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估計糖尿病對當前及未來疾病負擔的影響:全球分析

Estimating the Impact of Diabetes Mellitus on Present and Future Infectious Disease Burden: A Global Analysis

趙臨梅

April Meirie Hill

指導教授：林先和 博士

Advisor: Hsien-Ho Lin, M.D., Sc.D.

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摘要

引言：糖尿病是一種慢性疾病，過去數十年中全球皆不斷攀升並預計將持續增加至2045年。糖尿病被認為是多種傳染病的危險因子，但糖尿病對當前和未來傳染病負擔的影響尚未得到充分評估。本研究旨在量化糖尿病對呼吸道、胃腸道和泌尿道感染負擔的貢獻，並估計三種糖尿病盛行率情境對未來負擔的影響。

方法：我們進行了三種不同情境之糖尿病盛行率預測，包括「維持現狀」的趨勢、「遏制上升」和下降至歷史盛行率最低值的情境。我們採用人群可歸因分率（PAF）模型來計算當前和未來情境中可以歸因於糖尿病的比例。我們於大型群體研究使用隨機效應模型來計算風險的綜合估計值。

結果：在2019年，糖尿病佔呼吸道感染約15.25%的DALY，佔胃腸道感染6.67%的DALY，佔泌尿道感染6.29%的DALY。高收入國家在這三種傳染病的DALY中，糖尿病所佔比例最高，而可歸因疾病的比率在撒哈拉以南非洲、南亞和拉丁美洲及加勒比地區最高。大洋洲國家是糖尿病引起的感染疾病負擔最高的國家，其中糖尿病佔呼吸道感染DALY的比例高達34.73%，而可歸因於泌尿道和胃腸道感染的DALY在最負擔國家中佔16%-18%。如果糖尿病能夠控制於2019年相同的盛行率，則可以避免超過5500萬個呼吸道感染DALY、726萬個胃腸道感染DALY和255萬個泌尿道感染DALY。

結論：於全球各地區進行糖尿病控制都具有能夠減輕胃腸道、呼吸道和泌尿道感染負擔的潛力，但效益的實際大小因國家和不同感染疾病而異。

關鍵詞：糖尿病、疾病負擔、人口歸因比例、傳染性疾病、情境分析、風險因素分析

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Abstract

Introduction: Diabetes mellitus is a chronic condition that has been rising globally over the past few decades, and it is projected to continue increasing into 2045. Diabetes is considered a risk factor for several types of infectious diseases, but the impact of diabetes on present and future infectious disease burden has not been well-evaluated. This study aims to quantify the contribution of diabetes on the burden of respiratory, gastrointestinal, and urinary tract infections, and to estimate the effect of three scenarios of diabetes prevalence on the future burden.

Methods: We projected diabetes prevalence under three different scenarios, including a "business as usual" trend, a "stop the rise" in prevalence scenario, and a decline to the lowest historical value (a potential theoretical minimum exposure level). We used a population attributable fraction (PAF) model to calculate the proportion of disease that could be attributed to diabetes in the present and future scenarios. We calculated pooled estimates of risk from large, population-based cohort studies using a random-effects model.

Results: In 2019, diabetes accounted for approximately 15.25% of respiratory infection DALYs, 6.67% of gastrointestinal DALYs, and 6.29% of urinary tract infection DALYs. Countries in Oceania were disproportionately among the countries with the highest burden of diabetes-attributable infectious disease, with diabetes accounting for up to 34.73% of respiratory infection DALYs and 16% - 18% of DALYs due to urinary tract and gastrointestinal infections in the highest-burden nations. Without intervention, diabetes-related infectious diseases will rise to account for 22% of all respiratory infections, If the rise in diabetes prevalence can be stopped at 2019 levels, more than 55 million DALYs

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from respiratory infections, 7.26 million DALYs due to gastrointestinal infections, and 2.55 million DALYs from urinary tract infections can be avoided.

Conclusion: Diabetes control has the potential to reduce the burden of gastrointestinal, respiratory, and urinary tract infections globally and across all regions, though the magnitude of benefit varies by country and by infectious disease of interest.

Keywords: diabetes, burden of disease, population attributable fraction, infectious diseases, scenario analysis, risk factor analysis

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Chapter 1 Introduction

1.1 Background:

Diabetes mellitus is a chronic condition of global concern, as the prevalence of diabetes has more than doubled since 2000, from 4.6% of adults in 2000 to 10.5% in 2021.[1] These figures are projected to continue to rise, from an estimated prevalence of 537 million adults aged 20-79 years in 2021 to a projected increase to 783 million by 2045.[1] Characterized by elevated blood glucose, diabetes mellitus includes type 1 (T1DM), type 2 (T2DM), and gestational diabetes, but T2DM constitutes more than 90% of diabetes cases globally.[1,2] While there are many factors internal and external factors influencing the pathogenesis of diabetes, increased prevalence of T2DM is closely tied with lifestyle factors including obesity, a trend toward sedentary lifestyles, and unhealthy dietary behaviors like high intake of processed foods and refined carbohydrates.[2,3]

1.2 Diabetes and Infection

Chronic hyperglycemia can increase the risk of other diseases, including kidney disease, neuropathy, and heart disease. In addition to increasing the risk of other non-communicable diseases, diabetes also impacts infectious diseases by increasing a person's susceptibility to and severity of infection.[4] There are several physiological processes that may contribute to this increased infection risk, including immune cell dysfunction and poor immune response due to chronic inflammation and oxidative stress.[4–6] In addition to increased susceptibility to infection and higher risk of severe disease, people with diabetes may experience higher viral loads and longer infectious periods than their normoglycemic counterparts, which has implications for the spread of infectious disease within populations.[5,7]

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While the magnitude of increased risk due to diabetes differs by infection site, people with diabetes experience higher risk of most infectious diseases, including upper respiratory infections, surgical site infections, urinary tract infections, and skin and soft tissue infections (SSTIs).[6,8,9] There is also evidence of increased infection risk from drug resistant strains[10] and other uncommon pathogens.[11] Many systematic reviews and observational studies have explored the relationship between diabetes and both rare and common infectious diseases in a variety of settings and populations,[11–13] and the trends in older adults and hospitalized patients have garnered particular interest since people with diabetes are at increased risk of mortality due to infection.[14,15] However, while the evidence strongly supports a relationship between diabetes and risk of various infectious diseases, there are still many gaps in the literature that must be understood in the context of population health and global health priorities.

1.3 Confounders in the Relationship Between Diabetes and Infection

When evaluating the relationship between diabetes and the risk of infection, age and sex were common variables that most studies adjust for. However, complicating the relationship between diabetes and infectious diseases are several other confounders including vaccination rate, smoking, and other comorbid conditions like obesity. These factors, whose prevalence may be unequally distributed across people with and without diabetes, may lead to under or overestimation of the risk of infection among people with diabetes if they are not adequately measured.

Studies suggest that people with diabetes have higher rates of vaccination than people without diabetes,[16–21] which may be driven by public health and medical vaccination guidelines focusing on people with diabetes. While much of the literature has focused on

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the prevention of hospitalization or mortality,[19,22] vaccines have also been shown effective at reducing the risk of incident infection among people with diabetes, although some of this data has been found to be of low quality.[23,24] Estimates for the magnitude of risk reduction range from 25%-58% in people with diabetes, with similar reductions seen in the risk of incident infection and greater reductions seen in the risk of hospitalization.[19,22,25] Additionally, the relative decrease in hospitalizations and mortality as a result of vaccination may be greater in people with diabetes compared to people without diabetes.[19]

Smoking is a well-established independent risk factor for many types of infections, and is thought to increase infection risk in a dose-dependent relationship.[26,27] Urinary tract infections are thought to be a unique exemption from an increase in infection risk.[28,29] The body of evidence on whether smoking prevalence differs between people with and without diabetes is mixed, and these differences may be rooted in differences in smoking behaviors across cultures and ethnic groups. Studies out of the United States and Germany suggest that diabetes prevalence is similar or lower in people with diabetes and without diabetes,[30,31] with the studies out of Germany showing a lower prevalence of smoking among people with diabetes, though smokers with diabetes smoked more cigarettes per day than people without diabetes.[32] These potential differences in smoking behavior and the independent effect of smoking on infection risk suggest smoking is an important confounding factor to account for when considering the risk of diabetes and infection.

Finally, other comorbid conditions may be more common in people with diabetes, particularly since diabetes is considered an immune-suppressing condition. Many comorbid conditions independently increase the risk of infection compared to people without comorbid conditions.[33] Some of these conditions are more common among people with

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diabetes than people without diabetes (e.g. asthma, chronic obstructive pulmonary disease (COPD), obesity).[34–37] Thus, lack of adjustment for these other comorbid conditions may lead to an overestimation of risk among people with diabetes. Conversely, some comorbid conditions may be caused by or exacerbated by diabetes, such as chronic kidney disease or gastroparesis.[38] In instances where diabetes may fall along the causal pathway of the other comorbid conditions, further adjustment may be inappropriate and lead to an underestimation of the relationship between diabetes and infection.

Behavioral differences may add additional complications in discerning the relationship between diabetes and infection. Patients and providers may both exhibit different attitudes surrounding care seeking, diagnosis, and escalation of care.[12] Ruiz et al suggest the reason behind their study finding of higher hospitalization rate but lower in-hospital mortality may be a lower threshold for hospitalization in patients with diabetes compared to their counterparts without diabetes.[19] There is the possibility that people with chronic conditions (including diabetes) are more often recommended to visit their doctor than people without diabetes, which may influence case-finding and detection.[12] However, available studies suggest that when examining people with diabetes and people without diabetes, there may be no difference in the number of doctor's office visits annually.[16,39]

1.4 Global Implications

Like many other diseases of global concern, disease burden is unequally distributed globally. Of the estimated 537 million adults aged 20-79 years with diabetes, 80% live in low- and middle-income countries (LMICs),[1] where the burden of infectious diseases remains high.[40] LMICs are also projected to experience much of the rising burden of diabetes while being ill-prepared to handle the healthcare demands of the growing double

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burden of communicable and non-communicable diseases.[41] Poor healthcare infrastructure contributes to high rates of undiagnosed diabetes, and an estimated 87.5% of the people nearly 270 million people with undiagnosed diabetes live in LMICs.[1] This also has implications for health outcomes, since there is some evidence that suggests glycemic control is a driving factor in increasing the risk of infection among people with diabetes, with higher levels of glycemia being associated with increased risk and severity.[7,42]

Despite the burden of diabetes and infectious diseases borne by LMICs, most of the research on diabetes and infectious diseases comes from high-income nations, leaving large gaps in the literature regarding the impact of diabetes on global infectious disease burden.

1.5 Literature Gaps

While the relationship between diabetes and infectious diseases was well-accepted, there was not as much epidemiological evidence to support the association until the past decade, although this is now an a growing area of interest.[43] Many of the existing studies have methodological concerns that make it difficult to establish the causality and directionality of relationship, as infection may lead to transient hyperglycemia. Additionally, there have been few studies that quantify the impact of increased risk on infectious disease burden, particularly at a global level. Many of the available studies focus on specific populations (e.g. older adults, critically ill patients) or hospitalization outcomes (e.g. surgical site infections, sepsis). Additionally, while many studies support the link between diabetes and infectious diseases, few studies explore the impact of decreasing diabetes prevalence on infectious disease burden.

The Global Burden of Disease Study (GBD) is one of the largest undertakings of disease burden estimation, focusing on quantifying 369 causes of disease burden across

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communicable, non-communicable, and injury-related burdens.[40] However, while the GBD includes diabetes as a risk factor for tuberculosis, it has yet to publish estimates on the attributable burden of many infectious diseases due to diabetes. In addition to the GBD, other studies have produced estimates projecting the role that increased prevalence of diabetes may have on tuberculosis control, as well as support the role of diabetes management as the most effective strategy to reduce tuberculosis incidence.[44–46] Future projections from India and Indonesia, two countries with a high tuberculosis disease burden, show that diabetes will account for an growing proportion of incident tuberculosis cases and tuberculosis mortality.[45,47] Given the potential role of diabetes on tuberculosis transmission and control, as well as the growing body of evidence of the relationship between diabetes and infectious diseases, further exploration into the impact of diabetes on other infectious disease burden is warranted.

1.6 Study Aims

This study aims to quantify the present impact of diabetes on infectious disease burden among the global population and estimate how different scenarios of diabetes intervention may impact infectious disease globally. Our analysis will focus on T2DM since it is the predominant type of diabetes and can be controlled or prevented through various public health interventions. We will start with a brief overview of the epidemiological studies that quantify the associated risks of diabetes on incident infectious disease and mortality within the general population. Then, we will apply these estimates to the present disease burden and provide estimates for the impact of several future scenarios of diabetes prevalence on infectious disease burden due to three major classes of infectious diseases: respiratory infections, urinary tract infections, and gastrointestinal infections.

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Chapter 2 Methodology:

2.1 Selection of Infection Sites

The GDB was used to rank the highest-burden infectious causes by disability-adjusted life years (DALYs) in people over 20 years. DALYs are a sum of years of life lost (YLLs) and years lived with disability (YLDs), so they encompass two aspects of disease burden. Exclusion of those under 20 was done to better reflect the population at risk of T2DM and the disease burden that could be impacted by a changing prevalence of diabetes.

The cause list was assessed against the available literature to provide for comparability and consistency between the GBD reported causes and the available literature, as well as future estimates of disease burden. This resulted in the inclusion of both level 2 and level 3 GBD causes (Table 1).

Rankings were assessed by their overall global burden in DALYs, as well as their ranking in each of the GBD super regions. The GBD super regions were selected over the World Health Organization (WHO) regions due to the GBD's use of a "High-income" category, which separates high-income nations like the United States, Japan, and Australia from their geographic neighbors. High-income nations have different trends of communicable and non-communicable diseases,[48] thus using a hybrid system of grouping by geography and income status may highlight unique contributors to infectious disease burden that should be explored. The GBD region map is shown in Figure 1.

From the list of the infectious causes of DALYs, the top 10 causes globally and from each region were selected and evaluated according to the following inclusion criteria:

- Acute, infectious disease complications should account for the disease burden, compared to chronic health impacts resulting from infection
- Demonstrate a direct relationship with diabetes in the available literature.

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- Adequate research to support the risk relationship between diabetes and the infection site of interest, whether from systematic reviews, meta-analyses, or large cohort studies with sound research design

We excluded infectious diseases where much of the disease burden is due to chronic health burden, as this requires modeling both acute and chronic burden. Since we aimed to model the risk relationship and resulting disease burden due to diabetes, infectious causes also needed to have sufficient evidence of the relationship, which we defined as at least three studies that fit our inclusion criteria and supported a causal relationship between diabetes and the disease of interest. Several of the major global diseases were excluded on account of these criteria, including HIV/AIDS, malaria, and other tropical infectious diseases. We excluded HIV/AIDS and tuberculosis due to their long latency periods and chronic health outcomes. Malaria and other tropical diseases were excluded due to inadequate evidence of their relationship with diabetes. We also excluded COVID-19, as there are many unknowns making it difficult to project the future burden associated with it at the time. After applying the inclusion criteria and completing the literature search, three infection sites were selected: non-tuberculosis respiratory tract infections (lower and upper), diarrheal infections, and urinary tract infections and interstitial nephritis (UTIs).

2.2 Study Inclusion

Studies were selected based on predetermined inclusion and exclusion criteria. Inclusion criteria included (i) meta-analysis or systematic review of observational studies or (ii) original retrospective or prospective population-based cohort or case-control study of general-population, non-hospitalized adults (aged 18+) where the exposure of interest was diabetes (either T2DM or undefined diabetes) and the outcome of interest was incidence or

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mortality due to respiratory, urinary tract, or gastrointestinal infection. Original studies should be observational studies with a healthy comparator group, and measurement of diabetes was required to occur prior to the identification of infectious disease to control for the bidirectional relationship between hyperglycemia and infection. Exclusion criteria included (i) cross-sectional or case study designs, (ii) studies where hospitalization or intensive care unit admission was the sole outcome of interest, (iii) studies focused on specific populations (e.g. critically ill, pregnant, stroke patients), <18 years old population, or only included people with T1DM, (iv) studies that examined the relationship between diabetes and other comorbid conditions with infection, or (v) inclusive of a single pathogen.

2.3 Quality Assessment

Risk of bias associated with each outcome was assessed using the Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) tool.[49] The tool includes a set of signaling questions used to evaluate each study outcome for its risk of bias and assigns a score for each of its 7 domains (bias due to confounding, participant selection, intervention classification, deviation from intended intervention, missing data, outcome measurement, and reporting) as well as an overall rating. ROBINS-I also includes an additional assessment for the direction of bias either toward or away from the null hypothesis. Each outcome would be evaluated differently, as there was potential for different risks of bias depending on the outcome. Following individual assessment, the studies were collectively also assessed using the GRADE method.[50] Studies were required to receive a rating of "serious risk of bias" or higher to be included in the final pooling estimates.

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2.4 Statistical Analysis

2.4.1 Data Extraction

Extracted variables included: title, author, source of data, country, study design, population, length of follow-up, number of participants, risk ratio and confidence intervals, major study limitations, and included covariates. When available, ICD-9-CM and ICD-10-CM codes were extracted for comparison with the GBD-ICD code map to determine the best matching cause.

2.4.2 Study Pooling

If there were at least three estimates for an infection site, estimates were pooled using a DerSimonian and Laird random-effects model due to assumed heterogeneity and demographic differences across the populations in our studies.[51,52] We pooled adjusted estimates from each study and recorded their effect size and I^2. One study reported crude estimates from an age-sex-location matched cohort,[53] while the other studies all reported adjusted estimates. Infection sites (i.e. gastrointestinal, respiratory, and urinary tract infections) were analyzed separately, except in the case of lower and upper respiratory infections. When available, we generated separate estimates for all respiratory infections, lower respiratory infections, and upper respiratory infections. If studies reported lower and upper respiratory infections separately but did not report a joint estimate, we calculated a within-study estimate using a fixed effects model. Included measures of association were odds ratios (OR), incidence risk ratios (IRR), and hazard ratios (HR). Other crude measures of association, including standardized mortality ratios (SMRs) were not included in our study due to lack of adjustment for confounding.

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2.4.3 Data Sources

Data on T2DM prevalence from 1990-2019, as well as all infectious disease burden outcomes, by country, sex, and 5-year age group came from the 2009 Global Burden of Disease Study.[54] The United Nations population estimates were used for past and future population distributions from 1990-2045.[55] These data sources are publicly available. Relative risks for diabetes and the various sites of infection were calculated from meta-analyses of previous epidemiological studies according to the methodology previously described.

2.4.4 Present Situation

Diabetes prevalence estimates were available for age-standardized rates. All estimates for each year, country, sex, and 5-year-age group were calculated individually and then aggregated to produce regional, age group, or global estimates. While the GBD provides diabetes estimates starting at the 15-19 age group, we excluded ages <20 from our disease burden calculations. Since none of our identified studies include children or adolescents, we are unable to generalize the risk relationship demonstrated in the included studies to an adolescent population. However, as this group contributes to diabetes prevalence globally, we included them when calculating age-standardized diabetes prevalence or country-specific diabetes average. Age standardization was done via direct standardization against the WHO reference population 2000-2025.[56]

To calculate attributable disease burden, we used the population attributable fraction (PAF) method.[57] The PAF represents the proportional reduction in disease burden or mortality that would occur if the exposure to the risk (or prevalence of the risk factor) was reduced to zero or shifted to an alternative exposure scenario, and allows for calculating

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attributable and non-attributable disease burden. The PAF was calculated for each country-age-sex group and applied to disease burden data for historic and future diabetes prevalence under our three scenarios.

Outcomes were separated into the incidence of infection and mortality, which we used for calculating YLDs and YLLs respectively. Since there were not enough available outcomes for mortality due to UTIs and gastrointestinal infections, the risk relationship was assumed to be the same. YLDs and YLLs were calculated separately for respiratory infections and then combined to report the burden of disease in DALYs.

2.4.5 Future Prediction Model

Diabetes prevalence was modeled under three different scenarios of diabetes intervention and control to determine the impact of varying levels of diabetes control on the estimated future burden of infectious diseases.

Baseline/Business as Usual Scenario:

The “business as usual” scenario, in which the trend of diabetes prevalence was assumed to follow a similar trend to the past 10 years (2010-2019), was predicted using a linear regression model. Final values were assessed according to the difference between their initial and predicted final value in 2045, and the location-age-sex groups in the bottom and top 1% were compared against historical data for any potential inconsistencies in the trend that may contribute to extreme change.

Several locations and age groups demonstrated sharp increases or declines from 2015 to 2017, which are two of the years that the Global Burden of Disease study provided updates. Since differences in methodology, new data availability, or other causes may lead to artificial changes in prevalence or exaggerate true change, as well as have undue

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influence on future prediction models, any country that showed sharp, short-term declines or increases, particularly from 2015-2017, was rerun using historical data from 2005-2019 as a basis for the prediction model. This was done to ensure short-term changes in trend did not exert undue influence on future predictions.

Stop the Rise:

This target was based on the World Health Organization (WHO) diabetes target for 2025, which includes halting the rise of diabetes. While the World Health Organization target involved maintaining 2010 levels, we set the diabetes prevalence to stay at 2019 levels for each country-age-sex group from 2019 to 2045 due to aggressive intervention. This does not account for the influence of age structure on the all-age diabetes prevalence, so in the presence of an aging population, the country-specific diabetes prevalence may continue to rise.

In the case that the stop the rise scenario prevalence of diabetes was greater than the future trend of diabetes for that country-age-sex group, the lower estimate was used to calculate disease burden. This was done under the assumption that additional intervention would have a compounding effect on the trend of diabetes, lowering it further rather than raising it. However, due to heterogeneity across countries, we were unable to further adjust for the impact of intervention on diabetes prevalence.

Minimum Diabetes Prevalence Scenario:

The minimum prevalence of diabetes scenario was chosen as the lowest all-age diabetes prevalence across all countries and measurement years, as this suggests the potential minimum prevalence of T2DM. This scenario was selected as an alternative to a 0% all-age global prevalence of diabetes and represents the ideal scenario of diabetes

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prevalence on attributable burden. All age groups were assumed to decline at the same rate, where the all-age prevalence of diabetes would reach 0.44% (0.00438) by 2045. Groups could achieve a 0% prevalence of diabetes, but the lower bound was set at 0 as a negative prevalence of diabetes is not possible.

