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Estimated causal effects of common respiratory infections on cardiovascular risk: a meta-analysis

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/openhrt-2023-002501).

To cite: la Roi-Teeuw HM, van Smeden M, Bos M, *et al*. Estimated causal effects of common respiratory infections on cardiovascular risk: a meta-analysis. *Open Heart* 2023;**10**:e002501. doi:10.1136/openhrt-2023-002501

Received 23 September 2023
Accepted 2 November 2023

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ABSTRACT

Objective Literature supports associations between common respiratory tract infections (RTIs) and risk of cardiovascular diseases, yet the importance of RTIs for cardiovascular risk management remains less understood. This systematic review and meta-analysis aimed to estimate the causal effects of RTIs on occurrence of cardiovascular diseases in the general population.

Methods MEDLINE and EMBASE were systematically searched up to 4 November 2022. Eligible were all aetiological studies evaluating risk of cardiovascular outcomes after exposure to common RTIs within any follow-up duration. Evidence was pooled using random-effects models if data allowed. The ROBINS-E and GRADE approaches were used to rate risk of bias and certainty of evidence, respectively. All assessments were performed in duplicate.

Results We included 34 studies (65 678 650 individuals). Most studies had a high risk of bias. COVID-19 likely increases relative risk (RR (95% CI)) of myocardial infarction (3.3 (1.0 to 11.0)), stroke (3.5 (1.2 to 10)), pulmonary embolism (24.6 (13.5 to 44.9)) and deep venous thrombosis (7.8 (4.3 to 14.4)) within 30 days after infection (GRADE: moderate) and about twofold within 1 year (GRADE: low to moderate). Other RTIs also likely increase the RR of myocardial infarction (2.9 (95% CI 1.8 to 4.9)) and stroke (2.6 (95% CI 1.1 to 6.4)) within 30 days (GRADE: moderate), and to a lesser extent with longer follow-up.

Conclusions RTIs likely increase the risk of cardiovascular diseases about 1.5–5 fold within 1 month after infection. RTIs may, therefore, have clinical relevance as target for cardiovascular risk management, especially in high-risk populations.

PROSPERO registration number CRD42023416277.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Literature supports associations between common respiratory tract infections and risk of cardiovascular diseases, yet clear quantifications of the estimated causal effects of respiratory tract infections on the occurrence of cardiovascular diseases in the general community remain unknown.

WHAT THIS STUDY ADDS

⇒ In this systematic review and meta-analysis including data from over 65 million individuals from 34 aetiological studies, we found that common respiratory infections likely increase the risk of several cardiovascular diseases 1.5–5 fold within 30 days after infection. In studies with longer follow-up duration, this association appeared to be weaker.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Tackling respiratory infections—for instance, via vaccination or other preventive strategies—could be potential novel targets to reduce the burden of cardiovascular risk.

INTRODUCTION

Cardiovascular disease is a leading cause of morbidity and mortality worldwide.[1] Cardiovascular risk reduction, which constitutes a substantial task of all sectors in healthcare, traditionally focuses on reduction of well-established modifiable causal factors such as smoking, obesity, hypercholesterolaemia, hypertension and diabetes.[2 3] Recently, other eliciting factors have also been identified, in particular respiratory tract infections (RTIs).[3–5] This may offer new opportunities for cardiovascular risk reduction if the purported association between RTIs and cardiovascular diseases indeed is causal, potentially modifiable and substantial enough to be clinically relevant.

RTIs have been associated with an increased risk of developing cardiovascular disease. For example, an increase in cardiovascular events following an acute infection with SARS-CoV-2 has been widely observed.[6–8] Several studies suggest that the seasonal association between RTIs and ischaemic heart disease persists after controlling for potential confounders.[9 10] Also, pathophysiological mechanisms have been proposed, such as increased metabolic demands leading to hypoxaemia, systemic inflammatory responses leading to hypercoagulability and pathogens causing direct damage to cardiovascular tissues.[4 5 11] Risk and severity of RTIs can be reduced by vaccines against common pathogens such as influenza virus, respiratory syncytial virus, SARS-CoV-2 and pneumococci. However, clear quantitative estimates of the causal contribution of RTIs on the risk of cardiovascular diseases are lacking. Obtaining such estimates is essential to give an indication on whether preventive interventions, such as vaccination, could be useful, for instance, in patients with high risk of cardiovascular disease. Therefore, we systematically reviewed the published literature on the causal effects of RTIs on the occurrence of cardiovascular diseases in the context of community care.

METHODS

The review protocol was registered in PROSPERO (CRD42023416277). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines were followed (see online supplemental materials for a checklist of reported items).[12]

Search strategy and procedures

MEDLINE (via Ovid) and EMBASE were systematically searched for all relevant records except conference abstracts published up to 4 November 2022. Full search strategies can be found in online supplemental materials. Study selection, data extraction, assessments of risk of bias and certainty of evidence were performed independently by at least two researchers and discrepancies were discussed until consensus was reached. In studies reporting multiple results (from multiple designs, exposures, outcomes or analyses), each result was evaluated individually for eligibility and risk of bias.

