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Risk factors for community-acquired pneumonia in adults in Europe: a literature review

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ABSTRACT

Background Community-acquired pneumonia (CAP) causes considerable morbidity and mortality in adults, particularly in the elderly.

Methods Structured searches of PubMed were conducted to identify up-to-date information on the incidence of CAP in adults in Europe, as well as data on lifestyle and medical risk factors for CAP.

Results The overall annual incidence of CAP in adults ranged between 1.07 to 1.2 per 1000 person-years and 1.54 to 1.7 per 1000 population and increased with age (14 per 1000 person-years in adults aged ≥65 years). Incidence was also higher in men than in women and in patients with chronic respiratory disease or HIV infection. Lifestyle factors associated with an increased risk of CAP included smoking, alcohol abuse, being underweight, having regular contact with children and poor dental hygiene. The presence of comorbid conditions, including chronic respiratory and cardiovascular diseases, cerebrovascular disease, Parkinson's disease, epilepsy, dementia, dysphagia, HIV or chronic renal or liver disease all increased the risk of CAP by twofold to fourfold.

Conclusion A range of lifestyle factors and underlying medical conditions are associated with an increased risk of CAP in European adults. Understanding of the types of individual at greatest risk of CAP can help to ensure that interventions to reduce the risk of infection and burden of disease are targeted appropriately.

INTRODUCTION

Community-acquired pneumonia (CAP) is a cause of considerable morbidity and mortality in adults in developed countries, leading to high rates of hospitalisations, especially in the elderly.[1 2] The 2010 Global Burden of Disease Study reported that lower respiratory tract infections, including pneumonia, are the fourth most common cause of death globally, exceeded only by ischaemic heart disease, strokes and chronic obstructive pulmonary disease (COPD), and they are the second most frequent reason for years of life lost.[3] Within Europe, CAP is the leading cause of death due to infection,[2] with approximately 90% of deaths due to pneumonia occurring in people aged >65 years.[4] Pneumonia places a considerable burden on healthcare resources and society, with associated annual costs in Europe estimated at approximately €10 billion, mainly due to hospitalisation and lost working days.[5]

Several risk factors for CAP are recognised, including age >65 years,[1 6 7] smoking,[6] alcoholism,[7] immunosuppressive conditions,[7] and conditions such as COPD,[8] cardiovascular disease, cerebrovascular disease, chronic liver or renal disease, diabetes mellitus and dementia.[9] Although many European studies have reported on the incidence of CAP and associated risk factors, no comprehensive overviews of these data are currently available. This literature review was conducted to generate up-to-date information on the incidence of CAP in adults in Europe, and of the risk factors for contracting CAP. A secondary objective was to collect data on the rates of comorbidities in patients with CAP.

METHODS

The PubMed database was searched using the following search string: pneumonia AND English AND 2005/01/01–2012/07/31 AND risk NOT clinical trial, phase i OR clinical trial, phase ii OR clinical trial, phase iii OR controlled clinical trial OR randomised controlled trial OR case reports OR practice guideline OR editorial OR review OR cost OR cost effectiveness OR efficacy OR immunogenicity OR economic OR nosocomial. Additional searches used the same search string, but replaced 'risk' with either 'comorbidity' or 'co-morbidity'.

Papers were included if they reported observational studies performed in Western European countries (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, The Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, UK) and presented data from individuals aged >15 years on any of the following: incidence of CAP in at-risk individuals, defined as those with underlying risk factors for contracting CAP (table 1); risk factors for CAP; comorbidities in patients with CAP; pharmacotherapeutic agents associated with an increase or decrease in the risk of CAP; pathogens identified in patients with CAP. Studies that focused on nosocomial or healthcare acquired pneumonia were excluded.

Included papers were reviewed in full and data on the study setting and methodology, characteristics of the study population, incidence of CAP, risk factors for CAP (ORs or relative risks (RRs), and 95% CIs) reported in case-control studies, and observational data on rates of comorbidities, associated pharmacotherapies and pathogens were collected. If more than one paper reported different aspects of the same study, all relevant papers were included. Where the same data were reported in more than one paper, the earliest published paper was selected.

Analysis of the included papers was descriptive and no meta-analyses of data were performed. Unless otherwise stated, all data are reported as OR (95% CI) or RR (95% CI).

RESULTS

Included studies

Of the 3330 references identified, 3240 were excluded on the basis of the title or abstract. The

Table 1 Risk categories for community-acquired pneumonia included in the review

Immunocompetent at risk	Immunocompromised at risk
▶ Age ▶ Lifestyle – Alcoholism – Smoking ▶ Underlying diseases – Chronic heart disease – Chronic renal disease – Chronic liver disease – Chronic respiratory disease – Metabolic disease – CNS disease ▶ Prior IPD ▶ Previous pneumonia ▶ Other – Aspiration – Concomitant treatment	▶ Immunosuppression – Autoimmune diseases receiving steroid or immunosuppressive therapy or biological therapy – Cancer with immunosuppressive treatment – Waiting list for solid-organ transplantation (with or without immunosuppressive treatment) – Other immunosuppression ▶ Immunocompromised – Asplenia/splenic dysfunction – Primary immunodeficiencies ▶ HIV

CNS, central nervous system; IPD invasive pneumococcal disease.

authors identified one additional reference[10] that did not include the terms 'risk' or 'co-morbidity'/'comorbidity' in the title or abstract and was therefore not identified in the PubMed searches. However, it satisfied the other inclusion criteria. Final screening of the full papers identified 61 references meeting the inclusion and exclusion criteria, of which one paper[11] was later excluded due to data discrepancies that we were unable to resolve by correspondence with the author (figure 1).

Of the 60 publications, a majority (34) focused on hospitalised patients. Included studies were from Denmark (n=7), France (n=5), Germany (n=5), Greece (n=1), Italy (n=4), The Netherlands (n=3), Spain (n=23) and the UK (n=12). Study designs and populations are summarised in online supplementary table S1. Most studies included adults of all ages. However, five studies considered only patients aged ≥65 years,[12–16] two included patients aged 50–65 years,[17 18] two included patients aged ≥45 years[19 20] and single studies included patients aged ≥30 years,[21] ≥40 years[22] or 16–40 years.[23] Six studies included only patients infected with HIV.[24–29]

Most studies included patients with pneumonia of any aetiology, but six were performed in patients with pneumonia due to a specified bacterial agent: four studies in patients with *Legionella pneumophila* infection,[30–33] and one each in patients with *Haemophilus influenzae*[34] or Gram-negative bacteria[35] infections.

Incidence of CAP

The incidence of CAP was reported in 16 studies, from Denmark (n=2),[17 18] France (n=3),[24 26 29] Germany (n=1),[36] Italy (n=2),[27 37] Spain (n=5)[16 25 38–40] and the UK (n=3).[19 41 42] Data are summarised in table 2, with more details available in online supplementary table S2.

Differences in study populations and measures used for incidence rates make it difficult to make direct comparisons across studies. Nevertheless, several trends were apparent. The overall annual incidence of CAP in adults ranged between 1.07 to 1.2 per 1000 person-years and 1.54 to 1.7 per 1000 population[37 38 42 43] (table 2). Rates of hospitalisation for CAP

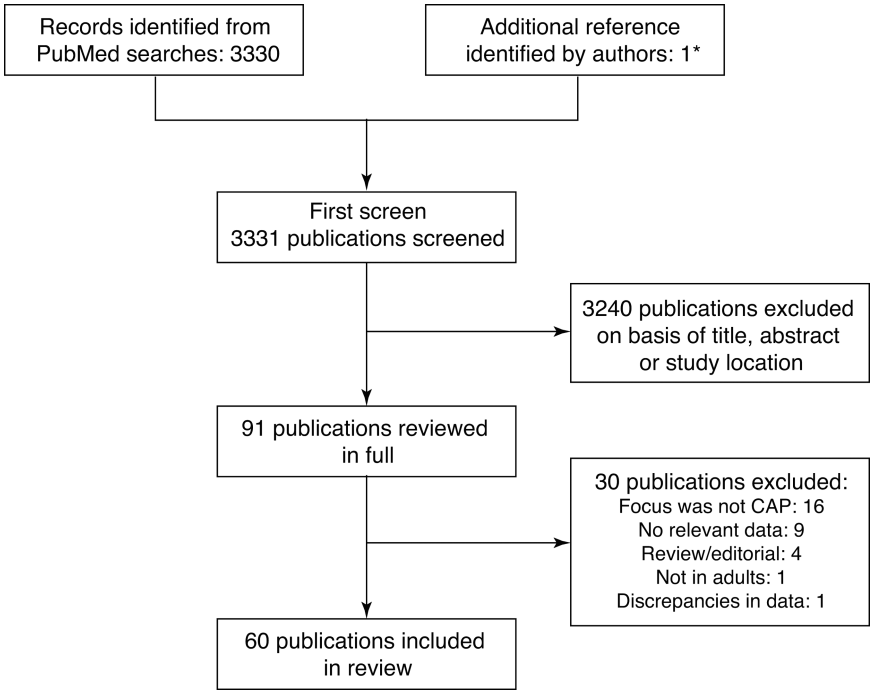

Figure 1 Summary of the study selection procedure. CAP, community acquired pneumonia. *One study did not include the terms 'risk' or 'co-morbidity'/'comorbidity' in either the title or abstract and so was not identified in the PubMed searches; however, 'risk factors' was included in the list of MeSH terms for the article.

Table 2 Incidence of community-acquired pneumonia (CAP) in adults in Europe

Study	Country; region	Study period	CAP incidence (95% CI)
Overall population			
Almirall *et al*[38]	Spain; east coast	1 November 1999–30 November 2000	Per 1000 population >14 years: 1.54
Gutierrez *et al*[39]	Spain; Alicante	15 October 1999–14 October 2001	Per 1000 person-years: Overall, 1.230 Men, 1.556 Women, 0.911
Rodriguez *et al*[42]	UK; national	1 January 2000–31 December 2005	Primary care patients, per 1000 person-years: Overall, 1.07 (1.04 to 1.09) Women, 0.93 (0.89 to 0.96) Men, 1.22 (1.18 to 1.26)
Viegi *et al*[37]*	Italy; national	15 February 1999–14 February 2000	Annual incidence per 1000 population: Overall, 1.703 Males, 1.692 Females, 1.713
Vila-Corcoles *et al*[16]	Spain; Tarragona	1 January 2002–30 April 2005	Age ≥65 years, per 1000 person-years: Overall, 14.0 (12.7 to 15.3) Men, 19.2 (17.1 to 21.6) Women, 10.0 (8.6 to 11.5)
Hospitalisation for CAP			
Bewick *et al*[41]	UK; Nottingham	September 2008–September 2010	Per 1000 population ≥16 years: Overall, 1.097
Ewig *et al*[36]	Germany; national	2005 and 2006	Per 1000 population/year ≥18 years: 2005, 2.75 2006, 2.96 Mean incidence: Men, 3.21 Women, 2.52
Kornum *et al*[17]	Denmark; Copenhagen and Aarhus	December 1993–April 2008	Per 1000 person-years, >50 years: Men, 4.2 Women, 3.4
Kornum *et al*[18]	Denmark; Copenhagen and Aarhus	December 1993–April 2008	Per 1000 person-years, >50 years: Men, 4.25 Women, 3.28
Patients with COPD			
Müllerova *et al*[19]	UK; England and Wales	1 January 1996–31 December 2005	Per 1000 patient-years: Overall, 22.4 (21.7 to 23.2) Women, 21.4 (20.4 to 22.5) Men, 23.1 (22.1 to 24.2)
Immunocompromised individuals			
Perez-Sola *et al*[40]†	Spain; national	February 2000–January 2006	Patients with rheumatic diseases treated with TNF antagonists, per 1000 patient-years: 5.97 (4.87 to 7.25)
HIV-infected individuals			
Bénard *et al*[24]	France; Aquitaine	2000–2007	Per 1000 patient-years: Overall: 12.0 (9.9 to 14.0)
Curran *et al*[25]	Spain; Barcelona	January 2000–December 2005	Cases/1000 patients/year: 2000, 30.90 2001, 31.80 2002, 25.70 2003, 21.90 2004, 20.50 2005, 24.00
Le Moing *et al*[26]	France; national	May 1997–December 2001	Hospitalisation for first episode of bacterial pneumonia in protease inhibitor-treated patients: 8/1000 patient-years (3–13)
Madeddu *et al*[27]‡	Italy; northern Sardinia	January 1999–December 2004	Per 1000 inpatients/year: 1999, 177 2004, 280
Saindou *et al*[29]	France; Lyon	1993–2004	Pneumococcal pneumonia, per 1000 patient-years: Cohort followed 1993–1 July 1996 (pre-HAART), 10.6 (5.4 to 15.7) Cohort followed before 1 July 1996–2004 (pre-HAART and HAART era), 1.5 (0.9 to 2.1) Cohort followed 1 July 1996–2004 (HAART era), 2.5 (1.4 to 3.6)

Incidence rates standardised per 1000 population or per 1000 person-years; original study data are available in online supplementary table S2.
*This study included data for 10 children aged <14 years.
†In this study, 'pneumonia' included fungal and viral aetiologies.
‡A majority of patients (84%) in this study were also intravenous drug users.
COPD, chronic obstructive pulmonary disease; HAART, highly active antiretroviral therapy; TNF, tumour necrosis factor.

were typically higher than overall incidence rates; for example, a German study[36] reported rates of 2.75 and 2.96 per 1000 population/year aged ≥18 years in 2005 and 2006, respectively (table 2). Overall CAP incidence and hospitalisation for CAP were higher in men than in women. The overall incidence per 1000 person-years in a UK study was 1.22 (1.18 to 1.26) in men compared with 0.93 (0.89 to 0.96) in women,[42] whereas a study in Denmark in men and women aged >50 years reported rates of hospitalisation for pneumonia per 1000 person-years of 4.2 in men and 3.4 in women.[17]

The incidence of CAP increased with age and with the presence of comorbidities (see online supplementary table S2). Among individuals aged ≥65 years in Spain, the incidence per 1000 person-years was 14.0 (12.7 to 15.3).[16] A study of patients with COPD reported the highest overall incidence of 22.4 (21.7 to 23.2) per 1000 person-years, with rates of 23.1 (22.1 to 24.2) and 21.4 (20.4 to 22.5) in men and women, respectively.[19]

High incidence rates were also reported in immunocompromised patients (table 2). Among patients with rheumatic diseases in Spain treated with tumour necrosis factor antagonists, the incidence per 1000 patient-years was 5.97 (4.87 to 7.25).[40] The incidence in patients with HIV in France, was 12.0 (9.9 to 14.0) per 1000 patient-years.[24] However, highly active antiretroviral therapy (HAART) appears to reduce the risk of CAP, with another French study reporting a reduction from 10.6 (5.4 to 15.7) per 1000 patient-years in the pre-HAART era to 2.5 (1.4 to 3.6) in the post-HAART era.[29]

Lifestyle factors and risk of CAP

The potential association between lifestyle factors and the risk of CAP was investigated in 12 case-control studies, performed in France (n=1),[30] Germany (n=1),[44] The Netherlands (n=1),[23 45] Spain (n=2)[12 38] and the UK (n=7).[19–22 42 46 47] Study details are summarised in online supplementary table S3.

