Comparing clinical trial population representativeness to real-world populations: an external validity analysis encompassing 43 895 trials and 5 685 738 individuals across 989 unique drugs and 286 conditions in England

Yen Yi Tan, Vaclav Papez, Wai Hoong Chang, Stefanie H Mueller, Spiros Denaxas, Alvina G Lai

Summary

Background Randomised controlled trials (RCTs) inform prescription guidelines, but stringent eligibility criteria exclude individuals with vulnerable characteristics, which we define as comorbidities, concomitant medication use, and vulnerabilities due to age. Poor external validity can result in inadequate treatment decision information. Our first aim was to quantify the extent of exclusion of individuals with vulnerable characteristics from RCTs for all prescription drugs. Our second aim was to quantify the prevalence of individuals with vulnerable characteristics from population electronic health records who are actively prescribed such drugs. In tandem, these two aims will allow us to assess the representativeness between RCT and real-world populations and identify vulnerable populations potentially at risk of inadequate treatment decision information. When a vulnerable population is highly excluded from RCTs but has a high prevalence of individuals actively being prescribed the same medication, there is likely to be a gap in treatment decision information. Our third aim was to investigate the use of real-world evidence in contributing towards quantifying missing treatment risk or benefit through an observational study.

Methods We extracted RCTs from ClinicalTrials.gov from its inception to April 28, 2021, and primary care records from the Clinical Practice Research Datalink Gold database from Jan 1, 1998, to Dec 31, 2020. We referred to the British National Formulary to classify prescription drugs into drug categories. We conducted descriptive analyses and quantified RCT exclusion and prevalence of individuals with vulnerable characteristics for comparison to identify populations without treatment decision information. Exclusion and prevalence were assessed separately for different age groups, individual clinical specialities, and for quantities of concomitant conditions by clinical specialities, where multimorbidity was defined as having two or more clinical specialties, and medications prescribed, where polypharmacy was defined as having five or more medications prescribed. Population trends of individuals with multimorbidity or polypharmacy were assessed separately by age group. We conducted an observational cohort study to validate the use of real-world evidence in contributing towards quantifying treatment risk or benefit for patients with dementia on anti-dementia drugs with and without a contraindicated clinical speciality. To do so, we identified the clinical specialities that anti-dementia drug RCTs highly excluded yet had corresponding high prevalence in the real-world population, forming the groups with highest risk of having scarce treatment decision information. Cox regression was used to assess if the risk of mortality outcomes differs between both groups.

Findings 43 895 RCTs from ClinicalTrials.gov and 5 685 738 million individuals from primary care records were used. We considered 989 unique drugs and 286 conditions across 13 drug-category cohorts. For the descriptive analyses, the median RCT exclusion proportion across 13 drug categories was 81·5% (IQR 76·7–85·5) for adolescents (aged <18 years), 26·3% (IQR 21·0–29·5) for individuals older than 60 years, 40·5% (IQR 33·7–43·0) for individuals older than 70 years, and 52·9% (IQR 47·1–56·0) for individuals older than 80 years. Multimorbidity had a median exclusion proportion of 91·1% (IQR 88·9–91·8) and median prevalence of 41·0% (IQR 34·9–46·0). Concomitant medication use had a median exclusion proportion of 52·5% (IQR 50·0–53·7) and a median prevalence of 94·3% (IQR 84·3–97·2), and polypharmacy had a median prevalence of 47·7% (IQR 38·0–56·1). Population trends show increasing multimorbidity with age and consistently high polypharmacy across age groups. Populations with cardiovascular or otorhinolaryngological comorbidities had the highest risk of having scarce treatment decision information. For the observational study, populations with cardiovascular or psychiatric comorbidities had highest risk of having scarce treatment decision information. Patients with dementia with an anti-dementia prescription and contraindicated cardiovascular condition had a higher risk of mortality (hazard ratio [HR] 1·20 [95% CI 1·13–1·28 ; p<0·0001]) compared with patients with dementia without a contraindicated cardiovascular condition. Patients with dementia with comorbid delirium (HR 1·25 [95% CI 1·06–1·48]; p<0·0088), intellectual disability (HR 2·72 [95% CI 1·53–4·81]; p=0·0006), and schizophrenia and schizotypal delusional disorders (HR 1·36 [95% CI 1·02–1·82]; p=0·036) had a higher risk of mortality compared with patients with dementia without these conditions.

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Institute of Health Informatics, University College London, London, UK (Y Y Tan MRes, V Papez PhD, W H Chang MSc, S H Mueller PhD, Prof S Denaxas PhD, A G Lai PhD)

Correspondence to:
Mr Yen Yi Tan, Institute of Health Informatics, University College London, London NW1 2DA, UK
yen.tan.16@ucl.ac.uk

Interpretation Overly stringent RCT exclusion criteria do not appropriately account for the heterogeneity of vulnerable characteristics observed in real-world populations. Treatment decision information is scarce for such individuals, which might affect health outcomes. We discuss the challenges facing the inclusivity of such individuals and highlight the strength of real-world evidence as an integrative solution in complementing RCTs and increasing the completeness of evidence-based medicine assessments in evaluating the effectiveness of treatment decisions.

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Introduction

Clinical prescription guidelines and regulations are derived from evidence-based medicine, which uses gold standard research evidence to inform treatment decisions for patients.[1] Randomised controlled trials (RCTs) rank among the top tier of evidence-based medicine available with a study design that minimises bias and confounding in the evaluation of the effectiveness of an intervention for a health condition.[2,3]

However, many RCTs select for populations with a single disease using stringent eligibility criteria, excluding individuals who have increased risk of an adverse event to the drug due to perceived vulnerabilities, such as older individuals, adolescents, individuals with concomitant conditions, multimorbidity, concomitant medication use, and polypharmacy.[4–11]

The main consequence of this exclusion is the scarcity of available treatment decision information for excluded populations. In other words, the effectiveness in terms of the net risk or net benefit towards a patient's health outcome of prescribing a course of treatment is unknown. This unknown is amplified in the context of concomitant conditions and medications. For example, a patient with atrial fibrillation might wish to know how anticoagulant use might affect their liver cirrhosis, but because most patients with hepatic conditions are under-represented or excluded in cardiovascular RCTs, this information is scarce.[12] Similarly, treatment risk or benefit information is important to clinicians as a factor to consider when making clinical treatment decisions, which will affect a patient's health outcome, but this is also scarce. Furthermore, vulnerabilities tend to overlap, the prevalence of chronic conditions increases with age, and drugs are prescribed for each condition separately. Although best efforts are made to account for the cumulative and interactive effects between multiple medications and conditions, these effects can still be easily missed.[13] Multimorbidity and polypharmacy are becoming the norm rather than the exception, with an increase observed particularly in individuals younger than 65 years.[14–17] The exclusion of adolescent individuals also results in off-label prescribing, yielding similar adverse risks. While newer RCTs work towards better inclusivity of such individuals,[18,19] the real-world equivalent of excluded populations—who tend to be the sickest and who require treatment the most—continues to grow.

It is necessary to understand the extent to which RCTs exclude vulnerable populations to identify the extent of the gap in treatment knowledge. We define vulnerable populations as individuals with medically complex or unfavourable characteristics which might give rise to complications, such as comorbidities, concomitant medication use, and vulnerabilities due to age. Concurrently, it is essential to evaluate the prevalence of these at-risk individuals in the real-world population as they continue to be prescribed the drugs in question. In doing so, we can identify at-risk populations and begin to contribute towards addressing gaps in treatment decision information by leveraging real-world evidence generation, an alternate avenue of evidence-based medicine increasingly recognised by regulatory bodies as an extension of RCTs.[20–23]

There were three aims of this study. Firstly, we sought to quantify the extent of exclusion of individuals with vulnerable characteristics from 43 895 RCTs registered on ClinicalTrials.gov from 13 different drug categories comprising 989 unique drugs. Secondly, we aimed to quantify the prevalence of individuals with vulnerable characteristics from population-representative electronic health records (EHRs) who are actively prescribed such drugs. In tandem, these two aims allowed us to assess the difference in representation between RCT and real-world populations and identify vulnerable populations potentially at risk of inadequate treatment decision information. When a vulnerable population is highly excluded from RCTs but has a high prevalence of individuals actively being prescribed the same medication, there is likely to be a gap in treatment decision information. Thirdly, we aimed to investigate the validity of using real-world evidence through an observational cohort study on patients with dementia on anti-dementia drugs and its use in contributing towards quantifying missing treatment risk or benefit information in patients with highly excluded comorbidities, thereby improving availability of treatment decision information for vulnerable patients. Specifically, we aimed to identify clinical specialities that are often excluded from anti-dementia drug RCTs yet had corresponding high prevalence in the real-world population, forming the