Study selection

Study eligibility criteria were specified a priori (see online supplemental materials for full details on study selection). We included studies with (1) a study design that enables comparison between RTI exposed and non-exposed individuals or periods, (2) a study population representative of (a subgroup of) the general population, (3) exposure defined as any symptomatic RTI relevant to community care—that is, not exclusively requiring diagnosis or treatment in secondary or tertiary care settings, (4) one of the listed cardiovascular outcomes and (5) extractable effect estimates such as relative risk (RR), incidence rate ratio (IRR), OR or HR with 95% CI or SE. Eligible outcomes were acute coronary syndromes (ACS; including acute myocardial infarction (AMI)), stroke, transient ischaemic accident (TIA), new-onset peripheral artery disease, venous thromboembolic events (VTE; including pulmonary embolism (PE) and deep venous thrombosis (DVT)), new-onset atrial fibrillation (AF) or any composite of the above outcomes which could also include associated mortality, within any follow-up duration.

Data extraction

Data were extracted as reported by the articles including any supplemental materials. A list of extracted items is provided in the study protocol. If studies reported on multiple time windows, we only extracted estimates for follow-up windows starting at exposure onset. If studies reported estimates with and without taking into account outcomes on the same day as the exposure onset, we extracted the latter to ensure that the exposure preceded the outcome.

Risk-of-bias assessment

Risk of bias was assessed using the Risk Of Bias In Non-randomized Studies - of Exposure (ROBINS-E) tool[13] for aetiological studies, which we adapted to also account for common sources of bias in case–control studies and self-controlled case series (online supplemental materials). This tool evaluates risk of bias across seven domains: confounding, exposure classification bias, selection bias, bias due to postexposure interventions, bias due to missing data, outcome classification bias and bias in selection of the reported result. We defined the following minimal set of confounders: age, sex, smoking status, diabetes mellitus, seasonality in case of ACS/AMI[14,15] and vaccination status in case of COVID-19 after January 2021 and influenza.

Data synthesis

Data were grouped according to predefined categories of exposures and outcomes. Estimates reported by the articles were summarised in Summary of Findings tables and visualised in forest plots. Because of anticipated heterogeneity in study designs, effect measure types, follow-up duration, confounder adjustment and other study characteristics, we initially anticipated to refrain from pooling estimates in meta-analyses, but rather to report ranges of RR estimates. However, we identified a substantial amount of studies and post hoc decided to pool estimates for some comparisons in order to achieve a better estimation of the quantitative effect including uncertainty measures. We only performed meta-analysis if at least three studies reported on the same exposure-outcome time window (up to 30 days or longer than 30 days) category in independent study cohorts. For studies reporting on multiple exposure types (eg, subanalyses on the type of RTI) or follow-up durations, we only included the combined exposure and longest follow-up duration, respectively, in the meta-analysis. We assumed that study-specific estimates of IRR, OR and HR could be approximately interpreted as RR given the low baseline risk of cardiovascular outcomes.[16] The Hartung-Knapp method for random effects pooling was used to obtain pooled estimates including 95% CI, prediction intervals and measures of heterogeneity (I^2 and tau^2 including SEs). Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) was used to assess the certainty of evidence, following the guidance for rating certainty when ROBINS-I is used (from which ROBINS-E is derived).[17] We assessed the certainty that RTIs would have an effect on cardiovascular outcomes greater than null (ie, RR>1), and used causal language (eg, 'likely

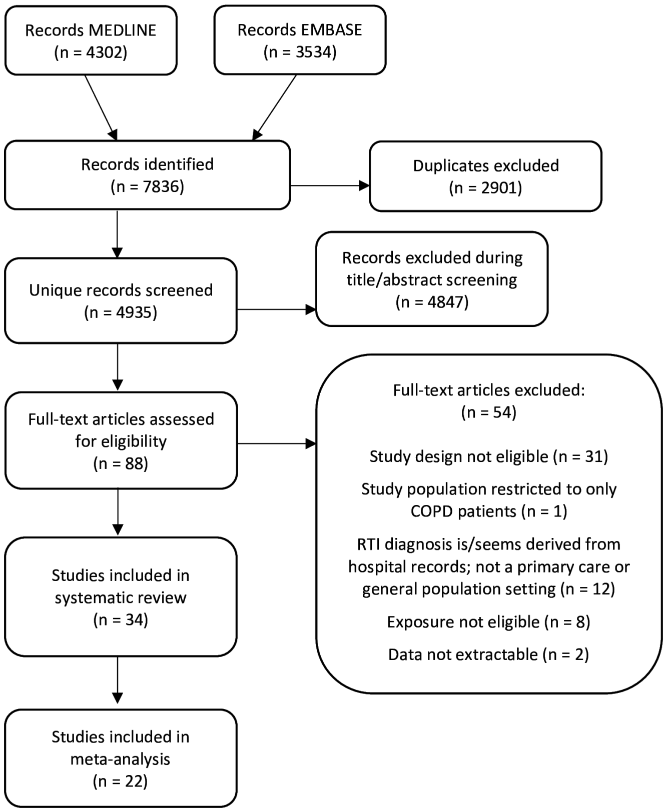

Figure 1 Flow chart of study selection. RTI, respiratory tract infection. COPD, chronic obstructive pulmonary disease.

increases', 'may increase') in line with the GRADE guidelines.[18] All analyses were performed in R using the metafor package.[19]

