Association Between Diabetes And Infection

by

© Waseem Abu-Ashour

A Thesis submitted to the

School of Graduate Studies

in partial fulfillment of the requirements for the degree of

Masters In Science Of Pharmacy
School Of Pharmacy

Memorial University of Newfoundland

May, 2016

St. John's Newfoundland and Labrador

ABSTRACT

Background:

The objective of the study was to assess the association between diabetes and infection.

Methods:

A systematic review and meta-analysis was conducted to summarize and quantify the association between diabetes and the risk of infections in the existing literature. Second, a cohort study was done to estimate the association between diabetes and infections occurring in primary care.

Results:

The systematic review and meta-analysis demonstrated that diabetes is associated with an increased risk of infection. Results were generally consistent across types of infections. Findings from the cohort study suggest that patients with diabetes have a small increased risk of developing certain infections compared to patients without diabetes in primary care.

Conclusion:

Diabetes is associated with an increased risk of infections. The relationship varies according to type of infection present. However, more research is needed to determine the implications of patient characteristics such as BMI and glycemic control on the risk of infections.

ACKNOWLEDGEMENTS

I would first like to thank my supervisor Dr. John-Michael Gamble of the School of Pharmacy here at Memorial University of Newfoundland. The door to Dr. Gamble's office was always open whenever I ran into a trouble or had a question about my research or writing. He consistently allowed this paper to be my own work, but steered me in the right the direction whenever he thought I needed it.

I would also like to thank my supervisory committee who were involved in my research project: Dr. Laurie Twells of School of Pharmacy/Faculty of Medicine, and Dr. James Valcour of Faculty of Medicine here at Memorial University of Newfoundland. Without their guidance and input, this project could not have been successfully conducted.

Finally, I must express my very profound gratitude to my parents Dr. Mohammed Abu-Ashour and Mrs. Heyam Abu-Ashour for providing me with unfailing support and continuous encouragement throughout my years of study and through the process of researching and writing this thesis. I would also like to mention my sisters for their continuing support; Wesam, Raneem, Salam, Leen and Rand. This accomplishment would not have been possible without all of them. Thank you.

Waseem Abu-Ashour.

Table of Contents

List of Tables

List of Figures

List of Symbols, Nomenclature or Abbreviations

aOR: Adjusted Odds Ratio

CCS: Case-Control Study

CI: Confidence Interval

cOR: Crude Odds Ratio

CPCSSN: Canadian Primary Care Sentinel Surveillance Network

CS: Cohort study

EMR: Electronic Medical Record

GI: Gastrointestinal

GU: Genitourinary

H&N: Head and Neck

HIV: Human Immunodeficiency Virus

I^2: I-squared

ICD-9: International Classification Disease

IPA: International Pharmaceutical abstracts

IRR: Incidence Rate Ratio

MeSH: Medical Subject Heading

MOOSE: Meta-analysis in Observational Studies in Epidemiology

NL-CPCSSN: Newfoundland and Labrador Canadian Primary Care Sentinel Surveillance Network

NOS: Newcastle-Ottawa Scale

PRISMA : Preferred Reporting Items for Systematic Reviews and Meta-analysis.

PY: Person-Year

RTI: Respiratory Tract Infection

SD: Standard Deviation

SSTI: Skin and Soft Tissue Infection

List of Appendices

Chapter 1

Introduction

1.1 Background:

1.1.1 Burden of Diabetes Mellitus:

Diabetes mellitus is a serious chronic condition with potentially devastating complications that affects all age groups worldwide. In the year 2015 more than 415 million people were diagnosed with diabetes mellitus globally. According to the International Diabetes Federation (IDF) this number is expected to rise to more than 640 million people by the year 2040 (1). Canada is one of the countries that will be significantly affected by this change. As of 2014, the estimated prevalence of diabetes in Canada was 6.7% of the population reflecting over 2 million Canadians living with diabetes (2).

Diabetes and its complications increase costs and service pressures on the healthcare system. Among adults aged 20 to 49 years, those who had diabetes were 2 to 3 times more likely to see a family physician or a specialist (2). Also, people with diabetes were 3

times more likely to require hospital admission in the preceding year with longer lengths of stay compared to those without diabetes (2). People with diabetes are over 3 times more likely to be hospitalized with cardiovascular disease, 12 times more likely to be hospitalized with end stage renal disease(ESRD) and over 20 times more likely to be hospitalized for a nontraumatic lower limb amputation compared to the general population (2). Obesity, hypertension, and dyslipidemia are the most commonly distinctive comorbidities associated with diabetes. However, there are other conditions found at higher rates in people with diabetes; depression, obstructive sleep apnea, fatty liver disease, cancer, fractures, cognitive impairment, low testosterone in men, periodontal disease and hearing impairment (3). Diabetes is the sixth leading cause of death in Canada (4). By 2050, the number of deaths directly attributable to diabetes in Canada is likely to increase to almost 17,500 deaths annually (5).

1.1.2 Definition:

Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action or both (6). Diabetes is associated with relatively specific long-term complications, due to persistence of hyperglycemia, affecting several body organs mainly the nerves, kidneys, eyes, as well as an increased risk for cardiovascular disease. Diabetes can be diagnosed based on glycated hemoglobin (A1C) criteria, fasting plasma glucose, random plasma glucose, or a 2-hour plasma glucose value after a 75 g oral glucose tolerance test (7,8).

1.1.3 Classification:

Diabetes can be classified into several categories. Type 1 diabetes encompasses diabetes that is primarily a result of pancreatic beta cell destruction and is prone to ketoacidosis (6). This form, previously called “insulin-dependent diabetes” or “juvenile-onset diabetes,” accounts for 5–10% of diabetes (9). It includes cases due to an autoimmune process and those for which the etiology of beta cell destruction is unknown.

Type 2 diabetes, previously referred to as “noninsulin- dependent diabetes” or “adult onset diabetes,” accounts for 90–95% of all diabetes (9). Type 2 diabetes may range from predominant insulin resistance with relative (rather than absolute) insulin deficiency to a predominant secretory defect with insulin resistance (6). At least initially, and often throughout their lifetime, these individuals may not need insulin treatment to survive. Distinguishing between type 1 and type 2 diabetes is important because management strategies differ, but it may be difficult at the time of diagnosis in certain situations. Clinical judgment with safe management and ongoing follow-up is a prudent approach.

In the past, gestational diabetes was defined as any degree of glucose intolerance that was first recognized during pregnancy (10), regardless of whether the condition may have predated the pregnancy or persisted after the pregnancy. A more accurate definition was undertaken. Gestational diabetes is diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes. Women with diabetes in the first trimester would be classified as having type 2 diabetes (9).

Other specific types include a wide variety of relatively uncommon conditions, primarily specific genetically defined forms of diabetes or diabetes associated with other diseases or drug use (6,9).

In 1997 and 2003, the Expert Committee on Diagnosis and Classification of Diabetes Mellitus (10,11) recognized a group of individuals whose glucose levels did not meet the criteria for diabetes but were too high to be considered normal. “Prediabetes” is a practical and convenient term referring to impaired fasting glucose, impaired glucose tolerance (12) or an A1C of 6.0% to 6.4%, each of which indicates an increased risk for the future development of diabetes and its complications. Impaired fasting glucose and impaired glucose tolerance should not be viewed as clinical entities in their own right but rather risk factors for diabetes and cardiovascular disease. Impaired fasting glucose and impaired glucose tolerance are associated with obesity (especially abdominal or visceral obesity) (13), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension.

1.1.4 Management Strategies:

People with type 1 diabetes require insulin for their survival. Standard treattment should be treated with multiple injections (three to four injections per day of different types of insulin) or a continuous subcutaneous insulin infusion system (14). Type 2 diabetes has traditionally been treated in a stepwise manner, starting with lifestyle modifications (such as diet and exercise) and later with pharmacotherapy. Several classes of oral agents are available for clinical use. These mainly include insulin seceratgogues, insulin sensitizers, and drugs that delay the absorption of carbohydrates from the gastrointestinal tract. Over time, many patients with type 2 diabetes will require insulin therapy. There are currently

seven broad classes of antidiabetic drugs currently approved for use in Canada: Insulin, Metformin, Sulfonylureas, Meglinides, α-Glucosidase Inhibitors, Thiazolidinediones, Incretins and Sodium Glucose Cotransporter 2 Inhibitors (14,15).

1.1.5 Complications:

Diabetes is associated with significant dysfunction of numerous metabolic pathways, which in the long run, will lead to complications that involve multiple systems of the body. Cardiovascular disease is the major cause of morbidity and mortality for individuals with diabetes. In fact, cardiovascular disease is the primary cause of death among people with type 1 and type 2 diabetes (16-18).

Hypertension affects the vast majority of individuals with type 2 diabetes and many of those with type 1 diabetes. (19) Diabetes is a considerable independent risk factors for myocardial infarction. Compared to individuals without diabetes, patients with diabetes have a 3-fold increased risk of acute coronary syndrome (20), and a 2-fold increased short and long-term mortality (21-24). Estimates of risk of ischemic stroke in people with diabetes range from a 2- to 3-fold increase in men and a 2- to 5-fold increase in women (25,26). Diabetes also doubles the risk of stroke recurrence, and stroke outcomes are significantly worse among patients with diabetes, with increased hospital and long-term stroke mortality, more residual neurological and functional disability, and longer hospital stays (27).

Heart failure, both systolic and diastolic, is also more prevalent in people with diabetes. It is recognized that diabetes can cause heart failure independently of ischemic heart disease

by causing a diabetic cardiomyopathy (28). Epidemiological studies have shown that the incidence of heart failure is 2- to 4-fold higher in people with diabetes compared to those without diabetes (29,30).

Another common finding in people with diabetes is kidney disease. Up to half of patients with diabetes demonstrate signs of kidney damage in their lifetime (31-33). Diabetes is the leading cause of kidney disease in Canada (34). Diabetic retinopathy is the most common cause of new cases of legal blindness in people of working age (35). Glaucoma, cataracts, and other disorders of the eye occur earlier and more frequently in people with diabetes. Previous data showed the prevalence rate of proliferative retinopathy to be 23% in people with type 1 diabetes, 14% in people with type 2 diabetes and on insulin therapy, and 3% in people receiving oral antihyperglycemic therapies (36). Neuropathy is yet another common complication with diabetes. Detectable sensorimotor polyneuropathy will develop within 10 years of the onset of diabetes in 40% to 50% of people with type 1 or type 2 diabetes (37). While clinical neuropathy is uncommon in people with type 1 diabetes within the first 5 years after the onset of diabetes, people with type 2 diabetes may have neuropathy at the time of diagnosis (38). Foot complications are a major cause of morbidity and mortality in persons with diabetes and contribute to increased healthcare utilization and costs (39-41).

In addition to these comorbidities, diabetes is also associated with other diseases or conditions at rates higher than those in people without diabetes (14). Erectile dysfunction affects approximately 34% to 45% of men with diabetes(42). Recent reports describe up to one-third of newly diagnosed men with diabetes have erectile dysfunction at presentation (43), with upward of 50% of men having erectile dysfunction by year 6 after

diagnosis (44). Diabetes is associated with increased risk of cancers of the liver, pancreas, endometrium, colon/rectum, breast, and bladder (45). Hip fracture risk is significantly increased in both type 1 and type 2 diabetes in both sexes (46). Type 1 diabetes is associated with osteoporosis, but in type 2 diabetes an increased risk of hip fracture is seen despite higher bone mineral density (47). Other conditions have been reported to occur more often in people with diabetes compared to people without, such as hearing impairment (48), obstructive sleep apnea (49-51), fatty liver disease (52,53), cognitive decline and dementia (54,55), as well as low testosterone levels in men (56). Such coexisting conditions and dysglycemia associated with diabetes, and the various treatments associated with these diseases, may also impact the susceptibility to infections in patients with diabetes.

Diabetes not only increases an individual's risk of numerous complications, it also decreases their quality of life and life expectancy (5-10 years) (57). Furthermore, the impact of living with diabetes extends to their families through economical and emotional burden, and society as a whole which reflects in an increase in healthcare system expidenture with 12% of global expidenture is spent on diabetes (>670 billion dollars) (1,58).

1.1.6 Diabetes and Infection:

Infection is a significant complication in patients with diabetes, hence it contributes to the morbidity, mortality and financial burden associated with the disease. For example, a cohort study conducted in the United States that examined diabetes and risk related

mortality, found infection related deaths in patients with diabetes to be almost 3 times higher than in patients without diabetes (59). Another study in Northern California, compared one year medical care costs for people with diabetes to those without and found that there was almost an excess cost of 5 million dollars spent due to infections (60). In addition to an increased risk of infection-related morbidy and mortality, it has been suggested that people with diabetes may be more susceptible to developing infections compared to those without diabetes. Although some rare infections have been shown to be more prevalent in people with diabetes, (e.g., pyelonephritis, malignant otitis externa, mucormycosis, etc.) (61), the association between diabetes and incident common infections is less clear.

Immunologic research has demonstrated several defects in host immune defense mechanisms in people with diabetes. Phagocytic capabilities of neutrophils are adversely affected by hyperglycemia, including impaired migration, phagocytosis, intracellular killing, and chemotaxis (62,63). Besides generalized impairments of immunity, other nonimmunologic, anatomically specific factors may contribute to an increased infection risk. For example, macrovascular disease and microvascular dysfunction may result in compromised local circulation leading to delayed response to infection and impaired wound healing (64). Unawareness of lower extremity trauma due to sensory neuropathy may result in inadequate attention to minor wounds and subsequent increased infection risk. Incomplete bladder emptying due to autonomic neuropathy permits urinary colonization by microorganisms, where high glucose concentration in the urine promotes the growth of some microorganisms (65).

The difficulties associated with estimating the actual risk of infection in diabetic patients are mainly due to the fact that diabetes is not solely a disturbance of glucose metabolism but instead a chronic inflammatory condition characterized by multiple alterations in lipid profiles and neuropathy as well as chronic vascular and renal diseases, with each of these changes altering the response to pathogens (66,67). The biological mechanisms described above are likely similar irrespective of the type of diabetes, especially in those with long standing disease; however, it is possible that the association between diabetes and infection may vary by etiology of diabetes.

Several studies have suggested that people with diabetes are at an increased risk of infection-related mortality (68,69,70), however very few studies have explored the relationship between diabetes and susceptibility to infections. Muller et al., conducted a 12 month cohort study measuring the increased risk of infections in adults with diabetes compared to those without (71). The study concluded there was an increased risk of infections (respiratory tract infection, urinary tract infection, skin and mucous membrane infection) in patients with diabetes,. However, there are several limitations worth mentioning. First the comparator group was patients without diabetes but with hypertension. They argued that these patients formed a good comparator group due to the need of regular check ups, providing regular follow up data compared to patients with diabetes. Moreover, they state that there is no known link between hypertension and infection. However, there is some evidence between cardiovascular disease and infection (72-75). Second, the age cut-off for diabetes diagnosis was 35 years arguing that it's 1-

2% in type diabetes potentially excluding younger patients with diabetes. Finally their outcome only included 3 types of infections; urinary tract, respiratory tract, and skin and mucous membrane infections.

Similarly Shah and Hux examined the association between diabetes and infection (68). They quantified the risk of infections and the mortality attributed to infectious disease in patients with diabetes. The risk ratio for infection in diabetics versus non-diabetics for infections was 1.21 (99% CI 1.20 –1.22). However, the study used an administrative dataset not primarily collected for research purposes and therefore missing critical information on confounders (glycemic control, comorbidities, life style factors, body max index, etc.). Also the study duration was only 1 year long.

Yet, not all studies agree on the presence of a relationship between diabetes and infection (76-78). In a case-control study Lipsky et al studied risk factors for acquiring pneumococcal infections in a general medical clinic. Diabetes was not shown to be among the risk factors for pneumococcal infections (76). However, the authors do state that the study population was not ideal considering them to be presumably high risk; elderly, from lower socioeconomic strata, and having several chronic medical conditions. Moreover, due to reliance on medical records, the study may have missed cases of pneumococcal infections, and undetectable pneumococcal vaccinations because of poor documentation. In another observational study, Dunkel et al examined risk factors for stump infection after lower limb amputation (77). Similarly, diabetes was not considered a risk factor for infection. However, what limits the extrapolation of the findings is that the study population was taken from a single institution in high income country. In

addition, all patients were given a single dose of prophylaxis antibiotic before surgery. The choice of antibiotic might differ between surgeons and if they treated patients with diabetes differently. This may have affected the occurrence of the outcome.

Although previous studies suggest that certain infections are more common in patients with diabetes, there still seems to be lack of current knowledge with regards to the association of diabetes with certain types of infections, presence in primary care, and the magnitude of this relationship. The focus of the current thesis is to address these important points.

1.2 Objectives:

The aim of this thesis is to address the current knowledge gap described above surrounding the relationship between diabetes (all types) and the risk of infection. Infection will be classified according to anatomical location of infection (local or generalized) and infectious agent (viral or bacterla/parasites). This will be achieved through two studies. The first study will summarize the literature describing the relationship between diabetes and the risk of infection using standard systematic review. Furthermore, the findings from published studies will be pooled into a summary risk estimate using standard meta-analysis techniques. The second study will estimate the

association between diabetes and the occurrence of infection within a primary care setting using a cohort study design. It will focus on common infections within primary care settings. Specific questions include:

Primary research question: What is the association between a new or current diagnosis of diabetes and common infectious diseases compared to those without diabetes?

Secondary research questions: In a primary care setting, compared to non-diabetics, what is the association between a new or current diagnosis of diabetes and the following infectious diseases?

1. Head and neck infections
2. Respiratory tract infections
3. Gastrointestinal infections
4. Genitourinary tract infections
5. Skin and soft tissue infections
6. Musculoskeletal infections
7. Viral infections

Determining a relationship between exposure and outcome to be causal or non-causal is crucial in epidemiological research. A group of conditions necessary to be present to provide the evidence of a causal relationship from non-causal are known as Hill's criteria

(79). The criteria are as follows; strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence and analogy. At the end of this thesis, it will be determined if and how the results of both studies meet these criteria.

References:

1) International Diabetes Federation. IDF Diabetes Atlas. 5th ed. Brussels: International Diabetes Federation, www.idf.org/diabetesatlas

2) Statistics Canada. CANSIM, table 105-0501 and Catalogue no. 82-221-X. Last modified: 2015-06-17. http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/health53a-eng.htm

3) American Diabetes Association. Initial evaluation and diabetes management planning. Sec. 3. In Standards of Medical Care in Diabetesd2015. *Diabetes Care* 2015;38 (Suppl.1):S17-S19.

4) Statistics Canada. Leading causes of death in Canada 2009;Catalogue no. 84-215-X. http://www.statcan.gc.ca/pub/84-215-x/2012001/tbl/T001-eng.pdf .

5) Canadian Agency for Drugs and Technologies in Health. Optimal therapy report: Current utilization of insulin products in Canada. *Compus* 2008;2:1-16.

6) Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Goldenberg R, Punthakee Z. Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome. *Can J Diabetes* 2013;37:S8-S11.

7) American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2014;37(Suppl.1):S81-S90.

8) The International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care* 2009;32:1327-1334.

9) American Diabetes Association. Classification and diagnosis of diabetes. Sec. 2. In Standards of Medical Care in Diabetesd2015. *Diabetes Care* 2015;38(Suppl.1):S8-S16.

10) The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997;20:1183-1197.

11) Genuth S, Alberti KG, Bennett P, et al. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003;26:3160-3167.

12) American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2012;35(Suppl.1):S64-71.

13) American Diabetes Association. Classification and diagnosis of diabetes. Diabetes care 2015; 38(Suppl.1):S8-16.

14) Executive summary: Standards of medical care in diabetes--2013. *Diabetes Care* 2013;36(Suppl.1):S4-10.

15) Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Harper W, Clement M, Goldenberg R et al. Pharmacologic Management of Type 2 Diabetes. *Can J Diabetes* 2013;S61-S68.

16) Roglic G, Unwin N, Bennett PH et al. The burden of mortality attributable to diabetes: realistic estimates for the year 2000. Diabetes Care 2005;28:2130-2135.

17) Morrish N, Wang S, Stevens L et al. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. Diabetologia 2001;44(Suppl.2):S14-21.

18) Booth G, Rothwell D, Fung K et al. Diabetes and cardiac disease. In: Hux JE, Booth G, Laupacis A. Diabetes in Ontario: An ICES Practice Atlas: Institute for Clinical Evaluative Sciences; 2002;5.95-5.127.

19) Campbell N, Gilbert R, Leiter L, et al. Hypertension in people with type 2 diabetes: update on pharmacologic management. *Can Fam Physician* 2011;57:997-1002.

20) Booth G, Kapral M, Fung K et al. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based

retrospective cohort study. *Lancet* 2006;368:29-36.

21) Donahoe S, Stewart G, McCabe C, et al. Diabetes and mortality following acute coronary syndromes. *JAMA* 2007;298:765-775.

22) Behar S, Boyko V, Reicher-Reiss H et al. Ten-year survival after acute myocardial infarction: comparison of patients with and without diabetes. SPRINT Study Group. Secondary Prevention Reinfarction Israeli Nifedipine Trial. Am Heart J 1997;133:290-296.

23) Kumler T, Gislason GH, Kober L et al. Diabetes is an independent predictor of survival 17 years after myocardial infarction: follow-up of the TRACE registry. *Cardiovasc Diabetol* 2010;9:22.

24) Malmberg K, Yusuf S, Gerstein HC et al. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. *Circulation* 2000;102:1014-1019.

25) Karapanayiotides T, Piechowski-Jozwiak B, van Melle G et al. Stroke patterns, etiology, and prognosis in patients with diabetes mellitus. Neurology 2004;62:1558e62.

26) Lehto S, Ronnemaa T, Pyorala K et al. Predictors of stroke in middle-aged patients

with non-insulin-dependent diabetes. *Stroke* 1996;27:63-68.

27) Idris I, Thomson GA, Sharma JC. Diabetes mellitus and stroke. Int J Clin Pract 2006;60:48e56.

28) Valle R, Bagolin E, Canali C et al. The BNP assay does not identify mild left ventricular diastolic dysfunction in asymptomatic diabetic patients. *Eur J Echocardiogr* 2006;7:40-44.

29) Shimabukuro M, Higa N, Oshiro Y et al. Diagnostic utility of brain-natriuretic peptide for left ventricular diastolic dysfunction in asymptomatic type 2 diabetic patients. *Diabetes Obes Metab* 2007;9:323-329.

30) Galderisi M. Diastolic dysfunction and diabetic cardiomyopathy: evaluation by Doppler echocardiography. *J Am Coll Cardiol* 2006;48:1548-1551.

31) Warram J, Gearin G, Laffel L et al. Effect of duration of type I diabetes on the prevalence of stages of diabetic nephropathy defined by urinary albumin/creatinine ratio. *J Am Soc Nephrol* 1996;7:930-937.

32) Reenders K, Nobel E, Hoogen H et al. Diabetes and its long-term complications in general practice: a survey in a well-defined population. *Fam Pract* 1993;10:169-172.

33) Weir MR. Albuminuria predicting outcome in diabetes: incidence of microalbuminuria in Asia-Pacific Rim. *Kidney Int* 2004;66:S38-39.

34) Canadian Institute for Health Information. Canadian Organ Replacement Register Annual Report: Treatment of End-Stage Organ Failure in Canada, 2000 to 2009. Ottawa, ON: Canada; 2011.

35) Kempen J, O'Colmain B, Leske M et al. The prevalence of diabetic retinopathy among adults in the United States. *Arch Ophthalmol* 2004;122:552-563.

36) Klein R, Klein BE, Moss SE. Epidemiology of proliferative diabetic retinopathy. *Diabetes Care* 1992;15:1875-1891.

37) Dyck P, Kratz K, Karnes J et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population based cohort: the Rochester Diabetic Neuropathy Study. Neurology 1993;43: 817-824.

38) Singleton J, Smith A, Bromberg M. Increased prevalence of impaired glucose tolerance in patients with painful sensory neuropathy. Diabetes Care 2001;24:1448-1453.

39) Boulton A, Armstrong D, Albert S et al. American Diabetes Association, American Association of Clinical Endocrinologists. Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of the American

Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. *Diabetes Care* 2008;31:1679-1685.

40) Davis W, Norman P, Bruce D et al. Predictors, consequences and costs of diabetes-related lower extremity amputations complicating type 2 diabetes: the Freemantle Diabetes Study. *Diabetologia* 2006;49:2634-2641.

41) O'Brien J, Patrick A, Caro J. Cost of managing complications resulting from type 2 diabetes mellitus in Canada. *BMC Health Serv Res* 2003;3:7.

42) Eardley I, Fisher W, Rosen RC et al. The multinational Men's Attitudes to Life Events and Sexuality study: the influence of diabetes on self-reported erectile function, attitudes and treatment-seeking patterns in men with erectile dysfunction. *Int J Clin Pract* 2007;61:1446-1453.

43) Al-Hunayan A, Al-Mutar M, Kehinde EO et al. The prevalence and predictors of erectile dysfunction in men with newly diagnosed with type 2 diabetes mellitus. *BJU Int* 2007;99:130-134.

44) Aversa A, Bruzziches R, Vitale C et al. Chronic sildenafil in men with diabetes and erectile dysfunction. *Expert Opin Drug Metab Toxicol* 2007;3:451-464.

45) Suh S, Kim KW. Diabetes and cancer: is diabetes causally related to cancer? *Diabetes*

Metab J 2011;35:193-198.

46) Janghorbani M, Van Dam R, Willett W et al. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. *Am J Epidemiol* 2007;166:495-505

47) Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes meta-analysis. *Osteoporos Int* 2007;18:427-444.

48) Bainbridge K, Hoffman H, Cowie C. Diabetes and hearing impairment in the United States: audiometric evidence from the National Health and Nutrition Examination Survey, 1999 to 2004. *Ann Intern Med* 2008;149:1-10.

49) Li C, Ford ES, Zhao G et al. Prevalence of self reported clinically diagnosed sleep apnea according to obesity status in men and women: National Health and Nutrition Examination Survey, 2005-2006. *Prev Med* 2010;51:18-23.

50) West S, Nicoll D, Stradling J. Prevalence of obstructive sleep apnoea in men with type 2 diabetes. Thorax 2006;61:945-950.

51) Foster G, Sanders M, Millman R et al. Sleep AHEAD Research Group. Obstructive sleep apnea among obese patients with type 2 diabetes. *Diabetes Care* 2009;32:1017-1019.

52) Clark J, Brancati F, Diehl A. The prevalence and etiology of elevated aminotransferase levels in the United States. *Am J Gastroenterol* 2003;98: 960-967.

53) El-Serag H, Tran T, Everhart J. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology* 2004;126:460-468.

54) Cukierman T, Gerstein H, Williamson J. Cognitive decline and dementia in diabetesdsystematic overview of prospective observational studies. *Diabetologia* 2005;48:2460-2469.

55) Biessels G, Staekenborg S, Brunner E et al. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol* 2006;5:64-74.

56) Dhindsa S, Miller M, McWhirter C et al. Testosterone concentrations in diabetic and nondiabetic obese men. *Diabetes Care* 2010;33:1186-1192.

57) Leal J, Gray A, Clarke P. Development of life-expectancy tables for people with type 2 diabetes. *Eur Heart J* 2009;30:834-839.

58) Zhang P, Zhang X, Brown J et al. Global healthcare expidenture on diabetes fro 2010 and 2030. *Diabetes Res Clin Pract* 2010;87:293-301.

59) Bertoni A, Saydah S, Brancati F. Diabetes and the risk of infection related mortality

in the U.S. *Diabetes Care* 2001;24:1044-1049.

60) Selby J, Ray G, Zhang D et al. Excess costs of medical care for patients with diabetes in a managed care population. *Diabetes Care* 1997;20:1396-1402.

61) Knapp S. Diabetes and infection. Is There a link? A mini review. *Gerontology* 2013;59:99-104.

62) Valerius N, Eff C, Hansen N et al. Neutrophil and lymphocyte function in patients with diabetes mellitus. *Acta Med Scand* 1982;211:463-467.

63) Delamaire M, Maugendre D, Moreno M et al. Impaired leucocyte functions in diabetic patients. *Diabet Med* 1997;14:29-34.

64) Pecoraro R, Ahroni J, Boyko E et al. Chronology and determinants of tissue repair in diabetic lower-extremity ulcers. *Diabetes* 1991;40:1305-1313.

65) Ellenberg M, Weber H. The incipient asymptomatic diabetic bladder. *Diabetes* 1967;16:331-335.

66) Donath M, Shoelson S. Type 2 Diabetes as an inflammatory disease. *Nat Rev Immunol* 2011;11:98-107.

67) Wellen K, Hotamisligil G. Inflammation, stress and diabetes. *J Clin Ivest* 2005;115:1111-1119.

68) Shah B, Hux J. Quantifying the risk of infectious diseases for people with diabetes. *Diabetes Care* 2003;26:510-513.

69) Emerging risk factors collaboration, Seshasai S, Kaptoge S et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 2011;364;829-841.

70) Bertoni A, Saydah S, Brancati F. Diabetes and the risk of infection-related mortality in the U.S. *Diabetes Care* 2001;24:1044-1049.

71) Muller L, Gorter K, Hak E et al. Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. *Clin Infect Dis* 2005;41:281-288.

72) Libby P, Ridker P, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002;105:1135-1143.

73) Ridker P. C-Reactive Protien and the risk of cardiovascular events among those at intermediate risk. *J Am Coll Cardiol* 2007;49:2129-2138.

74) Zhu J, Nieto F, Horne B et al. Prospective Study of Pathogen Burden and Risk of

Myocardial Infarction or Death. *Circulation* 2001;103:45-51.

75) Desvarieux M, Demmer R, Jacobs D et al. Periodontal bacteria and hypertension: the oral infections and vascular disease epidemiology study (INVEST). *J Hypertens* 2010;28:1413-1421.

76) Lipsky B, Boyko E, Inui T et al. Risk factors for acquiring pneumococcal infections. *Arch Intern Med* 1986;146:2179-2185.

77) Dunkel N, Belaieff W, Assal M et al. Wound dehiscence and stump infection after lower limb amputation: risk factors and association with antibiotic use. *J Orthop Sci* 2012;17:588-594.

78) Antonio N, Prieto D, Providencia L et al. Diabetes mellitus does not affect one-year outcome after heart transplantation. *Rev Port Cardiol* 2010;29:205-220.

79) Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965;58:295-300.

Chapter 2:

Diabetes and the Association of Infection: A Systematic Review and Meta-Analysis of Observational Studies

2.1 Introduction

The International Diabetes Federation estimates that there were almost 400 million people living with diabetes through out the world in 2014. The prevalence of diabetes is expected to increase to more than 590 million people by the year 2035 (1). Well-known complications of diabetes include microvascular (retinopathy, neuropathy, nephropathy) and macrovascular (coronary heart disease, cerebrovascular disease, and peripheral vascular disease) complications (2); however, there are numerous lesser-known complications. For example, diabetes is associated with increased rates of certain infection (3-5). Impairment of the immune system in people with diabetes such as impaired phagocytic function may be responsible for this increased risk of infection, although there is still some controversy around this relationship (4-8). Certain infections are more prevalent in people with diabetes (9). Studies have indeed suggested that individuals living with diabetes are at an increased risk of infection-related mortality

(10,11); this could explain why some physicians believe that patients with diabetes are more susceptible to infections, and tend to admit these patients to the hospital (3). However, not all studies support this association (12,13).

Although previous studies suggest that certain infections are more common in patients with diabetes, there is still a lack of substantive evidence to document the magnitude of this association. It is unclear whether diabetes is associated with an increase in the incidence of infections. To our knowledge, there has not been an attempt to summarize the existing evidence of the association between diabetes and infections, through a systematic review and meta-analysis. The justification for this review is as follows; it will help clarify the magnitude and precision of the effect; it will address gaps with regards to the current state of knowledge about the association between diabetes and certain types of infections; it will quanitify the heterogeneity among studies; and it will measure the quality of existing evidence on this association. Therefore, we aimed to to provide a rigourous summary of the evidence on the incidence of different types of infection (head and neck, respiratory, gastrointestinal, genitourinary, skin and soft tissue, musculoskeletal and viral) in patients with and without diabetes through conducting a comprehensive systematic review and meta-analysis.

