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Recent respiratory infection and risk of cardiovascular disease: case-control study through a general practice database

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Aims Respiratory infection may be associated with an increased risk of major cardiovascular events. This case-control study describes associations with these events of respiratory infection.

Methods and results The IMS Disease Analyzer Mediplus primary care database was used to identify all cases of first-time diagnosis of myocardial infarction (MI) or stroke and single matched controls. Details were extracted on visits for respiratory infection over the preceding year. A total of 11 155 MI cases and 9208 stroke cases were identified. For MI and stroke respectively, there were 326 and 260 respiratory infections during the month preceding the index date. There was strong evidence of an increased risk of both events in the 7 days following infection, for MI adjusted odds ratio (OR) 2.10 (95% confidence interval 1.38–3.21), for stroke OR 1.92 (95% confidence interval 1.24–2.97). The strength of these associations fell over time. The associations for MI occurred at all levels of initial underlying cardiovascular risk.

Conclusions There are strong associations between recent respiratory infection and major cardiovascular events, for MI at all levels of underlying risk. The benefits of reducing respiratory infection either through immunization or treating or preventing infection may be substantial.

Keywords Myocardial infarction • Stroke • Respiratory infection • Urinary tract infection • Case-control study

Introduction

It has for some years been recognized that there is an excess of deaths from coronary heart disease (CHD) and stroke during the winter months, over and above those directly attributable to deaths from respiratory disease.[1] Many early studies used serum levels of antibodies to respiratory-tract organisms, particularly of *Chlamydia pneumoniae*, to investigate associations with CHD more specifically, but established only modest risks for CHD[2] perhaps because these serological studies will have reflected many distant as well as some recent infections. Syrjanen *et al.*[3] reported a strong effect of recent infection in a case-control study of young survivors of stroke, though the numbers were very small. Mattila *et al.*[4] showed an association between dental health and myocardial infarction (MI), but the results of this and other studies of dental health are subject to strong confounding by social class which has not been completely allowed for.

In 1998, however, Meier *et al.*[5] reported a case-control study from the General Practice Research Database (GPRD), and found a significant association between respiratory infection within the previous month and MI. The risk was greatest for the first few days following the infection and then fell off, so that there was no observed excess risk after about 2 weeks. There was no association between recent urinary tract infection and MI,

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suggesting that it may be respiratory infection in particular that is responsible for the increased risk. The study did not consider people over the age of 75 and excluded all those with a range of clinical risk factors for CHD.

Another, much larger case-series study, using the same GPRD database, has recently confirmed the finding on MI and also reported an association with stroke. There was a moderately increased risk of MI after urinary tract infection[6] and a more pronounced risk of stroke. Recent immunization against influenza or pneumonia carried no excess risk.

To complement the GPRD data, Clayton *et al.*[7] have reported a clinical case-control study in which patients admitted with confirmed MI to the coronary care units of two hospitals and matched controls were compared for their experience of recent respiratory infection. The primary definitions of respiratory infection were minor symptoms such as cough, runny or blocked nose, or sore throat. These were not associated with MI. However, there was a strong association between recent pleuritic pain and/or fever with MI, i.e. with lower respiratory tract infection.

The present case-control study has been carried out in another general practice database, the IMS Disease Analyzer Mediplus database (IMS), to see if the GPRD findings for both MI and stroke can be replicated in a similar but separate database. The study has the additional advantages of, first, having no age restrictions (apart from the exclusion of a few events in those under 18). Secondly, the study includes extensive information on other risk factors for MI and stroke to establish whether the association between respiratory infection and cardiovascular disease can be seen at all levels of preceding risk. In other words, do the mechanisms responsible for the increase in cardiovascular disease following infection operate at all levels of prior risk?

Methods

The IMS database is a primary care database used widely in epidemiological research with recorded contacts of some two million patients with approximately 500 General Practioners (GPs). In order to be included in the database, GPs need to meet a minimum quality score based on a number of pre-specified criteria, e.g. the percentage of registered patients with completed demographic information.

