Obesity, diabetes, and hospitalization with pneumonia

PhD dissertation

Jette Brommann Kornum

Faculty of Health Sciences
Aarhus University

Department of Clinical Epidemiology, Aarhus University Hospital
Department of Endocrinology, Aalborg Hospital, Aarhus University Hospital
Department of Clinical Microbiology, Aalborg Hospital, Aarhus University Hospital

This PhD thesis is based on the following papers:

I. Kornum JB, Thomsen RW, Riis A, Lervang HH, Schønheyder HC, Sørensen HT. Type 2 diabetes and pneumonia outcomes: a population-based cohort study. *Diabetes Care* 2007; 30: 2251-2257.

II. Kornum JB, Thomsen RW, Riis A, Lervang HH, Schønheyder HC, Sørensen HT. Diabetes, glycemic control, and risk of hospitalization with pneumonia: a population-based case-control study. *Diabetes Care* 2008; 31: 1541-1545.

III. Kornum JB, Nørgaard M, Dethlefsen C, Due KM, Thomsen RW, Tjønneland A, Sørensen HT, Overvad K. Obesity and risk of subsequent hospitalization with pneumonia among Danes aged 50-64. *In preparation*

Preface

The present PhD thesis has been written on the basis of three studies, which were carried out while I was working at the Department of Clinical Epidemiology, Aarhus University Hospital.

This work was made possible due to a number of people. First of all, I would like to thank my supervisors: Reimar W. Thomsen for sharing his comprehensive knowledge and ideas with me in the field of infections and epidemiology, and for his commitment and support throughout the research process; Henrik T. Sørensen for patiently trying to teach me clinical epidemiology and the art of scientific writing; Henrik C. Schønheyder for patiently answering all my questions on microbiology, and Hans-Henrik Lervang for encouraging me to start this project and for his diabetological guidance.

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Jette Brommann Kornum, September 2009.

Contents

Introduction

Pneumonia is a major cause of morbidity, mortality, and costs of care worldwide. Combined with influenza, pneumonia is the eighth leading cause of death in the United States and the most frequent cause of death due to infectious diseases (1). During the past decade, hospitalizations with pneumonia have increased by 20–50% in Western populations (2-4).

Because of population growth, aging, and the increasing prevalence of obesity and physical inactivity, the prevalence of diabetes is rapidly increasing, a phenomenon referred to as "the diabetes epidemic" (5). Diabetes and hyperglycemia are generally thought to be risk factors for infections, but formal epidemiological evidence for any association between diabetes and pneumonia is limited (6). If such an association exists, it will place a large burden on health care systems globally in the future. Obesity, which is closely related to diabetes, has been suggested as a risk factor *per se* for pneumonia (7), but data on the association between obesity and pneumonia risk are sparse and inconsistent.

The three studies described in this thesis examine diabetes and obesity as risk factors for hospitalization with pneumonia, and the association among diabetes, hyperglycemia, and pneumonia in terms of outcome.

Introduction to pneumonia: incidence, risk factors, and prognosis

Pneumonia is defined as "inflammation and consolidation of lung tissue due to an infectious agent" (8). Symptoms suggestive of pneumonia are chills, fever, pleuritic chest pain, cough, and purulent sputum (8). Approximately 20% of patients with community-acquired pneumonia (CAP) are treated as inpatients (9) and 80% to 90% of hospitalized pneumonia cases are CAP (i.e., acquired outside a hospital setting) (3). The long list of potential microbiological agents in pneumonia consists of bacteria, viruses, fungi, and protozoa (10). The most frequent microbiological agent in CAP is *Streptococcus pneumonia*, which accounts for approximately half of all CAP cases requiring admission to a hospital (11;12). Other agents include but are not limited to *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Chlamydophila psittaci, Staphylococcus aureus*, *Legionella pneumophila*, gram-negative bacteria, and respiratory viruses (e.g., influenza virus, parainfluenza virus, adenovirus, respiratory syncytial virus, and coronavirus) (13). Still, in as many as 50% of pneumonia cases, a responsible agent is not found (14). The most common

mechanism through which the microbial agents can reach the lung is by aspiration from the oropharynx. Pneumonia can, however, also occur via inhalation of contaminated droplets, hematogenous spread, or direct spread from a contagious focus (15).

Incidence

Because of the lack of general population-based studies of the incidence of pneumonia, incidence estimates are almost always based on studies of pneumonia-related hospitalization rates. Based on data from the National Hospital Discharge Survey in the USA, Fry et al. reported that the rate of hospitalizations with pneumonia listed as a primary diagnosis increased by 29% between 1988–1990 and 2000–2002, from 17 to 22 episodes per 1000 in persons aged 65 years or older (2). They also found that the prevalence of hospitalized older adults with pneumonia, who had chronic cardiac disease, chronic pulmonary disease, or diabetes, rose from 66% during 1988–1990 to approximately 80% during 2000–2002. Trotter et al. used a database with information on all admissions to the National Health Service hospitals in England and found that the age-standardized incidence of hospitalizations with a primary diagnosis of pneumonia increased by 34%, from 1.48 to 1.98 per 1000 between 1997–1998 and 2004–2005 (4). A similarly increasing hospitalization rate has also been observed in Denmark. In their population-based study, Thomsen et al. found that the age-standardized rate of hospitalization for pneumonia rose by 50% (from 2.88 per 1000 to 4.42 per 1000) among adults between 1994 and 2003 (3). The increase occurred in all age groups and in both genders.

Risk factors for pneumonia

A risk factor for pneumonia can be defined as an antecedent event, condition, or characteristic that plays a necessary role in the occurrence of some cases of pneumonia (16). According to Rothman, multiple mechanisms can be responsible for a given disease (16). Producing a sufficient causal mechanism for pneumonia requires the joint action of a number of pneumonia risk factors or component causes (17). Exposure to the microbiological agent is only one of a large number of component causes; however, it is also a necessary component in all of the different causal mechanisms for pneumonia.

A number of risk factors have been associated with an increased risk of CAP (Table 1) (7;9;10;18-30). Several of these factors either increase exposure to microbiological agents, increase the likelihood of aspiration, or decrease immunity (31;32). The epidemiological

evidence of obesity and diabetes as risk factors for pneumonia will be discussed in detail on pages 12 and 24.

Table 1. Risk factors for pneumonia (7;9;10;18-30)

Increasing age	Stroke
Respiratory	Dementia
Asthma	Myasthenia gravis
Bronchiectasis	Amyotrophic lateral sclerosis
Chronic obstructive pulmonary disease/chronic bronchitis	*Cancer & immune system*
	Cancer
Congenital defects in ciliary activity	HIV/AIDS
Reduced forced expiratory volume in one second (FEV_1)	Malnutrition/underweight
	Congenital defects in host defenses
Previous respiratory infection	Neutropenia
Chronic renal failure	*Environmental/behavioral*
Rheumatoid arthritis	Frequent contact with children
Gastrointestinal	Crowding
Esophageal reflux	Cold climate/winter season
Tracheoesophageal fistula	Alcoholism
Esophageal diverticula	Smoking
Esophageal stricture	*Drugs*
Chronic liver disease	Immunosuppressive therapy
Congestive heart failure	Proton pump inhibitors
Central nervous system	Recemt antibiotic therapy

Prognosis

A prognosis is a qualitative or quantitative prediction of the outcome of a disease (16). Disease outcomes are often specific events, for example death or complications, or can be quantities such as disease progression, dyspnea, or quality of life (33). Prognostic studies include clinical studies of variables predictive of future events and studies of etiological risk factors (explanatory studies) (34).

In prediction studies, the aim is to predict the probability of the specified outcome with different combinations of predictors in a population (33). Predictors are factors associated (but not necessarily causally associated) with the outcome of a disease. For instance,

confusion may be a useful predictor of pneumonia prognosis but is not likely to be a cause of a poor prognosis. Examples of results from prediction studies used in the clinic are the Pneumonia Severity Index (PSI), CURB, and CURB-65 (described below). In explanatory studies, the aim is to evaluate the causal role of one or more factors while simultaneously controlling for the possible confounding effects of other factors (16).

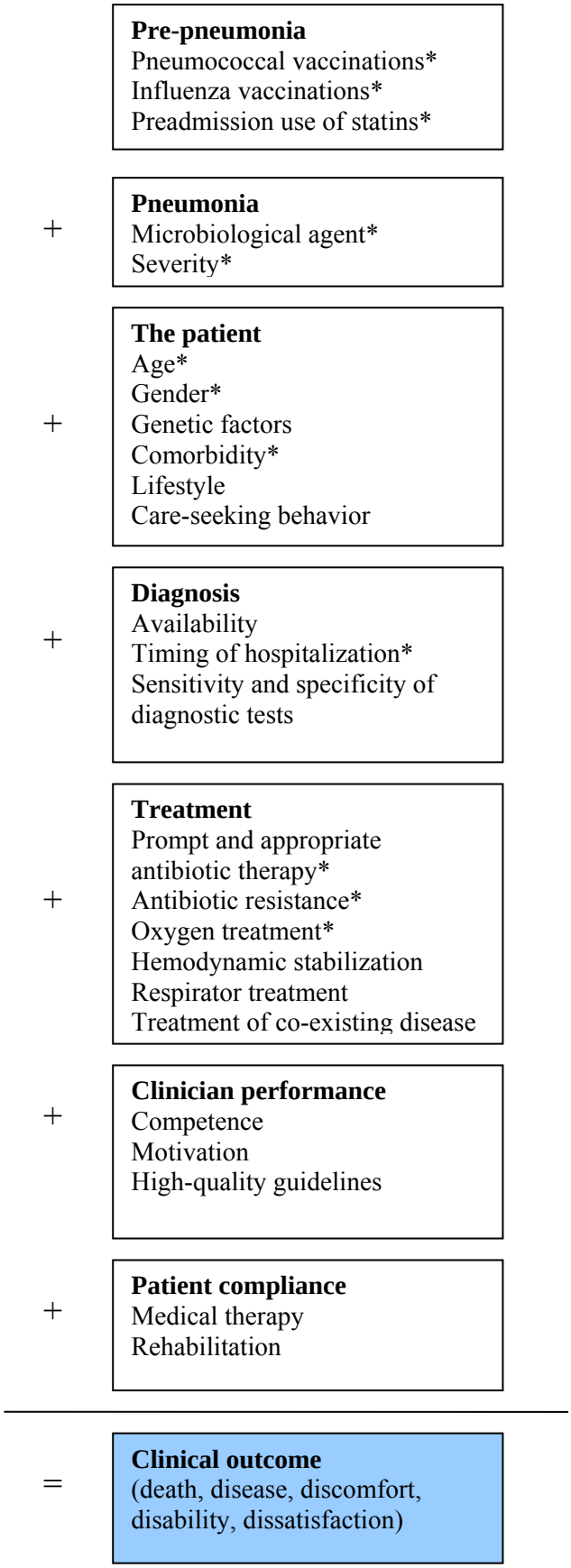
In the much-cited 1996 meta-analysis of CAP prognosis studies by Fine et al., the mortality (mostly in-hospital) ranged from 5.1% for combined hospitalized and ambulatory patients, to 13.6% for hospitalized patients, and to 36.5% for patients admitted to the intensive care unit (35). More recent cohort studies of CAP patients report unchanged average in-hospital mortality frequencies of 8–15% (12;36-39). In a recent population-based Danish study of 41,793 adults hospitalized with a first-time diagnosis of pneumonia, the mortality within 30 and 90 days of admission was 15.2% and 21.9%, respectively (3). In addition to mortality, patients with pneumonia are at risk of pulmonary complications and severe sepsis/bacteremia. In a US cohort study of all Medicare recipients aged 65 years or older and hospitalized with CAP (n = 623,718), 8–13% developed a pulmonary complication (defined as atelectasis, pneumothorax, empyema, and lung abscess), and 5–8% developed nonpulmonary organ dysfunction (40). Among patients hospitalized for CAP with available blood cultures, the proportion of patients with bacteremia is reported to be approximately 7–9% (41-43).

Scoring systems have been developed and validated to assess the severity of CAP and predict prognosis, including the PSI, CURB, and CURB-65. The PSI, developed in a cohort of 14,199 adult inpatients with CAP, stratifies patients into five risk classes according to the risk of dying within 30 days of presentation (44). In addition to abnormal physical findings (altered mental status, respiratory rate ≥30/min, systolic blood pressure <90 mmHg, temperature <35°C or ≥40°C, pulse ≥125/min), abnormal laboratory findings (arterial pH <7.35, urea ≥11 mmol/L, sodium <130 mmol/L, glucose ≥14 mmol/L, hematocrit <30%, PaO_2 <60 mmHg), and radiographic findings (pleural effusion), it also contains information on pre-existing comorbidity (neoplastic disease, liver disease, congestive heart failure, cerebrovascular disease, and renal failure) (44). CURB relies on the four adverse clinical prognostic predictors of **C**onfusion, **U**rea (>7 mmol/L), **R**espiratory rate (≥30/min), and **B**lood pressure, low (systolic <90 mmHg and/or diastolic ≤60 mmHg) at presentation (45). In a cohort of 267 inpatients with CAP, mortality ranged from 2.7% in the presence of no “core” predictors to

83% when all four “core” predictors were present (12). CURB-65 additionally includes age greater than 65 years as a predictor.

Other factors may also influence the prognosis of pneumonia (Figure 1). Factors substantiated by evidence from the literature are marked with an asterisk in the figure.

Figure 1 (46)



Factors that influence pneumonia outcomes. A modification of Sackett`s figure from "Clinical Epidemiology". Two new boxes ("Pre-pneumonia" and "The patient") have been added to the original figure, and the text has been adapted to pneumonia. Factors substantiated by evidence from the literature are marked with an asterisk.

Obesity: Definition, prevalence, and risk of pneumonia

Obesity increases overall mortality and is a well-known risk factor for serious chronic diseases such as cardiovascular disease, hypertension, osteoarthritis, obstructive sleep apnea, and certain forms of cancer (47). Furthermore, obesity is the most important modifiable risk factor for type 2 diabetes (see below). As reviewed by Falagas et al., obese individuals may also have increased susceptibility to infections compared with individuals of normal weight, with evidence especially for skin infections, postoperative infections, and other nosocomial infections (48).

Definition of obesity

Obesity can be defined as a "disease in which excess body fat has accumulated to such an extent that health may be adversely affected" (49). Body mass index (BMI) is an indirect measure of obesity. It is calculated as the weight in kilograms divided by the square of the height in meters and is often used to classify underweight, overweight, and obesity in adults. According to the World Health Organization (WHO), a BMI $\geq$25 kg/m^2 is defined as overweight, and a BMI $\geq$30 kg/m^2 as obese (49). It does, however, not take age, gender, bone structure, muscle mass, or fat distribution into consideration (50). For example, a lean person with high muscle mass may have a high BMI (an overestimation of body fat), whereas an elderly person with increased body fat and low muscle mass may have a normal or even low BMI (an underestimation of body fat) (50). Also, a woman would be more likely to have a greater percentage of body fat than a man with a comparable BMI.

Prevalence of obesity

Obesity is occurring at epidemic proportions. WHO estimates suggest that globally in 2005, approximately 1.6 billion adults were overweight, and at least 400 million adults were obese. Furthermore, WHO projects that by 2015, approximately 2.3 billion adults will be overweight and more than 700 million will be obese (at least 10% of the projected global population) (51). Obesity affects almost all age and socioeconomic groups and is present in both developed and developing countries (52). In the USA, 64.5% of all adults are overweight, and 30.5% are obese (53). In many European countries, more than 50% of the adult population is overweight, and 20–30% is obese. In addition, the prevalence has doubled or risen threefold in less than two decades (54). An obesity epidemic is also taking place in Denmark, where the

overall prevalence of an overweight BMI increased from 34% to 40% in men and from 17% to 27% in women between 1987 and 2001. During the same period, the overall prevalence of obesity more than doubled, in men from 6% to 12% and in women from 5% to 13% (55).

Obesity and risk of pneumonia

Pathophysiology

Obesity may increase the risk of pneumonia for several reasons, as described below.

Immunity

Obesity has been associated with impairments in host defense mechanisms (56-59). Chandra et al. reported that obese individuals show variable impairment of cell-mediated immune responses in vivo and in vitro, as well as reduction of intracellular bacterial killing by neutrophils (60). Conversely, increased T cell response and higher proliferative responses to mitogens have been observed in obese individuals after weight reduction (57). As reviewed by Lamas and Wolowczuk, impairments of the immune system have also been reported in several studies of obese animal models, including impaired T and B cell–mediated immune responses (57;59). The mechanisms linking obesity to impaired immune function are unclear. Malnutrition in obese individuals (because of consumption of diets high in fat) may adversely affect the immune response (57;61). It is also well-known that adipose tissue produces and releases a variety of proinflammatory and anti-inflammatory factors, but a link between the proinflammatory state of obesity and an increased risk of infections has not been determined (48).