Future Burden of Disease:

Historic diabetes prevalence was used to estimate the past attributable and non-attributable burden of infectious disease due to diabetes. We modeled the trend of non-attributable infectious disease into 2045 using a log-linear model. The log-linear accounts for a graduated decline toward a non-zero minimum of infectious disease burden over time and reflect the inability to achieve a negative disease burden. We used the future predicted non-attributable disease burden to model the total and attributable disease burden under our three scenarios.

2.5 Sensitivity Analysis

To test the robustness of our pooling study results, we conducted two sensitivity analyses. We repeated our analysis using a fixed-effects model to examine the impact of using a random-effects analysis on the results of our analysis. We also conducted influence analyses by removing each study from our meta-analysis for each of our major outcomes (all respiratory infections, upper respiratory infections, lower respiratory infections, gastrointestinal infections, and urinary tract infections).[58]

To test the robustness of our primary analysis, we repeated our statistical analysis under several scenarios. First, we separately analyzed lower and upper respiratory infections using only the studies that reported separate effect sizes to produce individual lower and upper respiratory infection results, as well as joint results to determine if there were significant differences. Additionally, if our leave-one-out analysis identified any

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studies that were more highly influential than others, we removed these to calculate our primary outcomes again.

Finally, we selected the most narrow definition of infectious disease shared between the available cohort studies and the GBD, so our results would reflect a conservative estimate of the true impacts of diabetes on those infectious outcomes. In our sensitivity analyses, we expanded the cause from "diarrheal diseases" to encompass the broader level three cause "enteric infections" (to include "invasive non-typhoidal Salmonella (iNTS)," "typhoid fever," and "paratyphoid fever") as well as "appendicitis" and "peptic ulcer diseases."

While one study (Carey et al. 2018) included "peritonitis" as a gastrointestinal infection outcome, the GBD study includes this within the "other digestive diseases" category along with other infectious and non-infectious causes. Given that there are nearly 100 distinct diseases represented within the "other digestive diseases" category, with many of these diseases having non-infectious etiologies as well as the fact that 25% of peritonitis cases or fewer are considered spontaneous bacterial peritonitis (SBP),[59,60] this cause was not included in our sensitivity analysis. Infectious etiologies are thought to play a role in approximately 70% of stomach ulcers and 70-90% of duodenal ulcers,[61] so the initial burden of disease values were set at 70% of initial values. Non-infectious etiologies of appendicitis are thought to only represent a small proportion of total appendicitis cases,[62,63] though the proportion of cases attributed to infection versus non-infectious or genetic causes has not been quantified. For this reason, no further adjustment was made to these values. The included ICD codes for gastrointestinal studies that included them can be found in Appendix 3.

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2.6 Uncertainty Analyses

Due to uncertainty related to estimation, we used a Monte Carlo simulation approach to randomly compute 1,000 sets of the PAF based on the uncertainty estimates of the risk exposures and RRs distributions. These distributions were drawn using a lognormal distribution for all outcomes. We calculated 95% uncertainty intervals of each outcome based on the resulting 1,000 distributions of estimated attributable burden, whether DALYs, YLDs, or YLLs. This simulation approach was repeated for each step of the statistical analysis that was previously described.

All statistical analysis was carried out using R version 4.0.3 and RStudio ver. 2023.03.2. Conversion between ICD-9 and ICD-10 codes was conducted using RStudio icd package 4.0.9. Visualizations were done using RStudio ver. 2023.03 and Flourish®.

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Chapter 3 Results

3.1 Search Results

We identified 6 studies on urinary tract infections,[8,16,39,53,64,65] 4 studies on gastrointestinal infections,[8,16,53,64] 5 studies on the incidence of respiratory infections (including both upper and lower),[8,16,39,53,64] and 5 studies on mortality due to respiratory infections.[66–70] One study included "infection mortality" which was composed of 75% lower respiratory infection outcomes in addition to 5% gastrointestinal infections and additional other infections,[8] but this outcome was excluded due to the inability to assign risk to our specific outcomes. There were 4 studies that reported the incidence of both lower and upper respiratory infections separately,[8,39,53,64] with one of the four studies also providing an "all respiratory infections" result, which is what we used in our combined lower and upper respiratory infection analysis.[64] Of the studies on respiratory infection mortality, 3 of the 5 focused on lower respiratory infections,[66,68,70] while 2 included both upper and lower respiratory infections.[67,69] There were no studies that reported separate upper respiratory infection mortality. These studies were population-based studies from Canada, China, Japan, Mexico, the Netherlands, the United Kingdom, and the United States. A summary of each study can be found in Appendix 1.

ICD-9-CM/ICD-10-CM codes were extracted from two studies for primary care visits on incidence risk of infection,[8,16] and included respiratory (n = 2), gastrointestinal (n = 1), and urinary tract (n = 1) infection outcomes. Four studies (Carey et al. 2018, Hine et al. 2017, Hirji et al. 2012, and Muller et al. 2005) reported different clinical classification methods,[8,39,64,65] with Carey et al 2018 only providing ICD codes for hospital visits but not for primary care visits. Shah and Hux 2003 did not report their included disease codes. Due

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to limited ICD codes availability, analysis of included codes did not provide meaningful comparisons between studies.

3.2 Quality Assessment

` The ratings for individual studies are presented in Figure 2-5, and the rationale for individual studies can be found in Appendix 2. All studies across all included outcomes were at serious risk of bias, with the primary domains of concern being bias due to confounding and bias due to measurement outcomes. Studies with serious risk of bias due to confounding neglected to adjust for key variables that may influence the results, with smoking,[39,53,65] vaccination,[8,39,53,64,66–70] obesity,[39,53,65] and other comorbid conditions (e.g. respiratory disease)[8,53,65–70] being commonly neglected confounders. One study adjusted for vaccination,[16] and two studies measured care-seeking behaviors.[16,39] Studies were generally at low risk of bias due to misclassification of outcomes or deviation from intended intervention, which is consistent with other studies of non-randomized observational outcomes. The most common missing data was on smoking status.[8,16,64] Some studies included various analytical techniques to address missing data, including the use of a missing indicator and complete case analysis.[16] Since diabetes could be diagnosed prior to the initiation of the study, most studies suffered from survivor bias, in which it is difficult to know how death among people with diabetes prior to the study initiation may impact results. Additionally, differences in care-seeking behavior or provider diagnosis may lead to bias, but few studies attempted to account for these factors. No study was excluded due to the critical risk of bias.

The collective body of evidence received a GRADE rating for the quality of evidence. Observational studies start with a “low” rating, but the body of evidence was

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upgraded to “moderate” due to evidence of a dose-response since there is evidence that higher blood glucose levels lead to a higher risk of infection across all of our study outcomes.[7,42,64,65,67]

3.3 Pooling Results

The forest plot generated for respiratory infections showed there was a slightly increased risk of upper respiratory infections due associated with diabetes (RR 1.16, 95% CI: 1.08-1.24) (Appendix 4). The risk of incident infection associated with lower respiratory infections was greater than upper respiratory infections (RR 1.36, 95% CI 1.26-1.48)), while the risk of general respiratory infections (including upper and lower) was 1.23 (95% CI: 1.17-1.29).

The pooled risk of mortality due to respiratory infection was 2.36 (CI 95% 1.65-3.37), with estimates ranging from 1.58-3.65. The risk of lower respiratory infection mortality was similar to overall respiratory infection (2.24, 95% CI: 1.43-3.51), but there were not enough studies to calculate an estimate for upper respiratory infection mortality. The highest mortality from respiratory infections was reported in a study from Mexico (RR: 3.65, 95% CI: 3.19-4.18), which showed greater than three times the risk of dying due to respiratory infection among people with diabetes. The risk of urinary tract infections among people with diabetes compared to the general population was 1.49 (95% CI: 1.27-1.55).

Heterogeneity was high across all meta-analyses with the exception of the gastrointestinal estimate. This was anticipated a priori due to the inclusion of studies from various countries and populations, as well as very large sample sizes with narrow confidence intervals.

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3.4 Present Situation

In 2019, the global age-standardized prevalence of T2DM was 5.31%, and the all-age prevalence of T2DM was 5.62%. In the Business as Usual scenario, the projected all-age prevalence of diabetes is 9.31%. If diabetes prevalence for each age group is maintained at 2019 levels, the 2045 all-age prevalence will be 6.91%. In the minimum prevalence scenario, the projected all-age prevalence of diabetes is 0.44% (Table 2).

Globally, among the 20+ years old global population in 2019, diabetes accounts for approximately 15.25% of all respiratory infection diseases, 6.67% of all gastrointestinal infections, and 6.29% of all urinary tract infections in 2019 (Table 3). Across all regions, diabetes contributes the largest percent of the disease burden due to gastrointestinal (8.66%), respiratory (19.50%), and urinary tract (8.68%) in the High-income region. The lowest percent of DALYs attributable to diabetes occurs in Central Europe, Eastern Europe, and Central Asia for gastrointestinal (3.36%) and respiratory tract (10.54%) infections, with Sub-Saharan Africa having the lowest percent of attributable urinary tract infections (3.19%). Latin America and the Caribbean have the highest rate of urinary tract infection DALYs due to diabetes, with 11.27 DALYs per 100,000, while diabetes contributes the highest rates of respiratory infections and gastrointestinal infections in Sub-Saharan Africa (165.19 per 100,000) and South Asia (106.29 per 100,000) respectively.

Analysis by country (Table 3) shows the highest rates of diabetes-attributable respiratory infections among islands in Oceania, including Palau (944.86 DALYs per 100,000) and Solomon Islands (805.94 DALYs per 100,000). In Niue, over 35% of all respiratory infection DALYs can be attributed to diabetes, while diabetes contributes 39.77 urinary tract infection DALYs per 100,000 in Barbados.

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3.5 Future Predictions of Diabetes

The regional prevalence percent of people with diabetes for the 20-49, 50-69, and 70+ age groups is expected to rise across all GBD regions, with the exception of the 70+ population of Southeast Asia, East Asia, and Oceania (SEAEAO). The sharpest increase is shown in the North Africa and the Middle East (MENA) and South Asia regions in the 70+ and 50-69 age groups, and South Asia for the 20-49 age group. Among the 70+ population in MENA, the prevalence of diabetes is projected to reach 41% under the current trend. The lowest prevalence of diabetes has historically been in the Sub-Saharan Africa region. This trend will continue for the 20-69 population, but the projected prevalence of diabetes in Sub-Saharan Africa will rise above that of SEA by 2045 (14.19% vs 22.51%).

Diabetes in the SEAEAO region is expected to decline in the 70+ age group, while the number of people with diabetes is predicted to more than double from around 24 million in 2015 to 55 million in 2045. Under these projections in the business as usual scenario, the total number of people with diabetes globally by 2045 is projected to be around 875 million (Figure 7). In comparison, stopping the rise of diabetes would prevent approximately 175 million cases of diabetes, with a large majority of those in the South Asia, Latin America, and MENA regions.

3.6 Impact of Diabetes on Infectious Disease Burden

The projected impact of diabetes on the sites of infection varies by region. With the exception of Sub-Saharan Africa, the other world regions show a trend toward increasing burden due to respiratory infections after a few decades of declining respiratory-related disease burden. In the high-income region, diabetes will contribute 36.5% of all respiratory infections by 2045 if there is no intervention (258 DALYs per 100,000, UI 95% :) (Figure 10a and Figure 10b).

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As shown in Figure 10b, between 2019 and 2045, the high-income nations will have the highest number of preventable DALYs due to respiratory infections associated with stopping the rise of diabetes compared to the other regions. Stopping the rise would prevent 7.26 million DALYs due to gastrointestinal infections, 2.55 million DALYs from urinary tract infections, and 41.24 million DALYs due to respiratory infections (Figure 11a, Figure 11b, and Figure 11c). A decline to our estimated minimum prevalence of diabetes would result in 37.07 million avoided DALYs from gastrointestinal infections, 12.65 million avoided DALYs from urinary tract infections, and 179.66 million avoided DALYs from respiratory tract infections. The minimum diabetes prevalence scenario would lead to a prevention of 6.90% of global respiratory infection DALYs, 6.38% of urinary tract infection DALYs, and 2.84% of global gastrointestinal infection DALYs. Of the avoided DALYs under both scenarios of diabetes control, South Asia experiences the largest reduction in DALYs from all three infection sites.

3.7 Sensitivity Analysis

In our primary model with fixed effects, there are minor differences seen in the point estimate for all respiratory infection incidence (RE: 1.23, 95% CI: 1.17 - 1.29 vs FE: 1.22 95% CI: 1.22 - 1.23), with similar results for individual lower and upper respiratory infections and gastrointestinal infections. The random-effect model remains more conservative, particularly for applications across the global population. All respiratory and lower respiratory infection mortality and urinary tract infections show some increase in the magnitude of risk using a random-effects model, though the direction of risk remained similar. This indicates heterogeneity underlying the cohort-specific estimates, which is

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consistent with a high I^2 (>80%) statistic for all estimates with the exception of gastrointestinal infections.

Influence analysis revealed relatively stable results for respiratory infections, lower respiratory infections, upper respiratory infections, and gastrointestinal infections. Our mortality outcomes showed more deviation upon removing each of the studies; however, we ultimately decided to keep all of these studies in our primary analysis, as each of these studies reflects racially diverse populations. Since there were no studies on mortality from upper respiratory infections, we assumed the effect size to be 1.0 when calculating mortality estimates in our sensitivity analysis. For urinary tract infections, the analysis revealed Shah and Hux 2003 was an influential study for urinary tract infections, and estimates varied when removing any study from both lower and total respiratory infection mortality.

Additionally, we conducted separate analyses of YLDs and YLLs for gastrointestinal and urinary tract infections. YLDs were calculated using the pooled results from our literature search and meta-analysis. YLLs were calculated using the values reported by Bragg et al 2023, which was the only included study to report mortality estimates for urinary tract infections and gastrointestinal infections.

A detailed presentation of the results is available in Appendix 5.

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Chapter 4 Discussion

If there is no intervention, the global prevalence of diabetes will almost double between 2019 and 2045, although some of this increase is driven by an aging population, as an increase is also seen in the global all-age prevalence of the Stop the Rise scenario. The Minimum Scenario leads to a reduction of 92.17% decrease in diabetes prevalence over 26 years, with the older population being the group to experience the largest reduction in prevalence. The overall feasibility of achieving either the Stop the Rise or the Minimum Prevalence scenario on a global scale is low. The Stop the Rise scenario was proposed by the World Health Organization in 2013, but only fourteen countries are on track to meet these targets.[71] However, these two scenarios were chosen as points of reference due to their 1) global health significance as a global target from the 75th World Health Assembly (Stop the Rise) and 2) their use for comparison against the Business as Usual scenario to illustrate and contextualize the role of diabetes on global infectious disease burden. Despite concern for feasibility, our study suggests that aggressive targets for diabetes control would have a significant impact on the global infectious disease burden.

The various regions show unique patterns in infectious disease distribution and the overall impact of diabetes on infectious disease burden. With the exception of Sub-Saharan Africa's declining trend of infectious disease DALYs, and South Asia in regard to gastrointestinal DALYs, the regions exhibit an increasing trend of infectious-disease-related burden. While this will be driven by an increasing disease burden that is not attributable to diabetes (Figure 9), a rising diabetes prevalence will exacerbate this trend (Figure 10a, Figure 10b). This is particularly evident when examining the graph of

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attributable disease of respiratory infections across most regions, and urinary tract infections in the high-income region.

Additionally, this analysis highlights the regional differences in diabetes burden and impact. In comparison, despite the relatively small proportion of diabetes-attributable infectious diseases in Sub-Saharan Africa, the DALYs associated with respiratory and gastrointestinal infections are comparable to or greater than many of the other regions. Thus, while the proportion of attributable disease is lower, diabetes control has the potential for meaningful impact across all regions in regard to respiratory, gastrointestinal, and urinary tract infections.

Further analysis at the country level shows that diabetes contributes significantly to the disease burden among island nations in Oceania (Table 3). In 2019, American Samoa, Niu, and Marshall Islands were within the top 5 countries that have the highest percent of gastrointestinal, respiratory, and urinary tract infections attributable to diabetes. These are also countries that have high rates of diabetes. Care should be taken when interpreting and applying regional and global estimates of disease burden, as focusing solely on regional burden can mask the challenges that smaller nations may face.

Looking at the future trend of the SEAEAO region actually shows a declining prevalence of diabetes over the next two decades, which is primarily driven by a declining trend in China and Indonesia. However, despite a declining prevalent percentage of people with diabetes, the prevalent number of people with diabetes continues to rise. This suggests the effect may be driven by factors other than a decline in diabetes incidence, such as improved life expectancy and healthcare access leading to a larger pool of healthy, non-diabetic adults. This is further supported by the growth highlighted in the cumulative

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preventable DALYs under the business as usual and the stop the rise scenario compared to the minimum prevalence of diabetes scenario. While the prevalence of diabetes will be around 14% in the 50+ population in SEA compared to 30.6% in Latin America and the Caribbean and 25% in the High-income region of the same population, the overall cumulative burden of DALYs due to respiratory infections in SEA is greater than Latin America and the High-income region combined.

These results support the use of diabetes intervention to not only address a growing non-communicable disease epidemic, but with the added benefit of reducing the burden of disease associated with infectious diseases. Additionally, the benefits of diabetes intervention may be greater than illustrated in this study. While there was not enough available data to create separate estimates for urinary tract infection or gastrointestinal infection mortality, the cohort study from Mexico suggests that the risk of mortality associated with both diseases may be significantly higher than their incident risk, with urinary tract infection mortality being as much as 10 times higher among people with diabetes.[67] Additionally, the risk may not be borne by all age groups equally. However, the existing literature on the risks of infection in different age groups is mixed, and more research is required before drawing significant conclusions.[16,67,72]

Based on the results of the risk of bias assessment, there is the need for further research into the relationship between diabetes and selected infectious diseases. The domains that indicate a serious risk of bias across almost all of the included studies. As urinary tract infections are less strongly influenced by factors such as vaccination or smoking, potential differences in providers' diagnostic behaviors may lead to a slightly skewed bias toward people with diabetes. Conversely, for respiratory diseases, the direction

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of bias is likely moderately skewed toward people without diabetes, as different vaccination behaviors may moderate some of the relationship between respiratory infections and diabetes. Additionally, while some studies did not account for smoking behaviors, only one study account for vaccination behaviors. Thus, the impact of vaccination on the body of evidence overall is less represented than that of smoking behaviors. The direction of bias on the effect size of gastrointestinal infections is unclear, due to the mixed relationship between diabetes risk and smoking, as well as the potential mediation effect of diabetes on infection via diabetes-induced comorbid conditions such as gastroparesis.

Other confounders such as smoking show a mixed association with diabetes, making the direction of bias difficult to predict.

4.1 Comparisons with Existing Literature

Although there are few studies that attempt a global analysis of the infectious disease burden attributable to diabetes, particularly for gastrointestinal infections, our results are largely consistent with the literature that does exist regarding respiratory infections. The GBD Tuberculosis Consortium estimates that 10.6% of tuberculosis cases in people without HIV could be attributed to diabetes globally,[73] while a modeling study from India suggests that, in 2017, 21.9% of the incident cases of TB could be attributed to diabetes. This number was projected to rise to 33% by 2050.[45] Bragg et al (2023) calculated the deaths from infection that were attributable to diabetes in Mexico City, and found that approximately 33% of infection-related mortality was attributable to diabetes, and over half of that figure was contributed by uncontrolled diabetes (defined as HbA1c ≥9.0%).[67] The Bragg estimates are higher than the final estimates for 2019 in this study, but their figures were likely influenced by their higher gastrointestinal and urinary tract infection effect size,

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while also including other infectious diseases that may have a stronger relationship with diabetes than those included in this study.

Our diabetes future projections are also comparable to other published estimates. While we assumed linearity of the relationship without including additional predictors in our business as usual scenario, our results are largely consistent with those of the International Diabetes Federation, which estimates there will be 783 million people with diabetes globally in 2045.[1] Our baseline estimate, approximately 875 million, is higher but also includes the global population over 80 years old, while the International Diabetes Federation excludes this subset of the population. While a more robust diabetes prediction model may estimate differences in the future prevalence of diabetes, we suspect that the trends in the impact of diabetes on infectious disease globally and over time would remain constant.

4.2 Sensitivity Analysis

We also conducted sensitivity analyses to determine the impact of our operational definitions and to address several of the limitations of this study. The sensitivity results are consistent with our analysis or suggest an underestimation of attributable disease burden. Pooling model and the inclusion or exclusion of selected studies had little impact on our overall results, while broader operant definitions of infectious causes and the use of separate gastrointestinal and urinary tract infection magnitudes of risk for calculating YLDs and YLLs calculation had a larger impact (Appendix 5).

4.3 Strengths

There are inadequate studies exploring the attributable burden of selected infectious diseases due to diabetes across different regions and countries. While some studies have

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attempted to quantify the burden of infectious disease contributed by diabetes within their study populations, this study's strength is that it produces estimates across 204 countries and territories, as well as by sex and age group.

Access to information on the relationship between diseases can lead to synergistic decision making and cross-collaboration that strengthens public health infrastructure and informs policymaking. This has been seen as a result of similar research detailing the relationship between tuberculosis and diabetes, as public health efforts have shifted toward incorporating diabetes management as a strategy for tuberculosis control.

4.4 Limitations

A primary limitation of this research is the data quality and availability, both regarding data sources as well as previously published research. The datasets utilized, including the GBD Study and the United Nations population predictions, are widely used by organizations and governments in global health. However, we acknowledge the concerns regarding the credibility and validity of the GBD results.

Another limitation of this research is the paucity of globally-representative literature examining the interactions between diabetes and the risk of infection. Much of the available research on the interactions between diabetes and the risk of infection comes from countries in North America and Europe, with the exception of studies examining respiratory infection mortality and diabetes. This may limit the generalizability of the findings to other regions of the world, as there is not enough data to determine if the risk between diabetes mellitus and infectious disease is constant across racial or ethnic groups. Particularly, the relationship between diabetes and respiratory infection mortality was stronger in Mexico and China than in the United States and the United Kingdom.

