Supplementary Materials

Xia *et al*. Associations between ticagrelor use and the risk of infections: A Mendelian randomization study

Table S1. STROBE-MR Checklist. (Skrivankova et al., 2021)

Item No.	Section	Checklist item	Manuscript section and paragraph
Title and abstract			
1	Title and abstract	Indicate Mendelian randomization (MR) as the study's design in the title and/or the abstract if that is a main purpose of the study.	Title and abstract
Introduction			
2	Background	Explain the scientific background and rationale for the reported study. What is the exposure? Is a potential causal relationship between exposure and outcome plausible? Justify why MR is a helpful method to address the study question.	Introduction, paragraph 1-2
3	Objectives	State specific objectives clearly, including prespecified causal hypotheses (if any). State that MR is a method that, under specific assumptions, intends to estimate causal effects.	Introduction, paragraph 3
Methods			
4	Study design and data sources	Present key elements of the study design early in the article. Consider including a table listing sources of data for all phases of the study. For each data source contributing to the analysis, describe the following:	Methods, section 1
	a	Setting: Describe the study design and the underlying population, if possible. Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection, when available.	Methods, section 2 and 4
	b	Participants: Report the eligibility criteria and the sources and methods of selection of participants. Report the sample size and whether any power or sample size calculations were carried out prior to the main analysis.	Methods, section 3; Table S2

	c	Describe measurement, quality control, and selection of genetic variants.	Methods, section 2
	d	For each exposure, outcome, and other relevant variables, describe methods of assessment and diagnostic criteria for diseases.	Methods, sections 2 and 4
	e	Provide details of ethics committee approval and participant informed consent, if relevant.	Methods, section 1
5	Assumptions	Explicitly state the 3 core instrumental variable (IV) assumptions for the main analysis (relevance, independence, and exclusion restriction), as well assumptions for any additional or sensitivity analysis.	Methods, section 1
6	Statistical methods: main analysis	Describe statistical methods and statistics used.	Methods, section 5
	a	Describe how quantitative variables were handled in the analyses (ie, scale, units, model).	Methods, section 5
	b	Describe how genetic variants were handled in the analyses and, if applicable, how their weights were selected.	Methods, section 5
	c	Describe the MR estimator (eg, 2-stage least squares, Wald ratio) and related statistics. Detail the included covariates and, in case of 2-sample MR, whether the same covariate set was used for adjustment in the 2 samples.	Methods, section 5
	d	Explain how missing data were addressed.	
	e	If applicable, indicate how multiple testing was addressed.	
7	Assessment of assumptions	Describe any methods or prior knowledge used to assess the assumptions or justify their validity.	Methods, section 3 and 5

8	Sensitivity analyses and additional analyses	Describe any sensitivity analyses or additional analyses performed (eg, comparison of effect estimates from different approaches, independent replication, bias analytic techniques, validation of instruments, simulations).	Methods, section 5
9	Software and preregistration		
	a	Name statistical software and package(s), including version and settings used.	Methods, section 5
	b	State whether the study protocol and details were preregistered (as well as when and where).	
Results			
10	Descriptive data		
	a	Report the numbers of individuals at each stage of included studies and reasons for exclusion. Consider use of a flow diagram.	Figure 1
	b	Report summary statistics for phenotypic exposure(s), outcome(s), and other relevant variables (eg, means, SDs, proportions).	Methods, section 2 and 4
	c	If the data sources include meta-analyses of previous studies, provide the assessments of heterogeneity across these studies.	
	d	For 2-sample MR: i. Provide justification of the similarity of the genetic variant–exposure associations between the exposure and outcome samples. ii. Provide information on the number of individuals who overlap between the exposure and outcome studies.	Results, section 1
11	Main results		

	a	Report the associations between genetic variant and exposure and between genetic variant and outcome, preferably on an interpretable scale.	Results, section 2
	b	Report MR estimates of the relationship between exposure and outcome and the measures of uncertainty from the MR analysis, on an interpretable scale, such as odds ratio or relative risk per SD difference.	Results, section 2 and 3
	c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.	
	d	Consider plots to visualize results (eg, forest plot, scatterplot of associations between genetic variants and outcome vs between genetic variants and exposure).	Figure 2
12	Assessment of assumptions		
	a	Report the assessment of the validity of the assumptions.	Results, section 3
	b	Report any additional statistics (eg, assessments of heterogeneity across genetic variants, such as I2, Q statistic, or E-value).	Results, section 3
13	Sensitivity analyses and additional analyses		
	a	Report any sensitivity analyses to assess the robustness of the main results to violations of the assumptions.	Results, section 3
	b	Report results from other sensitivity analyses or additional analyses.	Results, section 3
	c	Report any assessment of the direction of the causal relationship (eg, bidirectional MR).	Results, section 3

