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Risk Phenotypes of Diabetes and Association with COVID-19-Related Severity and Death - An Update of a Living Systematic Review and Meta-Analysis

Dissertation

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I. Summary (German)

Im Zusammenhang mit der COVID-19-Pandemie gibt es Hinweise darauf, dass Diabetes ein Risikofaktor für eine schlechte Prognose ist. Ziel dieser Studie ist es daher, die Hochrisiko-Phänotypen von Patienten mit Diabetes zu identifizieren, die mit dem Tod und Schweregrad von COVID-19 verbunden sind. Dies ist das erste Update eines kürzlich veröffentlichten systematischen Reviews und Metaanalyse von Beobachtungsstudien, das Phänotypen bei Menschen mit Diabetes in Bezug auf COVID-19-bedingten Tod und Schweregrad untersuchte. Bis Mai 2021 wurden vier verschiedene Datenbanken durchsucht. Die Literatur wurde von zwei unabhängigen Forschern gesichtet und die Daten wurden aus den relevanten Studien extrahiert. Das Bias-Risiko der Studien wurde mit dem QUIPS-Tool und die Vertrauenswürdigkeit der Evidenz mit dem GRADE-Tool bewertet. Wir berechneten die Gesamt-Relativen Risiken (SRR) mit 95%-Konfidenzintervallen (KI) unter Verwendung von Random-Effects Metaanalysen. Gemäß den Einschlusskriterien wurden 80 Artikel, davon 58 neue Studien, mit 90.000 Personen mit Diabetes eingeschlossen. Wir haben 143 Metaanalysen durchgeführt, 68 zu COVID-19-bedingten Tod und 75 zum Schweregrad von COVID-19. Es wurden Zusammenhänge mit hoher Vertrauenswürdigkeit der Evidenz zwischen männlichem Geschlecht, höherem Alter, Blutzuckerspiegel bei der Aufnahme, chronischer Insulin- und Metformineinnahme sowie vorbestehenden Komorbiditäten (CVD, CKD, COPD) und COVID-19-bedingten Todesfällen nachgewiesen. Unsere Ergebnisse liefern neue Erkenntnisse mit mittlerer bis hoher Vertrauenswürdigkeit der Evidenz für Adipositas (SRR: 1,54 [95% KI: 1,11, 2,15]; *n=9* Studien), mikrovaskuläre Komplikationen (SRR: 1,55 [95% KI: 1,08, 2,22]; *n*=3), Demenz/kognitive Beeinträchtigungen (SRR: 1,76 [95% KI: 1,21, 2,58]; *n*=4), Charlson-Index (SRR pro 1 Einheit: 1,33 [95% KI: 1,13, 1,57]; *n*=2), hohe CRP-Werte (SRR pro 5 mg/l: 1,07 [95% Kl: 1,02, 1,12]; *n*=7), AST (SRR: pro 5 U/l: 1,42 [95% Kl: 1,06, 1,90]; *n*=4), eGFR invers (SRR pro 10 ml/min/1,73 m²: 0,78 [95% KI: 0,64, 0,93]; *n*=3) und Lymphozytenzahl invers (SRR pro $1x10^9$/l: 0,29 [95% KI: 0,11, 0,73]; *n*=5) im Hinblick auf COVID-19-bedingten Tod. Es ergaben sich ähnliche Ergebnisse zwischen diesen Risikofaktoren und dem Schweregrad von COVID-19, allerdings wurden für diesen Endpunkt weitere Risikofaktoren identifiziert: Hypertonie (SRR: 1,28 [95% KI: 1,13, 1,44]; *n*=24) und HbA1c (SRR pro 10 mmol/mol: 1,12 [95% KI: 1,01, 1,24]; *n*=13). Unsere Ergebnisse deuten darauf hin, dass nicht der Diabetes an sich, sondern der

Schweregrad des Diabetes und die vorbestehenden Komorbiditäten die Prognose von COVID-19 bedingen.

II. Summary (English)

In the context of the COVID-19 pandemic, there is an indication that diabetes is a risk factor for poor prognosis. The aim of this research is therefore to determine the high-risk phenotypes of patients with diabetes that are associated with death and COVID-19-related severity and to quantify the risk. This is the first update of our recently published systematic review and meta-analysis of observational studies investigating phenotypes in individuals with diabetes regarding COVID-19-related death and severity. Until May 2021 four different databases were searched. The literature was screened by two independent researchers and data were extracted from eligible studies. The risk of bias of the studies was evaluated by the QUIPS tool and the certainty of evidence by the GRADE tool. We calculated summary relative risks (SRR) with a 95% confidence interval (CI) using random effects meta-analyses. According to the eligibility criteria, 80 articles, of which 58 were new studies, involving 90,000 individuals were included. We carried out 143 meta-analyses, 68 on COVID-19-related death and 75 on COVID-19-related severity. Associations with high certainty of evidence were demonstrated between male sex, older age, admission blood glucose level, use of chronic insulin and metformin, as well as pre-existing comorbidities (CVD, CKD, COPD) with COVID-19-related death. Our results generate new evidence with moderate to high certainty of evidence for obesity (SRR: 1.54 [95% CI: 1.11, 2.15]; *n*=9 studies), pre-existing microvascular complications (SRR: 1.55 [95% CI: 1.08, 2.22]; *n*=3), dementia/cognitive impairments (SRR: 1.76 [95% CI: 1.21, 2.58]; *n*=4), Charlson index (SRR per 1 unit: 1.33 [95% CI: 1.13, 1.57]; *n*=2), high levels of CRP (SRR per 5 mg/l: 1.07 [95% Cl: 1.02, 1.12]; *n*=7), AST (SRR per 5 U/l: 1.42 [95% Cl: 1.06, 1.90]; *n*=4), eGFR inversely (SRR per 10 ml/min/1,73 m²: 0.78 [95% Cl: 0.64, 0.93]; *n*=3) and lymphocyte count inversely (SRR per $1x10^9$/l: 0.29 [95% Cl: 0.11, 0.73]; *n*=5) related to COVID-19 death. There were similar results between these risk factors and the severity of COVID-19, but additional risk factors were identified for this endpoint: hypertension (SRR: 1.28 [95% Cl: 1.13, 1.44]; *n*=24) and HbA1c (SRR per 10 mmol/mol: 1.12 [95% Cl: 1.01, 1.24]; *n*=13). Our findings imply that it is not the diabetes per se, but that the prognosis of COVID-19 depends on the severity of diabetes and the pre-existing comorbidities.

III. List of Abbreviations

AKI	Acute kidney injury
ALT	Alanine aminotransferase
ARBS	Angiotensin-II type-1 receptors blockers
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
AT2R	Angiotensin-II type-2 receptor
BMI	Body mass index
CCI	Charlson comorbidity index
CG	Cockcroft–Gault
CI	Confidence interval
CKD	Chronic kidney disease
CKD – EPI	Chronic Kidney Disease Epidemiology Collaboration
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease-2019
CRP	C-reactive protein
CRRT	Continuous renal replacement therapy
CRS	Cytokine release syndrome
CVD	Cardiovascular diseases
Ct	Cycle-threshold
eGFR	estimated Glomerular filtration rate
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GLP-1-RA	GLP-1-Receptor-Agonists
HDL	High density lipoprotein

ICU	Intensive care unit
LDL	Low density lipoprotein
NPV	Negative predictive value
NSAIDs	Non-steroidal anti-inflammatory drugs
PCR	Polymerase chain reaction
PPV	Positive predictive value
QUIPS	Quality In Prognosis Studies
RoB	Risk of bias
RAAS	Renin-angiotensin-aldosterone system
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SRR	Summary relative risks
TNF α	Tumor necrosis factor a
T1D	Diabetes mellitus type 1
T2D	Diabetes mellitus type 2

IV. Table of Contents

List of Tables

List of Figures

Chapter 1 - Introduction

The World Health Organisation issued a pandemic alert precipitated by the rapid evolution of coronavirus disease-2019 (COVID-19), induced by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) after a cluster of pneumonia cases originated in Wuhan City, China in 2019. Given the rapid escalation of COVID-19 cases and its substantial effects on mortality, the healthcare infrastructure has been overwhelmed on a global basis. As it is suggested by the World Health Organisation (2), until January 2024 more than 774 million cases of SARS-CoV-2 infections and more than 7 million deaths have been reported worldwide since 2019. Consequently, the global economies have been strained to contain the outbreak, identify patients who are vulnerable to COVID-19 infection, and prevent the downgrade of economic growth.

Evidence from several systematic reviews and meta-analysis have indicated a two- to three-fold increased risk of mortality in patients with diabetes and COVID-19 compared to those without diabetes and COVID-19 (3, 4). Moreover, it has been postulated that diabetes is a risk factor for poor prognosis among individuals with COVID-19, in addition to other concomitant medical conditions (e.g. underlying cardiovascular diseases (CVD), respiratory diseases, hypertension, and obesity) (5). Therefore, individuals with diabetes present unique clinical challenges necessitating meticulous management. Diabetes, on the other hand, is a complex disease, thus there is growing evidence from recent studies that have discovered the associations between COVID-19 infection and specific phenotypes of diabetes with comorbidities and complications (6).

Diabetes Mellitus

Epidemiology

Diabetes mellitus is a metabolic disorder characterised by chronic hyperglycemia (7). About 537 million people worldwide have diabetes mellitus, corresponding to 10.5% of the world's population (8), while the prevalence has been rising more rapidly in low- and middle-income countries (9). The prevalence of diabetes mellitus in Europe lies at 9% and it is expected to increase by 1% by 2030, and the worldwide prevalence is estimated to increase to 12.5% by 2030 (8). Between 2000 and 2019, there was a 3% increase in diabetes mortality rates, and specifically, in lower-middle-income countries, the mortality rate due to diabetes increased by 13% (9), making it the ninth leading cause of mortality (10). This metabolic disorder accounted

for 6.7 million deaths in 2021, 1 every 5 seconds (8), and 32.6% of all deaths due to diabetes occurred before the age of 60 years (9).

Definition and Pathomechanisms of Diabetes Mellitus

Diabetes mellitus is a chronic metabolic disorder marked by chronic elevation of blood glucose levels (hyperglycemia) (7). It occurs either due to insufficient insulin production in the pancreas or when the body does not respond effectively to the insulin produced, or usually both (9). Insulin is a polypeptide hormone secreted by β-cells in the islets of Langerhans of the pancreas (11). The hormone regulates glucose levels in the bloodstream and induces glucose storage in the liver, muscles, and adipose tissue, resulting in overall weight gain (11). Thus, any change in physiological processes by insulin makes its synthesis and levels critical in the onset and progression of chronic diseases such as diabetes (11).

Diabetes mellitus can be categorised into four subgroups: type 1 (T1D), type 2 (T2D), gestational, and other specific types of diabetes (7). The focus of our study is on type 1 and 2 diabetes, therefore only individuals with these two types of diabetes fulfilled the inclusion criteria of the studies of our systematic review.

Diabetes mellitus Type 1 (T1D) is caused by β-cell destruction in the pancreas leading to an absolute deficiency of insulin, primarily due to immunological factors (7), resulting in hyperglycemia and ketosis. Incidence peaks in puberty and early adulthood, but onset can occur at any age (12). This type of diabetes accounts for about 5-10% of all cases of diabetes (7) and occurs most commonly in Europe and North America affecting approximately two million people (13). Like other organ-specific autoimmune diseases, T1D has human leukocyte antigen (HLA) associations (13). Two combinations that are of particular importance are present in 90% of children with T1D: DR4-DQ8 and DR3-DQ2 (13). First-degree relatives of these children are at greater risk of developing T1D than the relatives of children in whom the disease develops later (13). Three stages have been suggested for the progression of T1D (14). Stage 1 is characterized by β-cell autoimmunity, yet with normoglycemia and no symptoms. Dysglycemia appears in stage 2, followed by the symptoms in stage 3 (14).

Diabetes mellitus Type 2 (T2D) is the most common form of diabetes mellitus that accounts for 90-95% of all individuals with diabetes (7). It is expected that the number of cases of diabetes mellitus will increase to 643 million by 2030 (8). T2D is characterised by

carbohydrate and fat metabolism abnormalities (15). It is a heterogeneous syndrome and the causes are multifactorial, which include both genetic and environmental elements affecting β-cell function and insulin sensitivity in tissues (15). The condition is marked by deficient insulin secretion by pancreatic islet β-cells, tissue insulin resistance, and an inadequate compensatory insulin secretory response, leading to a progressive increase in plasma glucose levels (16). Insulin resistance is the inability of cells in muscles, fat, and liver to respond well to insulin thus preventing the take up of glucose from the blood. As a result, more insulin is produced in β-cells of the pancreas to prevent an increase in glucose levels. When the compensation mechanism reaches its peak, it results in diabetes mellitus. It is often associated with metabolic syndrome (7), which includes abdominal obesity, high triglycerides and low HDL cholesterol, elevated blood pressure, and elevated fasting plasma glucose (17).

Diagnostic Criteria of Diabetes Mellitus

The diagnosis of DM is based on the glucose level or the HbA1c level in the venous plasma (7). According to the American Diabetes Association diabetes can be defined according to the blood glucose and HbA1c levels as stated in Table 1.

Table 1: Diagnosis of Diabetes Mellitus	
Measured variable venous plasma glucose	
Random plasma glucose value	≥ 200 mg/dL (≥ 11.1 mmol/l)
Fasting plasma glucose	≥ 126 mg/dL (7.0 mmol/l) (fasting time 8–12 h)
OGTT 2h value in venous plasma	≥ 200 mg/dL (≥ 11.1 mmol/l)
Measured variable HbA1c:	
HbA1c	≥ 6.5 % (≥ 48 mmol/mol Hb)

Diagnosis of diabetes mellitus using venous plasma glucose and HbA1c levels - modified by ADA (18)

Risk Factors of Diabetes Mellitus

There are many factors that contribute to the development of T1D and T2D. Although the pathophysiology of diabetes mellitus has not been completely elucidated so far, it has been suggested that the disease has a major genetic component representing one of the non-modifiable factors (16). T1D is an autoimmune disorder strongly influenced by genetic factors. Individuals with a first-degree relative with T1D have a 1 in 20 lifetime risk of developing

T1D, compared to a 1 in 300 lifetime risk for the general population (19). Furthermore, T1D is the major type of diabetes in youth when the incidence rate increases from birth and peaks between the ages of 10-14 years during puberty and appears to stabilise in young adulthood (19). The incidence of T1D is increasing at an annual rate of 3-5%, implying that environmental exposure has changed over the last 60 years, either through the gradual introduction of a susceptibility factor or the removal of a protective factor (20). Outbreaks and seasonality of T1D may indicate an infectious cause, possibly related to increased sanitation and herd immunity loss (20). Environmental toxins and early childhood diet could also be risk factors (20).

T2D can be caused by modifiable and non-modifiable factors. The incidence and prevalence of T2D are found to vary widely depending on ethnicity and geographical region. East Asians, Native Americans and Hispanics have the highest risk of developing T2D (16). The most important risk factor that influences the development of insulin resistance and disease progression is obesity (16, 21). At closer analysis, a high BMI appears to contribute less to an increased risk of diabetes mellitus than the presence of increased visceral obesity and ectopic fat like liver fat (22). A wide variety of lifestyle factors, which can be modified, are also of great importance to the development of T2D (23). These factors include physical inactivity, a sedentary lifestyle, smoking, alcohol consumption, and diet (21, 24). A low-fiber diet with a high glycemic index is positively associated with a higher risk of developing the disease (25). A high intake of animal fat might be associated with a higher risk of developing T2D rather than vegetable fat intake (26). The socioeconomic status has also an impact on the development of diabetes mellitus and more specifically an inverse association has been reported worldwide, after separate analyses of high-, middle- and low-income countries (22). Low levels of socioeconomic status were associated with a 40-60% higher relative risk compared to high levels (22). Moreover, findings of the English Longitudinal Study of Ageing showed that people of a lower life course socioeconomic status group experienced a more than doubled risk of diabetes (27).

Although individual predisposition to diabetes mellitus due to non-modifiable risk factors has a strong genetic basis, evidence has been suggested that many cases could be prevented by changing the modifiable risk factors such as obesity, low physical activity, and an unhealthy diet (16, 24).

Symptoms and Complications of Diabetes Mellitus

The signs and symptoms of diabetes mellitus are often disregarded due to the disease's chronic course of progression. Considering the asymptomatic nature of diabetes in the early stages, it is essential to raise awareness of its warning signs (28). Classical symptoms include polyuria, polydipsia, and weight loss, as well as fatigue and confusion (28). In both types of diabetes, ketoacidosis leading to hyperosmolar coma is a potentially catastrophic emergency (29).

Individuals with diabetes are more susceptible to short- and long-term complications, including macro- and microvascular diseases (21). CVD is a primary cause of mortality and morbidity due to oxidative stress that enhances atherogenesis and low-density-lipoprotein (LDL) oxidation. (21). Diabetic nephropathy is a microvascular complication, whose progression can be prevented if detected in an earlier phase (21). It is the major cause of end-stage renal disease and its classical presentation is characterisied by hyperfiltration and albuminuria in the early stages, followed by a progressive decline in renal function (30). Another common complication is diabetes-related neuropathy, which is defined as loss of sensory function that begins distally in the lower extremities and is accompanied by pain and significant morbidity and it affects at least 50% of people with diabetes over time (31). It may be associated with sexual dysfunction, foot ulcers, amputations, as well as loss of protective sensation in the feet, which in turn leads to callous formation, ulceration, and gangrene (21). Diabetic retinopathy is the leading cause of vision loss in the elderly and is a common microvascular complication of diabetes (32). In the early stages of diabetic retinopathy, hyperglycemia and altered metabolic pathways cause oxidative stress and the development of neurodegeneration (32). Chronic hyperglycemia may cause microvascular damage to the retinal vessels, leading to edema and/or haemorrhage into the retina because of vascular permeability (21).

Furthermore, epidemiologic evidence has demonstrated that diabetes may be linked to an increased risk of developing cancer, such as colorectal, liver, bladder, breast, and kidney cancer (21). The reason behind this association may be due to the mutual risk factors contributing to both diseases like age, obesity, sedentary lifestyle, smoking, and diet (21). Hyperglycemia might also promote carcinogenesis through increased proliferation of colonic tumors as well as increased IGF-1 levels that have mitogenic and antiapoptotic actions on cancer cells (21).

Treatment of Diabetes Mellitus

Diabetes mellitus is a complex chronic disease and requires a multitude of interventions for successful management. The therapy depends on the type and severity of diabetes. Insulin therapy is necessary for T1D, as it is a disease primarily due to the absence of insulin (9). The first therapeutic use of insulin by Frederick Banting and Charles Best in 1921 was the revolution to the management of T1D, as it considerably changed the landscape of diabetes management (33). Insulin is the most effective anti-hyperglycemic agent (21). It provides effective glycemic control even when oral medication is inadequate (21). Its main mechanism is the suppression of hepatic glucose production, increasing postprandial glucose utilisation (21). It also improves insulin sensitivity and β-cell secretory function by the reduction of hyperglycemia. It can also suppress ketosis thus delaying diabetes complications (21).

For T2D on the other hand, there are conservative approaches, which are ineffective for T1D. These include a healthy diet and physical activity, as well as smoking cessation (9), which can be adequate treatments, especially in the initial stages. Therefore, patient awareness and education play a crucial role in successful disease prevention and management. When conservative measures are not adequate to control glucose levels, oral medication targeting insulin sensitivity or an increase in insulin secretion by the pancreas can be used as monotherapy or as a combination (34). The specific subclasses include biguanides, sulfonylureas, thiazolidinediones, α-glucosidase inhibitors, GLP-1 receptor agonists (GLP-1-RA), DPP-4 inhibitors, and SGLT-2 inhibitors (34). In advanced stages of the disease, insulin may also be necessary if glucose management is inadequate using oral medication (34).

Biguanides like metformin are one of the major classes of glucose-lowering drugs (21). Metformin belongs to the first-line therapy for diabetes mellitus (21). It has been proven efficient in lowering blood glucose, increasing insulin sensitivity, and reducing cardiovascular and hypoglycaemia risk (21), which improves macrovascular outcomes and reduces mortality rates in T2D (21) by 25% (35).

Sulfonylureas are second-line agents that stimulate insulin secretion, but they are dependent on the presence of enough β-cells with sufficient functional reserve (21). Glimepride, for example, was associated with a 23% lower risk of all-cause mortality and 17% reduction in cardiovascular death (36). One major adverse reaction is the higher rate of hypoglycaemia, especially in older adults (21).

Incretin-based therapies stimulate insulin secretion and suppress postprandial glucagon secretion (21). GLP-1-RA stimulate insulin production, inhibit glucagon release, and slow

nutrient absorption, increasing satiety (21). The use of GLP-1-RA was associated with a 12% reduction in the risk of cardiovascular mortality and 11% for all-cause mortality (36). DPP-4 inhibitors can improve the action of endogenous active GLP-1 by blocking its degradation by the DPP-4 enzyme. They protect pancreatic β-cells and promote normal glucagon secretion, hence slowing down the progression of diabetes mellitus (21). DPP-4 inhibitors are a relatively new class of drugs used to treat diabetes. Though many short-term studies have been encouraging, ongoing long-term clinical trials on humans are needed to provide further clarity to the complete safety profiles of these agents in terms of cardiovascular risk, and whether they may exert potential cardiovascular benefit (37) by reducing the cardiovascular mortality by 33% (38).

Thiazolidinediones are a class of insulin sensitisers, which control normal skeletal muscle and hepatic insulin sensitivity (21). They have a more durable action to regulate high glucose levels than sulfonylureas and metformin, and the risk of hypoglycemia is not increased as a monotherapy. In the UK Research General Practice Dababase it was demonstrated that pioglitazone was associated with a 39% decrease in the risk of all-cause mortality (39). According to another meta-analysis, the cardiovascular events in patients with diabetes were also reduced by 17% under medication with pioglitazone (40). They often cause fluid retention, therefore its use should be avoided in older patients with congestive or class III-IV heart failure (21).

Alpha-glucosidase inhibitors decrease carbohydrate absorption and improve glucose tolerance (21). According to a Cochrane meta-analysis, it was observed that α-glucosidase inhibitors reduced the HbA1c by 0.8% (41). The risk of CVD such as acute myocardial infarction is also reduced by 49% (41). However, their use should be avoided in patients with renal impairment (21).

SGLT-2 inhibitors are a new class of glucose-lowering agents that prevent renal-filtered glucose reabsorption back into circulation. As a result, urinary glucose elimination increases and blood glucose levels decrease (21). SGLT-2 inhibitors reduce HbA1c by 0.5-0.7% as well as the cardiovascular mortality by 14% (41). Adverse effects observed under this medication included genital infections and the occurrence of breast and bladder cancer (21).

The long-term treatment of diabetes has therefore the goal to prevent microangiopathic complications like retinopathy, nephropathy, neuropathy, and macroangiopathic complications such as myocardial infarction and stroke. If lifestyle changes do not yield improvement, drug treatment is initiated to reach the HbA1c target range of 6.5-7.5% (34).

Treatment targets can be less stringent in old age. Although there are many treatment options, individualised long-term treatment still presents a challenge (34). Part of the treatment is also the improvement of the patient's competence to deal with diabetes and the promotion of patient adherence to prevent hypoglycemia and weight gain (34).

Coronavirus – COVID-19

Epidemiology

The World Health Organisation (WHO) issued a pandemic alert precipitated by the rapid evolution of coronavirus disease-2019 (COVID-19) induced by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), after a cluster of pneumonia cases originated in Wuhan City, China in 2019. Given the rapid escalation of COVID-19 cases and its substantial effects on mortality, the healthcare infrastructure has been overwhelmed on a global basis. As it is suggested by WHO (2), more than 774 million cases of SARS-CoV-2 infections and more than 7 million deaths have been reported worldwide until January 2024. Consequently, the global economies have been strained to contain the outbreak, identify patients who are vulnerable to COVID-19 infection, and prevent the downgrade of economic growth.

Definition, Pathomechanism and Transmission of COVID-19

In December 2019, a cluster of pneumonia cases of unknown origin was reported in Wuhan, Hubei province in China (42). The novel strain of coronavirus belonged to the same family of viruses that caused severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) (42). The WHO declared on March 11, 2020, the novel coronavirus (COVID-19) outbreak a global pandemic (42). Coronavirus disease is an infectious disease caused by the SARS-CoV-2 virus (43).

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus of the genus Betacoronavirus with a crown-like appearance as seen under an electron microscope (*corona* is the Latin term for crown) because of the presence of spike glycoproteins on the envelope (44). It relies on its obligate receptor, angiotensin-converting enzyme 2 (ACE2) to enter cells (45). This receptor is known to be the causative agent of mild upper respiratory tract infections. The membrane structural proteins of the virus consist of the S (spike) protein that serves to bind to the host cell, the E (envelope) protein that is essential for the assembly of viral particles, and the M (matrix) protein that serves to provide structure and plays a role

in the assembly of viral particles as well (45). Non-membrane structural protein is the N (nucleocapsid) protein which forms the nucleocapsid together with the genome (45). After binding to ACE2, the cellular transmembrane protease serine 2 (TMPRSS2) mediates the S protein priming enabling the virus to enter the host cells (45). As soon as coronavirus enters the cell after binding through the spike proteins on ACE2 receptors, the reproduction cycle starts (46). This includes the uncoating of the virus and the release of its nucleic acid from the endosome into the cytoplasm, followed by the translation, replication, and transcription of the viral genetic material (46). After the assembly of the individual virus components, the newly formed viruses are released to infect further cells (46).

There are two stages of immune response induced by the virus (47). The initial stage involves the specific adaptive immune response and the second stage the uncontrolled inflammation (47). During the early stages of incubation, the adaptive response prevents the progression of the disease and aims to eliminate the virus (47). When this procedure is ineffective, the virus propagates, destructing the affected tissues, followed by the development of more severe disease (47). An uncontrolled inflammatory response may lead to acute respiratory distress syndrome (ARDS) (48). The mechanism is based on the release of a cytokine storm which may promote apoptosis or necrosis of T cells leading to their depletion (48). The severity of the disease can also be seen in the increased plasma levels of cytokines like IL-6, TNF, and IL-10, along with lower numbers of circulating $CD4^+$ and $CD8^+$ T cells (49). Due to ARDS, T-cell exhaustion impairs viral clearance (50).

COVID-19 has been rapidly expanding across the world with each country developing epidemiologic patterns in terms of frequency, hospitalisation, and death (51). The main route of transmission for SARS-CoV-2 is respiratory ingestion of virus-containing particles produced for example by breathing, coughing, talking, and sneezing (52). Transmission through contaminated surfaces cannot be ruled out, since replicable SARS-CoV-2 viruses can remain infectious on surfaces for some time under laboratory conditions (53). Furthermore, conjunctive as well as transmission through food and vertical transmission from mother to child could be gateways for infection (52).

Diagnosis of COVID-19

If infection with the SARS-CoV-2 coronavirus is suspected, samples should be taken from the upper respiratory tract, and if clinically indicated from the deep respiratory tract (52). The different sample types can be seen in Table 2.

Table 2: Sample Types of Infectious Material for COVID-19 Diagnosis	
Upper respiratory tract	Nasopharyngeal swab, oropharyngeal swab
Deep airways	Sputum, tracheal secretion
Alternative method	Mouth/throat and nasal vestibule swab

Diagnosis of COVID-19 using samples of infectious material of the respiratory tract (52)

PCR detection systems have been developed and validated for laboratory diagnostic testing to clarify suspected infection with SARS-CoV-2. They are considered the gold standard for diagnostics (52). It detects the virus directly and testing is indicated when there is a clinical suspicion consistent with SARS-CoV-2 infection based on history, symptoms, or findings. The threshold value of 10^6 copies/mL is based on the current state of research (52). Accordingly, it is not a clear threshold value but only an orientation value that must be considered in the context of clinical and temporal parameters (52).

In this context, the use of cycle threshold (Ct) values is employed for the diagnosis or prediction of SARS-CoV-2 infection (54). This approach holds considerable clinical importance since Ct values can be associated with the viral load, as they indicate how many amplification cycles are required for the target gene to reach a threshold level (54, 55). Consequently, comprehending the interpretation of Ct values and other influential factors becomes pivotal in understanding both the viral load and the severity of the disease (54). The relationship between the SARS-CoV-2 viral load and Ct values is inversely proportional, meaning that a lower Ct value is indicative of a higher viral load (54). This correlation suggests increased infectiousness associated with a higher viral load, as a low Ct indicates a higher concentration of genetic material, commonly associated with an increased risk of infection (54). Ct values between 17-24 are associated with higher viral load, whilst values between 24-35 are related to moderate viral load (54).

Antigen (Rapid) test formats are also available and they are based on the detection of viral protein in respiratory sample materials (52). In principle, the sensitivity of antigen tests is

lower in the early phase of infection than in the late phase (52). The analytical sensitivity of antigen tests is below the sensitivity of PCR (52). According to the Cochrane Dababase, antigen tests have an average sensitivity of 56.2% and specificity of 99.5%, whereas PCR achieves 95.2% and 98.9% respectively (56). For the detection of acute SARS-CoV-2 infection in symptomatic individuals, the WHO formulates a minimum detection limit for antigen tests equivalent to 10^6 (acceptable) or better 10^4 (desirable) genome copies/mL (52).

A positive antigen test result raises the suspicion of a transmission-relevant SARS-CoV-2 infection and requires a follow-up test by PCR to avoid false-positive results (52). Positive rapid test results in low prevalence areas require confirmation testing to avoid unnecessary quarantine measures (PPVs of 85% to 90% for antigen assays mean that between 1 in 10 and 1 in 7 positive results will be falsely positive). PPV refers to the percentage of people with real infection given that the test is positive (56). When the prevalence is higher (i.e. 20% or higher), false positives are less of a concern (PPVs range from 96% to 100%), but the impact of false negative results becomes more significant, and all test negatives may be considered for verification (56). Between 1 in 4 and 1 in 8 cases with negative rapid test results are SARS-CoV-2 missed cases (24 to 50 cases missed out of a total of 200 cases) (56). Negative predictive value (NPV) refers to the percentage of people with no real infection when they had a negative test result. The lower the NPV, the greater the potential impact on infection transmission from missed cases and the greater the impact of contact tracing delays (56). A negative result in the antigen test does not exclude infection, especially in the early (pre-symptomatic) phase (52). PCR tests should be used primarily in the clinical diagnostic context and negative antigen test results should be verified by PCR testing if a SARS-CoV-2 infection is still suspected (52).

Previous infections with SARS-CoV-2 can be indirectly detected using antibody detection (52). This method is suitable for the investigation of infection epidemiological questions. Various test formats like ELISA are available for the detection of a previous SARS-CoV-2 infection by means of antibody detection, with which IgM, IgA, IgG or total antibodies can be detected (52). Seroconversion occurs in the majority of patients in the second week after symptom onset (57). Therefore, due to low seroconversion rates in the early phase (week 1 to 2 after symptom onset) of infection, they are not recommended for acute diagnosis. The detection of SARS-CoV-2-specific antibodies indicates a previously experienced or still-existing SARS-CoV-2 infection (52).

Even though there was a positive correlation between SARS-CoV-2 viral load and its transmissibility (58), viral load alone is not sufficient to assess the contagiousness of a patient (52). This is influenced by other factors, such as the time since the onset of symptoms, the clinical course, and behavioural patterns of the infected person (52). The extent to which an infected person passes the virus on to others depends on the duration and type of contact, as well as on external circumstances such as room ventilation, air humidity, and air temperature as well as the susceptibility of the contact persons (52, 59).

Risk Factors of COVID-19

There are many predisposing previous diseases that make the risk assessment of COVID-19 infection complex. Severe courses of the disease can even occur in individuals without any comorbidity (48) and in younger patients (60). However, some factors predispose to a more severe course of COVID-19 infection. In the general population, it could be observed that the risk of a severe COVID-19 infection is steadily increasing from 50 years of age (52). Male sex (61), smoking (62), obesity (63) as well as pregnancy (64) were also associated with a more severe course of the disease. People with pre-existing conditions also had an increased risk of developing a more severe course of COVID-19 infection. These included CVD, chronic obstructive pulmonary disease (COPD), liver diseases and chronic kidney disease (CKD), neurological and psychiatric diseases (e.g. dementia), diabetes mellitus, cancer and weak immune system (63).

Symptoms and Complications of COVID-19

Men and women are equally affected by SARS-CoV-2 infection, however men develop more frequently a severe course of the disease and die twice as often compared to women (61). Presentation of symptoms for COVID-19 infection can be developed within 2-14 days after exposure (45). Approximately 80% of patients present with mild infection and can recover spontaneously, while 20% of patients develop severe disease and 6% become critically ill (65). COVID-19 can manifest itself not only in the lungs but also in other organ systems, depending on the density of ACE-2 receptors in the tissues (66). This receptor will in turn allow the entrance of the virus into the cells (66). It has also been observed, that besides cytopathic effects, the virus can cause excessive immune reactions and circulatory disorders due to hypercoagulability (66).

The most common manifestation of the virus is the infection of the respiratory system (67). The most frequently recorded symptoms in the German reporting system manifest as an upper respiratory tract infection with cough, fever, loss of smell and taste, and rhinitis (52).
Neurological symptoms include headaches, olfactory and gustatory disturbances, dizziness, confusion, and other impairments (68). COVID-19 infection may also be associated with gastrointestinal symptoms like nausea, loss of appetite, vomiting, abdominal pain, and diarrhea (69).

The course of the disease varies greatly in symptoms and severity, from asymptomatic infections to severe pneumonia with lung failure and death (52). This is suspected by the presence of decreased oxygen saturation, lymphopenia, and increased inflammation markers such as C-reactive protein (CRP), D-dimer, and ferritin (70). Pneumonia may develop, usually in the second week, which may progress to ARDS (67). This condition requires ventilation, and the oxygenation of the blood outside the body (67).

Some cases demonstrated cardiac involvement with elevated cardiac enzymes and troponin after infection with SARS-CoV-2 (71). A number of patients with a more severe course of the disease experienced CVD, including myocardial damage, myocarditis, acute myocardial infarction, heart failure, and venous thromboembolic events (71). Due to increased blood coagulation, there has been observed an association with an increased risk of thromboembolism in the lower extremities, pulmonary artery, and cerebrovascular embolism (72). In severely ill patients requiring ventilation, acute renal failure, which may require dialysis, has been observed (73). Some patients could also develop a hyperinflammatory syndrome 8-15 days after the onset of the disease, which can result in multi-organ failure and lead to death (52).

Intensive research is currently ongoing regarding the possible long-term health consequences (Post-COVID-19 syndrome) induced by SARS-CoV-2 infection. So far, the underlying mechanisms are not clear yet. Frequently reported symptoms include fatigue, exhaustion, shortness of breath, memory and concentration problems, muscle weakness and pain, sleep disturbances, anxiety, and depressive symptoms. Lung function deterioration, as well as impairments of liver and kidney function and the new occurrence of diabetes mellitus, are also observed (74, 75).

Treatment of COVID-19

The pathogenesis of COVID-19 is thought to be driven by two main processes (76). Earlier stages of the disease are primarily characterised by the replications of SARS-CoV-2 (76). Later in the clinical course, the immune response to SARS-CoV-2 seems to be deregulated which leads to tissue damage (76). Based on this scientific background, therapies directly targeting SARS-CoV-2 are applied in the early stages of infection in order to anticipate systematic inflammation, whilst immunosuppressive/anti-inflammatory therapies are likely to be more successful in the later stages of COVID-19 (77).

The therapy differs in patients who do not require hospitalisation or supplemental oxygen to those requiring hospital care (76). A meta-analysis reported an estimation of 20% of individuals with COVID-19 infection remained asymptomatic (78). Approximately 80% of patients with COVID-19 have mild to moderate symptoms that do not require medical intervention or hospitalisation (76). Those patients with mild symptoms are managed in an ambulatory care setting or at home (79). One of the main targets of supportive care when managing outpatients with COVID-19 is to reduce the risk of SARS-CoV-2 transmission and advise patients on when to seek an in-person evaluation (76). Proper nutrition and symptom management are important at this stage of the disease (76). Symptom management can be achieved using antipyretics, analgesics, or antitussives for fever, headache, myalgias, and cough (80). The avoidance of dehydration through regular intake of fluids is also important (76). Patients who are at high risk of progression to severe COVID-19 infection can be candidates for oral medication (77). Preferred therapies for the ambulatory control of the infection include antiviral medication like Ritonavir-boosted Nirmatrelvir, Remdesivir or Molnupiravir (77).

On the other hand, hospitalised patients receive the appropriate therapy according to the severity of the disease. For those patients who do not require oxygen supplementation, it is not recommended to receive dexamethasone or other systemic corticosteroids for the treatment of COVID-19 (80). Patients who are prone to a more severe course of the disease receive the antiviral drug Remdesivir (76). Hospitalised patients under conventional oxygen therapy receive the antiviral drug Remdesivir and most of them also receive dexamethasone. In case of rapid systemic inflammation, the therapy can be escalated using monoclonal antibodies like Baricitinib or Tocilizumab (76). The combination of all these medications, along with anticoagulant therapy to prevent any thrombosis complication, unless contraindicated, provides effective therapeutic management of COVID-19 infection (81).

Associations between Diabetes Mellitus and COVID-19

Most of the investigations regarding diabetes and COVID-19 explored in the literature are still contradictory, involve imprecise estimations, or are influenced by biased risk factors such as confounding. Further research into the diabetes-COVID-19 interaction is required to gain a thorough understanding of the phenotypes of diabetes in people with COVID-19 infection that led to a severe course of the disease or death. This could potentially elucidate treatment strategies that will in turn facilitate clinical practice and the crucial task of defining vulnerable groups. A summary of the findings, the calculation of more robust estimations, the consideration of the risk of bias, and the evaluation of the certainty of evidence should be explored in a systematic review and meta-analysis. Accordingly, this could provide the best available evidence for the identification of risk phenotypes of diabetes in association with COVID-19-related severity and death. As worldwide efforts to both mitigate the spread and treat COVID-19 are urgent, the scope of our work was to conduct and update our recent systematic review and meta-analysis among patients with co-occurring diabetes and COVID-19 to document death and severity rate (1). The early presumption and identification of risk phenotypes in individuals with diabetes with confirmed COVID-19 infection will be helpful to anticipate the imminent escalation in cases, adopting the appropriate supportive care and thereby reducing COVID-19-related death and severity.

Aim of Thesis

Evidence from a previously published meta-analyses from researchers of the German Diabetes Center elucidated that some phenotypes contribute to a more severe COVID-19 infection and COVID-19-related death. Of these phenotypes, male sex, older age (≥65 years), pre-existing CVD, CKD and COPD, diabetes treatment (insulin use and inverse association for metformin use) as well as high blood glucose at admission were associated with moderate to high certainty of evidence with a more severe COVID-19 infection course (1).

However, since the first publication of this meta-analysis numerous studies on this topic have been published, and thus, the aim of this thesis was to update the first systematic review and meta-analysis to enhance the level of certainty between risk phenotypes of people with diabetes and SARS-COVID-19 infection which led to severe COVID-19 infection and death.

Chapter 2 - Material and Methods

The protocol for this work was registered with PROSPERO (registration ID CRD42020193692) and the systematic literature review was conducted according to the PRISMA 2020 guideline (82). The results of this study were not published in this form but used as a basis for the next update of our systematic review (83).

Search Strategy and Databases

As COVID-19 has grown in importance around the world, new evidence is constantly becoming available, providing us with data regularly to update our living review. The literature search was conducted from the beginning of the pandemic up to 10 May 2021. The studies explored were extracted from PubMed, Epistemonikos, Web of Science, and the WHO COVID-19 Research Database. The predefined search terms are shown in Table 3.

Table 3: Search Strategy	
PubMed	
#1	diabetes mellitus[MeSH Terms]) OR diabetes OR diabetic*
#2	covid19 OR covid-19 OR covid OR corona OR new-corona OR novel-corona OR coronavir* OR SARS-CoV-2 OR nCoV OR 2019-nCoV
#3	Combine: #1 AND #2
Epistemonikos	
#1	advanced_title_en:(diabetes mellitus OR diabetes OR diabetic*) OR advanced_abstract_en:(diabetes mellitus OR diabetes OR diabetic*)
#2	advanced_title_en:(covid19 OR covid-19 OR covid OR corona OR new-corona OR novel-corona OR coronavir* OR SARS-CoV-2 OR nCoV OR 2019-nCoV) OR advanced_abstract_en:(covid19 OR covid-19 OR covid OR corona OR new-corona OR novel-corona OR coronavir* OR SARS-CoV-2 OR nCoV OR 2019-nCoV)
#3	Combine: #1 AND #2
Web of Science	
#1	TOPIC: (diabetes mellitus OR diabetes OR diabetic*)
#2	TOPIC: (covid19 OR covid-19 OR covid OR corona OR new-corona OR novel-corona OR coronavir* OR SARS-CoV-2 OR nCoV OR 2019-nCoV)
#3	Combine: #1 AND #2
COVID-19 Research Database	
#1	(tw:(diabetes mellitus OR diabetes OR diabetic*))
#2	(tw:(covid19 OR covid-19 OR covid OR corona OR new-corona OR novel-corona OR coronavir* OR SARS-CoV-2 OR nCoV OR 2019-nCoV))
#3	Combine: #1 AND #2

Key words used in the search strategy of eligible studies - modified by Schlesinger et al (1)

Through continuous search in PubMed using the email alert service based on our above-mentioned search terms, we identified studies published after the last update. Our most recent publication was on 28 April 2021 (1) for which the literature was updated until 10 October 2020. We did not use any limitations or filters. The studies were screened by the doctoral student and at least one other researcher independently, and discrepancies were resolved by discussion or by consulting a third researcher. All titles and abstracts were screened for

eligibility using the predefined inclusion and exclusion criteria, followed by the assessment of potentially relevant full texts. Reference lists from included studies and relevant systematic reviews on this topic were screened for additional studies.

The eligibility criteria are shown in Table 4. Studies of any design that reported risk estimates (HR, RR or OR with 95% Cl) for relationships between diabetes phenotypes with death, and severity of COVID-19 in diabetes patients with confirmed COVID-19 infection as defined by WHO (43) were included (Table 4). COVID-19-related severity was defined as a composite endpoint, consisting of death, ARDS, intensive care unit (ICU) admission, endotracheal intubation for mechanical ventilation, septic shock, multiple organ dysfunction or failure, or hospitalisation. The phenotypes include individual characteristics, diabetes-specific characteristics, underlying comorbidities or complications related to diabetes, as well as laboratory parameters as seen in Table 5.

Studies not containing primary clinical data (including modelling studies), letters, reviews, editorials, commentaries, guidelines, and articles not in English, which could not be translated, were excluded as mentioned in Table 4. If multiple studies of the same cohort/data set were found, we chose the one with the larger number of cases or/and best adjustment for confounders. Studies with mixed populations (including people without diabetes or without COVID-19) were not included. To avoid the exclusion of a study due to missing data, we successfully contacted the authors of four studies and for some studies, we obtained missing data or corrections for implausible data (84-87).

Table 4: Inclusion and Exclusion Criteria by the PICOS Statement		
	Inclusion criteria	**Exclusion criteria**
P (Population)	Individuals with diabetes and COVID-19 infection	Individuals without diabetes and/or without COVID-19 infection
I (Intervention/ exposure)	Exposed to any phenotypes; age, sex, BMI, smoking status, ethnicity, type of diabetes, duration of diabetes, glycaemic control, diabetes treatment, blood pressure/ hypertension, inflammatory biomarkers, liver enzymes, specific laboratory markers, macrovascular diseases (CVD, stroke etc.), microvascular diseases (nephropathy, neuropathy, retinopathy), respiratory diseases, cancer, immunosuppressive conditions, COVID-19 infection	COVID-19 treatment
C (comparison)	Not exposed to the phenotypes; age, sex, BMI, smoking status, ethnicity, type of diabetes, duration of diabetes, glycaemic control, diabetes treatment, blood pressure/ hypertension, inflammatory biomarkers, liver enzymes, specific laboratory markers, macrovascular diseases (CVD, stroke etc.),	

	microvascular diseases (nephropathy, neuropathy, retinopathy), respiratory diseases, cancer, immunosuppressive conditions, COVID-19 infection	
O (outcome)	COVID-19-related death and COVID-19-severity	No references to relevant COVID-19 outcomes
S (study design)	Observational studies and randomised controlled trials	Studies not containing primary clinical data (including modelling studies), letters, reviews, editorials, commentaries, guidelines, articles not in English, which could not be translated, studies with mixed populations (including people without diabetes or without COVID-19)

Search method using PICOS statement to identify inclusion and exclusion criteria of studies (own work)

Table 5: Extracted Data from Included Studies	
Categories	**Description**
Information of included publications	• The first author's last name • Date of publication • Study design • Geographic area • Number of participants • Number of cases
Patients' characteristics	• Age • Sex • BMI • Smoking status • Ethnicity
Diabetes-specific characteristics	• Type of diabetes • Duration of diabetes • Glycaemic control • Diabetes treatment
Metabolic parameters	• Blood pressure/ hypertension • Inflammatory biomarkers • Liver enzymes • Specific laboratory markers
Diabetes-related complications	• Macrovascular diseases (CVD: coronary heart diseases and stroke etc.) • Microvascular diseases (nephropathy, neuropathy, retinopathy)
Comorbidities	• Respiratory diseases

	• Cancer • Immunosuppressive conditions
Outcome	• Definition of outcome • Outcome assessment
Findings	• Crude risk estimates and 95% CIs • If available multivariable-adjusted risk estimates with 95% CIs • Confounders

Relevant data extracted from eligible studies - modified by Schlesinger et al (1)

Data Extraction and Risk of Bias Assessment

Relevant data were extracted by the doctoral student and controlled by another researcher using a pre-piloted form. Through discussion between the two researchers, and if necessary with a third researcher, discrepancies were resolved. The extracted data of interest are listed in Table 5.

The risk of bias (RoB) in the included studies was independently assessed by the doctoral student and two other researchers in pairs of two using the validated Cochrane tool, Quality in Prognosis Studies (QUIPS) (88). Any discrepancies were solved by discussion. The domains included in the QUIPS tool are as follows: study participation, prognostic factor measurements, study attrition, outcome measurements, study confounding, and statistical analysis as shown in Table 6.

Study participation refers to the adequate participation in the study by eligible people with confirmed COVID-19 and diagnosed diabetes mellitus. References are also made to the source of population indicating for example the region or the setting and the time period and place of recruitment, as well as to the baseline characteristics of the study sample and selection criteria. Study attrition refers to the adequate response rate for study participants during follow-ups, information about the participants who dropped out, and the reasons for loss to follow-up. The prognostic factor measurement domain includes the phenotypes explored in the study, the methods of phenotype assessment and if it is consistent for all study participants, as well as the report of continuous variables. Outcome measurement refers to the outcome definitions, as well as methods, and consistency of outcome measurements. Study confounding refers to all important confounders which should include age, sex, BMI/overweight/obesity, and at least

one comorbid condition, provided with their definitions and their valid and reliable measurement. Minimally adjusted models should take into consideration the important confounders. The statistical analysis domain consists of the sufficient presentation of data to assess the adequacy of the analysis, as well as an adequate statistical model such as multivariable logistic regression or Cox proportional hazard model (Table 6).

Table 6: Brief Description of QUIPS Tool Domains	
QUIPS	
Domains	**Description**
Study participation	Eligible people with confirmed COVID-19 and diabetes, region, setting, time period, place of recruitment, baseline characteristics and selection criteria
Study attrition	Reponse rate during follow-ups, reasons for loss to follow-up, information about the participants who dropped out
Prognostic factor measurements	Phenotypes explored, methods of phenotype assessment and consistency to all participants
Outcome measurements	Definitions, methods and consistency of outcome assessment
Study confounding	Defintions of all important confounders (age, sex, BMI/overweight/obesity and at least one comorbid condition), and valid and reliable measurement
Statistical analysis	Sufficient presentation of data to assess the adequacy of the analysis, adequate statistical model such as multivariable logistic regression or cox proportional hazard model

Short version of QUIPS Tool with a brief description of each domain – modified by Schlesinger et al (1). QUIPS, Quality In Prognosis Studies

Each domain was rated as low, moderate, or high risk of bias, or - if not applicable - no information, when not enough information was available. Determining the overall risk of bias in each study, we put special emphasis on the domains comprising study confounding, statistical analysis/reporting and study participation. We defined low risk of bias as the

statistical analysis including a minimal adjustment set (including age, sex, BMI, and at least one comorbid condition), moderate if one of the aforementioned confounders was missing, and high if more than one of the aforementioned confounders was missing and/or univariate analyses were performed. Studies were rated as high risk of bias if one of these domains was rated as high risk of bias. Studies were rated as low risk of bias, if all domains were rated as low risk of bias, or if confounding and statistical analysis/reporting were low risk of bias, and none of the other domains were rated as high risk of bias. In other cases, studies were rated as moderate risk of bias.

Certainty of Evidence

The certainty of evidence is defined as the "amount of confidence that a risk estimate of an association is correct or adequate to support a specific decision or recommendation". Two investigators assessed the certainty of the evidence of the associations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (89). The domains included in the GRADE tool are study design, risk of bias, inconsistency, indirectness, imprecision, publication bias, the magnitude of effects, dose–response relations, and the impact of residual confounding.

The certainty of evidence can be rated down by risk of bias, imprecision, inconsistency, indirectness, and publication bias. Risk of bias occurs when the results do not represent the true values due to limitations in the study design (90). Study limitations in observational studies are for example the failure to develop and apply appropriate eligibility criteria, flawed measurement of both exposure and outcome, and incomplete follow-up (91). The failure to adequately control confounding is another important factor that enhances the risk of bias and refers to the failure of accurate measurement of all known prognostic factors and failure to match for prognostic factors as well as the lack of adjustment in statistical analysis (91). Inconsistency refers to the heterogeneity between the studies. Authors may choose to rate down for inconsistency when the point estimates point to different directions and/or the 95% CIs of the different studies do not overlap (90). Criteria for evaluating inconsistency include similarity of point estimates, the extent of overlap of confidence intervals, and statistical criteria including heterogeneity tests such as I^2. The indirectness domain includes the interventions/exposures of interest in the population of interest. Evidence is most certain when studies directly compare these factors, hence certainty can be rated down if for example the population studied is different from those for whom the recommendation applies (90).

Publication bias is the domain that makes inferences about missing evidence (90). Even when individual studies were conducted with high-quality evidence such as randomised trials, publication bias can result in substantial overestimates of effect. Caution is warranted when the available evidence comes from a number of small studies, most of which have been commercially funded. Using the funnel plot, the pattern of data can be examined to identify publication bias (92). Imprecision focuses on the 95% CI around the best estimate of the relative effect (90). If a recommendation or clinical course of action would differ when comparing the upper versus the lower boundary of the Cl which represents the truth, then rating down for imprecision could be considered. At the same time even if Cls appear narrow, when the effects are large and both sample size as well as number of events are modest, then the imprecision rates down the certainty (93).

