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Sources of heterogeneity in case–control studies on associations between statins, ACE-inhibitors, and proton pump inhibitors and risk of pneumonia

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ABSTRACT

The heterogeneity in case–control studies on the associations between community-acquired pneumonia (CAP) and ACE-inhibitors (ACEi), statins, and proton pump inhibitors (PPI) hampers translation to clinical practice. Our objective is to explore sources of this heterogeneity by applying a common protocol in different data settings. We conducted ten case–control studies using data from five different health care databases. Databases varied on type of patients (hospitalised vs. GP), level of case validity, and mode of exposure ascertainment (prescription or dispensing based). Identified CAP patients and controls were matched on age, gender, and calendar year. Conditional logistic regression was used to calculate odds ratios (OR) for the associations between the drugs of interest and CAP. Associations were adjusted by a common set of potential confounders. Data of 38,742 cases and 118,019 controls were studied. Comparable patterns of variation between case–control studies were observed for ACEi, statins and PPI use and pneumonia risk with adjusted ORs varying from 1.04 to 1.49, 0.82 to 1.50 and 1.16 to 2.71, respectively. Overall, higher ORs were found for hospitalised CAP patients matched to population controls versus GP CAP patients matched to population controls. Prevalence of drug exposure was higher in dispensing data versus prescription data. We show that case–control selection and methods of exposure ascertainment induce bias that cannot be adjusted for and to a considerable extent explain the heterogeneity in results obtained in case–control studies on statins, ACEi and PPIs and CAP. The common protocol approach helps to better understand sources of variation in observational studies.

INTRODUCTION

During the past decade numerous case–control studies reported associations between commonly used drugs and a decreased or increased risk for community acquired pneumonia (CAP) [*1*, *2*]. Among these drugs are ACE-inhibitors (ACEi), statins, and proton pump inhibitors (PPI). Proposed mechanisms of action behind these associations are interference with aspiration and cough induction through ACE inhibition [*3*], immunomodulation by statins, and gastrointestinal bacteria overgrowth due to increased stomach pH by proton pump inhibition. Recent reviews and meta-analyses of ACEi and CAP [*4*], statins and CAP [*5*, *6*], as well as PPI and CAP [*7*] show a marked heterogeneity in findings. In these reviews, the most often mentioned explanation for differences in findings is unmeasured confounding in some or all of the studies reviewed. However, the case–control studies included in these meta-analyses differed also with respect to several other factors including source population (e.g. ethnicity), health care setting and data source, calendar time, and methods of exposure and outcome ascertainment [*8*, *9*]. In other words, besides confounding, selection bias and information bias may account for the observed heterogeneity and compromise causal inference [*10*].
To further explore the potential impact of the abovementioned biases on case–control study results, we planned ten case–control studies on ACEi, PPI, and statin-use and pneumonia risk using a common protocol but varying on (1) type of patients (hospitalised vs. non-hospitalised pneumonia cases), (2) case validity (hospitalisation with X-ray confirmations, ICD coding, or ICPC coding), and (3) exposure ascertainment (general practitioner prescriptions vs. pharmacy dispensing data). To avoid health care associated heterogeneity all studies were conducted in the Dutch health care setting and within the same time frame. This knowledge on sources of heterogeneity in case–control study findings and means of prevention are indispensable to translate epidemiological findings on drug associated CAP into clinical practice.

METHODS

Study populations

This project used data from the Dutch Mondriaan project, the Netherlands Primary Care Database coordinated by NIVEL (NPCD) [*11*], the PHARMO Record Linkage System, and a prospective cohort of CAP patients. Mondriaan is a private–public collaboration funded by the Dutch Top Institute Pharma and provides an infrastructure and system to collect data for pharmacoepidemiological research (http://www.projectmondriaan.nl). Mondriaan currently covers GP data from a population of over 1.2 million people [*12*]. The PHARMO RLS database (www.pharmo.nl) contains drug-dispensing data from community-pharmacies throughout the Netherlands in a standardised format linked to hospital discharge information. Table 1 provides the main characteristics of the abovementioned data sources. Using these different data sources we were able to design ten case–control studies in hospitalised and general practitioner (GP) settings as well as in regional and nationwide data sources by using a common protocol. These include ‘within database’ comparisons as well as ‘between databases’ where cases and controls are

sampled from the same data source or from different sources. This approach has been applied before [*13*].

[TABLE 1]

Within database; GP-case–GP-control

The first three case control sets were sampled from three Dutch general practitioner databases, the Leidsche Rijn General Practitioner (LRGP) database [*14*], the Almere Health Care group (AHC) general practitioner database, and the NPCD. In each case control study the cases and controls were selected from the same GP data source.