	d	When relevant, report and compare with estimates from non-MR analyses.	
	e	Consider additional plots to visualize results (eg, leave-one-out analyses).	Figure S1
Discussion			
14	Key results	Summarize key results with reference to study objectives.	Discussion, paragraph 1
15	Limitations	Discuss limitations of the study, taking into account the validity of the IV assumptions, other sources of potential bias, and imprecision. Discuss both direction and magnitude of any potential bias and any efforts to address them.	Discussion, paragraph 5
16	Interpretation		
	a	Meaning: Give a cautious overall interpretation of results in the context of their limitations and in comparison with other studies.	Discussion, paragraph 3 and 5
	b	Mechanism: Discuss underlying biological mechanisms that could drive a potential causal relationship between the investigated exposure and the outcome, and whether the gene-environment equivalence assumption is reasonable. Use causal language carefully, clarifying that IV estimates may provide causal effects only under certain assumptions.	Discussion, paragraph 2
	c	Clinical relevance: Discuss whether the results have clinical or public policy relevance, and to what extent they inform effect sizes of possible interventions.	Conclusion
17	Generalizability	Discuss the generalizability of the study results (a) to other populations, (b) across other exposure periods/timings, and (c) across other levels of exposure.	Discussion, paragraph 5

Other Information			
18	Funding	Describe sources of funding and the role of funders in the present study and, if applicable, sources of funding for the databases and original study or studies on which the present study is based.	Funding source section
19	Data and data sharing	Provide the data used to perform all analyses or report where and how the data can be accessed, and reference these sources in the article. Provide the statistical code needed to reproduce the results in the article or report whether the code is publicly accessible and, if so, where.	Data availability section
20	Conflicts of interest	All authors should declare all potential conflicts of interest.	Disclosure section

Table S2. Detailed information of the GWAS data

Contribution	Traits	Data Sources	Cases, n	Sample size	PMID	Dataset ID
Exposure	Ticagrelor AUCss	PLATO trial	-	3,753	25935875	-
Positive control	Coronary heart disease	UK Biobank + CARDIoGRAMplusC4D	122,733	547,261	29212778	MRCIEU: ebi-a-GCST005195
		FinnGen	21,012	218,792	-	FinnGen: I9_CHD
	Myocardial infarction	UK Biobank + CARDIoGRAMplusC4D	14,825	395,795	33532862	MRCIEU: ebi-a-GCST011365
		FinnGen	12,801	200,641	-	FinnGen: I9_MI
	Angina pectoris	UK Biobank	16,175	393,278	-	PheWeb: 411.3
		FinnGen	18,168	206,008	-	FinnGen: I9_ANGINA
Outcome	Upper respiratory infection	UK Biobank	2,335	408,782	-	PheWeb: 465
		FinnGen	43,385	260,405	-	FinnGen: J10_UPPERINFEC
	Pneumonia	UK Biobank	10,059	408,597	-	PheWeb: 480
		FinnGen	33,723	260,405	-	FinnGen: J10_PNEUMONIA
	Bacterial pneumonia	UK Biobank	6,710	405,248	-	PheWeb: 480.1
		FinnGen	9,878	233,465	-	FinnGen: J10_PNEUMOBACT
	Urinary tract infection	UK Biobank	12,491	392,427	-	PheWeb: 465
		FinnGen	19,479	250,959	-	FinnGen: N14_URETHRAOTH
	Sepsis	UK Biobank	11,643	486,484	-	MRCIEU: ieu-b-4980
		FinnGen	7,463	242,218	-	FinnGen: AB1_SEPSIS
	Sepsis in critical care	UK Biobank	1,380	431,365	-	MRCIEU: ieu-b-4982

MRCIEU: https://gwas.mrcieu.ac.uk/

PheWeb: https://pheweb.org/UKB-SAIGE/

FinnGen: https://r6.finngen.fi/

Table S3. Detailed information of instrumental variables

Exposure	Chr	Position	SNP	Minor allele	Major allele	MAF	Beta	SE	P-value	R-square	F-statistic
AUCss of ticagrelor	7	99421085	rs62471956	G	A	0.034	0.211	0.027	1.07E-14	0.0158	60.25
	7	98932759	rs147642358	G	A	0.022	0.250	0.036	5.51E-12	0.0126	47.81
	7	99274316	rs62471929	A	G	0.047	0.145	0.021	1.54E-11	0.0121	45.77
	7	100103523	rs140607780	G	A	0.016	0.273	0.041	3.47E-11	0.0116	44.16
	7	99543627	rs140104968	C	T	0.019	0.224	0.036	4.35E-10	0.0103	39.16
	7	99841354	rs117038461	C	T	0.017	0.232	0.038	9.40E-10	0.0099	37.64
AUCss of ARC	12	21402979	rs113681054	T	C	0.184	0.062	0.009	3.63E-13	0.0140	53.21
	4	70050302	rs188514203	A	G	0.015	0.186	0.030	7.07E-10	0.0101	38.20

