Trials

Clinical trial results in context: comparison of baseline characteristics and outcomes of 38510 RECOVERY trial participants versus a reference population of 346271 people hospitalised with COVID-19 in England

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Abstract:

Background:
Randomised trials are essential to reliably assess medical interventions. Nevertheless, interpretation of such studies, particularly when considering absolute effects, is enhanced by understanding how the trial population may differ from the populations it aims to represent.
Methods:
We compared baseline characteristics and mortality of RECOVERY participants recruited in England (n= 38510) with a reference population hospitalised with COVID-19 in England (n = 346271) from March 2020 - November 2021. We used linked hospitalisation and mortality data for both cohorts to extract demographics, comorbidity/frailty scores, and crude and age- and sex-adjusted 28-day all-cause mortality.
Results:
Demographics of RECOVERY participants were broadly similar to the reference population, but RECOVERY participants were younger (mean age [standard deviation]: RECOVERY 62.6 [15.3] vs reference 65.7 [18.5] years) and less frequently female (37% vs 45%). Comorbidity and frailty scores were lower in RECOVERY, but differences were attenuated after age stratification. Age- and sex-adjusted 28-day mortality declined over time but was similar between cohorts across the study period (RECOVERY 23.7% [95% confidence interval: 23.3%-24.1%]; vs reference 24.8% [24.6%-24.9%]), except during the first pandemic wave in the UK (March-May 2020) when adjusted mortality was lower in RECOVERY.
Conclusions:
Adjusted 28-day mortality in RECOVERY was similar to a nationwide reference

	population of patients admitted with COVID-19 in England during the same period but varied substantially over time in both cohorts. Therefore, the absolute effect estimates from RECOVERY were broadly applicable to the target population at the time, but should be interpreted in the light of current mortality estimates. Trial registration: ISRCTN50189673, NCT04381936
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Title:

Clinical trial results in context: comparison of baseline characteristics and outcomes of 38510 RECOVERY trial participants versus a reference population of 346271 people hospitalised with COVID-19 in England

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Abstract

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We compared baseline characteristics and mortality of RECOVERY participants recruited in England (n= 38510) with a reference population hospitalised with COVID-19 in England (n = 346271) from March 2020 - November 2021. We used linked hospitalisation and mortality data for both cohorts to extract demographics, comorbidity/frailty scores, and crude and age- and sex-adjusted 28-day all-cause mortality.

Results:

Demographics of RECOVERY participants were broadly similar to the reference population, but RECOVERY participants were younger (mean age [standard deviation]: RECOVERY 62.6 [15.3] vs reference 65.7 [18.5] years) and less frequently female (37% vs 45%). Comorbidity and frailty scores were lower in RECOVERY, but differences were attenuated after age stratification. Age- and sex-adjusted 28-day mortality declined over time but was similar between cohorts across the study period (RECOVERY 23.7% [95% confidence interval: 23.3%-24.1%]; vs reference 24.8% [24.6%-24.9%]), except during the first pandemic wave in the UK (March-May 2020) when adjusted mortality was lower in RECOVERY.

Conclusions:

Adjusted 28-day mortality in RECOVERY was similar to a nationwide reference population of patients admitted with COVID-19 in England during the same period but varied substantially over time in both cohorts. Therefore, the absolute effect estimates from RECOVERY were broadly applicable to the target population at the time, but should be interpreted in the light of current mortality estimates.

Trial registration: ISRCTN50189673, NCT04381936

List of abbreviations

95% CI: 95% confidence intervals

CRF: case-report form

HES: Hospital Episode Statistics

ICD-10: International Classification of Diseases and Related Health Problems, Tenth Revision

IQR: inter-quatile range

NHS: National Health Service

RCTs: randomised controlled trials

RECOVERY: Randomised Evaluation of COVID-19 Therapy

SD: standard deviation

Background

Randomised controlled trials (RCTs) are essential to reliably evaluate safety and efficacy of health interventions.(1,2) The use of randomisation (with allocation concealment) minimises the risk of bias but, inevitability, due to eligibility criteria, trial participants are rarely representative of the populations whose treatment they aim to inform. Nonetheless, the proportional estimates of treatment effects from the trial are usually generalisable to the broader population, unless there are good grounds for believing there may be systematic differences in the effectiveness of the intervention or in the biology of the target disease outside of the trial setting (e.g. the advent of a new variant that renders a pathogen resistant to the particular drug that was studied).(3) However, the estimates of *absolute* harm and benefit generated by such trials may not be directly generalisable, and assessment of the absolute rates of the relevant outcomes in the target population is useful to understand the likely absolute effects of the intervention in clinical practice.(4,5)

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is an ongoing, randomised, controlled, open-label, pragmatic, platform trial of potential therapies for patients hospitalised with COVID-19.(6) Eligibility criteria are broad and simple (i.e. hospitalisation for suspected or confirmed COVID-19), and trial procedures are streamlined to be feasible in local practice. Data collection by trial staff, using dedicated case-report forms (CRF), focuses on the minimum information needed, and is

complemented with extensive linkage to several healthcare systems data sources in the UK. The trial is taking place in all acute UK National Health Service (NHS) hospitals, and in several other countries globally.

Here, we aimed to compare the baseline characteristics (demographics and comorbidities) and all-cause 28-day mortality (the trial primary outcome) for RECOVERY participants with a reference population hospitalised with COVID-19, within England.

Methods

RECOVERY cohort

The RECOVERY trial design has been described previously.(6) Briefly, RECOVERY recruits patients admitted to hospital with confirmed or suspected COVID-19 who are considered suitable for inclusion by their attending clinical team. Recruitment was not targeted to any particular subgroups or aimed at achieving a representative sample of the target population; the aim was to recruit a large number of participants rapidly. Randomisation is performed via a short online CRF in which essential baseline data are collected. Follow-up data are collected using a simple CRF upon death, hospital discharge, or at 28 days from randomisation (whichever occurs sooner). In the UK, these data are complemented with linkage to national healthcare systems data sources. The protocol, data analysis plan, baseline characteristics and outcome derivation documentation, and published results are openly available at www.recoverytrial.net, and the trial is registered with ISRCTN (50189673) and ClinicalTrials.gov (NCT04381936). Written informed consent was obtained from all the patients or from a legal representative if they were unable to provide consent. The RECOVERY trial has been approved by the UK Medicines and Healthcare products Regulatory Agency and the Cambridge East Research Ethics Committee (reference 20/EE/0101).

For this analysis we included all RECOVERY participants recruited in England who had not withdrawn consent and had available healthcare systems data on hospital admissions (Hospital Episode Statistics [HES]),(7) with or without mortality data from official death records (Civil Registrations).(8) We excluded children aged <16 years due to difficulties in accessing linked healthcare systems data in this group in RECOVERY. HES data contained information on admissions to all NHS hospitals in England

(using standardised coding practices since the 1990s), namely admission and discharge dates and relevant diagnostic and procedure codes. Diagnostic codes are recorded using the *International Classification of Diseases and Related Health Problems, Tenth Revision* (ICD-10) clinical terminology, and can be assigned a position from 1 to 20; codes in position 1 usually indicate the primary cause of admission (or main cause of extension of hospital stay).(9) Civil Registrations included information on date of death and underlying and contributing causes of death (also coded using ICD-10). HES and Civil Registrations were linked and supplied by NHS England.(10)

Reference population

To derive a reference population of people hospitalised with COVID-19 in England (thus potentially eligible for RECOVERY), we used an anonymised database covering the entirety of England which includes linked HES and Civil Registrations data continuously collected since 1999. These data were linked and supplied by NHS England, and are analysed at the University of Oxford.(11) More information can be found in the NHS England Data Uses Register at http://digital.nhs.uk/services/data-access-request-service-dars/data-uses-register (reference: DARS-NIC-315419-F3W7K). Approval for the use of the datasets was provided by the Central and South Bristol Research Ethics Committee (ref 04/Q2006/176).

