School of Medicine
University of Dundee

Using epidemiology to quantify the applicability of trial evidence to inform guideline development

Dr Daniel Morales

Disclosures

I am funded by the Wellcome Trust.

I am a member of the EMA Pharmacovigilance Risk Assessment Committee.

The views are my own and not of any organization or committee I am affiliated with.

A known issue

- There are good reasons for exclusion
  - Optimize power
  - Constraints on trial recruitment
  - Constraints on trial duration
- Many reasons for exclusion
  - Disease severity, age and comorbidity, prescribing
- Exclusions are not always justified

Eligibility Criteria of Randomized Controlled Trials Published in High-Impact General Medical Journals

A Systematic Sampling Review

Harriette G. C. Van Spall, MD
Andrew Toren, MD
Alex Kiss, PhD
Robert A. Fowler, MD, MS

Context Selective eligibility criteria of randomized controlled trials (RCTs) are vital to trial feasibility and internal validity. However, the exclusion of certain patient populations may lead to impaired generalizability of results.

Objective To determine the nature and extent of exclusion criteria among RCTs published in major medical journals and the contribution of exclusion criteria to the representation of certain patient populations.

Data Sources and Study Selection The MEDLINE database was searched for RCTs published between 1994 and 2006 in certain general medical journals with a high impact factor. Of 4827 articles, 283 were selected using a series technique.

Data Extraction Trial characteristics and the details regarding exclusions were extracted independently. All exclusion criteria were graded independently and in duplicate as either strongly justified, potentially justified, or poorly justified according to previously developed and pilot-tested guidelines.

Data Synthesis Common medical conditions formed the basis for exclusion in 81.3% of trials. Patients were excluded due to age in 72.1% of all trials (60.1% in pediatric populations and 38.5% in older adults). Individuals receiving commonly prescribed medications were excluded in 54.1% of trials. Conditions related to female sex were grounds for exclusion in 39.2% of trials. Of all exclusion criteria, only 47.2% were graded as strongly

RANDOMIZED CONTROLLED trials (RCTs) are generally accepted as the most unbiased measures of efficacy for new interventions, drugs, or devices.[1] Results of well-conducted RCTs provide clinicians and health policy makers with the best evidence for adoption or rejection of new therapies.[2] The findings of RCTs published in major medical journals effect change in medical practice.[3] Much attention is paid to the internal validity of clinical trials.[4] How

Table 3. Justification of Exclusion Criteria

	No. (%) of Trials*
Grading of individual exclusion criteria	
Total number of exclusions	2709 (100.0)
Strongly justified	1275 (47.2)
Potentially justified	430 (15.9)
Poorly justified	1004 (37.1)
At least 1 poorly justified exclusion criterion	238 (84.1)
Category with poor justification	
Age	160 (78.4)
Medical comorbidity	149 (64.8)
Sex	70 (52.6)
Females	69 (62.2)
Males	1 (4.5)
Medication-related	56 (36.6)
Socioeconomic status	31 (79.5)
Percentage of poorly justified exclusion criteria	
≥10	228 (80.6)
≥25	174 (61.5)
≥50	83 (29.3)
≥75	24 (8.5)
Exclusions per trial, mean (SD)	9.5 (6.1)

*Unless otherwise indicated.

- Strongly justified in **only 47%** of RCTs
- Comorbidity (81%), age (72%), co-prescribing (54%) of exclusions

2709 exclusions

How many people are excluded?

