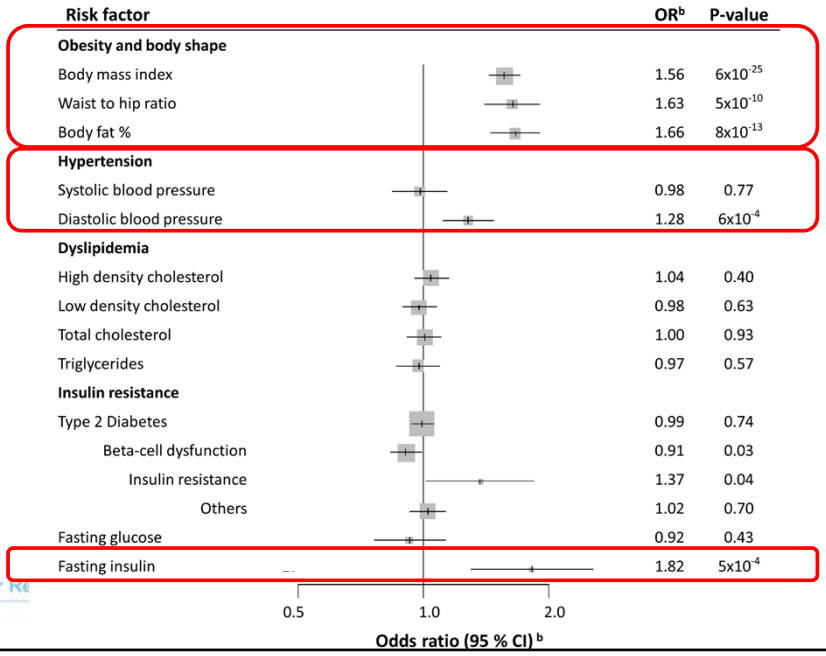
Causal effect estimates of obesity-related risk factors for RCC



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Causal effect estimates of obesity-related risk factors for RCC

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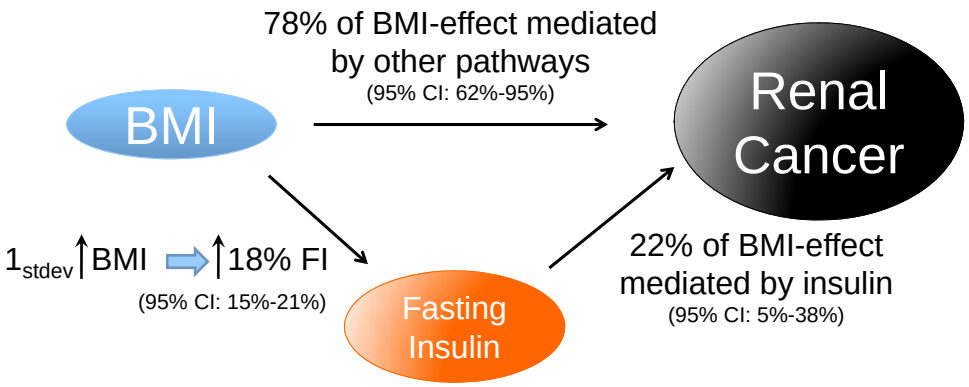
Obesity, insulin and renal cell carcinoma



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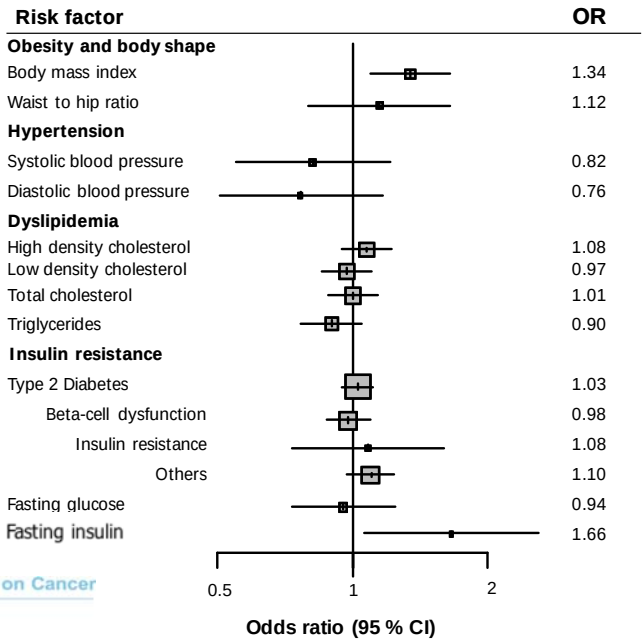
Causal estimates of obesity-related risk factors for pancreatic cancer



