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CANCER RESEARCH UK

UKRI MRC Integrative Epidemiology Unit

DISENTANGLING THE HEALTH EFFECTS OF NICOTINE AND NON-NICOTINE COMPONENTS OF TOBACCO SMOKE

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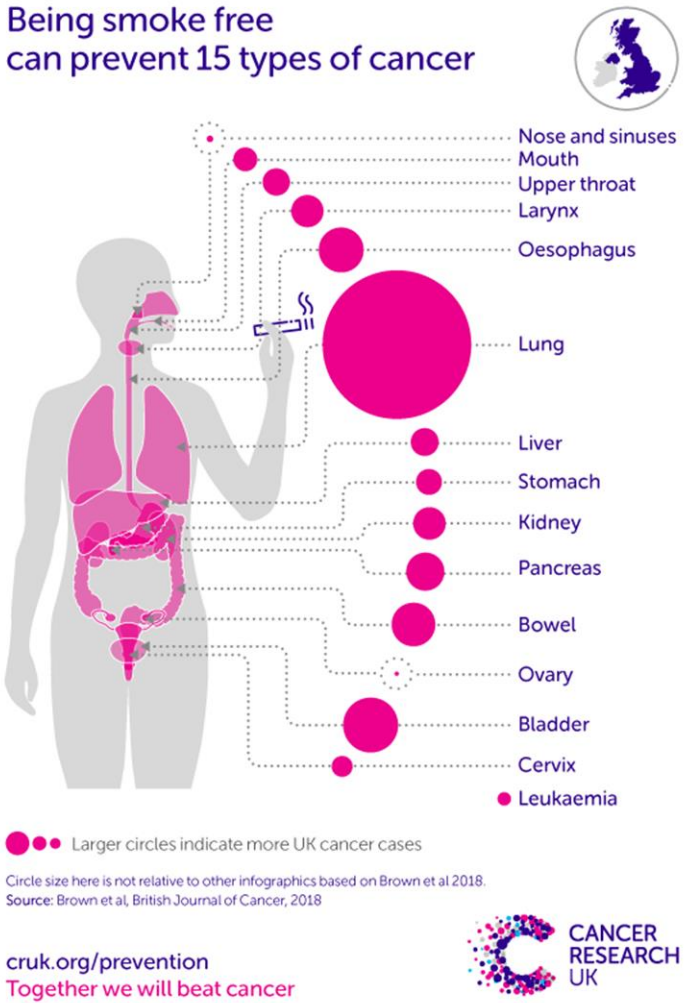
Disclosures

- This work is supported by:
  - The Medical Research Council (MRC) Integrative Epidemiology Unit at the University of Bristol
  - The Norwegian South-Eastern Regional Health Authority
  - Cancer Research UK
  - The European Research Council Advanced Grant (ART-Health)
  - The National Institute for Health Research (NIHR) Biomedical Research Centre at University Hospitals Bristol NHS Foundation Trust and the University of Bristol
- I have never received tobacco-related funding
- There are no financial repercussions in publishing the opposite findings

- All data and code are available on github: jkhouj/MVMRNicotine
  - v1.0.1: https://doi.org/10.5281/zenodo.10469666

Background

- Commercial tobacco smoking causes cancer and poor health
- What role does nicotine play?
  - IARC does not classify nicotine itself as carcinogenic unlike tobacco smoke
  - Nicotine may cause aggravation and recurrence of cancer (Sanner and Grimsrud, 2015)
  - Nicotine harms (impaired learning / affect) may be restricted to adolescent use (Holliday & Gould, 2016)
  - Nicotine use is *associated* with cardiovascular and respiratory outcomes (Mishra et al., 2015)



Background

- Nicotine use without tobacco (e.g., vapes) has become increasingly popular
- UK government's vaping excise duty proposed a tiered rate based on nicotine content
- This could send the message that nicotine itself is harmful in higher doses

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Table 3.A Proposed vaping duty tier structure

Tier	Rate structure	Comparisons to cigarettes
1	£1.00 per 10ml for nicotine-free liquids.	This is roughly 2.4% of the current total duty on the equivalent quantity of a typical cigarette.
2	£2.00 per 10ml on liquids that contain approximately the same or less nicotine (per ml) than in an average cigarette (0.1-10.9 mg).	This is roughly 4.7% of the current total duty on the equivalent quantity of a typical cigarette.
3	£3.00 per 10ml on liquids that contain roughly more nicotine per ml than in an average cigarette (11mg or more).	This is roughly 7.1% of the current total duty on the equivalent quantity of a typical cigarette. The maximum legal strength is 20mg/ml, however there is evidence that a significant number of illegal products above this limit are being sold.

Source: HMT/HMRC

Background

Smoking

Vaping

Mental / Physical Health

- It is increasingly important to understand the impact of nicotine use:
  - Does nicotine cause cancer?
  - Does nicotine impact lung and heart health?
  - Does nicotine impact cancer survival?
  - Does nicotine impact sleep and mental health?

