USING MENDELIAN RANDOMIZATION TO EXPLORE THE GATEWAY HYPOTHESIS

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Discloures

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RESEARCH REPORT

ADDICTION SSA

Using Mendelian randomization to explore the gateway hypothesis: possible causal effects of smoking initiation and alcohol consumption on substance use outcomes

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Epidemiology


Daily Mail

45p

DIANA: WHO THE FUCK STILL CARES?

IMMIGRATION SPIRALS AS WHITEHALL PARTIES

SEE PAGES 12-13

THE MAIL GET UPSET ON YOUR BEHALF

Health minister comes clean and tells Mail readers

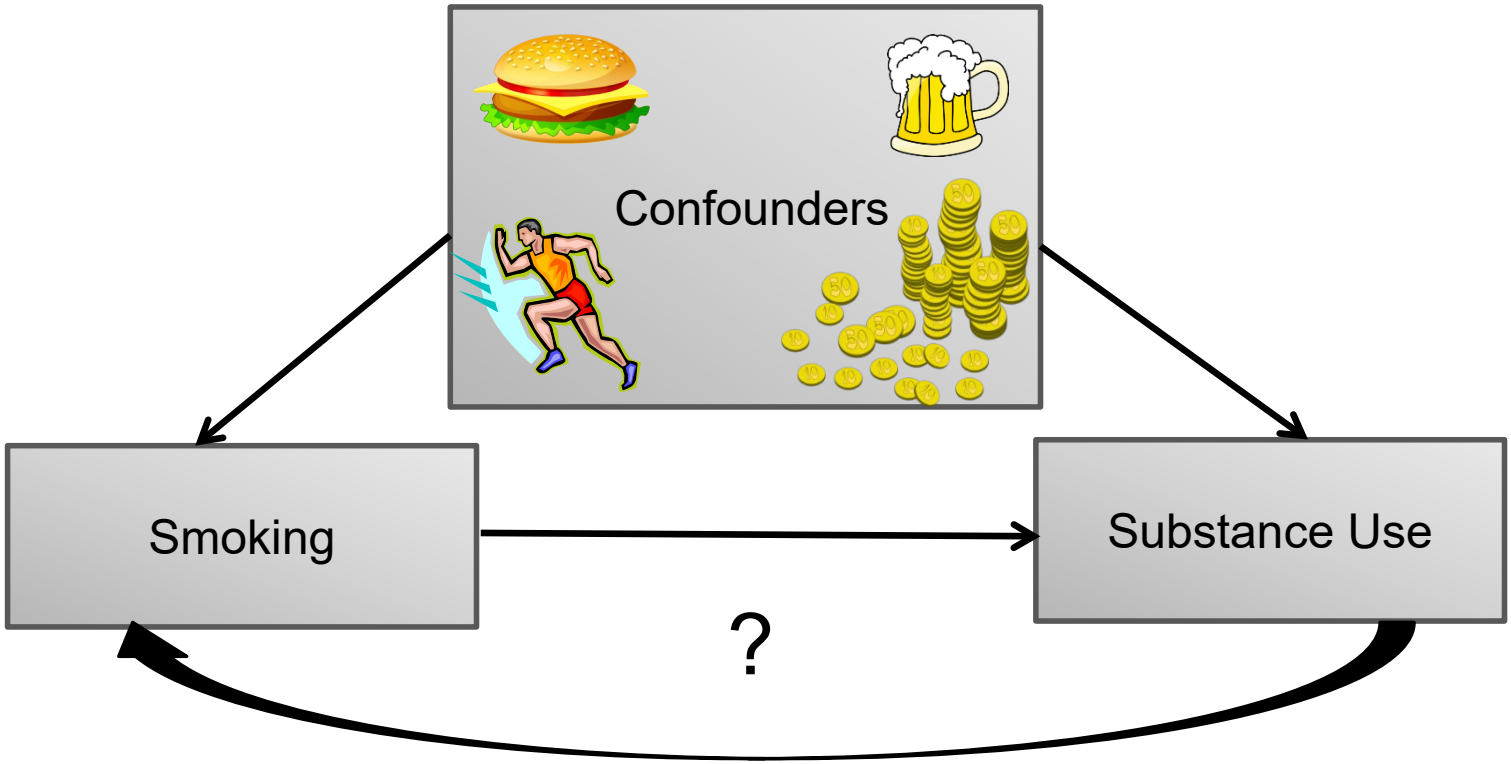
CANCER: READING THIS PAPER GIVES YOU DISEASE

