Further exploring the independent effects of smoking and alcohol use on head and neck cancer:

a multivariable Mendelian randomization study

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No conflicts of interest to declare

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Background

Increases risk of developing head and neck cancer (HNC)

Increases HNC risk but mostly among those who smoke

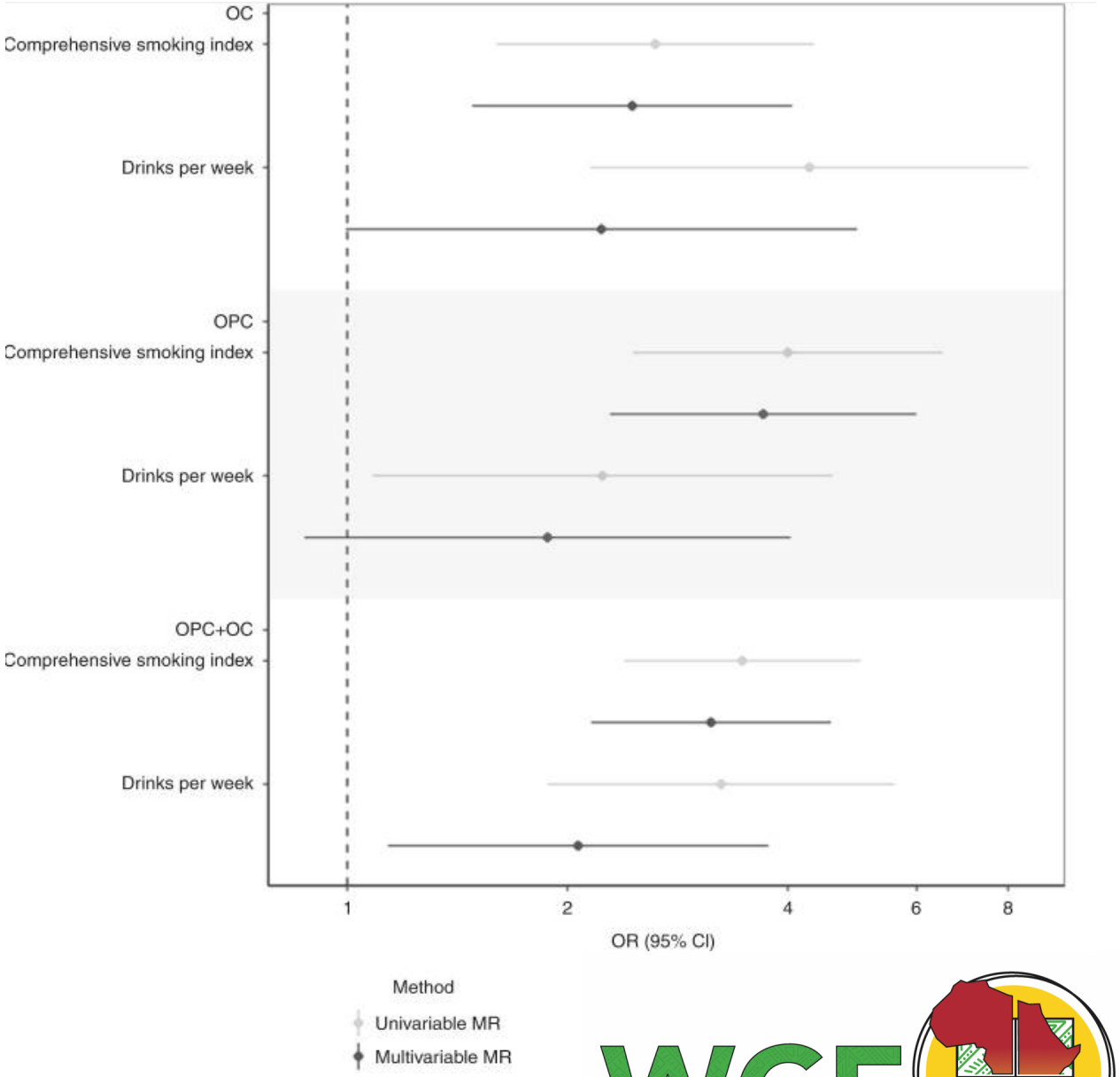
(Lander et al., 2024, Hashibe et al., 2008, 2009)

Observational research could be limited by confounding

Mendelian randomisation suggests independent effects on Oral, Oropharyngeal, HPV+ and HPV- HNC

(Gormley et al. 2020, Thakral et al. 2024)

Limited by sample size among subsites, lack of stratification and smoking measures used



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Aims and Methods

This study aimed to explore the independent effects of alcohol and tobacco use on head and neck cancer risk, including risk by subsite, using multivariable Mendelian randomisation