Background

- Previous research has focused on:
  - Animal research
  - People who smoke / use tobacco
- Difficult to explore due to:
  - Limited longitudinal evidence
  - Ethical issues and practicality of conducting a randomized controlled trial

Aim

To explore the **direct effect** of **nicotine** compared with the **non-nicotine** constituents of tobacco smoke (using genetic proxies for nicotine and for cigarettes smoked per day) on smoking-related health outcomes:

Lung cancer

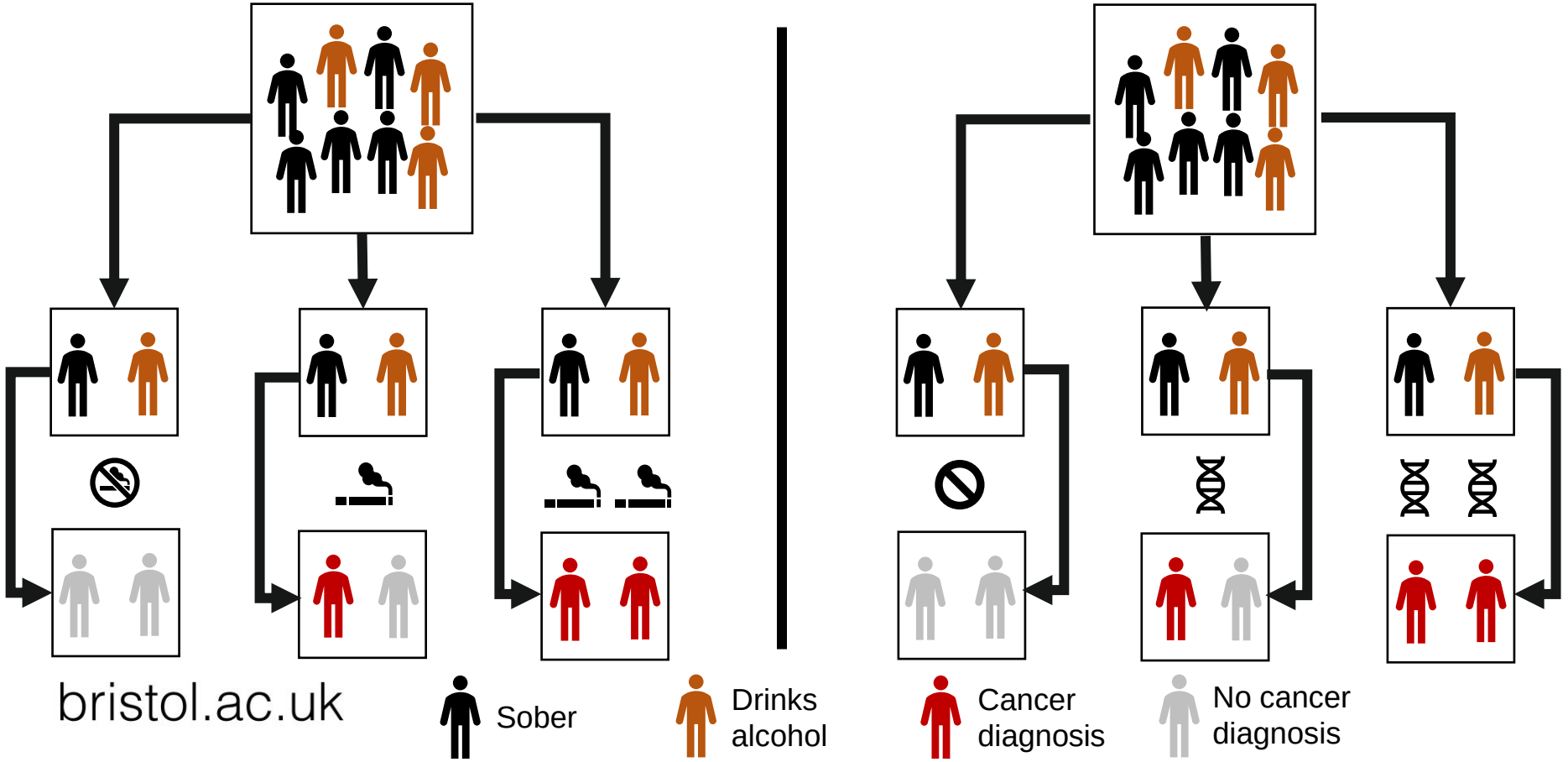
Chronic obstructive pulmonary disease

Lung function (FEV1 and FVC)

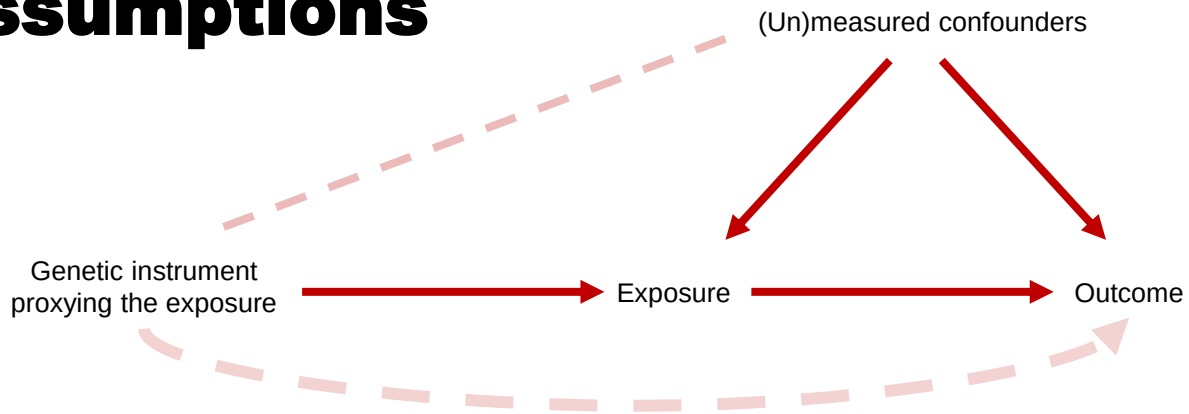
Coronary heart disease

Heart rate

RCT versus Mendelian randomization (MR)

