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Cigarette smoking and the occurrence of influenza – Systematic review

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SUMMARY

Objectives: The association of current smoking with influenza infection is not widely recognised. The aim of this systematic review was to summarise published evidence and quantify the risk of influenza infection in tobacco smokers compared to non-smokers.

Methods: We systematically searched MEDLINE, EMBASE, CINAHL, LILACS and Web of Science, from inception to 7 November 2017, to identify relevant randomised control trials, cohort and case-control studies. Study quality was assessed using the Newcastle–Ottawa Scale. We included studies defining influenza as a clinical syndrome and those using confirmatory microbiological tests. Pooled odds ratios (ORs) were estimated by using random effects model.

Results: The mean quality score across the nine included studies ($n = 40{,}685$ participants) was 5.4 of 9 (SD 1.07). Current smokers were over 5 times more likely to develop laboratory-confirmed influenza than non-smokers (pooled OR 5.69 (95% CI 2.79–11.60), 3 studies). For studies reporting the occurrence of an influenza-like illness (ILI), current smokers were 34% more likely to develop ILI than non-smokers (pooled OR 1.34 (95% CI 1.13–1.59), 6 studies).

Conclusion: Current smokers have an increased risk of developing influenza compared to non-smokers. The association was strongest in studies examining cases with laboratory confirmed influenza.

Introduction

Influenza is an acute viral respiratory tract infection affecting all ages and associated with a significant morbidity and mortality. It affects 10–20% of patients annually in developed countries.[1] The illness ranges from a mild self-limiting disease to a severe illness requiring hospitalisation. In the UK during an average influenza season, 1.3% and 0.1% of seniors aged 75 years or over consult their GP for an episode for respiratory illness attributable to influenza A and B respectively.[2] In hospital, Influenza accounts for an estimated 10% of the attributed respiratory admissions and deaths.[3] The primary mode of prevention in many countries is annual influenza vaccination targeting primarily selected populations considered at risk of complications or severe disease.[4,5]

Figures from the Office of National Statistics suggest that in the UK an estimated 15.8% of the adult population were current tobacco smokers in 2016.[6] Smokers have a significantly increased risk of chronic respiratory disease and acute respiratory infections.[7] Cigarette smoke produces structural changes in the respiratory tract, disrupting respiratory immune defences. These changes include peri-bronchiolar inflammation and fibrosis, increased mucosal permeability, impairment of the mucociliary clearance, changes in pathogen adherence and disruption of the respiratory epithelium.[8] Cigarette smoking is also associated with a variety of alterations in cellular and humoral immune system function which may predispose to infection.[9]

The association of tobacco smoking with influenza infection is not well established and currently, active smoking alone without associated co-morbidities does not identify an individual into a high-risk group requiring influenza vaccination. The aim of this systematic review was to summarise and quantify the risk of influenza infection in tobacco smokers compared to non-smokers.

Materials and methods

Search strategy and inclusion criteria

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement, we systematically

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searched online databases (MEDLINE, EMBASE, CINAHL, LILACS and Web of Science) using Medical Subject Headings to identify published and unpublished studies on the association between smoking and influenza from database inception to 7 November 2017. No restrictions on published language or date range were applied. We included randomised control trials (RCTs), cohort and case-control studies enrolling adults aged 18 years or above conducted in either community or hospital settings. Cross-sectional studies were excluded. The review protocol was registered on the PROSPERO database (CRD42018093933).[10]

Our primary outcome of interest was occurrence of influenza in smokers compared to non-smokers. Studies were included if they defined influenza either as a clinical syndrome defined using established criteria or fever plus acute onset of symptoms (an influenza-like illness (ILI)), or by using diagnostic laboratory-based influenza testing. Our exposure of interest was reported tobacco smoking including dose quantification and frequency, if reported.

Data extraction and quality assessment

We used the online Covidence® tool to consecutively screen the titles, abstracts then full text of studies against the inclusion criteria. Two independent assessors (HL, AH) screened all studies and disagreements were reviewed after discussion and involvement of a third reviewer if required. Data extraction of eligible studies was performed onto a standardised report form by each assessor. Study quality was independently assessed by two assessors (HL, AH) using the Newcastle–Ottawa Scale appropriate for the study design.

Statistical analysis

To compare the odds of developing influenza in smokers with non-smokers across the included studies, we estimated pooled odds ratios (ORs) with 95% confidence intervals (CIs) by using a random effects model. Heterogeneity was assessed taking into account the I^2 statistic. Pre-determined subgroup analyses were performed according to mode of influenza diagnosis used in the study; clinical versus laboratory-confirmed. Analyses were conducted using StataSE® version 15.