Exposures


Summary statistics from GSCAN 2 consortium exc. UK Biobank and 23&Me


15 smoking heaviness SNPs measured by cigarettes per day


10 drinking heaviness SNPs measured by drinks per week


European ancestry


Adjusted F-stats > 10


Warning: exact effect sizes not interpretable due to variable handling in GWAS

Saunders et al, 2022

SNPs = Single nucleotide polymorphisms

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Methods

Outcome

- HEADSpAcE GWAS of head and neck cancer & subsites (unpublished)
  - All head and neck cancers below (HNC)
  - Hypopharyngeal cancer (HPC)
  - Laryngeal cancer (LA)
  - Oral cancer (OC)
  - HPV- oropharyngeal cancer (OPC_NEG)
  - HPV+ oropharyngeal cancer (OPC_POS)
- Largest meta-GWAS of HNC and subsites
  - Widest range of HNC subsites
  - Sample size allowed for stratification by smoking and alcohol status

Smoking

Subsite	Ever controls	Ever cases	Never controls	Never cases
HNC	12593	8508	12587	2951
HPC	12593	463	12587	102
LA	12593	2371	12587	408
OC	12593	2494	12587	1001
OPC_NEG	12593	734	12587	214
OPC_POS	12593	1175	12587	805
				2530

Drinking

Subsite	Ever controls	Ever cases	Never controls	Never cases
HNC	22669	8732	1588	1745
HPC	22669	463	1588	45
LA	22669	2154	1588	372
OC	22669	2630	1588	627
OPC_NEG	22669	689	1588	118
OPC_POS	22669	1367	1588	386

Smoking and drinking

Subsite	Ever controls	Ever cases	Never controls	Never cases
HNC	11502	7239	1036	588
HPC	11502	419	1036	8
LA	11502	1997	1036	43
OC	11502	2135	1036	290
OPC_NEG	11502	631	1036	23
OPC_POS	11502	930	1036	149

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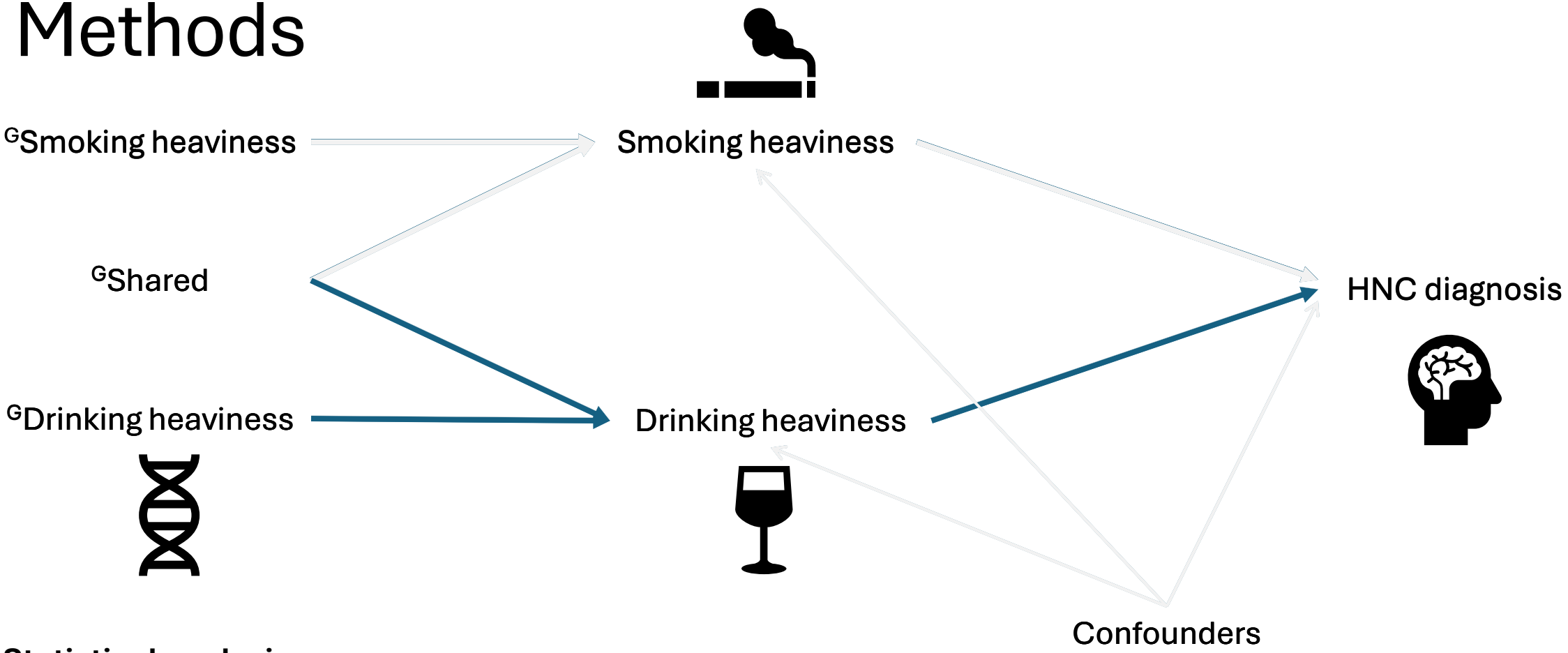
Methods