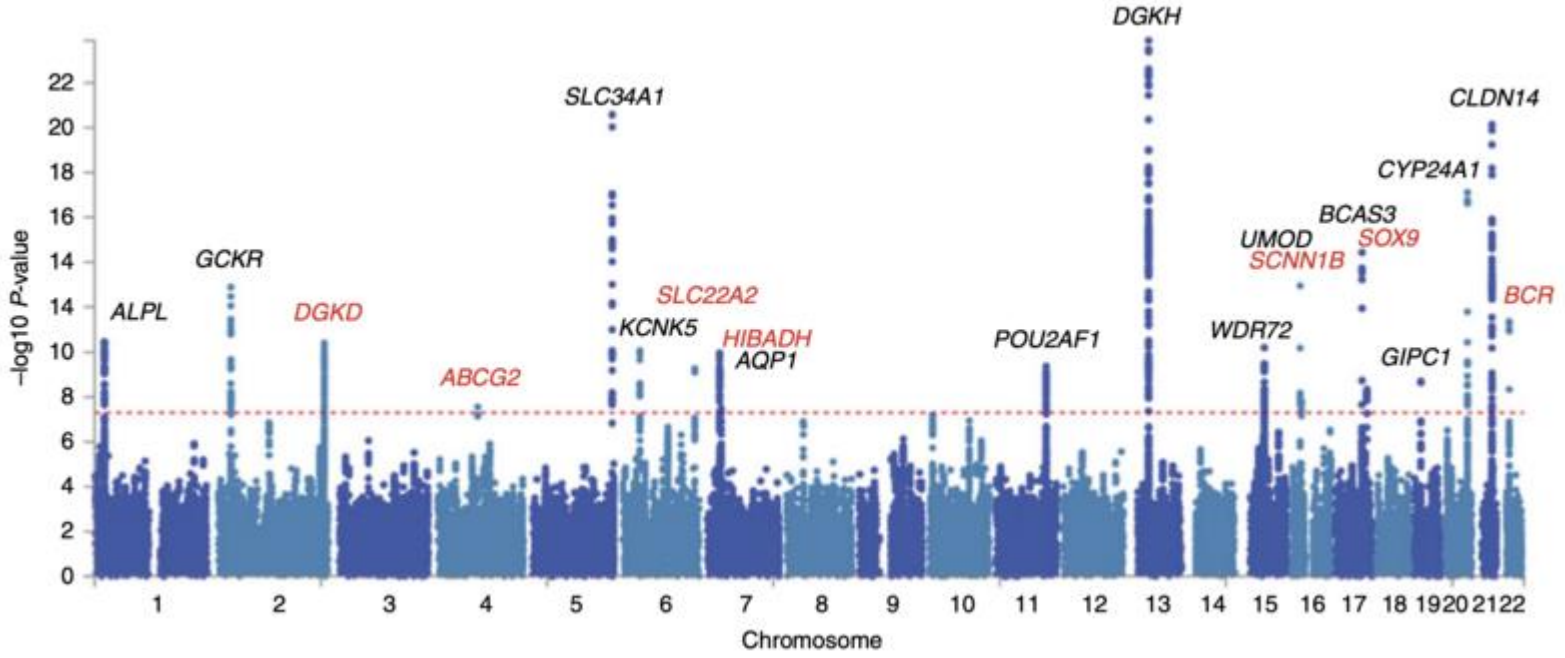


MR assumptions



1. The instrument (genetic variants) is associated with the exposure (relevance assumption)
2. There is no unmeasured (i.e., unaccounted for) confounding between the instrument and the outcome (independence assumption)
3. The association of the instrument and the outcome is entirely via the exposure (exclusion restriction assumption).

Identify genetic variants in GWAS



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Independence

- Population stratification or structure
  - Use homogenous groups e.g., European ancestry
- Intergenerational (dynastic) effects
- Assortative mating
- If independence is a potential issue, can use methods like multivariable MR

Pleiotropy robust methods

- Many methods have been developed to try account for pleiotropy e.g.,:
  - MR-Egger
  - Weighted Median
  - Weighted Mode
- These methods often lack power vs. traditional inverse variance weighted method (IVW)
- Triangulation
- Consistency in the direction of the effect across methods aids interpretation