The reference population was ascertained based on the presence of a COVID-19 ICD-10 code (U071 - "COVID-19, Virus identified", or U072 - "COVID-19, Virus not identified").(12) This approach was informed by preliminary cross-validation work (Annex III) using linked HES and SARS-CoV-2 testing data for RECOVERY participants, which showed 92% of RECOVERY participants recruited in England with a positive SARS-CoV-2 test (as captured in NHS England's COVID-19 Second Generation Surveillance System – SGSS dataset)(13) had an admission in the HES data which included one of these codes in the primary diagnostic position. We therefore restricted our reference population to individuals with relevant ICD-10 codes in the primary position to avoid inclusion of people in whom COVID-19 was not the main reason for care. The RECOVERY cohort largely overlaps the reference population, but given the anonymised nature of the national datasets it was not possible to identify them.

Analysis period

For each individual in RECOVERY and the reference population, we assigned an index date as the start of the earliest HES episode with U071/U072 in the first diagnostic position. For RECOVERY participants with index dates before 1st March 2020 (indicating long episodes before inclusion in the study; n=22), or no COVID-19 codes in their HES records (n=1465) we used randomisation date as the index date. We then restricted our analysis period to index dates between 1st March 2020 and 30th November 2021 inclusive. These analyses were not extended beyond this time-point as the launch of the high-dose dexamethasone comparison in the UK (only suitable to patients with oxygen or ventilation requirements) resulted in more selected patient populations being included in the trial.(14)

Baseline characteristic and outcomes

We used HES data in both cohorts to extract baseline clinical characteristics and demographics including age, sex, ethnicity, deprivation (quintile of Index of Multiple Deprivation 2019),(15) geographical location, Charlson Comorbidity Score (16,17) and its components, and Hospital Frailty Risk Score.(18) Comorbidities were defined as the presence of a relevant ICD-10 code in any diagnostic position recorded within 5 years before the index date (i.e. excluding the index episode). Further methodological details, including the ICD-10 codes used, are provided in Annex I. Geographical location data (including for deprivation assessments) were extracted from HES records and ascertained from full postcode in the RECOVERY HES data and lower-super output area of the postcode in the national HES data.

For outcomes, we calculated all-cause mortality within 28 days using linked HES and Civil Registrations data. Ascertainment of fact and date of death was based on these linked data sources (derivation methodology described elsewhere).(19) We considered death records occurring in either healthcare systems data source. We ignored reports of deaths of RECOVERY participants recorded only on the CRF data as there were no CRF data for the reference population.

Statistical analyses

This analysis is limited to RECOVERY participants in England with available HES data. To assess how this selection may have affected the cohort characteristics we first compared the characteristics of those recruited in England with those recruited in other UK nations (using CRF data for all characteristics

except ethnicity, and healthcare systems data in each nation for ethnicity). We then compared the characteristics of RECOVERY participants recruited in England who had available HES data with those who did not (using CRF data for all characteristics except ethnicity, for which we used healthcare systems data from primary care).

We compared baseline characteristics and 28-day mortality of the RECOVERY cohort with those of the reference population, in each case restricted to England only. Age was stratified into 4 groups: <60, 60-69, 70-79, and ≥80. We presented continuous parameters as mean with standard deviation (SD) or median with interquartile range (IQR) as appropriate (with visual assessment of frequency distribution for normality), and frequency counts and percentage distribution for categorical parameters. We compared age, sex, and region of residence by calculating a representativeness ratio - defined as the proportion of people within RECOVERY in each category divided by the proportion of people within the reference population in the same category – and presented these along with 95% confidence intervals [95% CI].(20) We also calculated a recruitment ratio defined as number of individuals included in RECOVERY divided by the number of individuals in the reference population. We then aggregated individuals in each cohort into three-month periods and conducted the same calculations as above for each time period separately.

The primary RECOVERY trial outcome of 28-day all-cause mortality was calculated starting from the index date in both cohorts, overall and over time (by three-month periods). We presented crude and age- and sex-adjusted mortality rates with 95% CI,(20) with adjustment performed using direct standardisation methods(20) (i.e. applying RECOVERY mortality rates to the reference population age and sex composition using the age groups mentioned above). Further methodological details are provided in Annex I.

We used Stata v17/MP to derive baseline characteristics and outcomes in HES and Civil Registrations data in both cohorts, and R v4.2.1 for all subsequent data management, statistical analysis, and plotting (further details are provided in Annex I).

Results

Baseline characteristics

Up until 1st September 2022, RECOVERY recruited 46010 participants, of which 44766 in the UK and 39952 in England. Of these, 39304 (98.4%) had available HES data, and 38780 were recruited within the analysis period (1st March 2020 – 30th November 2021). After excluding participants aged below 16 at the index date, a total of 38510 participants were finally included in our analysis (Figure 1). RECOVERY participants recruited in other UK nations had generally similar characteristics to those recruited in England (**Error! Reference source not found.**). People with no HES data available were younger, less frequently of white ethnicity, and had generally lower comorbidity burden and need for respiratory support at randomisation (Supplementary Table S2). The reference population included 346271 individuals (Figure 1); for every 100 people admitted with COVID-19 in England, 11 participants were recruited to RECOVERY. When considering geographical region, the proportion of relevant patients recruited to RECOVERY in London, West Midlands, and Yorkshire and The Humber was lower than in the other England regions (Figure 2).

Table 1 shows the baseline characteristics of both cohorts. RECOVERY participants were less frequently female (RECOVERY 37% vs reference population 45%) and were on average slightly younger than the reference population (mean age [SD]: 62.6 [15.3] vs 65.7 [18.5] years), with people aged 80+ and women underrepresented in RECOVERY throughout the analysis period (**Error! Reference source not found.** and **Error! Reference source not found.**3). RECOVERY participants were more frequently of White background (83% vs 79%) (Table 1 and **Error! Reference source not**

found.), but had similar deprivation status overall and throughout the study period (**Error! Reference source not found.**).

With respect to clinical conditions, RECOVERY participants had a lower prevalence of comorbidity (median Charlson Comorbidity Score [IQR]: RECOVERY 3.0 [1.0-5.0] vs reference population 4.0 [1.0-6.0]) and were less frail (median Hospital Frailty Risk Score [IQR]: 5.1 [1.8-11.4] vs 6.3 [1.8-16.3]) These differences were largely explained by the age structure of the two cohorts, with small differences remaining in the prevalence of some comorbidities, including cardiovascular disease, congestive heart failure, and dementia, after accounting for age (Supplementary Figures S4-S6).

Outcomes

Overall, the crude all-cause 28-day mortality in RECOVERY was 20.6% (95% CI: 20.2%-21.0%) and 24.8% (95% CI: 24.6%-25.0%) in the reference population, with mortality decreasing substantially in both cohorts from March 2021 onwards. After standardising the RECOVERY cohort to the age-sex composition of the national reference population, 28-day mortality in RECOVERY was similar to the reference population (23.7%, 95% CI: 23.3%-24.1%; **Error! Reference source not found.**). Age-stratified mortality rates were similar between the two cohorts, with the exception of March-May 2020 where mortality was lower in RECOVERY (Supplementary Figures S7-S8 and Supplementary Table S4). When mortality was assessed separately by comorbidity level and age, the difference in 28-day mortality between the two cohorts in March-May 2020 appeared to be mostly driven by older and more comorbid patients (Supplementary Figure S9).