2.2 Methods

2.2.1 Study Design:

We evaluated the relationship between diabetes and incident infections by conducting a systematic review and meta-analysis. The review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines during all stages of design, implementation and reporting (14,15).

2.2.2 Eligibility Criteria:

This review included observational studies assessing the association between diabetes and incident infections up to May 2014. Study designs that were eligible for inclusion were cohort studies, case-control studies, nested case-control or case-cohort studies. Other study designs such as systematic reviews and meta-analyses, case series, case reports, or cross-sectional studies were excluded from this review. Studies were included if the population studied was 18 years and older. Younger populations were excluded due to the fact that the immune system of this category is still developing, and this could affect our outcome of interest (16,17). Studies were required to report the number of incident infections in patients with diabetes and in patients without diabetes. Classification of the type of diabetes was based on the definition used in each study. Studies including any

type of diabetes were eligible including type 1 diabetes, type 2 diabetes, gestational diabetes, other, and unspecified diabetes.

2.2.3 Outcomes:

Outcomes were categorized in the following categories: infection (non specific), respiratory tract infections (RTI) (upper and lower), genitourinary tract infections (GU), skin and soft tissue infections (SSTI), gastrointestinal infections (GI), head and neck infections (H&N), viral infections, and any other infections not classified here. An outcome was placed into one of these body system categories, unless was specified by the study to be viral it was placed in the viral infection category.

2.2.4 Search Strategy:

The search strategy was carried out in collaboration with a research librarian experienced in systematic reviews. The following biomedical databases were searched from inception to December 31, 2013; PubMed, EMBASE, The Cochrane Library, International Pharmaceutical Science, and Web of Science. MeSH and free-text terms were used to search PubMed. EMTREE and free-text terms were used to search EMBASE. In searching the Cochrane Library, MeSH terms were used as well as free-text terms to capture items not indexed with MeSH. The remaining databases were searched using free-text terms. The search was restricted to English language. See Appendix 2.A for a sample of the search strategy.

2.2.5 Study Selection and Data Extraction:

Two independent reviewers screened titles and abstracts, and then went on to screen full texts. Identification of relevant studies was through use of a standardized study eligibility/relevance form. Discrepancies were resolved by consensus. If consensus was not achieved, a third reviewer was consulted. Data was extracted by one reviewer using a predesigned form information that included first author, contact details, journal citation, year of publication, study design, funding, sample size, data set used, study location and duration, duration of follow up, study population characteristics, statistical analysis used, the study specific measure of association, and the type of exposure (Appendix 2.B). An independent reviewer verified the accuracy of the extracted data.

2.2.6 Assessment of Risk of Bias:

The quality of the observational studies was appraised using the Newcastle-Ottawa Quality Assessment Scale (NOS) (18) according to the procedures recommended in the Cochrane Handbook of Systematic Reviews. One author assessed the methodological quality of all the selected studies. The NOS includes a "star system" in which a study is judged on three domains: selection of the study groups (four items); comparability of the groups (two items); and ascertainment of either the exposure or outcome (three items). If any item of NOS (for example, case definition or exposure ascertainment) is not reported, a zero score is given. Studies score one star for each area addressed, with scores between 0 and 9 (the highest level of quality). As per the NOS scale, study quality was classified according to the study score into poor (score 0-3), moderate (score 4-6) and high quality

(score 7-9).

2.2.7 Data Analysis:

For dichotomous outcome data, the results are expressed as odds ratio (OR) with corresponding 95% confidence intervals (CI). For continuous outcome data, the results are expressed as weighted mean difference (WMD) with 95% CIs, or as standardized weighted mean difference if outcomes are conceptually the same but measured in different ways.

As this review included only observational studies, we expected heterogeneity between studies, results were pooled across these studies using a random effects model. Heterogeneity was tested using the Chi-squared test and measured using the I-squared test. The Chi-squared test evaluates the observed differences in the results and whether they are compatible with chance alone. The I-squared test is used to quantify the inconsistency across studies. Sensitivity analyses were undertaken to explore the influence of different variables on the overall estimate of effect and as potential sources of heterogeneity including: study design (cohort versus case-control studies), quality of the study (low, moderate, high), sample size, patient characteristics, and exposure and outcome. Moreover, funnel plots were generated to assess the potential for publication bias. Analysis was conducted using Stata software (version 12.0).

2.3 Results

The study selection process is shown in Figure 1. There were a total of 345 studies: 243 cohort studies and 102 case-control studies. Most of the studies were conducted in North America (55%) followed by Europe (29%). The mean age of the participants was 61 years and ranged from 26 to 80 years. Specific and unspecified infections were identified from the included articles. Some studies reported a specific infection, while others reported multiple infections. Of all infections measured in the analysis, almost 45% were skin and soft tissue infections, followed by respiratory tract infections (9%) and genitourinary infections (8%).

According to the Newcastle-Ottawa Quality Assessment Scale (NOS), most of the studies (80.9%) included were of moderate quality (score 4-6). Other infections identified and characteristics of the studies are provided in Table 1. Table 2 clarifies specific infections reported by included studies. Types of infection with the odds ratio and 95%CIs found in this review are presented in Figure 2 (A-D). Funnel plots to express publication bias are shown in Appendix 2.C (1-8).

2.3.1 Skin and Soft Tissue Infections:

Our review found 176 studies (140 cohort studies, 36 case-control studies) that evaluated the association between diabetes and skin and soft tissue infections (SSTI). The pooled crude odds ratio (cOR) for an SSTI from cohort studies was 2.09 (95% CI 1.92-2.29),

with a comparable pooled adjusted odds ratio (aOR) of 2.16 (95% CI 1.95-2.39). Substantial between-study heterogeneity as indicated by high I^2 values was observed for both crude and adjusted results (I^2 = 91.8%, I^2 = 95.3% respectively). As for case-control studies, the cOR was 2.89 (95% CI 2.24-3.75), and the aOR was 2.61 (95% CI 2.17-3.13). Heterogeneity was less for the crude result (I^2 = 74.8%), and was not present for the adjusted result (I^2 = 0%). To decrease the heterogeneity between results, since skin and soft tissue infections is a relatively broad category and based on the studies found, these infections were categorized into surgical site infections (SSI) and other skin and soft tissue infections. As shown in Table 2, the results showed a positive association with diabetes, but heterogeneity was not decreased for the cohort studies for both groups (SSI: cOR 2.09, 95% CI 1.90-2.31, I^2 = 91.4%, aOR 2.33, 95% CI 2.03-2.67, I^2 = 93.9%; Other SSTI: cOR 2.22, 95% CI 1.67-2.95, I^2 = 91.8%), and was less for the case-control studies (SSI: cOR 3.12, 95% CI 2.37-4.11, I^2 = 0%, aOR 2.62, 95% CI 2.15-3.20, I^2 = 0%; Other SSTI: cOR 1.69, 95% CI 1.05-2.72, I^2 = 55.8%). Moreover, to lessen the marked heterogeneity, the 2 subgroups were further divided. SSI was categorized according to type of surgery into 9 categories. The results of each of these categories are shown in Table 3.

2.3.2 Respiratory Tract Infections:

Meta-analyses of the 49 study results of respiratory tract infections (RTI) (cohort studies=35, case-control studies=14) showed a positive association with diabetes. For cohort studies the (cOR) was 1.46 (95% CI 1.32-1.61) with considerable heterogeneity (I^2

= 84.9%), and the (aOR) was 1.35 (95% CI 1.28-1.43) with even higher heterogeneity (I^2 = 97.8%). Case-Control studies showed a (cOR) 2.06 (95% CI 1.71-2.48), and (aOR) 1.62 (95% CI 1.37-1.92). Heterogeneity was high as well for crude and adjusted results (I^2 = 95%, and I^2 = 85.9% respectively). Those infections were categorized into 3 subgroups; upper respiratory tract, lower respiratory tract and unspecified. Lower respiratory tract infections were further classified into tuberculosis and pneumonia to decrease the degree of heterogeneity between the studies. Details are shown in **Table 4**.

2.3.3 Genitourinary Tract Infections:

33 cohort studies found a cOR of 2.05 (95% CI 1.83-2.31, I^2 = 92.4%) and an aOR of 1.61 (95% CI 1.42-1.83, I^2 = 99.2%). Results of 11 case-control studies reported a cOR of 3.06 (95% CI 2.21-4.23, I^2 = 81.2%), and an aOR of 2.42 (95% CI 1.61-3.66, I^2 = 83.7%). This group was divided into urinary and genital. Each of these categories was further classified into subgroups (Table 5).

2.3.4 Blood-Stream Infections:

An association was apparent after adjustment between blood-stream infections and diabetes. 31 cohort studies reported a cOR of 1.75 (95% CI 0.84-3.65, I^2 = 99.7%) and an aOR of 1.73 (95% CI 1.49-2.01, I^2 = 94.2%). 10 case-control studies demonstrated a higher association with a cOR of 2.77 (95% CI 2.24-3.42, I^2 = 49.7%) and an aOR was 2.40 (95% CI 1.68-3.42, I^2 = 71.7%). Blood stream infections were also grouped

according to type of patients (Table 6).

2.3.5 Viral Infections:

Viral infections included 14 studies (cohort studies=10, case-control studies=4). The analysis of cohort studies revealed a cOR of 1.45 (95% CI 1.29-1.64, I^2 = 66.9%) and an aOR of 1.29 (95% CI 1.13-1.46, I^2 = 97.7%). Case-control studies showed a cOR of 1.13 (95% CI 0.43-2.93, I^2 = 99.9%) (Table 7).

2.3.6 Head and Neck Infections:

5 studies (cohort studies=3, case-control studies=2) reported head and neck infections (H&NI). Cohort studies gave a cOR of 1.33 (95% CI 1.08-1.65, I^2 = 29.9%), and an aOR of 1.17 (95% CI 1.13-1.22, I^2 = 45.4%). Case-control studies showed a cOR of 1.55 (95% CI 0.22-11.10, I^2 = 80.7%) (Table 8).

2.3.7 Gastrointestinal Infections:

There were 4 cohort studies and 6 case-control studies that reported a gastrointestinal infection. Cohort studies suggested an inverse relationship with a cOR of 0.79 (95% CI 0.66-0.94, I^2 = 0%), but the aOR was 1.48 (95% CI 1.40-1.57, I^2 = 64.5%). However, case-control studies showed a stronger association with a cOR of 2.44 (95% CI 1.26-4.71, I^2 = 89.9%) and an aOR of 3.61 (95% CI 2.94-4.43, I^2 = 0%) (Table 9).

2.3.8 Bone Infections:

7 studies (cohort studies=5, case-control studies=2) reported bone infections. Cohort studies gave a cOR of 2.43 (95% CI 1.48-3.99, $I^2 = 0\%$). There was insufficient data to pool results for the case-control studies here.

2.3.9 Unspecified Infections:

There were 67 studies (cohort studies=52 studies, case-control=15 studies) that reported infections with no specification of type as the outcome. The cOR was 1.91 (95% CI 1.64-2.23, $I^2 = 90.3\%$) and aOR was 1.81 (95% CI 1.64-2.00, $I^2 = 99.6\%$) for cohort studies. As for case-control, the cOR was 2.66 (95% CI 1.84-3.83, $I^2 = 73.7\%$) and aOR was 3.81 (95% CI 2.88-5.04, $I^2 = 0\%$). This was further analyzed according to types of patients (Table 10).

2.3.10 Other infections:

The pooled cOR for the 2 case-control studies that reported zygomycosis was 8.21 (95% CI 3.45-19.57, $I^2 = 0\%$).

2.4 Discussion

This quantitiative systematic review examined the association between diabetes and different types of infections. A total of 345 observational studies were identified that presented the existing evidence on the relationship between the diabetes and development of an infection. A persistent positive association was found when examining various classfications of infections and diabetes. The results from individual studies were heterogeneous, which might reflect differences in study quality, the populations studied and how diabetes and infection were measured.

Although the association between diabetes and the risk of developing different types of infections has long been postulated (9,19-21), convincing quantitative evidence has been lacking especially for common infections. In general a positive association between diabetes and infections is biological plausible given that certain microorganisms are known to be more common in patients with diabetes, mainly Staphylococcus, Group A&B Streptococcus (22-25). Moreover, hyperglycemia decreases function of neutrophils and monocytes by way of impaired chemotaxis, adherence, phagocytosis and other immune system impairment (5-7,26-28).

Moveover, there may be other mechanisms at play that increase the risk of certain types of infections in those with diabetes. Specifcally, diabetes is known to affect healing (29,30), and hyperglycaemia affects coagulation and fibrinolytic function(31), lipid

metabolism and endothelial function (32,33) thereby leading to increased skin and soft tissue infections. Persons with diabetes are also susceptible to pulmonary infections due to an increased risk of aspiration secondary to gastroparesis, diminished cough reflex, and higher rates of obstructive sleep apnea (34-36). Impaired lung functions in these patients contribute to acquiring this type of infection as well (37,38). This impairment is believed to involve microangiopathic changes in the basement membrane of pulmonary blood vessels and respiratory epithelium, as well as non-enzymatic glycosylation of tissue protein (39-42). Several factors are thought to predispose diabetic subjects to genitourinary infections (19,20,43,44). Reduced sensitivity and altered distensibility of the urinary bladder due to autonomic neuropathy can result in stagnation of urine and higher rates of catheterization (45). Moreover, glycosuria can create a favourable environment that promotes the growth of bacteria and yeast (e.g. Candida albicans) growth (46-48). Additionally, glycosuria impairs phagocytosis, reducing the ability to fight infection (49). People with diabetes may have increased susceptibility to blood stream infections for several reasons. Co-existing morbidities, such as microvascular and macrovascular complications, neuropathy, and diabetic foot disease play a role as well in acquiring blood stream infections. A correlation of head and neck infections was also linked to diabetes, where contributing factors involve higher salivary glucose, low salivary pH, microangiopathy, and abnormal collagen metabolism (19,20,26,28,50,51). The pathogenic link involves diabetes-induced changes in immune cell function causing. It was demonstrated in this review that viral infections are linked to diabetes. The association between diabetes and viral infections is supported by various diabetes specific in vitro defects in innate and adaptive immunity, and studies that showed that long-

standing diabetes is often accompanied by impaired cell-mediated immunity, which increases the risk to more severe and widespread infections. This could also be the case for gastrointestinal infections and other types that were shown in the review.

Although infection was associated with diabetes across all types of infections, there was a difference in magnitude of this association between these types of infections. Although the reasons for these differences are unclear, there are several potential explanatory factors. Certain infections (e.g., Head and Neck, Viral infecitons) had a small number of studies limited the power to detect differences in infections. Another factor that might play a role in this discrepancy is lack of information on type of diabetes, type of diabetic medications, and duration of diabetes which might have affected the outcome.

It is important to note that most of the studies included in this review were of moderate quality according to the risk of bias tool used. Furthermore, in an attempt to test for publication bias funnel plots were generated. Most of these plots were asymmetrical (skin and soft tissue, respiratory, genitourinary and blood-stream infections). Causes for asymmetry in these plots could be due to differences in individual studies included in this review; selection bias, true heterogeneity (size of effect differes according to study size, intensity of intervention and differences in underlying risk factors), methodological differences (poor analysis in smaller studies, inadequate analysis) and chance.

2.4.1 Strengths and Limitations:

To our knowledge, this is the first systematic review and meta-analysis that examines the association between diabetes and different types of infection. Strengths of this systematic review include a comprehensive search strategy, inclusion of patient important outcomes, inclusion of studies with an explicit temporal relationship whereby diabetes preceeded the infection, and a rigorous quality assessment of included studies. This review included a large number of observational studies with both general and specific populations resulting in a broad representation of the population at-risk, and may better reflect better the nature and frequency of unintended effects experienced in clinical practice.

Despite these positive aspects, some limitations must be noted here. Observational studies are methodologically challenging, difficult to interpret and susceptible to several types of bias and confounding, mainly selection bias (referral bias, volunteer bias, loss to follow up bias) and information bias (exposure ascertainment bias, outcome ascertainment bias). Some epidemiological studies of diabetes have used self-reported assessments of prevalent diabetes. Self reported measures of diabetes status have been previously shown to be over 99% specific and 66% sensitive compared with medical records (52). In addition, misclassification of patients with diabetes who did not know that they had the disease to the referent group of participants without diabetes is highly likely given that 46% of the estimated prevalence of diabetes is in people with undiagnosed disease (1).

Another important limitation to understand is that some studies did not have diabetes and/or infection as the primary exposure/outcome. None the less, the required information

needed to conduct our analysis was present in these studies.

The limitation of having a single reviewer assessing the quality of each study should be recognized. However, 2 reviewers besides the main reviewer verified data extraction.

The heterogeneity found in this review was somewhat high. Heterogeneity was explored across our results by grouping infections in several subtypes, and further grouping those into subcategories. This grouping managed to decrease heterogeneity of our results.

Finally, only studies in English in the review were included as translation of texts was not feasibile. However, our review managed to obtain over 340 studies. Although non-English studies were not included, others have shown excluding non-English studies appeared not to influence the results substantially (53,54).

2.5 Conclusion

In conclusion, our systematic review and meta-analysis quantified the association between diabetes and several types of common infections. The strength and significance of the association varied according to the type of infection studied. The knowledge generated from this review will help further inform physicians and researchers toward the best summary of evidence. However, more research is needed to explore the effects patient characteristics such as classificaiton of diabetes, BMI, and glycemic control may have on the risk of these types of infections.

References:

1) International diabetes federation atlas sixth edition: http://www.idf.org/diabetesatlas/update-2014

2) Morrish N, Wang S, Stevens L, et al. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia* 2001;44:S14-21.

3) Shah BR, Hux JE. Quantifying the risk of infectious diseases for people with diabetes. *Diabetes Care* 2003;26:510-513.

4) Calvet HM, Yoshikawa TT. Infections in diabetes. *Infect Dis Clin North Am* 2001;15:407-421.

5) Pozzilli P, Leslie RDG. Infections and diabetes: mechanisms and prospects for prevention. *Diabet Med* 1994;11:935-941.

6) Valerius NH, Eff C, Hansen NE, et al. Neutrophil and lymphocyte function in patients with diabetes mellitus. *Acta Med Scand* 1982;211:463-467.

7) Delamaire M, Maugendre D, Moreno M, et al. Impaired leucocyte functions in diabetic patients. *Diabet Med* 1997;14:29-34.

8) Balasoiu D, van Kessel KC, van Kats-Renaud HJ, et al. Granulocyte function in women with diabetes and asymptomatic bacteriuria. *Diabetes Care* 1997;20:392-395.

9) Knapp S. Diabetes and infection. Is there a link? A mini review. *Gerontology* 2013;59:99-104.

10) Seshasai S, Kaptoge S, Thomson A et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 2011;364;829-841.

11) Bertoni A, Saydah S, Bancati F. Diabetes and the risk of infection-related mortality in the U.S. *Diabetes Care* 2001;24:1044-1049.

12) Kaplan V, Angus D, Grifiin M, et al. Hospitalization community-acquired pneumonia in the elderly. *Am J Respir Crit Care Med* 2002;165:766-772.

13) Stegenga M, Vinvent JL, Vail G et al. Diabetes does not alter mortality or hemostatic and inflammatory responses in patients with severe sepsis. *Crit Care Med* 2010;38;539-545.

14) Moher D, Lebarati A, Tetzlaf J et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62;1006-1012.

15) Stroup D, Berlin J, Morton S et al. Meta-analysis of observational studies in epidemiology, a proposal for reporting. *JAMA* 2000;283:2008-2012.

16) Kovarik, J, Siegrist, CA. Immunity in early life. *Immunol Today* 1998;19:150-152.

17) Duramad P, Tager I, Holland N. Cytokines and other immunological biomarkers in children's environmental health studies. *Toxicol Lett* 2007;172:48-59.

18) The Newcastle-Ottawa Quality Assessment Scale (NOS): http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

19) Peleg A, Weerarathna T, McCarthy J et al. Common infections in diabetes: pathogenesis, management and relationship to glycemic control. *Diabetes Metab Res Rev* 2007;23:3-13.

20) Gupta S, Koirala J, Khardori R et al. Infections in diabetes mellitus and hyperglycemia. *Infect Dis Clin North Am* 2007;21:617-638.

21) Shilling A, Raphael J. Diabetes, hyperglycemia, and infections. *Best Pract Res Clin Anesthesiol* 2008;22:519-535.

22) Factor S, Levine O, Schwartz B et al. Invasive group A Streptococcal disease: risk factors for adults. *Emerg Infect Dis* 2003;9:970-977.

23) Davies H, McGeer A, Schwartz B et al. Invasive group A Streptococcal infections in Ontario, Canada. *N Engl J Med* 1996;335:547-554.

24) Ahluwalia A, Sood A, Sood A et al. Nasal Colonization with Staphylococcus aureus in patients with diabetes mellitus. *Diabet Med* 2000;17:487-491.

25) Boyko E, Lipsky B, Sandoval R et al. NIDDM and prevalence of nasal Staphylococcus aureus colonization. San Luis Valley Diabetes Study. *Diabetes care* 1989;12;189-192.

26) Loe H. Periodontal disease. The sixth complication of diabetes mellitus. *Diabetes Care* 1993;16:329-334.

27) Grossi SG, Skrepcinski FB, DeCaro T, et al. Treatment of periodontal disease in diabetics reduced glycated hemoglobin. *J Periodontol* 1997;68:713-719.

28) Tervonen T, Karjalainen K. Periodontal disease related to diabetic status. A pilot study of the response to periodontal therapy in type 1 diabetes. *J Clin Periodontol* 1997;24:505-510.

29) Porter J, Baur G, Taylor L. Lower-extremity imputations for ischemia. *Arch Surg* 1981;116:89-92.

30) Gibran N, Jang Y-C, Isik F et al. Diminished neuropeptide levels contribute to the impaired cutaneous healing response associated with diabetes mellitus. *J Surg Res* 2002;108:122-128.

31) Carr M. Diabetes mellitus a hypercoagulable state. *J Diabetes Complications* 2001;15:44-54.

32) Williams S, Goldfine A, Timimi F et al. Acute hyperglycemia attenuates endothelium dependent vasodilation in humans in vivo. *Circulation* 1998;97:1695-1701.

33) Ammar R, Gutterman D, Brooks L et al. Free radicals mediate endothelial dysfunction of coronary arterioles in diabetes. *Cardiovasc Res* 2000;47:595-601.

34) Incalzi R, Fuso L, Giordano A et al. Neuroadrenergic Denervation of the lung in type 1 diabetes mellitus complicated by autonomic neuropathy. *Chest* 2002;121:443-451.

35) American Diabetes Association. Initial evaluation and diabetes management planning. Sec. 3. In Standards of Medical
Care in Diabetes 2015. Diabetes Care 2015;38(Suppl.1):S17-S19.

36) Su V, Lui CJ, Wang HK et al. Sleep apnea and risk of pneumonia: a nationwide population-based study. *CMAJ* 2014;186: 415-421.

37) Farina J, Furio V, Fernandez-Acenero et al. Nodular fibrosis of the lung in diabetes mellitus. *Virchows Arch* 1995;427:61-63.

38) Watanabe K, Senju S, Toyoshima H et al. Thickness of the basement membrane of bronchial epithelial cells in lung diseases as determined by transbronchial biopsy. *Respir Med* 1997;91:406-410.

39) Sandler M, Bunn A, Stewart R. Cross-section study of pulmonary function in patients with insulin-dependent diabetes mellitus. *Am Rev Respir Dis* 1987;135:223-229.

40) Hsia C, Raskin P. The diabetic lung: relevance of alveolar microangiopathy for the use of inhaled insulin. *Am J Med* 2005;118:205-211.

41) Rosenstock J, Friberg T, Raskin P. Effect of glycemic control on microvascular complications in patients with type 1 diabetes mellitus. *Am J Med* 1986;81:1012-1018.

42) Reichard P, Berglund B, Britz A et al. Intensified conventional insulin treatment retards the microvascular complications of insulin-dependent diabetes mellitus (IDDM): the Stockholm diabetes intervention study (SDIS) after 5 years. *J Intern Med* 1991;230:101-108.

43) Rayfield EJ, Ault MJ, Keusch GT et al. Infection and diabetes: the case for glucose control. *Am J Med* 1982; 72:439–450.

44) Patterson JE, Andriole VT. Bacterial urinary tract infections in diabetes mellitus. *Infect Dis Clin North Am* 1997;11:735-750.

45) Hosking DJ, Bennett T, Hampton JR. Diabetic autonomic neuropathy. *Diabetes Care* 1978;27:1043-1054.

46) Wilson RM, Tomlinson DR, Reeves WG. Neutrophil sorbitol production impairs oxidative killing in diabetes. *Diabet Med* 1987;4:37-40.

47) Hostetter MK. Handicaps to host defense. Effects of hyperglycemia on C3 and Candida albicans. *Diabetes* 1990;39:271-2755.

48) Segal E, Soroka A, Schechter A. Correlative relationship between adherence of Candida albicans to human vaginal epithelial cells in vitro and candidal vaginitis. *Sabouraudia* 1984;22:191-200.

49) Ellenberg M, Weber H. The incipient asymptomatic diabetic bladder. *Diabetes* 1967; 16:331-335.

50) Finney LS, Finney MO, Gonzalez-Campoy JM. What the mouth has to say about diabetes. Careful examinations can avert serious complications. *Postgrad Med* 1997;102:117-126.

51) Seppala B, Sorsa T, Ainamo J. Morphometric analysis of cellular and vascular changes in gingival connective tissue in long-term insulin-dependent diabetes. *J Periodontol* 1997;68:1237-1245.

52) Okura Y, Urban LH, Mahoney DW et al. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. *J Clin Epidemiol* 2004;57:1096-103.

53) Morrison A, Moulton K, Clark M et al. English language restriction when conducting systematic reviews-based meta-analyses: systematic review of published studies. Canadian Agency for Drugs and Technologies in Health (CADTH) 2009.

54) Moher D, Pham B, Klassen T et al. What contributions do languages other than English make on results of meta-analyses. *J Clin Epidemiol* 2000;53:964-972.

Figure 1: Study Selection Process

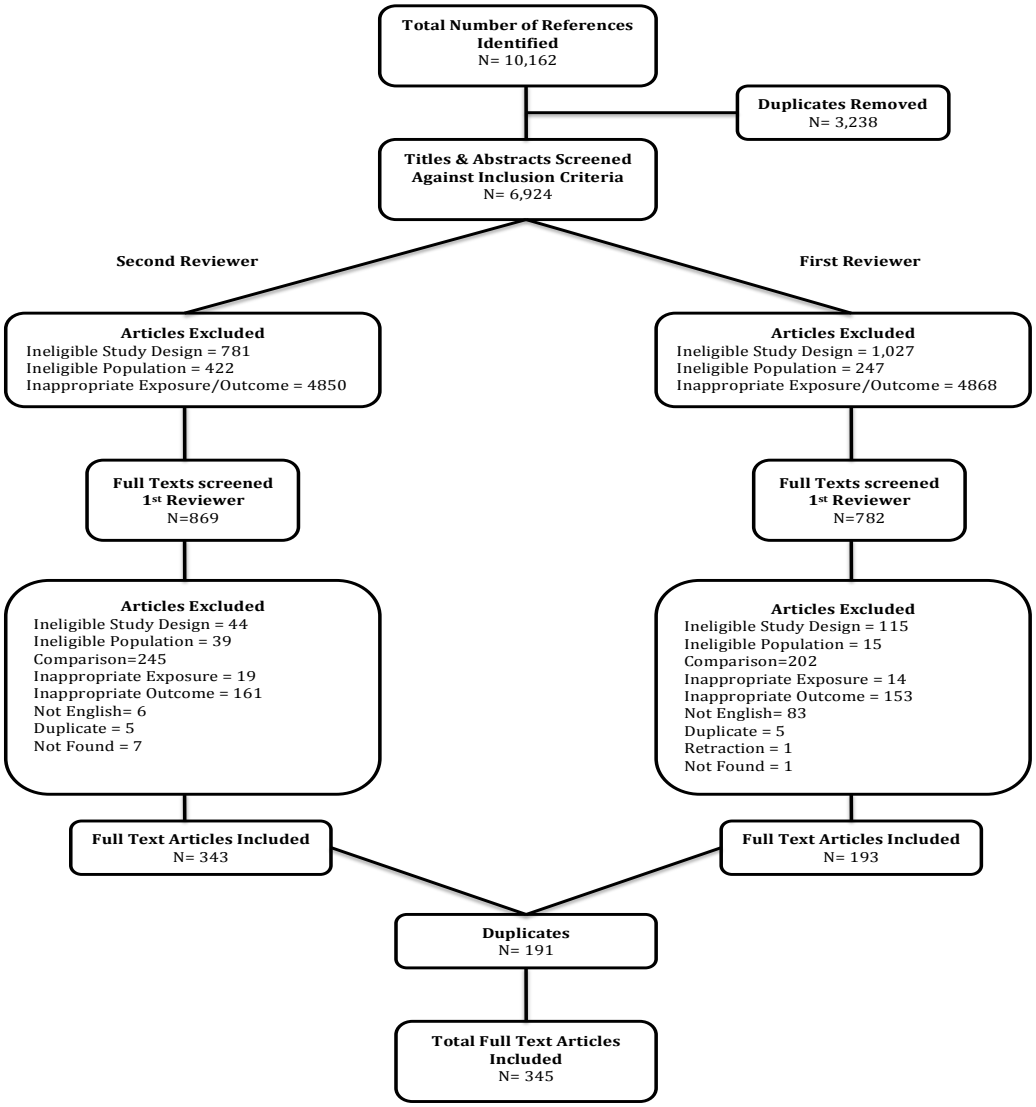


Table 1: Study Characteristics of Observational Studies Evaluating the Association Between Diabetes and Infection

CHARACTERISTICS	COHORT STUDIES N=243	CASE-CONTROL STUDIES N=102	Total N=345
Year of Study, n(%)			
<1990	4 (1.6)	1 (0.98)	5(1.4)
1990-1994	8 (3.3)	4 (3.9)	12(3.5)
1995-1999	8 (3.3)	12 (11.8)	20(5.8)
2000-2004	33 (13.6)	20 (19.6)	53(15.4)
2005-2009	64 (26.3)	34 (33.3)	98(96.1)
2010-2014	126 (51.8)	31 (30.4)	157(45.5)
Mean Age (range), no. of Studies	61.9 (28-80), n=172	55.9 (26-76), n=54	61 (26-80), n=226
Sex N%, no. of Studies (n)			
Male	16,615,301 (48.2)	763,173 (52)	17,378,474 (48.3)

Female	17,852,673 (51.8), n=221	703,693 (48), n=82	18,556,366 (51.7), n=303
Mean Follow up (yrs), no. of Studies	4.4, n=70	N/A	4.4, n=70
Setting, n(%)			
Hospital	216 (88.9)	85 (83.3)	301 (87.2)
Clinic	18 (7.4)	11 (10.8)	29 (8.4)
Hospital & Clinic	8 (3.3)	5 (4.9)	13 (3.8)
Long term facilities	1 (0.4)	1(1)	2 (0.6)
Region, n(%)			
Europe	62 (25.5)	38 (37.2)	100 (29)
Asia	61 (25.1)	18 (17.6)	79 (22.9)
North America	111 (45.7)	44 (43)	155 (44.9)
South America	7 (2.9)	2 (2)	9 (2.6)
Africa	2 (0.8)	0 (0)	2 (0.6)
Population, n(%)			
General population	71 (29.2)	54 (53)	125 (36.2)