Results

We identified 2579 references for screening of which 102 studies were assessed for full text eligibility. The main reasons for study exclusion were irrelevance ($n = 37$) and incorrect outcome ($n = 22$). Of the final eleven studies, six were cohort studies,[11–16] four were case control studies[17–20] and one was a RCT[21] – see Fig. 1. One study was subsequently excluded as it focussed on risk factors for Influenza A(H7N9), a predominantly avian influenza rarely causing infection in humans.[18] One further study was found on hand searching references[22] but subsequently excluded to avoid cohort duplication as it contained a sample of a study population already included in a larger study.[15] Of note, a study from 1969 by Finklea et al. stated that they found a statistically significant increase in morbidity among smokers, however was excluded following full text review as it did not report outcomes further.[23] Nine of the remaining ten studies reported odds ratios and were included in the pooled meta-analysis; see Table 1 for details of included studies.

Diagnostic criteria for an ILI varied across all seven studies that defined influenza infection clinically. Of these, two studies used established criteria to diagnose ILI, the European Centre for Disease Prevention and Control criteria plus fever ($n = 1$)[11] and the Dutch sentinel station criteria ($n = 1$).[21] One study defined ILI using ICD9 codes previously associated with culture-confirmed influenza.[16] Four studies defined ILI as acute onset of symptoms (within hours) of fever ($T > 37.5$ °C or $T > 38.0$ °C) and at least one symptom consistent with influenza (cough, sore throat, and myalgia).[12,13,15,20] Two of six studies diagnosed ILI following a visit to a medical practitioner[13,20] whilst the remaining relied on participant reported symptoms.

Of three studies reporting laboratory-confirmed influenza, each used a different method to identify cases; (i) real time reverse transcriptase PCR of nasopharyngeal and oropharyngeal swabs ($n = 1$),[17] (ii) complement fixation tests for antibodies to influenza A and B of paired acute and convalescent serum samples ($n = 1$),[14] and (iii) a combination of PCR, rapid antigen detection, direct fluorescent antibody detection and viral culture ($n = 1$)[19].

Quality of the studies and assessment of bias

The mean quality score across the included nine studies was 5.4 (SD 1.07) out of a possible maximum of 9; the average score for the cohort studies was 5.5 (SD 1.38) and the case-control studies 5.3 (SD 0.58). Domains most responsible for downgrading quality scores were exposure ascertainment, comparability of cohorts and outcome assessment. All studies assessed smoking status via participant completed questionnaires, potentially introducing both reporter and recall bias. Most studies had a restricted study population; age over 60 years ($n = 2$ studies)[14,21]; military personnel only ($n = 3$ studies)[12,13,20]; renal transplant recipients only ($n = 1$ study),[19] respondents to online surveys ($n = 2$ studies).[11,15] Individual study scores were not associated with the direction of the study result.

Statistical results

Across the studies of laboratory-confirmed influenza, the percentage of smokers amongst influenza cases ranged from 27% to 42% (mean 31.8%) compared to 3% to 14.2% (mean 10.5%) in the non-influenza controls. Relevant data on smoking rates were only available for four of the seven ILI studies. Across these four, 20.3% to 57.5% (mean 37.9%) of cases were smokers compared to 21.9% to 38.0% (mean 29.1%) of non-influenza controls.

From pooled odds ratios, current smokers were 55% more likely to develop influenza than non-smokers (OR 1.55 (95% CI 1.24–1.92), 9 studies, $n = 40\,685$ participants) (Fig. 2). There was substantial study heterogeneity ($I^2 = 78.7\%$). Sub-group analysis of studies of laboratory-confirmed influenza found current smokers were over 5 times more likely to develop influenza than non-smokers (OR 5.69 (95% CI 2.79–11.60), 3 studies, $n = 462$ participants). There was no heterogeneity in these studies suggested by the I^2 statistic ($I^2 = 0.0\%$) though one was conducted in the community and one involved only renal transplants recipients. In studies of ILI, current smokers were 34% more likely to develop ILI than non-smokers (OR 1.34 (95% CI 1.13–1.59), 6 studies, $n = 40{,}223$ participants). High heterogeneity remained across this group of studies ($I^2 = 72.4\%$).