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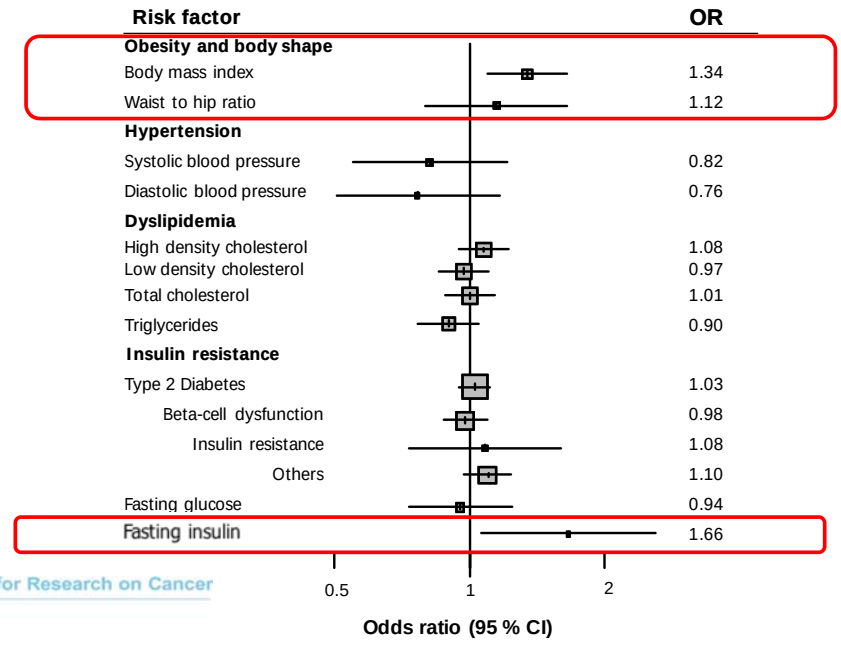
Causal estimates of obesity-related risk factors for pancreatic cancer



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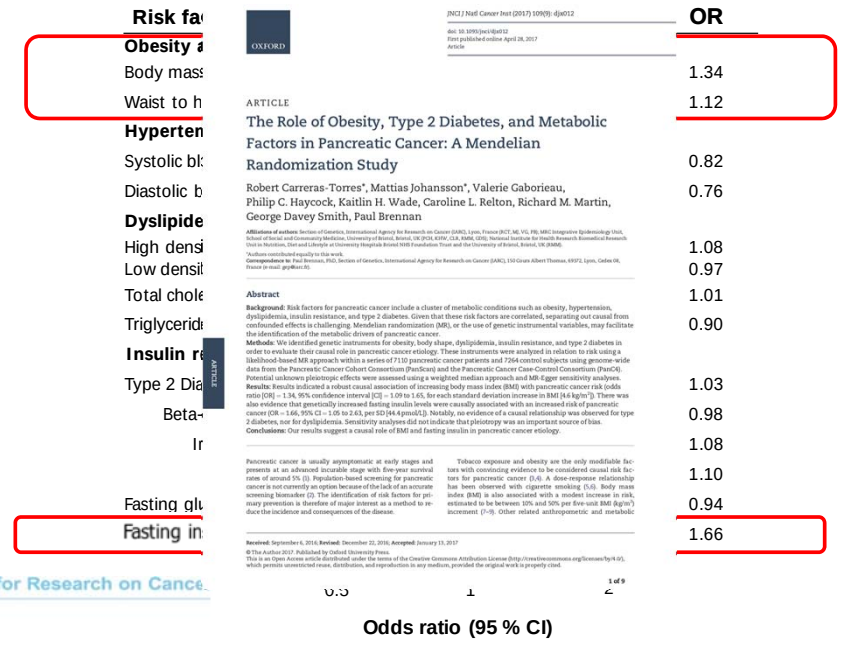
Causal estimates of obesity-related risk factors for pancreatic cancer



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Article

ARTICLE

The Role of Obesity, Type 2 Diabetes, and Metabolic Factors in Pancreatic Cancer: A Mendelian Randomization Study

Robert Carreras-Torres*, Mattias Johansson*, Valerie Gaborieau, Philip C. Haycock, Kaitlin H. Wade, Caroline L. Relton, Richard M. Martin, George Davey Smith, Paul Brennan

Abstract

Background: Risk factors for pancreatic cancer include a cluster of metabolic conditions such as obesity, hypertension, dyslipidemia, insulin resistance, and type 2 diabetes. Given that these risk factors are correlated, separating out causal from confounded effects is challenging. Mendelian randomization (MR), or the use of genetic instrumental variables, may facilitate the identification of the metabolic drivers of pancreatic cancer.