Pulmonary complications of obesity

Obesity has multiple adverse effects on the respiratory system. Increasing BMI is usually associated with a reduction in forced expiratory volume in one second (FEV_1), forced vital capacity, total lung capacity, functional residual capacity, and expiratory reserve volume (62). In addition, obesity can cause alterations in the pattern of ventilation (reduced ventilation at the lung bases) (47;63) and an increased work of breathing because of reduced chest wall compliance and respiratory muscle strength (62). The body fat distribution is also important. Particularly, abdominal obesity may restrict the descent of the diaphragm and limit lung expansion (64). Reduced lung function is a strong predictor for pneumonia-related hospitalization; an FEV_1 less than 60% of predicted levels is associated with a risk of pneumonia-related hospitalization more than three times higher than that for normal lung

function (25). As reviewed by McClean, several studies agree that the effect of weight gain on lung function is greater in men than in women, which may be because of sex-related differences in fat distribution (the mechanical effect of abdominal fat on the diaphragm in men) (63).

In addition, obese patients may have an increased risk of aspiration because of increased intra-abdominal pressure, a greater rate of gastroesophageal reflux, and a higher volume of gastric fluid (65). Last, obesity is a risk factor for respiratory diseases such as obstructive sleep apnea, obesity hypoventilation syndrome, and asthma (62). The latter is in turn a well-established risk factor for pneumonia (19;21;28;29).

Other complications of obesity

Elevated BMI is also related to other diseases that may increase the risk of pneumonia. These diseases include type 2 diabetes, heart failure, stroke, certain forms of cancer, and non-alcoholic fatty liver disease (47;66;67). Furthermore, abdominal obesity is a major contributor to the development of hypertension, elevated plasma insulin concentrations and insulin resistance, hyperglycemia, and hyperlipidemia (metabolic syndrome) (68). Hypertension, in turn, is a risk factor for end-stage renal disease (69). The link between obesity and diabetes is described on page 17.

Smoking and alcohol

As noted by Chiolero in his review, numerous cross-sectional studies indicate an association between smoking and low BMI (70). Results from studies on alcohol intake and body weight are inconclusive (71).

Studies on obesity and the risk of pneumonia

I searched PubMed to identify articles on the association between BMI/obesity and the risk of pneumonia, using the following terms:

- "obesity"[Mesh] AND "pneumonia"[Mesh] (yielded 55 articles).
- "body mass index"[Mesh] OR "body weight"[Mesh] OR "waist circumference"[Mesh] AND "pneumonia"[Mesh] (yielded 290 articles).
- "life style"[Mesh] AND "pneumonia"[Mesh] (yielded 17 articles)
- "pneumonia/epidemiology"[Mesh] AND "risk factors"[Mesh] (yielded 816 articles)

Limits were humans, adults, and English-, Danish-, Norwegian-, or Swedish-language articles. We included only studies examining obesity as a risk factor for pneumonia. Studies were excluded if they examined only hospital-acquired pneumonia, ventilator-associated pneumonia, or healthcare-associated pneumonia. The remaining six important studies are shown in Table 2.

Table 2. Studies on BMI and the risk of pneumonia

Author, year, country	Design	Included individuals	Outcome measure	Results (95%CI)
LaCroix et al., 1989, USA (23)	Cohort	2605 men (pneumonia hospitalization rate, 9.71 per 1000 person-years); 2869 women (pneumonia hospitalization rate, 6.89 per 1000 person-years)	Adj. RR of pneumonia-related hospitalization	"The risk of pneumonia was higher among persons with low BMI" (estimates not given).
Lange et al.,1995, Denmark (25)	Cohort	6158 men (pneumonia-related hospitalization, 216); 7265 women (pneumonia-related hospitalization, 189)	Adj. RR of pneumonia-related hospitalization	"The risk of pneumonia-related hospitalization rose significantly with decreasing BMI" (estimates not given).
Almirall et al., 1999, Spain (18)	Case-control	205 CAP cases, 475 population controls	Adj. OR for practitioner- or hospital-diagnosed CAP	BMI* Normal weight 1.0 Underweight 1.76 (0.85–3.67) Overweight 0.91 (0.52–1.59) Highly overweight 1.42 (0.63–3.24)
Baik et al., 2000, USA (7)	Cohort	26,429 men (CAP, 290); 78,062 women (CAP, 305)	Adj. RR for practitioner- or hospital-diagnosed CAP	BMI / Men / Women <21.0: 1.55 (0.87–2.75) / 1.00 (0.70–1.43) 21.0–22.9: 1.0 (ref.) / 1.00 (ref.) 23.0–24.9: 0.91 (0.62–1.36) / 0.61 (0.39–0.96) 25.0–26.9: 0.94 (0.63–1.39) / 1.53 (1.03–2.28) 27.0–29.9: 1.53 (1.04–2.26) / 1.87 (1.26–2.77) ≥30.0: 0.97 (0.57–1.67) / 2.22 (1.56–3.18)

Schnoor et al., 2007, Germany (28)	Case-control	1130 CAP cases; 989 population controls	Adj. OR for practitioner- or hospital-diagnosed CAP	BMI**	
				Normal weight	1.0
				Underweight	2.3 (1.3–3.9)
				Overweight	0.6 (0.5–0.7)
				Obese	0.7 (0.5–0.9)
Almirall et al., 2008, Spain (19)	Case-control	1336 CAP cases; 1326 population controls	Unadj. OR for practitioner- or hospital-diagnosed CAP	BMI	
				Normal weight	1
				Underweight	2.20 (1.57–3.09)
				Overweight	0.89 (0.72–1.09)
				Obese	0.79 (0.60–1.04)

adj. = adjusted, BMI = body mass index, CAP = community-acquired pneumonia, OR = odds ratio, RR = relative risk, unadj. = unadjusted.

*Cut-off points are defined by 20.7, 27.8, and 31.1 in males and 19.1, 27.3, and 32.3 in females.

**Cut-off points are defined by 20.1, 25.1, and 30.1 in males and 19.1, 24.1, and 30.1 in females.

As it appears from Table 2, only few studies have examined the association between obesity and the risk of pneumonia. In a US study, Baik et al. followed 26,429 men from the Health Professionals' Follow-up Study and 78,062 women from the Nurses' Health Study who were free of asthma, cardiovascular disease, cancer, and diabetes at baseline, and found that a BMI of ≥30 was associated with a greater risk of pneumonia among women (adjusted RR [relative risk] = 2.2; 95% CI 1.6–3.2) but not among men (RR = 1.0; 95% CI 0.6–1.7) (7). Chronic diseases developed during follow-up were not taken into account. Almirall's study including 205 CAP cases found a positive but imprecisely measured association between being "highly overweight" and risk of CAP (adjusted OR [odds ratio] 1.42; 95% CI 0.63–3.24) (18). In contrast, two more recent case-control studies found no association between obesity and pneumonia-related hospitalization (19;28). These studies were based on self-reported values of anthropometric data, which can be less accurate than clinical measurements (72;73). Moreover, other risk factors were not accounted for in one of the case-control studies (19). Finally, case-control studies based on questionnaires can be hampered by recall bias (18;19;28).

Comparison of the previous studies is also complicated because of different BMI categories and the fact that some studies only included pneumonia patients diagnosed by general practitioners; others included a combination of both practitioner- and hospital-diagnosed pneumonia patients.

In conclusion, obese individuals may have an increased risk of pneumonia, but available data are sparse and inconsistent. It is also unclear whether such a relation might be due to obesity *per se* or explained by other acquired diseases associated with obesity. In this thesis, the Danish cohort "Cancer, Diet and Health" in combination with medical and administrative registries served as valuable tools for examining the association between obesity and the risk of subsequent hospitalization with pneumonia.

The link between obesity and type 2 diabetes

Obesity, in particular abdominal obesity, is associated with insulin resistance, an important element of type 2 diabetes (Figure 2). Suggested mechanisms linking obesity to insulin resistance include (1) insulin itself, by inducing receptor downregulation; (2) free fatty acids; (3) intracellular lipid accumulation; and (4) circulating peptides produced by adipocytes, such as the cytokines TNF-α and IL-6, RBP4, as well as the adipokines adiponectin and resistin (74). In a cohort of 114,281 US women participating in the Nurses' Health Study, BMI was found to be the most important predictor of risk for diabetes; a risk was already increased with BMIs greater than 22.0 kg/m (75). Women with a BMI of 35 kg/m^2 or greater had a 93-fold higher risk of developing diabetes compared with women with a BMI of less than 22 kg/m^2. A similar positive association between increasing BMI and diabetes also exists among men. In a cohort of 51,529 US male health professionals, Chan et al. found that men with a BMI of ≥35 kg/m^2 had a 42-fold higher risk of diabetes compared with men with a BMI <23 kg/m^2 (76). As many as 80% of patients with type 2 diabetes are obese (74).

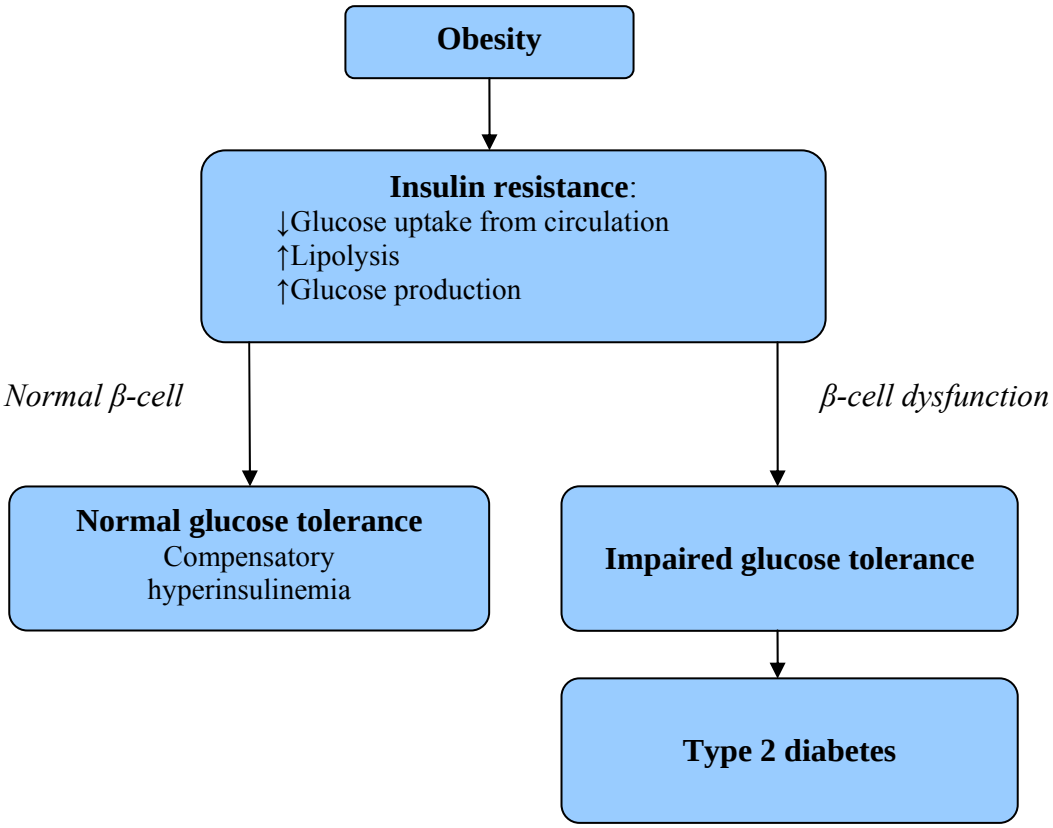


Figure 2. The link between obesity and type 2 diabetes.

Diabetes mellitus: definition, prevalence, and association with pneumonia

Diabetes is the fifth leading cause of death by disease in the USA (1). Moreover, adults with diabetes have rates of stroke and death from heart disease that are about 2–4 times higher than adults without diabetes. Diabetes is a leading risk factor for end-stage renal disease, adult blindness, and non-traumatic limb amputations (77). There is also growing evidence that individuals with diabetes are at an increased risk of common infections such as urinary tract infection, skin and mucous membrane infection, and perhaps pneumonia (78-81). Of particular interest here is the suggested association between diabetes and pneumonia.

Definition of diabetes mellitus

Diabetes mellitus refers to a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (82). Diabetes mellitus can be classified into type 1 and type 2 diabetes, other specific types, and gestational diabetes.

Type 1 diabetes accounts for about 5–10% of those with diabetes. It arises from pancreatic β-cell destruction, which usually leads to absolute insulin deficiency (82). Individuals with type 1 diabetes require insulin for survival and are prone to develop ketoacidosis. Although type 1 diabetes usually develops before the age of 30, it can develop at any age (83).

Type 2 diabetes accounts for about 90–95% of those with diabetes. It is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased hepatic glucose production (83). This form of diabetes was previously referred to as non–insulin-dependent diabetes or adult-onset diabetes; however, many patients with type 2 diabetes require insulin for control of glycemia. Because hyperglycemia develops gradually, type 2 diabetes often goes undiagnosed for many years. Ketoacidosis seldom occurs in this type of diabetes. Older age, obesity, physical inactivity, and a family history of diabetes increase the risk of type 2 diabetes (83).

Other specific types of diabetes include diabetes attributable to other causes (for example genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas, and drug- or chemical-induced diabetes) (82). Gestational diabetes mellitus is

defined as “any degree of glucose intolerance with onset or first recognition during pregnancy” (82).

Prevalence of diabetes

The total number of people with diabetes worldwide has been predicted to more than double between 2000 and 2030, from 171 million to 366 million (5). In the USA, approximately 9% of the population has diabetes (84), and the incidence of type 2 diabetes has doubled over the last 30 years (85). Based on recent data from The Danish National Diabetes Register (described on page 32), Carstensen et al. found that the prevalence of diabetes in Denmark is approximately 4% (86) and that the prevalence increases 6% annually.

Association of diabetes with pneumonia

Pathophysiology

Individuals with diabetes and/or hyperglycemia may have an increased risk and a worse prognosis of pneumonia for several reasons, described below.

Immunity

Aberrations in host defense mechanisms are assumed to predispose diabetic patients to an increased risk and worse prognosis of infections. Observations from in vitro studies suggest that diabetic patients have altered neutrophil function, such as impaired chemotaxis, phagocytosis, and bacterial killing (87-90). The decreased function may in part be an effect of hyperglycemia (91). Some studies have, for example, found that the degree of neutrophil dysfunction correlates with the degree of hyperglycemia (87;88;90). Furthermore, correction of impaired neutrophil function has been reported in diabetic persons after improved metabolic control by insulin treatment (87). As reviewed by Smith et al., cell-mediated abnormalities such as decreased CD4/CD8 lymphocyte ratios, changes in natural killer cell function, acquired defects in interleukin-2 production, and a reduced phagocytic function of monocytes, have also been reported in diabetic patients and could account for an increased risk of both bacterial and viral infections (92).

Metabolic derangement

The harmful effects of hyperglycemia on the immune system may increase the risk of infections in diabetic individuals. Conversely, infection may worsen glycemic control in patients with diabetes. In fact, infection is the most common precipitating factor in the

development of diabetic ketoacidosis and a hyperosmolar hyperglycemic state (93). A randomized, controlled study of surgical critically ill patients (that is, adults admitted to a surgical intensive care unit who were receiving mechanical ventilation) has shown that strict glycemic control with insulin therapy substantially reduced morbidity and mortality, including the risk of sepsis (94). The beneficial effects of intensive insulin therapy were later found to be associated with metabolic control rather than with the insulin dose (95). However, concerns have been raised regarding the potential harm of hypoglycemia in critically ill patients treated with intensive insulin therapy (96-98).

Complications of diabetes

The complications of diabetes affect multiple organ systems, and some may increase the risk and worsen the prognosis of pneumonia. Diabetic patients have an increased risk of aspiration of pathogens causing pneumonia due to gastroparesis, which is present in 30–50% of patients with longstanding diabetes (91;99). Aspiration may also occur in diabetic patients with hypoglycemic seizure, hyperosmolar nonketotic coma, or ketoacidosis because of depressed mental status (91). The risk of stroke is increased by a factor of 2 in diabetic men and is even higher in diabetic women (100), and stroke sequelae can also predispose an individual to aspiration.