ARC, AR-C124910XX; AUCss, area under the curve during steady-state; Chr, chromosome; MAF, minor allele frequency; SE, standard error; SNP, single-nucleotide polymorphism

Table S4. Genetic liability to serum ticagrelor AUCss and risk of coronary heart disease

Traits	Data sources	SNPs, n	OR	95% CI	P value
Coronary heart disease	UK Biobank + CARDIoGRAMplusC4D	5	0.810	0.749-0.877	1.96E-07
	FinnGen	6	0.785	0.638-0.965	2.17E-02
	Combied	**-**	**0.807**	**0.750-0.869**	**1.34E-08**
Myocardial infarction	UK Biobank + CARDIoGRAMplusC4D	6	0.921	0.841-1.008	7.26E-02
	FinnGen	6	0.669	0.513-0.871	2.88E-03
	Combied	**-**	**0.890**	**0.817-0.970**	**7.75E-03**
Angina pectoris	UK Biobank	6	0.874	0.769-0.994	3.95E-02
	FinnGen	6	0.823	0.642-1.055	1.25E-01
	Combied	**-**	**0.863**	**0.770-0.967**	**1.13E-02**

Significant threshold: P<1.67E-02 (0.05/3 outcomes)

Table S5. Genetic liability to serum AR-C124910XX AUCss and risk of coronary heart disease

Traits	Data sources	SNPs	OR	95% CI	P value
Coronary heart disease	UK Biobank + CARDIoGRAMplusC4D	1	1.145	0.847-1.549	3.78E-01
	FinnGen	2	1.811	1.286-2.552	6.80E-04
Myocardial infarction	UK Biobank + CARDIoGRAMplusC4D	2	1.411	1.087-1.832	9.80E-03
	FinnGen	2	2.332	1.540-3.529	6.27E-05
Angina pectoris	UK Biobank	0	-	-	-
	FinnGen	2	1.409	0.979-2.028	6.50E-02

Table S6. MR results based on the MR-Egger regression (bootstrap) and the weighted median methods

Traits	MR methods	UK Biobank		FinnGen		Combined		
		OR	95% CI	OR	95% CI	OR	95% CI	P value
Upper respiratory infection	MR-Egger	0.356	0.071-1.783	0.902	0.753-1.081	0.892	0.746-1.067	2.12E-01
	Weighted median	0.810	0.546-1.203	0.923	0.778-1.094	0.904	0.773-1.057	2.06E-01
Pneumonia	MR-Egger	0.691	0.300-1.589	0.904	0.743-1.100	0.892	0.737-1.079	2.38E-01
	Weighted median	0.845	0.698-1.023	0.927	0.781-1.099	0.889	0.783-1.010	7.08E-02
Bacterial pneumonia	**MR-Egger**	**0.683**	**0.283-1.649**	**0.796**	**0.561-1.129**	**0.779**	**0.563-1.079**	**1.33E-01**
	Weighted median	**0.864**	**0.698-1.069**	**0.791**	**0.585-1.070**	**0.839**	**0.705-0.999**	**4.80E-02**
Urinary tract infection	MR-Egger	1.229	0.665-2.272	0.840	0.649-1.086	0.889	0.701-1.126	3.29E-01
	Weighted median	1.069	0.913-1.252	0.848	0.674-1.068	0.993	0.872-1.131	9.17E-02
Sepsis	**MR-Egger**	**0.609**	**0.303-1.223**	**0.906**	**0.618-1.329**	**0.826**	**0.591-1.156**	**2.66E-01**
	Weighted median	**0.880**	**0.737-1.051**	**0.916**	**0.661-1.270**	**0.888**	**0.760-1.038**	**1.36E-01**