Methods: We identified genetic instruments for obesity, body shape, dyslipidemia, insulin resistance, and type 2 diabetes in order to evaluate their causal role in pancreatic cancer etiology. These instruments were analyzed in relation to risk using a likelihood-based MR approach within a series of 7110 pancreatic cancer patients and 7264 control subjects using genome-wide data from the Pancreatic Cancer Cohort Consortium (PanScan) and the Pancreatic Cancer Case-Control Consortium (PanCuA). Potential unknown pleiotropic effects were assessed using a weighted median approach and MR-Egger sensitivity analyses.

Results: Results indicated a robust causal association of increasing body mass index (BMI) with pancreatic cancer risk (odds ratio [OR] = 1.34, 95% confidence interval [CI] = 1.09 to 1.65, for each standard deviation increase in BMI [4.6 kg/m²]). There was also evidence that genetically increased fasting insulin levels were causally associated with an increased risk of pancreatic cancer (OR = 1.66, 95% CI = 1.05 to 2.63, per SD [44.4 pmol/L]). Notably, no evidence of a causal relationship was observed for type 2 diabetes, nor for dyslipidemia. Sensitivity analyses did not indicate that pleiotropy was an important source of bias.

Conclusions: Our results suggest a causal role of BMI and fasting insulin in pancreatic cancer etiology.

Pancreatic cancer is usually asymptomatic at early stages and presents at an advanced incurable stage with five-year survival rates of around 5% (1). Population-based screening for pancreatic cancer is not currently an option because of the lack of an accurate screening biomarker (2). The identification of risk factors for primary prevention is therefore of major interest as a method to reduce the incidence and consequences of the disease.

Tobacco exposure and obesity are the only modifiable factors with convincing evidence to be considered causal risk factors for pancreatic cancer (3,4). A dose-response relationship has been observed with cigarette smoking (5,6). Body mass index (BMI) is also associated with a modest increase in risk, estimated to be between 10% and 50% per five-unit BMI (kg/m²) increment (7–9). Other related anthropometric and metabolic

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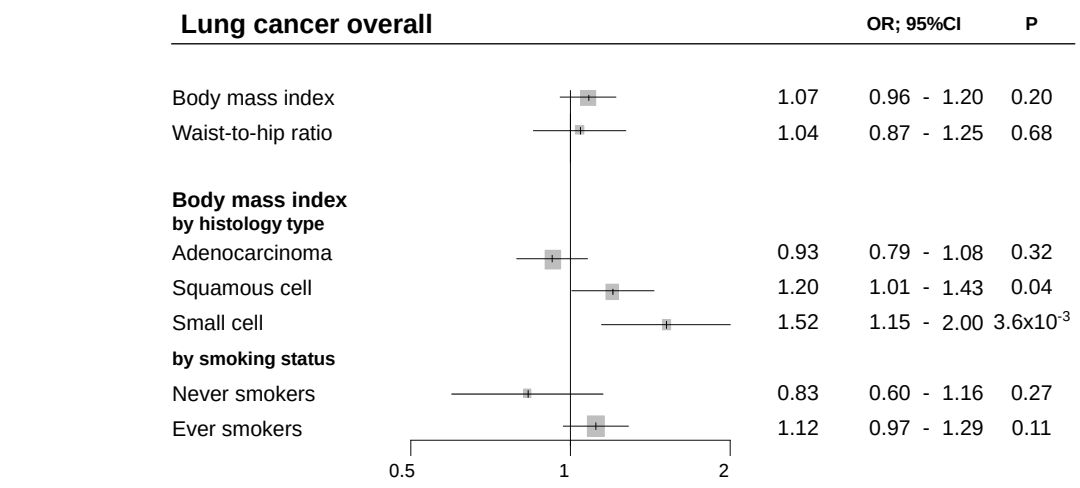
Obesity, body shape & lung cancer