Research in context

Evidence before this study

We searched PubMed, Google Scholar, and European PubMed Central from database inception to April 1, 2022, for external validity studies comparing randomised controlled trial (RCT) populations to real-world populations. Specifically, we used the following combination of keywords in our search criteria: "external validity", "clinical trials population", "real world population", "representativeness", and "exclusion criteria". The search was solely done in English and all publications considered were published in English. There were few studies that directly compared RCT populations derived from exclusion criteria to equivalent real-world populations. Most primary studies and meta-analyses have focused on examining the exclusion criteria for specific RCT niches (ie, RCTs of a single disease, a subset of diseases, a single drug, or a subset of drugs). While it was concluded that eligibility criteria were restrictive, there were no direct comparisons made as to the effect of such conclusions on actual patient populations. Studies examining a thorough range of physical and mental health conditions were not identified, with most studies limiting the number of comorbidities specified to ten or less. We did not identify any studies that considered all existing prescription drugs in the investigation and thus studies conducted systematically and to scale analysing all drug RCTs do not exist. Furthermore, we did not identify any studies that included methodology capable of systematically identifying populations with missing information in external validity and assessing the effect on outcomes of such missing information. Hence, there were no studies identified that quantified treatment risks to fill such gaps in treatment information. Very few studies demonstrate a population application for implementing real-world evidence to complement RCTs in evidence-based medicine.

Added value of this study

We present the largest scale external validity study comparing the representativeness of RCT populations derived from exclusion criteria to equivalent real-world populations. We systematically investigated 43 895 RCTs and 5·6 million electronic health records (EHR) pertaining to 989 prescription drugs and 286 clinically validated conditions. We quantify the exclusion proportion of vulnerable characteristics, which we define as comorbidities, concomitant medication use, and vulnerabilities due to age, across RCT groups and the prevalence of such characteristics in actual real-world populations actively prescribed these drugs. Detailed code lists for all conditions are available under open access. The use of nationwide EHRs with coverage of 15% of the UK population ensures that our data is representative of the general population and findings can be applied to similar demographics. We further present methodology to systematically identify populations at risk of having scarce treatment decision information due to poor external validity and demonstrate a scalable method for real-world evidence to contribute towards quantifying this missing treatment decision information, which might be a net risk or net benefit to the health outcomes of the patient. Our findings illustrate the extent of RCT exclusion by vulnerable characteristic for RCT groups and provide a direct comparison to prevalence in actual populations highlighting poor representativeness between RCT populations and real-world populations. A higher risk of mortality was associated with populations identified to not have treatment decision information, compared with community controls.

Implications of all the available evidence

By highlighting the poor representation between RCT populations and real-world populations, and demonstrating a systematic and scalable methodology to address gaps in treatment decision information, this work seeks to directly highlight the strength of leveraging real-world evidence to complement RCTs in increasing the completeness of evidence-based medicine generated for clinical prescription guidelines. The use of real-world evidence negates the added risks of conducting RCTs with clinically vulnerable individuals, and findings based on patient EHRs can contribute towards informing specific clinical prescription guidelines for current and future patients. This approach is especially important in formulating non-generic prescription guidelines for patients with multimorbidity and polypharmacy, by considering treatment risk or benefit based on a combination of conditions and drugs. In doing so, real-world evidence might contribute towards the goal of optimising and reducing risks involved with treatment decisions, hence contributing towards alleviating treatment dilemmas faced by clinicians and patients with multimorbidity. This approach will allow patients to assume greater responsibility of decision making with information on treatment risk or benefit, and minimise negative outcomes caused by adverse interactions between conditions and drugs.

groups with highest risk of having scarce treatment decision information. We then aimed to assess if the risk of mortality outcome differed between such patients with and without a contraindicated clinical speciality.

Methods

Data sources

Clinical trial records were obtained from the ClinicalTrials.gov database from Feb 29, 2000, to April 28, 2021.

EHRs were obtained from the Clinical Practice Research Datalink (CPRD) GOLD database, consisting of 6 163 418 individuals from 949 general practices across England during the study period of Jan 1, 1998, to Dec 31, 2020. These records include diagnoses and prescription events.

To categorise individual EHRs and RCTs by drug categories, we referred to the British National Formulary (BNF) chapters and identified 13 categories of prescription drugs specific to an organ system or

For more on the **British National Formulary** see http://www.medicinescomplete.com

condition type. A list of prescription drugs was extracted for each of the 13 drug categories. The categories include gastrointestinal; cardiovascular; respiratory; central nervous system; infections; endocrine system; obstetrics, gynaecology, and urinary-tract disorders; malignant disease and immunosuppression; nutrition and blood; musculoskeletal and joint diseases; eye; ear, nose, and oropharynx; and skin. Each category further consisted of subsections containing individual drug lists.

The first part of this study encompasses a descriptive analyses and the second part of this study encompasses cohort studies, and for simplicity we will refer to these as observational studies. The overall components of the methodology are shown in the appendix (p 1).

See Online for appendix

EHR phenotypes for 286 conditions were obtained from the open-access Health Data Research CALIBER phenotype library and have previously been validated.[24–26] Condition phenotypes were generated using Read codes version 2. The 286 conditions were mapped to 28 clinical specialities (appendix p 48).

For more on the **Health Data Research CALIBER phenotype library** see https://phenotypes.healthdatagateway.org/

EHR phenotypes for 133 prescription categories were generated by matching the drug lists and their corresponding chemical substances from each BNF subsection to the CPRD GOLD product dictionary on product name and drug substance, respectively (appendix p 2).

Information governance approval was obtained from the UK Medicines Healthcare Regulatory Authority Independent Scientific Advisory Committee (20_000204) Clinical Practice Research Datalink.

Procedures

Identification of clinical trial study groups and EHR cohorts for descriptive analyses

RCTs were filtered for the criteria of a randomised intervention trial investigating a drug or biological product. The filtering was done manually by YYT using MySQL (version 8.0.26; appendix p 53). To determine assignment of an RCT to a drug category group, the intervention name of each RCT was matched to the drug lists corresponding to each drug category group. A full list of drugs is available in the appendix (pp 38–47). Duplicate RCTs were removed by ensuring that each category of clinical trials only had a single instance of the unique NCT serial number used to identify clinical trials in ClinicalTrials.gov. Removing duplicates was carried out manually by YYT using Python (version 3.8.10).

All individuals who had at least one recorded prescription event corresponding to a drug category during the study period were considered eligible to be assigned to one or more of the 13 drug categories cohorts. Each drug category cohort consisted of individuals with a prescription event corresponding to a drug in the respective drug category. The earliest date of prescription of a drug falling within the assigned drug category was considered the index prescription date for the individual within the specific drug category cohort.

Clinical trial exclusion proportions and EHR cohort population prevalence analyses for descriptive analyses

RCTs in each drug category group were analysed to determine the proportion of RCTs with exclusion of the following criteria: concomitant conditions by clinical speciality and quantity; concomitant medication usage; and age. For concomitant conditions, individual conditions mapped to the 28 clinical specialities were matched to the exclusion criteria and a clinical speciality was considered excluded if at least one condition matched. Exclusion proportions were assessed by individual clinical speciality and quantity of concomitant clinical specialties, by grouping of 0, 1, 2–5, 6–10, and 11 or more clinical specialties. For concomitant medication use, keywords related to medication use concurrent to the RCT drug were matched to the exclusion criteria. Exclusion proportions were assessed by whether all medication use was excluded or not. For age, exclusion was determined by the minimum and maximum ages defined for each RCT. Exclusion proportions were assessed separately by the age thresholds of younger than 18 years, 60 years and older, 70 years and older, and 80 years and older.

Individuals in each drug category cohort were analysed to determine the proportion of individuals being actively prescribed a drug from the drug category while meeting the exclusion criteria outlined in the previous paragraph. For concomitant conditions, individuals with diagnoses of conditions mapped to the 28 clinical specialities before the index prescription date were recorded. Individuals with diagnoses in two or more clinical specialities were considered to have multimorbidity. This is not the true definition of multimorbidity[27] because it is quantified on a clinical speciality granularity, but acts as a proxy measure. Actual multimorbidity levels by individual condition granularity will be higher. Population prevalence was assessed by individual clinical specialty and quantity of concomitant clinical specialties, by grouping of 0, 1, 2–5, 6–10, and 11 or more clinical specialties. For concomitant medication, individuals with prescriptions before the index prescription date were recorded and was considered to have polypharmacy if an individual had five or more unique prescriptions. Population prevalence was assessed by the quantity of concomitant medication use, by grouping of 0, 1–4, 5–10, 11–20, and 21 or more. The age of an individual was recorded at the time of the index prescription date. Population prevalence was assessed separately by the age thresholds of younger than 18 years, 60 years and older, 70 years and older, and 80 years and older.