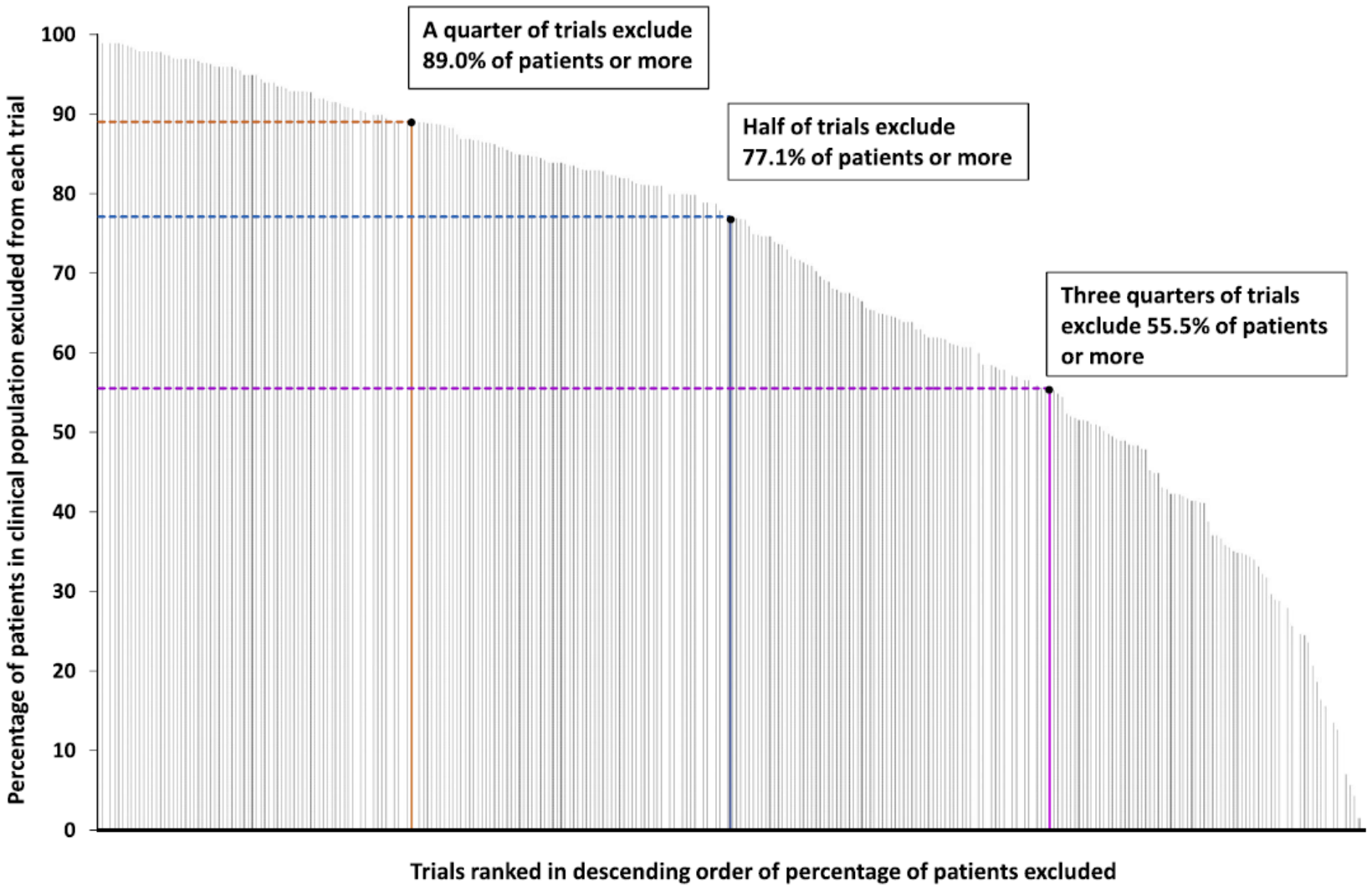
