Research

Type 2 diabetes mellitus and risk of community-acquired pneumonia: a systematic review and meta-analysis of observational studies

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Abstract

Background: People with type 2 diabetes are at greater risk for infections than those without type 2 diabetes. Our objective was to examine the association between type 2 diabetes and the risk of community-acquired pneumonia (CAP).

Methods: In this systematic review and meta-analysis, we searched MEDLINE, Embase, CINAHL, ProQuest theses and dissertations, Global Health, the Global Index Medicus of the World Health Organization, and Google Scholar. We included observational studies published in English or French between Jan. 1, 1946 (start of MEDLINE) and July 18, 2020. Two independent reviewers extracted data and assessed quality using the ROBINS-I tool. DerSimonian–Laird random-effects models were used to pool estimates of the association between type 2 diabetes and CAP.

Results: Our systematic review included 15 articles, reporting on 13 cohort studies and 4 case–control studies (14 538 968 patients). All studies reported an increased risk of pneumonia among patients with type 2 diabetes, and all were at serious risk of bias. When estimates were pooled across studies, the pooled relative risk was 1.64 (95% confidence interval [CI] 1.55–1.73); although there was a substantial amount of relative heterogeneity (I^2 94.2), the amount of absolute heterogeneity was more modest (T^2 0.008). The relative risk was 1.70 (95% CI 1.63–1.77, I^2 85.2%, T^2 0.002) among cohort studies (n = 13), and the odds ratio was 1.54 (95% CI 1.14–2.09, I^2 92.7%, T^2 0.07) among case–control studies (n = 4).

Interpretation: Type 2 diabetes may be associated with an increased risk of CAP; however, the available evidence is from studies at serious risk of bias, and additional, high-quality studies are needed to confirm these findings. **PROSPERO registration:** CRD42018116409

People with type 2 diabetes are at greater risk of infections, including urinary tract and genital infections, than people without diabetes.[1] The hyperglycemic environment in these patients, which is conducive to the growth and proliferation of bacteria, can lead to decreased T lymphocyte response and decreased neutrophil and macrophage function.[2,3] Patients with diabetes also exhibit worse infection outcomes than patients without diabetes.[1] Community-acquired pneumonia (CAP) is a common infection, which often requires hospital admission. In the United States, pneumonia is among the leading causes of hospital admission, especially among older adults.[4] Approximately 10% of patients admitted to hospital with a primary diagnosis of pneumonia die in hospital.[4]

Previous observational studies have examined the association between diabetes and the risk of pneumonia.[3,5–10] Although the literature generally suggests an increased risk,[1,5–7,9,10] previous studies have produced heterogeneous results, and there is a need to have a better understanding of the 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 clarify the risk of CAP associated with type 2 diabetes. Our objective was to determine if type 2 diabetes is associated with an increased risk of CAP via a systematic review and meta-analysis of observational studies.

Methods

Study design

We conducted a systematic review and meta-analysis. Our study protocol, which was written following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015[11] checklist, was registered with the International Prospective Register of Systematic Reviews (PROSPERO no. CRD42018116409). Postregistration protocol changes are specified below. The reporting of this knowledge synthesis follows the PRISMA[20] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[21,22]

Data sources and searches

We systematically searched Embase (Ovid; start year: 1974), MEDLINE (Ovid; start year: 1946), the Cumulative Index to Nursing and Allied Health Literature (CINAHL; start year: 1961), ProQuest theses and dissertations (EBSCO host; start year: 1997), Global Health (Ovid; start year: 1973), and the Global Index Medicus of the World Health Organization (start year: 1974) for studies published in English or French on type 2 diabetes (or studies on diabetes in general, because 85% of patients with diabetes have type 2 diabetes[23]) and pneumonia. We included studies published between Jan. 1, 1946 (the inception date of MEDLINE), and July 18, 2020.

The search strategy, constructed in consultation with a medical librarian, was developed in MEDLINE and then tailored to each database (Appendix 1, Supplemental Table S1, available at www.cmajopen.ca/content/9/1/E62/suppl/DC1). Briefly, we used MeSH terms for MEDLINE and CINAHL and Emtree terms for Embase for the concepts of type 2 diabetes (including terms for diabetes in general) and CAP. Search terms for diabetes in general were added after study registration. We also screened the first 10 pages of Google Scholar for any additional grey literature publications. Finally, we hand-searched references of relevant articles (including previous reviews in this area) for additional studies.