Cardiovascular Disease	72 (29.6)	18 (17.6)	90 (26.1)
Bone Disease	16 (6.6)	7 (6.9)	23 (6.7)
Kidney Disease	17 (7)	4 (3.9)	21 (6.1)
Malignancy	14 (5.8)	2 (2)	16 (4.6)
Gastrointestinal Disease	10 (4.1)	3 (2.9)	13 (3.8)
Spine Disease	10 (4.1)	2 (2)	12 (3.5)
Organ Transplant	7 (2.9)	4 (3.9)	11 (3.2)
Genitourinary Disease	8 (3.3)	1 (1)	9 (2.6)
Critically Ill	4 (1.6)	5 (4.9)	9 (2.6)
Pregnancy	4 (1.6)	0 (0)	4 (1.2)
Burn	3 (1.2)	0 (0)	3 (0.9)
Ophthalmologic	0 (0)	2 (2)	2 (0.6)
Respiratory Disease	2 (0.8)	0 (0)	2 (0.6)
Obesity	1 (0.4)	0 (0)	1 (0.3)
Breast Reconstruction	3 (1.2)	0 (0)	3 (0.9)
Autoimmune Disease	1(0.4)	0 (0)	1 (0.3)
Outcome, n(%)			
Unspecified Infections	36 (14.8)	12 (11.8)	48 (13.9)
Skin and Soft Tissue Infections	114 (46.9)	36 (35.3)	150 (43.5)
Respiratory Tract Infections	17 (7)	14 (13.7)	31 (9)
Genitourinary Infections	18 (7.4)	11 (10.8)	29 (8.4)

Gastrointestinal Infections	1 (0.4)	6 (5.9)	7 (2)
Head & Neck Infections	1 (0.4)	2 (2)	3 (0.9)
Blood Infections	16 (6.6)	10 (9.8)	26 (7.5)
Viral Infections	7 (2.9)	4 (3.9)	11 (3.2)
Bone Infections	2 (0.8)	2 (2)	4 (1.2)
Other Infections	1 (0.4)	4 (3.9)	5 (1.4)
Multiple Infections	30 (12.3)	1 (1)	31 (9)
Newcastle-Ottawa Scale (NOS), n(%)			
Weak (score 0-3)	0 (0)	0 (0)	0 (0)
Moderate (score 4-6)	197 (81)	82 (80.4)	279 (80.9)
Strong (score 7-9)	46 (19)	20 (19.6)	66 (19.1)

Table 2: Reported Infections in Included Studies

Type of Infection	Study Reported Infections
Skin and Soft Tissue	Surgical site=148 Unspecified=15 Peritonitis=7 Burn=3 Cellulitis=2 Erysipelas=2 Scabies=1
Respiratory	Pneumonia=29 Tuberculosis=19 Unspecified=5
Genitourinary	Urinary=46: Unspecified=34 Bacteruria=3 Cystitis=3 Pyelonephritis=3 Prostatitis=1 Urethritis=1

	Renal Abscess=1 Genital=10: Unspecified=4 Balanitis=1 Vaginitis=2 Chorioamenionitis=1 Endometritis=1 Vaginal Candidiasis=1
Gastrointestinal	Clostridium Difficile Associated Diarrhea=3 Liver Abscess=2 Diarrhea=1 Gastroenteritis=1 Enteric=1 Salmonellosis=1 Biliary tree=1 Unspecified=1
Head and Neck	Endophalmitis=3 Otitis Externa=2 Otitis Media=1

	Mastoditis=1
Musculoskeletal	Osteomyelitis=5 Joint=3
Viral	Herpes Zoster=8 Herpes Simplex=2 Influenza=2 Hepatitis=2 Human Papilloma=1 Human Immunodeficiency Disease=1 Unspecified=1
Other	Zygomycosis=3 Cardiovascular=2 Unspecified=2

Figure 2 (A): Cohort Studies Crude Results Odds Ratio (OR) by Infection Type:

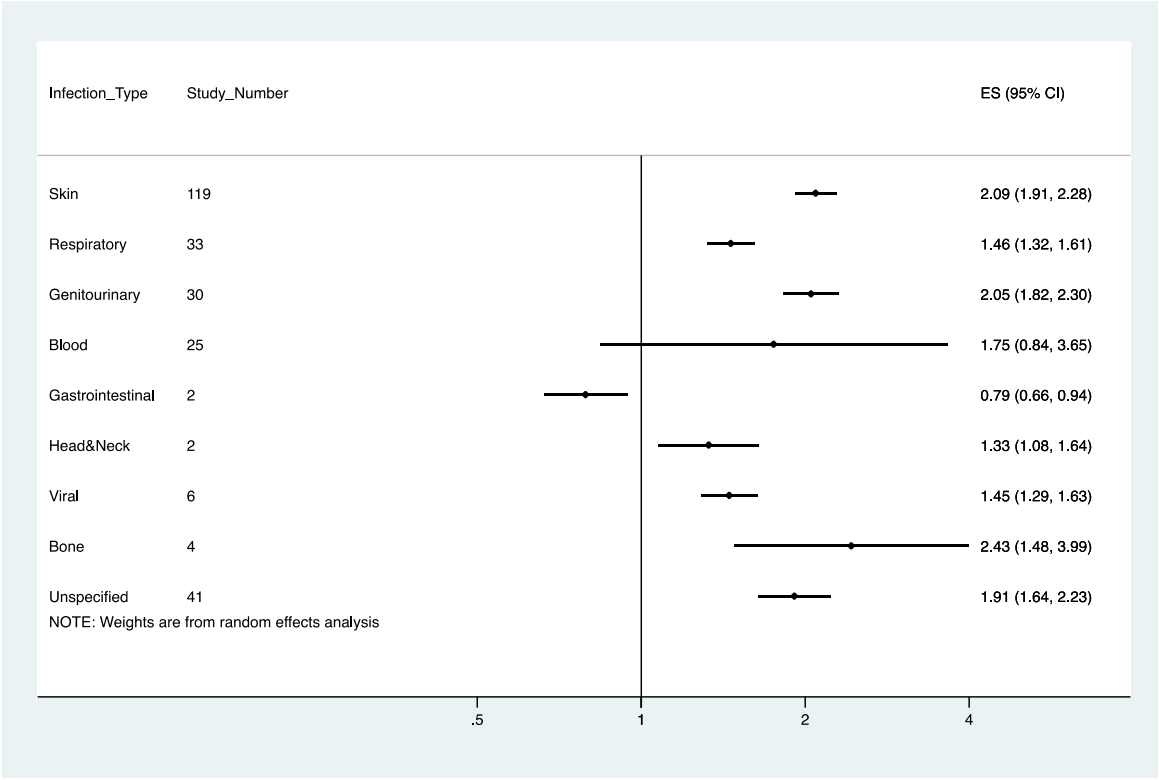


Figure 2 (B): Cohort Studies Adjusted Odds Ratio (OR) Results by Infection Type:

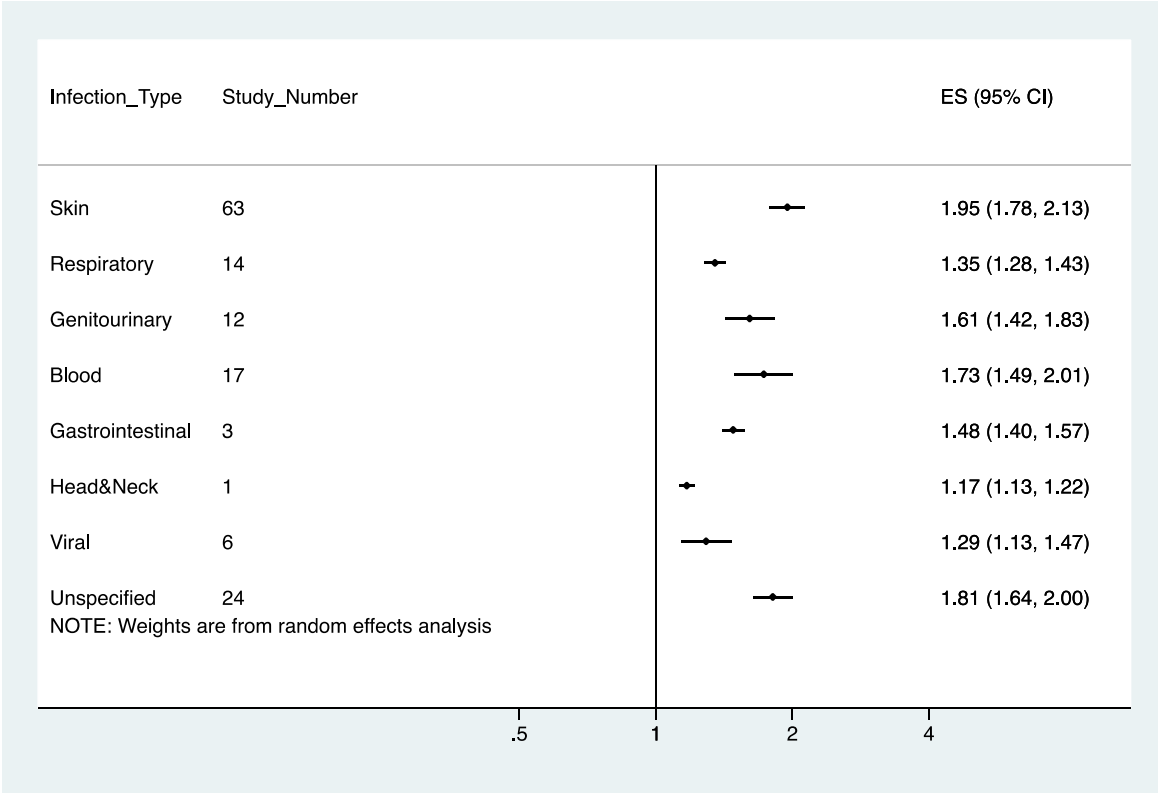


Figure 2 (C): Case-Control Studies Crude Odds Ratio (OR) Results by Infection Type:

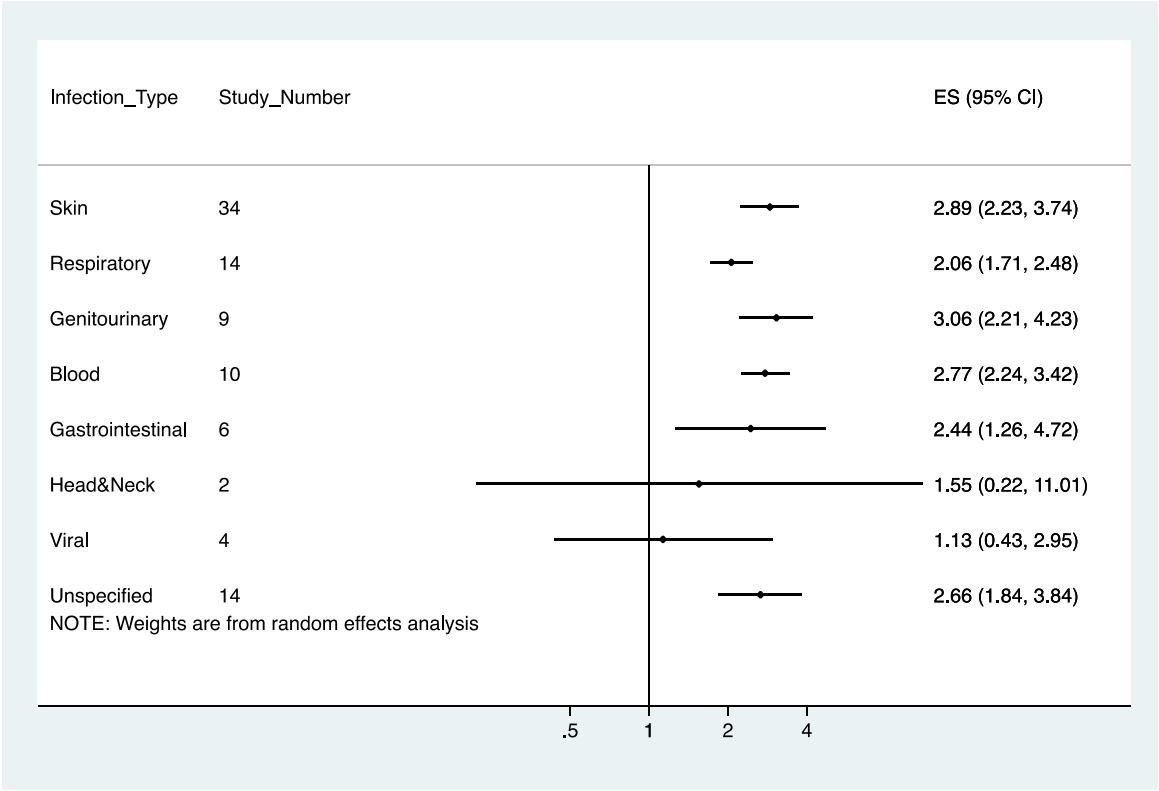


Figure 2 (D): Case-Control Studies Adjusted Odds Ratio (OR) Results by Infection Type:

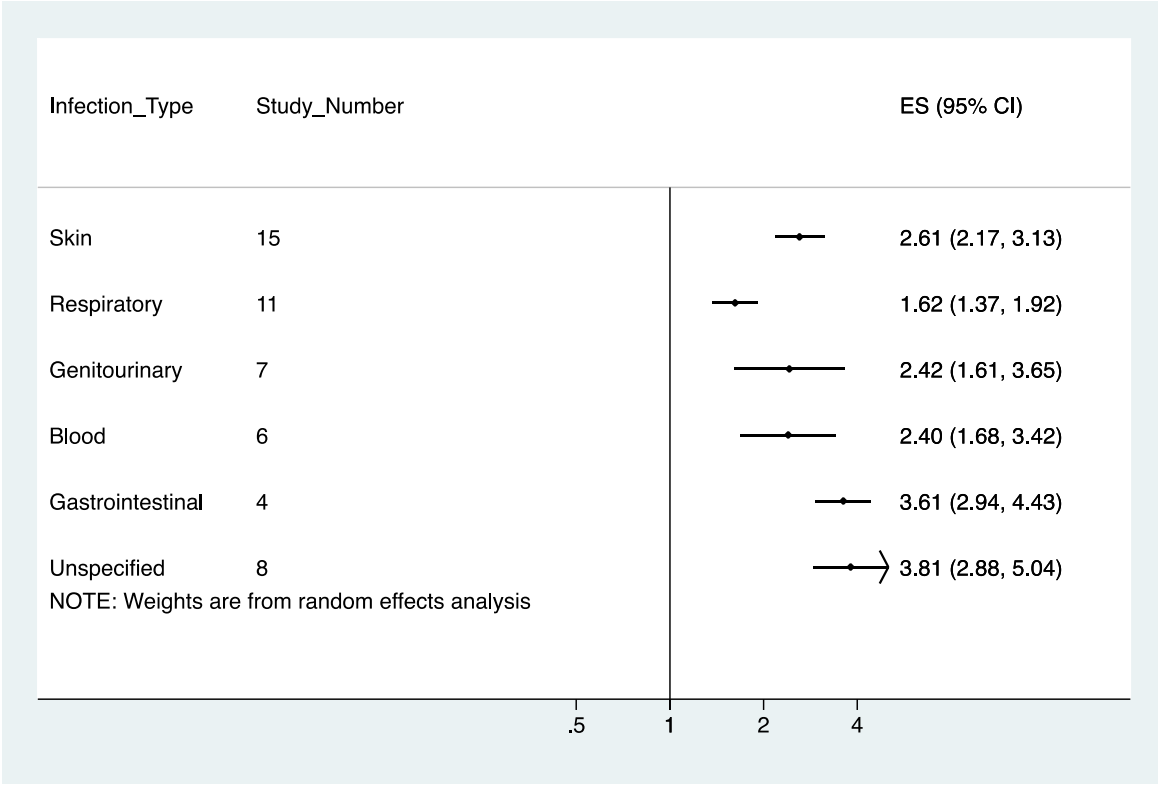


Table 3: Skin and Soft Tissue Infections:

Subgroup	Study Design	No of Studies	Crude OR (95% CI)	I^2	No of Studies	Adjusted OR (95% CI)	I^2
Surgical site Infections	Cohort	105	2.09 (1.90-2.31)	91.4%	56	2.02 (1.82-2.24)	86.4%
	Case-Control	30	3.12 (2.37-4.11)	0%	14	2.62 (2.15-3.20)	0%
General Surgery	Cohort	17	1.66 (1.19-2.31)	94.7%	6	1.65 (1.20–2.28)	72.2%
	Case-Control	5	4.28 (1.14-16.12)	94.9%	2	2.11 (1.37–3.26)	0%
Cardiovascular Surgery	Cohort	44	2.20 (1.93-2.50)	59.9%	29	2.08 (1.85–2.35)	75.3%
	Case-Control	15	2.71 (2.20-3.33)	18.2%	7	2.76 (2.13–3.57)	0%
Orthopedic Surgery	Cohort	16	2.50 (1.90-3.30)	73.0%	8	1.96 (1.16–3.34)	74.9%
	Case-Control	4	2.45 (1.66-3.62)	0%	2	2.32 (1.37–3.94)	0%
Spine Surgery	Cohort	12	3.03 (1.80-5.12)	87.0%	6	2.14 (1.44–3.18)	25.9%
	Case-Control	5	4.24 (2.57-7.00)	0%	3	4.15 (1.99–8.66)	I^2=0%
Skin Surgery	Cohort	3	1.65 (0.88-3.06)	51.3%	3	1.51 (1.07–2.13)	43.3%

Maxillo-Facial Surgery	Cohort	2	2.95 (1.28-6.83)	83.6%	2	4.01 (1.69–9.54)	84.0%
Gynecological Surgery	Cohort	2	1.28 (0.32-5.13)	85.4%		no studies identified	
Plastic surgery	Cohort	6	1.92 (1.18-3.13)	0%		no studies identified	
Ear Nose Throat surgery	Cohort	3	2.07 (0.80-5.38)	48%		no studies identified	
	Case-Control	6	2.30 (1.70-3.12)	96.3%	6	1.66 (1.30-2.12)	85.1%
Other Skin and Soft Tissue Infections	Cohort	14	2.22 (1.67-2.95)	91.8%	7	1.83 (1.73-1.94)	53%
	Case-Control	4	1.69 (1.05-2.72)	55.8%		no studies identified	
Peritonitis	Cohort	4	3.66 (1.18-11.36),	93.3%	2	1.37 (0.95-1.97)	0%
Erysipelas	Case-Control	2	1.24 (0.87-1.75)	0%		no studies identified	

Table 4: Respiratory Tract Infections:

Subgroup	**Study Design**	**No of Studies**	**Crude OR (95% CI)**	**I^2**	**No of Studies**	**Adjusted OR (95% CI)**	**I^2**
Upper Respiratory Tract Infections	Cohort		no studies identified		1	1.18 (1.17-1.19)	0%
Lower Respiratory Tract Infections	Cohort	30	1.45 (1.32-1.61)	83.4%	14	1.35 (1.28-1.43)	78.7%
	Case-Control	12	2.06 (1.71-2.50)	95.3%	10	1.60 (1.35-1.89)	86.7%
Tuberculosis	Cohort	10	1.35 (1.18-1.56)	84.3%	9	1.31 (1.20–1.42)	60%
	Case-Control	7	2.42 (1.86-3.15)	95.0%	6	1.86 (1.44-2.41)	87.1%
Pneumonia	Cohort	19	1.53 (1.29-1.83)	82.8%	6	1.43 (1.36-1.51)	70.1%
	Case-Control	6	1.61 (1.27-2.04)	78.9%	4	1.26 (1.21-1.31)	0%
Unspecified Respiratory Tract Infections	Cohort	2	1.50 (0.56-4.05)	85.7%		no studies identified	

Table 5: Genitourinary Infections:

Subgroup	Study Design	No of Studies	Crude OR (95% CI)	I^2	No of Studies	Adjusted OR (95% CI)	I^2
Genital Infections	Cohort	5	2.06 (1.20-3.52)	84.3%	4	1.41 (1.14-1.74)	98.6%
Male	Cohort	2	3.47 (2.93-4.11)	0%	2	1.28 (1.01-1.64)	98.8%
Female	Cohort	3	1.57 (0.60-4.14)	89.6%	3	1.49 (1.17-1.91)	92.6%
Urinary Infections	Cohort	25	2.00 (1.79-2.23)	90.9%	11	1.75 (1.52-2.00)	99.0%
	Case-Control	9	3.06 (2.21-4.23)	81.2%	7	2.59 (1.60-4.17)	86.0%
Urinary Tract Infections	Cohort	23	1.99 (1.77-2.24)	91.1%	9	1.49 (1.30-1.72)	98.8%
	Case-Control	8	2.98 (2.12-4.19)	82.7%	6	2.45 (1.48-4.05)	87.4%
Renal Infections	Cohort		no studies identified		2	2.40 (1.55-3.71)	98.4%
Bacteriuria	Cohort	3	1.94 (1.77-2.13)	0%	2	1.81 (1.66-1.97)	0%
Unspecified	Cohort	2	1.55 (1.11-2.18)	0%		no studies	

Genitourinary Infections						identified	

Table 6: Blood Infections:

Subgroup	**Study Design**	**No of Studies**	**Crude OR (95% CI)**	**I^2**	**No of Studies**	**Adjusted OR (95% CI)**	**I^2**
End Stage Renal Disease	Cohort	5	1.14 (0.24-5.44)	99.6%	5	1.71 (1.37-2.13)	80.7%
Cardiovascular Disease	Cohort	7	1.61 (1.46-1.78)	0%	4	1.36 (1.30-1.43)	0%
Critical Care Patients	Cohort	2	2.16 (1.48-3.17)	0%	2	1.92 (1.35-2.75)	0%
	Case-Control	3	4.10 (2.26-7.43)	0%	2	3.29 (1.42-7.62)	0%

Table 7: Viral Infections:

Subgroup	Study Design	No of Studies	Crude OR (95% CI)	I^2	No of Studies	Adjusted OR (95% CI)	I^2
Herpes Zoster (shingles)	Cohort	2	1.39 (1.34-1.43)	0%	4	1.42 (1.20-1.69)	97.2%
	Case-Control	3	0.96 (0.32-2.90)	99.9%		no studies identified	

Table 8: Head and Neck Infections:

Subgroup	Study Design	No of Studies	Crude OR (95% CI)	I^2	No of Studies	Adjusted OR (95% CI)	I^2
Endophalmitis	Case-Control	2	1.55 (0.22-11.10)	80.7%		no studies identified	

Table 9: Gastrointestinal Infections:

Subgroup	Study Design	No of Studies	Crude OR (95% CI)	I^2	No of Studies	Adjusted OR (95% CI)	I^2
Clostridium Difficile Associated Disease (CDAD)	Case-Control	3	1.66 (0.72-3.86)	86.6%		no studies identified	

Table 10: Unspecified Infections:

Subgroup	Study Design	No of Studies	Crude OR (95% CI)	I^2	No of Studies	Adjusted OR (95% CI)	I^2
Cardiovascular Disease	Cohort	15	1.92 (1.50-2.46)	92.6%	7	1.83 (1.40-2.41)	82.5%
Bone Disease	Cohort	4	1.69 (0.82-3.48)	83.2%	3	1.37 (0.93-2.00)	46.7%
End Stage Renal Disease	Cohort	2	1.91 (1.35-2.68)	0%	1	1.36 (1.21-1.52)	88.3%
Organ Transplant	Cohort	2	5.42 (2.10-14.02)	66.4%		no studies identified	

	Case-Control		no studies identified		2	6.90 (3.02-15.78)	0%
Cancer	Cohort	4	2.23 (1.23-4.04)	69.2%		no studies identified	
Critical Care Patients	Case-Control	2	2.30 (0.37-14.23)	79.2%		no studies identified	

Chapter 3:

Diabetes and the Occurrence of Infection in Primary Care: A Matched Cohort Study

3.1 Introduction

In 2014, the International Diabetes Federation estimated that over 385 million people were diagnosed with diabetes globally, and this number is expected to increase to more than 595 million people in the year 2035 (1). In Canada, the estimated prevelance of people with diabetes was 6.7% of the total population in 2014 (2). By 2019, that number is expected to grow to 3.7 million (2). Although diabetes is associated with chronic complications of the microvasculature and microvasculature (3) other non-traditional complications including connective tissues disorders and impaired immunity are becoming increasingly recognized (4).

Infection is a relatively frequent reason for hospitalization or a physician office visit in people with diabetes. In fact, 40% of all people with diabetes have at least one physician

claim, and nearly 6% have at least one hospitalization for an infectious disease each year (5). Moreover, infectious disease contributes to substantial financial costs in people with diabetes. A study that was done in North California estimated the proportion of costs spent on treating the complications associated with all types of diabetes across different age groups (<19->65 years). Costs were categorized into inpatient care, outpatient care (primary care, speciality, emergency, non-physician care), pharmacy and out of plan refferals and claims. They found that there was almost an excess cost of 5 million dollars spent due to infections over one year for people with diabetes compared to people without diabetes (6).

People with diabetes may be more susceptible to infectious disease than those without diabetes. Immunologic research has demonstrated several defects in host immune defense mechanisms in people with diabetes. Phagocytic capabilities of neutrophils are adversely affected by hyperglycemia, including impaired migration, phagocytosis, intracellular killing, and chemotaxis (7,8). Besides generalized impairments of immunity, macrovascular disease and microvascular dysfunction may result in compromised local circulation leading to delayed response to infection and impaired wound healing (9). Unawareness of lower extremity trauma due to sensory neuropathy may result in inadequate attention to minor wounds and subsequent increased infection risk. Incomplete bladder emptying due to autonomic neuropathy permits urinary colonization by microorganisms, where high glucose concentration in the urine promotes the growth of some microorganisms (10).

Given the paucity of studies that have explored the relationship between diabetes and the susceptibility to different types of infections in a primary care setting (5,11), it was sought to conduct a matched cohort study to measure the relationship between diabetes and susceptibility to common infections in primary care.

3.2 Methods

3.3.1 Study Design:

A matched cohort study using the Newfoundland and Labrador (NL) Canadian Primary Care Sentinel Surveillance Network (CPCSSN) database was conducted.

3.2.2 Data Source:

CPCSSN is Canada's first multi-disease electronic medical record (EMR)-based surveillance system (12). Participating community-based primary care clinics across Canada contribute information to CPCSSN on five chronic and mental health conditions (i.e., diabetes, chronic obstructive pulmonary disease, depression, hypertension, osteoarthritis) and three neurological conditions (i.e., alzheimers and related dementias, epilepsy, and parkinsons) (13). In NL, the Atlantic Practice Based Research Network

(APBRN) is a group of primary care providers that contribute information to CPCSSN. For this study, de-identified data was used from the NL-CPCSSN database. In NL there are almost 500 family physicians. Approximately 10% of those physicians contribute data to the CPCSSN dataset, representing around 45,000 patients by the end of 2013. Information available includes patient demographics (age, sex, socioeconomic status), health behaviors (smoking & alcohol intake), physiological data (e.g., blood pressure, body mass index) and laboratory data (e.g., cholesterol, HbA1c, fasting glucose, renal function), physician diagnoses, prescription medications, and vaccination. The sensitivity and specificity of diagnostic algorithms for diabetes in the database was very high with a 100% and 99%, respectively (14). The CPCSSN database has been used for several epidemiologic studies (15-18).

3.2.3 Inclusion Criteria:

All patients who had diabetes and were 18 years and older between January 1, 2008 and March 31, 2013 were included. Diabetes was defined using the CPCSSN validated algorithm based on International Classification of Disease (ICD-9) billing codes, problem lists, medications, and laboratory values (13) (Appendix 3.A). January 1, 2008 or the date a person was diagnosed with diabetes after January 1, 2008 was considered a persons cohort entry or index date. Controls were randomly selected from patients without diabetes that were alive on the date their matched patient with diabetes entered the cohort. Up to 8 controls were selected for each patient with diabetes and matched on index year.

3.2.4 Exclusion Criteria:

Patients with a diagnosis of malignancy; HIV infection; organ transplantation; use of immunosuppressive medications, ≥ 10 corticosteroids or antibiotics prescriptions in the year prior to the study cohort entry date were excluded from the study (11) (See Appendix 3.B for diagnostic codes).

3.2.5 Outcome Measures:

The primary outcome was the occurrence of one or more primary care physician visits for any infectious disease during follow-up. The CPCSSN dataset use ICD-9 codes for all diagnoses (encounter diagnosis, health condition, and family history). CPCSSN does not have a limit on ICD9 codes. Infection-related visits to the primary care physician were identified using ICD-9 codes, problem lists, and medications (Appendix 3.A).

Secondary outcomes included the number of head and neck infections, respiratory tract infections, gastrointestinal infections, genitourinary tract infections, skin and soft tissue infections, musculoskeletal infections and viral infections (See Appendix 3.A for diagnostic codes).

Patients were followed from their index date until March 31, 2014. Given multiple episodes of infection occurred throughout follow-up, a new episode was defined if a

patient was free of signs or symptoms for a 30-day period. A second episode occurring >30 days after the initial episode was considered to be a recurrence (Appendix 3.D).

3.2.6 Statistical Analysis:

Baseline characteristics among patients with new or existing diabetes were compared to those without diabetes using chi-square tests for categorical variables and t-tests for continuous variables. Crude and adjusted OR's were measured using univariate and multivariable conditional logistic regression analyses to determine if diabetes was independently associated with the occurrence of the primary and secondary outcomes. Potential confounding variables included in our statistical model were defined based on biological rationale, clinical experience, those available within the CPCSSN, and those used in other studies evaluating diabetes and infection. Specifically, adjustement was done for demographics (age, sex), the presence of comorbidities (microvascular disease [nephropathy, neuropathy, retinopathy], macrovascular disease [coronary artery disease, peripheral and cerebral vascular disease], heart failure, respiratory disease, dyslipidemia, fatty liver disease, and obesity), medications (acid inhibitors, respiratory system medications, anti-lipids and vaccines), lab tests, doctor visits, referral to specialists and number of infections in the year prior to enrollment in our statistical models (Appendix 3.D). Testing for presence of a multiplicative interaction was done using the likelihood ratio test between diabetes and age, sex, microvascular and macrovascular disease.

To test the robustness of our primary analysis sensitivity analyses was conducted. First,

restriction of follow-up period to 1 year was done and repeated the analyses for both the primary and secondary outcomes. Second, the analysis was repeated for the primary outcome evaluating 1 or more, 2 or more, and 3 or more infections. Third, given the high number of infection recurrences throughout follow-up, fixed effects conditional poisson regression model was used to quantify the association between diabetes and the number of infections, whereby adjusted incidence rate ratios were calculated. All analyses was conducted using Stata 12/MP with a p-value of < 0.05 considered statistically significant.

3.3 Results

A total of 1,779 patients who had diabetes and 11,066 patients without diabetes were followed for an average of 4.2 years. The average age of the total population was 45.1(SD 16.4) years and the majority were females (59%). Patients with diabetes were on average older, underwent more laboratory tests in the year prior to study entry, were more likely to receive vaccines, acid-suppressing medications and lipid-lowering medications, and were more likely to have existing macrovascular or microvascular disease at study entry compared to controls. However, number of infections and recurrences before 1-year entry to the study was higher in patients with no diabetes, but both groups were similar with regards to number of doctor visits on average (Table 1). Most patients with diabetes were treated with metformin constituting 60.5% of the group, while 22% were on insulin.

The proportion of patients with diabetes who had one or more primary care visits for an infection was similar to patients without diabetes (57% vs. 58%). Proportions were also comparable between groups within a 1-year follow-up period (33% vs. 32%) (**Table 2**). The rate of infections per 100 person-years (PYs) was similar between patients with diabetes and patients without (42.7 per 100PYs vs. 42.5 per 100PYs) (**Table 3**). Tables 2 and 3 display the proportions and rates for specific types of infections. Respiratory tract infections were the most common infections reported.

After controlling for potential confounding, patients with diabetes had an increased odds of any infection compared to patients without diabetes (adjusted OR=1.21, 95%CI 1.07-1.37, P value=0.002) (**Table 4**). There was no significant association between diabetes and head and neck infections (adjusted OR=1.10, 95%CI 0.87-1.39, P value=0.428). While the risk in patients with diabetes was increased in respiratory infections (adjusted OR=1.31, 95%CI 1.14-1.50, P value=<0.001), gastrointestinal infections (adjusted OR =1.41, 95%CI 1.13-1.75, P value=<0.001), genitourinary infections (adjusted OR=1.42, 95%CI 1.17-1.73, P value=<0.001), and finally skin and soft tissue infections (adjusted OR=1.65, 95%CI 1.36-2.01, P value=<0.001). There were no significant differences when examining musculoskeletal (adjusted OR=1.05, 95%CI 0.87-1.28, P value=0.606) or viral infections (adjusted OR=1.11, 95%CI 0.83-1.47, P value=0.485)

There was a significant interaction between diabetes and age for respiratory infections (likelihood ratio test for interaction p=<0.001) and viral infections (likelihood ratio test

for interaction p=0.006). A stronger association was shown between diabetes and respiratory infections (adjusted OR=1.24, 95%CI 1.08-1.42, P value=0.002) and viral infections (adjusted OR=1.48, 95%CI 1.07-2.06, P value=0.018) in patients ≥65; however, in patients <65 years there was a weak or no association (Respiratory infection: adjusted OR=1.07, 95%CI 0.91-1.25, P value=0.397; adjusted OR=1.15, 95%CI 0.86-1.53, P value=0.336).