Cases and controls

Cases were selected according to pre-defined criteria for MI or stroke and only those for whom this was a first-time diagnosis of the relevant outcome were considered. The criteria to be satisfied for accepting a case of MI were according to the READ coding system (a widely used standard set of clinical terms[8,9] approved by the National Health Service). In order to avoid the risk of retrospective recording of events in patients joining the practice only recently with the possibility of mistaken recall of symptoms and dates, and also to allow a sufficient period for exposures and other risk factors to have been recorded, cases had to be registered on the IMS database for at least 2 years prior to the date of diagnosis. Details of MIs and strokes which lead directly to a hospital admission are provided by the hospital to the patients' GP, who enters them, including the date of onset, into the database. He/she will enter details at the time if he/she saw the patient to begin with. If the patient was admitted to hospital as an emergency, there is invariably a summary sent to the GP shortly after the patient's discharge or death which includes date of onset. In addition to the date of diagnosis, there was a requirement for cases to have information on their year of birth, gender, and practice, which were the matching criteria for selecting controls. The only restriction on the age of cases was that they needed to be 18 or over at the date of the index event.

For each case, all potential controls were identified based on year of birth, gender, practice, and calendar time (to allow for seasonal variation). In order to match on calendar time, all potential controls had to be registered on the IMS database for at least 2 years on the day of the index MI or stroke of the case and to have no previous recorded diagnosis of the corresponding outcome by that date. A single control for each case was selected at random from among all potential controls before the exposure status or history of other risk factors was known. The controls were taken from the same population and were registered in the GP database using the same criteria as the cases but without the particular outcome of interest at the time of the case. The very few cases (approximately 1%) for whom there were no suitable control were excluded from the analysis usually because there were no controls with the same year of birth in the GP practice.

Measurement of risk factors

The index date for both cases and controls was taken as the date of the MI or stroke of the case. Before any data were extracted, the definition for the exposure of respiratory infection was established (based on the READ coding system using terms which included reference to diagnoses and symptoms such as 'Acute bronchitis', 'Pneumonia', and 'Productive cough'). Based on this definition, data for respiratory infection over the year preceding the index date were extracted for the most recent GP visit. To ensure the correct order of the timing of infection and outcome, any episode of respiratory infection recorded on the same day as the index date was excluded. In addition, information on GP visits specifically for pleuritic pain and/or pyrexia over the preceding year was extracted. A further objective of this study was to establish whether the findings from the Smeeth study[6] of an association between recent urinary tract infection and MI or stroke are confirmed in the IMS dataset. Therefore, information of presentations to the GP with urinary tract infection was also collected.

In order to adjust for possible confounding and to identify the most important contributors to the underlying risk of participants, details of other known risk factors recorded prior to the index date were also collected. Pre-defined criteria also based on the READ coding system were used to identify any history of hypertension, hyperlipidaemia, diabetes, CHD among first degree relatives, peripheral vascular disease, and chronic obstructive pulmonary disease. In addition, smoking status and body mass index (BMI) were taken from the most recent recorded entry on the database. Categorical risk factors that were not recorded for an individual while registered on the IMS database (at least 2 years) were assumed to be absent. Continuous measures such as BMI which were not recorded were taken as missing. The aim was to collect information on the most common factors expected to be strongly related to MI or stroke. Vaccinations against influenza and pneumococcal disease within the preceding year were also recorded.

Finally, for the outcome of MI, a previous history of stroke was recorded as a risk factor and, for the outcome of stroke, a previous history of MI was recorded. For the few cases with a recorded MI on the same day as a stroke (65 in total), it was assumed that the MI preceded the stroke but it made little difference to the results whether these cases and their controls were included or not.

Statistical methods

All individuals aged 18 and above with a new recording of MI or stroke on the IMS database in the 10 years up to June 2004 who met the eligibility criteria were included in the analysis. It was anticipated that in excess of 10 000 newly recorded cases of MI would be included, based on pre-defined criteria for MI. Therefore, the study was anticipated to provide excellent power to detect small associations even at low levels of reported respiratory infection. For example, a study of 10 000 MIs would have well in excess of 95% power (at 5% significance) to detect an odds ratio of 1.5 based on a prevalence of respiratory infection of 2% within the preceding 28 days among controls.

In all analyses, cases of MI and their controls were analysed separately from cases of stroke and their controls. The characteristics of the study population including history of respiratory infection and other relevant risk factors are described by case-control status.