RESULTS

Study selection and characteristics

A total of 4935 unique study records were identified in MEDLINE and EMBASE, of which 34 studies (65 678 650 individuals) were included in this review (figure 1).[20–53] Details on included and excluded studies are in online supplemental materials . Characteristics of the included studies are shown in table 1. Studies were conducted in 10 different countries. All studies were published within the last three decades with an increase in publications during COVID-19 pandemic years. Most studies used electronic health record data (n=20) or (Taiwanese or American) insurance data (n=11). Reported exposures were any RTI in most studies, or more specified RTI such as COVID-19 (n=13), pulmonary tuberculosis (n=3), rhinosinusitis (n=2) and influenza(-like illness) (n=3). Exposures were defined based on routine care diagnostic codes, symptoms, physical examination and/or laboratory tests. Three studies[20–22] used self-reported RTI exposure from interviews or questionnaires, and one study[23] used self-reported doctor's visit for RTI. Reported outcomes were AMI (n=17), ACS (n=4), stroke (n=14), TIA (n=4), PE (n=6), DVT (n=6), VTE (n=8), AF (n=4) or composites of these outcomes (n=4), generally defined by diagnostic codes from hospital, primary care or insurance databases.

One study used a natural language processing algorithm to encode confirmed VTE from radiology reports.[24] Follow-up times ranged widely from 1 day to 3 years. Three studies did not specify follow-up duration; these presumably entailed their complete study periods which ranged from 10 to 13 years.[25–27]

Risk of bias

Table 2 shows the results of the risk-of-bias assessment. Justifications for arriving at specific risk-of-bias judgements in individual studies are described in online supplemental materials. In short, risk of confounding bias was a major issue in particularly case–control and matched cohort studies. Risk of exposure classification bias was an issue in studies with self-reported exposures (recall bias) and studies in which outcome and exposure shared similar symptoms (such as dyspnoea or thoracic pain from ACS or PE and symptoms of RTIs). Risk of selection bias mainly arose from inappropriate sampling techniques for controls in case–control and matched cohort studies, and from (indirect) exclusion of non-survivors or more severely diseased individuals in self-controlled case series. Outcome classification bias was a concern in studies on PE, because RTI signs and symptoms may resemble those of PE and may, therefore, influence diagnostic workup. Studies that did not prespecify RTI as the exposure of interest in analyses exploring multiple associated factors were considered to be at risk of selective reporting bias. Risk of bias due to missing data or postexposure interventions was generally low. Overall, most studies had a high risk or very high risk of bias. Given the presumed direction of biases (if plausible), the risks of bias most probably led to risk of overestimation of the causal effect in 24 studies and risk of underestimation in two studies.

Various RTIs

Eighteen studies reported on the effect of various types of RTIs on AMI (n=9), stroke (n=6), DVT (n=2), VTE (n=2) and AF (n=1). Results are visualised in figure 2, and summarised in Summary of Findings tables in online supplemental materials. Prediction intervals and measures of heterogeneity of all meta-analyses can also be found in online supplemental materials. Some studies reported outcomes on multiple types of RTI, or outcomes with and without use of non-steroid anti-inflammatory drugs. RTIs probably increase risk of AMI (RR 2.9, 95% CI 1.8 to 4.9, moderate certainty) and stroke (RR 2.6, 95% CI 1.1 to 6.4, moderate certainty) within 30 days. It is also likely that RTIs increase the risk of DVT within 30 days (moderate certainty). RTIs may increase the long-term risk of AMI (very low certainty), stroke (very low certainty), VTE (low certainty) and AF (low certainty), although there were too few studies for meta-analysis and certainty of evidence was low or very low due to risk of bias in most studies. Studies on lower RTIs tended to have shorter follow-up duration and larger estimates, compared with studies on upper RTIs.