Skinny Kiera finally eats

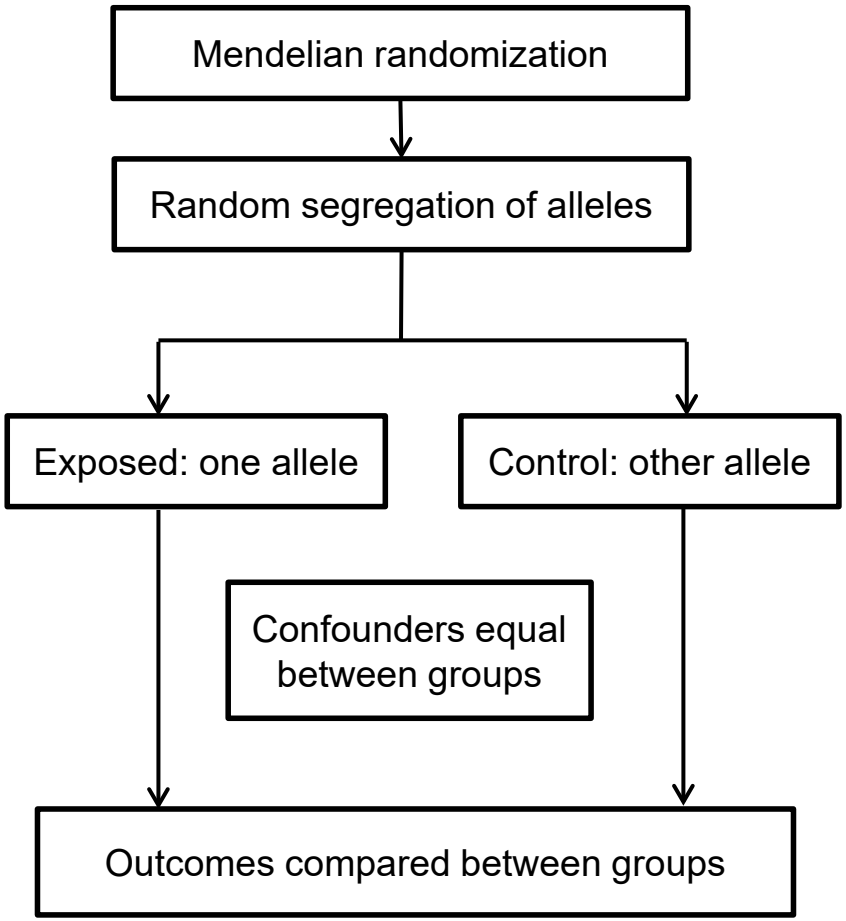

Seven cups of tea a day 'raises risk of prostate cancer by 50%'