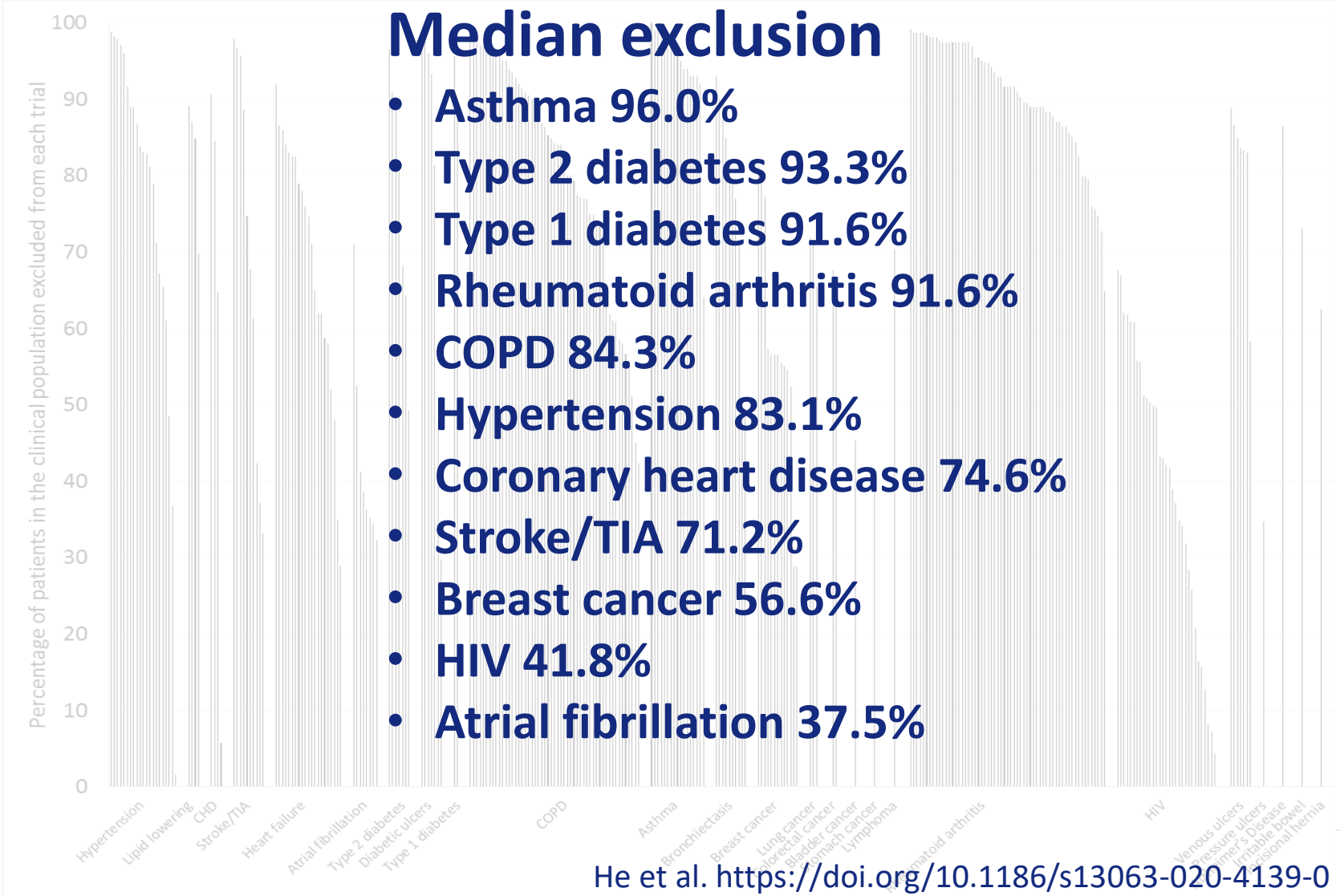