Table S7. Sensitivity analyses for the Mendelian randomization results

Traits	Data source	Heterogeneity		Reverse causality	Directional pleiotropy	
		I^2 statistic	P-value	Steiger test P-value	MR-Egger test P-value	MR-PRESSO global test P-value
Upper respiratory infection	UK Biobank	0.0%	4.57E-01	-	1.53E-01	5.18E-01
	FinnGen	12.6%	3.34E-01	-	2.09E-01	3.70E-01
Pneumonia	UK Biobank	37.8%	1.54E-01	-	7.54E-02	1.91E-01
	FinnGen	0.0%	9.87E-01	-	8.81E-01	9.80E-01
Bacterial pneumonia	UK Biobank	0.0%	4.91E-01	4.37E-206	1.17E-01	5.37E-01
	FinnGen	0.0%	7.99E-01	8.00E-108	8.86E-01	8.73E-01
Urinary tract infection	UK Biobank	0.0%	9.73E-01	-	5.19E-01	9.77E-01
	FinnGen	0.0%	7.36E-01	-	3.11E-01	7.79E-01
Sepsis	UK Biobank	0.0%	5.01E-01	9.06E-209	1.33E-01	5.59E-01
	FinnGen	0.0%	9.87E-01	1.14E-210	9.60E-01	9.88E-01

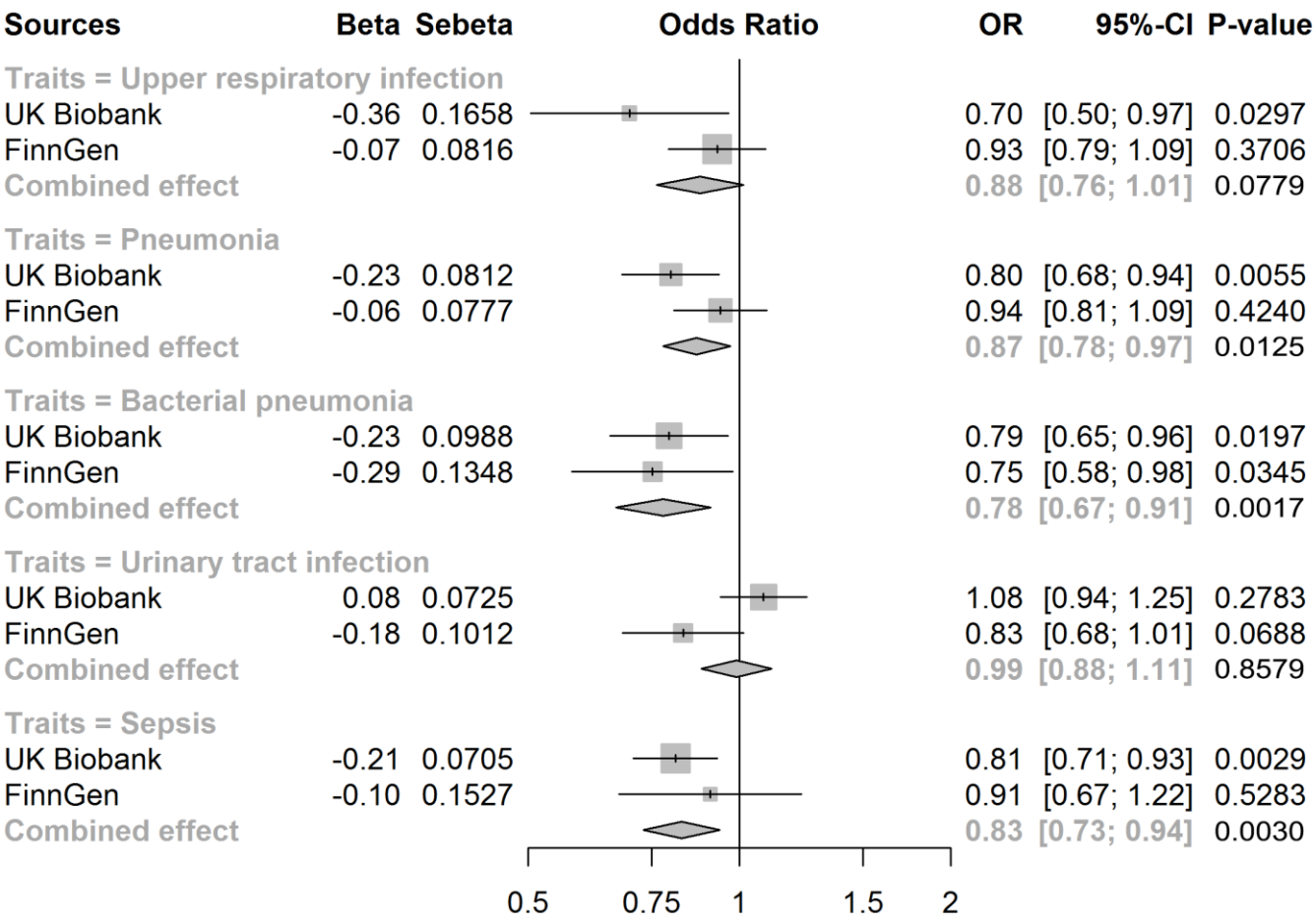

Figure S1. Inverse-variance weighted (IVW) Mendelian randomization results after excluding the proxy SNP rs7350033