There was consistent evidence that smoking was associated with an increased risk of CAP.[19–23 38 42 46 47] Compared with non-smokers (OR 1.00), the risk of CAP was increased in current smokers (crude ORs: 1.37 (1.14 to 1.64) to 1.81 (1.53 to 2.15); adjusted ORs: 0.99 (0.86 to 1.14) to 2.00 (1.20 to 3.36)) and former smokers (crude ORs: 1.34 (1.11 to 1.62) to 1.40 (1.17 to 1.68); adjusted OR: 1.04 (0.90 to 1.2)).

Compared with individuals who consumed no alcohol (OR 1.00), consumption of ≤40 g alcohol daily appeared to protect against CAP (21–40 g/day, crude ORs: 0.53 (0.22 to 1.25) and 0.88 (0.63 to 1.22)).[23 38] However, the risk increased in individuals with higher consumption (>41 g/day, crude OR: 1.59 (0.59 to 4.25)[23]; >80 g/day, crude OR: 2.34 (1.13 to 4.85)[38]) or with a history of alcohol abuse/alcoholism (crude ORs: 1.85 (1.19 to 2.88)[21] and 1.62 (0.91 to 2.91)[47]).

Being underweight was generally associated with an increased risk of CAP (crude ORs: 1.04 (0.57 to 1.89) to 2.20 (1.57 to 3.09)[23 38 44 47]) compared with normal bodyweight (OR 1.00). A reduced risk was seen in individuals classified as overweight (crude ORs: 0.6 (0.5 to 0.7) to 0.89 (0.72 to 1.09)[21 23 38 44 47]; adjusted ORs: 0.6 (0.5 to 0.7)[44] and 0.78 (0.67 to 0.90)[19]), whereas those classified as obese had either a lower risk (crude ORs: 0.66 (0.58 to 0.75) to 0.81 (0.66 to 0.99)[21 38 44 47]; adjusted ORs: 0.7 (0.5 to 0.9)[44] and 0.71 (0.60 to 0.85)[19]) or the same risk (crude OR 1.04 (0.57 to 1.89)[23]) as those of normal weight.

Household arrangements were also associated with the risk of CAP. Living in a household of over 10 people was associated with a crude OR of 2.20 (1.21 to 4.00).[38] Regular contacts with children also increased the risk of CAP (crude OR: 1.48 (1.26 to 1.75)[38]). Two studies found that having children in the household increased the adjusted OR from 1.00 for 'no children' to 3.2 (1.5 to 7.0)[44] or 3.41 (1.57 to 7.41)[23] for three or more children. There was no clear evidence regarding the influence of contact with pets; one study demonstrated an increased risk of CAP (crude OR 1.37 (1.18 to 1.60)[38]), whereas a study in young adults (aged 16–40 years) found a decreased risk (crude OR 0.85 (0.58 to 1.24)[23]).

Higher levels of education were associated with a lower risk of CAP.[23 38 44] Compared with individuals with a low level of education (OR 1.00), risk declined in those with an intermediate (secondary; crude ORs: 0.69 (0.41 to 1.19) to 0.86 (0.72 to 1.01)) or high level (university; crude ORs: 0.67 (0.41 to 1.10) to 0.78 (0.64 to 0.96)).[23 38] In another study, individuals with ≥12 years of education had a lower risk of CAP (adjusted OR 0.8 (0.6 to 1.1)) compared with those who had ≤9 years of education (OR 1.00).[44]

Two studies found that visiting the dentist was associated with a decreased risk of CAP (in the past month, crude OR 0.71 (0.55 to 0.92)[38]; in the past year, OR 0.59 (0.34 to 1.04)[23]). In contrast, one study found that frequent visits to the general practitioner in the previous year were associated with a substantial increase in the risk of CAP (1–4 visits, OR 1.00; ≥30 visits, crude OR 3.73 (3.14 to 4.42)).[21]

Comorbid conditions and risk of CAP

The association between comorbidities and the risk of CAP was investigated in 14 case-control studies (Denmark (n=1),[48] Germany (n=1),[44] The Netherlands (n=1),[23] Spain (n=2)[12 38] and the UK (n=9)[14 19–22 42 46 47 49] (see online supplementary table S4).

A history of respiratory disease was associated with an increased risk of CAP. A history of pneumonia increased the risk of a subsequent episode (crude ORs: 2.39 to 6.25 (1.83 to 21.40)[22 38 44]). Patients with chronic respiratory diseases, including COPD, bronchitis or asthma, had a twofold to fourfold increase in the risk of CAP (crude ORs: 2.17 (1.99 to 2.37) to 3.92 (3.67 to 4.18)[12 14 21–23 38 44 46 47]). Additional data also support this association. One study reported an adjusted OR of 2.47 (2.37 to 2.58) for chronic respiratory disease,[20] and another study reported adjusted RRs of 2.82 (2.45 to 3.24) for COPD and 1.58 (1.44 to 1.74) for asthma.[42] Patients with at least one respiratory tract infection in the past year were also at increased risk of CAP (crude ORs: 1.57 (1.35 to 1.84)[38] to 4.5 (3.7 to 5.4)[44]). In young adults, the risk of CAP increased in line with the number of infections over the previous 6 years (1–2 infections, adjusted OR 1.49 (0.87 to 2.56); >3 infections, adjusted OR 4.84 (1.24 to 18.9)).[23]

Chronic cardiovascular disease increased the risk of CAP up to threefold (crude ORs from 1.4 (1.2 to 1.5) to 3.2 (2.6 to 4.1)[12 21 22 38 44 46 47 49]). Additional studies supported an association between chronic heart disease (adjusted ORs: 1.63 (1.54 to 1.72)[46] and 1.66 (1.59 to 1.73)[20]) or heart failure (adjusted ORs: 2.19 (0.69 to 6.95)[12] and 1.37 (1.20 to 1.57)[19]; adjusted RR: 2.63 (2.21 to 3.14)[42]) and the risk of CAP.

Cerebrovascular disease/stroke and dementia approximately doubled the risk of CAP (for cerebrovascular disease/stroke, crude ORs: 1.86 (1.74 to 1.99) to 2.37 (2.19 to 2.57),[14 21 46 49] adjusted ORs: 1.08 (0.93 to 1.26)[19] and 1.68 (1.58 to 1.77),[20] adjusted RR: 1.42 (1.25 to 1.61)[42] for dementia, crude ORs: 2.12 (0.91 to 4.94) to 2.41 (2.11 to 2.75),[14 38 46] adjusted ORs: 2.64 (1.86 to 3.75)[19] and 2.68 (2.42 to 2.97)[20]). Other neurological or psychiatric conditions were also associated with an

increased risk of CAP in some studies (epilepsy, crude ORs: 2.81 (1.83 to 4.30) and 2.83 (1.11 to 7.21)[21 38]; Parkinson's disease, crude ORs: 1.82 (1.52 to 2.19) and 1.87 (1.60 to 2.19)[14 46]; multiple sclerosis, crude OR 3.20 (2.40 to 4.26)[46]). Crude ORs for CAP in patients with depression or bipolar disorder ranged from 1.75 (1.65 to 1.86) to 2.54 (1.03 to 6.26).[14 21 23] However, the association with depression may have been confounded by other factors, as other studies reported an adjusted OR of 1.13 (0.99 to 1.28)[19] or an adjusted RR of 1.30 (1.19 to 1.40).[42]

Two studies in elderly patients found a strong association between dysphagia and risk of CAP. A large database study in patients aged ≥65 years reported a crude OR of 2.10 (1.85 to 2.38),[14] whereas a small study in patients aged ≥70 years reported a crude OR of 16.3 (4.57 to 58.2) and an adjusted OR of 11.9 (3.03 to 46.9).[12]

Data from several studies suggested that diabetes mellitus was associated with a moderate increase in the risk of CAP (crude ORs: 1.43 (1.11 to 1.92) to 1.54 (1.44 to 1.65),[21 38 46] adjusted ORs: 1.07 (0.89 to 1.28)[19] and 1.33 (1.26 to 1.41),[20] adjusted RRs: 1.26 (1.21 to 1.31)[48] and 1.28 (1.13 to 1.44)[42]).

Cancer was also associated with a moderate increase in the risk of CAP (crude ORs: 1.42 (1.04 to 1.92)[38] and 1.70 (1.58 to 1.82),[46] adjusted ORs: 1.42 (1.3 to 1.56)[46] and 1.36 (1.24 to 1.49),[20] adjusted RR: 1.37 (1.22 to 1.54)[42]). One study reported a fivefold higher risk in patients with lung cancer (crude OR: 4.73 (3.58 to 6.25)).[46]

Chronic liver or renal disease increased the risk of CAP approximately twofold (chronic liver disease, crude ORs: 1.67 (0.99 to 2.82) to 2.24 (1.74 to 2.89),[38 44 46] adjusted ORs: 1.87 (1.43 to 2.44)[46] and 1.85 (1.48 to 2.31)[20]; chronic renal disease, crude ORs: 1.7 (1.1 to 2.8)[44] and 2.15 (1.81 to 2.56),[46] adjusted ORs: 1.72 (1.43 to 2.07)[46] and 1.78 (1.53 to 2.07)[20]).

Associations between conditions affecting immune function and the risk of CAP were reported. There was a moderate increase in risk in patients with rheumatoid arthritis (crude ORs: 1.46 (1.14 to 1.88)[21] and 2.02 (1.79 to 2.29),[46] adjusted ORs: 1.84 (1.62 to 2.10)[46] and 1.83 (1.64 to 2.03),[20] adjusted RR: 1.37 (1.12 to 1.69)[42]). Additionally, there was over a twofold increase in risk in patients with asplenia (adjusted OR: 2.58 (1.80 to 3.71)[46]) or with HIV or AIDS (adjusted ORs: 2.48 (1.34 to 4.58)[46] and 5.90 (2.55 to 13.64)[20]).

In addition to the above medical conditions, a moderate increase in risk of CAP was reported in patients with anaemia (adjusted RR: 1.43 (1.25 to 1.62)).[42]

Hospitalisation in the previous 5 years was associated with an increased risk of CAP (crude ORs: 1.6 (1.4 to 1.9)[44] and 1.68 (1.44 to 1.96)[38]). An adjusted RR of 1.77 (1.59 to 1.97) was calculated in patients with more than one hospitalisation in the previous year.[42] The risk of CAP was increased in patients who had undergone either bronchoscopy (crude OR: 2.09 (1.07 to 4.06)) or passage of a nasogastric tube (crude OR: 3.21 (1.17 to 8.77)) during the previous year.[38]

Comorbid conditions in patients with CAP

The frequency of comorbidities in patients diagnosed with CAP was presented in 39 studies (7 case-control studies of observational data,[15 19 45 50–53] and 31 observational, cohort studies[10 13 16 27 28 31–37 41 43 54–70]). Study details are summarised in online supplementary table S5.

The most common comorbidities were chronic respiratory diseases (up to 68% of patients), chronic heart disease (up to 47%) or heart failure (up to 46%), diabetes mellitus, cerebrovascular diseases and dementia (all up to 33%; table 3). Chronic liver and chronic renal diseases were observed in up to 20% and 27% of patients, respectively. The frequency of comorbidities was generally higher in patients aged ≥65 years compared with those aged <65 years, and in patients with COPD, chronic renal failure or cirrhosis compared with those without such conditions (see online supplementary table S5).

Table 3 Frequency of comorbid conditions in adults with community-acquired pneumonia

Comorbid condition	Number of cohorts with data*	Patients with condition (%)
Previous pneumonia	10	3.2–33.8
Chronic respiratory disease	25	9.7–68
COPD	21	9.4–62
Asthma	9	3–50.0
Chronic heart disease	23	10–47.2
Heart failure	27	1.0–46
Diabetes mellitus	48	4.9–33.0
Cerebrovascular disease/ stroke	26	3.2–33
Dementia	12	1.1–33.6
Cancer	33	4.3–18.0
Chronic liver disease	36	0.3–20
Chronic renal disease	39	0.5–26.7

*For studies that only reported data separately for each cohort, all cohorts were included; for studies that reported data for the overall study population, the summary data were used.
COPD, chronic obstructive pulmonary disease.

DISCUSSION

This review represents a comprehensive compilation of data about the incidence of and risk factors for CAP in adults in Western Europe.

Notwithstanding the heterogeneity of the populations studied and measures of incidence rates used, overall the annual incidence was 1.07–1.7 per 1000 population. Studies consistently showed that the incidence was higher in men than in women, and that it increased with age; in patients aged ≥65 years, an incidence rate of 14 cases per 1000 person-years was reported.[16] These findings are consistent with those of a recent review of European incidence rates published between 1990 and 2007.[1] Also in line with previous studies of CAP epidemiology, incidence rates were higher in patients with comorbidities such as COPD,[8] and in patients with HIV compared with those without HIV.[71] Possible explanations for the higher rates of hospitalisation for CAP compared with overall incidence rates include the inclusion of data from different countries (Italy,[37] Spain[38 43] and the UK[42] for overall incidence rates; Denmark,[17 18] Germany[36] and the UK[41] for hospitalisation) reflecting national differences in medical practice, and that Danish studies were performed in patients aged >50 years,[17 18] and so represent a population at increased risk of CAP.[1 2]

Importantly, this review included data obtained from observational and case-control studies. While observational studies provide valuable data on the rates of comorbidities observed in patients with CAP, they do not permit their identification as risk factors for infection. However, case-control studies of patients allow us to establish which comorbidities are indeed risk factors for CAP.

Pooled data from observational studies demonstrated the overall burden of CAP in patients with other medical conditions.[10 13 16 27 28 31–37 41 43 54–70] Chronic respiratory diseases,

cardiovascular diseases, cerebrovascular diseases, dementia and diabetes mellitus were the most frequently observed comorbidities. Up to two-thirds of patients had a chronic respiratory disease and almost half had a chronic cardiovascular disease, highlighting the need for appropriate management of these patients to reduce their risk of CAP.

Lifestyle factors such as smoking, high alcohol intake, being underweight, living in a large household or having regular contact with children were associated with an increased risk of CAP.[12 19–23 30 38 42 44 46 47] Smoking is an established risk factor for CAP,[6 72] probably due to its adverse effects on the respiratory epithelium and the clearance of bacteria from the respiratory tract.[73] Alcoholism has been associated with defects in innate and adaptive immunity,[74] and is a recognised CAP risk factor.[7] Smoking and excessive alcohol consumption are major health risks globally and are targets for interventions to reduce the global burden of disease.[75] Ensuring that patients make appropriate lifestyle changes would help to reduce the overall burden of CAP. Being underweight may predispose patients to CAP due to the consequences of undernutrition or underlying conditions on immune function.[6 44 72 76] Assessment of the nutritional status of vulnerable patients might help to identify those at increased risk of CAP. Regular contact with children has also been identified previously as a risk factor for CAP, possibly due to the high carriage of *Streptococcus pneumoniae* by children.[44 77] Appropriate measures for infection control may be advisable in vulnerable patients who are in regular contact with children.

Some lifestyle factors may provide protection against CAP. Young adults who consumed <40 g of alcohol per day had a lower risk of CAP than those who drank no alcohol,[23] potentially because individuals who consumed no alcohol had other comorbidities that increased the risk of CAP. However, light-to-moderate alcohol intake has been reported to reduce the risk of atherosclerosis and cardiovascular disease,[78 79] due to the antioxidant activities of alcohol,[78] and this may also protect against CAP. Adherence to good dental hygiene was also associated with a reduced risk of CAP. Poor oral care has previously been identified as a risk factor for nursing-home acquired pneumonia, possibly due to the colonisation of the oral cavity by respiratory pathogens,[80] and this risk may also be relevant for CAP. Finally, a higher level of education appeared to reduce the risk of CAP compared with a low level of education, as reported previously for invasive pneumococcal disease.[81] A similar protective association of higher educational levels has also been described in relation to cardiovascular risk factors.[82] Measures to reduce social and health inequalities could have the benefit of reducing costs associated with diseases like CAP.

