

Incidence and predictive factors of lower respiratory tract infections among the very elderly in the general population. The Leiden 85-plus Study.

Annemarie Sliedrecht,* † Wendy P.J. den Elzen,† Theo J.M. Verheij, MD, PhD,* Rudi G.J. Westendorp, MD, PhD,‡ Jacobijn Gussekloo, MD, PhD,†

*Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands.

†Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, The Netherlands

‡Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands

Corresponding author:

Dr. J. Gussekloo, MD, PhD

Department of Public Health and Primary Care

Leiden University Medical Center

Post zone V-0-P

P.O. Box 9600

2300 RC LEIDEN

The Netherlands

Tel: 0031-71-526 8444

Fax: 0031-71-526 8259

jgussekloo@lumc.nl

Running head: lower respiratory tract infections in old age

Word count: abstract 195 words, body of the text 2726 words

ABSTRACT

OBJECTIVES: To target preventive strategies in old age, we investigated which very elderly are predisposed to developing lower respiratory tract infections.

DESIGN: Prospective observational follow-up study.

SETTING: General population.

PARTICIPANTS: Unselected cohort of 587 participants aged 85 years in Leiden, the Netherlands.

MEASUREMENTS: As reported in the literature, predictive factors were selected and assessed at baseline. During a five year follow-up period, information on the development of lower respiratory tract infections was obtained from general practitioners or nursing home physicians. Associations between predictive factors were analysed with Cox regression and population attributable risks were calculated.

RESULTS: The incidence of lower respiratory tract infections among persons aged 85 through 90 years was 94 (95% CI 80-108) per 1000 person-years. After multivariate analysis, history of COPD, smoking, oral glucocorticosteroid use, severe cognitive impairment, history of stroke and declined functional status remained independently associated with the occurrence of lower respiratory tract infections. Smoking was the greatest contributor with a population attributable risk of 32%.

CONCLUSION: In the very old, smoking, COPD, stroke and declined functional status were associated with the occurrence of lower respiratory tract infections and provide means to target patients at risk of severe health complications.

Keywords: 'lower respiratory tract infections', 'predictive factors', 'aged 85 years and over'

INTRODUCTION

In the very elderly, the impact of lower respiratory tract infections is high, not only because of a high incidence, but also because elderly patients are likely to develop medical complications, be admitted to the hospital or die from lower respiratory tract infections.¹⁻⁵ Since the incidence of lower respiratory tract infections increases with age,^{1,2,6} timely diagnosis and treatment of lower respiratory tract infections and preventive strategies against its occurrence, for instance pneumococcal vaccination,⁷⁻¹⁰ should be emphasized.

For introducing these preventive strategies, it is important to know which subgroups of the very elderly population are predisposed to developing lower respiratory tract infections. Earlier studies have shown that increasing age,^{3,4} institutionalization,^{4,5} smoking,^{3,5,11} alcoholism,⁴ pulmonary disease,^{4,5,11} heart disease,^{4,5} neurological disease⁵ and immunosuppressive therapy⁴ may be contributing factors in the susceptibility of individuals to lower respiratory tract infections. However, until now no studies have been performed among the very elderly in the general population among whom the incidence is highest. Most previous studies that have investigated factors associated with lower respiratory tract infections included hospitalized patients and concerned the prognosis of patients with community acquired pneumonia (CAP) only.¹²⁻²⁰

The purpose of this study was to determine the incidence and predictive factors of lower respiratory tract infections among persons aged 85 years and over in the general population in order to provide more insight into which subgroups of the very elderly are at the highest risk of developing lower respiratory tract infections.

METHODS

Setting and study population

The Leiden 85-plus Study is an observational population-based prospective study of 85-year-old inhabitants of Leiden, the Netherlands. The overall aim was to investigate determinants and preventable causes of unsuccessful aging and to explore the possibilities for investing in successful aging.

Between September 1997 and September 1999, all inhabitants of Leiden who reached the age of 85 years were invited to participate in the study. There were no selection criteria concerning health or demographic characteristics. Participants were followed for five years until the age of 90 years or until death. At baseline, all participants were visited at their place of residence where face-to-face interviews were conducted, cognitive testing was performed, information on income, education and disabilities in daily activities was obtained, and a venous blood sample was drawn.