Fig. 2 Trials ranked in descending order of the percentage excluded in the clinical population studied

He et al. https://doi.org/10.1186/s13063-020-4139-0

How many people are excluded?



Median exclusion

- **Asthma 96.0%**
- **Type 2 diabetes 93.3%**
- **Type 1 diabetes 91.6%**
- **Rheumatoid arthritis 91.6%**
- **COPD 84.3%**
- **Hypertension 83.1%**
- **Coronary heart disease 74.6%**
- **Stroke/TIA 71.2%**
- **Breast cancer 56.6%**
- **HIV 41.8%**
- **Atrial fibrillation 37.5%**

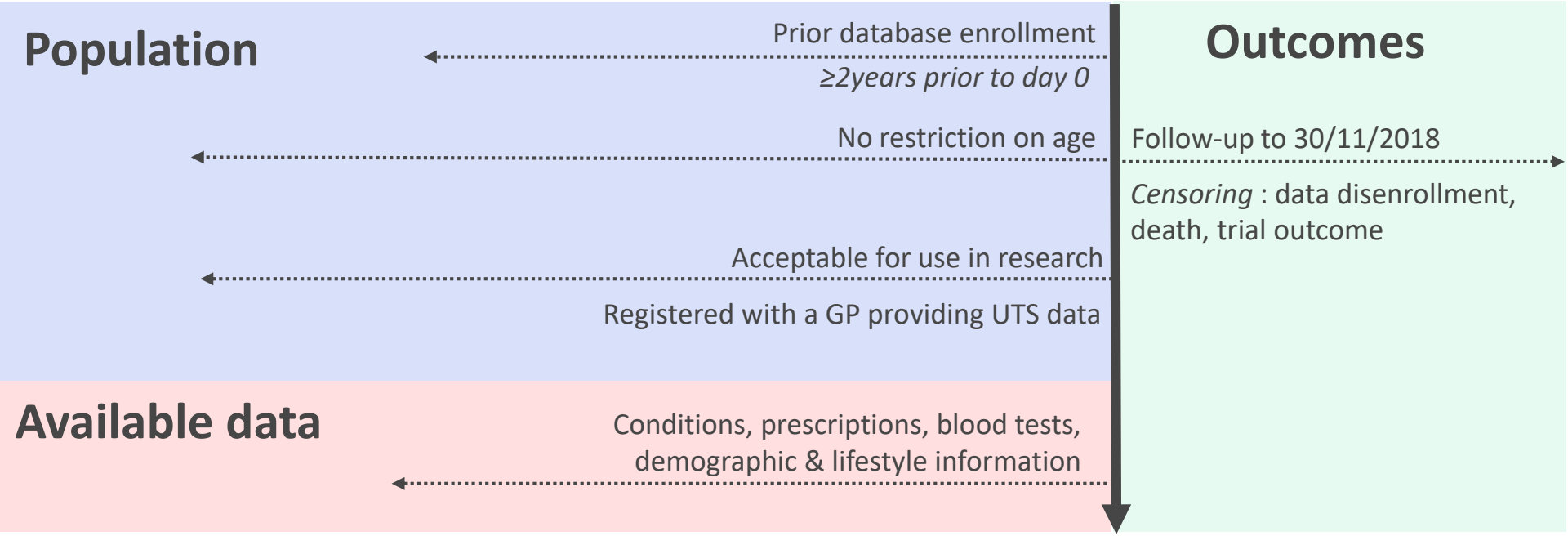
He et al. https://doi.org/10.1186/s13063-020-4139-0

Project

Large scale comparison of trial eligible vs trial ineligible populations

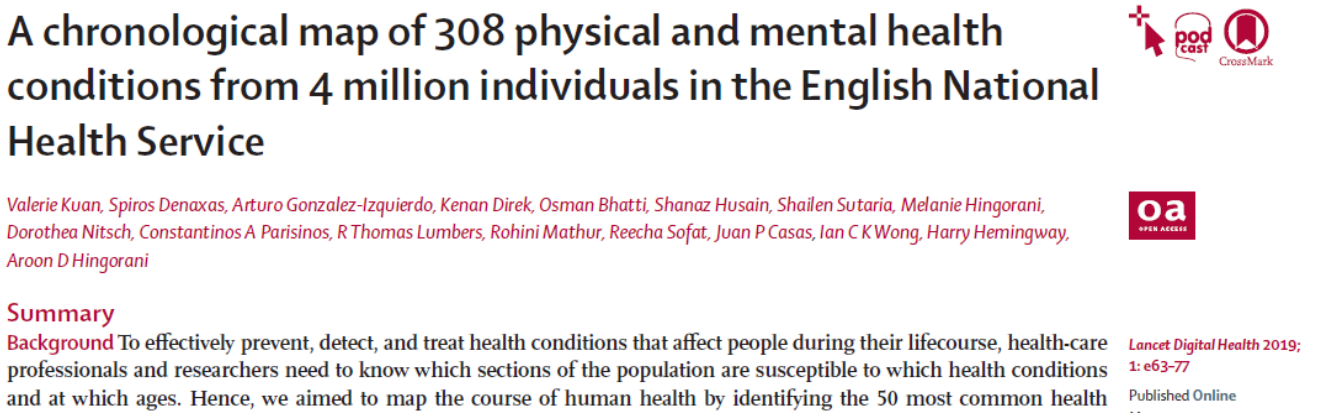
Tool built on top of data from CPRD linked to hospital / mortality data

