Supplementary Appendix

Manuscript: Early initiation of prophylactic anticoagulation for prevention of coronavirus disease 2019 mortality in patients admitted to hospital in the United States: cohort study

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Box 1. Levels, types, and doses of anticoagulation

Level	Type	Drug	Route	Dose
Prophylactic	Heparin	Heparin	SC	5000 units b.i.d. or t.i.d.
	LMWH	Enoxaparin	SC	40 mg q.d. or 30 mg b.i.d.
	LMWH	Fondaparinux	SC	2.5 mg q.d.
	LMWH	Dalteparin	SC	2500-5000 IU q.d.
	DOAC	Apixaban	Oral	2.5 mg b.i.d.
	DOAC	Rivaroxaban	Oral	10 mg q.d. or 2.5 mg b.i.d. for arterial disease
	DOAC	Dabigatran	Oral	220 mg q.d.
Therapeutic	Warfarin	Warfarin	Oral	Variable use INR
	Heparin	Heparin	IV	Variable use PTT
	LMWH	Enoxaparin	SC	>40 mg q.d.
	LMWH	Fondaparinux	SC	5, 7.5, 10 mg q.d.
	LMWH	Dalteparin	SC	≥5500 IU b.i.d.
	DOAC	Apixaban	Oral	5 mg b.i.d.
	DOAC	Rivaroxaban	Oral	≥15 mg q.d.
	DOAC	Dabigatran	Oral	150 mg b.i.d. or 75 mg b.i.d.*
	DOAC	Edoxaban	Oral	60 mg q.d. or 30 mg q.d.*

Abbreviations: q.d., once daily; b.i.d., twice daily; t.i.d., thrice daily; SC, subcutaneous; LMWH, low-molecular-weight heparin; DOAC, direct oral anticoagulant; INR, international normalized ratio; PTT, partial thromboplastin time; IU, international unit

*Assumed listed lower doses for dabigatran and edoxaban were for renal dosing

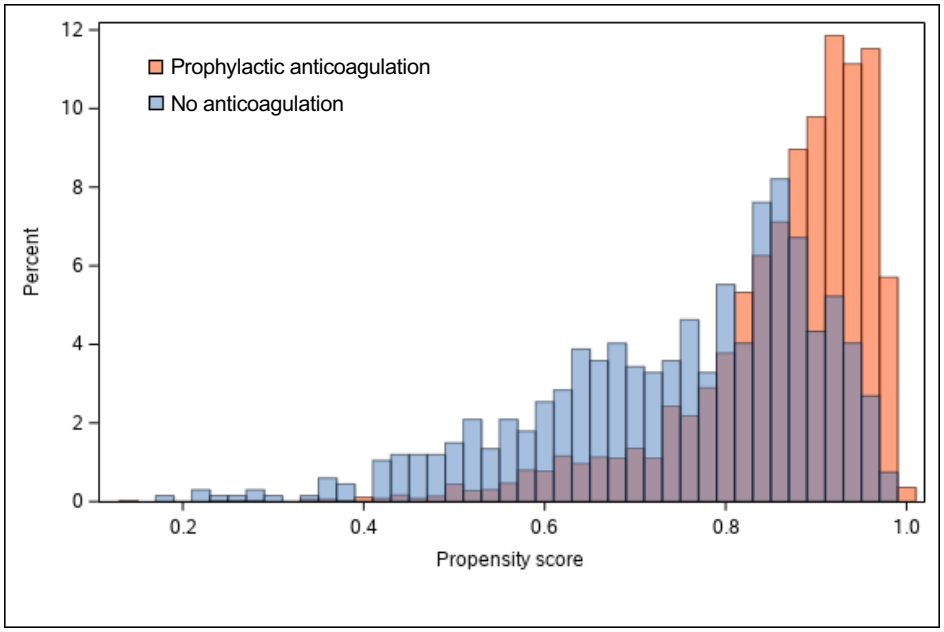
Box 2. Prognostic factors for venous thromboembolism and bleeding events previously identified*