Diabetes is a risk factor for end-stage renal disease. Immune cell dysfunction has been described in patients with chronic renal failure and hemodialysis, including impaired granulocyte activity, suppressed T-lymphocyte function, and impaired macrophage Fc receptor function (91).

Furthermore, patients with type 2 diabetes are more than twice as likely as patients without diabetes to develop congestive heart failure (101). Heart failure has been associated with a 1.9 times greater risk of pneumonia-related hospitalization (21) as well as a 1.4 times greater mortality following hospitalization with pneumonia (102). The universal micro- and macroangiopathy associated with diabetes may also worsen the risk and outcome of infections due to decreased tissue oxygenation and impaired leukocyte migration (32).

Impaired lung function has been suggested as a potential complication of diabetes (91;103), including reduction in lung diffusing capacity and spirometric parameters, such as total lung capacity, vital capacity, and FEV_1 to forced vital capacity. Interestingly, microangiopathic

changes have been reported in the basement membranes of pulmonary blood vessels and respiratory epithelium as well as glycosylation of tissue proteins (91). Finally, as mentioned on page 17, diabetes and obesity often coexist, and obesity may increase the risk of pneumonia (7).

Smoking and alcohol

The risk of type 2 diabetes is greater in smokers than in non-smokers (104;105). In the Physicians Health Study, a 70% higher risk of type 2 diabetes was reported for men who smoked >20 cigarettes per day compared with non-smokers (104). Similar results have been reported in women (105). Concerning the association between type 2 diabetes and alcohol, conflicting results exist (106).

Studies on diabetes, hyperglycemia, and pneumonia

I searched PubMed to identify articles on the association between diabetes and pneumonia as well as hyperglycemia and pneumonia, using the following terms:

- "diabetes mellitus"[Mesh] AND "pneumonia"[Mesh] (yielded 253 articles)
- "hyperglycemia"[Mesh] AND "pneumonia"[Mesh] (yielded 28 articles)
- "glucose"[Mesh] AND "pneumonia"[Mesh] (yielded 68 articles)
- "pneumonia/epidemiology"[Mesh] AND "risk factors"[Mesh] (yielded 816 articles)
- "pneumonia/epidemiology"[Mesh] AND "prognosis"[Mesh] (yielded 645 articles)

Limits were humans, adults, and English-, Danish-, Norwegian-, or Swedish-language articles. We included only studies examining diabetes as a risk or prognostic factor for pneumonia. Studies were excluded if they examined only hospital-acquired pneumonia, ventilator-associated pneumonia, or healthcare-associated pneumonia and if they were published more than 20 years ago. Relevant studies on diabetes and hyperglycemia as risk factors for pneumonia are shown in Table 3. Relevant studies on diabetes and hyperglycemia as prognostic factors are shown in Table 4.

Table 3. Studies on diabetes, hyperglycemia, and the risk of pneumonia

Author, year, country	Design	Included individuals	Outcome measure	Results (95% CI)
LaCroix et al., 1989, USA (23)	Cohort	Men, 2605 (DM, 8%); women, 2869 (DM, 10%)	Adj. RR (DM vs. other) of pneumonia-related hospitalization	Men, 1.0 (0.6–1.8) Women, 1.7 (1.1–2.7)
Koivula et al., 1994, Finland (22)	Cohort	4175 persons (DM, 13.%)	Adj. RR (DM vs. other) of outpatient visits or hospitalizations for pneumonia	"Diabetes was not significantly associated with pneumonia" (estimates not given)
Lange et al., 1995, Denmark (25)	Cohort	13,423 persons (distribution of DM not given)	Adj. RR (DM vs. other) of pneumonia-related hospitalization	No significant statistical association between DM and pneumonia-related hospitalization (estimates not given)
Almirall et al., 1999, Spain (18)	Case-control	205 CAP cases (DM, 9%), 475 population controls (DM, 6%)	Adj. OR (DM vs. other) for practitioner or hospital-diagnosed CAP	1.61 (0.69–3.72)
Shah et al., 2003, Canada (81)	Cohort	1,027,498 persons (DM, 50%)	Unadj. RR (DM vs. other) for hospitalization or physician claim for pneumonia	1.46 (1.42–1.49)*
Jackson et al., 2004, USA (21)	Cohort	46,237 persons (DM, 9%)	Adj. RR (DM vs. other) of 1) hospitalization for CAP 2) outpatients visit for CAP 3) all CAP	 1) 1.52 (1.29–1.78) 2) 0.90 (0.77–1.06) 3) 1.13 (1.01–1.27)
Muller et al., 2005, The Netherlands (80)	Cohort	26,328 (DM1 = 705, DM2 = 6712; hypertension = 18,911)	Adj. OR (DM vs patients with hypertension). For practitioner-diagnosed lower respiratory tract infection	1) For patients with DM1 1.42 (0.96–2.08) 2) For patients with DM2 1.32 (1.13–1.53)
Benfield et al., 2007, Denmark (78)	Cohort	10,063 persons (DM = 353)	1) Adj. RR (DM vs. other) of pneumonia-related hospitalization 2) Adj. RR of pneumonia-related hospitalization per mmol/L increase in plasma	1) 1.75 (1.23–2.48) 2) 1.06 (1.03–1.10)

			glucose	
Skull et al., 2008, Australia (107)	Case-cohort	1952 CAP cases (DM, 27%); 2927 cohort persons (DM, 25%)	Adj. RR (DM vs. other) of hospitalized CAP	1.22 (1.05–1.42)
Vila-Corcoles et al., 2008, Spain (108)	Cohort	11,241 persons (DM, 24%)	Adj. RR (DM vs. other) of outpatient visits or hospitalizations for CAP	1.04 (0.85–1.29)
Almirall et al., 2008, Spain (19)	Case-control	1336 CAP cases (DM, 10%); 1326 population controls (DM 7%)	Unadj. OR (DM vs. other) for practitioner- or hospital-diagnosed CAP	1.43 (1.11–1.92)

*99% confidence interval

adj. = adjusted, CAP = community-acquired pneumonia, DM = diabetes mellitus, OR = odds ratio, RR = relative risk, unadj. = unadjusted.

Table 4. Studies on diabetes, hyperglycemia, and outcome of pneumonia

Author, year, country	**Design**	**Included individuals**	**Measure of interest**	**Results (95% CI)**
LaCroix et al., 1989, USA (23)	Cohort	Men, 2605 (DM, 8%); women, 2869 (DM, 10%)	Adj. RR (DM vs. other) of pneumonia-related mortality on death certificate	Men, 1.5 (0.8–2.6) Women, 1.5 (0.6–3.6)
Marrie et al., 1992, Canada (109)	Cohort	1118 patients with CAP (DM, 8%)	Proportion of patients with DM among CAP patients with and w/o pneumococcal bacteremia	+ Bacteremia DM = 21.3% ÷ Bacteremia DM = 7%, P = 0.008
Lange et al., 1995, Denmark (25)	Cohort	6158 men (pneumonia-related hospitalization, 216); 7265 women (pneumonia-related hospitalization, 189); distribution of DM not given.	Adj. RR (DM vs. other) of pneumonia-related mortality on death certificate	No significant statistical association between DM and pneumonia-related death (estimates not given)
Fine et al., 1996, USA (35)	Meta-analysis of CAP prognosis	Total of 33,148 patients; 14,655 with data on DM	Unadj. summary OR (DM vs other) for mortality (method: Mantel and Haenszel)	1.3 (1.1–1.5)
Houston et al., 1997, USA (110)	Cohort	413 inpatients and outpatients with lower	Unadj. OR (DM vs. other) for 30-day	1.66 (0.54–5.07)

		respiratory tract infection (DM, 6%)	mortality	
Fine et al., 1997, USA (44)	Cohort	14,199 patients hospitalized with pneumonia (glucose ≥ 14 mmol/L, 9.6%)	Adj. 30-day hospital mortality	Glucose ≥ 14 mmol/L was a "significant predictor of mortality" (P< 0.05)
Akbar, 2001, Saudi Arabia (111)	Cohort	85 CAP patients with a positive sputum culture (DM, 31%)	In-hospital mortality (DM vs. other) following bacterial pneumonia	DM present: 31% DM not present: 20% (P = 0.2)
Kaplan et al., 2002, USA (40)	Cohort	623,718 CAP patients (DM, 17%)	Adj. OR (DM vs. other) for in-hospital mortality	0.96 (0.93–0.99)
McAlister et al., 2005, Canada (37)	Cohort	2471 CAP patients (DM, 16%) Admission glucose ≤6.1 33% 6.11–11.0 55% 11.01–13.99 5% ≥14.0 6%	1) Unadj. OR (DM vs. other) for in-hospital mortality 2) Adj. OR for in-hospital mortality	1) 1.00 (0.69-1.45) 2) Admission glucose (mmol/L) ≤6.1 1.0 (ref.) 6.11–11.0 1.20 (0.88–1.65) 11.01–13.99 1.79 (1.01–3.16) ≥14.0 1.69 (0.97–2.94)
Falguera et al., 2005, Spain (112)	Cohort	660 hospital-diagnosed CAP patients (DM, 16%)	Adj. OR (DM vs. other) 1) 30-day mortality 2) pleural effusion	1) 2.14 (1.09-4.19) 2) 2.01(1.23-3.28)
Benfield et al., 2007, Denmark (78)	Cohort	10,063 persons (DM = 353); 586 pneumonia episodes	Hospital-associated 28-day mortality	+DM 19% ÷DM 14%

*99% confidence interval

adj. = adjusted, DM = diabetes mellitus, MRR = mortality rate ratio, OR = odds ratio, RR = relative risk, unadj. = unadjusted.

Studies on diabetes, hyperglycemia, and the risk of pneumonia

Diabetes is thought to be a risk factor for pneumonia, but available data are inconclusive (Table 3). Four cohort studies, one case-cohort study, and two case-control studies have reported that diabetes is associated with a 1.13- to 1.75-fold increased risk of pneumonia (18;19;21;78;80;81;107); three cohort studies, however, failed to find an association (22;25;108). Two of these cohort studies examined a wide range of risk factors, and confounder-adjusted risk estimates for diabetes were not statistically significantly increased (estimates not given) (22;25). In the largest study to date on this topic, Shah et al. compared

all people with diabetes in Ontario, Canada, to age, sex, region, and income quintile-matched non-diabetic people (n = 513,749 in each group) and found that diabetes was associated with a 1.46 times (99% CI 1.42–1.49) increased risk of pneumonia-related hospitalization or physician claim for pneumonia (81). The study did not, however, clarify whether the result was influenced by a higher level of comorbidity among individuals with diabetes compared with individuals without diabetes. Jackson et al. reported that the adjusted RR for hospitalizations for CAP was 1.52 (95% CI 1.29–1.78) among persons with diabetes compared to persons without diabetes, based on 46,237 persons aged ≥65 years and enrolled in a single health maintenance organization in Washington state, USA (21). These findings may not apply to persons younger than 65 years of age or to the general population.

In fact, only a few of the previous studies were population based (18;22;81), and only one study distinguished between type 1 and 2 diabetes (80). Based on records from 195 general practices in Holland, Muller et al. compared patients with diabetes to an age-matched control group of hypertensive patients and 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) (80)]. However, the category "lower respiratory tract infection" included milder general practitioner-diagnosed cases of acute bronchitis, influenza, pleuritis, emphysema, or chronic obstructive pulmonary disease, and exacerbations of asthma, in addition to pneumonia. In the previous case-control studies, diabetes data were based on interviews or questionnaires and may therefore have been hampered by recall bias (18;19).

Very little is known about the influence of hyperglycemia on the risk of pneumonia (Table 3). Benfield et al. followed 10,063 individuals from the Danish general population and found that each 1 mmol/L increase in baseline plasma glucose was associated with a 6% (95% CI 1.03–1.10) increased RR of pneumonia (78). This result was based on a single non-fasting glucose measurement.

Studies on diabetes, hyperglycemia, and pneumonia outcomes

Whether diabetes worsens pneumonia prognosis remains controversial (Table 4). Fine's meta-analysis of pneumonia prognosis based on pre-1996 research found that diabetes was associated with a 1.3 times (95% CI 1.1–1.5) increased mortality following pneumonia (35). The meta-analysis did not consider possible confounders. A recent Spanish study of 660

patients with CAP found that diabetes was associated with markedly increased 30-day mortality [adjusted RR 2.14 (95% CI 1.09–4.19)] (112); that study relied on a cohort admitted to a single university hospital. In contrast, two larger cohort studies found similar in-hospital mortality among patients with and without diabetes (37;40). Based on 623,718 US patients aged over 65 and hospitalized for CAP, Kaplan et al. reported that the adjusted RR for in-hospital mortality associated with diabetes was 0.96 (95% CI 0.93–0.99) (40). In his study, patients with diabetes were identified only by earlier hospital diagnoses; thus, diabetic patients who were never previously hospitalized were missed. In a Canadian study of 2471 patients with CAP, including 401 patients with diabetes, McAlister et al. found that in crude analyses, a priori diabetes history did not predict in-hospital mortality (OR 1.00; 95% CI 0.69–1.45) (37). They did find that hyperglycemia on admission was associated with a poor prognosis for both diabetic and non-diabetic patients with CAP.

In studies of prognosis, observations of patients in a cohort should ideally begin at the same well-defined point in the course of a disease (113). Because of increased surveillance of diabetic patients, a different care-seeking behavior of diabetic patients, or both, physicians could be more likely to hospitalize diabetic patients in an earlier stage of the pneumonia infection, which could lead to lower-than-expected mortality from pneumonia. Information on pneumonia severity at presentation is therefore important for understanding the clinical course of pneumonia in diabetic vs. non-diabetic patients, but most studies lack these data (23;25;35;37;40;110;111). In addition, claims that pneumonia patients with diabetes are at an increased risk of developing bacteremia (109) have been hampered by missing data on the frequency of confirmation through blood cultures.

Evidence regarding increased pulmonary complications in diabetic patients with pneumonia remains limited (91;112), as are data on the prognostic value of acute hyperglycemia for diabetic patients with pneumonia (37) (Table 4). Nevertheless, admission glucose levels ≥14 mmol/L, but not a history of diabetes, constitutes one of the twenty factors included in the PSI (44). Finally, in prognostic studies, patients should be followed for a long enough period of time to allow most of the important outcome events to occur (113). Most deaths directly related to pneumonia are likely to occur within 30 days of presentation (114), while death within 90 days can be the result of pneumonia sequelae following the initial illness (38). Few studies have, however, followed the patients for 30 days or more, probably because of the difficulties in many countries with follow-up of patients in the post-discharge period (32).

In conclusion, because the prevalence of diabetes and the rate of pneumonia hospitalizations both are on the rise, it is important to clarify whether diabetes with associated hyperglycemia is a risk and prognostic factor for hospitalized pneumonia. More accurate data are needed to correctly define risk groups for pneumonia hospitalization and death; to qualify the debate on appropriateness of influenza and pneumococcal immunization in diabetic patients; to improve our understanding of the clinical course of pneumonia; and to predict pneumonia outcome more accurately among patients with diabetes/hyperglycemia. In this thesis, Danish health registries linked by a unique civil registration number functioned as a valuable tool for examining the impact of diabetes and hyperglycemia on pneumonia-related hospitalization, allowing a large sample size, a population-based design, and complete long-term follow-up of the patients.

Aims of the thesis

1. To examine whether type 2 diabetes increases risk of death, pulmonary complications, and bacteremia following pneumonia, and to assess the prognostic value of acute hyperglycemia at admission (*study I*).

2. To examine whether diabetes is a risk factor for hospitalization with pneumonia and to assess the impact of Hemoglobin A1c (HbA1c) level on such risk (*study II*).

3. To examine the association between obesity and the risk of subsequent hospitalization with pneumonia among men and women and to examine whether such association is explained by presence of other major chronic diseases in obese individuals *(study III)*.

Subjects and Methods

Data sources

Studies I and II

Studies I and II were based on population-based Danish medical and administrative registries. They were conducted in the Danish former counties of North Jutland and Aarhus, with a mixed rural and urban population of approximately 1.15 million people. In Denmark, the 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 (115). Use of civil registration numbers, assigned to every Danish resident since 1968, allows accurate linkage among Danish registries.

