

## **Diabetes, Glycemic Control and Risk of Hospitalization with Pneumonia: A Population-based Case-control Study**

Jette B. Kornum<sup>1</sup>, MD; Reimar W. Thomsen<sup>1</sup>, MD, PhD; Anders Riis<sup>1</sup>, MSc; Hans-Henrik Lervang<sup>2</sup>, MD, PhD; Henrik C. Schönheyder<sup>3</sup>, MD, DMSc; Henrik T. Sørensen<sup>1</sup>, MD, DMSc

<sup>1</sup>Department of Clinical Epidemiology, Aarhus University Hospital, Aalborg, Denmark

<sup>2</sup>Department of Endocrinology, Aarhus University Hospital, Aalborg, Denmark

<sup>3</sup>Department of Clinical Microbiology, Aarhus University Hospital, Aalborg, Denmark

### **Corresponding author:**

Jette B. Kornum,

E-mail: [j.kornum@rn.dk](mailto:j.kornum@rn.dk)

Running title: *Diabetes, glycemic control and risk of pneumonia*

Received 21 January 2008 and accepted 10 May 2008.

**Objective:** To examine whether diabetes is a risk factor for hospitalization with pneumonia and to assess the impact of HbA<sub>1c</sub> level on such risk.

**Research Design and Methods:** In this population-based case-control study we identified patients with a first-time pneumonia-related hospitalization between 1997 and 2005, using health care databases in Northern Denmark. For each case, ten sex- and age-matched population controls were selected from Denmark's Civil Registration System. We used conditional logistic regression to compute relative risk (RR) for pneumonia-related hospitalization among persons with and without diabetes, controlling for potential confounding factors.

**Results:** The study included 34,239 patients with a pneumonia-related hospitalization and 342,390 population controls. The adjusted RR for pneumonia-related hospitalization among persons with diabetes was 1.26 (95% confidence interval (CI) 1.21-1.31) compared with nondiabetic individuals. The adjusted RR was 4.43 (95% CI 3.40-5.77) for persons with type 1 diabetes and 1.23 (95% CI 1.19-1.28) for persons with type 2 diabetes. Diabetes duration  $\geq 10$  years increased the risk of a pneumonia-related hospitalization (adjusted RR 1.37; 95% CI 1.28-1.47). Compared with persons without diabetes, the adjusted RR was 1.22 (95% CI 1.14-1.30) for diabetic persons whose HbA<sub>1c</sub> level was  $< 7\%$ , and 1.60 (95% CI 1.44-1.76) for diabetic persons whose HbA<sub>1c</sub> level was  $\geq 9\%$ .

**Conclusions:** Type 1 and type 2 diabetes are risk factors for a pneumonia-related hospitalization. Poor long-term glycemic control among patients with diabetes clearly increases the risk of hospitalization with pneumonia.

**H**ospitalizations with pneumonia have increased by 20%-50% in Western populations during the past ten years (1,2). Combined with influenza, pneumonia is the 7th leading cause of death in the United States (3).

Diabetes is thought to be a risk factor for pneumonia, but available data are few and inconclusive (4-11). Diabetic persons may have increased susceptibility to pneumonia for several reasons. They are at increased risk of aspiration, hyperglycemia, decreased immunity, impaired lung function, pulmonary microangiopathy, and coexisting morbidity (12). Five cohort studies found that diabetes is a risk factor for pneumonia, with relative risks (RRs) ranging from 1.30 to 1.75 (4,6,8-10), while three studies failed to find an association (5,7,11). Existing studies have limitations: some included only patients older than 60 years (8,10,11), one did not adjust for comorbidity (9), and few were population-based (9,11). Only one study of respiratory tract infections distinguished between type 1 and type 2 diabetes (6).

Immunologic abnormalities in diabetic persons are related in part to the harmful effects of hyperglycemia (12). Recently, a cohort study encompassing 10,063 persons followed for 7 years found that each 1 mmol/l increase in baseline plasma glucose was associated with a 6% increase in the relative risk of pneumonia (4). However, this result was based on a single non-fasting glucose measurement. The impact of poor long-term glycemic control on risk of pneumonia-related hospitalization still remains uncertain.