In order to assess the impact of respiratory infection on risk of MI or stroke, the analysis accounted for the matched design of the study using conditional logistic regression, and therefore all odds ratios are adjusted for the matching factors of year of birth, gender, calendar time (and therefore seasonal variation), and practice, which may to some extent allow for socioeconomic status and other confounding factors. In addition, other recorded risk factors were included in the multivariable model if they were important independent predictors ($P < 0.01$) of at least one of the outcomes. This allowed for the comparative importance of risk factors to be compared between MIs and strokes.

The timing of any respiratory infection was considered in the following categories: 1–7, 8–28, 29–91, 92–365 days prior to the index date in order to be comparable to previous GPRD studies. An analysis considering infection within the first 3 days was also undertaken. The unexposed groups are those with no infection in the previous year.

A limited number of pre-specified subgroup analyses were undertaken in order to explore whether any association between respiratory infection and MI or stroke is consistent across all levels of underlying risk of coronary events. For these analyses, recent infection was considered as 1–28 days before the index date in order to give reasonable numbers for testing interactions. Patients were categorized into three groups reflecting approximate thirds of risk based on the presence of risk factors strongly related to outcome ($P < 0.01$) other than recent respiratory infection itself. This was done in two ways: by calculating a risk score based on the actual coefficients of the risk factors and a simpler score of the addition of number of risk factors present (either 0, 1, or ≥ 2). These two approaches yielded very similar results. In addition, many patients had no risk factors recorded and for stroke there were fewer individuals who had more than a single risk factor recorded. Therefore, results from the simple addition of risk factors are presented with separate odds ratios for the impact of respiratory infection within the preceding month calculated for each risk group. The presence of effect modification between respiratory infection and the three risk groups was assessed by a test of interaction. Since cases and controls were matched on age and gender, it was not possible to assess the independent association of these factors on outcome and so were not included in categorization above. However, the impact of age and gender on the association between respiratory infection and outcome was assessed using interaction tests.

Other analyses also considered the impact of urinary tract infection on outcome although, because of limited numbers, only the presence of infection within the preceding 28 days was considered as the exposure of interest. An analysis was also undertaken to assess the association between the specific symptoms of pleuritic pain and/or pyrexia with MI or stroke to add further information to the findings from the clinical study referred to previously.[7] Exposure was considered as any presentation to the GP with these symptoms (based on READ codes) in the 28 days prior to the index date.

The study complies with the Declaration of Helsinki and was approved by the Independent Scientific and Ethical Advisory Committee of the IMS Disease Analyzer Mediplus Database and the Ethics Committee of the London School of Hygiene & Tropical Medicine.

Results

There were 11 155 cases on the IMS database with a first-time diagnosis of MI who met the inclusion criteria of whom 61% were men (mean age 71 years) and 39% women (mean age 79 years) (*Table 1*). There were 9208 cases with a first-time diagnosis of stroke of whom 45% were men (mean age 76 years) and 55% women (mean age 81 years). For both MI cases and stroke cases, 13% presented in January. As expected, the recorded risk factors were more prevalent among the cases for both MI and stroke compared to the controls (*Table 2*).

Respiratory infection

In total, there were 934 (8.4%) MI cases with respiratory infection in the year before the index date [221 (2.0%) in the preceding month] compared to 736 (6.6%) controls [105 (0.9%) in the preceding month]. There was very strong evidence of an increased risk of an MI immediately following infection which reduced over time (trend test across the different time periods considered, $P < 0.001$) so that there was little increased risk beyond 1 month (*Tables 2* and *3*). After adjustment for other risk factors, the odds ratio of MI within 7 days of an infection was 2.10 (95% CI 1.38–3.21), whereas for 1–3 months and 3 months to 1 year, the odds ratios were 1.16 (95% CI 0.92–1.47) and 1.08 (95% CI 0.94–1.23), respectively. The risk was highest in the 3 days following infection [odds ratio 3.75 (95% CI 1.86–7.56)].

Further adjustment was made using the actual measurement of BMI although less than 40% of matched sets had a BMI reading for both cases and controls. BMI was a significant risk factor for MI [odds ratio 1.17 (95% CI 1.11–1.23) per 5 kg/m^2 increase] although this had little impact on the relationship between respiratory infection and MI.

