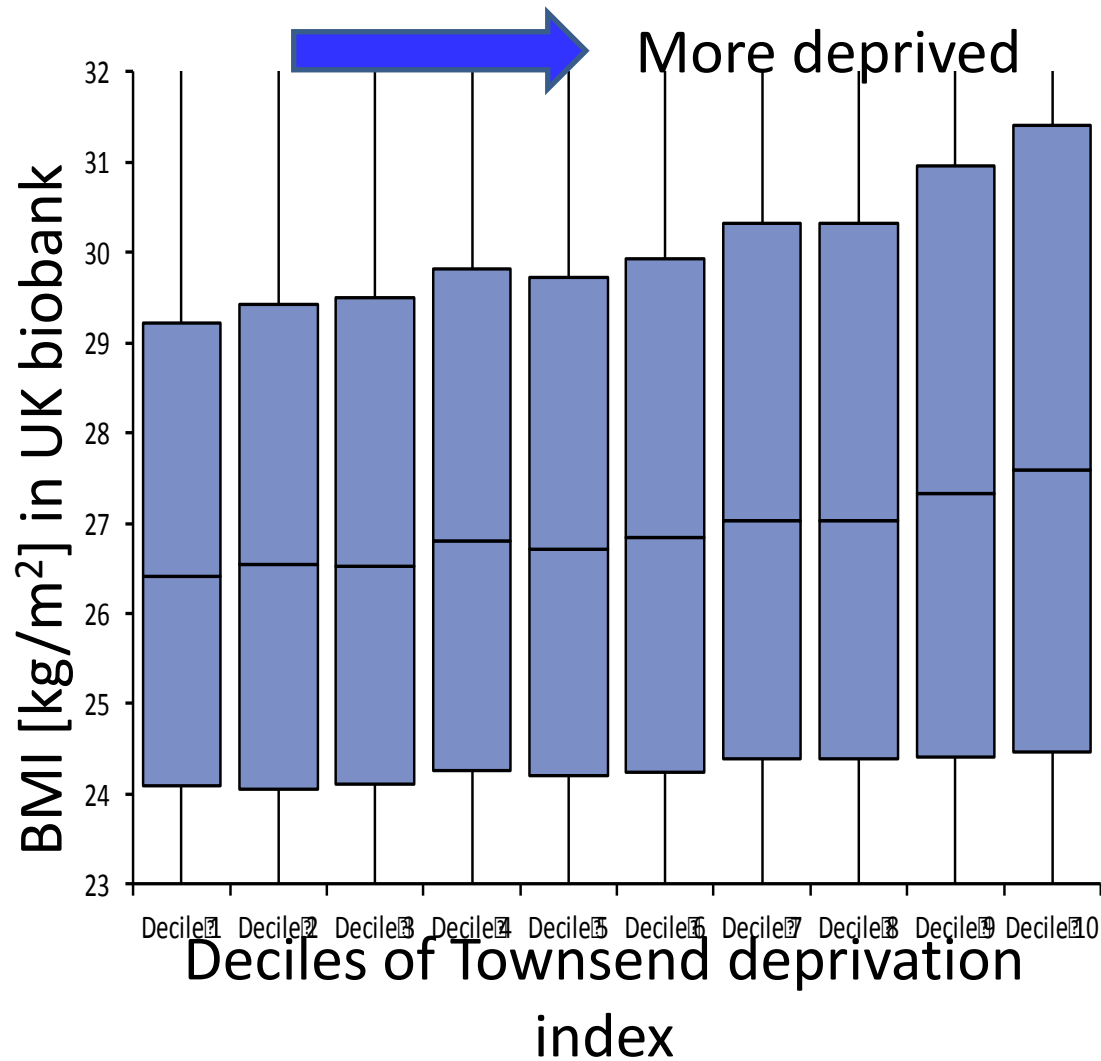
Genetic information to improve causal inference in observational epi