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Additionally, many of the included studies, especially the studies that included respiratory infections, were plagued by serious risk of bias due to confounding. Some studies did not adequately control for important confounders such as smoking, vaccination status, and other comorbid conditions like asthma or other respiratory diseases, all of which have been shown to individually impact the risk between diabetes and infectious disease. While the current research provides valuable insights into the potential burden of infectious diseases that may be attributed to diabetes, it is important to recognize these limitations and acknowledge the continued need for globally representative and rigorously designed research in this area.

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Chapter 5 Conclusion

Our study demonstrates the need to consider interventions to prevent the rise in diabetes both as a strategy to reduce chronic health disease burden and also to prevent infection disease burden due to various site-specific infections, including gastrointestinal, respiratory, and urinary tract infections. As diabetes is projected to continue to rise through 2045, the burden of infectious diseases attributable to diabetes will continue to rise. Care should be taken to examine trends at a country level as well as regional, since the highest-burden countries may not come from the highest-burden regions. While the total attributable burden associated with diabetes varies by region and infection site, stopping the rise in diabetes has the potential to prevent 55 million combined DALYs from gastrointestinal, respiratory, and urinary tract infections from 2019 - 2045, which has major implications for global health. Future studies may consider exploring the dose-response relationship of diabetes control and glycemia in the context of global infectious disease, as the burden of undiagnosed diabetes may further complicate projections of diabetes-attributable infectious disease burden.

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Chapter 6 Tables

Table 1: Ranking of infectious diseases by Global DALYs rate and total DALYs

Inclusion	Age	Disease	Global DALY Total	Global DALY Rate (per 100,000)
	20+ years	Tuberculosis	39461149.76	317.450
	20+ years	HIV/AIDS	38912549.28	313.037
	20+ years	Lower respiratory infections	33557506.61	269.958
	20+ years	Diarrheal diseases	27,376,900.64	220.240
	20+ years	Neglected tropical diseases and malaria	18939787.86	152.364
	20+ years	Other infectious diseases*	11506320.89	92.564
	20+ years	Periodontal diseases	7028197.942	56.539
	20+ years	Urinary tract infections and interstitial nephritis	4609992.253	37.086
	20+ years	Upper respiratory infections	3627738.265	29.184
	20+ years	Pancreatitis	3536801.355	28.452

Table 2: Definitions of three scenarios of diabetes prevalence

Description of Diabetes Scenarios				
Scenario	Description	2019 - Age standardized	2019 - All-age	2045 - All-age
Business as usual	Determined using a linear regression analysis of the past 10 years of T2DM prevalence	5.33%	5.62%	9.31%
Stop the rise	Diabetes prevalence remains at 2019 estimates through 2045	5.33%	5.62%	6.91%
Return to Lowest Historical Value	The lowest historical prevalence across all countries from 1990-2019 - a theoretic minimum risk exposure level	5.33%	5.62%	0.44%

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Table 3: Highest burden of attributable disease ranking by DALY rate and percent for gastrointestinal, urinary tract, and respiratory infections

Countries with the highest burden of disease attributable to diabetes 2019							
Attributable DALY's per 100,000				% of DALY's attributable to diabetes			
	Rate	Male	Female		%	Male	Female
Gastrointestinal							
Global	35.59	32.14	38.99	Global	6.67	6.40	6.90
1. Central African Republic	221.58	303.13	142.12	1. Niue	17.63	17.15	18.07
2. Solomon Islands	205.21	212.38	197.97	2. American Samoa	17.52	17.2	17.9
3. Kiribati	176.8	170.65	182.24	3. Marshall Islands	16.5	15.86	17.03
4. Lesotho	138.92	165.53	113.49	4. Fiji	15.43	15.15	15.77
5. India	119.17	93.77	145.88	5. Sri Lanka	14.51	13.35	15.54
6. Vanuatu	111.31	108.41	114.11	6. Mauritius	14.09	13.72	14.56
7. Eritrea	101.96	139.07	67.66	7. Palau	13.8	12.82	14.7
8. Papua New Guinea	101.2	127.55	73.31	8. Puerto Rico	13.53	13.73	13.34
9. Marshall Islands	98.24	84.76	112	9. Cook Islands	13.29	12.81	13.81
10. Niue	97.91	94.89	100.71	10. Seychelles	12.85	11.46	14.63
Respiratory							
Global	112.68	126.65	98.89	Global	15.62	15.62	15.63
1. Palau	32.12	31.54	32.59	1. Niue	32.12	31.54	32.59
2. Solomon Islands	31.53	27.09	34.12	2. American Samoa	31.53	27.09	34.12
3. Seychelles	28.43	28.99	28.12	3. Brunei Darussalam	28.43	28.99	28.12
4. Niue	28.97	26.84	30.5	4. Marshall Islands	28.97	26.84	30.5
5. Marshall Islands	27.69	27.41	27.97	5. Czechia	27.69	27.41	27.97
6. Malaysia	29.15	28.69	29.51	6. Cook Islands	29.15	28.69	29.51
7. Zimbabwe	35.38	35.5	35.27	7. Puerto Rico	35.38	35.5	35.27
8. Central African Republic	27.71	29.35	26.45	8. Grenada	27.71	29.35	26.45
9. Lesotho	28.09	27.51	28.59	9. Palau	28.09	27.51	28.59
10. Micronesia (Federated States of)	27.62	28.31	27.1	10. SVG	27.62	28.31	27.1
Urinary Tract Infection							
Global	5.63	5.40	5.87	Global	6.29	6.51	6.10
1. Barbados	39.77	47.41	33	1. American Samoa	16.35	16.99	15.8
2. Seychelles	31.11	31.28	30.91	2. Niue	15.16	15.83	14.64
3. American Samoa	26.3	25.93	26.65	3. Fiji	14.65	16.26	13.21
4. Saint Kitts and Nevis	25.27	38.98	12.59	4. Brunei Darussalam	14.35	17.12	12.59
5. U.S. Virgin Islands	24.13	22.53	25.47	5. Marshall Islands	13.21	13.58	12.94
6. SVG*	23.27	24.1	22.39	6. Bahrain	13.1	12.77	13.41
7. Portugal	22.97	18.79	26.58	7. Czechia	12.76	14.18	11.43
8. Puerto Rico	22.81	20.6	24.73	8. Puerto Rico	12.31	12.89	11.92
9. Armenia	21.7	25.35	18.99	9. Mauritius	11.65	11.89	11.41
10. Suriname	21.17	22.96	19.42	10. Saint Lucia	11.57	11.6	11.52

*Saint Vincent and the Grenadines

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Chapter 7 Figures

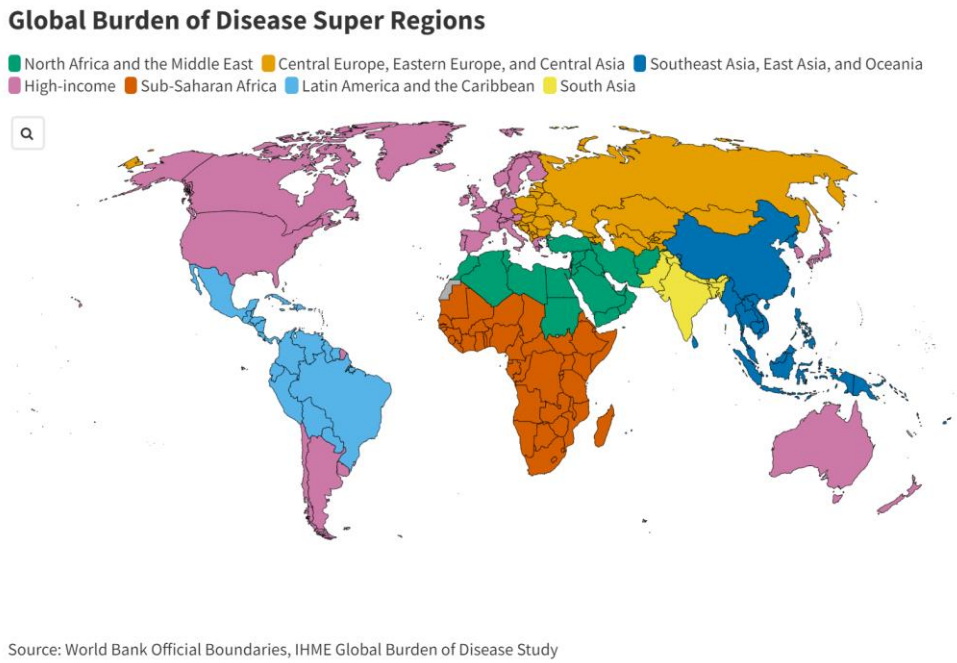

Figure 1: World map by Global Burden of Disease super region

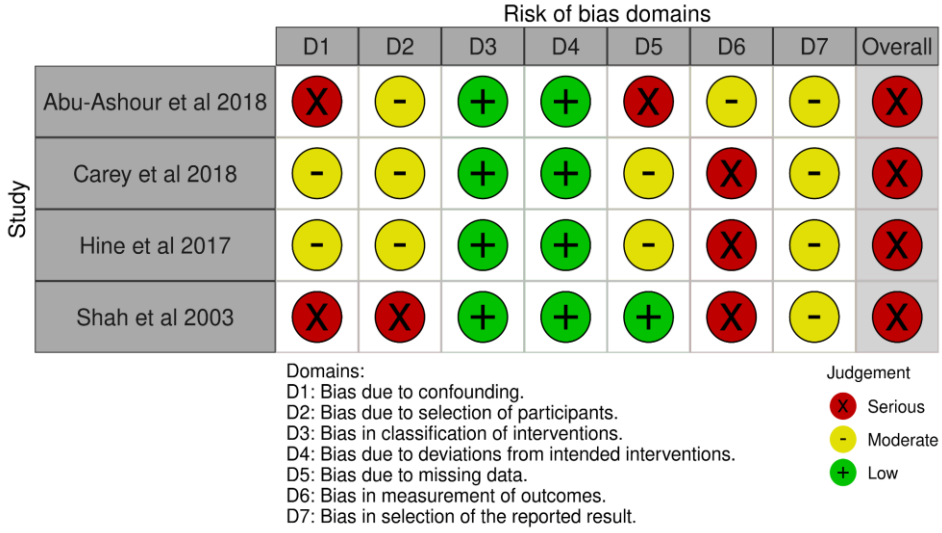

Figure 2: Traffic light plot of risk of ROBINS-I ratings for studies included in the gastrointestinal infections analysis

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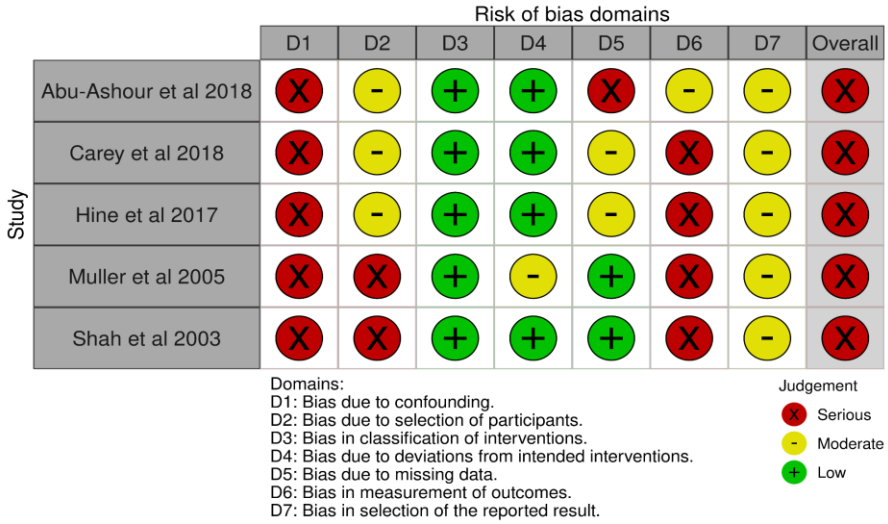

Figure 3: Traffic light plot for ROBINS-I for respiratory infection incidence

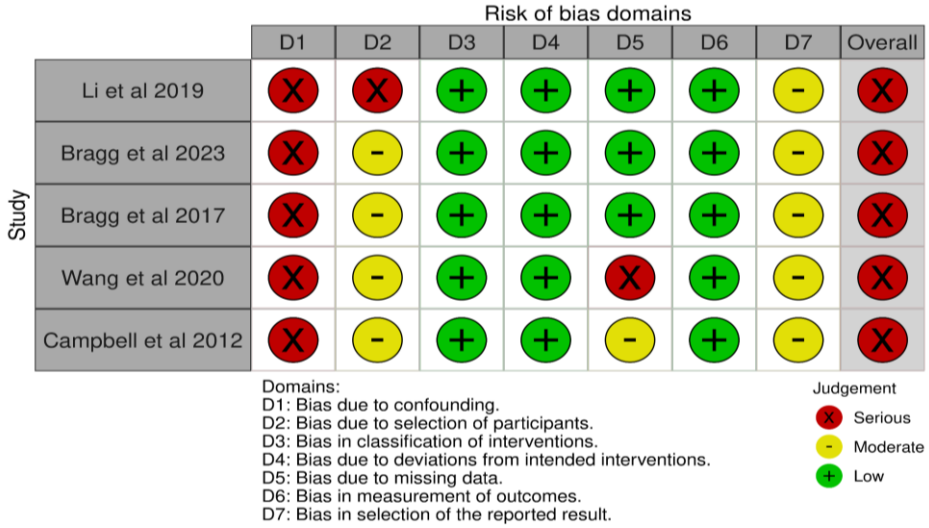

Figure 4: Traffic light plot of ROBINS-I results for respiratory infection mortality

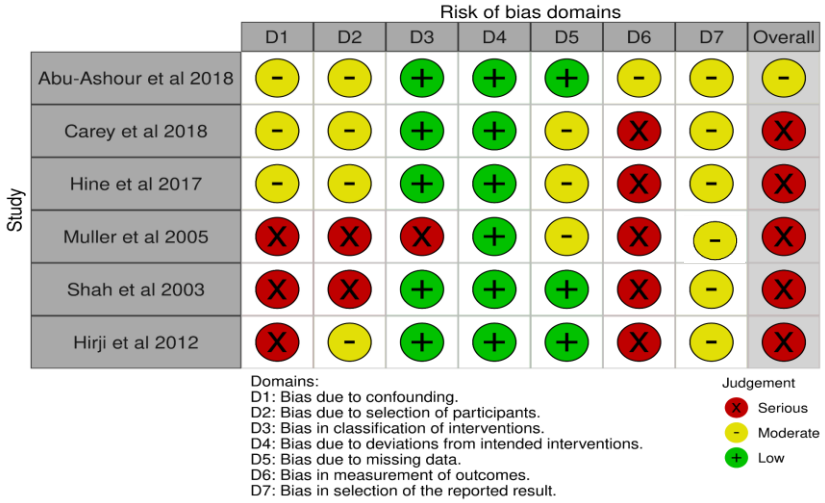

Figure 5: Traffic light plot of ROBINS-I results for urinary tract infections

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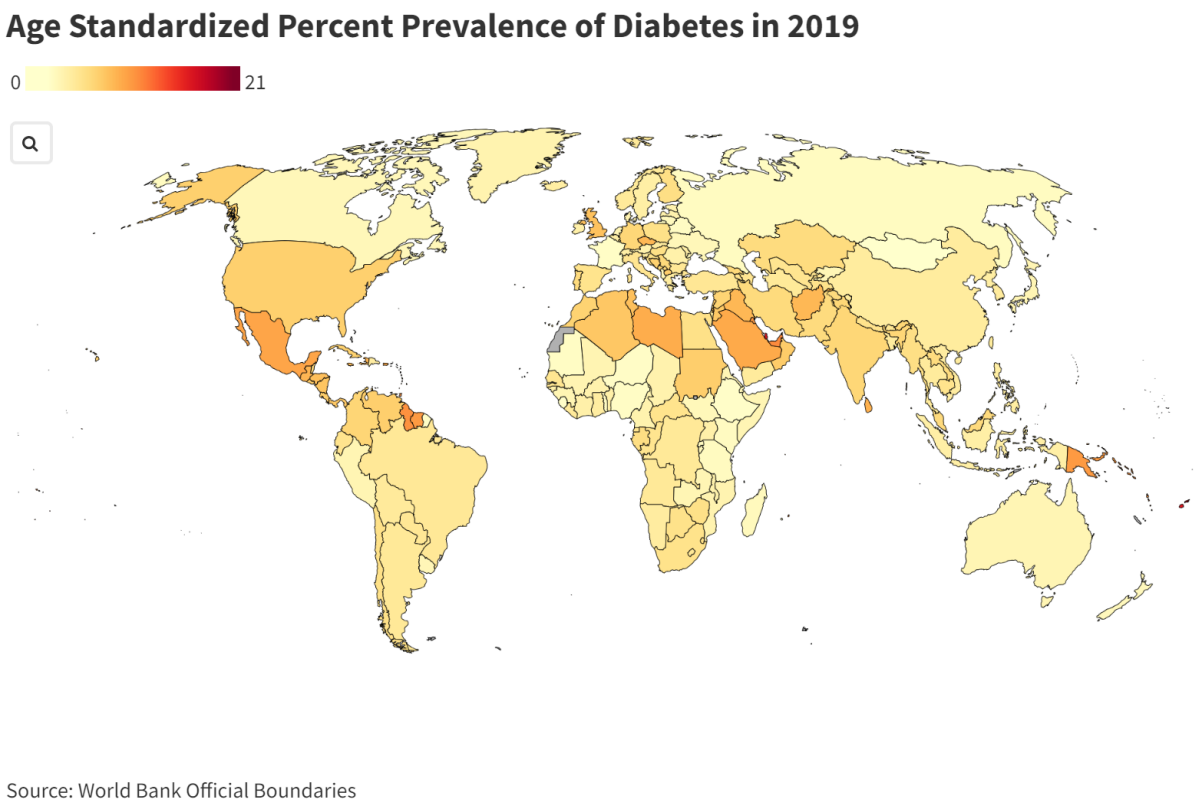

Figure 6: Age standardized prevalence of diabetes in each country in 2019

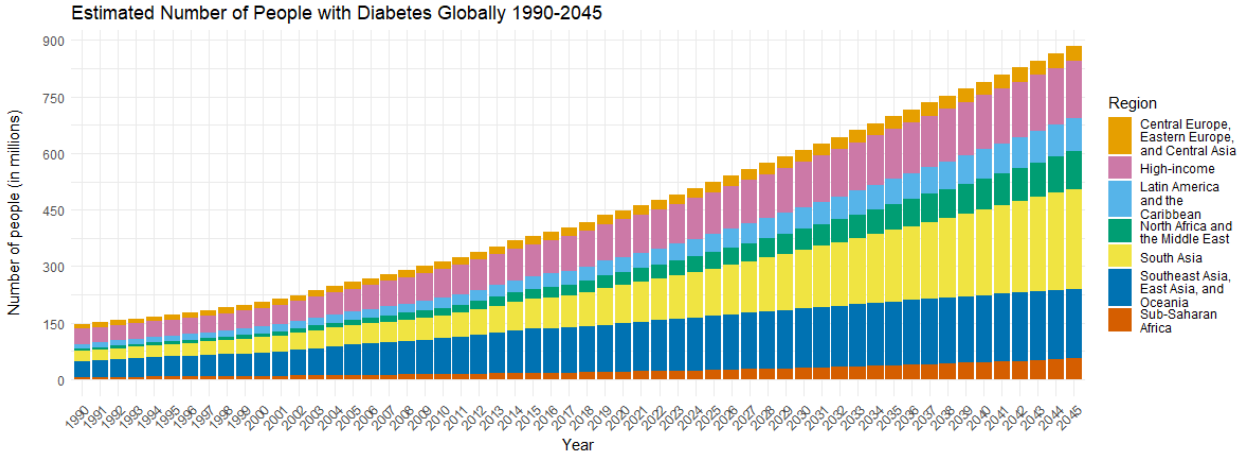

Figure 7: Trends in the predicted number of people living with diabetes, by region 1990-2045

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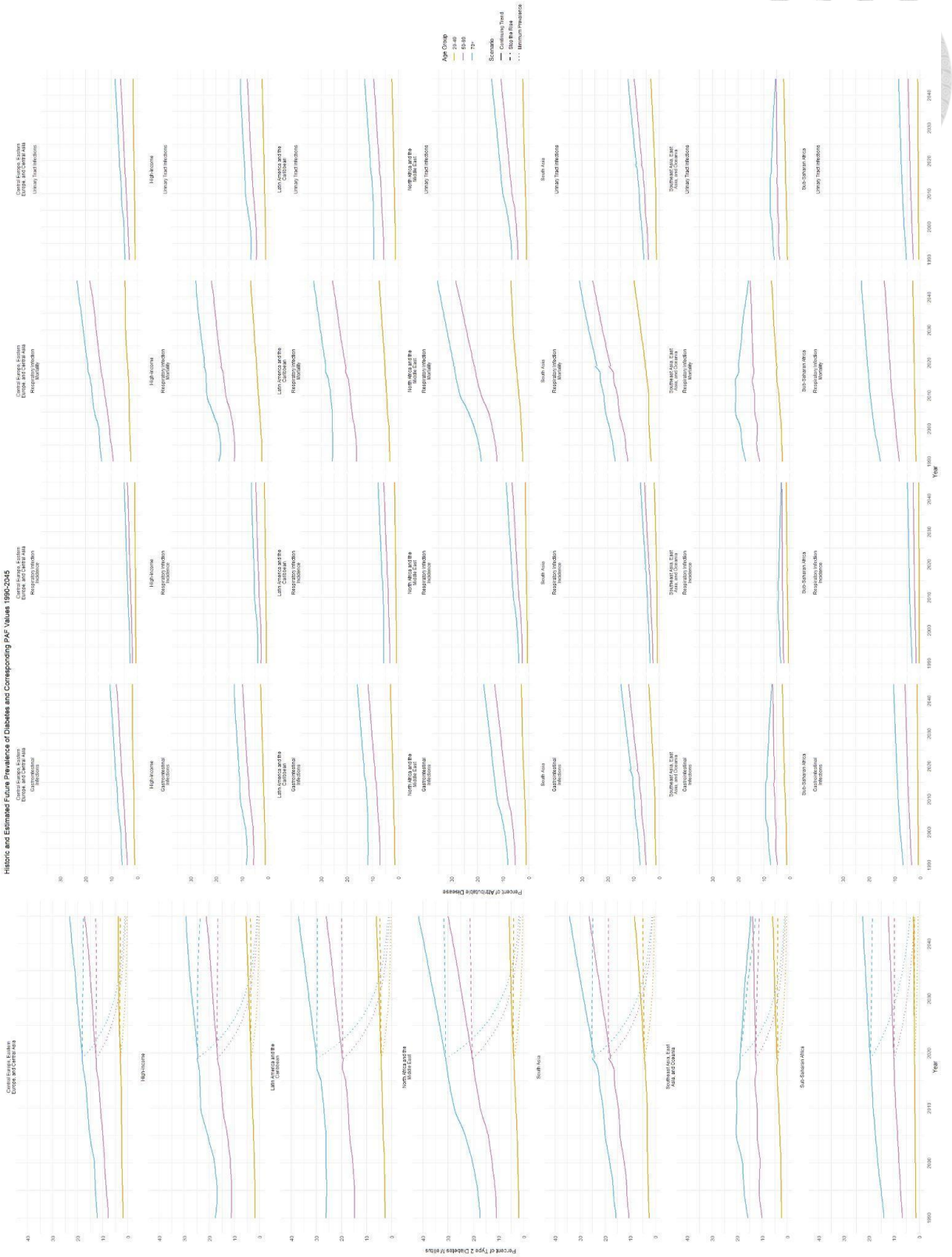