Pause

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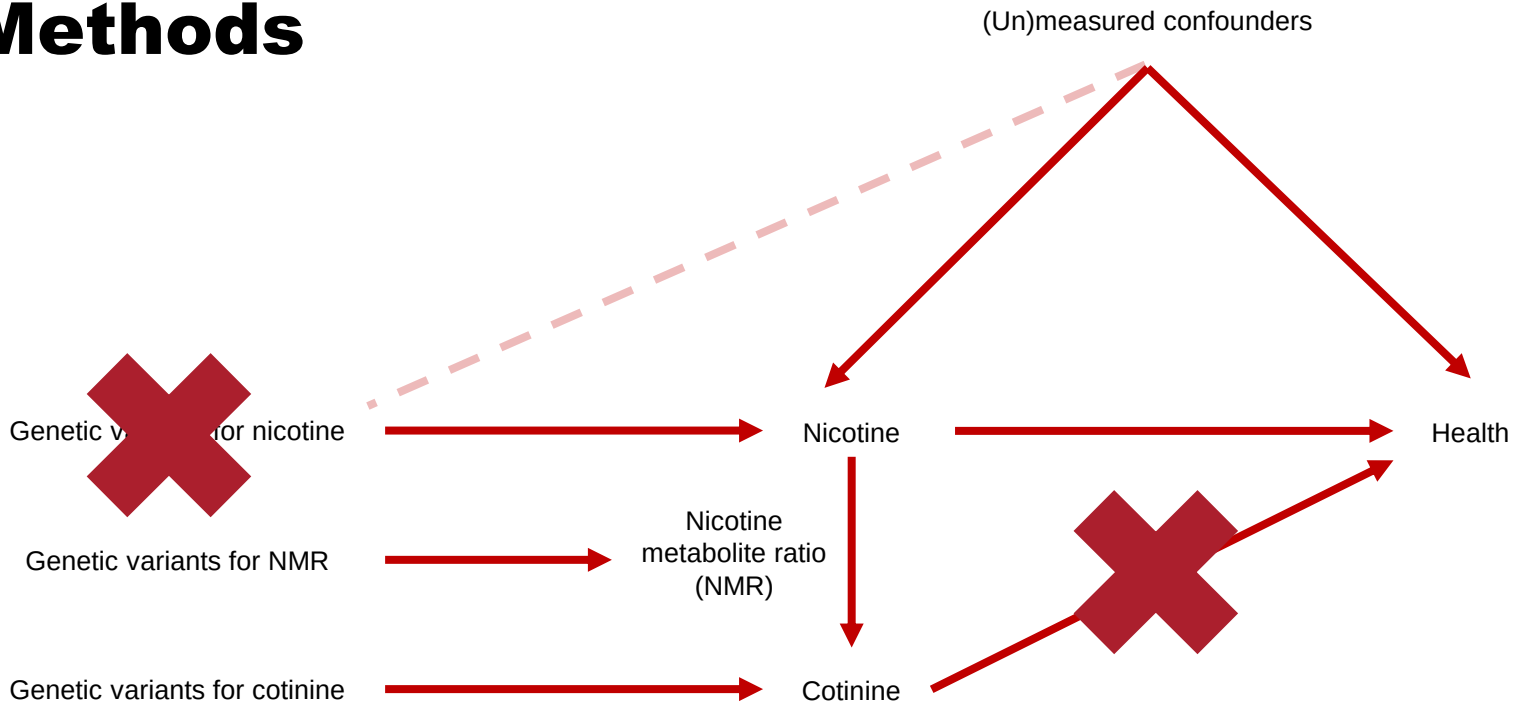