All participants gave informed consent; for people who were severely cognitively impaired, a guardian gave informed consent. The Medical Ethics Committee of Leiden University Medical Center approved the study.

Dates of death were obtained from the municipality. Specific data on causes of death were obtained from Statistics Netherlands, according to the International Classification of Diseases and Related Disorders, 10th revision (ICD-10). The assignment of causes of death was done independently of the risk factors that were determined at age 85 years.

Lower respiratory tract infection

The endpoint of this study was the development of the first lower respiratory tract infection during the follow-up period. This endpoint was considered present when a treating general practitioner or nursing home physician diagnosed a lower respiratory tract infection based on history taking, physical examination and clinical judgement. These data were gathered during annual interviews with participating physicians. The endpoint was also reached when a participant without clinical diagnosis of lower respiratory tract infection during follow-up died from pneumonia.

Selection of potentially predictive factors

Based on a search of the medical literature^{1,2,4-6,11-13} factors potentially associated with lower respiratory tract infections in the elderly were identified and selected for study. They were categorized as socio-demographic factors, functioning, co-morbidities and medication use. All potentially predictive factors were assessed when participants enrolled in the study at the age of 85 years.

Socio-demographic factors During baseline interviews, a research nurse collected information concerning participants' residency, income, level of education and smoking habits.

Functioning To assess cognitive function the Mini-Mental State Examination (MMSE) was used. Severe cognitive impairment was defined as a MMSE score below 19 points.²¹ In order to determine the presence of depressive symptoms, the Geriatric Depression Scale-15 (GDS-15) was performed; depressive symptoms were considered present in cases where a GDS-score was above 4 points. The GDS-15 was only administered to participants with sufficient cognitive function, i.e. to those with a MMSE score of 19 points or higher.²¹ Disability in basic activities of daily life (ADL) was determined using the Groningen Activity Restriction Scale (GARS). We defined disability as being unable to do any one of the following nine

basic ADL independently: walk inside, get out of bed, get into and out of a chair, use the toilet, wash hands and face, wash body, dress and undress, eat and drink, and make breakfast.²¹

Co-morbidities and medication use Information on participants' medical history was obtained by standardized interviews with their treating general practitioner or nursing home physician. Information on participant's use of medication was obtained by interviewing their pharmacists. We obtained clinical information on the presence of diabetes mellitus, hypertension, myocardial infarction, stroke, heart failure and cancer. The presence of COPD was considered present when the diagnosis of COPD was reported by the treating physician or when lung medication (Anatomical Therapeutic Chemical (ATC) code R03) was used at age 85 years. Information on the use of glucocorticosteroids, was obtained from the participants' pharmacists and was also coded according to the ATC classification.²² The presence of anemia was based on baseline hemoglobin level, which was determined by an automated system (Coulter Counter, Coulter Electronics, Hialeah, Fla). Anemia was defined according to WHO criteria: Hb < 7.5 mmol/L for women and Hb < 8.1 mmol/L for men.²³ Creatinine clearance and urea were determined as measures of renal function. Serum creatinine concentration was measured automatically according to the Jaffe method (Hitachi 747; Hitachi, Tokyo, Japan). Creatinine clearance was calculated from serum creatinine concentration and body weight, using the Cockcroft-Gault formula.²⁴ Low creatinine clearance was defined as creatinine clearance < 30 mL/min. Urea was measured in serum by means of a colorimetric method. Urea levels > 7.5 mmol/L were considered elevated urea levels. To further assess general health status, we determined C-reactive protein (CRP) levels with a fully automated Hitachi 911 analysis system. CRP levels > 5 mg/L were considered elevated CRP levels.

Data analyses

The incidence of lower respiratory tract infections from age 85 years onwards was calculated during 5 years of follow-up, using the life-table method. The number of first time lower respiratory tract infections was assigned to the nominator and the observed person-years at risk was assigned to the denominator.