Identification of vulnerable populations potentially at risk of inadequate treatment decision information for descriptive analyses

To identify vulnerable populations potentially at risk of inadequate treatment decision information, the degree of exclusion from RCTs was compared with the degree of prevalence in the real world. A high degree of exclusion

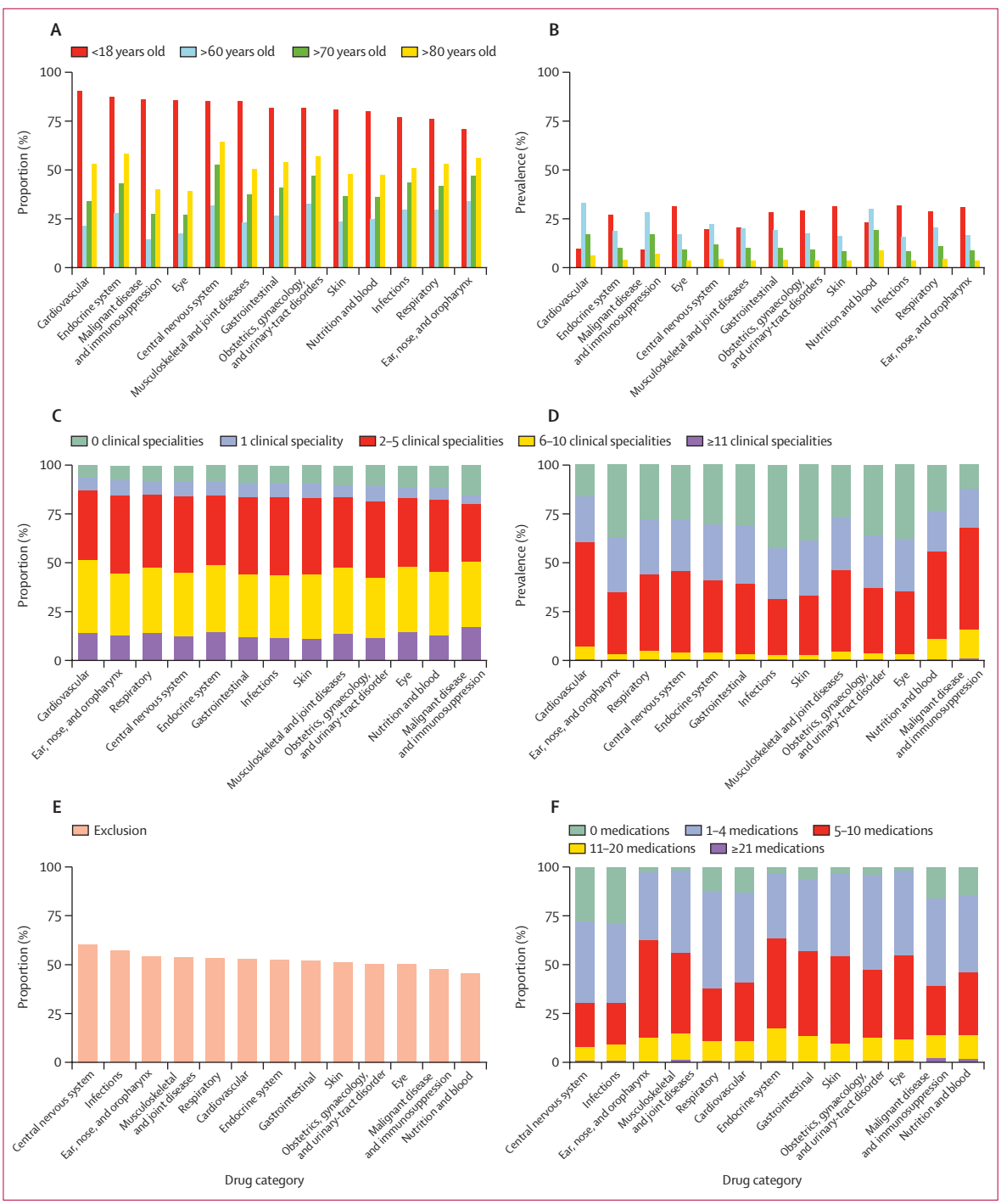
Figure 1: **Flowcharts for the assignment of RCTs to one or more of 13 drug categories (A) and for the selection of assignment of individuals to one or more of 13 drug categories (B)**

(A) Numbers represent unique RCTs in each group. (B) Numbers represent unique individuals in each group. RCT=randomised controlled trial. *The sum of each type of trial excluded exceeds the total number of trials excluded because the criteria are not exclusive to an individual trial, meaning a trial can have more than one exclusion criteria applied, of which only one is required for exclusion. †The sum of all the trials in the 13 drug categories exceeds the total unique count because a drug is not mutually exclusive to a category. ‡Counts of all individuals in each drug category do not sum to the total number of eligible individuals as some eligible individuals contributed to more than one drug categories.

from RCTs with a corresponding high degree of prevalence of individuals actively being prescribed the same medication in the real world suggests a probable gap in treatment decision information. For clinical specialities, a high degree or high correspondence was defined by a threshold of 50% or more RCT exclusion proportion and a threshold of 10% or more population prevalence. A moderate degree or moderate correspondence was defined by a threshold of 30·0–49·9% RCT exclusion proportion and 5·0–9·9% population prevalence.

Identification of multimorbidity and polypharmacy population trends for descriptive analyses

Multimorbidity and polypharmacy trends for separate age groups in each drug category were analysed to identify population trends. Population prevalence of individuals



with multimorbidity or polypharmacy was assessed separately by the age groups of younger than 18 years, 18–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years, 70–79 years, and 80 years or older.

Identification of clinical trial group for observational study and EHR cohort for observational study

The search method previously used to identify RCT groups was used, with the drug category restricted to anti-dementia drugs (donepezil, galantamine, rivastigmine, and memantine). For the EHR base cohort, all individuals who had an anti-dementia drug prescription, a previous dementia diagnosis, and at least a year of follow-up were considered eligible. The exposed population was identified as having a contraindicated condition before the index prescription date. The control non-exposed population was identified as individuals without a contraindicated condition before the index prescription date.

Identification of vulnerable populations potentially at risk of inadequate treatment decision information for observational study

The clinical specialities selected as the contraindications were identified through clinical speciality groups with a high degree of exclusion from RCTs and a corresponding high degree of prevalence in the real-world, suggesting a high likelihood of a gap in treatment decision information. The definition of a high degree is outlined in the descriptive analyses section.

Mortality risk assessment exposed and non-exposed control grouping

Individuals from both case and control groups were identified by propensity score matching by age, sex, primary care practice region, number of clinical specialities diagnosed, and number of prescriptions using the nearest-neighbour matching method (1:1 case: control match) with a calliper width of 0·2 of the standard deviation of the logit of the propensity score. Follow-up began at the anti-dementia drug prescription date (baseline) and ended at date of death, date of deregistration from the practice, end of follow-up period (10 years), or administrative end of follow-up (Dec 31, 2020), whichever happened first. Individuals are considered censored if lost to follow-up.

Statistical analysis

For the descriptive analyses, summary statistics of proportions and the medians of proportions across the individual categories were generated. The bootstrap percentile method was used to estimate 95% CIs for proportions.

For the observational study, Kaplan-Meier survival curves were plotted for comparison of the outcome, survival times, between exposed and non-exposed control individuals. Kaplan-Meier estimates were used for univariate descriptive analysis with the log-rank tests to determine significance between the survival expression of both groups. Log-rank p values were generated. The Cox proportional hazards regression model was used to estimate hazard ratios (HRs) of the risk of mortality between case and control individuals with corresponding p values and 95% CIs generated. The proportional hazards assumption was evaluated and determined to be met.

Data were processed and analysed using Python (version 3.8.10),[28] R (version 3.6.2), and MySQL (version 8.0.26).[29] A list of the packages used is in the appendix (p 50).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We identified 989 unique prescription drugs from the 13 drug categories (appendix pp 38–47). We identified 374 908 total RCTs from the inception of the ClinicalTrials.gov database. A total of 331 013 RCTs were excluded, resulting in 43 895 eligible RCTs assigned to 13 drug categories. We identified corresponding EHR cohorts for the drug categories from 5 685 738 eligible individuals with at least one recorded prescription record (figure 1).