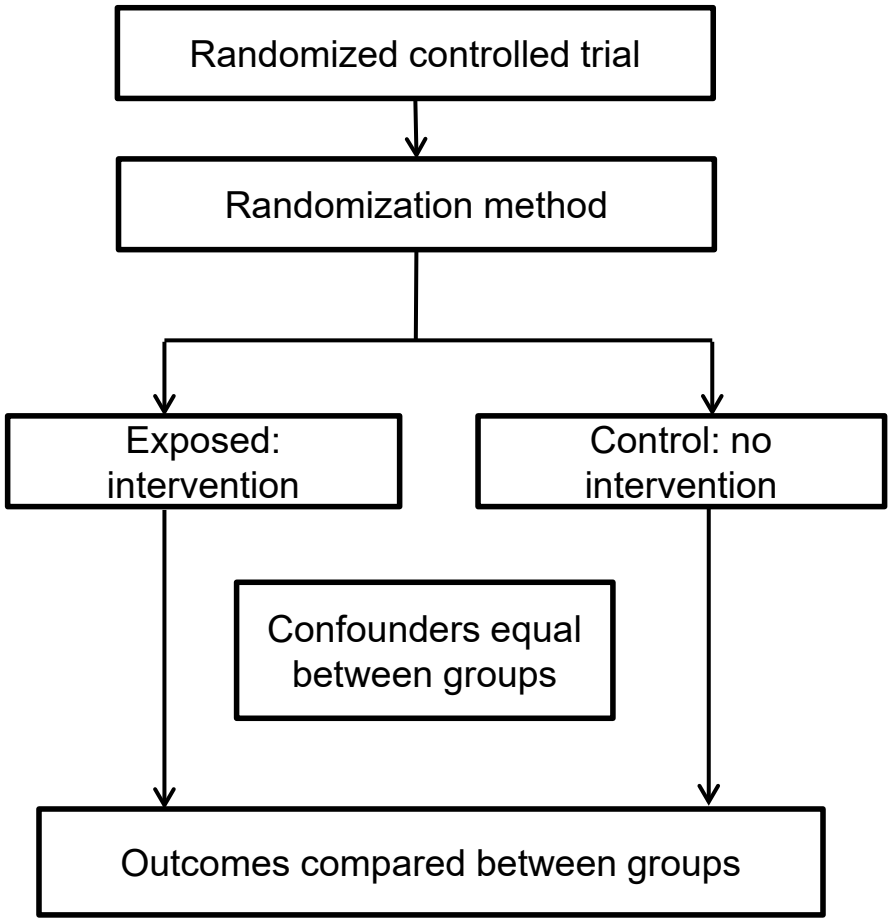
'Coffee and alcohol intake'

