

Online Data Supplement

Cardiovascular Outcomes Following a Respiratory Tract Infection among Adults with Non-CF Bronchiectasis: A General Population Based Study

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Appendix 1: Assumptions behind the self-controlled case series method

The self-controlled case series method relies on the following key assumptions. Firstly, recurrent outcome events must be independent i.e. having the first event does not influence the likelihood of a second event. Although this assumption is unlikely to be true for cardiovascular events, one way to avoid bias is to consider only the first occurrence of an event as a relevant outcome, which has previously been shown to be a valid approach. (1)

The second assumption is that the occurrence of the outcome event should not alter the probability of subsequent exposure. An example of this is if a recent cardiovascular event transiently changed the probability of developing a respiratory tract infection recorded in primary care. This would lead to either an abnormally low or high rate of events in the period leading up to the first respiratory tract infection which would be included in the baseline rate of events. This may result in an over or under estimate of the relative rate of events occurring in exposed periods compared to baseline periods. This possible bias can be overcome by removing a predefined period of time before exposure from all other baseline periods. (2) In our study, a two week period prior to first record of a respiratory tract infection was removed from the baseline period.

The final assumption made 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.(3) We restricted our outcomes events to non-fatal myocardial infarctions and strokes to overcome this potential bias.

References

1. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. *Stat Med* 2006; 25: 1768-1797.
2. 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: 885-893.
3. Whitaker HJ, Hocine MN, Farrington CP. The methodology of self-controlled case series studies. *Stat Methods Med Res* 2009; 18: 7-26.

Table E1a: 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) #	IRR (95% CI)%
1-91 days	125	1.56 (1.20- 2.02)	1.25 (1.02-1.53)	1.25 (0.98-1.91)
1-3 days	82	2.73 (1.41-5.27)	2.39 (1.21-5.62)	2.20 (1.19-6.43)
4-7 days	21	2.13 (1.46-2.74)	2.01 (1.22-2.78)	4.18 (1.85-9.43)
8-14 days	9	1.93 (1.11-2.08)	1.73 (1.09-2.13)	1.57 (1.05-4.92)
15-28 days	8	1.36 (0.87-2.11)	1.16 (0.77-2.19)	1.29 (0.74-2.42)
29-91 days	5	1.19 (0.73-1.51)	1.08 (0.69-1.53)	1.09 (0.54-2.05)
Baseline period	706	1.00	1.00	1.00

*Incidence Rate Ratio adjusted for age (10 year bands)

#Incidence Rate Ratio adjusted for age (10 year bands) and season

%Incidence Rate Ratio adjusted for age (2 year bands), season, calendar year, hypertension and diabetes mellitus

Table E1b: Adjusted incidence rate ratios of a first cardiovascular event in risk periods after a respiratory tract infection for individuals with more than six years of follow up

Risk period	Number of events	IRR (95% CI)%
1-91 days	34	1.19 (0.95-2.06)
1-3 days	12	1.76 (0.94-2.40)
4-7 days	9	3.53 (1.13-11.10)
8-14 days	5	2.65 (1.04-8.35)
15-28 days	5	1.51 (0.87-3.62)
29-91 days	3	1.03 (0.67-2.78)
Baseline period	579	1.00

Number of people prescribed azithromycin either prior to or during the study period (prescription length of 28 days or longer) =30