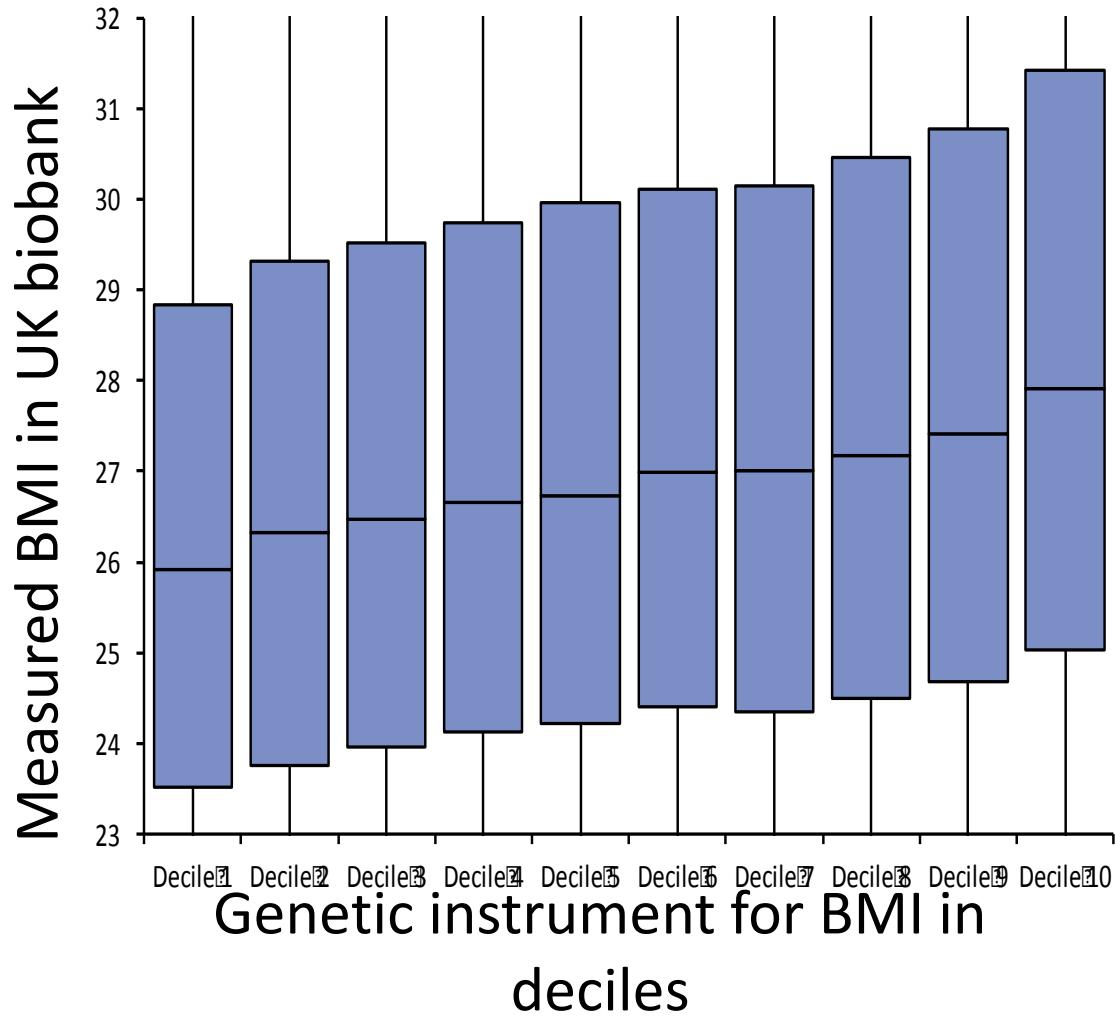
Traits inherited independent of each other & future environmental factors



