Reassessing the link between adiposity and head and neck cancer: a Mendelian randomization study

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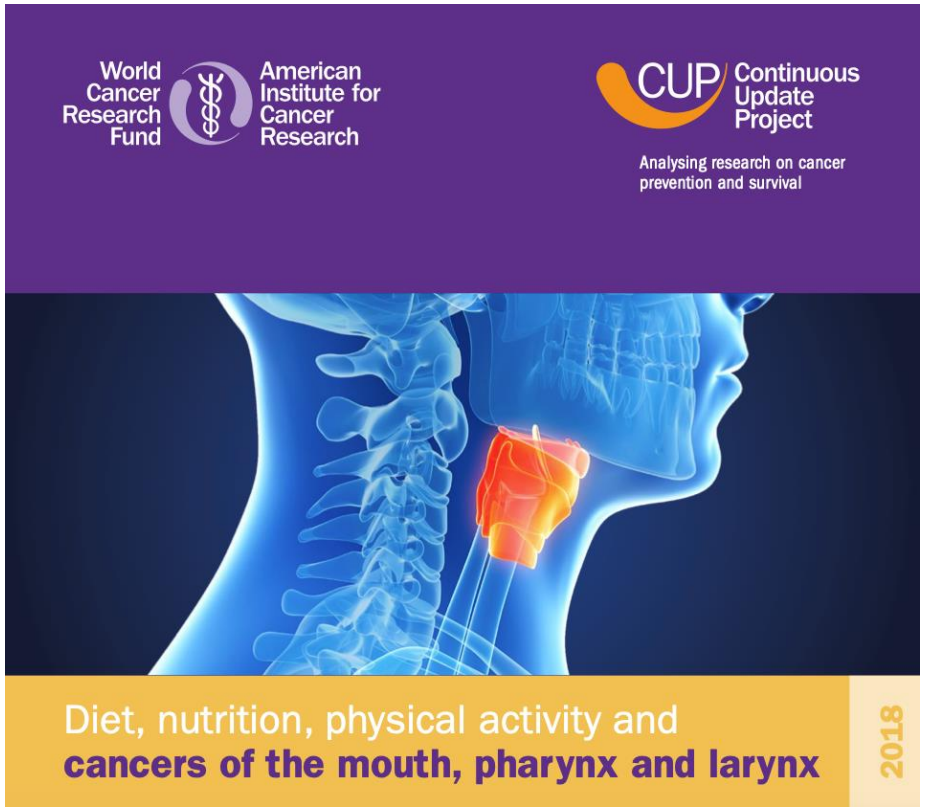
No conflicts of interest to declare

WCE
WORLD CONGRESS OF EPIDEMIOLOGY 2024

Background



2018

DIET, NUTRITION, PHYSICAL ACTIVITY AND CANCERS OF THE MOUTH, PHARYNX AND LARYNX

		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	Convincing		Alcoholic drinks
	Probable		Body fatness[1]

1 Body fatness marked by body mass index (BMI), waist circumference and waist-hip ratio.

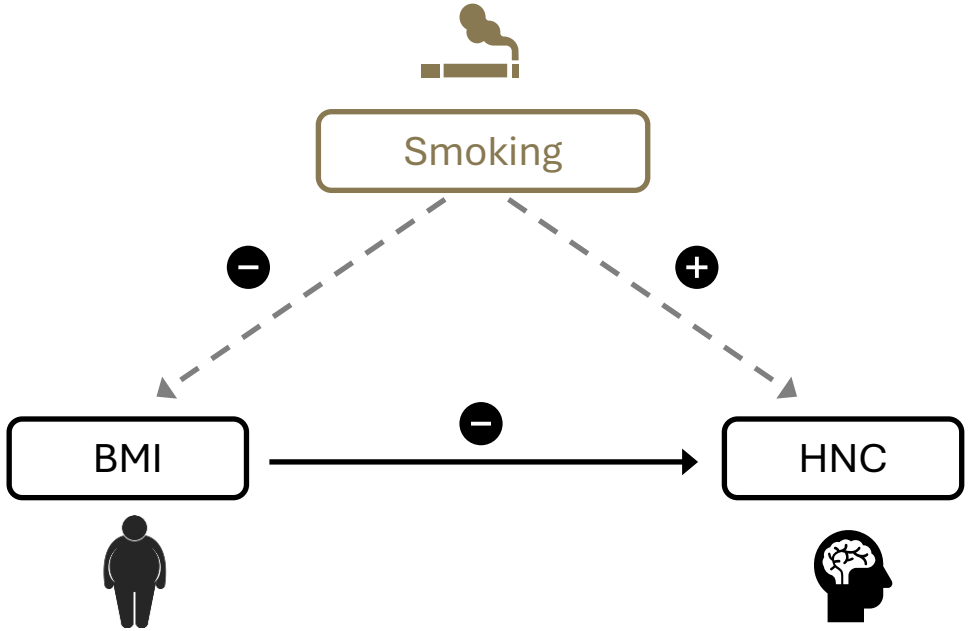
Diet, nutrition, physical activity and cancers of the mouth, pharynx and larynx. In: *Continuous Update Project Expert Report.* 2018.