Covariate	Included in model (✓/-)	Notes
Older age	✓	Age in model
Tachycardia	✓	Pulse in model
Thrombocytosis	✓	Platelet count in model
Leukocytosis	✓	Lymphocyte count in model
Fever	✓	Temperature in model
History of venous thromboembolism	✓	We did not include this variable directly, however, recent deep vein thrombosis/pulmonary embolism were likely excluded in our analysis due to the fact that anticoagulation prior to admission was an exclusion factor for this study
Malignancy	✓	Present in model as part of Charlson comorbidity index
Critical Illness	✓	Post-hoc analyses stratified by ICU status in first 24 hours
Infections	✓	HIV present in model as part of Charlson comorbidity index
C reactive protein	-	Not included in initial analysis due to lack of routine collection (>60% missing). We ran analyses including this variable which did not alter our findings
D dimer	-	Not included in initial analysis due to lack of routine collection (>45% missing). We ran analyses including this variable which did not alter our findings
Fibrinogen	-	Not included in initial analysis due to lack of routine collection (>50% missing)
Leg Edema	-	Not available in structured data
Barthel Index Score	-	Not available in structured data
Immobility	-	Not available in structured data
Paresis	-	Not available in structured data
Thrombophilia	-	Platelet count was included but not other aspects

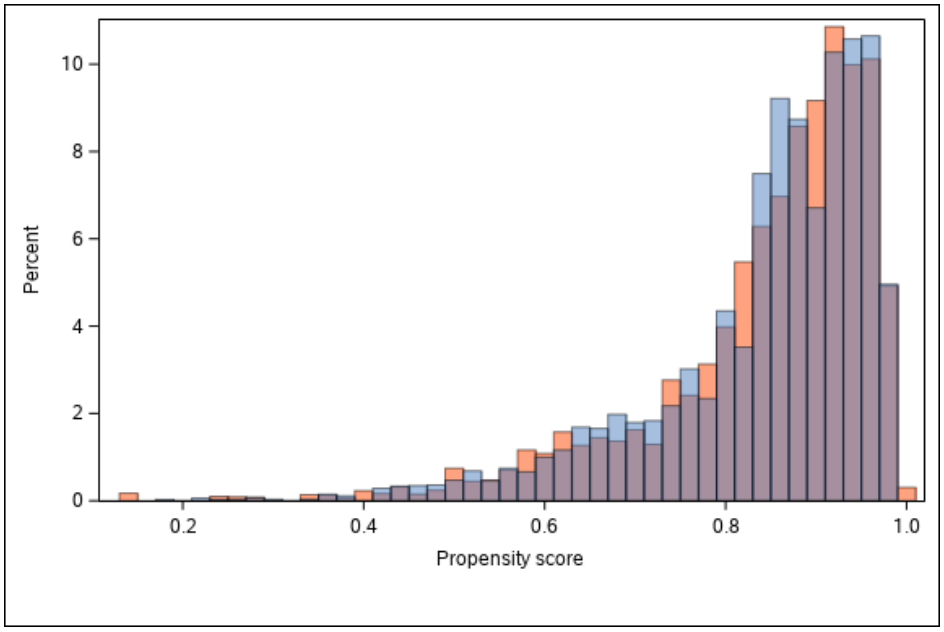
*List of covariates derived from Darzi AJ, et al. Prognostic factors for VTE and bleeding in hospitalized medical patients: a systematic review and meta-analysis. Blood. 2020 May 14;135(20):1788-1810

eFigure 1. Distribution of propensity scores by treatment group before and after weighting