We analysed RCT exclusion and real-world population prevalence for frequently excluded age thresholds (figure 2A, B). Adolescent individuals have the highest proportion of RCT exclusions, with the highest value of 90·3% (8281/9166; 95% CI 89·7–90·9; cardiovascular) and the lowest at 70·7% (2188/3097; 95% CI 69·0–72·2;

Figure 2: **Exclusion proportions and prevalence of individuals by vulnerable characteristics by drug category**

95% CIs are displayed as error bars where possible and are available in the appendix (pp 4–15). (A) RCT exclusion proportion of age groups by drug category. The denominator is the total number of RCTs for the drug category and the numerator is the number of RCTs excluding individuals in the specified age groups. (B) Real-world population prevalence of age groups by drug category. The denominator is the total number of individuals for the drug category cohort and the numerator is the number of individuals in the specified age groups. (C) RCT exclusion distribution of number of concomitant conditions at clinical speciality granularity by drug category. The denominator is the total number of RCTs for the drug category and the numerator is the number of RCTs excluding individuals with the specified number of clinical specialties concomitant to the indicated RCT condition. (D) Real-world population prevalence distribution of number of conditions at clinical speciality granularity by drug category. The denominator is the total number of individuals for the drug category cohort and the numerator is the number of individuals by specified clinical speciality count. (E) RCT exclusion proportion by concomitant medication use. The denominator is the total number of RCTs for the drug category and the numerator is the number of RCTs that exclude individuals with concomitant medication use. (F) Real-world population prevalence distribution of number of medications prescribed before to the index prescription by drug category. The denominator is the total number of individuals for the drug category cohort and the numerator is the number of individuals by specified medication prescription count. RCT=randomised controlled trial.

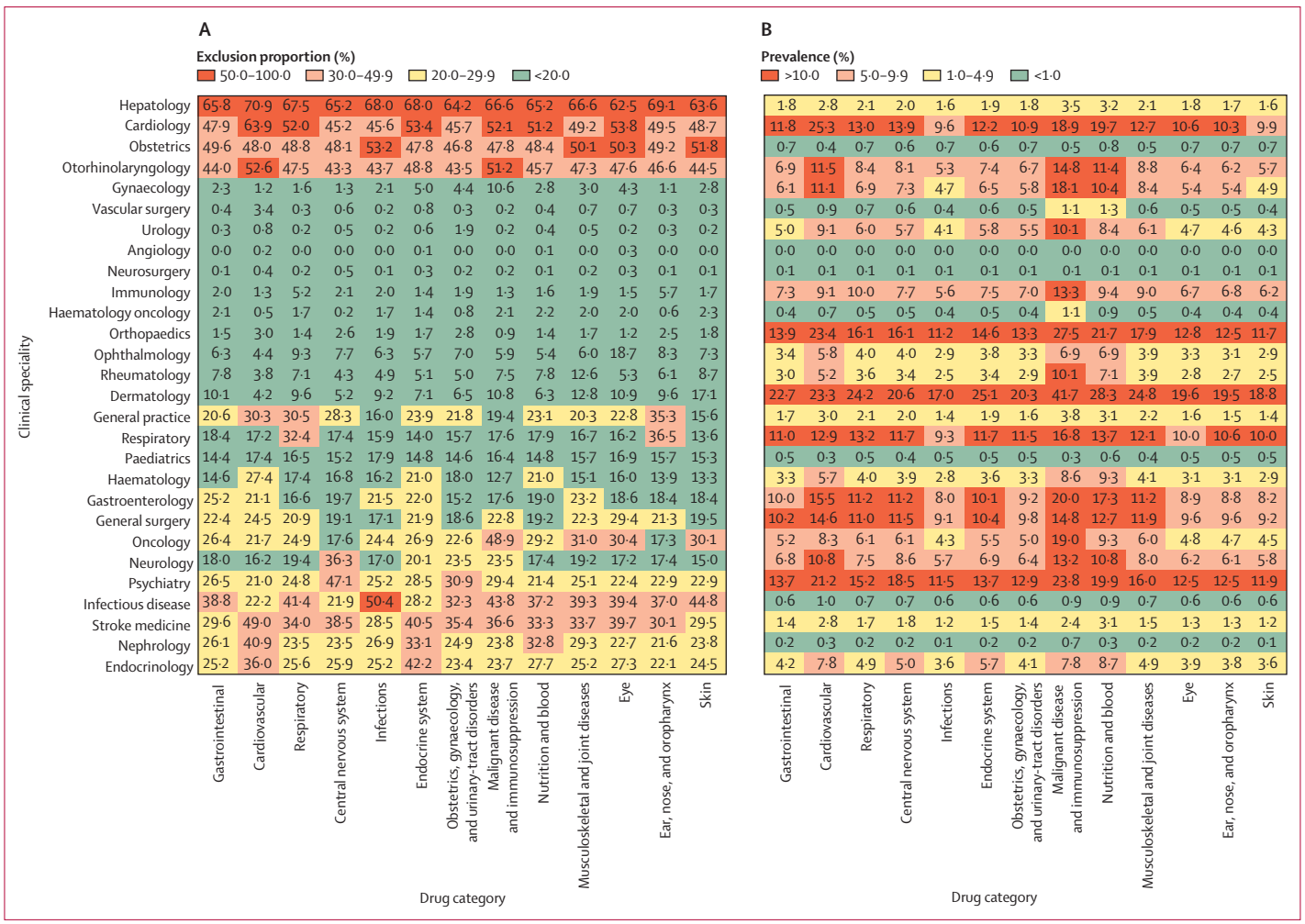


Figure 3: **Exclusion proportions and prevalence of individuals by clinical speciality by drug category**

All data and 95% CIs are available in the appendix (pp 16–25). (A) Heatmap of RCT exclusion proportions of each clinical speciality by RCTs in the respective drug category. The denominator is the total number of RCTs for the drug category. The numerator is the number of RCTs that exclude individuals with at least one condition mapped to the specified clinical specialty concomitant to the indicated RCT condition. For example, referring to the cell in the first row (hepatology) and first column (gastrointestinal), 65·8% represents the proportion of RCTs that exclude individuals with a hepatology condition (numerator) within all RCTs in the gastrointestinal drug category (denominator). (B) Heatmap of real-world population prevalence of individuals diagnosed with each clinical speciality assigned to the respective drug category cohort. The denominator is the total number of individuals for the drug category cohort. The numerator is the number of individuals who have been diagnosed with at least one condition mapped to the clinical speciality. For example, referring to the cell in the first row (hepatology) and first column (gastrointestinal), 1·8% represents the real-world population prevalence of individuals that have been diagnosed with a hepatology condition (numerator) within all individuals who have been prescribed a drug in the gastrointestinal drug category (denominator). The two examples given can be compared to ascertain the extent of exclusion of individuals with a specific clinical speciality from RCTs of a specific drug category in relation to the actual population prevalence of such individuals with a specific clinical speciality who are being prescribed drugs from the same specific drug category. RCT=randomised controlled trial.

ear, nose, and oropharynx) with a median of 81·5% (IQR 76·7–85·5). The exclusion proportion increases for older individuals with age, with the highest values of 33·7% (1043/3097; 95% CI 32·0–35·4; ear, nose, and oropharynx) with a median of 26·3% (IQR 21·0–29·5) for the older than 60 years group; 51·9% (5721/10969; 95% CI 50·9–52·8; central nervous system) with a median of 40·5% (IQR 33·7–43·0) for the older than 70 years group; and 63·8% (7015/10969; 95% CI 62·9–64·7; central nervous system) with a median of 52·9% (IQR 47·1–56·0) for the older than 80 years group. Adolescent individuals account for a median of 28·0% (IQR 19·3–30·8) of the real-world population across cohorts. The prevalence decreases for older individuals as age increases, with a median of 19·0% (IQR 16·5–22·2) for the older than 60 years group, 9·9% (IQR 8·5–11·7) for the older than 70 years group, and 3·6% (IQR 3·2–4·3) for the older than 80 years group.

We then analysed the RCT exclusion and real-world population prevalence for multimorbidity on a clinical speciality scale (figure 2C, D). RCTs across all drug categories had a median exclusion rate of 91·1% (IQR 88·9–91·8) of at least one concomitant clinical speciality. The median inclusion rate of RCTs for individuals with non-indicated RCT conditions is 9·0%

(IQR 8·1–10·7). Conversely, RCTs excluded up to 21 unique clinical specialities. RCTs are most likely to exclude common and chronic concomitant conditions, and the higher the number of clinical specialties excluded, the higher the likelihood that an individual with just one comorbidity will be excluded, drastically decreasing the pool of eligible participants. For the real-world population, multimorbidity is common, with a median prevalence of 41·0% (IQR 34·9–46·0). Individuals with two to five clinical specialities account for the largest prevalence in many cohorts. Of note, multimorbidity is counted from two to five clinical specialities here, as opposed to beginning at one clinical speciality in the exclusion analysis, because RCTs already select for individuals with an index condition.