The certainty of evidence can be rated up for large magnitude of effect, a dose-response gradient, and when residual confounding is taken into consideration (90). The presence of dose-response gradient increases our confidence in the findings of observational studies as it might indicate a cause-effect relationship between exposure and outcome (94). At the same time, with a sufficiently large effect on the outcome given a specific exposure one can reasonably deduce that we are confident that the association is close to the truth (94). Lastly, when confounders are considered when conducting a meta-analysis, which in fact underestimates the effect, then we can rate up the certainty of evidence (94).

The certainty of evidence can be classified as high, moderate, low, or very low. Evidence with a high certainty means that the inclusion of future studies is very unlikely to change the effect estimate, whereas a very low certainty of evidence means that the inclusion of future studies is likely to change the results (95). Moderate certainty means that the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. The definition of GRADE tool also suggests that further research is likely to have an important impact on our confidence in the estimate of effect and therefore change the estimate (95). Low certainty of evidence refers to the case that our confidence in the effect estimate is limited which suggests that the true effect may be substantially different from the estimate of the effect. Hence, any further research is very likely to have an important impact on our confidence in the estimate of effect, therefore increasing the likelihood of changing the estimate (95). Very low certainty of evidence indicates a very uncertain effect estimate that the true effect is likely to be substantially different from the effect estimate (95). Details are listed in Table 7.

Table 7: Certainty of Evidence Assessment using GRADE		
Quality level	**Definition**	**Previous definition**
High	We are very confident that the true effect lies close to that of the estimate of the effect	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	We have very little confidence in the estimate of the effect. The true effect is likely to be substantially different from the estimate of the effect	Any estimate of effect is very uncertain

Definitions of certainty of evidence of the GRADE Tool – modified by Balshem et al (95). GRADE, Grading of Recommendations Assessment, Development and Evaluation

Statistical Analysis

After collecting data of interest from different studies, we conducted meta-analyses separately for COVID-19-related death and COVID-19-related severity. We combined the data collected in the first version with the findings of the updated version. Summary relative risk (SRR) and 95% confidence intervals (Cl) were calculated by random-effects meta-analyses using the DerSimonian and Laird methods. Our analysis plan included the measurement of heterogeneity by calculating I^2. I^2 expresses the proportion of variability in a meta-analysis.

Furthermore, the meta-analyses were stratified by risk of bias due to confounding (low or moderate risk vs high risk of bias). The assessment of publication bias was demonstrated by generating funnel plots and applying Egger's test. For our statistical analysis, we use the Stata software version 15.1

Chapter 3 - Results and Evaluation

Literature Search

The databases used in our research provided in total 16,259 records. Duplicates were excluded and article titles and abstracts of 8,537 studies were screened. Out of these articles, 80 publications were finally included in our work, of which 58 were new publications (6, 84-86, 96-171) (Fig. 1).

Literature Search

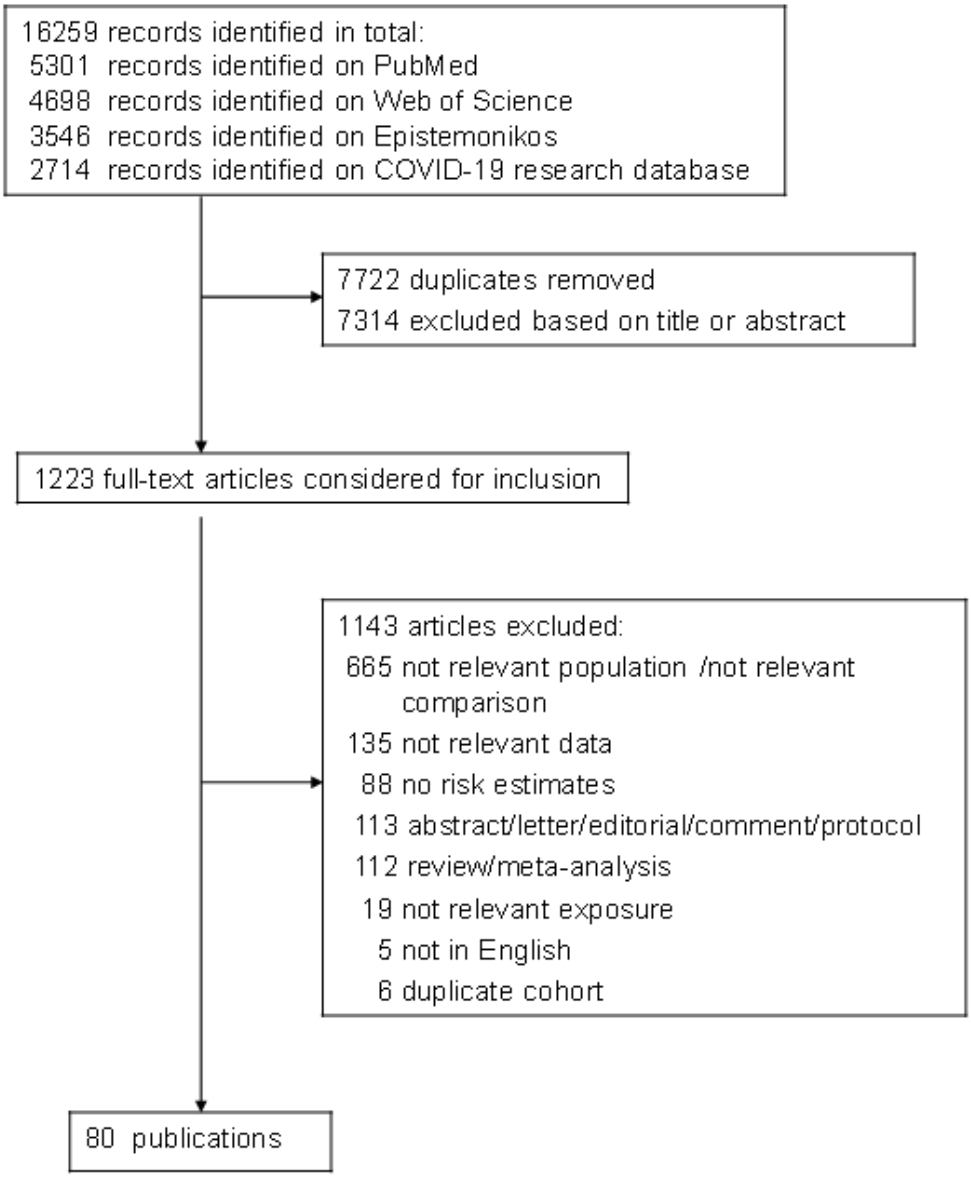


Fig. 1: Literature search flow chart - modified by Schlesinger et al (1)

Characteristics of Included Studies

The studies included 85,771 people with diabetes and confirmed SARS-CoV-2 infection, with COVID-19-related death as the endpoint and 90,869 for COVID-19-related severity (Fig. 2). The smallest study included in our analysis consisted of 24 individuals, and the largest one had 33,492. Using the data from these individuals, 143 meta-analyses were conducted, compared to 77 meta-analyses in our first version, of which 68 had COVID-19-related death and 75 severity as the endpoint. The publications used in our study were mostly conducted (n=43) in Asia (China, n=19; South Korea, n=9; Iran, n=8; Turkey, n=2; Saudi Arabia, n=2; Israel, n=1; India, n=1; Singapore, n=1), whereas 19 studies were undertaken in Europe (France, n=9; UK, n=4; Italy, n=3; Spain, n=3; Belgium, n=1; Sweden, n=1; Romania, n=1) (Fig. 3). Further, 17 studies were included from North America (USA, n=14; Mexico, n=3) and one study was performed in an international setting. The data used in the majority of the studies were collected mainly in a hospital setting based on hospital records (n=66), while some studies were based on data from the registry or insurance (n=14). Regarding the type of diabetes, data from individuals only with T2D were used in 36 publications, 3 only with individuals with T1D, while 14 publications included individuals with both T1D and T2D. In 27 studies, the types of diabetes that were included were not specified (Fig. 4). Further details regarding the characteristics of the studies are shown in Table 8.

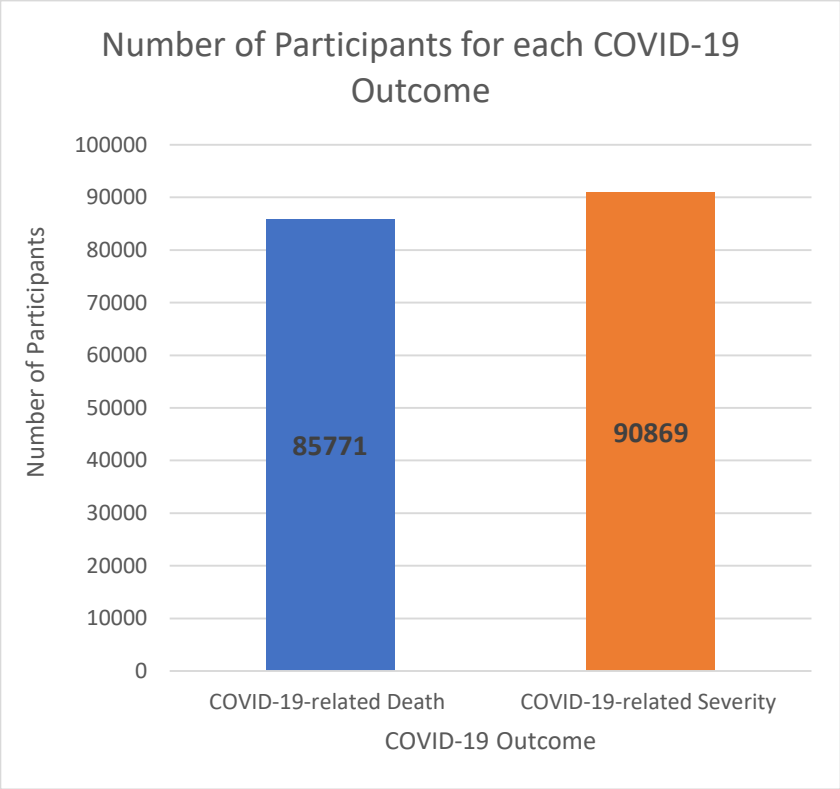


Fig. 2: Number of participants for each COVID-19 outcome (own work)

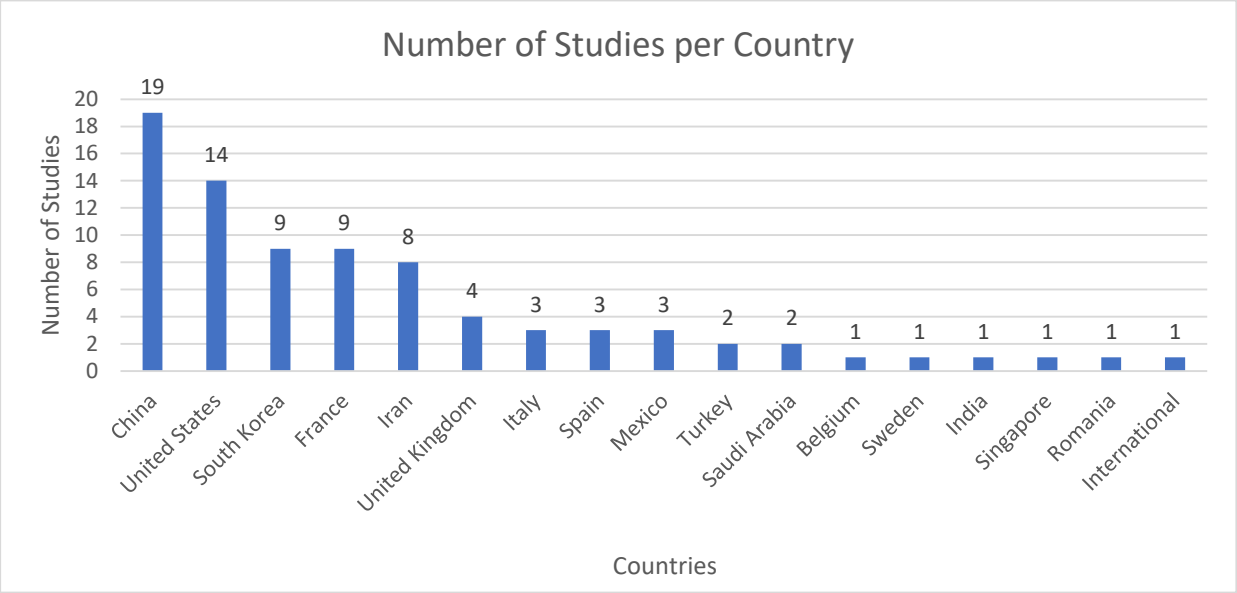


Fig. 3: Number of studies from different countries (own work)

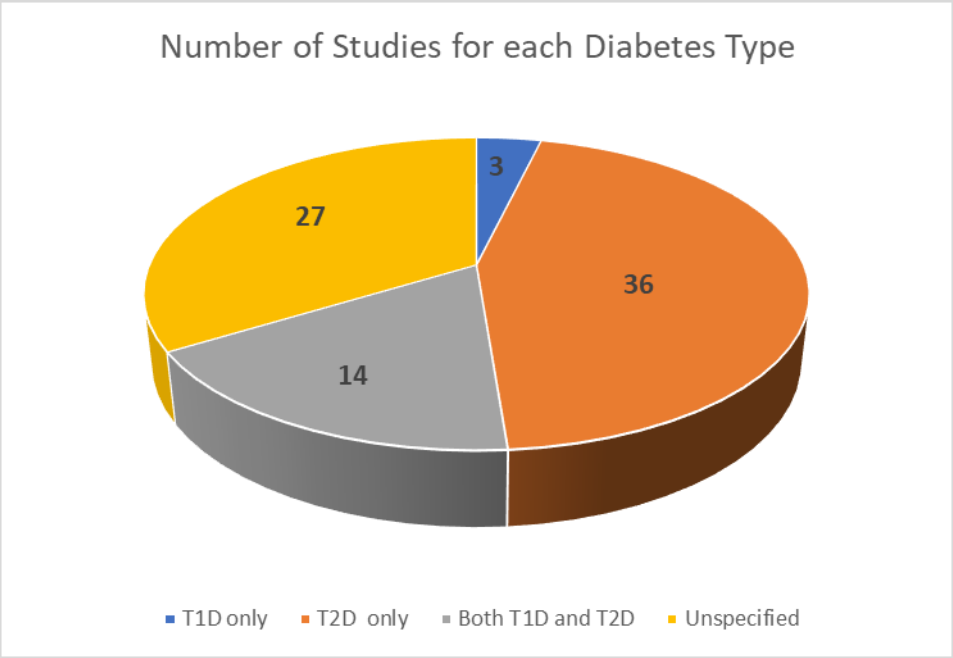


Fig. 4: Number of studies for each type of diabetes (own work)

Risk of Bias of the Included Studies

Using the QUIPS tool to assess the risk of bias in the studies that were included in our analyses, we concluded that n=17 studies had a low RoB, n=31 a moderate RoB, n=31 a high RoB, and n=1 had an unclear RoB, as shown in Fig. 5. The primary causes that led to a high RoB were an insufficient adjustment for confounding factors and/or inappropriate statistical analysis and reporting of the findings (Fig. 6). Studies that were rated as high risk of bias due to insufficient adjustment for confounding factors did not consider important confounders like age, sex, BMI/overweight/obesity, and at least on comorbid condition. Even though age and sex were considered in about 70 studies, the inclusion of all of the important confounders mentioned above was lacking. The estimates of these studies could therefore be overestimated. Appropriate statistical analyses include multivariable logistic regression or Cox proportional hazard model, as well as Weibull analysis. Most of the studies that performed with a low risk of bias conducted multivariable logistic regression, whereas the studies with a high risk of bias used univariate (unadjusted) methods or stepwise model selection, which were not adequate as a statistical model (172). Therefore, a multivariable regression allows us to have a different view of the relationship between the various variables and the outcome, hence comparisons can be more accurate.

Study Assessment for Risk of Bias Using QUIPS

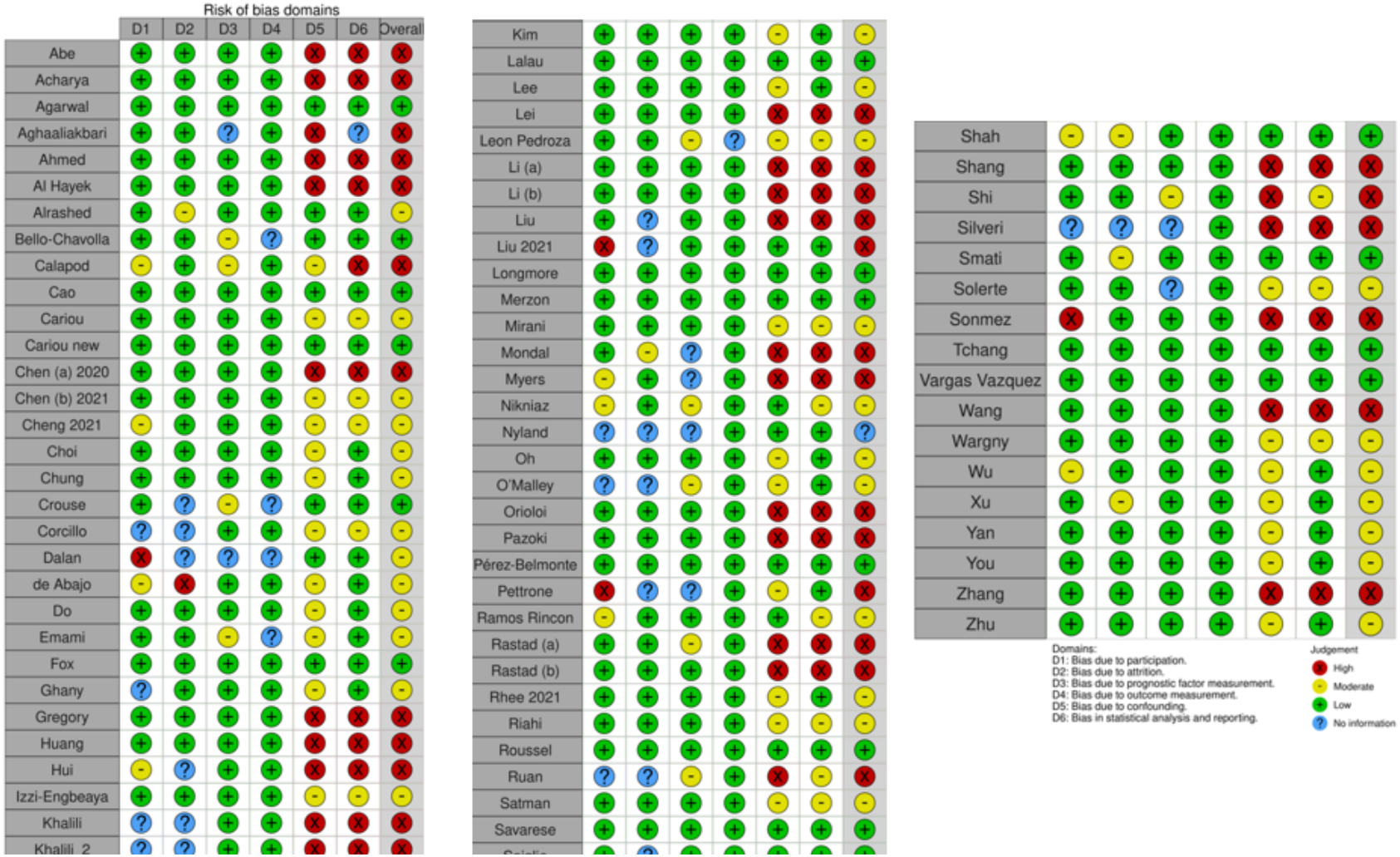


Fig. 5: Risk of bias of each study for each domain and overall - modified by Schlesinger et al (1)

Judgement Categories of Risk of Bias for Each QUIPS Domain

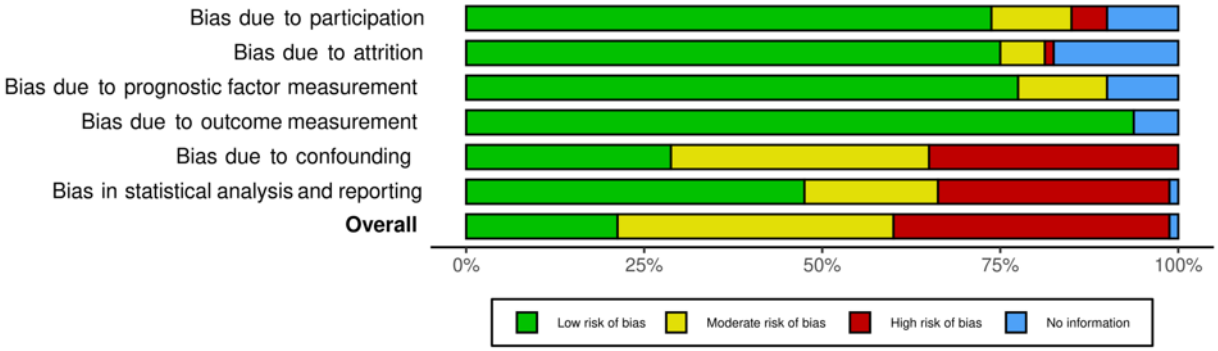


Fig. 6: Overall risk of bias and risk of bias judgements for each domain - modified by Schlesinger et al (1)

Table 8: Characteristics of Included Studies								
Author, year	**Country, setting, time period**	**Sex, mean age, type of diabetes**	**Number of participants / number of cases**	**Outcome**	**Outcome assessment**	**Relevant exposure**	**Exposure assessment**	**Considered important confounders**
Abe, 2020 (84)	USA, hospital-based	m/w, 56 years, ND	N=71/S: n= 52	Severe COVID (Composite ardiovascular complications)	Electronic medical records	General Factors, Diabetes-specific factors	Medical records	no
Acharya, 2020 (96)	South Korea, hospital-based	m/w, 69.8 years, T2D	N=55/ D: n=11	Death	Medical records	General Factors, Diabetes-specific factors, Comorbidities, Laboratory markers	Medical records	no
Agarwal, 2020 (97)	USA, hospital-based	m/w, 67.9 years, T1D + T2D	N=1279/ D: n=394	Death	Electronic health records	Diabetes-specific factors, Comorbidities	Electronic health records	yes
Aghaaliakbari, 2020 (98)	Iran, hospital-based	m/w, 64.4 years, ND	N=153/ D: n=40	Death	Medical records	General Factors, Diabetes-specific factors, Comorbidities, Other medication use	Medical records	no
Ahmed, 2021 (99)	UK, hospital-based	m/w, 76 years, T1D + T2D	N=140/ D: n=42	Death	Electronic medical records	General Factors, Diabetes-specific factors, Comorbidities	Electronic medical records	no
Alrashed, 2021 (101)	Saudi Arabia, hospital-based	m/w, 46.9 years (for the entire population, na for	N=126/ S: n= 103	Severe COVID	Electronic medical records	Other medication use	Electronic medical records	partly

		participants with diabetes), ND						
Al Hayek, 2020 (100)	Saudi Arabia, Hospital-based	m/w, 57.6 years, T2D	N=806/ S: n=387	Severe COVID (Hospitalisation)	Electronic medical records	General Factors, Diabetes-specific factors, Comorbidities	Electronic medical records	no
Bello-Chavolla, 2020 (102)	Mexico, National register data	m/w, 57.2 years, ND	N=9460 / D: n=2062	Death	Open source dataset of the General Directorate of Epidemiology of the Mexican Ministry of Health	General Factors, Comorbidities	Open-source dataset of the General Directorate of Epidemiology of the Mexican Ministry of Health	yes
Calapod, 2021 (103)	Romania, hospital-based	m/w, 66.3 years, T2D	N=138/ S: n=88	Severe COVID	Medical records	General Factors	Medical records	no
Cao, 2021 (104)	China, hospital-based	m/w, ND, ND	N=231/ ND	Severe COVID (severe pneumonia)	Electronic medical records	General Factors	Electronic medical records	yes
Cariou, 2020 (a) (106)	France,Hospital-based	m/w, 69.8 years, T1D + T2D	N=1317/D: n=140, S: n=382	Death, severe COVID (MV and/or death)	Medical files	General Factors, Diabetes-specific factors, Comorbidities, Other medication use, Laboratory markers	Medical files, if needed, general or specialist practitioner, regular pharmacist or biomedical laboratory	partly

Cariou, 2020 (b) (173)	France, hospital-based	m/w, 70.9 years, T2D	N=2449/D: n= 514	Severe COVID (MV and/or death)	Medical files	Other medication use	Medical files, if needed, general or specialist practitioner, regular pharmacist or biomedical laboratory	yes
Chen, 2020 (a) (174)	China, hospital-based	m/w, 66.0 years, ND	N=136/ D: n= 26, S: n= 93	Death, severe COVID (poor prognosis)	Electronic medical records, CT, evaluation by experienced clinicians	General Factors, Diabetes-specific factors, Comorbidities, Other medication use, Laboratory markers	Electronic medical records	no
Chen, 2020 (b) (107)	China, hospital-based	m/w, 63.4 years, T2D	N=138 /D: n=49	Death	Electronic medical records	Comorbidities, Laboratory markers	Electronic medical records	partly
Cheng, 2020 (109)	China, hospital-based	m/w, 63 years, T2D	N=103/ ND	Severe COVID	Electronic medical records	Diabetes-specific factors	Electronic medical records	partly
Choi, 2020 (175)	Korea, Health insurance data	m/w, ND, T1D + T2D	N=566/ D: n=68,S: n= 94	Death, severe COVID (Severe COVID or death)	HIRA database	Other medication use	HIRA database	partly
Chung, 2020 (111)	Korea, hospital-based	m/w, 66.3 years, ND	N=29/S: n=13	Severe COVID (Severe and critical outcome)	Electronic medical records	General Factors, Diabetes-specific factors	Electronic medical records	partly
Corcillo, 2020 (176)	UK, hospital-based	m/w, 68 years, T1D + T2D	N=187/S: n= 49	Severe COVID (Intubation)	Hospital medical records	Comorbidities	NHS Diabetic Eye Screening data	partly
Crouse, 2020 (113)	USA, hospital-based	m/w, ND, T1D + T2D	N=239 /deaths: n=45	Death	Electronic medical records	General Factors, Diabetes-specific factors	Electronic medical records	yes

Dalan, 2020 (177)	Singapore, hospital-based	m/w, ND, T2D	N=76/ ND	Severe COVID (MV)	Medical records	Diabetes-specific factors	Medical records	partly
de Abajo, 2020 (178)	Spain, hospital-based	m/w, 69.1 years (for the entire population, na for participants with diabetes), ND	N=1440/S: n= 182	Severe COVID (Admission to hospital)	Electronic primary health-care records	Other medication use	Hospital medical records	partly
Do, 2020 (179)	Korea, Health insurance data	m/w, 61 years, T2D	N=1865/ D: n= 150, S: n=85	Death, severe COVID (MV)	HIRA database	Analyses for death: Comorbidities Analyses for MV: General Factors, Diabetes-specific factors, Comorbidities	HIRA database	partly
Emami, 2021 (117)	Iran, hospital-based	m/w, 61.3 years, ND	N=458/ D: n= 50	Death	Hospital medical records	General Factors , Comorbidities	Hospital medical records	partly
Fox, 2020 (6)	USA, hospital-based	m/w, 66.4 years, ND	N=166/ D: n=45	Death	Hospital medical records	General Factors, Comorbidities	Hospital medical records	yes
Ghany, 2021 (118)	USA, hospital-based	m/w, ND, ND	N=593/ D: n=59, S: n=102	Death, severe COVID (ARDS)	Electronic medical records	Diabetes-specific factors	Electronic medical records	partly
Gregory, 2020 (85)	USA, hospital-based	m/w, 32 years, T1D	N=37/S: n=9	Severe COVID	Electronic medical records	General Factors, Diabetes-specific factors, Comorbidities,	Electronic medical records	no

						Other medication use		
Huang, 2020 (119)	China, hospital-based	m/w, 66 years, ND	N=256/ D: n= 54, S: 107	Death, severe COVID	Electronic medical records	Analyses for death: General Factors, Comorbidities, Laboratory markers Analyses for severity: Comorbities, Laboratory markers	Electronic medical records	no
Hui, 2020 (120)	China, hospital-based	m/w, 71 years, ND	N=55/ D: n= 44	Death	Electronic medical records	General Factors, Diabetes-specific factors	Electronic medical records	no
Izzi-Engbeaya, 2020 (121)	UK. hospital-based	m/w, 68.5 years, T1D + T2D	N=337/ S: n= 48	Severe COVID (Death/ICU)	Electronic medical records	General Factors, Diabetes-specific factors, Comorbidities, Other medication use, Laboratory markers	Electronic medical records	partly
Khalili, 2020 (122)	Iran, hospital-based	m/w, 66.4 years, T2D	N=127/ D: n=29	Death	Electronic medical records	General Factors, Diabetes-specific factors, Comorbidities	Electronic medical records	no

Khalili, 2021 (123)	Iran, hospital-based	m/w, 66.4 years, T2D	N=127/S: n= 36	Severe COVID (AKI)	Electronic medical records	General Factors, Diabetes-specific factors, Comorbidities, Other medication use	Electronic medical records	no
Kim, 2020 (124)	Korea, hospital-based	m/w, 68.3 years, ND	N=235/ D: n=44 S: n=65	Death, severe COVID	Electronic medical records	Diabetes-specific factors, Other medication use, Laboratory markers	Electronic medical records	partly
Lalau, 2020 (125)	France, hospital-based	m/w, 70.9 years, T2D	N=2449/S: n=857	Severe COVID (MV and/or death)	Medical files	Diabetes-specific factors	Medical files, if needed, general or specialist practitioner, regular pharmacist or biomedical laboratory	yes
Lee, 2021 (126)	Korea, Health insurance data	m/w, ND, T2D	N=1874/D: n= 133	Death	HIRA database	Other medication use	HIRA database	partly
Lei, 2020 (127)	China, hospital-based	m/w, 62.5 years, T1D + T2D	N=24/S: n= 5	Severe COVID (ICU admission)	Electronic medical records	General Factors, Diabetes-specific factors, Comorbidities, Laboratory markers	Electronic medical records	no
Leon Pedroza, 2021 (128)	Mexico, National register data	m/w, ND, T2D	N=33492/ ND	Death	SISVER	General Factors, Comorbidities	SISVER	partly

Li, 2020 (a) (180)	China, hospital-based	m/w, 65.0 years, T1D + T2D	N=132/D: n= 15, S: n=31	Death, severe COVID (in-hospital complications)	Electronic medical records	General Factors, Diabetes-specific factors, Comorbidities, Laboratory markers	Electronic medical records	no
Li, 2020 (b) (129)	China, hospital-based	m/w, 66.8 years, T2D	N=131/D: n=23	Death	Electronic medical records	Diabetes-specific factors	Electronic medical records	no
Liu, 2020 (a) (181)	China, hospital-based	m/w, 66.0 years, ND	N=64/S: n=12	Severe COVID (MV and/or death)	Electronic medical records	Diabetes-specific factors, Comorbidities, Other medication use, Laboratory markers	Electronic medical records	no
Liu, 2020 (b) (131)	China, hospital-based	m/w, 64.5 years, T2D	N=134/S: n= 82	Severe COVID	Medical records	Laboratory markers	Medical records	no
Longmore, 2021 (133)	International, hospital-based	m/w, ND, T1D + T2D	N=904 for D/ D: n=216 N=654 for MV/ S: n=144	Death, severe COVID (MV)	Electronic medical records	General Factors	Electronic medical records	yes
Merzon, 2020 (182)	Israel, Health insurance data	m/w, 61.8 years, ND	N=183, S: n=46	Severe COVID (Hospitalisation)	LHS electronic medical records	General Factors, Diabetes-specific factors, Comorbidities	LHS electronic medical records	yes

Mirani, 2020 (135)	Italy, hospital-based	m/w, 71 years, T2D	N=90/death: n=38	Death	Electronic medical records	General Factors, Diabetes-specific factors, Comorbidities, Other medication use, Laboratory markers	Electronic medical records	partly
Mondal, 2021 (86)	India, hospital-based	m/w, 59.4 years, T2D	N=196/ S: n= 26	Severe COVID (DKA)	Medical records	General Factors, Diabetes-specific factors	Medical records	no
Myers, 2021 (136)	USA, hospital-based	m/w, 68 years, T2D	N=3846/D: n=953	Death	Medical records	General Factors, Diabetes-specific factors, Comorbidities	Medical records	no
Nikniaz, 2021 (137)	Iran, hospital-based	m/w, 65.1 years, ND	N=317/D: n=67, S: n=71	Death, severe COVID (MV)	Electronic medical records	General Factors	Self-reported	partly
Nyland, 2021 (138)	USA, TriNetX COVID-19 Research Network	m/w, 62.2 years, T2D	N=12954/ death: n= 1067, S: n=3403	Death, severe COVID (Respiraroty complications)	TriNetX COVID-19 Research Network	Diabetes-specific factors	TriNetX COVID-19 Research Network	No information
Oh, 2020 (139)	Korea,Health insurance data	m/w, ND, T2D	N=2047/ D: n= 174	Death	NHIS-COVID-19 cohort database	General Factors, Diabetes-specific factors, Comorbidities	NHIS-COVID-19 cohort database	partly
O'Malley, 2020 (183)	USA, hospital-based	m/w, 39.9 years, T1D	N=113/S: n= 58	Severe COVID (Hospitalisation)	Electronic medical records	General Factors, Diabetes-	Electronic medical records	partly

						specific factors, Comorbidities		
Orioli, 2020 (141)	Belgium, hospital-based	m/w, 67 years, T1D+T2D	N=64/D: n=10	Death	Electronic medical records	General Factors, Comorbidities, Other medication use	Electronic medical records	no
Pazoki, 2021 (142)	Iran, hospital-based	m/w, 65 years, ND	N=176 /D: n= 54	Death	Electronic medical records	General Factors, Comorbidities, Laboratory markers	Electronic medical records	no
Perez-Belmonte 2020 (143)	Spain, hospital-based	m/w, 74.9 years, T2D	Metformin: N=498/D: n=158, S: n=179 DPP-4 i: N=210/ D: n=85, S: n=87 Insulin: N= 258 / D: n=97, S: n= 111	Death, Severe COVID (ICU, MV or death)	SEMI-COVID-19 Registry	Diabetes-specific factors	SEMI-COVID-19 Registry	yes
Pettrone, 2021 (144)	USA, hospital-based	m/w, ND, ND	N=79/S: n=55	Severe COVID (Hospitalisation)	Medical records	Diabetes-specific factors	Medical records	no
Ramos Rincon, 2021 (145)	Spain, hospital-based	m/w, 85.9 years, T2D	N=790/ death: n= 385	Death	SEMI-COVID-19 Registry	Diabetes-specific factors, Other medication use	SEMI-COVID-19 Registry	partly
Rastad, 2020 (a) (184)	Iran, hospital-based	m/w, 54.8 years (for the entire population, ND for participants with diabetes), ND	N=267/ ND	Death	Electronic medical records	Laboratory markers	Electronic medical records	no

Rastad, 2020 (b) (146)	Iran, hospital-based	m/w, 63.8 years, ND	N=455/ D: n= 79, S: n=65	Death, severe COVID (Ventilation)	Electronic medical records	General Factors, Diabetes-specific factors, Comorbidities, Other medication use	Electronic medical records	no
Rhee, 2021 (148)	Korea, Health insurance data	m/w, 61.8 years, ND	N=832/ S: n=34	Severe COVID (Intensive care or death)	HIRA database	Other medication use	HIRA database	partly
Riahi, 2020 (149)	USA, hospital-based	m/w, 66.4 years, T1D+T2D	N=166/ D: n= 45	Death	Hospital medical records	Diabetes-specific factors	Hospital medical records	partly
Roussell, 2021 (150)	France, hospital-based	m/w, 70.9 years, T2D	N=2449/ D: n=512, S: n=857	Death, severe COVID (MV and/or death)	Medical files	Diabetes-specific factors	Medical files, if needed, general or specialist practitioner, regular pharmacist or biomedical laboratory	yes
Ruan, 2021 (151)	UK, hospital-based	m/w, 62 years, T1D	N=196/ D: n= 53, S: n=68	Death, severe COVID (Death/ ICU)	Elecronic medical records	General Factors, Diabetes-specific factors, Comorbidities, Other medication use	Electronic medical records	no
Satman, 2021 (152)	Turkey, National register data	m/w, 53 years, T2D	N=18658/D: n= 1162, S: n=8172	Death, severe COVID (Hospitalsiation)	National COVID-19 registry of the Turkish Ministry of Health	General Factors, Diabetes-specific factors, Comorbidities, Other medication use	National COVID-19 registry of the Turkish Ministry of Health	partly

Savarese, 2020 (153)	Sweden, National register data	m/w, 72 years (for the entire population, ND for participants with diabetes), T1D + T2D	N=2692/ D: n= 846	Death	Cause of Death Registry	Other medication use	Swedish National Patient Registry	yes
Seiglie, 2020 (154)	USA, hospital-based	m/w, 66.7 years, ND	N=168/D: n=28, S: n=66	Death, severe COVID (MV)	Manual chart review	General Factors, Diabetes-specific factors	Manual chart review and Enterprise Data Warehouse (EDW)	yes
Shah, 2020 (155)	USA, hospital-based	m/w, 60.1 years (for the entire population, na for participants with diabetes), ND	N=228/ ND	Death, severe COVID (Death, new dialysis requirement, MV or ICU care)	Electronic medical records	Other medication use	Electronic medical records	yes
Shang, 2020 (156)	China, hospital-based	m/w, 59.0 years (for the entire population, na for participants with diabetes), ND	N=84/D: n=17	Death	Electronic medical records	Diabetes-specific factors	Electronic medical records	no
Shi, 2020 (185)	China, hospital-based	m/w, 64.0 years, ND	N=153/ D: n=31	Death	Electronic medical records	General Factors, Diabetes-specific factors, Comorbidities, laboratory parameters	Electronic medical records	no
Silverii, 2020 (158)	Italy, hospital-based	m/w, 73.3 years, T2D	N=159/ D: n= 59	Death	Electronic medical records	Diabetes-specific factors	Electronic medical records	no
Smati, 2020 (159)	France, hospital-based	m/w, 70.1 years, T2D	N=1965/D: n=190, S: n=546	Death, severe COVID (IMV or death)	Medical files	General Factors	Medical files, if needed, general or specialist practitioner, regular pharmacist or biomedical laboratory	yes

Solerte, 2020 (160)	Italy, hospital-based	m/w, 69.0 years, T2D	N=338/ D: n= 94, S: n=23	Death, severe COVID (MV)	Electronic medical records	General Factors, Diabetes-specific factors, Comorbidities, Other medication use	Electronic medical records	partly
Sonmez, 2021 (161)	Turkey, National register data	m/w, 61 years, T2D	N=9213/ S: n= 2065	Severe COVID (ICU admission)	National COVID-19 registry of the Turkish Ministry of Health	General Factors	National COVID-19 registry of the Turkish Ministry of Health	no
Tchang, 2021 (162)	USA, hospital-based	m/w, ND, ND	N=1134/ S: n=476	Severe COVID (Death/ ICU)	Electronic medical records	General Factors	Electronic medical records	yes
Vargas Vazquez, 2021 (163)	Mexico hospital-based	w/m, 57 years, T2D	N=109/ D: n= 34, S: n=52	Death, severe COVID	Electronic medical records	Diabetes-specific factors	Electronic medical records	yes
Wang, 2020 (164)	China, hospital-based	m/w, 66 years, T2D	N=67, S: n=51	Severe COVID (Poor therapeutic effect)	Electronic medical records	General Factors, Comorbidities	Electronic medical records	no
Wargny, 2021 (165)	France, hospital-based	m/w, 69.7 years, T1D + T2D	N=2796/ D: n= 577,S: n=800	Death, Severe COVID	Medical files	General Factors, Diabetes-specific factors, Comorbidities, Laboratory markers	Medical files, if needed, general or specialist practitioner, regular pharmacist or biomedical laboratory	partly

Wu, 2021 (166)	China, hospital-based	m/w, 59 years, T2D	N=946/ death: n= 106	Death	Electronic medical records	Comorbidities	Electronic medical records	partly
Xu, 2020 (167)	China, hospital-based	m/w, 66.0 years, T2D	N=114/ D: n=27	Death	Electronic medical records	Diabetes-specific factors	Electronic medical records	partly
Yan, 2020 (168)	China, hospital-based	m/w, ND, T2D	N=58/ S: n=21	Severe COVID	Electronic medical records	Diabetes-specific factors	Electronic medical records	partly
You, 2020 (169)	Korea, Health insurance data	m/w, ND, T2D	N=495/ ventilation: n=9, oxygen therapies: n=68, ICU admission: n=33	Severe COVID (Ventilation, oxygen therapy, ICU admission)	HIRA database	Diabetes-specific factors	HIRA database	partly
Zhang, 2020 (170)	China, hospital-based	m/w, 65.5 years, T2D	N:52/ S: n=21	Severe COVID	Electronic medical records	General Factors, Diabetes-specific factors, Comorbidities, Laboratory markers	Electronic medical records	no
Zhu, 2020 (171)	China, hospital-based	m/w, 62.7 years, T2D	N=810/ D: n=61, S: n=133	Death, severe COVID (ARDS)	Electronic medical records	Diabetes-specific factors	Electronic medical records	partly

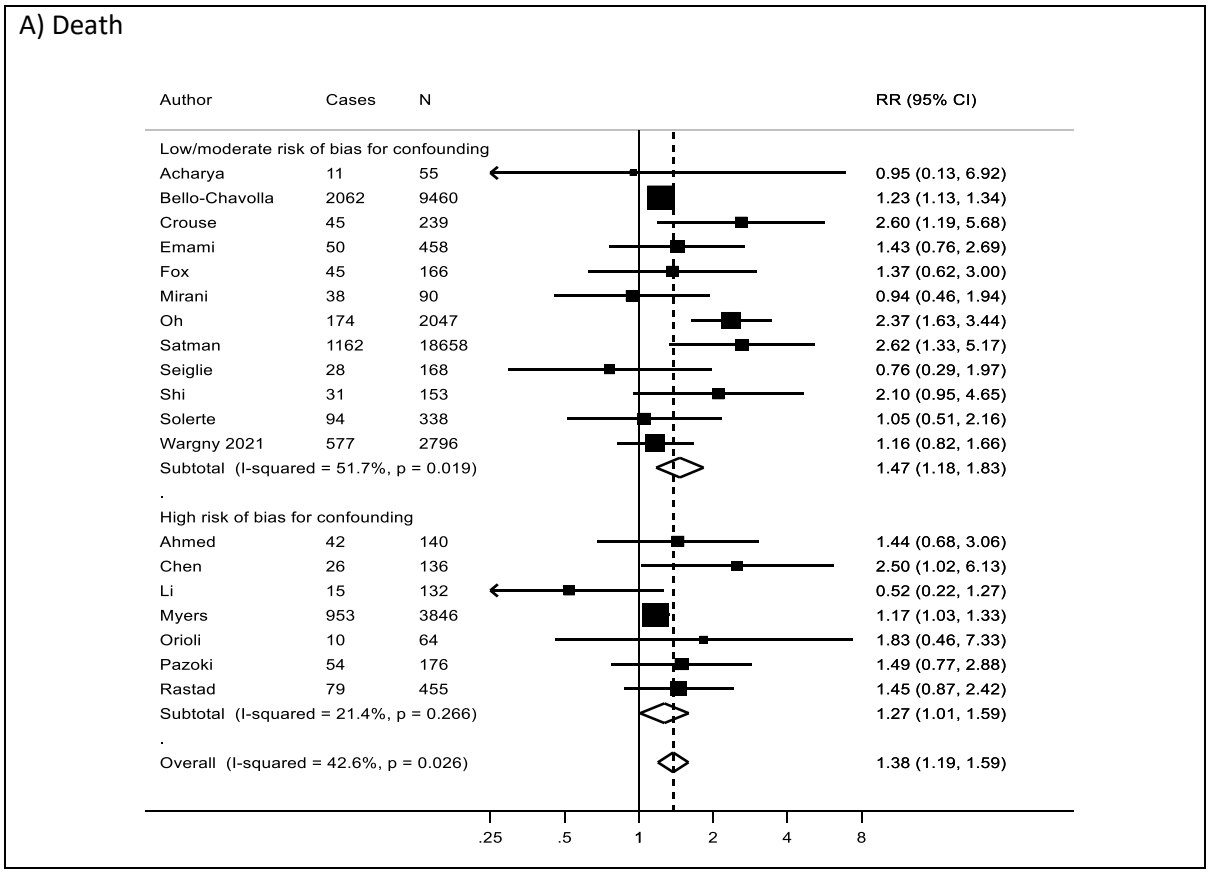
ND – not defined , *D= death, S= severity*

Considered important confounders: yes: minimal adjustment set (including age, sex, BMI, and at least one comorbid condition), partly: if one of the aforementioned confounders was missing, high: if more than one of the aforementioned confounders was missing and/or univariate analyses were performed – modified by Schlesinger et al (1)

General Risk Factors and COVID-19-Related Death and COVID-19-Related Severity in Individuals with Diabetes and COVID-19

Male sex compared to female sex was associated with an increased risk of COVID-19-related death (SRR: 1.38 [95% CI: 1.19, 1.59]; *n*=19 studies) with high certainty of evidence (Fig. 7). Similar results were observed for the outcome COVID-19-related severity (SRR: 1.24 [95% CI: 1.12, 1.39]; *n*=28 studies) but with moderate certainty of evidence. Moreover, the heterogeneity of studies for COVID-19-related severity was lower compared to COVID-19-related death (I^2 severity: 27%, I^2 death: 43%).

Meta-Analysis of Sex and COVID-19 Outcomes



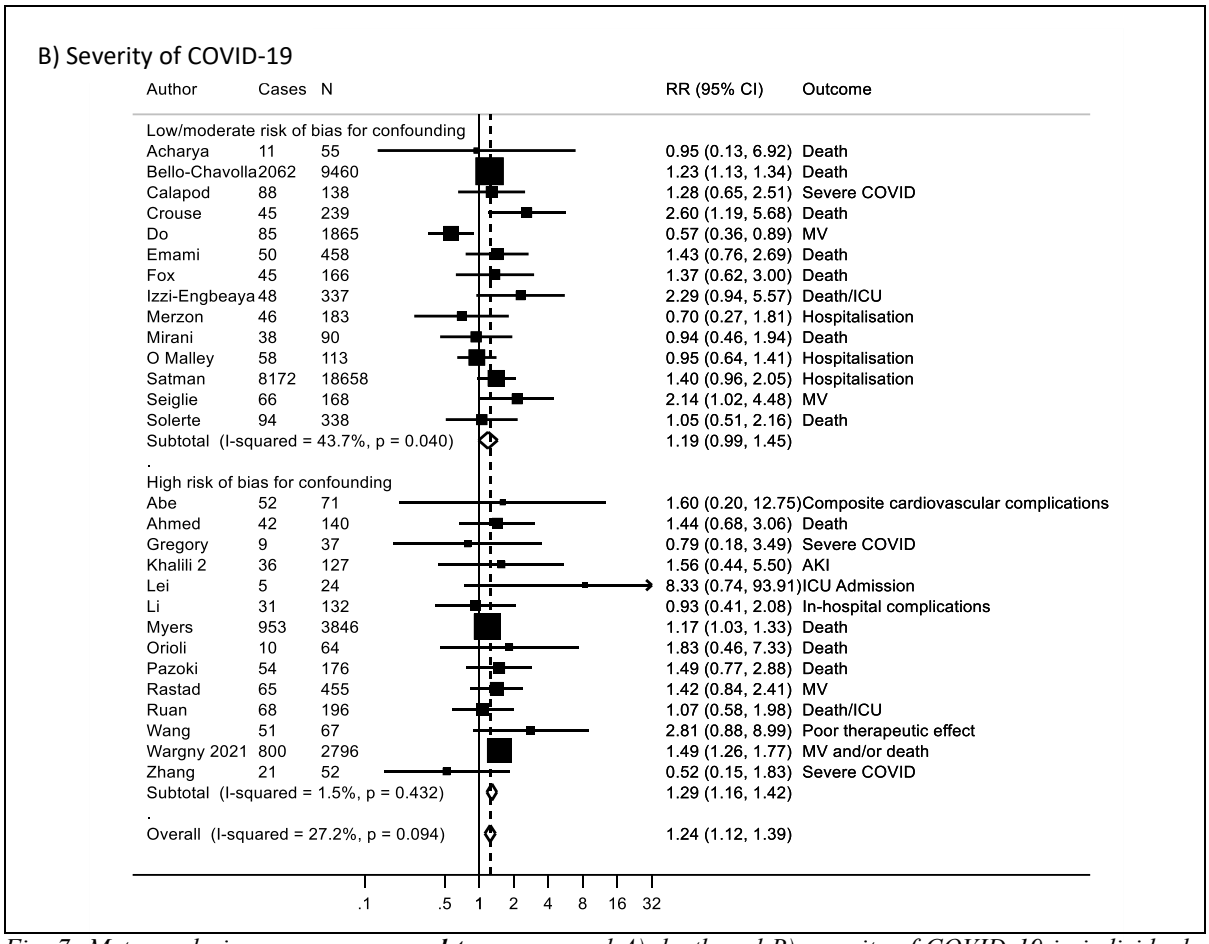


*Fig. 7: Meta-analysis on **men compared to women** and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

A factor that contributed to more than a two-fold risk to COVID-19-related death with high certainty of evidence was older age (≥65 years) (SRR: 2.67 [95% CI: 1.73, 4.12]; *n*=10 studies) when compared to individuals younger than 65 years old (Fig. 8). For every increase of 5 years, there is an approximate increase of 26% for COVID-19-related death (SRR: 1.26 [95% CI: 1.15, 1.38]; *n*=12 studies) (Fig. 30).

Regarding COVID-19-related severity, similar associations were observed and more specifically age ≥65 years (SRR: 1.92 [95% CI: 1.42, 2.61]; *n*=11 studies) was associated with the outcome with high certainty of evidence and every 5 years increase of age increased the relative risk by 22% (SRR: 1.22 [95% Cl: 1.11, 1.28]; n=18) with moderate certainty of evidence (Fig. 8, Fig. 31).