Given the rising incidence of pneumonia-related hospitalizations (1,2) and the increasing prevalence of diabetes (13), it is important to clarify whether diabetes and poor long-term glycemic control is a risk factor for pneumonia. We examined whether diabetes is associated with an increased risk

of pneumonia-related hospitalization and whether this risk is modulated by HbA1c level.

## RESEARCH DESIGN AND METHODS

We conducted this population-based case-control study in the Danish counties of North Jutland and Aarhus, with a mixed rural and urban population of approximately 1.15 million people. The Danish National Health service provides tax-supported health care for all residents, including free access to primary care and hospitals, and reimbursement of a portion of the cost of most prescription drugs (14). Civil registration numbers, unique identifiers assigned to each Danish citizen, which encode birth date and sex, allow accurate linkage among registries.

**Identification of patients hospitalized with pneumonia:** Hospital registries in Aarhus and North Jutland counties contain information on all hospitalizations since 1977 and on all outpatient visits since 1995. Data include dates of admission and discharge and up to 20 discharge diagnoses coded by physicians according to the International Classification of Diseases (10<sup>th</sup> revision (ICD-10) during the study period and 8<sup>th</sup> revision (ICD-8) before 1994). We identified all in-patients with the following first-time discharge diagnoses recorded between 1997 and 2005: pneumonia (J12.x-J18.x), legionellosis (A481.x.), and ornithosis (A709.x) (n=41,850) (2). We excluded 3,977 patients who lived in the counties less than 12 months before the admission date and also excluded eighteen patients born between 1894 and 1906 for whom we could not find controls, and 3,616 patients younger than 15 years of age, leaving 34,239 adult cases in the final analysis set.

**Selection of population controls:** The Central Population Registry, which is updated daily, contains electronic

records of all changes in vital status, including change of address, date of emigration, and date of death, for the entire Danish population since 1968. On the date of each patient's first pneumonia-related hospital admission (the index date), we randomly selected 10 controls from the Central Population Registry, matched by age (same year of birth), sex, and residence (the same county). We employed the risk set sampling technique (15), *i.e.*, eligible controls had to be alive and at risk of a first hospitalization with pneumonia as recorded in their hospital discharge history on the date the corresponding case was admitted.

**Data on diabetes:** For both cases and controls, we identified persons with diabetes from three databases: hospital registries, prescription databases, and the Danish National Health Service Registry. We used the hospital registries to identify all persons with a discharge or outpatient diagnosis of diabetes since 1977 based on the following ICD-codes: ICD-8 codes 249-250 (diabetes mellitus) and ICD-10 codes E10-14, (diabetes mellitus), O24 (diabetes mellitus in pregnancy except for O24.4 (diabetes mellitus arising in pregnancy)), and H36.0 (diabetic retinopathy) (16). From the prescription database, which tracks filled prescriptions for reimbursed drugs dispensed by pharmacies in North Jutland County since 1991 and in Aarhus County since 1996, we identified all persons with at least one recorded prescription for insulin or an oral antidiabetic drug. The Danish National Health Service Registry contains data on all citizens receiving health services, their providers, and specific health services received (17). This registry allowed us to identify persons who had at least one visit to a chiropodist for diabetic foot care, and/or who had at least five glucose-related services (blood glucose measurements performed in general practice) in one year, and/or 2 glucose-related services each year during five subsequent years.

Patients with diabetes were classified as type 1 (those with diabetes first recorded before age 30, using insulin monotherapy, and with no history of oral antidiabetes medications) or type 2 (the remaining diabetes patients). Duration of diabetes was computed as the time elapsed between the first record of diabetes treatment and the index date.

**Data on HbA<sub>1c</sub>:** We obtained information on HbA<sub>1c</sub> levels for diabetic persons through linkage with the counties' laboratory databases. These databases contain information on all specimens submitted for analysis by hospitals and practitioners, including the exact time of blood sample collection. One or more measurements in the 12 months preceding the index hospital admission date were available for 2,731 (61%) patients. One or more measurements in the 12 months preceding the index hospital admission date for the corresponding case were available for 16,605 (58%) controls with diabetes. The most recent HbA<sub>1c</sub> measurement before the index hospital admission date was used in our analysis.

