Risks of smoking and benefits of smoking cessation on hospitalisations for cardiovascular events and respiratory infection in patients with rheumatoid arthritis: a retrospective cohort study using the Clinical Practice Research Datalink

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ORIGINAL ARTICLE

ABSTRACT

Objectives To investigate the associations between smoking status, smoking cessation and hospitalisations for cardiovascular events (CVE) and respiratory tract infections (RTI) in an inception cohort of patients with rheumatoid arthritis (RA).

Methods The study was set within UK primary care electronic health records (the Clinical Practice Research Datalink) linked to hospital inpatient data (Hospital Episode Statistics). Patients with RA were followed from diagnosis to hospitalisation with a record of CVE or RTI, leaving their general practice, death, or 10 January 2012, whichever was earliest. Smoking status (never, current, former) was defined using primary care data and could vary over time. Survival analysis was performed using Cox regression (first event) and conditional risk set models (multiple RTIs).

Results 5677 patients were included in the cohort: 68% female, median age 61 years. The age-adjusted and sex-adjusted risks of hospitalisation for CVE or RTI were more than twice as high in current vs never smokers (CVE HR (95% CI) 2.19 (1.44 to 3.31); RTI 2.18 (1.71 to 2.78)). The risks for both outcomes were significantly higher in current compared with former smokers (CVE 1.51 (1.04 to 2.19), RTI 1.29 (1.04 to 1.61)). For each additional year of smoking cessation, the risk of first CVE and RTI hospitalisation fell significantly, approximately 25% and 15% respectively in the adjusted models.

Conclusions Patients with RA who smoke have an increased risk of hospitalisation with CVE or RTI compared with never and former smokers. The risk decreases for each additional year of smoking cessation. Patients with RA who smoke should be advised to stop smoking.

INTRODUCTION

Cigarette smoking is associated with an increased risk of developing rheumatoid arthritis (RA) and therefore there is a higher prevalence of smoking in RA populations. In the general population, cigarette smoking is known to increase the risk of cardiovascular disease (CVD) and respiratory tract infection (RTI). CVD is more prevalent in patients with RA than the general population, and RTIs also contribute significant morbidity. Cigarette smoking may contribute to the excess risk of CVD and RTI seen in RA populations.

How might this impact on clinical practice?

These results could be used to help encourage patients with RA to stop smoking.

Key messages

What is already known about this subject?

► Patients with rheumatoid arthritis (RA) are more likely to smoke and to experience cardiovascular events and respiratory tract infections than the general population.

What does this study add?

► Patients with rheumatoid arthritis who smoke have double the risk of a hospitalised cardiovascular event compared with patients with RA who have never smoked.

► The risk of a hospitalised respiratory infection is also increased for current smokers.

► In former smokers, the risk of both outcomes falls for each additional year of smoking cessation.

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compared with non-smokers (HR 1.98, 95% CI 1.8 to 2.3), while the risk of stroke was increased by almost 60% (HR 1.56, 95% CI 1.4 to 1.8). Ra is associated with an approximate 50% increased risk of incident cardiovascular disease (CVD), including increased risk of myocardial infarction, stroke and congestive heart failure. Similarly, both cigarette smoking and RA have been associated with an increased risk of RTI. Both current and former smoking have been shown to be associated with community-acquired pneumonia in the general population. In one study, patients with RA had approximately 90% greater risk of objectively confirmed RTI compared with matched controls (HR 1.88, 95% CI 1.4 to 2.5).

In the general population, there is evidence that smoking cessation is associated with a reduced risk of CVD: in the meta-analysis described above, the risk of ACE and stroke fell by 17% and 13% respectively for each decade of cessation. The risk of RTI also appears to decrease with smoking cessation, although the benefit was only apparent after 5 or 10 years of cessation and only in patients without chronic obstructive pulmonary disease (COPD). In a previous study, we found former smokers had a lower risk of cardiovascular mortality than current smokers, and the risk of death due to RTI fell for each additional year of smoking cessation in former heavy smokers. Smoking cessation could, therefore, potentially reduce the risk of developing CVD and RTI in patients with RA; however, this has not been studied previously.