The review also provides robust evidence that several comorbidities are associated with an increased risk of CAP, including a history of respiratory disease (including pneumonia) and cardiovascular disease. Patients with COPD are recognised as having a high risk of CAP[8] and are targets for vaccination against influenza and pneumococcal disease,[83 84] as are patients with chronic cardiovascular diseases.[84–86]

Patients with cerebrovascular disease or stroke, and neurological disorders (dementia, epilepsy, Parkinson's disease and multiple sclerosis) had approximately twice the risk of CAP compared with individuals without these conditions; dysphagia was also associated with a substantial increase in risk. The use of sedative medications and problems with swallowing might contribute to the risk of CAP in patients with dementia,[19 43] probably due to aspiration and its associated risk of pneumonia.[87] This could apply to patients with other neurological disorders.

Other comorbid conditions associated with an increased risk of CAP in the present study, including diabetes mellitus, cancer, chronic liver or renal disease, and impaired immune function, have previously been identified as risk factors for CAP.[9]

The main strength of this review is that many of the included publications were of case-control studies performed in large numbers of patients from registries or primary care databases, rather than small, single-centre studies, providing reassurance that the included studies provide a good representation of CAP in European populations.

This review also has some limitations. Patient registries and primary care databases are dependent on the quality of the information included in the records, and rely on the accuracy of the individuals responsible for entering diagnostic codes and demographic data. However, the inclusion of several thousand patients in such studies should help to minimise any potential introduced bias. Most of the included studies were based on patient populations in either Spain (23 studies[10 12 13 16 25 32 33 35 38–40 43 50 54–59 63 65 68 69]) or the UK (12 studies[14 19–22 41 42 46 47 49 53 66]), and this could limit the validity of the review for extrapolating the data to other European populations. Only those studies that were indexed in the PubMed database were included, and data from, for example, national surveillance databases were not included. Nevertheless, we believe it provides a good representation of the incidence and risk factors for CAP in European countries.

Lifestyle interventions, such as stopping smoking, reducing alcohol consumption, having regular dental checks and

Table 4 Bundles for lifestyle interventions to reduce the risk of CAP in adults

Risk factor	Evidence	Recommendation
Smoking	Risk of CAP increased in current and former smokers (9 studies)[19–23 38 42 46 47]	Smoking cessation
Alcohol consumption	Risk of CAP increased with high consumption or history of alcohol abuse (4 studies)[21 23 38 47]	Reduce alcohol consumption
Nutritional status	Being underweight was generally associated with an increased risk of CAP (4 studies)[23 38 44 47]	Dietary advice to ensure good nutritional status
Contact with children	Regular contact with children increased the risk of CAP (3 studies)[23 38 44]	Avoid contacts with children with lower respiratory tract infections
Dental hygiene	Risk of CAP decreased in individuals with a recent (within past year) dental visit (2 studies)[23 38]	Ensure regular dental visits
Vaccination against influenza and *Streptococcus pneumoniae*	Current guidelines[88 89]	Ensure compliance with guidelines

CAP, community-acquired pneumonia.

maintaining good nutritional status could help to reduce the burden of CAP. Patients with conditions such as chronic respiratory, cardiovascular and neurological diseases should be managed in accordance with current clinical guidelines to optimise their overall health status, and elderly patients should try to minimise contact with children who have acute viral respiratory infections. Finally, adults at risk of CAP should be vaccinated against influenza and pneumococcal pneumonia to reduce the risk of lower respiratory tract infections, in accordance with current guidelines (table 4).[88 89]

All but six of the studies included patients with pneumonia of any aetiology. *S pneumoniae* is the most frequently isolated pathogen from patients with CAP in Europe,[1] and has been estimated to be the cause of 30–50% cases of CAP requiring hospitalisation in adults in developed countries.[90] A 23-valent pneumococcal polysaccharide vaccine is recommended in some countries for the routine vaccination of adults aged ≥65 years, and for patients at increased risk of CAP.[85 86] However, there is little evidence that it is effective in elderly people or adults with chronic diseases.[91 92] A 13-valent pneumococcal conjugate vaccine (PCV-13) is available for the prevention of pneumonia and invasive pneumococcal disease caused by PCV-13 serotypes in adults aged ≥18 years.[93] Efficacy of PCV-13 for the prevention of a first episode of vaccine serotype-specific pneumococcal CAP in community-dwelling adults aged ≥65 years is being investigated in the ongoing Community Acquired Pneumonia Immunisation Trial in Adults.[94]

In conclusion, this review of risk factors for CAP in European adults has highlighted the range of lifestyle factors and underlying medical conditions that are associated with an increased risk of infection. Lifestyle factors included smoking, alcohol abuse, being underweight and regular contact with children, whereas patients with chronic respiratory or cardiovascular diseases, cerebrovascular disease, epilepsy, dementia, dysphagia, HIV, or chronic renal or liver disease were all at increased risk of CAP. Greater understanding of the types of individuals at risk of CAP can help to ensure that interventions to reduce the risk of infection and burden of disease are targeted appropriately.

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Supplementary Table S1. Methodology and patient demographics of studies included in the review.

Reference	Country; region	Study method	Study period	Population	Age (yrs [mean±SD])	Definition of CAP
Almirall 2008 [36]	Spain; east coast	Multicentre, prospective, population-based, case–control study	1 Nov 1999–30 Nov 2000	Primary care patients >14 yrs Cases, n=1336 Controls, n=1326	Cases: Male, 58.6±19.8; Female, 54.6±20.7 Controls: Male, 58.9±19.6; Female, 54.6±20.6	Chest X-ray confirmed
Almirall 2010 [37]	Spain; east coast	Multicentre, prospective, regional, population-based, observational case–control study	1 Nov 1999–30 Nov 2000	Primary care patients >14 yrs with chronic bronchitis, COPD or asthma requiring inhaled therapy Cases, n=473 Controls, n=235	Cases, 59.6±20.0 Controls, 60.9±20.7	Chest X-ray confirmed
Almirall 2013 [12]	Spain; Mataró	Single-centre, prospective, observational, case–control study	Feb 2008–Feb 2010	Patients ≥70 yrs with CAP requiring hospitalisation Cases, n=36 Controls, n=72	Cases, mean±SEM 81.22±0.77 Controls, mean±SEM 81.21±0.53	Chest X-ray confirmed and bacteriological identification
Bénard 2010 [24]	France; Aquitaine	Multicentre, prospective, cohort study	2000–2007	Patients with HIV, n=3336; 135 with bacterial pneumonia	Median, 39.6 [IQR 34.5–46.0]	Chest X-ray confirmed and bacteriological identification or successful antibacterial treatment
Bewick 2012 [38]	UK; Nottingham	Two-centre, prospective, observational cohort study	Sept 2008–Sept 2010	Patients ≥16 yrs hospitalised with CAP, n=920 (5.5% nursing home residents); 366 with pneumococcal pneumonia (6.8% nursing home residents)	Median, 71.7 [IQR 57.8–80.8]	Chest X-ray confirmed
Cabre 2010 [13]	Spain; Mataró	Single-centre, prospective, observational study	Jan 2001–Aug 2005	Patients ≥70 yrs with CAP requiring hospitalisation, n=134 (32% nursing home residents)	84.51±6.8	Chest X-ray confirmed
Carratalà 2007 [39]	Spain; Barcelona	Single-centre, prospective, observational study	1 Jan 2001–31 Dec 2004	Adult patients with CAP requiring hospitalisation, n=601	63.7±17.1	Chest X-ray confirmed
Che 2008 [30]	France; metropolitan	Multicentre, prospective, population-based, case–	1 Sept 2002–31 Sept 2004	Patients with sporadic Legionnaires' disease	57 [range, 18–93]	Chest X-ray confirmed and laboratory evidence

Reference	Country; region	Study method	Study period	Population	Age (yrs [mean±SD])	Definition of CAP
		control study		Cases, n=546 Controls, n=546		of *Legionella pneumophila* infection
Chidiac 2012 [31]	France; metropolitan	Multicentre, prospective, observational, cohort study	1 April 2006–30 June 2007	Patients hospitalised with community-acquired Legionnaires' disease, n=540	60 [range, 17–100]	Chest X-ray confirmed and laboratory evidence of *Legionella pneumophila* infection
Cillóniz 2011 [40]	Spain; Barcelona	Single-centre, prospective, observational cohort study	Jan 2003–Dec 2010	Patients with CAP admitted to ICU, n=362	63.4±16.5	Chest X-ray confirmed
Cillóniz 2012 [41]	Spain; Barcelona	Single-centre, prospective, observational cohort study	2001–2009	Adult patients hospitalised with pneumococcal pneumonia, n=626	63.6±18.9 46% ≤65 yrs	Clinical symptoms, chest X-ray confirmed and microbiological data
Curran 2008 [25]	Spain; Barcelona	Single-centre, prospective, observational cohort study	Jan 2000–Dec 2005	HIV patients ≥18 yrs hospitalised with bacterial pneumonia, n=161; 186 episodes	39.7±7.8	Clinical symptoms, chest X-ray confirmed and response to antibacterial therapy
de Roux 2006 [10]	Spain; Barcelona	Single-centre, prospective, observational cohort study	Oct 1996–Nov 2001	Patients hospitalised with CAP, classified according to alcohol abuse status Current, n=128 Former, n=54 None, n=1165	Current alcohol abuse, 58±14 Former alcohol abuse, 71±11 No alcohol abuse, 68±19	Clinical symptoms, chest X-ray confirmed and microbiological data
Ewig 2009 [42]	Germany; national (BQS)	Retrospective, observational study	2005 and 2006	Patients hospitalised with CAP, n=388,406	2005, 71.94±16.86 2006, 72.09±17.00 [Median, 2005 & 2006, 76 (IQR, 2005, 20; 2006, 19)]	ICD-10 (German modification) codes
Falguera 2009 [43]	Spain; Catalonia	Two-centre, prospective, observational cohort study	Jan 1995–Dec 2005	Patients ≥18 yrs hospitalised with CAP, n=3272; 61 with Gram-negative infections; 3211 with non-Gram-negative infections	64 [range, 18–100] Gram-negative infections, 69 Non-Gram-negative infections, 63	Clinical symptoms, chest X-ray confirmed and microbiological data
Garcia-Vidal 2009 [44]	Spain; Barcelona	Single-centre, prospective, observational cohort study	1 Jan 1995–31 Dec 2005	Patients hospitalised with CAP, n=1556; 146 with recurrent CAP (≥2 episodes of CAP in 3 yrs with asymptomatic period ≥1 month); 1410 with non-recurrent CAP	Recurrent CAP, 70.96±13.824 Non-recurrent CAP, 65.03±16.573	Clinical symptoms, chest X-ray confirmed and microbiological data

Reference	Country; region	Study method	Study period	Population	Age (yrs [mean±SD])	Definition of CAP
Giannella 2012 [45]	Spain; national	Multicentre, prospective, observational cohort study	Jan & Jun 2010 (1 week in each month)	Patients ≥16 yrs treated for CAP in the internal medicine department, n=591	Median, 77 [IQR 65–84]	Clinical symptoms, chest X-ray confirmed
Gulmez 2007 [46]	Denmark; County of Funen	Retrospective, observational, case–control study	1 Jan 2000–31 Dec 2004	Patients with a discharge diagnosis of CAP Cases, n=7642 Controls, n=34,176	Cases, 55.5±31.2 Controls, 56.5±29.5	ICD-10 codes
*Gutierrez 2005 [47]	Spain; Alicante	Single-centre, prospective, observational, cohort study	15 Oct 1999–14 Oct 2001	Patients ≥15 yrs with CAP, n=493	56.6 [range, 15–94]	Clinical symptoms, chest X-ray confirmed and microbiological data
*Gutierrez 2006 [48]	Spain; Alicante	Single-centre, prospective, observational, cohort study	15 Oct 1999–14 Oct 2001	Patients ≥15 yrs with CAP, n=493	56.6 [range, 15–94]	Clinical symptoms, chest X-ray confirmed and microbiological data
Hennessy 2007 [14]	UK; England and Wales (GPRD)	Nested, retrospective, observational, case–control study	1987–2002	Patients ≥65 yrs hospitalised for pneumonia Cases, n=12,044 Controls, n=48,176	Cases: Median, 81 [IQR, 74–86] Controls: Median, 75 [IQR, 70–81]	Diagnostic codes (Read codes) within the UK GPRD
Holm 2007 [49]	Denmark; Odense	Multicentre, prospective, observational study	9 Sept–1 Nov 2002; 6 Jan–25 April 2003	Primary care patients ≥18 yrs with a diagnosis of community-acquired LRTI, n=364; 48 with pneumonia	Overall: median, 50 [range 18–94] Pneumonia: median, 61 [range 22–88]	GP diagnosis of LRTI; chest X-ray confirmed
Klapdor 2012 [50]	Germany; national (CAPNETZ)	Multicentre, prospective, observational study	Jan 2002–Jun 2009	Patients ≥18 yrs with CAP, n=7803; 4083 <65 yrs (2.6% nursing home residents); 3720 ≥65 yrs (14.4% nursing home residents)	Overall: 60.9±18.5 [range 18–101] <65 yrs: Median, 47.0 [IQR 20.7] ≥65 yrs: Median, 76.0 [IQR 11.8]	Clinical symptoms, chest X-ray confirmed and microbiological data
Kofteridis 2009 [34]	Greece; Crete	Single-centre, retrospective, observational study	Jan 1996–Dec 2002	Adults hospitalised with community-acquired LRTI due to *Haemophilus influenzae* n=45	Median, 68 [range, 28–86]	Clinical symptoms, chest X-ray confirmed, and positive sputum culture for *H. influenzae*
Kornum 2008 [51]	Denmark; North Jutland and Aarhus	Multicentre, retrospective, population-based, case–control study	1997–2005	Adults ≥15 yrs with discharge diagnoses of pneumonia, legionellosis and ornithosis	Cases: Median, 74; IQR 61–82 Controls: Median, 74; IQR 61–82	Hospital discharge diagnosis codes (ICD-10)