Discussion

This study compared the characteristics of RECOVERY trial participants with people admitted to hospital due to COVID-19 in England. Our main findings were that RECOVERY participants were generally similar, but slightly younger, less frequently female, and had an overall lower comorbidity and frailty burden, much of which attributable to age differences. After adjustment for age and sex, 28-day mortality in the RECOVERY cohort was similar to that in the wider population of patients admitted to hospital with COVID-19 in England. This pattern was observed throughout the period studied, with the exception of March – May 2020 (corresponding to the first COVID-19 wave in the UK) when, even after adjusting for age and sex, 28-day mortality in RECOVERY was slightly lower than the reference population. The reasons for this are not fully explained by differences in measured frailty or comorbidity as assessed in our analyses and may be attributable to factors not captured in the datasets available in this study.

Older adults are frequently underrepresented in trials,(21) and have been excluded from over half of COVID-19 clinical trials and all major vaccine trials.(22) Although RECOVERY does not have an upper age limit (and some participants were aged over 100 years old), in our study RECOVERY participants were on average 3 years younger, with underrepresentation of people aged ≥80. RECOVERY participants were also less frequently female (37% vs 45%) but it is not possible to identify the possible reasons for this in the available data. We also found that comorbidity and frailty scores were lower in the RECOVERY cohort compared with the reference population. Most of these differences were attributable to age composition, but within older age groups comorbidities and the overall frailty risk scores remained slightly higher in the reference population. Clinical decision making about eligibility for randomised trials will inevitably result in differences between the trial cohort and the target population; however, the proportional estimates of treatment effect from trials are usually generalisable, unless there are substantial differences in the biology of the target disease or the effectiveness of the intervention in the non-trial context.(4,5)

While crude 28-day all-cause mortality was lower in RECOVERY, age- and sex-adjusted mortality were generally similar, with similar trends in both cohorts over time. The reduction seen from March 2021

onwards, consistent with previous reports,(23) may represent the effect of SARS-CoV-2 vaccination uptake, which greatly reduced the likelihood not only of hospital admission but also of death following hospitalisation.(24,25) Overall, the absolute effect estimates generated by RECOVERY were generalisable to the national population during the period studied. However, secular trends in mortality rates should be considered and the best estimate of the likely absolute effect size in current clinical practice requires application of the proportional treatment effect from the RECOVERY trial to current absolute event rates among patients hospitalised with COVID-19.(4,5)

Our study has a number of limitations. We were not able to determine baseline respiratory status (which has been shown to be an important determinant of the proportional and absolute benefits of corticosteroid treatment)(26) in our reference cohort, since there was low agreement between respiratory support status extracted from HES alone and that collected in the trial (based on a larger number of linked data sources) and used in published analyses (Annex IV). We also cannot be certain whether our reference population had clinically significant COVID-19, although we have mitigated this by including only people with a relevant ICD-10 code in the primary diagnostic position. Finally, our analysis was restricted to people admitted in England. Baseline characteristics were similar when comparing RECOVERY participants recruited across all UK nations, but may differ from non-UK countries. Finally, our analysis was restricted to the period from March 2020 to November 2021, due to changes to trial eligibility which could not be replicated in the reference population with the available data. However, recruitment to RECOVERY declined significantly from December 2021 onwards (along with national COVID-19 admissions), so that extending the analysis period to the time of writing (mid-2023) would add only a small number of additional deaths (~4%), which were unlikely to meaningfully influence interpretation of our results.

Conclusion

The RECOVERY trial recruited a broad patient population that was generally representative of people admitted to hospital due to COVID-19 in England during the same period, with respect to both baseline characteristics and subsequent mortality. 28-day mortality declined substantially in both the

RECOVERY and reference populations throughout the period studied. Estimates of current mortality rates from healthcare systems data combined with the proportional treatment effects from trials are needed to estimate the likely absolute effects of the treatments tested within current practice.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from all the patients or from a legal representative if they were unable to provide consent. The RECOVERY trial has been approved by the UK Medicines and Healthcare products Regulatory Agency and the Cambridge East Research Ethics Committee (reference 20/EE/0101). The RECOVERY trial has been approved by the UK Medicines and Healthcare products Regulatory Agency and the Cambridge East Research Ethics Committee (reference 20/EE/0101). The dataset used to build the reference population by the University of Oxford has been approved by the Central and South Bristol Research Ethics Committee (reference 04/Q2006/176).

Consent for publication

Not applicable.

Availability of data and materials

The RECOVERY trial protocol, consent form, statistical analysis plan, definition and derivation of clinical characteristics and outcomes, training materials, regulatory documents, and other relevant study

materials are available online at www.recoverytrial.net. Data will be made available in line with the Nuffield Department of Population Health policy and procedures. Those wishing to request access should complete the form available at http://www.ndph.ox.ac.uk/data-access and email it to data.access@ndph.ox.ac.uk. Nationwide anonymised English mortality (Civil Registrations) and hospitalisations (HES) data used to derive the reference population can be obtained upon application to NHS England at www.digital.nhs.uk. The statistical programming code used in this work is available for inspection and reuse at http://gitlab.ndph.ox.ac.uk/guilhermep/recovery-generalizability-representativeness.

Competing interests

Roche, AbbVie, Regeneron, and GSK have provided study drugs for evaluation in the RECOVERY trial. MM is an applicant on research grants from Novartis and Novo Nordisk (unrelated to this work). ML is in receipt of grants to University of Oxford from Novartis and Boehringer Ingelheim and grants to Protas from Regeneron, Sanofi, Moderna, FluLab, Google Ventures and Schmidt Futures (all unrelated to this work).

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CH). For the purpose of open access, the author(s) has applied a Creative Commons Attribution (CC BY) licence to any Author Accepted Manuscript version arising.

Authors' contributions

This manuscript was initially drafted by GPA, RG, MC, CH, and MM, and further developed and approved by all authors. GPA, RG, MC, CH, and MM conceptualised and designed this analysis. GPA and RG performed data derivation and analysis. GPA performed data visualisation. GPA, RG, CC, WS, AK, DM, RW, MN, KW, and MC contributed to data acquisition, management, and processing, together with the broader RECOVERY Collaborative Group. All authors contributed to data interpretation and critical review and revision of the manuscript.