Table 1 Study characteristics

Study	Country	Design	N*	Study population	Exposure	Outcome	FU†
Baylin *et al*[21] 2007	Costa Rica	SCCS	499	AMI survivors	RTI	AMI	6
Chang *et al*[38] 2016	Taiwan	CC	56 870	Unvaccinated adults	Influenza	AF	365
Chung *et al*[25] 2014a	Taiwan	MC	49 923	Adults	Tuberculosis	PE	–
Chung *et al*[26] 2014b	Taiwan	MC	50 840	Adults	Tuberculosis	ACS	–
Clavijo *et al*[39] 2021	Argentina	CC	661	Hospital attending patients	Mild COVID-19	VTE	90
Clayton *et al*[40] 2011	UK	CC	23 114	Adults	Lower RTI	DVT	365
Clayton *et al*[41] 2008	UK	CC	22 310 18 416	Adults	Lower RTI	AMI Stroke	365
Cohoon *et al*[42] 2018	USA	CC	2797	Care seeking patients	Different types of RTI	VTE	92
Ekker *et al*[22] 2022	Netherlands	SCCS	407	Stroke survivors aged <50 years	ILI	Stroke	1
Hao *et al*[43] 2013	Taiwan	MC	264 650	Adults	Rhinosinusitis	AMI	1096
Ho *et al*[44] 2021	Scotland	SCCS	1449	COVID-19 patients	COVID-19	AMI, DVT, PE, stroke	56
Huaman *et al*[35] 2017	USA	MC	4052	Adults	Tuberculosis	AMI	365
Katsoularis *et al*[29] 2022	Sweden	SCCS	1 057 174	COVID-19 patients	COVID-19	DVT, PE	180
Katsoularis *et al*[28] 2021	Sweden	SCCS	86 742	COVID-19 patients	COVID-19	AMI, stroke	28
Knight *et al*[45] 2022	UK	MC	47 580 340	Adults	COVID-19	AMI, DVT, PE, Stroke, TIA	343
Leibson *et al*[46] 2014	United States	CC	271	Nursing home residents	RTI	VTE	90
Meier *et al*[47] 1998	UK	SCCS CC	1922 9571	Adults aged <75 years without CVD risk factors	RTI	AMI	10 365
Paganini-Hill *et al*[23] 2003	USA	SCCS	192	Stroke survivors	RTI	Stroke	7
Pasha *et al*[24] 2021	USA	SCCS	54 354	COVID-19 patients	COVID-19	VTE	49
Penntinen *et al*[27] 1996	Finland	CC	323	Male farmers	Upper RTI	AMI	–
Rezel-Potts *et al*[37] 2022	UK	MC	857 300	Adults	COVID-19	IHD, VTE, AF‡, stroke	364
Ruane *et al*[20] 2017	Australia	SCCS	578	AMI survivors	Different types of RTI	AMI	35
Smeeth *et al*[48] 2006	UK	SCCS	3375§	DVT patients	Lower RTI	DVT	364
Smeeth *et al*[49] 2004	UK	SCCS	20921§ 22400§	AMI/stroke patients	Lower RTI	AMI Stroke	91
Torabi *et al*[50] 2022	UK	SCCS	2 062 144	COVID-19 patients	COVID-19	Arterial thrombosis, VTE, stroke	28
Wang *et al*[33] 2022	USA	MC	1 381 784	Adults	COVID-19	ACS, DVT, PE, AF, stroke, TIA	365
Warren-Gash *et al*[36] 2012	UK	SCCS	3927	AMI patients	Lower RTI, ILI	AMI	91
Wen *et al*[51] 2017	Taiwan	SCCS	9793	AMI patients	RTI	AMI	30
Wen *et al*[52] 2018	Taiwan	SCCS	29 518	Stroke patients	RTI	Stroke	30
Wu *et al*[53] 2012	Taiwan	MC	268 280	Adults	Rhinosinusitis	Stroke	1096
Xie *et al*[31] 2022a	UK	MC	112 026	Adults	COVID-19	VTE	30
Xie *et al*[34] 2022b	USA	MC	5 791 407	COVID-19 survivors/controls	COVID-19	ACS, VTE, AF, stroke, TIA	365
Xu[32] 2022	USA	MC	5 792 863	COVID-19 survivors/controls	COVID-19	Stroke, TIA	365
Yang *et al*[30] 2022	USA	SCCS	37 379	COVID-19 patients aged >65 years	COVID-19	Stroke	28

*The total number of analysed subjects, including controls for MC and CC designs. For SCCS, the number of analysed subjects with both exposure and outcome is presented if provided by the article, otherwise the size of the population on which the analysis was based (including subjects without exposure or outcome).
†Maximum number of days of follow-up between the exposure and outcome according to the study design of the article. These may deviate from the specific follow-up durations for which effect estimates are reported as presented in this review.
‡Including supraventricular tachycardias.
§Number of enrolled subjects, exact number of analysed subject after exclusion of subjects with an outcome on the same day as the exposure not reported
ACS, acute coronary syndrome; AF, atrial fibrillation; AMI, acute myocardial infarction; CC, case–control study; CVD, cardiovascular disease; DVT, deep venous thrombosis; FU, follow-up; IHD, ischaemic heart disease; ILI, influenza-like illness; MC, matched cohort study; PE, pulmonary embolism; RTI, respiratory tract infection; SCCS, self-controlled case series; TIA, transient ischaemic accident; VTE, venous thromboembolic event.

Table 2 Risk of bias assessment

Study	Outcome	Confounding	Exposure classification	Selection	Postexposure intervention	Missing data	Outcome classification	Selective reporting	Overall
Baylin *et al*[21] 2007	AMI								
Chang *et al*[38] 2016	AF								
Chung *et al*[25] 2014a	PE								
Chung *et al*[26] 2014b	ACS								
Clavijo *et al*[39] 2021	VTE								
Clayton *et al*[40] 2011	DVT								
Clayton *et al*[41] 2008	AMI								
Clayton *et al*[41] 2008	Stroke								
Cohoon *et al*[42] 2018	VTE		*				*		
Ekker *et al*[22] 2022	Stroke								
Hao *et al*[43] 2013	AMI								
Ho et al[44] 2021	AMI								
Ho *et al*[44] 2021	CVD								
Ho *et al*[44] 2021	DVT, stroke								
Ho *et al*[44] 2021	PE								
Huaman *et al*[35] 2017	AMI								
Katsoularis *et al*[29] 2022	DVT								
Katsoularis *et al*[29] 2022	PE								
Katsoularis *et al*[28] 2021	AMI								
Katsoularis *et al*[28] 2021	Stroke								
Knight *et al* 2022	AMI								
Knight *et al* 2022	DVT, stroke, TIA								
Knight 2022	PE								
Leibson 2014	VTE								
Meier 1998	AMI								
Paganini-Hill *et al*[23] 2003	Stroke								
Pasha *et al*[24] 2021	VTE								
Penntinen 1996	AMI								
Rezel-Potts *et al*[37] 2022	IHD								