Factors which predicted the occurrence of lower respiratory tract infections in participants after the age of 85 years were investigated with Cox regression proportional hazard models. Those factors associated with lower respiratory tract infections in the univariate Cox regression analysis with a p-value below 0.10 were included in a multivariate Cox regression model. Since the GDS-15 was only administered to participants without cognitive impairment (a MMSE score of 19 points or higher, n=491), the variable "depressive symptoms" was not included in the multivariate analysis.

The relative contribution of the different factors to the occurrence of lower respiratory tract infections was determined by population attributable risks (PAR), which combine the relative risk and the prevalence of the different factors.

Data analyses were conducted using SPSS for Windows, version 12.0 (SPSS inc., Chicago, Illinois, USA).

RESULTS

Study population

Between September 1997 and September 1999, 705 participants were eligible for participation in the Leiden 85-plus Study. Ninety-two participants refused to participate and 14 participants died before enrolment, resulting in a study population of 599 participants (response rate of 87%).²⁵

For the present study, 12 participants for which valid clinical information about lower respiratory tract infections was missing were excluded. Therefore, our study population consisted of 587 persons. By the end of the follow-up period, there were still 273 participants aged 90 years (Figure 1). During the 5-year follow-up period, 50 individuals refused further participation in the study and 264 individuals died. Primary causes of death were completed for 263 of the 264 participants. In total 39.5% died due to cardiovascular causes (ICD-10 I00-99) and 60.5% died due to noncardiovascular causes (all other ICD-10 codes). Of those, 17 participants had infection as primary cause of death, of whom 16 died due to pneumonia (ICD-10 J17). Of the deceased participants episodes of lower respiratory tract infections were registered until death occurred.

Table 1 shows the baseline characteristics of study participants at the age of 85 years (n = 587). One third of the population was male and 15% of participants were institutionalized. One third of the population was restricted in their daily activities and over 15% was severely cognitively impaired.

Incidence of lower respiratory tract infections

In 5 years' follow-up, 173 first episodes of lower respiratory tract infections were observed during 1845 person-years (py) at risk, resulting in an overall incidence of lower respiratory tract infections of 94 (95% CI 80-108) per 1000 py. During the follow-up period 53 participants had recurrent lower respiratory tract infections (9% of total population, 31% of participants with lower respiratory tract infections).

Predictive factors of lower respiratory tract infections

Table 2 shows the incidences of lower respiratory tract infections in various groups for all selected potentially predictive factors with concomitant univariate hazard ratios (HRs). The occurrence of lower respiratory tract infections was associated with (listed from highest to lowest HR) COPD, oral glucocorticosteroid use, medical history of stroke, severe cognitive impairment, smoking, disability in daily living, CRP >5 mg/L, institutionalization, depressive symptoms and male gender (table 2). Additional analyses showed that previous smokers (n=186) had a 1.92 (95% CI 1.37-2.68) increased risk to develop a lower respiratory tract infection compared to participants who had never smoked; for current smokers (n=92) this risk was 2.17 (95% CI 1.42-3.29). The occurrence of lower respiratory tract infections was not associated with socio-economic status (measured by income and educational level), renal function (measured by creatinine clearance and plasma level of urea) and diabetes mellitus (Table 2). Participants who had no influenza vaccination in the year before age 85 years had similar risks to develop lower respiratory tract infections as those who had an influenza vaccination (HR 0.82, 95% CI 0.56-1.20).

After multivariate analysis the following predictive factors remained significantly associated with the occurrence of lower respiratory tract infections (Table 3): COPD, oral glucocorticosteroid use, current and previous smoking, severe cognitive impairment, medical history of stroke and disability in daily living.

Population attributable risk

To further assess the relative contribution of the various factors to the occurrence of lower respiratory tract infections in the general population from age 85 years onwards, the Population Attributable Risk (PAR) of each variable that remained predictive of lower respiratory tract infections in the multivariate analysis was determined (Table 4). The highest PARs were revealed for current and previous smoking (32%), disability (21%), male gender (15%) and COPD (15%).