Background

Table 13. Summary of results from published pooled analysis [100] – BMI and head and neck cancer

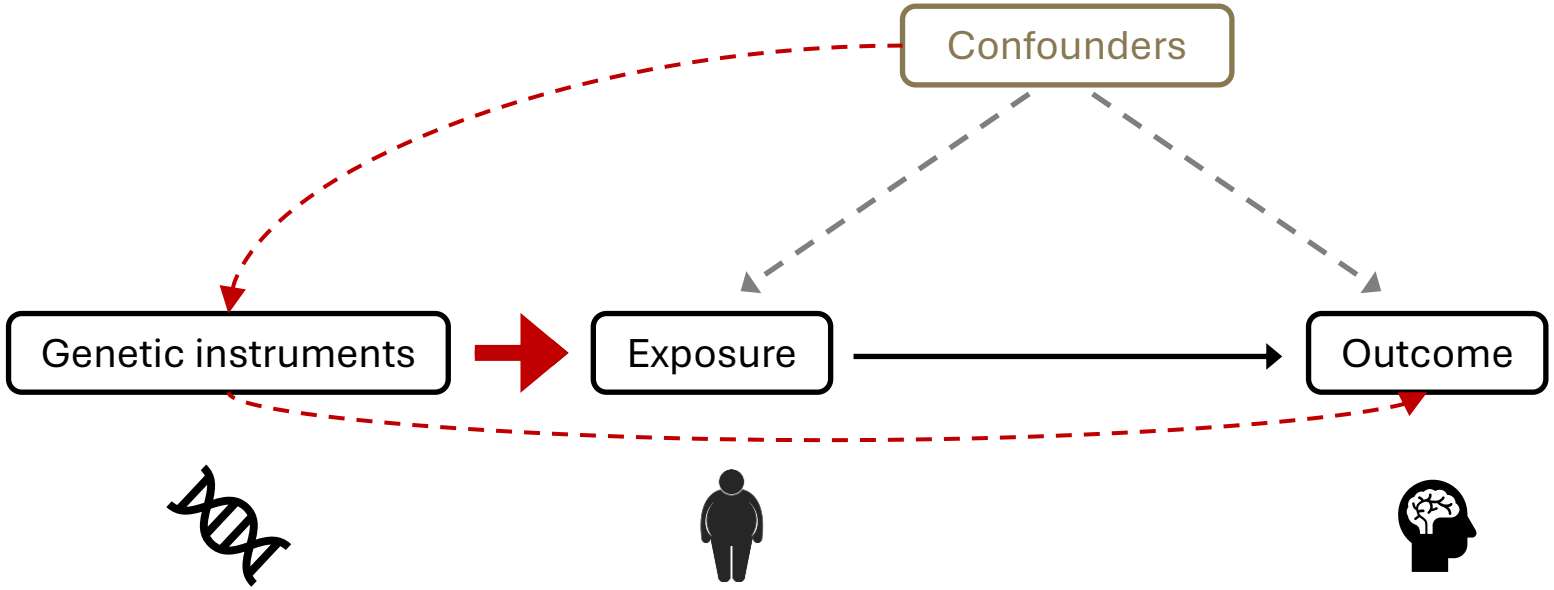
	No. Cases	HR (95% CI) Per 5 kg/m²	P trend
All	3,760	0.94 (0.90–0.98)	0.003

Link to Watts et al. meta-analysis on medRxiv which shows positive association among non-smokers in a larger sample (10,841 cases)



Gaudet MM, *et al. Int J Epidemiol* 2015, **44**(2):673-681.
Diet, nutrition, physical activity and cancers of the mouth, pharynx and larynx. In: *Continuous Update Project Expert Report.* 2018.