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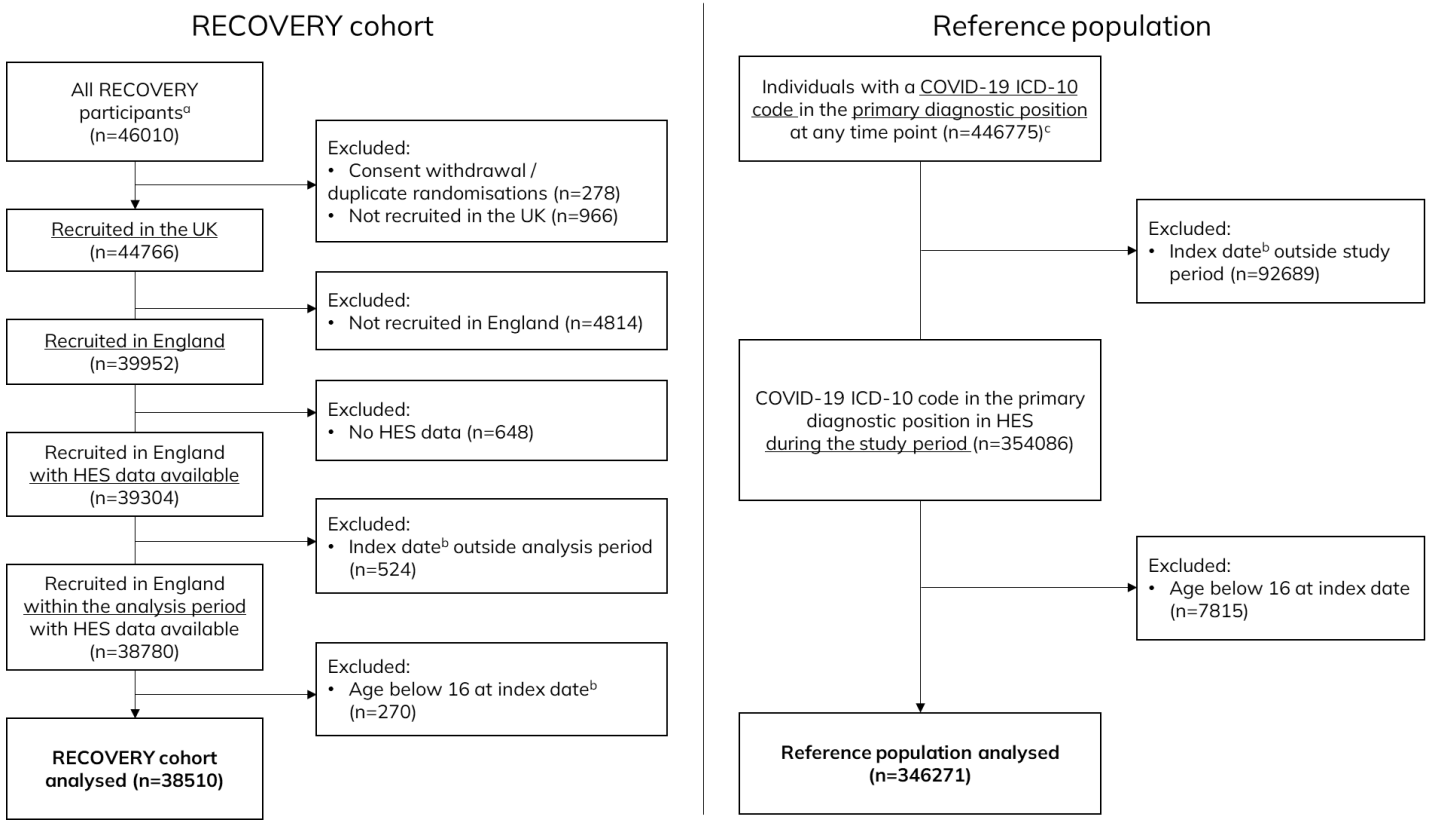
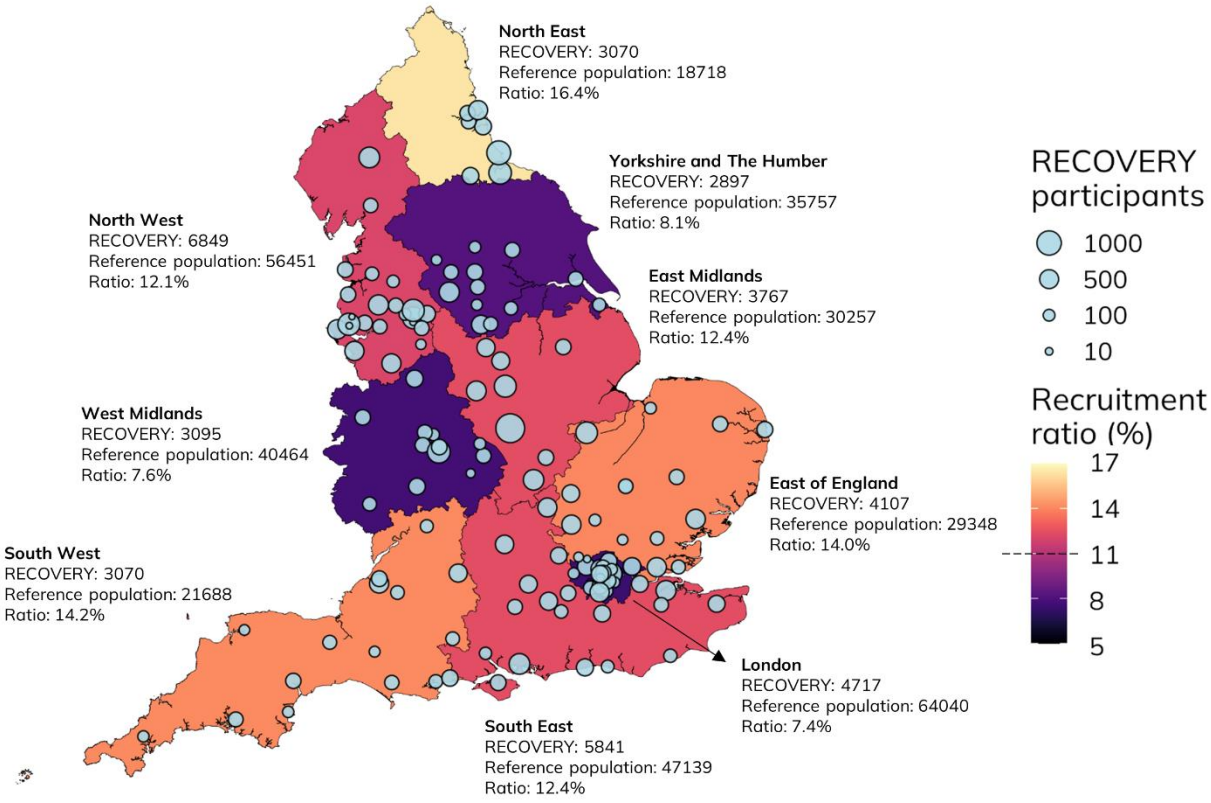
Figures

Figure 1 - CONSORT diagram depicting the cohort derivation process



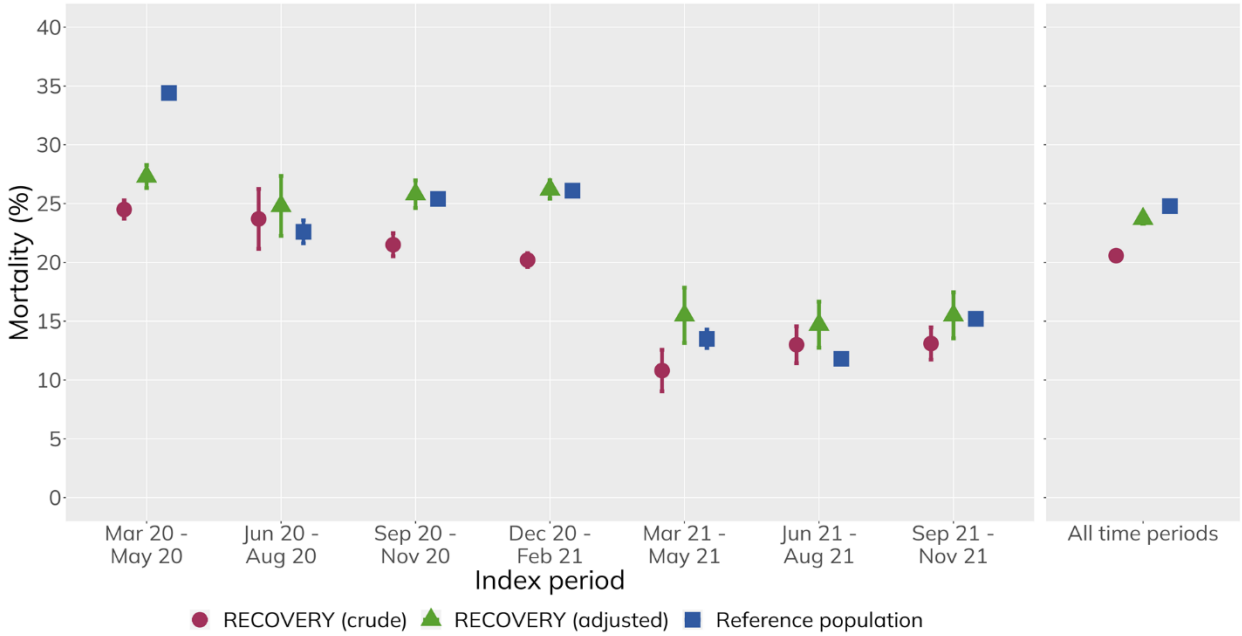
[a] Randomised up until the 1st September 2022; [b] Index date is the episode start date for the earliest episode with a COVID-19 ICD-10 code in the primary diagnostic position; [c] Up to June 2022 (latest data included in the raw extract)

Figure 2 - Geographical representativeness of the RECOVERY trial cohort in comparison with the national reference population



Number of RECOVERY participants plotted at the location of the recruiting NHS Trust hospital site. Recruitment ratios were calculated by dividing the number of RECOVERY participants recruited in each region by the number of individuals in the reference population in the same region, and are presented by region. The average recruitment ratio across all English regions was 11.1%. There were 1097 and 2409 individuals with missing residential area in HES data in the RECOVERY and the reference population cohort, respectively.