Statistical analysis

- Two-sample Mendelian Randomisation (MR)
- Two-sample Multivariable MR (MVMR)

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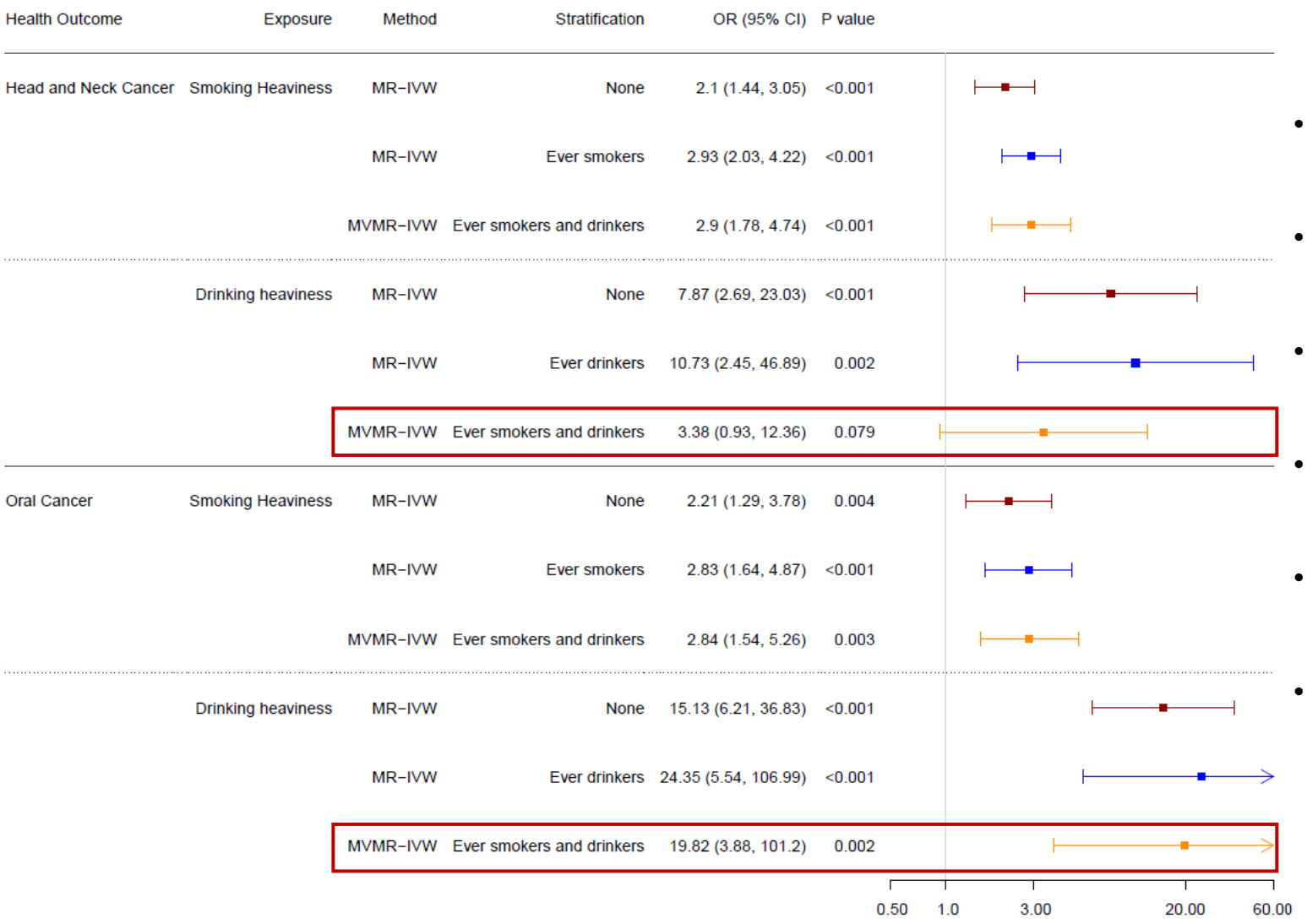
Results



- Independent effects of both smoking and drinking on head and neck cancer
- Limited impact of stratification by smoking / drinking status
- Removal of *ADH1B* (rs1229984) outlier attenuates drinking in overall
- However, effect is still clear for oral cancer
- Sensitivity results support these findings except…
- There is a clearer effect of drinking in MVMR-Egger