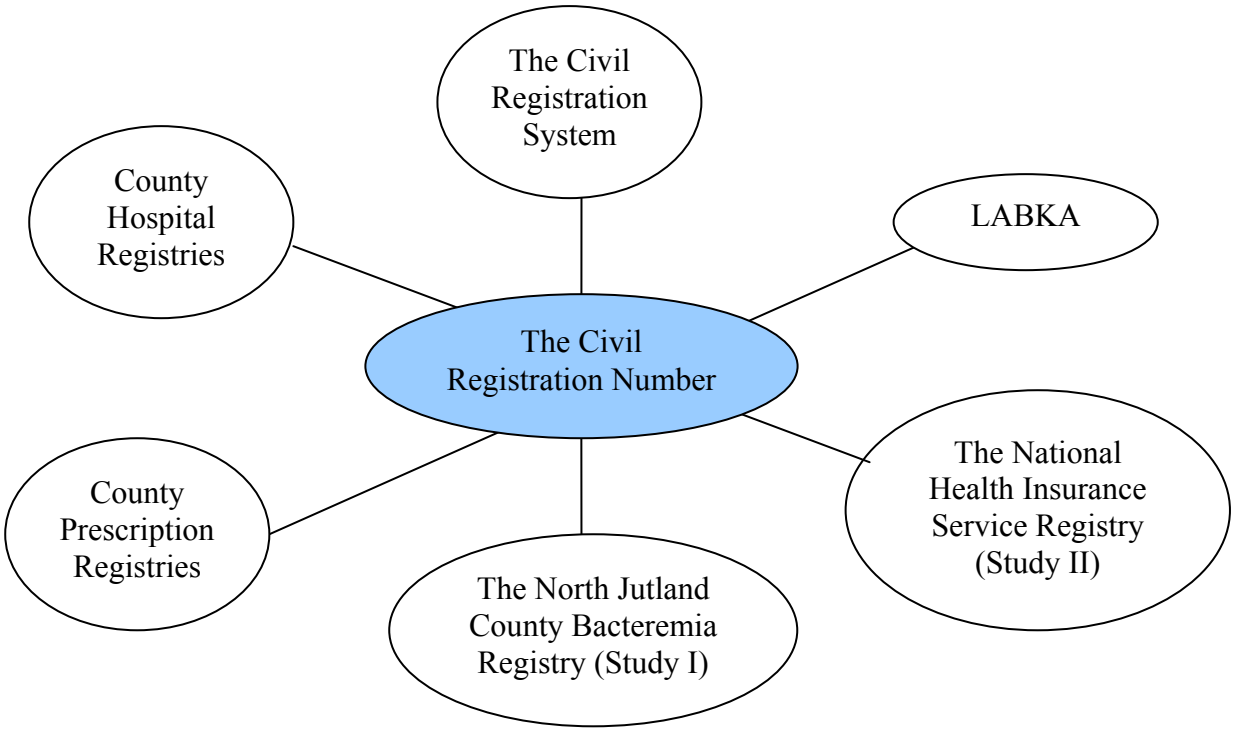


Figure 3. Data sources applied in *studies I–II*

The following data sources were used:

County Hospital Registries

The County Hospital Registries in Aarhus and North Jutland counties contain information on all discharges from non-psychiatric hospitals since 1977. Information on outpatient and emergency room visits was added from 1995 onwards. The County Hospital Registries compiles data for the National Registry of Patients. Data include civil registration number, dates of admission and discharge, the surgical procedures performed, and up to 20 discharge diagnoses classified by physicians according to the International Classification of Diseases, 8th revision (ICD-8) until the end of 1993 and according to the 10th revision (ICD-10) thereafter (116).

County Prescription Registries

Community pharmacies collect data on all prescriptions filled by ambulatory patients and forward data on reimbursable medicines to their local regional health service section (in North Jutland County since 1989 and in Aarhus County since 1996). Data include the patient's civil registration number and amount and type of drug prescribed according to the Anatomical Therapeutic Chemical (ATC) classification system (116).

The Laboratory Information Systems (LABKA)

The counties' laboratory databases contain information on all specimens submitted for analysis by hospitals and practitioners. Data from Aarhus County are considered complete from 1995, while data from North Jutland County are complete from 1997. At the time Study I was done (2006), laboratory data from Aarhus County were not yet available for research. Data include the patient's civil registration number, the test name, the test's IUPAC-code (International Union for Pure and Applied Chemistry) and/or a local analysis number, the result, and dates of ordering and carrying out the analysis (116).

The North Jutland County Bacteremia Registry

This bacteremia registry is maintained by the Department of Clinical Microbiology at Aalborg hospital. It stores prospectively collected data on all episodes of bacteremia in North Jutland County since 1992, including data on bacterial isolates and susceptibility patterns, the patient's civil registry number, age, sex, date of admission, clinical specialty, origin of infection, presumed focus of infection, and empirical antibiotic treatment. Since 1995, data on all blood cultures (positive or negative) taken in North Jutland County also have been stored electronically (117;118).

The National Health Insurance Service Registry (study II)

This registry contains information on all health services that are provided by general practitioners, dentists, physiotherapists, chiropodists, psychologists, and other specialists, and that are covered by the National Health Insurance. The individual provider is responsible for registering any given health care service (e.g., blood glucose measurements, ECG, mother/child care, and vaccinations). The registry holds no data regarding health status or diagnoses. The recorded data are from 1990 and onwards (116).

The Civil Registration System

This registry is updated daily and contains information on civil registration number, name, address, marital status, citizenship, kinship (parents/children), and date of death if any for the entire Danish population since 1968 (116;119).

Study III

Study III was based on the Danish cohort "Diet, Cancer and Health," and medical and administrative registries.

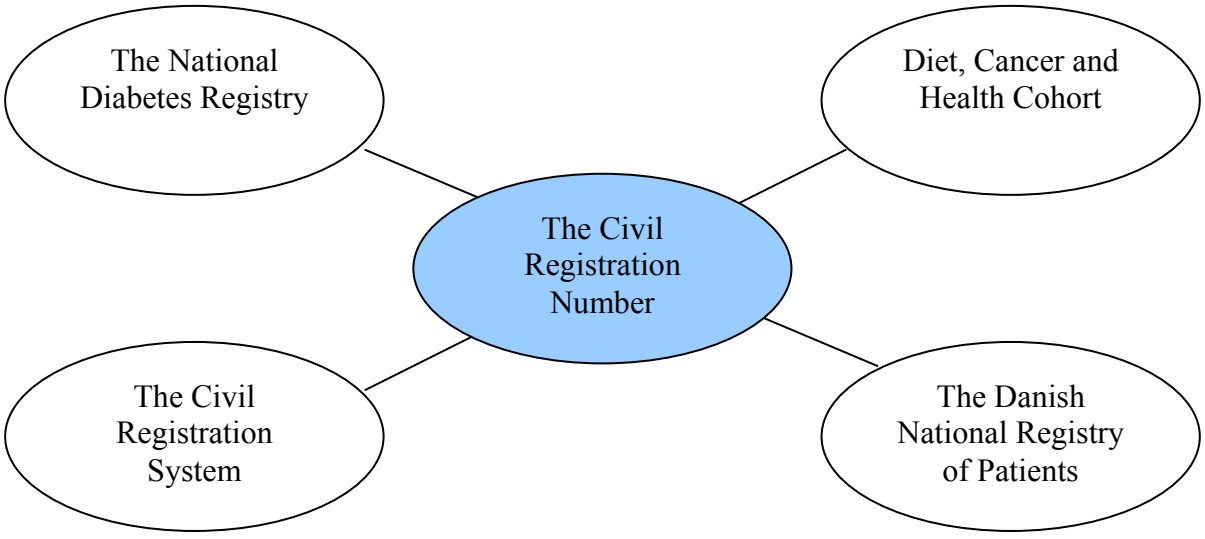


Figure 4. Data sources applied in *study III*

"Diet, Cancer and Health"

The overall aim of the "Diet, Cancer and Health" cohort is to examine the association between specific dietary components, foods, and nutrients, and risk of cancer, obesity, and chronic diseases (120). Between December 1993 and May 1997, a total of 160,725 persons (80,996 men and 79,729 women) were invited to participate in "Diet, Cancer and Health." Eligible participants were retrieved from the Civil Registration System. They were 50–64 years of age, born in Denmark, inhabitants of Copenhagen or Aarhus, and without a former cancer diagnosis registered in The Danish Cancer Registry. A total of 27,178 men and 29,875 women were enrolled in the study, representing 7% of the entire Danish population from ages 50 to 64 years. All participants completed a detailed food-frequency questionnaire (121;122) and a second baseline questionnaire on lifestyle and background (120). Anthropometrical measurements, including height and weight, were collected by a laboratory technician at enrolment.

The Danish National Registry of Patients

This registry receives data from the Hospital Registry of each county (please see page 30) (116).

The National Diabetes Registry

This registry contains information on individuals with diabetes in Denmark and covers the period 1996–2006. The registry links data from The Danish National Registry of Patients, The National Health Insurance Service Registry, and the nationwide Prescription Registry. Individuals are classified as having diabetes if one of the following criteria is met (86):

- Diagnosis of diabetes in the National Patient Registry, ICD-10: E10-14 (diabetes), H36.0 (diabetic retinopathy), O24 (diabetes in pregnancy except for O24.4, which is diabetes arising in pregnancy), or ICD-8: 249, 250 (diabetes)
- Chiropody for diabetic patients recorded in the National Health Insurance Service Registry
- Five blood glucose measurements within one year or two measurements per year in five consecutive years recorded in the National Health Insurance Service Registry

- Second purchase of oral glucose-lowering drugs recorded in the nationwide Prescription Registry within 6 months (except for women aged 20–39 years prescribed metformin alone)
- Second purchase of prescribed insulin recorded in the nationwide Prescription Registry

Study designs

Type 2 diabetes and pneumonia outcomes (study I)

We examined type 2 diabetes as a prognostic factor in an explanatory cohort study of adults with a first-time hospitalization with pneumonia in North Jutland and Aarhus counties between 1997 and 2004. Outcomes were 30-day and 90-day mortality, pulmonary complications, and bacteremia. The impact of admission hyperglycemia on 30-day and 90-day mortality following pneumonia was examined in a subcohort of pneumonia patients from North Jutland County. We adjusted for the following potential confounding factors: sex, age, level of comorbidity, history of alcoholism-related disorders, obesity, and pre-admission use of antibiotics and immunosuppressive drugs.

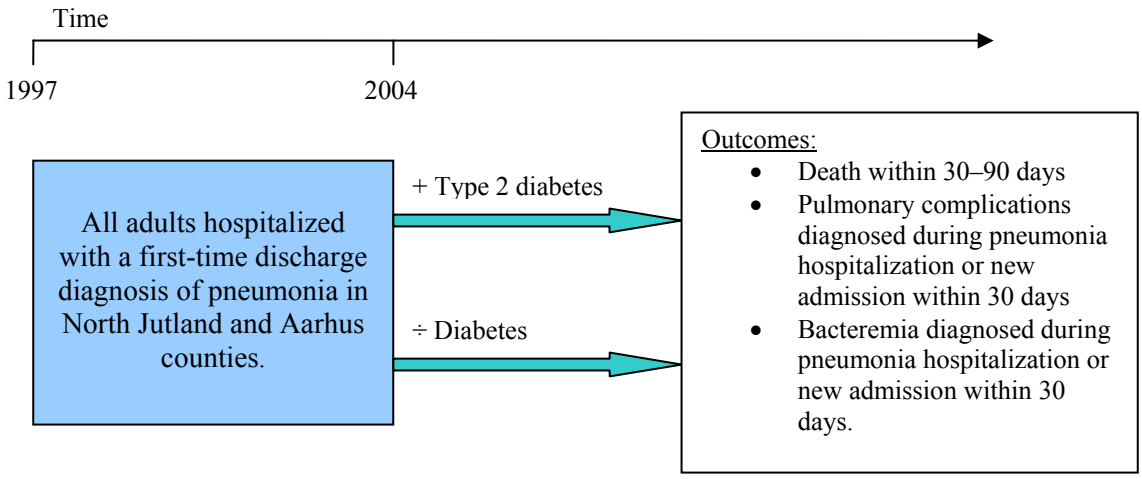


Figure 5. Pneumonia prognosis, cohort design (*study I*)

Diabetes, glycemic control, and risk of hospitalization with pneumonia (study II)

We examined diabetes (overall and categorized by type, duration, and HbA1c level) as a risk factor for hospitalization with pneumonia in a nested case-control study. The source

population consisted of all residents in the counties of North Jutland and Aarhus. Cases consisted of adults with a first-time hospitalization with pneumonia between 1997 and 2005. On the date of each patient's first pneumonia admission, we randomly selected 10 control persons from the Central Population Registry, matched by age, sex, and residence. The control persons were selected with the incidence density sampling technique (123); that is, the control persons had to be alive and at risk of a first hospitalization with pneumonia on the date the corresponding case was admitted. When using incidence density sampling, the estimated OR in a case-control design is an unbiased estimate of the RR. We adjusted for level of comorbidity, history of alcoholism-related disorders, pre-admission use of antibiotics or immunosuppressants, marital status, household presence of small children attending day-care centers, and degree of urbanization.

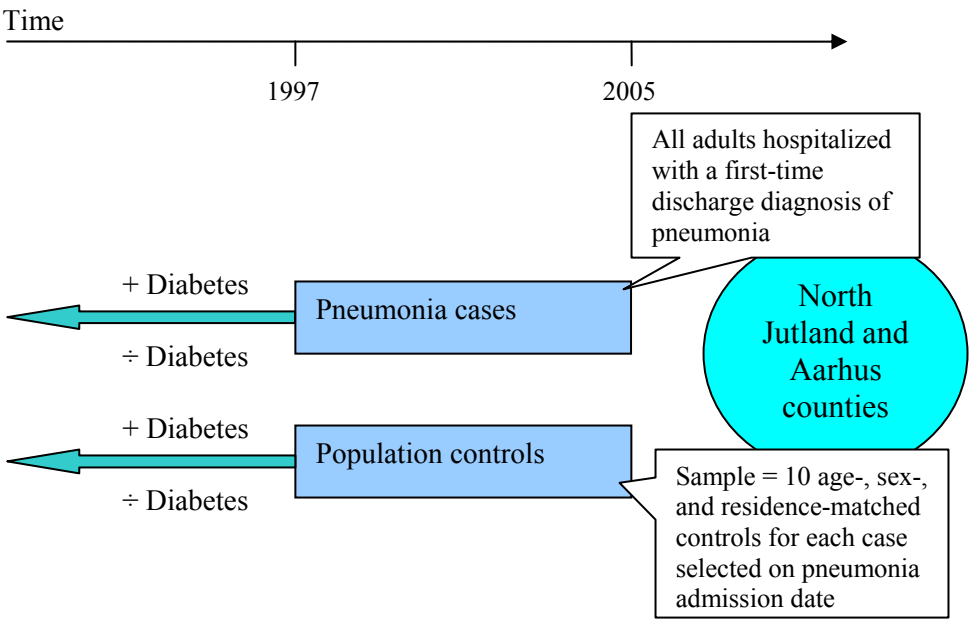


Figure 6. Pneumonia risk, case-control design (*study II*)

Obesity and risk of subsequent hospitalization with pneumonia among Danes aged 50 to 64

Study III was a cohort study. We examined whether obesity is associated with an increased risk of pneumonia-related hospitalization using the cohort "Diet, Cancer and Health." Participants with a prior pneumonia-related hospitalization and those with incomplete information on height and weight or potential confounders were excluded at baseline. We also excluded those who had other major chronic diseases diagnosed before enrolment (see page

39 for definition of other major chronic diseases). We adjusted for baseline smoking status, alcohol intake, schooling, and educational level. In a supplementary analysis we also adjusted for other major chronic diseases diagnosed during follow-up.