Figure 8: Predicted trend in diabetes prevalence and corresponding PAF 1990-2045

doi:10.6342/NTU202303883

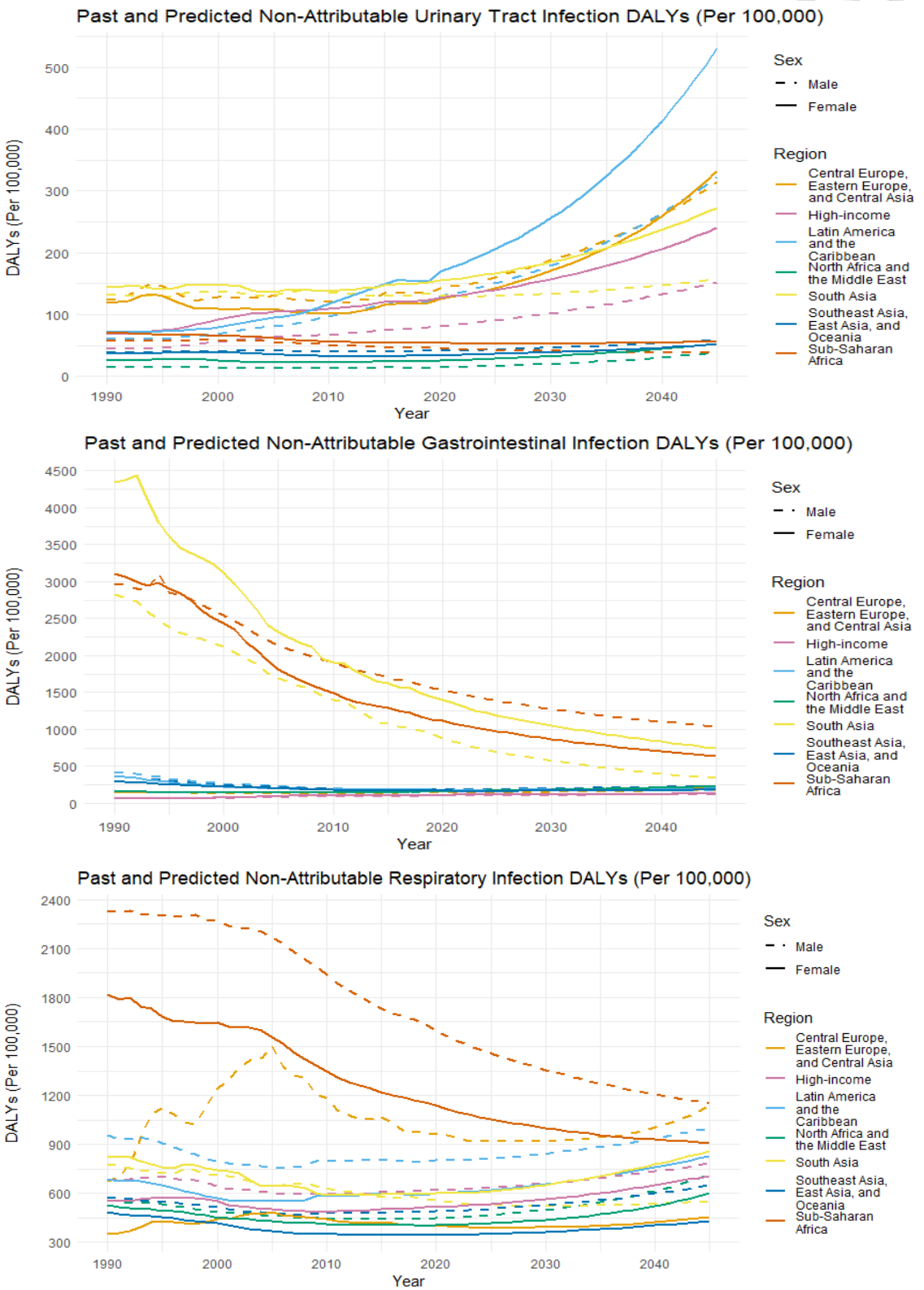

Figure 9: Trends in non-attributable infectious disease burden across regions and sex, 1990-2045

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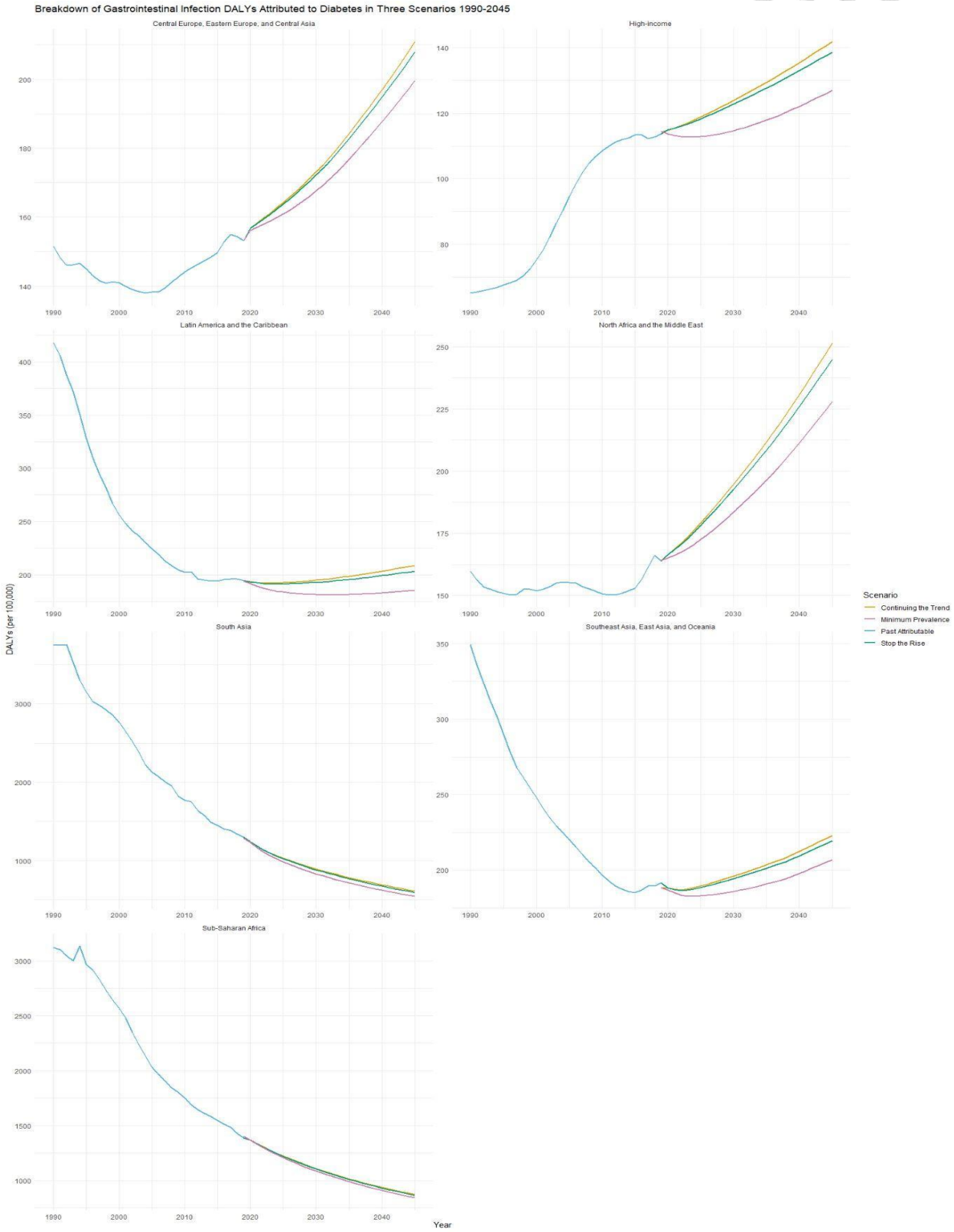

Figure 10a: Regional trends in historic and future diabetes-attributable disease burden for gastrointestinal infections, 1990-2045

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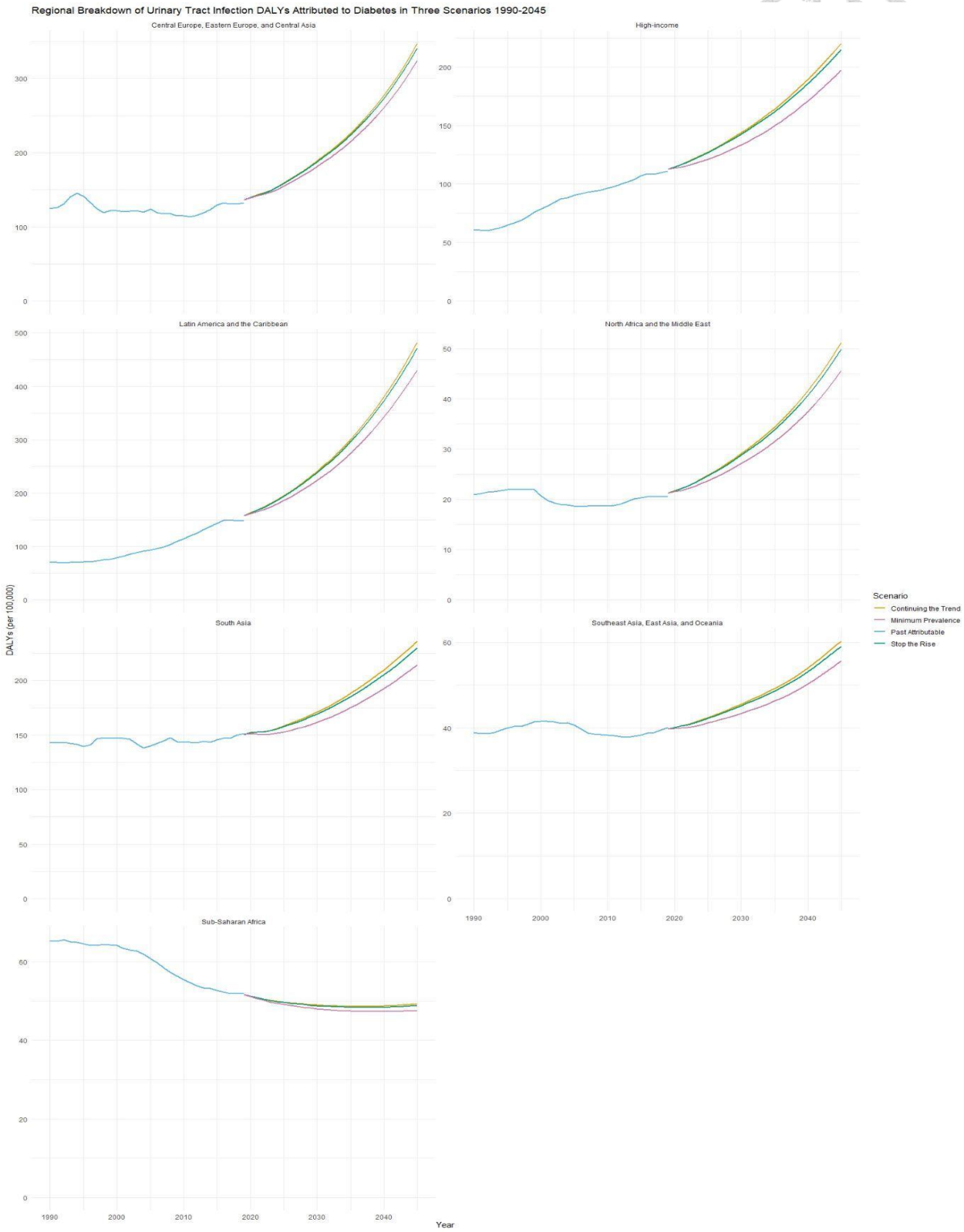

Figure 10b: Regional trends in historic and future diabetes-attributable disease burden for selected infection diseases, 1990-2045

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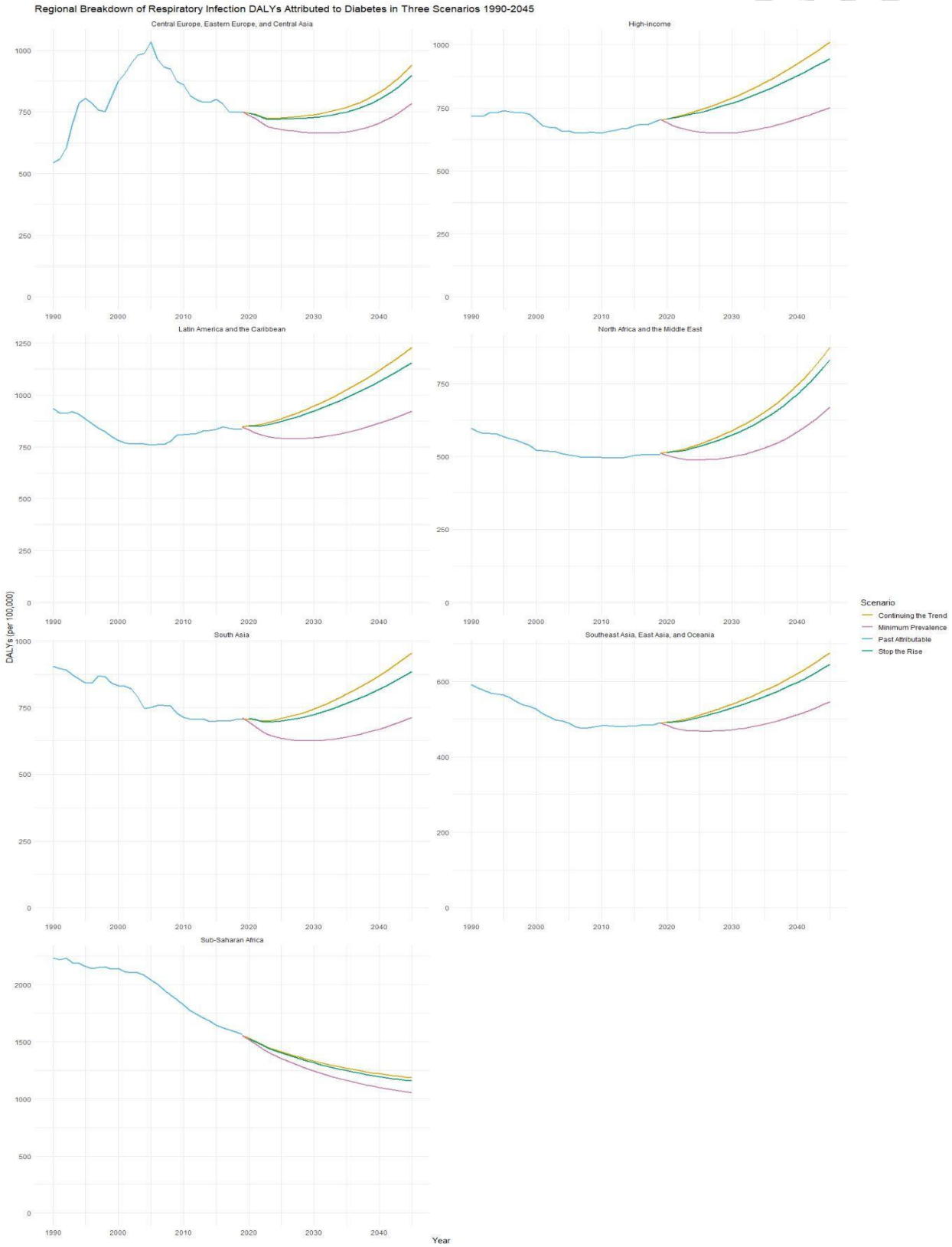

Figure 10c: Regional trends in historic and future diabetes-attributable disease burden for respiratory infections, 1990-2045

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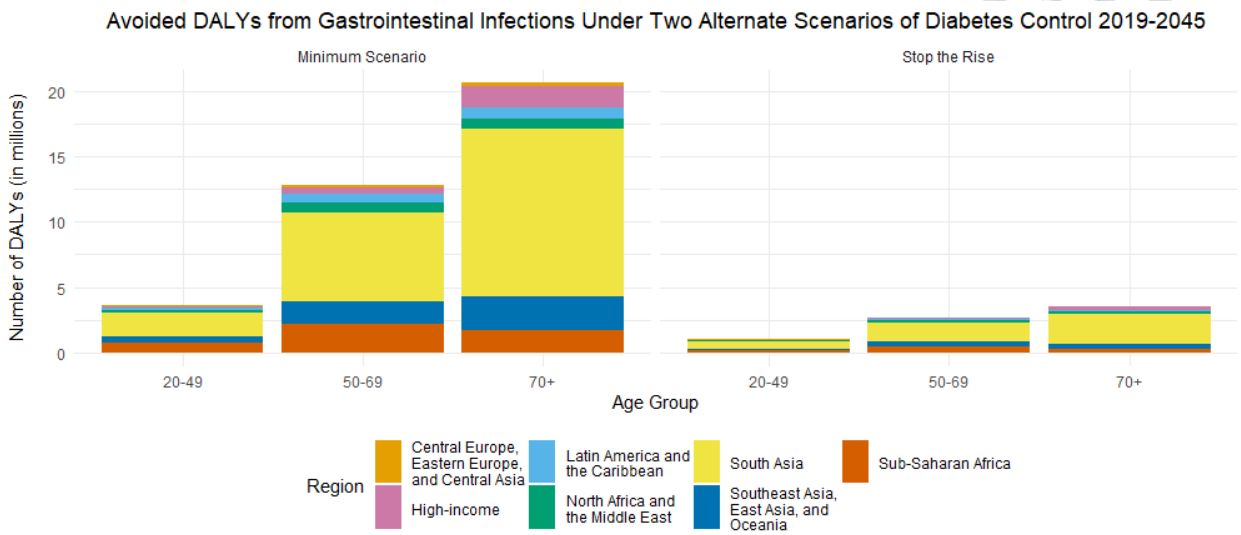

Figure 11a: Avoided DALYs under alternate scenarios of diabetes prevalence from 2019-2045 for gastrointestinal infections

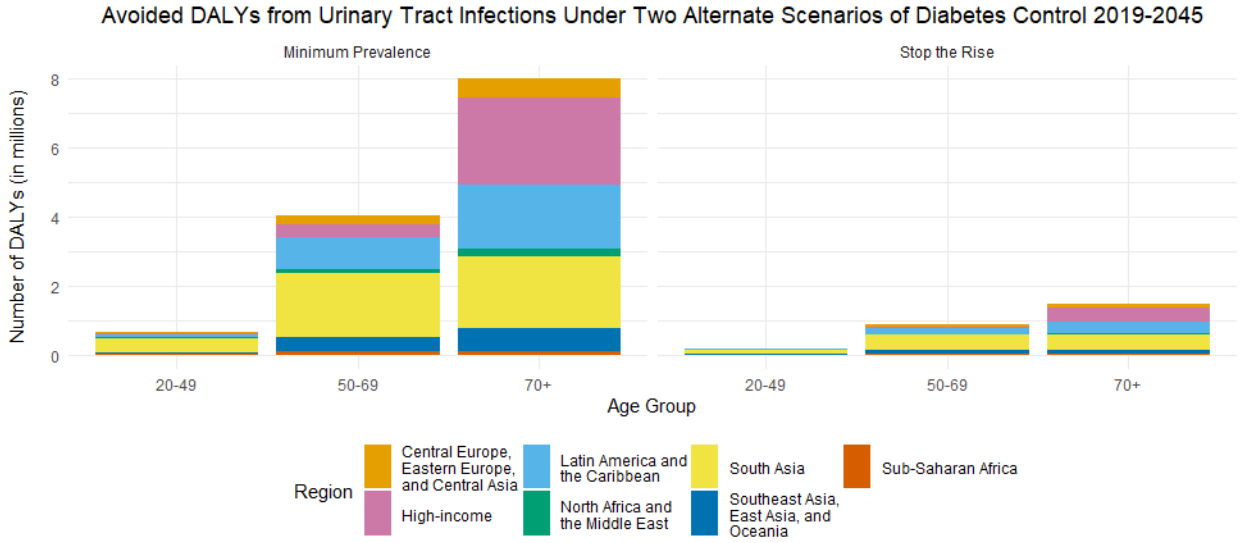

Figure 11b: Avoided DALYs under alternate scenarios of diabetes prevalence from 2019-2045 for urinary tract infections

doi:10.6342/NTU202303883

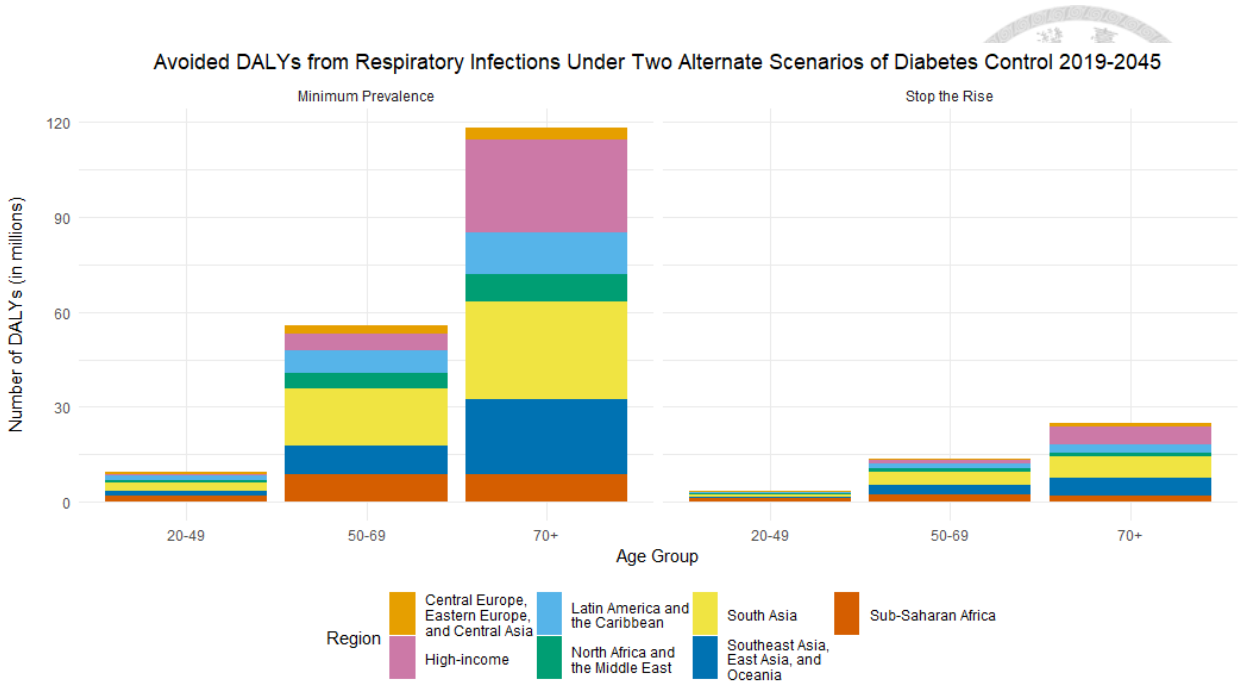

Figure 11c: Avoided DALYs under alternate scenarios of diabetes prevalence from 2019-2045 for respiratory tract infections