The aims of this study were to establish, in an inception cohort of patients with RA, (1) the proportions of CVE and RTI hospitalisations in patients with RA who smoke which might therefore be attributable to smoking, (2) the magnitude of any association between cigarette smoking and hospitalisations for major cardiovascular events (CVE) in patients without prior CVD, (3) the magnitude of any association between cigarette smoking and hospitalisations for RTI and (4) whether the risk of being hospitalised for CVE or RTI changes following smoking cessation.

METHODS

Design and setting

This was a retrospective cohort study set within the Clinical Practice Research Datalink (CPRD), a database of anonymised electronic health records (EHR) from UK primary care. CPRD contains routinely collected demographic, lifestyle and clinical data for almost 15 million patients. Clinical information is coded using the Read code system. The EHR provided by CPRD were linked to the National Health Service (NHS) Hospital Episodes Statistics (HES) inpatient dataset which covers all admissions to NHS hospitals in England. Within HES, the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) coding system is used to classify reasons for admission and important comorbidities and the OPCS Classification of Interventions and Procedures V4 (OPCS-4) coding system is used to classify procedures. To be eligible for linkage with HES, CPRD patients must have a valid NHS number and be registered with an English practice participating in the linkage scheme: 56% of CPRD practices are participating in HES linkage. Linkage is performed on behalf of CPRD by a trusted third party on the basis of NHS number, gender, date of birth and postcode.

Study population

Our study population has been described previously. To be included in the present study, individuals had to be recorded within CPRD, first diagnosed with RA within the study window (see below), aged 16 years or over at RA diagnosis and eligible for linkage with HES. Patients were excluded if they were prevalent cases of RA, were missing smoking status at baseline, or, for the CVE analysis, if they had a CVE in their HES record prior to RA diagnosis. A validated algorithm was used to identify highly probable cases of RA within CPRD. The date of RA diagnosis was defined as the date of their first RA Read code (code list available on ClinicalCodes.org) or disease-modifying antirheumatic drug (DMARD) prescription. To define incident RA, all patients were required to have at least 3 years of follow-up in CPRD prior to their RA diagnosis date. If the first DMARD prescription preceded the first RA Read code, an RA Read code needed to be recorded within 3 months of that first DMARD prescription. Patients diagnosed outside the study window (see below) were excluded. For the CVE analysis, patients were required to have at least 2 years of follow-up in the linked HES dataset prior to RA diagnosis in order to exclude those with a prior CVE.

Study window and follow-up

Linked data were available from 1 January 1998 to 10 January 2012. For the CVE analyses, the study window began on 1 January 2000 (to screen for CVE recorded up to 2 years prior to RA diagnosis) and for the RTI analyses, the study window began on 1 January 1998. For both analyses, the end of the study window was 10 January 2012. All eligible patients entered the cohort on their RA diagnosis date (baseline) and were followed until death, leaving their general practice, the occurrence of an outcome event of interest, the last data collection date for their general practice, or 10 January 2012, whichever was earliest.

Exposure

Smoking status was determined from the CPRD datasets based on Read codes, additional clinical information and prescriptions for smoking cessation therapy. Smoking status was defined as periods of never, former and current smoking and could vary throughout follow-up. Each period extended from the first record of a particular status until the first record of a different status (for further details see online supplementary figure S1). The
algorithm used to define smoking status is available to
download. 

For former smokers, the number of years of cessation
was defined. This value was reset to 0 at the start of each
new period of former smoking. As patients had variable
amounts of follow-up within CPRD prior to RA diagnosis,
information recorded more than 3 years prior to RA
diagnosis was not used. The maximum length of smoking
cessation at baseline was therefore 3 years. To account
for a potential interaction between amount smoked
and smoking cessation, amount smoked (light/heavy)
was also defined for inclusion in the smoking cessation
models. Smokers were categorised as heavy smokers if
they smoked more than 20 cigarettes or 10 cigars a day.

Outcomes
The outcomes of interest were hospitalisation for an
atherosclerotic CVE (myocardial infarction, stroke,
unstable angina, revascularisation surgery) and hospi-
talisation for RTI. Hospitalisation was defined as a re-
levant ICD-10 (CVE and RTI) or OPCS-4 (CVE only) code
(online supplementary table S1) recorded at any time
during an inpatient spell. We examined the time to first
admission for both outcomes. For RTI we also examined
the risk of recurrent events, counting each hospitalisa-
tion once only.