Figure 3 - All-cause 28-day mortality over time in RECOVERY and the reference population



Period		Mar 20 – May 20	Jun 20 – Aug 20	Sep 20 – Nov 20	Dec 20 – Feb 21	Mar 21 –May 21	Jun 21 – Aug 21	Sep 21 – Nov 21	All time periods
Number of individuals	RECOVERY	9634	1002	6208	16448	1160	1905	2153	38510
	Reference population	78180	6939	49431	127750	9319	32464	42188	346271
Recruitment ratio (%)		12.3	14.4	12.6	12.9	12.4	5.9	5.1	11.1
Deaths	RECOVERY	2364	237	1335	3330	125	248	283	7922
	Reference population	26855	1570	12557	33361	1255	3841	6405	85844
28-day mortality (95% CI)	RECOVERY, crude	24.5 (23.7 - 5.3)	23.7 (21.2 -26.2)	21.5 (20.5 -22.5)	20.2 (19.6 -20.8)	10.8 (9.0 -12.6)	13.0 (11.4 -14.6)	13.1 (11.7 -14.5)	20.6 (20.2 -21.0)
	RECOVERY, adjusted	27.3 (26.3 -28.3)	24.8 (22.3 -27.3)	25.8 (24.6 -27.0)	26.2 (25.4 -27.0)	15.5 (13.1 -17.9)	14.7 (12.7 -16.7)	15.4 (13.4 -17.4)	23.7 (23.3 -24.1)
	Reference population	34.4 (34.0 - 34.8)	22.6 (21.6 - 23.6)	25.4 (25.0 - 25.8)	26.1 (25.9 - 26.3)	13.5 (12.7 - 14.3)	11.8 (11.4 - 12.2)	15.2 (14.8 - 15.6)	24.8 (24.6 – 25.0)

28-day mortality is the proportion of people with death recorded within 28 days of their index date (with 95% confidence intervals included). Adjustment performed by applying RECOVERY 28-day mortality to an age- (5-year bands) and sex-standardised population using the reference population, in a rolling basis within each time period (for 28-day mortality and age and sex breakdown).

Tables

Table 1 - Baseline cohort characteristics

Characteristic	RECOVERY, N = 38510	Reference population, N = 346271
Age, mean (SD)	62.6 (15.3)	65.7 (18.5)
<60	16121 (41.9%)	123790 (35.7%)
60-69	8906 (23.1%)	56452 (16.3%)
70-79	7871 (20.4%)	69107 (20.0%)
80+	5612 (14.6%)	96922 (28.0%)
Sex		
Female	14060 (36.5%)	155441 (44.9%)
Male	24424 (63.5%)	190748 (55.1%)
Geographical region[a]		
London	4717 (12.2%)	64040 (18.5%)
North West	6849 (17.8%)	56451 (16.3%)
South East	5841 (15.2%)	47139 (13.6%)
West Midlands	3095 (8%)	40464 (11.7%)
Yorkshire and The Humber	2897 (7.5%)	35757 (10.3%)
East Midlands	3767 (9.8%)	30257 (8.7%)
East of England	4107 (10.7%)	29348 (8.5%)
South West	3070 (8%)	21688 (6.3%)
North East	3070 (8%)	18718 (5.4%)
Unknown/not resident in England	1097 (2.9%)	2409 (0.7%)
Ethnicity[a]		
White	29595 (83.3%)	253842 (78.9%)
Black	1171 (3.3%)	16909 (5.3%)

Asian	3263 (9.2%)	35785 (11.1%)
Other	1146 (3.2%)	11853 (3.7%)
Mixed	351 (1.0%)	3532 (1.1%)
Unknown	2984 (7.7%)	24350 (7.0%)
Index of multiple deprivation (quintile)		
1 (Most deprived)	9821 (25.5%)	94487 (27.3%)
2	8284 (21.5%)	78400 (22.6%)
3	7466 (19.4%)	65082 (18.8%)
4	6910 (17.9%)	57203 (16.5%)
5 (Least deprived)	5797 (15.1%)	48650 (14.0%)
Unknown	232 (0.6%)	2449 (0.7%)
Charlson score, median (IQR)	3.0 (1.0, 5.0)	4.0 (1.0, 6.0)
Myocardial infarction	2941 (7.6%)	34895 (10.1%)
Congestive heart failure	3158 (8.2%)	44007 (12.7%)
Peripheral vascular disease	2052 (5.3%)	24327 (7.0%)
Cerebrovascular disease	2603 (6.8%)	41812 (12.1%)
Chronic pulmonary disease	8160 (21.2%)	80492 (23.2%)
Rheumatic disease	1579 (4.1%)	17365 (5.0%)
Dementia	1234 (3.2%)	30314 (8.8%)
Peptic ulcer disease	710 (1.8%)	7693 (2.2%)
Liver disease (mild)	1515 (3.9%)	14674 (4.2%)
Liver disease (moderate-severe)	175 (0.5%)	2490 (0.7%)
Diabetes mellitus (without chronic complications)	6056 (15.7%)	59244 (17.1%)
Diabetes mellitus (with chronic complications)	1354 (3.5%)	16111 (4.7%)
Chronic kidney disease	3800 (9.9%)	54019 (15.6%)
Solid tumour	2463 (6.4%)	26844 (7.8%)
Metastatic cancer	589 (1.5%)	8287 (2.4%)

Lymphoma	389 (1.0%)	3238 (0.9%)
Leukaemia	320 (0.8%)	2775 (0.8%)
AIDS/HIV[b]	0 (0.0%)	0 (0.0%)
Hospital frailty score, median (IQR)	5.1 (1.8, 11.4)	6.3 (1.8, 16.3)
High-risk (>15)	6737 (17.5%)	94191 (27.2%)
Intermediate risk (5-15)	12751 (33.1%)	99402 (28.7%)
Low risk (<5)	19022 (49.4%)	152678 (44.1%)
Other comorbidities/demographics		
Renal replacement therapy	439 (1.1%)	4922 (1.4%)
Immunosuppression	1471 (3.8%)	15531 (4.5%)
Obesity	6147 (16.0%)	48749 (14.1%)
Severe mental illness	4268 (11.1%)	43969 (12.7%)
Alcohol-attributable diseases	945 (2.5%)	10909 (3.2%)

HES - Hospital Episode Statistics; IQR - interquartile range; SD - standard deviation

Data are shown as Mean (SD); n (%); or Median (IQR)

[a]Proportions for people with known and unknown geographical region and ethnicity were calculated separately, using the entire cohort as denominator for each calculation

[b]ICD-10 codes for AIDS/HIV are censored from HES data

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Table 1 - Baseline cohort characteristics