Reference	Country; region	Study method	Study period	Population	Age (yrs [mean±SD])	Definition of CAP
				Cases, n=34,239 Controls, 342,390		
++Kornum 2010 [17]	Denmark; Copenhagen and Aarhus	Multicentre, prospective, cohort study	Dec 1993–April 2008	Patients 50–64 yrs at enrolment hospitalised for pneumonia during median 11.8 yrs follow-up, n=48,551	Cases and controls Males: 50–54, 38% of cohort 55–59, 32% 60–64, 24% ≥65, 5% Females: 50–54, 36% 55–59, 32% 60–64, 26% ≥65, 6%	Hospital discharge diagnosis codes (ICD-10)
++Kornum 2012 [18]	Denmark; Copenhagen and Aarhus	Multicentre, prospective, cohort study	Dec 1993–April 2008	Patients 50–64 yrs at enrolment hospitalised for pneumonia during median 11.8 yrs follow-up, n=47,167	Median, 56 [5th–95th percentiles, 51–64]	Hospital discharge diagnosis codes (ICD-10)
Kothe 2008 [52]	Germany; national (CAPNETZ)	Multicentre, prospective, observational study	March 2003–Oct 2005	Patients with CAP, n=2647; 1298 <65 yrs (3.3% nursing home residents); 1349 ≥65 yrs (15.2% nursing home residents)	<65 yrs, 47.2±12.7 ≥65 yrs, 77.1±7.5	Clinical symptoms, chest X-ray confirmed and microbiological data
Le Moing 2006 [26]	France; national	Multicentre, prospective, observational cohort study	May 1997–Dec 2001	HIV patients receiving protease inhibitor therapy, n=1203; 29 hospitalised with pneumonia	Median, 36	Clinical symptoms, chest X-ray confirmed and microbiological data
Liapikou 2012 [53]	Spain; Barcelona	Single-centre, prospective, observational cohort study	2004–2008	Adult patients hospitalised with CAP, n=1379; 212 with COPD (5.7% nursing home residents); 1167 no COPD (10.2% nursing home residents)	Overall, 70±17 COPD, 73.4±8.8 No COPD, 69.4±17.9	Clinical symptoms, chest X-ray confirmed and microbiological data
Madeddu 2008 [27]	Italy; northern Sardinia	Single-centre, observational, retrospective analysis of consecutive patients	Jan 1999–Dec 2004	HIV patients hospitalised with CAP, n=76; 84 episodes	38.3±7.5 [range, 27–80]	Clinical symptoms, chest X-ray confirmed and microbiological data
**Manno 2009 [28]	Italy; Brescia	Single-centre, prospective, observational, cohort study	June 2000–Dec 2006	HIV patients hospitalised with CAP Patients with cirrhosis, n=29	Cirrhosis, 41.0±4.3 No cirrhosis, 37.3±6.2	Clinical symptoms, chest X-ray confirmed and microbiological data

Reference	Country; region	Study method	Study period	Population	Age (yrs [mean±SD])	Definition of CAP
				Patients without cirrhosis, n=73		
Migliorati 2006 [54]	Italy; Brescia	Single-centre, observational, retrospective analysis	Jan 2001–Dec 2002	Patients ≥15 yrs hospitalised with discharge diagnosis of pneumonia or pneumonia-related disease, n=148 (20% nursing home residents)	70.3±17.3	Chest X-ray confirmed
Molinos 2009 [55]	Spain; Asturias	Multicentre, prospective, observational study	April 2003–April 2004	Patients hospitalised with CAP, n=710; 244 with COPD; 466 no COPD (5% nursing home residents in both groups)	Overall, 67.14 [95% CI, 65.9–68.4] With COPD, 73.7 [95% CI, 72.5–74.9] No COPD, 63.6 [95% CI, 61.8–65.4]	Clinical symptoms, chest X-ray confirmed and microbiological data
Müllerova 2012 [19]	UK; England and Wales (GPRD)	Multicentre, population-based, retrospective, observational, cohort study	1 Jan 1996–31 Dec 2005	Patients ≥45 yrs with COPD, n=40,414	45–64, 37.1% of cohort 65–79, 49.9% ≥80, 13.3%	Diagnostic codes within the UK GPRD
		Multicentre, population-based, nested, case–control study in COPD patients	1 Jan 1996–31 Dec 2005	Patients ≥45 yrs with COPD; 1469 with CAP; 7345 without CAP	With CAP, 75.1±10.6 No CAP, 70.9±10.8	
Myint 2011 [56]	UK; national (2008 UK National COPD audit data)	Multicentre, retrospective, observational study	March–May 2008	Patients hospitalised with acute exacerbations of COPD, n=9338; 1505 with pneumonia (7% residential home residents); 7833 without pneumonia (5% residential home residents)	Overall, 73±10 With pneumonia: <65, 14% of cohort 65–74, 28% 75–84, 42% ≥85, 16% Without pneumonia: <65, 24% 65–74, 31% 75–84, 34% ≥85, 12%	Chest X-ray confirmed
Myles 2009 [22]	UK; national (THIN)	Multicentre, retrospective, population-based, nested case–control study	1 July 2001–1 July 2002	Primary care patients ≥40 yrs with pneumonia Cases, n=3709 Controls, n=22,174	Cases: 40–49, 10.6% of cohort 50–59, 15.9% 60–69, 16.6% 70–79, 24.3% ≥80, 32.8% Controls: 40–49, 10.6% 50–59, 16.0% 60–69, 16.6% 70–79, 24.3%	Database codes corresponding to ICD-9 codes

Reference	Country; region	Study method	Study period	Population	Age (yrs [mean±SD])	Definition of CAP
					≥80, 32.5%	
Nielsen 2012 [57]	Denmark; northern	Multicentre, retrospective, population-based, observational, case-control study	1 Jan 1997–12 Dec 2009	Patients ≥15 yrs hospitalised with CAP Cases, n=70,914 Controls, n=709,140	Median, 73 Cases and Controls: 15–39, 7.3% of cohort 40–64, 25.1% 65–79, 36.8% ≥80, 30.8%	ICD8/ICD10 classification
Perez-Sola 2011 [58]	Spain; national (BIOBADASER)	Multicentre, prospective, observational, cohort study	Feb 2000–Jan 2006	Patients with rheumatic diseases treated with TNF antagonists, n=6969; 101 with pneumonia	50±14	CDC criteria
Rodriguez 2009 [59]	UK; national (THIN)	Multicentre, cohort study with a nested case-control analysis using prospectively recorded data	1 Jan 2000–31 Dec 2005	Primary care patients 20–79 yrs with CAP Cases, n=7297 Controls, n=9993	Cases and Controls: 20–49, 27% of cohort 50–59, 17% 60–69, 23% 70–79, 32%	Read codes for diagnosis of pneumonia
Ruiz 2010 [35]	Spain; Basque country	Single-centre, prospective, observational, cohort study	Jan 1995–Dec 2007	Adults hospitalised with bacteraemic CAP due to Gram-negative bacteria, n=51	72.9±11.3	Clinical symptoms, chest X-ray confirmed
Saindou 2008 [29]	France; Lyon	Multicentre, prospective, observational, cohort study	1993–2004	Patients with HIV before and after introduction of HAART, n=4075	36.0±10.2	Clinical symptoms, chest X-ray confirmed and microbiological data
Sarkar 2008 [60]	UK; national (GPRD)	Multicentre, observational, cohort study with a nested case-control analysis using prospectively recorded data	May 1987–April 2002	Primary care patients ≥18 yrs with CAP Cases, n=80,066 Controls, n=799,872	Cases, 73.5±17.6 Controls, 49.5±18.3	Read codes for diagnosis of pneumonia
Schlienger 2007 [21]	UK; national (GPRD)	Multicentre, population-based, retrospective, nested case–control study	1 Jan 1995–30 April 2002	Primary care patients ≥30 yrs with CAP Cases, n=1253 Controls, n=4838	Cases: 30–39, 2.4% 40–49, 8.6% 50–59, 15.2% 60–69, 28.4% 70–79, 45.3% Controls: 30–39, 2.7% 40–49, 8.6% 50–59, 15.5% 60–69, 29.6% 70–79, 43.6%	Read codes for diagnosis of pneumonia
Schnoor 2007 [61]	Germany; national (CAPNETZ)	Multicentre, prospective, population-based, case–control study	1 June 2002–30 April 2005	Patients >18 yrs with CAP Cases, n=1137 (1.7%	Cases, 57.0±17.1 Controls, 57.5±17.2	Chest X-ray or clinical symptoms

Reference	Country; region	Study method	Study period	Population	Age (yrs [mean±SD])	Definition of CAP
				care home residents) Controls, n=1044 (1.3% care home residents)		
Sopena 2007 [32]	Spain; Barcelona	Single-centre, prospective, observational, cohort study	1994–2004	Adult patients hospitalised with community-acquired Legionnaires' disease, n=251; 138 sporadic cases; 113 outbreak cases	Sporadic cases, 56.6±15.5 Outbreak cases, 59.5±16.6	Laboratory evidence of acute infection with *Legionella pneumophila*
Sopena 2007 [33]	Spain; Barcelona	Single-centre, retrospective, observational, cohort study	1994–2004	Patients hospitalised with CAP due to *L. pneumophila,* n=158; 104 <65 yrs; 54 ≥65 yrs	<65, 65.9% of cohort ≥65, 34.1% ≥70, 13.9% ≥85, 1.9%	Laboratory evidence of infection with *L. pneumophila*
Teepe 2010 [23]	The Netherlands; Utrecht	Multicentre, prospective, population-based, case–control study	April 1999–Dec 2008	Primary care patients 16–40 yrs with CAP Cases, n=156 Controls, n=468	Cases, 34.3±4.4 Controls, 32.1±5.5	Chest X-ray or clinical symptoms
Thomsen 2008 [62]	Denmark; Aarhus and North Jutland	Multicentre, retrospective, population-based, observational, cohort study	1 Jan 1997–31 Dec 2004	Patients ≥15 yrs hospitalised with CAP, n=29,900; 1372 statin users; 28,528 statin non-users	Median, 73 [IQR 60–81] Statin users: 15–39, 0.4% 40–64, 30.8% 65–79, 56.9% ≥80, 12.0% Statin non-users: 15–39, 7.9% 40–64, 23.0% 65–79, 37.6% ≥80, 31.5%	Hospital discharge diagnosis
Trifiro 2010 [15]	The Netherlands; national (IPCI)	Multicentre, prospective, observational, population-based, nested case–control study	1 Jan 1996–31 Dec 2006	Patients ≥65 yrs with a first antipsychotic drug prescription, n=2560 Cases, n=258 Controls, n=1686	Cases, 83.6±7.4 Controls, 83.2±5.9	Database codes; chest X-ray or clinical symptoms
van de Garde 2006 [63]	The Netherlands; national (PHARMO)	Multicentre, prospective, observational, population-based, case–control study	1 Jan 1995–31 Dec 2000	Patients >18 yrs hospitalised with a discharge diagnosis of CAP Cases, n=1108 Controls, n=3817	Mean±SEM, 67±0.51 Cases: <40, 8.9% of cohort 40–49, 8.2% 50–59, 10.5% 60–69, 17.1% 70–79, 31.9%	Hospital discharge diagnosis (ICD-9 codes)

Reference	Country; region	Study method	Study period	Population	Age (yrs [mean±SD])	Definition of CAP
					80–89, 19.7% ≥90, 3.7% Controls: <40, 10.3% 40–49, 9.2% 50–59, 12.1% 60–69, 16.7% 70–79, 27.5% 80–89, 20.9% ≥90, 3.3%	
†van de Garde 2006 [64]	UK; England & Wales (GPRD)	Multicentre, retrospective, population-based, case–control study	1 June 1987–21 Jan 2001	Primary care patients ≥18 yrs with diabetes mellitus Cases, n=4719 Controls, n=15,322	Cases: <60, 11.1% of cohort 60–69, 16.6% 70–79, 32.5% 80–89, 34.4% ≥90, 5.4% Controls: <60, 11.6% 60–69, 20.0% 70–79, 37.0% 80–89, 28.9% ≥90, 2.5%	Read codes
†van de Garde 2007 [65]	UK; England & Wales (GPRD)	Multicentre, retrospective, population-based, case–control study	1 June 1987–21 Jan 2001	Primary care patients ≥18 yrs with diabetes mellitus Cases, n=4719 Controls, n=15,322	Cases: <60, 11.1% of cohort 60–69, 16.6% 70–79, 32.5% 80–89, 34.4% ≥90, 5.4% Controls: <60, 11.6% 60–69, 20.0% 70–79, 37.0% 80–89, 28.9% ≥90, 2.5%	Read codes
Viasus 2011 [66]	Spain; Barcelona	Single-centre, prospective, observational, cohort study	13 Feb 1995–30 April 2010	Adult patients with and without chronic renal disease, hospitalised with CAP, n=3800; 203 with renal disease (8.6% nursing home residents); 3597 with no renal disease (8.1% nursing home residents)	Renal disease: Median, 77 [IQR, 67–84] No renal disease: Median, 70 [IQR, 56–79]	Chest X-ray and clinical symptoms and microbiological data

Reference	Country; region	Study method	Study period	Population	Age (yrs [mean±SD])	Definition of CAP
Viasus 2011 [67]	Spain; Barcelona	Single centre, prospective, observational, cohort study	13 Feb 1995–31 Dec 2008	Patients with and without cirrhosis, hospitalised with CAP, n=3420; 90 with cirrhosis; 3330 with no cirrhosis	Cirrhosis, 61.8±13.0 No cirrhosis, 66.8±16.9	Chest X-ray and clinical symptoms
††Viegi 2006 [68]	Italy, national	Multicentre, prospective, observational, population-based study	15 Feb 1999–14 Feb 2000	Primary care patients with CAP, n=699; 548 diagnosed by GP (4.7% nursing home residents); 151 diagnosed by hospital (8.9% nursing home residents)	59.6±19.5 Patients diagnosed in community, 57.6±19.2 Patients diagnosed in hospital, 66.7±18.7 [10 patients in overall population were aged ≤14 yrs]	Chest X-ray and clinical symptoms
Vila-Corcoles 2009 [16]	Spain; Tarragona	Multicentre, prospective, observational, population-based, cohort study	1 Jan 2002–30 April 2005	Community-dwelling individuals ≥65 yrs, n=11,241	65–74, 55.2% of cohort 75–84, 34.3% ≥85, 10.5%	Chest X-ray and clinical symptoms
‡Vinogradova 2009 [69]	UK; national (QRESEARCH database)‡‡	Multicentre, retrospective, population-based, nested, case–control study	1 Jan 1996–31 Dec 2005	Primary care patients Cases, n=17,172 Controls, n=71,399	Cases: 0–4, 17.2% of cohort 5–14, 4.7% 15–44, 12.7% 45–64, 18.2% 65–74, 15.5% ≥75, 31.8% Controls: 0–4, 19.5% 5–14, 4.2% 15–44, 10.4% 45–64, 18.1% 65–74, 16.2% ≥75, 31.5%	Database codes (Read codes)
Vinogradova 2011 [20]	UK; national (QRESEARCH database)‡	Multicentre, retrospective, population-based, nested, case–control study	1 Jan 1996–31 Dec 2005	Primary care patients ≥45 yrs Cases, n=17,755 Controls, n=80,484	Cases: Median, 74 [IQR 62–82] 45–54, 12.3% of cohort 55–64, 16.3% 65–74, 20.9% 75–84, 29.9% ≥85, 20.6% Controls: 45–54, 12.5% 55–64, 16.7% 65–74, 21.7% 75–84, 30.8% ≥85, 18.4%	Database codes (Read codes)

Reference	Country; region	Study method	Study period	Population	Age (yrs [mean±SD])	Definition of CAP
Von Baum 2010 [70]	Germany; national (CAPNETZ)	Multicentre, prospective, observational study	1 June 2002–30 June 2007	Patients with CAP, n=5130 (6% nursing home residents); 67 with EB; 22 with PA; 1833 patients with no definite EB/PA	Overall, 60±18 With EB, 73±15 With PA, 64±17 No EB/PA, 58±18	Chest X-ray or clinical symptoms

BQS, The National Institute for Quality in Healthcare database; CAP, community-acquired pneumonia; CAPNETZ, Competence Network for Community-Acquired Pneumonia; CDC, Centers for Disease Control; COPD, chronic obstructive pulmonary disease; EB, Enterobacteriaceae; GP, General Practitioner; GPRD, General Practice Research Database; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; ICD, International Classification of Diseases; ICU, intensive care unit; IPCI, Integrated Primary Care Information; IQR, interquartile range; LRTI, lower respiratory tract infection; PA, *Pseudomonas aeruginosa*; SD, standard deviation; SEM, standard error of the mean; THIN, The Health Improvement Network; TNF, tumour necrosis factor; yr/yrs, year/years.