DISCUSSION

In this population-based prospective follow-up study of the very elderly, the incidence of lower respiratory tract infections was 94 per 1000 person years at risk. COPD, oral glucocorticosteroid use, smoking, severe cognitive impairment, medical history of stroke and disability in daily living were among the strongest predictive factors for developing lower respiratory tract infections between the age of 85 and 90 years. The population attributable risk was highest for smoking (32%).

In previous studies, the incidence of lower respiratory tract infections (defined as pneumonia and acute bronchitis) in persons aged 65 to 74 years was 42 per 1000 py,² and increased to 70 per 1000 py among persons aged 75 years and over.⁶ In the present study in persons from age 85 years onwards, the incidence of lower respiratory tract infections was 94 per 1000 py. Thus the outcome of our study corroborates these earlier findings and supports the hypothesis that the incidence of lower respiratory tract infections increases with age, even in the higher age ranges.³⁻⁵

It is well-known that patients with COPD have a higher rate of lower respiratory tract infections than those without COPD.^{3-5,11,26-28} Indeed, in our study population, the presence of COPD was a predictor of lower respiratory tract infections. Interestingly, however, smoking carries an equal risk and contributed even stronger to lower respiratory tract infections in our study. It is possible that clinically undiagnosed COPD in elderly current and previous smokers underlies part of these associations. An additional likely explanation is that smoking impairs immunological processes in the lung and directly causes an increased risk of respiratory tract infections in smokers.²⁹⁻³¹

In our study, factors reflecting declined functional status (severe cognitive impairment and disability in daily living) were also found to be predictors of lower respiratory tract infections from the age of 85 years onwards. Our results confirm the findings of the study by Lipsky et al., who found a relation between both dementia and stroke and pneumococcal pneumonia in patients, aged 50-80 years.⁵ Since more than one third of our population-based sample was restricted in their functioning, declined functional status importantly contributes to the occurrence of lower respiratory tract infections in the general population, reflected by a total PAR of 33%.

Lower respiratory tract infection is a known complication of clinical influenza infection, especially in the elderly. With influenza vaccination, the incidence of both influenza and its complications will be lowered. Therefore influenza vaccination will be offered especially to elderly at risk for lower respiratory tract infections. Interestingly, in this study we found that participants who had no influenza vaccination in the year before age 85 years had similar risks to develop lower respiratory tract infections as those who had received a vaccination (HR 0.82, 95% CI 0.56-1.20). This may be a positive vaccination effect, since those elderly who received the influenza vaccination were expected to have a higher risk of lower respiratory tract infections.

Although diabetes mellitus is reportedly associated with a greater predisposition to infections,³²⁻³⁵ we did not find any association between diabetes mellitus and lower respiratory tract infections. This finding is in line with the findings of three other investigations on this topic.^{3,5,11} Recently, a Dutch study showed that patients with type 2 diabetes mellitus had a higher risk of lower respiratory tract infections, compared to patients with hypertension (OR

1.3 (95% CI 1.1-1.5)).³⁵ Differences in age, type of diabetes and definition of lower respiratory tract infections possibly underlie the inconsistency with our data and might also explain the inconsistent findings.

The present study is a unique population-based sample of participants aged 85 years and over, with extensive baseline measurement and almost complete follow-up for morbidity and mortality. To our knowledge, we are the first to examine the incidence and predictive factors of lower respiratory tract infections in a large group of unselected 85-year-olds in a population-based setting.

It may be considered as a limitation of our study that lower respiratory tract infections were not diagnosed by standardized diagnostic procedure including chest radiography, sputum and blood cultures. In our study, however, all lower respiratory tract infections have been clinically diagnosed by general practitioners and nursing home physicians based on medical history taking, physical examination and clinical judgment during a consultation of the patient. In the preparation phase of the Leiden 85-plus Study, we decided to measure lower respiratory tract infections instead of pneumonia because this latter diagnosis is generally known to be inaccurate in elderly patients in primary care, since diagnostic procedures such as chest radiography, sputum, and blood cultures are not usually carried out³. Due to this design, we do not have any information about the incidence of the sub diagnosis viral pneumonia, bacterial pneumonia or acute bronchitis. This procedure, however, reflects usual primary care and enables generalization of our results to daily care.