We analysed the RCT exclusion and real-world population prevalence for concomitant medication use (figure 2E, F). RCTs did not specify the number or types of concomitant medication excluded; thus, we could only analyse exclusion of concomitant medication use in an excluded or non-excluded format. In almost all drug categories, more than half the RCTs exclude individuals with concomitant medication use with the median exclusion proportion being 52·5% (IQR 50·0–53·7). For the real-world population, polypharmacy is common, with a median prevalence of 47·7% (IQR 38·0–56·1). However, even more prominent is concomitant medication use, with a median prevalence of 94·3% (IQR 84·3–97·2).

The RCT exclusion proportion by clinical speciality was analysed to identify the clinical specialities most prominently excluded (figure 3A). We correspondingly analysed the real-world prevalence of each clinical speciality (figure 3B). This direct comparison between exclusion proportions and real-world prevalence allowed for the identification of groups of individuals with increased risk of not having treatment decision information. For example, if most RCTs for central nervous system drugs exclude individuals with a psychiatric condition, but there is a high prevalence of individuals with a psychiatric condition being prescribed central nervous system drugs, then there is the inference that individuals with a psychiatric condition are missing treatment decision information pertaining to the prescription of central nervous system drugs.

Clinical specialities with a high exclusion proportion and a similarly high prevalence include cardiology with median exclusion of 49·5% (IQR 45·7–52·1) and median prevalence of 12·2% (IQR 10·3–13·9), and otorhinolaryngology with median exclusion of 46·6% (IQR 43·7–47·6) and median prevalence of 7·4% (IQR 6·2–8·8). Clinical specialities with moderate levels of correspondence include oncology with median exclusion of 26·4% (IQR 21·7–30·1) and median prevalence of 5·5% (IQR 4·7–6·1), psychiatry with median exclusion of 25·1% (IQR 22·4–28·5) and median prevalence of 13·7% (IQR 12·5–18·5), and endocrinology with median exclusion of 25·3% (IQR 23·7–27·3) and median prevalence of 4·9% (IQR 3·8–5·7). Clinical specialities that had higher than average RCT exclusion proportion but not necessarily corresponding population prevalence include hepatology with median exclusion of 66·6% (IQR 64·2–68·0), obstetrics with median exclusion of 48·8% (IQR 47·8–50·1), infectious disease with median exclusion of 38·7% (IQR 28·2–41·4), and stroke medicine with median exclusion of 33·9% (IQR 29·6–38·5).

Across all drug category cohorts except for the malignant disease and immunosuppression group, there is a steeper increase of multimorbidity prevalence between the age groups of younger than 18 years to 50–59 years, compared with between the age groups of

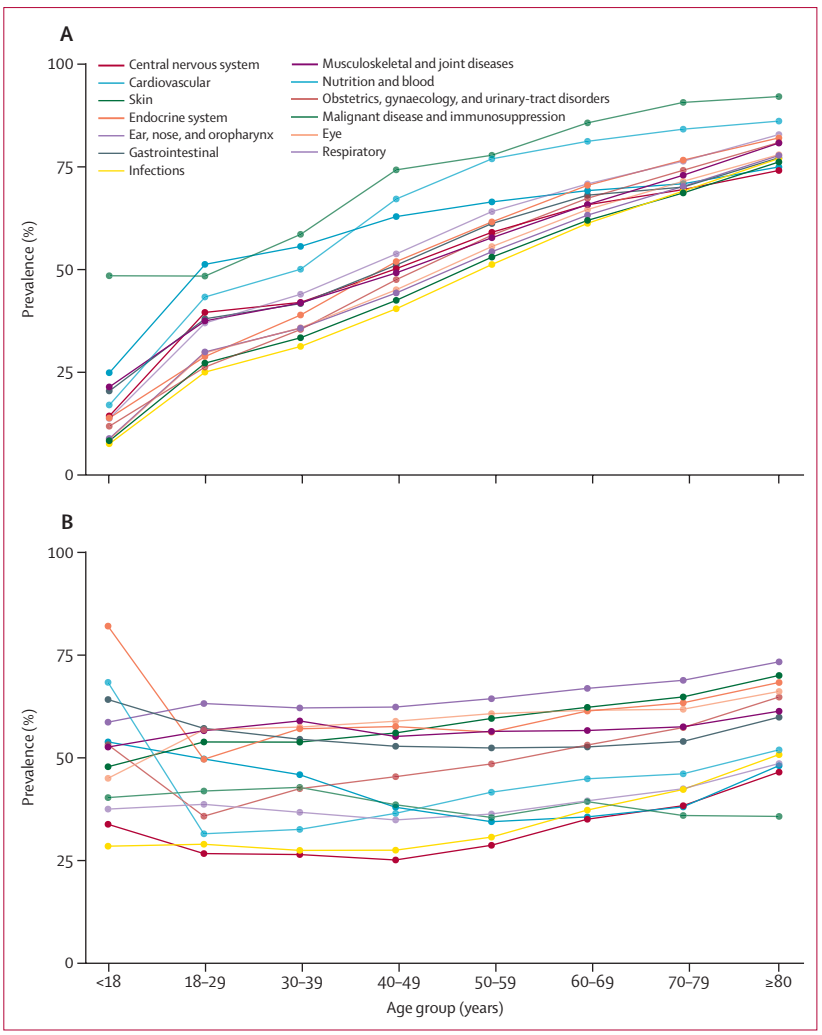
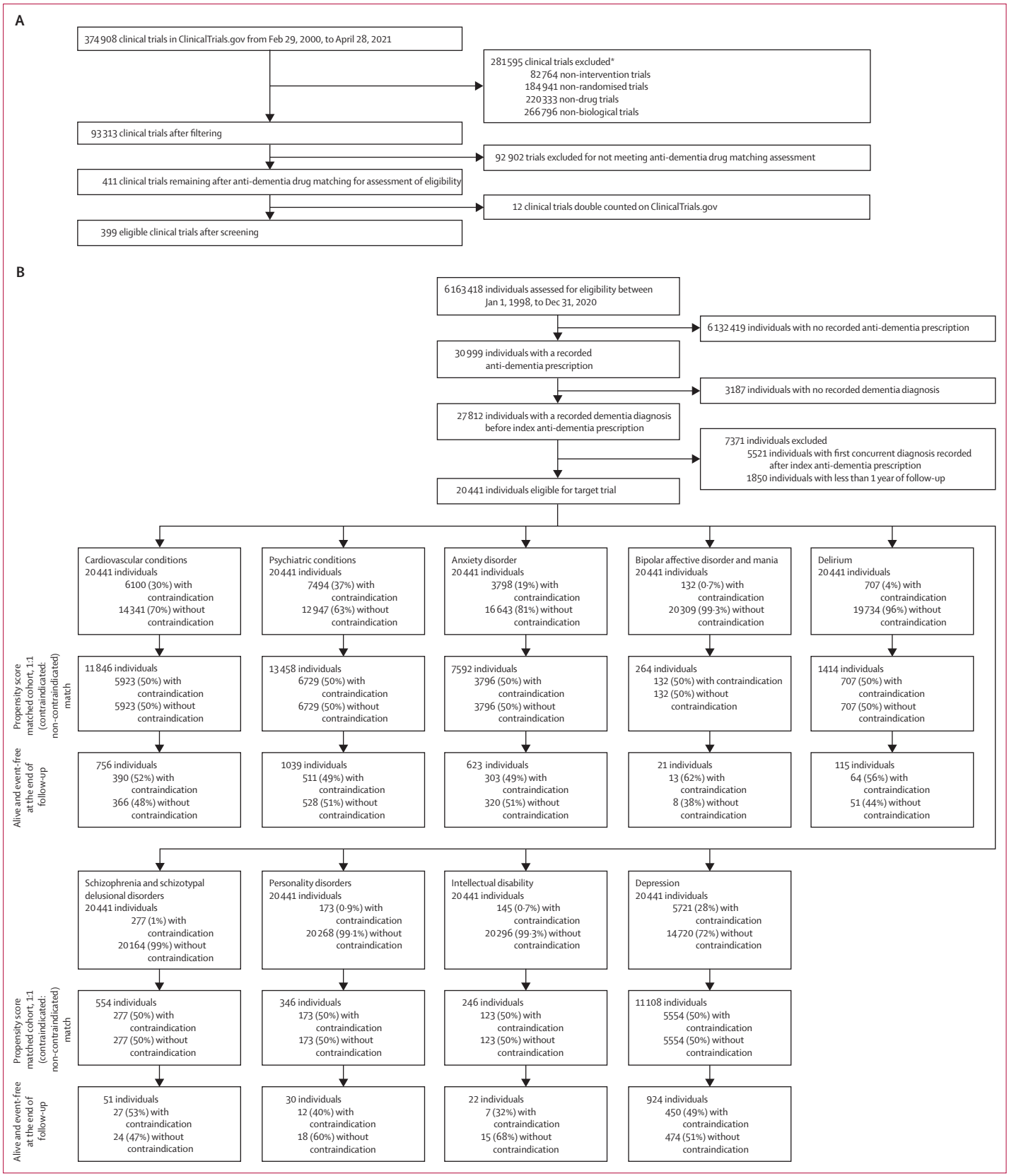


Figure 4: **Multimorbidity (two or more clinical specialities) and polypharmacy (five or more medications) trends by age groups by drug category**

All data and 95% CIs are available in the appendix (pp 26–29). (A) Multimorbidity real-world population prevalence trends across age groups by drug category cohorts. For each point, the denominator is the total number of individuals in the drug category cohort within the specified age group and the numerator is the number of individuals with multimorbidity. (B) Polypharmacy real-world population prevalence trends across age groups by drug category cohorts. For each point, the denominator is the total number of individuals in the drug category cohort within the specified age group and the numerator is the number of individuals with polypharmacy.