Covariates
Gender, socioeconomic status (SES), body mass index
(BMI) and year of diagnosis were included as time-inde-
dendent covariates. The quintile of Townsend score,17
at patient postal code level, was used as the indicator
of SES. BMI was calculated using each patient’s median
recorded height and a weight measurement recorded up
to 3 years prior or 1 year post-RA diagnosis (see Joseph
et al for more details). Year of diagnosis was a marker
for calendar year effects. This was categorised as before/
after 1 January 2000 to correspond approximately with
the introduction of biological therapies for RA in the UK.
For the CVE analysis, all person time was in the biologic
era and thus calendar year was not considered.

Age was a time-varying covariate. Asthma, COPD, type
2 diabetes and use of immunosuppressant DMARDs were
also included as time-varying covariates allowed to switch
from absent to present, but not back. Asthma and COPD,
included only in the RTI analysis, were defined using code
lists created by Doran et al. Read codes used to define
type 2 diabetes are available on ClinicalCodes.org. Use
of immunosuppressant DMARDs (methotrexate, azathio-
prine, ciclosporin, cyclophosphamide, leflunomide and
mycophenolate) was included as an indicator of disease
severity.

The following medications were time-varying covari-
ates, and switched between ‘on’ and ‘off’ according to the
prescription date and a calculated stop date: oral
glucocorticoids (GCs), non-steroidal anti-inflammatory
drugs (NSAIDs), cardiovascular medication, aspirin/
antiplatelet drugs and lipid regulators. The latter three
variables were included in the CVE analysis only. For oral
GCs, the stop date was calculated using an algorithm
which takes into account any recorded dosage and dura-
tion information. The remaining medications were
assigned the arbitrary length of 30 days per prescription.
Product code lists were defined for all medications based
on British National Formulary chapter20 and clinical
knowledge.

Analysis
Baseline characteristics according to clinical outcome
during follow-up were summarised using proportions
or median and IQR. Differences between groups were
examined using X² test or Kruskal-Wallis test. A signifi-
cance level of 0.05 was used throughout.

Crude incidence (first CVE and first RTI) and episode
(multiple RTIs) rates per 1000 person-years were calcu-
lated for each smoking status. The incidence rates were
then standardised, using direct standardisation, to match
the age/gender structure of the whole incident cohort.
Attributable risks (ie, the risk which can be attributed
to smoking status alone) were calculated as the differ-
ces in standardised incidence rates between the smoking
status categories. For CVE, the case fatality risk (CFR) was
calculated as the proportion of patients who died of any
cause within 30 days of the first CVE during follow-up,
excluding patients with <30 days between the CVE and
end of the linkage window.

The Cox proportional hazards regression model was
used to test the association between a) smoking status and
b) length of smoking cessation and the time to first event
for each outcome. Models were adjusted for age and
gender, then for all covariates. The proportional hazards
assumption was checked for each model by inspecting
Schoenfeld residuals. If necessary, interactions between
covariates and time were included in the models.

For multiple RTI, survival analysis with multiple failures
was performed using the conditional risk set model.21 22
This model stratifies each patient’s time from follow-up
start according to the number of previous events. The
risk of failure is calculated for each stratum including
only those patients who are still at risk (eg, a patient with
one event will be included in strata 1 (no prior events)
and 2 (one prior event) only). The time spent in hospital
with an RTI plus a 30-day lag-window after discharge was
excluded from the time at risk (online supplementary
figure S2). The analysis was limited to the first four RTI
events due to low numbers of patients in later strata.

