Cardiovascular outcomes following a respiratory tract infection amongst people with non-CF bronchiectasis: A general population based study

Authors: V Navaratnam[1,2], AA Root[3], I Douglas[3], L Smeeth[3], RB Hubbard[1], JK Quint[2,4]

1) Division of Epidemiology and Public Health, University of Nottingham, Nottingham, UK
2) Department of Respiratory Epidemiology, Occupational Medicine and Public Health, National Heart and Lung Institute, Imperial College London, UK
3) Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, UK

Correspondence to:

Dr Vidya Navaratnam

Nottingham Respiratory Research Unit,

Clinical Sciences Building,

Nottingham City Hospital,

Hucknall Road, Nottingham NG5 1PB, UK

vidya.navaratnam@nottingham.ac.uk

Tel: 0115823178

Keywords: Bronchiectasis, cardiovascular disease, myocardial infarction, stroke, epidemiology, self-controlled case series

Word count: 2977

Competing Interests: None declared

Funding: VN is funded by a National Institute for Health Research Academic Clinical Lectureship. RBH is funded by the GSK/BLF chair of Epidemiological Respiratory Research.

Abstract

Background: Studies suggest that people with bronchiectasis are at increased risk of cardiovascular co-morbidities. We aimed to quantify the relative risk of incident cardiovascular events following a respiratory tract infection amongst people with bronchiectasis.

Methods: Using UK electronic primary care records, we conducted a within-person comparison using the self-controlled case series method. We calculated the relative risk of first time cardiovascular events (either first myocardial infarction [MI] or stroke) following a respiratory tract infection compared with the individual's baseline risk.

Results: Our cohort consisted of 895 individuals with non-CF bronchiectasis with a first MI or stroke and at least one respiratory tract infection. There was an increased rate of first time cardiovascular events in the 91 day period after a respiratory tract infection (Incidence Rate Ratio [IRR] 1.56; 95% CI 1.20 to 2.02). The rate of a first cardiovascular event was highest in the first three days following a respiratory tract infection (IRR 2.73, 95% CI 1.41 to 5.27).

Conclusions: These data suggest that respiratory tract infections are strongly associated with a transient increased risk of first time MI or stroke amongst people with bronchiectasis. As respiratory tract infections are six times more common in people with bronchiectasis than the general population, the increased risk has a disproportionately greater impact in these individuals. These findings may have implications for including cardiovascular risk modifications in airway infection treatment pathways in this population.

(225 words)

Introduction

Bronchiectasis is a suppurative chronic lung disease characterized by repeated infections, and recent studies have shown that the incidence and prevalence of bronchiectasis in the UK [1] and USA [2] is increasing. Previous studies in the general population [3-5] and in people with COPD[6] have established an association between respiratory tract infections and cardiovascular events, and in previous work we have shown that people with bronchiectasis experience more cardiovascular co-morbidities compared to the general population.[7] It has been suggested that repeated lower respiratory tract infections result in an acute phase response and increased systemic inflammation which contributes to the increased cardiovascular risk seen. Although it is likely this association could be generalized to individuals with bronchiectasis, the occurrence of respiratory tract infections amongst people with bronchiectasis is far higher, and results in substantial morbidity and mortality. Hence quantifying the effect and magnitude of cardiovascular events following a respiratory tract infection is important.

Using routinely collected, anonymized UK primary care data, we conducted a within person comparison to assess the impact of respiratory tract infections on the risk of incident cardiovascular events amongst people with non-CF bronchiectasis.

Methods

Data source

We used anonymized electronic primary care data from the Clinical Practice Research Datalink (CPRD) (www.cprd.com). Information is recorded as part of routine care, and includes diagnostic and prescribing information. Studies have previously demonstrated that individuals who contribute to CPRD are broadly representative of UK general population.[8] Approval was obtained from the Independent Scientific Advisory Committee (ISAC), which oversees research involving CPRD data (protocol ref: 13_030R; available on request)

Study population

Our study population consisted of a dynamic cohort of individuals with a recorded diagnosis of bronchiectasis who were alive and contributing to CPRD at any point between the 1st of January 2000 and 31st of December 2013. We identified individuals with a record of bronchiectasis using pre-defined Read codes (H34..00, H34z.00, H340.00, A115.00, H341.00, P86.100) that have been previously been used in epidemiological studies.[1, 7] We excluded people with a co-existing diagnosis of cystic fibrosis (CF), anyone under 18 years of age at time of diagnosis and individuals who only had a record of bronchiectasis at time of death. All individuals had at least 12 months of electronic records that were of research quality prior to entry into the study. The start of our observation period was the latest of study start date or date of diagnosis of bronchiectasis. The end of the study observation period was the earliest of date of death, transfer out of practice, last date of data collection or study end date.