Characteristic	RECOVERY, N = 38,510	Reference population, N = 346,271
Age, mean (SD)	62.6 (15.3)	65.7 (18.5)
<60	16,121 (41.9%)	123,790 (35.7%)
60-69	8,906 (23.1%)	56,452 (16.3%)
70-79	7,871 (20.4%)	69,107 (20.0%)
80+	5,612 (14.6%)	96,922 (28.0%)
Sex		
Female	14,060 (36.5%)	155,441 (44.9%)
Male	24,424 (63.5%)	190,748 (55.1%)
Geographical region[a]		
London	4717 (12.2%)	64,040 (18.5%)
North West	6849 (17.8%)	56,451 (16.3%)
South East	5841 (15.2%)	47,139 (13.6%)
West Midlands	3095 (8%)	40,464 (11.7%)
Yorkshire and The Humber	2897 (7.5%)	35,757 (10.3%)
East Midlands	3767 (9.8%)	30,257 (8.7%)
East of England	4107 (10.7%)	29,348 (8.5%)
South West	3070 (8%)	21,688 (6.3%)
North East	3070 (8%)	18,718 (5.4%)
Unknown/not resident in England	1097 (2.9%)	2409 (0.7%)
Ethnicity[a]		
White	29,595 (83.3%)	253,842 (78.9%)
Black	1,171 (3.3%)	16,909 (5.3%)
Asian	3,263 (9.2%)	35,785 (11.1%)
Other	1,146 (3.2%)	11,853 (3.7%)
Mixed	351 (1.0%)	3,532 (1.1%)
Unknown	2,984 (7.7%)	24,350 (7.0%)
Index of multiple deprivation (quintile)		
1 (Most deprived)	9,821 (25.5%)	94,487 (27.3%)
2	8,284 (21.5%)	78,400 (22.6%)
3	7,466 (19.4%)	65,082 (18.8%)
4	6,910 (17.9%)	57,203 (16.5%)

5 (Least deprived)	5,797 (15.1%)	48,650 (14.0%)
Unknown	232 (0.6%)	2,449 (0.7%)
Charlson score, median (IQR)	3.0 (1.0, 5.0)	4.0 (1.0, 6.0)
Myocardial infarction	2,941 (7.6%)	34,895 (10.1%)
Congestive heart failure	3,158 (8.2%)	44,007 (12.7%)
Peripheral vascular disease	2,052 (5.3%)	24,327 (7.0%)
Cerebrovascular disease	2,603 (6.8%)	41,812 (12.1%)
Chronic pulmonary disease	8,160 (21.2%)	80,492 (23.2%)
Rheumatic disease	1,579 (4.1%)	17,365 (5.0%)
Dementia	1,234 (3.2%)	30,314 (8.8%)
Peptic ulcer disease	710 (1.8%)	7,693 (2.2%)
Liver disease (mild)	1,515 (3.9%)	14,674 (4.2%)
Liver disease (moderate-severe)	175 (0.5%)	2,490 (0.7%)
Diabetes mellitus (without chronic complications)	6,056 (15.7%)	59,244 (17.1%)
Diabetes mellitus (with chronic complications)	1,354 (3.5%)	16,111 (4.7%)
Chronic kidney disease	3,800 (9.9%)	54,019 (15.6%)
Solid tumour	2,463 (6.4%)	26,844 (7.8%)
Metastatic cancer	589 (1.5%)	8,287 (2.4%)
Lymphoma	389 (1.0%)	3,238 (0.9%)
Leukaemia	320 (0.8%)	2,775 (0.8%)
AIDS/HIV[b]	0 (0.0%)	0 (0.0%)
Hospital frailty score, median (IQR)	5.1 (1.8, 11.4)	6.3 (1.8, 16.3)
High-risk (>15)	6,737 (17.5%)	94,191 (27.2%)
Intermediate risk (5-15)	12,751 (33.1%)	99,402 (28.7%)
Low risk (<5)	19,022 (49.4%)	152,678 (44.1%)
Other comorbidities/demographics		
Renal replacement therapy	439 (1.1%)	4,922 (1.4%)
Immunosuppression	1,471 (3.8%)	15,531 (4.5%)
Obesity	6,147 (16.0%)	48,749 (14.1%)
Severe mental illness	4,268 (11.1%)	43,969 (12.7%)
Alcohol-attributable diseases	945 (2.5%)	10,909 (3.2%)

HES - Hospital Episode Statistics; IQR - interquartile range; SD - standard deviation

Data are shown as Mean (SD); n (%); or Median (IQR)

[a]Proportions for people with known and unknown geographical region and ethnicity were calculated separately, using the entire cohort as denominator for each calculation

[b]ICD-10 codes for AIDS/HIV are censored from HES data

Figure 1

Click here to access/download;Figure;figure_1_CONSORT_diagram_high_resolution.tif

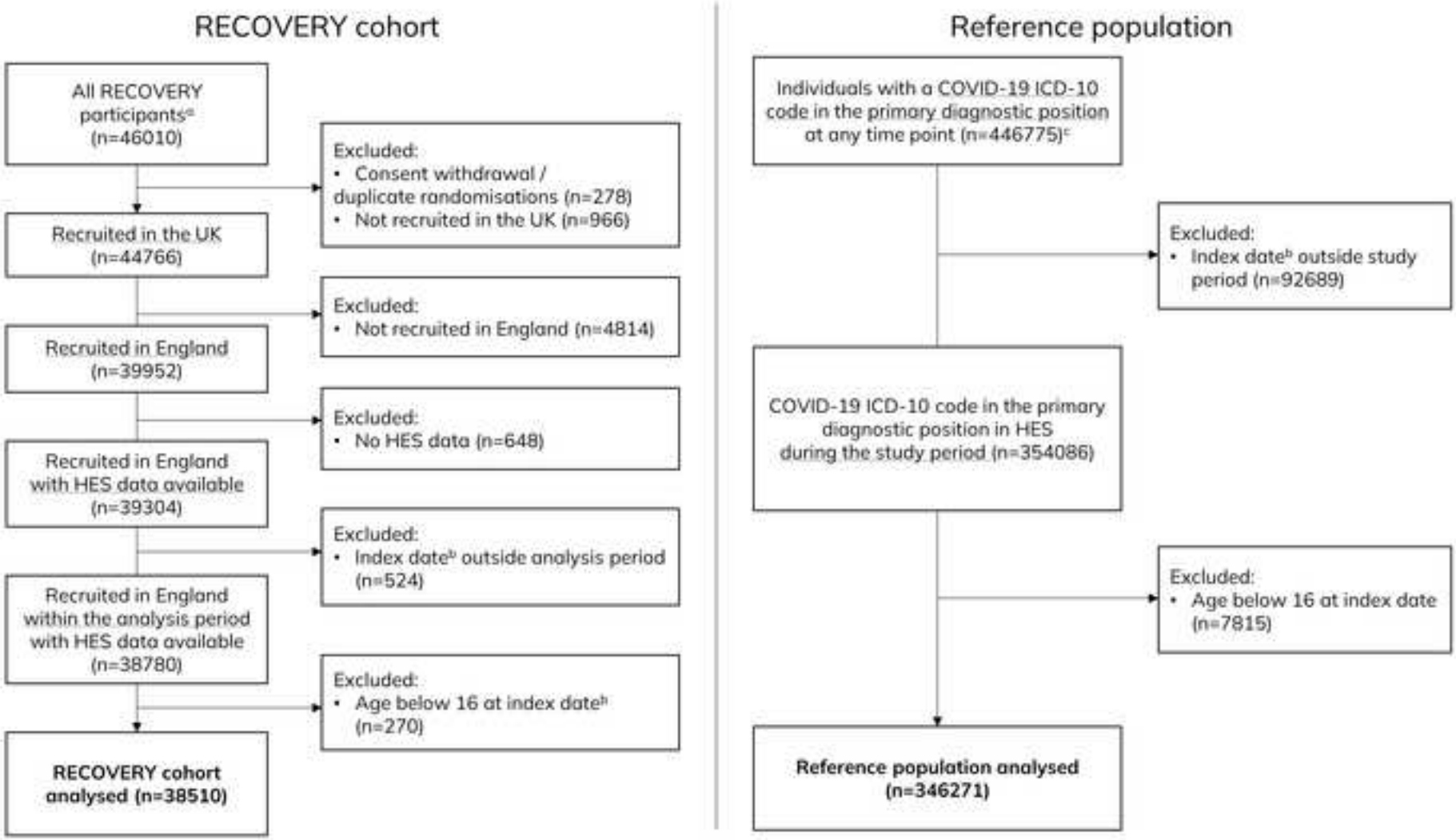


Figure 2

Click here to access/download;Figure;Figure_2_geographical_distribution_high_resolution.tif