*Different analyses relating to the same population; †Different analyses in the same population; ††Different analyses relating to the same population; **This paper refers to patients with cirrhosis as 'Cases' and those without cirrhosis as 'Controls'. However, there is no evidence of any matching of 'cases' and 'controls'; ††10 patients in this study were aged ≤14 years; ‡This study included patients of all ages; data for risk factors were only presented for the total population. In addition, 0.2% of cases had a diagnosis of 'postoperative pneumonia'. ‡‡The QRESEARCH database gathers anonymised patient data from >500 general practices in the UK that use the Egton Medical Information Systems clinical computer system.

Supplementary Table S2. Incidence of community-acquired pneumonia (CAP) in adults in Europe.

Study	Country; region	Study period	CAP incidence (95% CI)	Hazard ratio (95% CI)	CAP incidence (95% CI)
			Original study data		Standardised[+]
Overall population					
Almirall 2008 [36]	Spain; east coast	1 Nov 1999–30 Nov 2000	Per 1000 population >14 yrs: 1.54		
Gutierrez 2006 [48]	Spain; Alicante	15 Oct 1999–14 Oct 2001	Per 10,000 person-yrs: Overall, 12.30 15–44 yrs, 6.77 45–64 yrs, 10.83 65–74 yrs, 23.73 ≥75 yrs, 52.62 Males, 15.56 Females, 9.11		1.230 0.677 1.083 2.373 5.262 1.556 0.911
			Incidence due to *S. pneumoniae* per 10,000 person-yrs: Overall, 2.07 (1.66–2.58) 15–44 yrs, 0.97 45–64 yrs, 1.69 65–74 yrs, 4.64 ≥75 yrs, 10.06 Males, 2.38 Females, 1.77		 0.207 (0.166–0.258) 0.097 0.169 0.464 1.006 0.238 0.177
Rodriguez 2009 [59]	UK; national	1 Jan 2000–31 Dec 2005	Primary care patients, per 10,000 person-yrs: Overall, 10.7 (10.4–10.9) Women, 9.3 (8.9–9.6) Men, 12.2 (11.8–12.6)		 1.07 (1.04–1.09) 0.93 (0.89–0.96) 1.22 (1.18–1.26)
*Viegi 2006 [68]	Italy; national	15 Feb 1999–14 Feb 2000	Annual incidence per 1000 population: Overall, 1.703 Males, 1.692 Females, 1.713 ≤14 yrs, 0.734 15–44 yrs, 0.915 45–64 yrs, 1.627 >64 yrs, 3.338		
Vila-Corcoles 2009 [16]	Spain; Tarragona	1 Jan 2002–30 April 2005	Age ≥65 yrs, per 1000 person-yrs: Overall, 14.0 (12.7–15.3) 65–74 yrs, 10.0 (8.6–11.4) 75–84 yrs, 16.9 (14.6–19.4)		

Study	Country; region	Study period	CAP incidence (95% CI)	Hazard ratio (95% CI)	CAP incidence (95% CI)
			Original study data		Standardised[+]
			≥85 yrs, 29.4 (23.5–36.2) Men, 19.2 (17.1–21.6) Women, 10.0 (8.6–11.5) Chronic lung disease, 46.5 (40.0–53.9) Chronic heart disease, 25.5 (20.8–30.9) Diabetes mellitus, 15.0 (12.4–17.9) Smoking, 20.7 (15.8–26.7) Cancer, 29.2 (18.8–43.2) Chronic liver disease, 31.3 (19.0–48.5) Chronic renal disease, 27.2 (18.7–38.1) Corticosteroid therapy, 40.1 (31.9–49.6) Immunocompetent, 11.6 (10.4–12.9) Immunocompromised, 30.9 (25.8–36.6)		
Hospitalisation for CAP					
Bewick 2012 [38]	UK; Nottingham	Sept 2008–Sept 2010	Per 100,000 population ≥16 yrs: Overall, 109.7 16–24 yrs, 15.8 25–44 yrs, 31.7 45–64 yrs, 49.8 65–74 yrs, 288.4 75–84 yrs, 438.5 ≥85 yrs, 985.9		 1.097 0.158 0.317 0.498 2.884 4.385 9.859
Ewig 2009 [42]	Germany; national	2005 and 2006	Per 1000 population/yr ≥18 yrs: 2005, 2.75 2006, 2.96 18–19 yrs, 0.33 20–29 yrs, 0.44 30–39 yrs, 0.63 40–49 yrs, 0.77 50–59 yrs, 1.34 60–69 yrs, 2.98 70–79 yrs, 7.39 80–89 yrs, 17.62 ≥90 yrs, 35.81 Mean incidence: Males, 3.21 Females, 2.52		
Kornum 2010 [17]	Denmark; Copenhagen and Aarhus	Dec 1993–April 2008	Per 1000 person-yrs, >50 yrs: Men, 4.2 BMI group (kg/m^2): <22.5 5.2		

Study	Country; region	Study period	CAP incidence (95% CI)		Hazard ratio (95% CI)	CAP incidence (95% CI)
			Original study data			Standardised[+]
			22.5–24.9	3.6	1.4 (1.1–1.7)	
			25.0–29.9	3.9	1.0 (reference)	
			30.0–34.9	5.4	1.0 (0.8–1.1)	
			≥35	7.0	1.0 (0.8–1.3)	
					1.2 (0.8–1.7)	
			Women, 3.4			
			BMI group (kg/m^2):			
			<22.5	4.0	1.2 (1.0–1.4)	
			22.5–24.9	3.4	1.0 (reference)	
			25.0–29.9	3.0	0.8 (0.7–1.0)	
			30.0–34.9	2.9	0.7 (0.6–0.9)	
			≥35	4.3	0.8 (0.6–1.1)	
Kornum 2012 [18]	Denmark; Copenhagen and Aarhus	Dec 1993–April 2008	Per 1000 person-yrs, >50 yrs:			
			Men, 4.25			
			Alcohol (drinks/week):			
			0	7.02	1.40 (0.93–2.12	
			1–6	4.45	1.0 (reference)	
			7–20	3.67	0.94 (0.80–1.10)	
			21–34	3.79	0.90 (0.75–1.09)	
			35–50	5.34	1.14 (0.91–1.43)	
			>50	9.16	1.45 (1.11–1.90)]	
			Women, 3.28			
			Alcohol (drinks/week):			
			0	4.72	1.17 (0.82–1.68)	
			1–6	3.18	1.0 (reference)	
			7–20	3.19	1.03 (0.89–1.19)	
			21–35	4.03	1.08 (0.86–1.36)	
			>35	2.25	0.48 (0.25–0.93)]	
Patients with COPD						
Müllerova 2012 [19]	UK; England and Wales	1 Jan 1996–31 Dec 2005	Per 1000 patient-yrs:			
			Overall, 22.4 (21.7–23.2)			
			Women, 21.4 (20.4–22.5)			
			Men, 23.1 (22.1–24.2)			
			Age (yrs)			
			45–64, 11.3 (10.3–12.3)			
			65–79, 19.8 (18.9–20.8)			
			≥80, 46.1 (43.7–48.6)			
			Smoking			
			Current, 19.8 (18.7–21.0)			
			Former, 21.4 (20.2–22.8)			
			Non-smoker, 26.0 (24.3–27.8)			
			Unknown, 28.7 (25.9–31.9)			

Study	Country; region	Study period	CAP incidence (95% CI)	Hazard ratio (95% CI)	CAP incidence (95% CI)
			Original study data		Standardised[+]
			Asthma history Yes, 26.1 (24.4–27.9) No, 21.2 (20.4–22.1) Prior pneumonia Yes, 39.5 (35.4–44.1) No, 21.4 (20.6–22.1) COPD severity Mild, 18.2 (15.7–21.2) Moderate, 19.2 (18.4–20.0) Severe, 35.9 (33.8–38.1)		
Immunocompromised individuals					
†Perez-Sola 2011 [58]	Spain; national	Feb 2000–Jan 2006	Patients with rheumatic diseases treated with TNF antagonists, per 1000 patient-yrs: 5.97 (4.87–7.25)		
HIV-infected individuals					
Bénard 2010 [24]	France; Aquitaine	2000–2007	Per 1000 patient-yrs: Overall: 12.0 (9.9–14.0) Smoking: Current, 15.9 (13.1–19.3) Former, 7.9 (4.2–14.9) Never, 5.9 (3.5–10.0) CD4+ lymphocyte count (cells/μL): ≥500, 7.9 (5.8–10.8) 350–499, 7.4 (3.9–13.7) 200–349, 16.5 (9.5–28.4) <200, 28.8 (16.7–49.8)	 1.00 (reference) 0.48 (0.26–0.90) 0.50 (0.29–0.86) 1.00 (reference) 0.93 (0.54–1.60) 1.98 (1.25–3.15) 2.98 (1.80–4.94)	
Curran 2008 [25]	Spain; Barcelona	Jan 2000–Dec 2005	Cases/100,000 patients/yr: 2000, 3090 2001, 3180 2002, 2570 2003, 2190 2004, 2050 2005, 2400		 30.90 31.80 25.70 21.90 20.50 24.00
Le Moing 2006 [26]	France; national	May 1997–Dec 2001	Hospitalisation for first episode of bacterial pneumonia in protease inhibitor-treated patients: 0.8/100 patient-yrs (0.3–1.3)		 8 (3–13)
‡Madeddu 2008 [27]	Italy; northern Sardinia	Jan 1999–Dec 2004	Per 100 inpatients/yr: 1999, 17.7 2004, 28.0		 177 280
Saindou 2008	France; Lyon	1993–	Pneumococcal pneumonia, per 1000 patient-yrs:		

Study	Country; region	Study period	CAP incidence (95% CI)	Hazard ratio (95% CI)	CAP incidence (95% CI)
			Original study data		Standardised[+]
[29]		2004	Cohort followed 1993–1 July 1996 (pre-HAART), 10.6 (5.4–15.7) Cohort followed before 1 July 1996–2004 (pre-HAART and HAART era), 1.5 (0.9–2.1) Cohort followed 1 July 1996–2004 (HAART era), 2.5 (1.4–3.6)		

BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; *S. pneumoniæ*, *Streptococcus pneumoniae*; TNF, tumour necrosis factor; yr/yrs, year/years

[+] Incidence rates standardised per 1000 population or per 1000 person-years; *This study included data for 10 children aged <14 years; †In this study, 'pneumonia' included fungal and viral aetiologies; ‡A majority of patients (84%) in this study were also intravenous drug users

Supplementary Table S3. Risk factors identified in case–control studies of lifestyle factors and the risk of community-acquired pneumonia (CAP).

Citation	Study type	Definition of cases	Definition of controls	Risk factor(s)				
				Factor	Cases, %	Controls, %	Odds ratio (95% CI) Crude	Adjusted
Almirall 2008 [36]	Multicentre, prospective, population-based	Primary care patients with CAP n=1336	Randomly selected from primary care centres; matched 1:1 by sex, age (±5 yrs) and primary care centre n=1326	Body mass index				
				Normal	64.0	64.5	1.00 (ref)	
				Underweight	9.6	4.4	2.20 (1.57–3.09)	
				Overweight	17.8	20.2	0.89 (0.72–1.09)	
				Obese	8.6	10.9	0.79 (0.60–1.04)	
				Smoking				
				Never	41.0	48.5	1.00 (ref)	
				Current smoker	31.7	27.4	1.37 (1.14–1.64)	
				Ex-smoker	27.3	24.1	1.34 (1.11–1.62)	
				Alcohol intake in males, g/day				
				0	33.8	34.1	1.00 (ref)	
				0.1–20	41.3	43.7	0.95 (0.75–1.21)	
				21–40	12.9	14.8	0.88 (0.63–1.22)	
				41–80	8.3	5.9	1.42 (0.92–2.21)	
				>80	3.7	1.6	2.34 (1.13–4.85)	
				Education level				
				Low	37.7	33.4	1.00 (ref)	
				Middle	40.6	42.2	0.86 (0.72–1.01)	
				High	21.7	24.5	0.78 (0.64–0.96)	
				Contact with animals, excrement or viscera	11.5	9.0	1.78 (1.00–3.19)	
				Sudden temperature changes in the workplace[a]	8.7	2.8	3.28 (2.24–4.82)	2.64 (1.67–4.15)
				Living with >10 persons at home	2.6	1.2	2.20 (1.21–4.00)	
				Usual contact with children	35.4	27.0	1.48 (1.26–1.75)	1.48 (1.20–1.82)
				Contact with pets[b]	50.6	42.8	1.37 (1.18–1.60)	
				Dental dysaesthesia	23.3	19.7	1.24 (1.01–1.53)	
				Dental prosthesis	45.6	40.8	1.22 (1.04–1.42)	
				Visit to dentist in past month	8.7	11.8	0.71 (0.55–0.92)	0.69 (0.50–0.95)
Almirall 2013 [12]	Single-centre, prospective	Patients ≥70 yrs hospitalised with CAP n=36	Randomly selected from independently-living older subjects assigned to the local primary care centre; matched 2:1 by sex and age n=72	Barthel index <100	69.4	25.0	6.82 (2.81–16.6)	6.93 (2.13–22.5)
Che 2008 [30]	Multicentre, prospective, population-based	Patients with sporadic Legionnaires'	Selected from the same general practices as cases; matched (1:1) by sex, age	>3 (men)/>2 (women) units alcohol/day	NR	NR		1.83 (1.28–2.61)
				Living in block of flats vs.	NR	NR		2.54 (1.75–3.68)

Citation	Study type	Definition of cases	Definition of controls	Risk factor(s)				
				Factor	Cases, %	Controls, %	Odds ratio (95% CI) Crude	Odds ratio (95% CI) Adjusted
		disease n=546	(±10 yrs for cases <65 yrs; ±5 yrs for cases ≥65 yrs), underlying conditions and location of residence ≤5 km n=546	individual home				
				Travel within 10 days of infection:				
				Hotel	NR	NR		5.40 (3.16–9.22)
				Other accommodation				1.89 (1.28–2.78)
				Exclusive use of wash-hand basin for personal hygiene	NR	NR		1.96 (1.21–3.17)
Müllerova 2012 [19]	Multicentre, retrospective, population-based, nested	Patients ≥45 yrs with COPD and a diagnosis of CAP n=1469	Patients ≥45 yrs with COPD and no CAP; matched 1:5 on length of follow-up n=7345	Smoking				
				Non-smoker	20.4	17.5		1.0 (ref)
				Former	35.8	35.4		1.04 (0.90–1.2)
				Current	36.7	41.1		0.99 (0.86–1.14)
				Body mass index, kg/m^2				
				<18.5	NR	NR		1.15 (0.92–1.43)
				18.5-24.9	NR	NR		1.0 (ref)
				25.0–29.9	NR	NR		0.78 (0.67–0.90)
				≥30	NR	NR		0.71 (0.60–0.85)
Myles 2009 [22]	Multicentre, retrospective, population-based, nested	Primary care patients ≥40 yrs with a diagnosis of pneumonia n=3709	Selected from same general practices as cases; matched 6:1 by practice, sex and age (±3 yrs) n=22,174	Current smoker	26.8	18.8	1.7 (1.6–1.8)	
Rodriguez 2009 [59]	Multicentre, nested, prospectively collected data	Primary care patients 20–79 yrs with a diagnosis of pneumonia n=7297	Randomly selected from study population; frequency-matched for sex, yr of age and index date n=9993	Smoking			**Relative risk**	
				Non-smoker	25	33	1.00 (ref)	
				Former	25	23	1.14 (1.04–1.25)	
				Current	43	35	1.52 (1.40–1.65)	
Schlienger 2007 [21]	Multicentre, population-based, retrospective, nested	Primary care patients ≥30 yrs with a diagnosis of pneumonia n=1253	Randomly selected from study population; up to 4 per case, matched for sex, age (±2 yrs), general practice and index date n=4838	Smoking				
				Non-smoker	47.1	57.3	1.00 (ref)	
				Former	18.4	16.7	1.40 (1.17–1.68)	
				Current	22.0	15.8	1.81 (1.53–2.15)	
				Alcohol abuse	2.5	1.5	1.85 (1.19–2.88)	
				Body mass index, kg/m^2				
				<25	32.8	29.7	1.00 (ref)	
				25–29.9	29.1	37.4	0.70 (0.60–0.82)	
				≥30	13.7	15.4	0.81 (0.66–0.99)	
				GP visits in past yr				
				1–4	19.0	41.8	1.00 (ref)	
				5–14	1.1	1.3	1.85 (1.01–3.39)	
				15–29	8.9	7.1	2.82 (2.18–3.66)	