Inform guideline development



1,169,451 patients at 30/11/2015

Phenotypes



A chronological map of 308 physical and mental health conditions from 4 million individuals in the English National Health Service

Valerie Kuan, Spiros Denaxas, Arturo Gonzalez-Izquierdo, Kenan Direk, Osman Bhatti, Shanaz Husain, Shailen Sutaria, Melanie Hingorani, Dorothea Nitsch, Constantinos A Parisinos, R Thomas Lumbers, Rohini Mathur, Reecha Sofat, Juan P Casas, Ian C K Wong, Harry Hemingway, Aroon D Hingorani

Summary

Background To effectively prevent, detect, and treat health conditions that affect people during their lifecourse, health-care professionals and researchers need to know which sections of the population are susceptible to which health conditions and at which ages. Hence, we aimed to map the course of human health by identifying the 50 most common health

Lancet Digital Health 2019; 1: e63–77

Published Online

308 physical and mental health conditions that involve intensive use of health-care resources selected from:

- CPRD GOLD Read codes
- inpatient consultant episodes ICD-10 & OPSC-4 codes
- blood test values

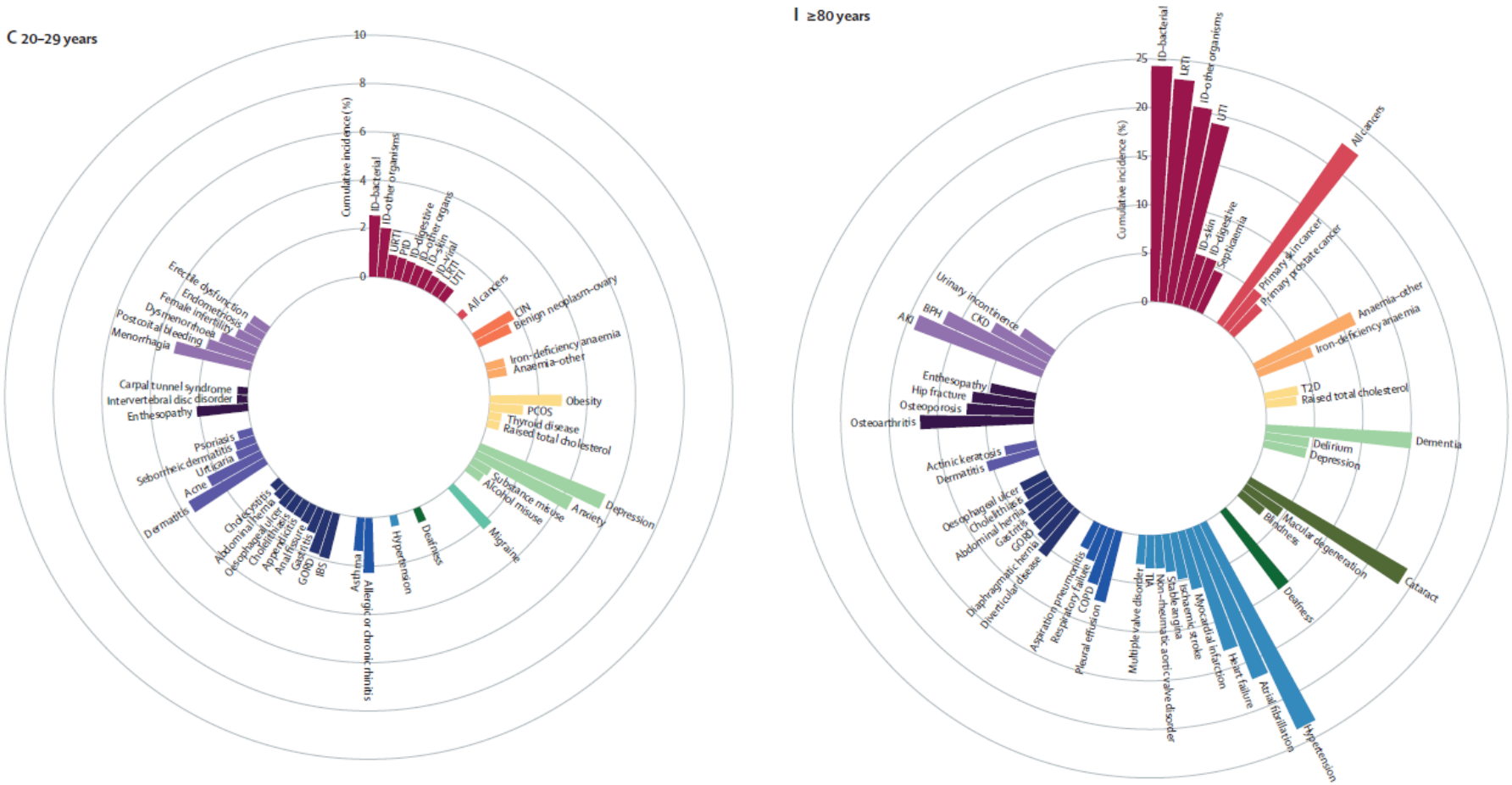
Included conditions with codes had either:

-more than 10 000 finished consultant episodes

-prevalence was greater than 0·01% and considered clinically important

https://www.caliberresearch.org/portal/phenotypes

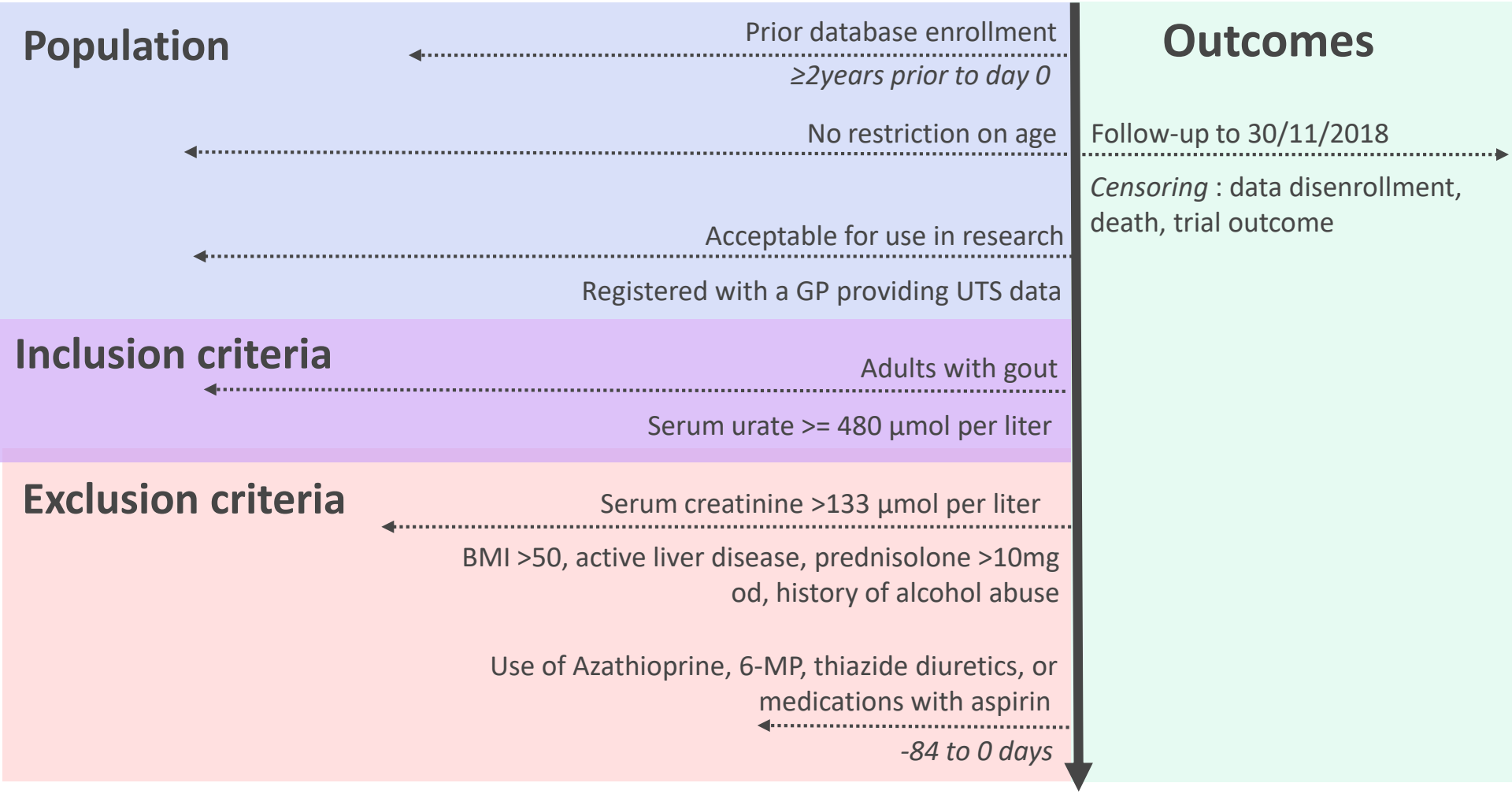
Sex-standardised cumulative incidence (%) of the top 50 diseases for individuals aged 20-29 years (left) and >=80 years (right)



