Type 2 Diabetes Mellitus and Risk of Community-acquired Pneumonia: A Systematic Review and Meta-analysis of Observational Studies

Short title: Type 2 Diabetes and Pneumonia: A Meta-analysis

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Word count: 2491; **Tables:** 2; **Figures:** 2; **Supplemental Tables:** 4; **Supplemental Figures:** 5;

Key words: Type 2 diabetes, Community-acquired Pneumonia, Meta-analysis, Epidemiology

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Results from this manuscript were presented as a poster presentation at the Society for Epidemiologic Research (SER) 2019 meeting in Minneapolis, MN on June 19th 2019.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts to declare.

ACKNOWLEDGEMENTS

We would like to thank Andrea Quaiattini, medical librarian at McGill University, for her help in developing the search strategy. Vanessa Brunetti is supported by the Doctoral Training Scholarship from the *Fonds de recherche du Québec – santé* (FRQ-S; Quebec Foundation for Health Research), the Drug Safety and Effectiveness Training (DSECT) Program Award, funded by the Canadian Institutes of Health Research (CIHR) and the David G. Guthrie Fellowship from the Faculty of Medicine at McGill University. Dr. Ayele is supported by the Postdoctoral Training Scholarship from the FRQ-S. Dr. Yu holds a *Chercheur-boursier clinicien* Junior I salary support award from the FRQ-S. Dr. Filion holds a *Chercher-boursier* Junior II salary support award from the FRQS and a William Dawson Scholar award from McGill University.

AUTHOR CONTRIBUTIONS

Dr. Filion conceived the study idea and supervised the study. Ms Brunetti developed the search strategy, performed the statistical analyses, and drafted the manuscript. Both Ms Brunetti and Dr. Tadesse Ayele performed the screening of relevant articles, data extraction, and quality assessment. Drs. Ernst and Yu provided substantive knowledge expertise. All authors were involved in study design, interpretation of data, and critically reviewed the manuscripts for intellectual content. Dr. Filion is the guarantor.

ABSTRACT

Background: Patients with type 2 diabetes mellitus are more likely to suffer from infections. Previous studies on the association between type 2 diabetes and community-acquired pneumonia (CAP) report mixed results, and previous knowledge syntheses did not specifically evaluate the risk of CAP in patients with type 2 diabetes. The purpose of this study was to conduct a systematic review and meta-analysis of observational studies on type 2 diabetes and CAP.

Methods: We systematically searched MEDLINE, EMBASE, CINAHL, ProQuest theses and dissertations, Global Health (Ovid), Global Index Medicus of the World Health Organization and Google scholar. We included observational studies published in English or French between January 1st 1946 and July 31st 2018. Two independent reviewers extracted data and conducted quality assessment of included studies using Robins-I tool. Dersimonian-Laird random-effects models were used to pool estimates.

Results: Our search identified 943 articles, of which 11 were included. All studies reported an increased risk of pneumonia in patients with type 2 diabetes; the presence of heterogeneity prevented the meta-analysis of data across study designs (I^2: 94.4). The pooled relative risk (RR) was 1.67 (95% CI 1.62, 1.72, I^2: 66.9%) among cohort studies and 1.29 (95% CI 1.15 – 1.44, I^2: 22.1%) among case-control studies. There was evidence of publication bias, and studies were of low quality, mainly due to inadequate control of confounding factors.

Interpretation: Type 2 diabetes is associated with an increased risk of CAP. Physicians should be aware of this increased risk when managing patients with type 2 diabetes.

INTRODUCTION

Type 2 diabetes mellitus is a metabolic condition characterized by insulin resistance or insufficient production of insulin, resulting in hyperglycemia[1]. Globally, the rate of type 2 diabetes mellitus is projected to increase from 285 to 439 million people with type 2 diabetes from 2010 to 2030[2]. An estimated 30.3 million Americans have type 2 diabetes, representing more than 9% of the total United States (US) population[3].

Patients with type 2 diabetes are at greater risk of infections, including urinary tract and genital infections[4]. The hyperglycemic environment in these patients, which is conducive to bacteria growth and proliferation, can lead to decreased T lymphocyte response and decreased neutrophil and macrophage function[5,6]. In addition to having an increased risk of infection, patients with diabetes also exhibit worse infection outcomes than patients without diabetes[4].

Community-acquired pneumonia (CAP) is a common infection, which often requires hospitalization. In the US, pneumonia is the second leading cause of hospitalization after childbirth. Approximately ten percent of patients hospitalized with a primary diagnosis of pneumonia die in hospital[7].

Previous observational studies have examined the association between diabetes and the risk of pneumonia[6,8-13]. While the literature generally supports an increased risk[4,8-10,12,13], previous studies have produced heterogeneous results, and there is a need to better understand potential sources of heterogeneity in this literature. In addition, the literature on the association between type 2 diabetes and CAP has not yet been synthesized. Given the increasing prevalence of type 2 diabetes and the clinical consequences of CAP, it is important to better understand the risk of CAP associated with type 2 diabetes. Our objective was to determine if type 2 diabetes mellitus is associated with an increased risk of CAP via a systematic review and meta-analysis of observational studies.

METHODS

Data sources and searches

Our study protocol, which was written following the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist (e-Table 1)[14], was registered with PROSPERO (CRD42018116409). The reporting of this knowledge synthesis follow the PRISMA and MOOSE guidelines[15,16].

We systematically searched Excerpta Medica database (Embase: Ovid), MEDLINE (Ovid), Cumulative Index of Nursing and Allied Health Literature (CINAHL), as well as ProQuest theses and dissertations (EBSCO host) for studies published in English or in French on type 2 diabetes and pneumonia. We included studies published between January 1st, 1946 (the start of Medline) and July 31st, 2018. The search strategy, which was constructed in consultation with a medical librarian and tailored to each database, is reported in detail in e-Table 2. Briefly, we used MeSH terms for MEDLINE and CINAHL and Emtree terms for Embase for the concepts of type 2 diabetes and CAP. In addition, we searched Global Health (Ovid) as well as Global Index Medicus of the World Health Organization for any relevant grey literature. We also screened the first 10 pages of Google Scholar for additional studies. Finally, we hand-searched references of relevant articles for additional studies.

Study selection

Studies were included if they fulfilled the following criteria: 1) observational design (cohort or case-control study); 2) study population aged ≥18 years; 3) reported at least one of the following two exposures: type 2 diabetes or diabetes with type not specified; and 4) reported at least one of the following two outcomes: CAP or unspecified pneumonia (i.e., did not explicitly differentiate between community-acquired and nosocomial [hospital- or ventilator-acquired). We excluded cross-sectional studies due to

their temporal ambiguity. We also excluded letters-to-the-editor, commentaries, editorials, case reports, case series, reviews and meta-analyses, animal studies, and basic science studies. In addition, we excluded conference abstracts as they typically have insufficient data to adequately assess study quality and because their results are often not final. Finally, we excluded studies that evaluated only type 1 diabetes and studies for which events were restricted to nosocomial pneumonia.