Mendelian randomisation



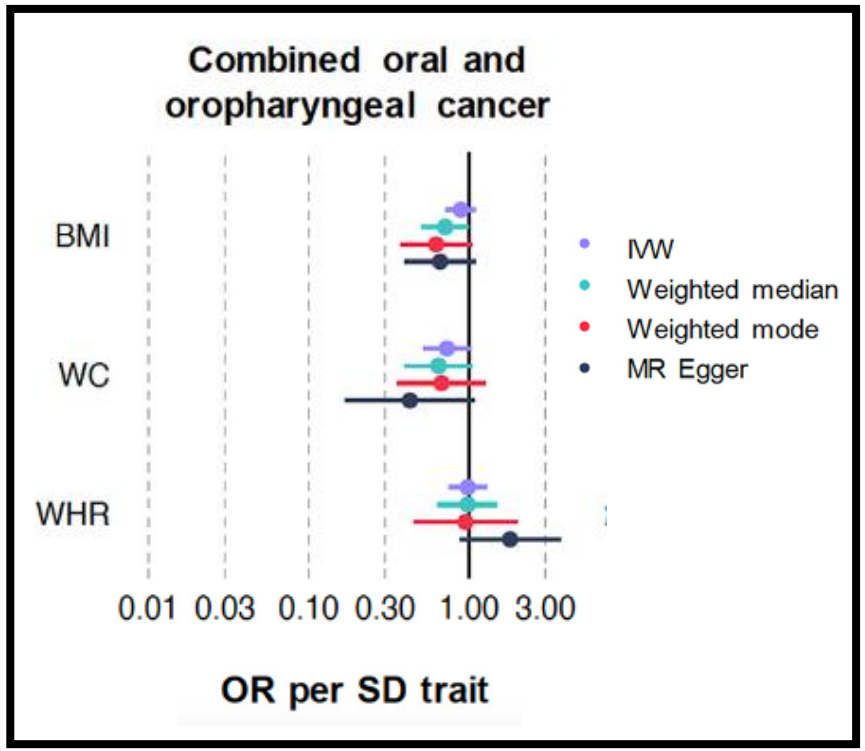
Background

eLife RESEARCH ARTICLE

Evaluating the effect of metabolic traits on oral and oropharyngeal cancer risk using Mendelian randomization

Mark Gormley[1,2]*, Tom Dudding[2], Steven J Thomas[2], Jessica Tyrrell[3], Andrew R Ness[4], Miranda Pring[2], Danny Legge[5], George Davey Smith[1], Rebecca C Richmond[1], Emma E Vincent[1,5†], Caroline Bull[1,5†]