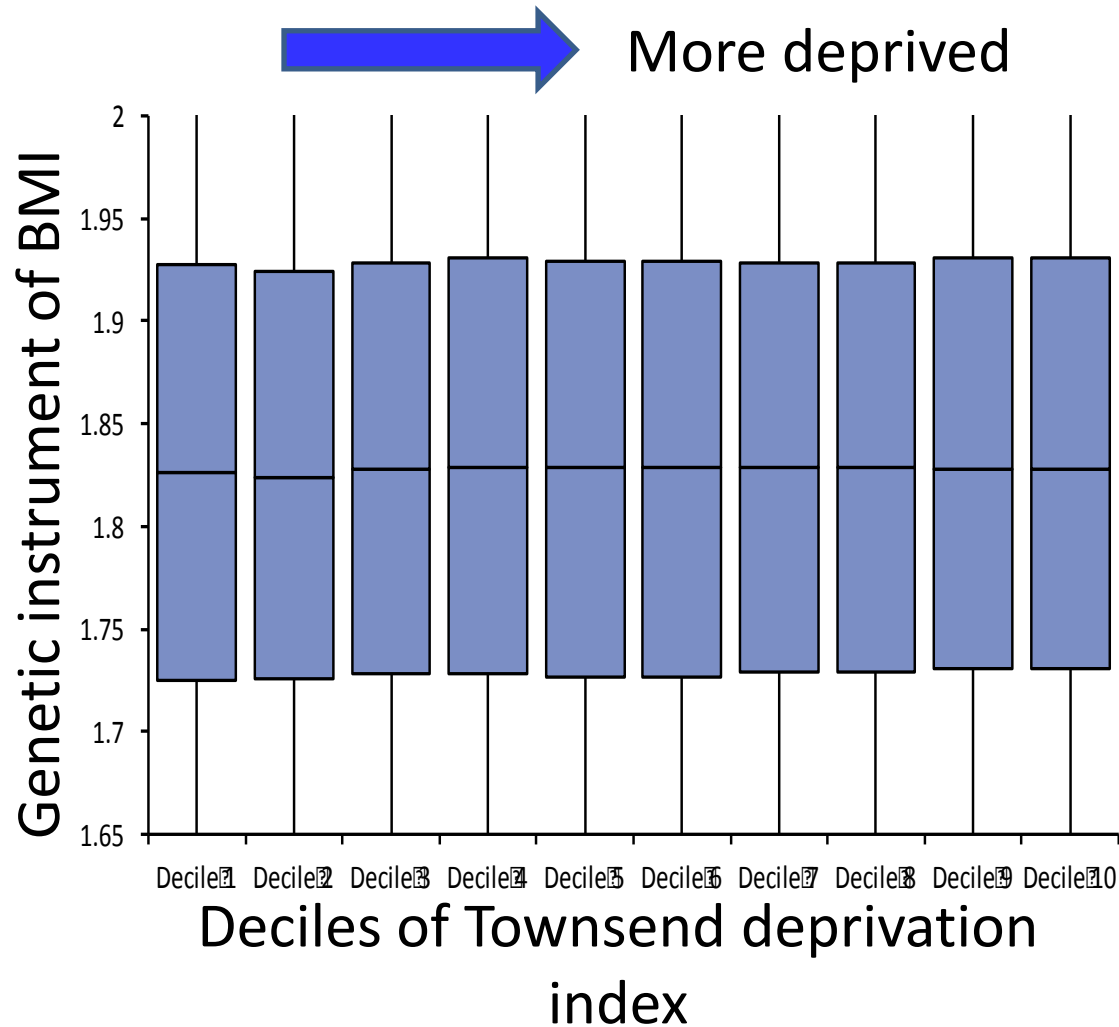
Example: Deprivation & measured BMI



Genetic instrument for BMI: 73 SNPs (GIANT Consortium)



Example: Deprivation & a genetic instrument for BMI



**CONFIRM CAUSAL RELEVANCE & GENERATE
MORE PRECISE ESTIMATES OF EFFECT VS SINGLE
EXPOSURE MEASURE (I.E. PREDICT THE EFFECT
OF INTERVENING)**

Relative risks for 5-unit BMI increment – Classical cohort studies

Cancer Sites

WCRF RR

Colorectum

1.05 [1.03;1.07]

Kidney

1.30 [1.25;1.35]

Pancreas

1.10 [1.07;1.14]