The final included study reported an unadjusted hazards ratio of 1.09 (95% CI 1.02–1.17, $p < 0.05$) for the occurrence of ILI in recent smokers, defined as >100 cigarettes in a lifetime and at least one in the last year, compared to non-smokers.[16]

Smoking frequency and duration were infrequently reported in the included studies therefore pooled analysis of a dose relationship was not possible. Of the included studies: Cruijff et al. reported no dose relationship between smoking and occurrence of influenza[21] and Kark et al. reported no association between the number of cigarettes smoked and ILI occurrence in either study group.[12,13] As part of the Influenzanet trial, Vandendijck et al. reported a RR of 1.30 (95% CI 1.15–1.46, $p < 0.0001$) of ILI in daily smokers and a RR of 1.13 (95% CI 0.95–1.35, $p = 0.1770$) in

Table 1
Table of included studies.

Lead author	Year published	Prospective/ retrospective	Study type	Country	Type of centres participating	ILI or laboratory confirmed diagnosis	How is influenza defined?	Number of participants included	How is smoking status measured?	Restricted population
Adler et al.[11]	2014	Prospective	Cohort	UK	Nationwide online flu survey	ILI	Influenza like illness based on participant self-reported symptoms. Two definitions used 1) ILI as per ECDC 2) ILI as ECDC plus fever	4532 participants	Self-reported questionnaire	Age >18
Choi et al.[17]	2014	Retrospective	Case-control	South Korea	One secondary care hospital	Laboratory	Pandemic 2009 H1N1 virus positive real time reverse transcriptase PCR using NP and OP swab samples.	33 cases, 132 controls	Self-reported questionnaire	Age >18
Cruijff et al.[21]	1999	Prospective	Randomised control trial	Netherlands	15 GP practices	ILI	Restricted to criteria for Dutch Sentinel stations in this analysis. Acute onset of symptoms, fever > 38°. At least one of cough, coryza, sore throat, frontal headache, myalgia.	1531 participants	Self-reported Questionnaire. Current, past, type and amount of smoking (1–9/day, 10–19/day, 20 plus)	>60 years, not vaccinated against influenza
Kark and Lebiush[12]	1981	Retrospective	Cohort	Israel	Israeli Defense Force Recruit Base	ILI	Mild – flu like illness reported by subject, no contact with doctors. Mod – flu like illness plus visited doctor. Severe – hospitalised with flu like illness.	173 participants	Self-reported questionnaire	Female healthy military recruits
Kark et al.[13]	1982	Retrospective	Cohort	Israel	Israeli Defense Force Recruit Base	ILI	Mild = symptoms but no time off work. Severe = hospitalised and stopped work	331 participants	Self-reported questionnaire	Male healthy military recruits
Nicholson et al.[14]	1999	Prospective	Cohort	UK	One county	Laboratory	Paired acute and convalescent serum samples tested by complement fixation for antibodies to influenza A and B. A 4-fold rise indicates infection.	427 (only 209 in non-vaccinated cohort)	Self-reported questionnaire	>60 years, not vaccinated against influenza
Pang et al.[20]	2015	Prospective	Case-control	Singapore	Four Armed Forces Camps	ILI (febrile respiratory illness)	FRI defined as temp >37.5, cough or sore throat, disease confirmed by healthcare worker at clinic. Nasal washings taken for etiological testing and multiplex PCR for viral detection.	7743 cases, 1247 controls	Self-reported questionnaire	Male healthy military recruits
Sparks et al.[19]	2014	Retrospective	Case-control	USA	Large tertiary care facility	Laboratory	Positive microbiological test for influenza (rapid antigen, direct fluorescent antibody, viral culture, and PCR) from NP, sputum or bronchoscopy samples	22 cases, 66 controls	Self-reported questionnaire	>18 years, renal transplant recipients
van Noort et al.[15]	2015	Prospective	Cohort	Netherlands, Belgium, Portugal, Italy	Online Flu survey – multinational in Europe	ILI	ILI = acute onset (within a few hours) of fever ($T > 38$) with muscle pain or headache and cough or sore throat.	24,666 participants	Self-reported questionnaire	
Woolpert et al.[16]	2014	Retrospective	Cohort	USA	Three US Military databases	ILI	First event ILI defined from ICD 9 codes recorded in the Military Health System Data Repository containing outpatient and inpatient encounters.	28,929 participants	Self-reported questionnaire – 'recent smokers' defined as >100 cigarettes in a lifetime and smoker within the past 12 months	Healthy US military employees, 18–49 years, vaccinated against influenza