**Data on confounding factors:** Data on confounding factors were collected from the hospital registries, the prescription databases, and the Danish Civil Registration System. Based on all available hospital diagnoses except diabetes, we computed a Charlson comorbidity index score for each person (18). Three comorbidity levels were defined: low (score of 0), medium (1-2), and high ( $\geq 3$ ). We also obtained data on several factors not included in the Charlson index, including history of alcoholism-related conditions (ICD-8 codes 291, 303, 979, 980, 577.10; ICD-10 codes F10, K86.0, Z72.1, R78.0, T51, K29.2, G62.1, G72.1, G31.2, I42.6), use of immunosuppressants within the year before the pneumonia-related admission (ATC-codes L01, L04, H02 AB), and use of systemic antibiotics within 90 days before the admission (ATC-code J01). The Central Population Registry provided data on marital

status (married, never married, divorced or widowed, marital status unknown), persons living with small children attending day care centers (younger than 6 years of age, yes/no), and degree of urbanization (residence in a rural area with a population of 0-10,000, in a provincial town with a population of 10,000-100,000, or in a city with more than 100,000 inhabitants).

**Statistical analysis:** We used conditional logistic regression to compute crude and adjusted odds ratios (ORs) as a measure of relative risk (RR) for pneumonia-related hospitalization among persons with and without diabetes, with associated 95% confidence intervals (CIs). Diabetes exposure was further categorized by type of diabetes, duration of diabetes (<5 years, ≥5-<10 years, ≥10 years), and HbA<sub>1c</sub> level (<7.0%, ≥7.0-<8.0%, ≥8.0-<9.0%, ≥9.0%, unknown). We adjusted for level of comorbidity, history of alcoholism-related conditions, pre-admission use of antibiotics or immunosuppressants, marital status, household presence of small children attending day care centers, and degree of urbanization. Stratified analyses were performed by sex, age group (15-39, 40-64, 65-79, ≥80 years), and level of comorbidity.

All analyses were conducted using Stata software (Version 9). The Danish Data Protection Agency approved the study (Record No. 2006-41-6226).

## RESULTS

**Descriptive data:** We identified 34,239 patients with a first-time pneumonia-related hospitalization (including 127 patients (0.37%) with legionellosis and 16 patients (0.05%) with ornithosis) and 342,390 population controls (Table 1). The study population was 53% male and 47% female, with a median age of 74 years. A total of 101 cases (0.3%) and 187 controls (0.1%) were diagnosed with type 1 diabetes, and 4,388 cases (12.8%), and 28,299 controls (8.3%)

were diagnosed with type 2 diabetes pre-dating the cases' pneumonia-related hospital admissions.

**Risk estimates:** The unadjusted RR for pneumonia-related hospitalization among diabetics compared to non-diabetic persons was 1.68 (95% CI 1.62-1.74) and the adjusted RR was 1.26 (95% CI 1.21-1.31) (Table 2). The adjusted RR was 4.43 (95% CI 3.40-5.77) for type 1 diabetic persons and 1.23 (95% CI 1.19-1.28) for type 2 diabetic persons. Diabetes duration ≥10 years increased the risk of pneumonia-related hospitalization (adjusted RR = 1.37 (95% CI 1.28-1.47)). Exclusion of possible diabetic complications, i.e. myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, and renal disease from the Charlson index and adjusting for the remaining disease categories only in the model, increased the effect of long-term diabetes (adjusted RR for diabetes duration ≥10 years = 1.62; 95% CI 1.52-1.74). Thus, approximately 40% of the apparent long-term diabetes effect was caused by a higher prevalence of renal, cardiovascular, and cerebrovascular disease. HbA<sub>1c</sub> level also influenced the risk of pneumonia-related hospitalization among diabetic persons. Compared with nondiabetic persons, the RR was 1.22 (95% CI 1.14-1.30) among diabetic persons with a HbA<sub>1c</sub> level <7%, and 1.60 (95% CI 1.44-1.76) among diabetic persons with a HbA<sub>1c</sub> level ≥9% (Table 2). Using only HbA<sub>1c</sub> measurements within 6 months instead of 12 months before admission yielded virtually identical risk estimates.