Different roles for obesity on lung cancer histology & smoking types

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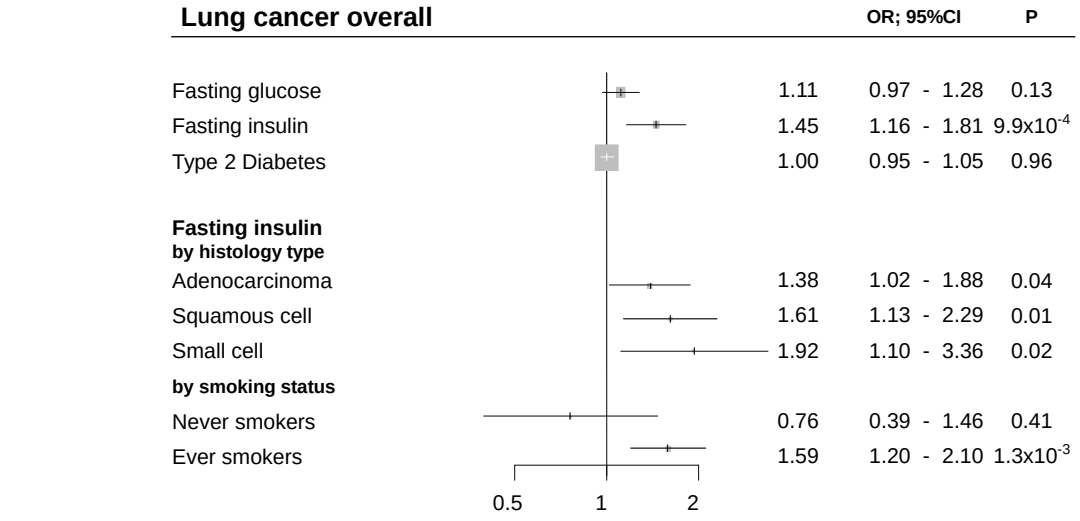
Diabetes-related factors and lung cancer



Fasting insulin consistently associated with lung cancer

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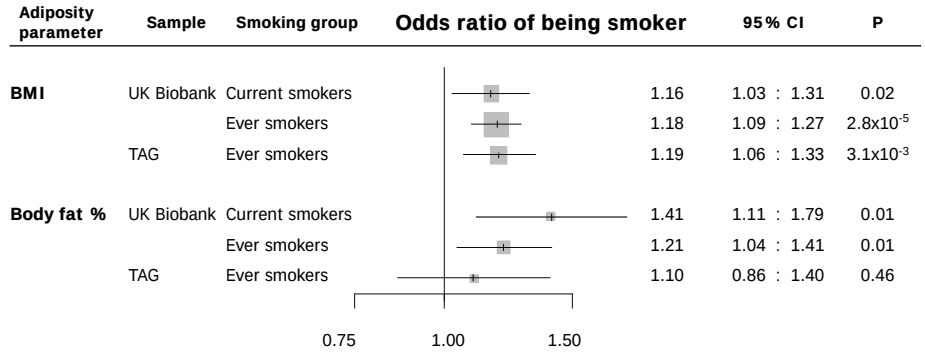
Inform targeted public health interventions

Accelerometry based physical activity & cancer risk	
Cancer Site or Type	**Relative Risk (95% CI)**
Colon and rectum	0.66 (0.53, 0.82)
Breast	0.59 (0.42, 0.84)
Breast ER +ve	0.53 (0.35, 0.82)
Breast ER -ve	0.78 (0.51, 1.22)
Prostate	0.49 (0.33, 0.72)

Role of obesity in smoking: MR in UKBB with replication in TAG



Each SD increase in BMI increases by 18% risk of being a smoker (& increases the intensity of smoking)

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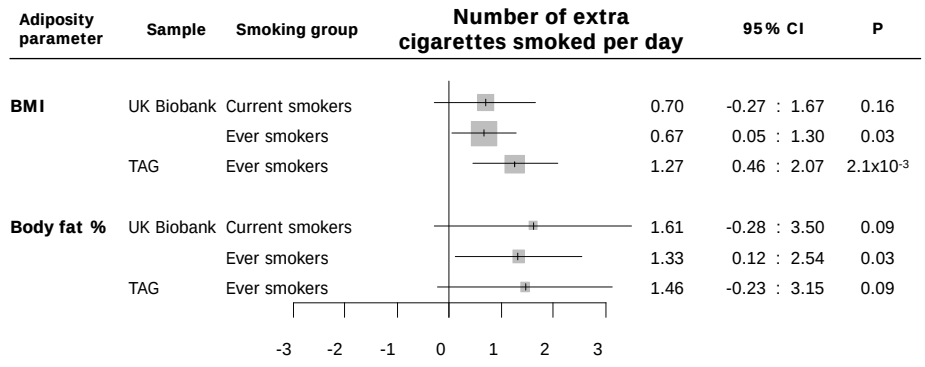
Role of obesity in smoking: MR in UKBB with replication in TAG