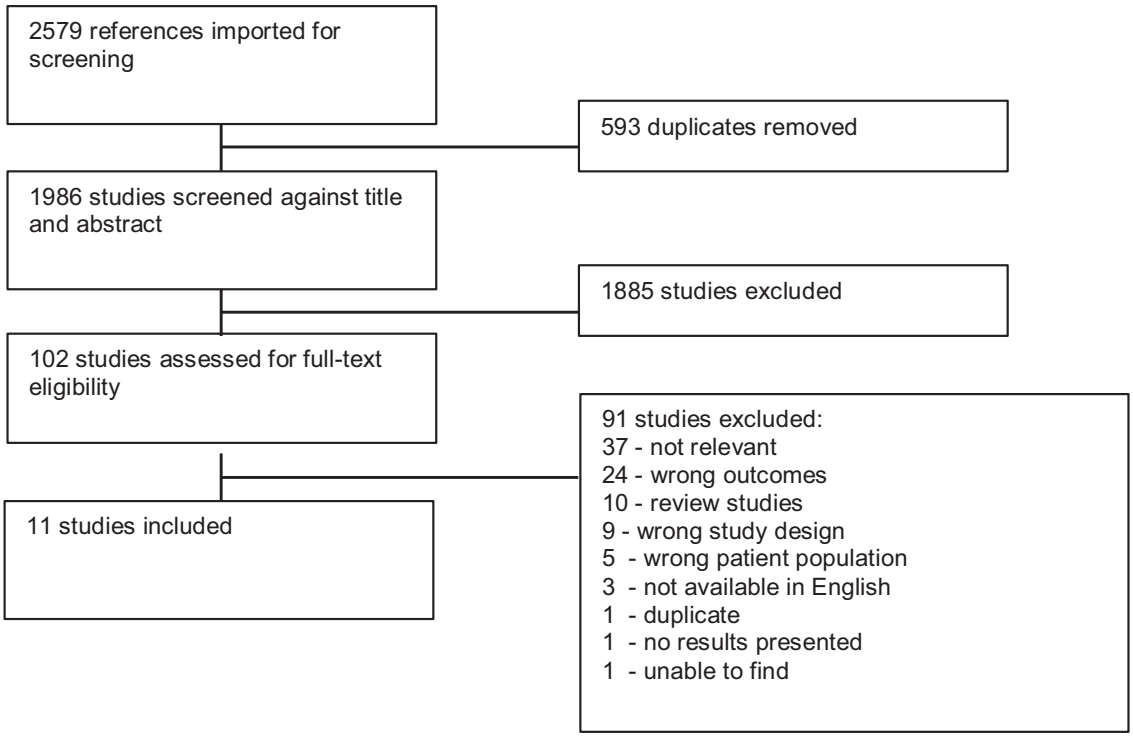

Fig. 1. Screening process.

occasional smokers compared to non-smokers, suggesting a stronger association with increased frequency of smoking.[22]

Discussion

Our main finding is that current smokers have an increased risk of developing influenza compared to non-smokers. This association was much stronger in all of the studies where influenza infection was confirmed microbiologically rather than based on a clinical diagnosis of an ILI.

Experimental data in animal models and in human cell culture suggest that tobacco smoke components can inhibit antiviral pathways and increase susceptibility to influenza via mechanisms involving oxidant stress but that this relationship is complex and dependent on chronicity of both exposure to tobacco and infection and the viral infective dose.[24] Consistent with these findings, an observational cohort study comparing local nasal mucosal responses to live attenuated influenza virus in healthy adults showed a suppressed IL-6 response and increased viral RNA in cells from nasal lavage fluid in smokers compared to non-smokers, suggesting smoke exposure has a measurable impact on the host's innate respiratory mucosal host defence to influenza.[25]