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Appendices

Appendix 1: Summary Results of Included Studies

Appendix table 1: Summary of Included Results						
Gastrointestinal infections						
Study	Country	Operational diagnosis method	Population (exposed)	Population (unexposed)	Unadjusted estimate (95% CI)	Adjusted estimate (95% CI)
Abu-Ashour et al 2018[a]	Canada	Primary care surveillance database	1,779	11,066	OR: 0.96 (0.86-1.06)	OR: 1.21 (1.07 – 1.37)
Carey et al 2018[b]	United Kingdom	Primary care database (CPRD)	96,630	191,822	NR	IRR: 1.58 (1.50-1.66)
Hine et al 2017[c]	United Kingdom	Primary care database (RCGP RSC)	34278	647330	NR	OR: 1.37 (1.19 – 1.57)
Shah et al 2003 [d]	Canada	Physician claim or hospital discharge for infection	401,661	401,661	OR: 1.50 (1.46–1.54)	NR
Incident Respiratory Infections - All						
Study	Country	Measurement	Population (exposed)	Population (unexposed)	Unadjusted estimate (95% CI)	Adjusted estimate (95% CI)
Abu-Ashour et al 2018[a]	Canada	Primary care surveillance database	1,779	11,066	OR: 0.84 (0.75 – 0.94)	OR: 1.30 (1.13 – 1.48)
Hine et al 2017[c]	United Kingdom	Primary care database (RCGP RSC)	34,278	647,330	NR	OR: 1.30 (1.26 – 1.34)
Incident Respiratory Infections - Lower						
Study	Country	Measurement	Population (exposed)	Population (unexposed)	Unadjusted estimate (95% CI)	Adjusted estimate (95% CI)
Carey et al 2018[a] – Pneumonia	United Kingdom	Primacy care database	96,630	191,822	NR	IRR: 1.59 (1.53-1.66)
Carey et al 2018[a] – Lower	United Kingdom	Primacy care database	96,630	191,822	NR	IRR: 1.24 (1.22-1.26)

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respiratory tract infection						
Hine et al 2017[c] - Bronchitis	United Kingdom	Primary care database (RCGP RSC)	34,278	647,330	NR	OR: 1.38 (1.32 – 1.44)
Hine et al 2017[c] – Influenza-like Illness	United Kingdom	Primary care database (RCGP RSC)	34,278	647,330	NR	OR: 1.21 (1.02 – 1.42)
Hine et al 2017[c] - Pneumonia	United Kingdom	Primary care database (RCGP RSC)	34,278	647,330	NR	OR: 1.43 (1.18 – 1.74)
Muller et al 2005[e]	Netherlands	Primary Care registry	6,712	18,811	NR	OR: 1.30 (1.11 – 1.52)
Shah et al 2003[d]	Canada	Health claims data	401,661	401,661	OR: 1.46 (1.42–1.49)	NR
Incident Respiratory Infections - Upper						
Study	Country	Measurement	Population (exposed)	Population (unexposed)	Unadjusted estimate (95% CI)	Adjusted estimate (95% CI)
Carey et al 2018[a] – Sinusitis (acute)	United Kingdom	Primacy care database	96,630	191,822	NR	IRR: 1.02 (0.97-1.07)
Carey et al 2018[a] – Upper respiratory tract infection (other)	United Kingdom	Primacy care database	96,630	191,822	NR	IRR: 1.16 (1.13-1.18)
Hine et al 2017[e]	United Kingdom	Primary care database (RCGP RSC)	34,278	647,330	NR	OR: 1.25 (1.19 – 1.30)
Muller et al 2005[e]	Netherlands	Primary Care registry	6,712	18,811	OR: 0.97 (0.87 – 1.09)	OR: 1.02 (0.91 – 1.14)
Shah et al 2003[d]	Canada	Health claims data	401,661	401,661	OR: 1.18 (1.17–1.19)	NR
Respiratory Infection Mortality - All						
Study	Country	Measurement	Population (exposed)	Population (unexposed)	Unadjusted estimate (95% CI)	Adjusted estimate (95% CI)

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Li et al 2019[f]	USA	NHANES survey + mortality files	1,909	8,834	3.90 (2.16 - 7.03)	3.56 (1.95 - 6.49)
Bragg et al 2023[g]	Mexico	Mexico City Prospective Study cohort + electronic death registry	22,493	108,504	NR	3.65 (3.19 – 4.18)
Bragg et al 2017[h]	China	China's Disease Surveillance Points system	30,280	482,589	NR	2.47 (1.80 – 3.38)
Wang et al 2020[i] – Male	Japan	Japan Collaborative Cohort Study	2,983	92,073	NR	1.39 (1.10–1.76)
Wang et al 2020[i] - Female	Japan	Japan Collaborative Cohort Study	689	54,442	NR	2.30 (1.71–3.11)
Campbell et al 2012[j] - Male	USA	Cancer Prevention Study-II (CPS-II)	40,116	715,061	NR	1.64 (1.08 – 2.9)
Campbell et al 2012[j] - Female	USA	Cancer Prevention Study-II (CPS-II)	26,090	560,598	NR	1.58 (1.45 – 1.73)
Incident Urinary Tract Infections						
Study	Country	Measurement	Population (exposed)	Population (unexposed)	Unadjusted estimate (95% CI)	Adjusted estimate (95% CI)
Abu-Ashour et al 2018[a]	Canada	Primary care surveillance database	1,779	11,066	OR: 1.10 (0.94 – 1.29)	OR: 1.48 (1.12 – 1.75)
Carey et al 2018[b]	United Kingdom	Primacy care database	96,630	191,822	NR	IRR: 1.46(1.42-1.49)
Hine et al 2017[e]	United Kingdom	Primary care database (RCGP RSC)	34,278	647,330	NR	OR: 1.59 (1.50-1.69)
Hirji et al 2012[k]	United Kingdom	Primary care database (GPRD)	135,920	135,920	OR: 1.57 (1.52–1.63)	OR: 1.53 (1.46–1.59)

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a: Covariates included: Age, sex, smoking status, comorbidities (including nephropathy, neuropathy, retinopathy, coronary artery disease, peripheral and cerebral vascular disease, heart failure, respiratory disease, dyslipidemia, fatty liver disease, obesity), several medications including inhaled corticosteroids, and number of infections in the previous year
b: Covariates included: Age, sex, duration of diabetes, practice region, BMI, smoking status, and Index of Multiple Deprivation (IMD) quintile**
c: Covariates included: Age, sex, socioeconomic status, smoking status and comorbidities (chronic kidney disease, asthma or chronic obstructive pulmonary disease, previous stroke or transient ischemic attack, peripheral vascular disease and heart failure or ischemic heart disease)
d: Shah et al 2003 reports crude rates from a cohort matched "1:1 for date of birth within 30 days, sex, region, and income quintile by ecological attribution of neighborhood-level census data"
e: Covariates included: Age, sex, type of health insurance, and comorbidities (pulmonary disease, cardiovascular disease, peripheral neuropathy, and neurologic disease)
f: Covariates include: sex, age, BMI, smoking status, and alcohol consumption
g: Covariates include: sex and age (5-year groups), geographic location (district), educational level, smoking status, alcohol consumption, height, weight, and waist and hip circumference.
h: Covariates include: sex and age (5-year groups), education level, smoking status, alcohol consumption, physical activity, BMI, and location
i: Covariates include: age, educational level, BMI, smoking status, alcohol consumption, physical activity, walking time, family history of diabetes
j: Covariates include: age, educational level, BMI, smoking status, alcohol consumption, vegetable intake, red meat intake, physical activity, and aspirin use
k: Covariates included: age, gender, study entry year, and past history of UTI
** Carey et al 2018 reported age-sex-location adjusted estimates and provided estimates with further adjustment, which were available in their supplementary materials

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Appendix 2: ROBINS-I Detailed analysis for included outcomes

Appendix Table 2: ROBINS-I Assessment of Bias Results			
Gastrointestinal Infections			
Study	Domain	Rating	Notes
Abu-Ashour et al 2018	Confounding	Serious	Confounding is expected. Rigorous sensitivity analysis was conducted on potential cofounding variables, but there may have been some adjustment for intermediary conditions (e.g. chronic kidney disease) and use of missing indicator for incomplete smoking status introduces an important source of bias.
	Participant Selection	Moderate	Since diabetes diagnosis occurred before study initiation, survivorship bias is introduced if people with diabetes die before study inclusion. Authors attempted to adjust for this by adjusting for number of infections in the year prior to the study period.
	Intervention Classification	Low	Intervention groups clearly defined and recorded at start of intervention / study initialization.
	Deviation from intervention	Low	Low chance of deviation from the assigned group outside of usual practice (i.e. new diagnosis of diabetes) during the study window.
	Missing data	Serious	Complete case analysis on smoking status was not conducted, nor was smoking status included in the final multivariate analysis or sensitivity analysis, so between group differences are unclear for this confounder.

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	Measurement of outcomes	Moderate	Differences in practitioner diagnosis, frequency of regular appointments, or patient care-seeking behaviors may influence outcome measurement. The study attempted to account for care-seeking behaviors and diagnosis using number of primary care visits in the year prior to the study. Differences between the two groups did not reach statistical significance.
	Reported result	Moderate	There is evidence that analyses are consistent with the initial plan, without indication that selection of reported analyses.
	Overall	Serious	Based on the handling of smoking data, the direction of bias may slightly favor the experimental group, since smoking is tied to diabetes.
Study	Domain	Rating	Notes
Carey et al 2018	Confounding	Moderate	Appropriate statistical analysis (multivariate regression) and sensitivity analysis conducted.
	Participant Selection	Moderate	Since diabetes diagnosis occurred before study initiation, survivorship bias is introduced but difficult to account for. Patients who were eligible but couldn't be matched were excluded, though sensitivity analysis showed no significant differences if they were included.
	Intervention Classification	Low	Intervention groups clearly defined and recorded at start of intervention / study initialization. Sensitivity analysis regarding people who developed diabetes during study period did not alter their findings.
	Deviation from intervention	Low	There is no evidence of deviation from standard practice of care or that this would have any significant impact.

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	Missing data	Moderate	Analysis excluded included only those with complete data, with sensitivity analysis on missing data showing no meaningful differences.
	Measurement of outcomes	Serious	Differences in practitioner diagnosis, frequency of regular appointments, or patient care-seeking behaviors may influence outcome measurement.
	Reported result	Moderate	Their reported result was only adjusted for age-sex-location, however they completed additional analysis which was available in the appendices that adjusted for BMI and socioeconomic status, or comorbid conditions for whole cohort analysis. While the results were not fully attenuated, and this may have been a sensitivity analysis.
	Overall	Serious	Due to practitioner knowledge of intervention status that may have led to differential diagnosis of outcomes, this direction of bias likely favors experimental group.
Study	Domain	Rating	Notes
Hine et al 2017	Confounding	Moderate	While there was risk of confounding, appropriate statistical analysis (multivariate logistic regression) and sensitivity analysis were conducted. However, there was control potential post-intervention variables (i.e. chronic kidney disease).
	Participant Selection	Moderate	Since diabetes diagnosis occurred before study initiation, survivorship bias is introduced but difficult to account for. In a study of this size (over 500,000), we anticipate the impact would not impart serious bias.
	Intervention Classification	Low	Intervention groups clearly defined and recorded at start of intervention / study initialization.

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	Deviation from intervention	Low	Low chance of deviation from the assigned group outside of usual practice (i.e. new diagnosis of diabetes) during the study window.
	Missing data	Moderate	Analysis included only those with complete data, with sensitivity analysis on missing data showing no meaningful differences.
	Measurement of outcomes	Serious	A recognized limitation of the study – differences in practitioner diagnosis or patient care-seeking behaviors may influence results, additionally diagnosis may occur based on subjective judgment versus quantitative proof of disease.
	Reported result	Moderate	There is evidence that analyses are consistent with the initial plan, without indication that selection of reported analyses.
	Overall	Serious	The direction of bias is difficult to predict since it revolves around societal factors (e.g. care seeking behaviors or differential diagnostic behaviors across practices) but may suggest bias favors experimental group.
Study	Domain	Rating	Notes
Shah et al 2003	Confounding	Serious	While there was matching for age-sex-region-socioeconomic status, there are additional variables that are important to adjust for, including other comorbid conditions like smoking or obesity that were not adjusted for.
	Participant Selection	Serious	Since diabetes diagnosis occurred before study initiation, survivorship bias is introduced but difficult to account for. Also, some participants with diabetes were excluded on the basis of no available matched pair, though the reasons for this are unclear. Additionally, the impact of this exclusion was not explored.

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	Intervention Classification	Low	Intervention group was clearly defined for a specific time period preceding the study, and intervention status would not have been impacted by outcomes.
	Deviation from intervention	Low	There is nothing to indicate that diagnostic behavior did not reflect usual practice, or that there would be systemic deviation from intervention.
	Missing data	Low	There is no evidence of missing data across groups
	Measurement of outcomes	Serious	Differences in practitioner diagnosis or patient care-seeking behaviors may influence results, additionally diagnosis may occur based on subjective judgment versus quantitative proof of disease.
	Reported result	Moderate	There is no indication of selection of the reported analysis and analysis seems to follow a predetermined plan.
	Overall	Serious	Due to lack of adjustment for additional variables of concern as well as excluded participants on a basis of matching without investigation of meaningful differences between the matched and unmatched participants. Direction of bias likely favors experimental due to lack of adjustment for comorbidities and detection bias.

Urinary Tract Infections			
Study	Domain	Rating	Notes

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Abu-Ashour et al 2018	Confounding	Moderate	Confounding is expected. Rigorous sensitivity analysis was conducted on potential cofounding variables, but there may have been some adjustment for intermediary conditions (e.g. chronic kidney disease). While a missing indicator was used for smoking status, a link between smoking and UTIs is inconclusive, so smoking is not considered a known confounder for UTIs.
	Participant Selection	Moderate	Since diabetes diagnosis occurred before study initiation, survivorship bias is introduced if people with diabetes die before study inclusion. Authors attempted to adjust for this by adjusting for number of infections in the year prior to the study period.
	Intervention Classification	Low	Intervention groups clearly defined and recorded at start of intervention / study initialization.
	Deviation from intervention	Low	Low chance of deviation from the assigned group outside of usual practice (i.e. new diagnosis of diabetes) during the study window.
	Missing data	Low	Data was reasonable complete, particularly for known confounders.
	Measurement of outcomes	Moderate	Differences in practitioner diagnosis, frequency of regular appointments, or patient care-seeking behaviors may influence outcome measurement. The study attempted to account for care-seeking behaviors and diagnosis using number of primary care

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			visits in the year prior to the study. Differences between the two groups did not reach statistical significance.
	Reported result	Moderate	There is evidence that analyses are consistent with the initial plan, without indication that selection of reported analyses. Specific subgroups of population not analyzed.
	Overall	Moderate	There is moderate risk of bias in this study due to probably baseline confounding associated with non-randomized studies and potential role of survivorship bias. However, there was rigorous sensitivity testing. Bias is likely to favor experimental due to survivorship bias.
Study	Domain	Rating	Notes
Carey et al 2018	Confounding	Moderate	Appropriate statistical analysis (multivariate regression) and sensitivity analysis conducted.
	Participant Selection	Moderate	Since diabetes diagnosis occurred before study initiation, survivorship bias is introduced but difficult to account for. Patients who were eligible but couldn't be matched were excluded, though sensitivity analysis showed no significant differences if they were included.
	Intervention Classification	Low	Intervention groups clearly defined and recorded at start of intervention / study initialization. Sensitivity analysis regarding

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			people who developed diabetes during study period did not alter their findings.
	Deviation from intervention	Low	There is no evidence of deviation from standard practice of care or that this would have any significant impact.
	Missing data	Moderate	Analysis excluded included only those with complete data, with sensitivity analysis on missing data showing no meaningful differences.
	Measurement of outcomes	Serious	Differences in practitioner diagnosis, frequency of regular appointments, or patient care-seeking behaviors may influence outcome measurement.
	Reported result	Moderate	Their reported result was only adjusted for age-sex-location, however they completed additional analysis which was available in the appendices that adjusted for BMI and socioeconomic status, or comorbid conditions for whole cohort analysis. While the results were not fully attenuated, and this may have been a sensitivity analysis.
	Overall	Serious	Due to practitioner knowledge of intervention status that may have led to differential diagnosis of outcomes. Direction of bias likely favors experimental due to detection bias.
Study	Domain	Rating	Notes

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Hine et al 2017	Confounding	Moderate	While there was risk of confounding, appropriate statistical analysis (multivariate logistic regression) and sensitivity analysis were conducted. However, there was control potential post-intervention variables (chronic kidney disease).
	Participant Selection	Moderate	Since diabetes diagnosis occurred before study initiation, survivorship bias is introduced but difficult to account for. In a study of this size (over 500,000), we anticipate the impact would not impart serious bias.
	Intervention Classification	Low	Intervention groups clearly defined and recorded at start of intervention / study initialization.
	Deviation from intervention	Low	Low chance of deviation from the assigned group outside of usual practice (i.e. new diagnosis of diabetes) during the study window.
	Missing data	Moderate	Analysis included only those with complete data, with sensitivity analysis on missing data showing no meaningful differences.
	Measurement of outcomes	Serious	A recognized limitation of the study – differences in practitioner diagnosis or patient care-seeking behaviors may influence results
	Reported result	Moderate	There is evidence that analyses are consistent with the initial plan, without indication that selection of reported analyses.

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	Overall	Serious	The direction of bias is difficult to predict since it revolves around societal factors (e.g. care seeking behaviors or differential diagnostic behaviors across practices) but may suggest bias favors experimental group.
Study	Domain	Rating	Notes
Muller et al 2005	Confounding	Serious	Multivariate analysis was used to address potential confounders including age, sex, socioeconomic status, and some comorbid conditions. However, this study neglected to control for several key confounding variables, including obesity.
	Participant Selection	Serious	Only people who had a physician contact over a 1-year period were included in the study, but this does not account for increased likelihood of people with diabetes to have physician contacts for routine management, or people are more likely to have physician contact if they have a disease concern. Additionally, due to the potential period of time between diagnosis and study initiation, there is also survivorship bias.
	Intervention Classification	Low	Intervention groups are clearly defined, with little room for misclassification.
	Deviation from intervention	Moderate	Those enrolled in the study report an average of 9 visits for people with diabetes and 7 visits for control subjects – which was reported as non-significant difference, but is greater than the 4 that would be recommended by Dutch primary care. This application of co-intervention may introduce case-finding bias.

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	Missing data	Low	No evidence of missing data, particularly missing data being different across groups
	Measurement of outcomes	Serious	Diagnosis of infection was subject to practitioner bias, particularly since they are aware of the intervention status of the patient. This study tracked practitioner-patient interactions to control for increased case-finding and care-seeking, with some differences between patients with type 2 diabetes and the control patients (9 vs 7).
	Reported result	Low	Additionally, non-significant results are reported and discussed, without attempt to include additional statistical analysis to reach significance.
	Overall	Serious	The direction of bias is unclear, since the different confounders that were not adjusted for may have different impacts (e.g. obesity + diabetes may increase risk, while increased vaccination in people with diabetes may decrease risk)
Study	Domain	Rating	Notes
Shah et al 2003	Confounding	Serious	While there was matching for age-sex-region-socioeconomic status, there are additional variables that are important to adjust for, including other comorbid conditions like obesity that were not adjusted for.