Meta-Analysis of Age >65 years Old and COVID-19 Outcomes

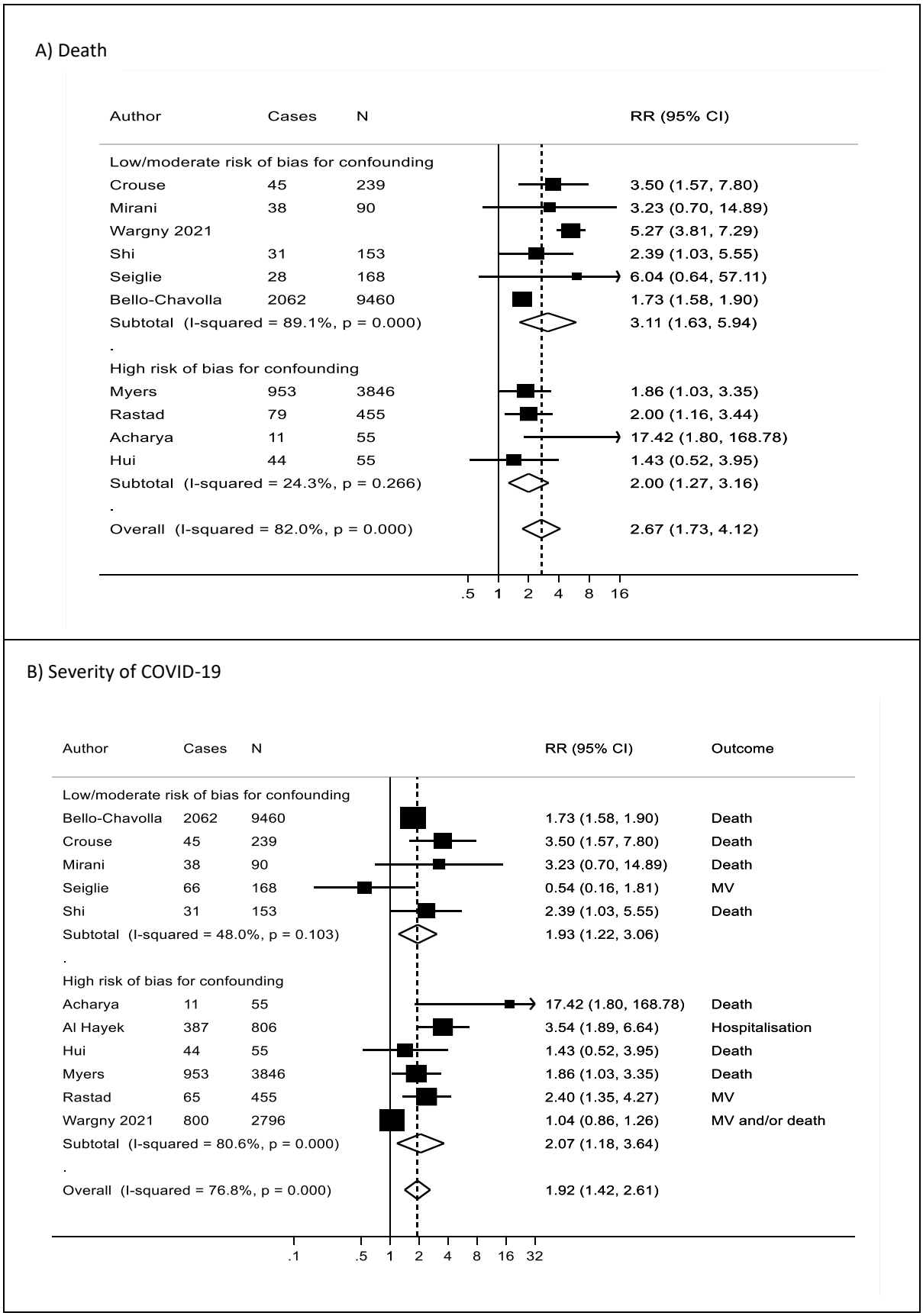


*Fig. 8: Meta-analysis on **age ≥65 years** and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

Furthermore, obesity in patients with diabetes was related to increased susceptibility to COVID-19-related death, and patients were exposed to 54% increased relative risk for this adverse outcome (SRR: 1.54 [95% CI: 1.11, 2.15]; *n*=9 studies; high certainty of evidence) (Fig. 9). On the other hand, BMI and smoking showed no clear associations with COVID-19-related death with moderate certainty of evidence (Appendix Fig. 1, Appendix Fig. 2)

Regarding COVID-19-related severity, obesity (SRR: 1.51 [95% CI: 1.19, 1.91]; *n*=13 studies) was associated with the outcome with moderate certainty of evidence (Fig. 9). On the other hand, BMI and overweight yielded no clear results for COVID-19-related severity with moderate certainty of evidence (Appendix Fig. 1, Appendix Fig. 3). The heterogeneity of the results for COVID-19-related death and severity, 60% and 70% respectively, was relatively high. Furthermore, there was evidence of publication bias for obesity with COVID-19-related severity, according to Egger's test, and the funnel plot shows that studies with null or negative findings were missing (Appendix Fig. 4).

Meta-Analysis of Obesity and COVID-19 Outcomes

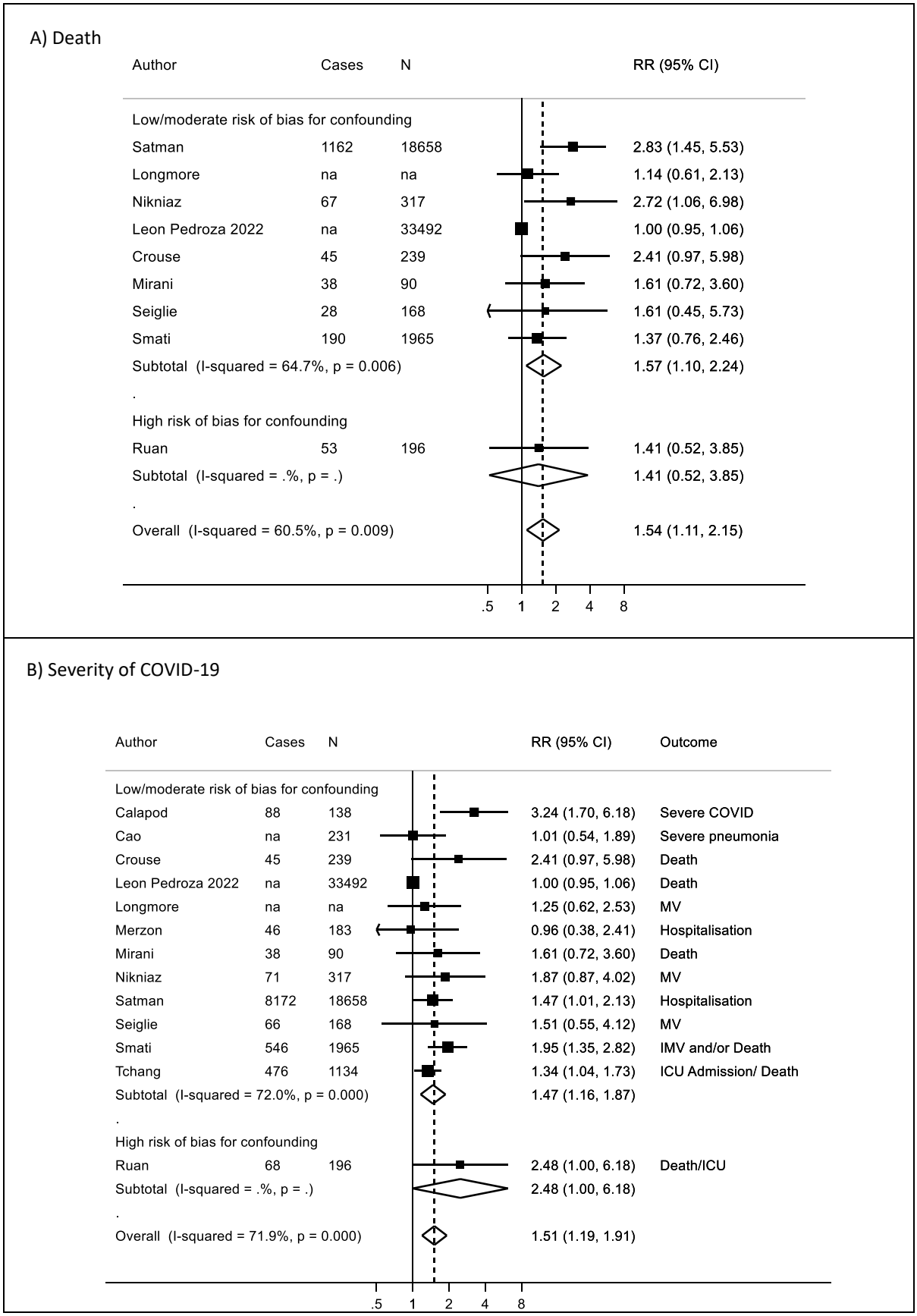


*Fig. 9: Meta-analysis on **obesity** compared to normal weight and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

Diabetes-Specific Risk Factors and COVID-19-Related Death and COVID-19-Related Severity in Individuals with Diabetes and COVID-19

Diabetes-Related Factors

Since the initial review, study scarcity limited the evidence strength on the independent prognostic value of diabetes type (SRR for COVID-19-related death: 1.35 [95% Cl: 0.58, 3.14]; *n*=3 and SRR for COVID-19-related severity (SRR: 1.14 [95% Cl: 0.63, 2.05]; *n*=4) and duration (SRR for COVID-19-related death: 1.47 [95% Cl: 0.16, 13.65]; *n*=2 and for COVID-19-related severity (SRR: 1.01 [95% Cl: 0.95, 1.07]; *n*=4), leading to imprecise estimates and very low certainty of evidence for these associations for both outcomes (Appendix Fig. 5, Appendix Fig. 6)

Diabetes-Related Laboratory Markers

The meta-findings show an association between high blood glucose levels at admission (glucose > 6 mmol/mol) and COVID-19-related death with a high certainty of evidence (SRR: 2.75 [95% Cl: 1.27, 5.97]; *n*=3). High blood glucose at admission (glucose >6 mmol/l) was also associated with COVID-19-related severity with high certainty of evidence (SRR: 2.79 [95% CI: 1.35, 5.75]; *n*=3 studies) (Fig. 10). The heterogeneity for this factor was 0% for both outcomes.

Every increase of blood glucose level was associated with COVID-19-related death and severity with a moderate certainty of evidence (SRR per 1 mmol/l for COVID-19-related death: 1.03 [95% Cl: 1.00, 1.06]; *n*=6 studies and SRR per 1 mmol/l for COVID-19-related severity: 1.03 [95% Cl: 1.00, 1.05]; *n*=8, SRR per 5 mmol/l for COVID-19-related death: 1.15 [95% Cl: 1.01, 1.31]; *n*=6 studies and SRR per 5 mmol/l for COVID-19-related severity: 1.13 [95% Cl: 1.00, 1.29]; *n*=8) (Fig. 11, Fig. 30, Fig. 31).

Meta-Analysis of Blood Glucose at Admission > 6 mmol/l and COVID-19 Outcomes

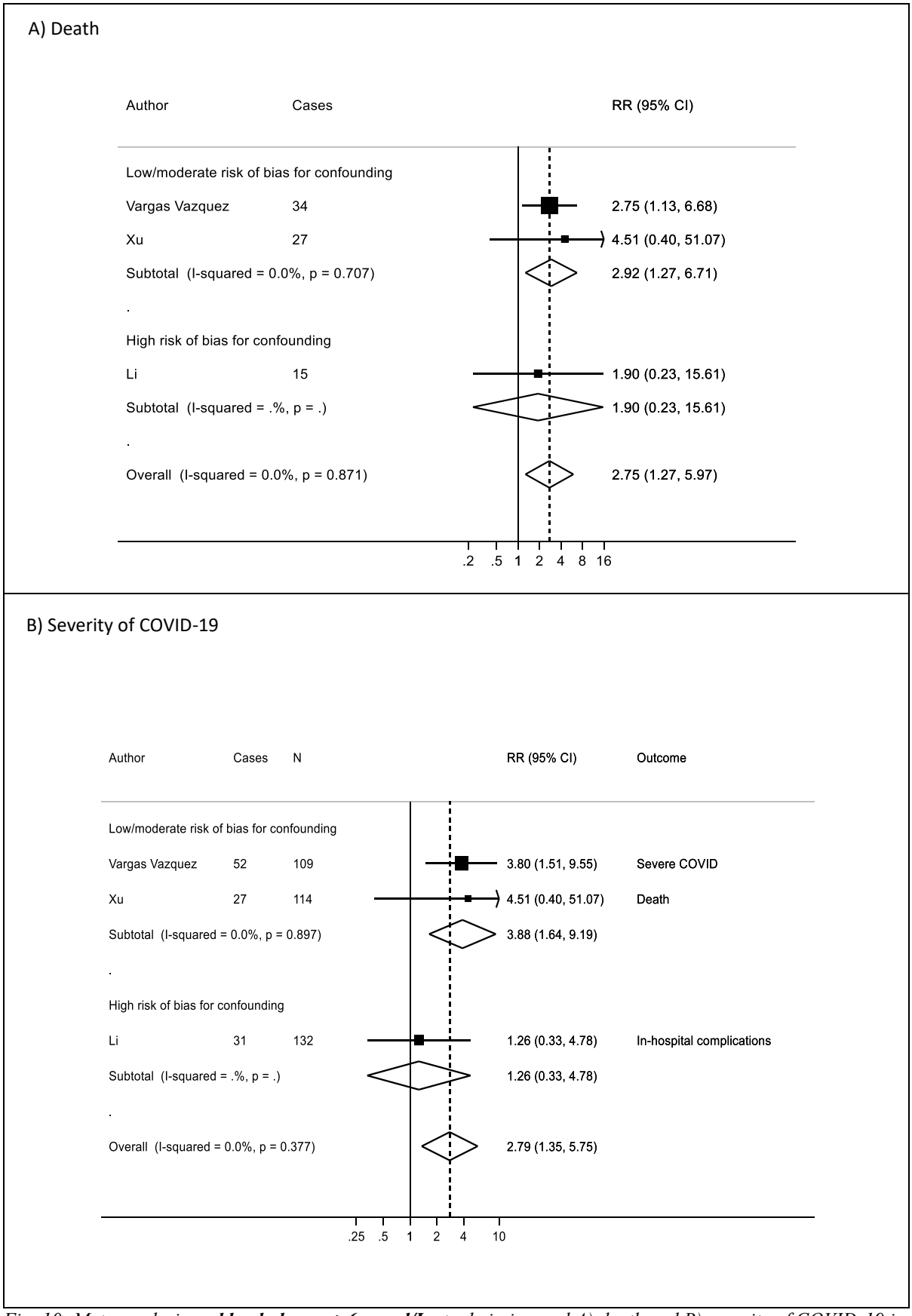


*Fig. 10: Meta-analysis on **blood glucose >6 mmol/L** at admission and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

Meta-Analysis of Blood Glucose Increase per 1 mmol/l and COVID-19 Outcomes

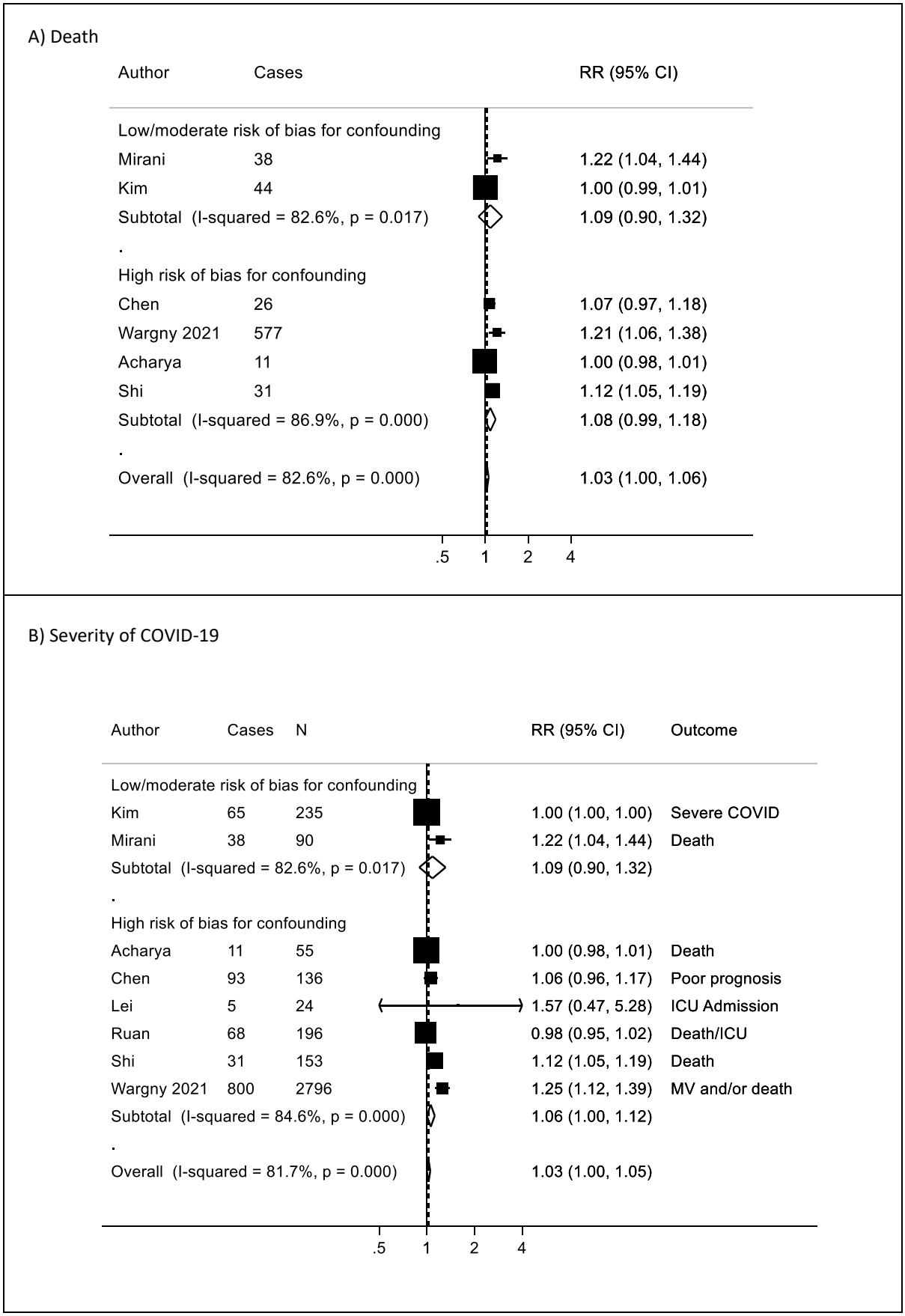
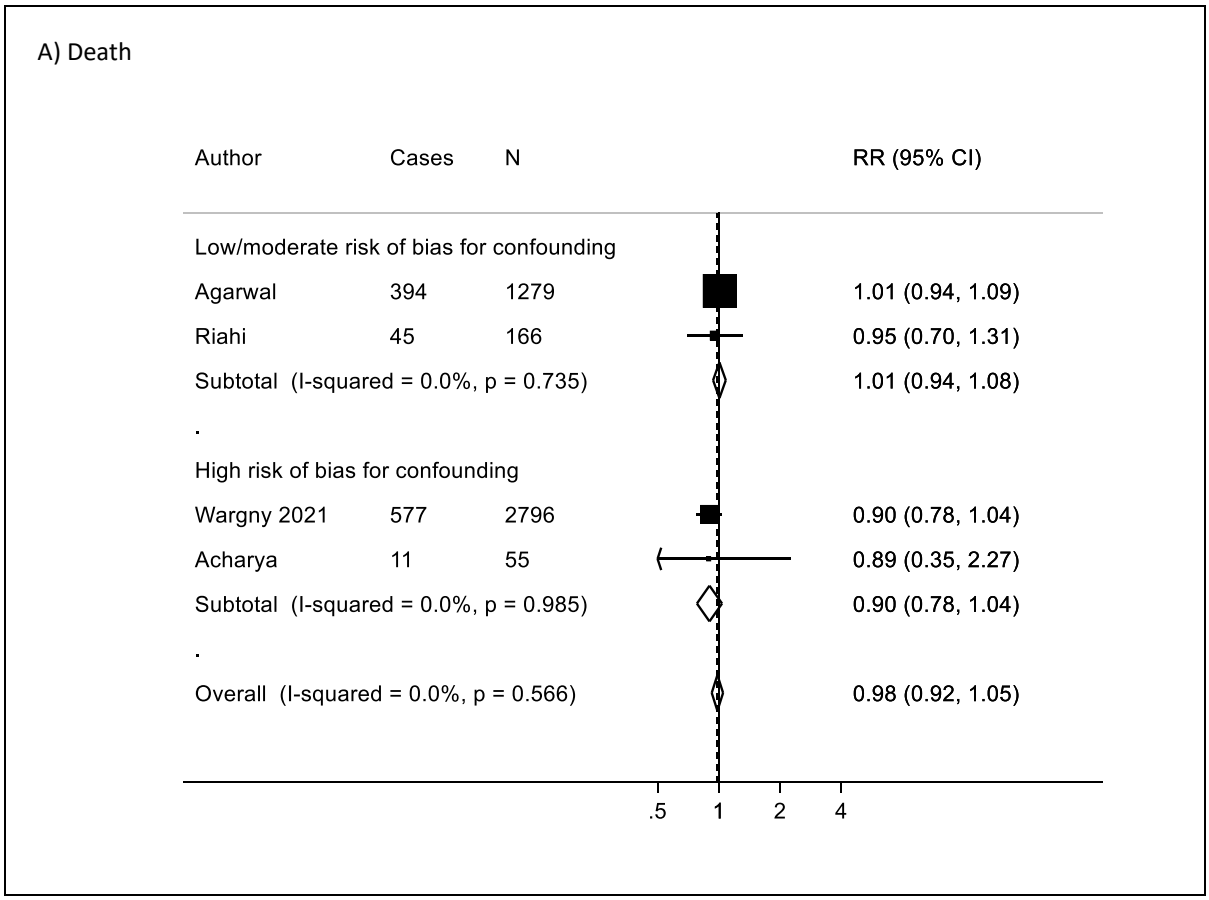


*Fig. 11: Meta-analysis on **blood glucose per 1 mmol/l** increase at admission and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (80)*

Findings on HbA1c differed between COVID-19-related death and severity. Even though higher HbA1c levels were not associated with COVID-19-related death (SRR for an increase per 20 mmol/mol: 0.98 [95% CI: 0.92, 1.05]; *n*=4 studies; high certainty of evidence), an increase per 20 mmol/mol showed a 12% higher relative risk of COVID-19-related severity (SRR for an increase per 20 mmol/mol: 1.12 [95% CI: 1.01, 1.24]; *n*=13 studies; moderate certainty of evidence) (Fig. 12). Even though the heterogeneity for the outcome COVID-19-related death was 0%, it was observed to be around 70% when considering COVID-19 severity. Moreover, Egger's test also suggested publication bias for HbA1c and COVID-19-related severity (Appendix Fig. 7).

Meta-Analysis of HbA1c per 20 mmol/mol and COVID-19 Outcomes



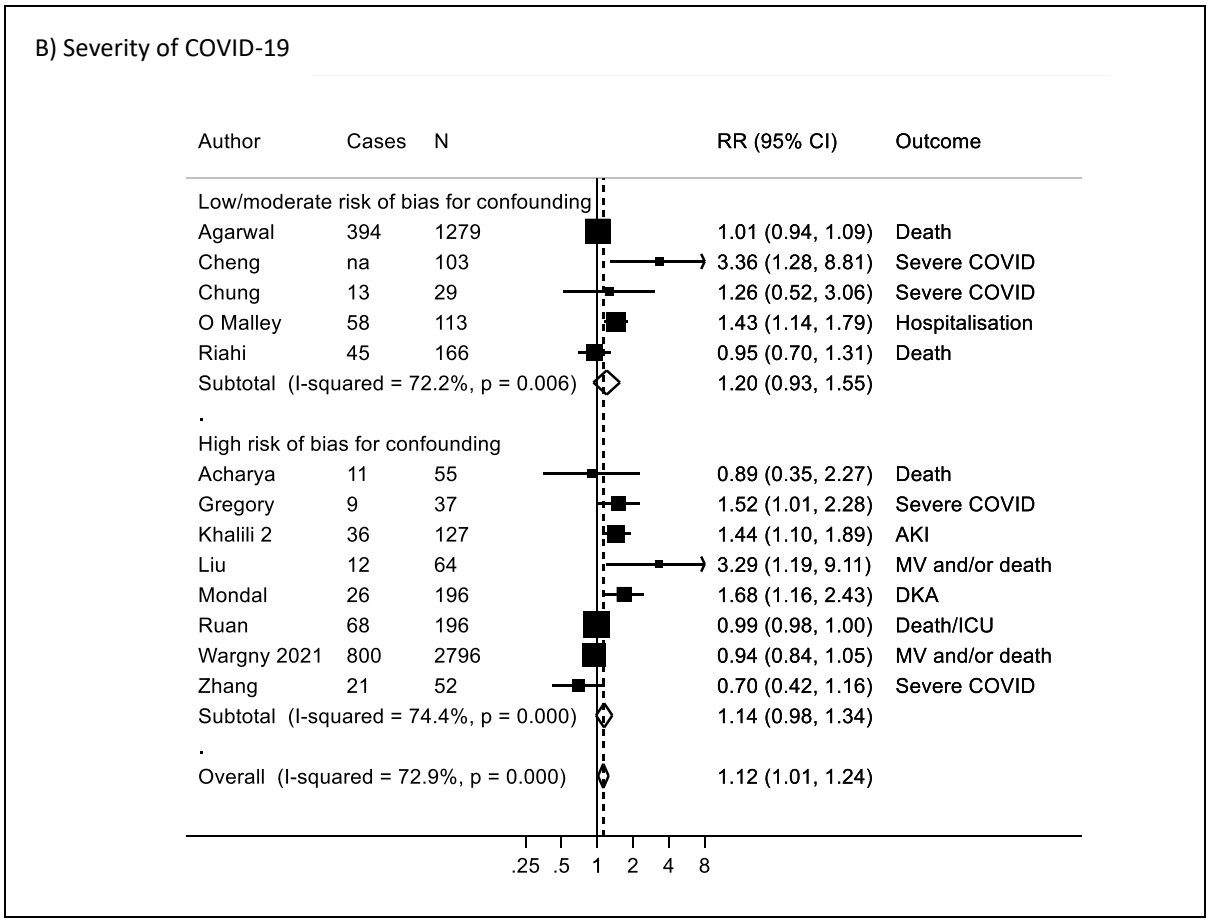


*Fig. 12: Meta-analysis on **HbA1c, per 20 mmol/mol** increase and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (80)*

Glucose-Lowering Medication

Several new studies regarding diabetes treatment have become available since the last published systematic review and meta-analysis. Evidence suggested that insulin use was associated with a 62% increased relative risk of COVID-19-related death (SRR: 1.62 [95% CI: 1.13, 2.33]; *n*=12 studies) (Fig. 13) compared to the individuals not receiving insulin, whereas metformin use was associated with a 32% lower relative risk (SRR: 0.68 [95% Cl: 0.51, 0.89]; *n*=11 studies) both with high certainty of evidence (Fig. 14).

Insulin use was also associated with a higher relative risk of COVID-19-related severity with high certainty of evidence (SRR: 1.49 [95% Cl: 1.12, 1.99]; *n*=16) (Fig. 13). Metformin showed however the opposite relationship with the outcome with moderate certainty of evidence (SRR: 0.75 [95% Cl: 0.58, 0.96]; *n*=15) (Fig. 14). The observations of DPP-4 inhibitors with the endpoint COVID-19-related severity indicated no clear associations with a moderate certainty of evidence (SRR: 0.95 [95% Cl: 0.80, 1.14]; *n*=13) (Appendix Fig. 8).

There were no clear associations between the risk of COVID-19-related death and the other diabetes medications and the certainty of evidence was low or very low (Fig. 30). For example, new evidence depicted that the use of GLP-1-RA was also associated with lower relative risk of COVID-19-related death with a low certainty of evidence (SRR: 0.71 [95% CI: 0.54, 0.94]; *n*=4 studies) when compared to individuals not receiving GLP-1-RA (Appendix Fig. 9).

Meta-Analysis of Insulin Use and COVID-19 Outcomes

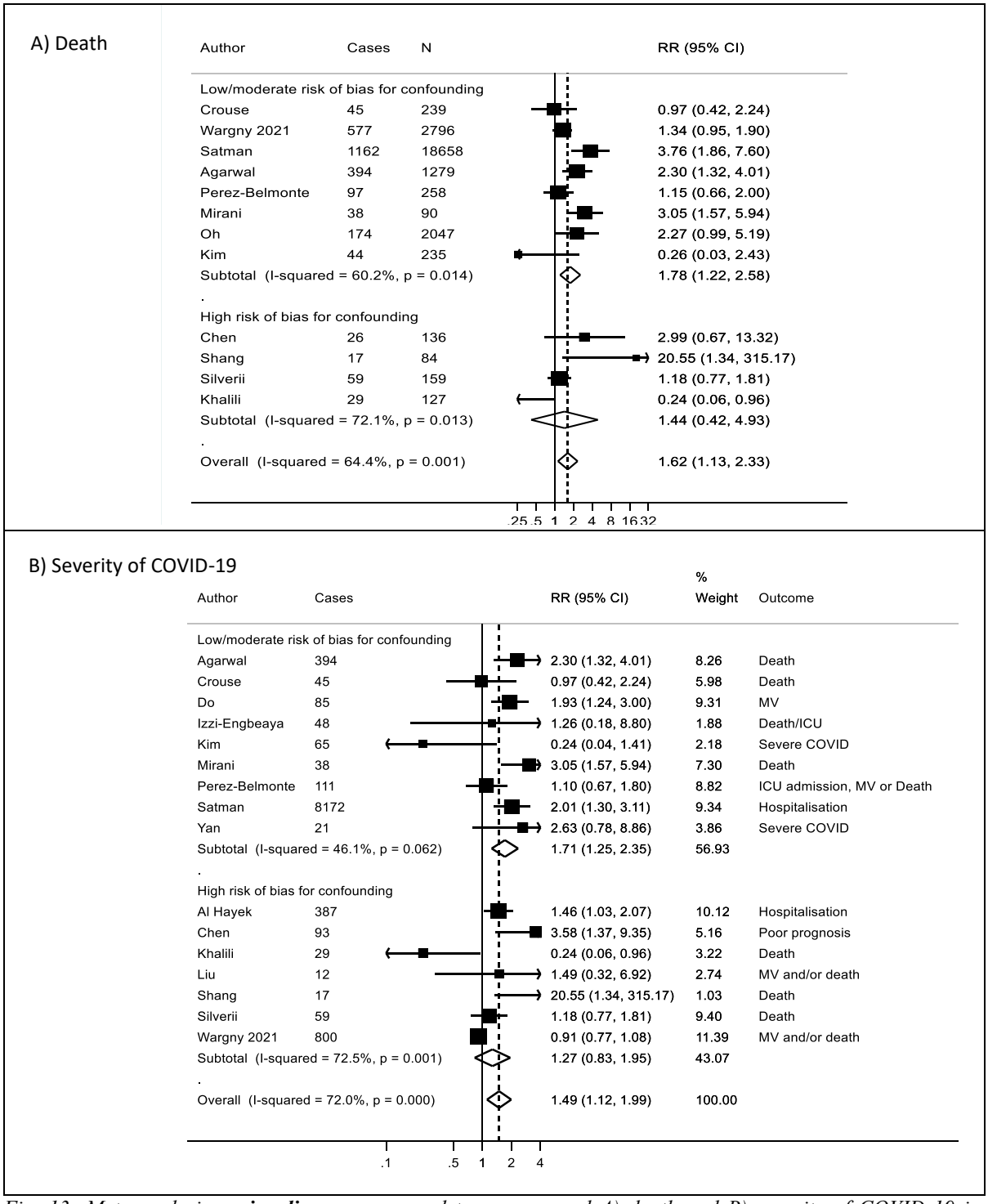


*Fig. 13: Meta-analysis on **insulin use** compared to non-use and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

Meta-Analysis of Metformin Use and COVID-19 Outcomes

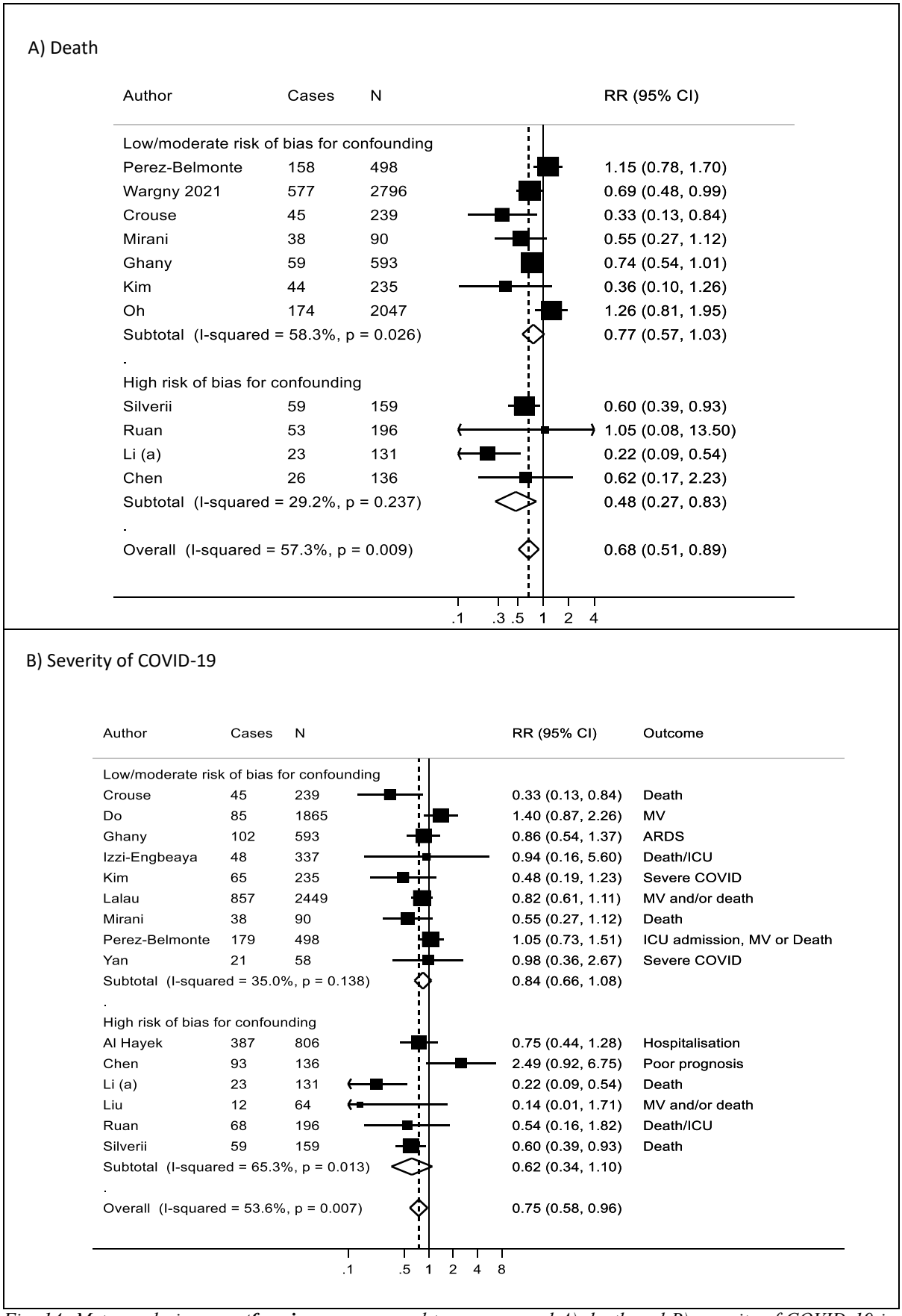


*Fig. 14: Meta-analysis on **metformin use** compared to non-use and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

Of note, no clear associations were observed between the medications SGLT-2, sulfonylurea/glinides/secretagogue use and thiazolidinedione with COVID-19-related death or severity (Appendix Fig. 10, Appendix Fig. 11, Appendix Fig. 12).

Laboratory Parameters on Admission and COVID-19-Related Death and COVID-19-Related Severity in Individuals with Diabetes and COVID-19

We evaluated the association between laboratory markers and COVID-19 outcomes that can be found in Fig. 30 and Fig. 31. Evidence suggested that higher estimated GFR (eGFR) was associated with decreased relative risk of COVID-19-related death with high certainty of evidence (SRR per 1 ml/min/1.73m²: 0.97 [95% Cl: 0.96, 0.99]; *n*=3 studies, SRR per 10 ml/min/1.73m²: 0.78 [95% Cl: 0.65, 0.94]; *n*=3 studies) in comparison to lower eGFR levels (Fig. 15, Fig. 30). Heterogeneity was especially high for laboratory markers, most likely due to differences in analytical methods and reference ranges used in the different labs. For example, the meta-analysis of eGFR indicated a heterogeneity of 69% and lymphocyte count 87% in comparison to factors sex which had a heterogeneity of 43% for COVID-19-related death.

eGFR had an inverse relationship also with the outcome COVID-19-related severity. A decrease in the level of eGFR was associated with an increase in the relative risk for the outcome (SRR per 1 mL/min/1.73 m^2: 0.98 [95% Cl: 0.97, 1.00]; *n*=3, SRR per 10 mL/min/1.73 m^2: 0.83 [95% Cl: 0.71, 0.96]; *n*=3) with high certainty of evidence (Fig. 15, Fig. 31).

Meta-Analysis of eGFR and COVID-19 Outcomes

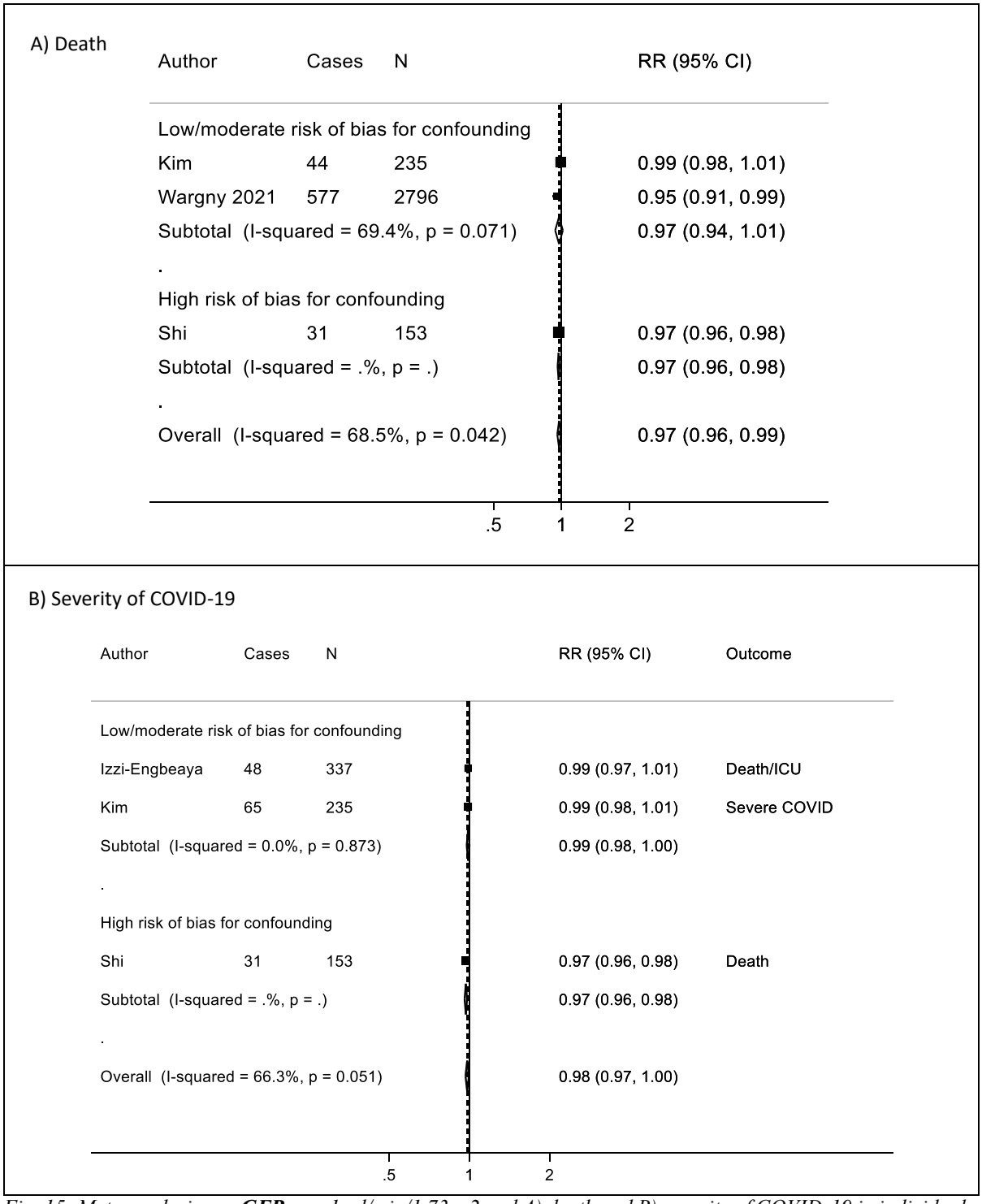


*Fig. 15: Meta-analysis on **eGFR**, per 1 ml/min/1.73 m2 and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

New evidence suggested that high CRP at admission was associated with increased relative risk of COVID-19-related death (SRR per 1 mg/l 1.01 [95% CI: 1.00, 1.02], *n*=7 studies, SRR per 5 mg/l 1.07 [95% CI: 1.02, 1.12], *n*=7 studies, moderate certainty of evidence). An increase in the CRP level per 10 mg/l was also associated with an increase in the relative risk

of COVID-19-related severity but in this case with high certainty of evidence (SRR for an increase per 1 mg/l 1.01 [95% CI: 1.00, 1.02], *n=6* studies, SRR for an increase per 5 mg/l: 1.06 [95% CI: 1.01, 1.11], *n*=6 studies) when compared to lower CRP levels (Fig. 16, Fig. 31). The heterogeneity for COVID-19-related death was 0% yet for severity 65%.

Meta-Analysis of CRP and COVID-19 Outcomes

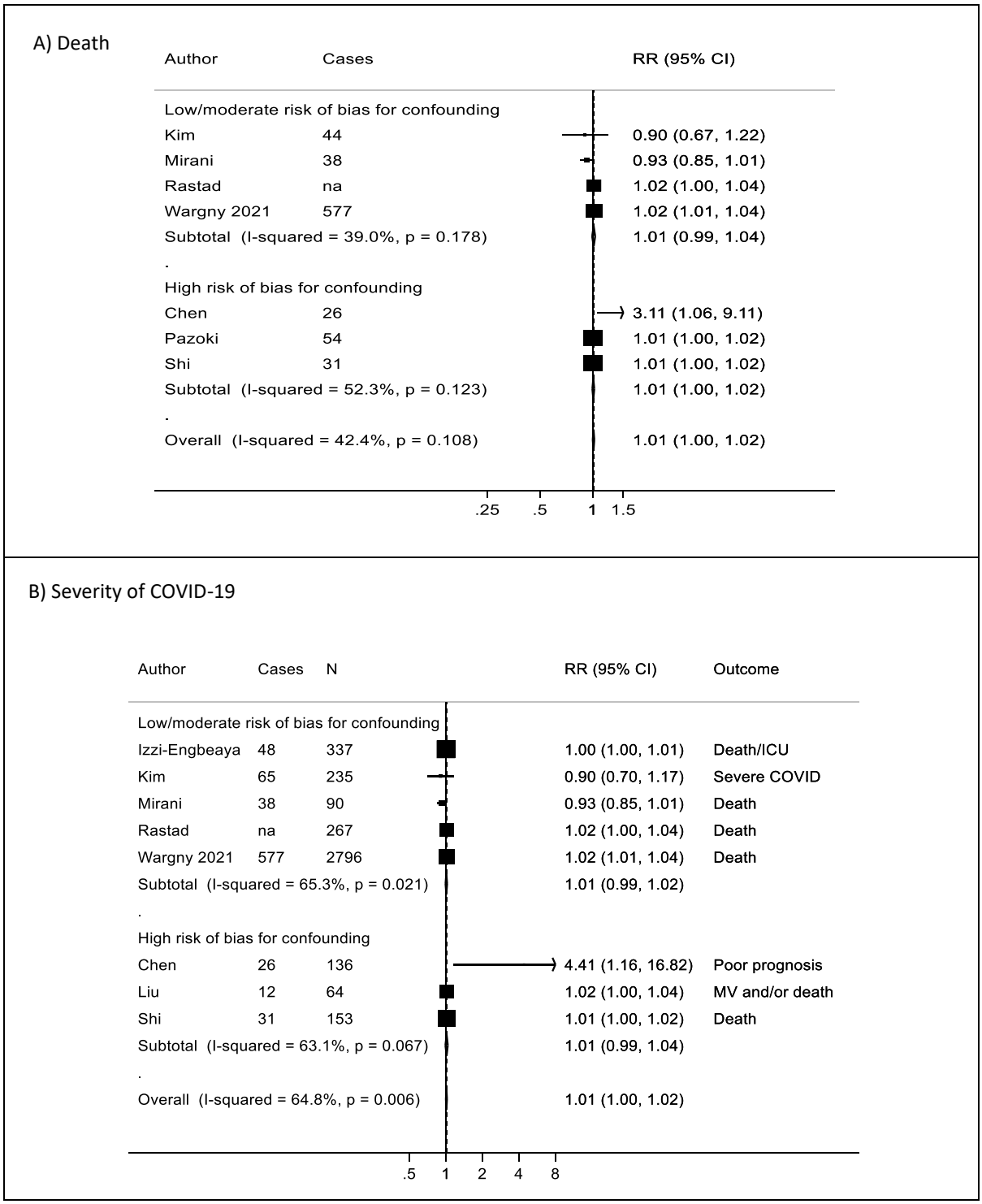
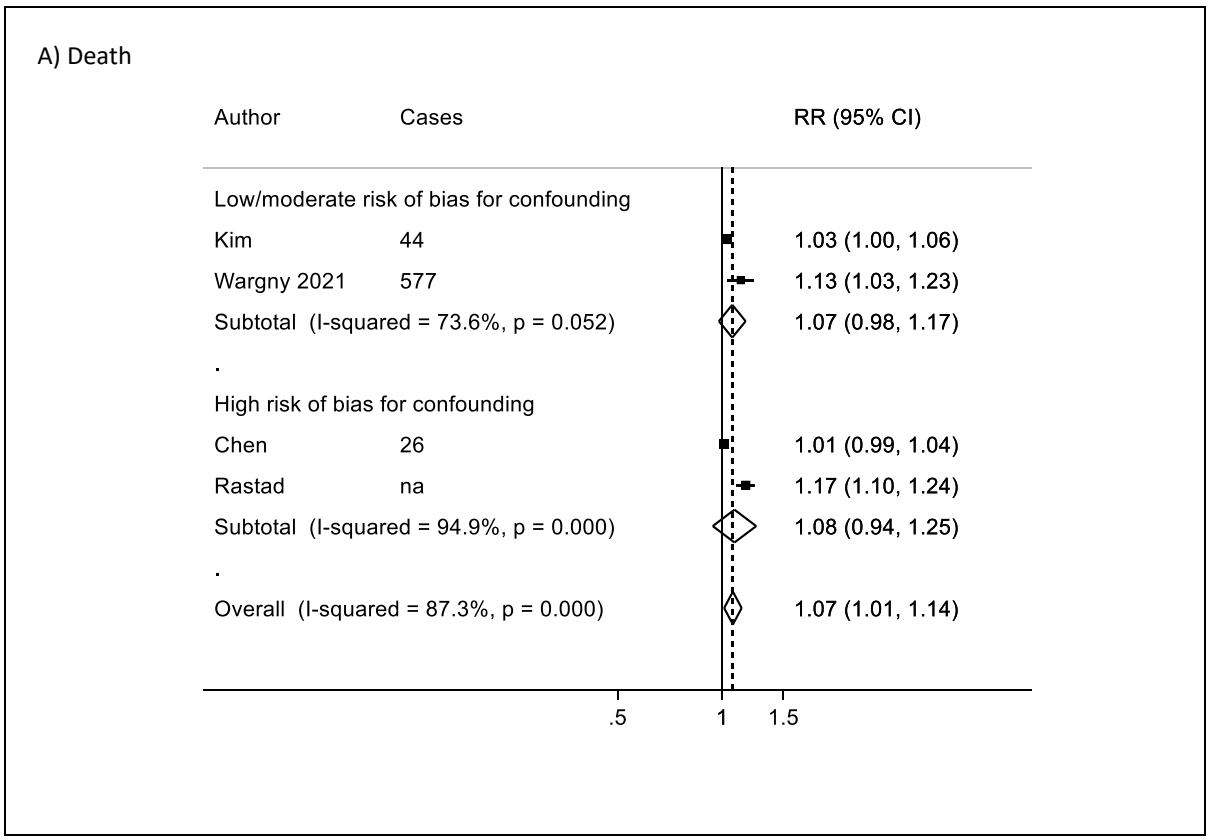


Fig. 16: Meta-analysis on ***C-reactive protein (CRP),*** *per 1 mg /dl and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

Besides eGFR and CRP, another factor related to COVID-19-related death was high aspartate aminotransferase (AST) levels at admission (SRR per 1 U/l: 1.07 [95% CI: 1.01, 1.14]; *n*=4, SRR per 5 U/l: 1.42 [95% CI: 1.06, 1.90]; *n*=4 studies; moderate certainty of evidence) (Fig. 17), whereas for ALT levels (alanine aminotransferase) no associations were observed (SRR for ALT per 1 U/l: 1.00 [95% CI: 0.96, 1.04]; *n*=3, SRR for ALT per 5 U/l: 1.00 [95% CI: 0.83, 1.20]; *n*=3, low certainty of evidence) (Appendix Fig. 13).

Furthermore, every increase of AST levels per 5 units/l was also associated with 46% increase in the relative risk of COVID-19-related severity with moderate certainty of evidence (SRR for an increase per 1 unit/l: 1.08 [95% CI: 1.02, 1.14], *n*=4 studies, SRR for an increase per 5 units/l: 1.46 [95% CI: 1.09, 1.95], *n*=4 studies) (Fig. 17, Fig. 31).