Epidemiology

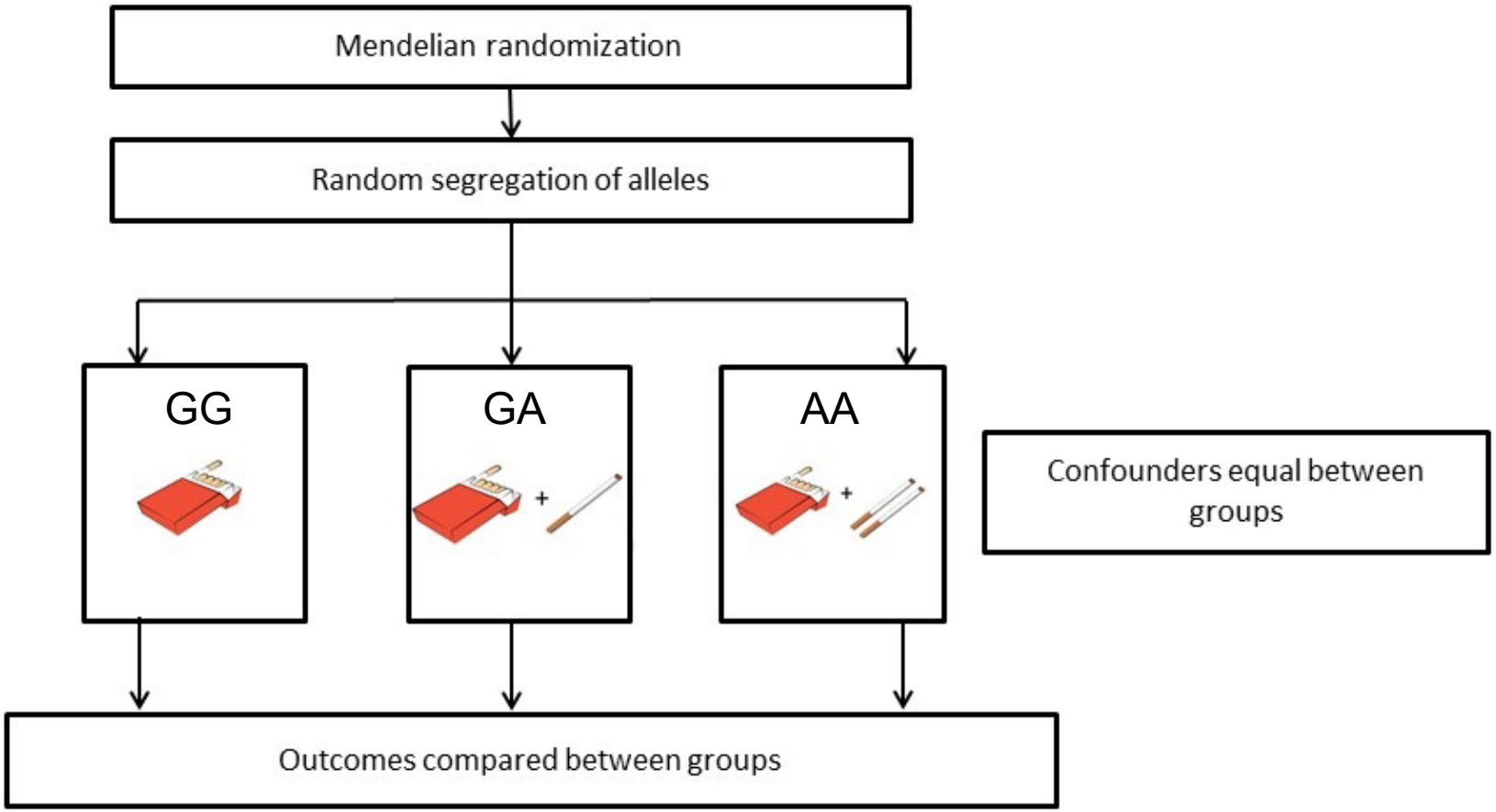


Mendelian Randomization

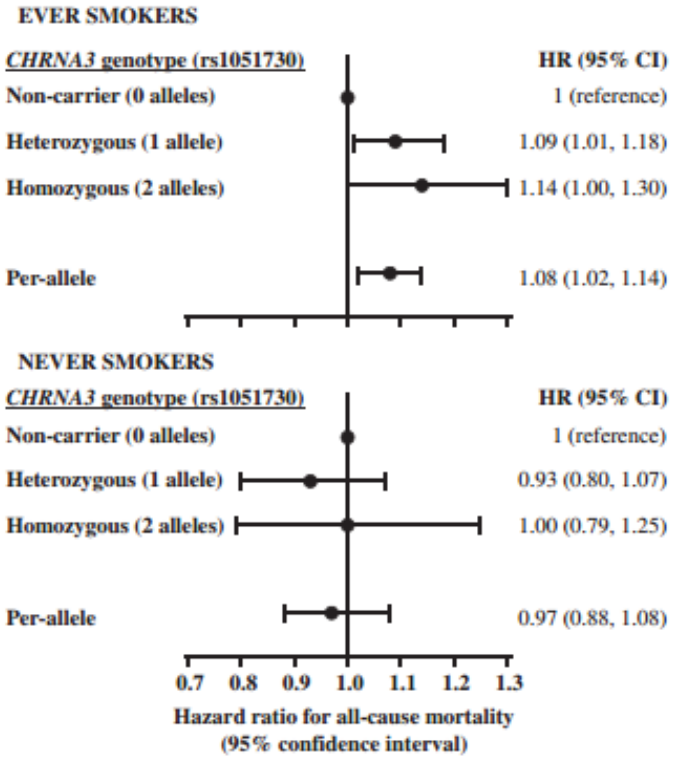


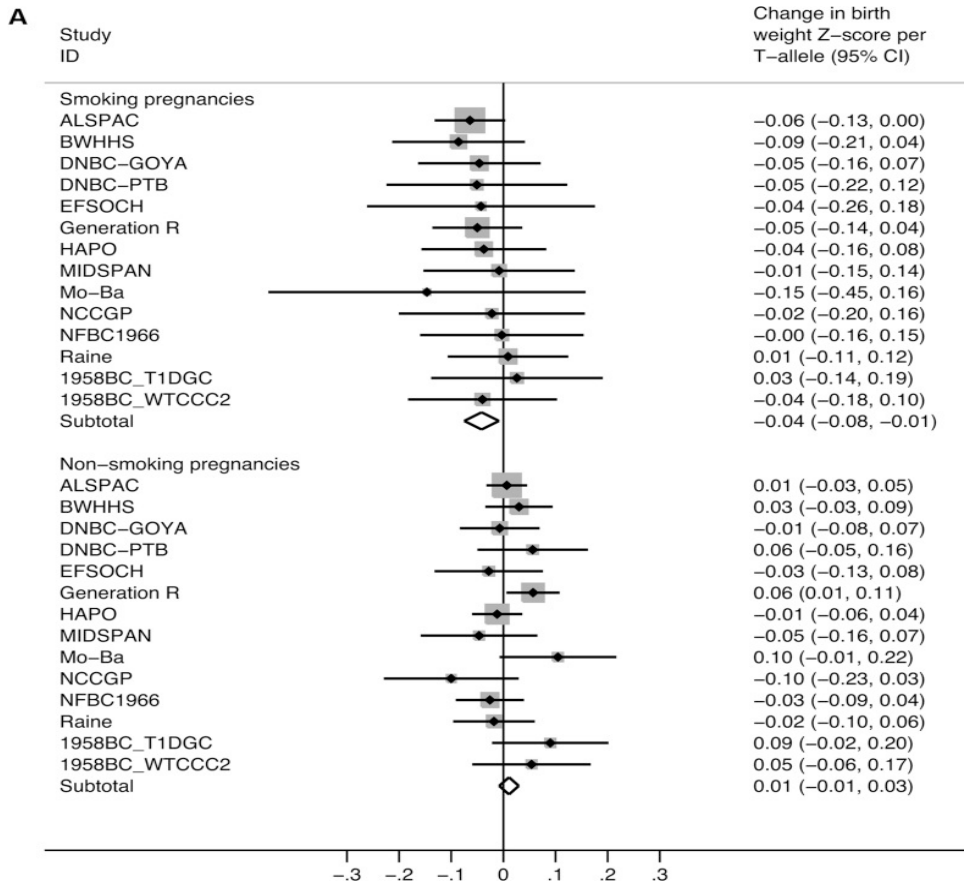


Smoking MR


Mendelian randomization
Random segregation of alleles
GG
GA
AA
Confounders equal between groups
Outcomes compared between groups

Smoking MR and Disease





Rode et al. (2014). Int J Epidemiol, 43, 1473-1483; Tyrrell et al. (2012). Hum Mol Genet, 21, 5344-5358.

G = E: What GWAS Can Tell Us about the Environment

Suzanne H. Gage[1,2], George Davey Smith[1,3], Jennifer J. Ware[1,3], Jonathan Flint[4], Marcus R. Munafò[1,2]*

1 MRC Integrative Epidemiology Unit (IEU) at the University of Bristol, Bristol, United Kingdom, 2 UK Centre for Tobacco and Alcohol Studies, School of Experimental Psychology, University of Bristol, Bristol, United Kingdom, 3 School of Social and Community Medicine, University of Bristol, Bristol, United Kingdom, 4 Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, United Kingdom