Study selection

We defined our inclusion criteria using the population, intervention, comparator and outcome (PICO) format of the *Cochrane Handbook for Systematic Reviews of Interventions*;[24] however, we defined an exposure instead of an intervention (Box 1). Studies were included if they fulfilled the following criteria: the study had an observational design (cohort or case–control

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Box 1: Study question formatted according to the PICO framework

P: Adults aged 18 years or older

I: Type 2 diabetes (exposure)

C: No diabetes

O: Community-acquired pneumonia

The PICO framework is described in the *Cochrane Handbook for Systematic Reviews of Interventions*.[24] Note: PICO = population, intervention, comparator and outcome.

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study); the study population was aged 18 years and older (population); the study reported data on type 2 diabetes or diabetes with type not specified (i.e., it did not explicitly differentiate between type 2 and type 1 diabetes; exposure); and the study reported data on CAP or unspecified pneumonia (i.e., it did not explicitly differentiate between CAP and nosocomial [hospital- or ventilator-acquired] pneumonia; outcome). We included studies for which the comparator group was patients without type 2 diabetes or without diabetes (comparator). We excluded cross-sectional studies because of their temporal ambiguity. We also excluded letters to the editor, commentaries, editorials, case reports, case series, reviews and meta-analyses, animal studies, basic science studies, conference abstracts (as they typically have insufficient data to adequately assess study quality and because their results are often not final) and studies that evaluated only type 1 diabetes or nosocomial pneumonia.

After removal of duplicates, 2 independent reviewers (V.C.B., H.T.A.) screened the titles and abstracts of the remaining studies for eligibility, with any article deemed potentially eligible by either reviewer carried forward for full-text review. The 2 reviewers conducted their full-text review independently and in duplicate, and they made the final decision about study inclusion by consensus.

Data extraction and quality assessment

The 2 reviewers independently extracted data in duplicate using a pilot-tested data extraction form. The following information was extracted: authors, year and location of study, study design, exposure and outcome definitions, follow-up duration, number of participants, baseline patient characteristics (mean age, sex), study outcomes, number of events by exposure group, crude and adjusted point estimates (odds ratios [ORs], rate ratios or hazard ratios [HRs]) and corresponding 95% confidence intervals [CIs], and variables included in statistical adjustment or matching.

We used an adapted version of the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool (adapted for exposure instead of intervention) to assess study quality. The predefined set of important confounders used to assess the potential level of confounding included age, sex, smoking status, alcohol use, history of asthma and history of chronic obstructive pulmonary disorder (COPD). Study quality was determined by the ROBINS-I domain with the greatest risk of bias. Quality assessment was conducted independently by 2 reviewers (V.C.B., H.T.A.), with disagreements resolved by consensus or by a third reviewer (K.B.F.).

Statistical analysis

Estimates were pooled across studies using DerSimonian–Laird random-effects models with inverse variance weighting.[25] We pooled estimates from the model, adjusting for the most covariates reported by each study; unadjusted estimates were used if a study did not report adjusted estimates. If a study reported results from distinct cohorts that were nonoverlapping, results from each of these cohorts were analyzed separately. For studies reporting HRs, we assumed that the hazard was proportional over the follow-up time and that the

HR therefore approximated the risk ratio;[26] if the hazards were constant, they would also have estimated the rate ratio. As pneumonia is a rare outcome,[27] we assumed that ORs accurately estimated the risk ratio, and thus we pooled ORs, rate ratios and HRs as relative risks.

We assessed heterogeneity quantitatively using the I^2 and T^2 statistics and qualitatively by comparing the exposure and outcome definitions of the different studies. We also estimated 95% prediction intervals (PIs) to facilitate the interpretation of results.[28] The inclusion of the T^2 statistic and 95% PIs were postregistration additions to our study protocol.

We conducted subgroup analyses by study type (cohort v. case–control), exposure definition (type 2 v. unspecified diabetes) and outcome definition (CAP v. unspecified pneumonia). Small-study effects (where smaller studies may show larger treatment effects in meta-analyses)[29] were assessed via visual inspection of funnel plots.[30] We also conducted 3 sensitivity analyses: a fixed-effects analysis to examine the impact of our model choice, influence analyses to examine the impact of individual studies on the overall measure of association, and an analysis converting reported ORs to risk ratios using the approach described by Cochrane.[26,31] All analyses were performed using Stata version 15.

Ethics approval

Ethics approval was not required for this systematic review, as our systematic review used publicly available aggregate data only.

Results

We identified 4454 publications through database searching, and we identified an additional 46 articles through other sources (Figure 1). After removal of duplicates, 4126 publications underwent title and abstract review. Fifteen studies met our inclusion criteria; these studies included a total of 14 538 968 patients.