Endometrium

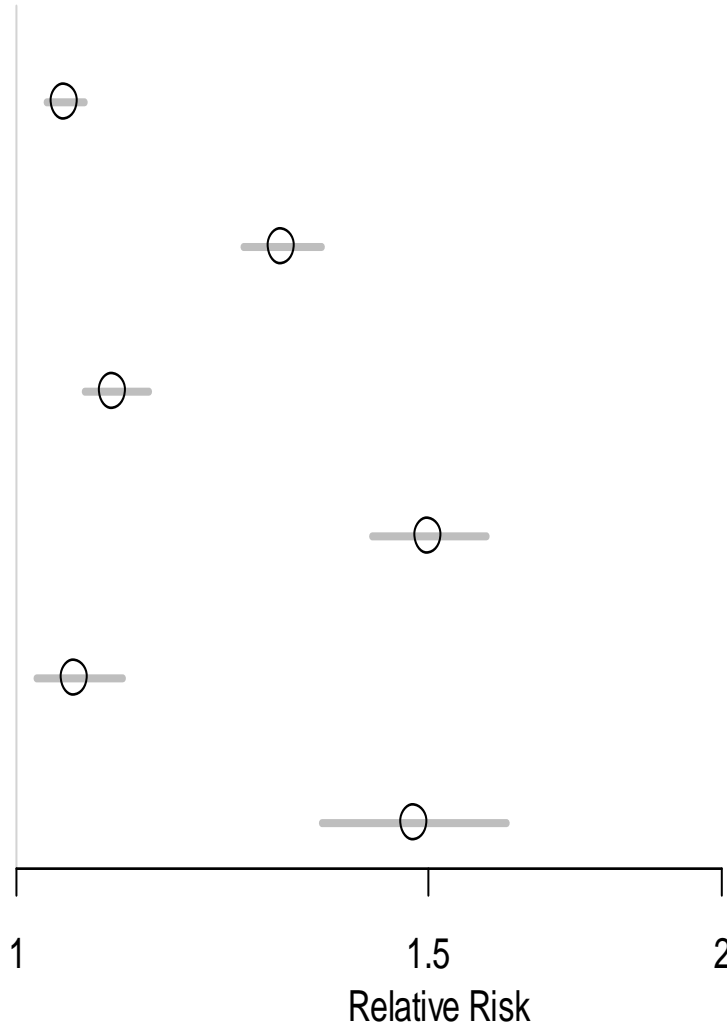
1.50 [1.42;1.59]

Ovary

1.06 [1.02;1.11]

Esophagus (Adeno)

1.48 [1.35;1.62]