Citation	Study type	Definition of cases	Definition of controls	Risk factor(s)				
				Factor	Cases, %	Controls, %	Odds ratio (95% CI) Crude	Odds ratio (95% CI) Adjusted
				≥30	71.0	49.8		
Schnoor 2007 [61]	Multicentre, prospective, population-based	Patients ≥18 yrs with a diagnosis of pneumonia n=1137	Randomly selected from local populations; frequency matched by sex and age (10-yr strata) n=1044	Children in household				
				None	NR	NR	1.00 (ref)	1.00 (ref)
				1	NR	NR	1.2 (0.9–1.6)	1.4 (1.0–2.0)
				2	NR	NR	2.1 (1.4–3.0)	2.2 (1.5–3.4)
				≥3	NR	NR	2.2 (1.1–4.2)	3.2 (1.5–7.0)
				Body mass index				
				Normal	NR	NR	1.00 (ref)	1.00 (ref)
				Underweight	NR	NR	2.1 (1.3–3.4)	2.3 (1.3–3.9)
				Overweight	NR	NR	0.6 (0.5–0.7)	0.6 (0.5–0.7)
				Obese	NR	NR	0.8 (0.6–1.1)	0.7 (0.5–0.9)
				School education				
				≤9 yrs	NR	NR	1.00 (ref)	1.00 (ref)
				10 yrs	NR	NR	0.6 (0.5–0.7)	0.6 (0.5–0.8)
				≥12 yrs	NR	NR	0.9 (0.7–1.1)	0.8 (0.6–1.1)
Teepe 2010 [23]	Multicentre, prospective, population-based	Patients 16–40 yrs with a diagnosis of CAP n=156	Randomly selected from same primary care practices; matched 3:1 within same age group n=468	Children in household				
				None	23.1	33.2	1.00 (ref)	1.00 (ref)
				1	23.8	27.1	1.26 (0.73–2.18)	1.02 (0.54–1.91)
				2	36.4	32.3	1.62 (0.98–2.68)	1.38 (0.77–2.46)
				≥3	16.8	7.4	3.26 (1.67–6.38)	3.41 (1.57–7.41)
				Current smoking	25.0	17.5	1.57 (1.00–2.46)	2.00 (1.20–3.36)
				Alcohol intake, g/day				
				0	26.7	20.3	1.00 (ref)	
				0.1–20.9	62.3	69.1	0.69 (0.44–1.07)	
				21.0–40.9	5.5	7.9	0.53 (0.22–1.25)	
				>41	5.5	2.6	1.59 (0.59–4.25)	
				Body mass index				
				Normal	55.9	53.3	1.00 (ref)	
				Underweight	3.3	3.8	1.04 (0.57–1.89)	
				Overweight	28.9	32.1	0.86 (0.57–1.31)	
				Obese	11.8	10.8	1.04 (0.57–1.89)	
				Education level				
				Low	22.6	16.6	1.00 (ref)	
				Middle	30.1	31.8	0.69 (0.41–1.19)	
				High	47.3	51.6	0.67 (0.41–1.10)	
				Contact with any pets	36.9	40.8	0.85 (0.58–1.24)	
				Visit to dentist in past yr	85.7	91.0	0.59 (0.34–1.04)	
van de Garde 2006 [64]	Multicentre, retrospective, population-based	Patients ≥18 yrs with diabetes mellitus and a first diagnosis of CAP n=4719	Randomly selected from diabetic patients without a record of pneumonia; up to 4 per case, matched for general practice, sex, age	Current smoking	12.7	9.2	1.48 (1.31–1.67)	
				Alcoholism	0.4	0.2	1.62 (0.91–2.91)	
				Body mass index, kg/m^2				
				20–24	14.6	14.5	1.00 (ref)	
				<20	5.3	3.0	1.73 (1.45–2.06)	

Citation	Study type	Definition of cases	Definition of controls	Risk factor(s)				
				Factor	Cases, %	Controls, %	Odds ratio (95% CI) Crude	Odds ratio (95% CI) Adjusted
			(±2 yrs) and index date n=15,322	25–30	22.9	32.2	0.71 (0.63–0.79)	
				>30	10.3	15.4	0.66 (0.58–0.75)	
*Vinogradova 2009 [69]	Multicentre, retrospective, population-based, nested	Patients with a diagnosis of pneumonia n=17,172	Patients from same database as cases without pneumonia; matched 5:1 by practice, age (±1 yr), sex and calendar time n=71,399	Non-smoker	69.9	73.3		1.00 (ref)
				Current smoker	19.2	12.4		1.61 (1.53–1.69)
				Townsend deprivation score				
				1st fifth (most affluent)	19.3	20.9		1.00 (ref)
				2nd fifth	19.0	20.4		1.00 (0.95–1.06)
				3rd fifth	19.2	19.1		1.08 (1.02–1.15)
				4th fifth	18.8	17.4		1.18 (1.11–1.25)
				5th fifth (most deprived)	20.7	18.4		1.27 (1.19–1.36)
Vinogradova 2011 [20]	Multicentre, retrospective, population-care based, nested	Patients ≥45 yrs with a diagnosis of pneumonia n=17,755	Randomly selected patients from same database as cases without pneumonia; matched 5:1 by practice, age (±1 yr), sex and calendar time n=80,484	Non-smoker	61.2	64.9		1.00 (ref)
				Current smoker	22.6	15.3		1.57 (1.50–1.64)
				Townsend deprivation score				
				1st fifth (most affluent)	19.6	21.6		1.00 (ref)
				2nd fifth	19.5	21.1		1.00 (0.95–1.06)
				3rd fifth	20.1	20.0		1.07 (1.01–1.13)
				4th fifth	18.9	17.4		1.13 (1.06–1.20)
				5th fifth (most deprived)	19.5	16.9		1.21 (1.14–1.30)

CI, confidence interval; COPD, chronic obstructive pulmonary disease; GP, general practitioner; NR, not reported; ref, reference; yr/yrs, year/years.

[a] Sudden work temperature change when coming in or out of a refrigerator, furnace or kitchen; [b] Increase in odds ratio of 1.19 (95% CI 1.097–1.30) for each additional animal.

* This study included patients of all ages (0–>75 years); data were only presented for all age groups.

Supplementary Table S4. Risk factors identified in case–control studies investigating the association between comorbid conditions and the risk of community-acquired pneumonia (CAP).

Citation	Study type	Definition of cases	Definition of controls	Risk factor(s)				
				Factor	Cases, %	Controls, %	Odds ratio (95% CI)	
							Crude	Adjusted
Almirall 2008 [38]	Multicentre, prospective, population-based	Primary care patients with CAP n=1336	Randomly selected from primary care centres; matched 1:1 by sex, age (±5 yrs) and primary care centre n=1326	Hospital admission in past 5 yrs	46.5	34.1	1.68 (1.44–1.96)	1.39 (1.14–1.70)
				Previous CAP:				
				Any	17.4	8.1	2.39 (1.88–3.05)	
				>2 episodes	1.3	0.2	6.25 (1.83–21.40)	
				Upper respiratory tract infection:				
				>1 in past yr	44.4	33.7	1.57 (1.35–1.84)	
				Any in past month	31.8	13.8	2.91 (2.40–3.53)	2.28 (1.81–2.89)
				Bronchoscopy in past yr	2.0	1.0	2.09 (1.07–4.06)	
				Nasogastric tube in past yr	1.2	0.4	3.21 (1.17–8.77)	
				Diabetes mellitus	10.1	7.2	1.43 (1.11–1.92)	
				Heart failure	8.6	4.9	1.81 (1.33–2.49)	
				Heart valve disease	4.4	2.6	1.70 (1.11–2.61)	
				Chronic bronchitis	16.2	6.1	2.96 (2.26–3.87)	1.81 (1.19–2.75)
				Asthma	28.1	14.3	2.33 (1.92–2.84)	1.67 (1.28–2.19)
				Non-active pulmonary tuberculosis	3.8	2.1	1.81 (1.13–2.89)	
				Epilepsy	1.3	0.5	2.83 (1.11–7.21)	5.95 (1.62–21.74)
				Dementia	1.3	0.6	2.12 (0.91–4.94)	
				Chronic liver disease	2.9	1.7	1.67 (0.99–2.82)	
				Cancer	7.9	5.7	1.42 (1.04–1.92)	
				HIV	1.1	0.2	7.49 (1.71–32.81)	
Almirall 2013 [12]	Single-centre, prospective,	Patients ≥70 yrs hospitalised with CAP n=36	Randomly selected from independently-living older subjects assigned to the local primary care centre; matched 2:1 by sex and age n=72	COPD/chronic bronchitis	50.0	27.8	2.60 (1.13–5.98)	3.80 (1.12–12.9)
				Chronic heart failure	44.4	21.1	2.99 (1.25–7.13)	2.19 (0.69–6.95)
				Oropharyngeal dysphagia	91.7	40.3	16.3 (4.57–58.2)	11.9 (3.03–46.9)
				Safety impairment	61.1	25.0	4.71 (2.00–11.1)	
				Efficacy impairment	83.3	33.3	10.0 (3.66–27.3)	
Hennessy 2007 [14]	Retrospective, nested	Patients ≥65 yrs hospitalised with pneumonia n=12,044	Randomly selected from same GP practice as cases; matched 4:1 based on time in study n=48,176	Any history of:				
				Bipolar disorder	0.3	0.2	2.50 (1.61–3.88)	
				COPD	20.2	6.2	3.92 (3.67–4.18)	
				Cerebrovascular disease	17.4	8.0	2.04 (1.91–2.17)	
				Depression	20.2	14.0	1.75 (1.65–1.86)	
				Dysphagia	3.8	1.8	2.10 (1.85–2.38)	
				Insomnia	22.5	14.7	1.55 (1.46–1.63)	

Citation	Study type	Definition of cases	Definition of controls	Risk factor(s)				
				Factor	Cases, %	Controls, %	Odds ratio (95% CI)	
							Crude	Adjusted
				Parkinson's disease	1.8	0.7	1.82 (1.52–2.19)	
				Poor nutritional status	1.0	0.3	2.84 (2.18–3.70)	
				Dementia	4.5	1.3	2.24 (1.97–2.54)	
Kornum 2008 [48]	Multicentre, retrospective, population-based,	Patients with discharge diagnoses (ICD-10) of pneumonia n=34,239	Randomly selected from same registry as cases; matched 10:1 by age (yr of birth), sex and residence (county) n=342,390				**Relative risk (95% CI)**	
				Diabetes mellitus				
				Absent	86.9	91.7	1.00 (ref)	1.00 (ref)
				Present	13.1	8.3	1.68 (1.62–1.74)	1.26 (1.21–1.31)
				Any diabetes				
				Age 15–39 yrs	NR	NR	3.93 (3.16–4.87)	3.21 (2.51–4.12)
				Age 40–64 yrs	NR	NR	2.63 (2.43–2.84)	1.65 (1.51–1.81)
				Age 65–79 yrs	NR	NR	1.64 (1.56–1.73)	1.22 (1.15–1.29)
				Age ≥80 yrs	NR	NR	1.33 (1.25–1.41)	1.11 (1.05–1.18)
				Type 1 diabetes, overall	0.3	0.1	5.55 (4.34–7.08)	4.43 (3.40–5.77)
				Age 15–39 yrs	NR	NR	6.41 (4.69–8.74)	5.15 (3.61–7.36)
				Age 40–64 yrs	NR	NR	4.67 (3.12–6.98)	3.43 (2.14–5.50)
				Comorbidity index				
				0	NR	NR	4.98 (3.67–6.74)	4.76 (3.43–6.61)
				1–2	NR	NR	3.35 (0.88–12.78)	3.15 (0.80–12.38)
				Type 2 diabetes	12.8	8.3	1.65 (1.59–1.71)	1.23 (1.19–1.28)
				Age 15–39 yrs	NR	NR	2.63 (1.94–3.58)	2.15 (1.51–3.06)
				Age 40–64 yrs	NR	NR	2.58 (2.39–2.79)	1.62 (1.47–1.77)
				Age 65–79 yrs	NR	NR	1.64 (1.56–1.73)	1.22 (1.15–1.29)
				Comorbidity index				
				0	NR	NR	1.62 (1.52–1.73)	1.45 (1.36–1.55)
				1–2	NR	NR	1.22 (1.15–1.29)	1.15 (1.07–1.22)
Müllerova 2012 [19]	Multicentre, retrospective, population-based, nested	Patients ≥45 yrs with COPD and a diagnosis of CAP n=1469	Patients ≥45 yrs with COPD and no CAP; matched 1:5 on length of follow-up n=7345	Myocardial infarction	12.0	9.5		1.00 (0.85–1.19)
				Congestive heart failure	27.5	16.3		1.37 (1.20–1.57)
				Cerebrovascular disease	15.1	10.9		1.08 (0.93–1.26)
				Dementia	3.6	1.0		2.64 (1.86–3.75)
				Peptic ulcer	18.4	14.6		1.22 (1.06–1.41)
				Peripheral vascular disease	8.2	5.7		1.27 (1.05–1.55)
				Connective tissue disease	45.8	38.2		1.16 (1.04–1.30)
				Diabetes mellitus	10.4	8.5		1.07 (0.89–1.28)
				Anxiety	25.7	21.4		1.09 (0.95–1.25)
				Depression	29.2	24.4		1.13 (0.99–1.28)
				COPD exacerbation				
				Severe	17.1	5.5		2.73 (2.32–3.20)
				Moderate	14.0	7.9		1.28 (1.13–1.46)
Myles 2009 [22]	Multicentre, retrospective, population-based,	Primary care patients ≥40 yrs with a diagnosis of	Selected from same general practices as cases; matched 6:1 by practice,	Ischaemic heart disease	17.0	13.3	1.4 (1.2–1.5)	
				Chronic lung disease	24.7	10.4	2.9 (2.7–3.2)	
				Charlson comorbidity index				