Kuan et al. Lancet Digital Health 2019;1: e63–77

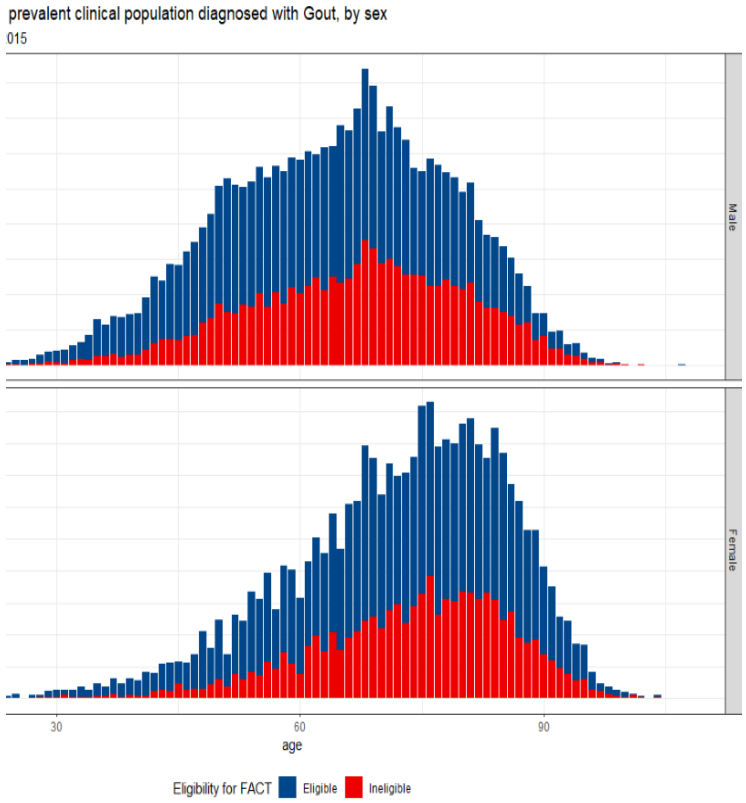
Febuxostat versus Allopurinol Controlled Trial (FACT)

RCT randomising 762 people with gout to receive febuxostat 80mg, febuxostat 120mg or allopurinol 300mg