Our findings were consistent when examining the odds of infections over a 1-year period (**Table 5**). Recurrence of any infection was also calculated in the study population for ≥1, ≥2 and ≥3 infections (Table 6). There was a consistent increase in the odds with number of recurrences. The odds of recurrences ≥2 infections was (adjusted OR=1.30, 95%CI 1.12-1.50, P value=<0.001), and recurrences ≥3 infections was (adjusted OR=1.51, 95%CI 1.27-1.79, P value=<0.001). In addition, through a fixed effects conditional poisson regression model, an increased incidence rate ratio (IRR) of any infection was found in patients with diabetes compared to those without diabetes (adjusted IRR=1.25, 95%CI 1.20-1.31, P value=<0.001).

3.4 Discussion

In the current study patients with diabetes have a 21% increased chance of developing a new infection compared to patients without diabetes in primary care practices over 4 years. The positive association between diabetes and the development of a community-acquired infection was observed within the first year of follow-up (37% relative odds increase). The strongest magnitude of association was found for skin and soft tissue infections (65% relative odds), followed by genitourinary (42% relative odds increase), gastrointestinal (41% relative odds increase), and respiratory infections (31% relative odds). A consistent, slightly stronger, measure of and association was observed in the one year follow up. However, no association was present for head and neck, musculoskeletal and viral infections. A gradient response was also present with the number of any infection and diabetes. Interestingly, we found that the number of infections and recurrences before 1-year entry to the study was higher in patients with no diabetes. Higher rates of infection in patients with no diabetes group here is likely due to the fact that they are on average younger than patients with diabetes (19).

Very few studies have explored the relationship between diabetes and the occurrence of general infections in a primary care setting (5,20-24). When comparing our results with other studies that examined this relationship in a primary care setting, they were consistent with most who have found increased rates of infections in patients with diabetes compared to patients without (5,20-23). For example, Shah and Hux examined the association between diabetes and different types of infections using administrative

databases from Ontario, Canada (5). They quantified the risk of infections in patients with diabetes. Despite the reliance on an administrative dateset and a short study duration (1 year), the authors found an increased risk of infectious disease in patients with diabetes, with an even higher risk ratio of infectious disease related hospitalization. Another cohort study done in Japan that examined risk factors for infection concluded that diabetes was one of the important risk factors. Using hospital records and community data the authors reported more than double the risk of infection in patients with diabetes compared to those without (21). The findings of this study may not be generalizable to primary care patients as the study population had autoimmune diseases. In addition important confounders that may affect the outcome, such as corticosteroid therapy, were not taken into consideration. A case-control study that conceded with our findings found more than double the risk of infection in patients with diabetes compared to patients without diabetes (22). Shortcomings of this study that should be noted are the small number of the study population included, and reliance on self-report of medical history and socioeconomic status.

In contrast, Lipsky et al studied risk factors for acquiring pneumococcal infections in a general medical clinic and found that diabetes was not a risk factors for developing pneumococcal infections (24). However, some limitations of the study should be noted. The authors do state that the study population was not ideal, presumably high risk, because they were elderly, from lower socioeconomic strata, and had several chronic medical problems. Moreover, because the study team relied on medical records, they may have missed cases of pneumococcal infections, and undetectable pneumococcal vaccinations may have occurred due to poor documentation .

Results of our secondary outcomes were consistent with other studies that looked at skin and soft tissue infections (5,11,25-32) with a magnitude of association ranging from [aOR=1.3-3.7], respiratory infections (5,11,29,33-43) [aOR=1.2-4.7], genitourinary infections [aOR=1.2-2.8] (5,11,44-50), and gastrointestinal infections (5,25,51) [aOR=1.3-1.5]. Despite shortcomings of these studies including non-generalizable populations (26,27,33,41,44,46,49,50), self reported symptoms (25,29), presence of misclassification bias (33,37,42,45,50) or selection bias (28) or reliance on hospital records (5,28-32,39,43), their results were consistent with the findings from this study.

There was no difference in the risk of head and neck, musculoskeletal, and viral infections in patients with diabetes and patients without, although few studies did find an increased risk of these types of infections (5,11,52-56). This might be due to the fact that there were a small number of infections in these categories compared to others above.

3.4.1 Strengths and Limitations:

This study has several limitations. First, patients with diabetes and control patients were different at baseline with regards to other risk factor (e.g., disease severity, presence of comorbidities, different medications and different dosages) that may have confounded the observed association between diabetes and infection. However, to minimize confounding adjustement was done for known differences between the comparison groups using multivariable analysis. Furthermore any differences in disease severity in patients with

diabetes which could not be ascertained due to the missingness of hemoglobuin A1C. Second, due to the fact that electronic medical records from routine clinical care were used to define the diagnosis of diabetes, the potential for misclassification of the diabetes (i.e., exposure) exists. Patients with a true diagnosis of diabetes may have been misclassified as not having the disease. Moreover, since over one-third of diabetes is undiagnosed in the community (57), the true number of patients with diabetes may have been underestimated. Alternatively, misclassification for our outcome, infection, may have also occurred. The ability to capture all patients with an infection and assessing some types infections occurrence in the general population setting is difficult. Some infections, such as viral, genital or other infections, are often treated by self-care, i.e., using products available over-the counter, symptomatic treatment, or no treatment at all. In addition, medical records from general practice were used to identify the occurrence of infections; it is possible that infections encountered in a hospital setting or treated at a specialist clinic may not be captured. Thus ascertaining such cases via clinical records may underestimate incidence. In addition, information was not available for vital status or hospitalizations which could have lead to not capturing patients who had an infection but were hospitalized without the knowledge of their primary care physician. Moreover, vitals can give a more of a clear picture of occurrence, worsening or improvement of an infection. Third, increased physician contact for patients with diabetes or differences in misclassification may have resulted in diagnosis bias. Physicians may have focused on and followed more closely, or treated patients with diabetes differently simply because of the misconception of patients with diabetes are more liable to infections (58). Fourth, comparison between different types of diabetes and the association of infection was not

investigated here. Type of diabetes is a possible effect modifier that could have affected the magnitude of measure of association. However, glycemic impairment is expected to be similar despite the different types of diabetes, and this does not seem to affect the etiology behind the occurrence of infection. Moreover, several studies that examined types of diabetes and infection found consistent results with regards to the presence of association (11,59,60). Fifth, although age was adjusted for in the model, residual confounding may still be present. Matching by age was impractical due to insufficient numbers. Finally using the CPCSSN dataset, is a rich source of data for primary care research, may have limited our generalizability. This dataset only includes physicians using electronic medical record, and this may differ from other physicians who do not use electronic medical records. Given these potential biases, the directionality depends on the type of bias. For example, misclassificaiton bias would direct the association towards the null; however, diagnostic bias may have shifted the association away from the null. Moreover, the CPCSSN dataset is from electronic medical records for clinical practice limiting the control of the researcher over the quality of the data.

Having said that, the study has distinctive strengths. First, a unique cohort of patients with diabetes treated in a primary care setting was studied. There seems to be minimal research done on the association between diabetes and infection in a primary care setting, Our study adds to the sparce literature in primary care setting. Second, the study had sufficient power to detect statistically significant associations for our primary outcome. Third, data was obtained from the CPCSSN database, which is designed specifically for primary care research, captures appropriate study variables and important prognostic markers (e.g.,

glycemic control, BMI, smoking and blood pressure) that are vital for the study design (17). In addition, a validated case definition was used to define diabetes status before outcome ascertainment (13), thus avoiding differential detection of undiagnosed diabetes in adults. Finally, our study included community-based comparison groups yesinstead of hospital-based and adjusted for comorbidities, vaccination status, which introduced potential bias in some studies (61-63).

3.5 Conclusion

In conclusion, our study supports a significant but weak association between diabetes and certain community-acquired infections including skin and soft tissues, gastrointestinal, genitourinary and respiratory infections. The implications of glucose control via antidiabetic medications on the risk of these infections remains to be determined.

References:

1) International diabetes federation atlas sixth edition: http://www.idf.org/diabetesatlas/update-2014

2) Statistics Canada. CANSIM, table 105-0501 and Catalogue no. 82-221-X. Last modified: 2015-06-17. http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/health53a-eng.htm

3) Morrish N, Wang S, Stevens L et al. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia* 2001;44:S14-21.

4) Diapedia Collective, The. Other complications of diabetes mellitus [internet]. 2015 Jan 21; Diapedia 71040851441 rev. no. 18. Available from: http://dx.doi.org/10.14496/dia.71040851441.18

5) Shah B, Hux J. Quantifying the risk of infectious diseases for people with diabetes. *Diabetes Care* 2003;26:510-513.

6) Selby J, Ray G, Zhang D et al. Excess costs of medical care for patients with diabetes in a managed care population. *Diabetes Care* 1997;20:1396-1402.

7) Valerius N, Eff C, Hansen N et al. Neutrophil and lymphocyte function in patients with diabetes mellitus. *Acta Med Scand* 1982;211:463-467.

8) Delamaire M, Maugendre D, Moreno M et al. Impaired leucocyte functions in diabetic patients. *Diabet Med* 1997;14:29-34.

9) Pecoraro R, Ahroni J, Boyko E et al. Chronology and determinants of tissue repair in diabetic lower-extremity ulcers. *Diabetes* 1991;40:1305-1313.

10) Ellenberg M, Weber H. The incipient asymptomatic diabetic bladder. *Diabetes* 1967;16:331-335.

11) Muller L, Gorter K, Hak E et al. Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. *Clin Infect Dis* 2005;41:281-288.

12)Birtwhistle R, Keshavjee K, Lambert-Lanning A, et al. Building a pan-Canadian primary care sentinel surveillance network: initial development and moving forward. *J Am Board Fam Med* 2009;22:412-422.

13) Greiver M, Keshavjee K, Martin K et al. Who are your patients with diabetes? EMR case definitions in the Canadian Primary Care setting. *Can Fam Physician* 2012;58:421-

422.

14) Kadhim-Saleh A, Green M, Williamson T et al. Validation of the Diagnostic Algorithms for 5 Chronic Conditions in the Canadian Primary Care Sentinel Surveillance Network (CPCSSN): A Kingston Primary Care Practice-based Research Network (PCPBRN). *J Am Board Fam Medicine* 2013;26:159-167.

15)Greiver M, Aliarzadeh B, Moineddin R et al. Diabetes Screening with Hemoglobin A1c Prior to a Change in Guideline Recommendations: Prevalence and Patient Characteristics. *BMC Fam Pract* 2011;12:1-7.

16)Greiver M, Barnsley J, Aliarzadeh B et al. Using a Data Entry Clerk to Improve Data Quality in Primary Care Electronic Medical Records: a pilot study. *Inform Prim Care* 2011;19:241-250.

17) Kotecha JA, Manca D, Lambert-Lanning A et al. Ethics and Privacy Issues of a Practice-based Surveillance System: Need for a National-level Institutional Research Ethics Board and Consent Standards. *Can Fam Physician* 2011;57:1165-1173.

18) Asghari et al. Does the Prevalence of Dyslipidemias Differ between Newfoundland and the Rest of Canada? Findings from the Electronic Medical Records of the Canadian

Primary Care Sentinel Surveillance Network. Front Cardiovasc Med. 2015; 2:1.

19) Touchie C. Report of the incidence and prevalence of diseases and other health related issues in Canada. A study for the MCC blueprint project. Medical Council of Canada 2013.

20) Crowson C, Hoganson D, Fitz-Gibbon P et al. Development and validation of a risk score for serious infection in patients with rheumatoid arthritis. *Arthritis Rheum* 2012;64:2847-2855.

21) Migita K , Arai T, Ishizuka N et al. Rates of serious intracellular infections in autoimmune disease patients receiving initial glucocorticoid therapy. *PLoS One* 2013 19;8:e78699.

22) Factor S, Levine O, Swhartz B et al. Invasive group A streptococcal disease: risk factors for adults. *Emerg Infect Dis* 2003;9:970-977.

23) Davis T, Weerarathne T, Foong Y et al. Community-acquired infections in type 2 diabetic patients and their nondiabetic partners. The Fremantle Diabetes Study. *J Diabetes Complications* 2005;19:259-263.

24) Lipsky B, Boyko E, Inui T et al. Risk factors for acquiring pneumococcal infections. *Arch Intern Med* 1986;146:2179-2185.

25) Baaten G, Roukens A, Geskus R et al. Symptoms of infectious diseases in travelers with diabetes mellitus: a prospective study with matched controls. *J Travel Med* 2010;17:256-263.

26) Heal C, Buettner P, Browning S. Risk factors for wound infection after minor surgery in general practice. *Med J Aust* 2006;185:255-258.

27) Kato H, Nakagami G, Iwahira Y et al. Risk factors and risk scoring tool for infection during tissue expansion in tissue expander and implant breast reconstruction. *Breast J* 2013;19:618-626.

28) Bykowski M, Sivak W, Cray J et al. Assessing the impact of antibiotic prophylaxis in outpatient elective hand surgery: a single-center, retrospective review of 8,850 cases. *J Hand Surg Am* 2011;36:1741-1747.

29) Nassel H, Ottosson C, Tornqvist H et al. The impact of smoking on complications after operatively treated ankle fractures--a follow-up study of 906 patients. *J Orthop Trauma* 2011;25:748-755.

30) Bartholomeeusen S, Vandenbroucke J, Truyers C. Epidemiology and comorbidity of erysipelas in primary care. *Dermatology* 2007;215:118-122.

31) Edmonston D, Foulkes G. Infection rate and risk factor analysis in an orthopaedic ambulatory surgical center. *J Surg Orthop Adv* 2010;19:174-176.

32) Bundy J, Gonzalez V, Barnard B et al. Gender risk differences for surgical site infections among a primary coronary artery bypass graft surgery cohort: 1995-1998. Am *J Infect Control* 2006;34:114-121.

33) Chen LK, Peng LN, Lin MH et al. Diabetes mellitus, glycemic control, and pneumonia in long-term care facilities: a 2-year, prospective cohort study. *J Am Med Dir Assoc* 2011;12:33-37.

34) Choudhry A, Al-Mudaimegh K, Turkistani A et al . Hajj-associated acute respiratory infection among hajjis from Riyadh. *East Mediterr Health J* 2006;12:300-309.

35) Dobler C, Flack J, Marks G. Risk of tuberculosis among people with diabetes mellitus: an Australian nationwide cohort study. *BMJ Open* 2012;13:2:e000666.

36) Picon P, Bassanesi S, Caramori M et al. Risk factors for recurrence of tuberculosis. *J Bras Pneumol* 2007;33:572-578.

37) Baker M, Lin H-H, Chang HY et al. The risk of tuberculosis disease among persons with diabetes mellitus: a prospective cohort study. *Clin Infect Dis* 2012;54:818-825.

38) Chen W, Shu W, Wang M et al. Pulmonary tuberculosis incidence and risk factors in rural areas of china: a cohort study. *PLoS One* 2013;8:e58171.

39) Alisjahbana B, Crevel R, Sahiratmadja E et al. Diabetes mellitus is strongly associated with tuberculosis in Indonesia. *Int J Tuberc Lung Dis* 2006;10:696-700.

40) Almiral J, Bolibar I, Balanzo X et al. Risk factors for community-acquired pneumonia in adults: a population-based case-control study. *Eur Respir J* 1999;13:349-355.

41) Treppenning M, Taylor G, Lopatin D et al. Aspiration pneumonia: dental and oral risk factors in an older veteran population. *J Am Geriatr Soc* 2001;49:557-563.

42) Wang Q, Ma A, Han X et al. Prevalence of type 2 diabetes among newly detected pulmonary tuberculosis patients in China: a community based cohort study. *PLoS One* 2013;18;8:e82660.

43) Jick S, Lieberman E, Rahman M et al. Glucocorticoid use, other associated factors, and the risk of tuberculosis. *Arthritis Rheum* 2006;55:19-26.

44) Boyko E, Fihn S, Scholes D et al. Risk of urinary tract infection and asymptomatic bacteriuria among diabetic and nondiabetic postmenopausal women. *Am J Epidemiol* 2005;161:557-564.

45) Gorter K, Hak E, Zuithoff N et al. Risk of recurrent acute lower urinary tract infections and prescription pattern of antibiotics in women with and without diabetes in primary care. *Fam Pract* 2010;27:379-385.

46) Goswami R, Dadhwal V, Tejaswi S et al. Species-specific prevalence of vaginal candidiasis among patients with diabetes mellitus and its relation to their glycaemic status. *J Infect* 2000;41:162-166.

47) Hirji I, Andersson S, Guo Z et al. Incidence of genital infection among patients with type 2 diabetes in the UK General Practice Research Database. *J Diabetes Complications* 2012;26:501-505.

48) Hirji I, Andersson S, Guo Z et al. Incidence of urinary tract infection among patients with type 2 diabetes in the UK General Practice Research Database (GPRD). *J Diabetes Complications* 2012;26:513-516.

49) Boyko E, Fihn S, Scholes D et al. Diabetes and the risk of acute urinary tract infection among postmenopausal women. *Diabetes Care* 2002;25:1778-1783.

50) Orlander J, Jick S, Dean A et al. Urinary tract infections and estrogen use in older women. *J Am Geriatr Soc* 1992;40:817-820.

51) Neal K, Slack R. Diabetes mellitus, anti-secretory drugs and other risk factors for campylobacter gastro-enteritis in adults: a case-control study. *Epidemiol Infect* 1997;119:307-311.

52) Weitzaman D, Shavit O,Stein M et al. A population based study of the epidemiology of Herpes Zoster and its complications. *J Infect* 2013;67:463-469.

53) Jih JS, Chen YJ, Lin MW et al. Epidemiological features and costs of herpes zoster in Taiwan: a national study 2000 to 2006. *Acta Derm Venereol* 2009;89:612-616.

54) Joesoef R, Harpaz R, Leung J et al. Chronic medical conditions as risk factors for herpes zoster. *Mayo Clin Proc* 2012;87:961-967.

55) Blumentals W, Nevitt A, Peng M et al. Body mass index and the incidence of influenza-associated pneumonia in a UK primary care cohort. *Influenza Other Respir Viruses* 2012;6:28-36.

56) Pezer M, Vidic V, Nikolic J et al. Risk factors in patients with herpes zoster infections: case-control study. *Cent Eur J Med* 2013;8:493-498.

57) Cowie C, Rust K, Byrd-Holt D et al. Prevalence of diabetes and impaired fasting glucose in adults in the U.S. population: National Health And Nutrition Examination Survey 1999-2002. *Diabetes Care* 2006;29:1263-1268.

58) Schneeberger C, Stolk R, DeVaries J et al. Differences in the pattern of antibiotic prescription profile and recurrence rate for possible urinary tract infections in women with and without diabetes. *Diabetes Care* 2008; 31:1380-1385.

59) Gorter K, Hak E, Zuitthoff N et al. Risk of recurrent acute lower urinary tract infections and prescription pattern of antibiotics in women with and without diabetes in primary care. *Fam Pract* 2010;27:379-385.

60) Leth R, Uldbjerg N, Norgaard M et al. Obesity, diabetes, and the risk of infections diagnosed in hospital and post discharge infections after cesarean section: a prospective cohort study. *Nordic Federation of Societies of Obstetrics and Gynecology* 2011;90:501-509.

61) BouterK, Diepersloot R, van Romunde L et al. Effect of epidemic influenza on ketoacidosis, pneumonia and death in diabetes mellitus: a hospital register survey of 1976–1979 in the Netherlands. *Diabetes Res Clin Pract* 1991;12:61-68.

62) Neuzil K, Reed G, Mitchel E et al. Influenza associated morbidity and mortality in young and middle-aged women. *JAMA* 1999;281:901-907.

63) Schanzer D, Langley J, Tam T. Co-morbidities associated with influenza-attributed mortality, 1994–2000, Canada. *Vaccine* 2008;26:4697-4703.

Tables:

Table 1: Baseline Characteristics for 12,845 Patients With and Without Diabetes Over 4-year Period:

Variable	Diabetes (n=1,779)	Non-Diabetes (n=11,066)	P value
Age			<0.001
Mean (SD)	57.5 (15.6)	43.1 (16.5)	
Median (IQR)	59.0 (20)	41.0 (26)	
Gender n, (%)			
Male	889 (50.0)	4,435 (40.1)	<0.001
Female	890 (50.0)	6,631 (59.9)	<0.001
Doctor Visits (Mean, SD)	3.7 (3.9)	3.3 (3.8)	0.015
Referral To a Specialist, n (%)			
0	1,568 (88.1)	9,927 (89.7)	0.05
1	133 (7.5)	755 (6.8)	0.338
≥2	78 (4.4)	384 (3.5)	0.064

Infection before 1-year entry, n (%) **0** **1** **≥2**	 1,385 (77.8) 203 (11.4) 191 (10.7)	 6,261 (56.6) 1,894 (17.1) 2,911 (26.3)	 <0.001 <0.001 <0.001
Lab Tests before 1-year entry **(Mean, SD)**	14.5 (46.3)	10.6 (33.2)	<0.001
Vaccines, n (%)	251 (14.1)	1,202 (10.9)	<0.001
Acid-suppressing Medications, n (%)	306 (17.2)	983 (8.9)	<0.001
Respiratory Medications, n (%)	173 (9.72)	1,140 (10.3)	0.482
Lipid-lowering Medications, n (%)	716 (40.2)	653 (5.9)	<0.001
Microvascular Disease, n (%)	29 (1.6)	23 (0.2)	<0.001
Macrovascular Disease, n (%)	76 (4.3)	111 (1)	<0.001
Heart Failure, n (%)	19 (1.1)	16 (0.1)	<0.001
Fatty Liver, n (%)	10 (0.6)	12 (0.1)	<0.001

Obesity, n (%)	61 (3.4)	129 (1.2)	<0.001
Respiratory Disease, n (%)	236 (13.3)	2,273 (20.5)	<0.001
Follow-up Time, years (Mean, SD)	4.2 (1.7)	4.2 (1.7)	0.788

Table 2: Proportion of New Infections in Patients with and without Diabetes Over 2 Follow-up Periods:

Infection Type	**4-year Follow-up Period**			**1-year Follow-up period**		
	Diabetes (n=1,779) n (%)	**Non Diabetes (n=11,066) n (%)**	**P value**	**Diabetes (n=1,779) n (%)**	**Non Diabetes (n=11,066) n (%)**	**P value**
Any Infection	1012 (56.9)	6428 (58.1)	0.354	584 (32.8)	3500 (31.6)	0.327
Head & Neck	118 (6.6)	817 (7.4)	0.280	39 (2.2)	298 (2.7)	0.252

Respiratory	462 (26.0)	3266 (29.5)	0.002	210 (11.8)	1381 (12.5)	0.445
Gastrointestinal	151 (8.5)	694 (6.3)	<0.001	69 (3.9)	245 (2.2)	<0.001
Genitourinary	203 (11.4)	1172 (10.6)	0.319	93 (5.2)	438 (4.0)	0.015
Skin & Soft Tissue	199 (11.2)	896 (8.1)	<0.001	78 (4.4)	269 (2.4)	<0.001
Musculoskeletal	185 (10.4)	1189 (10.7)	0.692	62 (3.5)	388 (3.5)	1.000
Viral	84 (4.7)	428 (3.9)	0.100	30 (1.7)	130 (1.2)	0.091

Table 3: New Infections Per 100 Person-Years in Patients With and Without Diabetes Over 2 Follow-up Periods:

Infection Type	Full Study Period (Mean, SD)			1 year study period (Mean, SD)		
	Diabetes	Non-Diabetes	P value	Diabetes	Non-Diabetes	P value
Any Infection	42.7 (63.0)	42.5 (59.9)	0.895	54.7 (99.3)	50.2 (94.6)	0.077
Head & Neck	2.1 (11.5)	2.2 (9.7)	0.771	2.6 (18.2)	3.0 (19.5)	0.318
Respiratory	13.4 (36.3)	13.9 (30.0)	0.589	16.2 (52.2)	16.3 (49.7)	0.943
Gastrointestinal	3.4 (15.0)	2.2 (11.1)	0.001	4.9 (27.9)	2.7 (19.4)	0.001
Genitourinary	4.8 (18.0)	4.2 (16.5)	0.148	6.9 (33.1)	4.9 (26.7)	0.016
Skin & Soft Tissue	4.1 (15.3)	2.4 (10.5)	<0.001	5.2 (26.3)	2.6 (17.4)	<0.001
Musculoskeletal	3.7 (14.4)	3.8 (14.5)	0.789	4.3 (25.1)	4.0 (22.3)	0.617
Viral	1.4 (7.1)	1.1 (6.6)	0.083	1.7 (13.5)	1.2 (11.4)	0.122

Table 4: Odds Ratio (OR) Between Diabetes and Infection: Crude and Covariate-Adjusted Results:

Type of Infection	Crude OR	95%CI	P value	Adjusted OR	95%CI	P value
Any Infection	0.96	0.86-1.06	0.399	1.21	1.07-1.37	0.002
Head & Neck	0.90	0.74-1.11	0.328	1.10	0.87-1.39	0.428
Respiratory	0.84	0.75-0.94	0.003	1.31	1.14-1.50	<0.001
Gastrointestinal	1.38	1.15-1.67	<0.001	1.41	1.13-1.75	<0.001
Genitourinary	1.10	0.94-1.29	0.238	1.42	1.17-1.73	<0.001
Skin & Soft Tissue	1.43	1.21-1.69	<0.001	1.65	1.36-2.01	<0.001
Musculoskeletal	0.97	0.82-1.14	0.714	1.05	0.87-1.28	0.606
Viral	1.21	0.95-1.55	0.115	1.11	0.83-1.47	0.485

Adjusted for age, sex, comorbidities (microvascular disease [nephropathy, neuropathy, retinopathy], macrovascular disease [coronary artery disease, peripheral and cerebral vascular disease], heart failure, respiratory disease, dyslipidemia, fatty liver disease, and obesity), medications (acid inhibitors, respiratory

system medications, anti-lipids and vaccines), lab tests, doctor visits, referral to specialists and number of infections in the year prior to enrollment

Table 5: Odds Ratio (OR) Between Diabetes and Infection Over 1-Year Period: Crude and Covariate-Adjusted Results:

Type of Infection	Crude OR	95%CI	P value	Adjusted OR	95%CI	P value
Any Infection	1.06	0.95-1.18	0.290	1.37	1.21-1.55	<0.001
Head & Neck	0.83	0.59-1.17	0.285	1.12	0.75-1.67	0.573
Respiratory	0.94	0.81-1.10	0.470	1.45	1.21-1.74	<0.001
Gastrointestinal	1.78	1.36-2.34	<0.001	1.71	1.22-2.39	0.002
Genitourinary	1.34	1.06-1.69	0.248	1.86	1.39-2.50	<0.001
Skin & Soft Tissue	1.81	1.40-2.34	<0.001	1.96	1.43-2.69	<0.001
Musculoskeletal	1.01	0.77-1.33	0.915	1.06	0.77-1.47	0.714

Viral	1.42	0.95-2.13	0.086	1.33	0.80-2.21	0.268

Adjusted for age, sex, comorbidities (microvascular disease [nephropathy, neuropathy, retinopathy], macrovascular disease [coronary artery disease, peripheral and cerebral vascular disease], heart failure, respiratory disease, dyslipidemia, fatty liver disease, and obesity), medications (acid inhibitors, respiratory system medications, anti-lipids and vaccines), lab tests, doctor visits, referral to specialists and number of infections in the year prior to enrollment

Table 6: Odds Ratio (OR) Between Diabetes and Any Infection Recurrence: Crude and Covariate-Adjusted Results:

Recurrences	**Crude OR**	**95%CI**	**P value**	**Adjusted OR**	**95%CI**	**P value**
≥1 Infection	0.96	0.86-1.06	0.399	1.21	1.07-1.37	0.002
≥2 Infection	0.92	0.82-1.04	0.196	1.30	1.12-1.50	<0.001
≥3 Infection	0.99	0.86-1.13	0.872	1.51	1.27-1.79	<0.001

Adjusted for age, sex, comorbidities (microvascular disease [nephropathy, neuropathy, retinopathy], macrovascular disease [coronary artery disease, peripheral and cerebral vascular disease], heart failure, respiratory disease, dyslipidemia, fatty liver disease, and obesity), medications (acid inhibitors, respiratory system medications, anti-lipids and vaccines), lab tests, doctor visits, referral to specialists and number of infections in the year prior to enrollment

Chapter 4

Summary

A popular notion among healthcare professionals is that patients with diabetes are more liable to developing infections. This view however, lacked the support of necessary substantive evidence. The magnitude and precession of the association between diabetes and infection was not established in the current literature. To address this gap, especially with certain types of infections, two complementary epidemiological studies were designed and presented in this thesis. The first study was a quantitative systematic review and meta-analyses, while the second study was a matched cohort study.

The first study (chapter 2) aimed to summarize and quantify the association between diabetes and infection through a systematic review and meta-analysis. An increased risk of numerous types of common infections in patients with diabetes was found; however, there existed much variation in results between studies. The results were most compelling for skin and soft tissue infections, genitourinary infections, and blood stream infections which had the strongest associations following a meta-analysis of studies with a similar design. The second study, the matched cohort study, aimed to estimate the association between diabetes and infection in a primary care setting. This study resulted in a small

increased risk in any infection in patients with diabetes compared to patients without diabetes. The highest increase in risk was seen in skin and soft tissue infections. An smaller but significant increased risk was also apparent in genitourinary, gastrointestinal, and respiratory infections.

These two studies complement each other: the systematic review summarized the current knowledge on the association of diabetes and infections from the literature that culminated in a meta-analysis, the second study, a matched cohort study examine this relationship in a primary care setting where most patients with diabetes are most often seen . Both of these studies add to the current evidence-based medicine literature.

4.1 Bradford Hill Considerations:

It is important in epidemiology to separate casual relationships between exposure and outcome from non-causal relationships. If a set of necessary casual criteria could be used to differentiate between causal and non-causal relationships, the presented research work would be solidified. A commonly set of criteria proposed by Sir Austin Bradford Hill was first described in 1965 to the Section of Occupational Medicine of the Royal Society of Medicine (1). Hill's lecture had a huge impact on epidemiologists and medical researchers. The list of casual criteria was considered a roadmap for researchers (2-4). Hill provided nine considerations to distinguish a casual relationship from a non-casual one as follows; strength, consistency, specificity, temporality, biological gradient,

plausibility, coherence, experimental evidence and analogy. These considerations were influenced by others before him (5,6). Hill's criteria as it is specifically related to this thesis will be reviewed here.

Strength of an association is shown through a quantitative measure of effect (e.g, relative risk, odds ratio, hazard ratio, absolute risk difference). Hill's argument is that strong associations are more likely to be casual than weak associations. According to Monson (7) a measure of association >1.5 is considered moderate to strong. In our cohort study, a weak association between the primary outcome, any infection, and diabetes was found(odds ratio (OR)= 1.21, 95%CI 1.07-1.37). When examining secondary outcomes of the study, only skin and soft tissue infections had a strong association (OR=1.65, 95%CI 1.36-2.01), while weak associations were present for genitourinary (OR=1.42, 95%CI 1.17-1.73), gastrointestinal (OR=1.41, 95%CI 1.13-1.75), and respiratory (OR=1.31, 95%CI 1.14-1.50). Our systematic review and meta-analysis showed strong associations with regards to secondary outcomes. Cohort studies revealed skin and soft tissue infections (OR=1.95, 95%CI 1.78-2.13, I^2=92.8%), blood stream (OR=1.73, 95%CI 1.49-2.01, I^2=94.2%), genitourinary (OR=1.61, 95%CI 1.42-1.83, I^2=99.2%) and unspecified infections (OR=1.81, 95%CI 1.64-2.00, I^2=99.6%) had strong associations. Case-control studies showed that skin (OR=2.61, 95%CI 2.17-3.13, I^2=0%), respiratory (OR=1.62, 95%CI 1.37-1.92, I^2=85.9%), blood (OR=2.40, 95%CI 1.68-3.42, I^2=71.7%), genitourinary (OR=2.42, 95%CI 1.61-3.65, I^2=83.7%), gastrointestinal (OR=3.61, 95%CI 2.94-4.43, I^2=0%), and non-specific (OR=3.81, 95%CI 2.88-5.04, I^2=0%) had strong associations.