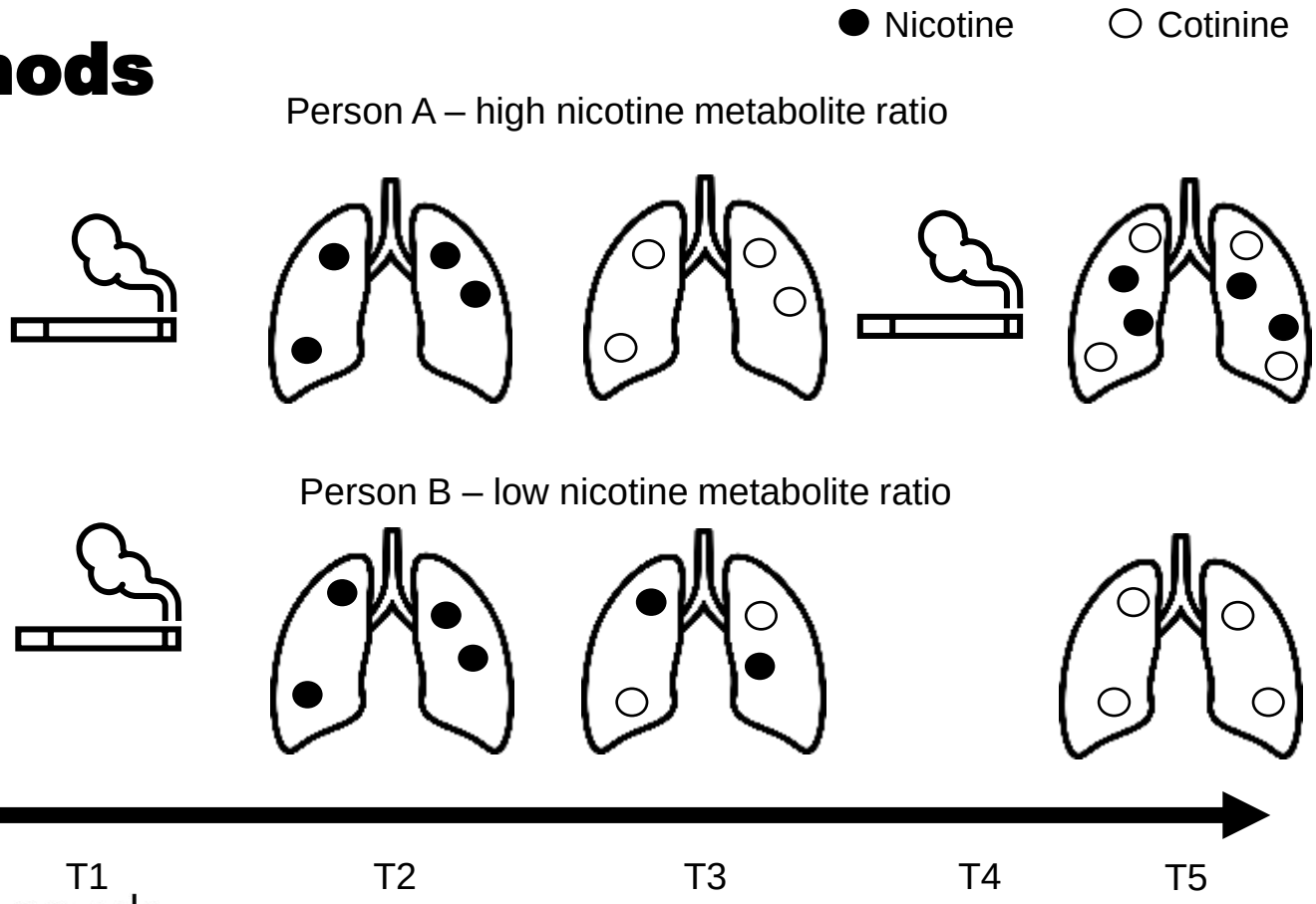
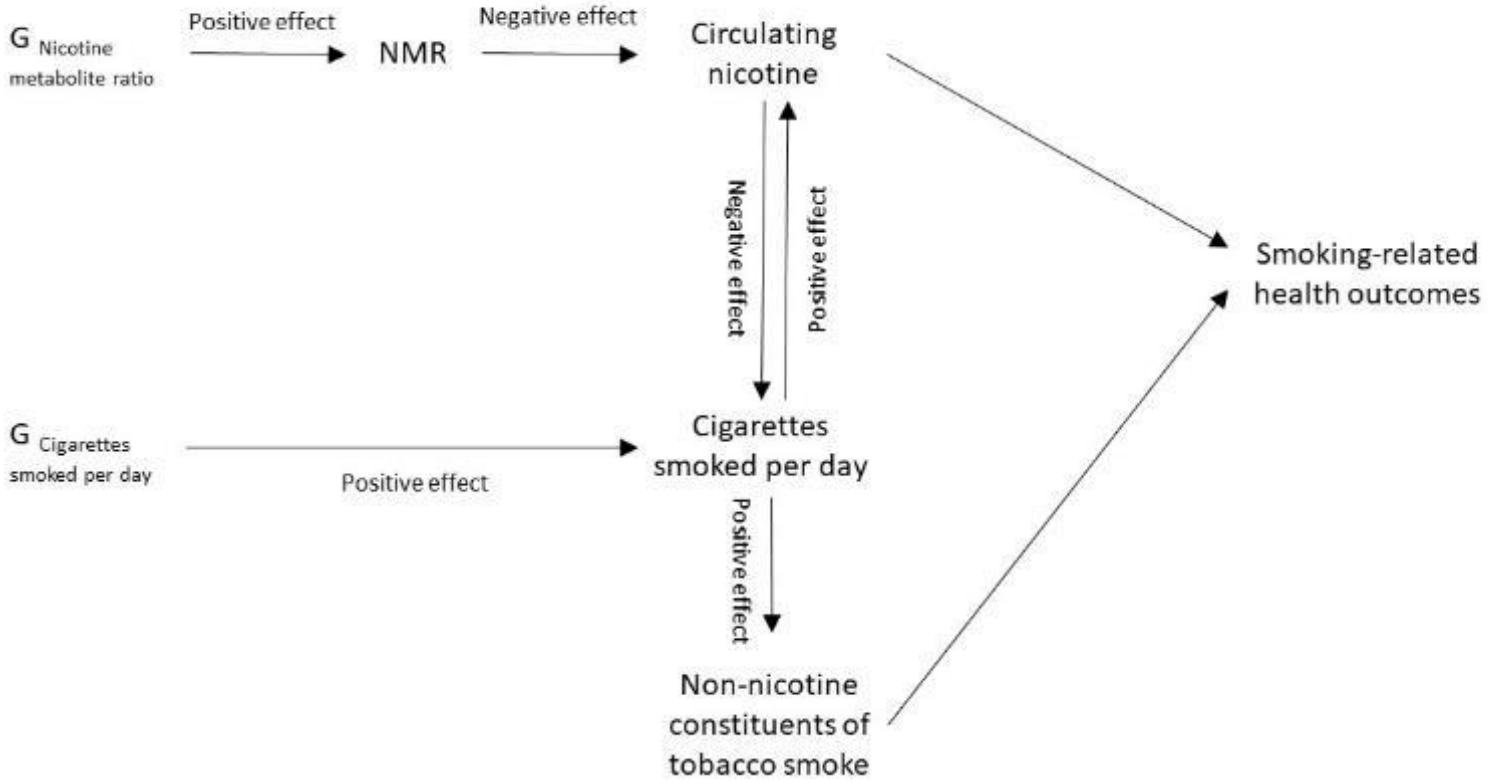
Methods