Within database; hospitalised cases–population controls

A fourth case control study was conducted in PHARMO to compare hospitalised cases with population controls.

Between database; hospitalised cases–population controls

A set of 504 hospitalised cases consisted of patients being hospitalised in the St. Antonius hospital, Nieuwegein, The Netherlands, and the Gelderse Vallei Hospital, Ede, The Netherlands (ANT). Case control studies five through seven were designed by comparing these hospitalised cases with controls from the abovementioned GP databases. The eighth study matched ANT hospital cases to population controls from PHARMO.

Between database; hospitalised cases–GP cases

We compared hospitalised ANT cases with GP cases in studies number nine ANT-AHC and ten ANT-NPCD.

Selection of cases and controls

Cases from databases were selected as all patients having a record for pneumonia (ICD-9 codes 481–487 in hospital based registries or ICPC-2 code R81 in GP based databases) between 2004 and 2010. Only first episodes of CAP during the study period were considered. All cases in the ANT set were hospitalised for radiographically confirmed pneumonia [*15*] in the same time period and clinical characteristics of these patients have been described elsewhere [*16, 17*].
Control subjects were eligible when they did not have a record for pneumonia in the 12 months prior to the index date of the corresponding case. All cases and controls had medication prescription and or dispensing data available for at least 6 months before index date. For each case we selected two up to five controls depending on the database while matching on sex and year of birth. If not enough appropriate controls were available, controls were matched on year of birth plus or minus 1 year. Controls were assigned the index date of the cases.

Drug exposure

In the GP based data sources LRGP and NPCD prescriptions by GPs of ACEi, statins and PPI were used to ascertain drug exposure. In AHC both prescriptions and dispensing information was available. For both ANT cases and PHARMO cases and controls dispensing information originating from community-pharmacies was used.

A subject was considered to be a user of these drugs when a dispensing date occurred less than 30 days prior to the index date or lasted over the index date. To explore potential false positive associations we also ascertained use of selective serotonin reuptake inhibitors (SSRI) in the majority of the studies. To our knowledge, SSRIs are not linked to an altered risk of acquiring pneumonia and may therefore act as a negative control. Exposure ascertainment has been performed independent of case or control status within a source.

Potential confounders

To adjust for confounding in multivariate conditional logistic regression analyses, the following clinical data were collected. For all subjects, the presence of co-morbidities was ascertained through drug-based proxies [*18*]. Patients who were using inhalation medication were considered to be suffering from asthma or chronic obstructive airway disease (COPD). Use of oral glucose lowering drugs and or insulin was considered a proxy for the presence of diabetes. Congestive heart failure was based on the use of diuretics in combination with digitalis. Besides co-morbidities also the use of morphine, non-steroidal anti-inflammatory drugs, antiplatelet drugs, and corticosteroids was assessed because these types of treatment have been associated with risk of pneumonia in other studies [*1*, *19*]. For all drugs, drug use was defined as two or more prescriptions/dispenses in the 182 days before the index date. In the GP based studies from LRGP and AHC we captured relevant ICPC-2 codes from medical records to include additional potential confounders including renal disease, malignancies, liver disease, cerebral vascular accident, and stroke. In LRGP, AHC, NPCD and PHARMO information on influenza vaccination in the year before index was available.

Statistical analysis

Continuous data are expressed as mean with standard deviation (SD), categorical data are presented as numbers with percentages. Conditional logistic regression was used to compute odds ratios (OR) for CAP and each drug of interest. We calculated crude ORs, semi-adjusted ORs, and fully-adjusted ORs. The semi-adjusted OR was calculated with confounders available in all sets as described above and including the other drugs of interest. Where applicable, influenza vaccination status and/or medical history based comorbidities were included as potential confounders additionally (fully-adjusted). To assess heterogeneity in ORs between the ten studies we applied Dersimonian-Laird analysis using RevMan 5.3 (Nordic Cochrane Institute, Copenhagen) to compute I^2 for heterogeneity based on the crude effect estimates. All other statistical analyses were conducted using IBM SPSS Statistics for Mac version 20 (Chicago, IL). A p value of <0.05 was considered statistically significant in all tests.

RESULTS

In this study we conducted ten different case control studies in different settings including 38,742 cases and 118,019 controls. Table 2 displays the patient characteristics, drug exposure, and identified comorbidities for all case–control combinations.