Adult diabetic persons under age 40 were three times more likely to be hospitalized with pneumonia than nondiabetic individuals of similar age, while the relative risk gradually decreased in elderly persons with diabetes (Table 3). After stratifying by level of comorbidity, the association between diabetes and the risk of pneumonia-related hospitalization was highest among persons

with no coexisting morbidity (adjusted RR = 1.51; 95% CI 1.41-1.61). The same trends were observed after further stratifying by diabetes type (Table 3).

## CONCLUSIONS

We found that type 1 diabetes was associated with a 4.4-fold increased risk of a pneumonia-related hospitalization, and type 2 diabetes was associated with a 1.2-fold increased risk. Poor long-term glycemic control and longer diabetes duration clearly increased the risk of pneumonia-related hospitalization. As well, the relative impact of diabetes was greatest in younger adults and in persons without coexisting morbidity.

Our data extend previous studies (4, 6, 8-10) suggesting that diabetes is a risk factor for pneumonia. A Dutch cohort study comparing diabetic patients with an age-matched control group of hypertensive patients, based on records from 195 general practices, showed that diabetic patients had a greater risk of lower respiratory tract infections. (Adjusted OR for patients with type 1 diabetes = 1.42 (95% CI 0.96-2.08) and for patients with type 2 diabetes = 1.32 (95% CI, 1.13-1.53) (6)). However, the category "lower respiratory tract infection" included milder general practitioner-diagnosed cases of acute bronchitis, influenza, pleuritis, emphysema or COPD, and exacerbations of asthma, in addition to pneumonia. In a Canadian cohort study, Shah *et al.* compared all persons with diabetes in Ontario to matched nondiabetic persons (n = 513,749 in each group) (9). In crude analyses, persons with diabetes had an increased risk of pneumonia-related hospitalization or physician claims for pneumonia treatment (RR = 1.46; 99% CI 1.42-1.49). The study did not clarify whether its result was influenced by a higher level of comorbidity among persons with diabetes compared to persons without diabetes. Jackson *et al.* reported that the adjusted RR for hospitalizations for CAP

(community-acquired pneumonia) was 1.52 (95% CI 1.29-1.78) among persons with diabetes compared to persons without diabetes, based on 46,237 persons aged  $\geq 65$  years enrolled in a single health maintenance organization in Washington State (8). These findings may not be generalizable to persons younger than 65 years of age or to the general population.

The main strengths of our study include its large size, population-based design, and adjustment for important confounders made possible through access to medical databases providing a complete medical and prescription history. As well, despite inevitable coding errors, the estimated predictive value of a discharge diagnosis of pneumonia in Denmark is 90% (2). The prevalence of type 2 diabetes cases identified in this study is higher than in our previous cohort study (19) (12.8% vs. 9.8%), due to improved identification of patients with untreated type 2 diabetes. Finally, by using highly valid algorithms to collect data on diabetes and possible confounding factors before the date of hospitalization for pneumonia, we were able to avoid the recall bias present in case-control studies based on interviews or questionnaires.

Limitations include the possibility that physicians are more likely to admit a diabetic patient with pneumonia to the hospital, compared to a nondiabetic patient. Such bias would lead to overestimation of the relative risk associated with diabetes. However, an earlier study showed that pre-admission use of antibiotics, levels of inflammatory markers, and proportions of patients with at least one blood culture were comparable among patients with type 2 diabetes and nondiabetic patients hospitalized with pneumonia (19). This suggests that there was not a severe bias associated with treatment of patients with type 2 diabetes. However, the possibility remains that estimates for patients with type 1 diabetes

were affected by increased surveillance. A previous cohort study examining diabetes as a risk factor for pneumonia-related hospitalizations and outpatient visits suggested that diabetic persons who develop pneumonia are more likely to be hospitalized than nondiabetic persons (hospitalizations for pneumonia, adjusted RR = 1.52; outpatient visits for pneumonia, adjusted RR = 0.90) (8).