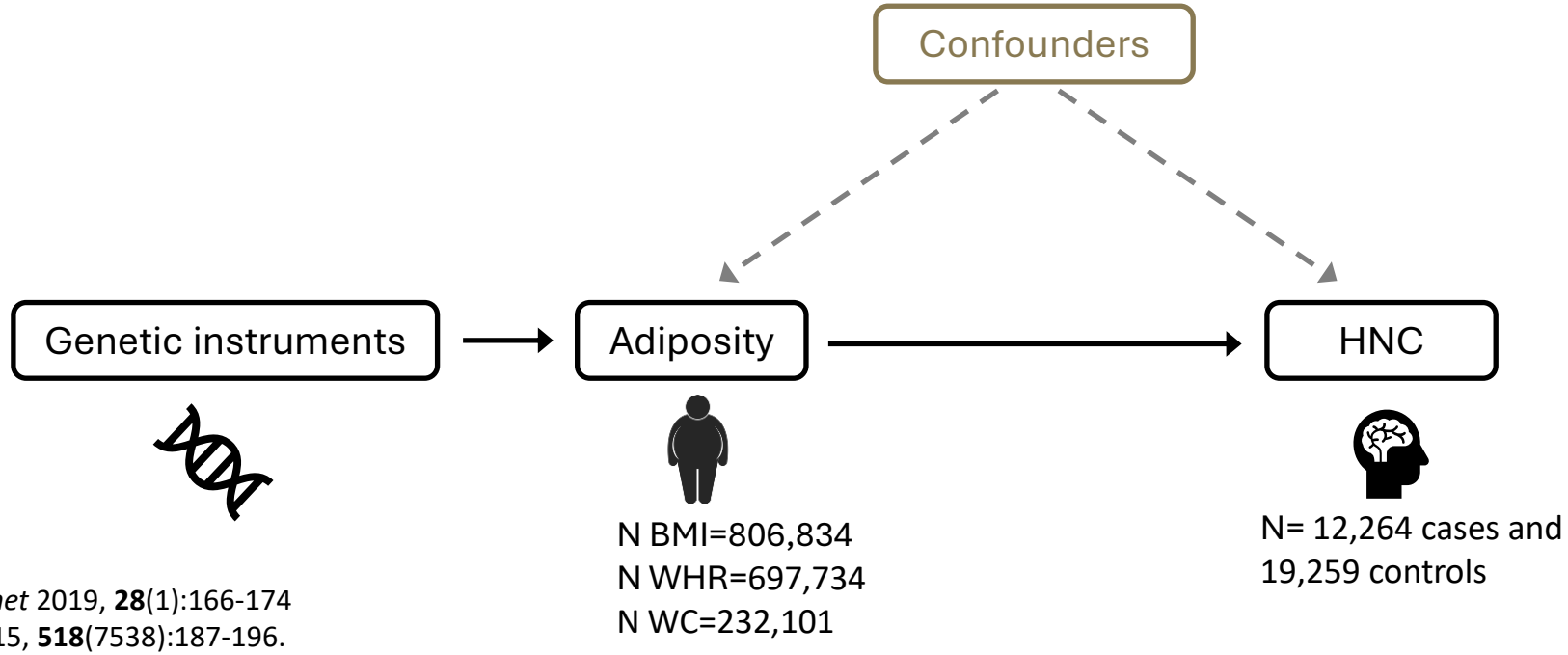
Abstract A recent World Health Organization report states that at least 40% of all cancer cases may be preventable, with smoking, alcohol consumption, and obesity identified as three of the most important modifiable lifestyle factors. Given the significant decline in smoking rates, particularly within developed countries, other potentially modifiable risk factors for head and neck cancer warrant investigation. Obesity and related metabolic disorders such as type 2 diabetes (T2D) and hypertension have been associated with head and neck cancer risk in multiple observational studies. However, adiposity has also been correlated with smoking, with bias, confounding or reverse causality possibly explaining these findings. To overcome the challenges of observational studies, we conducted two-sample Mendelian randomization (inverse variance weighted [IVW] method) using genetic variants which were robustly associated with adiposity, glycaemic and blood pressure traits in genome-wide association studies (GWAS). Outcome data were taken from the largest available GWAS of 6034 oral and oropharyngeal cases, with 6585 controls. We found limited evidence of a causal effect of genetically proxied body mass index (BMI; OR IVW = 0.89, 95% CI 0.72–1.09, p = 0.26 per 1 standard deviation in BMI [4.81kg/m^2]) on oral and oropharyngeal cancer risk. Similarly, there was limited evidence for related traits including T2D and hypertension. Small effects cannot be excluded given the lack of power to detect them in currently available GWAS.



Gormley M, *et al*. *Elife* 2023, **12**.

Aim

To assess the genetically predicted effect of adiposity on the risk of HNC and its subsites (oral, laryngeal, hypopharyngeal and oropharyngeal cancers) using a two-sample MR framework



Pulit SL, *et al*. *Hum Mol Genet* 2019, **28**(1):166-174
Shungin D, et al. *Nature* 2015, **518**(7538):187-196.