The results indicated that the risk of MI from respiratory infection did not depend upon age or gender (interaction *P*-values 0.70 and 0.34, respectively). Further, the association between recent infection and MI did not appear to depend on underlying prior risk (interaction *P*-value 0.23) with an increased risk of MI associated with infection seen in all three groups and the lower CI in each stratum above 1 (*Table 4*) in other words, infection increased risk in all risk groups.

There were 855 (9.3%) stroke cases with respiratory infection in the year before the index date compared to 735 (8.0%) controls. There was a similar association of respiratory infection with stroke as for MI, with an increased risk of a stroke immediately following infection which reduced steadily over time (trend test across the different time periods considered, $P < 0.001$) so that there was little increased risk beyond 1 month (*Tables 2* and *3*). After adjustment for other risk factors, the odds ratio of stroke within 7 days of an infection was 1.92 (95% CI 1.24–2.97) whereas for 1 to 3

Table 1 Baseline characteristics of cases and controls

	MIs		Strokes	
	Cases (n = 11155)	Controls (n = 11155)	Cases (n = 9208)	Controls (n = 9208)
Matching variables				
Gender				
Male	6825 (61.2%)	6825 (61.2%)	4179 (45.4%)	4179 (45.4%)
Female	4330 (38.8%)	4330 (38.8%)	5029 (54.6%)	5029 (54.6%)
Age (years)				
Mean (SD)	74 (13)	74 (13)	79 (14)	79 (14)
<60	1795 (16.1%)	1795 (16.1%)	911 (9.9%)	911 (9.9%)
60–69	2109 (18.9%)	2109 (18.9%)	1070 (11.6%)	1070 (11.6%)
70–79	3022 (27.1%)	3022 (27.1%)	2088 (22.7%)	2088 (22.7%)
80–89	2926 (26.2%)	2926 (26.2%)	3050 (33.1%)	3050 (33.1%)
≥90	1303 (11.7%)	1303 (11.7%)	2089 (22.7%)	2089 (22.7%)
Index month				
Dec–Feb	3279 (29.4%)	3279 (29.4%)	2613 (28.4%)	2613 (28.4%)
Mar–May	2664 (23.9%)	2664 (23.9%)	2225 (24.2%)	2225 (24.2%)
Jun–Aug	2480 (22.2%)	2480 (22.2%)	2220 (24.1%)	2220 (24.1%)
Sep–Nov	2732 (24.5%)	2732 (24.5%)	2150 (23.4%)	2150 (23.4%)
Other risk factors				
Hyperlipidaemia	1213 (10.9%)	791 (7.1%)	812 (8.8%)	660 (7.2%)
Hypertension	4276 (38.3%)	3424 (30.7%)	3739 (40.6%)	3037 (33.0%)
Diabetes	1467 (13.2%)	775 (7.0%)	1235 (13.4%)	706 (7.7%)
COPD	618 (5.5%)	507 (4.6%)	494 (5.4%)	408 (4.4%)
Family history CAD	1477 (13.2%)	1082 (9.7%)	799 (8.7%)	781 (8.5%)
Angina	2807 (25.2%)	1115 (10.0%)	1576 (17.1%)	1324 (14.4%)
Peripheral vascular disease	727 (6.5%)	370 (3.3%)	608 (6.6%)	352 (3.8%)
Smoking status				
Never[a]	6385 (57.2%)	7269 (65.2%)	6076 (66.0%)	6380 (69.3%)
Ex-smoker	2248 (20.2%)	2166 (19.4%)	1683 (18.3%)	1701 (18.5%)
Current	2522 (22.6%)	1720 (15.4%)	1449 (15.7%)	1127 (12.2%)
Previous stroke	465 (4.2%)	323 (2.9%)	–	–
Previous MI	–	–	772 (8.4%)	528 (5.7%)
Influenza vaccination[b]	3966 (35.6%)	3540 (31.7%)	3777 (41.0%)	3546 (38.5%)
Pneumococcal vaccination	165 (1.5%)	124 (1.1%)	145 (1.6%)	142 (1.5%)

[a]These numbers include 8036 patients in the MI dataset, and 7610 in the stroke dataset with no definite smoking status recorded.
[b]There were 45.9% of MI cases and 42.3% of controls aged 70 and above with a recorded influenza vaccination. There were 46.8% of stroke cases and 45.3% of controls aged 70 and above with a recorded influenza vaccination.

months and 3 months to 1 year, the odds ratios were 1.09 (95% CI 0.88–1.36) and 1.08 (95% CI 0.94–1.24), respectively. The risk was again highest in the 3 days following infection [odds ratio 4.07 (95% CI 1.99–8.34)].