Each SD increase in BMI increases smoking intensity by ≈ 1 extra cigarette per day

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Inform potential drug repurposing

Genetically-proxied inhibition of HMG-CoA reductase & ovarian cancer	
Cancer Site or Type	**Relative Risk (95% CI)**
Invasive epithelial OC	0.60 (0.43-0.83)
High grade serous carcinoma	0.70 (0.47-1.04)
Low grade serous carcinoma	1.49 (0.22-10.05)
Mucinous carcinoma	0.53 (0.12-2.42)
Endometrioid carcinoma	0.40 (0.19-0.83)
Clear cell carcinoma	0.61 (0.19-1.92)

Summary

- MR studies confirm causality of adiposity in oesophageal, gastric, pancreatic, renal, colorectal, endometrial, lung & ovarian cancers
- Observational studies underestimate its effect on risk
- Per SD higher insulin: 50-75% increase in kidney, pancreatic & lung cancers
- MR will identify additional causal pathways
- Adiposity influences smoking behaviour with implications for interventions
- Increased physical activity lowers risk of CR, breast & prostate cancer
- Statins protective in OC– potential use in high-risk women?
- Rapidly increasing genetic data will allow development of more powerful / specific instruments to better understand the role of adiposity

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CANCER RESEARCH UK MRC Integrative Epidemiology Unit

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OBESITY INCREASES THE RISK OF THESE CANCERS
MENINGIOMA
THYROID GLAND
BREAST
IN POSTMENOPAUSAL WOMEN
OESOPHAGUS
LIVER
STOMACH
CARDIA
GALLBLADDER
KIDNEY
OVARY AND ENDOMETRIUM
MULTIPLE MYELOMA
COLORECTUM
PANCREAS
Infographics produced by the IARC Handbooks of Cancer Prevention evaluation of cancers affected by obesity.

END

Excess Body Fatness by Cancer Site or Type *Lauby-Secretan et al. N Engl J Med 2016; 375:794-798*	
Cancer Site or Type	**Relative Risk of the Highest BMI Category* vs Normal BMI** (95% CI)**
Esophagus: adenocarcinoma	4.8 (3.0-7.7)
Gastric cardia	1.8 (1.3-2.5)
Colon and rectum	1.3 (1.3-1.4)
Liver	1.8 (1.6-2.1)
Gallbladder	1.3 (1.2-1.4)
Pancreas	1.5 (1.2-1.8)
Breast: postmenopausal	1.1 (1.1-1.2)
Corpus uteri	7.1 (6.3-8.1)
Ovary	1.1 (1.1-1.2)
Kidney: renal-cell	1.8 (1.7-1.9)
Meningioma	1.5 (1.3-1.8)
Thyroid	1.1 (1.0-1.1)
Multiple myeloma	1.5 (1.2-2.0)

**≥40 kg/m²; **18.5-24.9 kg/m²*

Summary: obesity, metabolic factors and cancer

- Per SD increase in BMI (4.6kg/m2):
  - 58% risk increase of kidney cancer (95%CI: 1.35-1.85) & 34% risk increase of pancreatic cancer (95%CI: 1.09-1.65)
  - Double the risk observed in traditional studies
- Per SD increase in fasting insulin (44.4 pmol/L:
  - 50-75% risk increase of kidney, pancreatic and lung cancer
  - also observed for endometrial cancer. (Nead et al. 2015)
  - potential risk factor for cancer overall

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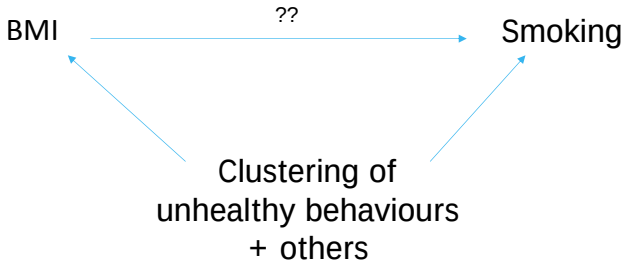
2nd Obesity and tobacco smoking