Data extraction and quality assessment

After removal of duplicates, two independent reviewers (VCB, HTA) screened titles and abstracts for eligibility, with any article deemed potentially eligible by either reviewer carried forward for full-text review. Both reviewers conducted full-text review independently, with final inclusion determined by consensus. Both reviewers independently extracted data using a pilot-tested data extraction form. The following information was extracted: authors, year and location of study, study design, exposure and outcome definitions, duration of follow-up, number of participants, baseline patient characteristics (mean age, sex), primary and secondary study endpoints, number of events by exposure group, crude and adjusted point estimates (odds ratio [OR], rate ratio [RR], or hazard ratio [HR]) and corresponding 95% confidence interval (CI), and variables included in statistical adjustment or matching.

We used an adapted version of the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool (adapted for exposure instead of intervention) to assess the quality of included studies. A predefined set of important confounders was used to assess the potential level of confounding; this set included age, sex, smoking status, alcohol use, history of asthma and chronic obstructive pulmonary disorder. Overall study quality was determined by the ROBINS-I domain with the greatest risk of bias. We included all observational studies meeting inclusion criteria in our study regardless of study quality.

Quality assessment was conducted independently by two reviewers (VCB and HTA), with disagreements resolved by consensus or by a third reviewer (KBF).

Data synthesis and analysis

Data were pooled across studies using DerSimonian and Laird random-effects models with inverse variance weighting[17]. We pooled the estimates from the most adjusted model reported by each study. If a study reported results from distinct cohorts that were non-overlapping, results from each of these cohorts were analysed separately. When pooling the results, the HR was converted to a RR using previously reported methods [18]. As pneumonia is a rare outcome[19], we assumed that ORs accurately estimated RRs, and thus ORs and RRs were pooled together. Heterogeneity was assessed quantitatively using the I^2 statistic, and qualitatively by comparing exposure and outcome definitions of the different studies. Sub-group analyses were conducted by study type (cohort vs case-control), exposure definition (type 2 vs unspecified diabetes), and outcome definition (community-acquired vs unspecified pneumonia). Publication bias was assessed via visual inspection of funnel plots[20]. We also conducted the following 2 sensitivity analyses: 1) fixed-effects analysis to examine the impact of our choice of modeling approach; 2) influence analyses to examine the impact of individual studies on the overall measure of association. All analyses were performed using Stata version 15[21].

RESULTS

Search results

We identified 1083 publications through database searching, with an additional 46 articles identified through other sources (Figure 1). After removal of duplicates, 943 publications underwent title and abstract review. Eleven studies met our inclusion criteria; these studies included a total of 14,397,109 patients.

Characteristics of the included studies are presented in Table 1. Eleven articles [8,9,11,13,22-26] reporting on 11 cohort and 2 case-control studies[10,12] were included. The article by Seminog et al.[13] reported results from 3 distinct cohorts (Linked English Hospital Episodes Statistics [LHES], Oxford Record Linkage Study 1 [ORLS] 1, and ORLS2) that were non-overlapping, and thus results from each of these cohorts were analysed separately but considered collectively when describing study characteristics. Both case-control studies were population-based studies conducted using registry data. All studies were published between 2004 and 2017, and most studies were conducted in Europe[6,8,10-13,22], with three studies in the US[24-26] and the other in Australia[9]. A total of 6 studies defined exposure as type 2 diabetes specifically[6,9-12,22], while the remaining 5 studies considered diabetes in general[8,13,24-26]. Exposure and outcome assessment varied between studies (e-Table 3). Most studies adjusted for age, sex, and socioeconomic status in their fully-adjusted models. Adjusted estimates were unavailable for 2 studies [9,24].

Quality assessment

The combined risk of bias for all studies was serious, as all studies presented a serious risk of bias in at least one of the ROBINS-I domains (e-Table 4). Three, 4 and 4 studies were respectively at serious, moderate and low risk of selection bias. All studies were either at low[8,10-13,22-24] or moderate[9] risk of information bias. All included studies were at a serious risk of bias for confounding, mainly because of inadequate control of important confounders. For instance, only two of the included studies controlled for a chronic obstructive pulmonary disorder [25,26], and only 4 controlled for smoking[8,11,25,26] and 4 for asthma[6,25] or other markers of pulmonary function[8,26]. As all studies presented a serious risk of bias, stratified analyses by study quality was not possible.

Diabetes and pneumonia

All included studies reported an increased risk of pneumonia in patients with diabetes (Table 2). Adjusted estimates ranged from 1.26 (95% CI 1.21, 1.31)[10] to 1.87 (95% CI 1.72, 2.04)[13]. Due to the presence of substantial heterogeneity (I^2: 94.4%), data were not pooled across designs. When data were pooled by study design, the pooled estimates for the association between diabetes and pneumonia were 1.67 (95% CI 1.62, 1.72; I^2: 66.9%) for cohort studies and 1.29 (95% CI 1.15, 1.44; I^2: 22.1%) for case-control studies. In subgroup analyses, the pooled estimate for studies where exposure was restricted to type 2 diabetes was 1.48 (95% CI 1.26, 1.74; I^2: 97.4%) and 1.70 (95% CI 1.59, 1.82; I^2: 55.8%) for studies of diabetes in general (e-Figure 1). Estimates also varied with outcome definition; studies of hospitalization for pneumonia had a RR of 1.57 (95% CI 1.32, 1.87; I^2: 97.8%) and those with any pneumonia diagnosis had a RR of 1.61 (95% CI 1.48, 1.75, I^2: 73.2%) (e-Figure 2).

In sensitivity analyses, fixed-effects models produced results that were consistent with those of our primary analysis (data not presented; cohort: 1.66, 95% CI 1.65, 1.67, I^2: 66.9%; case-control studies:

1.26, 95% CI 1.22, 1.32, I^2: 22.1%). Influence analyses with random effects suggested that the study by Kornum (2008) had the greatest impact on the overall estimate and heterogeneity (e-Figures 3 & 4; overall RR excluding Kornum: 1.67, 95% CI 1.61, 1.72, $I^2 = 64.2\%$). Asymmetry of our funnel plot revealed some evidence of publication bias (e-Figure 5).

INTERPRETATION

Our systematic review and meta-analysis was designed to assess the association between type 2 diabetes and CAP. All included studies reported an increased risk of pneumonia in patients with type 2 diabetes. Sub-group analyses by study type revealed that a greater risk was observed among cohort studies than among case-control studies. Estimates also varied with exposure and outcome definitions, with greater risks reported in studies that examined diabetes in general and in studies that examined any pneumonia diagnosis. Quality assessment revealed a low quality of included studies, mainly because of inadequate control of confounding.

The increased risk of CAP in patients with type 2 diabetes should be taken into consideration in clinical practice. Physicians may want to inform patients with type 2 diabetes to take preventative measures. Pneumococcal and influenza vaccination has been suggested as a cost-effective strategy to prevent CAP in patients with type 2 diabetes[27] and is suggested by most guidelines[28,29].