With regards to **consistency** of results, our cohort study coincides with other studies looking at the association of diabetes and infections. In addition to our cohort study, other observational studies examining the association between infections in the community and diabetes found the same conclusion with the measure of association ranging from [1.21-2.5] (8-12). In contrast, not all studies showed positive associations. Lipsky et al showed that diabetes was not considered a risk factor for pneumococcal infections. As for secondary outcomes, there was also consistency with the literature (13). The risk of skin and soft tissue was also increased in patients with diabetes with odds ratio ranging from 1.7-6.2 (10,14-18) among several other studies (19-22). Genitourinary infections was also shown to be increased in patients with diabetes in other studies (10,20,19-22). Numerous studies concluded positive association with respiratory infection and diabetes (10,19,20). Few studies coincided with our results in gastrointestinal infections (10,19,38).

To our knowledge, there is no systematic review that examined the association of all types of infections and diabetes. Jeon and Murray (39) conducted a systematic review and meta-analysis that looked at tuberculosis and diabetes. They concluded a positive association, as found in the systematic review and metat-analysis, in respiratory infection, with diabetes with cohort studies having a relative risk (RR=3.1, 95%CI 2.27-4.26) and case-control studies ranging from 1.16-7.83. Another systematic review done by Baker et al (40) examined the impact of diabetes on tuberculosis treatment. They concluded that diabetes increases the risk of relapse of tuberculosis. A narrative review done by Peleg et

al (41) studied common infections in diabetes. They concluded that diabetes is a risk factor for skin, respiratory and urinary infections.

With **temporality**, another consideration of Hill, the necessity for a cause to precede an effect in time is required for a casual relationship. Temporality can be applied in our case, where the occurrence of diabetes precedes the incidence of infection. However, due to the retrospective design of the studies included in the systematic review, temporality may not be ascertained completely.

Biological plausibility can be applied to the explanation of the observed association through known biological mechanisms. Defects in the immune system in patients with diabetes; decreased neutrophil capabilities, phagocytosis, chemotaxis, impaired migration (42,43), might have a role in the increased incidence of infection compared to patients without. Moreover, anatomically specific impairment could be considered another mechanism to add on the plausibility. Cardiovascular, neurological complications (44,45) and impaired lung function (46,47) increases risk of infections. Bradford Hill considers **coherence** if a cause and effect interpretation of association is clear when it does not conflict with what is known about the disease. In other words, the association is coherent with the current knowledge as is shown in the association studied here.

Biological gradient may also apply to association at hand. Although this thesis did not examine the association between glycemic control and infections, but a dose-response relationship is suggested by other literature. This suggests that the severity of diabetes,

reflected in poor glycemic control (hyperglycemia and increase in A1C), can be linked to the occurrence of infection (48). Animal studies showed that hyperglycemia can worsen immune function (49,50). In vitro studies in diabetic patients showed that diabetic cells, in comparison with controlled ones, had a reduced cellular immune function(51,52). Others have strengthened this theory through several observational studies (53-56).

In addition, **experimental evidence** (as interpreted by Bradford Hill) supports the association between diabetes and infections. People with diabetes have shown some evidence of histopathological changes that can give supplementary rationale to the present association between diabetes and infection. Diabetes can affect healing (57,58), and hyperglycaemia affects coagulation and fibrinolytic function (59), lipid metabolism and endothelial function (60,61). Impaired lung functions in these patients contribute to acquiring this type of infection as well (62,63). The pathophysiology of lung abnormalities in patients who have diabetes is believed to involve microangiopathic changes in the basement membrane of pulmonary blood vessels and respiratory epithelium, as well as non-enzymatic glycosylation of tissue protein (64-67).

The remaining Bradford Hill criteria including specificity and analogy, do not apply to the association studied here.

As discussed above, by reviewing Bradford Hill considerations, there is convincing evidence of casual relationship between diabetes and infection. However, while there

remains some controversy in the literature, more research is needed to strengthen the causal relationship between diabetes and infection.

4.2 Research and Clinical Implications:

Diabetes is a major public health issue and furthering our understanding of the risk of infection among patients living with diabetes has the potential to improve population health. The knowledge generated from this review will help further inform physicians and researchers and aid in a better understanding of the relationship between diabetes and the risk of infection. The implications of this research will impact health policy, clinical practice and epidemiological research.

4.2.1 Health Services:

The international diabetes federation reported in 2015 almost 415 million people were liing with diabetes. In 2040, number of patients living with diabetes is expected to increase to over than 640 million people. The cost of management these patients will affect the healthcare system expidenture. Health care expenses for people with diabetes is estimated to be generally 2-3 fold higher than for patients with no diabetes (68). This burden will be reflected in increase doctor visits, follow-up, management and hospital admissions. The results of both studies may influence health services policies by informing decision makers and those involved in developing clinical practice guidelines. Our findings regarding the link between diabetes and infection may impact policies in

institutions such as hospitals and nursing homes. In short, the results of this work will support evidence informed policy.

4.2.2 Clinical Practice:

Our findings can bridge to clinical practice as current clinical behavior, or current assumptions by clinicians regarding diabetes and infection, are supported by little evidence. As shown in the results the systematic review and cohort study in this thesis, patients with diabetes are more liable to certain types of infections compared to patients without diabetes. Hence, the study results may enhance evidence-based decision making at the point of care by healthcare professionals when treating patients with diabetes, especially with regard to decisions that may affect the immune system. This might be taken into consideration when managing infections in patients with diabetes with reagrds to choice of treatment, dosage, duration and follow-up.

4.2.3 Research:

As shown in the systematic review and meta-analysis and the cohort study done in this thesis, there is a relationship between diabetes and infection. However, some research needs to be done to focus on some points. Important questions to address in future research:

- Are patients with diabetes with uncontrolled blood sugar more liable to infection than patients with diabetes with controlled blood sugar?

- Is there any difference in the incidence of infection according to the type of diabetes?
- Do specific anti-diabeteic medications have a role in the occurrence of infections in patients with diabetes?
- What role do certain patient's characteristics (e.g, body mass index, diabetes complications, smoking, etc.) have in patients with diabetes in the occurrence of infections?

4.3 Conclusion:

The current thesis presents the results of two observational studies that examined the association between diabetes and the incidence of infection. The first study was a systematic review and meta-analysis used to summarize and quantify the association between diabetes and infection in the existing literature. This study concluded that diabetes is associated with an increased risk of infection. The association was present across all types of infections with skin soft tissue, genitourinary and blood infections having the strongest associations. The second study was a matched cohort study using a provincial dataset, to estimate the association between diabetes and infection in primary care. The study found that patients with diabetes have a small increase in risk of any infection compared to patients without diabetes. The highest risk was seen with skin and soft tissue infections, followed by genitourinary, gastrointestinal and respiratory infections.

References:

1) Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965;58:295-300.

2) Hussain S, Harris C. Molecular epidemiology of human cancer. *Toxicol Lett* 1998;103:219-225.

3) Spitzer W. Bias versus causality: Interpreting recent evidence of oral contraceptive studies. *Am J Obstet Gynecol* 1998;179:S43-S50.

4) Naschitz J, Kovaleva J, Shaviv N et al. Vascular disorders preceding diagnosis of cancer: distinguishing the causal relationship based on the Bradford-Hill guidelines. *Angiology* 2003;54:11-17.

5) Susser M. What is a cause and how do we know one? A grammar for pragmatic epidemiology. *Amer J Epidemiol* 1991;7:635-648.

6) Morabia A. On the origin of Hill's causal criteria. *Epidemiol* 1991;5:367-369.

7) Monson R. Occupational Epidemiology, 2nd edition. Boca Raton, Florida: CRC Press Inc.,1990.

8) Factor S, Levine O, Swhartz B et al. Invasive group A streptococcal disease: risk factors for adults. *Emerg Infect Dis* 2003;9:970-977.

9) Davis T, Weerarathne T, Foong Y et al. Community-acquired infections in type 2 diabetic patients and their nondiabetic partners. The Fremantle Diabetes Study. *J Diabetes Complications* 2005;19:259-263.

10) Shah B, Hux J. Quantifying the risk of infectious diseases for people with diabetes. *Diabetes Care* 2003;26:510-513.

11) Crowson C, Hoganson D, Fitz-Gibbon P et al. Development and validation of a risk score for serious infection in patients with rheumatoid arthritis. *Arthritis Rheum* 2012;64:2847-2855.

12) Migita K , Arai T, Ishizuka N et al. Rates of serious intracellular infections in autoimmune disease patients receiving initial glucocorticoid therapy. *PLoS One* 2013 19;8:e78699.

13) Lipsky B, Boyko E, Inui T et al. Risk factors for acquiring pneumococcal infections. *Arch Intern Med* 1986;146:2179-2185.

14) Bundy J, Gonzalez V, Barnard B et al. Gender risk differences for surgical site infections among a primary coronary artery bypass graft surgery cohort: 1995-1998. Am *J Infect Control* 2006;34:114-121.

15) Heal C, Buettner P, Browning S. Risk factors for wound infection after minor surgery in general practice. *Med J Aust* 2006;185:255-258.

16) Kato H, Nakagami G, Iwahira Y et al. Risk factors and risk scoring tool for infection during tissue expansion in tissue expander and implant breast reconstruction. *Breast J* 2013;19:618-626.

17) Bykowski M, Sivak W, Cray J et al. Assessing the impact of antibiotic prophylaxis in outpatient elective hand surgery: a single-center, retrospective review of 8,850 cases. *J Hand Surg Am* 2011;36:1741-1747.

18) Nassel H, Ottosson C, Tornqvist H et al. The impact of smoking on complications after operatively treated ankle fractures--a follow-up study of 906 patients. *J Orthop Trauma* 2011;25:748-755.

19) Baaten G, Roukens A, Geskus R et al. Symptoms of infectious diseases in travelers with diabetes mellitus: a prospective study with matched controls. *J Travel Med* 2010;17:256-263.

20) Muller L, Gorter K, Hak E et al. Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. *Clin Infect Dis* 2005;41:281-288.

21) Bartholomeeusen S, Vandenbroucke J, Truyers C. Epidemiology and comorbidity of erysipelas in primary care. *Dermatology* 2007;215:118-122.

22) Edmonston D, Foulkes G. Infection rate and risk factor analysis in an orthopaedic ambulatory surgical center. *J Surg Orthop Adv* 2010;19:174-176.

23) Boyko E, Fihn S, Scholes D et al. Risk of urinary tract infection and asymptomatic bacteriuria among diabetic and nondiabetic postmenopausal women. *Am J Epidemiol* 2005;161:557-564.

24) Gorter K, Hak E, Zuithoff N et al. Risk of recurrent acute lower urinary tract infections and prescription pattern of antibiotics in women with and without diabetes in primary care. *Fam Pract* 2010;27:379-385.

25) Goswami R, Dadhwal V, Tejaswi S et al. Species-specific prevalence of vaginal candidiasis among patients with diabetes mellitus and its relation to their glycaemic status. *J Infect* 2000;41:162-166.

26) Hirji I, Andersson S, Guo Z et al. Incidence of genital infection among patients with type 2 diabetes in the UK General Practice Research Database. *J Diabetes Complications* 2012;26:501-505.

27) Hirji I, Andersson S, Guo Z et al. Incidence of urinary tract infection among patients with type 2 diabetes in the UK General Practice Research Database (GPRD). *J Diabetes Complications* 2012;26:513-516.

28) Boyko E, Fihn S, Scholes D et al. Diabetes and the risk of acute urinary tract infection among postmenopausal women. *Diabetes Care* 2002;25:1778-1783.

29) Orlander J, Jick S, Dean A et al. Urinary tract infections and estrogen use in older women. *J Am Geriatr Soc* 1992;40:817-820.

30) Chen LK, Peng LN, Lin MH et al. Diabetes mellitus, glycemic control, and pneumonia in long-term care facilities: a 2-year, prospective cohort study. *J Am Med Dir Assoc* 2011;12:33-37.

31) Choudhry A, Al-Mudaimegh K, Turkistani A et al . Hajj-associated acute respiratory infection among hajjis from Riyadh. *East Mediterr Health J* 2006;12:300-309.

32) Dobler C, Flack J, Marks G. Risk of tuberculosis among people with diabetes mellitus: an Australian nationwide cohort study. *BMJ Open* 2012;13:2:e000666.

33) Picon P, Bassanesi S, Caramori M et al. Risk factors for recurrence of tuberculosis. *J Bras Pneumol* 2007;33:572-578.

34) Baker M, Lin H-H, Chang HY et al. The risk of tuberculosis disease among persons with diabetes mellitus: a prospective cohort study. *Clin Infect Dis* 2012;54:818-825.

35) Almiral J, Bolibar I, Balanzo X et al. Risk factors for community-acquired pneumonia in adults: a population-based case-control study. *Eur Respir J* 1999;13:349-355.

36) Treppenning M, Taylor G, Lopatin D et al. Aspiration pneumonia: dental and oral risk factors in an older veteran population. *J Am Geriatr Soc* 2001;49:557-563.

37) Wang Q, Ma A, Han X et al. Prevalence of type 2 diabetes among newly detected pulmonary tuberculosis patients in China: a community based cohort study. *PLoS One* 2013;18;8:e82660.

38) Neal K, Slack R. Diabetes mellitus, anti-secretory drugs and other risk factors for campylobacter gastro-enteritis in adults: a case-control study. *Epidemiol Infect* 1997;119:307-311.

39) Jeon C, Murray M. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. *PLoS Med* 2008;5:e152.

40) Baker M, Harries A, Jeon C et al. The impact of diabetes on tuberculosis treatment outcomes: a systematic review. *BMC Med* 2011;9:81.

41) Peleg A, Weerarathna T, McCarthy J et al. Common infections in diabetes: pathogenesis, management and relationship to glycaemic control. *Diabetes Metab Res Rev* 2007;23:3-13.

42) Valerius N, Eff C, Hansen N et al. Neutrophil and lymphocyte function in patients with diabetes mellitus. *Acta Med Scand* 1982;211:463-467.

43) Delamaire M, Maugendre D, Moreno M et al. Impaired leucocyte functions in diabetic patients. *Diabet Med* 1997;14:29-34

44) Pecoraro R, Ahroni J, Boyko E et al. Chronology and determinants of tissue repair in diabetic lower-extremity ulcers. *Diabetes* 1991;40:1305-1313.

45) Ellenberg M, Weber H. The incipient asymptomatic diabetic bladder. *Diabetes* 1967;16:331-335.

46) Sandler M, Bunn A, Stewart R. Cross-section study of pulmonary function in patients with insulin-dependent diabetes mellitus. *Am Rev Respir Dis* 1987;135:223-229.

47) Reichard P, Berglund B, Britz A et al. Intensified conventional insulin treatment retards the microvascular complications of insulin-dependent diabetes mellitus (IDDM): the Stockholm diabetes intervention study (SDIS) after 5 years. *J Intern Med* 1991;230:101-108.

48) Butler S, Btaiche I, Alaniz C. Relationship between hyperglycemia and infection in critically ill patients. *Pharmacotherapy* 2005;25:963-76.

49) Kwoun M, Ling P, Lydon E et al. Immunologic effects of acute hyperglycemia in non-diabetic rats. *J Parenter enteral Nutr* 1997;21:91-95.

50) Black C, Hennessey P, Andrassy R et al. Short term hyperglycemia depresses immunity through non-enzymatic glycosylation of circulating immunoglobulin. *J Trauma* 1998;30:830-832.

51) Bagdade J, Root R, Bulger R. Impaired leukocyte function in patients with poorly controlled diabetes. *Diabetes* 1974;23:9-15.

52) MacRury S, Gemmell C, Patterson K et al. Changes in phagocytic function with glycemic control in diabetic patients. *J Clin Pathol* 1989;42:1143-1147

53) Zerr K, Furnary A, Grunkemeier G et al. Glucose control lowers the risk of wound infection in diabetics after open heart operations. *Ann Thorac Surg* 1997;63:356-61.

54) Pomposelli J, Baxter J, Babineau T et al. Early postoperative glucose control predicts nosocomial infection rate in diabetic patients. *J Parenter Enteral Nutr* 1998;22:77-81.

55) Golden S, Peart-Vigilance C, Kao E et al. Perioperative glycemic control and the risk of infectious complications in a cohort of adults with diabetes. *Diabetes Care* 1999;22:1408-1414.

56) Furnary A, Zerr K, Grunkemeier G et al. Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. *Ann Thorac Surg* 1999;67:352-360.

57) Porter J, Baur G, Taylor L. Lower-extremity imputations for ischemia. *Arch Surg* 1981;116:89-92.

58) Gibran N, Jang Y-C, Isik F et al. Diminished neuropeptide levels contribute to the impaired cutaneous healing response associated with diabetes mellitus. *J Surg Res* 2002;108:122-128.

59) Carr M. Diabetes mellitus a hypercoagulable state. *J Diabetes Complications* 2001;15:44-554.

60) Williams S, Goldfine A, Timimi F et al. Acute hyperglycemia attenuates endothelium dependent vasodilation in humans in vivo. *Circulation* 1998;97:1695-1701.

61) Ammar R, Gutterman D, Brooks L et al. Free radicals mediate endothelial dysfunction of coronary arterioles in diabetes. *Cardiovasc Res* 2000;47:595-601.

62) Farina J, Furio V, Fernandez-Acenero et al. Nodular fibrosis of the lung in diabetes mellitus. *Virchows Arch* 1995;427:61-63.

63) Watanabe K, Senju S, Toyoshima H et al. Thickness of the basement membrane of bronchial epithelial cells in lung diseases as determined by transbronchial biopsy. *Respir Med* 1997;91:406-410.

64) Sandler M, Bunn A, Stewart R. Cross-section study of pulmonary function in patients with insulin-dependent diabetes mellitus. *Am Rev Respir Dis* 1987;135:223-229.

65) Hsia C, Raskin P. The diabetic lung: relevance of alveolar microangiopathy for the use of inhaled insulin. *Am J Med* 2005;118:205-211.

66) Rosenstock J, Friberg T, Raskin P. Effect of glycemic control on microvascular complications in patients with type 1 diabetes mellitus. *Am J Med* 1986;81:1012-1018.

67) Reichard P, Berglund B, Britz A et al. Intensified conventional insulin treatment retards the microvascular complications of insulin-dependent diabetes mellitus (IDDM): the Stockholm diabetes intervention study (SDIS) after 5 years. *J Intern Med* 1991;230:101-108.

68) International diabetes federation atlas sixth edition: http://www.idf.org/diabetesatlas/update-2014

Appendices:

Appendix 2.A: Search Strategy

Diabetes and The Occurrence of Infection: Search Strategy

Information source:

We searched the following biomedical databases: PubMed, EMBASE, The Cochrane Library via Wiley, International Pharmaceutical Abstracts via EBSCO, and Web of Science. There was no language restrictions.

Search:

MeSH and free-text terms were used to search PubMed. EMTREE and free-text terms were used to search EMBASE. The remaining databases were searched using free-text terms.

PubMed:

We conducted a MeSH term search (exploded) as well as a free-text search to allow identification of articles that have not been indexed with MeSH terms.

MeSH:

1. Diabetes mellitus [MeSH terms]
2. Infections [MeSH terms]
3. Cohort studies [MeSH terms]
4. Case-control studies [MeSH terms]
5. Retrospective studies [MeSH terms]
6. Observational study [Publication Type] [MeSH terms]
7. #1 AND #2
8. #3 OR #4 OR #5 OR #6
9. #7 AND #8

Free-Term Search (title and abstract):

1. Diabetes[Title/Abstract]
2. "Diabetes mellitus"[Title/Abstract]
3. Infection*[Title/Abstract]
4. Cohort[Title/Abstract]
5. Case-control[Title/Abstract]
6. Retrospective[Title/Abstract]
7. Observational[Title/Abstract]
8. #1 OR #2
9. #3 AND #8

10. #4 OR #5 OR #6 OR #7
11. #9 AND #10

#9 OR #11

EMBASE:

We conducted an EMTREE term (exploded) search as well as a free-text search to allow identification of articles that have not been indexed with EMTREE terms.

EMTREE:

1. 'Diabetes mellitus'/exp
2. 'Infection'/exp
3. 'Cohort analysis'/exp
4. 'Case control study'/exp
5. 'Retrospective study'/exp
6. 'Observational study'/exp
7. #1 AND #2
8. #3 OR #4 OR #5 OR #6
9. #7 AND #8

Free text search (title, abstract, keyword):

1. Diabetes:ti,ab,de
2. ‘Diabetes mellitus’:ti,ab,de
3. Infection:ti,ab,de
4. Cohort:ti,ab,de
5. ‘Case-control’:ti,ab,de
6. Retrospective$:ti,ab,de
7. Observational: ti,ab,de
8. #1 OR #2
9. #8 AND #3
10. #4 OR #5 OR #6 OR #7
11. #9 AND #10

#9 OR #11

The Cochrane Library:

Databases in the Cochrane Library include: Cochrane Central Register of Controlled Trials (clinical trials), Cochrane Database of Systematic Reviews (Cochrane reviews), Database of Abstracts of Reviews of Effects (systematic review quality assessments), Cochrane Methodology Register (control trial methods), Health Technology Assessment Database (technology assessments), NHS Economic Evaluation Database (economic evaluations), About The Cochrane Collaboration (Cochrane groups).

We conducted free-text searches. Results are limited to Cochrane Reviews (ALL) and Other Reviews.

Free term search (title, abstract, keyword):

1. Diabetes
2. "Diabetes mellitus"
3. Infection
4. Cohort
5. "Case-control"
6. Retrospective
7. Observational
8. #1 OR #2
9. #3 AND #8
10. #4 OR #5 OR #6 OR #7
11. #9 AND #10

International Pharmaceutical Science:

We searched using free-text with the "all text" scope.

1. Diabetes
2. “Diabetes mellitus”
3. Infection*
4. Cohort
5. “Case-control”
6. Retrospective
7. Observational
8. S1 OR S2
9. S3 AND S8
10. S4 OR S5 OR S6 OR S7
11. S9 AND S10

Web of Science:

We searched using free-terms in this database.

1. topic=Diabetes
2. topic= “Diabetes mellitus”
3. topic=Infection*
4. topic=Cohort
5. topic=“case-control”

6. topic=Retrospective
7. topic=Observational
8. #1 OR #2
9. #3 AND #8
10. #4 OR #5 OR #6 OR #7
11. #9 AND #10

Appendix 2.B: Individual Study Characteristics

Author	Year	Design	Patients (n)	Male (%)	Age, Mean (SD)	Diabetes Type	Outcome	NOS Score
Abbott	2001	Cohort	327993	52.2	63.2 (14.9)	unclear	Blood	6
Abdel-Fattah	2008	Case-Control	844	53.8	41.2 (29.4)	unclear	RTI	6
Acosta	2012	Case-Control	515	0	30.6 (4.7)	1	Blood	5
Acosta	2013	Cohort	1622474	0	–	1, 2, gestational	Blood	6
Adams	2013	Cohort	40491	37.2	–	1, 2	SSTI	6
Al-Asmary	2004	Case-Control	824	52.7	40.8 (29.6)	unclear	GU	6
Alisjahbana	2006	Case-Control	1010	52.5	–	unclear	RTI	7
Almirall	1999	Case-Control	680	–	–	unclear	RTI	7
Álvarez-Lerma	2003	Cohort	1765	66.7	61.2 (15.7)	insulin-treated	GU	6
Antonelli	2005	Case-Control	866	31.8	60.8 (12.6)	2	Viral	7
Apisarnthanarak	2003	Case-Control	60	46.7	–	unclear	SSTI	6
Apisarnthanarak	2007	Case-Control	230	30.9	–	unclear	Unspecified	6
Aragón-Sánchez	2010	Cohort	283	63.6	–	unclear	SSTI	6
Ariyaratnam	2010	Cohort	7420	79.2	–	unclear	SSTI	6
Ata	2010	Cohort	1060	–	–	unclear	SSTI	6
Baaten	2010	Cohort	304	45.4	–	unclear	Multiple	6
Bachoura	2011	Case-Control	1783	49.5	–	unclear	SSTI	5
Baillot	2010	Cohort	23499	70.7	63.8 (11.4)	unclear	SSTI	6
SA	2011	Cohort	500	59	62.1 (9.9)	unclear	SSTI	5
Bartholomeeusen	2007	Nested Case-Control	160000	–	–	unclear	SSTI	5
Bassetti	2012	Case-Control	495	58.2	61.8 (17.1)	unclear	Blood	5
Bedanova	2009	Cohort	150	82.7	54.1 (7)	unclear	Multiple	6
Bical	2004	Cohort	712	91	59.6 (9.3)	1, 2	SSTI	6
Bitkover	1998	Case-Control	111	–	64.2 (11.6)	unclear	SSTI	6
Borer	2012	Case-Control	464	70	–	unclear	Unspecified	6
Borger	1998	Cohort	12267	72.2	–	unclear	SSTI	6
Bower	2008	Case-Control	63	60.3	61 (10.6)	unclear	SSTI	5
Boyko	2005	Cohort	1017	0	–	1, 2	GU	6
Boyko	2002	Case-Control	1814	0	66.1 (6.2)	1, 2	GU	7
Bundy	2006	Cohort	3878	75.3	–	1, 2	SSTI	6
Caire	2011	Cohort	23	100	–	unclear	SSTI	5
Carson	2002	Cohort	146786	70.8	65 (3.7)	unclear	Multiple	6
Carton	1992	Cohort	101392	–	64.5 (14.4))	1, 2	Blood	7
Chen	2012	Cohort	109038	50.4	–	1, 2	GU	7
Chen L.	2011	Cohort	233	54.9	76.9 (10.5)	unclear	RTI	6
Chen S	2009	Cohort	195	–	–	unclear	SSTI	6
Choudry	2006	Cohort	1027	73	33.5 (11.7)	unclear	RTI	5
Chouw	2005	Cohort	246	54.1	51 (13)	unclear	SSTI	5
Dalrymple	2010	Cohort	119858	90.5	75.2 (6.5)	unclear	Unspecified	7
Daneman	2010	Cohort	587327	37.8	–	unclear	SSTI	6
Davis	2005	Cohort	120	50	64.3 (9.9)	2	Unspecified	8
de Souza	2007	Cohort	55	60	45.6 (10.4)	unclear	Unspecifie	6

							d	
Boer	2006	Case-Control	521	73.3	56	unclear	RTI	7
Deng	2004	Cohort	751	84.3	56	2	SSTI	6
Di Palo	1988	Cohort	3796	–	–	unclear	SSTI	5
Dixon	2009	Cohort	7224	–	65 (16.5)	unclear	SSTI	5
Dobler	2012	Cohort	19855283	49.3	–	1,2, gestational	RTI	7
Dupuy	1999	Case-Control	423	52.3	56.6 (1.3)	unclear	SSTI	5
Edmonston	2010	Case-Control	409	50.6	46.3	unclear	SSTI	6
Ennker	2009	Case-Control	3675	–	–	unclear	SSTI	5
Everhart	2013	Cohort	1875	–	–	unclear	SSTI	6
Factor	2003	Case-Control	450	–	–	unclear	Unspecifie d	6
Fakih	2007	Cohort	3578	32.5	67.2 (11)	unclear	SSTI	6
Farrow	2008	Cohort	105	98	55.2	unclear	SSTI	6
Fernandez-Sabe	2009	Case-Control	90	65.5	–	unclear	Other	6
Filsoufi	2009	Cohort	5798	37.6	64 (14)	unclear	SSTI	6
Floros	2011	Cohort	5649	–	64.5	unclear	SSTI	7
Flynn	2000	Cohort	98	67.3	–	2	SSTI	5
Friedman	2007	Case-Control	123	65	51.7 (14.5)	unclear	SSTI	6
George	2011	Cohort	556	58.1	57.7	unclear	SSTI	6
Gorter	2010	Cohort	6958	0	51 (17)	1, 2	GU	6
Goswami	2000	Cohort	166	0	31.5 (10.9)	1, 2	GU	6
Graf	2009	Case-Control	240	68.7	68	unclear	SSTI	5
Gude	2006	Case-Control	489	68	67 (11)	unclear	SSTI	6
Guvener	2002	Cohort	1090	70.8	59.6 (10.3)	unclear	Multiple	6
Hamilton	2013	Cohort	1139	–	64.1 (11.3)	2	Multiple	7
Heal	2006	Cohort	857	52.4	56.3 (16.5)	unclear	SSTI	6
Heal	2012	Cohort	953	54.3	59.3 (33)	unclear	SSTI	6
Herce	2013	Case-Control	105	60	73.3 (11)	unclear	SSTI	6
Iorio	2012	Cohort	4241	–	–	unclear	SSTI	6
Kadija	2011	Cohort	538	0	50 (14)	unclear	SSTI	6
Kanafani	2006	Nested Case-Control	81	54.3	51	unclear	SSTI	5
Kato	2013	Cohort	981	0	46.4	unclear	SSTI	6
Lai	2007	Case-Control	–	–	–	unclear	SSTI	6
Latham	2001	Case-Control	1044	68.6	63.7 (10.3)	unclear	SSTI	6
Ledur	2011	Cohort	717	67.4	61.9 (11)	unclear	Unspecifie d	5
Lee F.	2013	Nested Case-Control	66	40.9	–	unclear	SSTI	6
Li GQ	2013	Cohort	2061	50.5	51 (16.7)	unclear	SSTI	6
Marschall	2007	Case-Control	76	63.1	62.2 (16.3)	unclear	SSTI	5
Matsuda	2009	Cohort	11	68.7	61.8 (11.5)	unclear	SSTI	6
Mossad	1997	Case-Control	46	71.7	–	unclear	SSTI	5
Munoz	2008	Cohort	357	60.2	64.3 (12.7)	unclear	SSTI	6
Nakano	2008	Cohort	1500	72.7	67.8 (9.3)	unclear	SSTI	6
Schimmel	2010	Nested Case-Control	171	42.7	48.6 (15.1)	1, 2	SSTI	6
Simsek Yavuz	2008	Cohort	991	71.9	56.9 (13.1)	unclear	SSTI	5
Singh	1993	Cohort	701	87.9	58.5	unclear	SSTI	5
Siracuse	2013	Cohort	478	57.9	69	unclear	SSTI	5
Spelman	2000	Cohort	690	73.7	–	unclear	Multiple	5
Takoudes	2004	Cohort	728	0	29.7	1, 2	Multiple	6
Talbot	2004	Case-Control	152	–	–	unclear	SSTI	6
Trinh	2009	Case-Control	202	39.1	58.4 (16.4)	unclear	SSTI	6
Veeravagu	2009	Cohort	24774	94.8	–	unclear	SSTI	5