[TABLE 2]

PATIENT CHARACTERISTICS AND DRUG USE

Age and sex distributions differed between patients derived from GP databases and hospitalised patients. CAP patients in primary care were younger with a mean age of 46 ± 15 years in LRGP, 54 ± 18 in AHC, 61 ± 18 in NPCD compared to older hospitalised patients of 63 ± 18 years in ANT and 66 ± 17 in PHARMO. The proportion of males in primary care was 48 % in all three GP databases and was lower than in hospitalised settings with 52 % males in PHARMO and 59 % in ANT. Drug utilisation differed considerably between the cohorts for both the exposure to drugs of interest as well as other drugs that are a proxy for comorbidity (Table 2). Cases used more drugs than controls in all comparisons and hospitalised cases used more drugs than GP cases. We observed that drug use in GP controls with also dispensing data available (AHC) was similar to that of population controls with dispensing data but slightly higher compared to controls with GP prescription data.

ASSOCIATIONS WITH CAP

Overall, for all drugs under study the observed crude associations were highly heterogeneous over the ten case–control studies as I^2 values were high (ACEi 89 %, Statin 95 %, PPI 89 %) and all p values <0.0001 [*20*]. Figure 1 shows the crude, semi-adjusted and fully-adjusted ORs for use of ACEi, statin, PPI, and SSRI, respectively in the individual case–control studies. In the multi-variable analyses adjusting for all shared variables (semi-adjusted) the ORs were lower than those for crude analyses in all case–control studies. For ACEi use and pneumonia risk the semi-adjusted OR varied from 1.04 (95 % CI 0.98–1.10) in PHARMO–PHARMO to 1.49 (95 % CI 0.95–2.33) in ANT-AHC. The association between statin treatment and pneumonia varied from a protective effect [OR 0.82 (95 % CI 0.78–0.86)] to a small increased risk of 1.50 (95 % CI 1.09–2.07) in ANT-NPCD. PPI use was not significantly associated with pneumonia, the OR varied from 1.30 (95 % CI 0.99–1.72) in the case–control study ANT-PHARMO to an increased risk of 2.71 (95 % CI 1.99–3.69) in ANT-NPCD. The semi-adjusted association between the negative control (SSRI) and CAP ranged from 1.16 (95 % CI 1.06–1.27) in PHARMO–PHARMO to 2.47 (95 % CI 1.37–4.45) in ANT-NPCD. A further, full adjustment in the GP case–control studies did not change the effect estimates any further in a relevant way. See Appendix Table 3 for all other ORs, 95 % CI, and p values.

[FIGURE 1] [TABLE 3]

Overall, hospitalised cases matched to GP controls resulted in the highest ORs. The variation in ORs over the case–control studies showed a similar curving pattern (Fig. 1) for all drugs under study. The ORs for PPI were higher in all studies compared with the other drugs.

DISCUSSION

This is the first study to explore how associations between the frequently used drugs statins, ACEi, and PPIs and pneumonia risk are influenced by case–control selection and exposure ascertainment as inherent to the type of health care setting and data source. Our data show that the type of health care setting and the data source the cases and controls were selected from can largely impact the variation in ORs, consistently for all three drugs. Increasing the level of adjustment for confounding was not able to reduce this variation. These findings are very relevant when interpreting the impact of available studies and the proposed clinical implications of those findings.

Below we will discuss types of bias mostly related to differences in health care setting and data source. Firstly, selection bias seems to be an important source of the heterogeneity observed in our study. In our study ORs were consistently higher when studying hospitalised cases compared to patients diagnosed in primary care. In the Netherlands, the number of patients hospitalised for CAP is around 20 % of the number of patients who present with symptoms of pneumonia at the general practitioner [*21*]. National guidelines require only patients with severe CAP or antibiotic treatment failure to be referred to hospital [*22*] and therefore differences between hospitalised and non-hospitalised patients are to be expected i.e. age and co-morbidities. Indeed in the present study age is higher in hospitalised cases than in GP cases. Furthermore, cardiovascular morbidity and corresponding medication use (statins and ACEi) appeared to be associated independently with hospital referral when comparing primary care cases to hospitalised cases (case control studies nine and ten). Hospitalised ‘high risk’ pneumonia patients thus tend to use more drugs, which influences the observed association with pneumonia relative to population controls. This could cause a risk of overestimation of harm and also hold a risk of missing a preventive association when compared with control patients without pneumonia. This phenomenon is an example of selection bias often referred to as referral bias. A recent paper of Dublin et al. [*23*] report a similar observation on ACEi use and pneumonia with an increased risk for hospitalised patients versus a neutral OR for non-hospitalised patients.