Multiple imputation by chained equations was
performed for missing BMI and amount smoked data
using linear and logistic regression, respectively. All vari-
ables included in the final models were included in the
imputation model. Twenty datasets were imputed and
results were combined using Rubin’s rules.24

Stata/MP V.12.1 (StataCorp, College Station, Texas,
USA) was used for data handling and analysis. The study
was approved by the Independent Scientific Advisory
Committee (protocol reference 13_159).
RESULTS
Within CPRD, 40,605 patients with RA were identified using the validated algorithm,14 5904 of whom were registered with a practice participating in linkage and met our criteria for incident RA diagnosed during the study window (online supplementary figure S3). A further 227 patients were excluded because of missing smoking status at baseline, leaving a final cohort of 5677 patients. At baseline, there were 2288 (40%) never, 1935 (34%) former and 1454 (26%) current smokers. Former smokers were on average older (median age 60.9, 64.9 and 58 years for never, former and current smokers, respectively) and more likely to be male (never smokers 21%; former smokers 40%; current smokers 38%). Former smokers had a higher baseline prevalence of CVD and type 2 diabetes. The prevalence of asthma was 12% in never smokers, 14% in former smokers and 7% in current smokers (X² (2)=36, p<0.001). The prevalence of COPD was 1% in never smokers, 7% in former smokers and 6% in current smokers (X² (2)=36, p<0.001).

Cardiovascular events
Among the 5677 patients, 374 had fewer than 2 years of follow-up in HES and 224 had a CVE prior to RA diagnosis. Of the remaining 5079 patients, 198 (4%) patients had at least one CVE hospitalisation during follow-up. These patients were more likely to be current smokers at baseline (36% vs 25%) (table 1).

During 21843 person-years (pyr) of follow-up, the crude incidence rate of CVE hospitalisations was 9.1 (95% CI 7.9 to 10.4) per 1000 pyr. After adjusting for age and gender, current smokers had the highest incidence rate at 13.7 (9.1–18.3) per 1000 pyr (table 2). The 30-day CFR in the 194 patients with a CVE hospitalisation at least 30 days before the end of the linkage window was 12% (23 patients): never smokers 6% (3/51); former smokers 11% (11/99) and current smokers 20% (9/44). There

| Table 1 Baseline characteristics according to hospitalisation for major cardiovascular events |
|-----------------------------------------------|
| All patients | Never CVE | CVE | Test statistic |
|-----------------|-----------|-----|----------------|
| n patients (% total) | 5079 | 4881 (96%) | 198 (4%) | – |
| Baseline smoking status, n (%) | | | | |
| Never | 2048 (40%) | 1988 (41%) | 60 (30%) | – |
| Former | 1749 (34%) | 1682 (34%) | 67 (34%) | – |
| Current | 1282 (25%) | 1211 (25%) | 71 (36%) | X² (2)=14.4, p=0.001 |
| % female | 68.7 | 69.3 | 54.6 | X² (1)=19.2, p=0.000 |
| Median age (IQR) | 61.0 (50.9, 70.9) | 60.6 (50.4, 70.6) | 70.2 (63.5, 77.2) | KW (1)=101, p=0.0001 |
| Median BMI (IQR)* | 26.9 (23.8, 30.9) | 26.8 (23.8, 30.9) | 27.6 (24.8, 30.6) | KW (1)=1, p=0.26 |
| Townsend score quintile† | | | |
| 1 | 23.5 | 23.5 | 22.7 | – |
| 2 | 24.1 | 24.3 | 20.7 | – |
| 3 | 21.5 | 21.4 | 22.2 | – |
| 4 | 18.4 | 18.3 | 20.2 | – |
| 5 | 12.6 | 12.5 | 14.1 | X² (4)=1.9, p=0.754 |
| Type 2 diabetes | 10.7 | 10.5 | 15.2 | X² (1)=4.4, p=0.036 |
| Immunosuppressant DMARDs | 10.5 | 10.7 | 7.6 | X² (1)=1.9, p=0.167 |
| Oral glucocorticoids | 16.5 | 16.3 | 22.2 | X² (1)=4.9, p=0.027 |
| NSAIDs | 47.0 | 46.7 | 55.6 | X² (1)=6.0, p=0.014 |
| CVD medication | 25.4 | 24.6 | 43.9 | X² (1)=37.6, p=0.000 |
| Aspirin/antiplatelet drugs | 7.0 | 6.7 | 15.7 | X² (1)=23.6, p=0.000 |
| Lipid-lowering agents | 10.6 | 10.2 | 19.2 | X² (1)=16.1, p=0.000 |

Figures are percentages, unless otherwise stated.
*33% missing BMI.
†5% missing SES.