Characteristics of the included studies are described in Table 1. Fifteen articles[3,5,6,8,10,12–16,18] reporting on 13 cohort studies and 4 case–control studies[7,9,18,19] were included. The article by Seminog and Goldacre[10] reported results from 3 distinct cohorts (Linked English Hospital Episodes Statistics [LHES], Oxford Record Linkage Study 1 [ORLS1] and Oxford Record Linkage Study 2 [ORLS2]) that were non-overlapping, and thus we analyzed results from each of these cohorts separately but considered them collectively when describing study characteristics. The 4 case–control studies were population-based case–control studies. Six studies defined exposure as type 2 diabetes specifically,[3,6–9,15] while 9 studies considered diabetes in general.[5,10,12,13,16] The exposure and outcome assessment varied among studies (Appendix 1, Supplemental Table S2). Most studies adjusted for age, sex and socioeconomic status in their fully adjusted models. Adjusted estimates were unavailable for 4 studies.[6,16,18,19]

Quality assessment

The combined risk of bias for all studies was serious, as all studies presented a serious risk of bias in at least 1 of the ROBINS-I domains (Appendix 1, Supplemental Table S3). Four, 7 and 4 studies were at low,[7,12,13,15] moderate[5,8,10,14,16,18,19] and serious risk[3,6,9,17] of selection bias, respectively. All studies were either at low[3,5,7–10,12,15–17,19] or moderate[6,13,14,18] risk of exposure misclassification (classification of intervention in ROBINS-I). All included studies were at serious risk of bias for confounding because of inadequate control of important confounders; only 3 of the included studies controlled for COPD,[12,13,17] only 5 controlled for smoking[5,8,12–14] and only 4 controlled for asthma[3,12] or other markers of pulmonary function.[5,13] As all studies presented a serious risk of bias, it was not possible to perform stratified analyses by study quality.

Diabetes and pneumonia

All included studies reported an increased risk of pneumonia among patients with diabetes (Table 2). When estimates were pooled across all studies, the pooled relative risk was 1.64 (95% CI 1.55–1.73) (Figure 2). Although the amount of relative heterogeneity that was present was high (I^2 94.2%), the amount of absolute heterogeneity that was present was more modest (T^2 0.008). The 95% PI was 1.30 to 2.06.

The pooled relative risk was 1.70 (95% CI 1.63–1.77, I^2 85.2%, T^2 0.002, 95% PI 1.51–1.92) among cohort studies (n = 13) and the pooled OR was 1.54 (95% CI 1.14–2.09, I^2 92.7%, T^2 0.07, 95% PI 0.74–3.21) among case–control studies (n = 4). In subgroup analyses that included both cohort and case–control studies, 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%, T^2 0.033, 95% PI 0.90–2.42) and 1.76 (95% CI 1.64–1.88; I^2 80.5%, T^2 0.006, 95% PI 1.43–2.17) for studies of diabetes in general (Appendix 1, Supplemental Figure S1).

Estimates were similar by outcome definition; the pooled relative risk was 1.65 (95% CI 1.45–1.87; I^2 97.6%, T^2 0.023, 95% PI 1.10–2.47) for hospital admission for pneumonia and 1.64 (95% CI 1.53–1.76, I^2 63.3%, T^2 0.005, 95% PI 1.34–2.00) for studies with the outcome defined by a pneumonia diagnosis (Appendix 1, Supplemental Figure S2).

In sensitivity analyses, fixed-effects models produced results that were consistent with those of our primary analysis (Appendix 1, Supplemental Figure S3). Influence analyses, conducted using random-effects models, suggested that the study by Kornum and colleagues (2008)[7] had the greatest impact on the overall estimate and amount of heterogeneity (Appendix 1, Supplemental Figures S4 and S5; overall estimate excluding that study: 1.71, 95% CI 1.64–1.78, I^2 82.6%, T^2 0.002, 95% PI 1.51–1.93). Asymmetry of our funnel plot showed some evidence of small-study effects (Appendix 1, Supplemental Figure S6), although they were mainly due to 2 small studies. Finally, results were similar for our repeated primary analysis when ORs were converted to risk ratios (Appendix 1, Supplemental Table S4 and Figure S7).