Secondly, information bias due to outcome misclassification. Differences in level of case validity might provide another explanation for the observed variation in ORs. In our study, CAP cases from the ANT hospital were confirmed by infiltrates on a chest X-ray and clinical presentation of symptoms according to WHO criteria [*15*] whereas all GP based cases were selected based on ICPC-2 codes entered by GPs. The latter holds a chance that some CAP cases could have been missed or misclassified. ICD-9 coding in PHARMO originating from hospital databases could similarly lead to invalid cases if not all hospital admissions are correctly registered. We think, however, that ICD-9 of pneumonia in the present study is quite reliable. Not only because the positive predictive value of coding of pneumonia in hospital administrative database in the Netherlands is reported to be 88 % [*24*], but also due to the observation that in the ‘between database case–case comparison’ the associations in ANT cases and PHARMO cases are similar (ORs ~ 1.0; data not shown) and that patient characteristics and drug exposure rates were very comparable. This supports the assumption that ANT cases in our study are a representative sample of hospitalised pneumonia patients in general, and thus that case validity in PHARMO is sufficient. Reversely, this supports also that the ‘population-base principle’ holds and that ANT cases can be matched to population

controls from PHARMO. Based on the considerations above, we do not expect that misclassification of pneumonia is the major explanation for the observed variation between the ten case–control studies. Accordingly, we did not observe a regression to the null correlated with the level of case ascertainment.

Information bias due to exposure misclassification is another potential source of variation observed in the results of the ten case–control studies is the way of drug exposure ascertainment. For all three drugs under study as well as SSRIs, the prevalence of exposure was considerably higher in the ANT cases and subjects originating from the PHARMO database whereas lower and similar rates were observed in all three GP databases (parallel trend). Given that PHARMO holds dispensing data from community pharmacies compared to prescription data for the GP databases this could hold two possible explanations. First, not all prescribed medication is registered fully by the general practitioner or second, the patient fills prescriptions that do not originate from the general practitioner (e.g. medical specialist prescriptions). Consequently, for comparisons that include hospitalised patients with drug dispensing information matched to GP derived controls (case control studies 5–7), this could lead to an overestimation of the associations, especially for drugs typically prescribed by specialist doctors. One could argue that the relatively younger age of the GP population might be another explanation for lower drug use prevalence. However, this is not reflected by the prevalence of drug use in the GP based case control studies in AHC (prescribing + dispensing) versus in NPCD (prescribing only).

An advantage of our study is that we were able to conduct the ten case–control studies within the same time-frame and country, having the same healthcare system, treatment guidelines, refunding policies, socio economic situation, accessibility to health care facilities etcetera. This already rules out some important potential sources of heterogeneity. For example, through this we exclude ethnicity [*4*, *25*] or genetics [*2*, *26*] as a potential explanation for variation in results as has been suggested for the association between ACEi use and pneumonia [*27*]. In other words, this approach increases the likelihood of detecting methodology and data origin as source of biases leading to the heterogeneity in the case–control study findings [*28*].

So far, most studies on statins, PPIs and ACEi end with stating that unmeasured confounding cannot be ruled out. In our study, we show that the heterogeneity observed between studies seems to be more determined by the selection of cases and controls and exposure ascertainment rather that adjustment for confounding factors. This phenomenon is reflected by the observation of a similar pattern of variation between sets in calculated ORs for all drugs under study including a negative control. Such has recently also been illustrated by McCandless showing that the inability to adjust for so-called healthy behaviour in studies on statins and fracture risk only represents a minor source of variation in study findings [*29*].

LIMITATIONS

Some limitations of our study need to be addressed. First, our studies were conducted using healthcare data from the Netherlands, which may limit the generalizability of our findings. Second, for reasons of consistency, the exposure assessment was somewhat granular. We did not analyse dose effect relations of the individual drugs nor time relations (e.g. new vs. prevalent use). Nevertheless, we do not think that the

above limitations would change the conclusion from our study. Finally, we were limited in the number of potential confounders available in all ten datasets. This means that we can not exclude that residual confounding (e.g.: BMI, alcohol, smoking, the history of influenza) could still explain some variation in ORs observed between the ten case control studies [*30–32*]. To argue against this, when adding more confounders to our model, there were no major shifts in ORs.

FUTURE DIRECTIONS

We observed that over the ten case control studies a similar curving pattern of ORs is visible independent of the drug under study (Fig. 1). This does not only confirm biases independent of the drug under study but also could hold a possibility to study a specific drug relative to other drugs over studies. If an OR for a specific drug is persistently elevated relative to the OR of other drugs over ten different datasets this could suggest a true association. As an example, in our study the ORs for PPIs and pneumonia are relatively higher in each case control study compared to the other drugs under study. This could be interpreted as supportive to causality of PPI use being a risk factor for developing pneumonia. Today's extensive availability of electronic health care data, like in the Mondriaan project, facilitates addressing study questions with this approach by using a common protocol in multiple-databases.
In conclusion, we show that in case–control studies on statins, ACEi, PPIs and CAP, the case control selection and method of exposure ascertainment can induce spurious heterogeneity in study results to a considerable extent. Increasing the level of adjustment for confounding is not able to reduce this heterogeneity. The common protocol approach helps to better understand sources of variation in observational studies.