Our results support the hypothesis that the immunity of patients with type 2 diabetes may be compromised, leading to an increased risk of CAP, although this specific biological mechanism has not been established. The increased risk may be due to the impaired function of neutrophils and monocytes caused by hyperglycemia [27]. Patients with type 2 diabetes may be at greater risk of pneumonia because of increased susceptibility to *Staphylococcus aureus*, gram-negative organisms, and *Mycobacterium tuberculosis,* which may increase their risk of infection by pneumococcal pneumonia [30,31]. The increased susceptibility of patients with type 2 diabetes to these organisms is likely caused by their hyperglycemic environment[32,33,34], which in turn leads to impaired coagulation[35], endothelial function[36], fibrinolytic function[37], and structural and functional abnormalities[38], which may make them more susceptible to infections in general. Studies have also shown that there is increased adherence of microorganisms to mucosal and epithelial cells in diabetes[39]. It is also possible that the complications associated with

diabetes, such as disordered sleep patterns[40] and impaired lung function[41], may be involved in the mechanism behind the increased risk of pneumonia. Patients with type 2 diabetes also seem to have worse pneumonia outcomes as compared to patients without diabetes[27,42], as certain microorganisms may become more virulent in a hyperglycemic environment[39]. As such, attaining glycemic control may improve outcomes in these patients[38].

A previous meta-analysis on diabetes and the risk of all infections revealed an increased risk of lower respiratory tract infections in patients with diabetes (cohort: OR: 1.35, 95% CI: 1.28, 1.43, I^2: 79.4%; case-control: OR: 1.60, 95% CI: 1.35, 1.89, I^2: 86.7%)[4]. However, this study did not differentiate between diabetes types nor between nosocomial or community-acquired respiratory infections, and their meta-analysis contained substantial heterogeneity[4]. To our knowledge, the present study is the first systematic review and meta-analysis focused on the relationship between type 2 diabetes and CAP. Although the notion that type 2 diabetes is a risk factor for CAP is well known and accepted in a clinical setting, the literature on this topic is surprisingly sparse and of low to moderate quality. We found that the main limitation of included studies was inadequate control for important confounders, which may substantially bias the results. However, the increased risk of CAP in patients with type 2 diabetes was consistent across studies. Future research examining the biological mechanism behind the increased risk of CAP with type 2 diabetes is needed to fully understand this association and to develop appropriate preventative strategies.

This study has several strengths. First, our search strategy, which was developed with an experienced librarian, allowed us to comprehensively assess the available literature. Second, our study was conducted according to a pre-specified protocol registered at PROSPERO. Third, it included a detailed assessment of study quality, and included subgroup and sensitivity analyses to better understand sources of clinical and statistical heterogeneity in this literature.

Our study also has potential limitations. First, we found some evidence of publication bias. Second, the presence of substantial statistical heterogeneity prevented the meta-analysis of data across all studies. Stratification by study design reduced this heterogeneity. Some subgroup analyses also had important heterogeneity (by exposure and outcome definition); subsequent analyses determined that it was largely driven by one study, the exclusion of which greatly reduced the I^2 statistic. Third, several of the included studies were of modest quality, and systematic reviews are inherently affected by the limitations of their included studies. Fourth, although it is typically only used in cohort studies, we applied the ROBINS-I tool to case-control studies. However, both case-control studies were conducted using administrative data and thus were part of a well-defined underlying cohort. Our adaptation of the ROBINS-I for exposure instead of intervention allowed us to use it for these studies.

CONCLUSIONS

Our systematic review and meta-analysis demonstrates that patients with type 2 diabetes are at increased risk of CAP. Considering the substantial morbidity and mortality associated with CAP, patients should be informed to seek medical attention promptly if they develop symptoms to facilitate early detection and treatment. As hyperglycemia appears to increase the proliferation of bacteria, physicians and patients should be aware of the importance of attaining glycemic control to prevent resulting infections in this patient population.

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Table 1: **Study characteristics of studies examining the association between type 2 diabetes and the risk of community-acquired pneumonia**

Author, year	Country	Sample size	Mean age (SD)*	Male (%)†	Exposure	Primary Outcome	Mean duration of follow-up (years)
Cohort studies							
Benfield, 2007	Denmark	10,063	67.8/ 60.7 ‡	NR	diabetes	pneumonia hospitalization	7
Hamilton, 2013	Australia	6,450	63.6/ 66.1 §	48.8/NR ‡	type 2 diabetes	pneumonia hospitalization	12.06
Hine, 2017	UK	647,330	67.0/ 46.0 ‖	49.1	type 2 diabetes	pneumonia	1
Jackson, 2004	USA	46,237	NR	42.0	diabetes	Community-acquired pneumonia hospitalization	3
Lopes de Andres, 2017	Spain	901,136	77.08 (10.46)	60.1	type 2 diabetes	community-acquired pneumonia hospitalization	9
Muller, 2005	Netherlands	26,328	65.7 (12.7) / 63.1 (13.4) ‡	46.1/39.1 ‡	type 2 diabetes	pneumonia	1
O'Meara, 2005	USA	5888	75.0 / 72.6 §	42.3	diabetes	pneumonia hospitalization	10.7 |
Ray, 2017	USA	411	60.7/ 55.8/ 48.5/ 44.9 ¶	69.2/ 64.7/ 65.3/ 77.1 ¶	diabetes	pneumonia	NR
Seminog LHES, 2013	UK	11,220,545	64	NR	diabetes	pneumonia	4
Seminog ORLS1, 2013	UK	640,549	64	NR	diabetes	pneumonia	35

Seminog ORLS2, 2013	UK	508,965	62	NR	diabetes	pneumonia	3
Case-control studies							
Kornum, 2008	Denmark	376,629	74 (61-82) / 74 (61-82) #	52.9	type 2 diabetes	pneumonia hospitalization	NR
Thomsen, 2004	Denmark	6,578	67 (18-94) / 67 (17-94)**	47.3	type 2 diabetes	community-acquired pneumonia	9

Abbreviations: NR = not reported, UK = United Kingdom, USA = United States of America, SD = standard deviation
* Mean (SD) of entire population, unless otherwise specified.
† Entire population, unless otherwise specified
‡: Diabetes/no diabetes
§: Hospitalized/non-hospitalized
| : Median
||: Median: Diabetes/no diabetes
¶: Euglycemic with diabetes / Hyperglycemic with diabetes / Hyperglycemic without diabetes / No diabetes with normal glycaemia
#: Median (interquartile range [IQR]): Cases/controls
**: Median (full range): Cases/controls

Table 2: Measures of association of included studies examining the association between type 2 diabetes and the risk of community-acquired pneumonia

Author, year	No. events / No. exposed	No. events / No. unexposed	Measure of association	Unadjusted estimate (95% CI)	Adjusted estimate (95% CI)	Covariates (adjusted for or matched)
Cohort studies						
Benfield, 2007	90 / 353	1,104 / 9,710	HR	2.55 (1.86, 3.29)	1.75 (1.23, 2.48)	age, sex, smoking status, socioeconomic status (SES; education, income), cholesterol, triacylglycerol, hypertension, physical activity, lung function
Hamilton, 2013	181 / 1,294	435 / 5,156	RR	1.86 (1.55, 2.21)	-	-
Hine, 2017	34,278 *	613,052 †	OR	-	1.43 (1.18, 1.74)	age, sex, smoking status SES, comorbidities, general practice
Jackson, 2004	-	-	HR	-	1.52 (1.29, 1.78)	age, sex, smoking, CHF, ischemic heart disease, cancer, dementia, stroke, COPD, asthma, renal disease, use of prednisone or other immunosuppressive medication, no. outpatient visits in the year prior, hospitalization for pneumonia in year prior, home oxygen therapy, receipt of home healthcare