What is the clinical importance of our findings? Since most developed countries face population ageing and the incidence of lower respiratory tract infections increases with age, it is important to consider preventive and early clinical management strategies for lower respiratory tract infections in the very elderly. For very elderly at high risk for lower respiratory tract infections, two strategies of prevention are possible. First, elderly with changeable risk factors could be advised to reduce exposure to these factors; very elderly who currently smoke could be advised to stop or reduce smoking, and unnecessary use of glucocorticoids could be reduced. Second, those very elderly at risk could be firmly advised to apply for influenza and pneumococcal vaccination. Before giving these advices and changing current guidelines, however, effects of both strategies on reducing lower respiratory tract infections in very elderly people have to be studied in randomized intervention studies.

"The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non-exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article to be published in Thorax editions and any other BMJ PGL products to exploit all subsidiary rights, as set out in our licence <http://thorax.bmjournals.com/fora/licence.pdf> "

REFERENCES

1. Seppä Y, Bloigu A, Honkanen PO et al. Severity assessment of lower respiratory tract infection in elderly patients in primary care. *Arch Intern Med.* 2001; 161: 2709-2713.
2. Bont J, Hak E, Hoes AW et al. A prediction rule for elder primary care patients with lower respiratory tract infections. *Eur Respir J.* 2007; 29: 969-975.
3. Farr BM, Woodhead MA, Macfarlane JT et al. Risk factors for community-acquired pneumonia diagnosed by general practitioners in the community. *Respir Med.* 2000; 94: 422-427.
4. Koivula I, Sten M, Mäkelä PH. Risk factors for pneumonia in the elderly. *Am J Med.* 1994; 96: 313-320.
5. Lipsky BA, Boyko EJ, Inui TS et al. Risk factors for acquiring Pneumococcal infections. *Arch Intern Med.* 1986; 146: 2179-2185.
6. Hak E, Rovers MM, Kuyvenhoven MM et al. Incidence of GP-diagnosed respiratory tract infections according to age, gender and high risk co-morbidity: the Second Dutch National Survey of General Practice. *Family Practice.* 2006; 23: 291-294.
7. Posfay-Barbe KM, Wald ER. Pneumococcal vaccines: do they prevent infection and how? *Curr Opin Infect Dis.* 2004; 17: 177-184.
8. Bogaert D, Hermans PWM, Adrian PV et al. Pneumococcal vaccines: an update on current strategies. *Vaccine.* 2004; 22: 2209-2220.
9. Vila-Córcoles A, Ochoa-Gondar O, Hospital I et al. Protective effects of the 23-valent pneumococcal polysaccharide vaccine in the elderly population: the EVAN-65 study. *Clin Infect Dis.* 2006; 43: 860-868.
10. Christenson B, Hedlund J, Lundbergh P et al. Additive preventive effect of influenza and pneumococcal vaccines in elderly persons. *Eur Respir J.* 2004; 23: 363-368.
11. Almirall J, Bolívar I, Balanzó X et al. Risk factors for community-acquired pneumonia in adults: a population-based case-control study. *Eur respir J.* 1999; 13: 349-355.
12. Bauer TT, Ewig S, Marre R et al. CRB-65 predicts death from community-acquired pneumonia. *J Intern Med.* 2006; 260: 93-101.
13. Riquelme R, Torres A, El-Ebiary M et al. Community-acquired pneumonia in the elderly: a multivariate analysis of risk and prognostic factors. *Am J Respir Crit Care Med.* 1996; 154: 1450-1455.
14. Fernandez-Sabe N, Carratala J, Roson B et al. Community-acquired pneumonia in very elderly patients: causative organisms, clinical characteristics, and outcomes. *Medicine.* 2003; 82: 159-169.
15. Lim WS, Macfarlane JT. Defining prognostic factors in the elderly with CAP: a case controlled study of patients aged ≥ 75 yrs. *Eur Respir J.* 2001; 17: 200-205.
16. Naito T, Suda T, Yasuda K et al. A validation and potential modification of the pneumonia severity index in elderly patients with community-acquired pneumonia. *J Am Geriatr Soc.* 2006; 54: 1212-1219.
17. Brancati FL, Chow JW, Wagener MM et al. Is pneumonia really the old man's friend? Two-year prognosis after CAP. *Lancet* 1993; 342: 30-33.
18. Conte HA, Chen YT, Mehal W et al. A prognostic rule for elderly patients admitted with community-acquired pneumonia. *Am J Med.* 1999; 106: 20-28.
19. Fine MJ, Smith MA, Carson CA et al. Prognosis and outcomes of patients with community-acquired pneumonia. A Meta-analysis. *JAMA.* 1996; 275: 134-141.
20. Lim WS, Lewis S, Macfarlane JT. Severity prediction rules in CAP: a validation study. *Thorax.* 2000; 55: 219-223.
21. Bootsma-van der Wiel A, Gussekloo J, de Craen AJM et al. Disability in the oldest old: "can do" or "do do"? *J Am Geriatr Soc.* 2001; 49: 909-914.