Definition of outcomes

Our primary outcome was first record of a cardiovascular event, a composite outcome of first recorded diagnosis of myocardial infarction (MI) or stroke that occurred during the study observation period. Individuals with diagnoses of MI or stroke prior to the start of the study period were excluded (see Figure 1). The validity of recording of MI [9, 10] and stroke [10, 11] in electronic primary care records has previously been shown to be high. MI and stroke events that coincided with date of death were also excluded. One of the assumptions of the self–controlled case series method is that the outcome of interest must not censor the observation period. In our case, if a cardiovascular event increases the likelihood of death. However, there is evidence that the method is robust to this assumption.[12] We restricted out outcomes events to non-fatal MI and strokes to overcome this potential bias. Our secondary outcomes were incident MI and stroke events analyzed separately.

Definition of respiratory tract infection

We searched medical records for diagnoses of respiratory tract infections. The medical Read Codes used to identify respiratory tract infections were developed by two clinical epidemiologists, one of whom was a consultant respiratory physician[13], and were consistent with the United Kingdom's National Institute of Health and Care Excellence (NICE) guidelines for the diagnosis of lower respiratory tract infection and clinical diagnosis of community acquired pneumonia.[14] We excluded Read Codes suggestive of an exacerbation of chronic obstructive pulmonary disease (COPD)[15] as we have previously demonstrated that approximately 1/3rd of individuals with bronchiectasis also have a co-existing diagnosis of COPD.[1] Codes used to define respiratory tract infection can be found in the appendix and included report of these codes with and without treatment with antibiotics either by the GP (i.e. treated at home) or in hospital. Date of the respiratory tract infection was deemed to

be the date the patient visited the GP or hospital as was recorded in the electronic medical record.

Statistical analysis

We undertook a within person comparisons in our population of individuals with bronchiectasis who had both a first cardiovascular outcome and at least one respiratory tract infection during our study observation period. The self-controlled case series study design is similar with cohort methodology and is adapted from rate modelling using a Poisson distribution. This study design relies on within person comparisons in a population with both the exposure and outcome of interest.[12, 16] An advantage of the within person comparison method is that possible confounders such as smoking habit, hypertension, hyperlipidemia and diabetes mellitus, are removed.

The self-controlled case series method relies on several assumptions, an important one being that the occurrence of the outcome event should not alter the probability of subsequent exposure. In this study, a cardiovascular event should not change the subsequent probability of developing a respiratory tract infection. Such a change would alter the baseline rate of events and this may result in an over or under estimate of the relative rate of events occurring in exposed periods compared to baseline periods. If there is a transient change in the probability of post-outcome exposures, this bias can be overcome by removing a predefined period of time before exposure from all other baseline periods. [17] In our study, a two week period prior to first record of a respiratory tract infection was removed from the baseline period. All assumptions of the self-controlled case series method are detailed in Appendix 1.

Fixed effects conditional Poisson regression was used to generate incidence rate ratios comparing the rate of incident cardiovascular events during our pre-specified high risk intervals following a respiratory tract infection compared with all other observed periods for each individual. Our high risk interval was defined as extending up to 91 days after a respiratory tract infection, subdivided in to smaller periods of 1 to 3 days, 4 to 7 days, 8 to 14 days, 15 to 29 days and 29 to 91 days after an infection. These risk windows have previously been used to evaluate the risk of MI and stroke following acute infections in the general population.[4] For people who had repeated respiratory tract infections during the study observation period, each episode of infection was followed by a 91 day interval, subdivided into the smaller periods mentioned above, where individuals were considered at high risk. For those who had multiple records of respiratory tract infections within the high risk interval, only the first record of infection was used to define the start and end of the high risk interval. Since age varies with time, we adjusted for age in five year age bands over the age of 45. As seasonal patterns are seen in both cardiovascular events and respiratory tract infections, we then repeated the analyses controlling for the effect of seasonal variation by dividing up the study observation period into warmer months (April to September) and cooler months (October to March).