Lopes de Andres, 2017	233,715 *	677,621 †	RR	-	1.66 (1.65, 1.67)	age, sex
Muller, 2005	-	-	OR	1.31 (1.15, 1.50)	1.30 (1.11, 1.52)	age, sex, asthma, pulmonary disease (including tuberculosis acute bronchitis, disease, and asthma), insurance type, cardiovascular disease, peripheral neuropathy, neurologic disease
O'Meara	-	-	RR	-	1.34 (1.05, 1.70)	age, race, education level, smoking, prior vaccination for pneumonia, vaccination for influenza in the year prior, FEV1, FVC, maximal inspiratory pressure, 3MSE score, history of: MI, angina pectoris, CHD, claudication, CHF, CVA, COPD, pneumonia
Ray, 2017	7 / 47	15 / 292	OR	3.23 (1.24, 8.38)	-	-
Seminog LHES, 2013	-	-	RR	-	1.68 (1.65, 1.71)	age, sex, the time period in single calendar years, SES (region of residence deprivation score)
Seminog ORLS1, 2013	-	-	RR	-	1.87 (1.72, 2.04)	age, sex, the time period in single calendar years, SES (district of residence)

Seminog ORLS2, 2013	-	-	RR	-	1.76 (1.60, 1.92)	age, sex, the time period in single calendar years, SES (district of residence)
Case-control studies						
Kornum, 2008	4,489 / 32,975	29,750 / 343,654	OR	1.68 (1.62, 1.74)	1.26 (1.21, 1.31)	age (matched), sex (matched), SES (marital status, degree urbanization)
Thomsen, 2004	53 / 351	545 / 6,227	OR	1.9 (1.4, 2.6)	1.5 (1.1, 2.0)	age (matched), sex (matched), Charlson index score, alcohol related disease

Abbreviations: 3MSE = Modified Mini-Mental State Examination, CHD = coronary heart disease, CHF = congestive heart failure, CI = confidence interval, COPD = chronic obstructive pulmonary disease, CVA = cerebrovascular accident, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, MI = myocardial infarction, HR = hazard ratio, OR = odds ratio, RR = risk ratio,

* Total number of exposed patients

† Total number of unexposed patients

FIGURE LEGENDS

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram describing systematic search for studies of type 2 diabetes and the risk of community-acquired pneumonia

Figure 2. Forest plot of association between type 2 diabetes and risk of community-acquired pneumonia by study design. *Pooled analyses across study types not presented due to substantial heterogeneity (I^2: 94.4%)

Figure 1

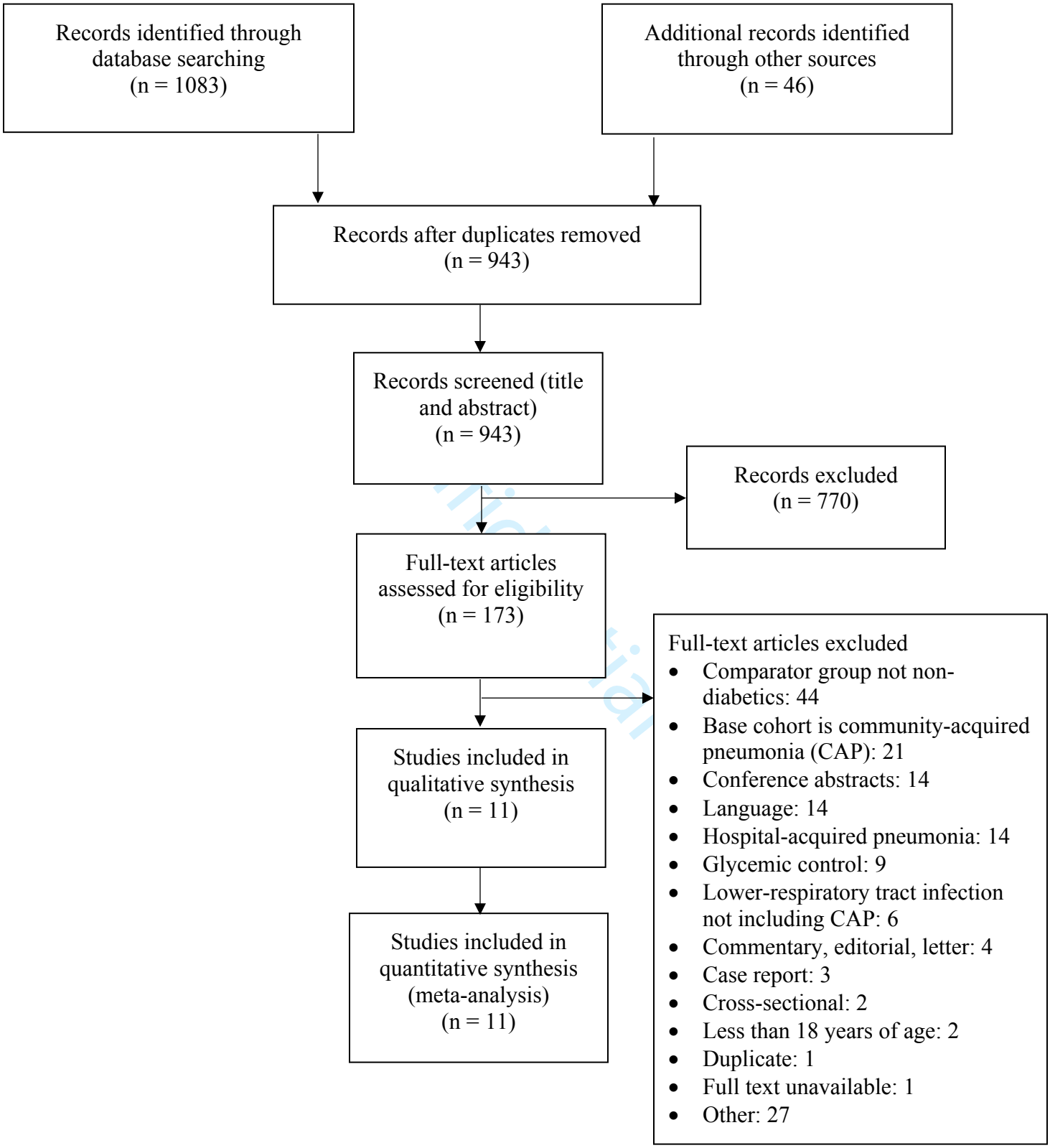
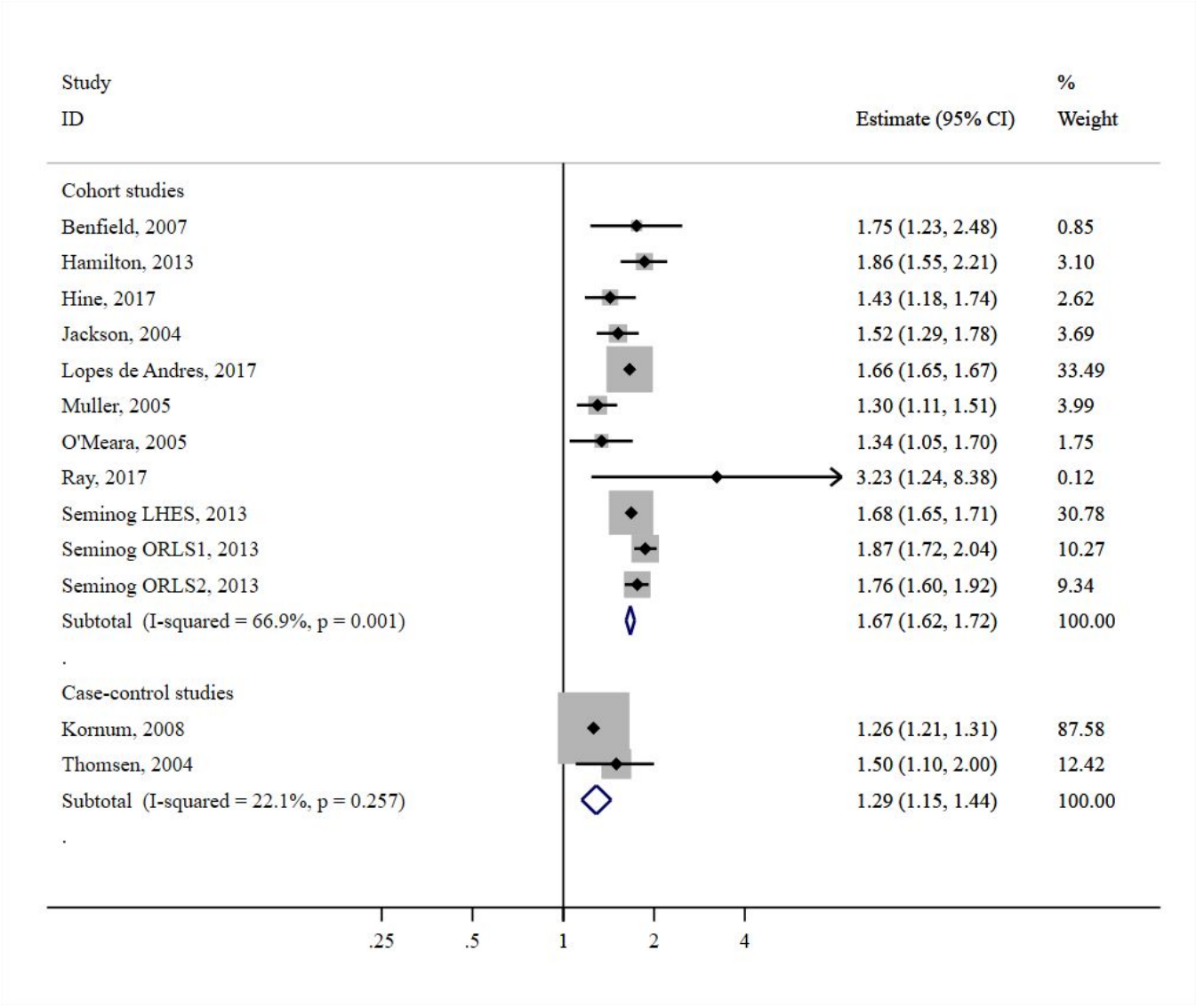