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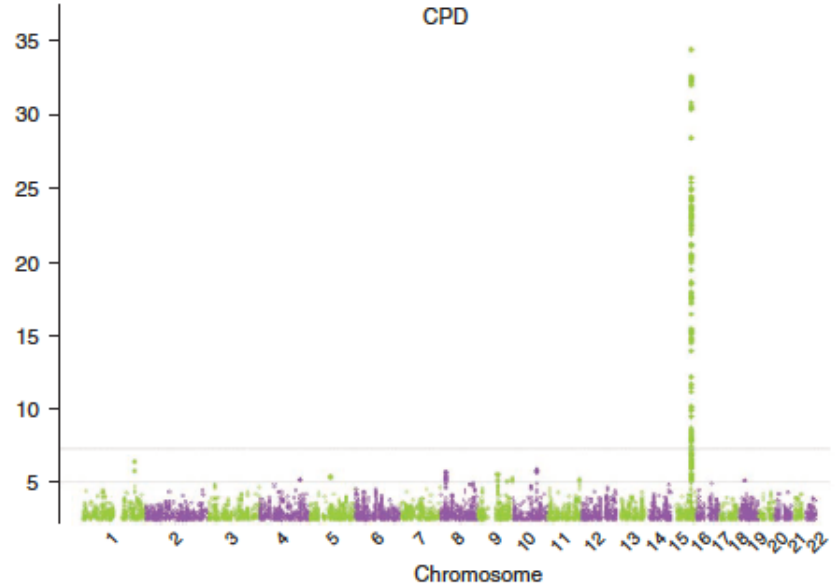
- Lung cancer
  (e.g., Spitz, 2008)
- COPD/emphysema
  (e.g., Pillai, 2009)
- Peripheral arterial disease
  (e.g., Thorgeirsson, 2008)



Gage et al. (2016). PLOS Genet, 12, e1005765.

Questions?

Mendelian Randomization

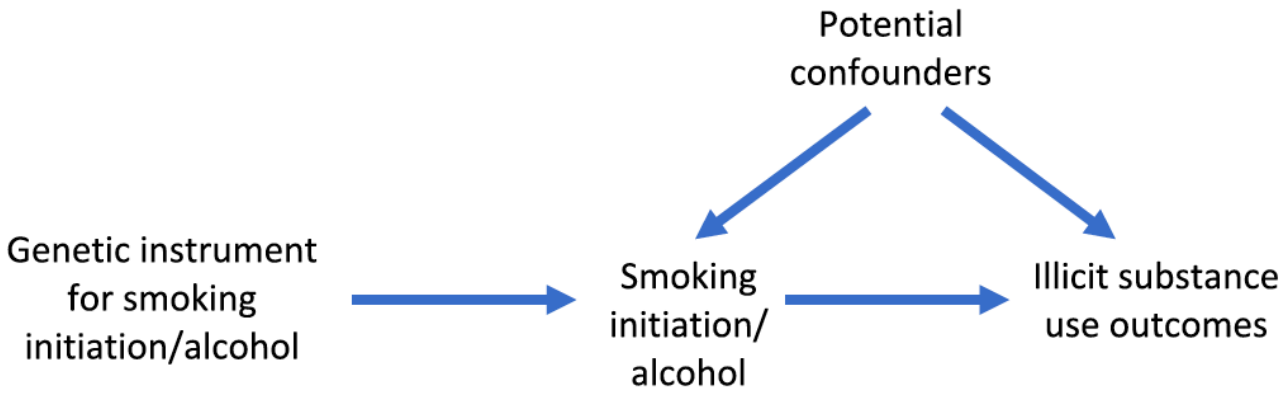


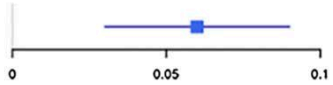
FIGURE 1 Bidirectional two-sample Mendelian randomization between smoking initiation/alcohol consumption and illicit substance use outcomes. A directed acyclic graph (DAG) for the causal effect between smoking initiation/alcohol consumption and illicit substance use outcomes. Evidence of a causal effect in the other direction may indicate a bidirectional effect or a common underlying risk factor