Secondary analyses

We repeated the analyses for the individual outcomes of first MI and stroke, in turn. Finally, we also explored the impact of co-existing COPD in the association of cardiovascular outcomes following a respiratory tract infection. The main analyses were repeated after excluding people with bronchiectasis who also had a diagnosis of COPD.

Power calculation

Prior to undertaking the analyses, we expected to identify approximately 800 individuals with bronchiectasis who had an incident cardiovascular event and at least one respiratory tract infection. With this sample size we calculated that we would have more than 80% power at 5% significance level to detect an incidence rate ratio of 1.5 or above in the first two weeks after an infection. All statistical analyses were conducted using Stata version 14 (Texas).

Results

From a cohort of 26,518 individuals with bronchiectasis, our final study population consisted of 895 individuals with bronchiectasis who had both a first cardiovascular event and at least one respiratory tract infection during the study observation period. (See Figure 1). 468 (52.9%) people were female, the median age at time of diagnosis of bronchiectasis was 63.7 years (Interquartile range [IQR] 50.0 to 72.1) and 235 (26.3%)were current -smokers (see Table 1). The mean observation period for the study population was 6.2 years (standard deviation [SD] 4.5). After controlling for the effects of age, the rate of incident cardiovascular events was 56% higher in the 91 day period after a record of respiratory tract infection (Incidence Rate Ratio [IRR] 1.56, 95% Confidence Interval [CI] 1.20 to 2.02). The rate of a first cardiovascular event was highest in the first three days following a respiratory tract infection (IRR 2.73, 95% CI 1.41 to 5.27) and fell after the first fourteen days (see Table 2). The rate of incident cardiovascular events remained higher after a respiratory tract infection after controlling for the effects on seasonality (see Table 2).

Secondary analyses

443 people with bronchiectasis had an incident myocardial infarction and least one episode of a respiratory tract infection during our study period. The age adjusted rate ratio for first myocardial infarction was substantially higher in the fourteen days following a respiratory

tract infection compared to periods without a respiratory tract infection. The rate ratio for first MI peaked in the first three days following a respiratory tract infection where it was over four times higher compared to baseline (see Table 3). 479 individuals with bronchiectasis and at least one respiratory tract infection had an incident stroke. The age adjusted rate ratio for first stroke was also higher after a respiratory tract infection, and was highest in the first three days (IRR 1.79, 95% CI 1.20-3.53); see Table 4). Additional adjustment for seasonality had little impact on the rate ratios for first MI and stroke (see Tables 3 and 4). After excluding individuals with co-existing COPD (n=464), we found marginal change to the age adjusted rate of incident cardiovascular events following a respiratory tract infection (see Table 5). Controlling for the effects of season in addition to age did not alter the rate ratios for incident cardiovascular event in this subset.

Due to the fact the SCCS is usually undertaken in studies of shorter follow up, we stratified the analysis on people with < and > 6 years FU since this is the mean and found the IRR is similar, between the two, suggesting the result is not being driven by unadjusted confounding amongst people with longer FU (Table 2b in Supplementary material). We also repeated the analysis using calendar year, 2 year age bands and season (Table 2a Supplementary material).