Figure 2



Supplemental material

Type 2 Diabetes Mellitus and Risk of Community-acquired Pneumonia: A Systematic Review and Meta-analysis of Observational Studies

e-Table 1: Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	e-Table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5-6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6
Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5-6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7 Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7 Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8 e-Table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-9 Table 2 Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-9 Figure 2 e-Figure 1 e-Figure 2 e-Figure 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8 e-Table 3

			e-Figure-5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-9 e-Figure 1 e-Figure 2 e-Figure 3 e-Figure 4
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

e-Table 2: Search strategy for observational studies of type 2 diabetes and the risk of community-acquired pneumonia - MEDLINE

Table 1: search strategy in MEDLINE	
Search number	Search terms
1	exp Diabetes mellitus, Type 2/
2	type 2 diabet*.mp.
3	type two diabet*.mp.
4	insulin resistance/
5	insulin resist*.mp.
6	glyc?emic control*.mp.
7	non insulin dependent diabet*.mp
8	t2dm.ti.
9	t2dm.ab.
10	t2dm.kw.
11	hypoglycemia/
12	hypoglyc?emia.mp.
13	hyperglycemia/
14	hyperglyc?emia.mp.
15	exp PNEUMONIA/
16	community acquired pneumonia.mp.
17	respiratory tract infections/
18	Community-Acquired Infections/
19	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
20	15 or 16 or 17 or 18
21	19 and 20

e-Table 3: Exposure and outcome definitions of included studies of association between type 2 diabetes and community-acquired pneumonia

Author, year	Exposure	Exposure definition	Primary Outcome	Outcome definition
Cohort studies				
Benfield, 2007	Diabetes	Self-reported	Pneumonia hospitalization	ICD-8 codes: 480 – 486 ICD-10 codes : A48.1, J12 – J18
Hamilton, 2013	Type 2 diabetes	Fasting plasma glucose (>7.8 mmol/l until 1999 and >7.0 mmol/l thereafter) urine samples	Pneumonia hospitalization	ICD-9-CM code :480.1, 480.2 480.8, 480.9, 481, 482.0–.9, 483.0, 485, 486 ICD-10 codes: J12.1, J12.2, J12.8, J12.9, J13, J14, J15.0, J15.1, J15.3, J15.4, J15.5, J15.6, J15.7, J15.8, J15.9, J18.0, J18.8, J18.9
Hine, 2017	Type 2 diabetes	Diagnostic, biochemical and prescription data entered before January 1 2014 (cohort entry)	Pneumonia	read code H20-28
Jackson, 2004	Diabetes	Any inclusion in the Group Health Cooperative diabetes registry	Community-acquired pneumonia hospitalization	ICD-9-CM codes: 480 – 487.0, 038.0, 038.2, 041.0, 041.2, 320.1
Lopes de Andres, 2017	Type 2 diabetes	ICD-9-CM codes: 250.x0, 250.x2	Community-acquired pneumonia hospitalization	ICD-9-CM codes: 480– 488, 507.0– 507.8
Muller, 2005	Type 2 diabetes	ICPC code DM1 (T90.1) or DM2 (T90.2)	Pneumonia	pneumonia (R81)