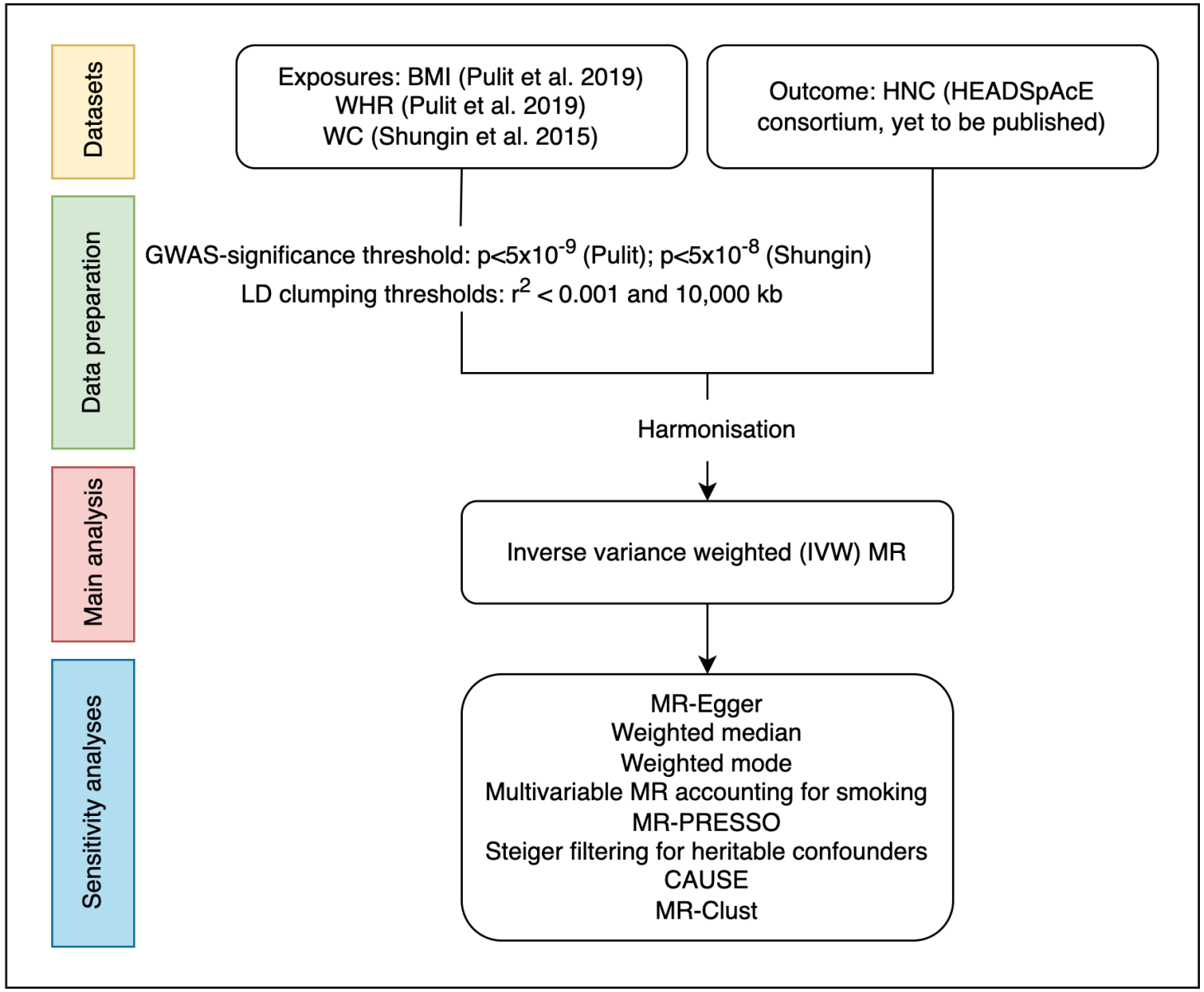
Methods

Mean F-statistics:

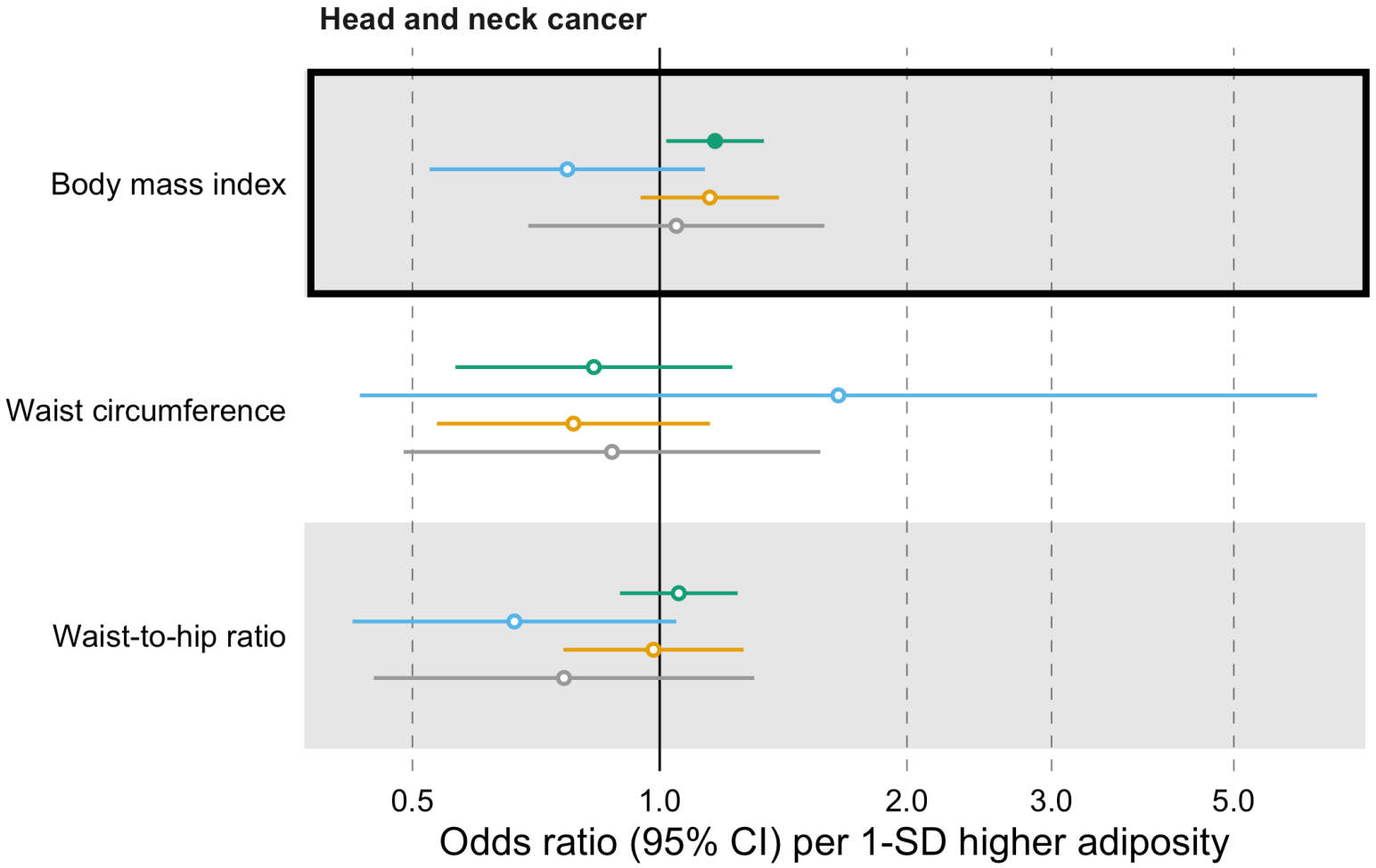
- BMI = 77
- WHR = 73
- WC = 50

Variance explained:

- BMI = 4.8%
- WHR = 3.1%
- WC = 0.8%



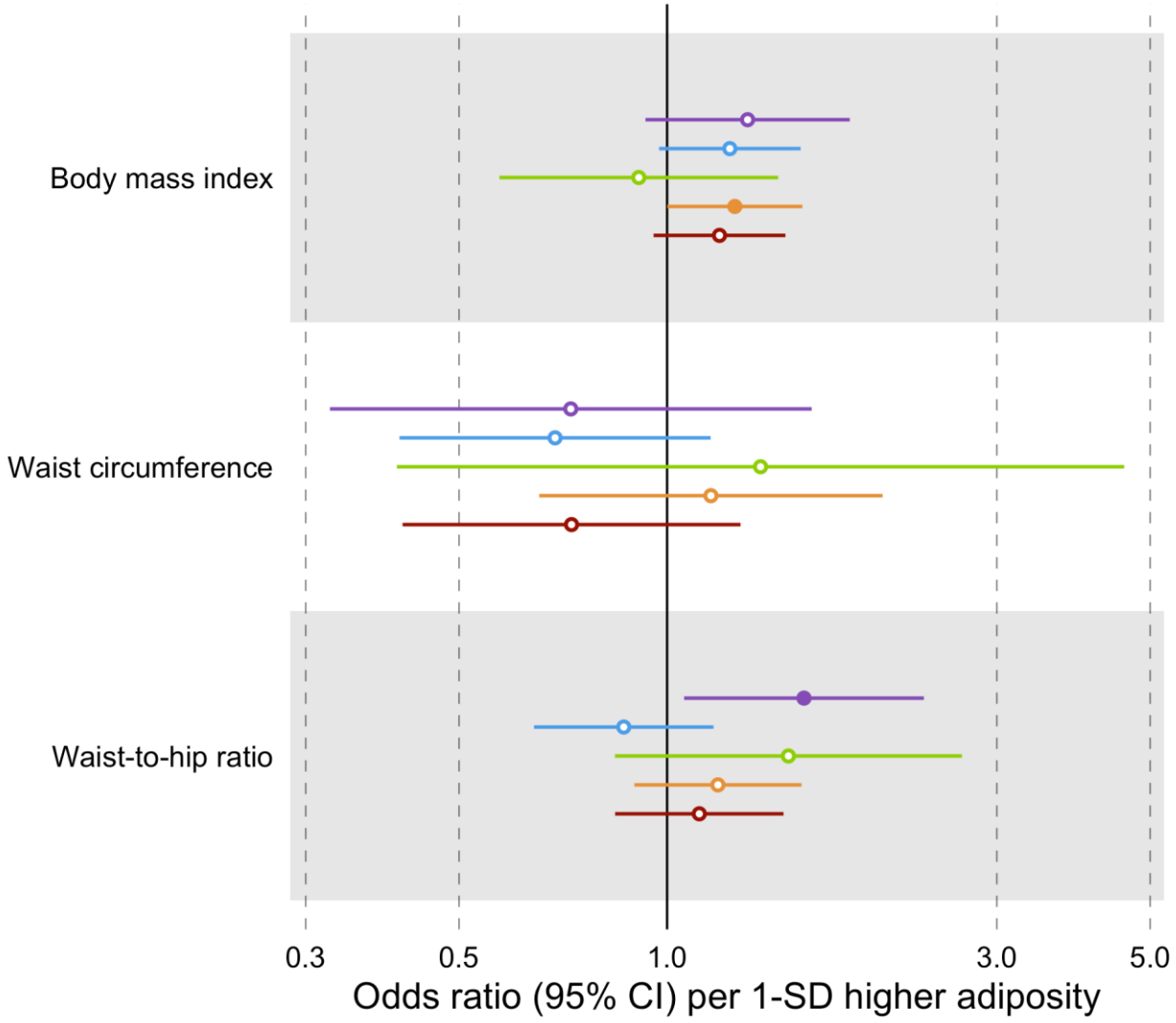
Univariable MR results



- BMI increases risk of HNC in IVW analysis only
- No evidence of other adiposity measures impacting HNC

method
- Inverse variance weighted
- MR Egger
- Weighted median
- Weighted mode

Univariable MR results by subsite



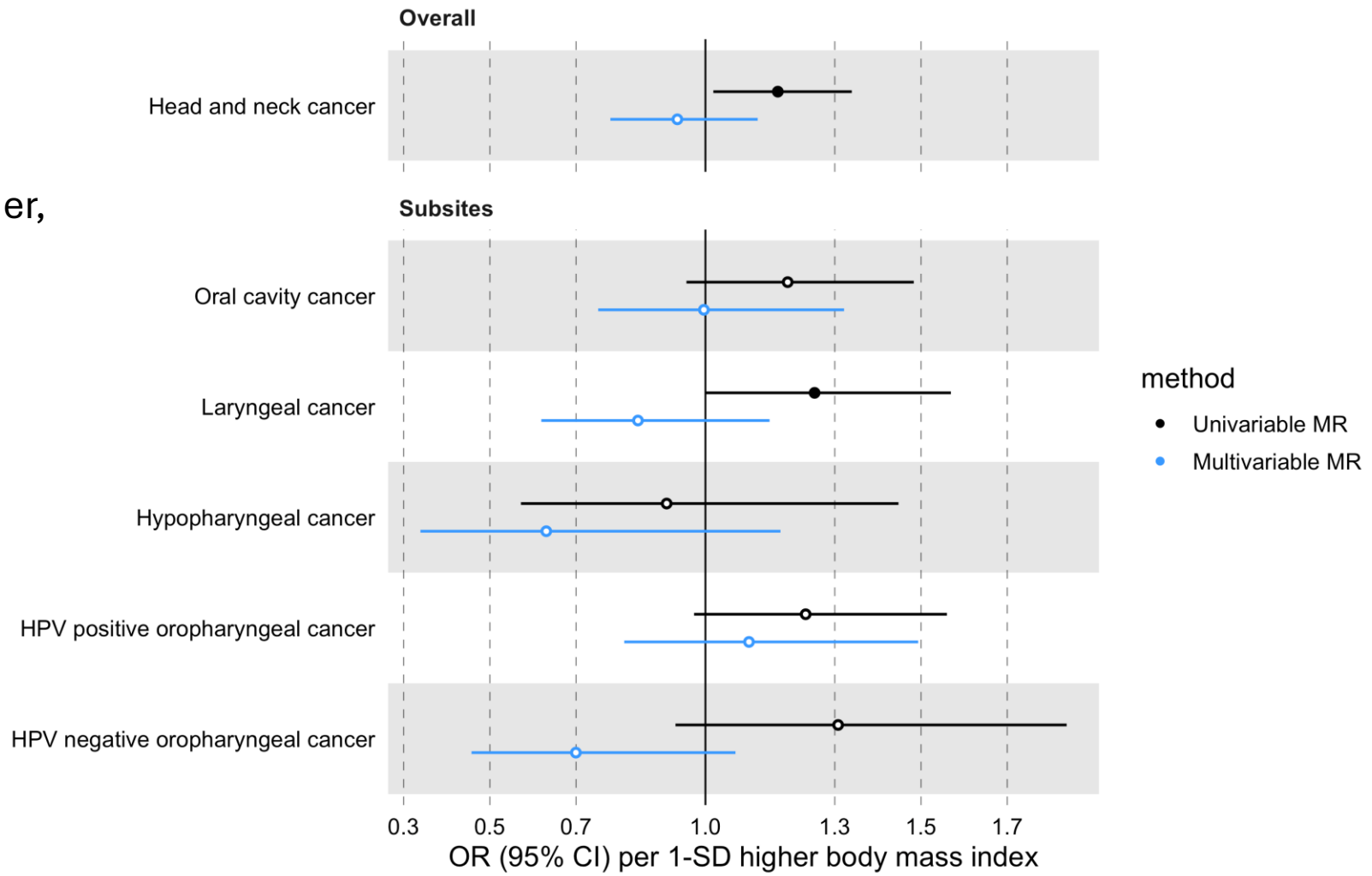
- No evidence of heterogeneity
- Some evidence for effects of:
  - BMI on LA
  - WHR on HPV- OPC