1. Smokers show lower BMI than non-smokers

   MR studies showed causality from smoking to lower BMI

   (Winslow et al. 2015; Taylor et al. 2014)

2. Higher BMI is observed in former smokers (Reverse causation)
3. BMI correlates with smoking intensity (Sneve et al. 2008; Date et al. 2015)



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Body fatness, weight gain & cancer (WCRF 2018)

BODY FATNESS AND WEIGHT GAIN AND THE RISK OF CANCER

WCRF/AICR GRADING		DECREASES RISK		INCREASES RISK	
		Exposure	Cancer site	Exposure	Cancer site
STRONG EVIDENCE	Convincing			Adult body fatness	Oesophagus (adenocarcinoma) 2016[1] Pancreas 2012[1] Liver 2015[1] Colorectum 2017[1] Breast (postmenopause) 2017[1,3] Endometrium 2013[4,5] Kidney 2015[1]
				Adult weight gain	Breast (postmenopause) 2017[1]
	Probable	Adult body fatness	Breast (premenopause) 2017[1,3]	Adult body fatness	Mouth, pharynx and larynx 2018[1] Stomach (cardia) 2016[2] Gallbladder 2015[2,7] Ovary 2014[2,5,6] Prostate (advanced) 2014[1,9]
		Body fatness in young adulthood	Breast (premenopause) 2017[1,6] Breast (postmenopause) 2017[1,6]		
LIMITED EVIDENCE	Limited – suggestive			Adult body fatness	Cervix (BMI ≥ 29 kg/m²) 2017[2,3]
STRONG EVIDENCE	Substantial effect on risk unlikely	None identified			

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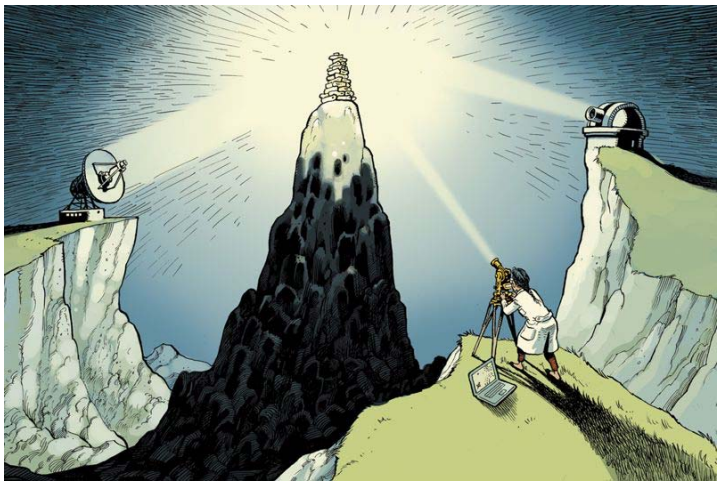
"Robust research needs many lines of evidence" (Triangulation)



Commentary: Marcus R. Munafò & George Davey Smith. *Nature 2018*

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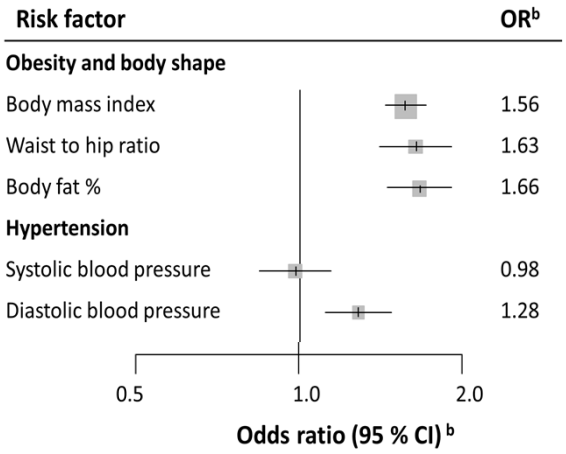
Triangulation for blood pressure in renal cancer

Genetically measured (MR)



Directly measured (Cohort)

Blood pressure measure	Relative risks (95% CI)
Univariate	
Systolic BP	1.15 (1.07– 1.23)
Diastolic BP	1.25 (1.17 – 1.33)
Mutually adjusted	
Systolic BP	0.94 (0.85 – 1.03)
Diastolic BP	1.31 (1.19 – 1.43)

*Cox-regression for directly measured BP in **UK Biobank** and the European Prospective Investigation into Cancer and nutrition (**EPIC**) study. Initial 5 years of follow-up excluded.*