Interpretation

Our systematic review and meta-analysis was designed to assess the association between type 2 diabetes and CAP. All
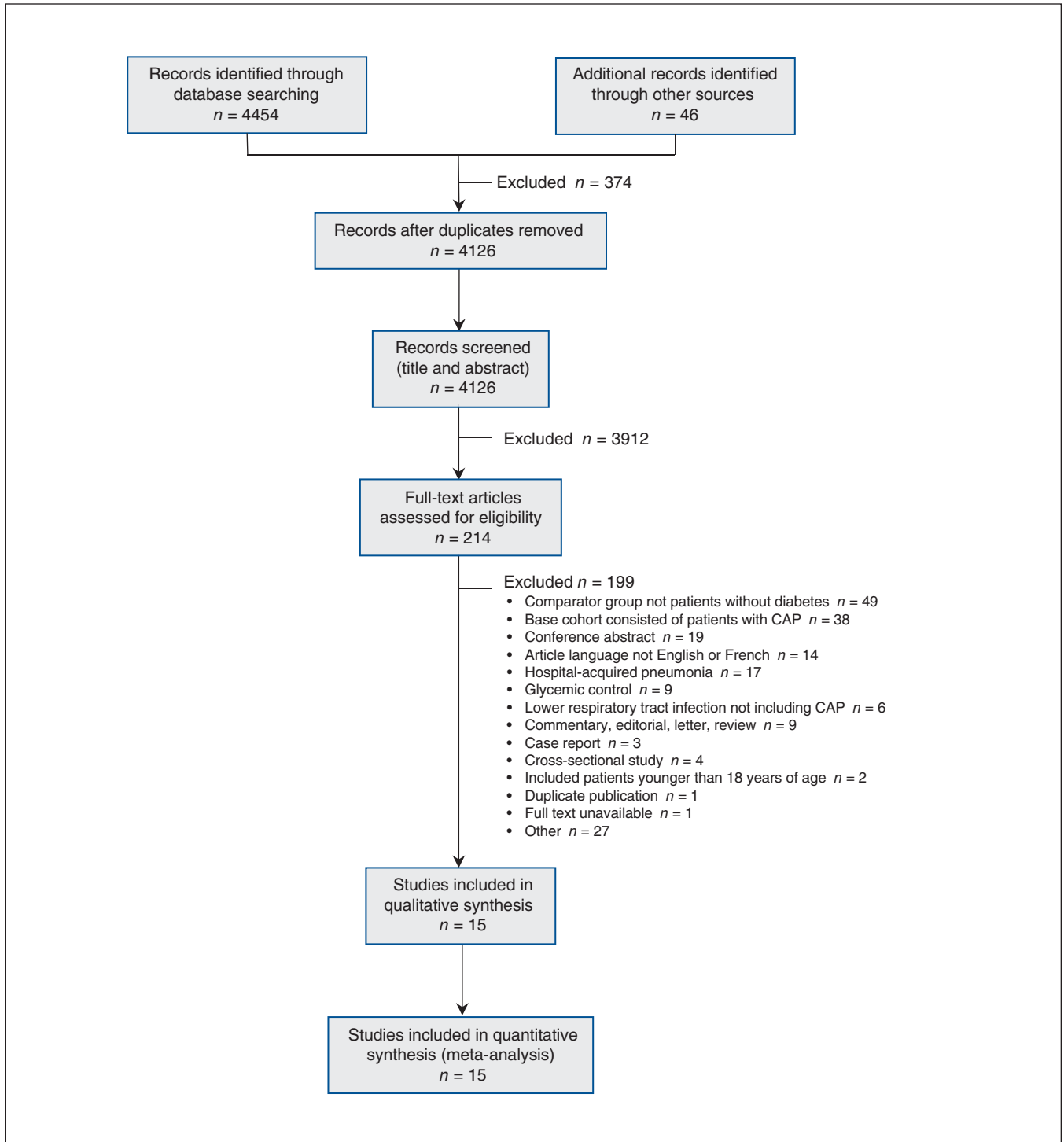
Figure 1: Flow diagram, based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline, describing the systematic search for studies of type 2 diabetes and the risk of community-acquired pneumonia (CAP). Note: Some of the studies captured in the literature search evaluated the association between change in glycemic control and risk of pneumonia, in patients with or without diabetes. The estimate derived from these studies did not answer the research question posed in the present study, and thus these studies were not included in the meta-analysis.

included studies reported an increased risk of pneumonia in patients with type 2 diabetes. When data were pooled across all studies, the pooled relative risk was 1.64 (95% CI 1.55–1.73). The corresponding 95% PI ranged from 1.30 to 2.06, suggesting that the increased risk would be found in this range in 95% of future clinical settings.[33] Quality assessment revealed that the included studies had a serious risk of bias, and thus our results should be interpreted with caution.