Continued

Table 2 Continued

Study	Outcome	Confounding	Exposure classification	Selection	Postexposure intervention	Missing data	Outcome classification	Selective reporting	Overall
Rezel-Potts *et al*[37] 2022	AF, stroke	High	Low	High	Low	Low	Low	Low	Very high
Rezel-Potts *et al*[37] 2022	PE, VTE, CVD	High	Some concerns	High	Low	Low	Some concerns	Low	Very high
Ruane *et al*[20] 2017	AMI	High	Very high	Some concerns	Low	Low	Low	Low	Very high
Smeeth 2006	DVT	High	Low	Low	Low	Low	Low	Low	High
Smeeth 2004	AMI	High	Some concerns	Some concerns	Low	Low	Low	Low	High
Smeeth 2004	Stroke	High	Low	Some concerns	Low	Low	Low	Low	High
Torabi 2022	ACS	High	Some concerns	Some concerns	Low	Low	Low	Low	High
Torabi 2022	Stroke	High	Low	Some concerns	Low	Low	Low	Low	High
Torabi 2022	VTE	High	Some concerns	Some concerns	Low	Low	Some concerns	Low	High
Wang *et al*[33] 2022	ACS	Low	Some concerns	High	Low	Low	Low	Low	High
Wang *et al*[33] 2022	AF, DVT, stroke, TIA	Low	Low	High	Low	Low	Low	Low	High
Wang *et al*[33] 2022	PE	Low	Some concerns	High	Low	Low	Some concerns	Low	High
Warren-Gash *et al*[36] 2012	AMI	Low	Some concerns	Some concerns	Low	Low	Low	Low	High
Wen 2017	AMI	Low	High	High	Low	Low	Low	Low	Very high
Wen 2018	Stroke	Low	High	High	Low	Low	Low	Low	Very high
Wu 2012	Stroke	High	Low	High	Low	Low	Low	Low	Very high
Xie *et al*[31] 2022a	VTE	High	Some concerns	High	Low	Low	Some concerns	Low	Very high
Xie *et al*[34] 2022b	ACS	Low	Some concerns	High	Low	Low	Low	Low	High
Xie *et al*[34] 2022b	AF, stroke, TIA	Low	Low	High	Low	Low	Low	Low	High
Xie *et al*[34] 2022b	PE, VTE	Low	Some concerns	High	Low	Low	Some concerns	Low	High
Xu[32] 2022	Stroke, TIA	Low	Low	High	Low	Low	Low	Low	High
Yang *et al*[30] 2022	Stroke	High	Low	Low	Low	Low	Low	Low	High

-Very high risk of bias, -High risk of bias, -Some concerns, -Low risk of bias

*Low risk of bias for the exposure upper respiratory tract infection.

ACS, acute coronary syndrome; AF, atrial fibrillation; AMI, acute myocardial infarction; CVD, cardiovascular disease (composite outcome); DVT, deep venous thrombosis; IHD, ischaemic heart disease; PE, pulmonary embolism; TIA, transient ischaemic accident; VTE, venous thromboembolic event.