Citation	Study type	Definition of cases	Definition of controls	Risk factor(s)				
				Factor	Cases, %	Controls, %	Odds ratio (95% CI)	
							Crude	Adjusted
	nested	pneumonia n=3709	sex and age (±3 yrs) n=22,174	score				
				0	29.1	50.9	1.0 (ref)	
				1–2	43.7	35.2	2.5 (2.3–2.7)	
				3–5	23.7	13.0	4.0 (3.6–4.4)	
				>5	3.5	1.0	7.9 (6.3–10.0)	
				Previous pneumonia	10.2	2.9	4.1 (3.6–4.8)	
Rodriguez 2009 [42]	Multicentre, nested, prospectively collected data	Primary care patients 20–79 yrs with a diagnosis of pneumonia n=7297	Randomly selected from study population; frequency-matched for sex, yr of age and index date n=9993				Relative risk (95% CI)	
				COPD	16	4		2.82 (2.45–3.24)
				Asthma	25	12		1.58 (1.44–1.74)
				Ischaemic heart disease	17	11		1.28 (1.16–1.42)
				Myocardial infarction	7	4		1.42 (1.22–1.65)
				Cerebrovascular disease	9	6		1.42 (1.25–1.61)
				Heart failure	7	2		2.63 (2.21–3.14)
				Diabetes mellitus	11	7		1.28 (1.13–1.44)
				Rheumatoid arthritis	4	2		1.37 (1.12–1.69)
				Cancer	12	7		1.37 (1.22–1.54)
				Anaemia	9	6		1.43 (1.25–1.62)
				Depression	28	19		1.30 (1.19–1.40)
				Gastrointestinal disease				
				GERD	15	11		1.07 (0.97–1.18)
				Dyspepsia	23	18		1.12 (1.03–1.22)
				Uncomplicated peptic ulcer	6	3		1.49 (1.26–1.75)
				Complicated peptic ulcer	4	2		1.82 (1.49–2.23)
				≥1 hospital admission in past yr	17	7		1.77 (1.59–1.97)
Schlienger 2007 [21]	Multicentre, population-based, retrospective, nested	Primary care patients ≥30 yrs with a diagnosis of pneumonia n=1253	Randomly selected from study population; up to 4 per case, matched for sex, age (±2 yrs), general practice and index date n=4838	Diabetes mellitus	15.2	11.0	1.45 (1.21–1.73)	
				Asthma or COPD	43.5	26.0	2.33 (2.03–2.67)	
				Ischaemic heart disease or chronic heart failure	18.8	10.7	2.28 (1.87–2.78)	
				Stroke	16.7	8.7	2.10 (1.74–2.53)	
				Venous thromboembolism or pulmonary embolism	2.6	1.7	1.55 (1.02–2.37)	
				Rheumatoid arthritis	8.7	6.3	1.46 (1.14–1.88)	
				Depression or bipolar disorder	13.9	8.9	1.77 (1.54–2.18)	
				Epilepsy	3.0	1.1	2.81 (1.83–4.30)	
Schnoor 2007 [44]	Multicentre, prospective, population-based	Patients ≥18 yrs with a diagnosis of pneumonia n=1137	Randomly selected from local populations; frequency matched by sex and age (10-yr strata)	Hospitalization in past 5 yrs	NR	NR	1.6 (1.4–1.9)	
				>1 respiratory infection in past yr	NR	NR	4.5 (3.7–5.4)	3.6 (2.9–4.5)
				Previous CAP	NR	NR	2.4 (2.0–2.9)	1.6 (1.3–2.1)

Citation	Study type	Definition of cases	Definition of controls	Risk factor(s)				
				Factor	Cases, %	Controls, %	Odds ratio (95% CI)	
							Crude	Adjusted
			n=1044	Chronic pulmonary disease	NR	NR	3.9 (3.1–4.9)	2.3 (1.7–3.0)
				Chronic heart disease	NR	NR	3.2 (2.6–4.1)	
				Chronic liver disease	NR	NR	2.1 (1.2–4.0)	
				Chronic renal disease	NR	NR	1.7 (1.1–2.8)	
Teepe 2010 [23]	Multicentre, prospective, population-based	Patients 16–40 yrs with a diagnosis of CAP n=156	Randomly selected from same primary care practices; matched 3:1 within same age group n=468	Asthma	12.2	5.8	2.27 (1.22–4.20)	2.69 (1.23–5.88)
				Sinusitis	15.4	9.0	1.84 (1.08–3.16)	
				Upper respiratory tract infections in past 6 yrs				
				0	75.0	83.8	1.00 (ref)	1.00 (ref)
				1–2	21.2	14.7	1.60 (1.01–2.55)	1.49 (0.87–2.56)
				>3	3.8	1.5	2.87 (0.95–8.71)	4.84 (1.24–18.9)
				Depressive disorder	5.8	2.4	2.54 (1.03–6.26)	
				GERD	3.2	1.1	3.07 (0.88–10.74)	
†van de Garde 2006 [47]	Multicentre, retrospective, population-based	Patients ≥18 yrs with diabetes mellitus and a first diagnosis of CAP n=4719	Randomly selected from diabetic patients without a record of pneumonia; up to 4 per case, matched for general practice, sex, age (±2 yrs) and index date n=15,322	Cardiovascular disease	46.4	23.6	2.81 (2.62–3.00)	
				Pulmonary disease	20.1	10.4	2.17 (1.99–2.37)	
†van de Garde 2007[49]	Multicentre, retrospective, population-based	Patients ≥18 yrs with diabetes mellitus and a first diagnosis of CAP n=4719	Randomly selected from diabetic patients without a record of pneumonia; up to 4 per case, matched for general practice, sex, age (±2 yrs) and index date n=15,322	History of stroke	25.1	12.4	2.37 (2.19–2.57)	
				Congestive heart failure	30.1	14.1	2.63 (2.43–2.84)	
*Vinogradova 2009 [46]	Multicentre, retrospective, population-based, nested	Patients with a diagnosis of pneumonia n=17,172	Patients from same database without pneumonia; matched 5:1 by practice, age (±1 yr), sex and calendar time n=71,399	Diabetes mellitus	7.8	5.4	1.54 (1.44–1.65)	1.36 (1.27–1.47)
				Chronic heart disease	18.9	12.0	1.91 (1.81–2.00)	1.63 (1.54–1.72)
				Ischaemic heart disease	13.6	9.8	1.54 (1.46–1.63)	
				No ischaemic disease	5.3	2.2	2.53 (2.31–2.76)	
				Chronic renal disease	1.2	0.5	2.15 (1.81–2.56)	1.72 (1.43–2.07)
				Chronic respiratory disease	26.0	12.4	2.62 (2.51–2.73)	2.42 (2.31–2.53)
				Treated asthma	13.6	5.7	2.65 (2.51–2.81)	
				Untreated asthma	2.9	2.4	1.19 (1.07–1.32)	
				Asplenia	0.3	0.1	2.88 (2.04–4.06)	2.58 (1.80–3.71)
				Chronic liver disease	0.5	0.2	2.24 (1.74–2.89)	1.87 (1.43–2.44)
				Sickle cell or coeliac disease	0.3	0.1	2.65 (1.87–3.75)	2.42 (1.68–3.49)
				HIV/AIDS	0.1	0	2.71 (1.50–4.90)	2.48 (1.34–4.58)
				Stroke or TIA	8.5	5.0	1.86 (1.74-1.99)	1.63 (1.52–1.75)

Citation	Study type	Definition of cases	Definition of controls	Risk factor(s)				
				Factor	Cases, %	Controls, %	Odds ratio (95% CI)	
							Crude	Adjusted
				Rheumatoid arthritis	2.3	1.1	2.02 (1.79–2.29)	1.84 (1.62–2.10)
				Parkinson's disease	1.3	0.7	1.87 (1.60–2.19)	1.82 (1.53–2.15)
				Multiple sclerosis	0.5	0.2	3.20 (2.40–4.26)	3.63 (2.70–4.88)
				Dementia	2.2	0.9	2.41 (2.11–2.75)	2.45 (2.13–2.81)
				Osteoporosis	3.8	2.2	1.84 (1.67–2.03)	1.57 (1.41–1.74)
				Any cancer	6.7	4.2	1.70 (1.58–1.82)	1.42 (1.30–1.56)
				Lung cancer	0.6	0.1	4.73 (3.58–6.25)	
				Immunosuppressed	4.5	4.1	1.12 (1.03–1.21)	1.40 (1.26–1.55)
Vinogradova 2011 [20]	Multicentre, retrospective, population-based, nested	Patients ≥45 yrs with a diagnosis of pneumonia n=17,755	Randomly selected patients from same database without pneumonia; matched 5:1 by practice, age (±1 yr), sex and calendar time n=80,484	Diabetes mellitus	11.0	7.6		1.33 (1.26–1.41)
				Chronic heart disease	29.7	17.8		1.66 (1.59–1.73)
				Chronic renal disease	1.8	0.7		1.78 (1.53–2.07)
				Chronic respiratory disease	30.4	14.1		2.47 (2.37–2.58)
				Chronic liver disease	0.8	0.3		1.85 (1.48–2.31)
				Sickle cell or coeliac disease	0.3	0.2		1.72 (1.23–2.39)
				HIV/AIDS	0.1	0		5.90 (2.55–13.64)
				Stroke or TIA	13.5	7.6		1.68 (1.58–1.77)
				Rheumatoid arthritis	3.3	1.6		1.83 (1.64–2.03)
				Parkinson's disease	2.2	1.1		1.98 (1.74–2.26)
				Multiple sclerosis	0.7	0.2		3.84 (3.02–4.89)
				Dementia	4.1	1.6		2.68 (2.42–2.97)
				Cancer	9.7	6.0		1.36 (1.24–1.49)

AIDS, autoimmunity deficiency syndrome; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GERD, gastro-oesophageal reflux; GP, general practitioner; HIV, human immunodeficiency virus; ICD, International Classification of Diseases; ref, reference; NR, not reported; RR, relative risk; TIA, transient ischaemic attack; yr/yrs, year/years.

†Separate analyses in the same population; *This study included patients of all ages (0–>75 years); data were presented only for all age groups.

Supplementary Table S5. Observational data for the rates of comorbid conditions in adults with community-acquired pneumonia (CAP). Data were available from both case–control and observational studies.

Citation	Population	Comorbid condition	Study cohorts (data are % of patients)		
Almirall 2010 [37]	Primary care patients with chronic bronchitis n=122	Upper respiratory tract infection in past month	46.3		
		Asthma	8.2		
		Previous CAP	23.8		
		Other respiratory disease	4.2		
		Diabetes mellitus	22.1		
		Heart failure	18.3		
		Depression	21.3		
		Cancer	9.8		
	Primary care patients with COPD n=94	Upper respiratory tract infection in past month	46.8		
		Asthma	50.0		
		Previous CAP	29.8		
		Diabetes mellitus	29.8		
		Heart failure	17.0		
		Depression	13.8		
		Cancer	13.8		
	Primary care patients with asthma n=256	Upper respiratory tract infection in past month	61.3		
		Previous CAP	21.5		
		Diabetes mellitus	12.9		
		Heart failure	9.8		
		Depression	14.5		
		Cancer	6.3		
Bewick 2012 [38]	Patients ≥16 yrs hospitalised with CAP		**All patients (n=920)**	**Pneumococcal CAP (n=366)**	
		COPD	26.5	25.7	
		Ischaemic heart disease	15.8	16.7	
		Diabetes mellitus	14.1	14.8	
		Cerebrovascular disease	11.2	12.3	
		Asthma	11.1	12.8	
		Congestive heart failure	8.0	7.1	
		Active malignancy	7.3	10.4	
		Dementia	3.5	5.7	
Cabre 2010 [13]	Patients ≥70 yrs with CAP requiring hospitalisation [**p≤0.01; ***p≤0.001 vs. safe swallow]		**All patients (n=134)**	**Safe swallow (n=60)**	**Oropharyngeal dysphagia (n=74)**
		Oropharyngeal dysphagia	55.2		
		Chronic pneumopathy	53.7	55.0	52.7

Citation	Population	Comorbid condition	Study cohorts (data are % of patients)		
		Heart failure	23.9	18.3	28.4
		Ischaemic heart disease	14.9	13.3	16.2
		Diabetes mellitus	30.6	28.3	32.4
		Chronic liver disease	3.0	3.3	2.7
		Cancer	12.7	11.7	13.5
		Dementia	33.6	13.3	50.0***
		Cerebrovascular disease	24.6	13.3	33.8**
		Chronic renal failure	26.7	26.7	26.8
Carratalà 2007 [39]	Adult patients with CAP requiring hospitalisation n=601	COPD	25.1		
		Chronic heart disease	26.8		
		Diabetes mellitus	16.6		
		Cerebrovascular disease	11.8		
		Cancer	4.7		
		Chronic renal failure	3.3		
		Chronic liver disease	3.7		
		Autoimmune disease	1.3		
Chidiac 2012 [31]	Patients hospitalised with community-acquired Legionnaires' disease n=540	Diabetes mellitus	15.7		
		Cancer	6.3		
Cillóniz 2011 [40]	Patients with CAP admitted to ICU n=362	Chronic respiratory disease	37		
		COPD	16		
		Asthma	6		
		Bronchiectasis	3		
		Chronic cardiovascular disease	14		
		Diabetes mellitus	20		
		Neurological disease	19		
		Chronic renal disease	6		
		Chronic liver disease	6		
Cillóniz 2012 [41]	Adult patients hospitalised with pneumococcal pneumonia [**p≤0.01; ***p≤0.001 vs. uncomplicated CAP]		**All patients (n=626)**	**Complicated CAP (n=235)**	**Uncomplicated CAP (n=391)**
		Chronic respiratory disease	44.2	NR	NR
		COPD	21.0	12.0***	26.2
		Asthma	6.6	8.2	5.7
		Bronchiectasis	10.3	11.2	9.8
		Other chronic respiratory disease	6.4	7.2	5.2
		Chronic cardiovascular disease	13.5	10.7	15.1
		Diabetes mellitus	16.9	14.7	18.3
		Neurological disease	14.0	14.1	14.0
		Chronic renal disease	5.0	3.9	5.7
		Chronic liver disease	6.1	9.4**	4.1

Citation	Population	Comorbid condition	Study cohorts (data are % of patients)		
		Alcohol abuse	16.8	20.2	14.8
de Roux 2006 [10]	Patients hospitalised with CAP (current alcohol abuse = daily consumption >80 g for men and 60 g for women during the past 2 yrs; former alcohol abuse = no abuse in past 1 yr) [*p<0.05 vs. no alcohol abuse]		**No abuse (n=1165)**	**Current abuse (n=128)**	**Former abuse (n=54)**
		COPD	32	42*	52*
		Chronic renal failure	8	2*	18*
		Neurological disease	17	9*	22
		Hepatic disease	3	20*	15*
		Neoplasm	9	9	22*
Ewig 2009 [42]	Patients hospitalised with CAP n=388,406	Cardiac disease	19.2		
		CNS disorders	13.8		
		Pulmonary disease (excluding COPD)	13.1		
		Diabetes mellitus	11.9		
		COPD	9.4		
		Renal disease	8.6		
		Dementia	6.0		
		Malignancy (excluding bronchial)	3.3		
		Lung cancer	1.6		
		Liver disease	1.5		
Falguera 2009 [43]	Patients hospitalised with CAP [**p≤0.01; ***p≤0.001 vs. no Gram-negative infections]		**All patients (n=3272)**	**Gram-negative infection (n=61)**	**No Gram-negative infection (n=3211)**
		≥1 comorbid condition	61	79**	61
		COPD	26	46***	25
		Congestive heart disease	22	21	22
		Diabetes mellitus	18	16	18
		Chronic renal disease		3	4
		Chronic liver disease		5	5
		Cerebrovascular disease		0	4
		Active neoplasm		8	8
Garcia-Vidal 2009 [44]	Patients hospitalised with CAP [***p≤0.001 vs. non-recurrent CAP]		**Recurrent pneumonia (n=146)**	**Non-recurrent pneumonia (n=1410)**	
		Any comorbid condition	91.8***	71.5	
		COPD	38.4***	25.1	
		Diabetes mellitus	17.8	16.9	
		Cancer	11.6	7.6	
		Cerebrovascular disease	4.8	3.2	
		Chronic heart disease	29.5	23.0	
		Chronic renal disease	3.4	3.2	
		Chronic liver disease	6.2	5.2	
		Dementia	6.2	3.6	