Figure 1: Identification of study population

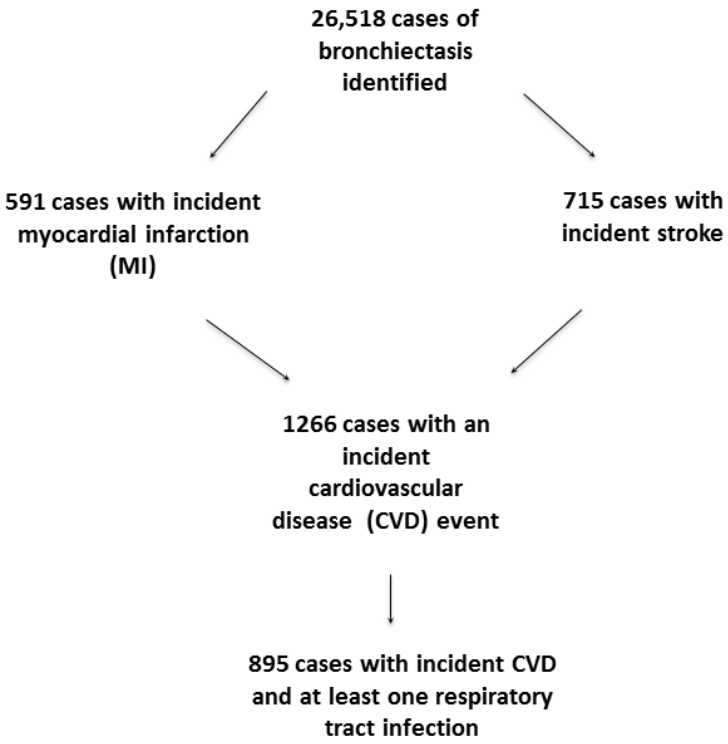

Figure 2: Pictorial representation of the SCCS

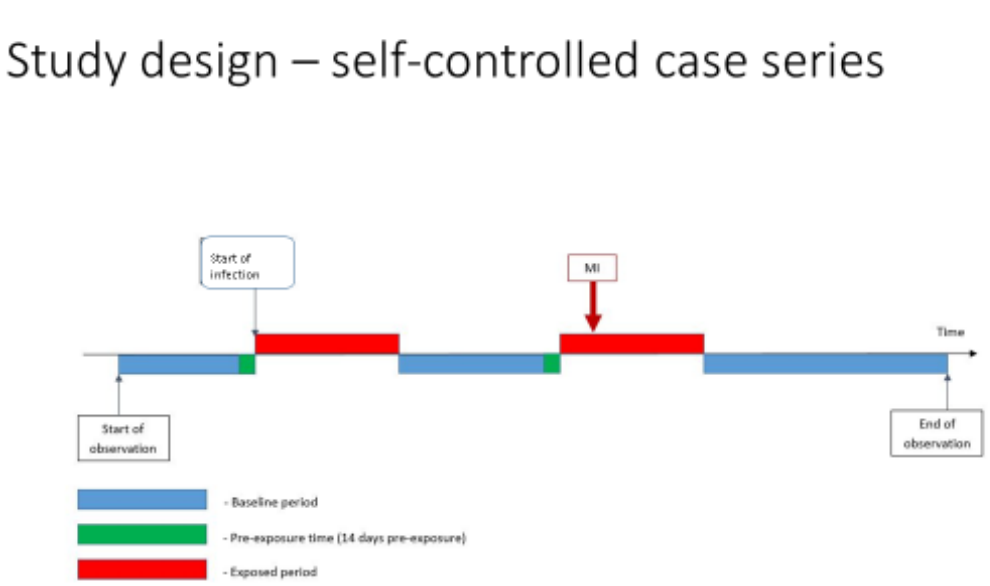

Table 1: Baseline characteristics of the bronchiectasis cohort

Characteristic		Number of people (n=895)
Sex (%)	Male	427 (47.1)
	Female	468 (52.9)
Age category (years) (%)	<45	146 (16.3)
	45-55	114 (12.7)
	56-65	187 (20.9)
	66-75	248 (27.7)
	>75	200 (22.4)
Mean observation period (years) (Standard deviation [SD])		6.2 (4.5)
Median number of respiratory tract infections during the study period (Interquartile range [IQR])		5 (2-10)
Smoking habit (%)	Never smoked	165 (18.4)
	Ex-smoker	478 (53.4)
	Current smoker	235 (26.3)
	Missing information	17 (1.9)

Table 2: Adjusted incidence rate ratios of a first cardiovascular event in risk periods after a respiratory tract infection