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

Author, year	Country	Study design	Sample size	Mean age, yr (SD)*	Male, %†	Exposure	Primary outcome	Mean duration of follow-up, yr
Cohort studies								
Jackson et al. 2004[12]	US	Retrospective cohort	46 237	NR	42.0	Diabetes	Hospital admission for CAP	3
Muller et al. 2005[3]	Netherlands	Prospective cohort	26 328	65.7 (12.7)/ 63.1 (13.4)‡	46.1/39.1‡	Type 2 diabetes	Pneumonia	1
O'Meara et al. 2005[13]	US	Prospective cohort	5888	75.0/72.6§	42.3	Diabetes	Hospital admission for pneumonia	10.7¶
Benfield et al. 2007[5]	Denmark	Retrospective cohort	10 063	67.8/60.7‡	NR	Diabetes	Hospital admission for pneumonia	7
Ehrlich et al. 2010[14]	US	Retrospective cohort	121 866§	57.2¶	50.1	Diabetes	Hospital admission for pneumonia	NR
Hamilton et al. 2013[6]	Australia	Prospective cohort	6450	63.6/66.1**	48.8/NR‡	Type 2 diabetes	Hospital admission for pneumonia	12.06
Seminog and Goldacre 2013[10] (LHES)	UK	Retrospective cohort	11 220 545	64	NR	Diabetes	Pneumonia	4
Seminog and Goldacre 2013[10] (ORLS1)	UK	Retrospective cohort	640 549	64	NR	Diabetes	Pneumonia	35
Seminog and Goldacre 2013[10] (ORLS2)	UK	Retrospective cohort	508 965	62	NR	Diabetes	Pneumonia	3
Hine et al. 2017[8]	UK	Retrospective cohort	647 330	67.0/46.0††	49.1	Type 2 diabetes	Pneumonia	1
López-de-Andrés et al. 2017[15]	Spain	Retrospective cohort	901 136	77.1 (10.5)	60.1	Type 2 diabetes	Hospital admission for CAP	9
Ray et al. 2017[16]	US	Retrospective cohort	411	47.0 (16.3)	73.8	Diabetes	Pneumonia	NR
Williams et al. 2017[17]	UK	Retrospective cohort	14 513	70.3 (10.8)	53.6	Diabetes	CAP	5
Case–control studies								
Farr et al. 2000[18]	UK	Population-based case–control	555	45.2	46.1	Diabetes	Pneumonia	NR
Thomsen et al. 2004[9]	Denmark	Population-based case–control	6578	67 (18–94)/ 67 (17–94)‡‡	47.3	Type 2 diabetes	CAP	9
van de Garde et al. 2006[19]	Netherlands	Population-based case–control	4925	67	55.0	Diabetes	Hospital admission for CAP	NR
Kornum et al. 2008[7]	Denmark	Population-based case–control	376 629	74 (61–82)/ 74 (61–82)§§	52.9	Type 2 diabetes	Hospital admission for pneumonia	NR

Note: CAP = community-acquired pneumonia, LHES = Linked English Hospital Episodes Statistics, NR = not reported, ORLS = Oxford Record Linkage Study, SD = standard deviation, UK = United Kingdom, US = United States.
*For entire population, unless otherwise specified.
†For entire population, unless otherwise specified.
‡Diabetes/no diabetes.
§Subcohort of patients for whom diabetes status was evaluated.
¶Median.
**Admitted to hospital/not admitted to hospital.
††Median: diabetes/no diabetes.
‡‡Median (full range): cases/controls.
§§Median (interquartile range): cases/controls.

Pneumococcal and influenza vaccination are recommended by most guidelines[23,33] and are suggested as a cost-effective strategy to prevent CAP in patients with type 2 diabetes.[34] Although the included evidence has important limitations, our results are compatible with current clinical treatment guidelines.[23,33] The increased risk of CAP in patients with type 2 diabetes should be taken into consideration in clinical practice, and prevention of pneumonia should be discussed by physicians.