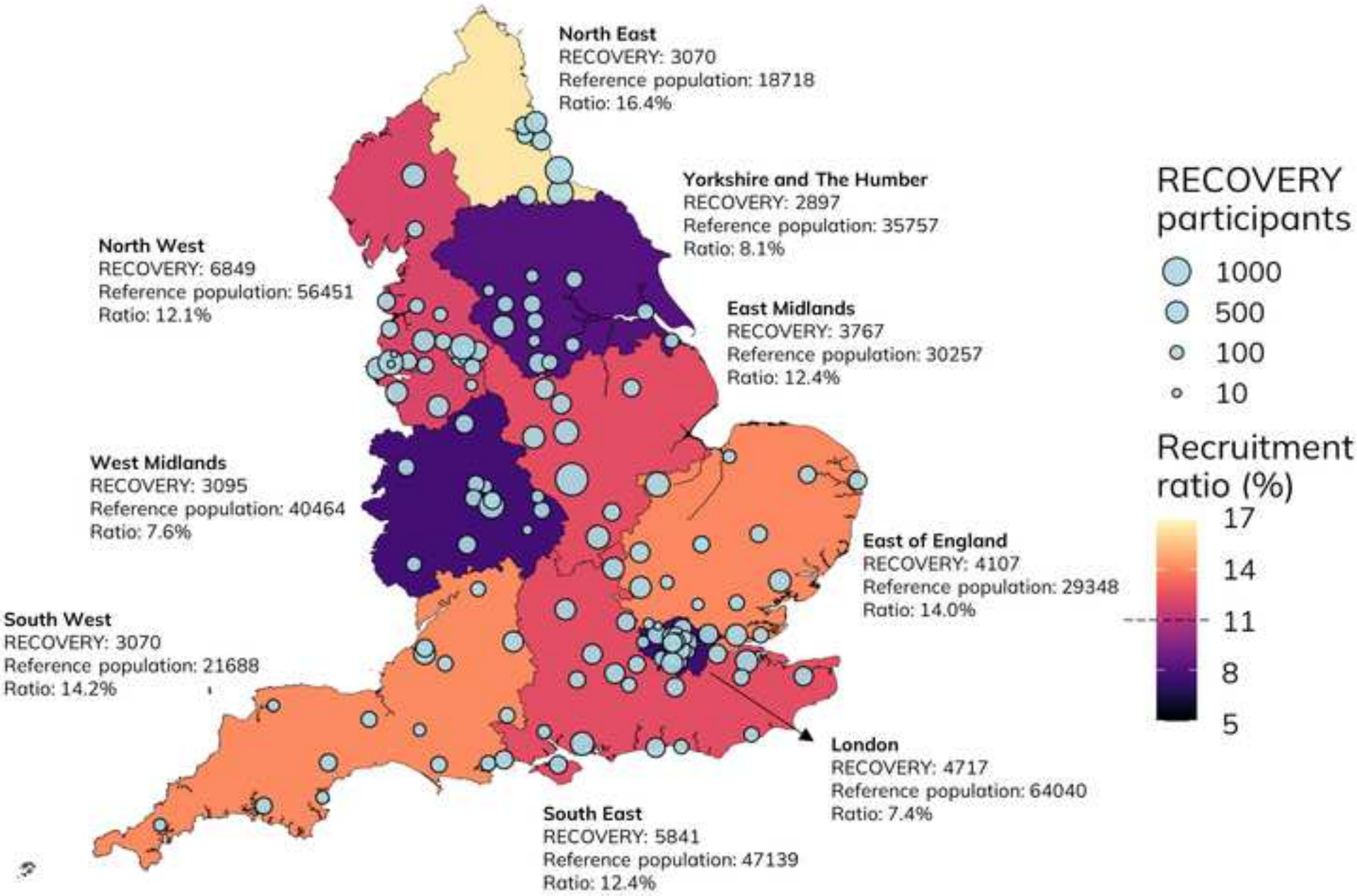
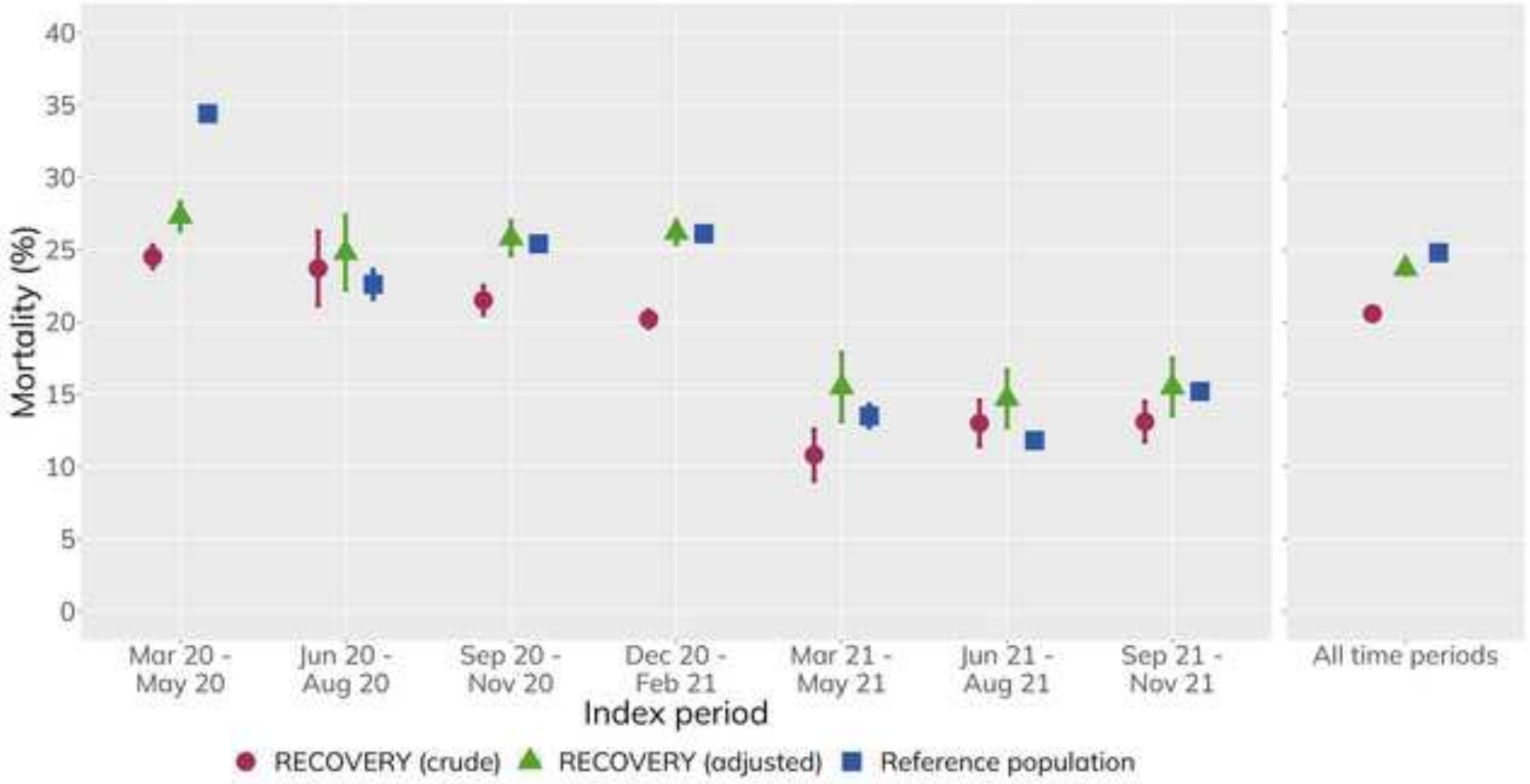