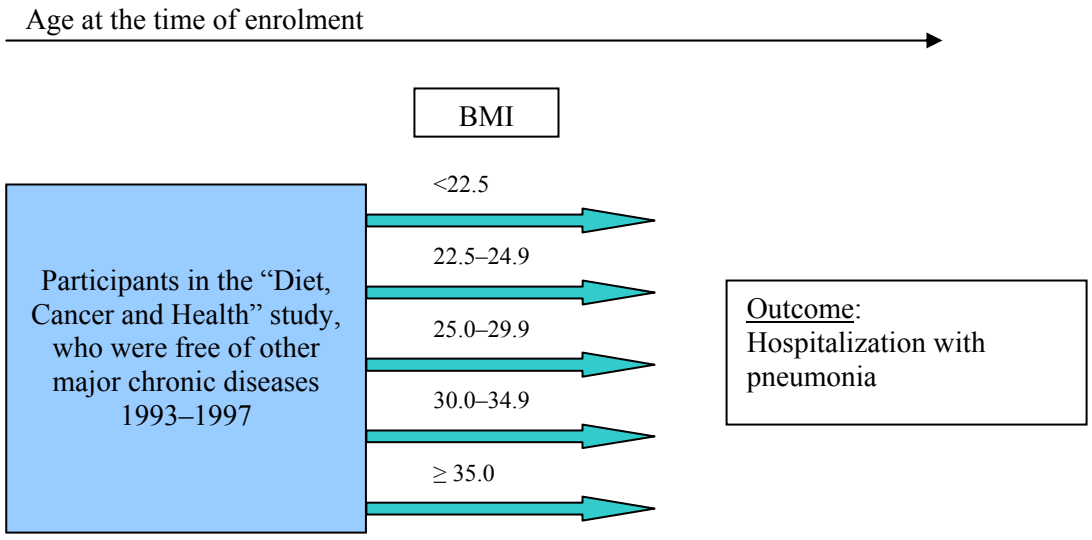


Figure 7. Pneumonia risk, cohort design (*study III*)

Definition of exposure, outcomes, and confounding factors

Diabetes

The way we identified individuals with diabetes differs among studies I–III, mainly because the availability of registry data improved over time.

In *study I*, we identified diabetic individuals from the hospital and prescription registries as follows:

- Hospital diagnosis of type 1 and 2 diabetes (ICD-8 codes 249-250 and ICD-10 codes E10-E11) and/or
- At least one prescription ever for insulin (ATC code A10A) or an oral anti-diabetes drug (ATC code A10B) (124)

In *study II*, we obtained access to the National Health Insurance Service Registry, and the definition of diabetes was extended as follows:

- Hospital diagnosis of diabetes ICD-8 249-250 (diabetes), ICD-10 codes E10-14 (diabetes), O24 (diabetes in pregnancy except for O24.4, which is diabetes arising in pregnancy), and H36.0 (diabetic retinopathy)
- At least one prescription for insulin (ATC code A10A) or an oral anti-diabetes drug (ATC code A10B)
- At least one visit to a chiropodist for diabetic foot care
- At least five glucose-related services (blood glucose measurements performed in general practice) in one year and/or two glucose-related services each year during five subsequent years (125)

In *study III*, we obtained information on diabetes from the National Diabetes Register (covers the period 1996–2006) (see description on page 32), the Danish National Registry of Patients (1977–2008), and from self-reported diabetes by questionnaire in the "Diet, Cancer and Health" cohort.

In *studies I and II*, we classified patients with diabetes as type I (those with diabetes first recorded before age 30 years, using insulin monotherapy, and with no history of oral anti-diabetes medications) or type 2 (the remaining diabetic patients). In *study II*, the duration of

diabetes was defined as the time elapsed between the first record of diabetes and the date of each patient's first pneumonia-related hospital admission.

Data on glucose and HbA1c levels

Information on glucose levels among pneumonia patients from North Jutland County (*study I*) and HbA1c levels among diabetic cases and controls from both counties (*study II*) were obtained from the counties' laboratory databases. We used the first glucose measurement taken on the day of admission or (if unavailable) on the following day. We used the most recent HbA1c measurement for diabetic persons obtained within 12 months preceding the index hospital admission date.

Anthropometric data

All anthropometric data in *study III* were collected at the two study clinics in Aarhus and Copenhagen. Height was measured with the participants standing without shoes and was recorded to the nearest half centimeter. Weight was measured using a digital scale with the participants wearing light clothing or underwear and was recorded to the nearest 100 g. BMI was calculated as a person's weight (measured in kg) divided by the square of their height (measured in meters).

Patients hospitalized with pneumonia

Data on pneumonia were obtained from the counties' hospital registries in *studies I and II*, and from the Danish National Registry of Patients in *study III*. We identified all adult (aged ≥ 15 years) patients with the following discharge diagnoses: pneumonia (codes J12.x–J18.x), legionellosis (A481.x), and ornithosis (A709.x). Because we were interested in first-time hospitalizations with pneumonia, in *studies I and II*, we removed hospitalizations for any recurrent episode of pneumonia during the study periods beginning in 1997 and all patients who had been hospitalized with pneumonia during 1992–1996 (ICD-8 codes used before 1994: 480.XX–486.XX, 0.73.XX, and 471.XX). In *study III*, all participants with a discharge diagnosis of pneumonia preceding enrolment in the cohort "Diet, Cancer and Health" were excluded.

In *study I*, we used the laboratory database to assess pneumonia severity among the North Jutland County patients. We obtained the first laboratory results available on the admission day or the following day.

Mortality

The main outcome in the prognostic study (*study I*) was death from any cause within 30 and 90 days following the admission date. We used all-cause mortality and not cause-specific mortality because among patients with underlying diseases, it can be difficult to distinguish between death because of pneumonia and death from the underlying disease. We ascertained the exact date of death from the Danish Civil Registration System.

Pulmonary complications and bacteremia

Secondary outcomes in *study I* were pulmonary complications and bacteremia. We ascertained pulmonary complications by tracing all diagnoses in the hospital registries documented for the index hospitalization or, if a patient was discharged before day 30, documented for re-hospitalizations up to 30 days post-admission. Pulmonary complications were defined as effusion (codes J90.9 and J91.9), empyema (J86.x), lung abscess (J85.x), or adult respiratory distress syndrome (J80.9) (45). For a subcohort of patients from North Jutland County, we identified all pneumonia patients with at least one blood culture and at least one episode of bacteremia occurring during the hospitalization for pneumonia or within 30 days following the admission date. This identification was achieved through linkage to the North Jutland County Bacteremia Registry.

Potential confounders

In *studies I and II*, data on potential confounding factors were collected from the counties' hospital registries (using both hospital discharge and outpatient visit diagnoses), the counties' prescription registries, and from the Danish Civil Registration System. To adjust for confounding by comorbidity, we computed for each individual the Charlson Comorbidity Index score (126) (described on page 53) based on all available hospital diagnoses except diabetes. Three comorbidity levels were defined: low (score of 0), medium (1–2), and high (≥ 3). We also obtained data on covariates potentially associated with pneumonia risk or prognosis that are not included in the Charlson index: a 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 was added in *study II*); use of systemic glucocorticoids and other 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). In *study I*, we also ascertained any history of obesity

(ICD-8 code 277.99; ICD-10 codes E65.x and E66.x). The Central Population Registry provided in *study II* data on marital status, persons living with small children attending day-care centers (younger than 6 years of age, yes/no), and degree of urbanization.

In *study III*, information on lifestyle factors was obtained from the questionnaires. In the food frequency questionnaire, alcohol intake (beer, wine, fortified wine, and spirits) was reported as the average amount consumed over the preceding year. To calculate total alcohol intake, all types of alcohol consumption were converted to "number of drinks," each containing 12 g of ethanol (127). From the lifestyle questionnaire, we obtained information on smoking status, schooling, and educational level.

Data on other major chronic diseases diagnosed during follow-up were collected from the Danish National Registry of Patients using hospital discharge or hospital outpatient visit diagnoses. For diabetes, we additionally obtained data from self-reports and from the Danish National Diabetes Register. To adjust for other major chronic diseases, we computed the cumulative Charlson comorbidity index score achieved during follow-up for each participants, while also including diagnoses of hypertension (ICD-8 codes 400-404; ICD-10 codes I10-I15), HIV (ICD-10 codes B20.X), and gastroesophageal reflux (ICD-8 codes 530.99; ICD-10 codes K21.X) with one point each. Three comorbidity levels were defined: low (score of 0), medium (1-2), and high (≥ 3).

Statistical analyses

Study I

In the analyses of the association between type 2 diabetes and mortality, follow-up extended for 90 days post-admission, or until death or migration, whichever came first. We constructed survival curves and computed cumulative mortality (after 30 and 90 days of follow-up) by 1 minus the Kaplan-Meier estimator. Survival curves were also constructed by comorbidity level. To compare mortality according to type 2 diabetes status, we used Cox's regression to estimate 30- and 90-day mortality rate ratios (MRRs), while controlling for sex, age (in categories of 15–39, 40–64, 65–79, and ≥80 years), level of comorbidity (low, medium, and high), history of alcoholism-related disorders, and pre-admission use of antibiotics and immunosuppressive drugs. Analyses were conducted with and without the obesity variable. We also adjusted for individual diseases instead of comorbidity level, first by computing the

relative mortality rates in our pneumonia cohort associated with different disease categories in the Charlson index, and then substituting log-transformed weights, based on these individual rates, for the Charlson index score levels in the mortality analysis.

Because we could not clearly discriminate between CAP and hospital-acquired pneumonia, we computed 30-day MRRs for type 2 diabetes separately for patients with pneumonia listed as the primary discharge diagnosis and for those with pneumonia listed as a secondary discharge diagnosis. In accordance with Fry et al. (2), we assumed that primary discharge codes for pneumonia represented hospital admissions because of pneumonia and that secondary discharge codes represented a mixture of hospital admissions precipitated by pneumonia and hospital-acquired pneumonia. To examine how much of the apparent effect of diabetes was caused by hyperglycemia, we included admission glucose level in the model for the North Jutland subcohort, both as a categorical and a continuous variable.

Because of the lack of accurate data on person-time to pulmonary complications/bacteremia, we used logistic regression to estimate adjusted RR for pulmonary complications/bacteremia following pneumonia in patients with type 2 diabetes versus patients without diabetes.

Finally, in the last analysis among all pneumonia patients in the North Jutland subcohort, we computed 30- and 90-day MRRs for different glucose level categories (≤6.1, 6.11–11.0, 11.01–13.99, ≥14 mmol/L) using Cox's regression and controlling for confounders. Stratified analyses were performed according to the presence of diabetes.

Study II

We used conditional logistic regression to compute ORs as a measure of RR, with associated 95% CIs, for hospitalizations with pneumonia among persons with and without diabetes. An OR is approximately equal to the RR when the outcome is rare (128).

Diabetes exposure was further categorized by type of diabetes, duration of diabetes (<5 years; ≥5–<10 years; ≥10 years), and HbA1c level (<7.0%; ≥7.0–<8.0%; ≥8.0–<9.0%; ≥9.0%; unknown). We adjusted for level of comorbidity (low, medium, and high), history of alcoholism-related conditions, pre-admission use of antibiotics or immunosuppressants, marital status (married, never married, divorced or widowed, marital status unknown), household presence of small children attending day-care centers, 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). Stratified analyses were performed by sex, age group (15–39, 40–64, 65–79, ≥80 years), and level of comorbidity.

Study III

We divided the participants according to BMI (<22.5, 22.5-24.9, 25.0-29.9, 30.0-34.9, and 35+) similar to groupings used by the WHO (49). (Because of the few participants with BMI <18.5, we used a different cut-point for the lowest BMI category). We defined normal weight as BMI = 22.5-24.9, overweight as BMI = 25.0-29.9, moderate obesity as BMI = 30.0-34.9 and severe obesity as BMI ≥35.0. We used age as the underlying time variable, with follow-up starting at age at study enrolment. Follow-up extended until age on April 10, 2008, or until age at pneumonia diagnosis, death or migration, whichever occurred first. We computed pneumonia incidence rates by dividing the number of events by the accumulated person-time of follow-up within the groups of BMI, separately for men and women. Cox's regression was used to compute hazard ratios (HRs) as a measure of relative risk for hospitalization with pneumonia according to BMI (reference: 22.5-24.9). We controlled for baseline smoking status (never; former, current <15, 15-25, or >25 g of tobacco/day), alcohol intake (modelled as a restricted cubic spline and an indicator for those who do not drink), schooling (7, 8-10, and >10 years), and educational level (no education, short, middle, long).

To examine whether an association between obesity and pneumonia is explained by other major chronic diseases, in a supplementary analysis we also added the level of our modified Charlsons score achieved during follow-up as a time-dependent variable (Charlson score level low, medium, and high).

Results

Below is a summary of the main results obtained in each of the three studies.

Study I. Type 2 diabetes and pneumonia outcomes

The cohort included 29,900 adult patients with a first-time hospitalization for pneumonia. Of these patients, 2931 (9.8%) had type 2 diabetes, and 92 patients (0.3%) with type 1 diabetes were excluded, leaving 29,808 patients in the final analysis. The median age was 75 years among the diabetic patients and 73 years among the non-diabetic patients. As expected, patients with type 2 diabetes were more likely to have congestive heart failure (23% vs. 10%), a history of myocardial infarction (16% vs. 9%), peripheral vascular disease (13% vs. 7%), cerebrovascular disease (22% vs. 13%), renal disease (6% vs. 3%), and obesity (12% vs. 2%) compared with non-diabetic patients.

Type 2 diabetes and mortality

The cumulative mortality among diabetic patients was 19.9% vs. 15.1% among other patients after 30 days (mortality difference = 4.8%; 95% CI 3.3%–6.3%) and 27.0% vs. 21.6% after 90 days (mortality difference = 5.3%; 95% CI 3.7%–7.0%). Patients with diabetes had higher cumulative mortality, independent of the measured comorbidity level (Figure 8). Adjusted 30- and 90-day MRRs for diabetic pneumonia patients were 1.16 (95% CI 1.07–1.27) and 1.10 (1.02–1.18), compared with non-diabetic pneumonia patients (Table 5). Further adjustment for obesity yielded virtually identical 30- and 90-day MRRs [1.18 (95% CI 1.08–1.29) and 1.12 (1.04–1.20)], as did adjustment for individual disease categories in lieu of Charlson index score levels (1.17 and 1.11, respectively). Patients with type 2 diabetes were slightly more likely than other pneumonia patients to have pneumonia listed as a non-primary discharge diagnosis (40.5% vs. 35.8%). The adjusted 30-day MRR was 1.18 (95% CI 1.05–1.34) for diabetic patients with pneumonia listed as a secondary discharge diagnosis and 1.13 (1.00–1.27) for those with pneumonia listed as the primary discharge diagnosis.

In the North Jutland cohort, there was no association between diabetes and mortality after adjustment for confounding [30-day MRR 0.98 (95% CI 0.86–1.11); 90-day MRR 0.97 (95% CI 0.87–1.09)]. Among the subset of patients with bacteremic pneumonia, mortality from diabetes was slightly lower, with MRRs of 0.86 (95% CI 0.54–1.38) and 0.92 (95% CI 0.62–1.36), respectively. After the categorical variable for the glucose level at admission was added

to the regression model, the adjusted 30-day and 90-day MRRs for patients with diabetes decreased, respectively, from 0.98 and 0.97 to 0.82 (95% CI 0.71–0.95) and 0.89 (95% CI 0.79–1.00).

Type 2 diabetes, pulmonary complications, and bacteremia

The cumulative incidence of recorded pulmonary complications was 2% among patients with or without diabetes. The overall adjusted RR for pulmonary complications was 1.02 (95% CI 0.75–1.40). Overall, 60.2% of patients with diabetes and 59.7% of other pneumonia patients had at least one blood culture. *Streptococcus pneumoniae* was the pathogen in 51.1% of all bacteremia episodes. Among pneumonia patients with blood cultures available, the adjusted RR for bacteremia in diabetic versus non-diabetic patients was 1.02 (95% CI 0.78–1.33). Patients with diabetes were similar to their non-diabetic counterparts in their risk of pneumococcal bacteremia (adjusted RR 1.17; 95% CI 0.84–1.62), but had a greater risk of bacteremia due to gram-positive pathogens other than *Streptococcus pneumoniae* (adjusted RR 1.69; 95% CI 1.02–2.80) and a lower risk for gram-negative bacteremia (adjusted RR 0.72; 95% CI 0.42–1.23).

Hyperglycemia at admission and mortality

Ninety percent of patients with type 2 diabetes and 71% of non-diabetic patients in the North Jutland subcohort (N = 13,574) had blood glucose values measured at admission or on the following day. An admission glucose level greater than or equal to 14 mmol/L was a predictor of death in those with type 2 diabetes (adjusted 30-day MRR 1.46; 95% CI 1.01–2.12), but an even stronger predictor in those without diabetes (adjusted 30-day MRR 1.91; 95% CI 1.40–2.61) (Table 6).