Table 2 (part 1 of 2): Measures of association of included studies examining the association between type 2 diabetes and the risk of community-acquired pneumonia					
Study	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						
Jackson et al. 2004[12]	–	–	HR	–	1.52 (1.29–1.78)	Age, sex, smoking status, CHF, ischemic heart disease, cancer, dementia, stroke, COPD, asthma, renal disease, use of prednisone or other immunosuppressive medication, no. of outpatient visits in the previous year, hospital admission for pneumonia in in the previous year, home oxygen therapy, receipt of home health care
Muller et al. 2005[3]	–	–	OR	1.31 (1.15–1.50)	1.30 (1.11–1.52)	Age, sex, asthma, pulmonary disease (including tuberculosis, acute bronchitis and asthma), insurance type, cardiovascular disease, peripheral neuropathy, neurologic disease
O'Meara et al. 2005[13]	–	–	Risk ratio	–	1.34 (1.05–1.70)	Age, race, education level, smoking status, prior vaccination for pneumonia, vaccination for influenza in the previous year, FEV_1, FVC, maximal inspiratory pressure, 3MSE score, history of: MI, angina pectoris, CAD, claudication, CHF, CVA, COPD, pneumonia
Benfield et al. 2007[5]	90/353	1104/9710	HR	2.55 (1.86–3.29)	1.75 (1.23–2.48)	Age, sex, smoking status, SES (education, income), cholesterol, triacylglycerol, hypertension, physical activity, lung function
Ehrlich et al. 2010[14]	–	–	HR	–	1.92 (1.84–1.99)	Age, sex, smoking status, race or ethnicity, education, alcohol, BMI, no. of outpatient visits occurring in the 12 mo before baseline
Hamilton et al. 2013[6]	181/1294	435/5156	Rate ratio	1.86 (1.55–2.21)	–	–
Seminog and Goldacre 2013[10] (LHES)	–	–	Rate ratio	–	1.68 (1.65–1.71)	Age, sex, the time period in single calendar years, SES (region of residence deprivation score)
Seminog and Goldacre 2013[10] (ORLS1)	–	–	Rate ratio	–	1.87 (1.72–2.04)	Age, sex, the time period in single calendar years, SES (district of residence)
Seminog and Goldacre 2013[10] (ORLS2)	–	–	Rate ratio	–	1.76 (1.60–1.92)	Age, sex, the time period in single calendar years, SES (district of residence)
Hine et al. 2017[8]	34 278*	613 052†	OR	–	1.43 (1.18–1.74)	Age, sex, smoking status, SES, comorbidities, general practice
López-de-Andrés et al. 2017[15]	NR/223 715	NR/677 621	Rate ratio		1.66 (1.65–1.67)	Age, sex, year of discharge
Ray et al. 2017[16]	7/47	15/292	OR	3.23 (1.24–8.38)	–	–
Williams et al. 2017[17]	–	–	OR	–	1.74 (1.44–2.10)	Age, sex, smoking status, BMI, prior diagnosis of pneumonia, exacerbation frequency, pharmacotherapy, comorbidities, GOLD stage

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

Study	No. events/ no. exposed	No. events/ no. unexposed	Measure of association	Unadjusted estimate (95% CI)	Adjusted estimate (95% CI)	Covariates (adjusted for or matched)
Case–control studies						
Farr et al. 2000[18]	–	–	OR	2.50 (0.34–14.11)	–	–
Thomsen et al. 2004[9]	53/351	545/6227	OR	1.9 (1.4–2.6)	1.5 (1.1–2.0)	Age (matched), sex (matched), Charlson Comorbidity Index score, alcohol-related disease
van de Garde et al. 2006[19]	134/393	974/4532	OR	1.88 (1.66–2.10)	–	–
Kornum et al. 2008[7]	4489/32 975	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 of urbanization)

Note: BMI = body mass index, CAD = coronary artery 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, GOLD = Global Initiative on Obstructive Lung Disease, HR = hazard ratio, LHES = Linked English Hospital Episodes Statistics, MI = myocardial infarction, NR = not reported, OR = odds ratio, ORLS = Oxford Record Linkage Study, SES = socioeconomic status, 3MSE = Modified Mini-Mental State Examination.
*Total no. of exposed patients.
†Total no. of unexposed patients.

The specific biological mechanism behind the increased risk of CAP in patients with type 2 diabetes has not been established. The increased risk may be due to the impaired function of neutrophils and monocytes caused by hyperglycemia.[2,3,34] Patients with type 2 diabetes may be at greater risk of pneumococcal pneumonia because of increased susceptibility to certain organisms probably caused by their hyperglycemic environment.[35–39] It is also possible that complications associated with diabetes, including disordered sleep patterns and impaired lung function, may be involved in this mechanism.[40,41] Patients with type 2 diabetes also appear to have worse pneumonia outcomes,[34,42] as certain microorganisms may become more virulent in a hyperglycemic environment.[43] Thus, attaining glycemic control may improve outcomes in these patients.[44]

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 studies: OR 1.35, 95% CI 1.28–1.43, I^2 79.4%; case–control studies: OR 1.60, 95% CI 1.35–1.89, I^2 86.7%).[1] However, this study did not differentiate between diabetes types nor between nosocomial and community-acquired respiratory infections.[1] 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 consists of studies at serious risk of bias. We found that the main limitation of the included studies was inadequate control for confounding. Future research examining the biological mechanism behind the increased risk of CAP in patients with type 2 diabetes is needed to understand this association fully and to develop appropriate preventive strategies.