A
374 908 clinical trials in ClinicalTrials.gov from Feb 29, 2000, to April 28, 2021
281 595 clinical trials excluded*
82 764 non-intervention trials
184 941 non-randomised trials
220 333 non-drug trials
266 796 non-biological trials
93 313 clinical trials after filtering
92 902 trials excluded for not meeting anti-dementia drug matching assessment
411 clinical trials remaining after anti-dementia drug matching for assessment of eligibility
12 clinical trials double counted on ClinicalTrials.gov
399 eligible clinical trials after screening
B
6 163 418 individuals assessed for eligibility between Jan 1, 1998, to Dec 31, 2020
6 132 419 individuals with no recorded anti-dementia prescription
30 999 individuals with a recorded anti-dementia prescription
3187 individuals with no recorded dementia diagnosis
27 812 individuals with a recorded dementia diagnosis before index anti-dementia prescription
7371 individuals excluded
5521 individuals with first concurrent diagnosis recorded after index anti-dementia prescription
1850 individuals with less than 1 year of follow-up
20 441 individuals eligible for target trial
Cardiovascular conditions
20 441 individuals
6100 (30%) with contraindication
14 341 (70%) without contraindication
Psychiatric conditions
20 441 individuals
7494 (37%) with contraindication
12 947 (63%) without contraindication
Anxiety disorder
20 441 individuals
3798 (19%) with contraindication
16 643 (81%) without contraindication
Bipolar affective disorder and mania
20 441 individuals
132 (0·7%) with contraindication
20 309 (99·3%) without contraindication
Delirium
20 441 individuals
707 (4%) with contraindication
19 734 (96%) without contraindication
Propensity score matched cohort, 1:1 (contraindicated: non-contraindicated) match
11 846 individuals
5923 (50%) with contraindication
5923 (50%) without contraindication
13 458 individuals
6729 (50%) with contraindication
6729 (50%) without contraindication
7592 individuals
3796 (50%) with contraindication
3796 (50%) without contraindication
264 individuals
132 (50%) with contraindication
132 (50%) without contraindication
1414 individuals
707 (50%) with contraindication
707 (50%) without contraindication
Alive and event-free at the end of follow-up
756 individuals
390 (52%) with contraindication
366 (48%) without contraindication
1039 individuals
511 (49%) with contraindication
528 (51%) without contraindication
623 individuals
303 (49%) with contraindication
320 (51%) without contraindication
21 individuals
13 (62%) with contraindication
8 (38%) without contraindication
115 individuals
64 (56%) with contraindication
51 (44%) without contraindication
Schizophrenia and schizotypal delusional disorders
20 441 individuals
277 (1%) with contraindication
20 164 (99%) without contraindication
Personality disorders
20 441 individuals
173 (0·9%) with contraindication
20 268 (99·1%) without contraindication
Intellectual disability
20 441 individuals
145 (0·7%) with contraindication
20 296 (99·3%) without contraindication
Depression
20 441 individuals
5721 (28%) with contraindication
14 720 (72%) without contraindication
Propensity score matched cohort, 1:1 (contraindicated: non-contraindicated) match
554 individuals
277 (50%) with contraindication
277 (50%) without contraindication
346 individuals
173 (50%) with contraindication
173 (50%) without contraindication
246 individuals
123 (50%) with contraindication
123 (50%) without contraindication
11 108 individuals
5554 (50%) with contraindication
5554 (50%) without contraindication
Alive and event-free at the end of follow-up
51 individuals
27 (53%) with contraindication
24 (47%) without contraindication
30 individuals
12 (40%) with contraindication
18 (60%) without contraindication
22 individuals
7 (32%) with contraindication
15 (68%) without contraindication
924 individuals
450 (49%) with contraindication
474 (51%) without contraindication

50–59 years to 80 years and older (figure 4A). In the malignant disease and immunosuppression cohort, the initial multimorbidity prevalence for the younger than 18 years age group is already high, with almost half the adolescent individuals having multimorbidity. However, the overall trend for all drug category cohorts is clear: multimorbidity prevalence increases with age.

There are two polypharmacy trends among the cohorts (figure 4B). The first is a continuous gradual increase in polypharmacy prevalence with age, which can be seen in the ear, nose, and oropharynx; musculoskeletal and joint diseases; skin; respiratory; eye; and infections groups. There is a marginal decrease between the age groups of 18–29 years to 40–49 years in most of these groups before increasing again. The second trend is a U-shape beginning with high polypharmacy prevalence in the younger than 18 years age group, before a sharp decrease in the 18–29 years age group followed by an increase with age, which can be seen in the endocrine system; cardiovascular; nutrition and blood; gastrointestinal; obstetrics, gynaecology, and urinary-tract disorders; and central nervous system groups. The outlier is the malignant disease and immunosuppression group, which fluctuates but has an overall decrease in polypharmacy prevalence with age.

To estimate the potential of unknown treatment risks caused by broad RCT exclusion criteria, we identified all eligible anti-dementia drug RCTs (n=399; figure 5A). We identified the corresponding real-world cohorts, resulting in a base cohort of 20 441 eligible individuals with an anti-dementia prescription and previous dementia diagnosis (figure 5B). No participants had any missing data. Baseline characteristics are shown in the appendix (p 52).

We analysed anti-dementia drug RCT exclusion proportion by clinical speciality and compared this with its population prevalence (figure 6). Individuals with a comorbidity in stroke medicine with exclusion of 71·7% (286/399; 95% CI 66·9–76·0) and prevalence of 12·8% (2626/20441; 95% CI 12·4–13·3), in cardiology with exclusion of 61·4% (245/399; 95% CI 56·4–66·2) and prevalence of 62·6% (12806/20441; 95% CI 62·0–63·3%), in psychiatry with exclusion of 69·9% (279/399; 95% CI 65·1–74·3) and prevalence of 36·8% (7518/20441; 95% CI 36·1–37·4), and in otorhinolaryngology with exclusion of 52·6% (210/399; 95% CI 47·6–57·6) and prevalence of 31·8% (6499/20441; 95% CI 31·2–32·4) are highly excluded from these RCTs and highly prevalent in the real-world population, supporting a gap in ascertaining the risks of prescribing anti-dementia medication to such individuals, who are currently taking the medication. Cardiology and psychiatry have the highest corresponding exclusion proportions and population prevalence.

We chose to evaluate the cohort with a cardiovascular comorbidity, firstly due to high exclusion and prevalence, and secondly as previous studies have postulated that anti-dementia drugs are associated with adverse cardiovascular events, thus exacerbating treatment risks in individuals with pre-existing cardiovascular conditions.[30,31] Contraindicated cardiovascular conditions include atrial

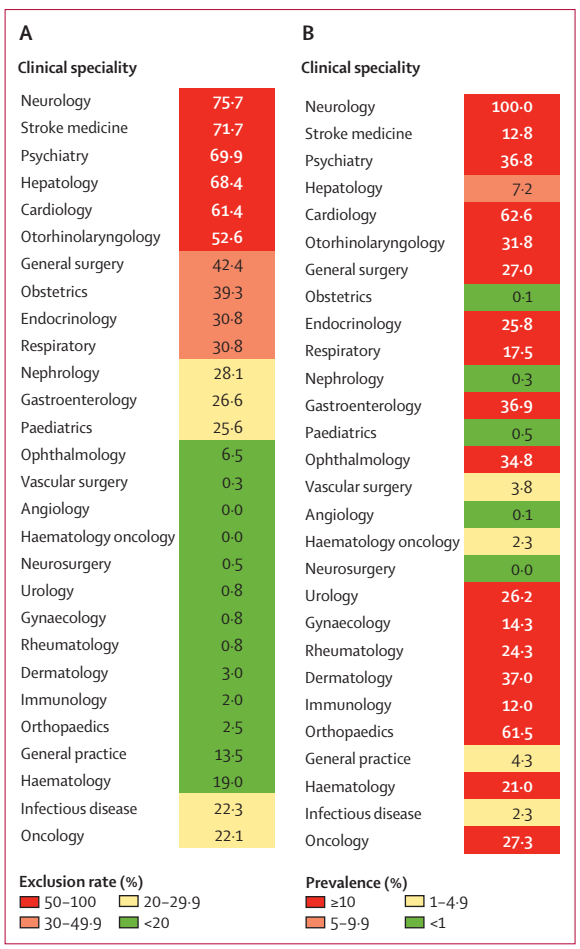


Figure 6: **Observational study heatmaps of anti-dementia drug RCT exclusion proportions (A) and of real-world anti-dementia drug prescribed population prevalence (B) for each clinical speciality**
95% CIs are displayed as error bars where possible and are available in the appendix (p 31–35). (A) The numerator is the number of RCTs that exclude individuals with at least one condition mapped to the specified clinical specialty concomitant to the indicated RCT condition. (B) The denominator is the total number of individuals with an anti-dementia drug prescription and a prior dementia diagnosis. The numerator is the number of individuals who have been diagnosed with at least one condition mapped to the specified clinical speciality. Neurology has a 100% prevalence as all individuals had a dementia diagnosis. RCT=randomised controlled trial.