Citation	Population	Comorbid condition	Study cohorts (data are % of patients)	
Giannella 2012 [45]	Patients ≥16 yrs treated for CAP in internal medicine department n=591	COPD	37.4	
		Congestive heart failure	21.3	
		Diabetes mellitus	25.2	
		Cerebrovascular disease	17.9	
		Dementia	16.6	
		Cancer	13.0	
		Chronic renal failure	13.2	
		Chronic liver failure	8.3	
		Autoimmune disease	3.6	
		HIV	3.7	
Gulmez 2007 [46]	Patients with a discharge diagnosis of CAP n=7642	History of:		
		CAP	15.5	
		COPD	18.8	
		Peptic ulcer	7.2	
		Diabetes mellitus	7.9	
		Renal failure	1.9	
		Hepatic cirrhosis	0.75	
		Ischaemic heart disease	15.4	
		Heart failure	14.4	
		Stroke	11.0	
		Alcohol-related diagnosis or drug use	4.1	
		Psychiatric disorder	7.2	
Gutierrez 2005 [47]	Patients ≥15 yrs with CAP n=493	Any comorbid condition	46	
		COPD	20.1	
		Diabetes mellitus	19.9	
		Dementia	10.5	
		Immunosuppression	5.3	
		Neoplasia	4.3	
		Congestive heart failure	4.1	
		Chronic renal failure	3.4	
Holm 2007 [49]	Primary care patients ≥18 yrs with a diagnosis of community-acquired LRTI		**All patients (n=364)**	**Confirmed pneumonia (n=48)**
		COPD	9	21
		Cardiac disease	9	10
Klapdor 2012 [50]	Patients ≥18 yrs with CAP [***p≤0.001 vs. patients <65 yrs]		**Age <65 yrs (n=4083)**	**Age ≥65 yrs (n=3720)**
		Any comorbidity	46.6	88.2***
		Chronic respiratory disease	28.6	44.0***
		Congestive heart failure	5.9	34.4***
		Other heart disease	12.6	49.7***
		Cerebrovascular disease	3.9	20.8***

Citation	Population	Comorbid condition	Study cohorts (data are % of patients)	
		Other chronic neurological disorder	5.0	10.0***
		Renal insufficiency	2.9	15.2***
		Chronic liver disease	3.7	2.9
		Diabetes mellitus	8.1	26.7***
		Cancer	5.4	13.9***
Kofteridis 2009 [34]	Adults hospitalised with community-acquired LRTI due to *Haemophilus influenzae* n=45	Patients with ≥1 comorbid condition	100	
		COPD	62	
		Bronchiectasis	18	
		Solid tumour	9	
		Haematological malignancy	7	
		Cardiovascular disease	36	
		Ischaemic heart disease	27	
		Cerebrovascular disease	7	
		Peripheral vascular disease	2	
		Chronic renal disease	2	
		Diabetes mellitus	29	
		Chronic liver disease	7	
		Alcoholism	36	
Kothe 2008 [52]	Patients with CAP [***p≤0.001 vs. patients <65 yrs]		**Age <65 yrs (n=1298)**	**Age ≥65 yrs (n=1349)**
		Chronic pulmonary disease	30.0	42.6***
		Chronic heart disease	12.8	47.2***
		Congestive heart failure	6.4	37.9***
		Chronic liver disease	3.9	3.3
		Chronic renal failure	2.9	13.3***
		Cerebrovascular disease	4.1	22.3***
		Other neurological disorder	6.6	10.1***
		Diabetes mellitus	8.3	28.1***
Liapikou 2012 [53]	Adults hospitalised with CAP [**p≤0.01 vs. patients without COPD]		**No COPD (n=1167)**	**With COPD (n=212)**
		Heart failure	23.0	26.4
		Chronic liver disease	4.1	5.7
		Malignancy	5.7	13.2**
		Renal failure	6.7	9.0
		Neurological disease	27.2	21.7
		Diabetes mellitus	20.2	25.9
		Pneumonia in previous yr	17.5	33.8**
Madeddu 2008 [27]	HIV patients hospitalised with CAP n=76; 84 episodes	Chronic hepatitis		
		HBV	7.9	
		HCV	77.6	
Manno 2009 [28]	HIV patients hospitalised with		**No cirrhosis**	**With cirrhosis**

Citation	Population	Comorbid condition	Study cohorts (data are % of patients)	
	CAP [***p≤0.001 vs. no cirrhosis]		**(n=73)**	**(n=29)**
		Other comorbidities (diabetes mellitus, cancer, heart, renal, neurological and pulmonary disease)	8.2	17.2
		Alcohol abuse	6.9	55.6***
		Intravenous drug use	34.6	53.6
		Pneumonia within past month	9.6	17.2
		AIDS	31.5	41.4
Migliorati 2006 [54]	Patients ≥15 yrs hospitalised with a discharge diagnosis of pneumonia or pneumonia-related disease n=148	≥1 previous episode of pneumonia	14	
		≥1 comorbidity	87	
		COPD	34	
		Asthma	3	
		Other respiratory disease	5	
		Liver disease	15	
		Congestive heart failure	24	
		Cardiac arrhythmia	3	
		Cancer	10	
		Obesity	13	
		Renal failure	9	
		Neuromuscular disease	5	
		Alcohol abuse	14	
		Dementia or other cerebrovascular disease	26	
		Arterial hypertension	39	
		Diabetes mellitus	27	
		Malnutrition	9	
Molinos 2009 [55]	Patients hospitalised with CAP [*p<0.05 vs. no cirrhosis]		**No COPD (n=466)**	**With COPD (n=244)**
		Cardiac disease	18	23
		Renal disease	6	9
		Hepatic disease	4	4
		Cerebrovascular disease	9	8
		Diabetes mellitus	14	20*
		Alcohol abuse	11	18*
Müllerova 2012 [19]	Patients ≥45 yrs with COPD n=1469	Asthma	45.4	
		Myocardial infarction	12.0	
		Congestive heart failure	27.5	
		Cerebrovascular disease	15.1	

Citation	Population	Comorbid condition	Study cohorts (data are % of patients)	
		Dementia	3.6	
		Peptic ulcer	18.4	
		Peripheral vascular disease	8.2	
		Connective tissue disorder	45.8	
		Diabetes mellitus	10.4	
		Anxiety	25.7	
		Depression	29.2	
		Lung cancer	2.0	
		Renal disease	4.1	
Myint 2011 [56]	Patients hospitalised with acute exacerbations of COPD [***p≤0.001 vs. no pneumonia]		**No pneumonia (n=7833)**	**With pneumonia (n=1505)**
		Number of comorbidities		
		0	24	19
		1	32	32
		2	25	27
		≥3	19	23***
Nielsen 2012 [57]	Patients ≥15 yrs hospitalised with CAP n=70,914	Previous myocardial infarction	9.5	
		Congestive heart failure	10.5	
		Peripheral vascular disease	8.6	
		Cerebrovascular disease	15.0	
		Dementia	2.2	
		Chronic pulmonary disease	20.4	
		Connective tissue disease	5.3	
		Peptic ulcer disease	8.7	
		Liver disease	2.3	
		Diabetes mellitus	12.2	
		Renal disease	3.8	
		Solid cancer	18.0	
		Charlson comorbidity index score		
		0	37.1	
		1–2	40.4	
		≥3	22.6	
		Alcoholism-related disorders	6.1	
Ruiz 2010 [35]	Adults hospitalised with bacteraemic CAP due to Gram-negative bacteria n=51	Cardiac disease	43.1	
		Pulmonary disease	35.3	
		Renal disease	17.6	
		Hepatic disease	15.9	

Citation	Population	Comorbid condition	Study cohorts (data are % of patients)	
		Neurological disease	21.6	
		Diabetes mellitus	21.6	
		>1 comorbid condition	43.1	
Sarkar 2008 [60]	Primary care patients ≥18 yrs with CAP n=80,066	Alcoholism	2.3	
		Dementia	14.4	
		Stroke	19.2	
		Diabetes mellitus	4.9	
		Cirrhosis	0.3	
		Renal failure	0.5	
		Congestive heart failure	10.5	
		Myocardial infarction	9.3	
		COPD or asthma	22.4	
		Cancer	7.3	
		Previous CAP	3.2	
Sopena 2007 [32]	Adults hospitalised with community-acquired Legionnaires' disease [*statistically significant vs. sporadic cases; p-value not given]		**Sporadic cases (n=138)**	**Outbreak cases (n=113)**
		Alcohol abuse	26.8	16.5
		Any underlying disease	55.1	49.6
		Chronic lung disease	19.6	9.7*
		Chronic heart disease	12.4	11.5
		Diabetes mellitus	15.2	23.9
		Liver cirrhosis	5.9	8.8
		Neoplasm	7.3	8.8
		HIV infection	11.6	1.8*
		Chronic renal failure	2.2	1.8
Sopena 2007 [33]	Adults hospitalised with CAP due to *Legionella pneumophila* [**p≤0.01; ***p≤0.001 vs. age ≥65 yrs]		**Age <65 yrs (n=104)**	**Age ≥65 yrs (n=54)**
		Alcohol abuse	35.0***	9.3
		Any underlying disease	46.2***	75.9
		Chronic pulmonary disease	10.6***	35.2
		Diabetes mellitus	7.7**	27.8
		Neuromuscular disease	1.0***	20.4
		Neoplasm	6.7	13.0
		Heart failure	1.0***	14.8
		HIV infection	15.4***	0
		Liver cirrhosis	4.9	1.9
		Chronic renal failure	2.9	1.9

Citation	Population	Comorbid condition	Study cohorts (data are % of patients)	
		Risk of aspiration	0**	5.6
Thomsen 2008 [62]	Patients ≥15 yrs hospitalised with CAP		**Statin users (n=1372)**	**Statin non-users (n=28,528)**
		Previous myocardial infarction	43.6	7.9
		Congestive heart failure	23.2	10.2
		Peripheral vascular disease	20.9	6.9
		Cerebrovascular disease	24.6	13.7
		Dementia	1.1	2.1
		Chronic pulmonary disease	23.8	19.4
		Connective tissue disease	4.8	4.7
		Peptic ulcer disease	9.8	8.7
		Liver disease	1.0	2.0
		Diabetes mellitus	29.1	9.4
		Renal disease	6.7	3.0
		Cancer	14.1	15.8
		Alcoholism-related disorders	2.8	5.0
		Charlson comorbidity index score		
		0	13.6	41.2
		1–2	47.9	39.8
		≥3	38.5	19.0
Trifiro 2010 [15]	Patients ≥65 yrs with a first antipsychotic drug prescription n=258	Previous myocardial infarction	1.9	
		Previous cerebrovascular event	17.8	
		Heart failure	21.3	
		Swallowing problems	2.7	
		COPD	19.4	
		Diabetes mellitus	22.5	
		Chronic renal disease	2.7	
		Chronic hepatic disease	3.9	
		Cancer (excluding lung cancer)	14.0	
		Parkinson's disease	11.6	
van de Garde 2006 [63]	Patients >18 yrs hospitalised with a discharge diagnosis of CAP n=1108	Heart failure	11.4	
		Respiratory disease	41.0	
		Diabetes mellitus	12.1	
Viasus 2011 [66]	Adults hospitalised with CAP [***p≤0.001 vs. no renal disease]		**No renal disease (n=3597)**	**Chronic renal disease (n=203)**
		Any comorbid condition	63.3	82.3***

Citation	Population	Comorbid condition	Study cohorts (data are % of patients)	
		Chronic pulmonary disease	27.7	28.6
		Chronic heart disease	22.5	46.8***
		Diabetes mellitus	20.0	33.0***
		Chronic liver failure	6.3	3.4
		Cerebrovascular disease	7.3	18.7***
	Adults hospitalised with CAP [**p≤0.01; ***p≤0.001 vs. no haemodialysis]		**No haemodialysis (n=2091)**	**On haemodialysis (n=44)**
		Any comorbid condition	59.3	81.8**
		Chronic pulmonary disease	25.6	27.3
		Chronic heart disease	20.2	50.0***
		Diabetes mellitus	19.8	29.5
Viasus 2011 [67]	Patients hospitalised with CAP [**p≤0.01; ***p≤0.001 vs. no cirrhosis]		**No cirrhosis (n=3330)**	**Cirrhosis (n=90)**
		Alcohol abuse	17.9	35.6***
		Any comorbid condition	68.5	58.9
		COPD	27.3	22.2
		Chronic heart disease	25.4	14.4**
		Diabetes mellitus	20.1	27.8
		Chronic renal failure	6.2	4.4
*Viegi 2006 [68]	Primary care patients with CAP [**p≤0.01; ***p≤0.001 vs. patients diagnosed by GP]		**GP diagnosed (n=548)**	**Hospital diagnosed (n=151)**
		Heart disease	17.3	45.0***
		Neurological disease	6.9	16.9***
		Diabetes mellitus	10.5	12.2
		Hypertension	30.2	43.0**
		Cancer	9.1	7.9
		Chronic bronchitis	22.3	40.8**
		Asthma	8.7	16.4**
		Emphysema	18.9	34.5***
Vila-Corcoles 2009 [16]	Community-dwelling individuals ≥65 yrs with CAP n=473	Chronic lung disease	36.2	
		Diabetes mellitus	25.4	
		Chronic heart disease	20.9	
		Chronic liver disease	4.0	
		Cerebrovascular disease	5.1	
		Chronic renal disease	6.8	

Citation	Population	Comorbid condition	Study cohorts (data are % of patients)		
		Cancer	5.1		
von Baum 2010 [70]	Patients with CAP, with/without EB or PA [*p<0.05; **p≤0.01; ***p≤0.001 vs. no EB/PA]		**No EB/PA (n=1833)**	**Confirmed EB (n=67)**	**Confirmed PA (n=22)**
		Chronic respiratory disease	37	45	68**
		Renal failure	6	22***	NR
		Congestive heart failure	14	46***	NR
		Cerebrovascular disease	5	33***	32***
		Other chronic neurological disorder	3	15***	18***
		Diabetes mellitus	13	30***	27*
		Enteral tube feeding	0.5	4.5***	23***

AIDS, acquired immune deficiency syndrome; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; EB/PA, Enterobacteriaceae and/or *Pseudomonas aeruginosa*; GP, General Practitioner; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICU, intensive care unit; LRTI, lower respiratory tract infection; NR, not reported; yr/yrs, year/years.

*This study included 10 patients aged ≤14 years.