Data Sets

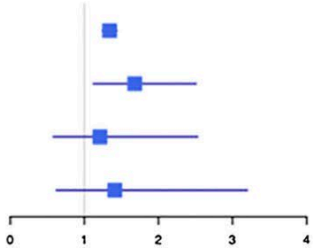
- Smoking initiation - Liu et al. (2019)
- Drinks per week - Liu et al. (2019)
- Cannabis use - Pasman et al. (2018)
- Cannabis dependence - Agrawal et al. (2017)
- Cocaine dependence - Gelernter et al. (2014)
- Opioid dependence - Gelernter et al. (2014)

Smoking Initiation

Exposure	Outcome	N SNPs	Beta (95% CI)	P value
Smoking Initiation	Drinks per week	72	0.06 (0.03 to 0.09)	9.44 x 10−06

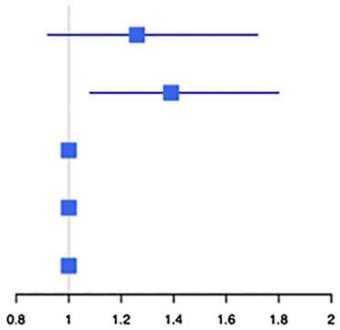


Exposure	Outcome	N SNPs	OR (95% CI)	P value
Smoking Initiation	Cannabis use	144	1.34 (1.24 to 1.44)	1.95 x 10−14
Smoking Initiation	Cannabis dependence	133	1.68 (1.12 to 2.51)	0.01
Smoking Initiation	Cocaine dependence	190	1.21 (0.58 to 2.53)	0.60
Smoking Initiation	Opioid dependence	155	1.41 (0.62 to 3.20)	0.41



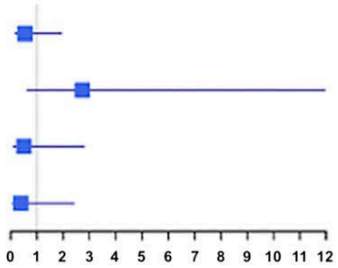
Smoking Initiation

Exposure	Outcome	N SNPs	OR (95% CI)	P value
Drinks per week	Smoking Initiation	22	1.26 (0.92 to 1.72)	0.15
Cannabis use	Smoking Initiation	4	1.39 (1.08 to 1.80)	0.01
Cannabis dependence	Smoking Initiation	9	1.00 (0.99 to 1.01	0.60
Cocaine dependence	Smoking Initiation	27	1.00 (1.00 to 1.00)	0.42
Opioid dependence	Smoking Initiation	7	1.00 (0.99 to 1.01)	0.80



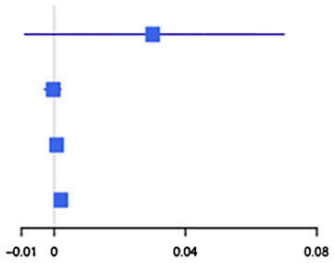
Alcohol Consumption

Exposure	Outcome	N SNPs	OR (95% CI)	P value
Drinks per week	Cannabis use	20	0.55 (0.16 to 1.93)	0.35
Drinks per week	Cannabis dependence	41	2.73 (0.62 to 11.95)	0.18
Drinks per week	Cocaine dependence	68	0.50 (0.09 to 2.79)	0.43
Drinks per week	Opioid dependence	47	0.38 (0.06 to 2.41)	0.30



Cannabis Use

Exposure	Outcome	N SNPs	Beta (95% CI)	P value
Cannabis use	Drinks per week	22	0.03 (–0.009 to 0.07)	0.14
Cannabis dependence	Drinks per week	4	–0.0003 (–0.003 to 0.002)	0.80
Cocaine dependence	Drinks per week	9	0.0007 (–0.0007 to 0.001)	0.08
Opioid dependence	Drinks per week	27	0.002 (0.0005 to 0.002)	8.61 x 10–03



Limitations

- Low statistical power for some phenotypes
- Less stringent p-value threshold for some phenotypes
- Evidence of horizontal pleiotropy
- What are “smoking initiation” SNPs capturing?

Future Directions

Smoking as "independent" risk factor for suicide: illustration of an artifact from observational epidemiology?