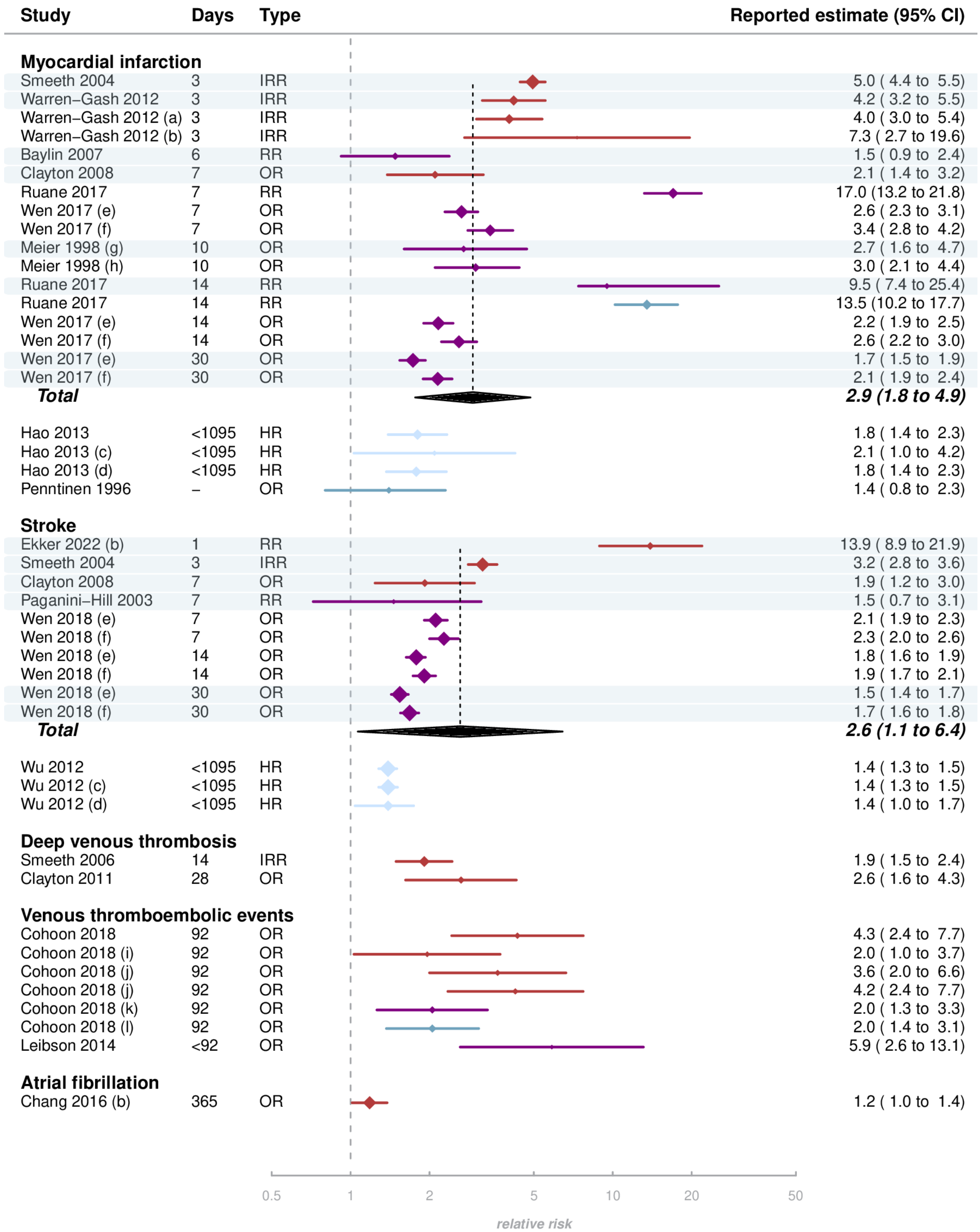

Figure 2 Forest plot for effect of respiratory infections on cardiovascular outcomes. The dashed line represents the reference value of no effect (estimate=1). Highlighted studies are included in meta-analysis. Legend: ■ Lower respiratory tract infections, ■ Respiratory tract infections, ■ Upper respiratory tract infections, ■ Rhinosinusitis; details on exposure status: (a) non-influenza infections, (b) influenza(-like) infections, (c) acute rhinosinusitis, (d) chronic rhinosinusitis, (e) without non-steroid anti-inflammatory drug (NSAID) use, (f) with NSAID use, (g) based on self-controlled case series, (h) based on case–control analysis, (i) bronchitis, (j) pneumonia, (k) bronchitis and upper respiratory tract infections, (l) upper respiratory infections including infections of the mouth, ear, nose and throat. FU, follow-up; IRR, incidence rate ratio; RR, relative risk.

COVID-19

Thirteen studies reported on the effect of COVID-19 on cardiovascular outcomes (figure 3, online supplemental materials). Various (combinations of) cardiovascular outcomes were studied, including many analyses on venous thrombosis. Three studies excluded day 0 outcomes[28–30] and three other studies only considered 30-day COVID-19 survivors and excluded outcomes up to 30 days after baseline for both COVID-19 patients and controls.[31–33] Six studies were performed before