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Conflict of interest

Mark C. H. de Groot: The University of Utrecht has received funding from Top Institute Pharma to pay part of my salary. This public private partnership (funding: 50 % Government, 25 % Academia, 25 % pharmaceutical industry) supports project T6-101-1 Mondriaan, The Dutch healthcare landscape as a 'population laboratory' (www.tipharma.com). My employer received unrestricted support from the Innovative Medicine Initiative Joint Undertake (IMI-PROTECT: www.imi.europa.eu) under Grant Agreement No. 115004, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution. Olaf H. Klungel received unrestricted research support from IMI-PROTECT and IMI-EU2P for development of educational presentations. Hubert G. M. Leufkens has no personal funding to declare. Liset van Dijk has received unrestricted grants from Bristol

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APPENDIX

See Table 3.

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TABLES

Table 1 Main characteristics of datasources

Datasource	**Population numbers and geography**	**Type of case**	**Case selection method**	**Exposure assessment**	**Comorbidity and other patient characteristics**
LRGP	Approx. 20,000; Utrecht region	Primary care diagnosis	Administrative data; ICPC coded	GP prescriptions; ATC code	Medication based + ICPC coded diagnoses
AHC	Approx. 260,000; Almere region	Primary care diagnosis	Administrative data; ICPC coded	GP prescriptions + community pharmacy dispensings; ATC code	Medication based + ICPC coded diagnoses
NPCD	Approx. 340,000; Nationwide	Primary care diagnosis	Administrative data; ICPC coded	GP prescriptions; ATC code	Medication based
PHARMO	Approx. 3,000,000; Nationwide	Hospitalisation	Administrative data; ICD-9 coded	Community pharmacy dispensings; ATC code	Medication based
ANT	800 bed teaching hospital; Utrecht region	Hospitalisation	Prospective cohort	Community pharmacy dispensings; ATC code	Medication based

LRGP Leidsche Rijn General Practitioner database, AHC Almere Health Care group general practitioner database, NPCD Netherlands Primary Care Database, PH PHARMO database, ANT Cases Antonius Hospital

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Table 2 Characteristics of case control studies, patient characteristics and prevalence of exposures and potential confounders

	Within database approach								Between database approach						
Setting	GP case - GP control						Hosp case-pop control		Hosp case-pop control						Hosp Case- GP case
Source	LRGP	LRGP	AHC	AHC	NPCD	NPCD	PHARMO	PHARMO	ANT	ANT-LRGP	ANT-AHC	ANT-NPCD	ANT-PHARMO	AHC	NPCD
Study	1		2		3		4		10 9 8 7 6 5						
CAP status	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Control	Control	Control	Case	Case
Patients	798	2347	4198	12405	12398	61959	20844	41308	504	1333	1112	2515	2016	1259	2513
Age Mean(SD)	46.3 (15.4)	45.4 (14.3)	53.5 (17.6)	53.6 (17.6)	60.8 (18.2)	60.7 (18.2)	66.1 (17.1)	65.9 (17.1)	63.4 (18.1)	60.1 (16.5)	62.8 (18)	63.5 (18)	63 (18.1)	63.2 (17.8)	63.6 (18)
Sex Female	(52.3)	(52.3)	(52.6)	(52.6)	(51.8)	(51.8)	(48.2)	(48.6)	(41.7)	(43.4)	(39.8)	(41.4)	(41.5)	(40.9)	(41.3)
Exposure of interest															
ACEi	47 (5.9)	95 (4)	415 (9.9)	750 (6)	1335 (10.8)	5144 (8.3)	3231 (15.5)	5669 (13.7)	89 (17.8)	117 (8.8)	108 (9.7)	221 (8.8)	315 (15.6)	203 (16.1)	305 (12.1)
Statin	73 (9.1)	134 (5.7)	561 (13.4)	1008 (8.1)	1518 (12.2)	6314 (10.2)	4037 (19.4)	8362 (20.2)	126 (25.1)	161 (12.1)	131 (11.8)	301 (12.0)	461 (22.9)	260 (20.7)	391 (15.6)
PPI	68 (8.5)	92 (3.9)	683 (16.3)	890 (7.2)	1641 (13.2)	4373 (7.1)	5297 (25.4)	6198 (15)	123 (24.6)	116 (8.7)	110 (9.9)	193 (7.7)	328 (16,3)	268 (21.3)	372 (14.8)
SSRI	-	-	-	-	446 (3.6)	1545 (2.5)	1111 (5.3)	1573 (3.8)	24 (4.8)	-	-	46 (1.8)	48 (2.4)	-	80 (3.2)
Confounders based on drug use															
Diabetes	34 (4.3)	67 (2.9)	359 (8.6)	628 (5.1)	974 (7.9)	3455 (5.6)	2585 (12.4)	3894 (9.4)	77 (15.4)	82 (6.2)	76 (6.8)	166 (6.6)	209 (10.4)	159 (12.6)	232 (9.2)
Opiate	2 (0.3)	2 (0.1)	29 (0.7)	35 (0.3)	170 (1.4)	474 (0.8)	654 (3.1)	700 (1.7)	21 (4.2)	5 (0.4)	1 (0.1)	18 (0.7)	32 (1.6)	18 (1.4)	43 (1.7)
COPD	116 (14.5)	82 (3.5)	939 (22.4)	771 (6.2)	1865 (15)	2883 (4.7)	5501 (26.4)	3512 (8.5)	128 (25.5)	68 (5.1)	83 (7.5)	119 (4.7)	123 (6.1)	330 (26.2)	506 (20.1)
HeartFailure	17 (2.1)	14 (0.6)	171 (4.1)	190 (1.5)	895 (7.2)	2341 (3.8)	2873 (13.8)	3134 (7.6)	31 (6.2)	15 (1.1)	16 (1.4)	85 (3.4)	81 (4)	56 (4.4)	171 (6.8)
Oral_gc	31 (3.9)	8 (0.3)	230 (5.5)	95 (0.8)	567 (4.6)	511 (0.8)	2550 (12.2)	725 (1.8)	48 (9.6)	11 (0.8)	15 (1.3)	25 (1)	30 (1.5)	81 (6.4)	77 (3.1)
NSAIDS	56 (7)	81 (3.5)	388 (9.2)	690 (5.6)	729 (5.9)	2595 (4.2)	1876 (9)	2865 (6.9)	40 (8)	61 (4.6)	58 (5.2)	89 (3.5)	100 (5)	112 (8.9)	144 (5.7)
Platelets	50 (6.3)	77 (3.3)	460 (11)	830 (6.7)	1464 (11.8)	5674 (9.2)	4231 (20.3)	7905 (19.1)	114 (22.8)	108 (8.1)	111 (10)	292 (11.6)	393 (19.5)	262 (20.8)	403 (16)