(Un)measured confounders
Genetic v or nicotine
Nicotine
Health
Genetic variants for NMR
Nicotine metabolite ratio (NMR)
Genetic variants for cotinine
Cotinine

Methods


Nicotine
Cotinine
Person A – high nicotine metabolite ratio
Person B – low nicotine metabolite ratio
T1
T2
T3
T4
T5

Methods


G Nicotine metabolite ratio
Positive effect
NMR
Negative effect
Circulating nicotine
Negative effect
Positive effect
Smoking-related health outcomes
G Cigarettes smoked per day
Positive effect
Cigarettes smoked per day
Positive effect
Non-nicotine constituents of tobacco smoke

Methods

- Multivariable Mendelian randomisation (MVMR)

- Summary-level genome-wide association data

- Exposures:
  - GSCAN (Liu et al., 2019)
    - Cigarettes per day (CPD)
  - Buchwald et al. (2020)
    - NMR

Int J Epidemiol. 2019 Jun 1;48(3):713-727. doi: 10.1093/ije/dyy262.

An examination of multivariable Mendelian randomization in the single-sample and two-sample summary data settings

Eleanor Sanderson [1 2], George Davey Smith [1 2], Frank Windmeijer [1 3], Jack Bowden [1 2]

Methods

– UK Biobank (ever, current, former, never)
  - Forced vital capacity (FVC)
  - Forced expiratory volume in 1 second (FEV-1)
  - Chronic obstructive pulmonary disease (COPD)
  - Coronary heart disease (CHD)
  - Heart rate (HR)
– International Lung Cancer COnsortium – ILCCO (ever, never)
  - Lung cancer

Why stratify by smoking status?

- Genetic variants identified in ever/current smokers
- Binary diagnoses explored in ever smokers (as people may quit)
- Acute outcomes only measurable in current smokers
- Former smokers can help to explore recoverable effects
- Never smokers can help us determine if there is something wrong with the model

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Results

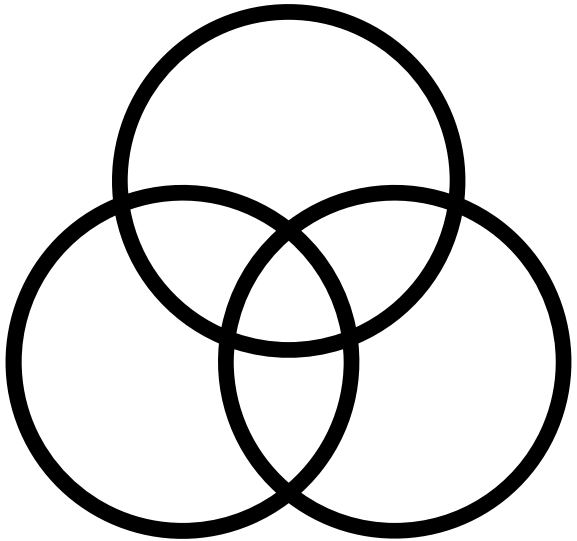
	Ever smokers	Current Smokers	Former Smokers	Never Smokers
	International Lung Cancer Consortium			
N	40,187	N/A	N/A	9,859
Lung Cancer (case rate)	57%	N/A	N/A	24%
	UK Biobank			
N	213,341	49,721	163,620	258,056
Coronary Heart Disease (case rate)	11%	11%	11%	6%
Chronic Obstructive Pulmonary Disease (case rate)	3%	6%	2%	<1%
Forced Expiratory Volume (mean litres [SD])	2.82 (0.78)	2.78 (0.83)	2.83 (0.76)	2.88 (0.78)
Forced Vital Capacity (mean litres [SD])	3.78 (0.97)	3.81 (1.02)	3.78 (0.96)	3.78 (0.99)
Heart Rate (mean beats per minute [SD])	69.05 (11.38)	71.27 (11.58)	68.40 (11.23)	68.93 (11.10)