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	Participant Selection	Serious	Since diabetes diagnosis occurred before study initiation, survivorship bias is introduced but difficult to account for. Also, some participants with diabetes were excluded on the basis of no available matched pair, though the reasons for this are unclear. Additionally, the impact of this exclusion was not explored.
	Intervention Classification	Low	Intervention group was clearly defined for a specific time period preceding the study, and intervention status would not have been impacted by outcomes.
	Deviation from intervention	Low	There is nothing to indicate that diagnostic behavior did not reflect usual practice, or that there would be systemic deviation from intervention.
	Missing data	Low	There is no evidence of missing data across groups
	Measurement of outcomes	Serious	Differences in practitioner diagnosis or patient care-seeking behaviors may influence results, diagnosis or treatment for UTIs in people with diabetes may occur based on subjective judgment versus quantitative proof of disease.
	Reported result	Moderate	There is no indication of selection of the reported analysis and analysis seems to follow a predetermined plan.
	Overall	Serious	Due to lack of adjustment for additional variables of concern as well as excluded participants on a basis of matching without

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			investigation of meaningful differences between the matched and unmatched participants.
Study	Domain	Rating	Notes
Hirji et al 2012	Confounding	Serious	While there was matching for age, gender and index year, there was no adjustment for other confounders like comorbid conditions (e.g. obesity). They include previous UTI incidence as a confounder, since some evidence suggests that one UTI increases the risk of another
	Participant Selection	Moderate	Since diabetes diagnosis occurred before study initiation, survivorship bias is introduced but difficult to account for. However, in a study of this size, we might anticipate that impact to be low.
	Intervention Classification	Low	Intervention group was clearly defined for a specific time period preceding the study, and based on the measurement of intervention status, it would not have been impacted by the outcome.
	Deviation from intervention	Low	There is no indication that clinical practice differed from standard practice.
	Missing data	Low	There is no evidence of missing data across groups

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	Measurement of outcomes	Serious	Differences in practitioner diagnosis or patient care-seeking behaviors may influence results, diagnosis or treatment for UTIs in people with diabetes may occur based on judgments influenced by knowledge of intervention status.
	Reported result	Moderate	Analysis seems to follow a predetermined plan, and all indicated analyses are reported. Included appropriate sensitivity analysis.
	Overall	Serious	Due to lack of adjustment for additional confounders like comorbid conditions, as well as the potential for knowledge of the intervention to influence outcome measurement (particularly in the case of detection bias).
Respiratory Tract Infections - All			
Study	Domain	Rating	Notes
Abu-Ashour et al 2018	Confounding	Serious	Confounding is expected. Rigorous sensitivity analysis was conducted on potential cofounding variables, but there may have been some adjustment for intermediary conditions (e.g. chronic kidney disease) and use of missing indicator for incomplete smoking status introduces an important source of bias.
	Participant Selection	Moderate	Since diabetes diagnosis occurred before study initiation, survivorship bias is introduced if people with diabetes die before study inclusion. Authors attempted to adjust for this by adjusting for number of infections in the year prior to the study period.

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	Intervention Classification	Low	Intervention groups clearly defined and recorded at start of intervention / study initialization.
	Deviation from intervention	Low	Low chance of deviation from the assigned group outside of usual practice (i.e. new diagnosis of diabetes) during the study window.
	Missing data	Serious	Complete case analysis on smoking status was not conducted, nor was smoking status included in the final multivariate analysis or sensitivity analysis, so between group differences are unclear for this confounder and lead to serious risk of bias.
	Measurement of outcomes	Moderate	Differences in practitioner diagnosis, frequency of regular appointments, or patient care-seeking behaviors may influence outcome measurement. The study attempted to account for care-seeking behaviors and diagnosis using number of primary care visits in the year prior to the study. Differences between the two groups did not reach statistical significance.
	Reported result	Moderate	There is evidence that analyses are consistent with the initial plan, without indication that selection of reported analyses.
	Overall	Serious	Based on the handling of smoking data, the direction of bias may slightly favor the experimental group, since smoking is tied to diabetes.
Incident Respiratory Infections – Lower			
Study	Domain	Rating	Notes

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Carey et al 2018	Confounding	Serious	Appropriate statistical analysis (multivariate regression) and sensitivity analysis conducted. No consideration of key comorbid conditions (e.g. respiratory diseases) potential differential vaccination rates (e.g. if vaccination against respiratory infections occurs more often in people with diabetes).
	Participant Selection	Moderate	Since diabetes diagnosis occurred before study initiation, survivorship bias is introduced but difficult to account for. Patients who were eligible but couldn't be matched were excluded, though sensitivity analysis showed no significant differences if they were included.
	Intervention Classification	Low	Intervention groups clearly defined and recorded at start of intervention / study initialization. Sensitivity analysis regarding people who developed diabetes during study period did not alter their findings.
	Deviation from intervention	Low	There is no evidence of deviation from standard practice of care or that this would have any significant impact.
	Missing data	Moderate	Analysis excluded included only those with complete data, with sensitivity analysis on missing data showing no meaningful differences.
	Measurement of outcomes	Serious	Differences in practitioner diagnosis, frequency of regular appointments, or patient care-seeking behaviors may influence outcome measurement.

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	Reported result	Moderate	Their reported result was only adjusted for age-sex-location, however they completed additional analysis which was available in the appendices that adjusted for BMI and socioeconomic status, or comorbid conditions for whole cohort analysis. While the results were not fully attenuated, and this may have been a sensitivity analysis.
	Overall	Serious	Due to concerns over lack of adjustment for vaccination rates and other comorbid conditions like respiratory diseases.
Study	Domain	Rating	Notes
Hine et al 2017	Confounding	Serious	While there was risk of confounding, appropriate statistical analysis (multivariate logistic regression) and sensitivity analysis a conducted. However, there was control potential post-intervention variables (chronic kidney disease) and no consideration of potential differential vaccination rates (e.g. if vaccination against respiratory infections occurs more often in people with diabetes)
	Participant Selection	Moderate	Since diabetes diagnosis occurred before study initiation, survivorship bias is introduced but difficult to account for. In a study of this size (over 500,000), we anticipate the impact would not impart serious bias.
	Intervention Classification	Low	Intervention groups clearly defined and recorded at start of intervention / study initialization.

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	Deviation from intervention	Low	Low chance of deviation from the assigned group outside of usual practice (i.e. new diagnosis of diabetes) during the study window.
	Missing data	Moderate	Analysis included only those with complete data, with sensitivity analysis on missing data showing no meaningful differences.
	Measurement of outcomes	Serious	A recognized limitation of the study – differences in practitioner diagnosis or patient care-seeking behaviors may influence results
	Reported result	Moderate	There is evidence that analyses are consistent with the initial plan, without indication that selection of reported analyses.
	Overall	Serious	The direction of bias is difficult to predict since it revolves around societal factors (e.g. care seeking behaviors or differential diagnostic behaviors across practices) but may suggest bias favors experimental group.
Study	Domain	Rating	Notes
Muller et al 2005	Confounding	Serious	Multivariate analysis was used to address potential confounders including age, sex, socioeconomic status, and comorbid conditions. However, this study neglected to control for several key confounding variables, including obesity, vaccination, and smoking.

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	Participant Selection	Serious	Only people who had a physician contact over a 1-year period were included in the study, but this does not account for increased likelihood of people with diabetes to have physician contacts for routine management, or people are more likely to have physician contact if they have a disease concern. Additionally, due to the potential period of time between diagnosis and study initiation, there is also survivorship bias.
	Intervention Classification	Low	Intervention groups are clearly defined, with little room for misclassification.
	Deviation from intervention	Moderate	Those enrolled in the study report an average of 9 visits for people with diabetes and 7 visits for control subjects – which was reported as non-significant difference, but is greater than the 4 that would be recommended by Dutch primary care. This application of co-intervention may introduce case-finding bias.
	Missing data	Low	No evidence of missing data, particularly missing data being different across groups
	Measurement of outcomes	Serious	Diagnosis of infection was subject to practitioner bias, particularly since they are aware of the intervention status of the patient. This study tracked practitioner-patient interactions to control for increased case-finding and care-seeking, with some differences between patients with type 2 diabetes and the control patients (9 vs 7).

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	Reported result	Low	Additionally, non-significant results are reported and discussed, without attempt to include additional statistical analysis to reach significance.
	Overall	Serious	The direction of bias is unclear, since the different confounders that were not adjusted for may have different impacts (e.g. obesity + diabetes may increase risk, while increased vaccination in people with diabetes may decrease risk)
Study	Domain	Rating	Notes
Shah et al 2003	Confounding	Serious	While there was matching for age-sex-region-socioeconomic status, there are additional variables that are important to adjust for, including other comorbid conditions like smoking or obesity that were not adjusted for.
	Participant Selection	Serious	Since diabetes diagnosis occurred before study initiation, survivorship bias is introduced but difficult to account for. Also, some participants with diabetes were excluded on the basis of no available matched pair, though the reasons for this are unclear. Additionally, the impact of this exclusion was not explored.
	Intervention Classification	Low	Intervention group was clearly defined for a specific time period preceding the study, and intervention status would not have been impacted by outcomes.

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	Deviation from intervention	Low	There is nothing to indicate that diagnostic behavior did not reflect usual practice, or that there would be systemic deviation from intervention.
	Missing data	Low	There is no evidence of missing data across groups
	Measurement of outcomes	Serious	Differences in practitioner diagnosis or patient care-seeking behaviors may influence results, additionally diagnosis may occur based on subjective judgment versus quantitative proof of disease.
	Reported result	Moderate	There is no indication of selection of the reported analysis and analysis seems to follow a predetermined plan.
	Overall	Serious	Due to lack of adjustment for additional variables of concern as well as excluded participants on a basis of matching without investigation of meaningful differences between the matched and unmatched participants.
Incident Respiratory Infection - Upper			
Study	Domain	Rating	Notes
Carey et al 2018	Confounding	Serious	Appropriate statistical analysis (multivariate regression) and sensitivity analysis conducted. No consideration of key comorbid conditions (e.g. respiratory diseases).

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	Participant Selection	Moderate	Since diabetes diagnosis occurred before study initiation, survivorship bias is introduced but difficult to account for. Patients who were eligible but couldn't be matched were excluded, though sensitivity analysis showed no significant differences if they were included.
	Intervention Classification	Low	Intervention groups clearly defined and recorded at start of intervention / study initialization. Sensitivity analysis regarding people who developed diabetes during study period did not alter their findings.
	Deviation from intervention	Low	There is no evidence of deviation from standard practice of care or that this would have any significant impact.
	Missing data	Moderate	Analysis excluded included only those with complete data, with sensitivity analysis on missing data showing no meaningful differences.
	Measurement of outcomes	Serious	Differences in practitioner diagnosis, frequency of regular appointments, or patient care-seeking behaviors may influence outcome measurement.
	Reported result	Moderate	Their reported result was only adjusted for age-sex-location, however they completed additional analysis which was available in the appendices that adjusted for BMI and socioeconomic status, or comorbid conditions for whole cohort analysis. While the results were not fully attenuated, and this may have been a sensitivity analysis.

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	Overall	Serious	Due to concerns over lack of adjustment for vaccination rates and other comorbid conditions like respiratory diseases. Direction of bias likely favors the comparator group, although direction and magnitude is unclear since some neglected confounders may result in differential direction of bias.
Study	Domain	Rating	Notes
Muller et al 2005	Confounding	Serious	Multivariate analysis was used to address potential confounders including age, sex, socioeconomic status, and comorbid conditions. However, this study neglected to control for several key confounding variables, including obesity, vaccination, and smoking.
	Participant Selection	Serious	Only people who had a physician contact over a 1-year period were included in the study, but this does not account for increased likelihood of people with diabetes to have physician contacts for routine management, or people are more likely to have physician contact if they have a disease concern. Additionally, due to the potential period of time between diagnosis and study initiation, there is also survivorship bias.
	Intervention Classification	Low	Intervention groups are clearly defined, with little room for misclassification.
	Deviation from intervention	Moderate	Those enrolled in the study report an average of 9 visits for people with diabetes and 7 visits for control subjects – which was reported as non-significant difference, but is greater than the 4 that would be recommended by Dutch primary care. This application of co-intervention may introduce case-finding bias.

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	Missing data	Low	No evidence of missing data, particularly missing data being different across groups
	Measurement of outcomes	Serious	Diagnosis of infection was subject to practitioner bias, particularly since they are aware of the intervention status of the patient. This study tracked practitioner-patient interactions to control for increased case-finding and care-seeking, with some differences between patients with type 2 diabetes and the control patients (9 vs 7).
	Reported result	Low	Additionally, non-significant results are reported and discussed, without attempt to include additional statistical analysis to reach significance.
	Overall	Serious	The direction of bias is unclear, since the different confounders that were not adjusted for may have different impacts (e.g. obesity + diabetes may increase risk, while increased vaccination in people with diabetes may decrease risk)
Study	Domain	Rating	Notes
Hine et al 2017	Confounding	Moderate	While there was risk of confounding, appropriate statistical analysis (multivariate logistic regression) and sensitivity analysis a conducted. However, there was control potential post-intervention variables (chronic kidney disease). While this study does not account for vaccination, routine vaccination for upper respiratory infections is not standard.

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	Participant Selection	Moderate	Since diabetes diagnosis occurred before study initiation, survivorship bias is introduced but difficult to account for. In a study of this size (over 500,000), we anticipate the impact would not impart serious bias.
	Intervention Classification	Low	Intervention groups clearly defined and recorded at start of intervention / study initialization.
	Deviation from intervention	Low	Low chance of deviation from the assigned group outside of usual practice (i.e. new diagnosis of diabetes) during the study window.
	Missing data	Moderate	Analysis included only those with complete data, with sensitivity analysis on missing data showing no meaningful differences.
	Measurement of outcomes	Serious	A recognized limitation of the study – differences in practitioner diagnosis or patient care-seeking behaviors may influence results
	Reported result	Moderate	There is evidence that analyses are consistent with the initial plan, without indication that selection of reported analyses.
	Overall	Serious	The direction of bias is difficult to predict since it revolves around societal factors (e.g. care seeking behaviors or differential diagnostic behaviors across practices) but may suggest bias favors experimental group.

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Study	Domain	Rating	Notes
Shah et al 2003	Confounding	Serious	While there was matching for age-sex-region-socioeconomic status, there are additional variables that are important to adjust for, including other comorbid conditions like smoking or obesity that were not adjusted for.
	Participant Selection	Serious	Since diabetes diagnosis occurred before study initiation, survivorship bias is introduced but difficult to account for. Also, some participants with diabetes were excluded on the basis of no available matched pair, though the reasons for this are unclear. The impact of excluding unmatched patients was not explored.
	Intervention Classification	Low	Intervention group was clearly defined for a specific time period preceding the study, and intervention status would not have been impacted by outcomes.
	Deviation from intervention	Low	There is nothing to indicate that diagnostic behavior did not reflect usual practice, or that there would be systemic deviation from intervention.
	Missing data	Low	There is no evidence of missing data across groups
	Measurement of outcomes	Serious	Differences in practitioner diagnosis or patient care-seeking behaviors may influence results, additionally diagnosis may occur based on subjective judgment versus quantitative proof of disease.

doi:10.6342/NTU202303883

	Reported result	Moderate	There is no indication of selection of the reported analysis and analysis seems to follow a predetermined plan.
	Overall	Serious	Due to lack of adjustment for additional variables of concern (smoking and obesity would lead to bias toward the experimental group) as well as excluded participants on a basis of matching without investigation of meaningful differences between the matched and unmatched participants.
Respiratory Infection Mortality			
Study	Domain	Rating	Notes
Li et al 2019	Confounding	Serious	While there was matching based on a number of important confounders, including other respiratory disease and vaccination were missing.
	Participant Selection	Serious	There's an unknown amount of time between diagnosis (intervention) and the start of the study, which could lead to survivorship bias. It's also not clear whether the rate ratio is held constant over time or if it also increases with age.
	Intervention Classification	Low	There is little chance for misclassification of outcomes, and the groups are clearly defined at the start. Those who are ambiguous are excluded, although new research al f so means to include this group.

doi:10.6342/NTU202303883

	Deviation from intervention	Low	There's no indication that any of the participants would have received treatment that deviated from standard clinical procedure.
	Missing data	Low	Missing data was identified and underwent sensitivity analysis to determine whether it different significantly from the observed data.
	Measurement of outcomes	Low	Measurement of death due to infectious cause is unlikely to be strongly influenced by knowledge of the people's intervention status.
	Reported result	Moderate	Data analysis is consistent with the described methods, results are reported regardless of significance
	Overall	Serious	This study neglects to address a number of important confounding variables, including obesity and vaccination status, but the direction of bias is unclear as vaccination is suggested to be higher in a population with diabetes, which would suggest bias toward the null, while lack of adjustment for BMI would bias it toward the experimental in this population.
Study	Domain	Rating	Notes
Bragg et al 2023	Confounding	Serious	Adjustment was done for some relevant confounders, but major confounders like pre-existing respiratory disease and vaccination rate was neglected

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	Participant Selection	Moderate	There's a varying amount of time between diagnosis (intervention) and the start of the study, which could lead to survivorship bias. However, it's thought that, given the large sample size, this may be relatively small percentage of the population
	Intervention Classification	Low	The intervention group criteria were clearly defined in the beginning with specific guidelines, and group assignment is unlikely to be tied with the outcome.
	Deviation from intervention	Low	There's no indication that any of the participants would have received treatment that deviated from standard clinical procedure, though their participation in this study may have led to their diagnosis of unknown diabetes sooner. However, systematic differences in level of care are unlikely.
	Missing data	Low	This study was missing 4.5% of its initial study population due to missing information on covariates. This might be considered reasonably complete.
	Measurement of outcomes	Low	Measurement of death due to infectious cause is unlikely to be strongly influenced by knowledge of the participant's intervention status, particularly since death registry was used as a data source.
	Reported result	Moderate	Results seem soundly generated without attempts to generate biased results or subgroups.

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	Overall	Serious	This is primarily driven by lack of adjustment for vaccination and survivorship bias in participant selection. The direction of bias is likely slightly toward comparator on the basis of vaccination.
Study	Domain	Rating	Notes
Wang et al 2020	Confounding	Serious	Adjustment was done for some relevant confounders, but major confounders like pre-existing respiratory disease and vaccination rate were neglected (respiratory disease was also an outcome in this story)
	Participant Selection	Moderate	Since diabetes diagnosis occurred before study initiation, survivorship bias is introduced but difficult to account for. Patients who were eligible but couldn't be matched were excluded, though sensitivity analysis showed no significant differences if they were included.
	Intervention Classification	Low	The intervention group criteria were clearly defined in the beginning with specific guidelines, and group assignment is unlikely to be tied with the outcome.
	Deviation from intervention	Low	There's no indication that any of the participants would have received treatment that deviated from standard clinical procedure, though their participation in this study may have led to their diagnosis of unknown diabetes sooner. However, systematic differences in level of care are unlikely.

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	Missing data	Serious	Those without an intervention status (missing diabetes status) at baseline were excluded, which constituted 15,529 (~14%). It's hard to predict the direction of this and to adjust for who would be missing intervention status.
	Measurement of outcomes	Low	Measurement of death due to infectious cause is unlikely to be strongly influenced by knowledge of the participant's intervention status, particularly since death registry was used as data source.
	Reported result	Moderate	Results seem soundly generated without attempts to generate biased results or subgroups.
	Overall	Serious	This is primarily driven by lack of adjustment for vaccination and survivorship bias in participant selection, as well as high proportion of missing data due to intervention status without ability to properly adjust for it.
Study	Domain	Rating	Notes
Bragg et al 2017	Confounding	Serious	Adjustment was done for some relevant confounders, but key ones such as respiratory disease/asthma and vaccination rate were neglected
	Participant Selection	Moderate	There's a varying amount of time between diagnosis (intervention) and the start of the study, which could lead to survivorship bias. However, in a study of this size, the proportion of cases may be negligible.

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	Intervention Classification	Low	The intervention group criteria were clearly defined in the beginning with specific guidelines, and group assignment is unlikely to be tied with the outcome.
	Deviation from intervention	Low	There's no indication that any of the participants would have received treatment that deviated from standard clinical procedure, though their participation in this study may have led to their diagnosis of unknown diabetes sooner. However, systematic differences in level of care are unlikely.
	Missing data	Low	This study was missing (n = 22) for data, which is negligible from a population of over 500,000.
	Measurement of outcomes	Low	Measurement of death due to infectious cause is unlikely to be strongly influenced by knowledge of the participant's intervention status, particularly since death registry was used as data source. <5% did not have official medical death records, so these were ascertained by other standardized procedures.
	Reported result	Moderate	Results seem soundly generated without attempts to generate biased results or subgroups.
	Overall	Serious	This is primarily driven by lack of adjustment for vaccination and other key confounders. The direction of bias is likely slightly toward experimental on the basis of comorbid conditions, given the study population showed more comorbid conditions in the diabetes group.
Study	Domain	Rating	Notes

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Campbell et al 2012	Confounding	Serious	Adjustment was done for some relevant confounders, but major confounders like pre-existing respiratory disease and vaccination rate were neglected
	Participant Selection	Moderate	There's a varying amount of time between diagnosis (intervention) and the start of the study, which could lead to survivorship bias. However, in a study of this size, the proportion of cases may be negligible.
	Intervention Classification	Low	The intervention group criteria were clearly defined in the beginning with specific guidelines, and group assignment is unlikely to be tied with the outcome.
	Deviation from intervention	Low	There's no indication that any of the participants would have received treatment that deviated from standard clinical procedure, though their participation in this study may have led to their diagnosis of unknown diabetes sooner. However, systematic differences in level of care are unlikely.
	Missing data	Moderate	About 11% of participants were excluded for some reason, but the most common was missing data. No sensitivity analysis was done to determine if there were significant differences between the included and excluded groups.
	Measurement of outcomes	Low	Measurement of death due to infectious cause is unlikely to be strongly influenced by knowledge of the people's intervention status.