LRGP Leidsche Rijn General Practitioner database, *AHC* Almere Health Care group general practitioner database, *NPCD* Netherlands Primary Care Database, *PH* PHARMO database, *ANT* Cases Antonius Hospital

ACEi angiotensin converting enzyme inhibitor, *PPI* proton pump inhibitor, *SSRI* selective serotonin re-uptake inhibitor

Oral_gc oral glucocorticoid, *NSAIDs* Non steroidal anti-inflammatory drug, Platelets: anti-coagulation drugs

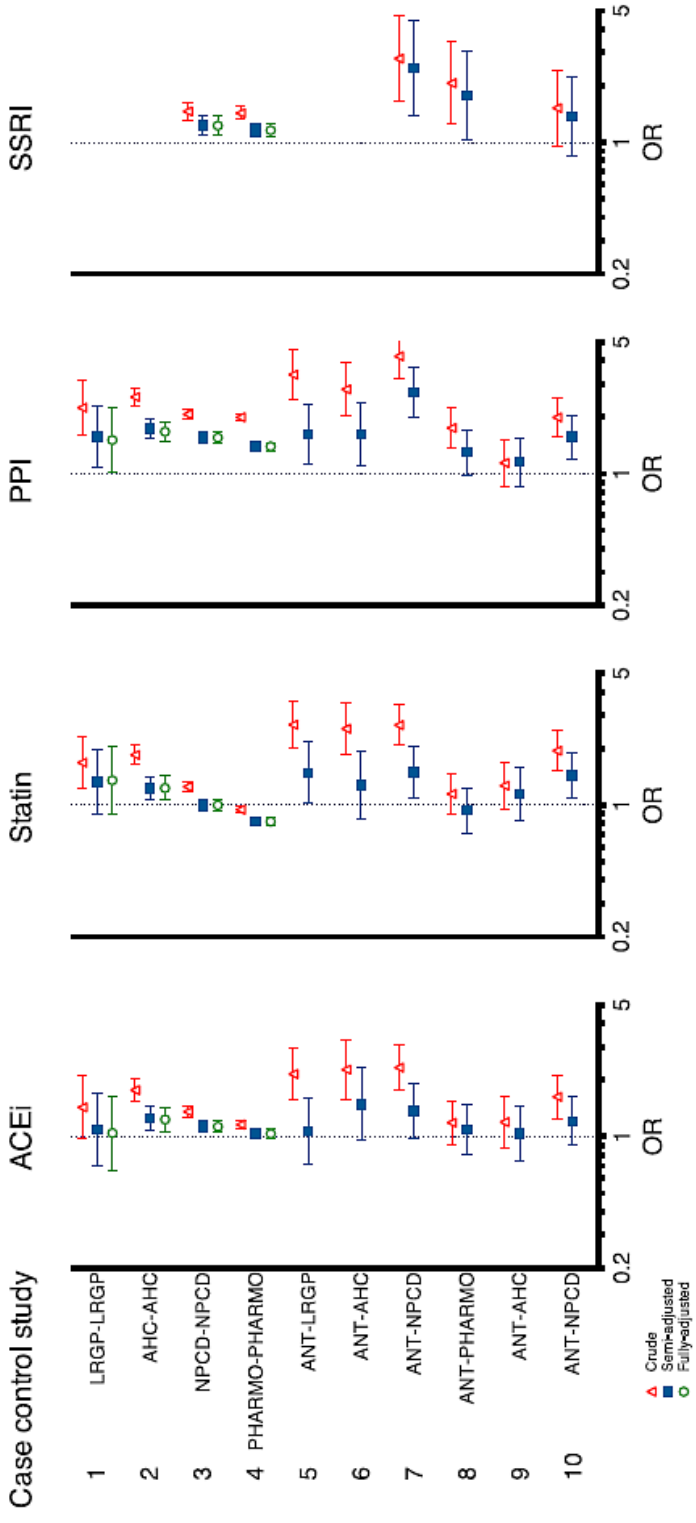

Fig. 1 Unadjusted, semi-adjusted, and fully adjusted ORs with 95 % CIs for the association of ACEi, statin, PPI or SSRI drug use and the risk of pneumonia in ten independent case–control studies Un-adjusted: drug of interest. Semi-adjusted: drug of interest + other drugs of interest (ACEi, Statins, PPI) + exposure derived confounding (diabetes, opiates, COPD, heart failure, oral glucocorticoids, NSAIDs, platelet inhibitors). Fully-adjusted in studies 1 and 2: semi-adjusted + influenza vaccination + medical history coded disease (heart failure, diabetes, renal disease, malignancies, lung disease, liver disease, cerebral vascular accident/stroke). Fully-adjusted in studies 3 and 4: semi-adjusted + influenza vaccination

Table 3