Risk period	Number of events	IRR (95% CI)*	IRR (95% CI) #
1-91 days	125	1.56 (1.20 to 2.02)	1.25 (1.02-1.53)
1-3 days	82	2.73 (1.41-5.27)	2.39 (1.21-5.62)
4-7 days	21	2.13 (1.46-2.74)	2.01 (1.22-2.78)
8-14 days	9	1.93 (1.11-2.08)	1.73 (1.09-2.13)
15-28 days	8	1.36 (0.87-2.11)	1.16 (0.77-2.19)
29-91 days	5	1.19 (0.73-1.51)	1.08 (0.69-1.53)
Baseline period	706	1.00	1.00

*Incidence Rate Ratio adjusted for age

#Incidence Rate Ratio adjusted for age and season

Table 3: Adjusted incidence rate ratios of first myocardial infarction in risk periods after a respiratory tract infection

Risk period	Number of events	IRR (95% CI)*	IRR (95% CI) #
1-3 days	36	4.26 (2.00-9.06)	4.25 (1.99-9.04)
4-7 days	10	2.28 (1.03-5.54)	2.27 (1.03-5.55)
8-14 days	7	1.30 (0.78-2.46)	1.29 (0.76-2.49)
15-28 days	5	1.04 (0.69-2.81)	1.05 (0.68-2.46)
29-91 days	4	1.05 (0.73-1.50)	1.03 (0.71-1.52)
Baseline period	347	1.00	1.00

*Incidence Rate Ratio adjusted for age #Incidence Rate Ratio adjusted for age and season

Table 4: Adjusted incidence rate ratios of first stroke in risk periods after respiratory tract infection

Risk period	Number of events	IRR (95% CI)*	IRR (95% CI) #
1-3 days	48	1.79 (1.20-3.53)	1.77 (1.15-3.56)
4-7 days	13	1.59 (1.12-4.75)	1.58 (1.12-4.76)
8-14 days	10	1.32 (0.96- 3.09)	1.29 (0.94-3.09)
15-28 days	3	1.14 (0.79-4.15)	1.14 (0.77-4.17)
29-91 days	4	0.98 (0.62-3.31)	0.95 (0.60-3.32)
Baseline period	383	1.00	1.00

*Incidence Rate Ratio adjusted for age #Incidence Rate Ratio adjusted for age and season

Table 5: Adjusted incidence rate ratios of a first cardiovascular event in risk periods after a respiratory tract infection excluding people with a co-existing diagnosis of COPD

Risk period	Number of events	IRR (95% CI)*
1-3 days	42	2.38 (1.77-4.76)
4-7 days	17	2.30 (1.46-3.89)
8-14 days	5	1.61 (1.15-2.24)
15-28 days	4	1.36 (0.67-2.76)
29-91 days	2	0.97 (0.55-2.16)
Baseline period	352	1.00

*Incidence Rate Ratio adjusted for age

Discussion

Our population based study found that amongst people with non-CF bronchiectasis, a respiratory tract infection is strongly associated with a transient increase in the rate of incident cardiovascular events. The rate of first cardiovascular events was over two-fold higher in the first three days following a respiratory tract infection and remained almost double up to two weeks after, compared to periods without infection. While the rates of both first MI and stroke were elevated after a respiratory tract infection, the effect was most pronounced with first MI. The impact of respiratory tract infection on cardiovascular risk was greatest in the first week after the infection, suggesting a narrow window for risk factor modification. Although a substantial number of individuals with bronchiectasis in our population also had a co-existing record of COPD, our secondary analyses showed that the association persists after excluding this subset of people. The age-standardized (standardized to the 2004 UK population) rate of respiratory tract infections in the entire bronchiectasis cohort (n=26,415) was 632.7 per 1000 person years. This was approximately six times higher than the age-standardized rate of community acquired lower respiratory tract infections in the general population.[13] Hence the relative risk of a cardiovascular event occurring following a respiratory tract infection in a patient with bronchiectasis is six-fold higher than the relative risk of a cardiovascular event occurring following a systemic respiratory tract infection in the general population.