Risk of stroke from respiratory infection did not depend upon age or gender (interaction P-values 0.74 and 0.50, respectively). There was a suggestion that the impact of respiratory infection on stroke was less in those at higher underlying risk (*Table 4*), although the evidence for this was not strong (interaction $P = 0.021$).

There was no evidence of a link between BMI and risk of stroke, and adjustment for BMI had no impact on the association between respiratory infection and stroke.

There was no evidence of an association between vaccination against influenza and pneumococcal disease with risk of MI or stroke.

Urinary tract infection and other analyses

Urinary tract infection was less common than respiratory infection with only 40 infections reported in the 28 days preceding the index date among MI cases and their controls and a further 40 reported among the stroke cases and their controls. There was little evidence of an association with subsequent MI. However, by contrast with MI, there was evidence of increased risk of stroke in the month following urinary tract infection after adjustment for

Table 2 Association of exposures with MI and stroke adjusted for matching factors only

Exposure	MIs					Strokes				
	Cases ($n = 11155$)	Controls ($n = 11155$)	Odds ratio	95% CI	*P*-value	Cases ($n = 9208$)	Controls ($n = 9208$)	Odds ratio	95% CI	*P*-value
Respiratory tract infection										
1–7 days before index date[a]	84 (0.8%)	34 (0.3%)	2.55	1.71–3.80	<0.0001[b]	60 (0.7%)	34 (0.4%)	1.80	1.18–2.74	<0.0001[b]
8–28 days	137 (1.2%)	71 (0.6%)	1.97	1.48–2.63		104 (1.1%)	62 (0.7%)	1.74	1.26–2.39	
29–91 days	195 (1.8%)	151 (1.4%)	1.34	1.08–1.67		188 (2.0%)	178 (1.9%)	1.08	0.88–1.34	
92–365 days	518 (4.6%)	480 (4.3%)	1.12	0.98–1.27		503 (5.5%)	461 (5.0%)	1.12	0.98–1.27	
None in previous year	10221	10419	1	–		8353	8473	1	–	
Urinary tract infection										
1–28 days before index date	20 (0.2%)	20 (0.2%)	1.00	0.54–1.86	1.00	30 (0.3%)	10 (0.1%)	3.00	1.47–6.14	0.003
None in previous month	11135	11135	1	–		9178	9198	1	–	
Fever/pleurisy										
1–28 days before index date	18 (0.2%)	10 (0.1%)	1.80	0.83–3.90	0.14	8 (0.1%)	9 (0.1%)	0.89	0.34–2.30	0.81
None in previous month	11137	11145	1	–		9200	9199	1	–	

[a]For MI, there were 43 cases and 11 controls with respiratory infection between 1 and 3 days prior to the index data, OR = 4.07 (95% CI 2.10–7.91). For stroke, there were 35 stroke cases and 10 controls with a respiratory infection between 1–3 days prior to the index data, OR = 3.53 (95% CI 1.75 to 7.13).
[b]Trend test across time periods.

other risk factors, including respiratory infection, with an adjusted odds ratio of 2.67 (95% CI 1.29–5.54).

There was a suggestion of an increased risk of MI in the month following presentation of fever and/or pleurisy but numbers were too small to provide conclusive evidence [adjusted odds ratio 1.64 (95% CI 0.72–3.76)]. There was no evidence of an increased risk of stroke in the month following presentation of fever and/or pleurisy.

Discussion

Our results strengthen the evidence for a strong association between recent respiratory infection and both MI and stroke. Thus, the odds ratios for infection three days prior to the index date were 3.75 for MI and 4.07 for stroke. The fact that there was also increased risk of MI (and stroke) associated with respiratory infection when the interval between the two was more than a week or so reduces the possibility that the infection was in some way a prodromal manifestation of the subsequent cardiovascular event. There were only limited numbers of urinary tract infections, and, although our results on this were uncertain with no good evidence on MI, they demonstrated a possible association with stroke which is consistent with the Smeeth study.[6] Numbers of cases of pleuritic pain and/or fever were also limited, although there was a suggestion of an association with MI but not with stroke and we have therefore been unable to clearly confirm the strong association between recent pleuritic pain and/or fever with MI that we found in our clinical study.[7]

Our definitions of respiratory infection were likely to be more stringent than previous studies and this may be the main reason that the prevalence in controls in our study was lower than we had anticipated. However, there was still more than adequate power for the main results. We had less power for interaction analyses than anticipated, including assessing the effects of underlying risk according to the number of clinical risk factors (*Table 4*), although here too several of the findings were clear and significant.