We also may have underestimated the duration of diabetes due to undetected type 2 diabetes. However, such misclassification is unlikely to be greater among cases than among controls. As well, lack of data precluded adjustment for pneumococcal and influenza vaccinations, which may reduce the risk of pneumonia. If patients with diabetes were vaccinated at higher rates than others, however, the relative risk of pneumonia-related hospitalizations would be underestimated and would not alter our conclusions.

We found a difference in risk estimates for pneumonia-related hospitalization by type of diabetes, which agrees with the study by Muller *et al* (6). Patients with type 1 diabetes may be more likely to seek medical attention and to be hospitalized due to problems with glucose regulation triggered by pneumonia and risk of ketoacidosis. In addition to increased surveillance, the higher risk of pneumonia-related hospitalization in patients with type 1 diabetes compared to those with type 2 diabetes could also arise from different disease pathogenesis. Unlike type 2 diabetes, type 1 diabetes is characterised by reduced or totally absent insulin secretion. Insulin may itself have anti-inflammatory effects (20). Duration of diabetes has an impact on the risk of pneumonia-related hospitalizations, due perhaps to worsening of microangiopathic changes in the basement membranes of pulmonary blood vessels and respiratory epithelium in diabetic persons (12).

We found that diabetes combined with a HbA<sub>1c</sub> level  $\geq 9\%$  is associated with a 60% increased risk of pneumonia-related hospitalization, while diabetes combined with a HbA<sub>1c</sub> level  $< 7\%$  was associated with a 22% increased risk, compared to persons without diabetes. These results confirm observations from in vitro studies, in which hyperglycemia was associated with abnormalities in neutrophil function such as impaired chemotaxis, phagocytosis, and bacterial killing (21). At the same time, our results do not support the claim that “Infections are no commoner in well-controlled diabetics than in non-diabetic” (22), but rather indicate that the increased susceptibility to pneumonia among diabetic persons has a multifactorial etiology.

We found that the relative risk of pneumonia-related hospitalization declined with age among diabetic persons. Young adults generally have a low incidence of hospitalized pneumonia, which may explain why the relative impact of diabetes is higher.

In conclusion, our data, combined with previous results, provide strong evidence that diabetes is associated with a 25%-75% increase in the relative risk of pneumonia-related hospitalization. Longer duration of diabetes and poor glycemic control increase the risk of pneumonia-related hospitalization. These results emphasize the value of influenza and pneumococcal immunization, particularly for patients with longer diabetes duration, and the importance of improved glycemic control to prevent pneumonia-related hospitalization among diabetic patients.

## ACKNOWLEDGMENTS

This study received financial support from the Western Danish Research Forum for Health Sciences, from “Klinisk Epidemiologisk Forskningsfond”, and from “Århus Universitetshospitals Forskningsinitiativ”, Denmark.