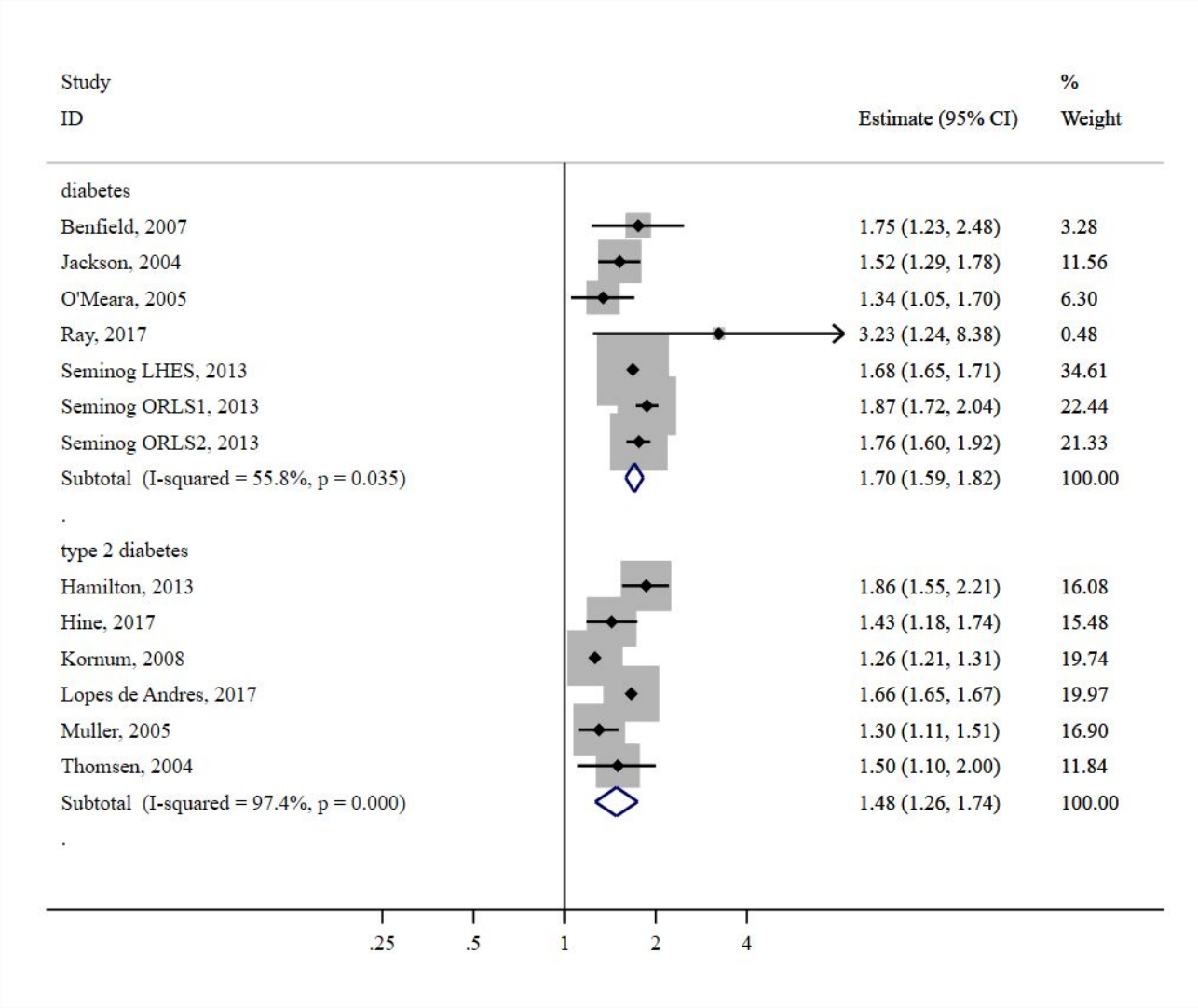
O'Meara, 2005	Diabetes	Diabetes mellitus at baseline from fasting plasma glucose of at least 126mg/dL or the use of insulin or oral hypoglycemic agents	Pneumonia hospitalization	ICD-9-CM codes: 481. 482, 486
Ray, 2017	Diabetes	The presence of DM in clinical notes	Pneumonia	medical record review of culture results
Seminog LHES, 2013	Diabetes	ICD-7 code: 260, ICD-8 code: 250 ICD-9 code: 250 ICD-10 codes: E10–E14	Pneumonia	ICD-10 codes J13, pneumonia specified as S. pneumoniae; A40.3, septicaemia attributable to S. pneumoniae; and G00.1,
Seminog ORLS1, 2013	Diabetes	Idem	Pneumonia	Idem
Seminog ORLS2, 2013	Diabetes	Idem	Pneumonia	Idem
Case-control studies				
Kornum, 2008	Type 2 diabetes	ICD-8 codes: 249– 250 ICD-10 codes: E10– E14 , O24 (diabetes in pregnancy except for O24.4	Pneumonia hospitalization	ICD-10 codes: J12.x – J18.x ICD-8 codes: not mentioned
Thomsen, 2004	Type-2 diabetes	Previous hospitalization with diabetes or earlier prescriptions for insulin or an oral antidiabetic drug	Community-acquired pneumonia	Patients older than 15 years with a first hospitalization for community-acquired pneumococcal bacteremia

e-Table 4: Quality assessment of studies examining the association between type 2 diabetes and risk of community-acquired pneumonia

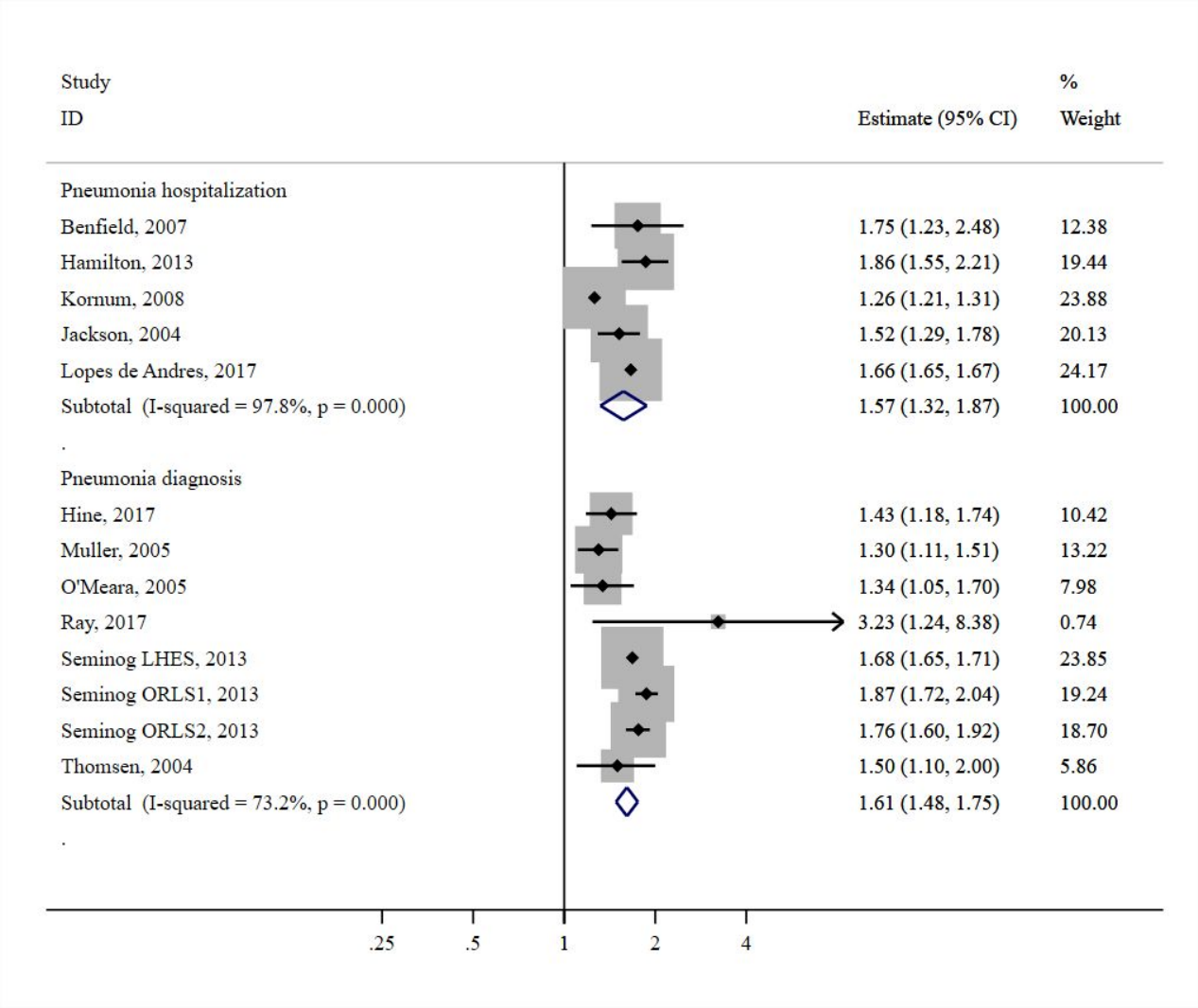
Study	Outcome	Confoun-ding	Selection of participants into the study	Classification of interventions	Deviations from intended intervention	Missing data	Measurement of outcomes	Reported result	Overall
Cohort study									
Benfield et.al. 2007	Pneumonia related death	Serious	Moderate	Low	Low	Low	Serious	Serious	Serious
Hamilton et.al. 2013	Pneumonia	Serious	Serious	Moderate	Low	Low	Serious	Moderate	Serious
Hine et.al. 2016	Pneumonia	Serious	Moderate	Low	Low	Moderate	Serious	Serious	Serious
Jackson et. al. 2004	Community-acquired pneumonia hospitalization	Serious	Low	Low	Serious	Moderate	Moderate	Moderate	Serious
Lopes-de-Andres	Community-acquired pneumonia hospitalization	Serious	Low	Low	Low	Moderate	Low	Moderate	Serious
Muller et.al. 2005	Infections including Pneumonia	Serious	Serious	Low	Serious	Low	Serious	Serious	Serious
O'Meara et. Al, 2005	Pneumonia hospitalization	Serious	Low	Serious	Low	Low	Moderate	Moderate	Serious
Ray et.al. 2017	Pneumonia	Serious	Moderate	Low	Serious	Serious	Serious	Serious	Serious
Seminog	Pneumonia	Serious	Moderate	Low	Low	Low	Serious	Moderate	Serious