Meta-Analysis of AST and COVID-19 Outcomes



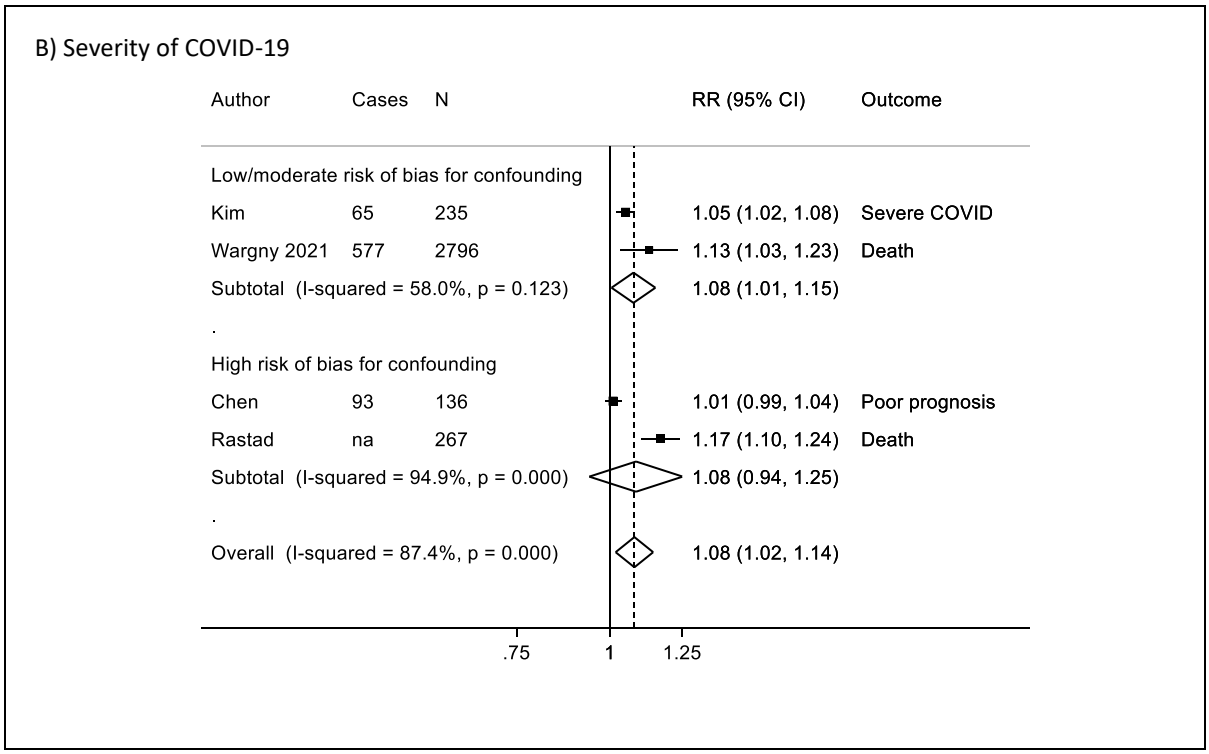


*Fig. 17: Meta-analysis on **AST per 1 U/l** and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

As for the lymphocyte count, there has been an inverse relationship between this factor and COVID-19-related death (SRR: 0.29 [95% CI: 0.11, 0.73], *n*=5 studies) with a moderate certainty of evidence. This indicates that individuals with high lymphocyte count were prone to more adverse COVID-19 outcomes. Lymphocyte count was also associated with an inverse relationship with COVID-19-related severity (SRR: 0.38 [95% CI: 0.20, 0.71], *n*=6 studies) but in this case with high certainty of evidence (Fig. 18).

Meta-Analysis of Lymphocyte Count and COVID-19 Outcomes

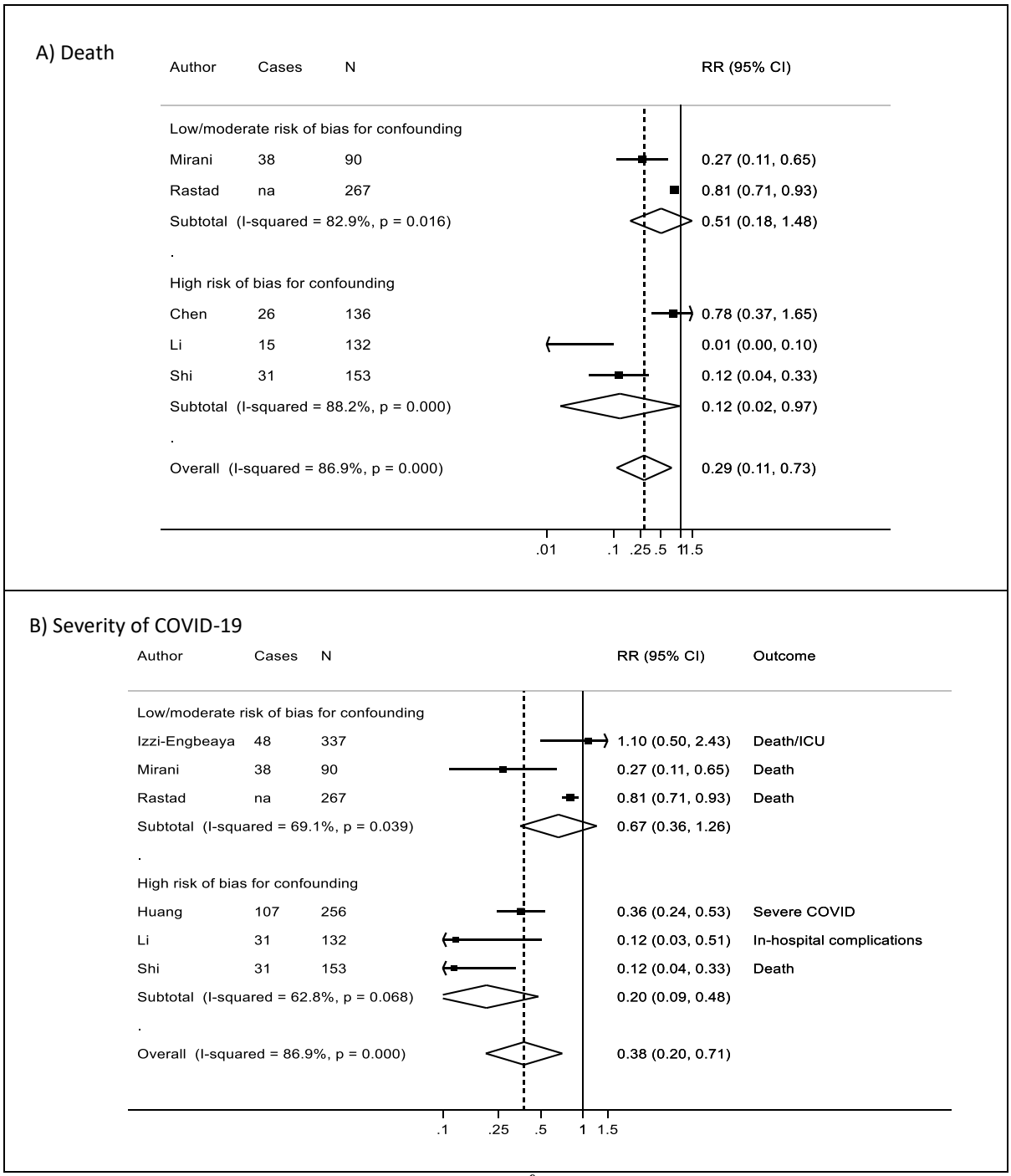


Fig. 18: Meta-analysis on ***lymphocyte count, per 1x10^9/l*** *and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

Platelet count yielded no clear associations with COVID-19-related death or severity with moderate certainty of evidence, yet procalcitonin level increase per 1 ng/ml was associated with 20% (SRR: 1.20 [95% Cl: 1.06, 1.35]; *n*=2) increase in the relative risk of COVID-19-related death but no associations were observed for COVID-19-related severity with low certainty of evidence (Appendix Fig. 14, Appendix Fig. 15).

A factor that showed a reverse relationship when considering studies with a low and high risk of bias was haemoglobin. Even though the overall risk of COVID-19-related death was decreased per 5g/dL increase in haemoglobin with low certainty of evidence, a study with low/moderate risk of bias indicated an increase in the relative risk per 1g/dL increase in haemoglobin level with precision (RR: 1.55 [95% Cl: 1.07, 2.25]; *n*=1), whereas the study with a high risk of bias depicted a decrease in the relative risk of the adverse outcome (RR: 0.54 [95% Cl: 0.39, 0.74]; *n*=1) (Fig. 30, Appendix Fig. 16).

Regarding COVID-19-related severity, creatinine observations were associated with moderate certainty of evidence (SRR for an increase per 1 μmol/L: 1.00 [95% CI: 1.00, 1.01], *n*=6 studies, SRR for an increase per 10 μmol/L: 1.03 [95% CI: 1.01, 1.06], *n*=6 studies) (Fig. 31, Appendix Fig. 17). An increase in the neutrophils per $1*10^9$/L was associated with the adverse outcome but the certainty of evidence was low (SRR: 1.24 [95% Cl: 1.18, 1.29]; n=4) (Appendix Fig. 18). D-Dimer was not associated with COVID-19-related severity with moderate certainty of evidence (Appendix Fig. 19).

Moreover, some factors were only associated with COVID-19-related severity and not with death. These included IL-6 (SRR for an increase per 1 pg/ml: 1.01 [95% CI: 1.01, 1.02], *n*=3 studies, SRR for an increase per 5 pg/dl: 1.07 [95% CI: 1.04, 1.10], *n*=3 studies) with moderate certainty of evidence (Fig. 19, Fig. 31) and erythrocyte sedimentation rate. However, erythrocyte sedimentation rate indicated an association with low certainty of evidence (SRR for an increase per 1 mm/h: 1.04 [95% CI: 1.02, 1.06], *n*=2 studies) (Appendix Fig. 20).

Meta-Analysis of IL-6 and COVID-19 Outcomes

A) Death

No data

B) Severity of COVID-19

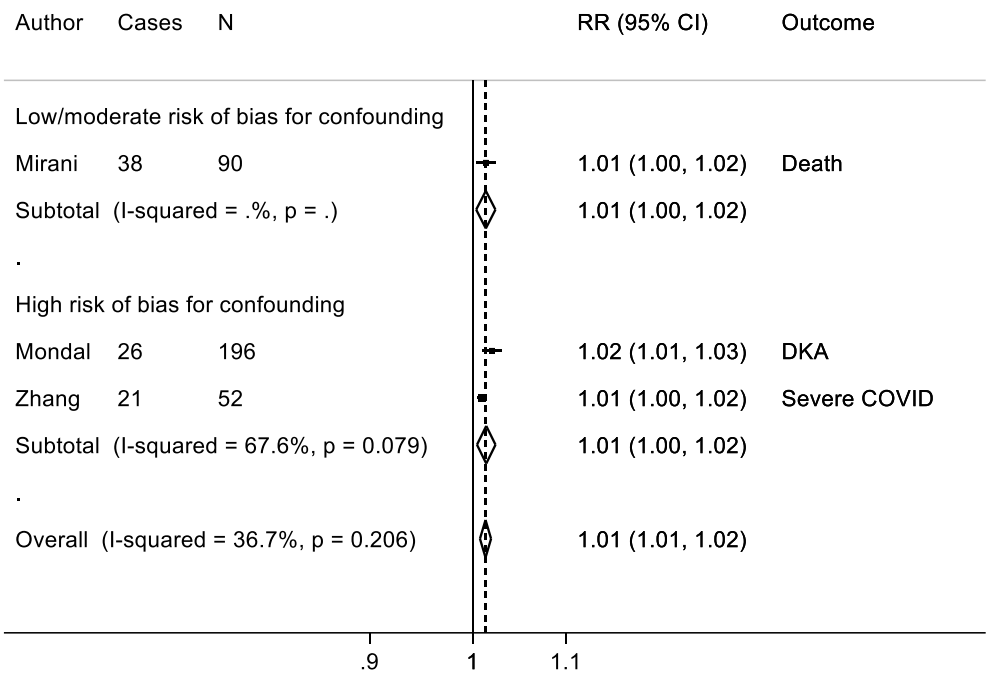


*Fig. 19: Meta-analysis on **IL-6, per 1 pg/ml** and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al* (1)

Comorbidities, Complications and COVID-19-Related Death and COVID-19-Related Severity in Individuals with Diabetes and COVID-19

The presence of pre-existing CVD was associated with COVID-19-related death, increasing the relative risk by 33% (SRR: 1.33 [95% Cl: 1.11, 1.59]; *n*=14 studies) (Fig. 20). It was observed that CKD (relative risk increased by 75%) and COPD (relative risk increased by 31%) were also related to COVID-19-related death (CKD: SRR: 1.75 [95% Cl: 1.36, 2.25]; *n*=14 studies; COPD: SRR: 1.31 [95% Cl: 1.17, 1.47], *n*=9 studies) compared to individuals without these comorbidities (Fig. 21, Fig. 22). All three associations were evaluated as high certainty of evidence.

Results for COVID-19-related severity were similar with a high certainty of evidence for CKD (SRR: 1.67 [95% Cl: 1.36, 2.05]; *n*=18 studies (Fig. 21) and a moderate certainty of evidence for CVD (SRR: 1.31 [95% Cl: 1.11, 1.55]; *n*=18 studies (Fig. 20). Regarding the outcome for CVD and COVID-19-related severity, publication bias was observed according to Eager's test (Appendix Fig. 21). COPD, on the other hand, did not show clear associations with the outcome with moderate certainty of evidence (SRR: 1.18 [95% Cl: 0.95, 1.48]; *n*=12) (Fig. 22). The heterogeneity of these results was similar for both outcomes, except for COPD which had a 0% heterogeneity when considering COVID-19-related death and 54% for COVID-19-related severity.

Meta-Analysis of CVD and COVID-19 Outcomes

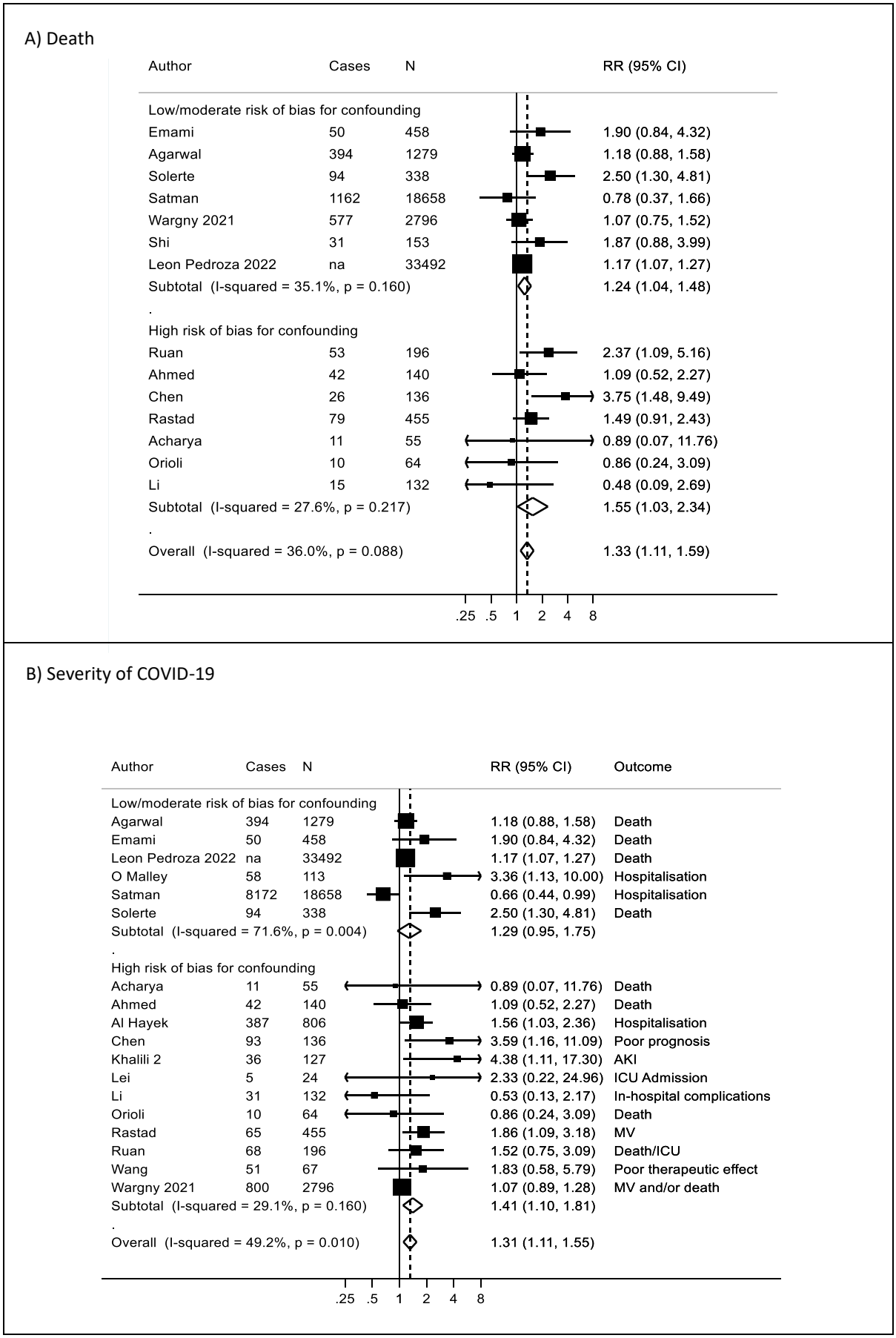


*Fig. 20: Meta-analysis on pre-existing **cardiovascular disease (CVD)** compared to no CVD and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al* (1)

Meta-Analysis of CKD and COVID-19 Outcomes

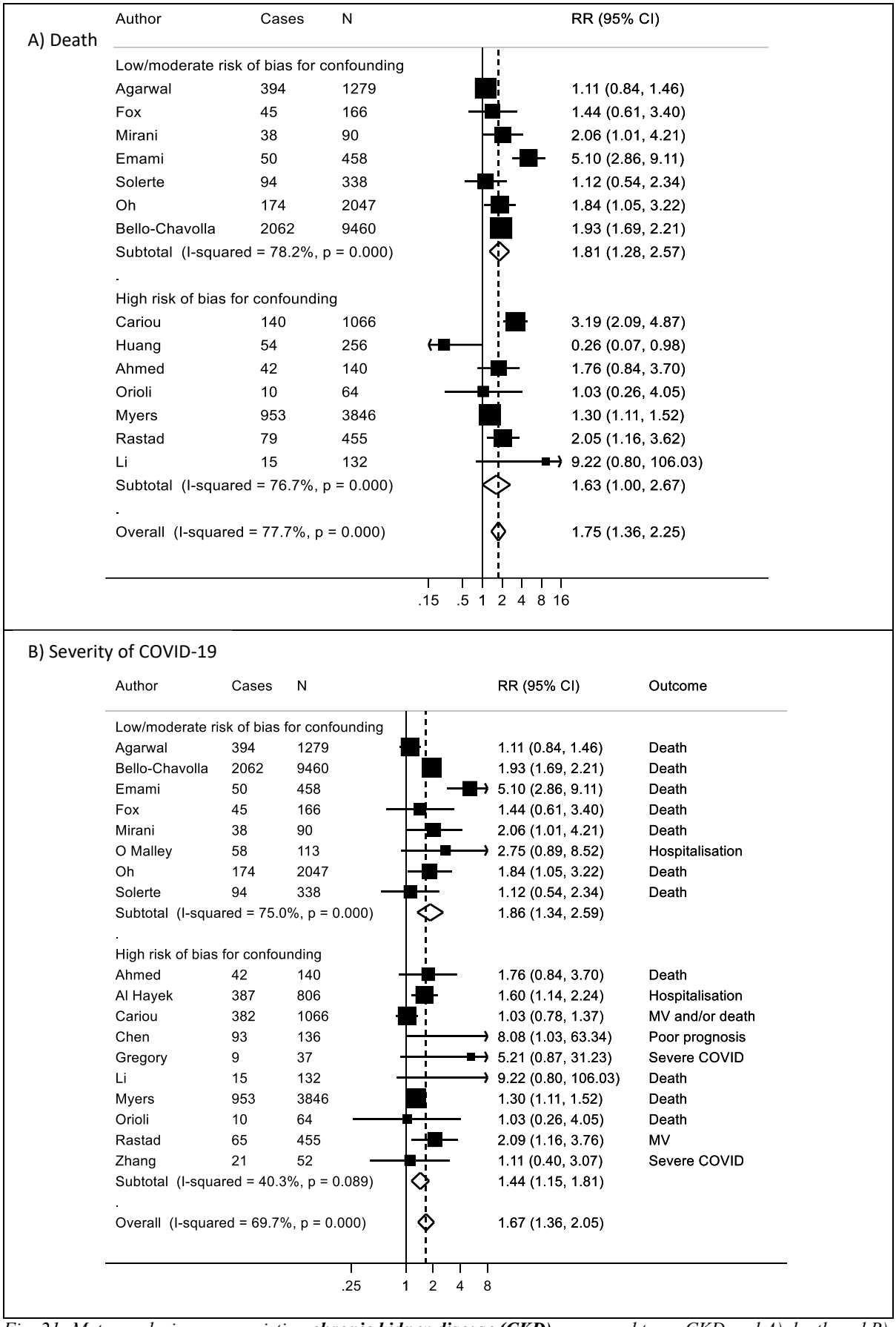


*Fig. 21: Meta-analysis on pre-existing **chronic kidney disease (CKD)** compared to no CKD and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

Meta-Analysis of COPD and COVID-19 Outcomes

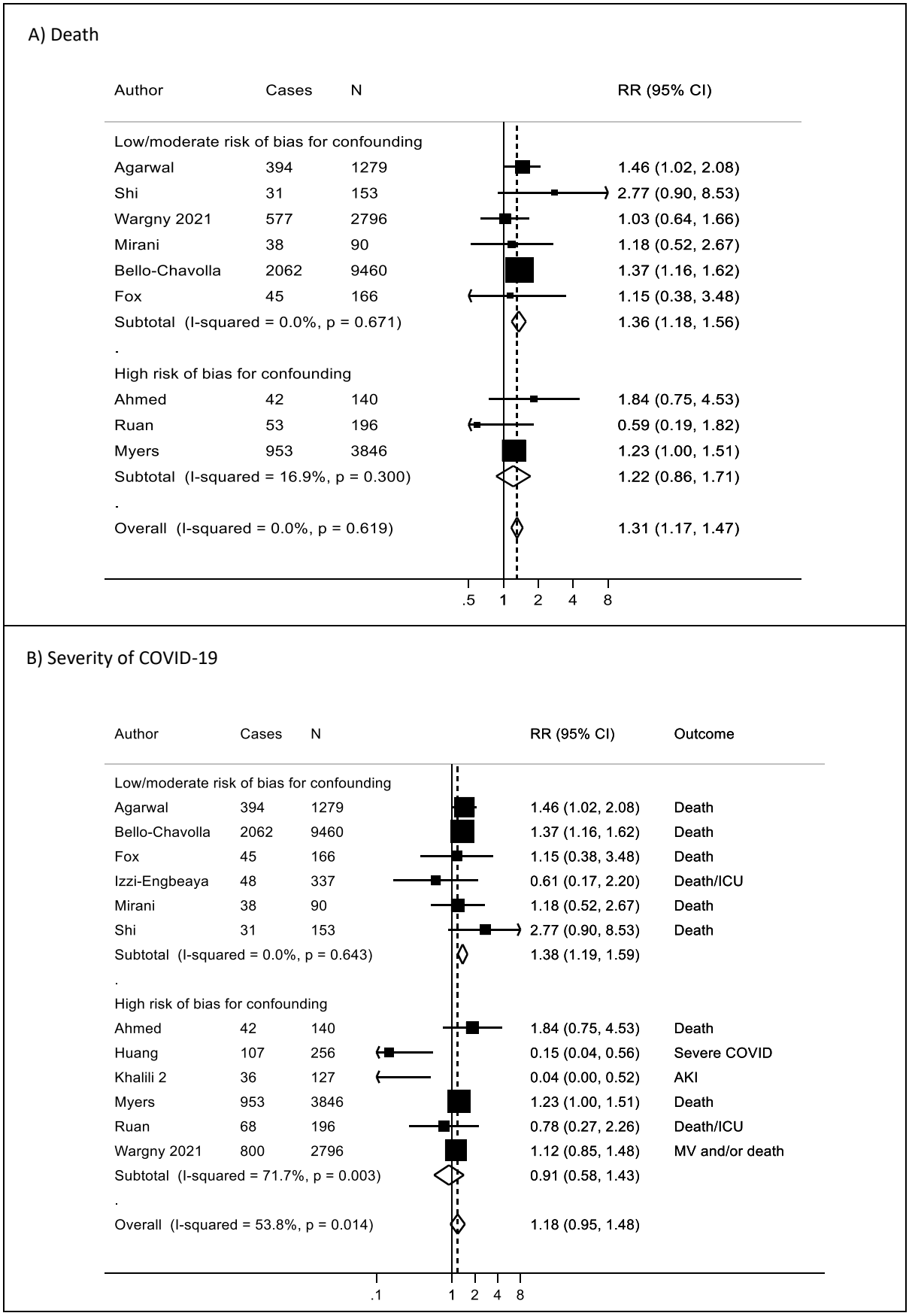


*Fig. 22: Meta-analysis on pre-existing **chronic obstructive pulmonary disease (COPD)** compared to no COPD and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

New observations with moderate certainty of evidence indicated that dementia (including cognitive impairments) (SRR: 1.76 [95% Cl: 1.21, 2.58; *n*=4 studies) (Fig. 23), pre-existing microvascular complications (SRR: 1.55 [95% Cl: 1.08, 2.22]; *n*=3 studies) (Fig. 24) and the per unit increase of the Charlson index (SRR: 1.33 [95% Cl: 1.13, 1.57]; *n*=2 studies) (Fig. 25) were associated with an increased relative risk of COVID-19-related death. Coronary artery disease (CAD) (SRR: 1.78 [95% Cl: 1.21, 2.64]; *n*=5 studies) and heart failure (SRR: 1.48 [95% Cl: 1.19, 1.83]; *n*=5 studies) did not show clear associations with COVID-19-related death as the certainty of evidence for these factors was low (Appendix Fig. 22, Appendix Fig. 23).

Meta-Analysis for Dementia and COVID-19 Outcomes

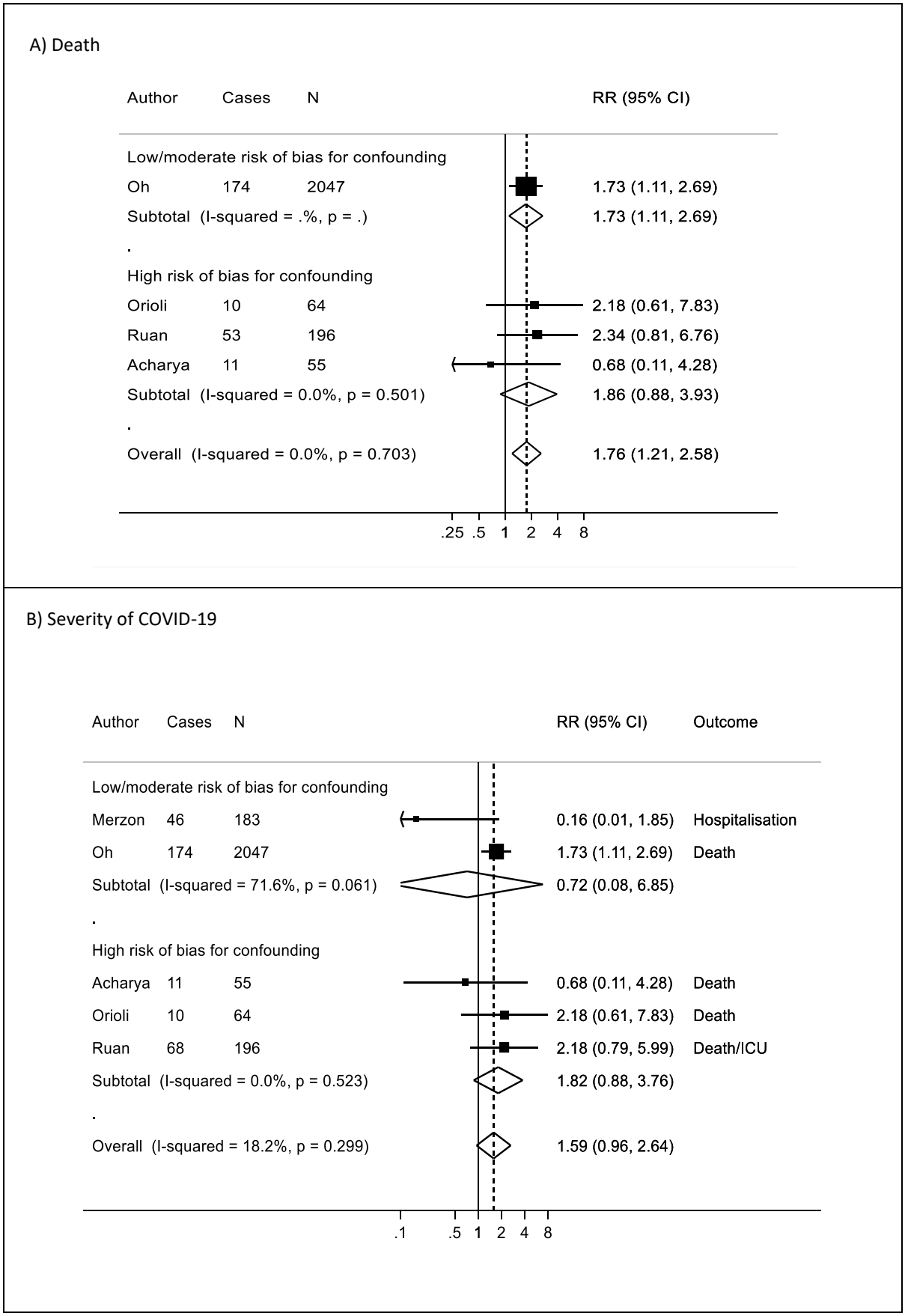


*Fig. 23: Meta-analysis on pre-existing **dementia/cognitive impairment** compared to no dementia and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (80)*

Meta-Analysis for Microvascular Disease and COVID-19 Outcomes

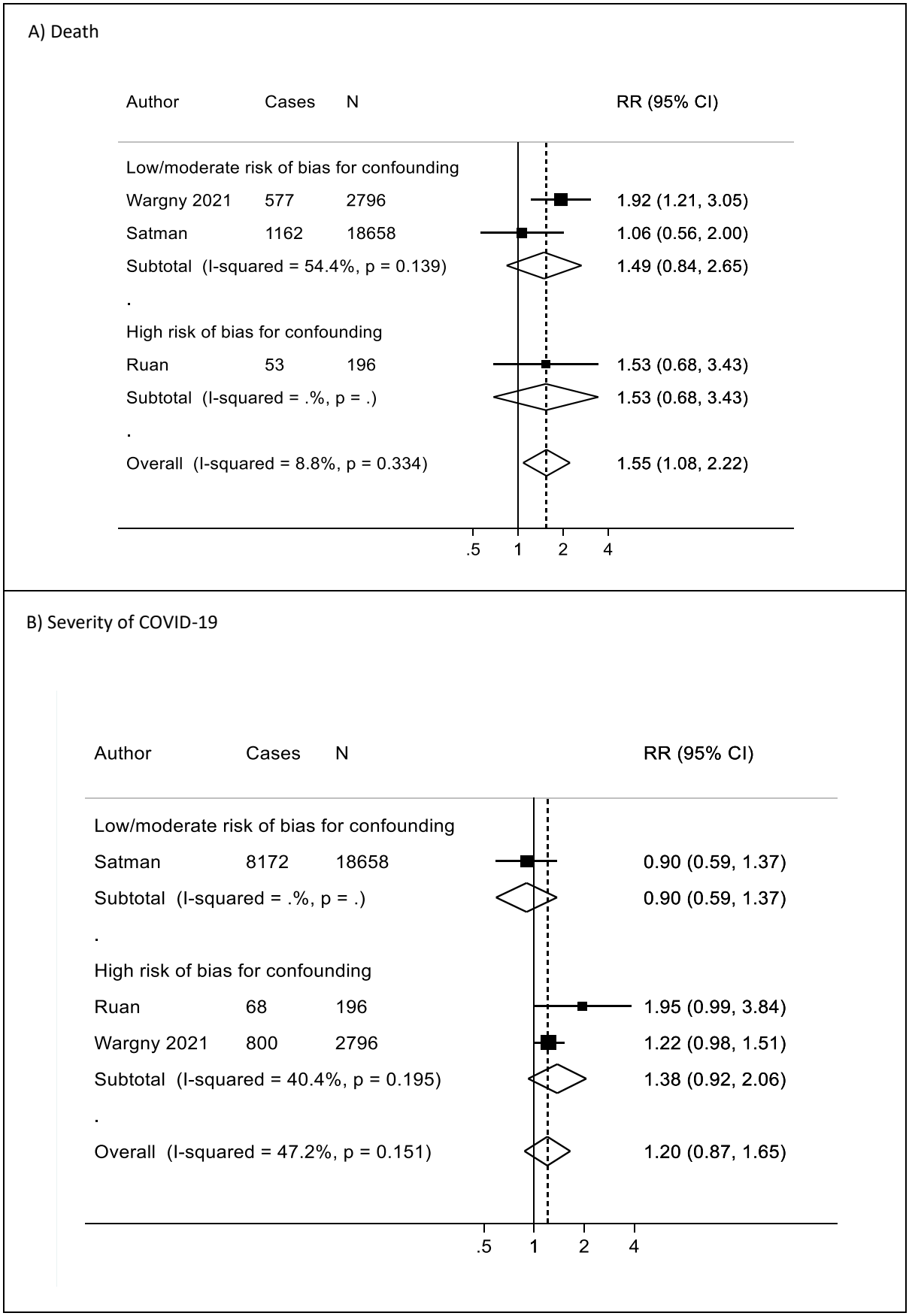


*Fig. 24: Meta-analysis on pre-existing **microvascular disease (MVD)** compared to no CKD and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

Meta-Analysis of Charslon Index and COVID-19 Outcomes

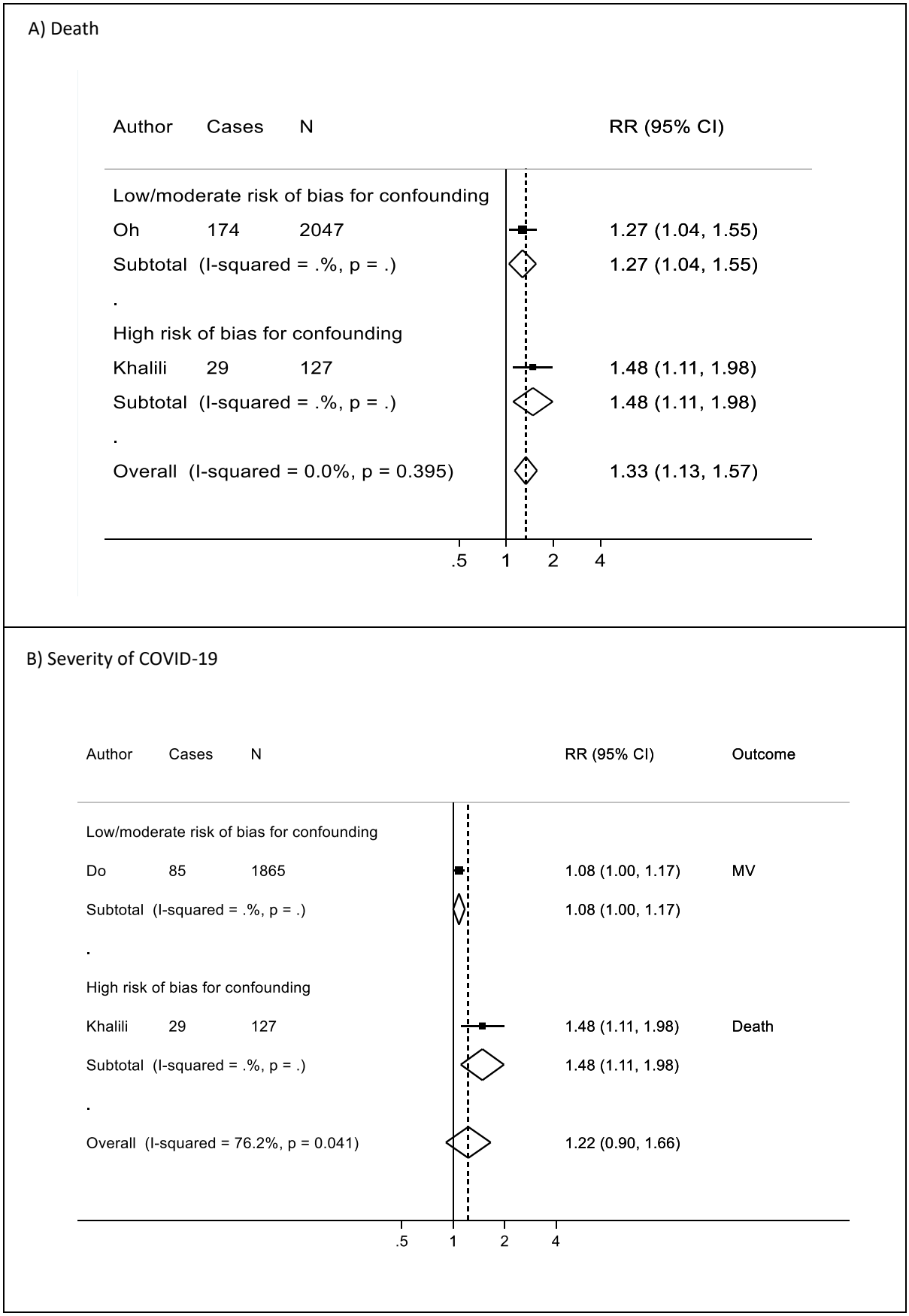
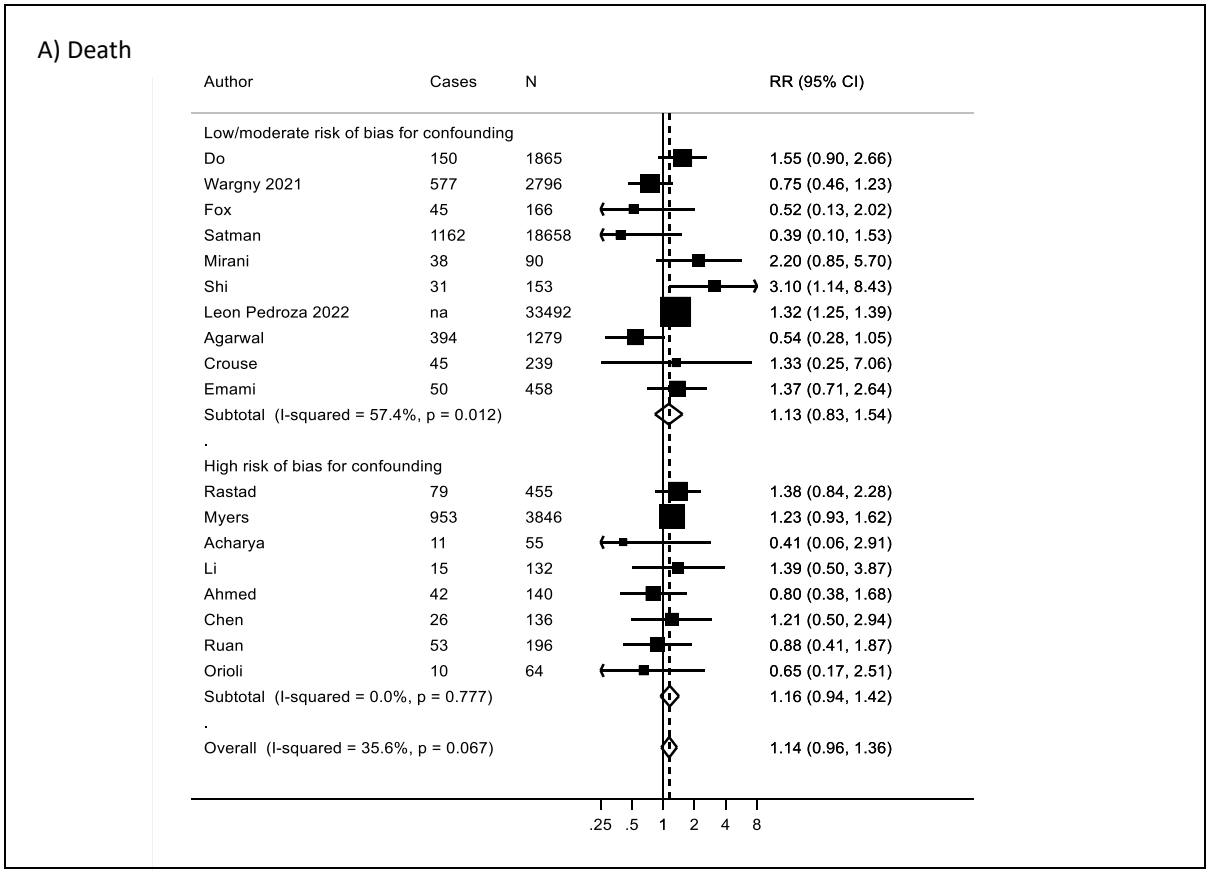


*Fig. 25: Meta-analysis on **Charlson index, per 1 unit** compared to no comorbidities and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

Regarding hypertension, it was associated only with COVID-19-related severity (SRR: 1.28 [95% Cl: 1.13, 1.44]; *n*=24 studies, high certainty of evidence) (Fig. 26) compared to those not suffering from hypertension. No relationship was observed between hypertension and COVID-19-related death and according to Egger's test it was suggested that publication bias existed for these results (Appendix Fig. 24).

Meta-Analysis of Hypertension and COVID-19 Outcomes



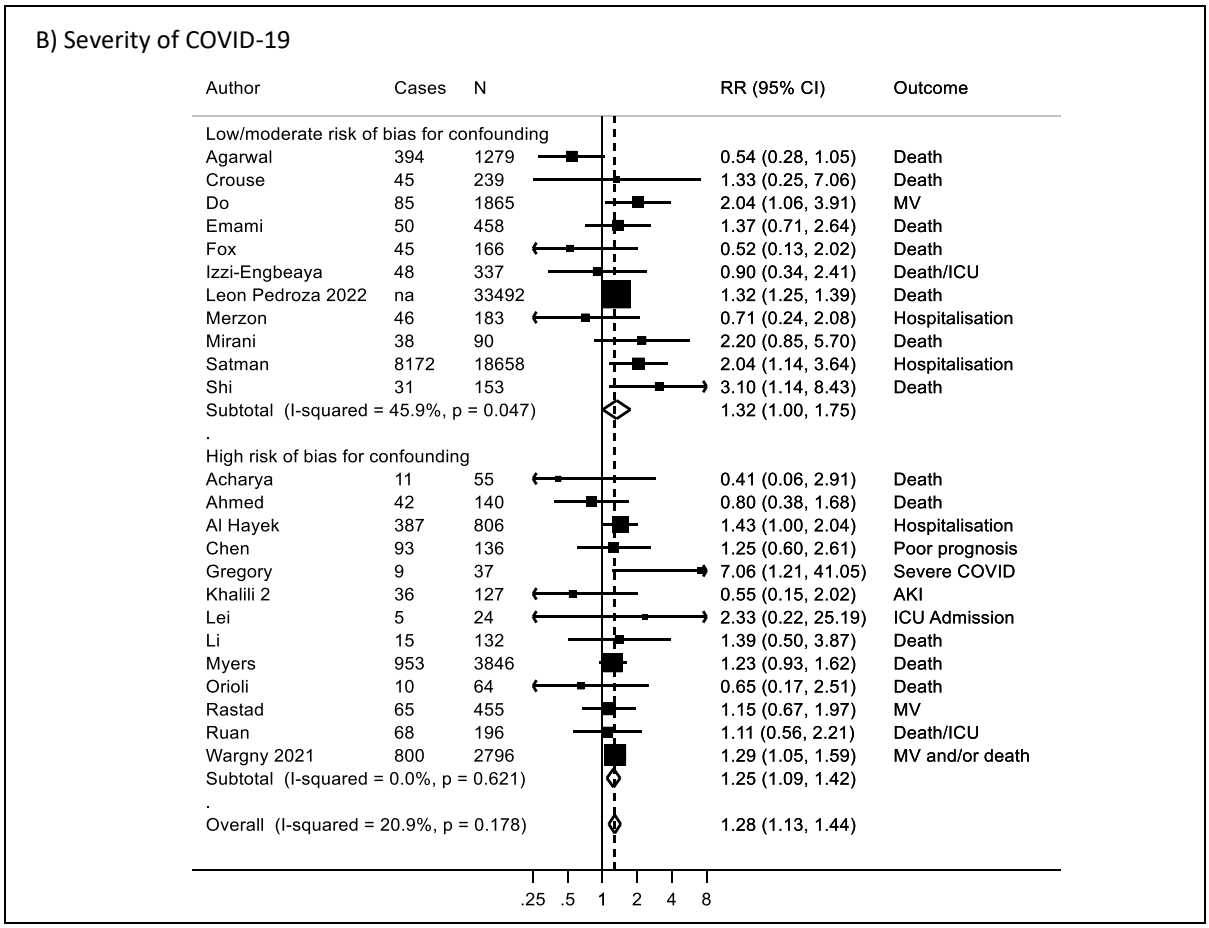


*Fig. 26: Meta-analysis on **hypertension** compared to no hypertension and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

Moreover, chronic pulmonary diseases (SRR: 1.52 [95% Cl: 1.19, 1.96]; *n*=6 studies, moderate certainty of evidence) were associated with a 52% higher relative risk of COVID-19-related severity in comparison to individuals who were not affected from chronic pulmonary diseases (Fig. 27). There were indications that individuals with obstructive sleep apnea were more prone to suffer from COVID-19-related severity in comparison to those who were not affected, but the certainty of evidence was low (SRR: 1.36 [95% Cl: 1.04, 1.76]; *n*=2) (Appendix Fig. 25)

Meta-Analysis of Chronic Pulmonary Diseases and COVID-19 Outcomes

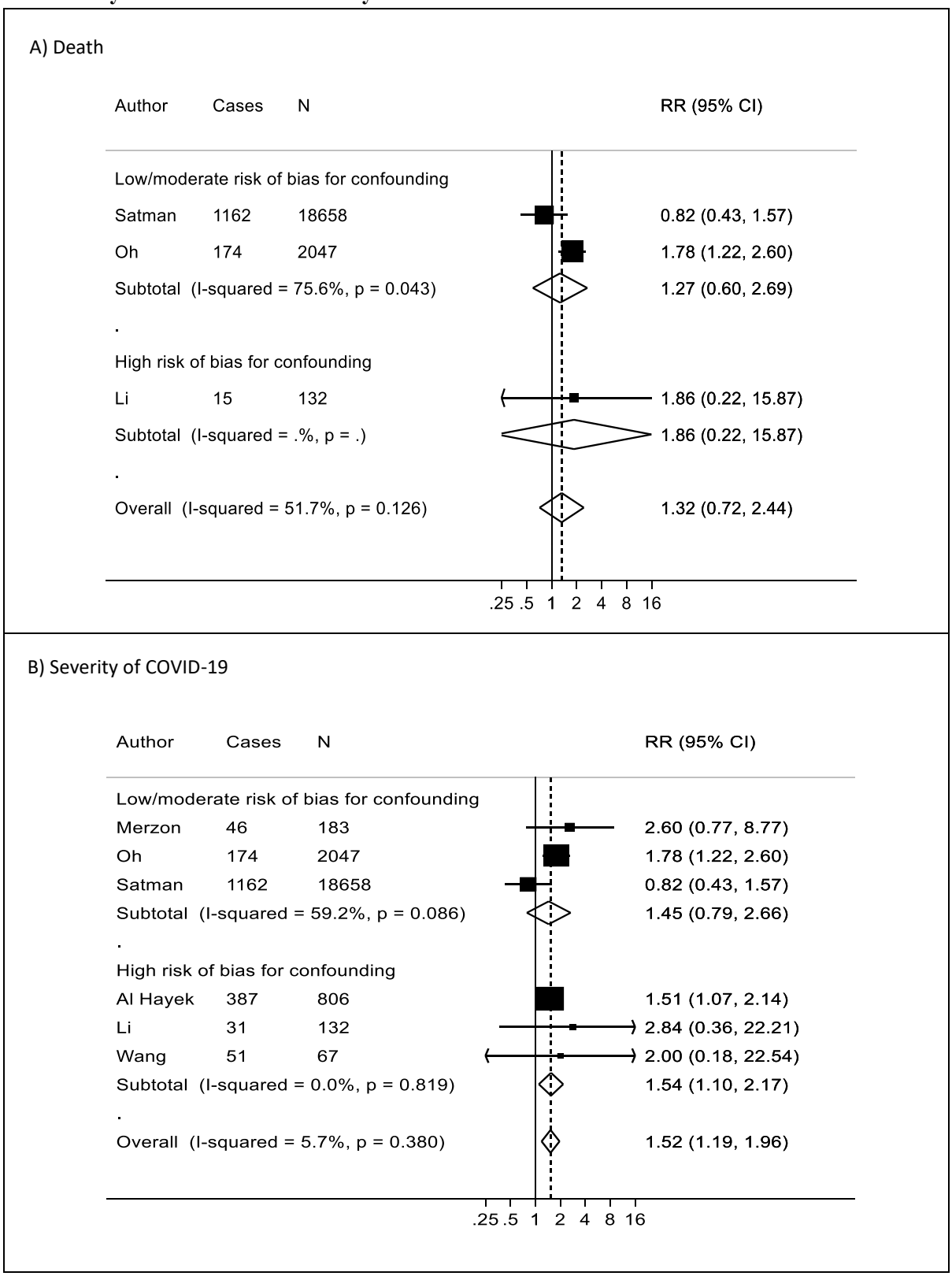


*Fig. 27: Meta-analysis on pre-existing **chronic pulmonary disease** (not specified) compared to no chronic pulmonary disease and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

Non-Glucose-Lowering Medication and COVID-19-Related Death and COVID-19-Related Severity in Individuals with Diabetes and COVID-19

As for medication other than diabetes treatment, the use of acetylsalicylic acid was associated with COVID-19-related death with moderate certainty of evidence (SRR: 2.47 [95% CI: 1.41, 4.31]; *n*=2 studies) (Fig. 28). There were indications that individuals prescribed with statins were related to an increased susceptibility for COVID-19-related death with moderate certainty of evidence compared to those who were not under this medication. However these findings were imprecisely estimated (SRR for COVID-19-related death: 1.31 [95% Cl: 0.88, 1.95]; *n*=6 studies) (Fig. 29).