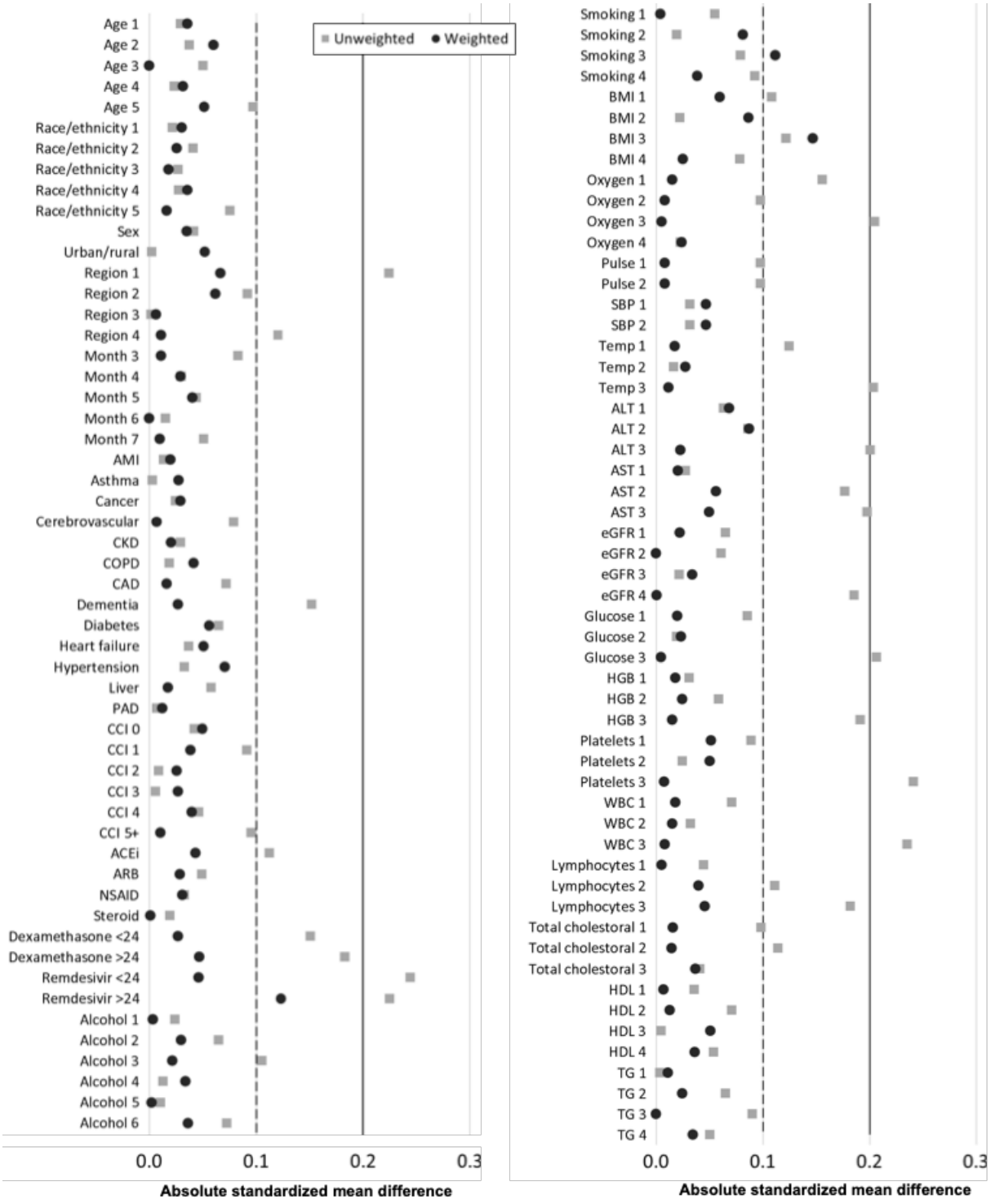
(a) Unweighted



(b) Weighted

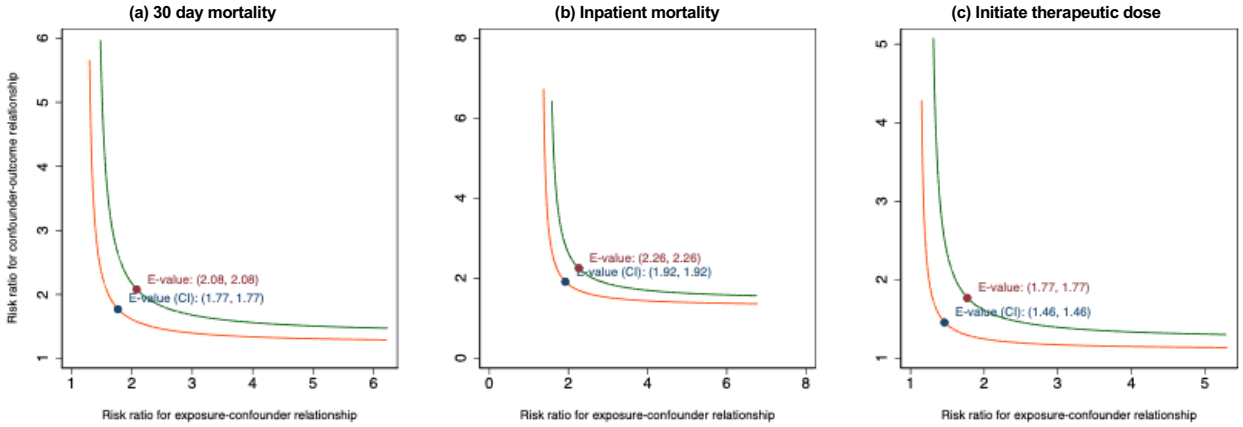


eFigure 2. Balance between treatment groups before and after weighting



Note: Covariates with standardised differences of <0.2 in the weighted sample were considered balanced

eFigure 3. E-value demonstrating required strength of unmeasured confounder to explain observed associations