Vilar-Compte	2000	Case-Control	3372	–	50 (17.1)	unclear	SSTI	6
Wasson	2013	Case-Control	388	89.7	61.5	unclear	SSTI	7
Wukich	2011	Cohort	1462	39.5	48.2 (15.8)	unclear	SSTI	5
Zacharias	1996	Cohort	2317	69.1	62 (10.9)	unclear	SSTI	6
John	2001	Cohort	171	64.9	53.5 (6.8)	1, 2	Unspecified	6
Hata	2011	Cohort	55492	46.8	60.1 (16.5)	unclear	Viral	7
Heymann	2008	Nested Case-Control	111189	44.4	–	unclear	Viral	6
Muller	2005	Cohort	26328	41.1	63.5 (13.4)	1, 2	Multiple	7
Hirji	2012	Cohort	271840	53.9	62.6 (13.5)	2	GU	8
Hirji	2012	Cohort	271840	53.9	62.6 (13.6)	2	GU	8
Holley	1991	Cohort	60	66.7	48.5 (15)	unclear	SSTI	6
Hoy	1985	Cohort	268	59.7	–	unclear	GU	5
Hu	2014	Cohort	20655	52.2	–	unclear	RTI	6
Hu	2004	Case-Control	1810	0	66.2 (6.3)	unclear	GU	6
Ikegami	2012	Cohort	346	48	51.5 (11.8)	unclear	RTI	6
Jackson	1995	Case-Control	864	50.5	–	unclear	Unspecified	6
Jackson	2004	Cohort	1017	0	–	1, 2	GU	6
Kaandorp	1995	Case-Control	4907	30.6	–	unclear	Other	6
Kaiserman	2005	Cohort	159634	46.2	65.7 (0.05)	unclear	Viral	6
Kang	2012	Cohort	93931	–	–	unclear	GU	5
Karamanos	2013	Cohort	81165	42	52.5 (13.8)	unclear	Multiple	6
Ko	2011	Cohort	1000887	46.9	61 (12.6)	unclear	GU	8
Kontoyiannis	2005	Case-Control	81	51.9	51.3	unclear	Other	6
Kornum	2008	Case-Control	376629	52.9	–	1, 2	RTI	6
Kuo	2013	Cohort	253349	51.1	55.4 (8.8)	2	RTI	8
Lau	2014	Cohort	166715	52.6	–	unclear	Viral	8
Lee CH	2013	Cohort	70782	83	54.5 (22.9)	unclear	RTI	7
Lee JH	2013	Case-Control	162	69.7	–	unclear	GU	5
Lee MC	2013	Cohort	99806	52.5	61.9 (14.2)	1, 2	TB	7
Leegaard	2011	Case-Control	17224	53.3	–	1, 2	RTI	6
Lehmann	2000	Case-Control	92	57.6	–	unclear	H&N	5
Leth	2011	Cohort	2492	0	32.1 (4.7)	1,2, gestational	Unspecified	6
Leung	2008	Cohort	42116	34.7	72.6	unclear	RTI	6
Lipsky	1986	Case-Control	193	–	–	unclear	Unspecified	7
Lui S.A	2007	Cohort	994	93.1	51.5 (11.7)	unclear	SSTI	5
Lola	2011	Cohort	172	77.3	66 (10)	unclear	Unspecified	6
Ma	2012	Cohort	376	48.7	73.1 (3.4)	unclear	SSTI	6
McKane	2014	Cohort	2551	57.1	65.4 (16)	unclear	Blood	7
Michalia	2009	Cohort	343	71.7	52 (17.4)	1, 2	Blood	6
Monaghan	2011	Case-Control	5736	62.1	51.8 (22.2)	unclear	GU	4
Montague	2001	Cohort	491	100	–	unclear	SSTI	5
Montan	1998	Case-Control	277	30.7	74.7	unclear	H&N	6
Myers	2012	Cohort	148	41.9	57.3 (10)	1, 2	Unspecified	6
Nassaji-Zavareh	2007	Cohort	300	48.3	51.8 (22.5)	unclear	Other	6
Neal	1997	Case-Control	825	39.5	44.2 (17.3)	unclear	GI	5
Halleberg Neyman	2011	Cohort	86	29.1	80 (11.1)	unclear	GU	6
Platt	1986	Cohort	1478	51.1	–	unclear	GU	5
Partikaki	2008	Cohort	561	67.4	55.5 (18.7)	unclear	Blood	6
Ryan	1997	Case-Control	111	–	–	unclear	Blood	5
Scholes	2005	Case-Control	788	0	32.9 (9.8)	unclear	GU	6

Sheiner	2009	Cohort	199093	0	28.5 (6)	gestational, other	GU	6
Singh	2009	Case-Control	100	–	–	unclear	Other	5
Strom	2000	Case-Control	546	61.9	–	unclear	Other	6
Suputtamongkol	1999	Case-Control	580	59.1	51.5 (15.5)	unclear	Blood	6
Terpenning	2001	Case-Control	358	–	–	unclear	RTI	6
Thomsen	2005	Case-Control	14487	–	–	1, 2	Blood	7
Thomse	2007	Case-Control	73780	54.2	–	1, 2	GI	7
Thomsen	2011	Case-Control	4357	49.1	–	1, 2	Blood	7
Toure	2013	Cohort	390	60.5	–	1, 2	Blood	5
Vidal	2012	Cohort	4388	66.1	50.1 (14.5)	unclear	GU	6
Viglino	1994	Cohort	1990	55.9	58 (14.5)	unclear	Multiple	6
Wang H.E	2012	Cohort	30183	44.8	–	unclear	Blood	6
Wilson	1998	Cohort	389	100	–	unclear	SSTI	5
Yang C.H	2012	Cohort	886	74.5	45.2	unclear	Unspecified	5
Simsir	2010	Cohort	2027	100	64.3 (10.1)	unclear	Blood	5
Antonio	2010	Cohort	114	65.8	53.1 (11.7)	unclear	Unspecified	5
Antoniou	2014	Cohort	989302	64.4	–	unclear	Viral	7
Blumentals	2012	Cohort	1074315	47.8	–	2	Viral	7
Clech	2007	Nested Case-Control	3281	60.7	–	unclear	GU	5
Gajewska	2005	Cohort	45	0	–	unclear	Viral	6
Heilmann	2013	Cohort	1297	69.6	67 (12.7)	unclear	SSTI	5
Higgins	2009	Cohort	136	81.6	50.6 (11.3)	unclear	Unspecified	6
Hu C.C	2012	Cohort	76362	61.5	62.2 (15.2)	unclear	H&N	7
Jaar	2000	Cohort	4005	52.3	59.4 (15.4)	1, 2	Blood	6
Lee CH	2012	Cohort	140	72.1	47.5 (15)	unclear	Bone	6
Lee P.Y	2010	Cohort	260	76.1	58.3 (14.2)	unclear	SSTI	5
Liao	2006	Cohort	337	17.5	–	unclear	SSTI	7
Matros	2010	Cohort	21191	34.3	65	unclear	SSTI	6
Memmel	2004	Cohort	1256	60.8	39.4 (10.5)	unclear	Multiple	5
Michalopoulos	2011	Case-Control	84	73.8	64.3 (11.5)	unclear	Blood	5
Pablos-Mendez	1997	Case-Control	42656	58.2	–	1, 2	RTI	5
Perez	2006	Case-Control	75723	50.4	–	unclear	RTI	5
Pull ter Gunne	2009	Cohort	3174	40.1	55.6 (15.5)	unclear	SSTI	5
Wang I.K	2012	Cohort	898	41	56 (14.6)	unclear	Blood	6
Wilson	1995	Cohort	823	100	–	unclear	SSTI	4
Yamashita	2000	Cohort	367	70	63.5 (10.4	1, 2	Unspecified	6
Thomsen	2004	Case-Control	6578	47.3	–	1, 2	Blood	7
Coskun	2000	Cohort	117	71	55	unclear	SSTI	5
Khurram	2004	Case-Control	57	57.9	46.5 (17.2)	unclear	Unspecified	5
Wang Q	2013	Case-Control	13057	63.9	50.6 (17.5)	2	RTI	7
Thanni	2004	Cohort	90	58.9	40 (17)	unclear	SSTI	5
Bailey	1970	Cohort	1797	0	–	unclear	GU	5
Baynes	1993	Case-Control	773	61.2	–	unclear	SSTI	7
Picon	2007	Cohort	610	61.6	36 (14)	unclear	RTI	4
Pezer	2013	Case-Control	109	–	–	unclear	Viral	6
Yoon	2013	Case-Control	344	0	54 (15.6)	unclear	GU	7
Jackson	2013	Nested Case-Control	4730	–	–	unclear	RTI	6
Shah	2003	Cohort	1830820	51.7	60.9 (11.6)	unclear	Multiple	8
Weitzman	2013	Cohort	2020709	–	–	unclear	Viral	7
Limmathurotsa	2010	Cohort	–	–	–	unclear	Unspecifie	7

kul							d	
Seminog	2013	Cohort	–	–	–	unclear	Unspecifie d	7
Abdul-Jabbar	2012	Cohort	6628	48.1	56.5	unclear	SSTI	5
Acott	2009	Cohort	38989	–	61.3	unclear	Multiple	6
Adrenito	2008	Cohort (Macthed cohort?)	54	74.1	52.8	1, 2	SSTI	6
Adetayo	2012	Cohort	297	–	51.7 (9.5)	unclear	Multiple	5
Alserius	2008	Cohort	605	79	66 (9)	2	SSTI	7
Altiparmak	2002	Case-Control	35	65.7	32.8 (10.3)	unclear	Unspecifie d	6
Alvarsson	2012	Cohort	194	54.5	78.4	unclear	Unspecifie d	6
Al-Zaru	2010	Cohort	216	78.1	60.4 (9.1)	unclear	SSTI	6
Appaduray	2013	Cohort	519	–	55 (17.7)	1, 2	Unspecifie d	6
Aseeri	2008	Case-Control	188	43.6	–	1, 2	GI	6
Atilgan	2014	Case-Control	305	65.9	25.7 (20.5)	unclear	Unspecifie d	5
Backes	2014	Cohort	191	68.6	–	unclear	SSTI	6
Baker	2012	Cohort	17715	49.6	–	unclear	RTI	6
Behnke	2014	Cohort	396	53.3	57 (17)	unclear	SSTI	5
Benin	2003	Case-Control	438	42	–	1, 2	Unspecifie d	6
Bevilacqua	2011	Cohort	65	35.4	59.2 (14.6)	unclear	Blood	5
Birgand	2013	Cohort	552	82.5	–	unclear	SSTI	6
Bolognesi	2008	Cohort	751340	38.8	67.9 (11.5)	unclear	Multiple	6
Bonds	2013	Cohort	254	53.9	56 (14)	unclear	SSTI	5
Bowen	2005	Cohort	164	65.7	47 (18)	unclear	Unspecifie d	7
Bozic	2014	Case-Control	587	55	–	unclear	Bone	6
Bykowski	2011	Cohort	2755	37	52.9 (15)	unclear	SSTI	6
Calderwood	2013	Cohort	524892	31.8	–	unclear	SSTI	6
Carignan	2012	Case-Control	240	100	–	unclear	Multiple	7
Chelemer	2002	Cohort	533	74.8	–	unclear	Unspecifie d	6
Chen C-H	2006	Cohort	756	58.6	40.7 (12.2)	unclear		6
Chung S.D	2014	Cohort (Macthed cohort)	30426	53.1	–	unclear	SSTI	7
Chung C.P	2012	Cohort	169	0	63.8 (12.1)	unclear	GU	6
Colombier	2013	Case-Control	222	73.4	64 (12)	unclear	SSTI	6
Copeland	1994	Case-Control	73	0	67.6	unclear	SSTI	5
Crowson	2012	Cohort	584	27.7	57.5 (15.1)	unclear	Unspecifie d	7
Daniels	2010	Cohort	243	21.4	55.1	unclear	Infection	4
Menezes	2008	Case-Control	240	56.7	44.63	unclear	SSTI	5
Demura	2009	Cohort	110	59.1	–	unclear	SSTI	4
Donati	2014	Cohort	2782	67.8	–	unclear	Unspecifie d	6
Dowesy	2008	Cohort	2206	44.2	–	unclear	Bone	7
Dublin	2009	Case-Control	3360	50.8	–	unclear	RTI	7
Dunkel	2012	Cohort	289	68.8	–	unclear	Unspecifie d	5
Dziedzic	2009	Cohort	659	48.5	69.6 (12.4)	unclear	RTI	6
Einsiedel	2013	Cohort	613	43.3	45.8 (15.7)	uncelar	Multiple	7
Estrada	2003	Cohort	1574	66.8	63.5 (10.4)	unclear	Unspecifie d	6
Fernandez-Fresnedo	2001	Cohort	107	71	51.4 (8.6)	1, 2	Unspecifie d	4
Filsoufi	2007	Cohort	2725	76.4	65.4 (10.6)	unclear	Multiple	7

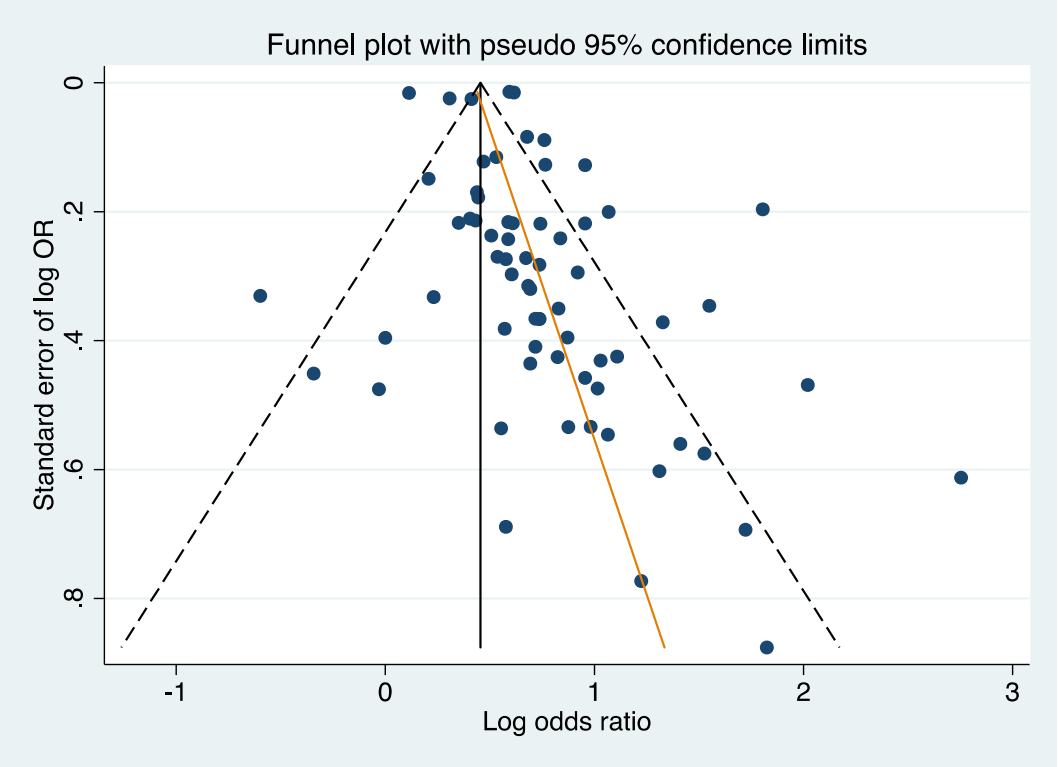
Flores-Maldonado	2001	Cohort	261	15.3	40 (12)	unclear	SSTI	6
Friedman	2007	Cohort	4633	97	66.3	unclear	SSTI	6
Frisch	2010	Cohort	3112	46.2	56.5 (16)	unclear	Multiple	6
Fusconi	2006	Cohort	115	–	–	unclear	SSTI	5
Gali	2012	Cohort	574	–	60.6 (13)	unclear	Unspecified	6
Gansera	2006	Cohort	8666	78.6	65.1 (9.3)	unclear	SSTI	4
Garber	1998	Cohort	360	100	59	unclear	GU	6
Garcia	2013	Cohort	92	73.9	54 (12.2)	2	Unspecified	5
Haraway	2013	Cohort	135	21.5	57	unclear	SSTI	6
Harness	2010	Cohort	3003	31.2	–	unclear	SSTI	6
Hayes	2014	Cohort	187	61.5	–	1, 2	Blood	6
Hermsen	2011	Case-Control	352	59.1	60.3	unclear	Unspecified	6
Hirotani	1999	Cohort	420	75.7	64	unclear	SSTI	7
Hong	2014	Cohort	53249	48.4	–	unclear	GI	6
Hughes	2013	Cohort	2110	65.5	71 (8.7)	unclear	Multiple	4
Itagaki	2013	Cohort	1526360	73.3	64.8 (10.7)	unclear	SSTI	6
Jeon	2012	Cohort	13800	47.4	–	unclear	SSTI	6
Ji	2010	Cohort	393	70	74.2(3.1)	unclear	Multiple	6
Ji	2009	Cohort	441	66.9	71.8 (3)	unclear	Multiple	6
Jick	2006	Case-Control	2463	52.2	–	unclear	RTI	8
Jih	2009	Cohort	1000000	49.6	–	unclear	Viral	7
Joesoef	2012	Case-Control	675350	54.2	–	unclear	Viral	8
Jovanovic	2006	Cohort	69	91.3	–	unclear	SSTI	4
Kline	2009	Cohort	81	64.2	47.1	unclear	SSTI	6
Kluytmans	1995	Case-Control	160	75.6	62.7 (9.6)	unclear	SSTI	5
Lee S-E	2010	Cohort	355	0	72.1	unclear	SSTI	5
Lee S-C	2004	Case-Control	101	55.4	63.7 (14.1)	unclear	Blood	5
Lehtinen	2010	Nested Case-Control	469	39.9	51.6 (15.3)	unclear	SSTI	6
Lemaire	2009	Cohort	1749	60.1	–	unclear	Blood	5
Linney	2010	Case-Control	284	47.2	75.6 (12.5)	unclear	GI	5
Malone	2002	Cohort	5031	95	61 (13)	unclear	SSTI	6
Mangrulkar	2009	Cohort	489	58.7	–	unclear	Unspecified	5
Masgala	2012	Case-Control	200	24	71.5 (16.8)	unclear	Unspecified	5
Matsa	2001	Cohort	765	78.2	–	unclear	SSTI	5
McCampbell	2002	Cohort	191	–	–	unclear	Multiple	5
Mekhail	2011	Cohort	707	42.3	46 (15)	unclear	SSTI	4
Memon	2013	Cohort	60	38.3	43.8 (11.8)	unclear	SSTI	6
Michalopoulos	2003	Case-Control	140	73.3	64.1 (9.9)	unclear	Blood	7
Migita	2013	Cohort	604	40.7	59.6 (16.8)	unclear	Unspecified	7
Miller	2007	Cohort	763	0	–	1, 2	SSTI	5
Minakata	2012	Cohort	1421	77.4	68.3 (9.1)	unclear	Multiple	7
Mittal	2014	Cohort	1651	62.7	76 (12)	unclear	Unspecified	6
Mohamed	2009	Cohort	7733	76.5	64.9 (10.9)	unclear	Unspecified	7
Mulaudzi	2009	Cohort	217	65	63.9	unclear	SSTI	6
Murphy	1992	Cohort	238	76.5	62.3 (10.8)	unclear	Unspecified	5
Nasell	2011	Cohort	1782	46	–	unclear	SSTI	7
Nelson	2014	Cohort	851	49.9	50 (13.7)	unclear	SSTI	5
Olsen	2002	Cohort	1695	64.9	–	unclear	SSTI	6

Olsen	2008	Case-Control	273	–	52.4	unclear	SSTI	6
Osterhoff	2014	Cohort	261	73.2	46 (18.6)	unclear	SSTI	6
Ovaska	2013	Case-Control	262	44	56	unclear	SSTI	6
Powe	1999	Cohort	4918	52.3	59.1 (15.8)	unclear	Blood	6
Puskas	2012	Cohort	3527	70.9	62.6 (10.6)	unclear	SSTI	6
Ramos	2008	Cohort	995	35	56.5 (15.9)	unclear	Unspecified	4
Ridderstolpe	2001	Cohort	2992	72.4	65.4 (10.5)	unclear	SSTI	6
Risnes	2010	Nested Case-Control	551	79.3	62.9 (9.5)	unclear	SSTI	5
Rocco	2013	Cohort	1016	53.4	70.3 (13.1)	unclear	Unspecified	6
Russo	2002	Cohort	2345	75.9	65.7	unclear	SSTI	6
Safdar	2005	Nested Case-Control	376	43.2	–	unclear	GU	5
Sajja	2012	Cohort	3072	86.8	58.2 (8.6)	unclear	SSTI	7
Sanderson	1990	Cohort	260	54.6	50.6	unclear	Multiple	5
sato	2010	Cohort	273	73.2	65.9 (11.9)	unclear	Multiple	6
Schwartz	2004	Cohort	2063	99.6	–	unclear	SSTI	6
Sepher	2009	Cohort	316	–	62	unclear	Unspecified	6
Shields	2013	Cohort	586	54.9	–	unclear	SSTI	7
Simon	2005	Cohort	76	89.5	50.4 (2)	unclear	Unspecified	6
Singh	2012	Cohort	903	15.8	48.1 (11.4)	unclear	SSTI	6
Song	2012	Cohort	6848	26	66.9 (12.6)	unclear	SSTI	5
Spinier	1998	Cohort	138	80.4	61.3 (12.2)	unclear	Unspecified	5
Swenne	2005	Cohort	374	77.2	65.6 (8.4)	unclear	SSTI	7
Tamayo	2012	Cohort	1610	39.1	67.8 (10.5)	unclear	RTI	7
Tang	2004	Cohort	30102	72.6	–	unclear	SSTI	4
Telzak	1991	Case-Control	155	51.6	67	unclear	GI	5
ter Gunne	2009	Cohort	3174	40.1	55.6 (15.5)	unclear	SSTI	6
Togo	2007	Cohort	535	67.7	62.1 (10.5)	unclear	Multiple	5
Torres	2006	Cohort	863	–	68.1(10.7)	unclear	SSTI	5
Trieman	1994	Cohort	1023	67.3	66	unclear	SSTI	5
Trick	2000	Case-Control	127	–	–	unclear	SSTI	5
Troidle	2003	Cohort	162	53.7	55.4 (11.3)	1, 2	SSTI	6
Vergidis	2012	Case-Control	50	–	58.5	unclear	Bone	5
Walcott	2014	Cohort	399	41.6	52.9 (0.8)	unclear	SSTI	7
Wallaert	2012	Cohort	1977	67.2	–	unclear	SSTI	8
Wang H.	2013	Cohort	707	32.7	72.5 (10.2)	unclear	Multiple	6
Weichman	2013	Cohort	546	–	49.5 (11.1)	unclear	Unspecified	5
Whang	2000	Cohort	900	84.3	–	unclear	Multiple	6
Wilson	2003	Case-Control	258	–	–	unclear	SSTI	6
Wlazlo	2013	Cohort	226	64.6	59.2 (11.5)	unclear	SSTI	7
Wong-McClure	2012	Case-Control	636	48.1	56.2	unclear	GI	6
Wu-H	2007	Case-Control	1180	63	60.5 (17.9)	unclear	RTI	5
Wukich	2010	Cohort	1000	44.3	46.7	unclear	SSTI	6
Yamamoto	1992	Cohort	566	60.8	48	unclear	SSTI	5
Yamauchi	2013	Cohort	1438	58.8	67 (10)	unclear	Multiple	6
Yavuz	2006	Cohort	991	71.9	57 (13.1)	unclear	SSTI	6
Horne	2008	Case-Control	247	–	–	unclear	SSTI	4
Howard	2009	Cohort	136	44.1	54.6 (15.5)	unclear	SSTI	5
Kuy	2013	Cohort	106	58.5	62 (14)	unclear	SSTI	5
Orlander	1992	Case-Control	22778	0	60	unclear	GU	6
Raja	2013	Cohort	909	66.1	62.3 (13.5)	unclear	Multiple	6

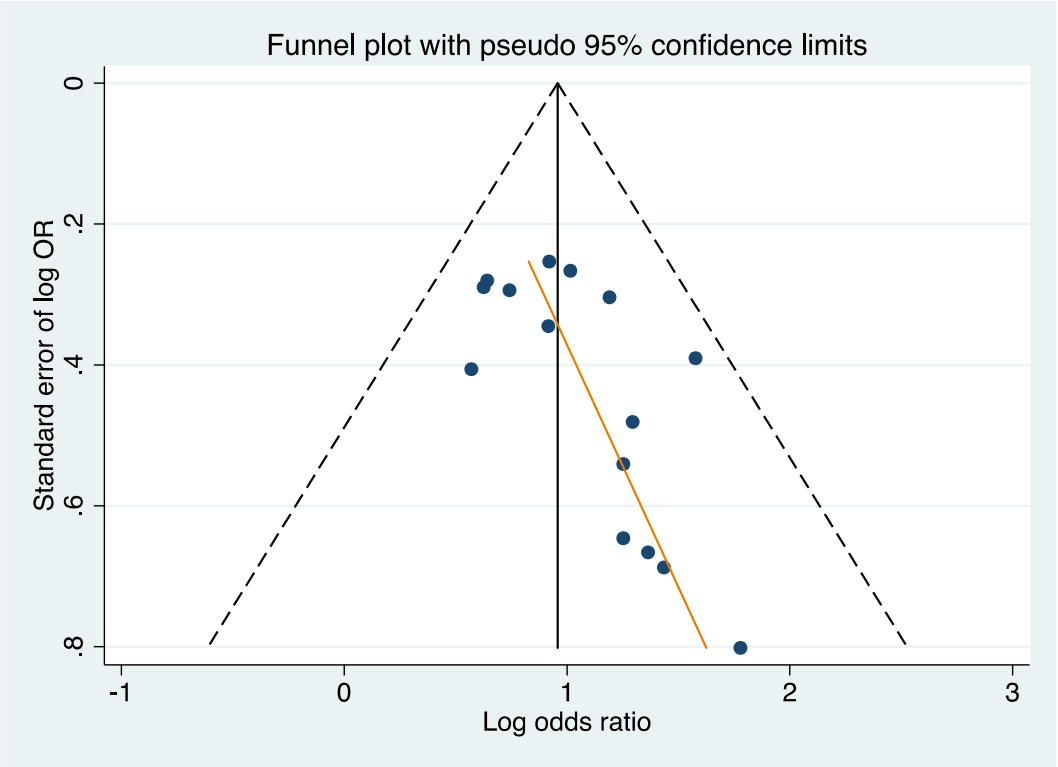
Chen W.	2013	Cohort	177527	51	–	unclear	RTI	6
Menderes	2010	Cohort	1000	0	29.8 (5.9)	gestational	SSTI	6
Topal	2012	Cohort	162	51.2	65.6 (10.5)	unclear	RTI	4
Guler	2006	Case-Control	204	43.1	47.7 (16.7)	unclear	GU	5
Ricci	2014	Cohort	335	44.8	57	unclear	SSTI	6
Steele	2012	Cohort	22288	19.3	44.2 (9.8)	1, 2, gestational	Multiple	6
Chaichana	2014	Cohort	817	45.6	56 (14)	unclear	SSTI	7
Hashimoto	2008	Cohort	242	54.5	–	unclear	Blood	6
Park	2012	Cohort	770	74.8	37.9	unclear	SSTI	6
Troutman	2001	Nested Case-Control	56	69.6	–	unclear	SSTI	4
Trussell	2008	Cohort	1482	71.9	67.1 (10.4)	unclear	SSTI	6

Appendix 2.C: Publication Bias Funnel Plots:

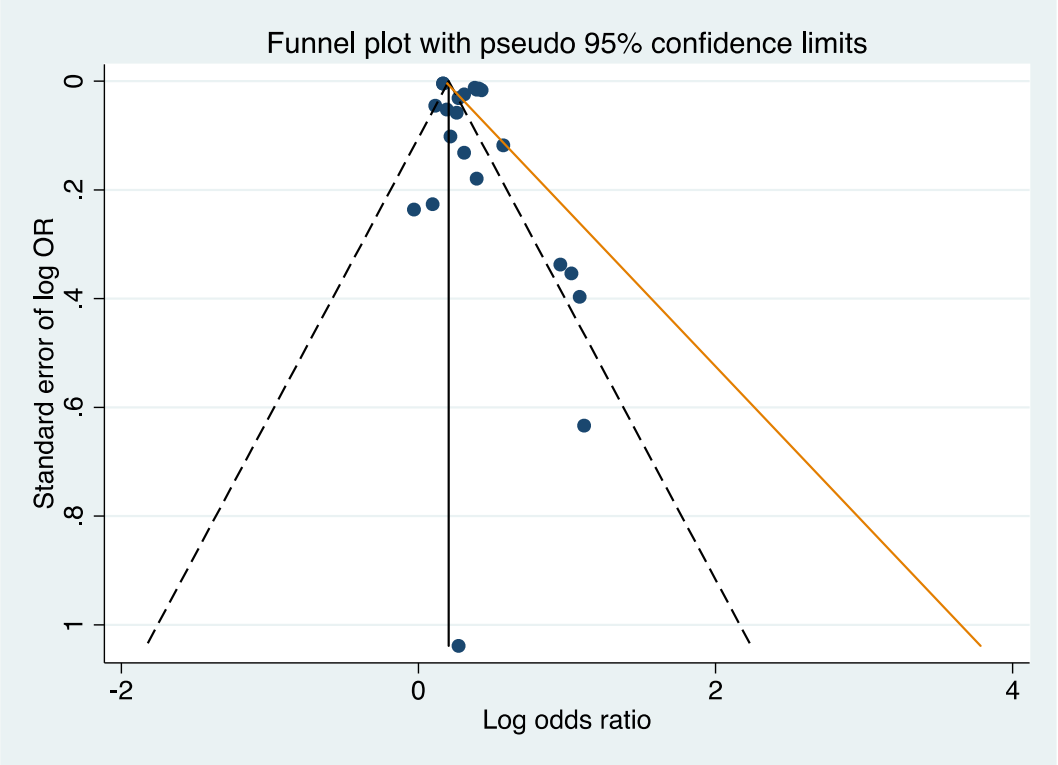
(1) SSTI Infections/Cohort Studies:



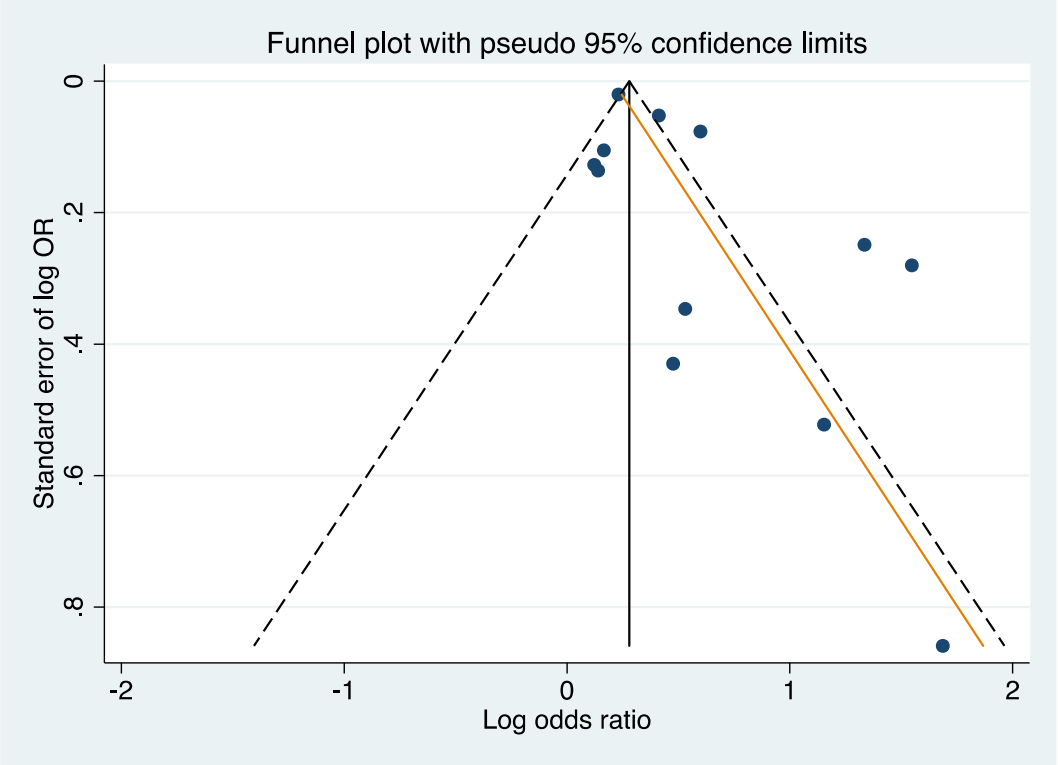
(2) SSTI Infections/Case-Control Studies:



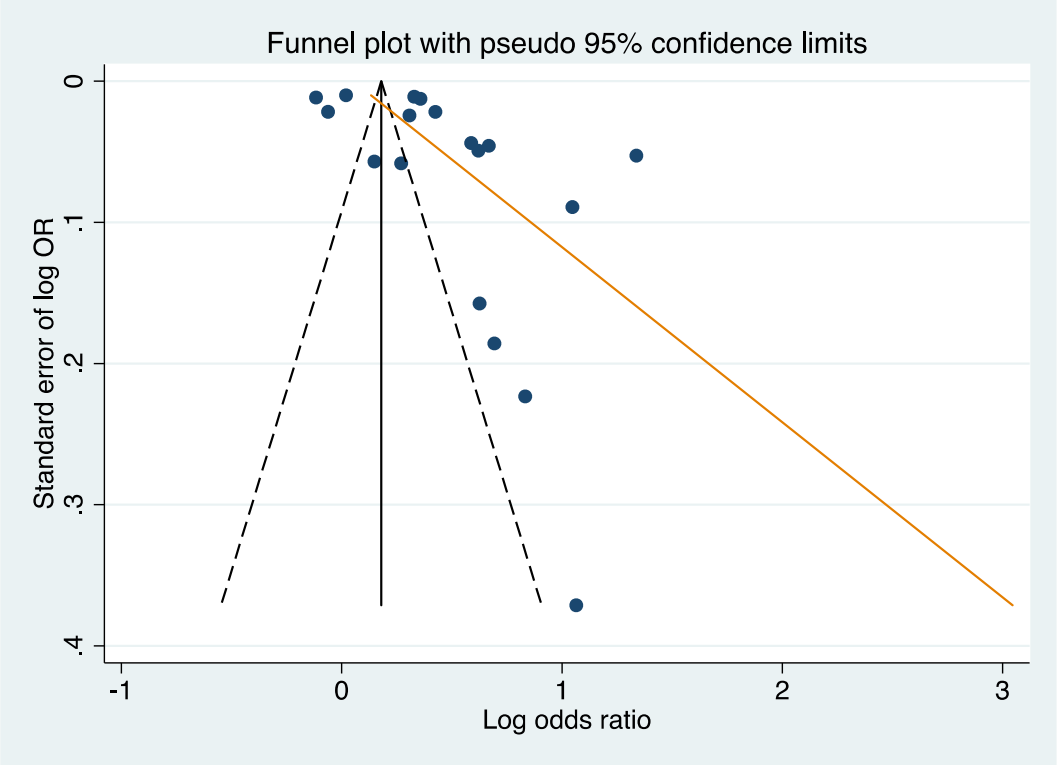
(3) RTI Infections/Cohort Studies:



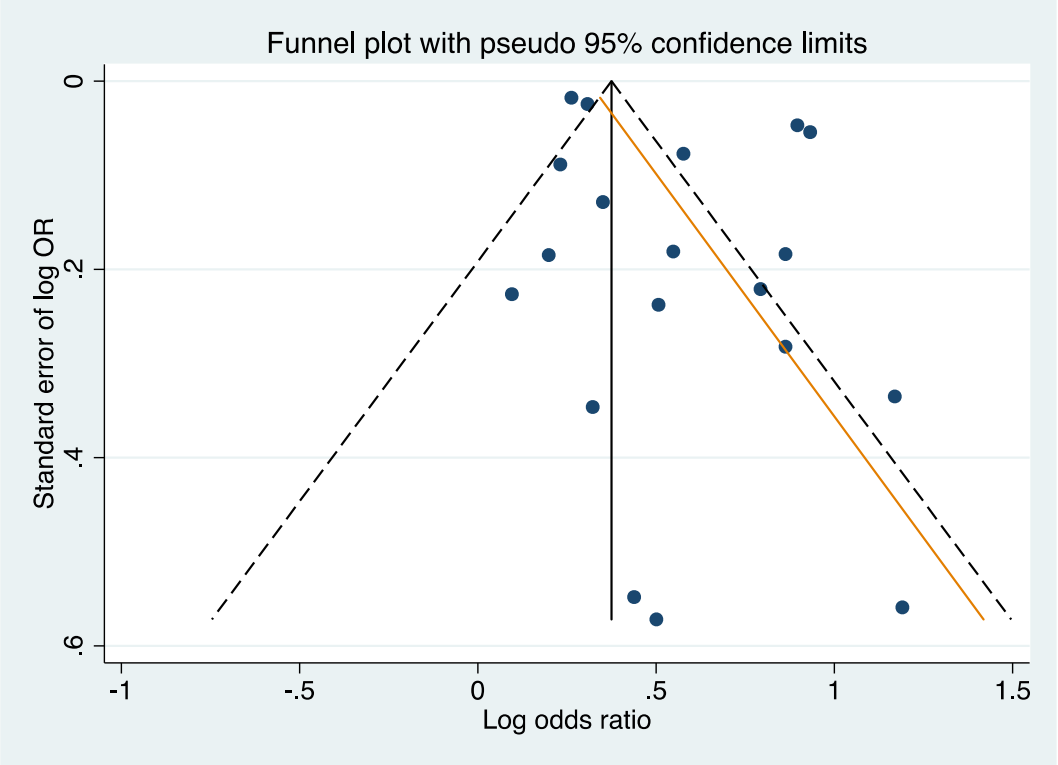
(4) RTI Infections/Case-Control Studies:



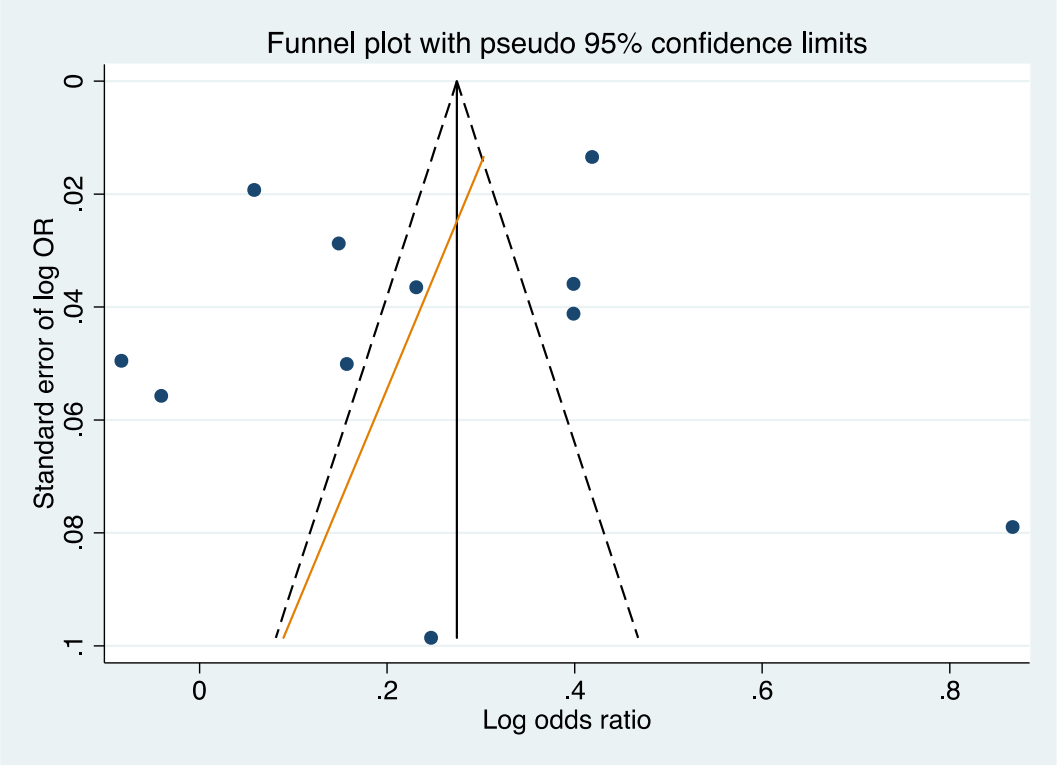
(5) Genitourinary Infections/Cohort Studies:



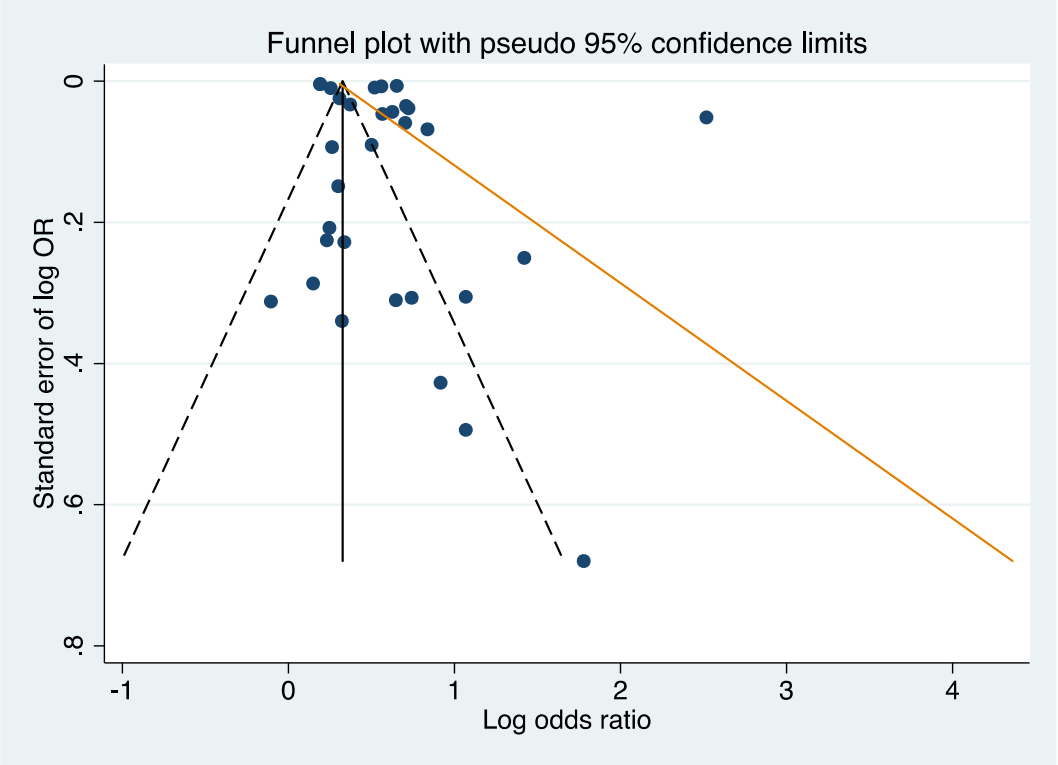
(6) Blood Infections/Cohort Studies:



(7) Viral Infections/Cohort Studies:



(8) Unspecified Infections/Cohort Studies:



Appendix 3.A: Exposure and Outcome Case Definitions:

Exposure/Outcome				**Classification of Variables**
Diabetes				CPCSSN Validated Case Definition using problem list (Diabetes, NIDDM, DM), Diagnostic codes (ICD-9: 250.0-250.9), medication list (insulin, oral antidiabetic agents, ATC code A10), and lab test results (HbA1c>7%, fasting BS>7)
Infection	**Any infection-Related Visit**			Any record in EMR for any infection plus ICD-9 codes: 001-139, 320-326, 391.1, 391.2, 421, 451, 685, 461.0-461.3, 461.8, 461.9, 473.0-473.3, 473.8, 473.9, 460, 472.2, 462, 472.1, 463, 474.00, 464.3, 464.5, 464.0, 476.0, 464.2, 476.1, 464.1, 491.8, 466, 490, 491, 480-486, 510 + (041.0-041.9), 010-018, 590.0-590.3, 590.8, 590.9, 595, 597, 601.0, 601.1, 601.9, 604, 607.1, 112.2, 611.0, 614.0-614.5, 614.7, 615.9, 616.0, 616.1, 616.81, 090-099, V02.7, 647.1, 110-118, 680, 681-682, 683, 684, 686, 728, 727.00, 727.02, 727.05. 727.06, 729.4, 730.0-730.2, 730.3, 382.2, 711.0-711.9, 003, 005, 004, 006, 009.0, 009.1, 531-535, 540-543, 567, 370.3, 370.4, 372.0-372.3, 373.0, 373.1, 373.4-373.6, 373.8, 373.9, 076, 380.0, 380.1, 381.0-381.5, 382.0-382.9, 384.0, 384.1, 383.0, 383.1, 383.9, 052, 053, 054, 055, 056, 072, 487, 488, 070, J01, J02, J04, J05, D01, D06, G01, P01, P02, P03, A07A
Infection	**Respiratory Tract Infections**	**Upper respiratory tract infection**	Sinusitis	Any record in EMR plus ICD-9: 461.0-461.3, 461.8, 461.9, 473.0-473.3, 473.8, 473.9
			Naso-pharyngitis	Any record in EMR plus ICD-9: 460, 472.2
			Pharyngitis	Any record in EMR plus ICD-9: 462, 472.1
			Tonsillitis	Any record in EMR plus ICD-9: 463, 474.00
			Epiglottitis	Any record in EMR plus ICD-9: 464.3, 464.5
			Laryngitis	Any record in EMR plus ICD-9: 464.0, 476.0
			Laryngo-	Any record in EMR plus ICD-9: 464.2, 476.1

			tracheitis	
			Tracheitis	Any record in EMR plus ICD-9: 464.1, 491.8
		Lower respiratory tract infection	Bronchitis	Any record in EMR plus ICD-9: 466, 490, 491
			Pneumonia	Any record in EMR plus ICD-9: 480-486
			Empyema	Any record in EMR plus ICD-9: 510 + (041.0-041.9)
			Tuberculosis	Any record in EMR plus ICD-9: 010-018
	Genitourinary Tract Infection	**Urinary tract infection**	Pyelonephritis	Any record in EMR plus ICD-9: 590.0-590.3, 590.8, 590.9
			Cystitis	Any record in EMR plus ICD-9: 595
			Urethritis	Any record in EMR plus ICD-9: 597
			Prostatitis	Any record in EMR plus ICD-9: 601.0, 601.1, 601.9
		Genital infection	Epididymitis	Any record in EMR plus ICD-9: 604
			Balanitis	Any record in EMR plus ICD-9: 607.1, 112.2
			Pelvic Inflammatory Disease	Any record in EMR plus ICD-9: 611.0, 614.0-614.5, 614.7, 615.9, 616.0, 616.1, 616.81
			Syphilis	Any record in EMR plus ICD-9: 090-099
			Gonorrhea	Any record in EMR plus ICD-9: V02.7, 647.1
	Skin and Soft Tissue Infection		Mycoses	Any record in EMR plus ICD-9: 110-118
			Carbuncle and Furuncle	Any record in EMR plus ICD-9: 680
			Cellulitis	Any record in EMR plus ICD-9: 681-682
			Lymphadenitis	Any record in EMR plus ICD-9: 683
			Impetigo	Any record in EMR plus ICD-9: 684
			Other	Any record in EMR plus ICD-9: 686
	Musculoskeletal Infection		Myositis	Any record in EMR plus ICD-9: 728
			Synovitis	Any record in EMR plus ICD-9: 727.00, 727.02, 727.05. 727.06
			Fasciitis	Any record in EMR plus ICD-9: 729.4
			Osteomyelitis	Any record in EMR plus ICD-9: 730.0-730.2

		Periostitis	Any record in EMR plus ICD-9: 730.3
		Petrositis	Any record in EMR plus ICD-9: 382.2
		Arthropathy Associated Infection	Any record in EMR plus ICD-9: 711.0-711.9
	Gastrointestinal Infection	Salmonela (food poisoning)	Any record in EMR plus ICD-9: 003, 005
		Shigellosis	Any record in EMR plus ICD-9: 004
		Amebiasis	Any record in EMR plus ICD-9: 006
		Gastroenteritis	Any record in EMR plus ICD-9: 009.0, 009.1
		Ulcer	Any record in EMR plus ICD-9: 531-535
		Appendicitis	Any record in EMR plus ICD-9: 540-543
		Peritonitis	Any record in EMR plus ICD-9: 567
	Head & Neck Infections	Conjunctivitis	Any record in EMR plus ICD-9: 370.3, 370.4, 372.0-372.3
		Blepharitis	Any record in EMR plus ICD-9: 373.0, 373.1, 373.4-373.6, 373.8, 373.9
		Trachoma	Any record in EMR plus ICD-9: 076
		Otitis Externa	Any record in EMR plus ICD-9: 380.0, 380.1
		Otitis Media	Any record in EMR plus ICD-9: 381.0-381.5, 382.0-382.9
		Myringitis	Any record in EMR plus ICD-9: 384.0, 384.1
		Mastoditis	Any record in EMR plus ICD-9: 383.0, 383.1, 383.9
	Viral Infections	Chickenpox	Any record in EMR plus ICD-9: 052
		Herpes Zoster	Any record in EMR plus ICD-9: 053
		Herpes Simplex	Any record in EMR plus ICD-9: 054
		Measles	Any record in EMR plus ICD-9: 055
		Rubella	Any record in EMR plus ICD-9: 056
		Mumps	Any record in EMR plus ICD-9: 072
		Influenza	Any record in EMR plus ICD-9: 487, 488
		Hepatitis	Any record in EMR plus ICD-9: 070

	Medications		Anti-infectives	Any record in EMR plus ATC code: J01, J02, J04, J05, D01, D06, G01, P01, P02, P03, A07A

Appendix 3.B: Diagnostic Codes for Exclusion:

Category		**Classification of Variables**
Neoplasms		Any record in EMR plus ICD-9: 140-239
AIDS/HIV		Any record in EMR plus ICD-9: 042-044
Organ Transplant	Kidney	Any record in EMR plus ICD-9: 55.6
	Liver	Any record in EMR plus ICD-9: 50.51
	Heart	Any record in EMR plus ICD-9: 37.52, 37.60, 37.65-37.67
Medication use	Immunosuppressant	Any record in EMR plus ATC code: L04
	Corticosteroids	Any record in EMR plus ATC code: H02

Appendix 3.C: Timeline of Subject Recruitment and Follow-up:

<table>
<tr><th>2007</th><th>2008</th><th>2009</th><th>2010</th><th>2011</th><th>2012</th><th>2013</th><th>2014</th></tr>
<tr><td rowspan="3">Covariate measurement</td><td colspan="6"></td><td rowspan="2"></td></tr>
<tr><td colspan="6">Cohort Entry Starts</td></tr>
<tr><td colspan="6">Cohort Entry Ends</td><td>End of study: Minimum one year follow up</td></tr>
</table>

Covariate Measurement Period: Starts January 1, 2007 to March 31, 2013.

Cohort Entry Period: Starts January 1, 2008 to March 31, 2013.

End of Study: Study will end March 31, 2014, which ensure at least one-year follow up.

Appendix 3.D: Case Definitions for Potential Confounders and Effect Modifiers:

Category	Variable Name	Classification of Variable
Demographic	ID	De-identified ID
	Age	Birth year
	Sex	Sex
Lab Values	HbA1c	HbA1c
	Temperature >37.5 C	Temperature
	WBC > 10,000 mcL	WBC count
	Fasting Glucose	Fasting Glucose
	BMI	BMI
	Lipids	Lipids
	Urine albumin creatinine ratio	Urine albumin creatinine ratio
Health Services Utilization	Number of primary care physicians visits	Number of visits
	Referrals to specialist	Number of referrals
	Number of lab tests ordered	Number of lab tests
Medications	Anti-diabetic Medications	Any record in EMR plus ATC code: A10A, A10B
	Immunosuppressant	Any record in EMR plus

			ATC code: L04
	Corticosteroids		Any record in EMR plus ATC code: H02
	Immunoglobulins		Any record in EMR plus ATC code: J06
	Vaccines		Any record in EMR plus ATC code: J07
	Drugs for Acid-related Disorders		Any record in EMR plus ATC code: A02A, A02B, A02X
	Respiratory System Agents		Any record in EMR plus ATC code: R01-R07
	Lipid Modifying Agents		Any record in EMR plus ATC code: C10
Diabetes Comorbidities	Microvascular	Nephropathy	Any record in EMR plus ICD-9: 250.40-250.43, 583.81, 581.81
		Neuropathy	Any record in EMR plus ICD-9: 250.60-250.63, 337.1, 357.2, 536.3, 353.5
		Retinopathy	Any record in EMR plus

			ICD-9: 250.50-250.53, 362.00-362.07, 369.00-369.90, 366.41, 265.41
	Macrovascular	Peripheral vascular disease	Any record in EMR plus ICD-9: 443.9, 441, 785.4, V43.4, 38.48
		Cerebrovascular disease	Any record in EMR plus ICD-9: 430-438
		Myocardial infarction	Any record in EMR plus ICD-9: 410, 412
		Congestive heart failure	Any record in EMR plus ICD-9: 428
	Non-Alcoholic Fatty Liver Disease		Any record in EMR plus ICD-9: 571.8
	Obesity		Any record in EMR plus ICD-9: 278, 783.1, V77.8
Respiratory disease			Any record in EMR plus ICD-9: 460-519

Appendix 3.E: Odds Ratio (OR) of All Covariates for All Types of Infection:

Any Infection:

Variable	Crude OR	95%CI	P value	Adjusted OR	95%CI	P value
Diabetes	0.96	0.86-1.06	0.399	1.21	1.07-1.37	0.002
Age:						
18-29 Years	1.01	0.89-1.14	0.890	0.97	0.85-1.10	0.636
30-39 Years	1.20	1.05-1.36	0.006	1.14	1.00-1.31	0.048
40-49 Years	1.12	0.99-1.27	0.080	1.10	0.96-1.25	0.174
50-59 Years						
60-69 Years	0.94	0.82-1.09	0.443	0.95	0.82-1.11	0.535
≥70 Years	0.86	0.73-1.00	0.058	0.77	0.65-0.91	0.002
Sex (Female)	0.70	0.65-0.76	<0.001	0.73	0.68-0.80	<0.001
Microvascular	1.70	0.85-3.39	0.130	1.53	0.75-3.12	0.244
Macrovascular	0.77	0.56-1.05	0.104	0.75	0.54-1.05	0.091
Respiratory Disease	2.32	2.09-2.58	<0.001	1.45	1.28-1.64	<0.001
Doctor Visits:						
≤12 Visits						
>12 Visits	2.18	1.94-2.18	<0.001	1.33	1.02-1.73	0.033
Referral:						
0-1						

≥2	1.45	1.17-1.80	0.001	1.06	0.84-1.32	0.621
Lab Number:						
0-29						
30-59	1.21	1.03-1.41	0.017	0.99	0.84-1.17	0.947
60-89	1.17	0.93-1.47	0.167	0.96	0.75-1.22	0.734
90-119	1.05	0.77-1.43	0.757	0.84	0.61-1.16	0.301
120-149	1.40	0.88-2.18	0.148	1.02	0.64-1.62	0.935
≥150	1.76	1.21-2.56	0.003	1.16	0.79-1.71	0.449
Infection Before 1 Year Of Entry:						
0						
1	1.76	1.58-1.97	<0.001	1.60	1.42-1.79	<0.001
≥2	3.12	2.82-2.46	<0.001	2.54	1.26-2.85	<0.001
Vaccines	1.35	1.19-1.53	<0.001	1.09	0.95-1.25	0.193
Drugs For Acid Related Disorders	1.56	1.37-1.78	<0.001	1.24	1.08-1.44	0.003
Respiratory Med	2.02	1.76-2.31	<0.001	1.22	1.04-1.43	0.012
Lipid Medications	1.00	0.89-1.13	0.966	1.07	0.92-1.24	0.356
Chf	1.42	0.64-3.14	0.384	1.20	0.52-2.74	0.671
Fatty Liver Disease	1.12	0.43-2.96	0.810	0.81	0.29-2.20	0.675
Obesity	1.39	1.00-1.92	0.048	1.15	0.82-1.62	0.418

Head&Neck Infections:

Variable	Crude IRR	95%CI	P value	Adjusted IRR	95%CI	P value
Diabetes	0.90	0.74-1.11	0.328	1.10	0.87-1.39	0.428
Age:						
18-29 Years	0.94	0.74-1.18	0.579	0.84	0.66-1.08	0.170
30-39 Years	1.07	0.85-1.35	0.565	1.00	0.78-1.27	0.990
40-49 Years	1.08	0.86-1.36	0.494	1.01	0.79-1.28	0.934
50-59 Years						
60-69 Years	0.96	0.73-1.27	0.788	0.96	0.72-1.38	0.785
≥70 Years	0.92	0.68-1.24	0.576	0.78	0.56-1.08	0.139
Sex (Female)	0.80	0.69-0.92	0.002	0.83	0.71-0.97	0.017
Microvascular	1.11	0.41-3.00	0.834	0.77	0.27-2.19	0.628
Macrovascular	1.13	0.64-2.01	0.700	1.04	0.57-1.91	0.885
Respiratory Disease	2.11	1.80-2.48	<0.001	1.42	1.17-1.74	<0.001
Doctor Visits:						
≤12 Visitis						
>12 Visits	1.91	1.34-2.74	<0.001	1.30	0.89-1.89	0.176
Referral:						
0-1						
≥2	1.64	1.15-2.34	0.006	1.28	0.89-1.86	0.185

Lab Number:						
0-29						
30-59	1.39	1.01-1.92	0.046	1.09	0.78-1.53	0.615
60-89	0.54	0.29-1.00	0.050	0.37	0.20-0.70	0.002
90-119	0.67	0.30-1.50	0.332	0.54	0.24-1.22	0.867
120-149	1.01	0.34-2.97	0.991	0.91	0.30-2.72	0.867
≥150	1.25	0.59-2.63	0.562	0.71	0.33-1.55	0.395
Infection Before 1 Year Of Entry:						
0						
1	1.68	1.35-2.08	<0.001	1.48	1.18-1.85	0.001
≥2	2.72	2.28-3.26	<0.001	2.14	1.74-2.63	<0.001
Vaccines	1.73	1.41-2.13	<0.001	1.44	1.15-1.80	<0.001
Drugs For Acid Related Disorders	1.60	1.29-1.98	<0.001	1.51	1.25-1.81	<0.001
Respiratory Med	1.78	1.44-2.19	<0.001	1.29	1.02-1.63	0.030
Lipid Medications	1.01	0.80-1.27	0.925	1.00	0.76-1.32	0.983
Heart Failure	1.37	0.38-4.98	0.631	1.50	0.39-5.71	0.552
Fatty Liver Disease	3.69	0.79-17.21	0.096	2.10	0.42-10.58	0.368
Obesity	1.52	0.94-2.47	0.090	1.07	0.64-1.79	0.794

Respiratory Infections:

Variable	Crude OR	95%CI	P value	Adjusted OR	95%CI	P value
Diabetes	0.84	0.75-0.94	0.003	1.31	1.14-1.50	<0.001
Age:						
18-29 Years	1.45	1.27-1.66	<0.001	1.38	1.19-1.59	<0.001
30-39 Years	1.73	1.51-1.98	<0.001	1.65	1.43-1.91	<0.001
40-49 Years	1.40	1.22-1.61	<0.001	1.37	1.18-1.59	<0.001
50-59 Years						
60-69 Years	0.93	0.79-1.09	0.369	0.97	0.82-1.15	0.733
≥70 Years	0.79	0.65-0.95	0.011	0.73	0.60-0.89	0.002
Sex (Female)	0.64	0.59-0.70	<0.001	0.68	0.62-0.75	<0.001
Microvascular	0.95	0.49-1.84	0.883	0.84	0.41-1.69	0.620
Macrovascular	0.63	0.44-0.91	0.014	0.84	0.57-1.23	0.370
Respiratory Disease	2.55	2.30-2.82	<0.001	1.86	1.65-2.11	<0.001
Doctor Visits:						
≤12 Visits						
>12 Visits	1.81	1.45-2.26	<0.001	1.17	0.92-1.48	0.198
Referral:						
0-1						

≥2	1.87	1.51-2.31	<0.001	1.48	1.18-1.85	0.001
Lab Number:						
0-29						
30-59	1.23	1.03-1.47	0.023	1.16	0.96-1.39	0.131
60-89	1.08	0.83-1.39	0.561	0.95	0.73-1.25	0.743
90-119	1.35	0.95-1.92	0.090	1.29	0.89-1.86	0.177
120-149	1.54	0.95-2.49	0.076	1.28	0.77-2.10	0.337
≥150	1.24	0.83-1.85	0.290	0.92	0.61-1.41	0.719
Infection Before 1 Year Of Entry:						
0						
1	1.55	1.37-1.74	<0.001	1.30	1.14-1.46	<0.001
≥2	2.73	2.46-3.03	<0.001	1.96	1.74-2.22	<0.001
Vaccines	1.01	0.89-1.16	0.854	0.88	0.76-1.01	0.080
Drugs For Acid Related Disorders	1.34	1.17-1.54	<0.001	1.18	1.02-1.37	0.027
Respiratory Med	1.87	1.64-2.13	<0.001	1.06	0.91-1.23	0.467
Lipid Medications	0.71	0.62-0.82	<0.001	0.88	0.74-1.04	0.139
Heart Failure	0.92	0.40-2.14	0.852	1.13	0.47-2.74	0.779
Fatty Liver Disease	0.73	0.24-2.21	0.581	0.56	0.18-1.75	0.318
Obesity	1.37	0.99-1.89	0.056	1.13	0.81-1.60	0.468

Gastrointestinal Infections:

Variable	Crude OR	95%CI	P value	Adjusted OR	95%CI	P value
Diabetes	1.38	1.15-1.67	<0.001	1.41	1.13-1.75	<0.001
Age:						
18-29 Years	0.75	0.58-0.95	0.019	0.79	0.64-0.95	0.080
30-39 Years	0.73	0.57-0.94	0.014	0.76	0.61-0.92	0.043
40-49 Years	0.95	0.75-1.22	0.703	0.92	0.90-1.31	0.504
50-59 Years						
60-69 Years	0.94	0.71-1.23	0.638	0.89	0.87-1.33	0.443
≥70 Years	1.04	0.78-1.38	0.801	0.94	0.89-1.39	0.706
Sex (Female)	1.15	0.99-1.34	0.074	1.16	0.99-1.35	0.070
Microvascular	2.93	1.10-7.78	0.031	2.21	0.77-6.31	0.138
Macrovascular	1.05	0.59-1.86	0.872	0.79	0.43-1.46	0.461
Respiratory Disease	1.22	1.02-1.46	0.032	0.98	0.79-1.23	0.891
Doctor Visits:						
≤12 Visits						
>12 Visits	2.46	1.78-3.41	<0.001	2.05	1.46-2.90	<0.001
Referral:						
0-1						
≥2	1.11	0.72-1.72	0.619	0.87	0.55-1.37	0.549
Lab Number:						

0-29						
30-59	0.69	0.47-1.01	0.060	0.60	0.40-0.89	0.012
60-89	0.75	0.42-1.34	0.334	0.62	0.34-1.14	0.125
90-119	0.92	0.44-1.94	0.837	0.79	0.37-1.69	0.548
120-149	1.17	0.48-2.87	0.731	0.91	0.36-2.31	0.850
≥150	1.60	0.80-3.19	0.182	1.19	0.58-2.45	0.631
Infection Before 1 Year Of Entry:						
0						
1	1.44	1.16-1.79	0.001	1.47	1.17-1.84	0.120
≥2	1.67	1.38-2.02	<0.001	1.71	1.36-2.13	<0.001
Vaccines	1.23	0.97-1.54	0.082	1.04	0.81-1.34	0.745
Drugs For Acid Related Disorders	2.22	1.79-2.76	<0.001	1.89	1.49-2.38	<0.001
Respiratory Med	1.02	0.80-1.31	0.840	0.78	0.58-1.03	0.083
Lipid Medications	1.31	1.04-1.64	0.021	0.93	0.71-1.22	0.618
Heart Failure	0.71	0.15-3.29	0.666	0.45	0.09-2.15	0.319
Fatty Liver Disease	0.39	0.05-3.17	0.379	0.24	0.03-2.05	0.191
Obesity	1.34	0.75-2.38	0.471	1.22	0.67-2.24	0.510

Genitourinary Infections:

Variable	Crude OR	95%CI	P value	Adjusted OR	95%CI	P value
Diabetes	1.10	0.94-1.29	0.238	1.42	1.17-1.73	<0.001
Age:						
18-29 Years	1.06	0.77-1.29	0.552	0.94	0.76-1.16	0.580
30-39 Years	0.97	0.79-1.19	0.791	0.82	0.66-1.02	0.080
40-49 Years	1.04	0.85-1.28	0.691	0.98	0.79-1.22	0.889
50-59 Years						
60-69 Years	1.04	0.83-1.31	0.727	1.00	0.78-1.27	0.975
≥70 Years	1.19	0.94-1.52	0.150	0.93	0.71-1.21	0.585
Sex (Female)	0.31	0.27-0.36	<0.001	0.32	0.27-0.37	<0.001
Microvascular	0.89	0.36-2.23	0.809	0.59	0.22-1.54	0.281
Macrovascular	1.15	0.72-1.84	0.549	1.21	0.73-2.02	0.460
Respiratory Disease	1.77	1.54-2.03	<0.001	1.09	0.92-1.30	0.315
Doctor Visits:						
≤12 Visits						
>12 Visits	2.52	1.93-3.28	<0.001	1.63	1.22-2.18	0.001
Referral:						
0-1						
≥2	1.16	0.84-1.59	0.920	0.84	0.60-1.17	0.308
Lab Number:						

0-29						
30-59	1.37	1.05-1.81	0.022	1.09	0.81-1.46	0.572
60-89	0.98	0.65-1.49	0.944	0.72	0.46-1.12	0.146
90-119	1.05	0.60-1.85	0.866	0.71	0.39-1.27	0.248
120-149	0.67	0.23-1.91	0.450	0.37	0.12-1.12	0.079
≥150	1.48	0.82-2.67	0.192	0.86	0.46-1.61	0.648
Infection Before 1 Year Of Entry: 0						
1	1.65	1.38-1.98	<0.001	1.55	1.28-1.88	<0.001
≥2	2.81	2.41-3.27	<0.001	2.43	2.04-2.90	<0.001
Vaccines	1.36	1.14-1.63	<0.001	0.99	0.81-1.21	0.948
Drugs For Acid Related Disorders	1.79	1.49-2.14	<0.001	1.36	1.11-1.67	0.003
Respiratory Med	1.81	1.52-2.17	<0.001	1.25	1.01-1.54	0.038
Lipid Medications	1.03	0.85-1.25	0.770	0.98	0.77-1.25	0.882
Heart Failure	1.91	0.76-4.78	0.167	1.41	0.53-3.72	0.490
Fatty Liver Disease	4.42	1.30-15.07	0.017	4.66	1.20-18.17	0.027
Obesity	1.61	1.04-2.51	0.033	1.32	0.81-2.14	0.261

Skin&Soft Infections:

Variable	Crude OR	95%CI	P value	Adjusted OR	95%CI	P value
Diabetes	1.43	1.21-1.69	<0.001	1.65	1.36-2.01	<0.001
Age:						
18-29 Years	0.89	0.71-1.10	0.286	0.95	0.76-1.20	0.678
30-39 Years	1.04	0.84-1.30	0.696	1.07	0.86-1.35	0.533
40-49 Years	1.05	0.84-1.32	0.636	1.08	0.86-1.35	0.527
50-59 Years						
60-69 Years	0.88	0.68-1.14	0.334	0.86	0.66-1.11	0.249
≥70 Years	1.17	0.90-1.51	0.240	1.04	0.79-1.37	0.778
Sex (Female)	1.05	0.91-1.20	0.497	1.07	0.93-1.23	0.323
Microvascular	2.84	1.27-6.34	0.011	1.86	0.80-4.28	0.146
Macrovascular	1.24	0.77-1.99	0.378	1.04	0.63-1.72	0.880
Respiratory Disease	1.65	1.41-1.93	<0.001	1.33	1.10-1.61	0.004
Doctor Visits:						
≤12 Visits						
>12 Visits	2.42	1.79-3.26	<0.001	1.89	1.37-2.60	<0.001
Referral:						
0-1						
≥2	1.02	0.70-1.49	0.901	0.80	0.54-1.18	0.263
Lab Number:						

0-29						
30-59	1.48	1.11-1.99	0.009	1.32	0.98-1.79	0.070
60-89	0.62	0.36-1.06	0.081	0.51	0.29-0.88	0.015
90-119	1.96	1.13-3.41	0.017	1.65	0.93-2.93	0.088
120-149	0.51	0.15-1.70	0.276	0.43	0.13-1.45	0.174
≥150	1.25	0.61-2.56	0.549	0.98	0.46-2.09	0.965
Infection Before 1 Year Of Entry: 0						
1	1.29	1.06-1.56	0.011	1.25	1.02-1.53	0.033
≥2	1.73	1.47-2.05	<0.001	1.53	1.26-1.87	<0.001
Vaccines	1.20	0.98-1.48	0.075	1.01	0.82-1.26	0.907
Drugs For Acid Related Disorders	1.44	1.17-1.78	0.001	1.19	0.95-1.49	0.125
Respiratory Med	1.47	1.19-1.82	<0.001	1.03	0.81-1.31	0.809
Lipid Medications	1.10	0.88-1.36	0.019	0.87	0.67-1.12	0.276
Heart Failure	1.12	0.31-3.96	0.863	0.71	0.19-2.66	0.613
Fatty Liver Disease	0.84	0.18-3.90	0.824	0.60	0.12-2.91	0.524
Obesity	1.90	1.18-3.06	0.002	1.44	0.87-2.36	0.152

Musculoskeletal Infections:

Variable	Crude OR	95%CI	P value	Adjusted OR	95%CI	P value
Diabetes	0.97	0.82-1.14	0.714	1.05	0.87-1.28	0.606
Age:						
18-29 Years	0.59	0.48-0.72	<0.001	0.57	0.47-0.70	<0.001
30-39 Years	0.80	0.65-0.97	0.024	0.76	0.62-0.93	0.008
40-49 Years	1.40	1.16-1.68	<0.001	1.40	1.15-1.69	0.001
50-59 Years						
60-69 Years	0.87	0.70-1.09	0.227	0.88	0.70-1.11	0.273
≥70 Years	0.43	0.32-0.58	<0.001	0.38	0.27-0.51	<0.001
Sex (Female)	0.65	0.57-0.73	<0.001	0.62	0.54-0.71	<0.001
Microvascular	2.21	1.04-4.69	0.039	2.12	0.97-4.67	0.061
Macrovascular	0.71	0.40-1.26	0.240	0.83	0.45-1.51	0.539
Respiratory Disease	1.23	1.07-1.43	0.005	0.97	0.81-1.16	0.734
Doctor Visits:						
≤12 Visits						
>12 Visits	1.51	1.11-2.04	0.008	1.15	0.83-1.59	0.400
Referral:						
0-1						
≥2	2.02	1.52-2.68	<0.001	1.75	1.30-2.35	<0.001
Lab Number:						

0-29						
30-59	1.03	0.78-1.36	0.815	0.92	0.69-1.23	0.579
60-89	1.58	1.10-2.27	0.013	1.41	0.97-2.05	0.074
90-119	0.96	0.57-1.63	0.895	0.85	0.50-1.46	0.565
120-149	0.99	0.45-2.17	0.983	0.72	0.32-1.60	0.417
≥150	1.11	0.61-2.03	0.724	0.82	0.44-1.53	0.536
Infection Before 1 Year Of Entry: 0						
1	1.21	1.01-1.44	0.033	1.16	0.96-1.40	0.113
≥2	1.57	1.35-1.82	<0.001	1.46	1.23-1.74	<0.001
Vaccines	1.06	0.88-1.29	0.514	1.03	0.84-1.27	0.757
Drugs For Acid Related Disorders	1.56	1.29-1.87	<0.001	1.38	1.13-1.69	0.002
Respiratory Med	1.24	1.02-1.50	0.028	0.96	0.77-1.20	0.755
Lipid Medications	0.97	0.79-1.18	0.758	0.97	0.77-1.23	0.802
Heart Failure	1.60	0.59-4.31	0.354	2.52	0.89-7.13	0.081
Fatty Liver Disease	2.12	0.63-7.10	0.223	1.70	0.49-5.93	0.403
Obesity	1.25	0.80-1.95	0.320	1.01	0.63-1.62	0.963

Viral Infections:

Variable	Crude OR	95%CI	P value	Adjusted OR	95%CI	P value
Diabetes	1.21	0.95-1.55	0.115	1.11	0.83-1.47	0.485
Age:						
18-29 Years	0.73	0.53-1.00	0.048	0.72	0.52-1.00	0.055
30-39 Years	0.73	0.53-1.01	0.059	0.69	0.49-0.97	0.035
40-49 Years	0.99	0.73-1.35	0.958	1.02	0.74-1.40	0.907
50-59 Years						
60-69 Years	1.13	0.80-1.58	0.490	1.03	0.73-1.46	0.860
≥70 Years	1.06	0.73-1.54	0.742	0.84	0.57-1.26	0.404
Sex (Female)	0.86	0.71-1.05	0.140	0.84	0.68-1.03	0.090
Microvascular	3.32	0.96-11.44	0.058	2.15	0.58-8.00	0.254
Macrovascular	1.14	0.53-2.47	0.740	0.82	0.36-1.85	0.635
Respiratory Disease	1.70	1.36-2.11	<0.001	1.31	1.00-1.72	0.051
Doctor Visits:						
≤12 Visits						
>12 Visits	1.48	0.95-2.32	0.085	1.10	0.68-1.78	0.698
Referral:						
0-1						
≥2	0.82	0.46-1.46	0.507	0.63	0.35-1.15	0.133
Lab Number:						

0-29						
30-59	1.43	0.96-2.11	0.074	1.16	0.77-1.75	0.462
60-89	0.99	0.55-1.79	0.976	0.76	0.41-1.41	0.382
90-119	1.07	0.46-2.48	0.869	0.81	0.34-1.94	0.645
120-149	2.13	0.83-5.45	0.114	1.90	0.72-4.99	0.191
≥150	0.60	0.18-2.00	0.407	0.43	0.13-1.46	0.176
Infection Before 1 Year Of Entry: 0						
1	1.18	0.89-1.57	0.240	1.11	0.82-1.49	0.503
≥2	1.68	1.33-2.13	<0.001	1.40	1.06-1.86	0.017
Vaccines	2.27	1.76-2.92	<0.001	1.99	1.52-2.61	<0.001
Drugs For Acid Related Disorders	1.48	1.11-1.96	0.007	1.13	0.83-1.54	0.425
Respiratory Med	1.65	1.25-2.19	<0.001	1.17	0.84-1.63	0.354
Lipid Medications	1.32	0.98-1.76	0.063	1.08	0.77-1.52	0.660
Heart Failure	0.58	0.07-4.74	0.612	0.42	0.05-3.54	0.428
Fatty Liver Disease	10.24	2.43-43.19	0.002	12.28	2.79-54.14	<0.001
Obesity	1.93	1.05-3.54	0.033	1.67	0.89-3.13	0.107

Appendix 3.F: Odds Ratio (OR) Of All Covariates For All Types Of Infection 1-Year Period:

Any Infection:

Variable	Crude OR	95%CI	P value	Adjusted OR	95%CI	P value
Diabetes	1.06	0.95-1.18	0.290	1.37	1.21-1.55	<0.001
Age:						
18-29 Years	1.27	1.12-1.45	<0.000	1.24	1.09-1.43	0.002
30-39 Years	1.18	1.04-1.35	0.012	1.13	0.98-1.30	0.086
40-49 Years	1.26	1.10-1.44	0.001	1.24	1.07-1.42	0.003
50-59 Years						
60-69 Years	1.05	0.91-1.23	0.482	1.07	0.92-1.26	0.369
≥70 Years	1.17	0.99-1.38	0.063	1.05	0.88-1.25	0.610
Sex (Female)	0.69	0.63-0.75	<0.001	0.72	0.66-0.78	<0.001
Microvascular	2.60	1.36-4.97	0.004	2.12	1.06-4.25	0.033
Macrovascular	1.00	0.72-1.40	0.989	0.93	0.65-1.33	0.695
Respiratory Disease	2.19	1.99-2.41	<0.001	1.48	1.31-1.66	<0.001
Doctor Visits:						
≤12 Visits						
>12 Visits	2.48	2.00-3.07	<0.001	1.61	1.28-2.03	<0.001
Referral:						

0-1						
≥2	1.47	1.20-1.80	<0.001	1.09	0.88-1.35	0.435
Lab Number:						
0-29						
30-59	1.04	0.89-1.23	0.602	0.87	0.73-1.03	0.104
60-89	1.11	0.87-1.41	0.400	0.89	0.69-1.15	0.386
90-119	0.98	0.70-1.37	0.909	0.78	0.55-1.11	0.165
120-149	1.20	0.75-1.92	0.443	0.86	0.53-1.40	0.550
≥150	1.54	1.07-2.22	0.019	1.01	0.69-1.48	0.945
Infection Before 1						
Year Of Entry:						
0						
1	1.64	1.46-1.84	<0.001	1.48	1.25-1.47	<0.001
≥2	2.65	2.40-2.93	<0.001	2.14	1.91-2.40	<0.001
Vaccines	1.32	1.17-1.50	0.026	1.04	0.91-1.19	0.561
Drugs For Acid	1.61	1.41-1.83	<0.001	1.28	1.12-1.48	<0.001
Related Disorders						
Respiratory Med	1.88	1.66-2.14	<0.001	1.16	1.00-1.34	0.047
Lipid Medications	0.98	0.86-1.11	0.333	0.96	0.82-1.12	0.605
Heart Failure	1.54	1.03-2.30	0.034	1.63	0.75-3.56	0.217
Fatty Liver	1.48	0.60-3.67	0.391	1.19	0.48-2.97	0.708
Disease						
Obesity	1.29	0.94-1.78	0.115	1.04	0.74-1.45	0.823

Head&Neck Infections:

Variable	Crude OR	95%CI	P value	Adjusted OR	95%CI	P value
Diabetes	0.83	0.59-1.17	0.285	1.12	0.75-1.67	0.573
Age:						
18-29 Years	1.40	0.96-2.04	0.082	1.23	0.82-1.85	0.312
30-39 Years	1.26	0.85-1.87	0.253	1.13	0.74-1.73	0.564
40-49 Years	1.64	1.13-2.40	0.010	1.53	1.03-2.27	0.033
50-59 Years						
60-69 Years	0.97	0.60-1.58	0.911	1.05	0.63-1.74	0.849
≥70 Years	1.24	0.76-2.04	0.392	1.21	0.71-2.06	0.484
Sex (Female)	0.76	0.60-0.97	0.030	0.85	0.65-1.09	0.201
Microvascular	1.46	0.30-6.98	0.638	0.96	0.19-4.88	0.959
Macrovascular	1.08	0.37-3.15	0.895	0.93	0.29-2.97	0.903
Respiratory Disease	2.06	1.59-2.68	<0.001	1.24	0.90-1.71	0.192
Doctor Visits:						
≤12 Visits						
>12 Visits	1.86	1.04-3.32	0.036	1.10	0.59-2.06	0.762
Referral:						
0-1						
≥2	2.49	1.53-4.03	<0.001	1.85	1.10-3.13	0.021
Lab Number:						

0-29						
30-59	1.70	1.09-2.66	0.009	1.44	0.90-2.32	0.130
60-89	0.91	0.40-2.06	0.593	0.69	0.29-1.64	0.404
90-119	0.31	0.04-2.39	0.238	0.37	0.04-2.61	0.297
120-149	0.67	0.08-5.27	0.533	0.69	0.08-5.73	0.732
≥150	1.12	0.38-3.37	0.546	0.87	0.28-2.70	0.813
Infection Before 1 Year Of Entry:						
0						
1	1.58	1.11-2.24	0.010	1.42	0.98-2.04	0.060
≥2	3.36	2.53-4.45	<0.001	2.76	1.99-3.82	<0.001
Vaccines	1.45	1.03-2.03	0.033	1.14	0.78-1.66	0.489
Drugs For Acid Related Disorders	1.38	0.96-1.96	0.079	1.02	0.69-1.52	0.905
Respiratory Med	1.70	1.22-2.39	0.002	1.07	0.73-1.59	0.717
Lipid Medications	0.80	0.53-1.21	0.298	0.87	0.54-1.40	0.557
Heart Failure	1.21	0.14-10.45	0.863	1.17	0.12-11.07	0.893
Fatty Liver Disease	4.18	0.26-67.62	0.313	4.10	0.16-106.71	0.396
Obesity	1.11	0.42-2.91	0.835	0.86	0.30-2.46	0.778

Respiratory Infections:

Variable	Crude OR	95%CI	P value	Adjusted OR	95%CI	P value
Diabetes	0.94	0.81-1.10	0.470	1.45	1.21-1.74	<0.001
Age:						
18-29 Years	1.41	1.17-1.70	<0.001	1.38	1.14-1.69	0.001
30-39 Years	1.45	1.20-1.75	<0.001	1.37	1.12-1.67	0.002
40-49 Years	1.35	1.11-1.63	0.002	1.30	1.06-1.59	0.010
50-59 Years						
60-69 Years	0.86	0.68-1.09	0.218	0.92	0.72-1.17	0.501
≥70 Years	0.96	0.75-1.23	0.735	0.93	0.71-1.21	0.595
Sex (Female)	0.69	0.62-0.78	<0.001	0.77	0.68-0.87	<0.001
Microvascular	1.48	0.66-3.33	0.342	1.13	0.47-2.70	0.697
Macrovascular	0.59	0.34-1.01	0.056	0.67	0.38-1.19	0.267
Respiratory Disease	2.86	2.52-3.24	<0.001	1.97	1.69-2.30	<0.001
Doctor Visits:						
≤12 Visits						
>12 Visits	2.51	1.95-3.24	<0.001	1.56	1.18-2.06	0.002
Referral:						
0-1						
≥2	1.35	1.03-1.77	0.030	0.95	0.71-1.27	0.735
Lab Number:						

0-29						
30-59	1.31	1.04-1.63	0.019	1.15	0.91-1.46	0.248
60-89	1.17	0.83-1.63	0.364	0.95	0.66-1.35	0.767
90-119	1.03	0.64-1.67	0.902	0.89	0.54-1.47	0.652
120-149	1.12	0.57-2.19	0.741	0.79	0.39-1.60	0.523
≥150	1.67	1.01-2.74	0.044	1.20	0.70-2.04	0.503
Infection Before 1 Year Of Entry:						
0						
1	1.63	1.39-1.93	<0.001	1.30	1.10-1.55	0.003
≥2	2.87	2.51-3.29	<0.001	1.90	1.62-2.22	<0.001
Vaccines	1.19	1.00-1.41	0.053	0.93	0.77-1.13	0.475
Drugs For Acid Related Disorders	1.76	1.49-2.08	<0.001	1.48	1.23-1.78	<0.001
Respiratory Med	2.13	1.81-2.51	<0.001	1.12	0.93-1.35	0.243
Lipid Medications	0.70	0.58-0.86	0.001	0.71	0.55-0.90	0.005
Heart Failure	0.97	0.35-2.69	0.948	0.82	0.27-2.48	0.720
Fatty Liver Disease	0.82	0.17-3.90	0.804	0.55	0.11-2.81	0.473
Obesity	1.61	1.07-2.44	0.023	1.25	0.80-1.96	0.318

Gastrointestinal Infections:

Variable	Crude OR	95%CI	P value	Adjusted OR	95%CI	P value
Diabetes	1.78	1.36-2.34	<0.001	1.71	1.22-2.39	0.002
Age:						
18-29 Years	0.85	0.57-1.27	0.440	0.94	0.61-1.44	0.774
30-39 Years	0.72	0.47-1.10	0.127	0.77	0.50-1.20	0.255
40-49 Years	1.03	0.69-1.53	0.876	0.97	0.64-1.46	0.884
50-59 Years						
60-69 Years	1.22	0.80-1.87	0.359	1.15	0.73-1.80	0.549
≥70 Years	1.64	1.08-2.49	0.020	1.38	0.88-2.18	0.161
Sex (Female)	1.17	0.91-1.49	0.211	1.16	0.89-1.50	0.263
Microvascular	5.25	1.60-17.24	0.006	3.41	0.95-12.21	0.059
Macrovascular	1.61	0.68-3.80	0.279	1.01	0.40-2.55	0.977
Respiratory Disease	1.17	0.88-1.55	0.284	0.84	0.59-1.20	0.344
Doctor Visits:						
≤12 Visits						
>12 Visits	2.50	1.51-4.15	<0.001	1.80	1.03-3.13	0.038
Referral:						
0-1						
≥2	1.19	0.65-2.19	0.574	0.95	0.49-1.83	0.877
Lab Number:						

0-29						
30-59	0.56	0.31-0.99	0.048	0.46	0.26-0.84	0.011
60-89	0.57	0.22-1.47	0.249	0.38	0.14-1.05	0.062
90-119	0.83	0.28-2.48	0.746	0.61	0.20-1.89	0.396
120-149	0.71	0.16-3.17	0.650	0.61	0.13-2.88	0.530
≥150	1.45	0.52-4.01	0.474	1.06	0.35-3.18	0.912
Infection Before 1 Year Of Entry:						
0						
1	1.28	0.90-1.82	0.164	1.41	0.98-2.05	0.067
≥2	1.95	1.45-2.61	<0.001	2.27	1.59-3.22	<0.001
Vaccines	1.27	0.88-1.82	0.195	0.93	0.62-1.38	0.722
Drugs For Acid Related Disorders	2.66	1.92-3.67	<0.001	1.93	1.35-2.75	<0.001
Respiratory Med	1.16	0.80-1.68	0.425	0.93	0.60-1.44	0.737
Lipid Medications	1.71	1.22-2.39	0.002	1.03	0.68-1.55	0.897
Heart Failure	1.04	0.12-9.20	0.970	0.52	0.06-4.83	0.569
Fatty Liver Disease	-	-	-	-	-	-
Obesity	0.92	0.32-2.65	0.872	1.00	0.33-3.05	0.993

Genitourinary Infections:

Variable	Crude OR	95%CI	P value	Adjusted OR	95%CI	P value
Diabetes	1.34	1.06-1.69	0.248	1.86	1.39-2.50	<0.001
Age:						
18-29 Years	1.04	0.77-1.42	0.786	0.98	0.70-1.38	0.929
30-39 Years	0.82	0.58-1.15	0.244	0.73	0.51-1.05	0.093
40-49 Years	1.16	0.84-1.61	0.353	1.14	0.81-1.61	0.449
50-59 Years						
60-69 Years	1.05	0.73-1.51	0.774	0.97	0.66-1.43	0.877
≥70 Years	1.62	1.14-2.31	0.007	1.28	0.87-1.90	0.206
Sex (Female)	0.34	0.27-0.43	<0.001	0.35	0.28-0.45	<0.001
Microvascular	1.78	0.56-5.61	0.324	1.11	0.32-3.85	0.871
Macrovascular	2.00	1.04-3.85	0.037	2.20	1.06-4.56	<0.034
Respiratory Disease	1.87	1.52-2.30	<0.001	1.14	0.88-1.47	0.330
Doctor Visits:						
≤12 Visits						
>12 Visits	2.65	1.83-3.85	<0.001	1.55	1.03-2.35	0.037
Referral:						
0-1						
≥2	1.01	0.63-1.61	0.955	0.77	0.47-1.27	0.317
Lab Number:						

0-29						
30-59	1.32	0.91-1.92	0.137	1.03	0.69-1.55	0.865
60-89	1.11	0.61-2.01	0.739	0.80	0.42-1.51	0.489
90-119	1.22	0.59-2.51	0.585	0.67	0.32-1.43	0.303
120-149	0.94	0.27-3.25	0.929	0.41	0.11-1.57	0.194
≥150	1.69	0.72-3.97	0.230	0.92	0.36-2.30	0.854
Infection Before 1 Year Of Entry:						
0						
1	2.17	1.64-2.85	<0.001	2.13	1.58-2.86	<0.001
≥2	3.30	2.61-4.16	<0.001	3.02	2.30-3.96	<0.001
Vaccines	1.59	1.22-2.07	<0.001	1.11	0.83-1.48	0.483
Drugs For Acid Related Disorders	2.10	1.61-2.72	<0.001	1.50	1.11-2.02	0.008
Respiratory Med	1.72	1.31-2.26	<0.001	1.09	0.80-1.51	0.574
Lipid Medications	1.07	0.79-1.44	0.658	0.77	0.53-1.13	0.187
Heart Failure	2.95	0.88-9.86	0.080	1.91	0.53-6.91	0.323
Fatty Liver Disease	5.14	1.01-26.09	0.048	4.32	0.77-24.03	0.095
Obesity	1.28	0.63-2.57	0.495	1.04	0.49-2.21	0.908

Skin&Soft Infections:

Variable	Crude OR	95%CI	P value	Adjusted OR	95%CI	P value
Diabetes	1.81	1.40-2.34	<0.001	1.96	1.43-2.69	<0.001
Age:						
18-29 Years	1.08	0.74-1.58	0.682	1.24	0.83-1.86	0.290
30-39 Years	1.15	0.78-1.69	0.476	1.23	0.82-1.85	0.321
40-49 Years	1.16	0.78-1.71	0.465	1.21	0.81-1.82	0.352
50-59 Years						
60-69 Years	1.43	0.94-2.17	0.097	1.31	0.84-2.03	0.227
≥70 Years	1.27	0.80-2.01	0.312	1.07	0.65-1.75	0.787
Sex (Female)	1.05	0.83-1.33	0.676	1.06	0.83-1.35	0.656
Microvascular	5.92	1.88-18.63	0.002	3.74	1.05-13.26	0.041
Macrovascular	1.63	0.68-3.92	0.270	1.05	0.40-2.70	0.925
Respiratory Disease	1.81	1.40-2.36	<0.001	1.50	1.08-2.10	0.016
Doctor Visits:						
≤12 Visits						
>12 Visits	3.14	1.93-5.11	<0.001	2.36	1.40-4.00	0.001
Referral:						
0-1						
≥2	1.50	0.89-2.55	0.129	1.06	0.60-1.86	0.838
Lab Number:						

0-29						
30-59	1.47	0.94-2.30	0.088	1.31	0.82-2.08	0.340
60-89	0.43	0.15-1.21	0.110	0.32	0.11-0.95	0.081
90-119	1.37	0.57-3.26	0.477	1.07	0.43-2.65	0.996
120-149	0.76	0.17-3.35	0.716	0.65	0.14-2.93	0.495
≥150	0.95	0.27-3.34	0.934	0.86	0.23-3.19	0.619
Infection Before 1 Year Of Entry:						
0						
1	1.23	0.87-1.73	0.232	1.27	0.89-1.82	0.182
≥2	1.73	1.31-2.28	<0.001	1.61	1.15-2.25	0.05
Vaccines	0.91	0.62-1.33	0.628	0.69	0.46-1.05	0.084
Drugs For Acid Related Disorders	1.41	0.99-2.01	0.057	1.06	0.72-1.56	0.755
Respiratory Med	1.48	1.04-2.11	0.029	0.98	0.66-1.47	0.931
Lipid Medications	1.46	1.03-2.07	0.033	1.16	0.76-1.75	0.492
Heart Failure	3.04	0.55-16.81	0.202	1.42	0.20-10.18	0.727
Fatty Liver Disease	-	-	-	-	-	-
Obesity	1.84	0.78-4.33	0.161	1.30	0.53-3.18	0.570

Musculoskeletal Infections:

Variable	Crude OR	95%CI	P value	Adjusted OR	95%CI	P value
Diabetes	1.01	0.77-1.33	0.915	1.06	0.77-1.47	0.714
Age:						
18-29 Years	0.65	0.46-0.90	0.010	0.68	0.48-0.97	0.013
30-39 Years	0.80	0.57-1.11	0.175	0.82	0.58-1.16	0.246
40-49 Years	1.45	1.07-1.97	0.017	1.47	1.07-2.02	0.022
50-59 Years						
60-69 Years	0.90	0.63-1.28	0.560	0.97	0.67-1.40	0.524
≥70 Years	0.30	0.16-0.56	<0.001	0.29	0.16-0.55	<0.001
Sex (Female)	0.62	0.50-0.77	<0.001	0.61	0.49-0.76	<0.001
Microvascular	2.10	0.74-5.94	0.163	1.81	0.59-5.49	0.296
Macrovascular	0.67	0.23-1.92	0.459	0.87	0.29-2.60	0.800
Respiratory Disease	1.60	1.27-2.03	<0.001	1.23	0.91-1.65	0.175
Doctor Visits:						
≤12 Visits						
>12 Visits	1.83	1.17-2.85	0.007	1.31	0.81-2.12	0.271
Referral:						
0-1						
≥2	1.67	1.08-2.58	0.021	1.31	0.83-2.09	0.247
Lab Number:						

0-29						
30-59	0.73	0.46-1.15	0.174	0.65	0.40-1.05	0.078
60-89	1.21	0.70-2.09	0.496	1.03	0.58-1.84	0.921
90-119	0.90	0.41-1.97	0.803	0.79	0.35-1.75	0.558
120-149	0.86	0.25-2.95	0.810	0.52	0.14-1.93	0.329
≥150	0.73	0.28-1.89	0.516	0.46	0.17-1.24	0.125
Infection Before 1 Year Of Entry:						
0						
1	1.06	0.78-1.43	0.726	0.96	0.70-1.33	0.830
≥2	1.62	1.28-2.05	<0.001	1.35	1.02-1.79	0.036
Vaccines	0.86	0.62-1.20	0.370	0.82	0.57-1.16	0.267
Drugs For Acid Related Disorders	1.92	1.45-2.56	<0.001	1.68	1.22-2.30	0.001
Respiratory Med	1.63	1.21-2.18	0.001	1.11	0.79-1.56	0.553
Lipid Medications	1.25	0.92-1.71	0.152	1.31	0.90-1.92	0.160
Heart Failure	-	-	-	-	-	-
Fatty Liver Disease	1.78	0.37-8.61	0.475	1.69	0.33-8.54	0.528
Obesity	1.57	0.83-2.99	0.167	1.26	0.64-2.50	0.503

Viral Infections:

Variable	Crude OR	95%CI	P value	Adjusted OR	95%CI	P value
Diabetes	1.42	0.95-2.13	0.086	1.33	0.80-2.21	0.268
Age:						
18-29 Years	0.52	0.31-0.87	0.013	0.52	0.29-0.91	0.023
30-39 Years	0.49	0.28-0.85	0.012	0.48	0.26-0.89	0.019
40-49 Years	0.83	0.50-1.37	0.466	0.85	0.50-1.46	0.557
50-59 Years						
60-69 Years	0.60	0.33-1.08	0.091	0.55	0.29-1.04	0.067
≥70 Years	0.58	0.30-1.14	0.114	0.60	0.29-1.26	0.177
Sex (Female)	0.91	0.64-1.29	0.602	0.83	0.57-1.20	0.324
Microvascular	11.92	1.07-132.18	0.043	5.39	0.41-70.53	0.199
Macrovascular	-	-	-	-	-	-
Respiratory Disease	1.90	1.30-2.78	0.001	1.88	1.14-3.11	0.014
Doctor Visits:						
≤12 Visits						
>12 Visits	1.27	0.53-3.07	0.593	1.10	0.41-2.97	.852
Referral:						
0-1						
≥2	0.76	0.27-2.16	0.609	0.55	0.17-1.74	0.308
Lab Number:						

0-29						
30-59	0.83	0.43-1.60	0.578	0.77	0.38-1.56	0.469
60-89	0.83	0.31-2.17	0.701	0.54	0.18-1.55	0.251
90-119	0.40	0.05-3.12	0.383	0.30	0.04-2.50	0.268
120-149	1.67	0.34-8.18	0.524	1.74	0.33-9.20	0.511
≥150	-	-	-	-	-	-
Infection Before 1 Year Of Entry:						
0						
1	1.29	0.81-2.06	0.274	1.27	0.76-2.13	0.364
≥2	1.40	0.94-2.09	0.093	1.23	0.74-2.04	0.419
Vaccines	1.83	1.17-2.87	0.008	2.05	1.24-3.39	0.005
Drugs For Acid Related Disorders	1.30	0.78-2.15	0.315	0.98	0.55-1.74	0.957
Respiratory Med	1.19	0.70-2.02	0.528	0.60	0.31-1.15	0.125
Lipid Medications	1.22	0.72-2.04	0.457	0.97	0.51-1.83	0.922
Heart Failure	-	-	-	-	-	-
Fatty Liver Disease	17.09	1.76-165.65	0.014	19.24	1.81-204.58	0.005
Obesity	3.77	1.59-8.95	0.003	2.22	1.26-8.25	0.015