GEORGE DAVEY SMITH ANDREW N. PHILLIPS JAMES D. NEATON

It may be argued that smoking is a plausible causal factor for suicide. The risk of being murdered has therefore also been analysed according to smoking status. As there are only 222 deaths due to homicide, smoking has been classified into three groups—no cigarettes, 1–39, and 40+. The relative rates (and 95% CI) of being murdered, adjusted for income and race which are both associated with risk of murder, are: 1·00, 1·71 (1·29–2·28), and 2·04 (1·32–3·15), respectively.

"Unless the provisional wing of the health education lobby has moved on to a direct action phase, during which they shoot smokers, this association is very unlikely to be causal".

Shared genetic liability

RESEARCH ARTICLE

Association of genetic liability to smoking initiation with e-cigarette use in young adults: A cohort study

Jasmine N. Khouja[1,2,3]*, Robyn E. Wootton[1,2], Amy E. Taylor[2,4], George Davey Smith[1,2], Marcus R. Munafò[1,3,4]

Outcome *p*-value threshold	*n*	OR	95% CI	*p*
Ever e-cigarette use by age 24	2,894			
5×10^{-8}		1.24	1.14, 1.34	<0.001
0.0005		1.27	1.17, 1.38	<0.001
0.005		1.36	1.26, 1.48	<0.001
0.05		1.39	1.28, 1.51	<0.001
0.5		1.39	1.28, 1.51	<0.001

Shared genetic liability

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0.05		1.39	1.28, 1.51	<0.001
0.5		1.39	1.28, 1.51	<0.001

Shared genetic liability

Outcome *p*-value threshold	*n*	OR	95% CI	*p*
11 or more sexual partners by age 23*	2,505			
5×10^{-8}		1.15	1.05, 1.26	0.003
0.0005		1.12	1.02, 1.23	0.019
0.005		1.18	1.08, 1.29	<0.001
0.05		1.25	1.14, 1.37	<0.001
0.5		1.30	1.19, 1.43	<0.001
Been in trouble with the law since 23rd birthday	2,928			
5×10^{-8}		1.00	0.79, 1.28	0.988
0.0005		1.12	0.88, 1.43	0.352
0.005		1.11	0.87, 1.41	0.407
0.05		1.04	0.82, 1.33	0.745
0.5		0.90	0.71, 1.15	0.394
Enjoys taking risks at age 24	2,932			
5×10^{-8}		1.06	0.98, 1.14	0.154
0.0005		1.05	0.98, 1.14	0.163
0.005		1.11	1.03, 1.19	0.005
0.05		1.09	1.01, 1.17	0.029
0.5		1.08	1.01, 1.16	0.033

Shared genetic liability

Outcome *p*-value threshold	*n*	OR	95% CI	*p*
Hyperactivity at age 7	5,227			
5×10^{-8}		1.02	0.96, 1.08	0.511
0.0005		1.10	1.04, 1.16	0.001
0.005		1.14	1.08, 1.20	<0.001
0.05		1.14	1.08, 1.21	<0.001
0.5		1.15	1.08, 1.21	<0.001
Conduct disorder at age 7	5,334			
5×10^{-8}		1.10	1.03, 1.17	0.004
0.0005		1.11	1.04, 1.19	0.001
0.005		1.11	1.04, 1.18	0.002
0.05		1.08	1.01, 1.15	0.021
0.5		1.08	1.01, 1.15	0.017
Oppositional defiant disorder at age 7	5,325			
5×10^{-8}		1.02	0.96, 1.08	0.496
0.0005		1.08	1.02, 1.14	0.013
0.005		1.04	0.98, 1.10	0.200
0.05		1.04	0.98, 1.10	0.173
0.5		1.02	0.96, 1.08	0.529

Conclusions

- Mendelian randomization is an increasingly popular and effective tool for causal inference
- Our results suggest that smoking may play a causal role in subsequent cannabis use, and potentially dependence
- Potential pleiotropic effects of “smoking initiation” SNPs suggest a need for triangulation of evidence

Questions?