Even though the observed percentage of MIs and strokes which resulted from respiratory infection is low (less than 2% among cases), the absolute number of MIs and strokes which could potentially be prevented is substantial, because these are common conditions. As discussed above, the definition of infection was stringent and it is also not possible to record those infections which did not lead to a visit to the GP. Further, previous studies have suggested that many coronary deaths annually may be attributable to respiratory infection.[1,10]

Advantages of the study

First, our study is based on an entirely separate general practice database, so that the replication and consistency of the main findings compared with the GPRD studies adds to confidence that there may be a true causal association between recent respiratory infection and major vascular events. The numbers in our study are of course substantial. Secondly, we did not impose an age restriction on eligibility (apart from excluding a few cases in those under 18 years of age). Thirdly, we have included extensive data on well-known risk factors for CHD. While not all cases and controls had information about all risk factors, the expected associations between these and MI or stroke support the

Table 3 Multivariable predictors of myocardial infarction and stroke in addition to matching factors

Risk factor	MIs			Strokes		
	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
Recent respiratory infection						
1–7 days[a]	2.10	1.38–3.21	<0.0001[b]	1.92	1.24–2.97	<0.0001[b]
8–28 days	1.93	1.42–2.63		1.76	1.27–2.45	
29–91 days	1.16	0.92–1.47		1.09	0.88–1.36	
92–365 days	1.08	0.94–1.23		1.08	0.94–1.24	
None	1	–		1	–	
Angina						
No	1	–		1	–	
Yes	2.93	2.70–3.19	<0.0001	1.05	0.96–1.15	0.25
Smoking status						
Never	1	–		1	–	
Ex-smoker	1.06	0.98–1.14	0.18	0.96	0.89–1.05	0.40
Current smoker	1.71	1.58–1.86	<0.0001	1.36	1.24–1.49	<0.0001
Diabetic						
No	1	–		1	–	
Yes	1.81	1.64–2.00	<0.0001	1.74	1.57–1.93	<0.0001
Hypertension						
No	1	–		1	–	
Yes	1.28	1.20–1.36	<0.0001	1.38	1.29–1.47	<0.0001
Peripheral vascular disease						
No	1			1	–	
Yes	1.59	1.38–1.83	<0.0001	1.54	1.33–1.77	<0.0001
Family history of CAD						
No	1	–		1	–	
Yes	1.27	1.15–1.39		0.95	0.85–1.07	0.39
Hyperlipidaemia						
No	1	–	0.004	1	–	
Yes	1.17	1.05–1.31		1.02	0.91–1.15	0.72
Previous stroke						
No	1	–	0.006	–	–	–
Yes	1.25	1.07–1.47				
Previous MI						
No	–	–	–	1	–	
Yes				1.42	1.25–1.61	<0.0001
Urinary tract infection in previous month						
No	1	–		1	–	
Yes	1.03	0.53–2.01	0.93	2.67	1.29–5.54	0.008

[a]For MI: OR = 3.75 (95% CI 1.86–7.56) for RRI 1–3 days prior to the index date. For stroke: OR = 4.07 (95% CI 1.99–8.34) for RRI 1–3 days prior to the index date.
[b]Trend test across time periods.

general quality of the risk factor data. It is sometimes suggested that incidence in individuals who are at high risk to begin with will not be significantly affected by an additional risk factor. The inclusion of data on risk factors has enabled us to consider this point, and whether the association between recent respiratory infection and either MI or stroke operates at all levels of risk, i.e. do the mechanisms such as increased thrombotic tendency confer additional hazard, regardless of the level of risk due to conventional clinical risk factors? The first GPRD study[5] excluded those with risk factors. The second GPRD study,[6] being a case-

Table 4 Effect of respiratory infection within the preceding month on myocardial infarction and stroke in according to number of significant ($P < 0.01$) risk factors present[a]