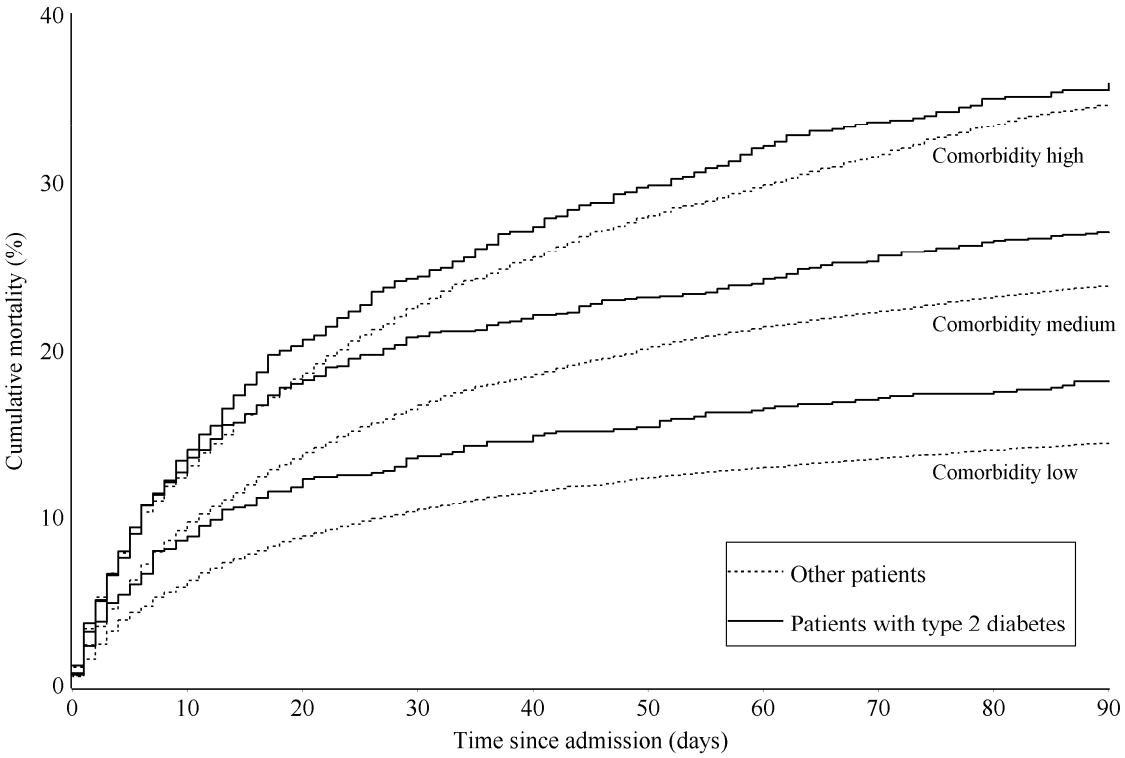


Figure 8. Mortality curves for patients with type 2 diabetes compared with other patients hospitalized with pneumonia, according to level of the Charlson index score. Solid line: patients with type 2 diabetes. Dashed line: other pneumonia patients.

Table 5. Unadjusted and adjusted mortality within 30 and 90 days among patients hospitalized for pneumonia

Exposure	*n*	No. of deaths	Mortality	Unadjusted MRR (95% CI)	Adjusted MRR* (95% CI)
30-day					
No diabetes	26,877	4048	15.1%	1.0 (ref.)	1.0 (ref.)
Type 2 diabetes	2931	582	19.9%	1.36 (1.25–1.48)	1.16 (1.07–1.27)
90-day					
No diabetes	26,877	5818	21.6%	1.0 (ref.)	1.0 (ref.)
Type 2 diabetes	2931	791	27.0%	1.30 (1.21–1.40)	1.10 (1.02–1.18)

Data are *n* unless otherwise indicated. *Adjusted for sex, age group, level of comorbidity, alcoholism-related disorders, and use of antibiotics and immunosuppressive drugs before admission.

Table 6. Unadjusted and adjusted mortality within 30 days among pneumonia patients with available blood glucose values on admission.

	n	No. of deaths	Cumulative mortality	Unadjusted MRR (95% CI)	Adjusted MRR* (95% CI)
30-day					
Level of glucose					
All patients (n = 10,414)					
≤6.1 mmol/L	5129	727	14.2%	1.0 (ref.)	1.0 (ref.)
6.11–11.0 mmol/L	4446	903	20.3%	1.49 (1.36–1.65)	1.37 (1.25–1.51)
11.01–13.99 mmol/L	383	86	22.5%	1.68 (1.35–2.10)	1.49 (1.19–1.86)
≥14 mmol/L	456	107	23.5%	1.79 (1.46–2.20)	1.71 (1.40–2.10)
Patients with type 2 diabetes (n = 1307)					
≤6.1 mmol/L	279	52	18.6%	1.0 (ref.)	1.0 (ref.)
6.11–11.0 mmol/L	545	95	17.4%	0.93 (0.66–1.30)	0.96 (0.69–1.35)
11.01–13.99 mmol/L	188	40	21.3%	1.18 (0.78–1.78)	1.24 (0.82–1.88)
≥14 mmol/L	295	65	22.0%	1.24 (0.86–1.78)	1.46 (1.01–2.12)
Other patients (n = 9107)					
≤6.1 mmol/L	4850	675	13.9%	1.0 (ref.)	1.0 (ref.)
6.11–11.0 mmol/L	3901	808	20.7%	1.56 (1.41–1.73)	1.43 (1.29–1.59)
11.01–13.99 mmol/L	195	46	23.6%	1.81 (1.34–2.44)	1.65 (1.23–2.23)
≥14 mmol/L	161	42	26.1%	2.07 (1.51–2.82)	1.91 (1.40–2.61)

*Adjusted for sex, age group, level of comorbidity, alcoholism-related conditions, and use of antibiotics and immunosuppressive drugs before admission.

Study II. Diabetes, glycemic control, and risk of hospitalization with pneumonia

We identified 34,239 patients with a first-time pneumonia-related hospitalization and 342,390 population controls (median age: 74 years). A total of 101 cases (0.3%) and 187 controls (0.1%) were diagnosed with type 1 diabetes, and 4388 cases (12.8%) and 28,299 controls (8.3%) were diagnosed with type 2 diabetes pre-dating their pneumonia-related hospital admissions.

Table 7 shows the RRs for pneumonia-related hospitalizations. The unadjusted RR for pneumonia-related hospitalization among diabetic individuals compared with non-diabetic individuals was 1.68 (95% CI 1.62–1.74) and the adjusted RR was 1.26 (95% CI 1.62–1.74). The adjusted RR was 4.43 (95% CI 3.40–5.77) for individuals with type 1 diabetes and 1.23 (95% CI 1.19–1.28) for individuals with type 2 diabetes. Diabetes duration ≥10 years increased the risk of pneumonia-related hospitalization (adjusted RR = 1.37; 95% CI 1.28–1.47)). HbA1c level also influenced the risk of pneumonia-related hospitalization among diabetic individuals. Compared with non-diabetic individuals, the RR was 1.22 (95% CI 1.14–1.30) among diabetic individuals with an HbA1c level <7 %, and 1.60 (95% CI 1.44–1.76) among diabetic individuals with an HbA1c level ≥9%. Using only HbA1c measurements within 6 months instead of 12 months before admission yielded virtually identical risk estimates.

Adult diabetic individuals aged <40 years were three times more likely to be hospitalized with pneumonia than non-diabetic individuals of similar age, while the RR gradually decreased in elderly individuals with diabetes (Table 8). After stratifying by level of comorbidity, the association between diabetes and the risk of pneumonia-related hospitalization was highest among individuals with no coexisting morbidity (adjusted RR = 1.51; 95% CI 1.41–1.61). The adjusted RR for pneumonia listed only as a primary discharge diagnosis was 1.20 (95% CI 1.15–1.26) among diabetic individuals compared with non-diabetic individuals.

Table 7. Unadjusted and adjusted relative risks (RRs) for hospitalizations associated with pneumonia.

Exposure	Unadjusted RR (95% CI)	Adjusted RR* (95% CI)
Diabetes		
Absent	1.0 (ref.)	1.0 (ref.)
Present	1.68 (1.62–1.74)	1.26 (1.21–1.31)
Diabetes type		
Diabetes absent	1.0 (ref.)	1.0 (ref.)
Type 1 diabetes	5.55 (4.34–7.08)	4.43 (3.40–5.77)
Type 2 diabetes	1.65 (1.59–1.71)	1.23 (1.19–1.28)
Duration of diabetes		
Diabetes absent	1.0 (ref.)	1.0 (ref.)
<5 years	1.60 (1.53–.68)	1.21 (1.14–1.27)
≥5–<10 years	1.60 (1.51–1.70)	1.24 (1.16–1.32)
≥10 years	1.93 (1.81–2.06)	1.37 (1.28–1.47)
HbA1c		
Diabetes absent	1.0 (ref.)	1.0 (ref.)
Diabetes present, HbA1c <7%	1.64 (1.54–1.74)	1.22 (1.14–1.30)
Diabetes present, HbA1c ≥7–<8%	1.62 (1.48–1.76)	1.23 (1.12–1.36)
Diabetes present, HbA1c ≥8–<9%	1.77 (1.59–1.97)	1.29 (1.15–1.44)
Diabetes present, HbA1c ≥9%	2.26 (2.07–2.48)	1.60 (1.44–1.76)
Diabetes present, HbA1c unknown	1.58 (1.50–1.66)	1.21 (1.14–1.28)

*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 8. RRs for hospitalization associated with pneumonia according to presence of diabetes 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)

*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.

Study III. Obesity and risk of subsequent hospitalization with pneumonia among Danes ages 50 to 64

Descriptive data

Of 57,053 participants in the "Diet, Cancer and Health" cohort, we excluded 331 individuals because of a missing baseline questionnaire or missing variables, 826 individuals who had experienced a hospitalisation for pneumonia before enrolment, and an additional 7,339 individuals who had other major chronic diseases diagnosed before enrolment, leaving 48,557 individuals (22,580 men and 25,977 women) for our analysis.

Among the individuals included in our cohort, 1,088 men and 1,025 women had a first episode of pneumonia-related hospitalization during a median follow-up period of 11.8 and 11.9 years, respectively. The corresponding incidence rates of hospitalizations with pneumonia were 4.2 per 1000 person-years for men and 3.4 per 1000 person-years for women. At enrolment 50% of the participating men were overweight, 12% moderately obese and 2% severely obese. Among women 34% were overweight, 10% moderately obese and 3% severely obese. Compared with participants of normal weight, obese participants were less likely to be smokers but more likely to be former smokers, to be less educated, and to be diagnosed with other major chronic diseases during follow-up. Furthermore, obese men reported higher alcohol intake compared with men of normal weight, while obese women reported lower alcohol intake (data not shown).

Risk estimates

Compared with men of normal weight, adjusted HRs were 1.4 (95% CI 1.2-1.7) for men with moderate obesity, and 2.0 (95% CI 1.4-2.8) for men with severe obesity (Table 9). Among women the associations were weaker with adjusted HRs of 0.8 (95% CI 0.6-1.0) for women with moderate obesity, and 1.2 (95% CI 0.8-1.6) for women with severe obesity.
All adjusted HRs were close to the crude estimates, suggesting little confounding by smoking status, alcohol intake, schooling, and educational level together.

Further adjustment for other major chronic diseases diagnosed during follow-up attenuated the association between obesity and pneumonia hospitalization risk. Thus, the adjusted HRs decreased to 1.0 (95% CI 0.8-1.3) among men with moderate obesity, and 1.2 (95% CI 0.8-

1.7) among men with severe obesity. Among women the corresponding adjusted HRs decreased to 0.7 (95% CI 0.6-0.9) for women with moderate obesity, and 0.8 (95% CI 0.6-1.1) for women with severe obesity.

Table 9. Incidence rates and hazard ratio (HR) with 95% confidence intervals (CIs) of hospitalization with pneumonia among men and women according to body mass index (BMI).

	Body mass index (kg/m^2)				
	<22.5	22.5-24.9	25.0-29.9	30.0-34.9	35+
Men					
Incidence rate*	5.2	3.6	3.9	5.4	7.0
Crude HR (95% CI)**	1.5 (1.2-1.8)	1.0 (ref.)	1.1 (0.9-1.2)	1.5 (1.2-1.8)	2.1 (1.5-3.0)
Adjusted HR (95% CI) †	1.4 (1.1-1.7)	1.0 (ref.)	1.1 (0.9-1.3)	1.4 (1.2-1.7)	2.0 (1.4-2.8)
Adjusted HR (95% CI) ‡	1.4 (1.1-1.7)	1.0 (ref.)	1.0 (0.8-1.1)	1.0 (0.8-1.3)	1.2 (0.8-1.7)
Women					
Incidence rate*	4.0	3.4	3.0	2.9	4.3
Crude HR (95% CI)**	1.3 (1.1-1.5)	1.0 (ref.)	0.8 (0.7-1.0)	0.8 (0.6-1.0)	1.2 (0.8-1.6)
Adjusted HR (95% CI) †	1.2 (1.0-1.4)	1.0 (ref.)	0.9 (0.7-1.0)	0.8 (0.6-1.0)	1.2 (0.8-1.6)
Adjusted HR (95% CI) ‡	1.2 (1.0-1.4)	1.0 (ref.)	0.8 (0.7-1.0)	0.7 (0.6-0.9)	0.8 (0.6-1.1)

*Incidence per 1000 person-years. **The crude HR was calculated with the use of Cox´s regression, with age as the underlying time variable. †Multivariable-adjusted model was based on the crude model with additional adjustment for smoking status, alcohol intake, schooling, and educational level.‡Multivariable-adjusted model as specified above and with additional adjustment for other major chronic diseases diagnosed during follow-up

Strengths and weaknesses of the studies

Considerations about research design

We examined *diabetes/hyperglycemia as prognostic factors for pneumonia (study I)* in a cohort design of pneumonia patients exposed and unexposed to diabetes. A cohort study has the advantage of making it possible to compute the absolute risk of the outcome. A disadvantage of cohort studies based on primary data collection is that they are inefficient (because many more individuals must be enrolled than experienced the outcome) as well as time consuming and expensive, because of resources necessary to study many people over time (113). This cohort study was, however, based on already existing data from medical and administrative registries in Denmark, which allowed a large sample size, a population-based design, and complete follow-up for mortality.

We examined *diabetes as a risk factor for pneumonia-related hospitalization (study II)* in a nested case-control design using medical and administrative registries. Alternatively, we could have performed a cohort study based on the same registries starting with a diabetic and a control cohort. Still, the control of confounding would have been more complicated because confounders (e.g., the use of immunosuppressive drugs) may be variably present and the study participants may shift from one confounder category to another (e.g., having small children). The nested case-control design enabled us to address the research question with smaller sample sizes comparing the odds of having diabetes among pneumonia cases and only a sample of the source population in Aarhus and North Jutland counties. Because we sampled the controls with the incidence density technique, the controls provided an estimate of the proportion of the total person-time for exposed and unexposed cohorts in the source population (16). Thus, the estimated OR was an unbiased estimate of the incidence rate ratio and mirrored the result that the underlying cohort would provide (123).

Obesity as risk factors for pneumonia-related hospitalization (study III) can also be examined in both a cohort and a case-control design. In this context, a nested case-control study, in which BMI is measured close to the index hospital admission date, may be preferred. Deciding which study design to choose also, however, depends on the availability of primary or secondary data. Concerning our intended obesity study, The Danish National Registry of Patients/hospital registries did not contain information on BMI or other anthropometric

measurements. Nevertheless, at the time *study III* was planned, we obtained access to the cohort *"Diet, Cancer and Health"* (described on page 31), which contains detailed information on anthropometric measurements, lifestyle factors, and history of hospital diagnoses for all participants at enrolment. Nevertheless, the cohort lacks data on certain other confounders (e.g., use of immunosuppressants and other drugs), and participants may have shifted exposure (because of weight gain or weight loss) or confounder category during long-term follow-up (see the next section).

Considerations about bias, confounding and chance

Before deciding whether the associations found in our studies are likely to be causal, we needed to assess the impact of potential bias in selection or measurement/information, confounding factors, and statistical chance (113). The precision of the estimates of associations was described by the 95% CIs in the results section.