Meta-Analysis of Acetylsalicylic Acid (ASA) and COVID-19 Outcomes

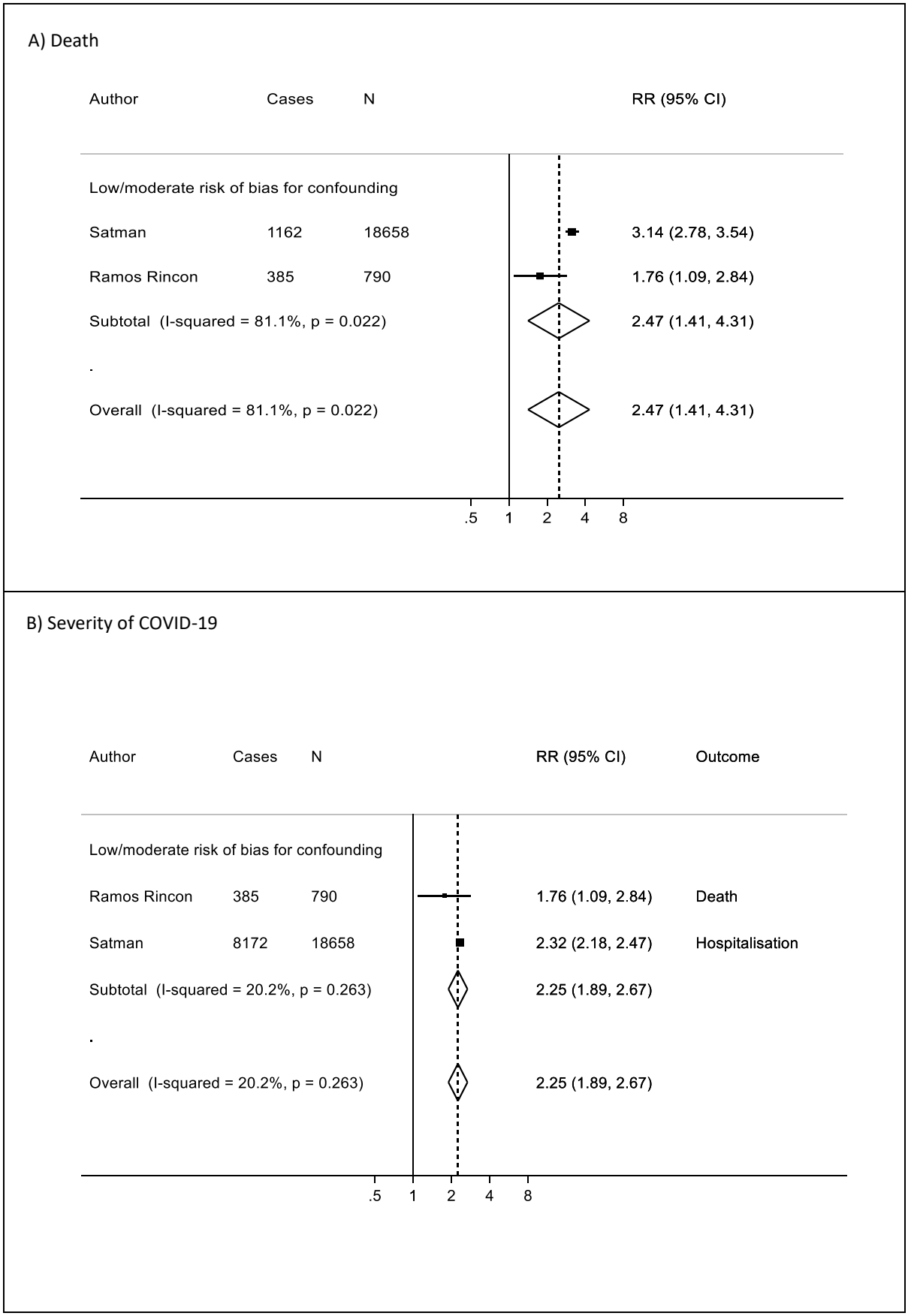


*Fig. 28: Meta-analysis on use of **acetylsalicylic acid (ASA)** compared to non-use and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

Meta-Analysis of Statins and COVID-19 Outcomes

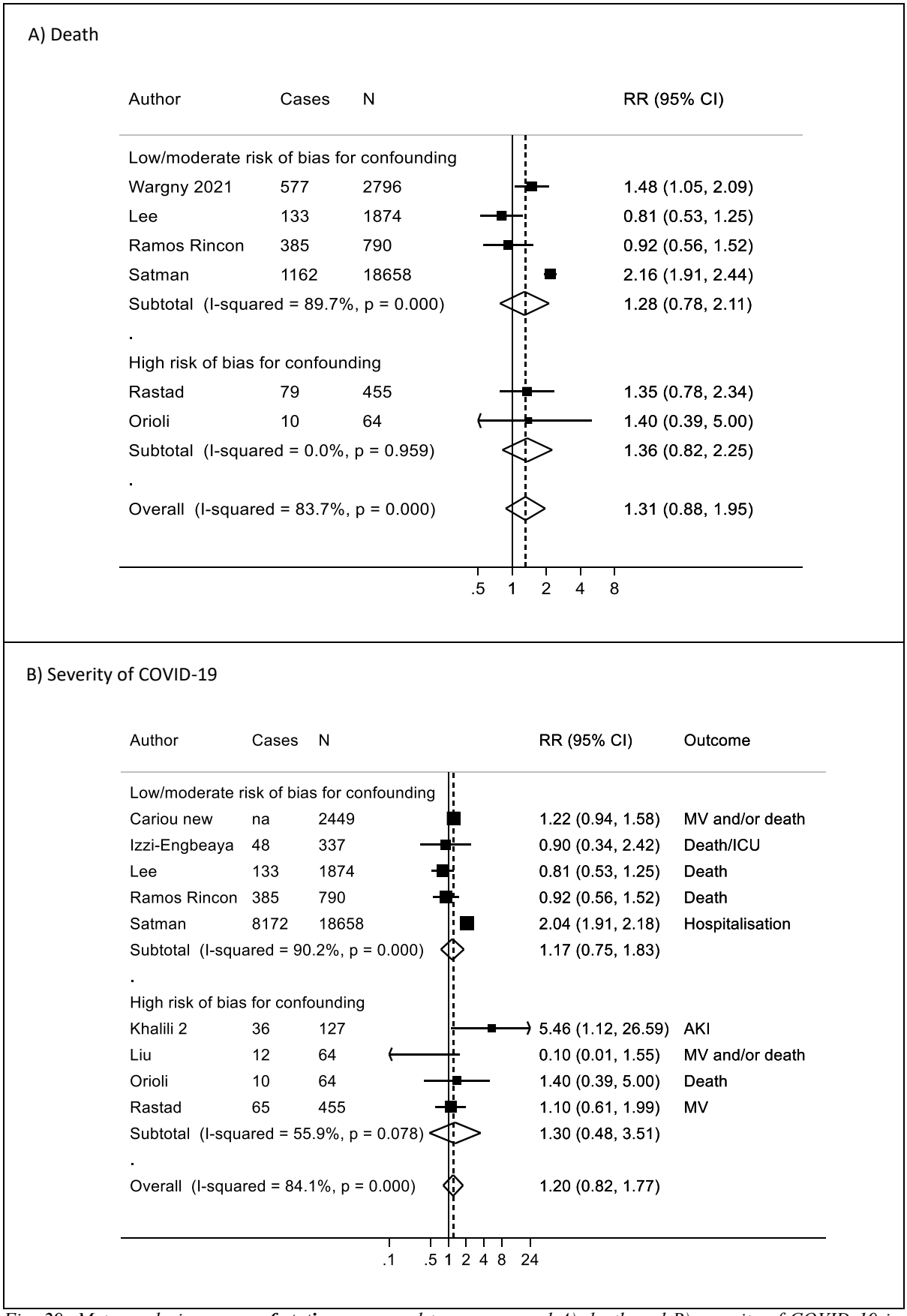


*Fig. 29: Meta-analysis on **use of statins** compared to non-use and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

The only medication associated with COVID-19-related severity with a high certainty of evidence was the use of ASA (SRR: 2.25 [95% CI: 1.89, 2.67]; *n*=2 studies) compared to the non-use of ASA (Fig. 28).

Other drug use that also demonstrated an association with both outcomes, yet with imprecisely calculated estimations and low certainty of evidence was the use of beta-blockers. After stratifying due to risk of bias, it could be observed that the use of beta-blockers exhibited a higher risk of COVID-19-related severity in a study with low/moderate risk of bias with precise results (RR: 3.21 [95% Cl: 1.53, 6.73]; *n*=1), yet studies with high risk of bias indicated a reduced relative risk (RR: 0.76 [95% Cl: 0.23, 2.54]; *n*=2) (Appendix Fig. 26).

Lastly, the use of renin inhibitors generated opposite associations with death and severity in co-occurrence with COVID-19 infection, however, based on a low certainty of evidence in this case as well. RAAS inhibitors increased the relative risk of severe infection (SRR: 1.03 [95% CI: 0.83, 1.28; *n*=20 studies, low certainty of evidence). At the same time, studies with low/moderate risk of bias due to confounding exhibited a reduced relative risk of COVID-19-related severity (RR: 0.80 [95% Cl: 0.64, 1.00]; *n*=11), but the studies with high risk of bias due to confounding increased the risk compared to the non-use of renin inhibitors (RR: 1.45 [95% Cl: 1.07, 1.98]; *n*=9) (Appendix Fig. 27).

Summary of Findings

In the following section, the overall results of our systematic review and meta-analyses are presented. In Fig. 30, Fig. 31 the summary risk estimates for diabetes risk phenotypes associated with COVID-19-related death and COVID-19-related severity respectively are shown. Factors are categorised into sections that include general factors, diabetes-specific factors, laboratory parameters, and lastly, comorbidities and complications and non-glucose lowering medication.

Risk Factors Associated with COVID-19-Related Death

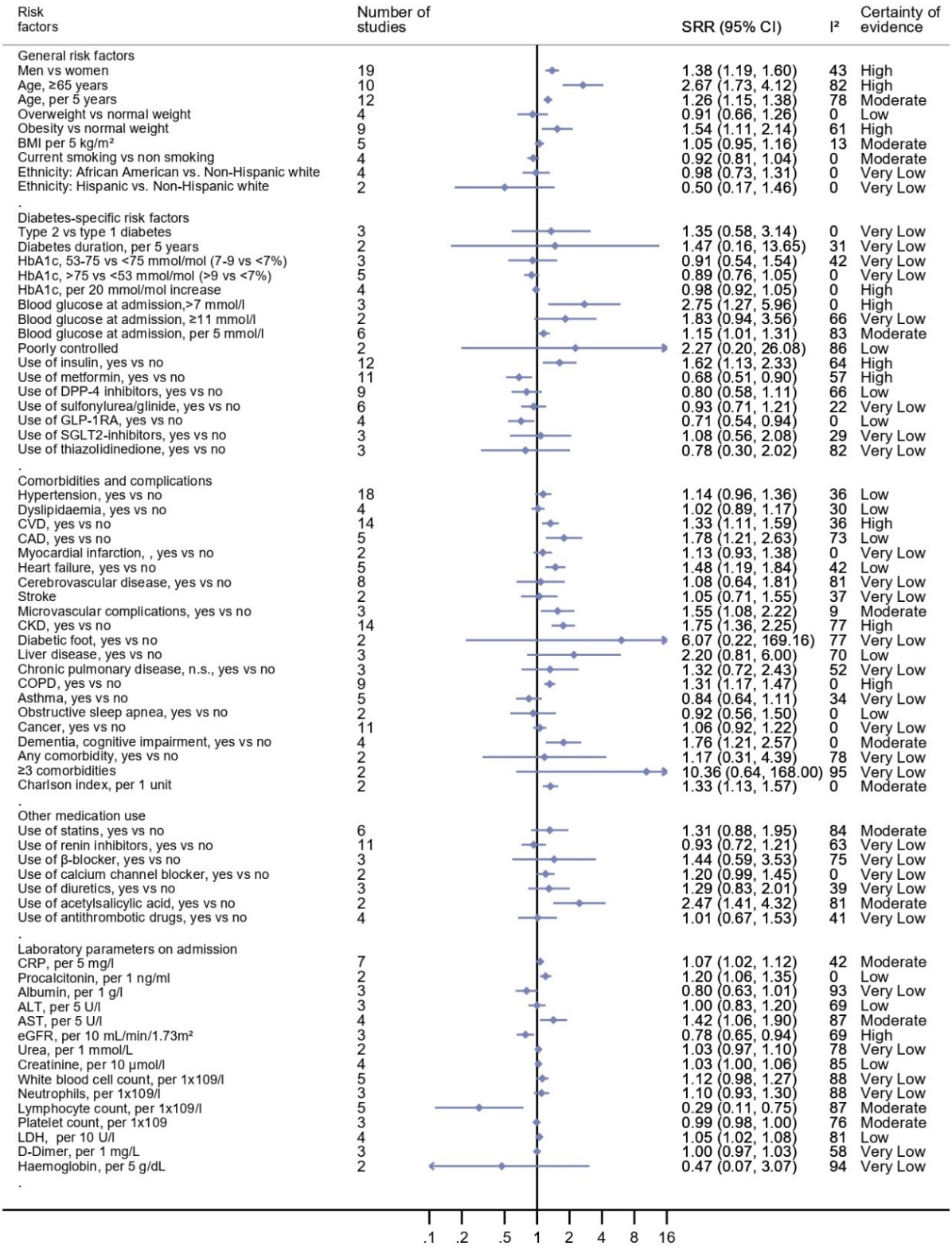


Fig. 30: Risk factors in individuals with diabetes associated with COVID-19-related death - modified by Schlesinger et al (80)

Risk Factors Associated with COVID-19-Related Severity

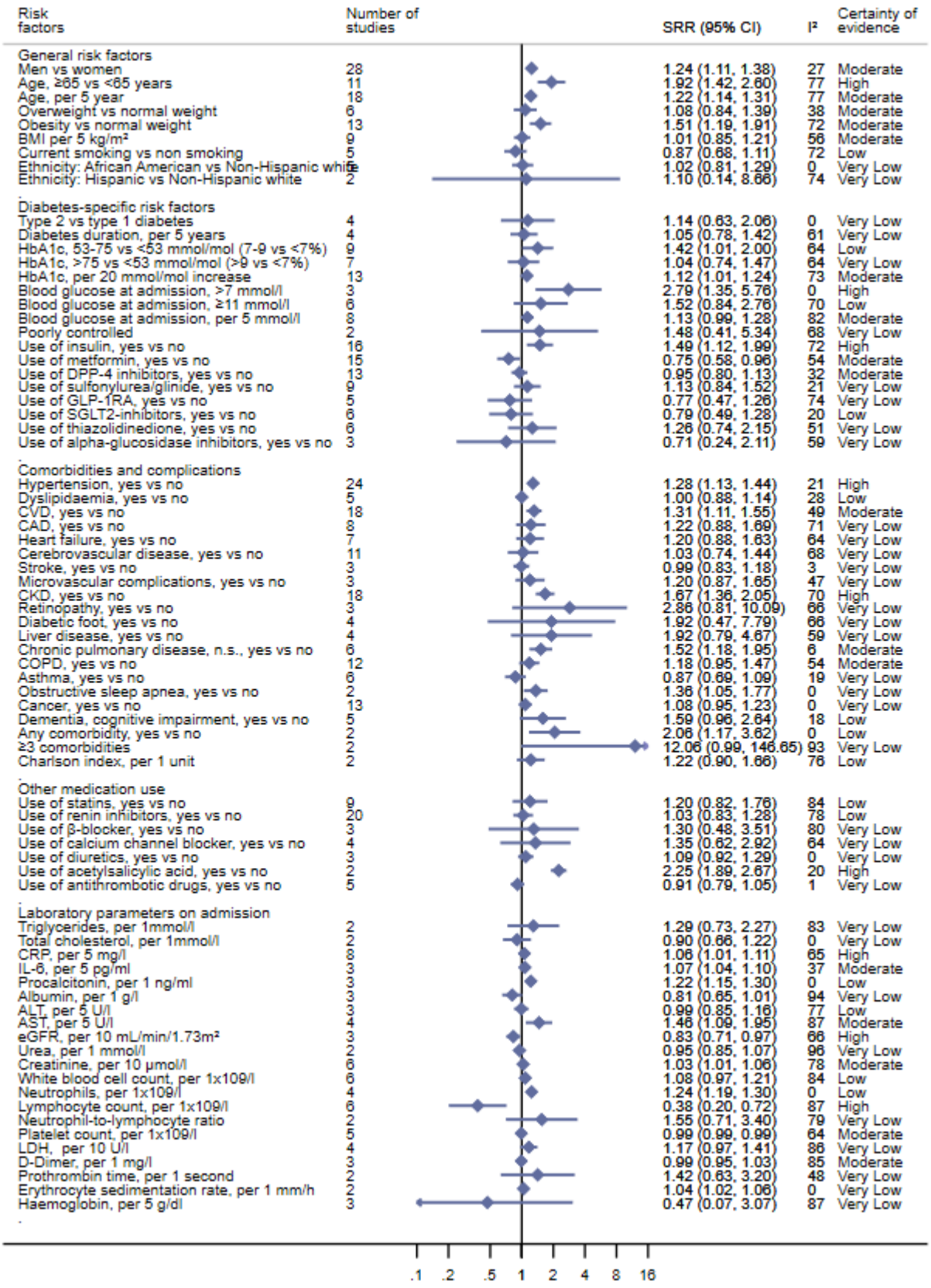


Fig. 31: Risk factors in individuals with diabetes associated with COVID-19-related severity - modified by Schlesinger et al (80)

Chapter 4 - Discussion and Conclusion

In this updated systematic review and meta-analysis, data from 58 new studies were analysed and 153 meta-analyses were performed. This study aimed to investigate the relationship between diabetes phenotypes and COVID-19-related death and severity. Our results showed that several factors were found to be associated with an increased relative risk of COVID-19-related death and severity in individuals with diabetes with moderate to high certainty of evidence. These included male sex, older age, higher blood glucose levels at admission, insulin use, and inverse relationships with metformin use. Furthermore, pre-existing comorbidities such as CVD, CKD, and COPD also increased the relative risk of COVID-19-related death and severity. New evidence supported the hypothesis that obesity, pre-existing microvascular complications, dementia/cognitive impairments, and the Charlson index were associated with COVID-19-related death and severity. Additionally, higher values of laboratory markers such as CRP and AST were associated with an increased relative risk, and higher eGFR and lymphocyte count at admission with a decreased relative risk of COVID-19 outcomes. Previous use of statins and acetylsalicylic acid also indicated an association with an increased relative risk of COVID-19-related death and severity. It was noted that two factors, high HbA1c levels, and hypertension, were only associated with COVID-19-related severity, but not with COVID-19-related death. In summary, our updated systematic review and meta-analyses identified several diabetes phenotypes that are associated with an increased relative risk of COVID-19-related death and severity. These findings may have important implications for the understading, management, and prevention of COVID-19 in individuals with diabetes.

Comparison with Other Studies

General Risk Factors

As mentioned in the previous version of our systematic review (1), male sex and age over 65 years were positively associated with worse COVID-19 outcomes in people with diabetes. After considering more studies in our updated version of the systematic review and meta-analyses, the increase in the relative risk of COVID-19-related death and severity in older individuals was lower than initially observed (COVID-19-related death - initial review SRR: 3.49 [95% Cl: 1.82, 6.69]; n=6 studies; updated version SRR: 2.67 [95% Cl: 1.73, 4.12]; n=10 studies), but still identified older age as a risk factor. In the general population, older age has also been reported to be an important predictor of death after COVID-19 infection (186). In

the study of Bonanad, age groups above 50, and especially above 60 years, had an increased risk of mortality compared to the immediately younger age groups. For example, the largest increase in mortality risk was observed in patients aged 60-69 years compared to those aged 50-59 years (OR: 3.13 [95% Cl: 2.61, 3.76]) (186).

Furthermore, male sex was associated with a 38% (SRR: 1.38 [95% Cl: 1.19, 1.60]) higher relative risk of experiencing COVID-19-related death and 24% (SRR: 1.24 [95% Cl: 1.12, 1.39]) of severity. In a study that included the general population (187), male sex was also associated with severe COVID-19 disease (RR: 1.18 [95% CI: 1.10, 1.27]), a higher need for intensive care (RR: 1.38 [95% CI: 1.09 ,1.74]) and with death (RR: 1.50 [95% CI: 1.18, 1.91]). Wenham suggested that immunological differences, hormonal disparities, social factors, and lifestyle habits can play a role in the vulnerability of men and women regarding COVID-19 prognosis (188). Smoking seems to be a factor that differs in prevalence between males and females. Increased smoking levels in the male population could be a potential factor that increases the risk of adverse COVID-19 outcomes (188). Due to the protective effects of the X chromosome and sex hormones, which are crucial for both innate and adaptive immunity, women are less vulnerable to viral infections (189). On the other hand, data from the State Council Information Office in China also indicate that more than 90% of healthcare professionals in the province of Hubei are women, highlighting the character of the healthcare field and the risk borne by the majority of women health professionals (188). This fact suggests that women are more likely to get infected with COVID-19 as they are in the frontline in hospitals, hence increasing the chance of suffering from adverse COVID-19-related outcomes.

In this update of the living systematic review and meta-analysis it was observed that the course of COVID-19 disease among patients with diabetes and confirmed SARS-COV-2 was affected by obesity, identifying it as a risk factor for both outcomes. The risk of obese individuals with diabetes experiencing adverse outcomes was around 50% (SRR for COVID-19-related death: 1.54 [95% Cl: 1.11, 2.14], SRR for COVID-19-related severity: 1.51 [95% Cl: 1.19, 1.91]) higher than those who were not obese. In our study, we identified moderate statistical heterogeneity between the study findings. Possible reasons for the heterogeneity could be the fact that the population observed for this meta-analysis originated from different countries and continents, like USA, Europe and Asia, with different lifestyle and food preferences. Therefore, the risk of obesity differs depending on the lifestyle of each culture. For example, obese individuals with diabetes observed in a study in Romania experienced a more than threefold increase in the risk of suffering from a severe course of COVID-19 infection (103), but a study observing individuals in China (162) found that individuals with diabetes and

obesity experienced a 30% increase in the relative risk of COVID-19-related severity. Similar results have been observed in the general population (190).

Obesity can be defined using the BMI as an indicator (191). BMI is a proxy of body fat based on height and weight applied to adult men and women. BMI has four categories, and more specifically underweight individuals have a BMI value of <18.5 kg/m², normal weight ranges between 18.5 kg/m² and 24.9 kg/m², overweight individuals have a BMI of 25 kg/m² to 29.9 kg/m², and obesity is indicated by values 30 kg/m² and above (191). The relationship between BMI per 5 kg/m² and COVID-19-related death and severity was not clear in our meta-analysis (SRR for COVID-19-related death: 1.05 [95% Cl: 0.95, 1.16] and SRR for COVID-19-related severity: 1.01 [95% Cl: 0.84, 1.20]). According to the study of Mahamat-Saleh that included the general population infected with COVID-19, the SSR was 1.12 [95% CI: 1.07, 1.17], I^2=68%, n=25) per 5 kg/m^2 increase in BMI, indicating that individuals with obesity and the corresponding BMI value of 30 kg/ m² and above are exposed to about 12% higher relative risk of developing COVID-19-related outcomes. For persons with BMI ≥30 kg/m^2 compared to those with BMI <30 kg/m^2 it was observed that they had almost 50% increase in the relative risk for adverse outcomes (SSR: 1.45 [95% CI: 1.31, 1.61], I^2=91%, n=54, high certainty of evidence) (190).

Of note, regarding ethnicity, no associations were observed between African Americans in comparison to Non-Hispanic White and COVID-19 outcomes (Appendix Fig. 28). Based on a study in the general population, African American/Black and Hispanic populations experience disproportionately higher rates of SARS-CoV-2 infection, hospitalization, and COVID-19-related mortality compared to non-Hispanic White populations, but not higher case-fatality rates (moderate- to high certainty of evidence) (192).

Diabetes-Specific Risk Factors

For some factors, such as type and duration of diabetes, there is limited availability of evidence due to the lack of studies. Therefore, the very low certainty of the evidence and the imprecise estimations did not lead to robust results on these factors. The study included in our review with low/moderate risk of bias indicated a lower relative risk of COVID-19-related severity in individuals with T2D compared to T1D (RR: 0.37 [95% Cl: 0.04, 3.44]), but 95% CI were very wide. Studies with a high risk of bias indicated an increased relative risk of COVID-19-related severity for T2D compared to T1D (RR: 1.24 [95% Cl: 0.67, 2.27]), but again findings were imprecisely estimated (Appendix Fig. 5). Controversial findings were found in

population-based studies that covered the entire population of people with diabetes (but not all with confirmed SARS-CoV-2 infection). On the one hand, findings indicated an increased relative risk for patients with T2D compared to T1D (193), while it was simultaneously observed in another study that no differences existed by type of diabetes (194). In this study of McGurnaghan et al. (194), comparisons with the population without diabetes depicted that the risk of fatal or serious COVID-19 infection was higher for T1D than for T2D (OR for T1D: 2.40 [95% Cl: 1.82, 3.16]; OR for T2D: 1.37 [95% Cl: 1.28, 1.47]. This elevated risk in T1D is probably due to the longer duration of diabetes, as in the older age bands the cumulative incidence was higher in T1D than T2D, and because no clear difference in the risk by type was found among individuals with diabetes once age, sex, and diabetes duration were adjusted for (194). The age factor could also be used as an argument that T2D may develop a more critical course of COVID-19 infection, as the overall age distribution of individuals with T2D is higher. Another study demonstrated that both types of diabetes were related to the severity of COVID-19, with a 3-fold increase in the risk of both types compared to individuals with no diabetes (85).

Regarding HbA1c, we did not observe an association between HbA1c levels and COVID-19-related death, but we identified a relationship between the factor and COVID-19-related severity (SRR per 20mmol/mol: 1.12 [95% Cl: 1.01, 1.24]). For severity, 13 studies were available, while for death only 4 studies were available. Positive associations between higher HbA1c levels and COVID-19-related severity were also observed in population-based studies (including also persons without SARS-CoV-2 infection and/or individuals without diabetes) (194-196). In detail, compared to people with an HbA1c of 48–53 mmol/mol (6.5–7.0%), people with an HbA1c of 86 mmol/mol (10.0%) or higher had an increased relative risk of COVID-19-related mortality (HR: 2.23 [95% CI: 1.50, 3.30] in T1D and 1.61 [95% CI: 1.47, 1.77] in T2D). This indicates that individuals with T1D and high levels of HbA1c are more susceptible to adverse COVID-19-related outcomes, perhaps due to impairment of the immune system due to hyperglycemia (180). In addition, in people with T2D, COVID-19-related mortality was significantly higher in those with an HbA1c of 59 mmol/mol (7.6%) or higher than in those with an HbA1c of 48–53 mmol/mol with an increase in the relative risk for approximately 22% (HR: 1.22 [95% CI: 1.15, 1.33] for 59–74 mmol/mol (7.6–8.9%) and 35% (HR: 1.36 [1.24, 1.50]) for 75–85 mmol/mol (9.0–9.9%) (194).

Additionally, a dose-response meta-analysis among the general population yielded a linear relationship between blood glucose levels and COVID-19-related severity (197), which was also observed in our meta-analysis including only persons with diabetes (SRR per 5 mmol/l

for COVID-19-related death: 1.15 [95% Cl: 1.01, 1.32], SRR for COVID-19-related severity: 1.13 [95% Cl: 1.00, 1.29]), both with moderate certainty of evidence). Blood glucose could therefore be a sign of poorly controlled diabetes but at the same time an indicator of the COVID-19 effect on blood glucose levels. In our meta-results, we identified two studies referring to poorly controlled diabetes and COVID-19 outcomes. We observed with low certainty of evidence that poorly controlled diabetes was associated with an increased relative risk of COVID-19-related death after considering the study with low/moderate risk of bias (RR: 7.69 [95% CI: 2.32, 25.52]) (Appendix Fig. 29). The study with a high risk of bias that we included in our analysis, indicated, however, a low risk of COVID-19-related death (RR: 0.63 [95% CI: 0.15, 2.64]) with imprecise results. Similar results were observed for the outcome of COVID-19-related severity. There was an indication of heterogeneity of results perhaps due to the different laboratory methods of blood glucose measurement. Based on another study including individuals with diabetes (171), the survival rate in hospitalized patients with T2D with well-controlled blood glucose (glycemic variability within 3.9 to 10.0 mmol/L) was associated with markedly lower mortality compared to individuals with poorly controlled blood glucose (upper limit of glycemic variability exceeding 10.0 mmol/L) (HR: 0.14 [95% CI: 0.03, 0.6]) during hospitalization. The study of Lazarus et al. (197) indicated that the observed associations were also present in patients without a prior history of diabetes.

Furthermore, in our update of the systematic review, we identified several studies on the chronic use of different glucose-lowering drugs, including insulin, metformin, DPP-4 inhibitors, sulfonylurea/glinides, GLP-1-RA, SGLT-2 inhibitors, thiazolidinediones, and α-glucosidase inhibitors. Based on our results, insulin was identified as a risk factor for adverse COVID-19 outcomes, but metformin use reduced the relative risk of COVID-19-related death and severity with moderate to high certainty of evidence. The use of insulin enhanced the risk of adverse COVID-19 outcomes with an average increase in the relative risk of 62% (SRR: 1.62 [95% Cl: 1.13, 2.33]) for COVID-19-related death and 49% (SRR: 1.49 [95% Cl: 1.12, 1.99]) for COVID-19-related severity. Metformin use was associated with a reduction in the relative risk of COVID-19-related outcomes. Associations between insulin prescription and mortality were reported in previous observational studies and the relationship could be related to the late prescription of insulin during the course of diabetes disease, i.e at a later medical management stage (198). A study including individuals with diabetes and COVID-19 infection admitted to hospitals in 68 centers spread across France (199) also observed that individuals treated with insulin experienced a higher relative risk of COVID-19-related death (OR: 1.44

[95% CI: 1.01, 2.06]) and a reduced relative risk when treated with metformin (OR: 0.71 [95% CI: 0.54, 0.94]).

Mostly due to the serious or even very serious risk of bias, inconsistency between studies, and imprecise estimates, low certainty of evidence was observed for other glucose-lowering medications. For example, the results for DPP-4 inhibitors showed no relationship with COVID-19-related severity (SRR: 0.95 [95% Cl: 0.80, 1.14]) or COVID-19-related death (SRR: 0.80 [95% Cl: 0.58, 1.11]). Based on Appendix Table 1 and Appendix Table 2, which refer to GRADE, inconsistent results were observed between DPP-4 inhibitors and COVID-19-related severity (I^2: 32%) and serious imprecision as well as inconsistency of COVID-19-related death (I^2: 66%). Similarly, no clear associations were observed between SGLT-2 inhibitors use and COVID-19-related death (SRR: 1.08 [95% CI: 0.56, 2.07]) or COVID-19-related severity (SRR: 0.79 [95% CI: 0.49, 1.28]) when compared to the non-users of this medication.

A nationwide population study from England (200) observed similar results on glucose-lowering medications and COVID-19-related death. Differences were observed in SGLT-2 inhibitors that showed a decreased relative risk of COVID-19-related death (HR: 0.82 [95% Cl: 0.74, 0.91]) and a higher relative risk for DPP-4 inhibitors (HR: 1.07 [95% Cl: 1.01, 1.13]). The indications for use of DPP-4 inhibitors include older people and particularly people with frailty (198). This suggests that it is not the use of DPP-4 inhibitors per se that poses an elevated risk for COVID-19-related death but the aging population receiving the drug. At the same time, SGLT-2 inhibitors are prescribed to younger patients as these drugs provoke the risk of volume depletion, and they are therefore avoided for the elderly (200). Additional studies to validate these findings are warranted as possible residual confounding factors could have led to these results.

Alpha-glucosidase inhibitors were not clearly associated with COVID-19-related severity with low certainty of evidence as well (SRR: 0.71 [95% CI: 0.24, 2.12]) (Appendix Fig. 30). A meta-analysis examining the impact of preadmission use of glucose-lowering medications and mortality among patients with COVID-19 in T2D indicated that alpha-glucosidase inhibitors were mortality-neutral 0.61 [95% CI: 0.26, 1.45], I^2: 77%), indicating that they were not associated with an increase or a decrease in the mortality (201).

Laboratory Parameters

In this update of the living systematic review, we identified that some laboratory markers at admission like CRP, AST, eGFR, and lymphocyte count could be identified as predictors of COVID-19 outcomes.

Low lymphocyte count was associated with COVID-19-related death and COVID-19-related severity. A decrease in the lymphocyte count by $1x10^9$/L was associated with about 71% (SRR: 0.29 [95% Cl: 0.11, 0.75]) increase in the relative risk of COVID-19-related death and about 62% (SRR: 0.38 [95% Cl: 0.20, 0.71]) of COVID-19-related severity. The findings of other studies were consistent with our results that low lymphocyte count was associated with worse COVID-19 outcomes (202). More specifically, the meta-analysis of 28 studies indicated that lymphopenia (<1500 lymphocytes/µl) had a threefold higher risk of adverse outcomes compared to better outcomes (OR: 3.33 [95% Cl: 2.51, 4.41]) (202).

Our systematic review and meta-analysis indicated that an increase in CRP levels at admission is associated with adverse COVID-19-related death or COVID-19-related severity with moderate or high certainty of evidence, respectively. A 5 mg/l increase in CRP levels was associated with an increased relative risk by 7% (SRR: 1.07 [95% Cl: 1.02, 1.12]) for COVID-19-related death and by 6% (SRR: 1.06 [95% Cl: 1.01, 1.11]) for severity. A meta-analysis of 20 studies including 4843 COVID-19 patients reporting elevated CRP levels (>10 mg/L) on outcomes showed that the risk of poor outcomes was nearly fourfold higher in comparison to lower CRP levels (OR: 3.97 [95% Cl: 2.89,5.45]) (202). CRP is a non-specific acute phase reactant produced by the liver after induction by IL-6 (202). CRP is used as a biomarker for different inflammatory and infectious conditions, therefore elevated CRP levels are directly correlated with inflammation and severe disease (202). It is therefore suggested that CRP can be an effective and sensitive biomarker in predicting the COVID-19 disease progression (202). IL-6 is promptly and transiently produced after infections and tissue injuries, contributing to host defense through the stimulation of acute phase responses, haematopoiesis, and immune reactions (203).

eGFR is another factor that was inversely associated with COVID-19 outcomes with high certainty of evidence. In our meta-analysis, we observed that low eGFR levels were associated with poor COVID-19 outcomes (SRR for COVID-19-related death: 0.78 [95% Cl: 0.64, 0.93], SRR for COVID-19-related severity: 0.83 [95% Cl: 0.71, 0.96]) indicating that decreasing renal function contributes to worse outcomes. Other studies also suggested that reduced eGFR and oliguria are associated with kidney injury and CKD, leading to worse COVID-19

outcomes (204). More specifically, the odds of kidney non-recovery was greater for lower baseline eGFR, with OR: 2.09 [95% CI: 1.09, 4.04], 4.27 [95% CI: 1.99, 9.17], and 8.69 [95% CI: 3.07, 24.55] for baseline GFR 31-60, 16-30, ≤15 mL/min/1.73 m^2, respectively, compared to eGFR>60 mL/min/1.73 m^2. No references were made in every study we included in our analysis regarding the calculation of eGFR. These different methods of eGFR calculation could be a possible explanation for the heterogeneity of the results for both COVID-19 outcomes.

In detail, renal function can be assessed by the GFR. It describes the flow rate of filtered fluid through the kidneys (205) and in principle, GFR is the product of the number of nephrons times the average single-nephron GFR (206). In the routine care of patients is vital to measure accurate renal function. Kidney disease progression can be determined by the renal function status therefore therapeutic measures can be taken to prevent toxic drug accumulation in the body (205). The gold standard measurement involves the injection of inulin and its clearance by the kidneys (205). It is neither absorbed nor secreted by the renal tubules (207).

Alternatively, GFR can be calculated using creatinine levels in serum and urine (205). The Cockcroft–Gault (CG) equation was then developed to estimate creatinine clearance (207). Creatinine clearance is the volume of blood plasma cleared of creatinine per unit time (205). It is cost-effective and less time-consuming than the use of inulin for the GFR calculation (205). Creatinine is the product of the breakdown of dietary meat and creatinine phosphate found in skeletal muscle (205). However, CG uses serum creatinine adjusted for age, weight, serum creatinine, and gender (207). With age, there is a change in both renal physiology and muscle mass, affecting eGFR calculation and reducing reliability in older patients (207). Studies have also shown that creatinine clearance overestimates GFR due to the secretion of creatinine from the tubules in normal people (207). Another creatinine-based method of calculating eGFR includes the CKD-EPI (CKD Epidemiology Collaboration) equation, which allows more accurate measurements and has gained worldwide acceptance for implementation into clinical practice (207).

Moreover, in our updated meta-analyses, we observed that increased levels of AST were associated with severe COVID-19-related outcomes. An increase of 5 U/L of AST levels increased the relative risk of COVID-19-related severity by 46% (SRR: 1.46 [95% Cl: 1.09, 1.95]) and of death by 42% (SRR 1.42 [95% Cl: 1.06, 1.90]). Findings of a systematic review and meta-analyis on liver enzymes and COVID-19 outcomes are consistent with our results. The meta-analysis included 18 studies that reported elevated AST levels (>40 U/L) and

outcomes giving a sample size of 6383 patients for evaluation. Yet the associations observed in this study were stronger as elevated AST values were associated with nearly a threefold more relative risk of poor outcomes in COVID-19 patients (elevated AST (>40 U/L) (SRR: 2.75 [95% CI: 2.30, 3.29]. Similarly, in a meta-analysis of 13 studies with elevated ALT (>40 U/L) and outcomes including 6019 patients, it was found a twofold increased likelihood of poor outcomes (SRR: 1.71 [95% Cl: 1.32, 2.20]) (202). In our study, we did not observe robust results regarding ALT levels and the outcomes.

Comorbidities, Complications, and Other Non-Glucose-Lowering Medication Use

These new findings indicated that the most prevalent comorbidities, CVD, CKD, and COPD are risk factors for the severe course of COVID-19 infection in patients with diabetes. Meta-analyses and systematic reviews based on the general population observed similar results as well (208-211).

COPD is associated with COVID-19-related death with high certainty of evidence, yet the associations with COVID-19-related severity were not clear (SRR for COVID-19-related death: 1.31 [95% Cl: 1.17, 1.47], SRR for COVID-19-related severity: 1.18 [95% Cl: 0.95, 1.48]). After stratification by risk of bias due to confounding, we could observe that studies with low/moderate risk of bias due to confounding indicated an increased risk of COVID-19-related severity (RR: 1.38 [95% CI: 1.19, 1.59]) and studies with a high risk of bias due to confounding demonstrated a reduced risk of the outcome (RR: 0.91 [95% CI: 0.58, 1.43]) but the latter was characterized by small effect size and imprecise results. A systematic review and meta-analysis investigating the relationship between COPD and asthma with in-hospital mortality in the general population with COVID-19 found that hospitalized COVID-19 patients with COPD had a higher relative risk of death compared to those without COPD (OR: 2.29 [95% CI: 1.79, 2.93]), indicating a stronger association in comparison to our results (209).

Furthermore, patients with CVD are at a higher risk of developing poor outcomes after COVID-19 infection. The findings of our study suggested that they are exposed to around 30% higher relative risk for both COVID-19 outcomes with moderate to high certainty of evidence. In a meta-analysis including in-hospital patients, except pediatric population, the relative risk of developing severe COVID-19 or death was higher in patients with risk factors for CVD (hypertension: OR 2.50 [95% CI: 2.15, 2.90]; diabetes 2.25 [95% CI: 1.89,2.69]) and CVD: (3.11 [95% Cl: 2.55, 3.79) (208). Therefore, our results are consistent with the associations based on the general population.

Based on our observations, patients with diabetes and CKD are exposed to a higher risk for adverse COVID-19 outcomes (SRR for COVID-19-related death: 1.75 [95% Cl: 1.36, 2.25], SRR for COVID-19-related severity: 1.67 [95% Cl: 1.36, 2.05]) with high certainty of evidence. In the meta-analysis of Singh et al. (211), the comorbidities CKD, acute kidney injury (AKI) and continuous renal replacement therapy (CRRT) utilisation were higher in patients with severe COVID-19. More specifically, among critically ill patients with comorbidities, the incidence rate of AKI after COVID-19 infection was found to be around 24% (incidence rate: 0.24 [95% Cl: 0.20, 0.27]).

In our study, we provided evidence to support that microvascular complications of diabetes are risk factors for COVID-19-related death with moderate certainty of evidence (SRR: 1.55 [95% Cl: 1.08, 2.22]). As explained below, studies including the general population indicated similar results (112, 212, 213).

One common microvascular complication of diabetes is diabetic retinopathy. Our results suggested that diabetic retinopathy was associated with an increased relative risk of COVID-19-related severity (SRR: 2.86 [95% Cl: 0.81, 10.08]) with imprecise results, but not death (Appendix Fig. 31). The certainty of evidence for both outcomes was low, suggesting that the results are prone to change upon the inclusion of more studies. In the study of Gall (214), diabetic retinopathy was associated with the development of diabetic nephropathy and end-stage renal disease. It is not surprising, then, that diabetic retinopathy frequently coexists with extra-retinal microvascular complications (215). Furthermore, diabetic retinopathy is associated with an increased risk of CVD and mortality in T1D and T2D (216), implying that retinopathy manifests generalised microvascular damage and endothelial dysfunction. A study suggested that COVID-19 patients with diabetes, in whom diabetic retinopathy was present, experienced a five-fold increased risk of intubation (112), indicating a double risk in comparison to our results. However, further studies are warranted to explore the relationship between past COVID-19 positivity and changes in diabetic retinopathy.

Diabetic nephropathy and albuminuria are other examples of microvascular complications of diabetes mellitus. Microalbuminuria is defined as a urinary albumin measurement between 20 and 200mg/L, and macroalbuminuria as >200 mg/L (217). Albuminuria is a risk factor for diabetic nephropathy, as well as CVD (217). It was proposed as a manifestation of systemic microvascular damage by the Steno hypothesis (218), and thus, it is a useful clinical marker of generalised endothelial dysfunction and microvascular damage in the course of diabetes disease (219). When compared to non-diabetic individuals with CKD, individuals with

diabetic nephropathy have a higher risk of developing severe COVID-19 outcomes (213), reflected in the negative linear relationship between eGFR and adverse outcomes (220). Our results therefore correlate with the observations of studies based on the general population.

Peripheral neuropathy is another complication of diabetes mellitus with microvascular involvement. However, due to the lack of studies examining the impact of peripheral neuropathy on COVID-19 outcomes, we were not able to analyse the relationship between these factors in our current version of systematic review.

The findings of our study indicated that individuals with diabetes and hypertension were more vulnerable to COVID-19-related severity with high certainty of evidence and more specifically they had 28% (SRR: 1.28 [95% Cl: 1.13, 1.44]) higher relative risk of developing adverse outcomes. However, we did not observe any associations with COVID-19-related death. A meta-analysis of 186 studies representing more than a million patients with COVID-19 observed similar associations (175). Patients with COVID-19 and hypertension had more than 40% increased relative risk of death after COVID-19 infection compared to individuals with no hypertension (SRR: 1.42 [95% CI: 1.30, 1.54], n=127, low certainty of evidence) (190).

Furthermore, we observed that dementia in individuals with diabetes is a risk factor for COVID-19-related death with moderate certainty of evidence. Dementia was associated with a SRR of 76% for a worse outcome after COVID-19 infection (SRR: 1.76 [95% Cl: 1.21, 2.58]). Individuals with dementia are susceptible to serious COVID-19 outcomes, once infected with the disease, as confirmed in a study with the general population (221).

It is well established that the comorbidities of patients are associated with worse clinical outcomes after COVID-19 infection, as explained in the above section. Therefore, it remains crucial to use a tool as a thorough assessment of comorbidities to evaluate the risk of patients infected with COVID-19. The Charlson Comorbidity Index (CCI) is a simple, validated, and widely used method of estimating the risk of death from a comorbid disease that has been used as a predictor of long term prognosis and survival (222). CCI was originally created to predict death within one year of hospitalisation. Scores are based on a number of comorbidities, each of which is assigned a weighted integer ranging from one to six based on the severity of the morbidity (223). Higher CCI was associated with increased mortality and disease severity after COVID-19 infection. It is found that CCI score above 0 was associated with an increased disease severity and death when controlled for age and sex (224).

In our study, we observed that for each increase in CCI, the relative risk of COVID-19-related death increased by 33% (SRR: 1.33 [95% Cl: 1.13, 1.57]; n=2). General-population-based

scores suggested similar results to our results, and more specifically the rate of comorbidities like hypertension, CVD, COPD had strong associations with the severity and prognosis of COVID-19 (225). In the context of the COVID-19 outbreak, CCI scoring can be very useful in forecasting the need for ICU admission, respiratory support, or the likelihood of hospital readmission. Adequate treatment should not be delayed especially in people with comorbidities, as they are exposed to a higher risk of developing a more severe course of the disease. In order to plan comprehensive treatment and allocate valuable resources to individuals with higher risk, it is critical to identify them upon hospital admission using clinical scores like CCI.

Non-Glucose-Lowering Medication

The last category explored in our study was the use of non-glucose-lowering medications as risk factors of adverse COVID-19 outcomes. The chronic use of statins suggested an increase in the relative risk of COVID-19-related death by 31% with moderate certainty of evidence (SRR: 1.31 [95% Cl: 0.88, 1.95]; *n*=6). In a meta-analysis of observational studies, it was suggested that no clear reductions were observed in either in-hospital mortality (OR: 0.97 [95% CI: 0.92, 1.03]) or COVID-19 severity (OR: 1.09 [95% CI: 0.99, 1.22]) among statin users compared to non-users (226). On the other hand, findings from another systematic review and meta-analysis observed that in-hospital statin use led to a significant reduction of all-cause mortality in COVID-19 cases (OR: 0.54 [95% CI: 0.50, 0.58]) (227). Therefore, the current state of findings is controversial regarding the beneficial or detrimental effect of chronic statin use, indicating that further research is warranted for more robust results.

Another non-glucose-lowering drug that led to an increase in the risk of worse COVID-19 outcomes was the chronic use of ASA, aspirin. ASA was associated with both COVID-19-related death and severity with moderate and high certainty of evidence respectively (SRR for COVID-19-related death: 2.47 [95% Cl: 1.41, 4.31], SRR for COVID-19-related severity: 2.25 [95% Cl: 1.89, 2.67]). The heterogeneity of the results for COVID-19-related death was around 80% but for COVID-19-related severity 20%. Studies based on the general population suggested that the use of non-steroidal anti-inflammatory drugs (NSAIDs) like ASA can lead to the progression of pulmonary infections (228). Similar outcomes were also observed in a small group of young individuals taking NSAIDs for COVID-19 symptoms (229). Experts in the UK suggested that prolonged illness or complications of respiratory infections may be

more common under NSAIDs medication and respiratory, septic, and cardiovascular complications (229).

Interestingly, the results regarding RAAS inhibitors show some discrepancies. We identified 11 studies on COVID-19-related death and 20 studies on severity. No clear relationship was observed with low certainty of evidence (SRR for COVID-19-related death: 0.93 [95% Cl: 0.72, 1.21]), SRR for COVID-19-related severity: 1.03 [95% Cl: 0.83, 1.28]). Nonetheless, in a meta-analysis after stratification by risk of bias due to confounding, we found an inverse association for renin inhibitor use with COVID-19 outcomes in studies with low/moderate risk (RR for COVID-19-related death: 0.80 [95% Cl: 0.67, 0.97], RR for COVID-19-related severity: 0.80 [95% Cl: 0.64, 1.00], yet an increased risk in studies with a high risk of bias due to confounding (RR for COVID-19-related death: 1.52 [95% Cl: 0.81, 2.86], RR for COVID-19-related severity: 1.45 [95% Cl: 1.07, 1.98]). The findings at the general population level also indicated a lower relative risk for chronic use with COVID-19-related severity (OR: 0.68 [95% CI: 0.53, 0.88]), supporting our findings in studies after adjustment for important confounders (230).

Potential Mechanisms of Higher Vulnerability Between Diabetes Phenotypes and Adverse COVID-19 Outcomes

A common pathway between diabetes and COVID-19 infection is the body's inflammatory state. Diabetes, a chronic inflammatory condition, is characterized by metabolic and vascular dysfunction, likely contributing to the increased susceptibility to infection. Possible mechanisms involve the raising of blood glucose levels, triggering oxidative stress and subclinical inflammation, as well as the ACE2 binding on acinar cells and tissue damage. Moreover, hyperglycemia limits lymphocyte proliferation, exacerbating the infection (231). Through the release of glucocorticoids and catecholamines, SARS-CoV-2 infection raises stress and glucose levels in diabetic patients as well as insulin resistance contributing to the weakening of the immunological response and perhaps raising the infection risk (232). The figure below (Fig. 32) demonstrates the COVID-19 mechanism of action in individuals with diabetes (231).

COVID-19 Mechanism of Action in Individuals with Diabetes

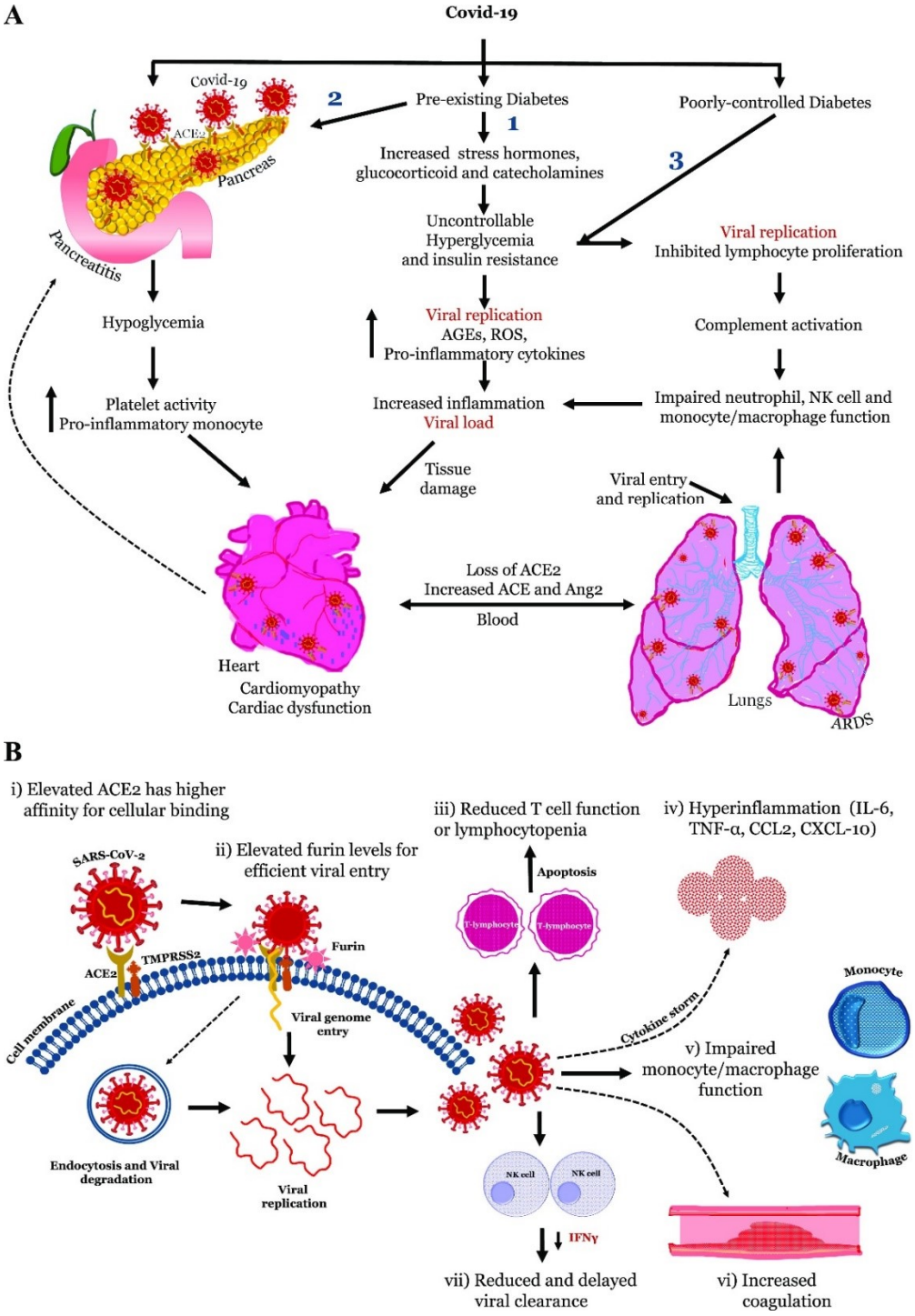


*Fig. 32: **A**: Mechanism of action of Coronavirus disease 2019 (COVID-19) in diabetes. ACE2, angiotensin-converting enzyme 2; AGE, advanced glycation end products; ANG 2, angiotensin 2; ARDS, acute respiratory distress syndrome; ROS, reactive oxygen species. **B**: Potential inflammatory mechanisms of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals with type 2 diabetes (T2D). CCL2, C-C motif chemokine ligand 2/monocyte chemotactic protein-1; CXCL-10, C-X-C motif chemokine 10; IFNγ, interferon-γ; TMPRSS2, transmembrane serine protease 2; TNF-α, tumor necrosis factor-α – modified by Narasimhulu et al (231)*

In our systematic review and meta-analysis, we identified several risk factors in individuals with diabetes contributing to worse COVID-19 outcomes. High blood glucose in diabetes deregulates the immune system, leading to elevated ACE2 for viral binding and furin levels for viral entry, reduced T cell function, or lymphopenia (233). These factors could lead to cytokine storm, impaired macrophage function, as well as increased coagulation on the endothelial level and reduced viral clearance (212). Therefore, high blood glucose, high HbA1c levels, and poor glycaemic control are associated with the impaired host defenses of our immune system, increased hospitalisation, and severity of infectious diseases amplifying hyperimmune responses post-COVID-19 infection (195).