One of the strengths of our study is the large population of people with bronchiectasis and length of our observation period, which enabled us to quantify the risk of incident cardiovascular events after a respiratory tract infection. An advantage of the self-controlled case series method is that it eliminates confounding by factors that vary between individuals

such as smoking, hypertension, hyperlipidemia and diabetes mellitus, due to the fact that each person acts as their own control.[18] Furthermore, within-comparison between time periods relative to the exposure also removes the possibility of reverse causation. It is possible that there is some misclassification between cardiovascular and infective events, however this is unlikely to account for the relationship we have seen in this study. In addition to the above, all key assumptions of the self-controlled case series methodology were met. We only used first time diagnoses of cardiovascular events as the risk of a subsequent event is likely to be different to the first. Studies have established the validity of medical diagnoses within CPRD to be high [10, 19] and the use of prospectively collected information from electronic primary care records minimizes the potential of recall or observer bias.

Our study has a number of limitations that need to be taken into consideration. Although we have studied a UK bronchiectasis population, the results are likely to be generalizable to other bronchiectasis populations worldwide, particularly in countries where the etiology of bronchiectasis is similar to the UK. [20] A potential limitation is the validity of diagnosis of bronchiectasis. Although we were unable to validate the diagnosis of bronchiectasis, only a small number of Read codes that have previously been published [1] were used to identify people with bronchiectasis. 70.7% of bronchiectasis patients who had a CV event also had a respiratory tract infection, suggesting that around one third of the initial cohort did not have clinically significant bronchiectasis. This is in keeping with previous studies and likely due to the increase in CT scans occurring in older individuals leading to a diagnosis of non-clinically significant disease.

In order to improve the specificity of our bronchiectasis population, we excluded anyone who was under 18 years of age at time of diagnosis of bronchiectasis and those who also had a

recorded diagnosis of cystic fibrosis. As we did not have access to radiological information from our cohort, it is not possible to confirm if the diagnosis of bronchiectasis was made according to current guidelines. However, bronchiectasis is usually diagnosed in a secondary care setting after patients have had radiological confirmation with a computed tomography scan, as demonstrated by the recent British Thoracic Society bronchiectasis audit.[20] Therefore it is unlikely that a diagnosis of bronchiectasis would present in primary care records without confirmation from healthcare providers in secondary care. Further reassurance of the external validity of diagnosis of bronchiectasis is supported by the fact that the demographic features of our cohort are consistent with the UK population of patients with bronchiectasis.[21-23] Our bronchiectasis cohort is also likely to represent individuals with a diagnosis of bronchiectasis in their primary care records across the disease spectrum. It is possible that by excluding people with bronchiectasis before the age of 18 that we have disproportionately excluded those with primary ciliary dyskinesia making the results less applicable to that group, however we are not able to test this.

Another potential limitation of our study is we used date of diagnosis of respiratory tract infection rather than date of onset, which could not be determined accurately. This is likely to result in underestimation of the duration of the increased risk of first MI or stroke. Furthermore, we will not have captured all respiratory tract infections in people with bronchiectasis as some patients may have rescue antibiotics at home to self-medicate at onset of symptoms. It is important to note that the exposure in our study was a respiratory tract infection that precipitated consultation with primary care, the severity of which will vary between individuals. We were unable to use the British Thoracic Society guideline definition of infective exacerbation of bronchiectasis [24] as our exposure definition due to the small number of people who met these criteria. We also did not have information on disease

severity or secondary care records to assess if disease severity or hospitalization influenced the effect of respiratory tract infections on the risk of incident cardiovascular outcomes. Therefore it is likely that our findings are actually an underestimate of the risk of cardiovascular disease following airway infection in people with bronchiectasis.

To our knowledge, this is the first study to demonstrate that amongst a population of people with bronchiectasis, an acute respiratory tract infection is associated with a transient increased risk of incident cardiovascular outcomes. Our findings are consistent with studies that have shown that in the general population[3-5] and amongst people with COPD[6], the risk of MI and stroke are higher after a respiratory tract infection. Using routine primary care data, studies have shown that the relative risk for both MI[3, 4] and stroke[4] were substantially higher in the first few days after a respiratory tract infection, especially following influenza infection.[25] More recently, a study using two separate community based cohorts demonstrated that episodes of pneumonia that resulted in a hospital admission was associated with a short and longer term risk of cardiovascular disease.[26] It has also been demonstrated that the risk of MI and stroke is higher following an exacerbation of COPD. [6]