Influenza vaccination is currently recommended for risk groups considered more likely to develop serious complications of influenza, such as pneumonia or severe disease. Tobacco smoke exposure is significantly associated with the development of pneumonia in current smokers. Evidence on smoking as a risk factor the development of influenza complications, such as pneumonia, is limited.[26] Smoking may affect the severity of influenza infection. Gualano et al. found that mice exposed to cigarette smoke and then infected with influenza A(H3N1) had a worse response to infection than mice not exposed to smoke beforehand.[27] In contrast Han et al. found decreased mortality and an increased early cytokine response in smoke exposed mice compared to air exposed controls after infection with pandemic influenza A(H1N1),[28] indicating a possible difference in the relationship between influenza strains. Published epidemiological evidence on the severity of influenza in smokers is inconsistent. Kark et al. reported the rate of severe influenza increased from 30% in non-smokers to 54% in heavy smokers with a statistically significant chi-square test for linear trend across the group ($p < 0.0001$). However they used place of treatment not clinical parameters to define severe illness.[13] Wong et al. in 2013 found that smoking may increase influenza-associated mortality in an elderly cohort.[29] During the 2009 H1N1 influenza pandemic, smoking was associated with an over 2-fold increased risk of intensive care admission in peri-partum women hospitalised with ILI (OR 2.77, 95% CI 1.19–6.45).[30] In contrast a study examining risk factors for severe outcomes in patients hospitalised with pandemic 2009 H1N1 influenza did not find smoking to be a significant risk factor, demonstrating conflicting evidence even within a pandemic year.[31]

Two of the three studies of laboratory-confirmed influenza were conducted within a hospitalised cohort whilst all six of the ILI studies were community based. Hospitalised patients represent a cohort with higher severity disease compared to those treated in the community. Epidemiological studies suggest that smoking may increase the risk of hospitalisation from influenza; Ward et al. found adults who were current or previous smokers had twice the risk of hospitalisation from pandemic 2009 influenza A H1N1 infection compared to non-smokers (current smokers OR 2.0 (95% CI 1.3–3.2).[32] A case-control study by Godoy et al. of adults with confirmed RT-PCR influenza examined the risk of hospitalisation between smokers and non-smokers. They found smokers were at an increased risk of hospitalisation and that the association was strongest in current smokers than previous smokers.[33]

The greater size of effect between smoking and influenza from our results in the laboratory-confirmed studies might therefore partly reflect both an increased risk of developing influenza and developing more severe disease with smoking. However, the size of effect in the community study by Nicholson et al. where influenza was confirmed microbiologically (OR 4.4), was very similar to the study by Choi et al. conducted within a hospitalised cohort (5.5), suggesting the observed association relates primarily to the risk of *developing* influenza regardless of disease severity.