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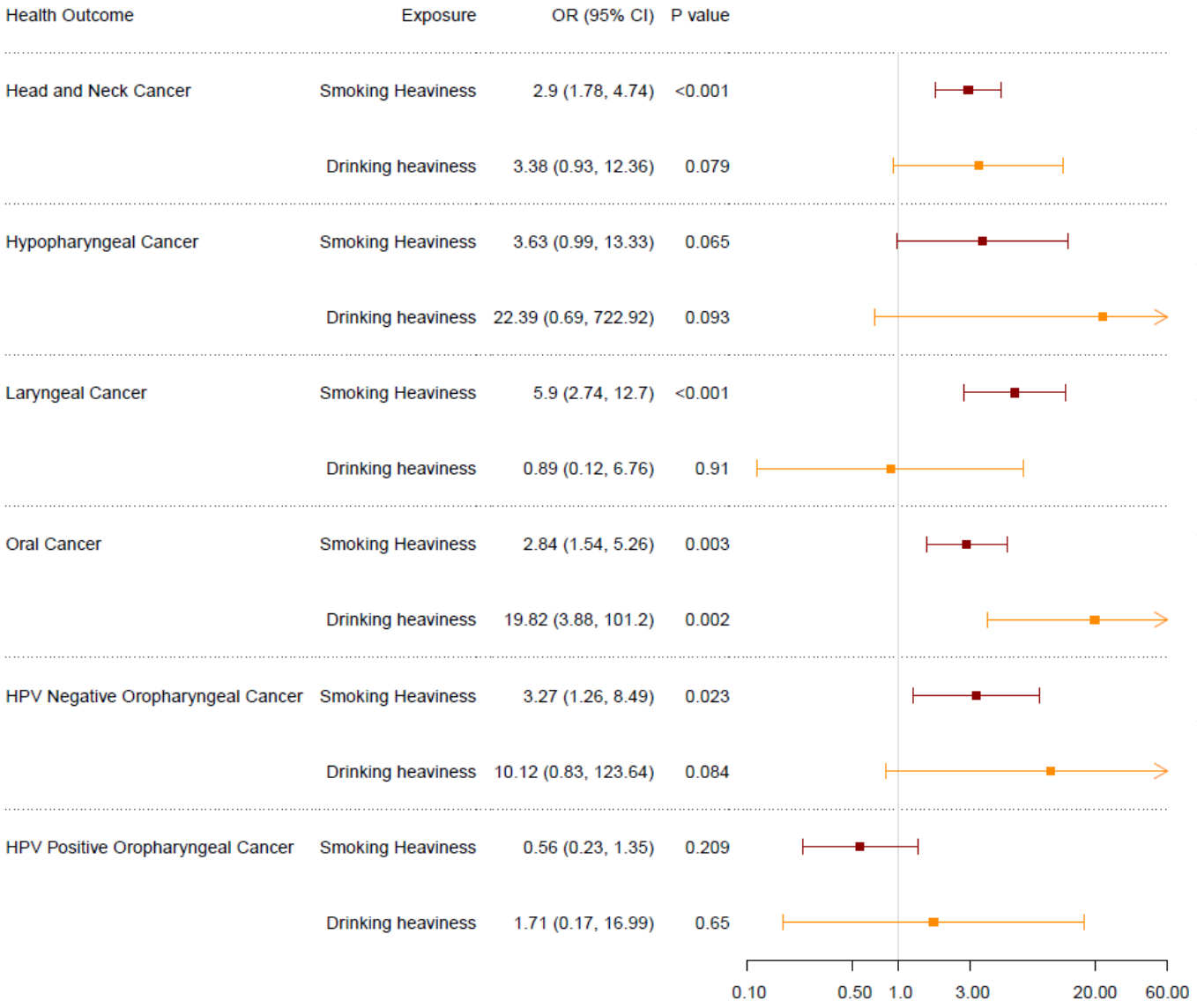
Results - subsites



MVMR-IVW among drinkers and smokers, outlier removed

- Smoking appears to be important across most subsites - HPV positive OPC is an exception
- Alcohol appears to be an important factor for oral cancer specifically
- MVMR-Egger showed clearer evidence of an effect of drinking on HNC, HPC and LA
- Heterogeneity across subsites:
  - Smoking I^2 = 76.0%, Q =16.66 (p=.002)
  - Drinking I^2 = 45.4%, Q =7.32 (p=.12)
- Some evidence of pleiotropy in results among never smokers – smoking heaviness, OC and HPV- OPC

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Discussion

- Heavier smoking leads to increased HNC risk across subsites (except HPV+)
- Strong evidence of an effect of heavier drinking on OC

- Larger sample size and power
- Additional stratifications to prior work

- Some evidence of pleiotropy and bias (potentially due to stratification)
- Caution should be taken interpreting the effect sizes

Conclusion: there are independent effects of smoking and alcohol on HNC, indicating both should be targeted for prevention

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