22. Guidelines for ATC Classification and DDD Assignment. Oslo, Norway: World Health Organization Collaborating Centre for Drug Statistics Methodology, 1996.
23. Nutritional anaemias. Report of a WHO scientific group. World Health Organ Tech Rep Ser 1968; 405:5-37.
24. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976; 16: 31–41.
25. der Wiel AB, van Exel E, de Craen AJ et al. A high response is not essential to prevent selection bias: results from the Leiden 85-plus study. *J Clin Epidemiol*. 2002; 55: 1119-1125.
26. Monto AS, Millicent WH, Ross HW. The Tecumseh study of respiratory illness. VIII. Acute infection in chronic respiratory disease and comparison groups. *Am Rev Respir Dis*. 1975; 111:27-36.
27. McNamara MJ, Phillips IA, Williams OB. Viral and *Mycoplasma pneumoniae* infections in exacerbations of chronic lung disease. *Am Rev Respir Dis*. 1969; 100:19-24.
28. Westerberg SC, Smith CB, Renzetti AD. *Mycoplasma* infections in patients with chronic obstructive pulmonary disease. *J Infect Dis*. 1973; 127:491-7.
29. Stringer KA, Tobias M, O'Neill HC et al. Cigarette smoke extract-induced suppression of caspase-3-like activity impairs human neutrophil phagocytosis. *Am J Physiol Lung Cell Mol Physiol*. 2007; 292: L1572-1579.
30. Baik I, Curhan GC, Rimm EB et al. A prospective study of age and lifestyle factors in relation to community-acquired pneumonia in US men and women. *Arch Intern Med*. 2000; 160: 3082-3088.
31. Klement E, Talkinton DF, Wasserzug O et al. Identification of risk factors for infection in an outbreak of *Mycoplasma pneumoniae* respiratory tract disease. *Clin Infect Dis*. 2006; 43: 1239-1245.
32. Shah BR, Hux JE. Quantifying the risk of infectious disease for people with diabetes. *Diabetes Care*. 2003; 26: 510-513.
33. Calvet HM, Yoshikawa TT. Infections in diabetes. *Infect Dis Clin North Am*. 2001; 15: 407-421.
34. Pozzilli P, Leslie RDG. Infections and diabetes: mechanisms and prospects for prevention. *Diabet Med*. 1994; 11: 935-941.
35. Muller LM, Gorter KJ, Hak E et al. Increased risk of infection in patients with diabetes mellitus type 1 or 2. *Ned Tijdschr Geneesk*. 2006; 150: 549-553. Dutch.