The increasing proportion of COVID-19 patients presenting with hyperglycemia despite the absence of a diabetes diagnosis is an indication either of previously undiagnosed diabetes or for the bidirectional relationship between COVID-19 and diabetes (234). Insulin receptor signaling could be affected by enhanced angiotensin II actions due to ACE2 down-regulation after viral entry (234). SARS-CoV-2 binding to ACE2 receptors on pancreas cells could induce acute diabetes (235). Patients with diabetes and SARS-CoV-2 - ACE2 interaction experience damage and hypoglycemia, which increases platelet activity and proinflammatory monocyte movement, all of which are related to cardiovascular problems (236, 237). In detail, the cardiovascular system is under stress through the initial lung immune responses causing vessel dilation, endothelial permeability, and leucocytopenia, making CVD patients more susceptible to adverse COVID-19 outcomes (208).

A study suggested that the organ involvement of SARS-CoV-2 correlated with organ expression of ACE2 (235). Organs abundant with ACE2 were lung, kidney, heart, and islets of the pancreas. Pancreatic islets exhibited abundant ACE2, suggesting an impact on the endocrine function, leading to acute diabetes. This could therefore cause acute impairment in insulin secretion, possibly triggered by a plethora of pro-inflammatory cytokines like IL-6 damaging pancreatic β-cells. Many other viruses such as enteroviruses, Coxsackie B virus, retroviruses, rubella, mumps, cytomegalovirus, Epstein-Barr and varicella zoster virus have been also implicated in the development of T1D in humans (238).

A factor that was observed in our meta-analysis and is suggested to initiate a series of reactions that block ACE2, thereby leading to virus penetration inhibition (239) is metformin, a first-line medication for managing hyperglycemia in T2D (240). Metformin's anti-inflammatory effects are believed to mitigate obesity-induced inflammation that is associated with lower levels of the anti-inflammatory cytokine IL10, favourably influencing the clinical outcomes

after COVID-19 infection (241). Some mechanisms discussed include increasing levels of IL10 (240), improved glucose control (242), reduction in insulin resistance (243), and reduction in body weight (244).

Obesity exacerbates the inflammatory state in individuals with diabetes, exacerbating pronounced inflammation driven by elevated cytokine levels like IL-6 and TNF-α (245, 246). The humoral system's immediate defense responses against pathogens are weakened (233), and interferon-gamma production by T lymphocytes is compromised due to increased glycated end-products (247). A restrictive pulmonary pattern and reduced lung volume, indicating reduced lung capacity, along with diminishing cardiorespiratory reserves, as well as vascular endothelial dysfunction, potentially increasing the risk of excessive pulmonary vascular injury following COVID-19 infection are observed in obese individuals (248).

Endothelial dysfunction, a common diabetes-related complication, involves altered vasomotor tone, procoagulant state promotion, increased vessel permeability, and abnormal cytokine expression (212). The endothelium is the innermost lining of blood vessels and functions as a paracrine organ, controlling vascular homeostasis through factor secretion while also influencing vascular tone, platelet aggregation, local responses to inflammation, and angiogenesis (212). Microvascular complications may contribute to worse COVID-19 outcomes.

The pulmonary vasculature appears to be a site of diabetic microvascular damage (249), reducing physiological reserve for oxygenation (212) and people with diabetes are more likely to develop respiratory problems like asthma, fibrosis, and COPD (250). It is suggested that pre-existing endothelial dysfunction and microvascular disease in diabetes could exacerbate vascular insults during COVID-19 infection (212). COPD, linked to irreversible airway obstruction and often caused by smoking, is a significant comorbidity associated with severe COVID-19 infections (209). The higher mortality noted in individuals with COPD could be related to increased comorbidities (251) and smoking, which is considered to be an up-regulator of the ACE2 receptor, facilitating SARS-CoV-2 adhesion (252). The genes associated with ACE2 expression were more likely to be present in individuals with COPD, possibly related to inflammatory signaling (253).

Direct invasion of immune cells due to ACE2 expression (254) as well as the association of elevated cytokines to lymphocyte-induced apoptosis (255) explain the lymphocyte involvement in the course of COVID-19 disease. Low lymphocyte count, particularly a

decrease in $CD4^+$ T helper cells and $CD8^+$ cytotoxic T lymphocytes was associated with adverse COVID-19 outcomes correlated with disease progression (256).

Other immune cells like neutrophils are also associated with worse infection as their function is affected by NSAIDs like ASA. As a result, the clearance of bacteria and inflammation resolution can be delayed and pulmonary complications like pleural empyema, excavation, and abscess were enhanced (257). Experts in the UK suggested prolonged illness or complications of respiratory infections under NSAID medication, possibly due to the anti-inflammatory properties, thus slowing down the recovery process (229). On the other hand, ASA, with anti-inflammatory and antithrombotic effects, could be useful against COVID-19. Bianconi's study (258) suggested that ASA's anti-inflammatory mechanisms involve COX enzymes acetylation and NF-κB proinflammatory pathway suppression, addressing viral-induced inflammation. ASA's antithrombotic effects through inhibition of platelet generation by TXA2, a potent vasoconstrictor, and a stimulator of platelet reactivity, counteract the detrimental activity of COVID-19 of hypercoagulability and platelet aggregability (258).

As previously mentioned, the cytokine storm is a hallmark of severe COVID-19. Autonomic neuropathy in diabetes is associated with impaired negative feedback of the inflammatory response, therefore contributing to the excessive COVID-19 inflammation. However, further studies investigating this association are required to confirm the hypothesis (259).

Based on evidence, the risk of COVID-19-related neurological complications can be enhanced especially in individuals with pre-existing neurological deficits, for example by more specific mechanistic aspects of dementia (260). A study using data of the UK Biobank, in particular, found that individuals who are homozygous for APOE 4 experienced a more than twofold risk of COVID-19-related hospitalisation than individuals with the most common APOE 3/3 genotype (260). APOE 4 is associated with increased blood-brain barrier permeability leading to a more extensive CNS inflammation in response to SARS-CoV-2 infection. APOE4 is known to exacerbate microglia-mediated neuroinflammation and neurogeneration (261). Furthermore, APOE 4 has been linked to increased cytokine production in response to inflammatory stimuli, which may exacerbate the already inflammatory response associated with COVID-19, resulting in a cytokine storm, and in turn lung damage, multi-organ failure, and severe COVID-19 outcomes (261).

Furthermore, cytokine storm can lead to tissue injury, including liver damage with elevated AST and ALT levels (262). Liver dysfunction is likely due to secondary damage from systemic

inflammation, the use of hepatotoxic drugs like ritonavir, and COVID-19-related hypoxia ((202), (263)).

Although COVID-19 primarily affects the lungs, kidneys are also found to be affected, particularly in patients with CKD due to their persistent proinflammatory state (45). The cellular components ACE2, TMPRSS2, and cathepsin L (CTSL), essential for virus entry, are highly expressed in kidneys (264). Especially IL-6 is speculated to lead to renal inflammation, increased vascular permeability, and volume depletion (265). The upregulation of IL-6 after injured renal tubular epithelium in AKI is associated with lung-kidney bidirectional damage, leading to higher alveolar-capillary permeability and pulmonary hemorrhage (266). ARDS may also promote renal medullary hypoxia, which in turn insults tubular cells (266). As a result, GFR reduction occurs due to renal vein congestion, hypotension, and renal hypoperfusion (265).

As demonstrated in Fig. 32, COVID-19 infection can deregulate clotting cascades, leading to extensive microthrombosis in coronary and pulmonary circulation (267). These mechanisms may contribute to endothelial dysfunction in hypertension (268), potentially predisposing to severe COVID-19 (269). Guzik's study suggests an association between hypertension, $CD8^+$ T cell dysfunction, inefficient viral combat, cytokine overproduction, and a potential association with COVID-19 (270).

RAAS inhibitors, which include ACE inhibitors and ARBS, represent the backbone of the treatment of hypertension, and upregulate ACE2, the cell-entry target of SARS-CoV-2 (269), raising concern for increased susceptibility to adverse COVID-19 outcomes (271). It has been also observed that statins increase the cellular expression of ACE2 (272). Evidence supports that ACE2 is not upregulated in nasal ciliary cells of patients who received RAAS inhibitors (273). ACE2 reduces inflammation in lung diseases, diabetes, and hypertension, while its polymorphisms linked to these conditions warrant further investigation for increased COVID-19 risk (271). No clear associations with outcomes were observed in our RAAS inhibitor observations. Stratification by risk of bias suggested a decreased COVID-19 relative risk in low/moderate bias studies. In more detail, RAAS, critical in maintaining vascular tone and regulating pressure, involves renin, angiotensin, and aldosterone (44). Renin hydrolyses liver-secreted protein angiotensinogen to angiotensin I. ACE converts Ang I into Ang II, which has a vasoconstrictive role on all blood vessels (44). ACE2 is the only known human homologue of ACE and it is able to convert Ang II to Ang- (1-7), which opposes the pressor, proliferative, and profibrotic functions of Ang II (44).

RAAS, and particularly its key effector Ang II, therefore play a critical role in hypertension development, contributing to endothelial dysfunction, oxidative stress, and inflammation (274). RAAS inhibitors activate protective axes, including the activation of ACE2, and the activation of the type 2 Ang II receptor (AT2R), which exerts a protective role in the cardiovascular system through vasodilation and NO production (275). These mechanisms produce anti-proliferative, anti-inflammatory, and anti-remodeling effects (275). In a cohort of hospitalised COVID-19 patients, the ARB telmisartan reduced the CRP levels, ICU admission, and time to death compared to usual care (276). According to the evidence-based viewpoint of Cappuccio, neither ACE inhibitors nor ARBS are associated with severe COVID-19 infection (277).

Strengths and Limitations

The doctoral thesis has several strengths and limitations that will be discussed in the following section. Firstly, our study is the most comprehensive report focusing only on individuals with diabetes infected with SARS-CoV-2 and investigates a broad spectrum of risk phenotypes. We registered a protocol for our study. The literature search and screening, the data extraction, and the evaluation of the risk of bias, and the certainty of evidence were conducted independently by two researchers. A large amount of data from four different literature databases was reviewed and thoroughly evaluated. The assessment of the risk of bias of the included studies using the validated QUIPS tool, as well as the certainty of evidence using the GRADE tool allowed us to examine the trustworthiness of the results.

However, it remains possible that some factors may have affected our results, thus, the limitations of our study have to be acknowledged and warrant consideration. Given the nature of our study, we cannot infer causality from our results since the design of our study is observational. Moreover, some data were collected from studies that were rated as high risk of bias (37%), mainly due to inadequate adjustment and selection of confounders. After stratification of all meta-analyses by adjustment status, our findings were robust, except for some factors like haemoglobin and renin inhibitor use as described above. Inconsistent and imprecise meta-analyses were detected as a result of the influence of the risk of bias and the high heterogeneity of the studies. Another limitation is the lack of consideration of COVID-19 treatment, which could possibly affect our results. Since the beginning of the pandemic, tremendous research has been conducted on the possible prevention of a severe phase of COVID-19 infection. Vaccination trials have reached their maximum during the pandemic to

provide the best possible prevention plan for the uncontrollable spread of the disease. However, in 2020, in which most of the studies included in our project were published, most of the individuals did not receive any vaccination. As a result, we were unable to take into account the effect of vaccination on COVID-19 outcomes. Furthermore, we obtained information on drug prescriptions, but there is no guarantee of patient adherence to chronic treatment. Hence, the effect of non-adherence in our results is difficult to measure. Additionally, the majority of our studies were conducted in a hospital setting, signifying the severity of the course of the disease. As a result, it is difficult to transfer the findings to patients with diabetes with a milder course of COVID-19 infection, who did not receive any hospital treatment. The results may not represent all of the infected population, especially the asymptomatic cases. Individuals who were asymptomatic after SARS-CoV-2 infection may have not been tested for the virus, therefore it was not possible to include all infected individuals with diabetes in the study. Another aspect that could not be addressed in the meta-analysis is the fact that SARS-CoV-2 evolved over time, and certain results could in theory also depend on the pathogeneity of the virus strain, which was probably worse in the first year of the pandemic than later. As for the risk phenotypes investigated with a comparatively smaller sample of studies, we are highly supportive of ongoing research to generate more data and decipher the interaction between risk phenotypes and COVID-19 with a higher certainty of evidence.

Future Clinical Relevance

In view of these results, effective management of diabetes and COVID-19 infection requires the appreciation by both clinicians and policymakers that care has to take into account the complexity of the chronic disease and possible adverse outcomes after COVID-19 infection. It is likely that it is not diabetes per se, but the comorbidities of individuals with diabetes, along with the infection with COVID-19, which induce systemic inflammatory reactions that lead to adverse COVID-19 outcomes. Policymakers in each country should be guided to target individuals with diabetes who are exposed to a higher risk of worse COVID-19 outcomes and set priorities when it comes to preventive measures and disease management therapies. For example, for the vaccination programs, risk phenotypes of individuals with diabetes should be a guide to identify the vulnerable groups and prioritise these patients for early vaccination. There should also be increased vigilance in clinics with diabetes patients and the threshold of testing for COVID-19 should be lowered.

Furthermore, the entire world was dealing with the major challenge of the mismatch of resources in supply and demand to provide adequate medical support to individuals suffering from severe COVID-19 infection. Hence, it is crucial to maximise the production of medical equipment to conserve supplies, provide useful frameworks for enhancing COVID-19 care, and critically evaluate the overall patients' conditions to provide the available resources firstly to vulnerable individuals like individuals with diabetes and comorbidities. Any patient with diabetes, who has also comorbidities, should be seriously considered after COVID-19 infection as they need extra monitoring and their individual threshold for hospital admission and ICU is lowered (4). Moreover, healthcare systems should focus on the management of diabetes to stabilise the disease progression, thus reducing their vulnerability to adverse COVID-19 outcomes in case of infection. As for older individuals with diabetes, there is a need for closer interactions between specialists of geriatric individuals and primary care (198). This additional expertise in the multidisciplinary team should be beneficial for balancing the progression of multiple comorbidities, prescribing appropriate medication to counteract any possible negative interactions, and controlling any complications after COVID-19 infection. For our future update, some factors mentioned above like antihypertensive treatment and microvascular complications could be potential risk factors for further investigation.

Conclusion

Finally, the updated version of this living systematic review and meta-analysis provides insight into the associations between diabetes risk phenotypes and COVID-19 severity and death. The overall risks of fatal or critical COVID-19 infection in individuals with diabetes were substantially elevated in those with male sex, older age, and obesity, as well as higher HbA1c levels, and high blood glucose at admission were associated with COVID-19 endpoints with high certainty of evidence. Regarding medications, chronic use of insulin and metformin (inversely), the use of statins and acetylsalicylic acid was also associated with COVID-19-related death and severity. The presence of pre-existing comorbidities such as CVD, CKD, COPD, microvascular complications, dementia/cognitive impairments, a comorbidity index, hypertension, and the high levels of the laboratory markers CRP and AST, low eGFR, and low lymphocyte count at admission were all associated with a more severe COVID-19 infection in individuals with diabetes and confirmed SARS-CoV-2 infection. These findings add to the body of knowledge and have important implications for people with diabetes to reinforce the consensus that some risk phenotypes of diabetes can lead to an acute life-threatening condition in combination with COVID-19 infection. Our findings can be used to launch international

guidance on the identification of vulnerable individuals with diabetes with COVID-19 infection and can be the stimulus to identify the lack of resources within healthcare systems and set collaborative targets.

Chapter 5 – References

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Chapter 6 - Appendix

Appendix Table 1: Certainty of Evidence for Associations Between Phenotypes of Individuals with Diabetes and SARS-CoV-2 Regarding COVID-19-Related Death

Certainty assessment							Relative risk (95% CI)	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Male sex								
19	observational studies	not serious [a]	not serious	not serious	not serious	None	**RR 1.38** (1.19 to 1.59)	⊕⊕⊕⊕ HIGH
Age >65 years								
10	observational studies	not serious [a]	not serious	not serious	not serious	strong association	**RR 2.67** (1.73 to 4.12)	⊕⊕⊕⊕ HIGH
Age per 5 years								
12	observational studies	not serious [b]	not serious	not serious	not serious	dose response gradient	**RR 1.26** (1.15 to 1.38)	⊕⊕⊕◯ MODERATE
BMI, per 5 kg/m²								
5	observational studies	not serious	serious [c]	not serious	not serious	None	**RR 1.05** (0.95 to 1.16)	⊕⊕⊕◯ MODERATE
Overweight								
4	observational studies	not serious	not serious	not serious	very serious [d]	none	**RR 0.91** (0.66 to 1.27)	⊕⊕◯◯ LOW
Obesity								
9	observational studies	not serious	not serious	not serious	not serious	None	**RR 1.54** (1.11 to 2.15)	⊕⊕⊕⊕ HIGH
Smoking (smoker vs not smoker)								
4	observational studies	not serious	serious [c]	not serious	not serious	none	**RR 0.92** (0.81 to 1.04)	⊕⊕⊕◯ MODERATE
Ethnicity: African American vs. Non-Hispanic white								
4	observational studies	very serious [e]	not serious	not serious	very serious [d]	None	**RR 0.98** (0.73 to 1.31)	⊕◯◯◯ VERY LOW

Appendix Table 1: Certainty of Evidence for Associations Between Phenotypes of Individuals with Diabetes and SARS-CoV-2 Regarding COVID-19-Related Death

Certainty assessment							Relative risk (95% CI)	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Ethnicity: Hispanic vs. Non-Hispanic white								
2	observational studies	not serious	not serious	not serious	extremely serious [d,f]	None	**RR 0.50** (0.17 to 1.44)	⊕◯◯◯ VERY LOW
Type 2 vs T1D								
3	observational studies	extremely serious [g]	not serious	not serious	very serious [d]	none	**RR 1.35** (0.58 to 3.13)	⊕◯◯◯ VERY LOW
Diabetes duration, per 5 years								
2	observational studies	extremely serious [g]	not serious	not serious	extremely serious [h]	none	**RR 1.47** (0.13 to 13.79)	⊕◯◯◯ VERY LOW
HbA1c, 53-75 vs <53 mmol/mol (7-9 vs <7%)								
3	observational studies	serious [i]	not serious	not serious	very serious [d]	none	**RR 0.91** (0.54 to 1.54)	⊕◯◯◯ VERY LOW
HbA1c, >75 vs <53 mmol/mol (>9 vs <7%)								
5	observational studies	extremely serious [g]	not serious	not serious	serious [j]	none	**RR 0.89** (0.76 to 1.05)	⊕◯◯◯ VERY LOW
HbA1c per 20 mmol/mol increase								
4	observational studies	not serious	not serious	not serious	not serious	none	**RR 0.98** (0.92 to 1.05)	⊕⊕⊕⊕ HIGH
Blood glucose at admission >7 mmol/l								
3	observational studies	not serious	not serious	not serious	serious [k]	strong association	**RR 2.75** (1.27 to 5.97)	⊕⊕⊕⊕ HIGH
Blood glucose at admission >11 mmol/ l								

Appendix Table 1: Certainty of Evidence for Associations Between Phenotypes of Individuals with Diabetes and SARS-CoV-2 Regarding COVID-19-Related Death

Certainty assessment							Relative risk (95% CI)	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
5	observational studies	extremely serious [g]	not serious	not serious	serious [j]	none	**RR 1.83** (0.89 to 3.37)	⊕◯◯◯ VERY LOW
Blood glucose at admission, per 5 mmol/l								
6	observational studies	very serious [e]	not serious	not serious	not serious	dose response gradient	**RR 1.15** (1.01 to 1.32)	⊕⊕⊕◯ MODERATE
Poorly controlled								
2	observational studies	serious [i]	serious [l]	not serious	extremely serious [h]	strong association	**RR 2.27** (0.20 to 26.39)	⊕⊕◯◯ LOW
Use of insulin								
12	observational studies	not serious	not serious	not serious	not serious	none	**RR 1.62** (1.13 to 2.33)	⊕⊕⊕⊕ HIGH
Use of metformin								
11	observational studies	not serious	not serious	not serious	not serious	none	**RR 0.68** (0.51 to 0.89)	⊕⊕⊕⊕ HIGH
Use of DPP-4 inhibitors								
9	observational studies	not serious	serious [m]	not serious	serious [j]	none	**RR 0.80** (0.58 to 1.11)	⊕⊕◯◯ LOW
Use of sulfonylurea/glinide								
6	observational studies	very serious [e]	not serious	not serious	very serious [d]	none	**RR 0.93** (0.71 to 1.21)	⊕◯◯◯ VERY LOW
Use of GLP1-RA								
4	observational studies	very serious [e]	not serious	not serious	not serious	none	**RR 0.71** (0.53 to 0.93)	⊕⊕◯◯ LOW

Appendix Table 1: Certainty of Evidence for Associations Between Phenotypes of Individuals with Diabetes and SARS-CoV-2 Regarding COVID-19-Related Death

Certainty assessment							Relative risk (95% CI)	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Use of SGLT-2 inhibitors								
3	observational studies	serious [i]	not serious	not serious	very serious [d]	none	**RR 1.08** (0.56 to 2.07)	⊕◯◯◯ VERY LOW
Use of thiazolidinedione								
3	observational studies	serious [i]	serious [n]	not serious	very serious [d]	none	**RR 0.78** (0.30 to 2.01)	⊕◯◯◯ VERY LOW
Hypertension								
18	observational studies	serious [i]	not serious	not serious	serious [j]	none	**RR 1.14** (0.96 to 1.36)	⊕⊕◯◯ LOW
Dyslipidaemia								
4	observational studies	very serious [e]	not serious	not serious	not serious	none	**RR 1.02** (0.89 to 1.18)	⊕⊕◯◯ LOW
Total CVD								
14	observational studies	not serious	not serious	not serious	not serious	none	**RR 1.33** (1.11 to 1.59)	⊕⊕⊕⊕ HIGH
CAD								
5	observational studies	very serious [e]	not serious	not serious	not serious	none	**RR 1.78** (1.21 to 2.64)	⊕⊕◯◯ LOW
Myocardial infarction (MI)								
2	observational studies	very serious [e]	not serious	not serious	serious [j]	none	**RR 1.13** (0.92 to 1.37)	⊕◯◯◯ VERY LOW
Heart failure (HF)								
5	observational studies	very serious [e]	not serious	not serious	not serious	none	**RR 1.48** (1.19 to 1.83)	⊕⊕◯◯ LOW
Cerebrovascular disease								

Appendix Table 1: Certainty of Evidence for Associations Between Phenotypes of Individuals with Diabetes and SARS-CoV-2 Regarding COVID-19-Related Death

Certainty assessment							Relative risk (95% CI)	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
8	observational studies	very serious [e]	serious [o]	not serious	very serious [d]	none	**RR 1.08** (0.64 to 1.80)	⊕◯◯◯ VERY LOW
Stroke								
2	observational studies	very serious [e]	not serious	not serious	very serious [d]	none	**RR 1.05** (0.71 to 1.55)	⊕◯◯◯ VERY LOW
Microvascular complications								
3	observational studies	not serious	not serious	serious [p]	not serious	none	**RR 1.55** (1.08 to 2.22)	⊕⊕⊕◯ MODERATE
CKD								
14	observational studies	not serious [a]	not serious	not serious	not serious	none	**RR 1.75** (1.36 to 2.25)	⊕⊕⊕⊕ HIGH
Diabetic foot								
2	observational studies	extremely serious [g]	not serious	not serious	extremely serious [h]	strong association	**RR 6.07** (0.22 to 170.87)	⊕◯◯◯ VERY LOW
Liver disease								
3	observational studies	serious [i]	not serious	not serious	very serious [d]	strong association	**RR 2.20** (0.81 to 6.02)	⊕⊕◯◯ LOW
Chronic pulmonary diseases, not specified								
3	observational studies	not serious	not serious	not serious	very serious [d]	none	**RR 1.32** (0.72 to 2.44)	⊕◯◯◯ VERY LOW
COPD								
9	observational studies	not serious [a]	not serious	not serious	not serious	none	**RR 1.31** (1.17 to 1.47)	⊕⊕⊕⊕ HIGH
Asthma								

Appendix Table 1: Certainty of Evidence for Associations Between Phenotypes of Individuals with Diabetes and SARS-CoV-2 Regarding COVID-19-Related Death

Certainty assessment							Relative risk (95% CI)	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
5	observational studies	very serious [e]	not serious	not serious	serious [j]	none	**RR 0.84** (0.64 to 1.11)	⊕◯◯◯ VERY LOW
Obstructive sleep apnea								
2	observational studies	not serious	not serious	not serious	very serious [d]	none	**RR 0.92** (0.56 to 1.49)	⊕⊕◯◯ LOW
Cancer								
10	observational studies	very serious [e]	not serious	not serious	serious [j]	none	**RR 1.06** (0.92 to 1.22)	⊕◯◯◯ VERY LOW
Dementia/cognitive impairment								
4	observational studies	serious [i]	not serious	not serious	not serious	none	**RR 1.76** (1.21 to 2.58)	⊕⊕⊕◯ MODERATE
Any comorbidity								
2	observational studies	extremely serious [g]	serious [q]	not serious	very serious [d]	none	**RR 1.17** (0.31 to 4.37)	⊕◯◯◯ VERY LOW
≥3 comorbidities								
2	observational studies	very serious [e]	very serious [r]	not serious	extremely serious [h]	strong association	**RR 10.36** (0.64 to 168.30)	⊕◯◯◯ VERY LOW
Charlson index per 1 unit								
2	observational studies	serious [i]	not serious	not serious	not serious	none	**RR 1.33** (1.13 to 1.57)	⊕⊕⊕◯ MODERATE
Use of statins								
6	observational studies	not serious	not serious	not serious	serious [j]	none	**RR 1.31** (0.88 to 1.95)	⊕⊕⊕◯ MODERATE
Use of renin inhibitors								

Appendix Table 1: Certainty of Evidence for Associations Between Phenotypes of Individuals with Diabetes and SARS-CoV-2 Regarding COVID-19-Related Death

Certainty assessment							Relative risk (95% CI)	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
11	observational studies	serious [i]	not serious	not serious	very serious [d]	none	**RR 0.93** (0.72 to 1.21)	⊕◯◯◯ VERY LOW
Use of beta-blockers								
3	observational studies	very serious [e]	serious [s]	not serious	very serious [d]	none	**RR 1.44** (0.59 to 3.54)	⊕◯◯◯ VERY LOW
Use of calcium channel blocker (CCB)								
2	observational studies	extremely serious [g]	not serious	not serious	serious [j]	none	**RR 1.20** (0.99 to 1.45)	⊕◯◯◯ VERY LOW
Use of diuretics								
3	observational studies	very serious [e]	not serious	not serious	serious [j]	none	**RR 1.29** (0.83 to 2.02)	⊕◯◯◯ VERY LOW
Use of acetylsalicylic acid (ASA)								
2	observational studies	not serious	serious [t]	not serious	serious [u]	strong association	**RR 2.47** (1.41 to 4.31)	⊕⊕⊕◯ MODERATE
Use of antiplatelet/anticoagulant								
4	observational studies	very serious [e]	not serious	not serious	very serious [d]	none	**RR 1.01** (0.67 to 1.54)	⊕◯◯◯ VERY LOW
CRP, per 5 mg/l								
7	observational studies	very serious [e]	not serious	not serious	not serious	dose response gradient	**RR 1.07** (1.02 to 1.12)	⊕⊕⊕◯ MODERATE
Procalcitonin, per 1 ng/ml								
2	observational studies	very serious [e]	not serious	not serious	serious [f]	dose response gradient	**RR 1.20** (1.06 to 1.35)	⊕⊕◯◯ LOW
Albumin, per 1 g/l								

Appendix Table 1: Certainty of Evidence for Associations Between Phenotypes of Individuals with Diabetes and SARS-CoV-2 Regarding COVID-19-Related Death

Certainty assessment							Relative risk (95% CI)	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
3	observational studies	very serious [e]	not serious	not serious	serious [j]	none	**RR 0.80** (0.63 to 1.01)	⊕◯◯◯ VERY LOW
ALT, per 5 unit/l								
3	observational studies	very serious [e]	not serious	not serious	not serious	none	**RR 1.00** (0.83 to 1.20)	⊕⊕◯◯ LOW
AST, per 5 unit/l								
4	observational studies	very serious [e]	not serious	not serious	not serious	dose response gradient	**RR 1.42** (1.06 to 1.90)	⊕⊕⊕◯ MODERATE
eGFR per 10 mL/min/1.73 m^2								
3	observational studies	serious [i]	not serious	not serious	not serious	dose response gradient	**RR 0.78** (0.64 to 0.93)	⊕⊕⊕⊕ HIGH
Urea, per 1 mmol/L								
2	observational studies	extremely serious [g]	not serious	not serious	serious [f]	none	**RR 1.03** (0.96 to 1.09)	⊕◯◯◯ VERY LOW
Creatinine, per 10 µmol/l								
4	observational studies	very serious [e]	not serious	not serious	not serious	none	**RR 1.03** (1.00 to 1.06)	⊕⊕◯◯ LOW
White blood cell count, per 1x10^9/l								
5	observational studies	very serious [e]	serious [v]	not serious	serious [j]	none	**RR 1.12** (0.98 to 1.27)	⊕◯◯◯ VERY LOW
Neutrophils, per 1x10^9/l								
3	observational studies	extremely serious [g]	serious [w]	not serious	serious [j]	none	**RR 1.10** (0.93 to 1.29)	⊕◯◯◯ VERY LOW
Lymphocyte count, per 1x10^9/l								

Appendix Table 1: Certainty of Evidence for Associations Between Phenotypes of Individuals with Diabetes and SARS-CoV-2 Regarding COVID-19-Related Death

Certainty assessment							Relative risk (95% CI)	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
5	observational studies	very serious [e]	serious [x]	not serious	not serious	strong association dose response gradient	**RR 0.29** (0.11 to 0.73)	⊕⊕⊕◯ MODERATE
Platelet count, per 1x10^9/l								
3	observational studies	serious [i]	not serious	not serious	not serious	none	**RR 0.99** (0.98 to 1.00)	⊕⊕⊕◯ MODERATE
Lactatdehydrogenase, per 10 unit/l								
4	observational studies	very serious [e]	not serious	not serious	not serious	none	**RR 1.05** (0.97 to 1.13)	⊕⊕◯◯ LOW
D-Dimer, per 1 mg/L								
3	observational studies	serious [i]	serious [c]	not serious	serious [f]	none	**RR 1.00** (0.97 to 1.03)	⊕◯◯◯ VERY LOW
Haemoglobin, per 5 g/dL								
2	observational studies	serious [i]	very serious [y]	not serious	extremely serious [h]	strong association	**RR 0.47** (0.07 to 2.98)	⊕◯◯◯ VERY LOW

Appendix Table 1: Certainty of Evidence for Associations Between Phenotypes of Individuals with Diabetes and SARS-CoV-2 Regarding COVID-19-Related Death

Certainty assessment							Relative risk (95% CI)	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		

a. High proportion (>25-50%) of evidence from studies with high risk of bias; however, in stratified analysis clear association in low/moderate Rob studies.
b. Very high proportion (>50-90%) of evidence from studies with high risk of bias; however, in stratified analysis clear association in low/moderate Rob studies.
c. One study with strong association included, but it has a small weight
d. 95% CI includes the null value and includes important benefit AND harm
e. Very high proportion (>50-90%) of evidence from studies with high risk of bias
f. Number of participants: n<400
g. Extremely high proportion (>90-100%) of evidence from studies with high risk of bias
h. 95% CI includes the null value and includes important benefit AND harm and is extremely wide
i. High proportion (>25-50%) of evidence from studies with high risk of bias
j. 95% CI includes the null value and includes important benefit OR harm
k. Only three studies and wide 95% CI
l. RR ranged from 0.63 to 7.69 and minimal overlap of 95% CIs
m. RR ranged from 0.13 to 1.48 and minimal overlap of 95% CIs
n. RR ranged from 0.32 to 1.37 and minimal overlap of 95% CIs
o. RR ranged from 0.15 to 5.32 and minimal overlap of 95% CIs
p. Microvascular diseases not further explained and indirectness is possible.
q. RR ranged from 0.57 to 2.20 and minimal overlap of 95% CIs
r. RR ranged from 2.57 to 44.22 and no overlap of 95% CIs
s. One study with strong harmful and one with strong beneficial association included.
t. RR ranged from 1.76 to 3.14 and minimal overlap of 95% CIs
u. Only two studies and wide 95% CI
v. RR ranged from 0.76 to 1.54 and partly no overlap of 95% CIs
w. RR ranged from 0.76 to 1.24 and partly no overlap of 95% CIs
x. RR ranged from 0.01 to 0.81 and partly no overlap of 95% CIs
y. RR ranged from 0.54 to 1.55 and no overlap of 95% Cis

Certainty of evidence for associations between phenotypes of people with diabetes and COVID-19-related death - modified by Schlesinger et al (80)

Appendix Table 2: Certainty of Evidence for Associations Between Phenotypes of Individuals with Diabetes and SARS-CoV-2 Regarding COVID-19-Related Severity

Certainty assessment							Relative risk (95% CI)	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Male sex								
28	observational studies	serious [a]	not serious	not serious	not serious	none	**RR 1.24** (1.12 to 1.39)	⊕⊕⊕◯ MODERATE
Age >65 years								
11	observational studies	not serious [b]	not serious	not serious	not serious	none	**RR 1.92** (1.42 to 2.61)	⊕⊕⊕⊕ HIGH
Age per 5 years								
18	observational studies	very serious [c]	not serious	not serious	not serious	dose response gradient	**RR 1.22** (1.11 to 1.28)	⊕⊕⊕◯ MODERATE
BMI, per 5 kg/m²								
9	observational studies	not serious	serious [d]	not serious	not serious	none	**RR 1.01** (0.84 to 1.20)	⊕⊕⊕◯ MODERATE
Overweight								
6	observational studies	not serious	not serious	not serious	serious [e]	none	**RR 1.08** (0.84 to 1.39)	⊕⊕⊕◯ MODERATE
Obesity								
13	observational studies	not serious	not serious	not serious	not serious	publication bias suspected	**RR 1.51** (1.19 to 1.91)	⊕⊕⊕◯ MODERATE
Smoking (smoker vs not smoker)								
5	observational studies	not serious	serious [f]	not serious	serious [e]	none	**RR 0.87** (0.68 to 1.11)	⊕⊕◯◯ LOW
Ethnicity: African American vs. Non-Hispanic white								

Appendix Table 2: Certainty of Evidence for Associations Between Phenotypes of Individuals with Diabetes and SARS-CoV-2 Regarding COVID-19-Related Severity

Certainty assessment							Relative risk (95% CI)	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
5	observational studies	very serious [c]	not serious	not serious	serious [e]	none	**RR 1.02** (0.81 to 1.29)	⊕◯◯◯ VERY LOW
Ethnicity: Hispanic vs. Non-Hispanic white								
2	observational studies	not serious	serious [g]	not serious	extremely serious [h]	none	**RR 1.10** (0.14 to 8.67)	⊕◯◯◯ VERY LOW
Type 2 vs T1D								
4	observational studies	extremely serious [i]	not serious	not serious	very serious [j]	none	**RR 1.14** (0.63 to 2.05)	⊕◯◯◯ VERY LOW
Diabetes duration, per 5 years								
4	observational studies	extremely serious [i]	not serious	not serious	very serious [j]	none	**RR 1.05** (0.77 to 1.40)	⊕◯◯◯ VERY LOW
HbA1c, 53-75 vs <53 mmol/mol (7-9 vs <7%)								
9	observational studies	very serious [c]	not serious	not serious	not serious	none	**RR 1.42** (1.01 to 2.00)	⊕⊕◯◯ LOW
HbA1c, >75 vs <53 mmol/mol (>9 vs <7%)								
7	observational studies	very serious [c]	serious [k]	not serious	very serious [j]	none	**RR 1.04** (0.73 to 1.46)	⊕◯◯◯ VERY LOW
HbA1c per 20 mmol/mol increase								
13	observational studies	very serious [c]	not serious	not serious	not serious	dose response gradient	**RR 1.12** (1.01 to 1.24)	⊕⊕⊕◯ MODERATE
Blood glucose at admission >7 mmol/l								
3	observational studies	serious [a]	not serious	not serious	serious [l]	strong association dose response gradient	**RR 2.79** (1.35 to 5.75)	⊕⊕⊕⊕ HIGH
Blood glucose at admission >11 mmol/ l								

Appendix Table 2: Certainty of Evidence for Associations Between Phenotypes of Individuals with Diabetes and SARS-CoV-2 Regarding COVID-19-Related Severity

Certainty assessment							Relative risk (95% CI)	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
6	observational studies	very serious [c]	not serious	not serious	serious [e]	dose response gradient	**RR 1.52** (0.84 to 2.67)	⊕⊕◯◯ LOW
Blood glucose at admission, per 5 mmol/l								
8	observational studies	very serious [c]	not serious	not serious	not serious	dose response gradient	**RR 1.13** (1.00 to 1.29)	⊕⊕⊕◯ MODERATE
Poorly controlled								
2	observational studies	serious [a]	not serious	not serious	very serious [j]	none	**RR 1.48** (0.41 to 5.33)	⊕◯◯◯ VERY LOW
Use of insulin								
16	observational studies	not serious [b]	not serious	not serious	not serious	none	**RR 1.49** (1.12 to 1.99)	⊕⊕⊕⊕ HIGH
Use of metformin								
15	observational studies	serious [a]	not serious	not serious	not serious	none	**RR 0.75** (0.58 to 0.96)	⊕⊕⊕◯ MODERATE
Use of DPP-4 inhibitors								
13	observational studies	not serious	serious [m]	not serious	not serious	none	**RR 0.95** (0.80 to 1.14)	⊕⊕⊕◯ MODERATE
Use of sulfonylurea/glinide								
9	observational studies	very serious [c]	not serious	not serious	serious [e]	none	**RR 1.13** (0.84 to 1.51)	⊕◯◯◯ VERY LOW
Use of GLP1-RA								
5	observational studies	serious [a]	not serious	not serious	very serious [j]	none	**RR 0.77** (0.47 to 1.25)	⊕◯◯◯ VERY LOW
Use of SGLT-2 inhibitors								

Appendix Table 2: Certainty of Evidence for Associations Between Phenotypes of Individuals with Diabetes and SARS-CoV-2 Regarding COVID-19-Related Severity

Certainty assessment							Relative risk (95% CI)	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
6	observational studies	not serious	not serious	not serious	very serious [j]	none	**RR 0.79** (0.49 to 1.28)	⊕⊕◯◯ LOW
Use of thiazolidinedione								
6	observational studies	serious [a]	not serious	not serious	very serious [j]	none	**RR 1.26** (0.74 to 2.15)	⊕◯◯◯ VERY LOW
Use of alpha-glucosidase inhibitors								
3	observational studies	very serious [c]	not serious	not serious	very serious [j]	none	**RR 0.71** (0.24 to 2.12)	⊕◯◯◯ VERY LOW
Hypertension								
24	observational studies	not serious [b]	not serious	not serious	not serious	none	**RR 1.28** (1.13 to 1.44)	⊕⊕⊕⊕ HIGH
Dyslipidaemia								
5	observational studies	very serious [c]	not serious	not serious	not serious	none	**RR 1.00** (0.88 to 1.14)	⊕⊕◯◯ LOW
Total CVD								
18	observational studies	serious [a]	not serious	not serious	not serious	none	**RR 1.31** (1.11 to 1.55)	⊕⊕⊕◯ MODERATE
CAD								
8	observational studies	very serious [c]	serious [n]	not serious	serious [e]	none	**RR 1.22** (0.88 to 1.68)	⊕◯◯◯ VERY LOW
Heart failure (HF)								
7	observational studies	very serious [c]	not serious	not serious	serious [e]	none	**RR 1.20** (0.88 to 1.62)	⊕◯◯◯ VERY LOW
Cerebrovascular disease								

Appendix Table 2: Certainty of Evidence for Associations Between Phenotypes of Individuals with Diabetes and SARS-CoV-2 Regarding COVID-19-Related Severity

Certainty assessment							Relative risk (95% CI)	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
11	observational studies	very serious [c]	serious [o]	not serious	very serious [j]	none	**RR 1.03** (0.74 to 1.45)	⊕◯◯◯ VERY LOW
Stroke								
3	observational studies	extremely serious [i]	not serious	not serious	not serious	none	**RR 0.99** (0.83 to 1.18)	⊕◯◯◯ VERY LOW
Microvascular complications								
3	observational studies	very serious [c]	not serious	not serious	serious [e]	none	**RR 1.20** (0.87 to 1.65)	⊕◯◯◯ VERY LOW
CKD								
18	observational studies	not serious [b]	not serious	not serious	not serious	none	**RR 1.67** (1.36 to 2.05)	⊕⊕⊕⊕ HIGH
Retinopathy								
3	observational studies	very serious [c]	not serious	not serious	very serious [p]	strong association	**RR 2.86** (0.81 to 10.08)	⊕◯◯◯ VERY LOW
Diabetic foot								
4	observational studies	very serious [c]	serious [q]	not serious	very serious [j]	none	**RR 1.92** (0.47 to 7.74)	⊕◯◯◯ VERY LOW
Liver disease								
4	observational studies	very serious [c]	not serious	not serious	very serious [j]	none	**RR 1.92** (0.79 to 4.68)	⊕◯◯◯ VERY LOW
Chronic pulmonary diseases, not specified								
6	observational studies	serious [a]	not serious	not serious	not serious	none	**RR 1.52** (1.19 to 1.96)	⊕⊕⊕◯ MODERATE
COPD								

Appendix Table 2: Certainty of Evidence for Associations Between Phenotypes of Individuals with Diabetes and SARS-CoV-2 Regarding COVID-19-Related Severity

Certainty assessment							Relative risk (95% CI)	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
12	observational studies	not serious [b]	not serious	not serious	serious [e]	none	**RR 1.18** (0.95 to 1.48)	⊕⊕⊕◯ MODERATE
Asthma								
6	observational studies	very serious [c]	not serious	not serious	serious [e]	none	**RR 0.87** (0.69 to 1.09)	⊕◯◯◯ VERY LOW
Obstructive sleep apnea								
2	observational studies	extremely serious [i]	not serious	not serious	not serious	none	**RR 1.36** (1.04 to 1.76)	⊕◯◯◯ VERY LOW
Cancer								
13	observational studies	very serious [c]	not serious	not serious	serious [e]	none	**RR 1.08** (0.95 to 1.24)	⊕◯◯◯ VERY LOW
Dementia/cognitive impairment								
5	observational studies	serious [a]	not serious	not serious	serious [e]	none	**RR 1.59** (0.96 to 2.64)	⊕⊕◯◯ LOW
Any comorbidity								
2	observational studies	extremely serious [i]	not serious	not serious	not serious	strong association	**RR 2.06** (1.17 to 3.61)	⊕⊕◯◯ LOW
≥3 comorbidities								
2	observational studies	very serious [c]	serious [r]	not serious	extremely serious [p]	strong association	**RR 12.06** (0.99 to 146.39)	⊕◯◯◯ VERY LOW
Charlson index per 1 unit								
2	observational studies	serious [a]	not serious	not serious	serious [e]	none	**RR 1.22** (0.90 to 1.66)	⊕⊕◯◯ LOW
Use of statins								

Appendix Table 2: Certainty of Evidence for Associations Between Phenotypes of Individuals with Diabetes and SARS-CoV-2 Regarding COVID-19-Related Severity

Certainty assessment							Relative risk (95% CI)	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
9	observational studies	serious [a]	not serious	not serious	serious [e]	none	**RR 1.20** (0.82 to 1.77)	⊕⊕◯◯ LOW
Use of renin inhibitors								
20	observational studies	serious [a]	not serious	not serious	serious [e]	none	**RR 1.03** (0.83 to 1.28)	⊕⊕◯◯ LOW
Use of beta-blockers								
3	observational studies	very serious [c]	serious [s]	not serious	very serious [j]	none	**RR 1.30** (0.48 to 3.49)	⊕◯◯◯ VERY LOW
Use of calcium channel blocker (CCB)								
4	observational studies	very serious [c]	serious [s]	not serious	very serious [j]	none	**RR 1.35** (0.62 to 2.90)	⊕◯◯◯ VERY LOW
Use of diuretics								
3	observational studies	extremely serious [i]	not serious	not serious	serious [e]	none	**RR 1.09** (0.92 to 1.29)	⊕◯◯◯ VERY LOW
Use of acetylsalicylic acid (ASA)								
2	observational studies	not serious	not serious	serious [t]	not serious	strong association	**RR 2.25** (1.89 to 2.67)	⊕⊕⊕⊕ HIGH
Use of antiplatelet/anticoagulant								
5	observational studies	very serious [c]	not serious	not serious	serious [e]	none	**RR 0.91** (0.79 to 1.05)	⊕◯◯◯ VERY LOW
Triglycerides, per 1mmol/L								
2	observational studies	extremely serious [i]	serious [u]	not serious	very serious [j]	none	**RR 1.29** (0.73 to 2.27)	⊕◯◯◯ VERY LOW

Appendix Table 2: Certainty of Evidence for Associations Between Phenotypes of Individuals with Diabetes and SARS-CoV-2 Regarding COVID-19-Related Severity

Certainty assessment							Relative risk (95% CI)	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Total cholesterol, per 1mmol/L								
2	observational studies	extremely serious [i]	not serious	not serious	very serious [j]	none	**RR 0.90** (0.66 to 1.22)	⊕◯◯◯ VERY LOW
CRP, per 5 mg/l								
8	observational studies	serious [a]	not serious	not serious	not serious	dose response gradient	**RR 1.06** (1.01 to 1.11)	⊕⊕⊕⊕ HIGH
IL-6, per 5 pg/ml								
3	observational studies	very serious [c]	not serious	not serious	not serious	dose response gradient	**RR 1.07** (1.04 to 1.10)	⊕⊕⊕◯ MODERATE
Procalcitonin, per 1 ng/ml								
3	observational studies	extremely serious [i]	not serious	not serious	not serious	dose response gradient	**RR 1.22** (1.15 to 1.30)	⊕⊕◯◯ LOW
Albumin, per 1 g/l								
3	observational studies	very serious [c]	not serious	not serious	serious [e]	none	**RR 0.81** (0.65 to 1.01)	⊕◯◯◯ VERY LOW
ALT, per 5 unit/l								
3	observational studies	very serious [c]	not serious	not serious	not serious	none	**RR 0.99** (0.85 to 1.16)	⊕⊕◯◯ LOW
AST, per 5 unit/l								
4	observational studies	very serious [c]	not serious	not serious	not serious	dose response gradient	**RR 1.46** (1.09 to 1.95)	⊕⊕⊕◯ MODERATE
eGFR per 10 mL/min/1.73 m²								
3	observational studies	serious [a]	not serious	not serious	not serious	dose response gradient	**RR 0.83** (0.71 to 0.96)	⊕⊕⊕⊕ HIGH

Appendix Table 2: Certainty of Evidence for Associations Between Phenotypes of Individuals with Diabetes and SARS-CoV-2 Regarding COVID-19-Related Severity

Certainty assessment							Relative risk (95% CI)	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Urea, per 1 mmol/L								
2	observational studies	extremely serious [i]	serious [v]	not serious	not serious	none	**RR 0.95** (0.84 to 1.06)	⊕◯◯◯ VERY LOW
Creatinine, per 10 µmol/l								
6	observational studies	very serious [c]	not serious	not serious	not serious	dose response gradient	**RR 1.03** (1.01 to 1.06)	⊕⊕⊕◯ MODERATE
White blood cell count, per 1x10^9/l								
6	observational studies	serious [a]	serious [w]	not serious	not serious	none	**RR 1.08** (0.96 to 1.20)	⊕⊕◯◯ LOW
Neutrophils, per 1x10^9/l								
4	observational studies	extremely serious [i]	not serious	not serious	not serious	dose response gradient	**RR 1.24** (1.18 to 1.29)	⊕⊕◯◯ LOW
Lymphocyte count, per 1x10^9/l								
6	observational studies	serious [a]	not serious	not serious	not serious	strong association dose response gradient	**RR 0.38** (0.20 to 0.71)	⊕⊕⊕⊕ HIGH
Neutrophil-to-lymphocyte ratio								
2	observational studies	very serious [c]	serious [v]	not serious	very serious [j,x]	none	**RR 1.55** (0.71 to 3.42)	⊕◯◯◯ VERY LOW
Platelet count, per 1x10^9/l								
5	observational studies	serious [a]	not serious	not serious	not serious	none	**RR 0.99** (0.99 to 1.00)	⊕⊕⊕◯ MODERATE
Lactatdehydrogenase, per 10 unit/l								
4	observational studies	serious [a]	not serious	not serious	serious [e]	none	**RR 1.17** (0.97 to 1.41)	⊕◯◯◯ VERY LOW