Note: SD = standard deviation

https://doi.org/10.1371/journal.pgen.1011157.t001

Results

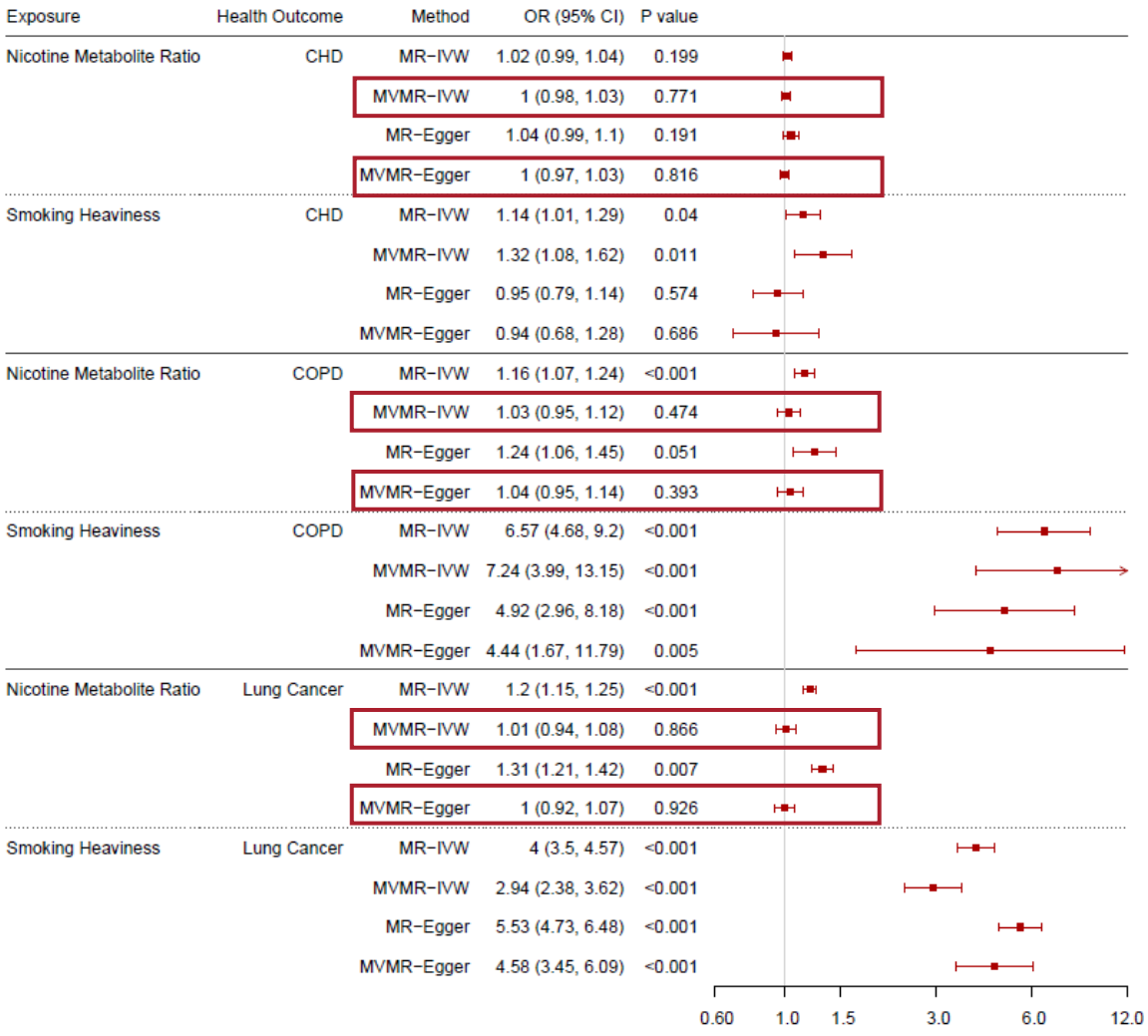
- Strong instrument = conditional F-stat >10
  - NMR = 30.17 to 49.08
  - CPD = 33.96 to 34.17
- Interpreting the results
  - Higher NMR = lower nicotine exposure
  - In the MVMR results, flip the estimate
  - E.g. OR 1.2 indicates decreased risk of the outcome with increased nicotine exposure



Results

Findings:

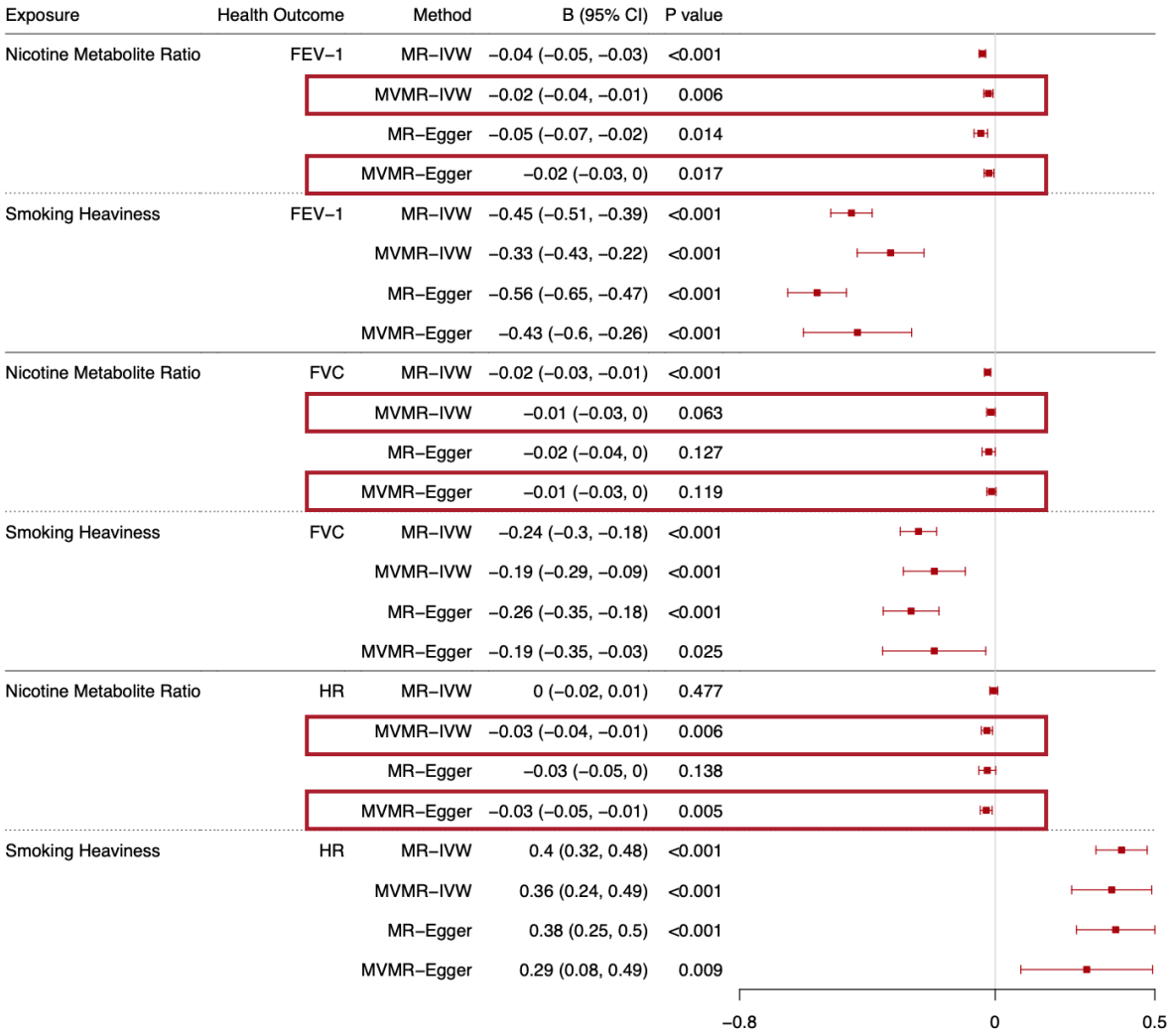
- Binary outcomes among ever smokers
- Nicotine exposure does not appear to cause CHD, COPD or lung cancer
- Lung cancer = negative control