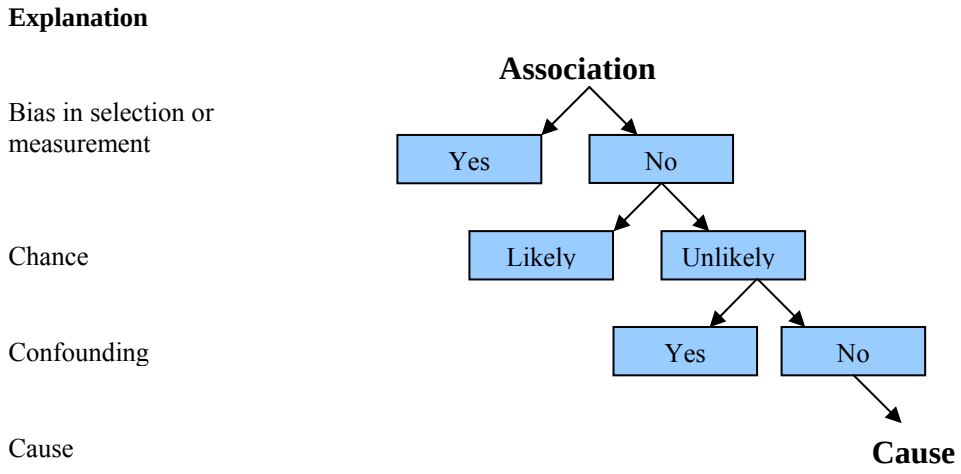


Figure 9. Association and cause. From Fletcher *Clinical Epidemiology: The Essentials* (113).

Study I. Type 2 diabetes and pneumonia outcomes

Selection bias

Selection bias occurs when the association between exposure and outcome differs for participants and non-participants in a study (16). Because of the unique civil registration numbers and the use of population-based registries, we had in this cohort study complete follow-up in terms of the outcomes of death, pulmonary complications, and for the North

Jutland subcohort, bacteremia. Thus, selection bias arising from differential loss-to-follow-up related to diabetes exposure or outcome was not a problem.

The validity of our estimates depended on the data quality for the pneumonia and diabetes diagnoses. Despite inevitable coding errors, the estimated positive predictive value of a discharge diagnosis of pneumonia in Denmark is 90% (95% CI 82–95%) (3). In comparison, the estimated positive predictive value of a pneumonia discharge diagnosis in Holland is 88% (95% CI 80–95) (129), whereas it is 70% (95% CI 0.51–0.89) in the U.S. Veterans Affairs Hospital discharge database (130) (both are based on the International Classification of Diseases, 9th Revision, Clinical Modification).

Information bias

Information bias can arise if the information collected about or from study participants is erroneous (16). The errors may result in misclassification of the exposure, the outcome, or the confounders. Misclassifications can be either non-differential (the errors are evenly distributed among comparison groups) or differential (the errors are unevenly distributed among comparison groups). Only *differential* misclassifications lead to systematic errors.

A previous study suggests that 80–90% of individuals with known diabetes in Denmark can be identified by combining discharge diagnoses from the Danish National Patient Registry with prescription data (131). Still, it is plausible that we missed some diabetic patients in our *study I* cohort who had not been hospitalized previously or treated with anti-diabetic drugs. This oversight could have led to conservative mortality estimates if there were a number of diabetes patients among our unexposed group. It also could have led to an overestimation of the type 2 diabetes–mortality association if the patients we identified with type 2 diabetes had particularly high diabetic disease severity. The predictive value of a diagnosis of diabetes based on the diabetes algorithm applied in *study I* was 97% (95% CI 89–100%) in another study (124).

There are no misclassifications of the outcome death. It is possible, however, that diabetic patients are more likely to have bacteremia or pulmonary complications diagnosed compared with other patients because of the increased surveillance of patients with a known chronic disease. This factor would have caused an overestimation of the RR of these complications

associated with diabetes. The identical proportions of patients with at least one blood culture taken (60.2% vs. 59.7%) argues against differential surveillance.

Confounding

Confounding can be defined as "distortion in an effect measure introduced by an extraneous variate" (17). For example, in this cohort study, the effect of diabetes could be mixed with the effect of another factor (e.g., age) in the outcome of pneumonia. To act as a confounder in a study of diabetes and mortality, a factor must fulfill three criteria (16), as follows. It must (1) be associated with the outcome (mortality); (2) be associated with the exposure (diabetes); and (3) not be an effect of the exposure (diabetes). Residual confounding in our studies could have arisen from misclassification and inappropriate categorization of the confounding factors that we included and controlled for, whereas unmeasured confounding could have arisen because of known confounding factors, which we could not control for. Unknown confounding could, as the term indicates, arise because of confounding by unknown factors.

To control for comorbidity, we used the Charlson Comorbidity Index. This index includes 19 disease categories, selected and weighted according to their associated RR of 1-year mortality in a cohort of 604 medical patients (126). The comorbidity index was subsequently tested for its ability to predict 10-year mortality in a cohort of breast cancer patients (126). Other weights may have been applied if the index had been developed for a different population (132). Furthermore, because the index was developed on the basis of a relatively small number of patients, rare diseases may not have been considered for inclusion in the index (133).

Comorbidity may be coded more completely in patients with diabetes for two reasons: Diabetes is a chronic disease that can lead to frequent contact with the health care system and thereby facilitate early diagnosis and coding of comorbid diseases. Conversely, patients in contact with the health care system for a comorbid disease may be more likely to have diabetes diagnosed. Such a differential misclassification of comorbidity may lead to underestimation of the comorbidity adjusted RRs between diabetic and non-diabetic patients but would of course not influence the crude RRs. Because diabetes was the exposure, diabetes was excluded from the Charlson index (two of the nineteen disease categories relate to diabetes) and included as a separate variable in the analyses. These circumstances may have weakened the index's ability to predict mortality. To counter these potential limitations, we

alternatively adjusted for individual disease categories in lieu of Charlson index score levels. This adjustment left our estimates virtually unchanged. Furthermore, we found with each increased level of the Charlson index score a stepwise increase in the adjusted MRR among patients hospitalized with pneumonia [adj. 30-day MRR for index low: 1.0 (ref.), index medium: 1.3 (95% CI 1.2–1.4), and index high: 1.7 (95% CI 1.6–1.9)].

The Charlson index contains disease categories such as myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, and renal disease that might be an effect of diabetes. It is therefore debatable whether these conditions should be considered confounding factors because they might be regarded as intermediates in the causal pathway from diabetes to pneumonia (16). Still, in our studies, we sought to examine the impact of diabetes without the influence of these diabetes-related diseases.

Lack of data precluded adjustment for pneumococcal and influenza vaccinations. Nevertheless, the overall uptake of pneumococcal vaccine in the North Jutland region has been as low as 2 per 1000 people/year since 1997 (124). Thus, we do not expect that pneumococcal vaccination had a major impact on our estimates. In the case of influenza, vaccination is recommended and provided free of charge for all patients >65 years of age regardless of the presence of diabetes or other comorbidities, and almost 70% of our pneumonia patients were >65 years of age. In our study, it was possible that patients with diabetes were vaccinated at higher rates than other patients with pneumonia. If vaccination has a beneficial effect on pneumonia outcome, as has been recently suggested (134;135), we then would have underestimated the relative diabetes-related mortality and our study's conclusion would be unaltered. Finally, we did not have data on antibiotic treatment or other medical treatments during the hospital stay. Nevertheless, *Streptococcus pneumoniae* was the microbiological agent in 51.1% of all bacteremia episodes in our study. In Denmark, *S. pneumoniae* is almost always penicillin sensitive [the resistance of S. *pneumoniae* to penicillins is between 0.4% and 0.8% in Denmark (136)], and penicillin continues to be recommended as the drug of choice for treating pneumonia in Denmark (137).

Comment on CAP and hospital-acquired pneumonia

We are aware that it is important to distinguish between community- and hospital-acquired pneumonia. Because diagnoses at the time of hospital admission were unavailable in the registry, we could not clearly distinguish between community- and hospital-acquired cases.

The crude mortality rates from hospital-acquired pneumonia range from 30% to as high as 70% (138). Thomsen et al. found that based on a random sample of 100 hospitalizations with pneumonia, 13% of pneumonia episodes in the hospital registry from North Jutland County were hospital acquired (3). If patients with diabetes were relatively more susceptible to hospital-acquired pneumonia because of more frequent hospitalizations, failure to discriminate between community- and hospital-acquired disease could partly explain the greater diabetes-related mortality found in our study compared with that in the study by Kaplan (40). To address the community vs. hospital-acquired question further, we performed a subanalysis in which we differentiated between primary and secondary discharge diagnoses. However, a similarly increased mortality associated with type 2 diabetes was observed regardless of whether pneumonia was listed as the primary discharge diagnosis [30-day MRR = 1.13 (95% CI 1.00–1.27) or as any-listed discharge diagnoses (adjusted 30-day MRR = 1.16 (95% CI 1.07–1.27)].

Study II. Diabetes, glycemic control, and risk of hospitalization with pneumonia

Selection bias

Selection bias in our case-control study could have arisen if diabetes increased the risk of being diagnosed as a pneumonia case because of a lower threshold for admitting diabetic patients with infections. Such a bias would lead to overestimation of the RR associated with diabetes. However, concerning type 2 diabetes, among patients with type 2 diabetes and non-diabetic patients with pneumonia, *study I* showed comparable levels of preadmission use of antibiotics (39% vs. 39%), levels of inflammatory markers [median C-reactive protein 85 mg/L (interquartile range, IQR, 32–176 mg/L) vs. 88 mg/L (IQR 34–181 mg/L); leukocyte 12.7 10^9/L (IQR 9.5–17.2 10^9/L) vs. 12.1 10^9/L (IQR 8.9–16.2 10^9/L), and PaO_2 (median PaO_2 8.1 kPa; IQR 6.8–9.7kPa) vs. 8.2 kPa, (IQR 6.9–9.7 kPa)], and proportion of patients with at least one blood culture (60.2% vs. 59.7%). These results suggest that there was no severe bias associated with admission of patients with type 2 diabetes. However, for type 1 diabetes, the possibility remains that increased surveillance affected risk estimates. In fact, unpublished laboratory data from *study I* showed that pneumonia patients with type 1 diabetes had lower levels of C-reactive protein upon admission [median C-reactive protein 69 mg/L (interquartile range, IQR, 29–175 mg/L) vs. 88 mg/L (IQR 34–181 mg/L)] and lower pneumonia-related mortality (90-day MRR = 0.34; 95% CI 0.13–0.90). Patients with type 1 diabetes may be more likely to seek medical attention and to be hospitalized because of problems with glucose regulation triggered by pneumonia and risk of ketoacidosis.

Information bias

Because of improved identification of patients with untreated type 2 diabetes, the prevalence of type 2 diabetes cases identified in *study II* was higher than in *study I* (12.8% vs. 9.8%). Nevertheless, the possibility remains that we missed a few diet-treated patients with type 2 diabetes who never had been hospitalized or who received one of the health services mentioned on page 36. Such a misclassification would be non-differential and would diminish any observed difference in risk estimates. By using highly valid algorithms to collect data on diabetes and possible confounding factors before the date of hospitalization for pneumonia (131), we avoided the recall bias present in case-control studies based on interviews or questionnaires. The categorization of diabetes into type and duration of diabetes was based on registry data and may not be entirely correct (partly because the hospital registry first was established in 1977 and the prescription registries in 1991 and 1996, respectively).

Confounding

The Charlson index was not developed to predict the risk of subsequent diseases, including pneumonia. However, it includes most important risk factors for pneumonia, such as chronic obstructive pulmonary disease, asthma, cardiovascular disease, cerebrovascular disease, liver disease, dementia, AIDS, renal disease, and cancer. Furthermore, similar to *study I*, we found with each increased level of Charlson index score a stepwise increase in the adjusted RR for pneumonia-related hospitalization in both this study and in study III.

Pneumococcal and influenza vaccinations may reduce the risk of pneumonia (139;140). If patients with diabetes were vaccinated at higher rates than others, the RR of pneumonia-related hospitalization would be underestimated and would not alter our conclusion. We adjusted for marital status, an important aspect of social support that may be related both to having a chronic disease like diabetes (141) and to infections (142). Unfortunately, we did not have data on other socio-economic factors such as income, education, and occupation. Moreover, we did not have data on smoking and alcohol consumption in the hospital registries. If more patients with diabetes were smokers and alcohol users than non-diabetics, these factors would lead to an overestimation of the RR of pneumonia-related hospitalization. Nevertheless, we adjusted for proxy measures for smoking and alcohol abuse such as chronic pulmonary disease and a history of alcoholism-related disorders.

Study III. Obesity and risk of subsequent hospitalization with pneumonia among Danes aged 50 to 64

Selection bias

Because we used population-based registries to ascertain the outcome hospitalized pneumonia, we had virtually complete follow-up.

Information bias

In *study III*, all height and weight measurements were performed by a laboratory technician at baseline, which reduces the potential bias toward a higher risk of pneumonia at lower BMI ranges resulting from possible understated weight in obese individuals (143). Erroneous measurements would probably be independent of a later diagnosis of pneumonia and thus a non-differential misclassification. The BMI may, however, have changed during follow-up because of weight gain or weight loss. If participants gained weight during follow-up, the association between baseline obesity and risk of pneumonia would have been overestimated. The association could, however, also have been overestimated if participants lost weight due to an undiagnosed underlying subclinical condition.

Because of the increased surveillance of patients with chronic diseases, physicians may be more likely to admit an obese patient with pneumonia compared with a patient of normal weight. Such bias would lead to an overestimation of the RR associated with obesity. Unfortunately, we did not have complete data on pneumonia severity upon hospital admission in obese vs. normal-weight patients to evaluate the extent of such bias.

Confounding

We modified the Charlson index by including three other diseases associated with risk of pneumonia thereby including most important diseases acting as risk factors for pneumonia. Nevertheless, inaccuracy of discharge data and presence of diagnoses not included in the Index may have reduced our ability to control for the influence of some chronic diseases. Furthermore, the Charlson index contains diseases that might be an effect of obesity, including diabetes, myocardial infarction, congestive heart failure, liver disease, cerebrovascular disease, dementia, chronic pulmonary disease and renal disease. (See discussion on page 56.)

Because we based our information on self-reported smoking and alcohol use at the time of enrolment, we cannot exclude residual confounding if this information was wrongly reported or if smoking or drinking habits changed over time. Still, alcohol use and smoking did not act as strong confounders in this study. Finally, lack of data precluded adjustment for medications including use of systemic antibiotic therapy, immunosuppressive drugs, and pneumococcal and influenza vaccination.

Discussion

Diabetes as a risk factor for hospitalization with pneumonia

Our data extend previous studies suggesting that diabetes is a risk factor for pneumonia with RRs ranging from 1.25–1.75 (19;21;78;80;81;107). We observed a difference in risk estimates for pneumonia-related hospitalization by type of diabetes. In comparison, the only previous study that distinguished between type 1 and 2 diabetes found that patients with type 1 and 2 diabetes had a 1.32 (95% CI 1.13–1.53) and 1.42 times (95% CI 0.96–2.08) greater risk of general practitioner-diagnosed "lower respiratory tract infection" (80). We found the highest RR estimates among young diabetic adults and among diabetic individuals without coexisting morbidity, which is in line with findings for pneumococcal bacteremia (117). Our findings of an increased risk of pneumonia-related hospitalization due to poor long-term glycemic control and longer diabetes duration have, to the best of our knowledge, not previously been reported.

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 characterized by reduced or totally absent insulin secretion. Insulin levels are often higher in the face of insulin resistance in type 2 diabetes and insulin may itself have anti-inflammatory effects (144). The observation that longer diabetes duration increased the risk of pneumonia-related hospitalization could be due to worsening of the described microangiopathic changes in the basement membranes of pulmonary blood vessels and respiratory epithelium in diabetic persons (91). Diabetes combined with an HbA1c level ≥9% was associated in our study with a 60% increased risk of pneumonia-related hospitalization, while diabetes combined with an HbA1c <7% was associated with an only 22% increased risk of pneumonia-related hospitalization. These results agree with observations from in vitro studies in which hyperglycemia was associated with abnormalities in neutrophil function (145) (page 19). Nevertheless, our results also show that even individuals with well-controlled diabetes have a higher risk of pneumonia-related hospitalization compared with non-diabetic individuals, indicating that the increased susceptibility to pneumonia among diabetic individuals has a multifactorial cause.