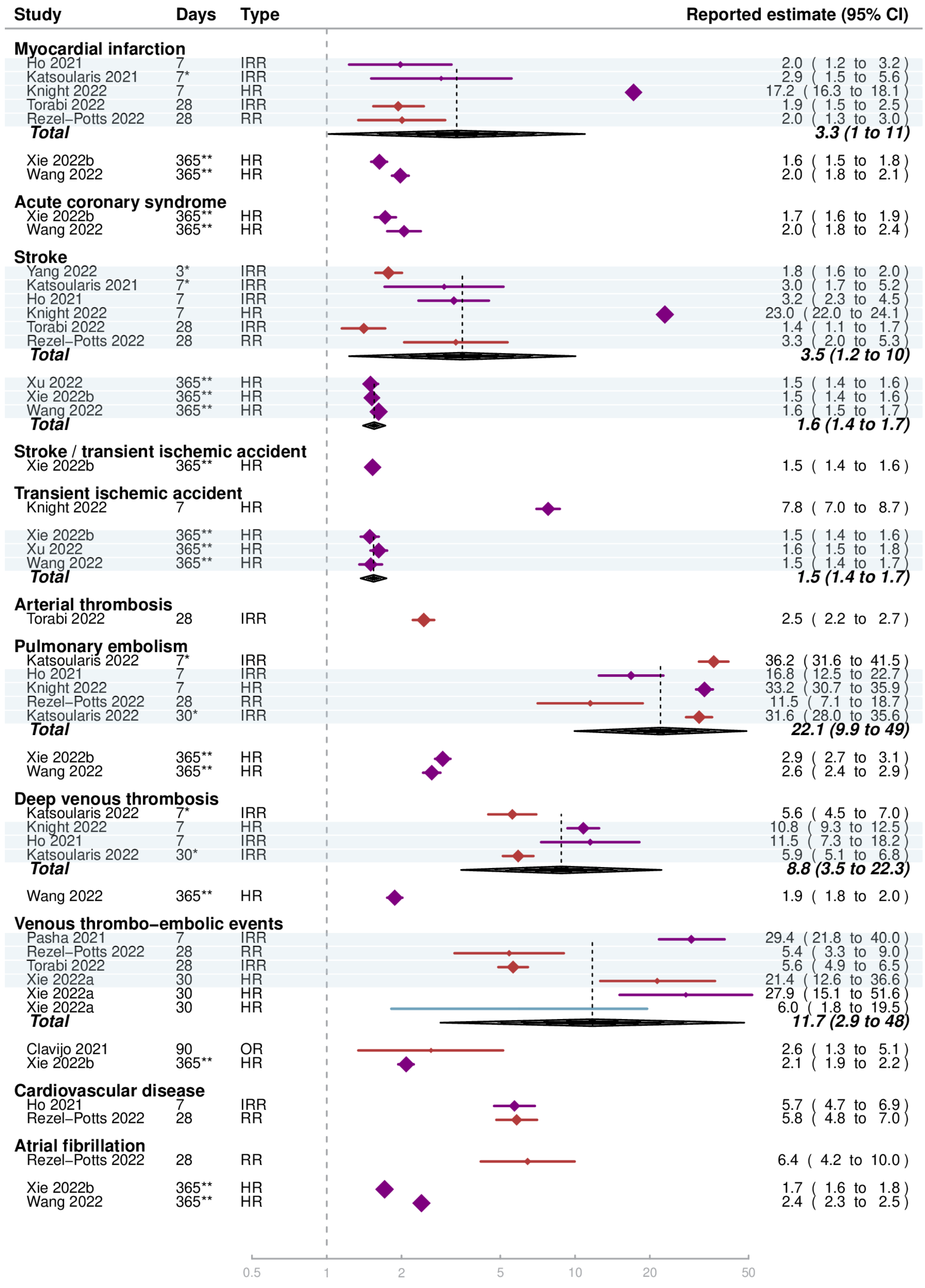

Figure 3 Forest plot for effect of COVID-19 infection on cardiovascular outcomes. The dashed line represents the reference value of no effect (estimate=1). Highlighted studies are included in meta-analysis. Legend: ■ only not (fully) vaccinated individuals (as specified by the article, or if the study population was enrolled before 15 January 2021), ■ both vaccinated and not vaccinated individuals with estimate unadjusted for vaccination status, ■ only fully vaccinated individuals. *Excluding day 0 (outcomes on the same day as COVID-19 diagnosis). **Excluding days 0–30 (outcomes within 30 days after COVID-19 diagnosis). FU, follow-up; IRR, incidence rate ratio; RR, relative risk.

the global widespread COVID-19 vaccination campaigns in January 2021. Of the remaining studies, only two studies took into account COVID-19 vaccination status by restricting the analysis to either only vaccinated or not vaccinated individuals.[33 34] COVID-19 likely increases the risk of AMI (RR 3.3, 95% CI 1.0 to 11.0), stroke (RR 3.5, 95% CI 1.2 to 10.0), PE (RR 22.1, 95% CI 9.9 to 49.0) and DVT (RR 8.8, 95% CI 3.5 to 22.3) within 30 days with moderate certainty of evidence. COVID-19 may increase the risk of VTE (11.7, 95% CI 2.9 to 48.0) and AF within 30 days (low certainty). Long-term risks are likely to increase for stroke (RR 1.6, 95% CI 1.4 to 1.7), TIA (RR 1.5, 95% CI 1.4 to 1.7), PE, DVT, VTE and AF (moderate certainty). Long-term risks may also be increased for ACS (low certainty).

Tuberculosis

Three studies compared individuals with a diagnosis of pulmonary tuberculosis to controls without any diagnosis of tuberculosis during the study period with respect to cardiovascular outcomes. Tuberculosis likely increase the long-term risk of PE (moderate certainty): Chung and colleagues found an HR of 2.46 (95% CI 1.10 to 5.51) within the study period.[25] Two studies reported on risk of ACS and AMI, respectively, and found HR of 1.40 (95% CI 1.14 to 1.72) and 2.43 (95% CI 1.50 to 4.10), respectively.[26 35] We rated the certainty that tuberculosis increases the long-term risk of ACS as low (online supplemental materials).

DISCUSSION

This review on the causal effects of RTIs on cardiovascular outcomes in the general population identified 34 studies including over 65 million individuals, which reported on various cardiovascular events and types of RTI. Risk of bias in effect estimates was generally high to very high, therefore, the quantitative effect estimates should be interpreted with caution. We found moderate certainty of evidence that RTIs increase the short-term risk of arterial thrombosis, which is likely to increase about 1.5–5 fold within 1 month. Within 1 year, there may still be an increased risk of cardiovascular diseases due to RTIs. COVID-19 may cause even higher increased risk, in particular for venous thrombosis, but there was considerable heterogeneity between reported estimates. Studies showed a trend of lower effect estimates with longer follow-up durations, which could be suggestive of a dose–response effect under the assumption that viral or bacterial load decreases over time. However, the type of RTI was also associated with the follow-up duration in the individual studies, which could also be suggestive of a relation between RTI severity and the risk of cardiovascular disease, or such trends could arise from other causes (eg, missing events due to follow-up loss). Overall, our results support a causal effect of RTI on cardiovascular risk.