Appendix Table 2: Certainty of Evidence for Associations Between Phenotypes of Individuals with Diabetes and SARS-CoV-2 Regarding COVID-19-Related Severity

Certainty assessment							Relative risk (95% CI)	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
D-Dimer, per 1 mg/L								
3	observational studies	not serious	serious [s]	not serious	not serious	none	**RR 0.99** (0.95 to 1.03)	⊕⊕⊕◯ MODERATE
Prothrombin time per 1 second								
2	observational studies	extremely serious [i]	not serious	not serious	very serious [j,x]	none	**RR 1.42** (0.63 to 3.20)	⊕◯◯◯ VERY LOW
Erythrocyte sedimentation rate, per 1 mm/h								
2	observational studies	extremely serious [i]	not serious	not serious	serious [x]	dose response gradient	**RR 1.04** (1.02 to 1.06)	⊕◯◯◯ VERY LOW
Haemoglobin, per 5 g/dL								
3	observational studies	serious [a]	serious [v]	not serious	extremely serious [h]	strong association	**RR 0.47** (0.07 to 2.98)	⊕◯◯◯ VERY LOW

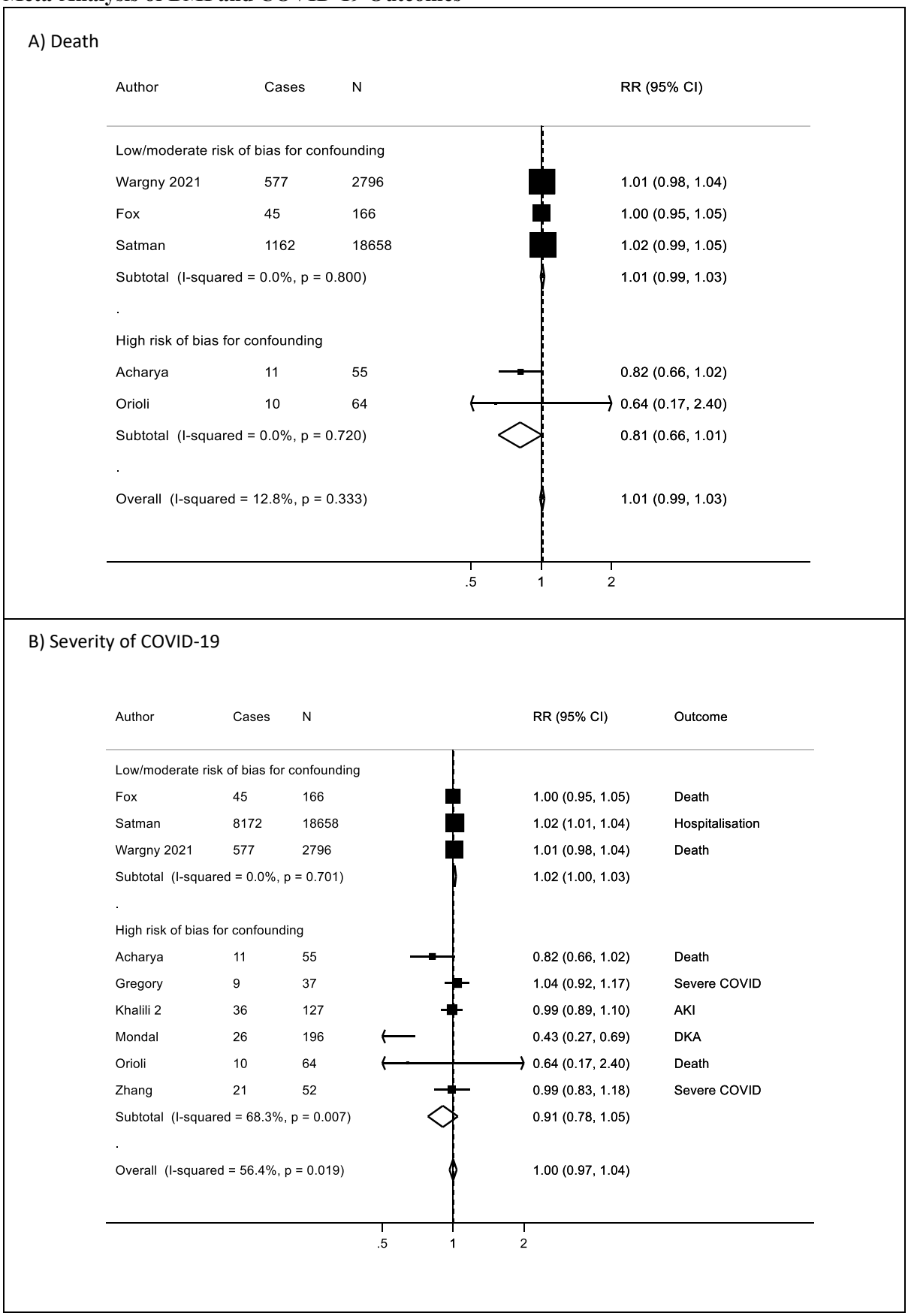
Appendix Table 2: Certainty of Evidence for Associations Between Phenotypes of Individuals with Diabetes and SARS-CoV-2 Regarding COVID-19-Related Severity

Certainty assessment							Relative risk (95% CI)	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		

CI: Confidence interval; RR: Risk ratio
a. High proportion (>25-50%) of evidence from studies with high risk of bias
b. Very high proportion (>50-90%) of evidence from studies with high risk of bias; however, in stratified analysis clear association in low/moderate Rob studies.
c. Very high proportion (>50-90%) of evidence from studies with high risk of bias
d. One study with strong association included
e. 95% CI includes the null value and includes important benefit OR harm
f. RR ranged from 0.70 to 3.82 and partly no overlap of 95% CI
g. One study with strong harmful and one with strong beneficial association included
h. 95% CI includes the null value and includes important benefit AND harm AND is extremely wide
i. Extremely high proportion (>90-100%) of evidence from studies with high risk of bias
j. 95% CI includes the null value and includes important benefit AND harm
k. RR ranged from 0.57 to 4.95 and partly no overlap of 95% CI
l. Only three studies and wide 95% CI
m. RR ranged from 0.13 to 2.54 and partly no overlap of 95% CI
n. RR ranged from 0.43 to 4.70 and partly no overlap of 95% CI
o. RR ranged from 0.23 to 5.32 and partly no overlap of 95% CI
p. 95% CI includes the null value and includes important benefit OR harm AND is extremely wide
q. RR ranged from 0.67 to 49.82 and partly no overlap of 95% CI
r. Only two studies and one of them implausibly large effect
s. One study with strong harmful and one with strong beneficial association included
t. Two studies with heterogeneous outcomes: one on hospitalization, one on death
u. RR ranged from 0.97 to 1.73 and only minimal overlap of 95% CI
v. I^2 >75% and partly no overlap of 95% CIs
w. RR ranged from 0.76 to 1.54 and partly no overlap of 95% CI
x. number of participants: n<400

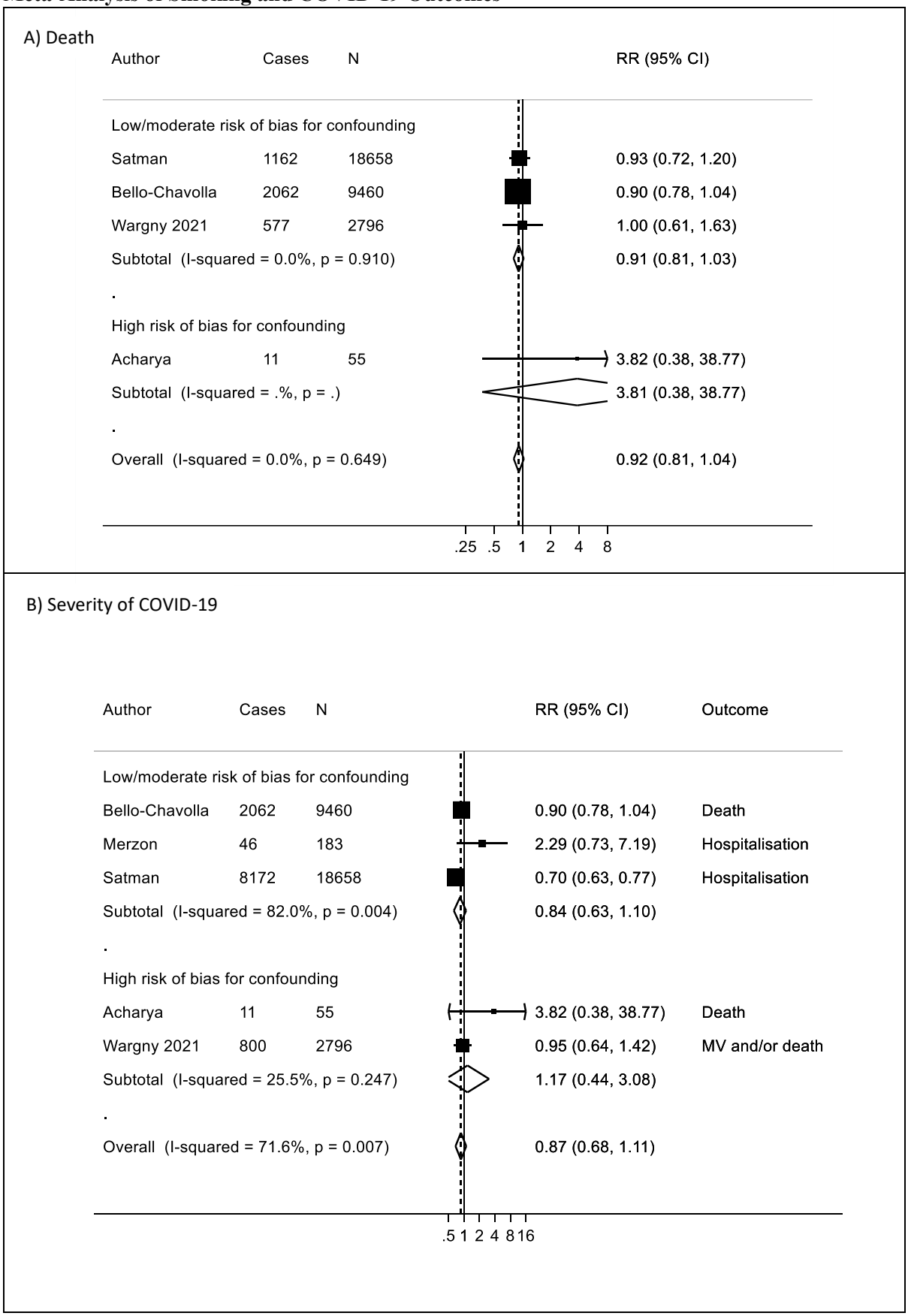
Certainty of evidence for associations between phenotypes of people with diabetes and COVID-19-related severity - modified by Schlesinger et al (80)

Meta-Analysis of BMI and COVID-19 Outcomes



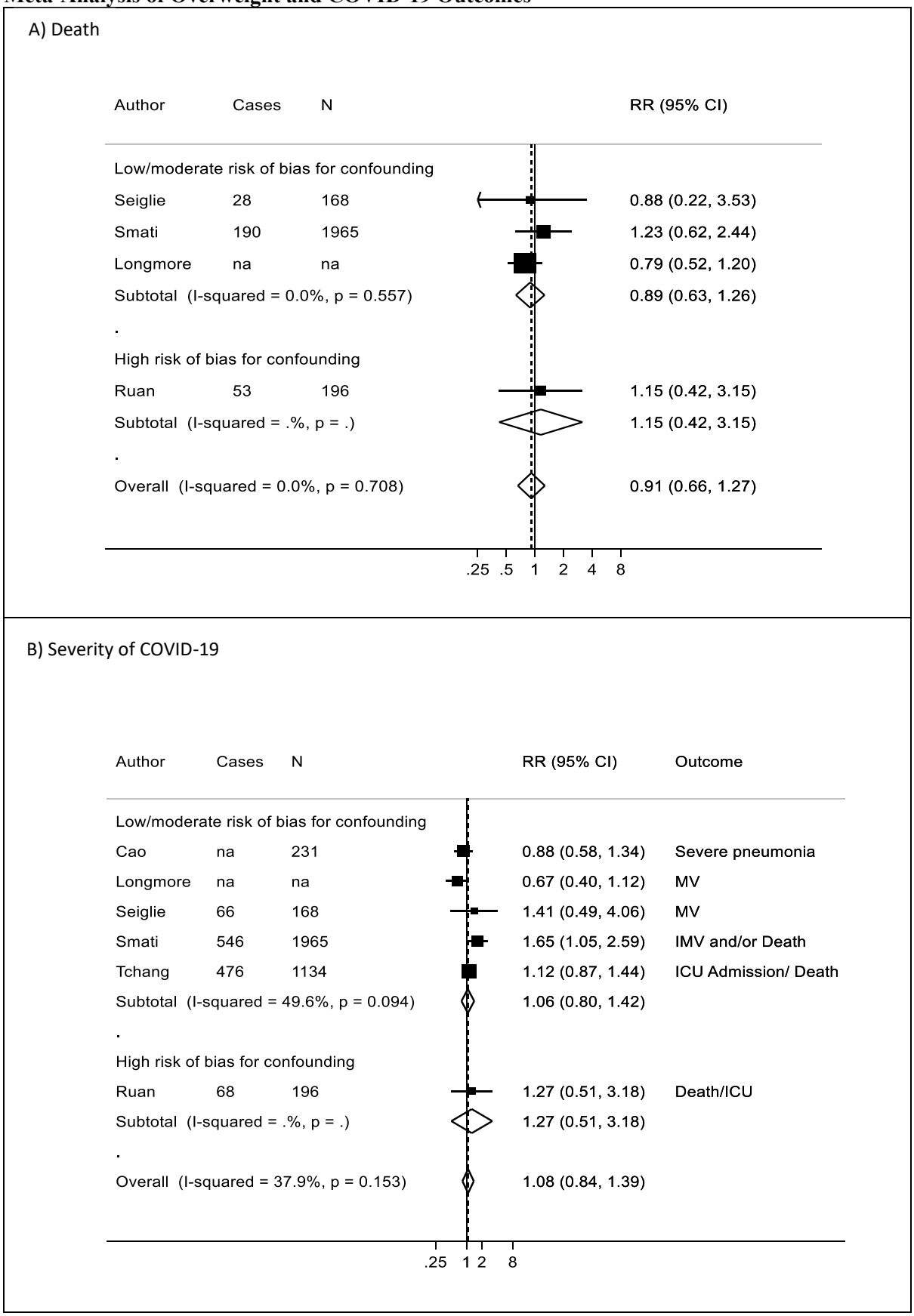
*Appendix Fig. 1: Meta-analysis on **BMI**, per 1 kg/m² increase and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (80)*

Meta-Analysis of Smoking and COVID-19 Outcomes



*Appendix Fig. 2: Meta-analysis on **smoking** compared to non-smoking and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (80)*

Meta-Analysis of Overweight and COVID-19 Outcomes



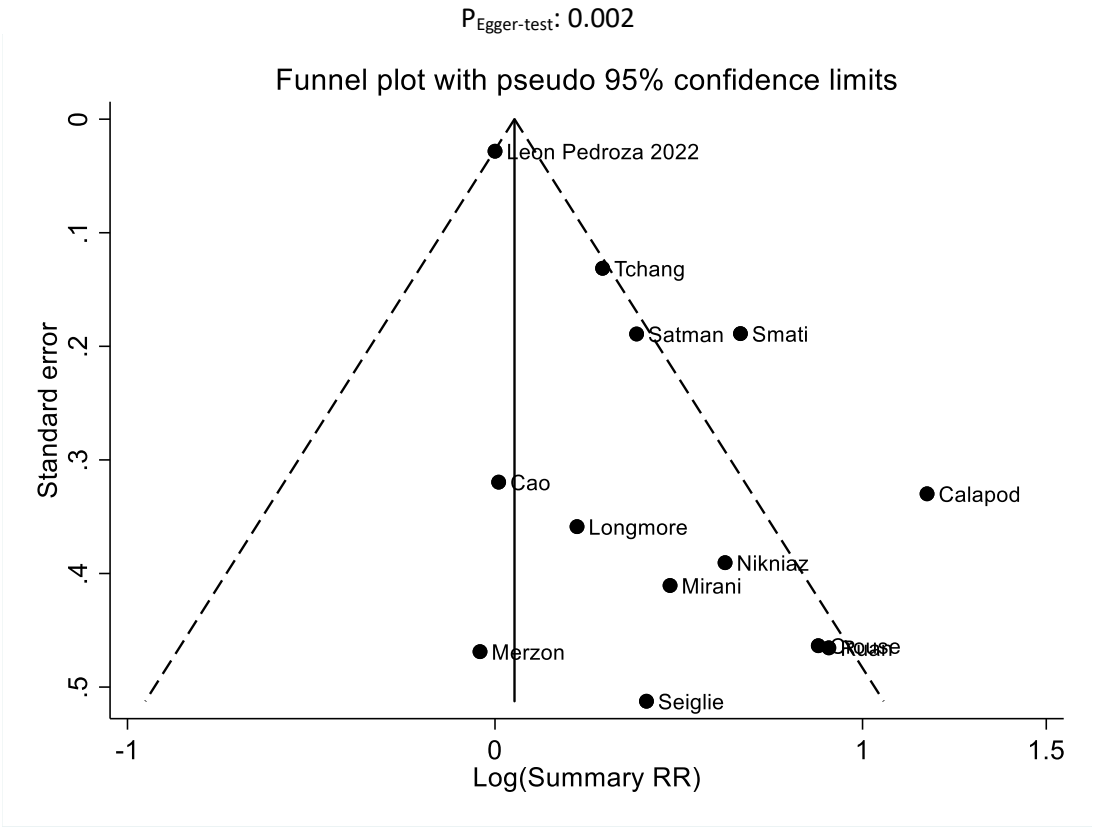
*Appendix Fig. 3: Meta-analysis on **overweight** compared to normal weight and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (80)*

Funnel Plot of Obesity and COVID-19 Outcomes

A) Death

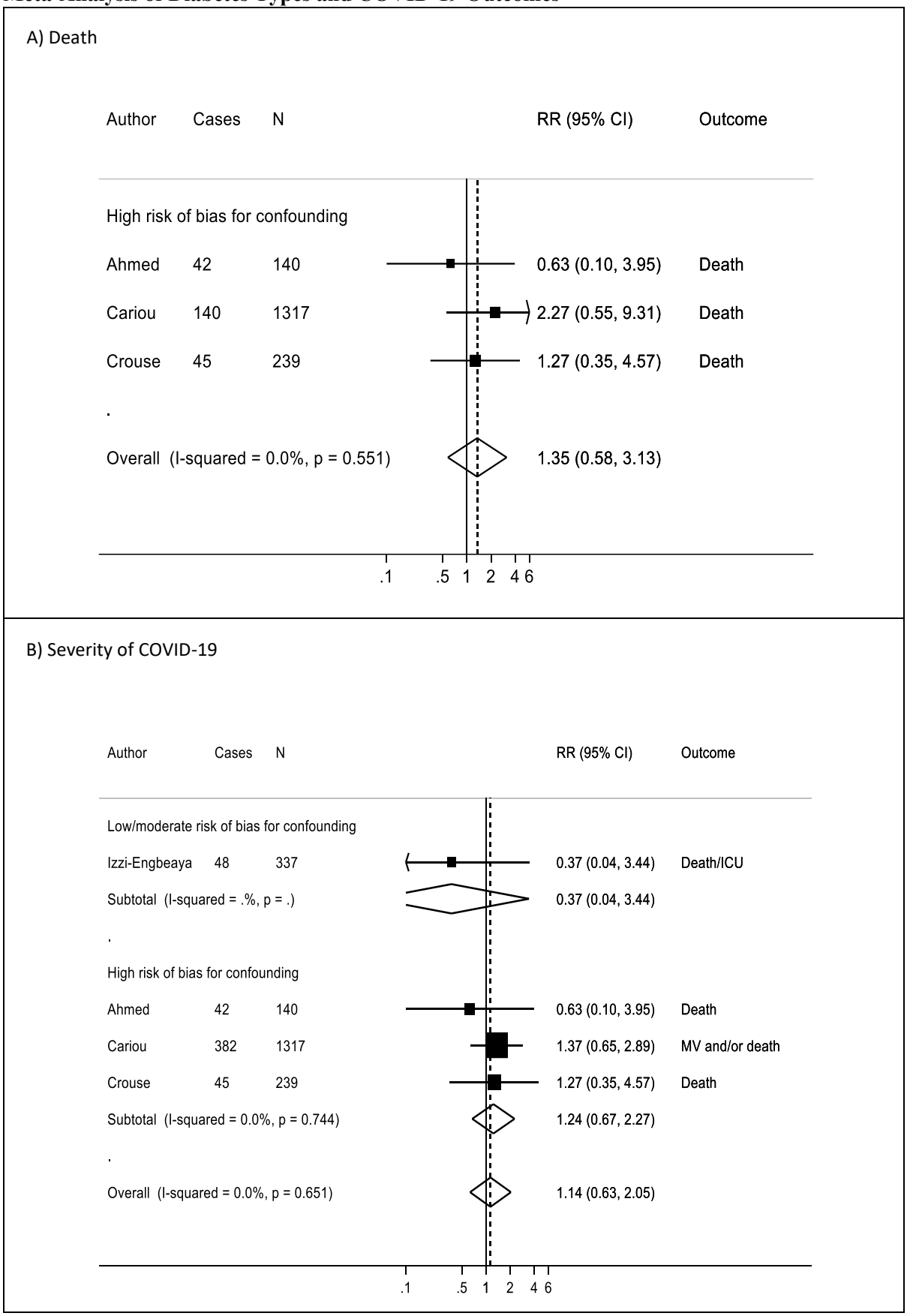
Analysis not conducted: <10 studies available

B) Severity of COVID-19



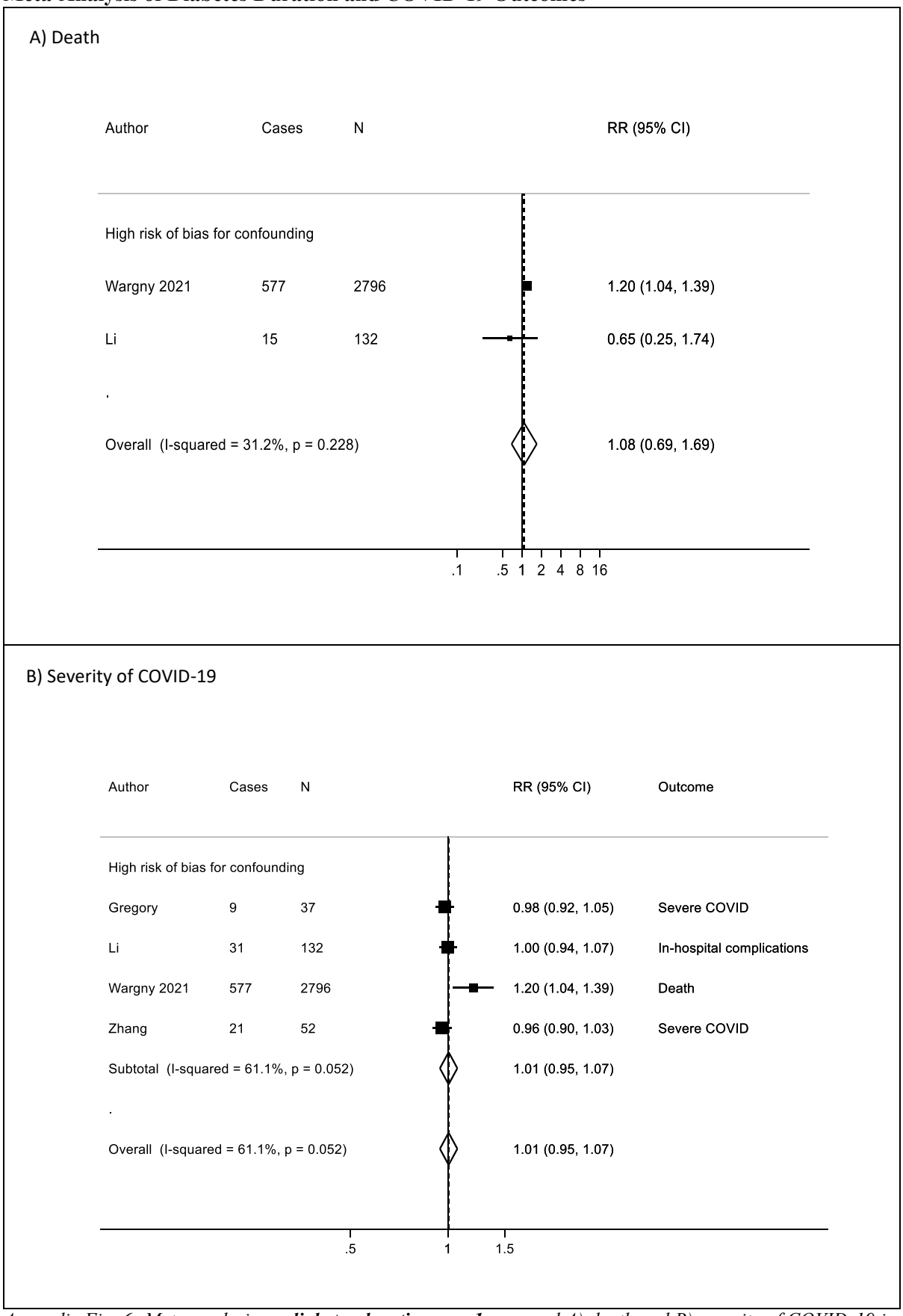
*Appendix Fig. 4: Funnel plot for association between **obesity** and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (80)*

Meta-Analysis of Diabetes Types and COVID-19 Outcomes



*Appendix Fig. 5: Meta-analysis on **type 2 vs type 1 diabetes** and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

Meta-Analysis of Diabetes Duration and COVID-19 Outcomes



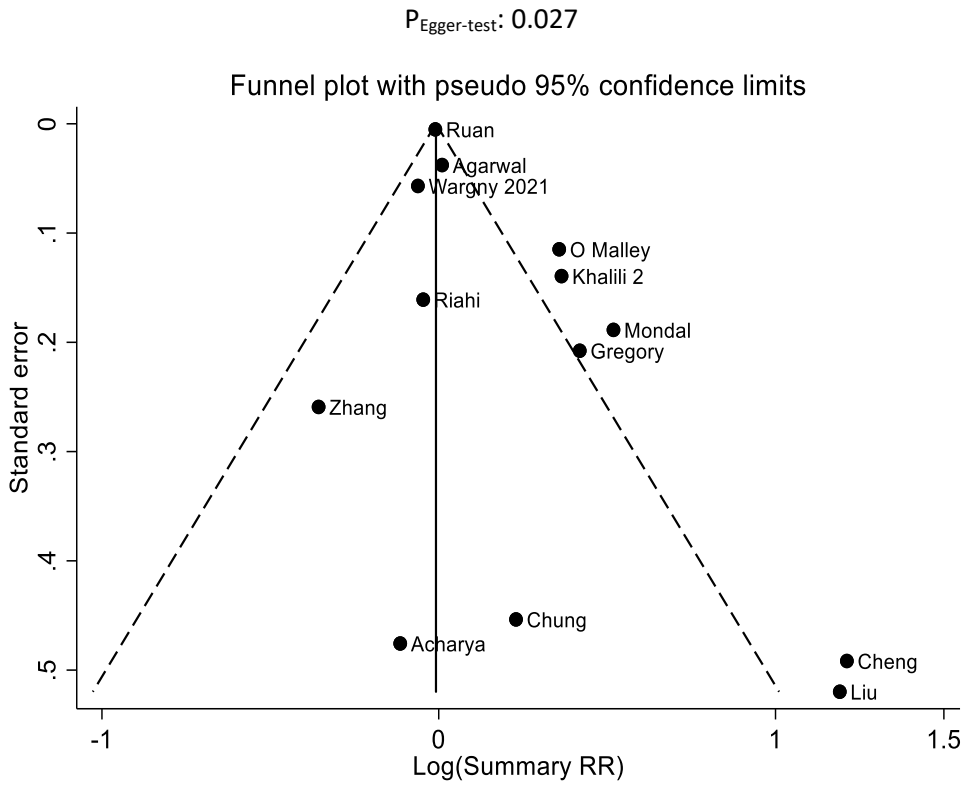
*Appendix Fig. 6: Meta-analysis on **diabetes duration, per 1 year** and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

Funnel Plot of HbA1c and COVID-19 Outcomes

A) Death

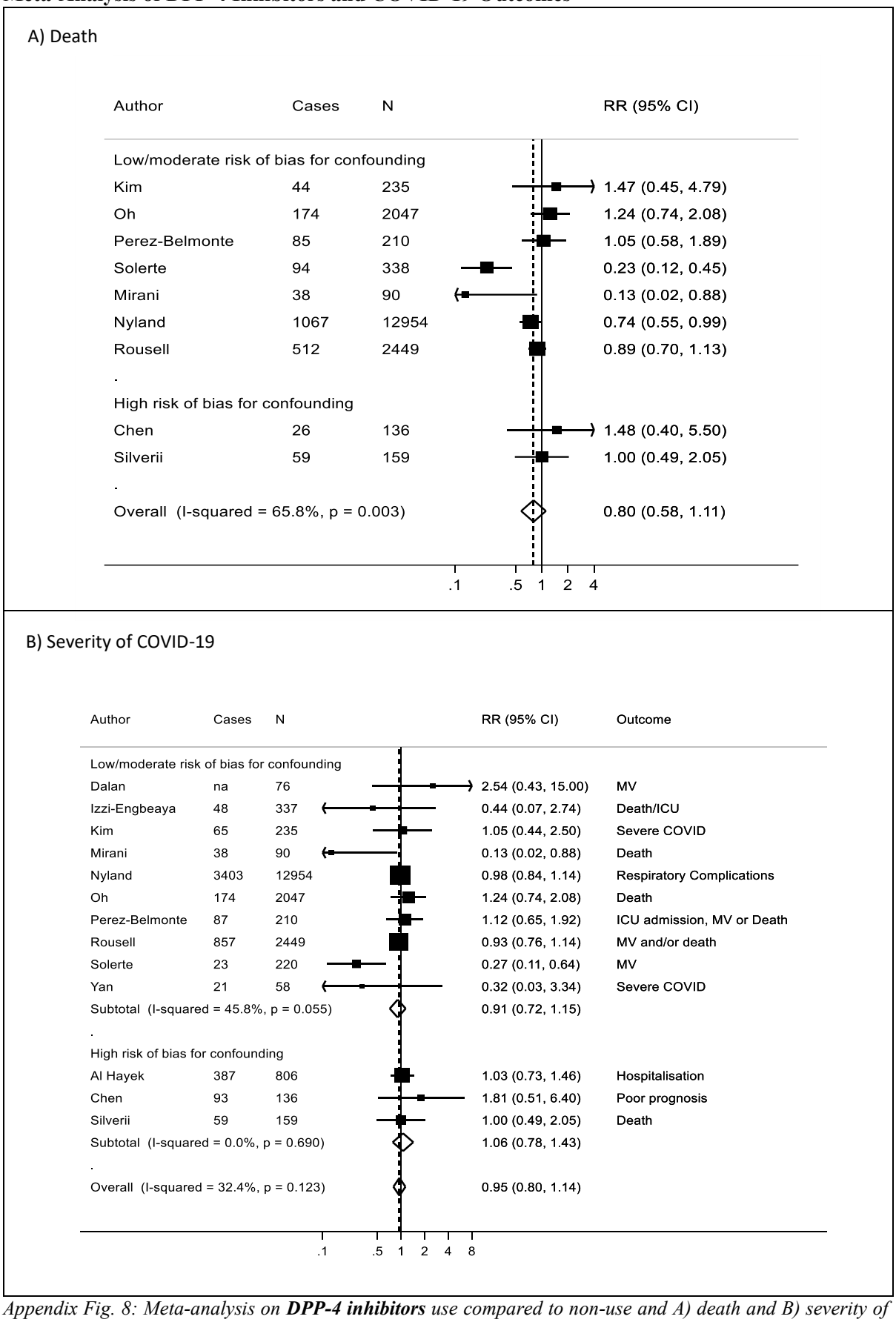
Analysis not conducted: <10 studies available

B) Severity of COVID-19



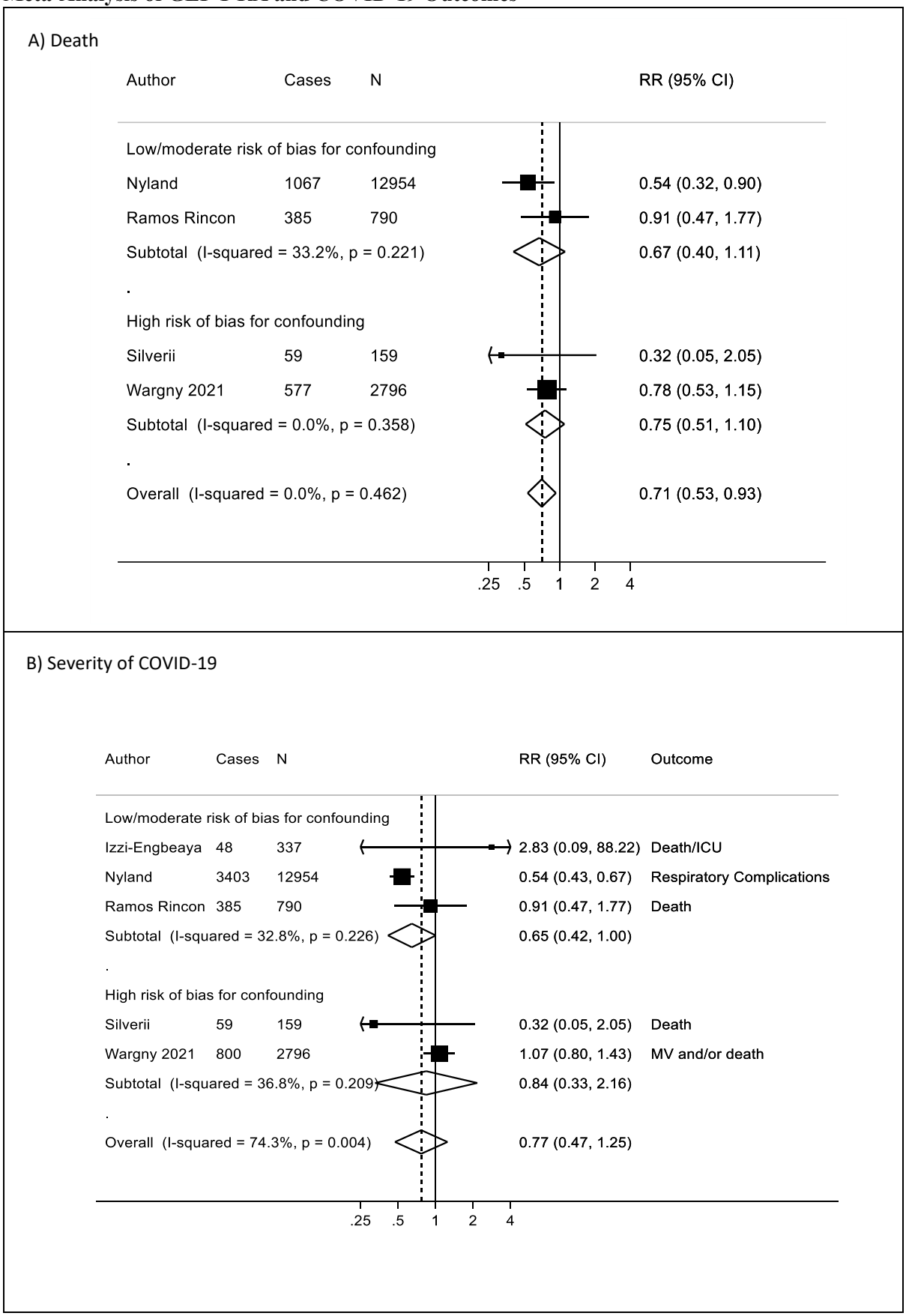
*Appendix Fig. 7: Funnel plot for association between **HbA1c** per 1% increase and A) death and B) severity of COVID-19 in individuals with diabetes and COVID -19 - modified by Schlesinger et al (80)*

Meta-Analysis of DPP-4 Inhibitors and COVID-19 Outcomes



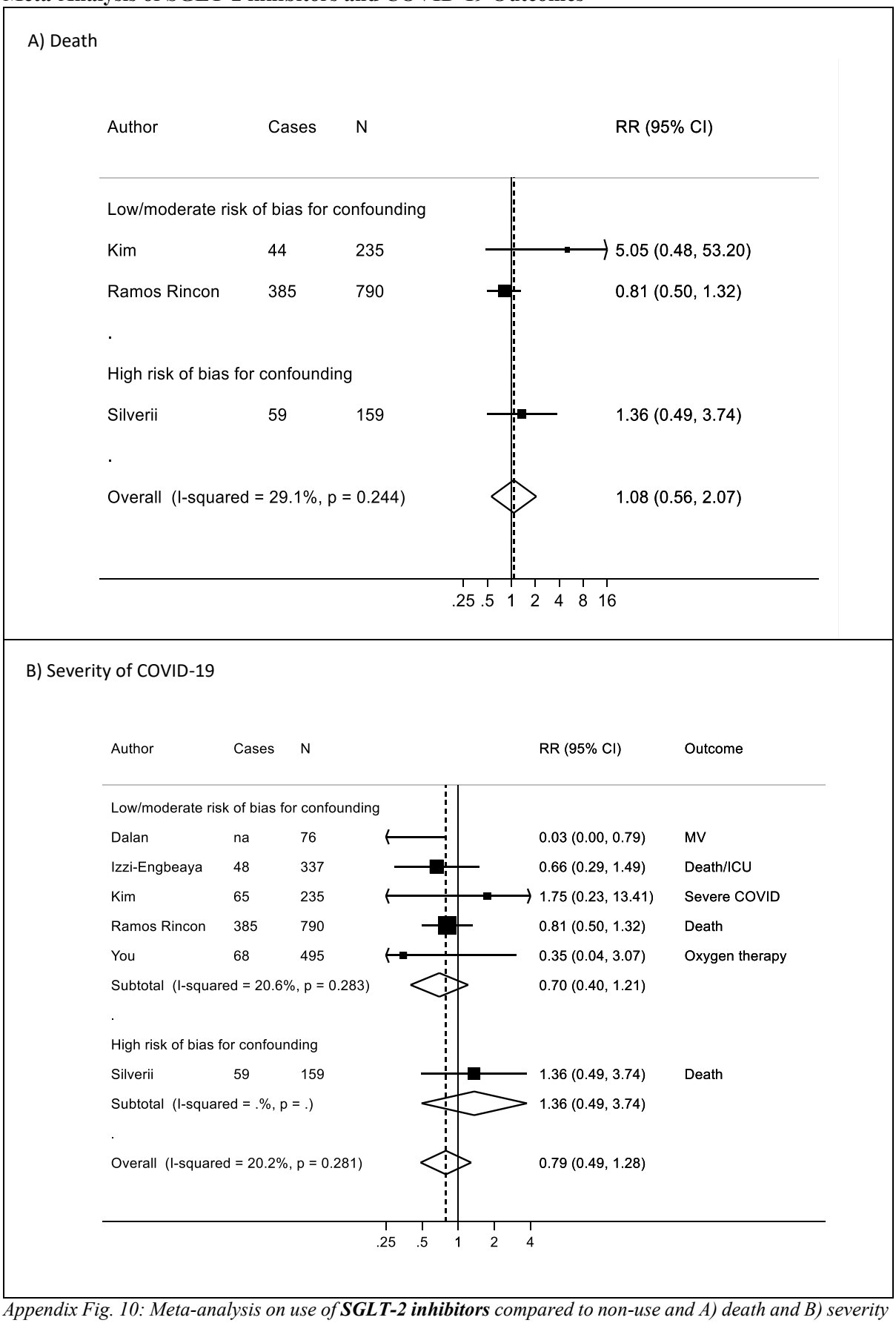
*Appendix Fig. 8: Meta-analysis on **DPP-4 inhibitors** use compared to non-use and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

Meta-Analysis of GLP 1-RA and COVID-19 Outcomes



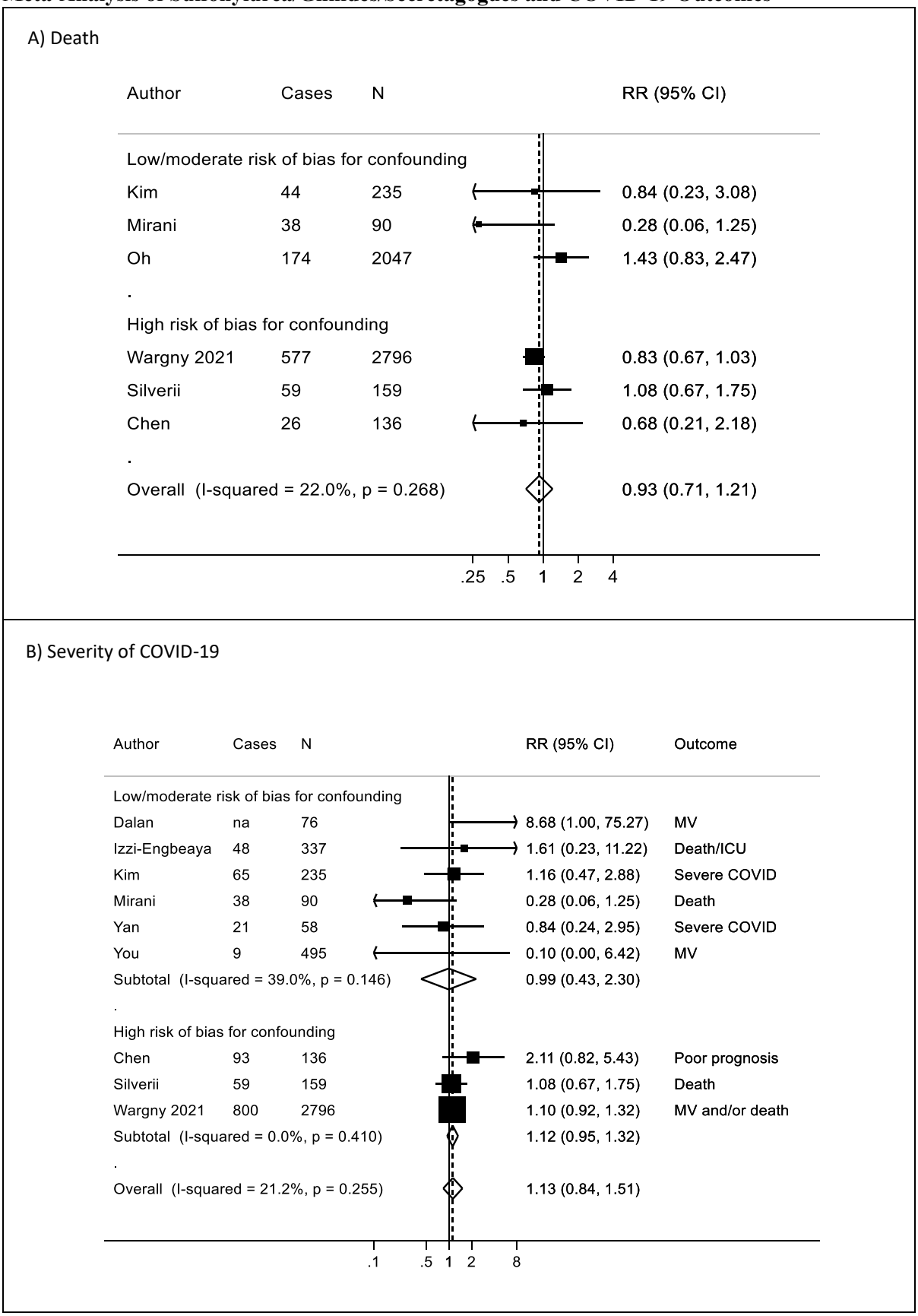
*Appendix Fig. 9: Meta-analysis on use of **GLP 1-RA** compared to non-use and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (80)*

Meta-Analysis of SGLT-2 inhibitors and COVID-19 Outcomes



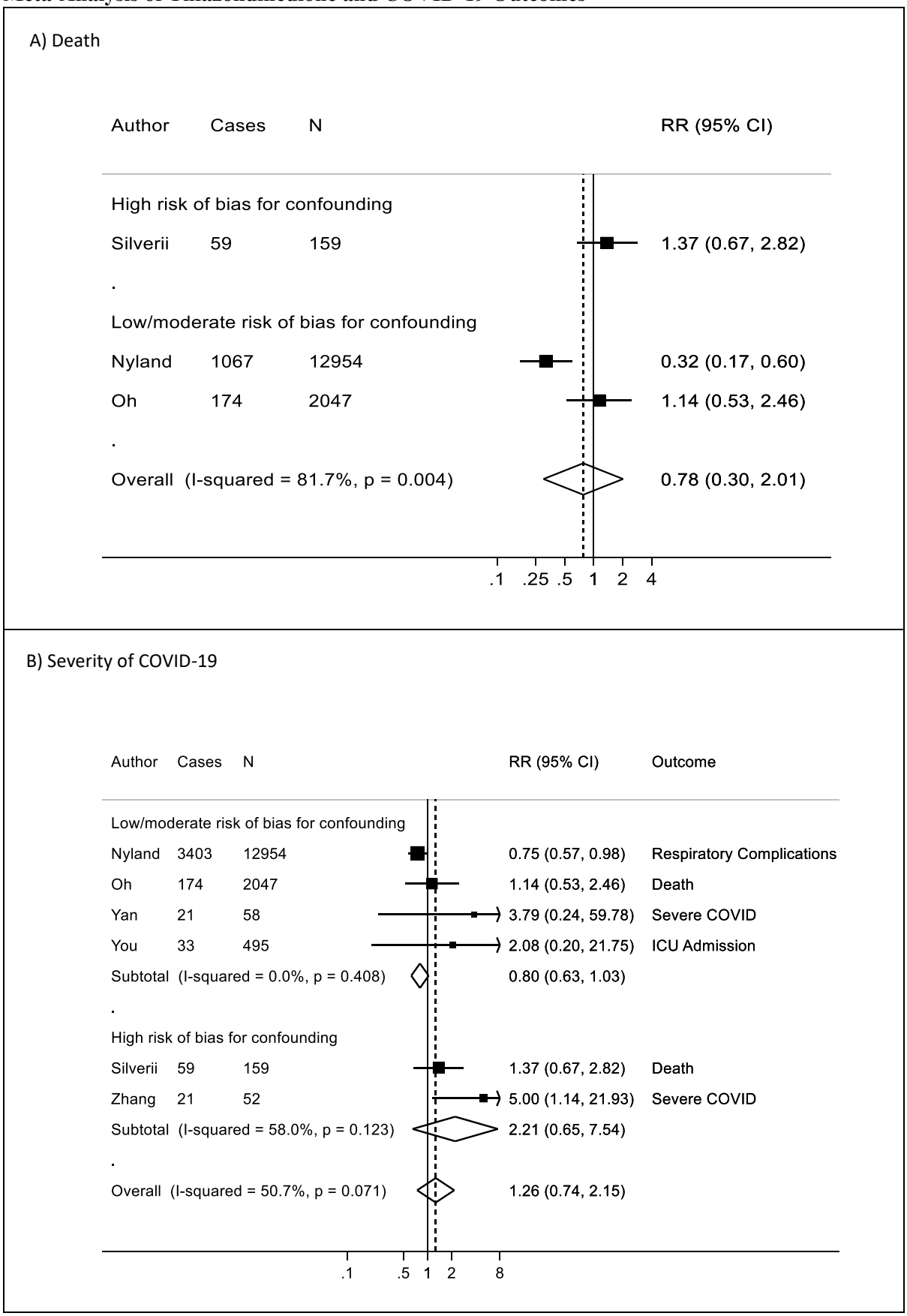
*Appendix Fig. 10: Meta-analysis on use of **SGLT-2 inhibitors** compared to non-use and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (80)*

Meta-Analysis of Sulfonylurea/Glinides/Secretagogues and COVID-19 Outcomes



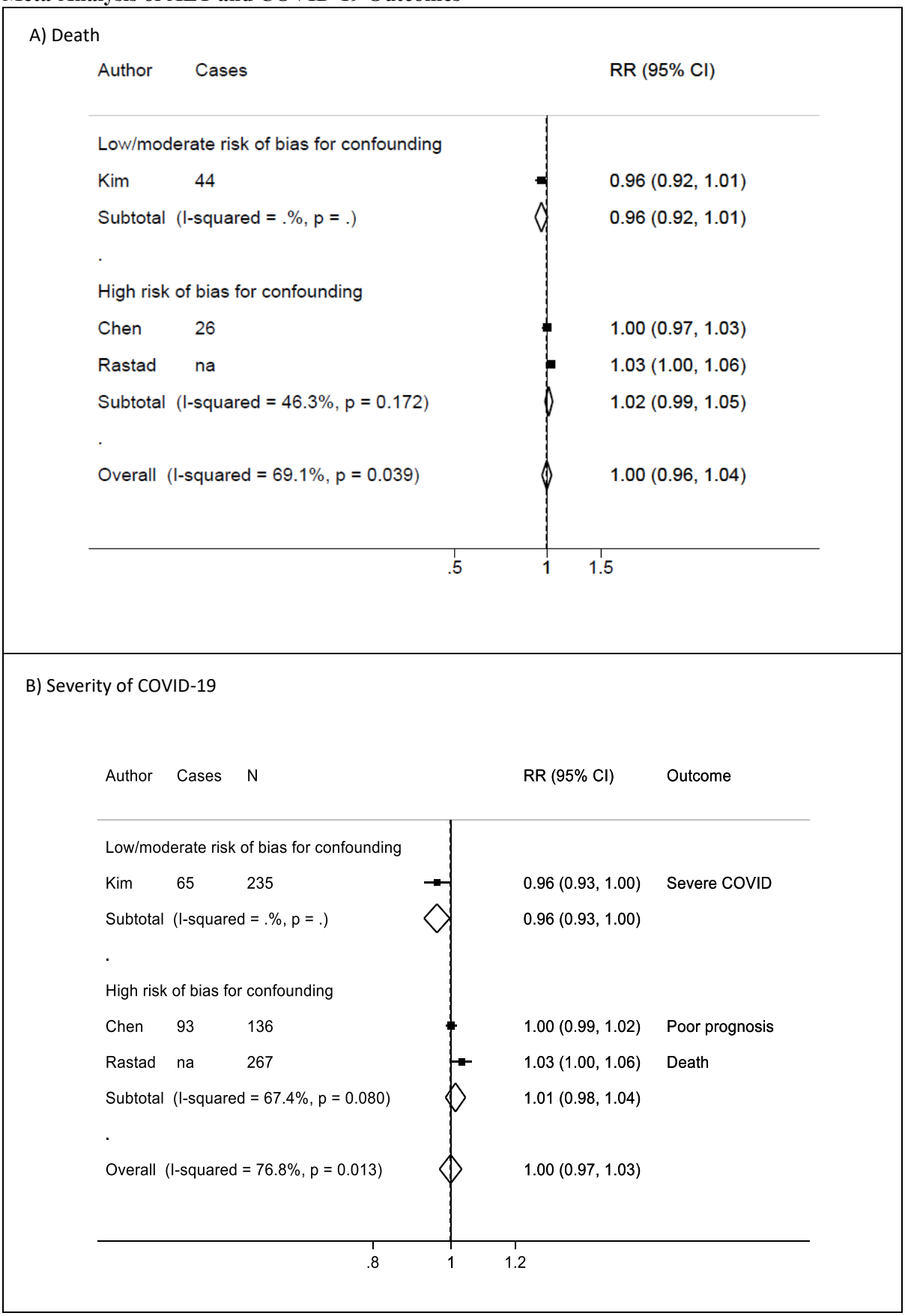
*Appendix Fig. 11: Meta-analysis on use of **sulfonylurea/glinides/secretagogues** compared to non-use and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