Figure 3

Click here to access/download;Figure;Figure_3_mortality_timeseries_high_resolution.tif



Period		Mar 20 – May 20	Jun 20 – Aug 20	Sep 20 – Nov 20	Dec 20 – Feb 21	Mar 21 –May 21	Jun 21 – Aug 21	Sep 21 – Nov 21	All time periods
Number of individuals	RECOVERY	9634	1002	6208	16448	1160	1905	2153	38510
	Reference population	78180	6939	49431	127750	9319	32464	42188	346271
Recruitment ratio (%)		12.3	14.4	12.6	12.9	12.4	5.9	5.1	11.1
Deaths	RECOVERY	2364	237	1335	3330	125	248	283	7922
	Reference population	26855	1570	12557	33361	1255	3841	6405	85844
28-day mortality (95% CI)	RECOVERY, crude	24.5 (23.7 - 5.3)	23.7 (21.2 -26.2)	21.5 (20.5 -22.5)	20.2 (19.6 -20.8)	10.8 (9.0 -12.6)	13.0 (11.4 -14.6)	13.1 (11.7 -14.5)	20.6 (20.2 -21.0)
	RECOVERY, adjusted	27.3 (26.3 -28.3)	24.8 (22.3 -27.3)	25.8 (24.6 -27.0)	26.2 (25.4 -27.0)	15.5 (13.1 -17.9)	14.7 (12.7 -16.7)	15.4 (13.4 -17.4)	23.7 (23.3 -24.1)
	Reference population	34.4 (34.0 - 34.8)	22.6 (21.6 - 23.6)	25.4 (25.0 - 25.8)	26.1 (25.9 - 26.3)	13.5 (12.7 - 14.3)	11.8 (11.4 - 12.2)	15.2 (14.8 - 15.6)	24.8 (24.6 - 25.0)

Ethics approval

Ethics approval

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6-7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	N/A
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8-9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	N/A
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			N/A
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	N/A
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	N/A
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	N/A
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	N/A

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9-10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9-10
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11
	13b	For each group, losses and exclusions after randomisation, together with reasons	11
Recruitment	14a	Dates defining the periods of recruitment and follow-up	8
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	22
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	19
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	12
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	12
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14-15
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14-15
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	14-15
Other information			
Registration	23	Registration number and name of trial registry	4,6
Protocol	24	Where the full trial protocol can be accessed, if available	6
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	17

Citation: Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Medicine. 2010;8:18.

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see www.consort-statement.org.

The RECORD statement

	Item No.	STROBE items	Location in manuscript where items are reported	Page numbers	RECORD items	Location in manuscript where items are reported	Page numbers
Title and abstract							
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Title and abstract	1,3	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between	Abstract Abstract + title Abstract	1,3 1,3 3

	Item No.	STROBE items	Location in manuscript where items are reported	Page numbers	RECORD items	Location in manuscript where items are reported	Page numbers
					databases was conducted for the study, this should be clearly stated in the title or abstract.	Abstract	3
Introduction							
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction	5-6			
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction	5-6			
Methods							
Study Design	4	Present key elements of study design early in the paper	Abstract, methods	3, 8-12			
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Abstract, methods, supplementary methods, Figure 2	3, 8-12, 22 Supplement: 1-3			
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of	Methods, supplementary methods (Annex I	8-11, 21 Supplement: 1-3, 8-11	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to	Methods, Figure 1, supplementary methods (Annex I	8-11, 21 Supplement: 1-3, 8-11

	Item No.	STROBE items	Location in manuscript where items are reported	Page numbers	RECORD items	Location in manuscript where items are reported	Page numbers
		participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	in the Supplement) N/A N/A N/A N/A N/A		identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or	in the Supplement) Annex III in the Supplement	Supplement: 53-58

	Item No.	STROBE items	Location in manuscript where items are reported	Page numbers	RECORD items	Location in manuscript where items are reported	Page numbers
					other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Figure 1	21
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Methods, supplementary methods (annex I)	10-12; supplement: 3-25	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Methods, supplementary methods (annex I)	Supplement: 3-25
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement).	Methods, supplementary methods (annex I)	8-12; supplement: 1-25			

	Item No.	STROBE items	Location in manuscript where items are reported	Page numbers	RECORD items	Location in manuscript where items are reported	Page numbers
		Describe comparability of assessment methods if there is more than one group	Methods, supplementary methods (annex I)	8-12; supplement: 1-25			
Bias	9	Describe any efforts to address potential sources of bias	Methods, supplementary methods (annex I), annex III	8-12; supplement: 1-25, 53-58			
Study size	10	Explain how the study size was arrived at	Results, Figure 1	13, 21			
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Methods	11-12			
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed	Methods Methods N/A (only people with follow-up data available	11-12 11-12 8-12, 21			

	Item No.	STROBE items	Location in manuscript where items are reported	Page numbers	RECORD items	Location in manuscript where items are reported	Page numbers
		(d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	were included in the cohort) N/A (only people with follow-up data available were included in the cohort) N/A N/A	8-12, 21			
Data access and cleaning methods					RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	Methods, supplementary methods (annex I)	8-10, supplement: 1-3

	Item No.	STROBE items	Location in manuscript where items are reported	Page numbers	RECORD items	Location in manuscript where items are reported	Page numbers
					RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Methods, supplementary methods (annex I)	Supplement: 1-25
Linkage		..			RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Methods, supplementary methods (annex I)	8-10, supplement: 1-3
Results							
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the	Results, Figure 1	13, 21	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.*, study population selection) including filtering	Methods, Figure 1, supplementary methods (Annex I)	8-10, 21, supplement: 1-3

	Item No.	STROBE items	Location in manuscript where items are reported	Page numbers	RECORD items	Location in manuscript where items are reported	Page numbers
		study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram			based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.		
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	Results, Table 1, Figure 2, Supplementary tables S1, S2, S4; supplementary figures S1-S6 Table 1, Figure 1, Figure 2, Supplementary figure S3 Methods, Results, Figure 3, Supplementary figures S7-S9	13, 14, 22, 23, 24; supplement: 36-49 21,22,24-26; supplement: 46 8-10, 13-14, 23; supplement: 50-52			

	Item No.	STROBE items	Location in manuscript where items are reported	Page numbers	RECORD items	Location in manuscript where items are reported	Page numbers
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	Results, Figure 3, Supplementary tables S4-S5, Supplementary figure S7 N/A N/A	13-14, 23; supplement: 50-52			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Methods, Results, Figure 3, Supplementary tables S3-S4, Supplementary figures S7-S9 Methods, Table 1 N/A	11-12,13-14, 23; supplement: 42,43, 50-52 11-12, 24-26			

	Item No.	STROBE items	Location in manuscript where items are reported	Page numbers	RECORD items	Location in manuscript where items are reported	Page numbers
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Methods, Results, Figure 3, Supplementary tables S1-S4, Supplementary figures S1-S9	11-12, 13-14; supplement: 36-52			
Discussion							
Key results	18	Summarise key results with reference to study objectives	Discussion	15			
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion	16-17	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	16-17	

	Item No.	STROBE items	Location in manuscript where items are reported	Page numbers	RECORD items	Location in manuscript where items are reported	Page numbers
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion, conclusion	16-17			
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion, conclusion	16-17			
Other Information							
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Declarations	19			
Accessibility of protocol, raw data, and programming code		..	Methods, declarations supplementary methods (annex I)	8-10,18, supplement: 26-34	RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol,	Methods, data availability statement	8-10,18, supplement: 26-34

	Item No.	STROBE items	Location in manuscript where items are reported	Page numbers	RECORD items	Location in manuscript where items are reported	Page numbers
					raw data, or programming code.		

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.