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

Antoni Torres,¹ Willy E Peetermans,² Giovanni Viegi,^{3,4} Francesco Blasi⁵

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¹Servei de Pneumologia, Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), CIBER de Enfermedades Respiratorias (CIBERes), University of Barcelona, Barcelona, Spain

²Department of Internal Medicine, University Hospital, KU Leuven, Leuven, Belgium

³CNR Institute of Clinical Physiology, Pisa, Italy

⁴CNR Institute of Biomedicine and Molecular Immunology, Palermo, Italy

⁵Department of Pathophysiology and Transplantation, University of Milan, IRCCS Fondazione Cà Granda Ospedale Maggiore, Milan, Italy

Correspondence to

Professor Antoni Torres, Servei de Pneumologia, Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), CIBER de Enfermedades Respiratorias (CIBERes), University of Barcelona, 08036 Barcelona, Spain; ATORRES@clinic.ub.es

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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
<ul style="list-style-type: none"> ▶ Age ▶ Lifestyle <ul style="list-style-type: none"> – Alcoholism – Smoking ▶ Underlying diseases <ul style="list-style-type: none"> – Chronic heart disease – Chronic renal disease – Chronic liver disease – Chronic respiratory disease – Metabolic disease – CNS disease ▶ Prior IPD ▶ Previous pneumonia ▶ Other <ul style="list-style-type: none"> – Aspiration – Concomitant treatment 	<ul style="list-style-type: none"> ▶ Immunosuppression <ul style="list-style-type: none"> – 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 <ul style="list-style-type: none"> – Asplenia/splenic dysfunction – Primary immunodeficiencies ▶ HIV

CNS, central nervous system; IPD invasive pneumococcal disease.

authors identified one additional reference¹⁰ 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 paper¹¹ 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 years²² 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 bacteria³⁵ 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.

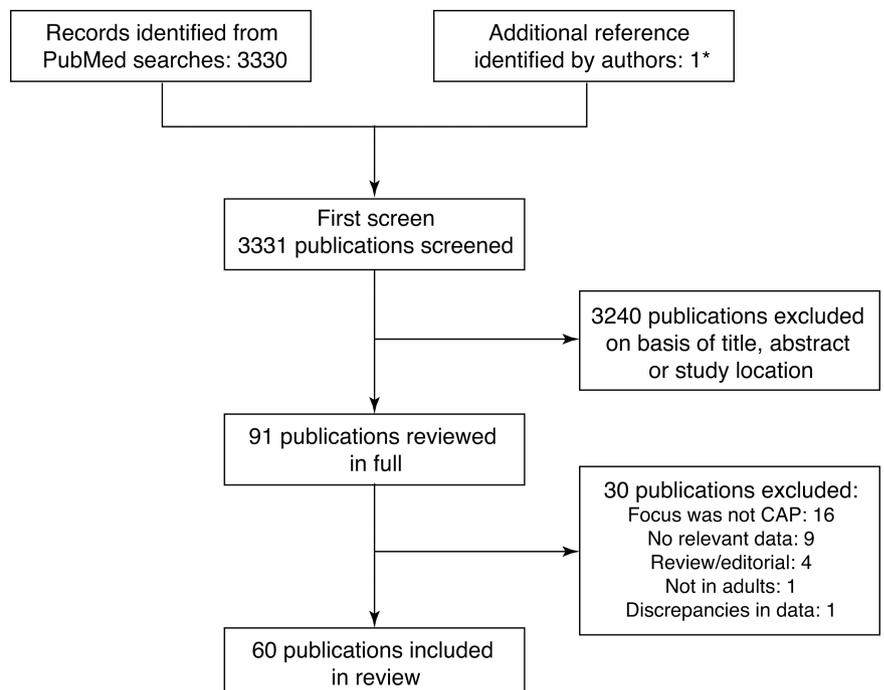


Table 2 Incidence of community-acquired pneumonia (CAP) in adults in Europe

Study	Country; region	Study period	CAP incidence (95% CI)
Overall population			
Almirall <i>et al</i> ³⁸	Spain; east coast	1 November 1999–30 November 2000	Per 1000 population >14 years: 1.54
Gutierrez <i>et al</i> ³⁹	Spain; Alicante	15 October 1999–14 October 2001	Per 1000 person-years: Overall, 1.230 Men, 1.556 Women, 0.911
Rodriguez <i>et al</i> 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 <i>et al</i> ^{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 <i>et al</i> 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 <i>et al</i> ⁴¹	UK; Nottingham	September 2008–September 2010	Per 1000 population ≥16 years: Overall, 1.097
Ewig <i>et al</i> 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 <i>et al</i> ¹⁷	Denmark; Copenhagen and Aarhus	December 1993–April 2008	Per 1000 person-years, >50 years: Men, 4.2 Women, 3.4
Kornum <i>et al</i> 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 <i>et al</i> 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 <i>et al</i> ^{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 <i>et al</i> ²⁴	France; Aquitaine	2000–2007	Per 1000 patient-years: Overall: 12.0 (9.9 to 14.0)
Curran <i>et al</i> 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 <i>et al</i> 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 <i>et al</i> ^{27‡}	Italy; northern Sardinia	January 1999–December 2004	Per 1000 inpatients/year: 1999, 177 2004, 280
Saindou <i>et al</i> 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 study³⁶ 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

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.

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).

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 UK⁴² for overall incidence rates; Denmark,^{17 18} Germany³⁶ and the UK⁴¹ 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 CAP⁸ 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 <i>Streptococcus pneumoniae</i>	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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