Note: Required strength of unmeasured confounder represented in area to the right of curve

eTable 1. Sensitivity of IPT-weighted hazard ratios and 95% confidence intervals by capping of propensity score

			Cutoff used to cap propensity score		
Outcome	**No of patients**	**No of events**	**No cap (primary analysis)**	**1st/99th centile**	**5th/95th centile**
30 day mortality					
Prophylactic anticoagulation	3627	513	0.73 (0.66-0.81)	0.76 (0.68-0.84)	0.79 (0.71-0.88)
No anticoagulation	670	109	ref	ref	ref
Inpatient mortality					
Prophylactic anticoagulation	3627	418	0.69 (0.61-0.77)	0.71 (0.63-0.80)	0.74 (0.65-0.83)
No anticoagulation	670	92	ref	ref	ref
Initiate therapeutic anticoagulation					
Prophylactic anticoagulation	3627	573	0.81 (0.73-0.90)	0.82 (0.74-0.92)	0.87 (0.78-0.97)
No anticoagulation	670	92	ref	ref	ref

Note. Propensity score distributions were capped at 1st/99th centile and 5th/95th centile. For example, if an individual had a propensity score lower than the 5th centile, their propensity score was set to the 5th centile.

Abbreviations: IPT, inverse probability of treatment

eTable 2. Sensitivity of IPT-weighted hazard ratios and 95% confidence intervals by use of robust variance estimation or stabilized weights

			Primary analysis (ATE weight)		Stabilized ATE weight	
Outcome	**No of patients**	**No of events**	**Default variance**	**Robust variance**	**Default variance**	**Robust variance**
30 day mortality						
Prophylactic anticoagulation	3627	513	0.73 (0.66-0.81)	0.73 (0.55-0.97)	0.73 (0.60-0.89)	0.73 (0.55-0.97)
No anticoagulation	670	109	ref	ref	ref	ref
Inpatient mortality						
Prophylactic anticoagulation	3627	418	0.69 (0.61-0.77)	0.69 (0.50-0.93)	0.68 (0.55-0.84)	0.68 (0.50-0.93)
No anticoagulation	670	92	ref	ref	ref	ref
Initiate therapeutic anticoagulation						
Prophylactic anticoagulation	3627	573	0.81 (0.73-0.90)	0.81 (0.61-1.07)	0.81 (0.66-0.98)	0.81 (0.61-1.07)
No anticoagulation	670	92	ref	ref	ref	ref

Abbreviations: IPT, inverse probability of treatment; ATE, average treatment effect

eTable 3. Sensitivity analyses expanding exposure ascertainment window from 24 to 48 hours

	Primary analysis (24 hours)			48 hours		
Outcome	**No of patients**	**No of events**	**IPT-weighted HR (95% CI)**	**No of patients**	**No of events**	**IPT-weighted HR (95% CI)**
30 day mortality						
Prophylactic anticoagulation	3627	513	0.73 (0.66-0.81)	3369	492	0.81 (0.72-0.91)
No anticoagulation	670	109	ref	364	66	ref
Inpatient mortality						
Prophylactic anticoagulation	3627	418	0.69 (0.61-0.77)	3369	413	0.88 (0.77-1.00)
No anticoagulation	670	92	ref	364	54	ref
Initiate therapeutic anticoagulation						
Prophylactic anticoagulation	3627	573	0.81 (0.73-0.90)	3369	470	0.65 (0.58-0.73)
No anticoagulation	670	92	ref	364	46	ref

Note. Lower sample size in the "48 hour" models due to the exclusion of patients who experienced any outcome or discharged during the exposure ascertainment window, which was expanded to 48 hours.