Odds ratios of associations of ACEi, Statin, PPI, and SSRI and CAP

Case control study	ACEi						PPI					
	Crude		Semi-adjusted		Fully adjusted		Crude		Semi-adjusted		Fully adjusted	
	OR	p value	OR	p value	OR	p value	OR	p value	OR	p value	OR	p value
1 LRGP–LRGP	1.43 (0.98–2.1)	0.0664	1.09 (0.7–1.69)	0.713	1.04 (0.66–1.65)	0.8608	2.24 (1.6–3.14)	<0.0001	1.58 (1.08–2.3)	0.0191	1.51 (1.03–2.23)	0.0361
2 AHC–AHC	1.77 (1.55–2.01)	<0.0001	1.25 (1.08–1.46)	0.0034	1.23 (1.06–1.44)	0.0069	2.56 (2.3–2.85)	<0.0001	1.73 (1.53–1.95)	<0.0001	1.68 (1.48–1.89)	<0.0001
3 NPCD–NPCD	1.36 (1.27–1.45)	<0.0001	1.13 (1.06–1.22)	0.0006	1.13 (1.05–1.21)	0.001	2.07 (1.95–2.21)	<0.0001	1.56 (1.46–1.67)	<0.0001	1.56 (1.45–1.67)	<0.0001
4 PHARMO–PHARMO	1.16 (1.1–1.21)	<0.0001	1.04 (0.98–1.1)	0.1951	1.04 (0.98–1.1)	0.195	1.99 (1.91–2.08)	<0.0001	1.4 (1.33–1.47)	<0.0001	1.4 (1.33–1.47)	<0.0001
5 ANT-LRGP	2.15 (1.58–2.93)	<0.0001	1.07 (0.71–1.59)	0.7707	–	–	3.36 (2.49–4.53)	<0.0001	1.62 (1.12–2.33)	0.0101	–	–
6 ANT-AHC	2.27 (1.58–3.26)	<0.0001	1.49 (0.95–2.33)	0.0813	–	–	2.81 (2.03–3.88)	<0.0001	1.62 (1.1–2.4)	0.0142	–	–
7 ANT-NPCD	2.33 (1.77–3.07)	<0.0001	1.37 (0.97–1.92)	0.0724	–	–	4.2 (3.23–5.47)	<0.0001	2.71 (1.99–3.69)	<0.0001	–	–
8 ANT-	1.18	0.216	1.09	0.61	–	–	1.75	<0.00	1.3	0.061	–	–