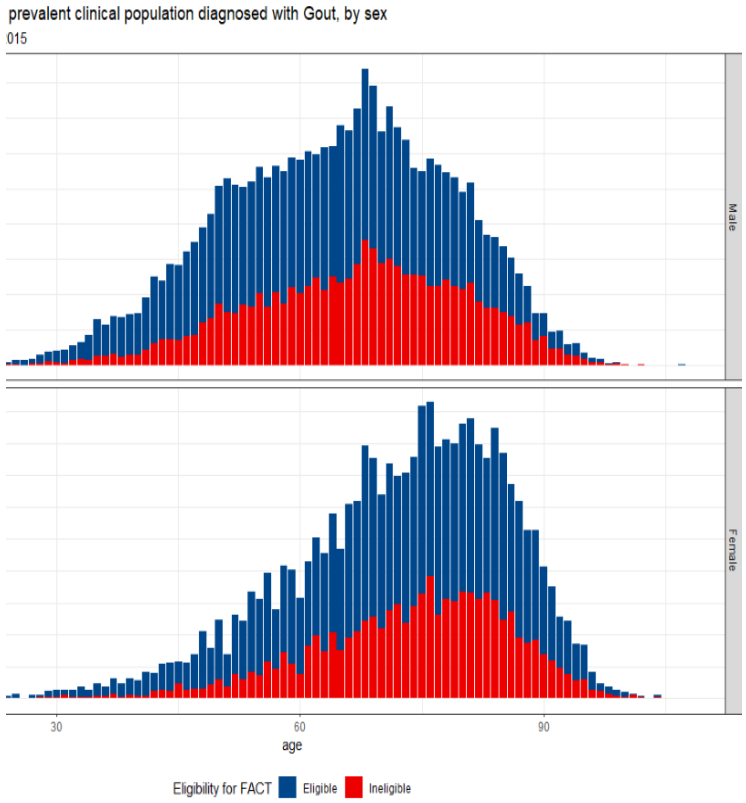
32,844 gout patients at 30/11/2015

Characteristics of FACT eligible vs ineligible gout patients



	Eligible		Ineligible	
	n	%	n	%
Prevalent clinical population (n=32,844)				
Alcohol Problems	1086	5.2	2329	19.4
Barrett's oesophagus	242	1.2	188	1.6
Cerebrovascular disease	1440	6.9	1126	9.4
CKD - all	3734	17.9	4179	34.7
CKD_Stage_3a	3141	15.1	1459	12.1
CKD_Stage_3b	585	2.8	1785	14.8
CKD_Stage_4	2	0.0	771	6.4
CKD_Stage_5	6	0.0	164	1.4
Coronary heart disease	3119	15.0	2446	20.3
Diabetes	3550	17.1	2886	24.0
Gastritis and duodenitis	1550	7.4	1174	9.8
Heart failure	981	4.7	965	8.0
Hypertension	9886	47.5	8163	67.8
Liver disease		0.0	648	5.4
Oesophagitis and oesophageal ulcer	1813	8.7	1318	11.0
Peptic ulcer disease	807	3.9	744	6.2
Peripheral arterial disease	633	3.0	663	5.5
None of the Above	6789	32.6	1323	11.0

Characteristics of FACT eligible vs ineligible gout patients



	Eligible		Ineligible	
	n	%	n	%
Prevalent clinical population (n=32,844)				
Alcohol Problems	1086	5.2	2329	19.4
Barrett's oesophagus	242	1.2	188	1.6
Cerebrovascular disease	1440	6.9	1126	9.4
CKD - all	3734	17.9	4179	34.7
CKD_Stage_3a	3141	15.1	1459	12.1
CKD_Stage_3b	585	2.8	1785	14.8
CKD_Stage_4	2	0.0	771	6.4
CKD_Stage_5	6	0.0	164	1.4
Coronary heart disease	3119	15.0	2446	20.3
Diabetes	3550	17.1	2886	24.0
Gastritis and duodenitis	1550	7.4	1174	9.8
Heart failure	981	4.7	965	8.0
Hypertension	9886	47.5	8163	67.8
Liver disease		0.0	648	5.4
Oesophagitis and oesophageal ulcer	1813	8.7	1318	11.0
Peptic ulcer disease	807	3.9	744	6.2
Peripheral arterial disease	633	3.0	663	5.5
None of the Above	6789	32.6	1323	11.0

Future work

- Build phenotypes specific to certain trial criteria that could be added to the portal
- Implement further phenotypes as they become available
- Phenotype development requires a community approach to maintain
- Feed into guideline development

Acknowledgements

Megan McMinn

Bruce Guthrie

Emily Jefferson

Shahzad Mumtaz

Chris Hall

Magalie Guignard-Duff