**REFERENCE:**

1. Fry AM, Shay DK, Holman RC, Curns AT, Anderson LJ: Trends in hospitalizations for pneumonia among persons aged 65 years or older in the United States, 1988-2002. *JAMA* 294:2712-2719, 2005
2. Thomsen RW, Riis A, Nørgaard M, Jacobsen J, Christensen S, McDonald CJ, Sørensen HT: Rising incidence and persistently high mortality of hospitalized pneumonia: a 10-year population-based study in Denmark. *J Intern Med* 259:410-417, 2006
3. Kochanek KD, Murphy SL, Anderson RN, Scott C: Deaths: final data for 2002. *Natl Vital Stat Rep* 53:1-115, 2004
4. Benfield T, Jensen JS, Nordestgaard BG: Influence of diabetes and hyperglycaemia on infectious disease hospitalisation and outcome. *Diabetologia* 50:549-554, 2007
5. Lipsky BA, Boyko EJ, Inui TS, Koepsell TD: Risk factors for acquiring pneumococcal infections. *Arch Intern Med* 146:2179-2185, 1986
6. Muller LM, Gorter KJ, Hak E, Goudzwaard WL, Schellevis FG, Hoepelman AI, Rutten GE: Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. *Clin Infect Dis* 41:281-288, 2005
7. Lange P, Vestbo J, Nyboe J: Risk factors for death and hospitalization from pneumonia. A prospective study of a general population. *Eur Respir J* 8:1694-1698, 1995
8. Jackson ML, Neuzil KM, Thompson WW, Shay DK, Yu O, Hanson CA, Jackson LA: The burden of community-acquired pneumonia in seniors: results of a population-based study. *Clin Infect Dis* 39:1642-1650, 2004
9. Shah BR, Hux JE: Quantifying the risk of infectious diseases for people with diabetes. *Diabetes Care* 26:510-513, 2003
10. O'Meara ES, White M, Siscovick DS, Lyles MF, Kuller LH: Hospitalization for pneumonia in the Cardiovascular Health Study: incidence, mortality, and influence on longer-term survival. *J Am Geriatr Soc* 53:1108-1116, 2005
11. Koivula I, Sten M, Makela PH: Risk factors for pneumonia in the elderly. *Am J Med* 96:313-320, 1994
12. Koziel H, Koziel MJ: Pulmonary complications of diabetes mellitus. Pneumonia. *Infect Dis Clin North Am* 9:65-96, 1995
13. Green A, Christian HN, Pramming SK: The changing world demography of type 2 diabetes. *Diabetes Metab Res Rev* 19:3-7, 2003
14. Nielsen GL, Sørensen HT, Zhou W, Steffensen FH, Olsen J: The Pharmacoepidemiologic Prescription Database of North Jutland - a valid tool in pharmacoepidemiological research. *Int J Risk Safety Med* 203-205, 1997
15. Wacholder S, McLaughlin JK, Silverman DT, Mandel JS: Selection of controls in case-control studies. I. Principles. *Am J Epidemiol* 135:1019-1028, 1992
16. Drivsholm TB, Frederiksen K, de Fine ON, Odegaard B, Kristensen JK: [The prevalence of diabetes in Denmark. Development of a method for a registry-based assessment]. *Ugeskr Laeger* 165:2887-2891, 2003
17. Olivarius NF, Hollnagel H, Krasnik A, Pedersen PA, Thorsen H: The Danish National Health Service Register. A tool for primary health care research. *Dan Med Bull* 44:449-453, 1997

18. Charlson ME, Pompei P, Ales KL, MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 40:373-383, 1987
19. Kornum JB, Thomsen RW, Riis A, Lervang HH, Schönheyder HC, Sørensen HT: Type 2 diabetes and pneumonia outcomes: a population-based cohort study. *Diabetes Care* 30:2251-2257, 2007
20. Das UN: Is insulin an antiinflammatory molecule? *Nutrition* 17:409-413, 2001
21. Pozzilli P, Leslie RD: Infections and diabetes: mechanisms and prospects for prevention. *Diabet Med* 11:935-941, 1994
22. Larkin JG, Frier BM, Ireland JT: Diabetes mellitus and infection. *Postgrad Med J* 61:233-237, 1985

Table 1. Characteristics of cases with a first-time hospitalization for pneumonia and population controls from North Jutland and Aarhus Counties, Denmark, 1997-2005.