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	Reported result	Moderate	Results seem soundly generated without attempts to generate biased results or subgroups.
	Overall	Serious	This is primarily driven by lack of adjustment for key confounders.

doi:10.6342/NTU202303883

Appendix 3: ICD Codes from Select Gastrointestinal Studies

Gastrointestinal Infections			
Source	Definition	ICD Codes	Corresponding GBD Cause List
Abu-Ashour et al 2018	Salmonella	ICD-9: 003, 005	Invasive Non-typhoidal Salmonella (iNTS) / Diarrheal diseases
	Shigellosis	ICD-9: 004	Diarrheal diseases
	Amebiasis	ICD-9: 006	Diarrheal diseases
	Gastroenteritis	ICD-9: 009.0, 009.1	Diarrheal diseases
	Ulcer	ICD-9: 531-535	Peptic ulcer disease
	Appendicitis	ICD-9: 540-543	Appendicitis
	Peritonitis	ICD-9: 567	Other digestive diseases
Carey et al 2018	Cholera	ICD-10: A00	Diarrheal diseases
	Typhoid and paratyphoid fevers	ICD-10: A01	Typhoid fever / Paratyphoid fever
	Other salmonella infections	ICD-10: A02.0, A02.2	Diarrheal diseases
	Shigellosis	ICD-10: A03	Diarrheal diseases
	Other bacterial intestinal infections	ICD-10: A04	Diarrheal diseases
	Other bacterial foodborne intoxications, not elsewhere classified	ICD-10: A05	Diarrheal diseases
	Amebiasis	ICD-10: A06	Diarrheal diseases
	Other protozoal intestinal diseases	ICD-10: A07	Diarrheal diseases
	Viral and other specified intestinal infections	ICD-10: A08	Diarrheal diseases
	Infectious gastroenteritis and colitis, unspecified	ICD-10: A09	Diarrheal diseases

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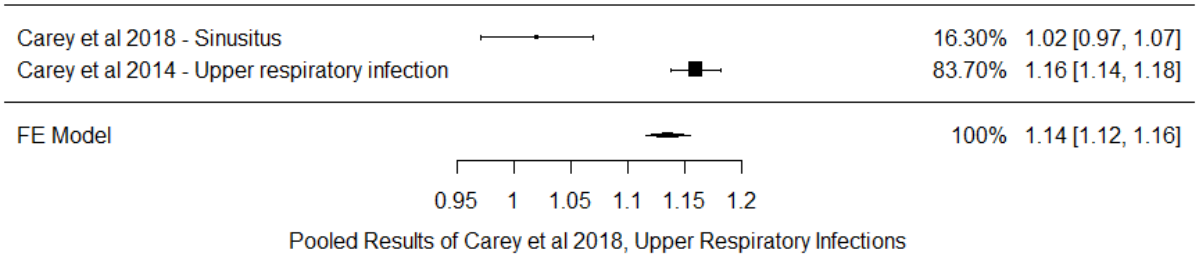
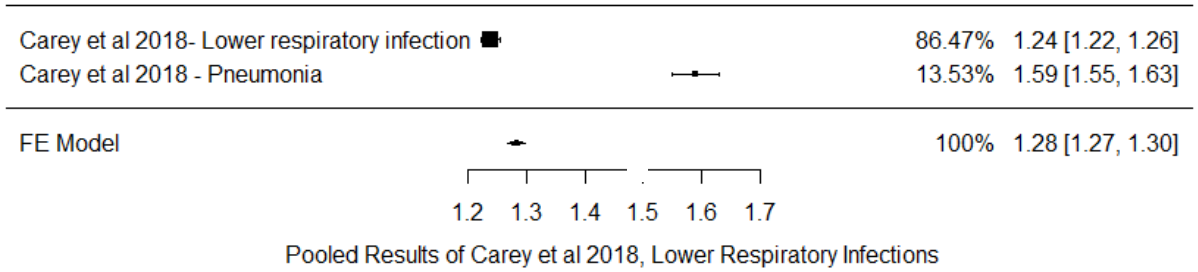
Appendix 4: Pooling results and forest plots



Pooled Results of Carey et al 2018, Upper Respiratory Infections



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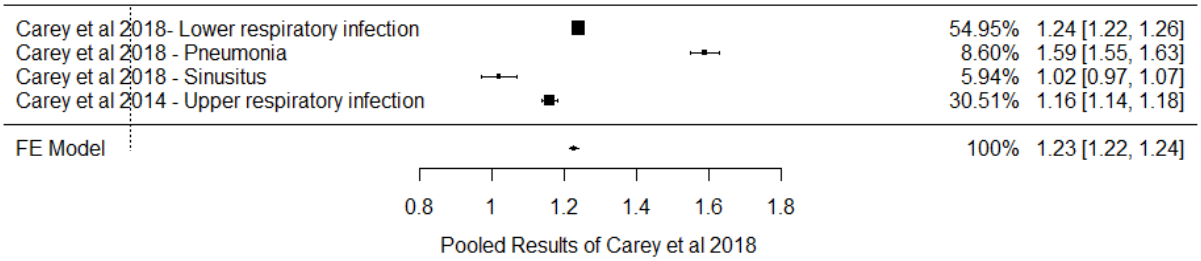

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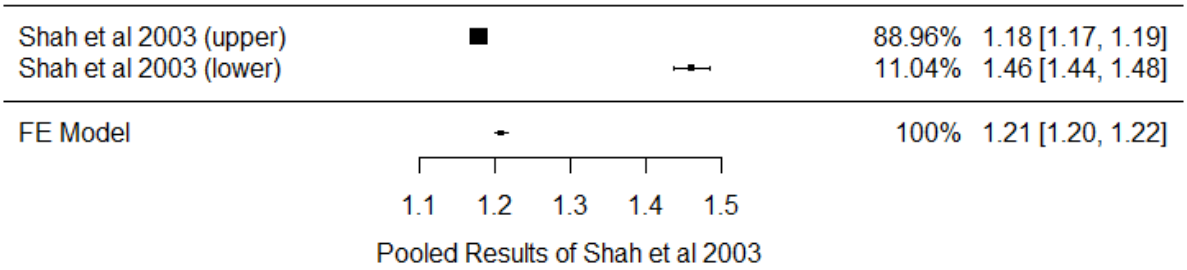
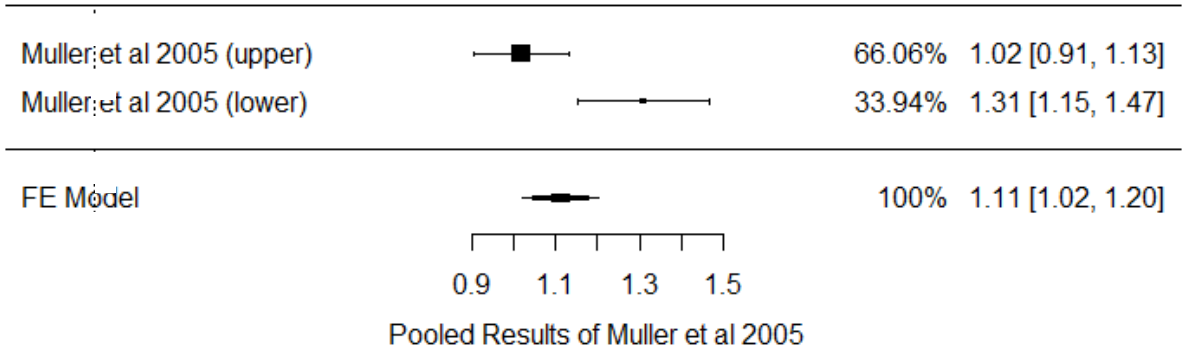
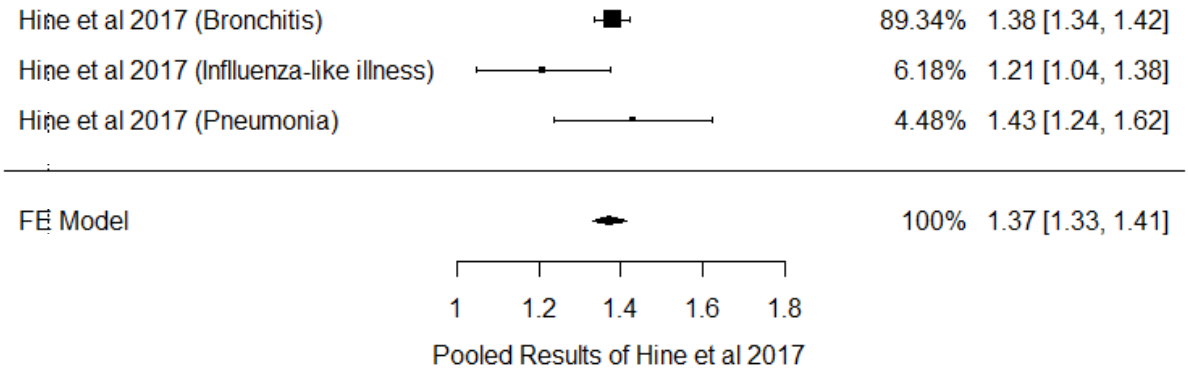


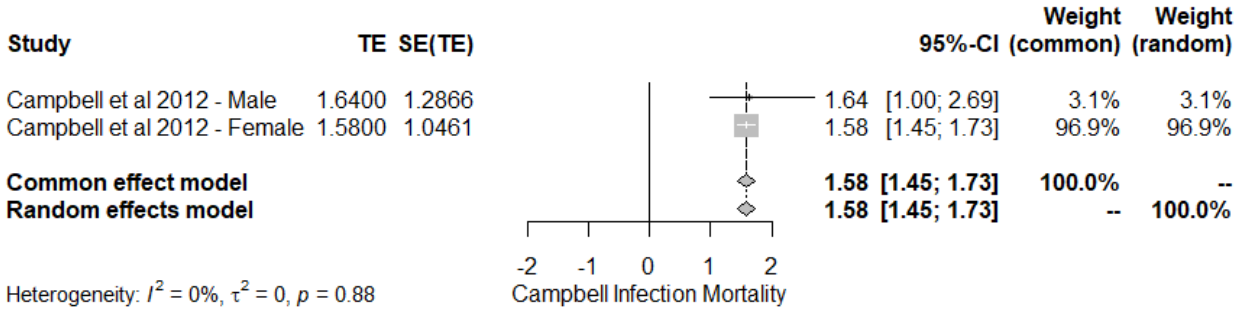
Pooled Results of Shah et al 2003

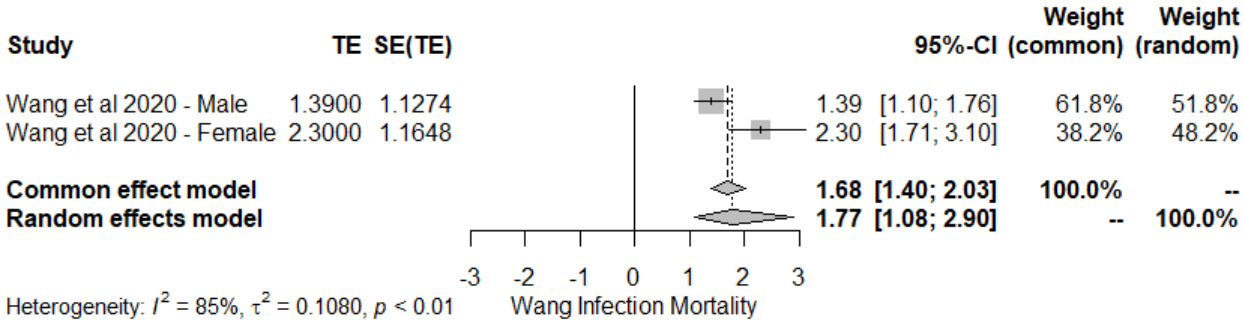


Pooled Results of Muller et al 2005

doi:10.6342/NTU202303883







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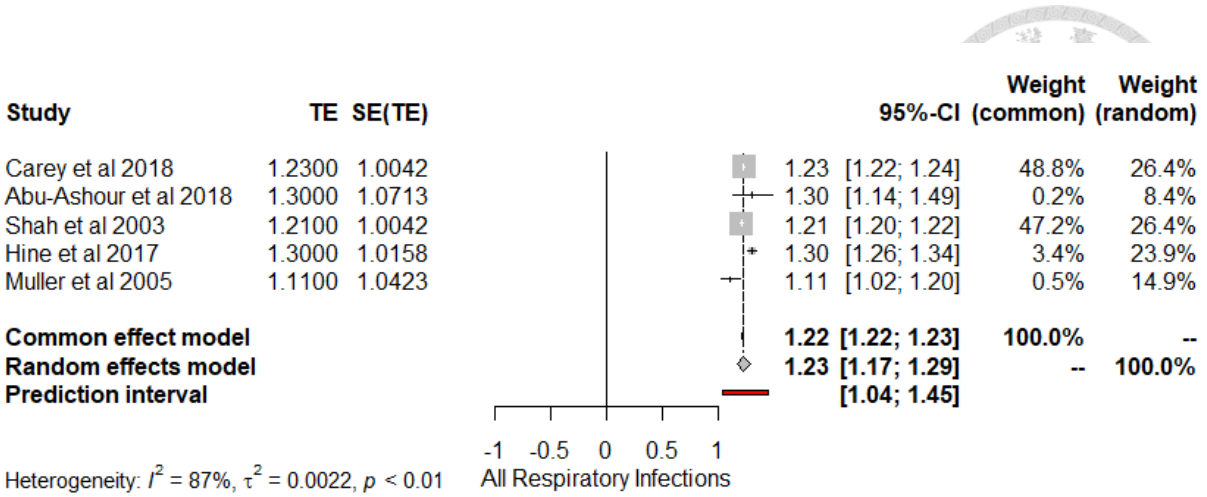

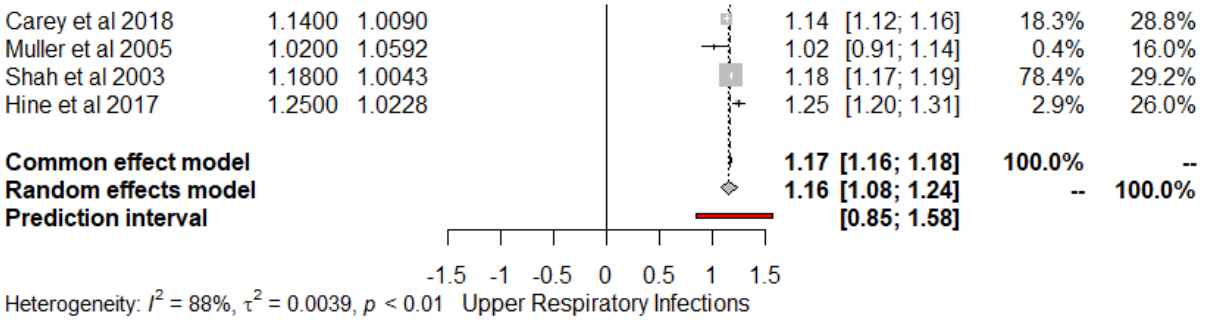

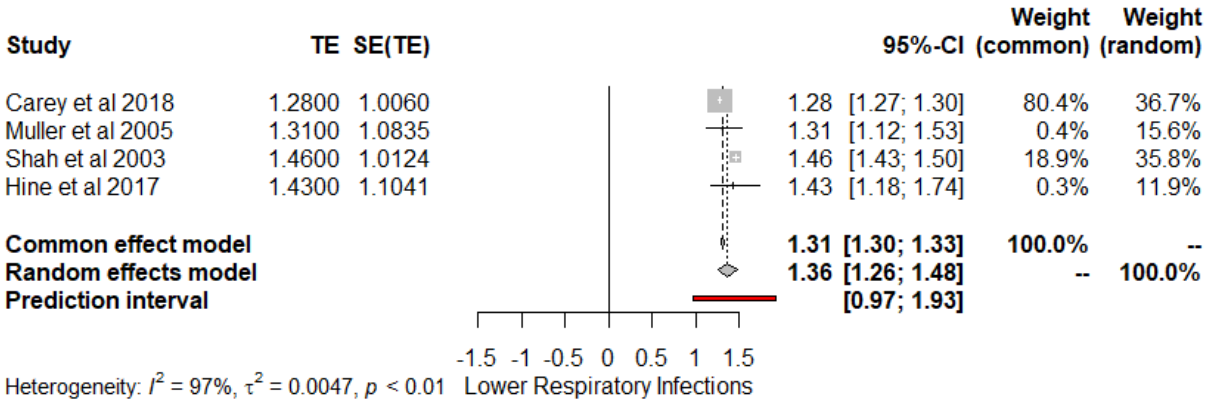

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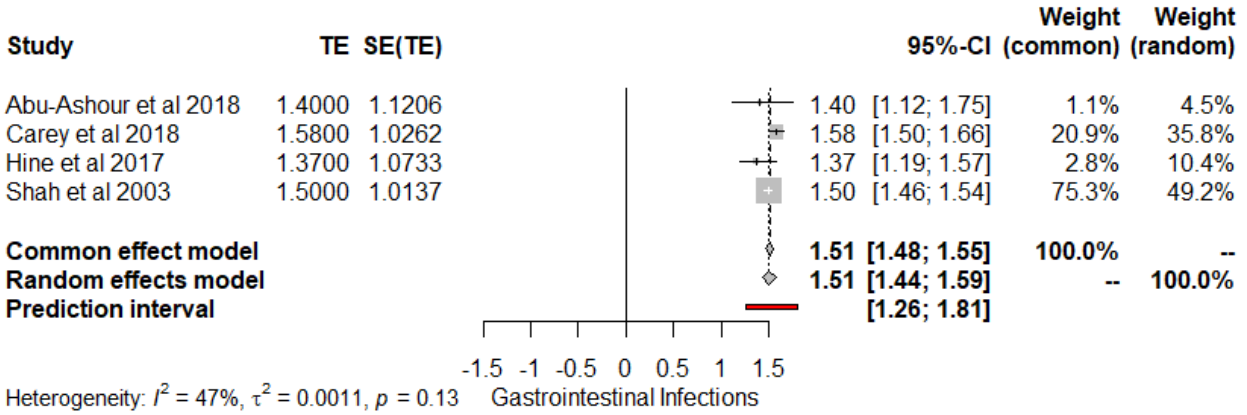

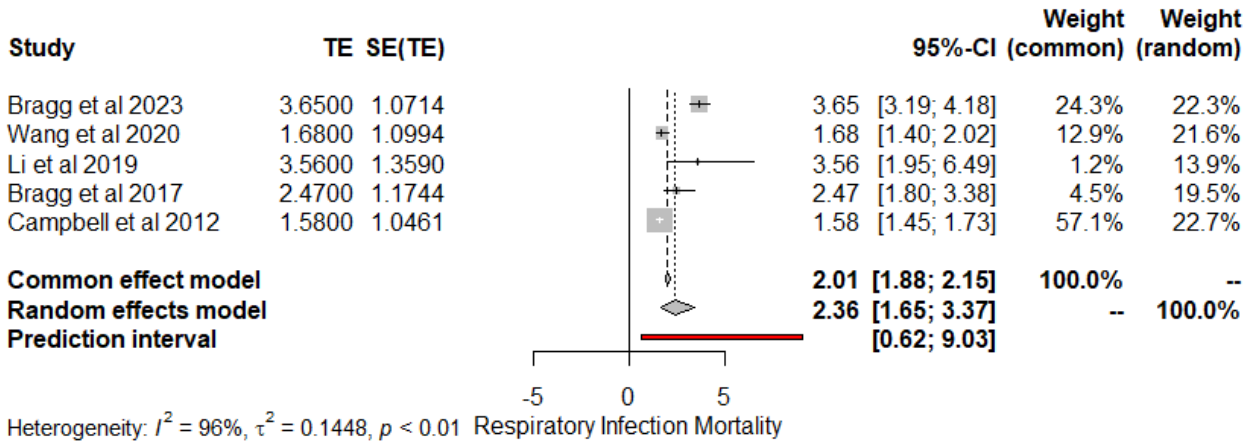

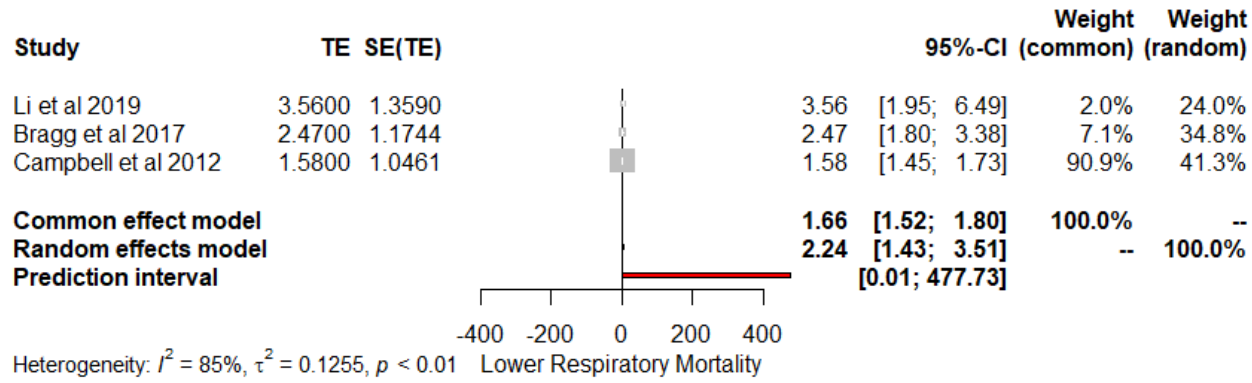

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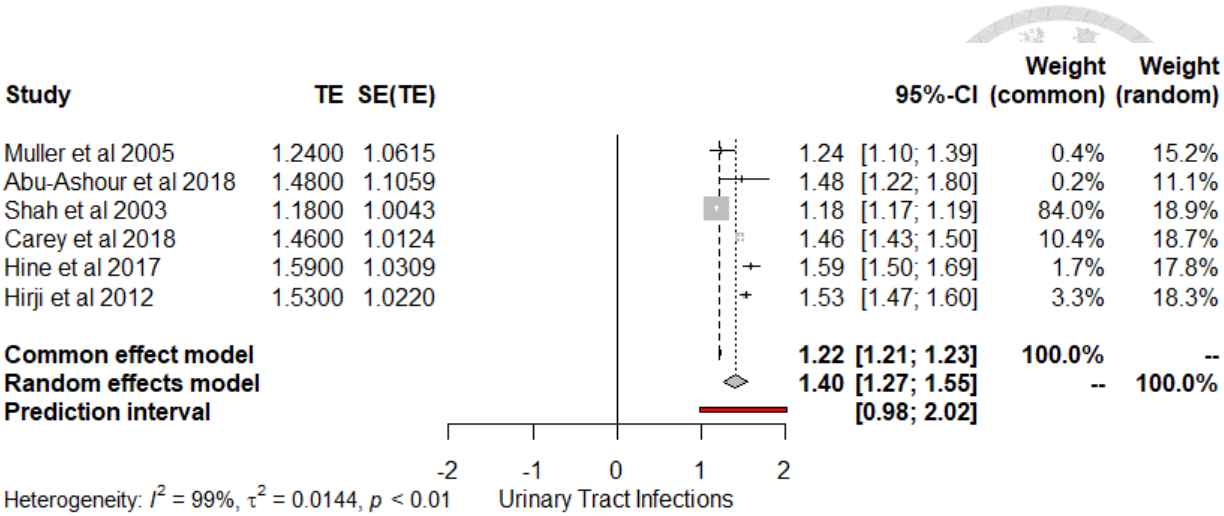