Type 2 diabetes, hyperglycemia, and outcomes following pneumonia-related hospitalization

Our finding of a 16% increased 30-day mortality associated with type 2 diabetes is consistent with results from previous cohort studies (23;110;111) and with the 1996 meta-analysis of CAP prognosis by Fine et al. (unadj. OR = 1.3; 95% CI 1.1–1.5). In comparison, a recent Spanish study found that diabetes was associated with a 2-fold increased 30-day mortality (112). This study relied, however, upon a cohort admitted to a single university hospital and may have included diabetic patients with greater disease severity compared to our population-based cohort. Hyperglycemia on admission was, in our study, associated with a poor prognosis in both diabetic and non-diabetic patients with pneumonia [adj. 30-day MRRs for glucose level ≥14 mmol/L were 1.46 (95% CI 1.01–2.12) and 1.91 (1.40–2.61), respectively], which agrees with the few previous studies on hyperglycemia and outcome of pneumonia (37;44). Of importance, like McAlister et al., we observed that the risk of mortality was substantially increased at much lower glucose levels than the level (≥14 mmol/L) incorporated in the PSI (44).

After we controlled for admission glucose level in the subset of patients with available glucose measurements, type 2 diabetes no longer predicted increased mortality following pneumonia. The analysis suggests that most of the effect on mortality associated with type 2 diabetes is mediated through glucose level. The impact of hyperglycemia on mortality was lower among patients with type 2 diabetes than that among other patients. In non-diabetic patients, hyperglycemia could signal physiological stress and thus greater pneumonia severity (146). Furthermore some non-diabetic patients with hyperglycemia could have been undiagnosed and therefore untreated diabetic patients (146), experiencing a poor outcome following pneumonia. By contrast, in diabetic patients, hyperglycemia could be the result of poorly controlled diabetes, stress, or both because we did not know the baseline concentration of glucose (147). In addition, patients with type 2 diabetes might be more likely to receive insulin for hyperglycemia during pneumonia-related hospitalization, potentially improving their outcome (94).

The elevated mortality that we observed in diabetic patients did not appear to be mediated through more pulmonary complications. Rather, we found that patients with diabetes had more underlying renal disease and considerably higher levels of urea nitrogen and creatinine

at the time of admission. Urea nitrogen level on admission has been shown to predict CAP outcome and is included in prognosis prediction rules such as the PSI score (44). We did not observe an elevated risk of bacteremia in diabetic pneumonia patients. In the subgroup of bacteremic pneumonia patients, mortality estimates for those with diabetes were actually below one, confirming previous findings for diabetic patients with pneumococcal bacteremia (124).

Study III: Obesity and risk of subsequent hospitalization with pneumonia among Danes aged 50 to 64

In contrast to our findings, Baik et al. found that obesity was associated with an elevated risk of pneumonia among women in the Nurses' Health study (adjusted RR = 2.2; 95% CI 1.6–3.2) but not among men in the Health Professionals' Follow-up Study (RR = 1.0; 95% CI 0.6-1.7) (7). Compared with our study, the US studies included younger women (aged 27 to 44 years) and elder men (aged 44-79). If the relative impact of obesity is greatest in younger adults, this age difference could explain part of the different risk estimates according to sex between the above studies and our study. Furthermore, the Nurses' Health Study II was based on self-reported physician-diagnosed pneumonia with the risk of over- or underreporting, while we use population-based hospital registries to obtain information on hospitalization with pneumonia. Unlike our study, two recent case-control studies reported a slightly reduced risk of pneumonia among obese individuals (19;28). A reason, for the lower risk associated with obesity in the mentioned case-control studies compared with our study, could be that the height and weight measurements in our study were performed at baseline and in particular obese participants may have gained further weight during follow-up causing an overestimation. In the case-control studies information on self-reported height and weight were collected close to the index pneumonia episodes. Part of the lower risk estimates in the case-control studies could, however, also be explained by lacking adjustment for smoking (19) or residual confounding because of inappropriate categorisation of the smoking variable (28).

After we added other major chronic diseases to the regression model, obesity no longer predicted higher risk of pneumonia and even tended to predict a lower risk among women. The results of this analysis suggest that much of the increased pneumonia risk associated with obesity is explained by presence of other chronic diseases (see the paragraph "Other complications of obesity" on page 12).

Interestingly, we found that obesity was more strongly related to the risk of pneumonia among men than among women. This sex difference remained after adjustment for other major chronic diseases and thus could not solely be due to difference in the burden of chronic diseases. The reasons for this sex difference are unclear. Differences in fat distribution may play a role as abdominal obesity, which is more prevalent in men than in women (148), may restrict the descent of the diaphragm and cause reduced ventilation at the lung bases (63). Reasons may also include other biological factors, residual confounding or the play of chance.

Main conclusions

Based on the results in the three studies and an evaluation of potential bias, confounding, and chance, we draw the following main conclusions:

Study I

Type 2 diabetes was a predictor for increased mortality from pneumonia, although this was largely explained by differences in patient age and comorbidity. Type 2 diabetes did not predict pulmonary complications or bacteremia. Admission glucose levels of >11 mmol/L in type 2 diabetic patients and of >6 mmol/L in other patients predicted increased mortality.

Study II

Type 1 diabetes was associated with 4.4-fold higher risk of a pneumonia-related hospitalization, and type 2 diabetes was associated with a 1.2-fold higher risk. Poor long-term glycemic control and longer diabetes duration clearly increased the risk of pneumonia-related hospitalization. Also, the relative impact of diabetes was greatest in younger adults and in individuals without coexisting morbidity.

Study III

Obesity was associated with a markedly increased risk of subsequent hospitalization with pneumonia among men but not among women. This higher risk was apparently explained by presence of other chronic diseases in obese individuals.

Perspectives

As the prevalence of obesity and diabetes continues to rise, the burden and health care costs of pneumonia due to obesity and diabetes are likely to increase. Nevertheless, obesity and type 2 diabetes can largely be prevented through lifestyle interventions, including increased physical activity and a healthy diet. Prevention of obesity and related type 2 diabetes is a difficult task and requires a large effort from the individual, the health care system, and society in general.

Influenza and pneumococcal vaccinations are important interventions against pneumonia. Influenza vaccine may reduce the risk of pneumonia by 53% in the elderly (140), while the current pneumococcal polysaccharide vaccine (PPV23) may reduce risk of pneumococcal bacteremia (139;149;150). The effectiveness of PPV23 in preventing non-bacteremic pneumonia is doubtful (149;150). It appears that the introduction of a new 7-valent pneumococcal conjugate vaccine (PCV7) for all infants has reduced the incidence of both bacteremic and non-bacteremic pneumococcal disease in the United States (151), including in elderly individuals. Thus, persons with diabetes and obesity might well benefit from the 2007 introduction of universal PCV7 for children aged ≤12 months in Denmark. Other preventive measures in the diabetic or obese individual would be to avoid other risk factors for pneumonia, including crowding, smoking, heavy alcohol intake, and probably excessive weight gain and unnecessary antibiotic use.

The fact that every fourth patient with type 2 diabetes dies within 90 days following pneumonia hospitalization is of great clinical and public health concern. It suggests that the current hospitalization routines and surveillance during and after pneumonia-related hospitalization in Denmark can be improved. Implementation of up-to-date clinical guidelines for correct treatment of pneumonia and sepsis are important. Examples are the new electronic guidelines for pneumonia treatment in the North and Central Denmark Regions (152), guidelines for pneumonia treatment from the Institute for Rational Pharmacotherapy (153), or nationwide guidelines for the correct treatment of sepsis in the national patient safety campaign “Operation Life” (154). Interventions such as pneumococcal and influenza vaccinations and statin therapy have recently been associated with improved survival following pneumonia (134;135;155), but our knowledge about prognostics factors for pneumonia specifically in diabetic patients is limited. Clinicians should predict that diabetic

and other patients with high blood glucose on admission will have an increased risk of death, while future studies may foster our understanding by examining the impact of long-term glycemic control, insulin vs. oral anti-diabetic treatment, and preadmission use of statins on pneumonia outcomes in diabetic patients. Studies that examine the specific causes of death in diabetic patients hospitalized with pneumonia are also needed.

The hope is that the findings in this thesis will contribute to continuous improvements in our ability to predict, understand, and change the risk and prognosis for pneumonia in patients with diabetes and obesity.

Summary

Pneumonia is a major clinical and public health problem. Pneumonia-related hospitalizations have increased by 20–50% in Western populations during the past 10 years, and reported in-hospital mortality remains high at 5% to 15%. Concurrently, the prevalence of obesity and diabetes is increasing globally. Patients with diabetes may have an increased risk and worse outcome of pneumonia due to hyperglycemia, decreased immunity, impaired lung function, chronic complications of diabetes, and an increased risk of aspiration. Obese individuals may also have an increased risk of pneumonia, but it is unclear whether such a relation might be due to obesity *per se* or explained by other acquired diseases associated with obesity.

The aims of this thesis were to examine (1) whether type 2 diabetes increases the risk of death and complications among patients hospitalized with pneumonia and to assess the prognostic value of admission hyperglycemia (*study I*); (2) whether diabetes is a risk factor for hospitalization with pneumonia and to assess the impact of glycemic control on such risk (*study II*); and (3) whether obesity increases the risk of hospitalization with pneumonia among men and women taking the presence of other major chronic diseases into account (*study III*). The three studies were based on Danish medical and administrative databases.

In *study I*, we conducted a population-based cohort study of 29,900 adults with first-time hospitalization for pneumonia. Overall, 10% of patients had type 2 diabetes. Mortality 30 and 90 days post-admission was higher among diabetic than other patients: 19.9% vs. 15.1% and 27.0% vs. 21.6%, respectively, corresponding to slightly increased adjusted 30- and 90-day MRRs of 1.16 (95% CI 1.07–1.27) and 1.10 (1.02–1.18). Presence of type 2 diabetes did not predict pulmonary complications or bacteremia. An admission glucose level ≥14 mmol/L was a strong predictor of death in those with type 2 diabetes (adjusted 30-day MRR 1.46; 95% CI 1.01–2.12), but an even stronger predictor in those without diabetes (adjusted 30-day MRR 1.91; 95% CI 1.40–2.61). In *study II*, we included 34,239 hospitalized pneumonia cases and 10 sex- and age-matched population controls per case in a population-based case-control study. Persons with type 1 and type 2 diabetes had a 4.4 (95% CI 3.4–5.8) and 1.2 (95% CI 1.2–1.3) times higher risk of pneumonia-related hospitalization compared with other individuals. Compared with non-diabetic individuals, diabetic persons whose HbA1c level was <7% had a 22% increased risk for pneumonia, while diabetic persons whose HbA1c level was ≥9% had a 60% increased risk. In *study III*, we examined the association of BMI with the

risk of an incident pneumonia-related hospitalization among 48,557 individuals from the Danish "Diet, Cancer and Health" study. We found that the risk of pneumonia was increased 1.4 (95% CI 1.2-1.7)-fold in men with moderate obesity and 2.0 (95% CI 1.4-2.8)-fold in men with severe obesity, compared with men of normal weight. Among women, severe obesity was associated with a 1.2 (95% CI 0.8–1.6)-fold increased risk, whereas women with moderate obesity had no increased risk of pneumonia (HR = 0.8; 95% CI 0.6-1.0). After we added other major chronic diseases to the regression model, obesity no longer predicted higher risk of pneumonia and even tended to predict a lower risk among women.

In conclusion, our studies show that type 2 diabetes predicts slightly increased mortality, but not pulmonary complications or bacteremia following pneumonia. Hyperglycemia on admission is a strong predictor for mortality following pneumonia in both diabetic and other patients. Our data, combined with previous results, provide strong evidence that diabetes is a risk factor for hospitalized pneumonia, in particular if associated with poor long-term glycemic control. Finally, obesity is associated with a markedly increased risk of subsequent hospitalization with pneumonia among men but not among women. This higher risk is apparently explained by presence of other chronic diseases in obese individuals.

Dansk resumé

Pneumoni udgør et betydeligt klinisk og samfundsmæssig problem. Antallet af indlæggelser med pneumoni er steget med 20-50% over de sidste 10 år i den vestlige verden. Dødeligheden efter indlæggelse med pneumoni er vedvarende høj, dvs. mellem 5 og 15%. Samtidig ses en global stigning i prævalensen af fedme og diabetes. Patienter med diabetes kan have øget risiko og forværret prognose for pneumoni på grund af hyperglykæmi, nedsat immunforsvar, nedsat lungefunktion, sendiabetiske komplikationer, og en øget risiko for aspiration. Fedme øger muligvis også risikoen for pneumoni, men det er uklart om en evt. sammenhæng mellem fedme og lungeinfektioner skyldes fedme i sig selv eller andre kroniske sygdomme relateret til fedme.

Formålet med denne afhandling har været at klarlægge 1) om type 2 diabetes øger risikoen for død og komplikationer hos patienter indlagt med pneumoni, samt at bestemme den prognostiske værdi af hyperglykæmi målt ved indlæggelsen (studie I), 2) om diabetes er en risikofaktor for indlæggelse med pneumoni, og om den glykæmiske regulering har indflydelse på pneumonirisikoen (studie II), og 3) sammenhængen mellem fedme og risikoen for at blive indlagt med pneumoni og at undersøge om en evt. sammenhæng kan forklares ved forekomsten af andre kroniske sygdomme hos individer med fedme. (studie III). Studierne er baserede på danske kliniske og administrative databaser.

Studie I var et kohortestudie omfattende 29.900 voksne med en førstegangsindlæggelse med diagnosen pneumoni. Ti procent af patienterne havde type 2 diabetes. Vi fandt at dødeligheden hhv. 30 og 90 dage efter indlæggelse med pneumoni var højere hos patienter med type 2 diabetes end hos andre patienter: 19,9% mod 15,1% og 27,0% mod 21,6%, svarende til justerede 30- og 90-dages mortalitets rate ratioer (MRR´er) på 1,16 (95% konfidensinterval (KI) 1,07-1,27) og 1,10 (95% KI 1,02-1,18). Type 2 diabetes var ikke en prædiktor for lungekomplikationer eller bakteriæmi inden for 30 dage efter indlæggelse. Et blodsukkerniveau ≥14 mmol/l målt ved indlæggelsen var en stærk prædiktor for død efter pneumoni hos patienter med type 2 diabetes (justeret 30-dags MRR 1,46, 95% KI 1,01-2,12), men en endnu stærkere prædiktor hos patienter uden kendt diabetes (justeret 30-dag MRR 1,91, 95% CI 1,40-2,61). I studie 2 inkluderede vi 34,239 indlagte pneumoni-cases og 10 køns- og alders-matchede kontroller per case udtrukket via CPR-registeret. Vi fandt at personer med type 1 hhv. type 2 diabetes havde en 4,4 (95% KI 3,4-5,8) og 1,2 (95% KI 1,2-

1,3) gange øget risiko for at blive indlagt med pneumoni sammenlignet med ikke-diabetikere. Sammenlignet med personer uden kendt diabetes havde diabetikere med et HbA1c niveau på <7% en 22% højere risiko for indlæggelse med pneumoni, mens diabetikere med et HbA1c niveau på ≥9% havde en 60% øget risiko. I studie III undersøgte vi sammenhængen mellem fedme og risikoen for at blive førstegangs-indlagt med pneumoni i en follow-up-undersøgelse af 48,557 personer inkluderet i den danske Kost, kræft og helbred kohorte. Vi fandt at risikoen for pneumoni var øget 1,4 (95% KI 1,2-1,7) gange blandt mænd med moderat fedme og 2,0 (95% KI 1,4-2,8) gange hos mænd med svær fedme, sammenlignet med normal-vægtige mænd. Hos kvinder var svær fedme associeret med en 1,2 (95% KI 0,8-1,6) gange øget risiko, mens kvinder med moderat fedme ikke havde en øget risiko for pneumoni (HR = 0,8; 95% KI 0,6-1,0). Efter justering for andre store kroniske sygdomme diagnosticeret under follow-up var fedme ikke længere associeret med øget pneumoni risiko og blandt kvinder fandt vi tilmed en nedsat pneumoni risiko.

Sammenfattende viser vore resultater at type 2 diabetes prædikterer let øget dødelighed, men ikke lungekomplikationer eller bakteriæmi efter indlæggelse med pneumoni. Hyperglykæmi målt ved indlæggelsen er en stærk prædiktor for øget pneumoni-dødelighed både hos personer med og uden kendt diabetes. Vores data kombineret med tidligere studier giver stærk evidens for, at diabetes er en risikofaktor for indlæggelse med pneumoni, især i forbindelse med dårlig glykæmisk regulering. Endelig tyder vores resultater på, at fedme er associeret med en betydelig øget risiko for en pneumoni-relateret indlæggelse blandt mænd men ikke blandt kvinder. Den højere risiko kan tilsyneladende forklares ved forekomsten af andre kroniske sygdomme hos personer med fedme.

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Appendices