outcome

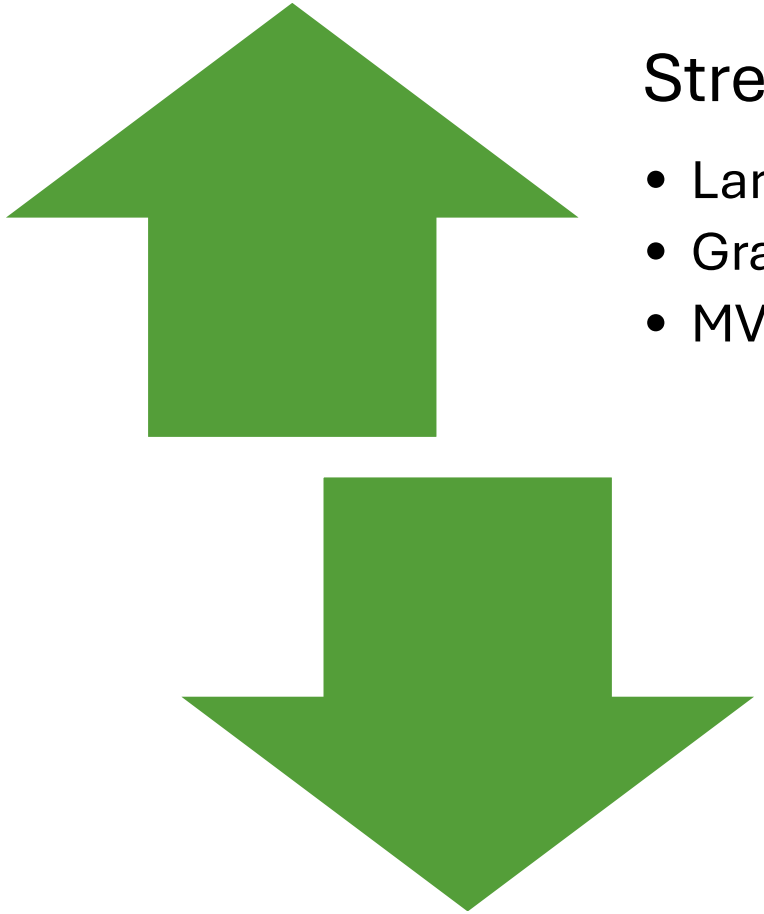
- HPV negative oropharyngeal cancer
- HPV positive oropharyngeal cancer
- Hypopharyngeal cancer
- Laryngeal cancer
- Oral cavity cancer

Multivariable MR results

- Multivariable MR can account for other, potentially correlated exposures
- Effects of BMI accounting for comprehensive smoking index
- When accounting for smoking, the effects attenuate



Strengths and limitations



Strengths

- Large sample size
- Granular data on subsites
- MVMR rather than stratified MR analysis

Limitations

- Untestable MR assumptions (independence and exclusion restriction)
- European ancestry only
- Unclear biology underlying BMI-smoking link

Conclusions

- Our results suggest that adiposity does not play an important role in HNC risk.
- Although we did not find strong evidence of a causal effect of adiposity on HNC, it is important to remember obesity is an established risk factor for multiple cancers and other chronic diseases.
- Hence there is still value in aiming to reduce the levels of excess adiposity in the population.

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