Table 1. Baseline characteristics of the study population at age 85 years (n = 587)

	n (%)
<i>Socio-demographic factors</i>	
Male	199 (34%)
Institutionalized*	104 (18%)
Minimum income	93 (16%)
Primary school only	380 (65%)
Smoking (current or previous)	278 (48%)
No yearly influenza vaccine before 85 years old	133 (24%)
<i>Functioning</i>	
Severe cognitive impairment (MMSE < 19)	96 (16%)
Depressive symptoms (GDS-15 > 4)	75 (15%)
Disability in daily living†	201 (34%)
<i>Co-morbidities and medication use</i>	
Diabetes mellitus	85 (15%)
Hypertension	226 (39%)
Myocardial infarction	62 (11%)
Stroke	59 (10%)
Heart failure	74 (13%)
Chronic obstructive pulmonary disease	69 (12%)
Cancer	104 (18%)
Anemia□□	149 (27%)
Oral glucocorticosteroid use	11 (2%)
Creatinine clearance < 30 mL/min	41 (8%)
Urea > 7.5 mmol/L	233 (42%)
CRP > 5 mg/L	188 (34%)

MMSE = 'Mini-Mental State Examination'; GDS-15 = 'Geriatric depression scale' with 15 items (only administered to participants with MMSE-score \geq 19 (n = 491)); CRP = 'C-reactive protein'.

* Institutionalized = nursing- or retirement home resident.

† Disability in daily living = unable to do any one of nine basic activities of daily living independently, according to the Groningen Activity restriction Scale

□□ Hb_{female} < 7.5 mmol/L, Hb_{male} < 8.1 mmol/L.

Table 2. Incidences of lower respiratory tract infections in index- and reference groups with the corresponding hazard ratios after univariate Cox regression analysis.

	N	Incidence in index group, per 1000 py (95% CI)	Incidence in reference group*, per 1000 py (95% CI)	HR (95% CI)
<i>Socio-demographic factors</i>				
Male	199	128.5 (98.4 – 158.6)	79.2 (63.9 – 94.5)	1.55 (1.14–2.10)
Institutionalized†	104	153.0 (105.0 – 201.1)	84.3 (70.0 – 98.5)	1.73 (1.21-2.48)
Minimum income	93	92.8 (57.8 – 127.8)	93.4 (78.1 – 108.7)	1.00 (0.66-1.50)
Only primary school	380	101.6 (83.3 – 120.0)	79.6 (58.3 – 100.8)	1.27 (0.92-1.76)
Smoking, current or previous	278	133.0 (107.5 – 158.6)	63.5 (48.2 – 78.9)	2.00 (1.47-2.73)
No yearly influenza vaccine < 85 yr	133	79.3 (52.6 – 105.9)	97.1 (80.4 – 113.8)	0.82 (0.56-1.20)
<i>Functioning</i>				
Severe cognitive impairment, MMSE < 19	96	178.9 (122.0 – 235.7)	82.7 (68.7 – 96.6)	2.10 (1.46-3.02)
Depressive symptoms, GDS-15 > 4	69	126.3 (79.5 – 173.1)	75.8 (61.5 – 90.2)	1.61 (1.06-2.44)
Disability in daily living‡	201	147.0 (113.8 – 180.3)	73.9 (59.3 – 88.5)	1.94 (1.43–2.62)
<i>Co-morbidities and medication use</i>				
Diabetes mellitus	85	95.6 (56.5 – 134.7)	93.3 (78.4 – 108.3)	1.00 (0.65-1.56)
Hypertension	226	101.5 (77.9 – 125.1)	89.0 (71.8 – 106.3)	1.13 (0.84-1.53)
Myocardial infarct	62	118.0 (64.9 – 171.1)	91.1 (76.7 – 105.6)	1.26 (0.78-2.03)
Stroke	59	206.2 (129.9 – 282.6)	85.2 (71.3 – 99.0)	2.26 (1.50-3.39)
Heart failure	74	115.6 (66.1 165.0)	90.3 (75.9 – 104.8)	1.23 (0.78-1.94)
Chronic obstructive pulmonary disease	69	270.6 (184.5 – 356.6)	79.2 (65.8 – 92.6)	3.07 (2.13-4.41)
Cancer	104	110.6 (71.7 – 149.5)	91.0 (76.1 – 106.0)	0.86 (0.58-1.27)
Anaemia¶	149	106.3 (74.5 – 138.0)	87.2 (71.5 – 102.9)	1.19 (0.84-1.69)
Oral glucocorticosteroid use	11	266.3 (69.0 – 463.5)	91.5 (77.6 – 105.4)	2.77 (1.30–5.89)
Creatinine clearance < 30 mL/min	41	121.6 (52.8 – 190.4)	89.5 (75.0 – 104.0)	1.35 (0.75–2.44)
Urea > 7.5 mmol/L	233	105.3 (80.8 – 129.8)	83.1 (66.0 – 100.2)	1.23 (0.90-1.68)
CRP > 5 mg/L	188	138.7 (105.7 – 171.7)	73.5 (58.7 – 88.4)	1.82 (1.33-2.49)
<i>Overall incidence of lower respiratory tract infections</i>		93.8 (79.8-107.7)		