Discussion of results in the context of other literature

Few systematic reviews have been conducted on the risk of cardiovascular diseases after RTI. Two reviews on the risk of AMI after influenza found results similar to this review.[54 55] One other review on the association between COVID-19 or influenza and atherosclerosis did not clearly define the setting or outcomes of interest.[56] The results of this review of epidemiological studies are further consistent with pathophysiological hypotheses on the effects of inflammation on cardiovascular disease, most of which are not pathogen-specific,[4 5 11] and the increased risk of cardiovascular disease with other inflammatory diseases such as rheumatoid arthritis.[57]

One possible way of understanding the impact of the potential estimated causal effects of RTIs on cardiovascular risk could be to compare our findings in the light of the causal effects of other well-known factors that are currently targeted for risk management. For instance, a twofold increased RR of cardiovascular diseases is equivalent to the difference between a smoker and a non-smoker, or systolic blood pressure increased with 40 mm Hg, or serum cholesterol levels increased with 155 mg/dL (4 mmol/L).[57] The estimated RRs of RTIs may, thus, be in the same range as the RRs of other well-known causal factors (although evidence from direct comparisons is lacking, and ethically impossible to achieve).

A clinically important difference is that the effect of RTIs—unlike effects of smoking or increased lipid levels—is likely more limited in duration as the exposure is only temporal. The exact time window of the increased risk after an acute RTI is unknown, but would probably be within weeks to months after infection according to literature.[36 37] Some RTIs may also become chronic, such as rhinosinusitis, and may as such have prolonged effects. Furthermore, there may be interactions between infection and metabolic risk factors of cardiovascular disease. For example, COVID-19 may also induce diabetes, hypertension and dyslipidaemia, and statin treatment may reduce the risk of infections.[58 59] However, it remains unclear to what extent RTIs could induce long-term changes to the cardiovascular and metabolic system. We found one study on this topic and this study could not identify sustainable measurable differences in blood pressure, biomarker concentrations or arterial stiffness between COVID-19 patients and controls, even though the former group reported residual symptoms at 6 months postinfection.[60]

Strengths and limitations of this review

A strength of this review is the extensive risk of bias assessment using the ROBINS-E. In fact, using this tool revealed that most studies currently performed on the association of RTIs and cardiovascular disease suffer from a high risk of bias, mainly due to incomplete adjustment for confounding bias. Importantly, we did not formally assess the risk of publication bias. Statistical methods to identify publication bias are often based on sample size, but these methods are less useful for observational studies compared with trials, as smaller observational studies may have better data quality.[16]

Implications

This review identifies a need for better understanding of the causal effects of RTI on cardiovascular outcomes, given the high risk of bias in many published studies. This may be inherent to the difficult nature of aetiological designs to appropriately address the causal effect. In addition, residual confounding will always remain in observational studies. We would, however, welcome future aetiological studies that focus on extensive confounder adjustment, in particular regarding vaccination status and calendar time, and dedicated selection of controls.[16]

In addition, research may also focus more on intervention studies concerning preventive strategies aimed to mitigate the cardiovascular risk caused by RTIs, such as vaccination or preventive therapies (eg, anticoagulants, colchicine, others) in targeted populations. Indeed, a systematic review of randomised controlled trials showed that influenza vaccination in patients with existing ACS is associated with reduction of major adverse cardiovascular events, as was also suggested by reviews on matched-cohort and case–control studies.[61–63] In line with this, observational studies suggest benefits from pneumococcal and SARS-CoV-2 vaccination in various populations, but no trials have been performed.[64 65] Vaccines for respiratory syncytial virus have recently been developed and no studies evaluating cardiovascular outcomes are yet available. Trials have shown that prophylactic anticoagulants can reduce the risk of cardiovascular diseases in hospitalised COVID-19 patients without other indications for anticoagulants, but no benefits were found in non-hospitalised patients.[66] No similar trials on other preventive therapies or for other RTI were identified, but recently one trial on therapeutic dose heparin prophylaxis for community-acquired pneumonia hospitalised patients was registered (NCT05848713). Further research is needed on the effectiveness of vaccinations and other preventive therapies in targeted populations. The benefits of vaccination and anticoagulation in the above-mentioned trials were found in populations with existing cardiovascular disease, high risk of cardiovascular disease or exposure to severe RTI requiring hospitalisation. The potential role of mild RTI as a target in primary prevention remains less clear.

CONCLUSIONS

Common respiratory infections, including upper and lower RTI, influenza and COVID-19, likely increase the risk of cardiovascular diseases about 1.5–5 fold within 1-month postinfection in the general population. These infections could, therefore, be further researched for their clinical relevance as target for cardiovascular risk management, especially in individuals with established cardiovascular disease or high cardiovascular risk.

Acknowledgements We are grateful to Drs. René Spijker, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, for his contribution to the performance of the systematic search.

Contributors HMIR-T conceptualised the study, wrote the protocol, performed the search, study selection, data extraction, risk of bias assessment, descriptive synthesis, meta-analysis, certainty of evidence rating and critically appraised the results, and wrote the first draft of the manuscript. SMdW developed the search string and performed duplicate title/abstract screening. MB performed duplicate full-text screening, data extraction and risk of bias assessment. BY performed duplicate certainty of evidence rating. G-JG, MvS and FR gave feedback during the whole process, critically appraised the results and the manuscript, and contributed to manuscript writing. All authors agreed to the final manuscript. HMIR-T is the guarantor.

Funding This project was funded by The Netherlands Organisation for Health Research and Development 'ZonMw', grant number 08391052110003.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data and R codes are available on reasonable request.

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