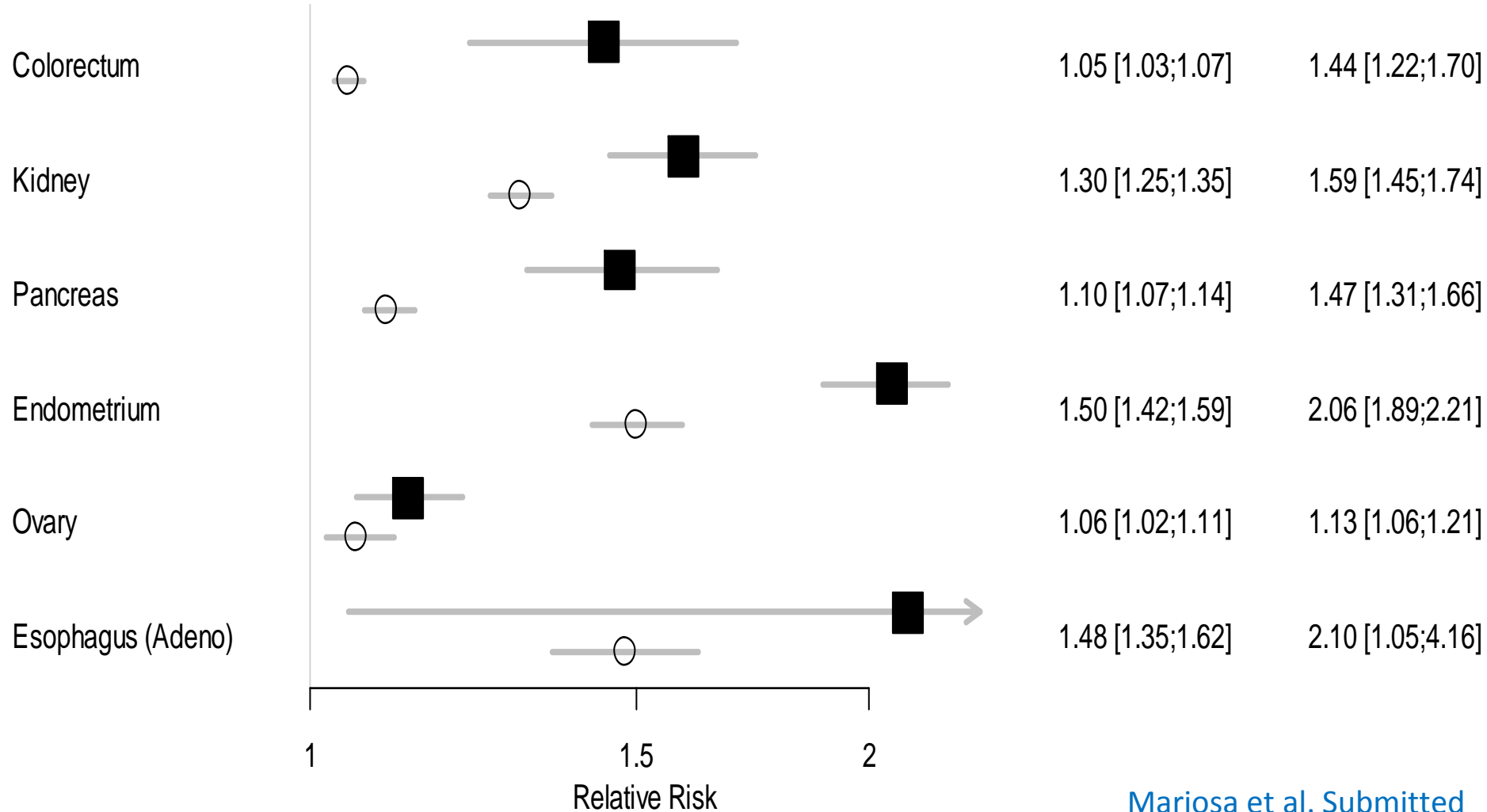


Relative risks for 5-unit BMI increment – Mendelian randomization

Cancer Sites

WCRF RR

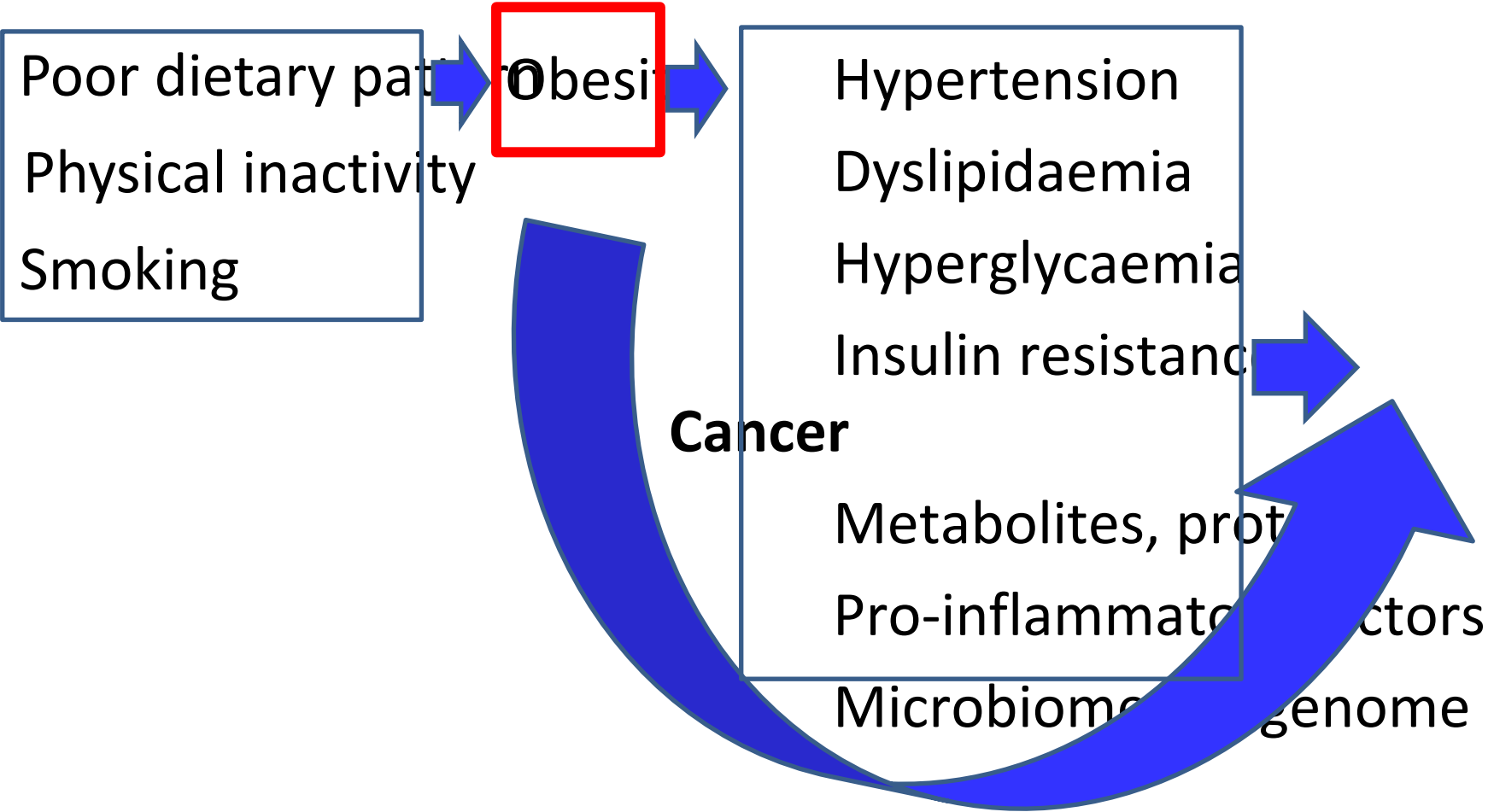
MR RR



- Reducing population adiposity & maintaining fat loss in individuals are difficult
- Could upstream factors or causal intermediates be intervened on to diminish the effects of adiposity?

IDENTIFY MOLECULAR MECHANISMS

Can genetics help untangle the causal pathway?



Causal effect estimates of obesity-related risk factors for RCC

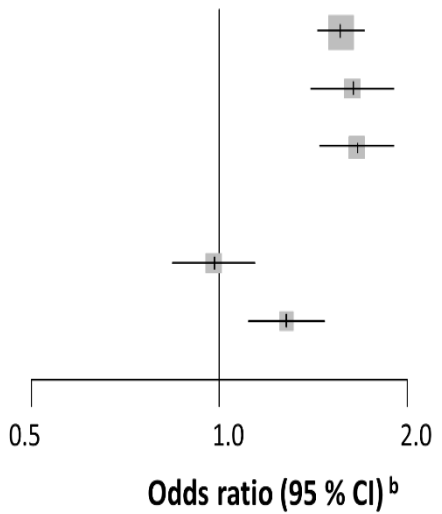
Risk factor	OR ^b	P-value
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Obesity and body shape

Body mass index	1.56	6×10^{-25}
Waist to hip ratio	1.63	5×10^{-10}
Body fat %	1.66	8×10^{-13}

Hypertension

Systolic blood pressure	0.98	0.77
Diastolic blood pressure	1.28	6×10^{-4}



Causal effect estimates of obesity-related risk factors for RCC

Risk factor	OR ^b	P-value
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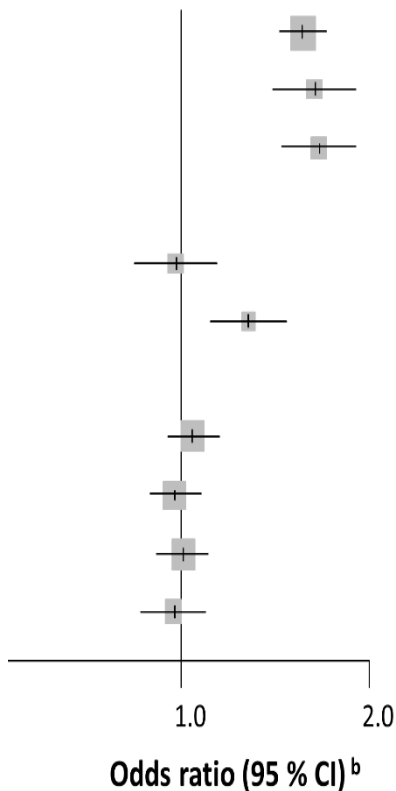
Dyslipidemia

High density cholesterol	1.04	0.40
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Low density cholesterol	0.98	0.63
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Total cholesterol	1.00	0.93
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

Triglycerides	0.97	0.57
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Causal effect estimates of obesity-related risk factors for RCC

Risk factor OR^b P-value





Obesity and body shape

Body mass index		1.56	6x10 ⁻²⁵
Waist to hip ratio		1.63	5x10 ⁻¹⁰
Body fat %		1.66	8x10 ⁻¹³






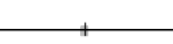
Hypertension

Systolic blood pressure		0.98	0.77
Diastolic blood pressure		1.28	6x10 ⁻⁴

Dyslipidemia

High density cholesterol		1.04	0.40
Low density cholesterol		0.98	0.63
Total cholesterol		1.00	0.93
Triglycerides		0.97	0.57

Insulin resistance

Type 2 Diabetes		0.99	0.74
Beta-cell dysfunction		0.91	0.03
Insulin resistance		1.37	0.04
Others		1.02	0.70
Fasting glucose		0.92	0.43
Fasting insulin		1.82	5x10 ⁻⁴

0.5 1.0 2.0

Odds ratio (95 % CI)^b