Case control study	ACEi						PPI					
	Crude		Semi-adjusted		Fully adjusted		Crude		Semi-adjusted		Fully adjusted	
	OR	p value	OR	p value	OR	p value	OR	p value	OR	p value	OR	p value
PHARMO	(0.91–1.55)	6	(0.8–1.48)	29			(1.37–2.24)	01	(0.99–1.72)	3		
9 ANT-AHC	1.2 (0.87–1.64)	0.2688	1.04 (0.74–1.46)	0.8321	–	–	1.14 (0.86–1.52)	0.3696	1.16 (0.86–1.55)	0.3466	–	–
10 ANT-NPCD	1.63 (1.24–2.13)	0.0005	1.21 (0.9–1.63)	0.2152	–	–	1.99 (1.56–2.54)	<0.0001	1.57 (1.2–2.05)	0.001	–	–

Case control study	Statins						SSRI					
	Crude		Semi-adjusted		Fully adjusted		Crude		Semi-adjusted		Fully adjusted	
	OR	p value	OR	p value	OR	p value	OR	p value	OR	p value	OR	p value
1 LRGP–LRGP	1.68 (1.22–2.32)	0.0015	1.33 (0.89–1.98)	0.1642	1.36 (0.9–2.04)	0.1448	–	–	–	–	–	–
2 AHC–AHC	1.85 (1.65–2.08)	<0.0001	1.23 (1.06–1.42)	0.0055	1.23 (1.07–1.43)	0.005	–	–	–	–	–	–
3 NPCD–NPCD	1.25 (1.18–1.33)	<0.0001	1.01 (0.94–1.08)	0.8915	1 (0.93–1.07)	0.9936	1.46 (1.31–1.63)	<0.0001	1.23 (1.1–1.38)	0.0003	1.23 (1.1–1.38)	0.0003
4 PHARMO–	0.95 (0.91–	0.0138	0.82 (0.78–	<0.0001	0.82 (0.78–	<0.0001	1.43 (1.32–	<0.0001	1.16 (1.06–	0.0009	1.16 (1.06–	0.0009

Case control study	Statins						SSRI					
	Crude		Semi-adjusted		Fully adjusted		Crude		Semi-adjusted		Fully adjusted	
	OR	p value	OR	p value	OR	p value	OR	p value	OR	p value	OR	p value
PHARMO	0.99)		0.86)		0.86)		1.55)		1.27)		1.26)	
5 ANT-LRGP	2.68 (2.01–3.57)	<0.0001	1.49 (1.02–2.16)	0.0384	–	–	–	–	–	–	–	–
6 ANT-AHC	2.54 (1.85–3.51)	<0.0001	1.28 (0.85–1.93)	0.2413	–	–	–	–	–	–	–	–
7 ANT-NPCD	2.66 (2.08–3.41)	<0.0001	1.5 (1.09–2.07)	0.0133	–	–	2.79 (1.66–4.68)	0.0001	2.47 (1.37–4.45)	0.0026	–	–
8 ANT-PHARMO	1.15 (0.9–1.45)	0.2597	0.94 (0.71–1.24)	0.659	–	–	2.06 (1.25–3.42)	0.0048	1.77 (1.02–3.06)	0.041	–	–
9 ANT-AHC	1.27 (0.95–1.69)	0.102	1.14 (0.83–1.58)	0.4199	–	–	–	–	–	–	–	–
10 ANT-NPCD	1.94 (1.52–2.48)	<0.0001	1.44 (1.09–1.9)	0.0096	–	–	1.52 (0.96–2.42)	0.0771	1.37 (0.85–2.21)	0.1994	–	–

LRGP Leidsche Rijn General Practitioner database, AHC Almere Health Care group general practitioner database, NPCD Netherlands primary care database, PH PHARMO database, ANT Cases Antonius Hospital
ACEi angiotensin converting enzyme inhibitor, AT2 angiotensin receptor antagonists; PPI proton pump inhibitor, SSRI selective serotonin re-uptake inhibitor
Un-adjusted: drug of interest

Semi-adjusted: drug of interest + other drugs of interest (ACEi, Statins, PPI) + exposure derived confounding (diabetes, opiates, COPD, heart failure, oral glucocorticoids, NSAIDs, platelet inhibitors)
Fully-adjusted in studies 1 and 2: semi-adjusted + influenza vaccination + medical history coded disease (heart failure, diabetes, renal disease, malignancies, lung disease, liver disease, cerebral vascular accident/stroke)
Fully-adjusted in studies 3 and 4: semi-adjusted + influenza vaccination