et.al 2013									
Case-control study									
Kornum et.al. 2008	Pneumonia Hospitalization	Serious	Low	Low	Low	Low	Moderate	Moderate	Serious
Thomsen et.al 2004	Hospitalization for CAP	Serious	Serious	Low	Low	Serious	Serious	Serious	Serious
Overall									**Serious**

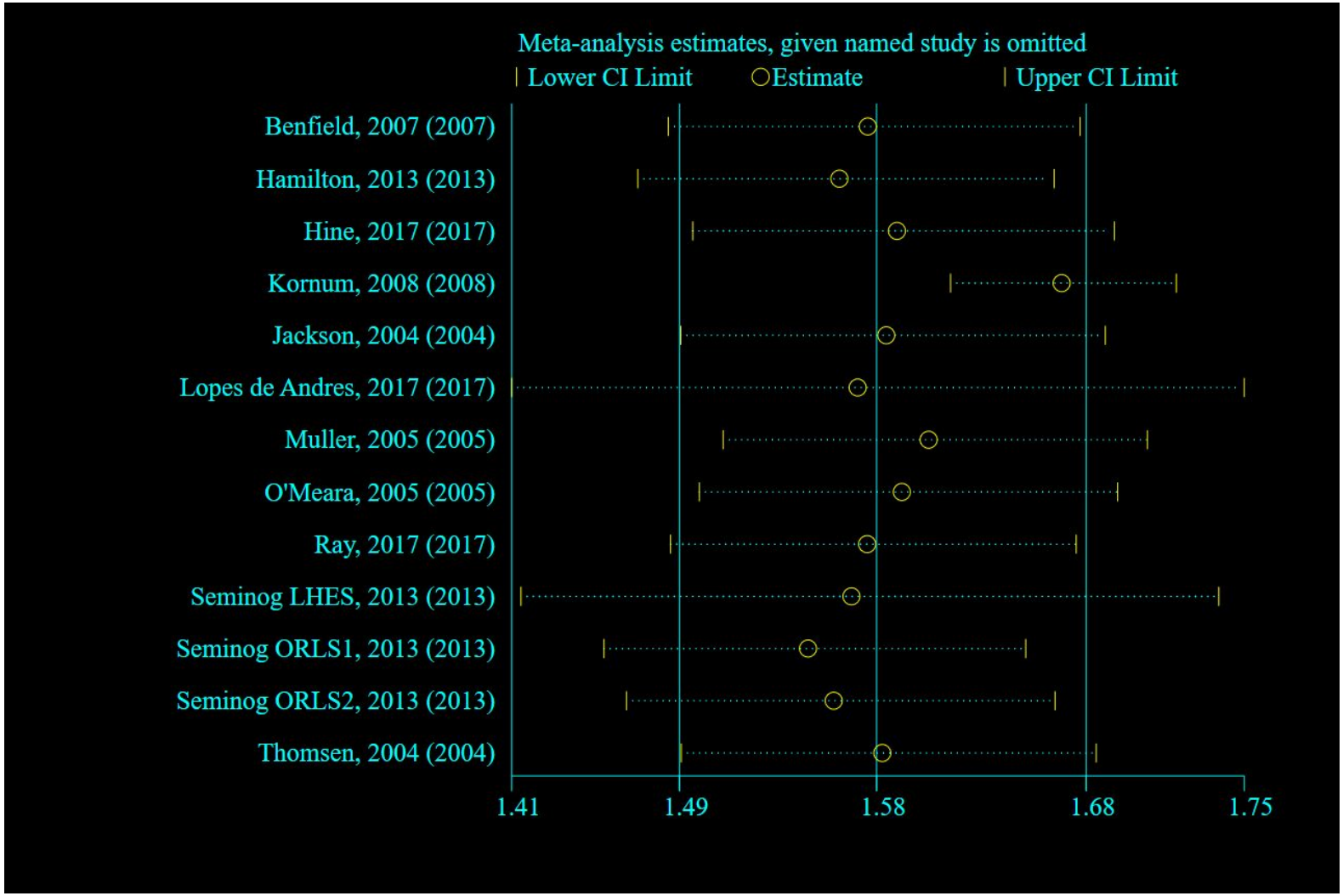
e-Figure 1: Forest plot of association between type 2 diabetes and risk of community-acquired pneumonia by exposure definition