Never CVE, no hospitalised CVE during follow-up; CVE, at least one hospitalised CVE during follow-up; CVE, cardiovascular event; n, number; BMI, body mass index; DMARDs, disease-modifying antirheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs; CVD, cardiovascular disease; X², chi-squared test; KW, Kruskal-Wallis test; SES, socioeconomic status.
was no meaningful difference in CFR according to length of smoking cessation: cessation <3 years 10% (3/29); cessation 3 years or longer 11% (8/70).

In the fully adjusted Cox regression models, the risk of CVE hospitalisation was more than doubled in current versus never smokers (HR 2.23 (95% CI 1.46 to 3.40)) (table 3). After adjusting for all covariates, current smokers were at significantly higher risk than former smokers (HR 1.51 (95% CI 1.04 to 2.19)) and former smokers were at significantly higher risk than never smokers (HR 1.47 (95% CI 1.04 to 2.08)).

The risk of CVE hospitalisation associated with being a former smoker decreased approximately 25% for each additional year of cessation (table 3). To meet the proportional hazards assumption, an interaction between length of cessation and follow-up time (before/after 5 years) was included in the model; the results therefore represent only the first 5 years after RA diagnosis.

### Respiratory tract infection

Of the 5677 patients included in this analysis, 560 (9.9%) patients had at least one, 135 (2.4%) had at least two, 58 (1.0%) had at least three and 27 (0.5%) had at least four hospitalised RTIs. The maximum number of hospitalised RTI recorded was 14. Those with a hospitalised RTI were more likely to be ever smokers (71% vs 58%) and to have asthma (18% vs 10.9%) or COPD (13.4% vs 3.2%) (table 4).

During 25622 pyr of follow-up, the crude incidence rate (counting only the first event) was 21.9 (95% CI 20.1 to 23.7) per 1000 pyr. The age-adjusted and sex-adjusted incidence rates were similar in former and current smokers, each with an attributable risk of 14 (95% CI 12 to 15) additional events per 1000 pyr compared with never smokers (table 5). In total, there were 836 hospitalised RTI recorded during 26666 pyr of follow-up, giving a crude episode rate of 31.4 (95% CI 29.3 to 33.5) per 1000 pyr. Former smokers had the highest adjusted episode rate. There were 6.7 (95% CI 4.1 to 9.3) additional RTI admissions per 1000 pyr in former compared with current smokers.

Considering only the first RTI hospitalisation, current smoking was associated with a significantly increased risk of hospitalisation compared with never smoking in the fully adjusted Cox regression models (HR 1.78 (95% CI 1.38 to 2.29)) (table 6). Current smoking had a 29% increase in risk compared with former smokers; and former smoking had a 38% increase in risk compared with never smokers.

Each additional year of smoking cessation was associated with an approximately 15% decreased risk of first hospitalised RTI independent of the amount previously smoked (table 6). As for CVE, the results of the smoking cessation models represent only the first 5 years of follow-up.

### Table 2

| Smoking status | Unadjusted, Age-adjusted and sex-adjusted | Attributable risk |
|----------------|-------------------------------------------|------------------|
|                | HR (95% CI) | HR (95% CI) | per 1000 pyr (95% CI) |
| All            | 9.4 (8.1 to 10.6) | – | – |
| Never          | 6.3 (4.4 to 8.1) | Ref | – |
| Former         | 11.8 (8.8 to 13.2) | 4.7 (3.5 to 5.9) | |
| Current        | 13.7 (9.1 to 18.3) | 7.4 (6.1 to 8.7) |  |

pyr, person-years; CI, confidence interval; ref, reference.