The increased risk of cardiovascular outcomes following respiratory tract infections in bronchiectasis may be due to a number of reasons; one of which is shared risk factors such as hypoxia and transient increase in systemic inflammation. It has been hypothesized that respiratory tract infections contribute to progression of atherosclerotic plaques[27], coupled with elevated levels of inflammatory cytokines[28] precipitate cardiovascular events. Arterial stiffness has been shown to rise acutely during infective exacerbations of COPD[29], increasing the risk of MI and stroke following airway infection in this population. Aortic stiffness has previously been shown to be elevated in people with bronchiectasis [30] raising

the possibility that this mechanism contributes to the increased risk in cardiovascular outcomes seen in our study.

51% of people with bronchiectasis in our cohort also had a diagnosis of COPD, which is also associated with increased risk of cardiovascular disease. However, our secondary analyses, excluding individuals co-existing diagnoses of COPD suggests that the increased cardiovascular risk following infection still persists.

In conclusion, our study has quantified the increased risk of incident cardiovascular outcomes, which amongst people with bronchiectasis is more than double in the first seven days following a respiratory tract infection compared to periods without an infection. This increased relative cardiovascular risk in people with bronchiectasis is substantially higher compared to the risk of MI or stroke following community acquired respiratory tract infections in the general population. These data suggest recurrent respiratory tract infections contribute to the increased cardiovascular comorbidities in people with bronchiectasis and clinical trials of targeted anti-platelet or statins into prevention of respiratory infection related vascular events are warranted.

References

1. Quint JK, Millett ER, Joshi M, Navaratnam V, Thomas SL, Hurst JR, Smeeth L, Brown JS. Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. *Eur Respir J* 2016: 47(1): 186-193.
2. Seitz AE, Olivier KN, Adjemian J, Holland SM, Prevots R. Trends in bronchiectasis among medicare beneficiaries in the United States, 2000 to 2007. *Chest* 2012: 142(2): 432-439.
3. Meier CR, Jick SS, Derby LE, Vasilakis C, Jick H, Meier CR, Jick SS, Derby LE, Vasilakis C, Jick H. Acute respiratory-tract infections and risk of first-time acute myocardial infarction. *The Lancet* 1998: 351(9114): 1467-1471.
4. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med* 2004: 351(25): 2611-2618.