Abbreviations: IPT, inverse probability of treatment; HR, hazard ratio; CI, confidence interval

eTable 4. Sensitivity analyses excluding direct oral anticoagulants from the treated group

	Primary analysis			Excluding DOACs		
Outcome	**No of patients**	**No of events**	**IPT-weighted HR (95% CI)**	**No of patients**	**No of events**	**IPT-weighted HR (95% CI)**
30 day mortality						
Prophylactic anticoagulation	3627	513	0.73 (0.66-0.81)	3600	506	0.73 (0.65-0.81)
No anticoagulation	670	109	ref	697	116	ref
Inpatient mortality						
Prophylactic anticoagulation	3627	418	0.69 (0.61-0.77)	3600	415	0.69 (0.61-0.77)
No anticoagulation	670	92	ref	697	95	ref
Initiate therapeutic anticoagulation						
Prophylactic anticoagulation	3627	573	0.81 (0.73-0.90)	3600	563	0.79 (0.71-0.88)
No anticoagulation	670	92	ref	697	102	ref

Abbreviations: DOAC, direct oral anticoagulant; IPT, inverse probability of treatment; HR, hazard ratio; CI, confidence interval

eTable 5. Effect of prophylactic anticoagulation separately for subcutaneous heparin and enoxaparin

	Subcutaneous heparin			Enoxaparin		
Outcome	**No of patients**	**No of events**	**IPT-weighted HR (95% CI)**	**No of patients**	**No of events**	**IPT-weighted HR (95% CI)**
30 day mortality						
Prophylactic anticoagulation	1094	230	0.73 (0.64-0.84)	2506	276	0.78 (0.68-0.89)
No anticoagulation	670	109	ref	670	109	ref
Inpatient mortality						
Prophylactic anticoagulation	1094	196	0.69 (0.60-0.80)	2506	219	0.72 (0.62-0.84)
No anticoagulation	670	92	ref	670	92	ref
Initiate therapeutic anticoagulation						
Prophylactic anticoagulation	1094	171	0.96 (0.81-1.13)	2506	392	0.79 (0.70-0.89)
No anticoagulation	670	92	ref	670	92	ref

Abbreviations: IPT, inverse probability of treatment; HR, hazard ratio; CI, confidence interval

STROBE and RECORD statements

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
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	(a) Title & Abstract (b) Abstract	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 databases was conducted for the study, this should be clearly stated in the title or abstract.	1.1: Abstract 1.2: Abstract – Setting & Participants 1.3: N/A
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Background (Para 1)		
Objectives	3	State specific objectives, including any prespecified hypotheses	Background (End of Para 2)		
Methods					
Study Design	4	Present key elements of study design early in the paper	Methods (Study design and population)		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods (Study design and population; Exposure, outcomes and follow-up)		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of 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	(a) Methods (Study design and population)	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to 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	6.1: Methods (Study design and population) 6.2: N/A 6.3: N/A

		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		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 other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Methods (Forms and doses of anticoagulation; Exposure, outcomes, and follow-up, Covariates; Figure 1)	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.	7.1: Methods (Forms and doses of anticoagulation; Exposure, outcomes, and follow-up, Covariates; Figure 1)
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods (Forms and doses of anticoagulation; Exposure, outcomes, and follow-up, Covariates; Figure 1)		
Bias	9	Describe any efforts to address potential sources of bias	Methods (Propensity score model; Statistical methods; Sensitivity analyses)		
Study size	10	Explain how the study size was arrived at	Methods (Study design and population; Figure 2)		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Methods (Propensity score model; Statistical methods)		
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	(a-c) Methods (Covariates; Propensity score model; Statistical methods, Sensitivity analyses) (d) N/A		

		(c) Explain how missing data were addressed (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	(e) Methods (Sensitivity analyses)		
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. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	12.1: Methods (Study design and population; Covariates; Ethics; Data sharing; Funding; Contributorship) 12.2: Methods (Covariates)
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.	N/A
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 study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	(a-c) Results (Patient characteristics, Figure 2)	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering 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.	13.1: Results (Patient characteristics, Figure 2)
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on	(a) Results (Patient characteristics, Table 1) (b) Table 1		

		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)	(c) Results (Patient characteristics)		
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 (Absolute and relative risks)		
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	(a) Results (Absolute and relative risks; Figure 3; Table 2) (b) Results (Table 1) (c) Results (Absolute and relative risks; Table 2)		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Results (Sensitivity analyses; Supplementary Appendix)		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Discussion (Key findings)		
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 (Strengths and limitations)	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	19.1 Discussion (Comparison with other evidence; Strengths and limitations)

				eligibility over time, as they pertain to the study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion (Throughout)		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion (Strengths and limitations)		
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	Funding		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Data sharing