This study has several strengths. Our search strategy, which was developed with an experienced librarian, allowed us to assess the available literature comprehensively. Our study was conducted according to a prespecified protocol registered at PROSPERO. It included a detailed assessment of study quality and included subgroup and sensitivity analyses to gain a better understanding of sources of clinical and statistical heterogeneity in this literature. Finally, the inclusion of 95% PIs strengthens the clinical interpretation of our results.

Limitations

Our study has potential limitations. We found some evidence of small-study effects. Although this appears to be due to 2 small studies, publication bias and small-study effects are inherent limitations of all knowledge syntheses. The estimated I^2 statistics suggest the presence of substantial statistical heterogeneity; however, this statistic is a relative measure, and the T^2 statistics suggest a modest amount of absolute heterogeneity. Some subgroup analyses also had important heterogeneity (by exposure and outcome definition); subsequent analyses determined that it was largely driven by 1 study,[7] the exclusion of which greatly reduced the I^2 statistic. All of the included studies had a serious risk of bias, which prevented us from conducting subgroup analyses by study quality, and systematic reviews are inherently affected by the limitations of the included studies. We applied the ROBINS-I tool to case–control studies. However, our adaptation of the ROBINS-I tool for exposure instead of intervention allowed us to use it for the case–control studies as they were part of a well-defined cohort.