Results

Findings:

- Continuous outcomes among current smokers
- Nicotine exposure does not appear to cause poor lung function
- Nicotine does appear to cause increased HR



Sensitivity results – never smokers

- Some effects found among never smokers in the smoking heaviness analyses
- No effects found among never smokers in the NMR analyses
- No evidence of issues with pleiotropy or population stratification for NMR

Former smokers

- The findings suggest that there are likely lasting detrimental effects of smoking
- These are unlikely to be attributable to nicotine exposure
- Effects seen in the univariable MR attenuate to the null in the multivariable MR when we account for smoking heaviness

Bonus results

Disentangling the effects of nicotine versus non-nicotine constituents of tobacco smoke on major depressive disorder:A multivariable Mendelian randomization study

Chloe Burke, Gemma Taylor, Tom P Freeman, Hannah Sallis, Robyn E Wootton, Marcus R Munafò, Christina Dardani, Jasmine Khouja

doi: https://doi.org/10.1101/2024.06.25.24309292

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Bonus results

- Major depressive disorder (MDD) in UK Biobank
- Weak evidence to suggest nicotine could increase risk of MDD
- More clear effect of the other constituents of tobacco smoke

Bonus results

Greater nicotine exposure per cigarette:

- Chronotype
  - More likely to be an evening person
- Getting up
  - Find it harder to get up in the morning
- Napping
  - Less likely to nap
- Narcolepsy
  - Less likely to have narcolepsy
- Sleep duration
  - More likely to sleep for longer

Interpretation

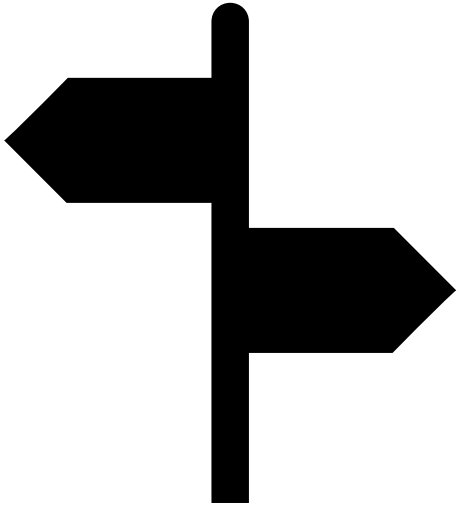
- Nicotine may be helpful to stay awake
- Aligns with nicotine being a stimulant
- BUT is nicotine good for sleep quality?
- Impact of nicotine or impact of withdrawal?

Discussion - Limitations

- Interpretation of effects of nicotine can be difficult where withdrawal may have an impact
- Collider bias due to stratification
- Potential pleiotropy / issues due to population stratification
- Unable to use non-European ancestry data
- Adjustment for BMI in NMR GWAS – impact analyses where BMI is a plausible covariate

Discussion – Future work

- Psychotic experiences
- Cognitive outcomes
- Open to collaborations
- BUT need to have outcome data stratified by smoking status



If you're interested in learning MR

- Bristol short courses:
- Mendelian Randomisation
- Advanced Mendelian Randomisation
- And more…

https://www.bristol.ac.uk/medical-school/study/short-courses/

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THANKS FOR LISTENING

Thanks to my collaborators and the students working on these projects

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