| Characteristic*               | Cases         | Population controls |
|-------------------------------|---------------|---------------------|
| n                             | 34,239        | 342,390             |
| Diabetes                      |               |                     |
| Absent                        | 29,750 (86.9) | 313,904 (91.7)      |
| Present                       | 4,489 (13.1)  | 28,486 (8.3)        |
| Sex                           |               |                     |
| Male                          | 18,112 (52.9) | 181,120 (52.9)      |
| Female                        | 16,127 (47.1) | 161,270 (47.1)      |
| Median age, years (IQR)       | 74 (61-82)    | 74 (61-82)          |
| Comorbidity index             |               |                     |
| Index low (0)                 | 15,439 (45.1) | 242,645 (70.9)      |
| Index medium (1-2)            | 13,432 (39.2) | 83,088 (24.3)       |
| Index high (3+)               | 5,368 (15.7)  | 16,657 (4.9)        |
| Alcoholism-related conditions | 1,732 (5.1)   | 4,955 (1.5)         |
| Systemic antibiotic therapy   | 11,852 (34.6) | 34,734 (10.1)       |
| Immunosuppressants            | 5,994 (17.5)  | 21,681 (6.3)        |
| Marital status                |               |                     |
| Married                       | 15,863 (46.3) | 178,814 (52.2)      |
| Never married                 | 4,225 (12.3)  | 38,601 (11.3)       |
| Divorced or widow             | 14,064 (41.1) | 124,353 (36.32)     |
| Unknown                       | 87 (0.3)      | 622 (0.2)           |
| Living with small children    | 1,273 (3.7)   | 11,124 (3.3)        |
| Degree of urbanization        |               |                     |
| Rural                         | 6,011 (17.6)  | 61,278 (17.9)       |
| Provincial town               | 15,528 (45.4) | 157,907 (46.1)      |
| City                          | 12,700 (37.1) | 123,205 (36.0)      |

\*Data are n (%), except for age, which is shown as a median (interquartile range).

Table 2. Relative risks (RRs) for hospitalizations associated with pneumonia.

| Exposure                                   | Cases         | Population controls | Unadjusted RR (95%CI) | Adjusted RR* (95% CI) |
|--|---------------|---------------------|-----------------------|-----------------------|
| Diabetes                                   |               |                     |                       |                       |
| Absent                                     | 29,750 (86.9) | 313,904 (91.7)      | 1.0 (ref.)            | 1.0 (ref.)            |
| Present                                    | 4,489 (13.1)  | 28,486 (8.3)        | 1.68 (1.62-1.74)      | 1.26 (1.21-1.31)      |
| Diabetes type                              |               |                     |                       |                       |
| Diabetes absent                            | 29,750 (86.9) | 313,904 (91.7)      | 1.0 (ref.)            | 1.0 (ref.)            |
| Type 1 diabetes                            | 101 (0.3)     | 187 (0.1)           | 5.55 (4.34-7.08)      | 4.43 (3.40-5.77)      |
| Type 2 diabetes                            | 4,388 (12.8)  | 28,299 (8.3)        | 1.65 (1.59-1.71)      | 1.23 (1.19-1.28)      |
| Duration of diabetes                       |               |                     |                       |                       |
| Diabetes absent                            | 29,750 (86.9) | 313,904 (91.7)      | 1.0 (ref.)            | 1.0 (ref.)            |
| <5 years                                   | 1,941 (5.7)   | 12,903 (3.8)        | 1.60 (1.53-1.68)      | 1.21 (1.14-1.27)      |
| ≥5-<10 years                               | 1,324 (3.9)   | 8,817 (2.6)         | 1.60 (1.51-1.70)      | 1.24 (1.16-1.32)      |
| ≥10 years                                  | 1,224 (3.6)   | 6,766 (2.0)         | 1.93 (1.81-2.06)      | 1.37 (1.28-1.47)      |
| HbA <sub>1c</sub>                          |               |                     |                       |                       |
| Diabetes absent                            | 29,750 (86.9) | 313,904 (91.7)      | 1.0 (ref.)            | 1.0 (ref.)            |
| Diabetes present HbA <sub>1c</sub> <7%     | 1,149 (3.4)   | 7,500 (2.2)         | 1.64 (1.54-1.74)      | 1.22 (1.14-1.30)      |
| Diabetes present HbA <sub>1c</sub> ≥7-<8%  | 607 (1.8)     | 3,999 (1.2)         | 1.62 (1.48-1.76)      | 1.23 (1.12-1.36)      |
| Diabetes present HbA <sub>1c</sub> ≥8-<9%  | 407 (1.2)     | 2,442 (0.7)         | 1.77 (1.59-1.97)      | 1.29 (1.15-1.44)      |
| Diabetes present HbA <sub>1c</sub> ≥9%     | 568 (1.7)     | 2,664 (0.8)         | 2.26 (2.07-2.48)      | 1.60 (1.44-1.76)      |
| Diabetes present HbA <sub>1c</sub> unknown | 1,758 (5.1)   | 11,881 (3.5)        | 1.58 (1.50-1.66)      | 1.21 (1.14-1.28)      |

Data are n (%). \*RR adjusted for level of comorbidity, alcoholism-related conditions, use of systemic antibiotic therapy and immunosuppressants before index hospitalization, marital status, household presence of small children attending day care centers, and degree of urbanization.