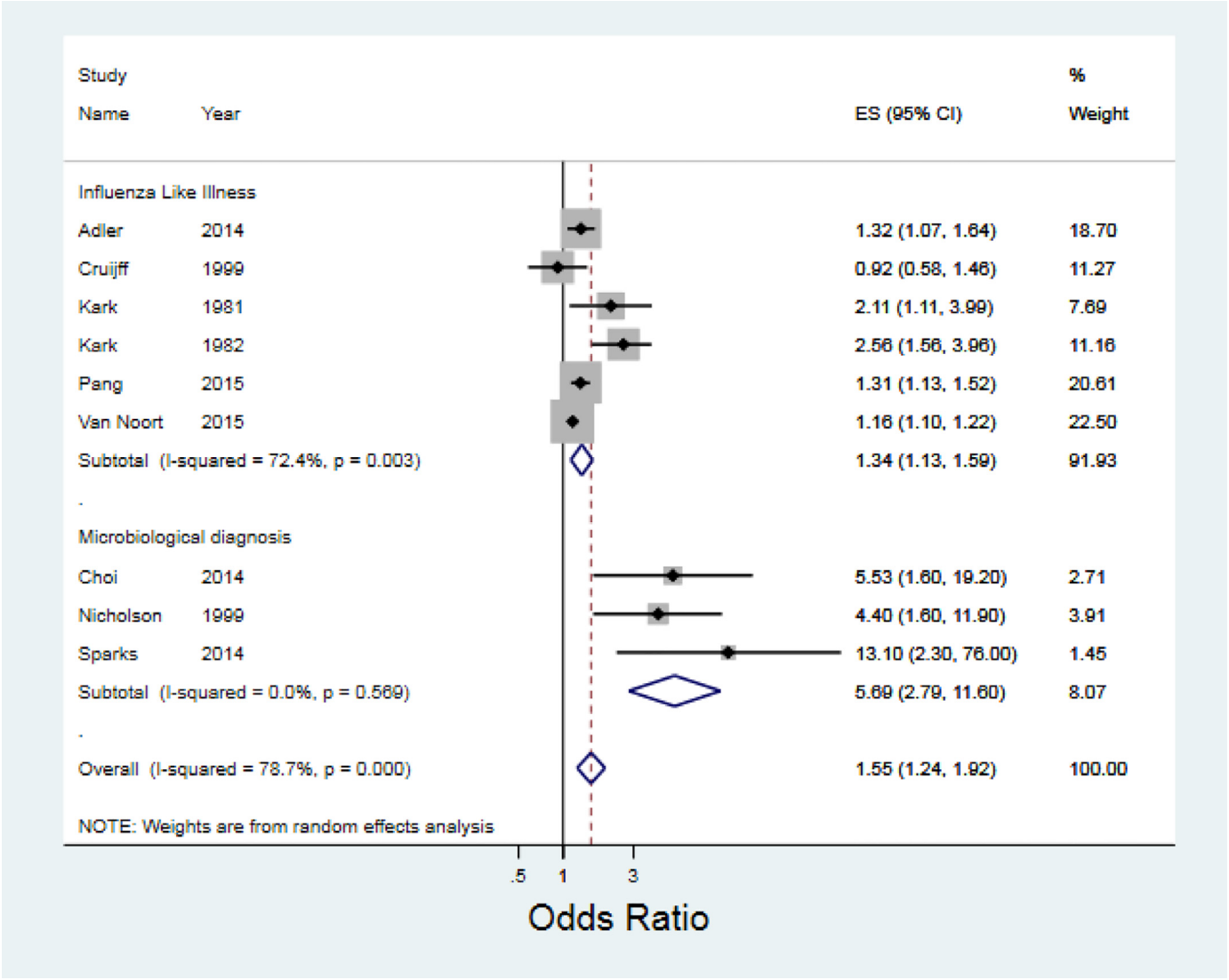

Fig. 2. Meta-analysis of pooled odds ratios from included studies using a random effects model and further subdivided by influenza like illness and laboratory confirmed influenza (microbiological diagnosis).

The specificity of ILI in identifying influenza infection is recognised to be poor even with established definitions of ILI.[34] A range of pathogens other than influenza can present as an ILI, including Respiratory Syncytial Virus (RSV), Human Rhinovirus (HRV) and bacterial pathogens. Published evidence regarding the risks of RSV and HRV infections in adult smokers is limited.[35,36] Epidemiological evidence from a prospective population-based cohort study of residents in Tennessee found that HRV positive cases were more likely to be smokers compared to those presenting with respiratory virus-negative acute respiratory illness (OR 2.31; 95% CI 1.68–3.19).[37] A meta-analysis of risk factors for RSV-associated LRTI in children under 5 years found an association with maternal smoking (OR 1.36; 95% CI 1.24–1.50).[38] In contrast, in a pooled analysis of two longitudinal studies of adults with COPD, smoking status was not a risk factor for RSV infection.[39] More generally, a cross sectional study of Norwegian adults found serum antibiotics to one or more of seven respiratory virus were commoner in smokers compared to non-smokers (adjusted odds ratio 1.7, 95% CI 1.3–2.4) with Influenza A and B antibodies having the first and third highest prevalence, respectively.[40] Together, these studies suggest that smoking may be more strongly associated with influenza infection than with other respiratory viral infections that can present as an ILI. This may partly explain the stronger association between smoking and laboratory-confirmed influenza, compared to smoking and ILI.

Strengths and limitations

Our study was performed in accordance with the PRISMA statement using validated search filters encompassing broad search terms to identify eligible studies. Authors were contacted for further data where appropriate. A range of study types were included with no restriction by healthcare setting nor mode of influenza diagnosis, thus reflecting the breadth of influenza infection, most of which occurs in the community where diagnostic investigations are generally limited. All except one of the studies were observational and susceptible to the effect of unmeasured confounders and smoking status recall and reporter bias. The varied definitions of influenza used may alter our estimates of the true effect size of smoking on influenza. We explored this effect through sub-group analysis of studies using clinical versus microbiological methods for influenza diagnosis. We were unable to determine whether influenza subtypes were differentially associated with tobacco smoking due to a lack of relevant studies. Similarly, we were unable to comment on a dose response relationship, or whether the risk of influenza infection decreases following smoking cessation.

Implications and future research

In many countries, influenza vaccination is offered to older adults or adults in specific clinical risk groups. The risk of developing disease complications in smokers was outside the scope of this work. However, the strong association between influenza infection and current smoking highlighted by this review raises the issue of whether current smoking should be considered an indication for influenza vaccination. Investigation of the risk of influenza infection in ex-smokers and in smokers of newer electronic cigarettes with different vapour compositions is warranted.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Role of the funder/sponsor

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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