### Table 3

| Smoking status | Unadjusted, HR (95% CI) | Age-adjusted and sex-adjusted, HR (95% CI) | Fully adjusted*, HR (95% CI) |
|----------------|------------------------|---------------------------------------------|-------------------------------|
| Current vs never | 1.64 (1.1 to 2.44) | 2.19 (1.44 to 3.31) | 2.23 (1.46 to 3.40) |
| Current vs former | 0.81 (0.57 to 1.15) | 1.35 (0.94 to 1.93) | 1.51 (1.04 to 2.19) |
| Former vs never | 2.02 (1.44 to 2.83) | 1.62 (1.15 to 2.29) | 1.47 (1.04 to 2.08) |

| Smoking cessation | Per year since cessation, HR (95% CI) | Per year since cessation, HR (95% CI) | Per year since cessation, HR (95% CI) |
|-------------------|--------------------------------------|--------------------------------------|--------------------------------------|
| Light smoker      | 0.80 (0.69 to 0.92) | 0.76 (0.66 to 0.88) | 0.77 (0.66 to 0.91) |
| Heavy smoker      | 0.78 (0.67 to 0.91) | 0.74 (0.63 to 0.86) | 0.73 (0.62 to 0.87) |

| Interaction†‡ | Per year since cessation, HR (95% CI) | Per year since cessation, HR (95% CI) | Per year since cessation, HR (95% CI) |
|---------------|--------------------------------------|--------------------------------------|--------------------------------------|
| Light smoker  | 1.31 (0.65 to 2.65) | 1.68 (0.82 to 3.45) | 1.80 (0.79 to 4.10) |
| Heavy smoker  | 0.98 (0.84 to 1.13) | 0.97 (0.83 to 1.12) | 0.95 (0.80 to 1.12) |

HR, hazard ratio; CI, confidence interval

*Adjusted for gender, age, Townsend score, use of immunosuppressant disease-modifying antirheumatic drugs, use of oral glucocorticoids, use of non-steroidal anti-inflammatory drugs, type 2 diabetes, use of cardiovascular drugs, use of aspirin/antiplatelet drugs, use of lipid regulators and body mass index.

†At the time of cessation.

‡Interaction between years of cessation and amount smoked.
Using the conditional risk set model for the analysis of recurrent events, the age-adjusted and sex-adjusted HR for current versus never smokers was 2.18 (95% CI 1.74 to 2.74); for current versus former smokers was 1.20 (95% CI 0.99 to 1.46) and for former versus never smokers was 1.81 (95% CI 1.51 to 2.18).

DISCUSSION

In this cohort of 5677 patients with RA, current smokers had double the risk both of hospitalisation for major CVE and hospitalisation for RTI compared with never smokers. Compared with former smokers, current smokers had an approximately 50% increased risk of hospitalisation for major CVE and 30% increased risk of hospitalisation for RTI. Within former smokers, the risk of hospitalisation for each of the outcomes decreased for each additional year of cessation.

Compared with never smokers, we found that current smoking was associated with seven additional CVE per 1000 pyr follow-up and a more than doubling of the risk of CVE in the regression models. These results are in agreement with a number of previous studies.\textsuperscript{25–27} For example, a meta-analysis found a risk ratio of 1.50 (95% CI 1.15 to 1.84) for current versus non-smokers.\textsuperscript{27} The difference in magnitude could relate to the definition of

| Table 4 | Baseline characteristics according to hospitalisation for respiratory tract infection |
|---------|-------------------------------------------------------------------------------------|
|         | All patients | Never RTI | RTI | Test statistic |
| No. of patients (% total) | 5677 | 5117 (90%) | 560 (10%) | – |
| Baseline smoking status, n (%) | | | | |
| Never | 2288 (40%) | 2128 (42%) | 160 (29%) | – |
| Former | 1935 (34%) | 1720 (34%) | 215 (38%) | – |
| Current | 1454 (26%) | 1269 (25%) | 185 (33%) | X$^2$ (2)=38, p=0.000 |
| % female | 67.8 | 68.6 | 61.1 | X$^2$ (1)=13, p=0.000 |
| Median age (IQR) | 61.4 (51.2, 71.3) | 60.3 (50.2, 70.1) | 70.8 (62.6, 77.4) | KW (1)=245, p=0.0001 |
| Median BMI (IQR)\textsuperscript{*} | 26.8 (23.8, 30.9) | 26.9 (23.8, 30.8) | 26.6 (23.7, 31.6) | KW (1)=0, p=0.92 |
| Townsend score quintile† | | | | |
| 1 | 23.1 | 23.5 | 19.8 | – |
| 2 | 24 | 24.4 | 20.3 | – |
| 3 | 21.8 | 21.4 | 25 | – |
| 4 | 18.3 | 18 | 21.4 | – |
| 5 | 12.9 | 12.8 | 13.6 | X$^2$ (4)=12.9, p=0.012 |
| Immunosuppressant DMARDs | 10 | 10.4 | 6.4 | X$^2$ (1)=8.9, p=0.003 |
| Glucocorticoids | 16.7 | 15.6 | 27 | X$^2$ (1)=46.9, p=0.000 |
| Type 2 diabetes | 10.7 | 10.4 | 13.6 | X$^2$ (1)=5.2, p=0.022 |
| Asthma | 11.6 | 10.9 | 18 | X$^2$ (1)=25.2, p=0.000 |
| COPD | 4.3 | 3.2 | 13.4 | X$^2$ (1)=127.9, p=0.000 |