Figure 5: **Flowchart for selection of RCTs (A) and eligible individuals (B) for anti-dementia drug observational study**
(A) Flowchart for selection of eligible RCTs for anti-dementia drugs. (B) Flowchart for selection of eligible individuals for analysis of survival outcomes between individuals with dementia and an anti-dementia drug prescription and specified contraindication or absence of a specified contraindication. RCT=randomised controlled trial. *The sum of each type of trial excluded exceeds the total number of trials excluded because the criteria are not exclusive to an individual trial, meaning a trial can have more than one exclusion criteria applied, of which only one is required for exclusion. RCT=randomised controlled trial.

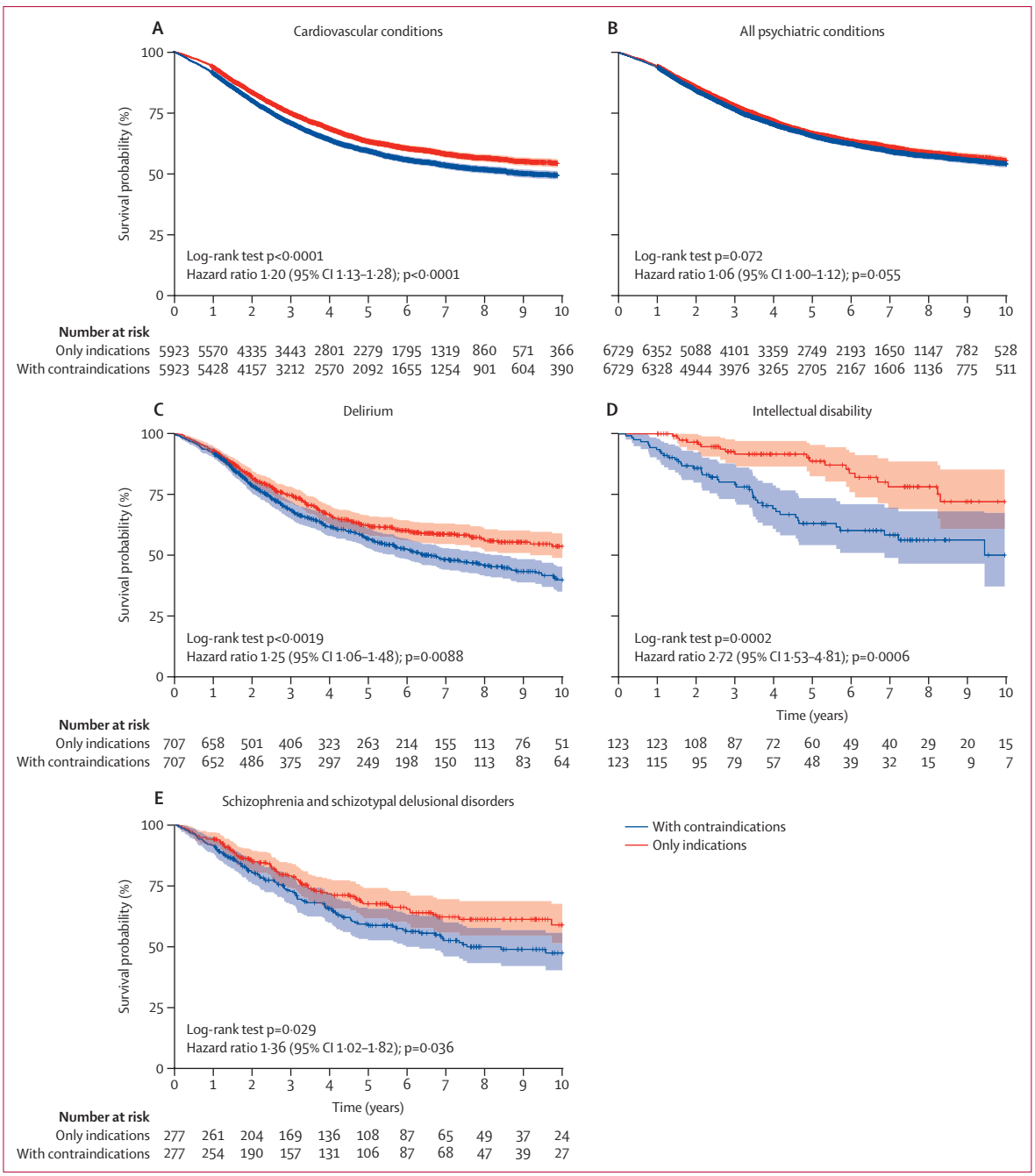


***Figure 7*: Observational study Kaplan-Meier survival curves with hazard ratios of propensity-matched cohorts for each specified condition, with and without contraindications**

Hazard ratios from Cox proportional hazards regression analyses are outlined. (A) Cardiovascular conditions. (B) All psychiatric conditions. (C) Delirium. (D) Intellectual disability. (E) Schizophrenia and schizotypal delusional disorders.

fibrillation, atrioventricular block (complete, first degree, and second degree), coronary heart disease, heart failure, myocardial infarction, ischaemic stroke, transient ischaemic attack, ventricular tachycardia, and supraventricular tachycardia. Individuals with a contraindicated cardiovascular condition had a higher risk of mortality (HR 1·20 [95% CI 1·13–1·28]; p<0·0001; figure 7A) compared with individuals with other comorbidities. The median follow-up time was 6·04 years (IQR 3·15–8·50) for the exposed group and 6·02 years (IQR 3·21–8·20) for the non-exposed control group.

We chose a second cohort with a psychiatric comorbidity to validate our approach without prior postulations. Individuals who had a contraindicated psychiatric

condition did not have a significant difference in mortality risk compared with individuals with other comorbidities (figure 7B). We further analysed individual non-lifestyle psychiatric conditions to nullify the effect of condition dilution. We found that individuals with dementia with comorbid delirium (HR 1·25 [95% CI 1·06–1·48]; p<0·0088), intellectual disability (2·72 [95% CI 1·53–4·81]; p=0·0006), and schizophrenia and schizotypal delusional disorders (1·36 [95% CI 1·02–1·82]; p=0·036) had a higher risk of mortality than individuals with other comorbidities (figure 7C–E). The median follow-up time for the exposed and non-exposed control groups for delirium are 6·43 years (IQR 3·24–9·40) and 6·04 years (IQR 3·20–8·44), for intellectual disability are 6·59 years (IQR 3·39–7·73) and 5·47 years (IQR 3·39–8·84), and for schizophrenia and schizotypal delusional disorders are 6·72 years (IQR 3·61–9·55) and 5·62 years (IQR 3·26–8·51). Using observational studies for specific conditions and medication, we were able to quantify the identified risks at different granularities.

Discussion

To our knowledge, this is the largest external validity study on RCTs to date and the first to be done at scale. Overall, we found that representation of individuals with vulnerable characteristics between RCT and real-world populations was vastly lacking. Further to systematically identifying groups of at-risk individuals, we used an observational study and successfully evaluated the mortality risk for patients with dementia with identified at-risk comorbidities who were on anti-dementia drug treatment, hence validating the use of real-world evidence in contributing towards quantifying treatment risk or benefit. Such treatment risks or benefits were previously unknown.

We demonstrate that overly stringent RCT exclusion criteria do not appropriately account for the heterogeneity of vulnerable characteristics observed in real-world populations. The adolescent and older populations are highly excluded but combined make up approximately 50% of the real-world population. Similarly, individuals with concomitant conditions and medication use are frequently excluded, yet multimorbidity prevalence is as high as 67·7%, the prevalence of concomitant medication use is as high as 98·5%, and polypharmacy prevalence is as high as 62·5%. This prominent difference is likely to lead to poor external validity and a scarcity of evidence-based medicine that accurately quantifies treatment risk or benefit in such under-represented individuals, especially in the context of concomitant conditions and medication use. Our findings agree with studies that have demonstrated poor external validity in landmark RCTs[32] and patient adverse events from following clinical guidelines,[13] questioning the translatability of RCT findings to heterogeneous populations.