Some of the included studies examined diabetes in general rather than being restricted to type 2 diabetes, which may introduce exposure misclassification. However, 85% of patients with diabetes have type 2 diabetes;[23] thus, we deemed it appropriate to include such studies. We presented the I^2 for all subgroups for transparency, although it may be biased in small samples.[45] We included only studies
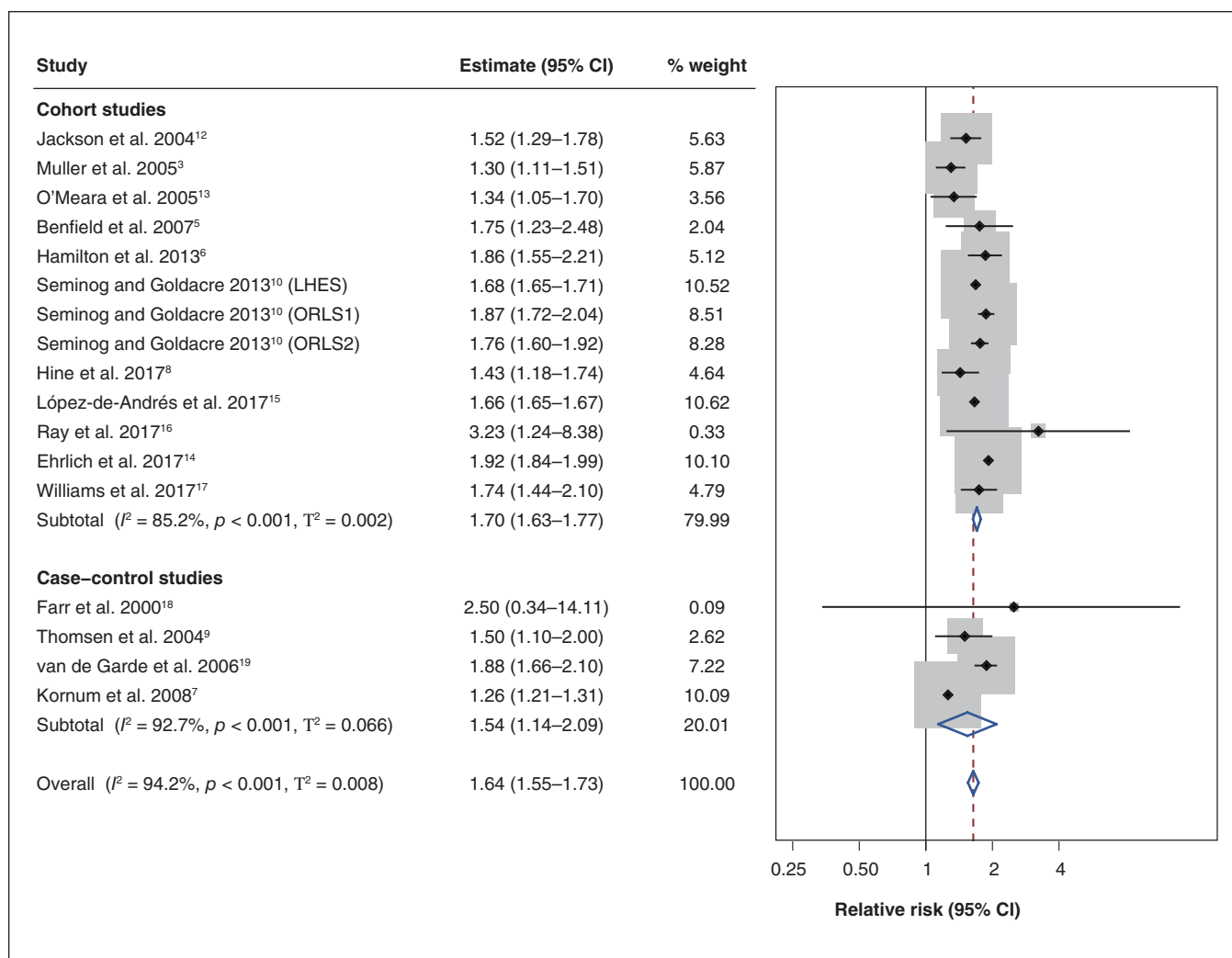
Study	Estimate (95% CI)	% weight
Cohort studies		
Jackson et al. 2004[12]	1.52 (1.29–1.78)	5.63
Muller et al. 2005[3]	1.30 (1.11–1.51)	5.87
O'Meara et al. 2005[13]	1.34 (1.05–1.70)	3.56
Benfield et al. 2007[5]	1.75 (1.23–2.48)	2.04
Hamilton et al. 2013[6]	1.86 (1.55–2.21)	5.12
Seminog and Goldacre 2013[10] (LHES)	1.68 (1.65–1.71)	10.52
Seminog and Goldacre 2013[10] (ORLS1)	1.87 (1.72–2.04)	8.51
Seminog and Goldacre 2013[10] (ORLS2)	1.76 (1.60–1.92)	8.28
Hine et al. 2017[8]	1.43 (1.18–1.74)	4.64
López-de-Andrés et al. 2017[15]	1.66 (1.65–1.67)	10.62
Ray et al. 2017[16]	3.23 (1.24–8.38)	0.33
Ehrlich et al. 2017[14]	1.92 (1.84–1.99)	10.10
Williams et al. 2017[17]	1.74 (1.44–2.10)	4.79
Subtotal ($I^2 = 85.2\%$, $p < 0.001$, $T^2 = 0.002$)	1.70 (1.63–1.77)	79.99
Case–control studies		
Farr et al. 2000[18]	2.50 (0.34–14.11)	0.09
Thomsen et al. 2004[9]	1.50 (1.10–2.00)	2.62
van de Garde et al. 2006[19]	1.88 (1.66–2.10)	7.22
Kornum et al. 2008[7]	1.26 (1.21–1.31)	10.09
Subtotal ($I^2 = 92.7\%$, $p < 0.001$, $T^2 = 0.066$)	1.54 (1.14–2.09)	20.01
Overall ($I^2 = 94.2\%$, $p < 0.001$, $T^2 = 0.008$)	1.64 (1.55–1.73)	100.00

Relative risk (95% CI)

Figure 2: Forest plot of association between type 2 diabetes and risk of community-acquired pneumonia by study design. Note: CI = confidence interval, LHES = Linked English Hospital Episodes Statistics, ORLS = Oxford Record Linkage Study. DerSimonian–Laird random-effects models were used to pool estimates across studies. The shaded areas represent the weight of the study in the overall estimate. The 95% prediction intervals were 1.51–1.92 for cohort studies, 0.74–3.21 for case–control studies and 1.30–2.06 overall.

published in English or French, which may have introduced language bias, a form of selection bias. Because of insufficient data and data variability, we were unable to examine how the distributions of characteristics such as age and sex affected study-specific measures of association. Finally, our search of the grey literature may have been incomplete as our search strategy was not tailored to the grey literature.

Conclusion

The available evidence suggests that type 2 diabetes is associated with an increased risk of CAP. However, this evidence is from studies at serious risk of bias, and additional high-quality studies are needed to confirm these findings. While awaiting such studies, health care providers should inform patients to seek medical attention promptly if they develop symptoms of CAP to facilitate early detection and treatment, given the morbidity and mortality associated with CAP. 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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