Never RTI=no hospitalised RTI during follow-up; RTI=at least one hospitalised RTI during follow-up. Figures are percentages, unless otherwise stated.\textsuperscript{*}33% missing BMI.\textsuperscript{19} 10.5% missing SES.\textsuperscript{19}

RTI, respiratory tract infection; n, number; BMI, body mass index; DMARDs, disease-modifying antirheumatic drugs; COPD, chronic obstructive pulmonary disorder; X$^2$, chi-squared test; KW, Kruskal-Wallis test; SES, socioeconomic status.

| Table 5 | Adjusted incidence rate of hospitalisations for respiratory tract infection according to smoking status |
|---------|-----------------------------------------------------------------|
|         | Age-adjusted and sex-adjusted rate per 1000 pyr | Attributable risk per 1000 pyr |
| Smoking status (95% CI) | (95% CI) | (95% CI) |
| First RTI hospitalisation | | |
| All | 22.8 (21 to 24.7) | – |
| Never | 14.2 (11.8 to 16.6) | Ref |
| Former | 27.7 (24.4 to 30.9) | 13.5 (11.6 to 15.3) |
| Current | 27.8 (22.3 to 33.2) | 13.6 (11.7 to 15.5) |
| All RTI hospitalisations | | |
| All | 32.2 (30 to 34.3) | – |
| Never | 17.3 (14.7 to 20) | Ref |
| Former | 43 (39.1 to 46.8) | 25.6 (23.4 to 27.9) |
| Current | 36.3 (30.3 to 42.2) | 18.9 (16.8 to 21.1) |

Table shows incidence rates for the first RTI hospitalisations during follow-up and episode rates for all RTI hospitalisations during follow-up. pyr, person-years; ref, reference; CI, confidence interval; RTI, respiratory tract infection; Ref, reference.
smoking exposure and the reference category used. Our results are more similar to another CPRD-based study of patients with psoriasis (HR 2.22 (95% CI 2.07 to 2.38) for current vs never smokers), which also allowed smoking status to vary through time.

In this study, we investigated both the risk of CVE according to smoking status, and the change in risk with increasing length of smoking cessation. The reference category in this second model was patients who have <1 year of smoking cessation, therefore this result should not be interpreted as a decrease in risk compared with current smoking. Additionally, the change in risk is relative to the previous year’s risk rather than the original risk. Taken together the results suggest that overall, current smokers have a higher risk of CVE than former smokers, and within former smokers the risk of CVE decreases approximately 25% for each additional year of cessation. Cohort studies set within the general population have also demonstrated a reduced risk of CVE following smoking cessation in older populations, although the risk was not significantly lower than current smoking until 52 or 102 years after cessation.

Table 6 Cox regression analysis for time to first hospitalised respiratory tract infection after rheumatoid arthritis diagnosis