Stratifying by age, we observed a steeper increase in multimorbidity between younger groups, suggesting that more individuals are developing multimorbidity at a younger age, contrary to the narrative that multimorbidity is only prominent in older individuals.[15] A stark increase in overall multimorbidity across the population is evident when comparing against previous primary care studies,[16,17] reinforcing the idea that multimorbidity is becoming normalised.

We identified two opposing trends in polypharmacy prevalence across age groups. The first is an increase in polypharmacy prevalence with age, which is expected and in line with an increase in multimorbidity prevalence with age. However, for several drug categories the polypharmacy prevalence for the adolescent group (aged <18 years) is higher than all other age groups, suggesting that paediatric conditions pertaining to these drug category prescriptions are more severe or result in complications or conditions which require additional drugs. It is also important to consider if widespread off-label prescribing and its negative consequences for paediatric patients has contributed to this increase.[33] Widespread off-label prescribing reflects the extent to which adolescent individuals are excluded from RCTs, without a baseline for whether a drug that is indicated for their condition is suitable.

On a clinical speciality granularity, we observe that populations with a cardiovascular or otorhinolaryngology comorbidity are most at-risk of having scarce treatment decision information. Our intention for undertaking the analysis at a clinical speciality and drug category granularity was to capture the overall picture of representativeness without losing the ability to summarise findings appropriately. The identification of clinical specialities with populations for which treatment decision information is missing presents the opportunity to further investigate, on an individual condition and drug level, if the scarcity of treatment decision information has a profound negative effect on the at-risk population. A high exclusion proportion alone might yield important findings, as the at-risk population might be small but clinically relevant. For example, individuals with atrial fibrillation and liver cirrhosis are a small population relative to the full hepatology clinical specialty, of which most patients on cardiovascular drugs have a comorbidity to,[34] but are still clinically relevant.[35]

Arguably, an analysis on a condition-by-condition basis is likely to yield more applicable findings. We chose a population being prescribed anti-dementia drugs with a previous dementia diagnosis. Although high exclusion and prevalence were observed for the clinical specialities of stroke medicine, psychiatry, cardiology, and otorhinolaryngology, we focused on cardiology and psychiatric comorbidities due to their high co-occurrence with dementia[36,37] and scarcity of clinical guidelines. Furthermore, previous studies have hypothesised that anti-dementia drugs are associated with adverse cardiovascular events, thus exacerbating treatment risks in individuals with pre-existing cardiovascular conditions and providing a reference point for our findings.[30,31] Our

focus was on investigating, firstly, if RCT exclusion and corresponding prevalence could identify this gap in treatment knowledge for individuals with cardiovascular comorbidities, and secondly, if real-world evidence could confirm this risk in patient outcomes. We then pivoted to psychiatric conditions to ascertain the importance of increasing granularity.

Our approach successfully identified a high proportion of both RCT exclusion and prevalence for the cardiology clinical speciality. More importantly, our observational study showed that individuals who had a cardiovascular comorbidity had worse outcomes than individuals with any other comorbidities. Our approach also identified a high proportion of both RCT exclusion and prevalence for the psychiatric clinical speciality. We found a significant difference in mortality risk between individuals with comorbid delirium, intellectual disability, or schizophrenia and schizotypal delusional disorders than in individuals with any other comorbidities. By identifying contra-indicated comorbidities and ascertaining a risk on mortality outcomes, real-world evidence highlights that contraindicated comorbidities must be considered during the treatment decision process. The findings of association between contraindicated comorbidities and poorer mortality outcomes relative to the treatment does not unequivocally equate to absolute treatment risk or benefit, but it reveals how RCT-excluded comorbidities affect mortality and hence the possibility that they might negatively interact with an individual's treatment. To establish causality between contraindicated comorbidities and treatment, further in-depth individual studies are required. In this sense, the importance of RCTs is still evident, but so is the importance of real-world evidence in identifying treatment gaps and providing focus and direction for urgent investigation. Currently, inadequate treatment information from RCTs means that individuals continue to have negative health outcomes due to contraindicated comorbidities to their treatment that have not been identified.

Real-world evidence can hence be leveraged in addition to RCTs to increase the completeness of evidence-based medicine generated for clinical prescription guidelines. Currently, systematic reviews of RCTs top the hierarchy of evidence-based medicine used to inform such guidelines because of their rigorous compilation of evidence from individual RCTs. Our study highlights the scarcity of external validity of individual RCTs, and although systematic reviews make reliability and bias assessments of the study design components of each individual RCT,[38] there is still no consideration of imbalanced exclusion criteria. Conversely, some systematic reviews actively exclude studies that include vulnerable populations,[39] showing that this issue of external validity permeates into the highest level of RCT evidence.

Increased completeness of evidence-based medicine will better cater to specific prescription guidelines for both patients with a single disease and patients with comorbidities. Current guidelines on the management of dementia acknowledge the challenges of multi-morbidity but stop short of providing specific guidelines for individual comorbidities, instead referring to generic multimorbidity guidelines.[40–42] The American Psychological Association guidelines make references to potential cardiovascular side effects from anti-dementia medication in the context of single disease, but such considerations are unhelpful to patients who have other treatments and conditions to consider, who cannot make informed treatment decisions without quantified risk information.

Our study highlights the ability to systematically identify and rank populations who face gaps in treatment knowledge and highlights the benefits of real-world evidence in contributing towards addressing these gaps. Working towards quantifying treatment risks for individuals with comorbidities will allow patients to assume responsibility in making informed treatment decisions and will alleviate the dilemma that clinicians face in the absence of risk information. Real-world evidence strengthens external validity, given appropriate control of confounding, as analyses are retrospectively carried out on the at-risk population to which the same findings would apply.

Our study has several limitations. While we analysed RCT data comprehensively from ClinicalTrials.gov, other smaller but innovative RCT registries might provide a further variety of RCTs not picked up by ClinicalTrials.gov. The level of detail in ClinicalTrials.gov eligibility criteria is not uniform across studies; there is no requirement to justify exclusion criteria and amendments can be made to eligibility criteria between initial submission and RCT execution. Moreover, although we assessed the effect of variables such as condition count, medication count, sex, practice location, and age, further variables such as socioeconomic factors and demographic factors could also have been included through data linkage, leaving possible residual unmeasured confounding, a limitation of all observational studies. The next logical steps for further investigation include expanding with other RCT registries and analysing trends for further components such as geographical differences in RCTs and variations in RCT characteristics.

Because it is unfeasible to conduct RCTs for every possible combination of multimorbidity for all ages and unethical to subject adolescent individuals to increased risks in the name of inclusivity, RCTs specific to vulnerable populations will require additional framework and safety precautions. Furthermore, barriers to entry might hinder participation of such individuals, such as the willingness of a funding body to absorb such risks, or the implications of factors such as non-adherence from polypharmacy or premature cessation of participation.[14,43–47] Furthermore, there are limitations when conducting RCTs for rare conditions or conditions that take place over a long period of time, alongside with the

consideration of costs, manpower, and time required for each RCT.

Integration of real-world evidence provides a seamless solution in complementing RCTs by applying retrospective treatment risk or benefit findings from target populations, thereby negating the risks involved in conducting an RCT for the same goal.

The use of patient EHRs can inform specific prescription guidelines for current and future patients, optimising treatment decisions and decreasing the risk of treatment decisions. Other studies have also begun to work towards using real-world-evidence-data-driven approaches to minimise restrictive eligibility criteria for RCTs, demonstrating the broad application of real-world evidence.[48]

Contributors

YYT and AGL formulated the research question. AGL obtained funding for the study. YYT, VP, and AGL designed the study and analysis plan. YYT, VP, WHC, and SHM prepared the data. YYT did the statistical analysis. YYT, WHC, SHM, and AGL designed and reviewed statistical methodology. YYT and SD prepared the electronic health record code lists. YYT and AGL drafted the initial and early versions of the manuscript. All authors critically reviewed the early and final versions of manuscript. YYT and AGL have accessed and verified the underlying data reported in the manuscript. All authors had access to all the data reported in the study. The corresponding author had the final responsibility to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The data used in this study are available on successful ethics application to the Clinical Practice Research Datalink (https://cprd.com/primary-care-data-public-health-research; enquiries@cprd.com). All summarised data and results are available in the appendix. The code used in our analysis is available at https://zenodo.org/record/7022506; doi: 10.5281/zenodo.7022506.

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