5. Clayton TC, Capps NE, Stephens NG, Wedzicha JA, Meade TW. Recent respiratory infection and the risk of myocardial infarction. *Heart* 2005: 91(12): 1601-1602.
6. Donaldson GC, Hurst JR, Smith CJ, Hubbard RB, Wedzicha JA. INcreased risk of myocardial infarction and stroke following exacerbation of copd. *Chest* 2010: 137(5): 1091-1097.
7. Navaratnam V, Millett ER, Hurst JR, Thomas SL, Smeeth L, Hubbard RB, Brown J, Quint JK. Bronchiectasis and the risk of cardiovascular disease: a population-based study. *Thorax* 2016. 72(2):161-166.
8. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, Smeeth L. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015: 44(3): 827-836.
9. Bhattarai N, Charlton J, Rudisill C, Gulliford MC. Coding, recording and incidence of different forms of coronary heart disease in primary care. *PLoS One* 2012: 7(1): e29776.
10. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol* 2010: 69(1): 4-14.
11. Zhou EH GK, Graham DJ, Ding Y, Levenson M, Rose M, Davillier SF, Hammad TA. Validation of Stroke in the Clinical Practice Research Datalink (CPRD). *Pharmacoepidemiology and Drug Safety* 2013: 22(S1): 234.
12. Whitaker HJ, Hocine MN, Farrington CP. The methodology of self-controlled case series studies. *Stat Methods Med Res* 2009: 18(1): 7-26.
13. Millett ER, Quint JK, Smeeth L, Daniel RM, Thomas SL. Incidence of community-acquired lower respiratory tract infections and pneumonia among older adults in the United Kingdom: a population-based study. *PLoS One* 2013: 8(9): e75131.
14. (NICE) NIfHaCE. Pneumonia in adults: diagnosis and management. 2014.
15. Rothnie KJ, Mullerova H, Hurst JR, Smeeth L, Davis K, Thomas SL, Quint JK. Validation of the Recording of Acute Exacerbations of COPD in UK Primary Care Electronic Healthcare Records. *PLoS One* 2016: 11(3): e0151357.
16. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. *BMJ* 2016: 354.
17. Pratt NL, Roughead EE, Ramsay E, Salter A, Ryan P. Risk of hospitalization for stroke associated with antipsychotic use in the elderly: a self-controlled case series. *Drugs & aging* 2010: 27(11): 885-893.
18. Farrington CP. Relative Incidence Estimation from Case Series for Vaccine Safety Evaluation. *Biometrics* 1995: 51(1): 228-235.
19. Hansell A, Hollowell J, Nichols T, McNiece R, Strachan D. Use of the General Practice Research Database (GPRD) for respiratory epidemiology: a comparison with the 4th Morbidity Survey in General Practice (MSGP4). *Thorax* 1999: 54(5): 413-419.
20. Lonni S, Chalmers JD, Goeminne PC, et al. Etiology of Non–Cystic Fibrosis Bronchiectasis in Adults and Its Correlation to Disease Severity. *Annals of the American Thoracic Society*. 2015;12(12):1764-1770. doi:10.1513/AnnalsATS.201507-472OC.
21. Hill AT, Routh C, Welham S. National BTS bronchiectasis audit 2012: is the quality standard being adhered to in adult secondary care? *Thorax* 2013.
22. Hill AT, Welham S, Reid K, Bucknall CE. British Thoracic Society national bronchiectasis audit 2010 and 2011. *Thorax* 2012: 67(10): 928-930.
23. Evans IE, Bedi P, Quinn TM, Hill AT. Bronchiectasis severity is an independent risk factor for vascular disease in a Bronchiectasis Cohort. *Chest* 2016.;151(2):383-388.
24. Pasteur MC, Bilton D, Hill AT. British Thoracic Society guideline for non-CF bronchiectasis. *Thorax* 2010: 65 Suppl 1: i1-58.
25. Warren-Gash C, Hayward AC, Hemingway H, Denaxas S, Thomas SL, Timmis AD, Whitaker H, Smeeth L. Influenza Infection and Risk of Acute Myocardial Infarction in England and Wales: A CALIBER Self-Controlled Case Series Study. *The Journal of Infectious Diseases* 2012: 206(11): 1652-1659.
26. Corrales-Medina VF, Alvarez KN, Weissfeld LA, Angus DC, Chirinos JA, Chang C-CH, Newman A, Loehr L, Folsom AR, Elkind MS, Lyles MF, Kronmal RA, Yende S. Association Between Hospitalization for Pneumonia and Subsequent Risk of Cardiovascular Disease. *Jama* 2015: 313(3): 264-274.

27. Harskamp RE, van Ginkel MW. Acute respiratory tract infections: a potential trigger for the acute coronary syndrome. *Ann Med* 2008: 40(2): 121-128.
28. Wedzicha JA, Seemungal TA, MacCallum PK, Paul EA, Donaldson GC, Bhowmik A, Jeffries DJ, Meade TW. Acute exacerbations of chronic obstructive pulmonary disease are accompanied by elevations of plasma fibrinogen and serum IL-6 levels. *Thromb Haemost* 2000: 84(2): 210-215.
29. Patel ARC, Kowlessar BS, Donaldson GC, Mackay AJ, Singh R, George SN, Garcha DS, Wedzicha JA, Hurst JR. Cardiovascular Risk, Myocardial Injury, and Exacerbations of Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory and Critical Care Medicine* 2013: 188(9): 1091-1099.
30. Gale NS, Bolton CE, Duckers JM, Enright S, Cockcroft JR, Shale DJ. Systemic comorbidities in bronchiectasis. *Chron Respir Dis* 2012: 9(4): 231-238.

Author's Contributions

VN, ID and JKQ conceived and designed the study. VN and JKQ were involved in the acquisition of the data. VN, AAR and JKQ were involved in the analyses of the data. VN, AAR, ID, LS, RBH, and JKQ were involved in the interpretation of the data and in writing or revising the manuscript before submission.

VN takes responsibility for the integrity of the work in this manuscript and is the guarantor of the manuscript.