| Smoking status                          | Unadjusted, HR (95% CI) | Age-adjusted and sex-adjusted, HR (95% CI) | Fully adjusted*, HR (95% CI) |
|-----------------------------------------|-------------------------|-------------------------------------------|-----------------------------|
| Current vs never                        | 1.62 (1.28 to 2.06)     | 2.18 (1.71 to 2.78)                       | 1.78 (1.38 to 2.29)         |
| Current vs former                       | 0.79 (0.64 to 0.97)     | 1.34 (1.09 to 1.67)                       | 1.29 (1.04 to 1.61)         |
| Former vs never                         | 2.06 (1.69 to 2.52)     | 1.62 (1.32 to 1.99)                       | 1.38 (1.12 to 1.7)          |
| Smoking cessation                       |                         |                                           |                             |
| Per year since cessation, light smoker  | 0.92 (0.84 to 1.01)     | 0.86 (0.78 to 0.94)                       | 0.84 (0.76 to 0.92)         |
| Per year since cessation, heavy smoker  | 0.91 (0.82 to 1)        | 0.83 (0.75 to 0.92)                       | 0.83 (0.75 to 0.92)         |
| Heavy vs light smoker†                  | 1.43 (0.9 to 2.27)      | 1.95 (1.21 to 3.14)                       | 1.37 (0.82 to 2.26)         |
| Interaction‡                           | 0.98 (0.9 to 1.08)      | 0.96 (0.88 to 1.06)                       | 0.99 (0.9 to 1.09)          |

HR, hazard ratio; CI, confidence interval.
*Adjusted for gender, age, Townsend score, year of diagnosis use of immunosuppressant disease-modifying anti-rheumatic drugs, use of oral glucocorticoids, type 2 diabetes, body mass index, asthma and chronic obstructive pulmonary disease.
†At the time of cessation.
‡Interaction between years of cessation and amount smoked.

The risk of hospitalised RTI was also significantly higher in former smokers than never smokers. In the regression models, former smokers had a lower risk of first RTI than current smokers, although the two groups were more similar when considering multiple RTI. The risk of RTI hospitalisation decreased approximately 15% for each additional year of cessation. Few studies have investigated the association between smoking cessation and RTI in the general population: one study demonstrated a decreased risk of hospitalisation for bacterial pneumonia associated with former smoking, but only for those without COPD who had stopped smoking >10 years previously.

Strengths of our study include the large sample size which enabled us to investigate recurrent RTI hospitalisations. Through linkage with HES, we were able to capture all inpatient spells that occurred within England for our cohort. This is the first study to investigate the association between smoking cessation and risk of CVE or RTI in an RA population. Use of prospectively collected EHRs enabled us, for the first time, to define smoking status longitudinally for each patient and allow the status to vary with time. By defining smoking status in this way, the amount of misclassification in smoking status should be markedly reduced compared with using only baseline information.

There are limitations to the study. As discussed previously, it is likely that some misclassification is still present in our definition of smoking status. It is difficult to assess the impact of potential misclassification, which could result from errors in patient reporting or GP recording of status, or from the frequency of data capture. Those at greater risk of outcomes could be asked about their smoking behaviour more frequently, thus may have fewer classification errors. A second limitation is that the analysis included only events that led to hospitalisation or...
that occurred while hospitalised, and events were not captured if the patient did not survive to be admitted. We have previously published on the link between smoking and CV and respiratory mortality in this cohort. For CVE hospitalisations, we aimed to capture incident CVE only and excluded patients with a prior CVE record in their HES dataset. However, 25% of participants were using cardiovascular medication at baseline suggesting that there may have been some prevalent CVD. Excluding these patients would have limited the generalisability of the analysis. The CPRD is considered broadly representative of the UK population and it is likely that these results are generalisable to all patients with RA within the UK. However, as discussed previously, diagnosis of RA was based on an algorithm which has a sensitivity of 84% and specificity of 86% and so a proportion of patients may have been falsely included or excluded. In addition, as we did not include a comparison group without RA, we cannot comment about RA-specific effects. Finally, there is the risk of unmeasured confounding as certain information about RA is not routinely captured in primary care, including direct measures of RA severity and exposure to biologic therapies. We included use of immuno-suppressant DMARDs as a proxy measure of RA severity. While there have been conflicting findings, there is some evidence that smoking is associated with more severe RA.

In conclusion, current smoking was associated with a doubling of the risk of hospitalisation both for major CVEs and RTI after adjusting for age and gender. For both outcomes, the risk associated with being a former smoker was lower than for current smokers and decreased for each additional year of cessation. Promoting smoking cessation among patients with RA could therefore reduce the risk of CVE and RTI for these patients. Materials designed to raise awareness of the link between RA and smoking in patients with RA have recently been developed and could help to promote this message.

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