Number of risk factors	Infections in preceding month	MI			Stroke		
		Cases	Controls	Odds ratio (95% CI)[b]	Cases	Controls	Odds ratio (95% CI)[b]
None	No. of infections (%) Total patients	52 (1.7%) 3001	34 (0.7%) 4933	2.73 (1.75–4.27)	69 (1.9%) 3679	41 (0.9%) 4757	2.45 (1.65–3.65)
One	No. of infections (%) Total patients	71 (1.9%) 3810	43 (1.1%) 3853	1.68 (1.13–2.49)	63 (1.7%) 3646	39 (1.2%) 3347	1.59 (1.06–2.40)
Two or more	No. of infections (%) Total patients	98 (2.3%) 4344	28 (1.2%) 2369	1.85 (1.20–2.84)	32 (1.7%) 1883	16 (1.4%) 1104	1.08 (0.59–2.00)
Total	No of infections (%) Total patients	221 (2.0%) 11155	105 (0.9%) 11155	2.01 (1.57–2.57)	164 (1.8%) 9208	96 (1.0%) 9208	1.81 (1.39–2.36)

[a]For MI: angina, smoking status, diabetic status, hypertension, peripheral vascular disease, family history of CAD, hyperlipidaemia, and previous stroke. For stroke: smoking status, diabetic status, hypertension, peripheral vascular disease, previous MI, and urinary tract infection.
[b]From conditional logistic regression model. The odds ratio for all patients is adjusted for number of risk factors. Interaction between infection and risk group: (i) MI, $P = 0.23$ (ii) stroke, $P = 0.021$.

series study in which cases were their own controls, could therefore not consider different levels of risk (although there was of course no possibility of confounding by risk factor differences). For MI, there are significantly raised ORs associated with respiratory infection at all levels of risk, suggesting that the mechanism(s) responsible operate at all levels of prior underlying heart attack risk. This may also be true for stroke, although the strength of the association may be less at high rather than low levels of risk.

Disadvantages of the study

Case control studies are always susceptible to uncertainties of whether controls are fully comparable to cases in all respects apart from the exposure under consideration. However, both cases and controls had to have been on a doctor's list for at least 2 years, and selection of closely matched controls from the same database as the cases in the unselected IMS population means that this disadvantage may not be of material significance. We have not been able to check on the accuracy of recordings of infection and outcome events (a condition of using the database being that individual patients may not be identified), but any inaccuracies are likely to have resulted in underestimates of the strength of associations. Missing information on some of the risk factors has to be considered and the decision to classify the risk factor as absent if not recorded. However, as already indicated, the expected associations of all the risk factors with heart attacks suggest that this may not have been an important limitation. For example, there were more patients with a missing recording of smoking status (a known risk factor for MI and stroke) among the controls indicating the decision to consider these as non-smokers to be reasonable. Finally, it is possible that other risk factors on which information was not collected may have influenced the association between infection and MI or stroke. However, information on the most common risk factors for MI or stroke was collected and any other, less common potential confounders with limited associations with MI or stroke, are unlikely to alter the results substantially.

Conclusions

There is irrefutable evidence of a strong association between recent respiratory infection and MI and also of stroke. Two further research approaches would show whether this association is one of cause and effect. The first is work on mechanisms through which infection might increase the incidence of major arterial events—for example, on increased thrombogenic potential and on the extent and stability of underlying vessel wall disease and atheromatous plaques. The second is through intervention studies. So far, several studies have failed to demonstrate an effect of antibiotics,[11,12] which may not be surprising since the evidence is that viruses are responsible for most respiratory infections and antibiotics would probably need to be given very early on and might well be largely ineffective once an inflammatory response was underway. Antiviral agents can reduce the duration and severity of established influenza, for example, and also appear to have a marked effect in reducing influenza in a prophylactic context in exposed groups not yet clinically affected.[13] In view of the strong evidence that respiratory infections increase the risk of MIs and strokes, it may therefore be that aborting or preventing attacks of influenza will reduce vascular events and there are some studies suggesting that this is so, although the evidence is still not conclusive.[14–18] MIs and strokes occur more frequently during the winter months. Since there may be a large number of vascular deaths attributable to respiratory infection, over and above those directly attributable to respiratory disease,[1] the benefits of reducing respiratory infection, particularly during the winter months, could be substantial.

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