Table 3. RRs for hospitalization associated with pneumonia according to presence of diabetes (overall, type 1, and type 2), stratified by age, sex, and level of comorbidity.

|                    | Unadjusted RR (95% CI) | Adjusted RR* (95% CI) |
|--------------------|------------------------|-----------------------|
| Diabetes (overall) |                        |                       |
| Age (years)        |                        |                       |
| 15-39              | 3.93 (3.16-4.87)       | 3.21 (2.51-4.12)      |
| 40-64              | 2.63 (2.43-2.84)       | 1.65 (1.51-1.81)      |
| 65-79              | 1.64 (1.56-1.73)       | 1.22 (1.15-1.29)      |
| 80+                | 1.33 (1.25-1.41)       | 1.11 (1.05-1.18)      |
| Sex                |                        |                       |
| Male               | 1.67 (1.60-1.75)       | 1.25 (1.19-1.32)      |
| Female             | 1.69 (1.60-1.77)       | 1.26 (1.20-1.33)      |
| Comorbidity index  |                        |                       |
| Index low (0)      | 1.68 (1.58-1.79)       | 1.51 (1.41-1.61)      |
| Index medium (1-2) | 1.22 (1.15-1.30)       | 1.15 (1.08-1.22)      |
| Index high (3+)    | 1.15 (0.99-1.32)       | 1.11 (0.95-1.28)      |
| Type 1 diabetes    |                        |                       |
| Age (years)        |                        |                       |
| 15-39              | 6.41 (4.69-8.74)       | 5.15 (3.61-7.36)      |
| 40-64              | 4.67 (3.12-6.98)       | 3.43 (2.14-5.50)      |
| 65-79              | -                      | -                     |
| 80+                | -                      | -                     |
| Sex                |                        |                       |
| Male               | 5.05 (3.68-6.94)       | 3.97 (2.81-5.60)      |
| Female             | 6.38 (4.35-9.36)       | 5.28 (3.49-8.00)      |
| Comorbidity index  |                        |                       |
| Index low (0)      | 4.98 (3.67-6.74)       | 4.76 (3.43-6.61)      |
| Index medium (1-2) | 3.35 (0.88-12.78)      | 3.15 (0.80-12.38)     |
| Index high (3+)    | -                      | -                     |
| Type 2 diabetes    |                        |                       |
| Age (years)        |                        |                       |
| 15-39              | 2.63 (1.94-3.58)       | 2.15 (1.51-3.06)      |
| 40-64              | 2.58 (2.39-2.79)       | 1.62 (1.47-1.77)      |
| 65-79              | 1.64 (1.56-1.73)       | 1.22 (1.15-1.29)      |
| 80+                | 1.33 (1.25-1.41)       | 1.11 (1.05-1.18)      |
| Sex                |                        |                       |
| Male               | 1.64 (1.57-1.72)       | 1.23 (1.17-1.29)      |
| Female             | 1.66 (1.57-1.74)       | 1.24 (1.17-1.31)      |
| Comorbidity index  |                        |                       |
| Index low (0)      | 1.62 (1.52-1.73)       | 1.45 (1.36-1.55)      |
| Index medium (1-2) | 1.22 (1.15-1.29)       | 1.15 (1.07-1.22)      |
| Index high (3+)    | 1.15 (0.99-1.32)       | 1.11 (0.95-1.28)      |

\*RR adjusted for level of comorbidity (except when stratified by this variable), alcoholism-related conditions, use of systemic antibiotic therapy and immunosuppressants before index hospitalization, marital status, household presence of small children attending day care centers, and degree of urbanization.