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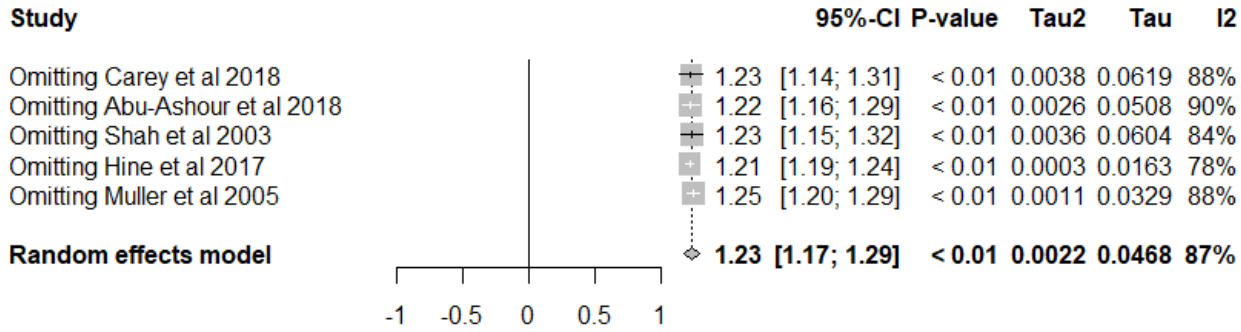
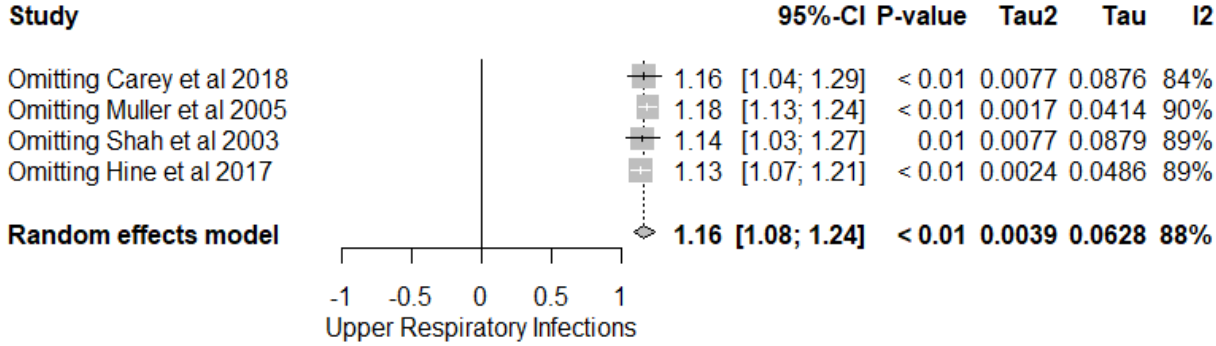
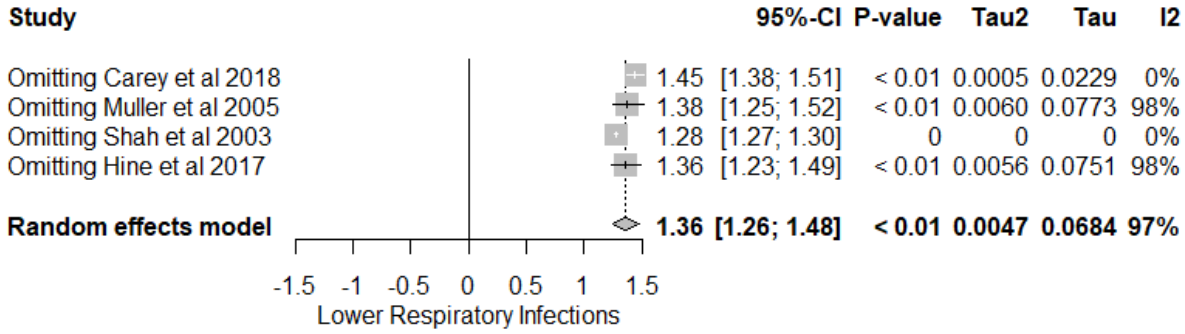
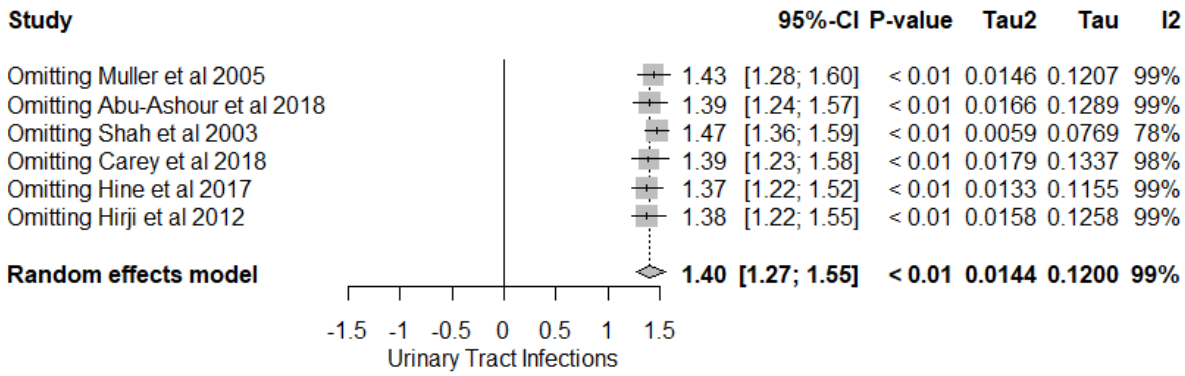
Appendix 5: Sensitivity Analysis

Influence Analysis









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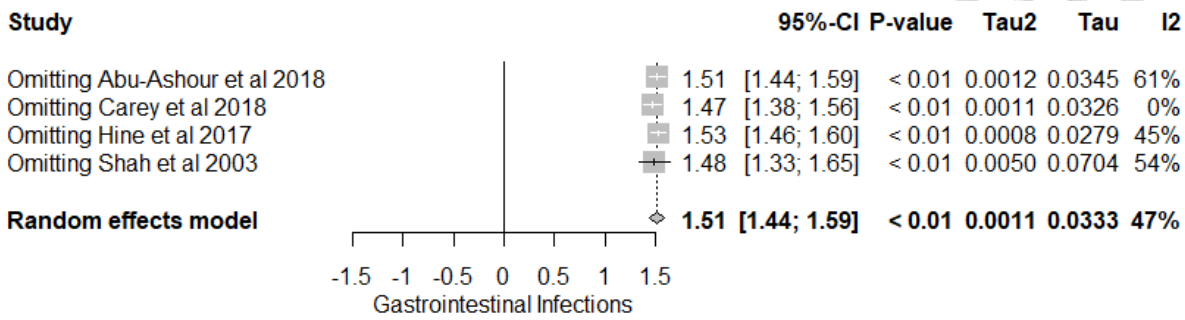

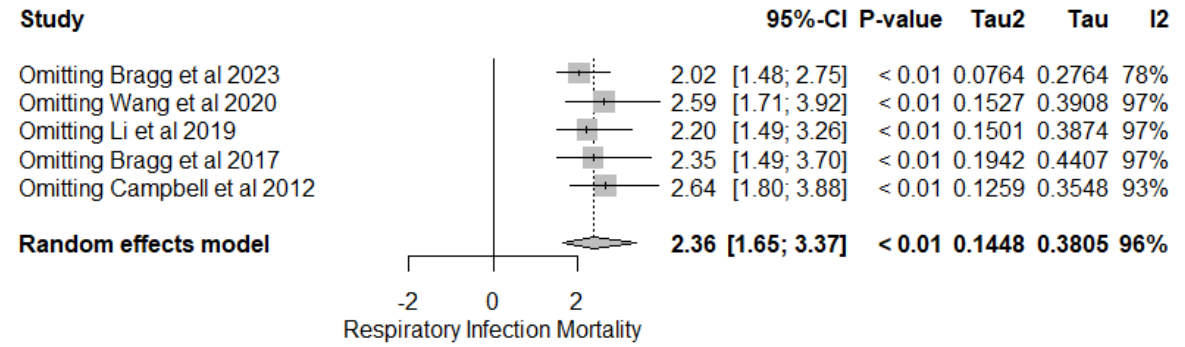

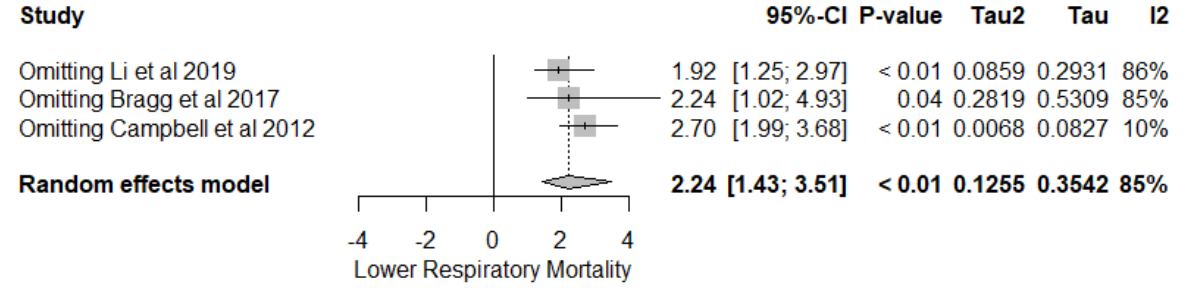

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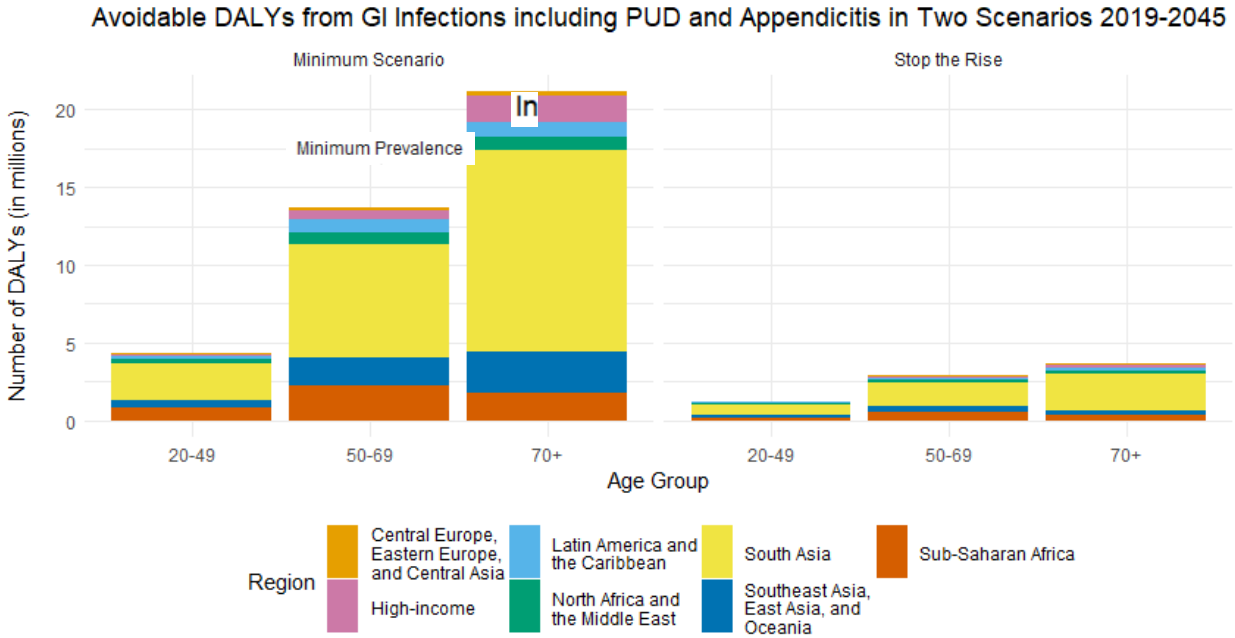

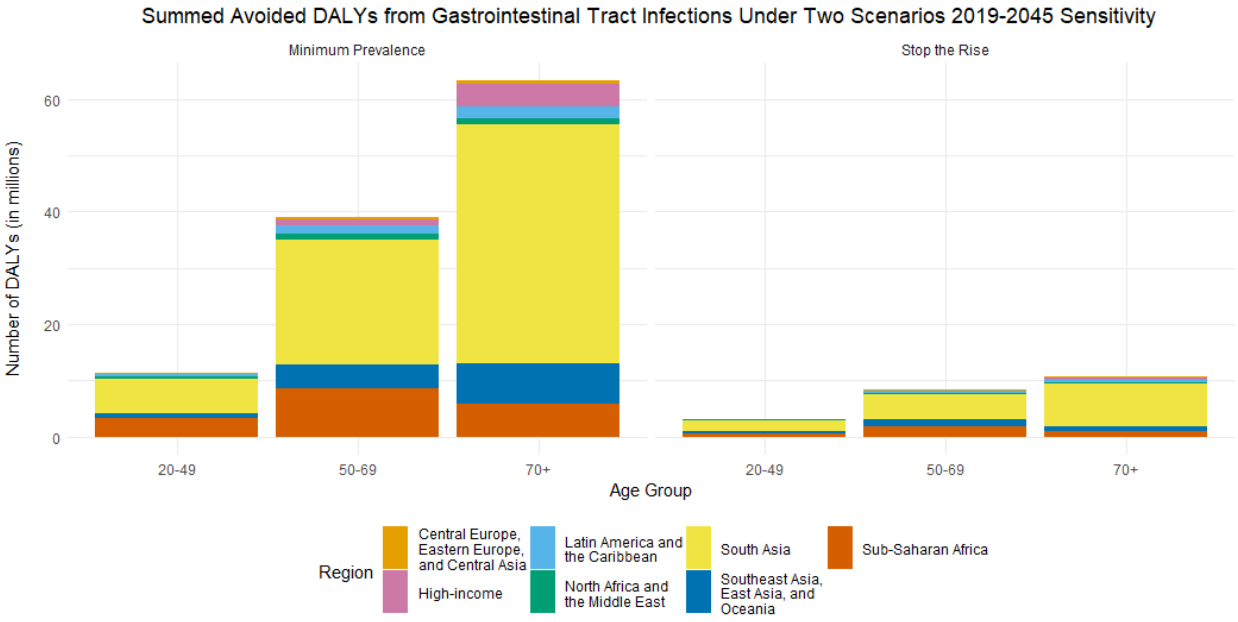

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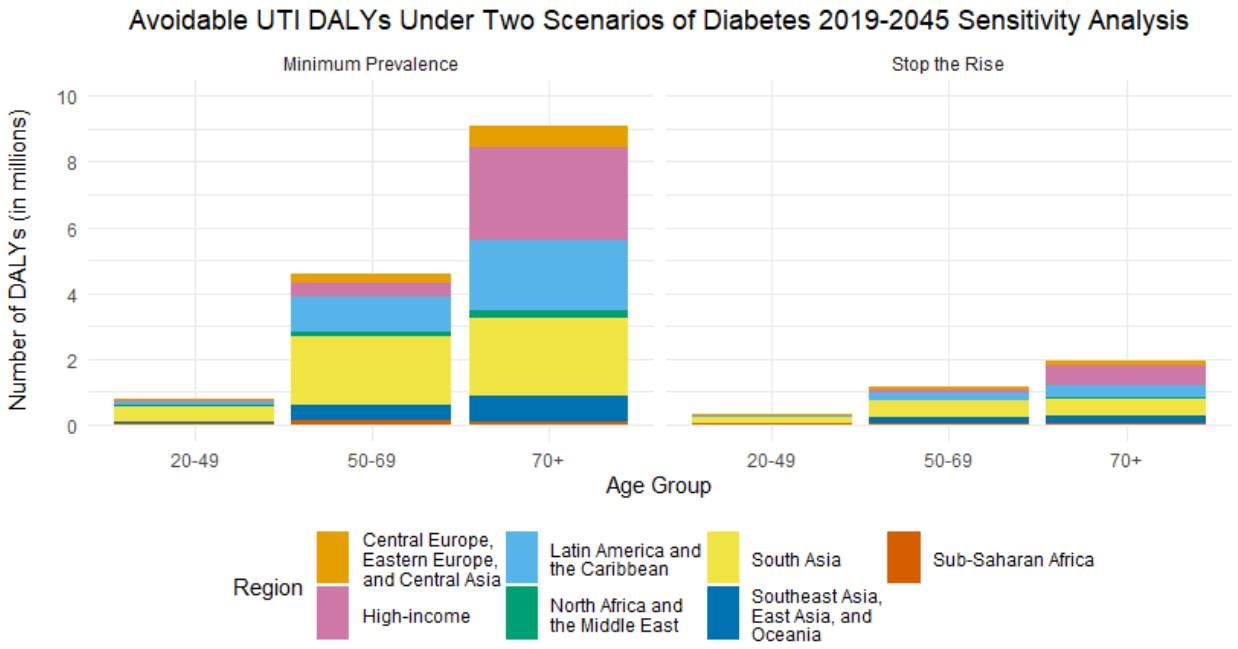

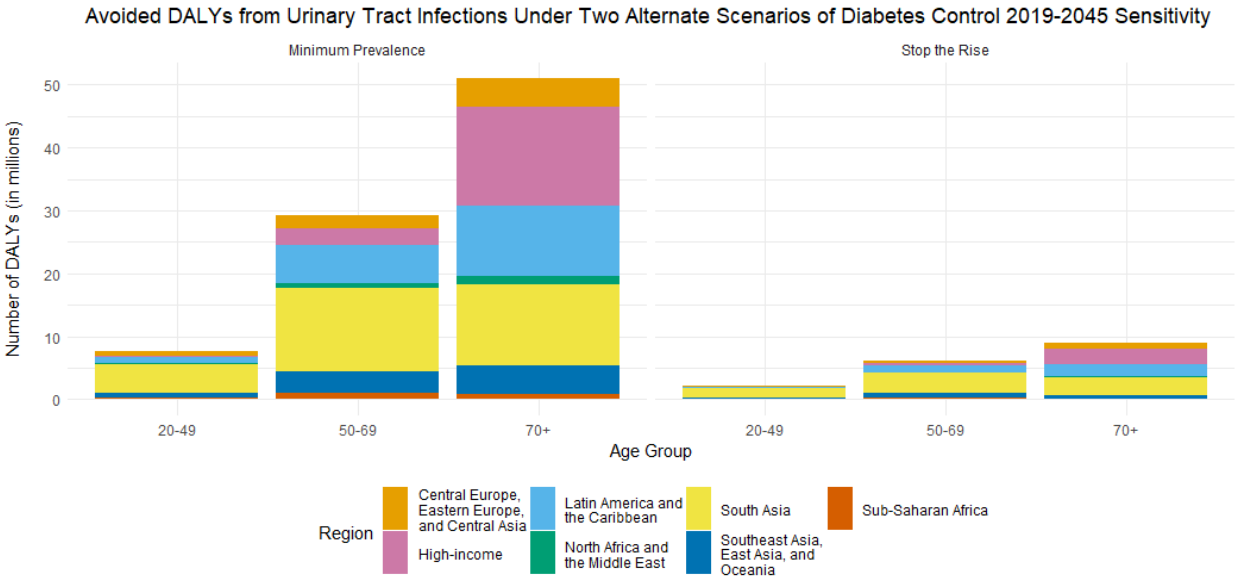

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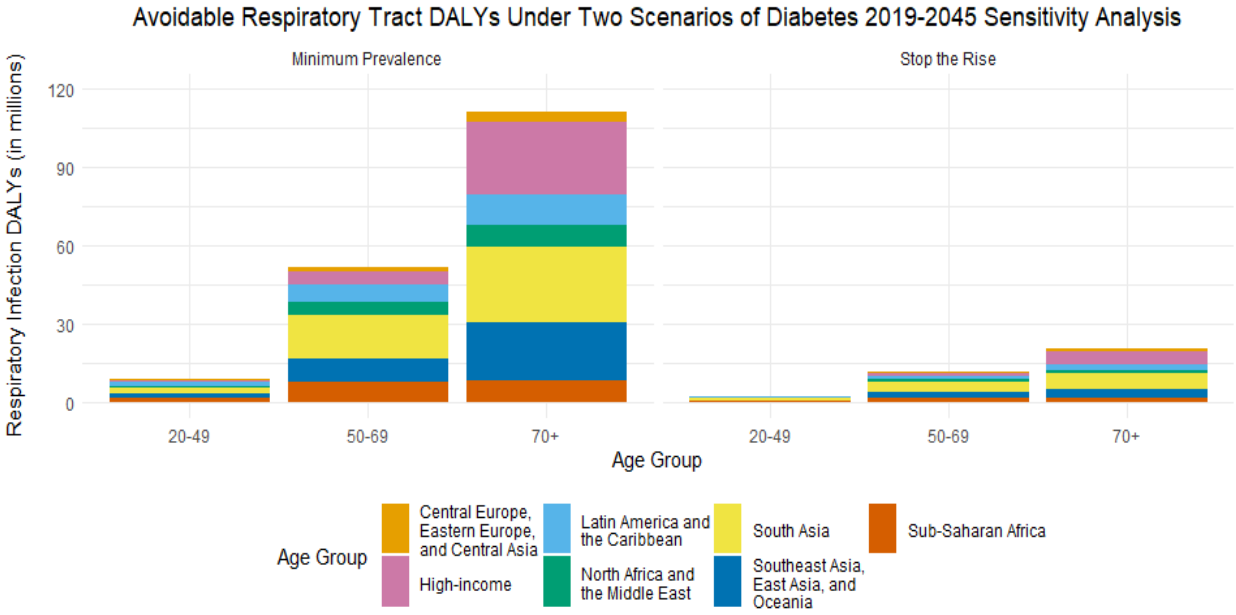

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