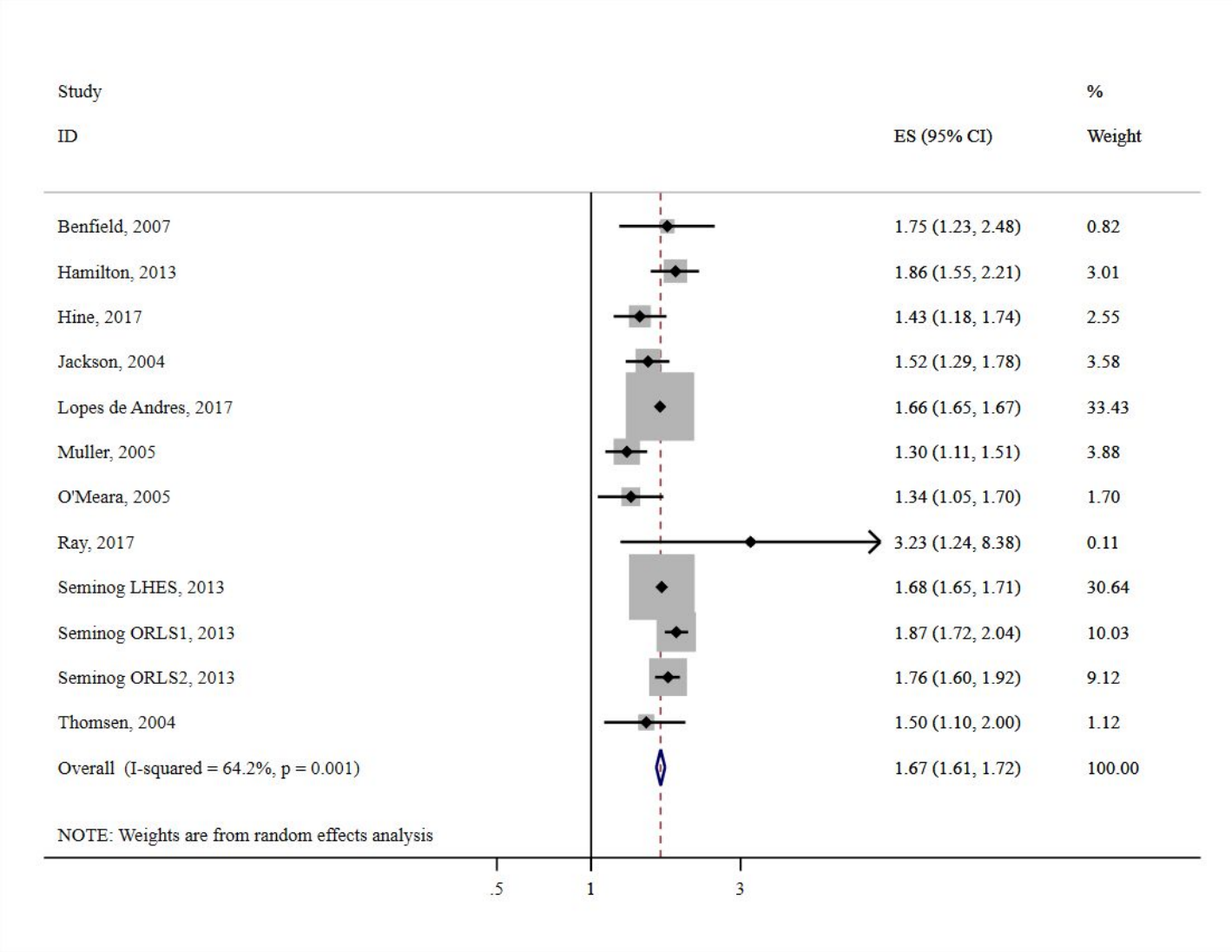
e-Figure 2: Forest plot of association between type 2 diabetes and risk of community-acquired pneumonia by outcome definition



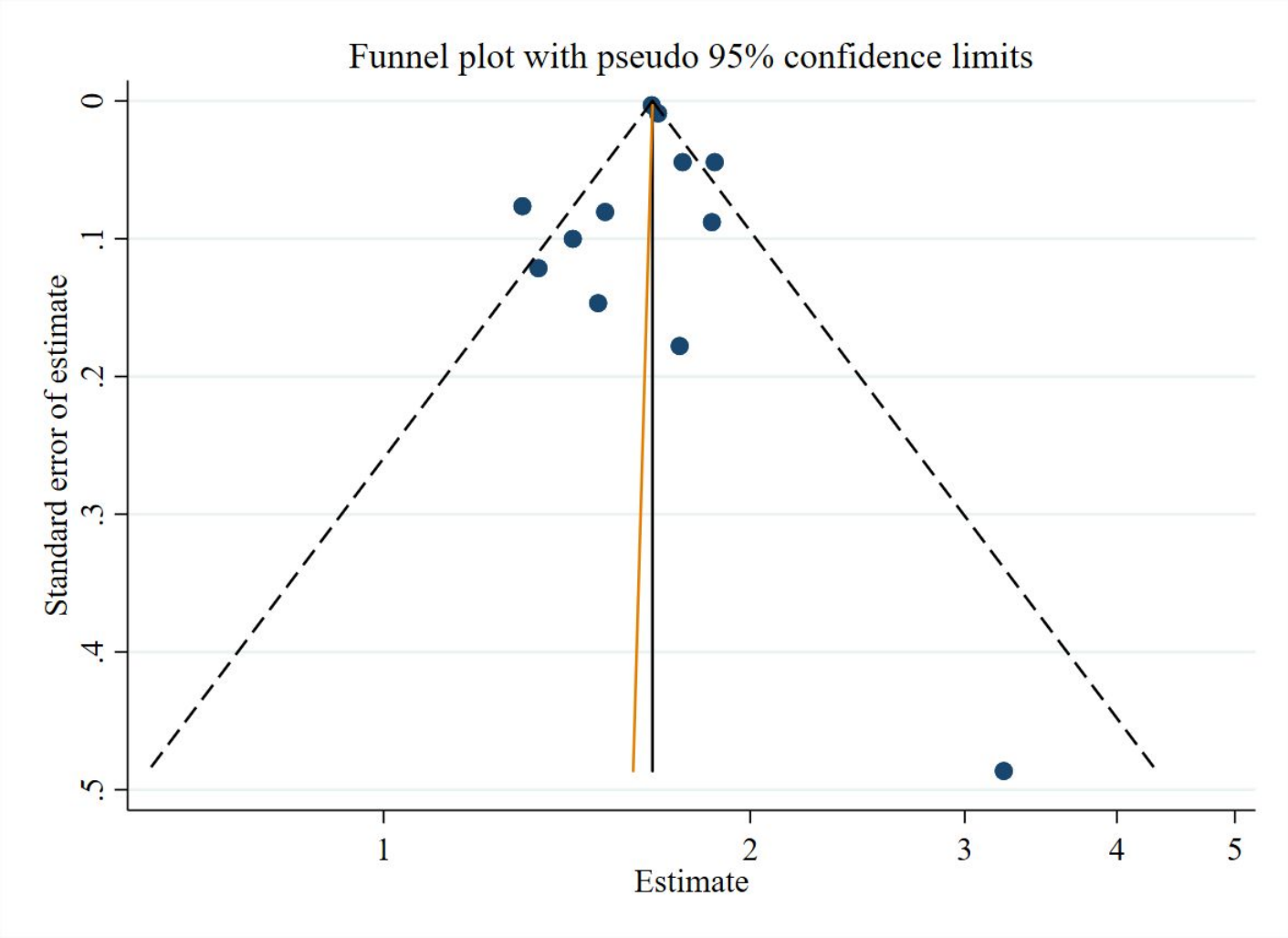
e-Figure 3: Influence analysis



e-Figure 4: Forest plot of association between type 2 diabetes and risk of community-acquired pneumonia excluding study by Kornum et al. (2008)



e-Figure 5: Funnel plot for assessment of publication bias of included studies on type 2 diabetes and community-acquired pneumonia



Type 2 Diabetes Mellitus and Risk of Community-acquired Pneumonia: A Systematic Review and Meta-analysis of Observational Studies

Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist

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FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14