py = 'person-years'; CI = 'confidence interval'; HR = 'hazard ratio'; yr = year; MMSE = 'Mini-Mental State Examination'; GDS-15 = 'Geriatric Depression Scale' with 15 items (only administered to participants with MMSE-score ≥ 19 (n = 491)); CRP = 'C-reactive protein'.

* Definition of reference groups: females, living independently, pension or other extra incomes, additional education after primary school, non-smoking, yearly influenza vaccine, not severely cognitively impaired (MMSE ≥ 19), no depressive symptoms (GDS-15 ≤ 4), not disabled (see definition[§]), no co-morbidity, no oral glucocorticosteroid use, CRP ≤ 5 mg/L, creatinine clearance ≥ 30 mL/min, urea ≤ 7.5 mmol/L.

† Institutionalized = nursing- or retirement home resident.

‡ Disability in daily living = being unable to do any one of the nine basic activities of daily living independently.

¶ $\text{Hb}_{\text{female}} < 7.5 \text{ mmol/L}$, $\text{Hb}_{\text{male}} < 8.1 \text{ mmol/L}$.

Table 3. Factors associated with increased risk of developing lower respiratory tract infections after age 85 years, by multivariate Cox regression analysis.

	<i>HR (95% CI)</i>
<i>Socio-demographic factors</i>	
Male	1.3 (0.90 – 1.9)
Institutionalized*	1.1 (0.72 – 1.7)
Smoking, current or previous	1.9 (1.3 – 2.8)
<i>Functioning</i>	
Severe cognitive impairment, MMSE < 19	1.7 (1.1 – 2.8)
Disability in daily living†	1.6 (1.1 – 2.3)
<i>Co-morbidities and medication use</i>	
Chronic obstructive pulmonary disease	3.4 (2.3 – 5.0)
Stroke <85 years	1.7 (1.1 – 2.7)
Oral glucocorticosteroid use	2.3 (1.0 – 5.0)
CRP >5 mg/L	1.4 (1.0 – 1.9)

HR = 'hazard ratio'; CI = 'confidence interval'; MMSE = 'Mini Mental State Examination'; CRP = 'C-reactive protein'.

* Institutionalized = nursing- or retirement home resident.

† Disability in daily living = unable to do any one of nine basic activities of daily living independently, according to the Groningen Activity Restriction Scale.

Table 4. Population Attributable Risks (PAR) of the occurrence of lower respiratory tract infections after the age of 85 years, for factors that remained predictive after multivariate analysis.

	<i>PAR (%)</i>
<i>Socio-demographic factors</i>	
Male (n = 199)	15 %
Institutionalized* (n = 104)	10 %
Smoking, current or previous (n = 278)	32 %
<i>Functioning</i>	
Severe cognitive impairment, MMSE < 19 (n = 96)	12 %
Disability in daily living† (n = 201)	21 %
<i>Co-morbidities and medication use</i>	
Stroke (n = 59)	9 %
Chronic obstructive pulmonary disease (n = 69)	15 %
Oral glucocorticosteroid use (n = 11)	2 %
CRP > 5 mg/L (n = 188)	11 %

PAR = 'population attributable risk'; MMSE = 'Mini-Mental State Examination'; CRP = 'C-reactive protein'.

* Institutionalized = nursing- or retirement home resident.

† Disability in daily living = unable to do any one of nine basic activities of daily living independently, according to the Groningen Activity Restriction Scale.

FIGURE 1. The number of participants from age 85 through 90 years in the Leiden 85-plus Study