Meta-Analysis of Thiazolidinedione and COVID-19 Outcomes



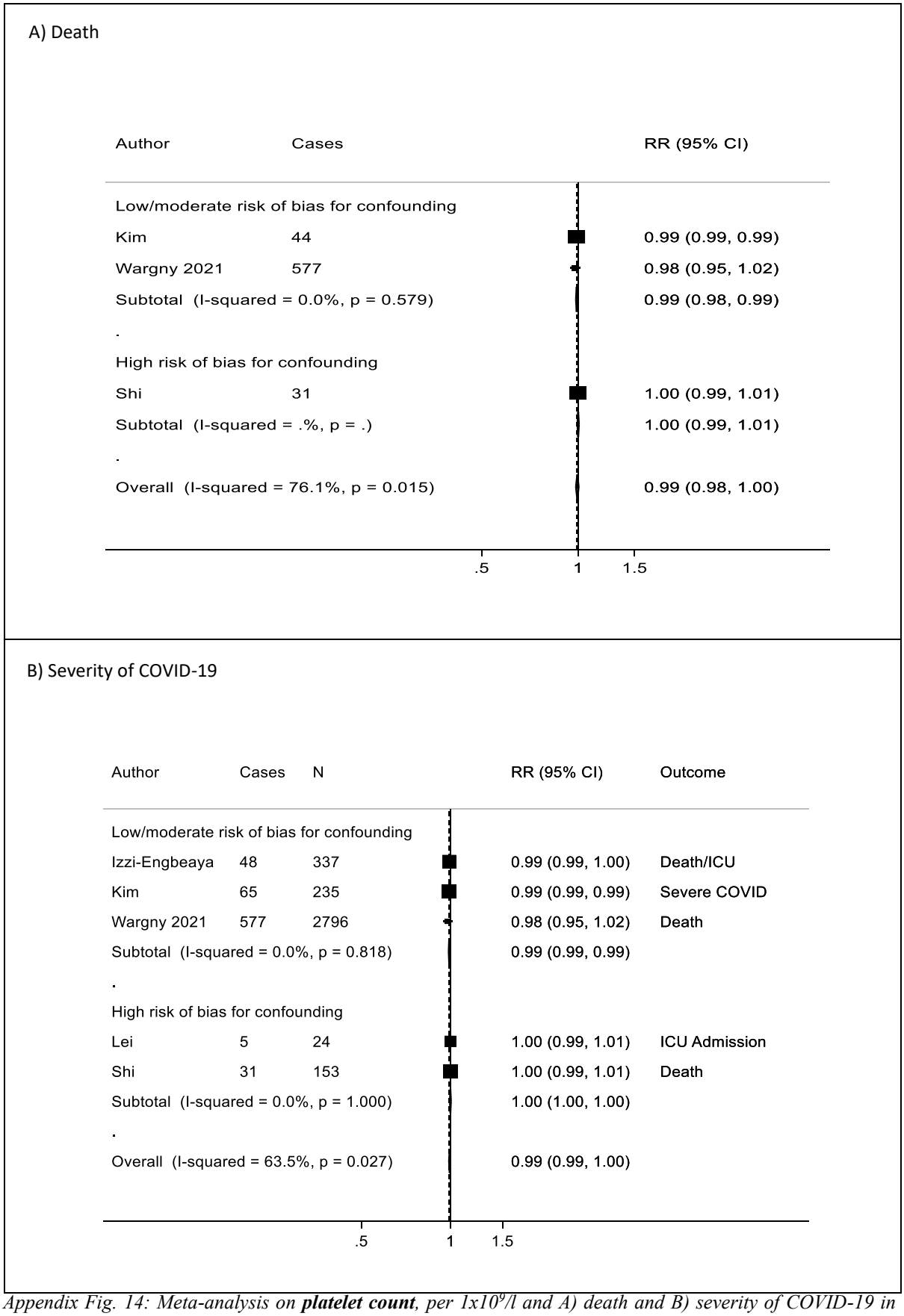
*Appendix Fig. 12: Meta-analysis on use of **thiazolidinedione** compared to non-use and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

Meta-Analysis of ALT and COVID-19 Outcomes



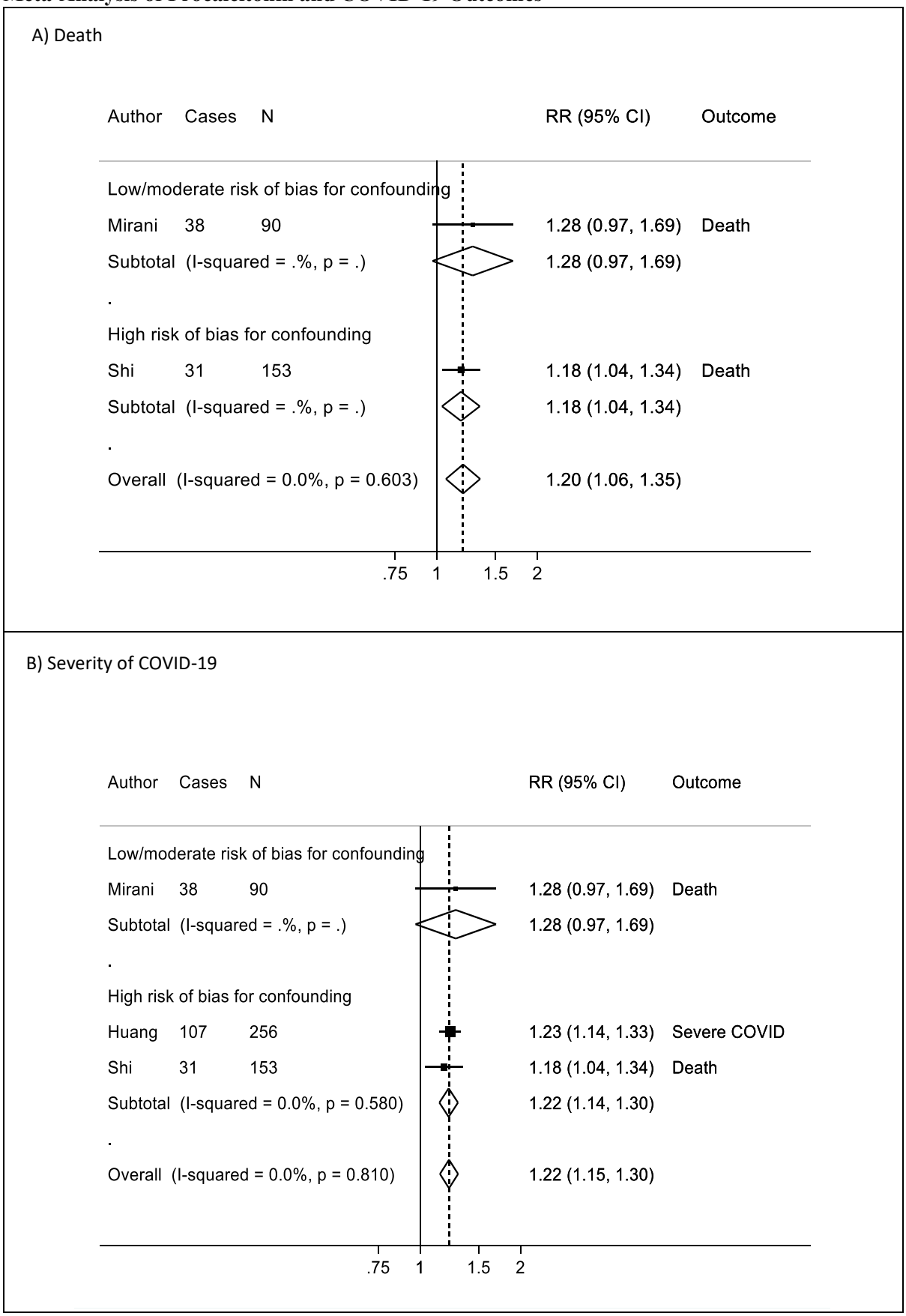
*Appendix Fig. 13: Meta-analysis on **ALT**, per 1 U/l and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 (1)*

Meta-Analysis of Platelet Count and COVID-19 Outcomes



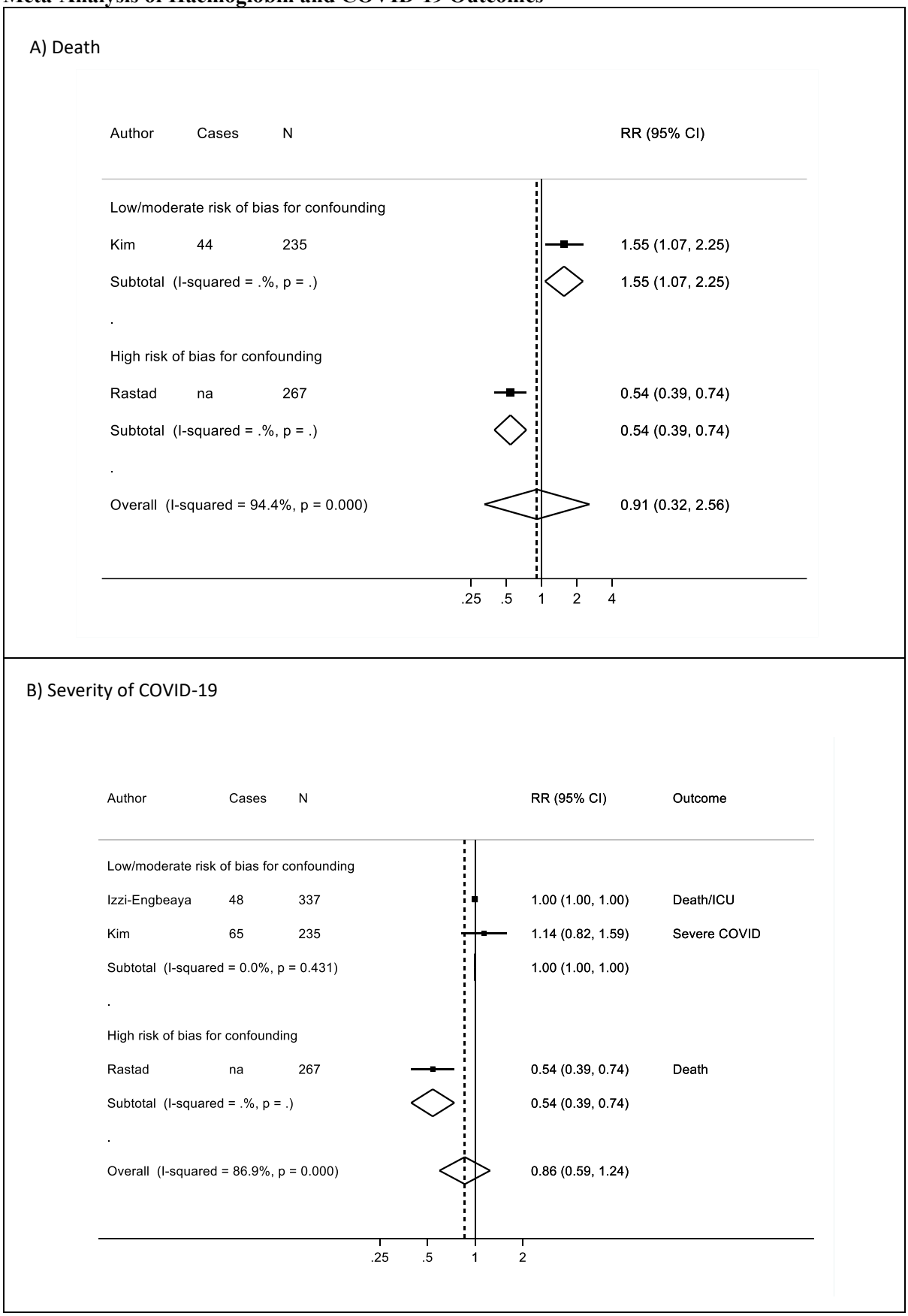
*Appendix Fig. 14: Meta-analysis on **platelet count**, per 1x10^9/l and A) death and B) severity of COVID-19 in patients with diabetes and COVID-19 - modified by Schlesinger et al (1)*

Meta-Analysis of Procalcitonin and COVID-19 Outcomes



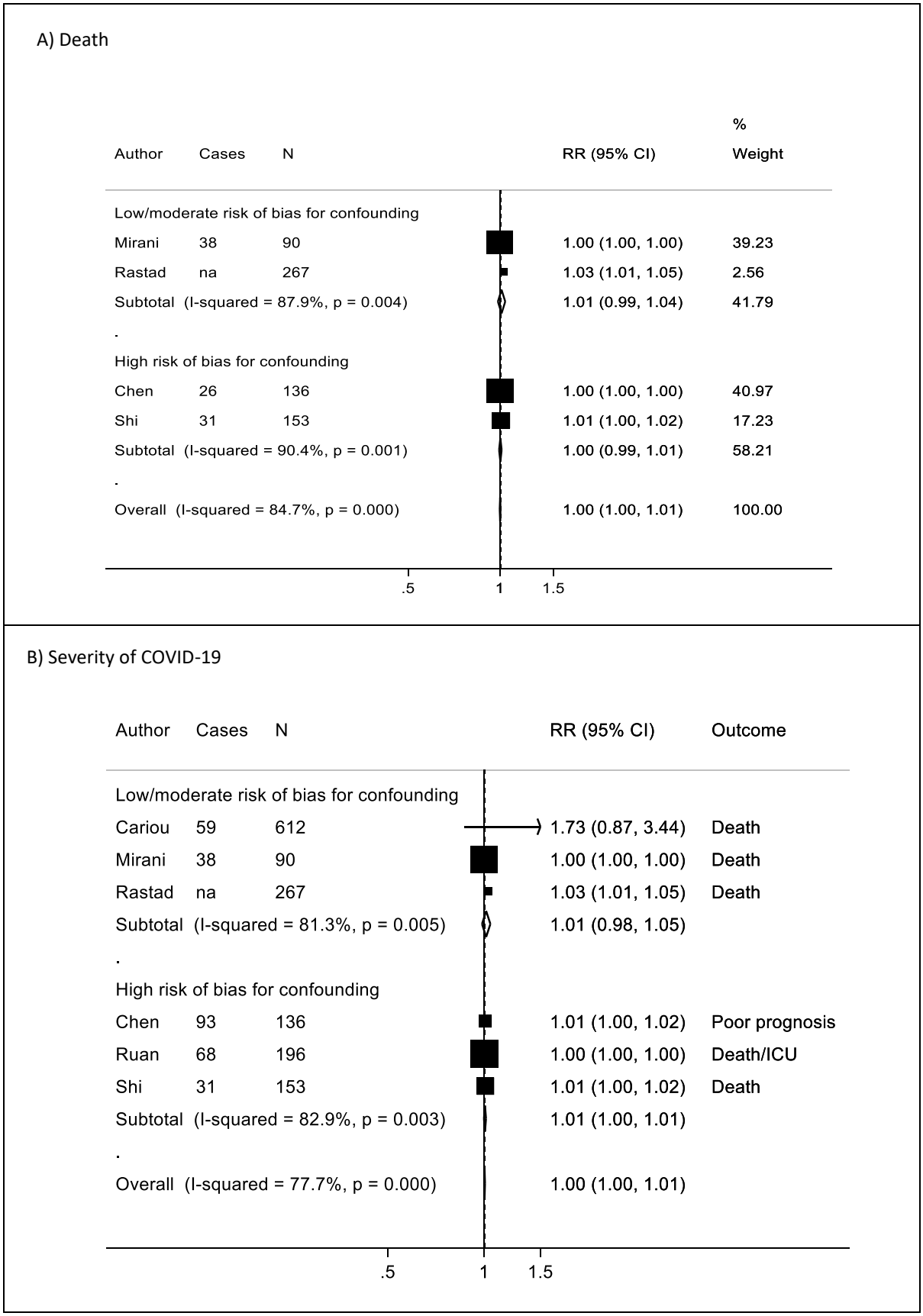
*Appendix Fig. 15: Meta-analysis on **procalcitonin**, per 1 ng/ml and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

Meta-Analysis of Haemoglobin and COVID-19 Outcomes



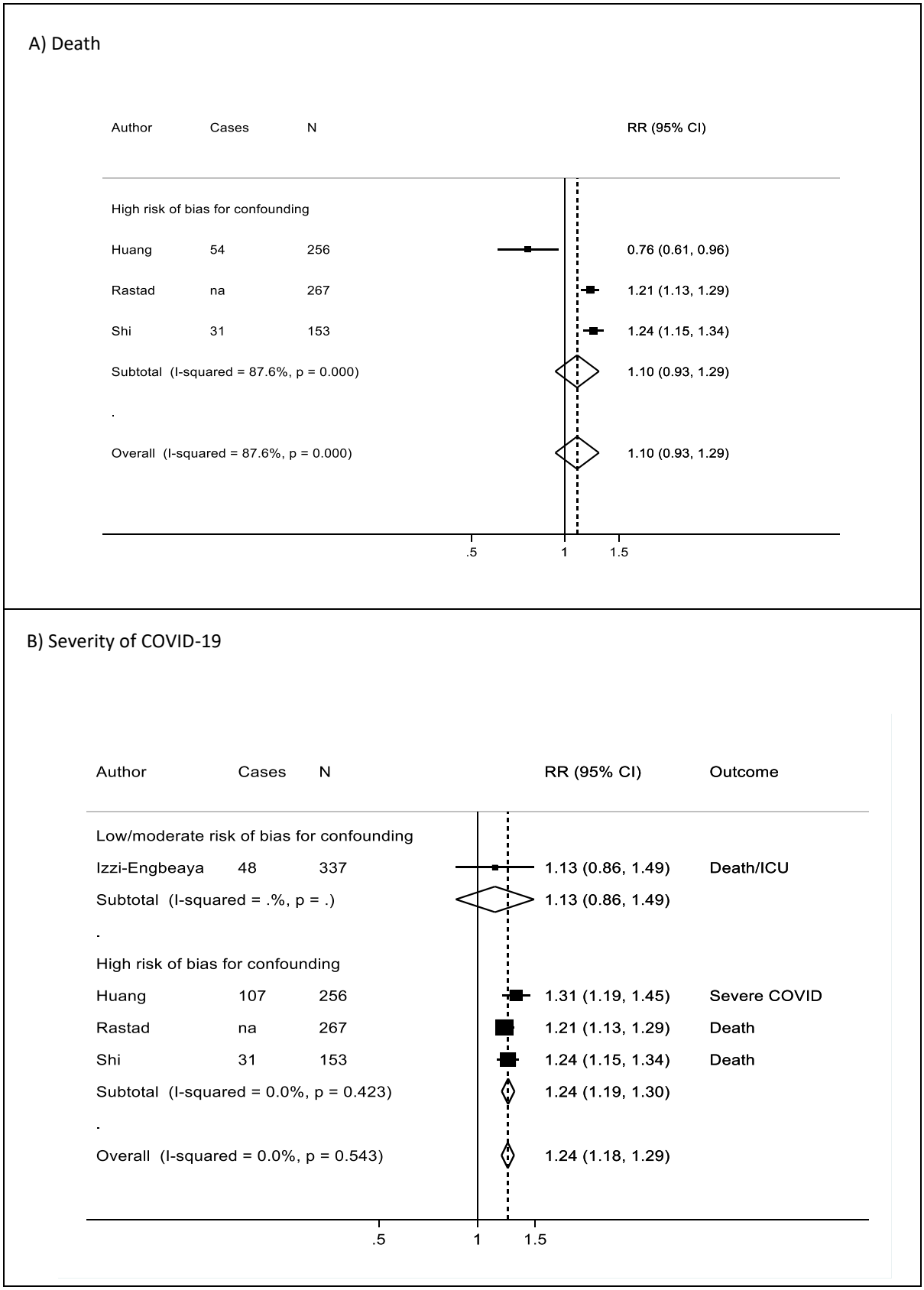
*Appendix Fig. 16: Meta-analysis on **haemoglobin**, per 1 g/dl and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

Meta-Analysis of Creatinine and COVID-19 Outcomes



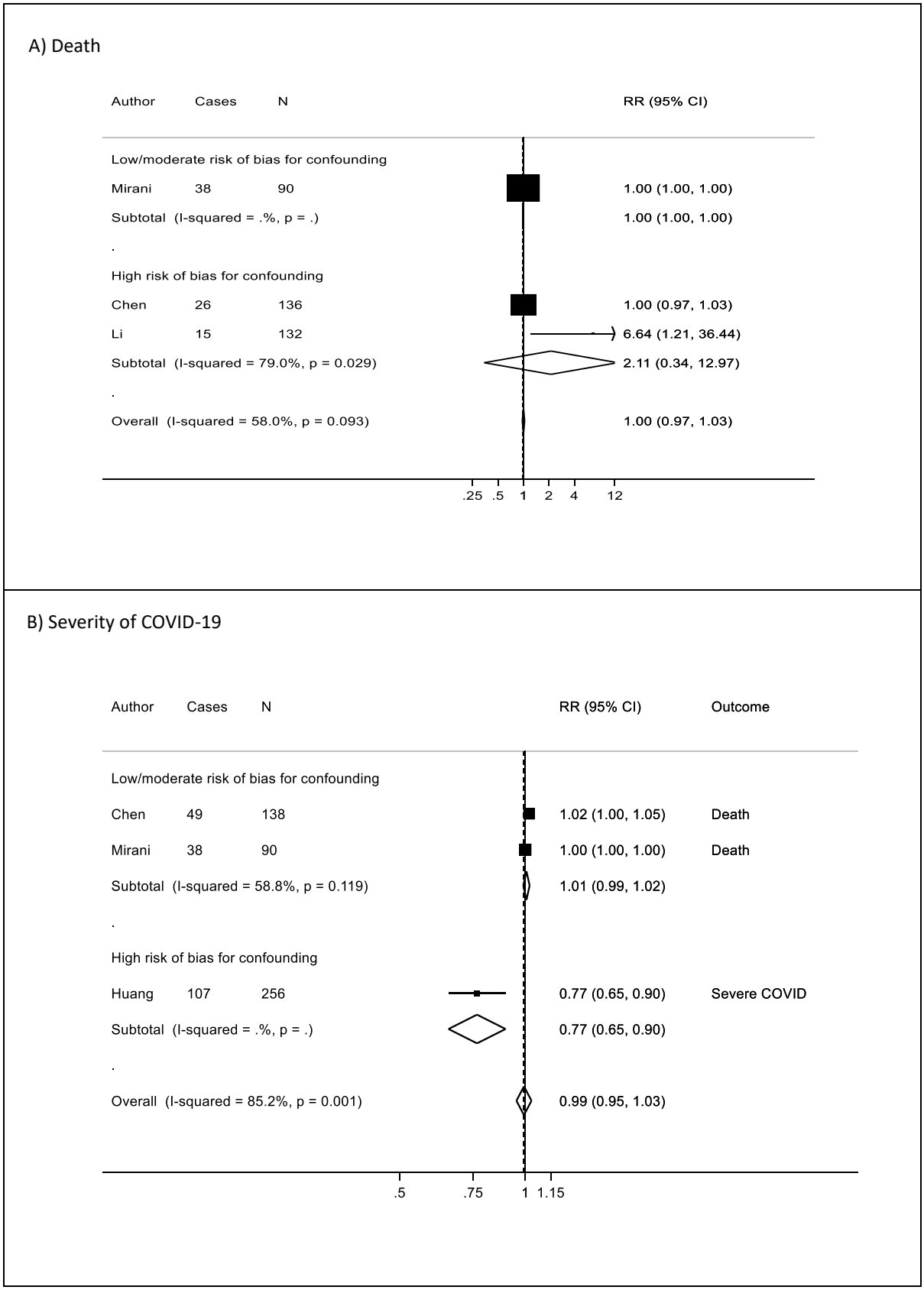
*Appendix Fig. 17: Meta-analysis on **creatinine**, per 1 µmol/l and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

Meta-Analysis of Neutrophils and COVID-19 Outcomes



*Appendix Fig. 18: Meta-analysis on **neutrophils**, per 1 g/dl and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

Meta-Analysis of D-dimers and COVID-19 Outcomes



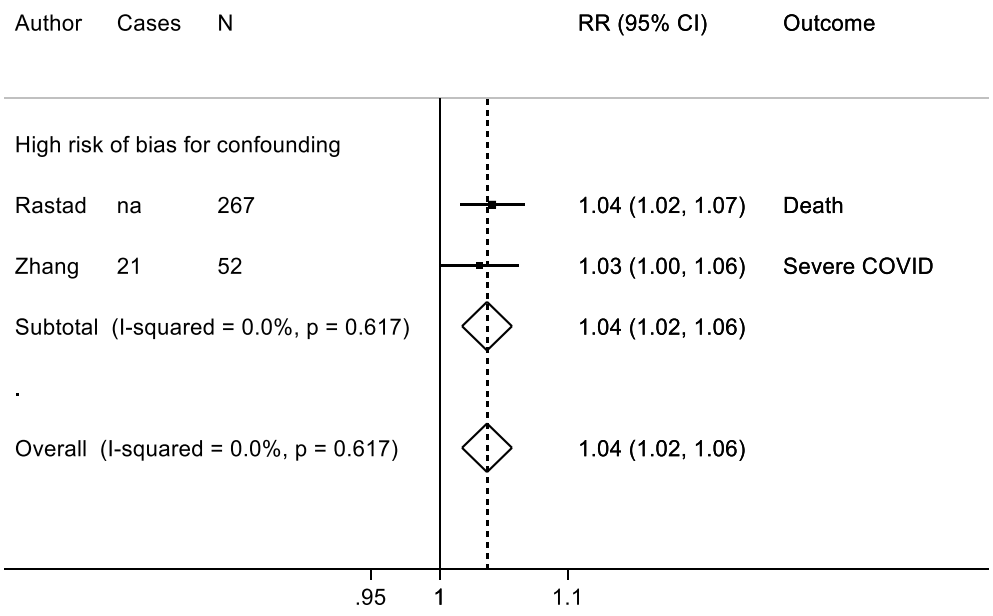
*Appendix Fig. 19: Meta-analysis on **D-Dimers** and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 (1)*

Meta-Analysis of Erythrocyte Sedimentation Rate and COVID-19 Outcomes

A) Death

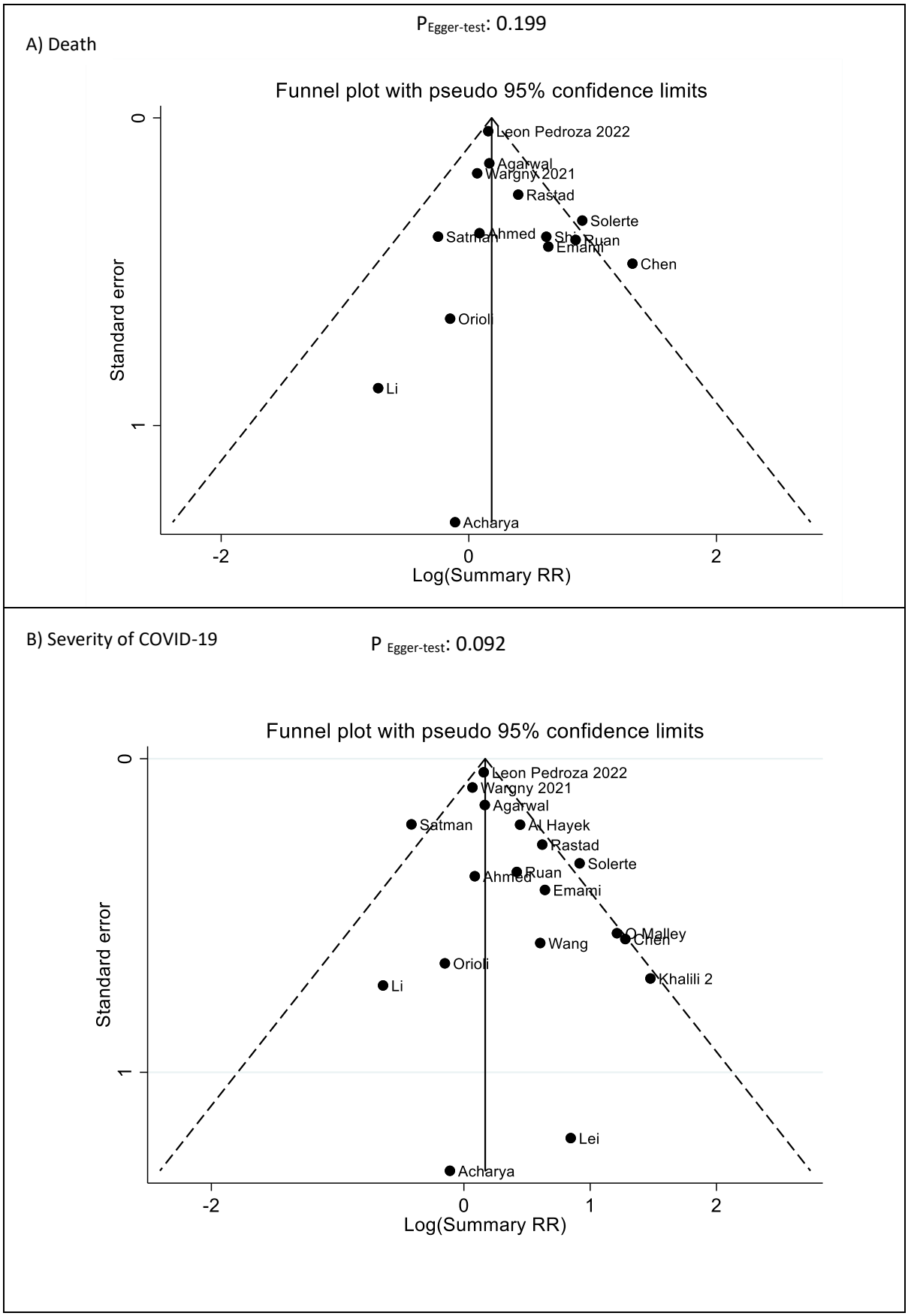
no data

B) Severity of COVID-19



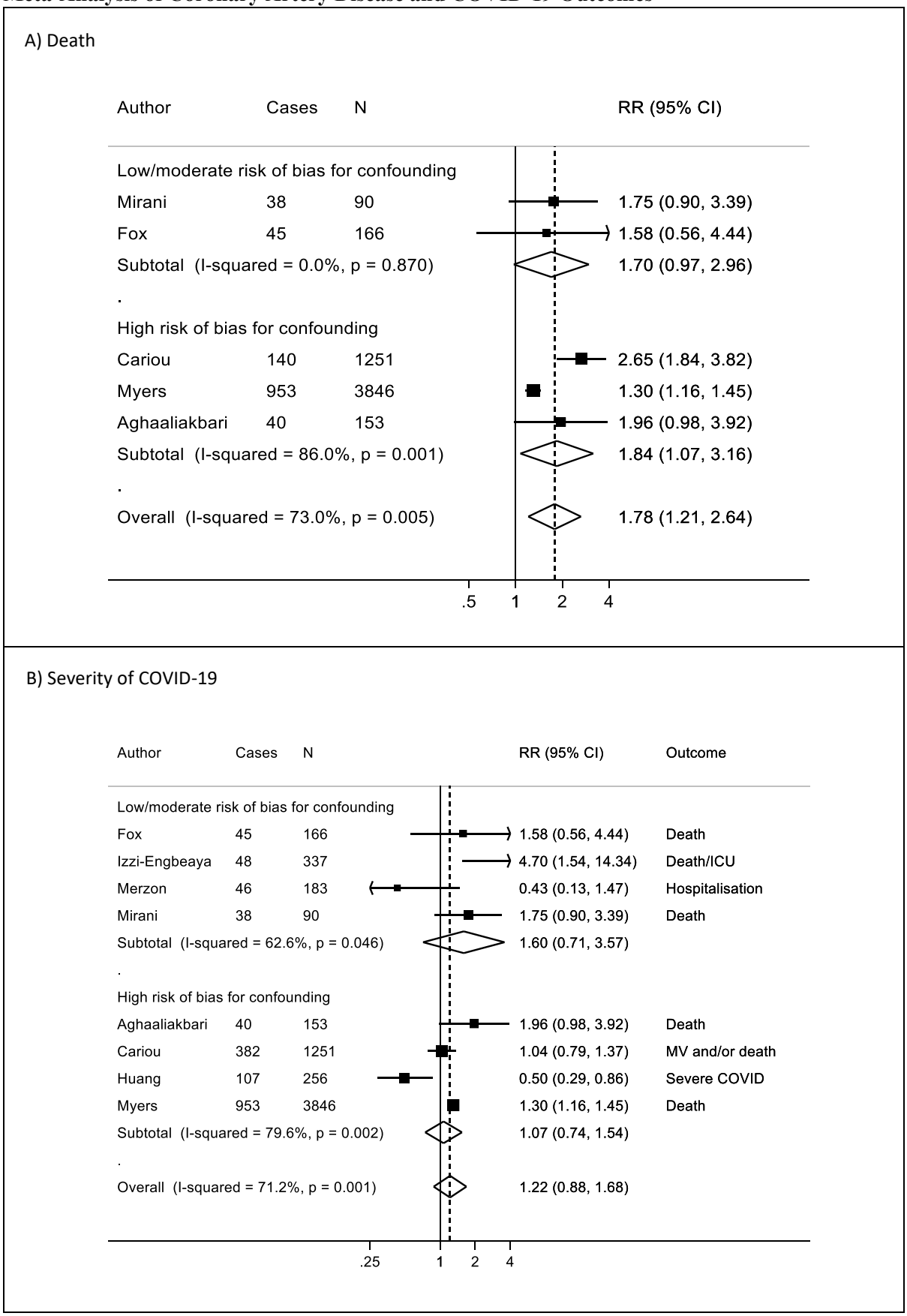
*Appendix Fig. 20: Meta-analysis on **erythrocyte sedimentation rate**, per 1 mm/h and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 (1)*

Funnel Plot for CVD and COVID-19 Outcomes



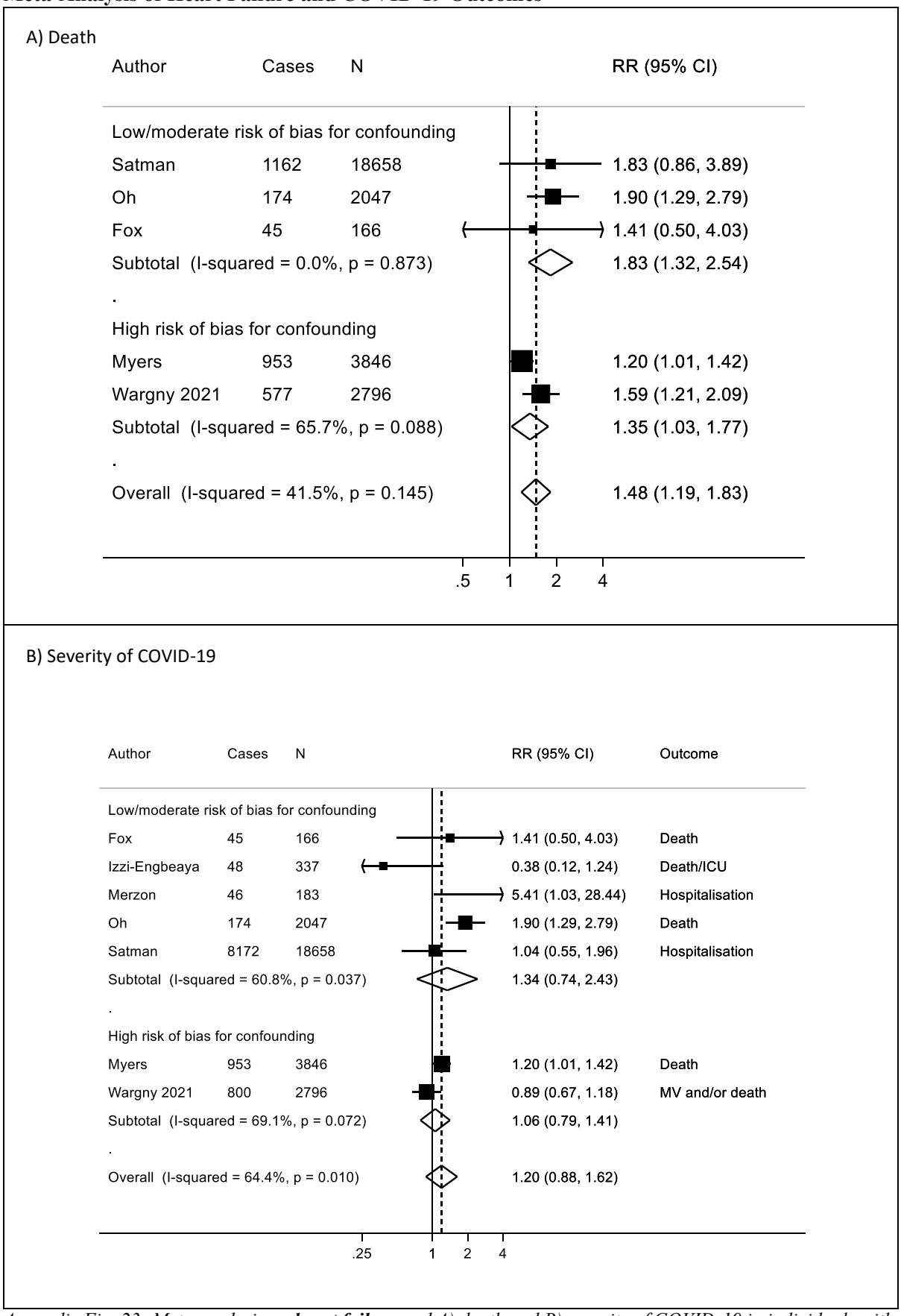
*Appendix Fig. 21: Funnel plot for association between **CVD** and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (80)*

Meta-Analysis of Coronary Artery Disease and COVID-19 Outcomes



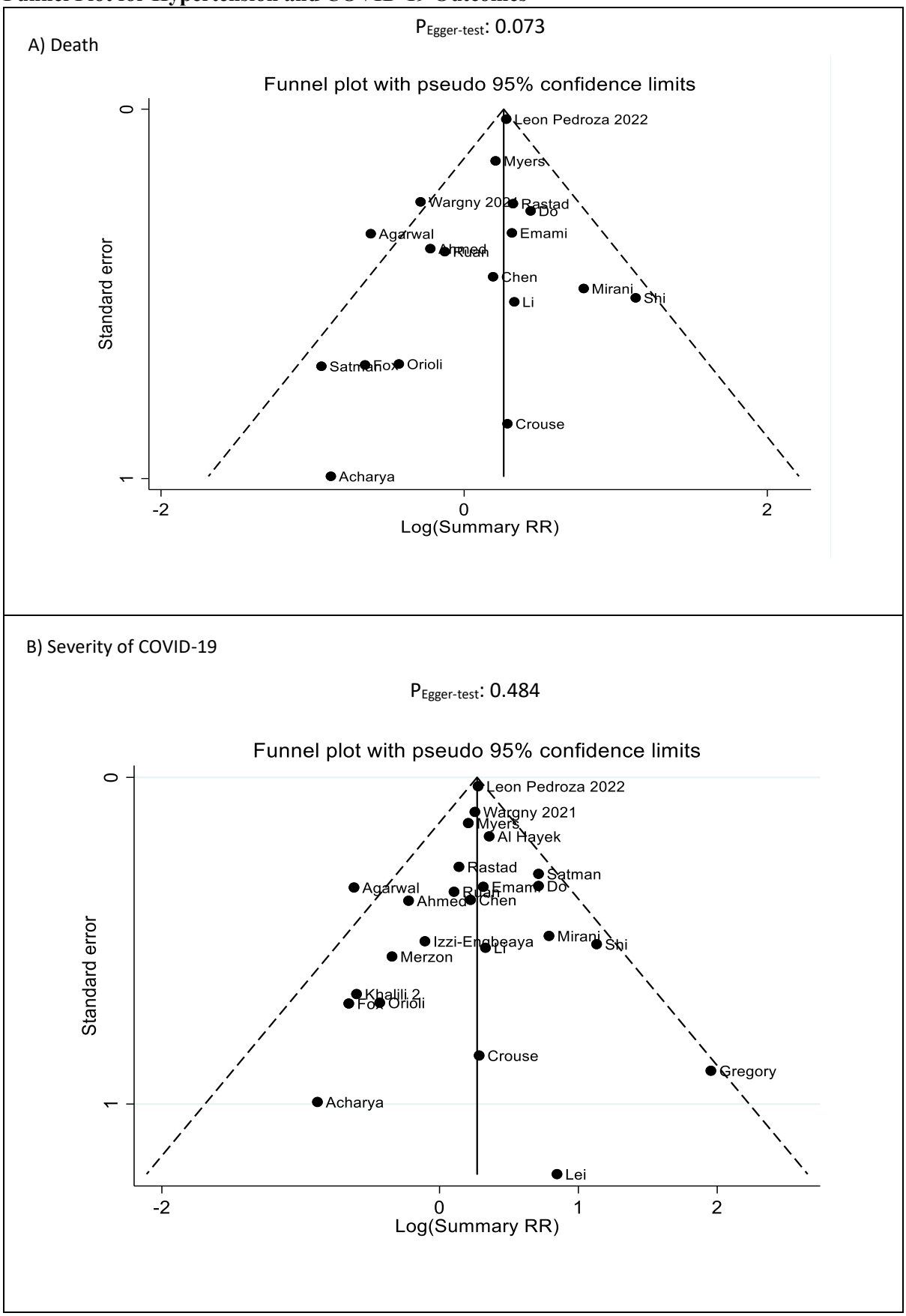
*Appendix Fig. 22: Meta-analysis on **coronary artery disease (CAD)** and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (80)*

Meta-Analysis of Heart Failure and COVID-19 Outcomes



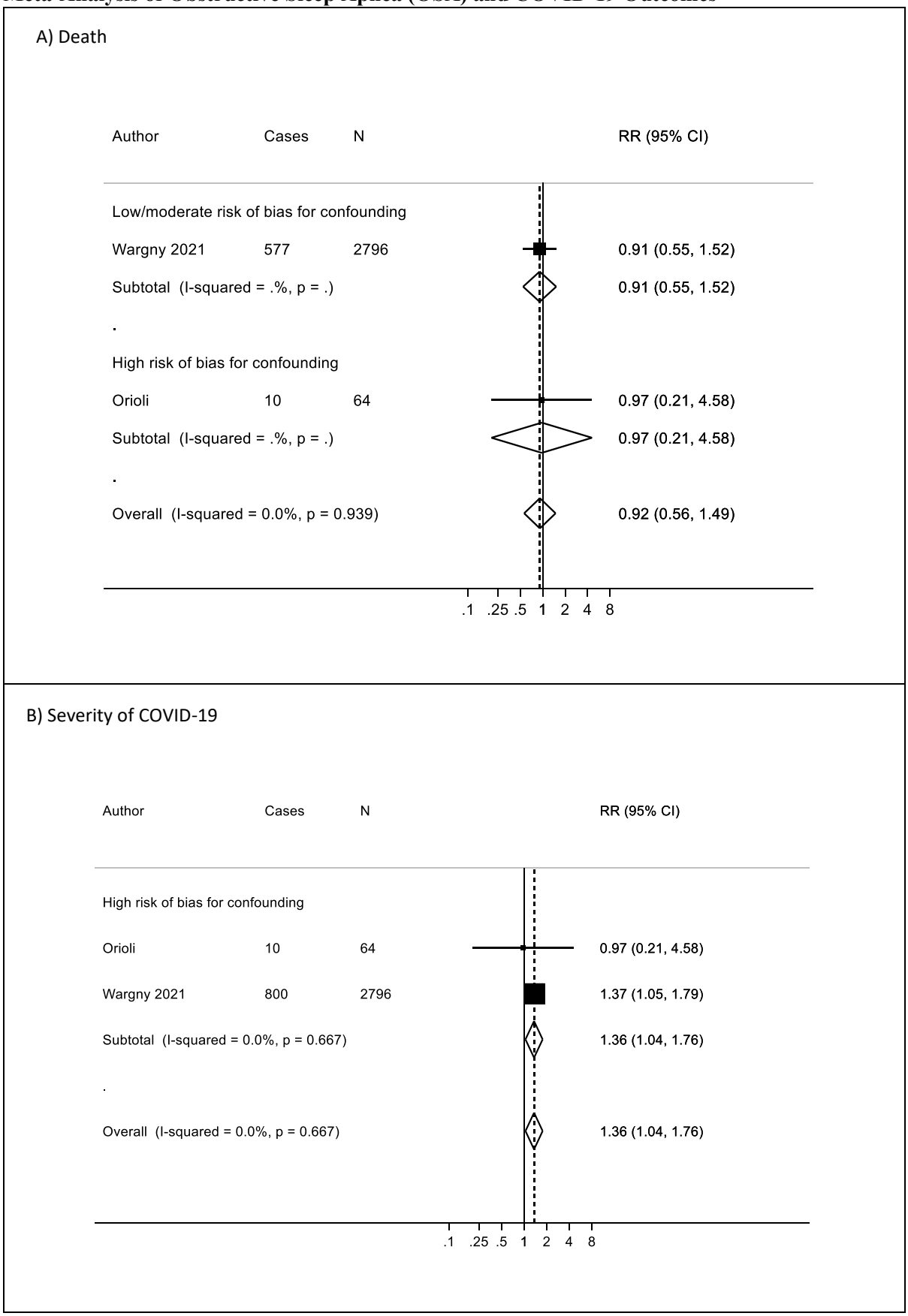
*Appendix Fig. 23: Meta-analysis on **heart failure** and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (80)*

Funnel Plot for Hypertension and COVID-19 Outcomes



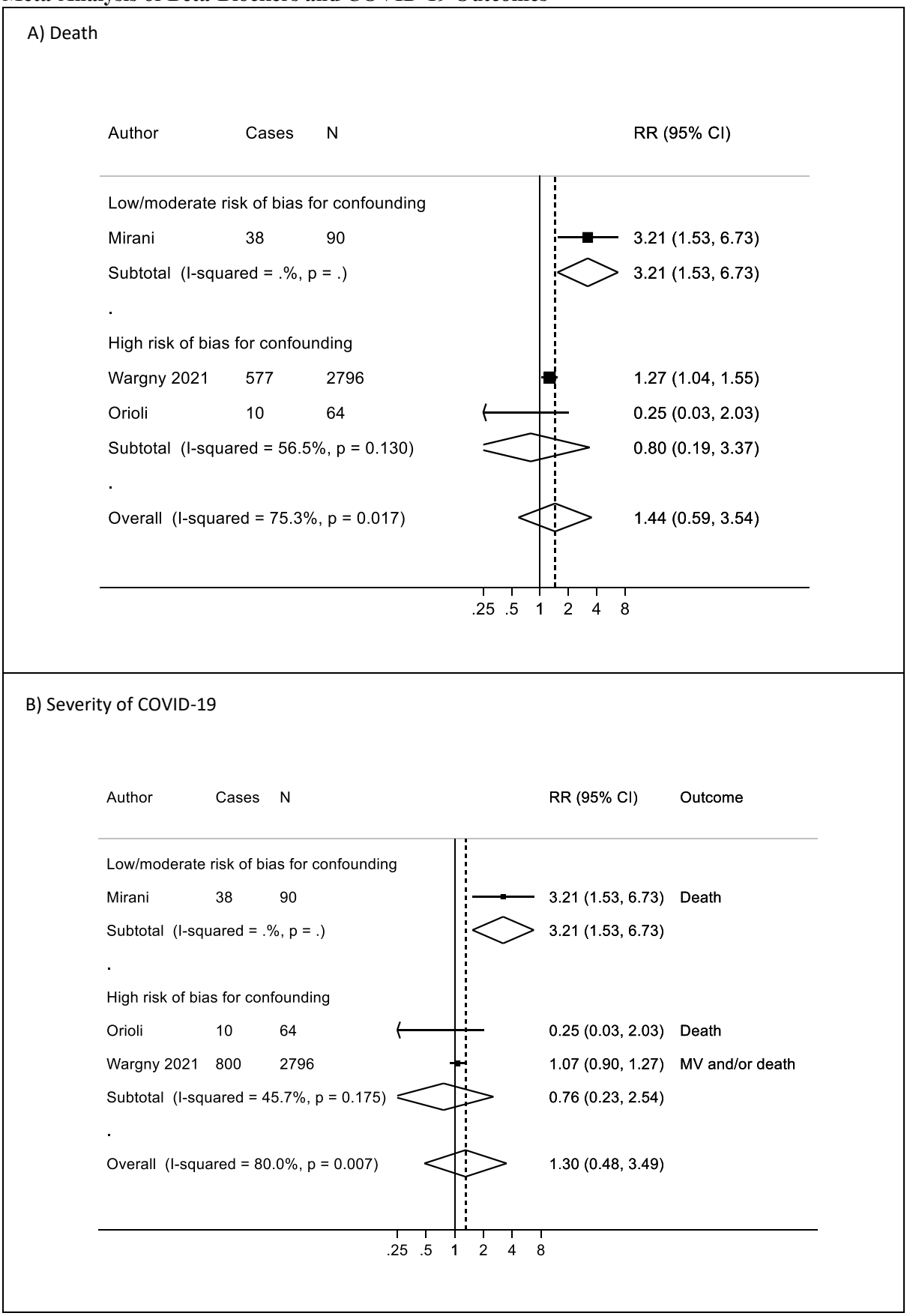
*Appendix Fig. 24: Funnel plot for association between **hypertension** and A) death and B) severity of COVID-19 in individuals with diabetes and COVID -19 - modified by Schlesinger et al (80)*

Meta-Analysis of Obstructive Sleep Apnea (OSA) and COVID-19 Outcomes



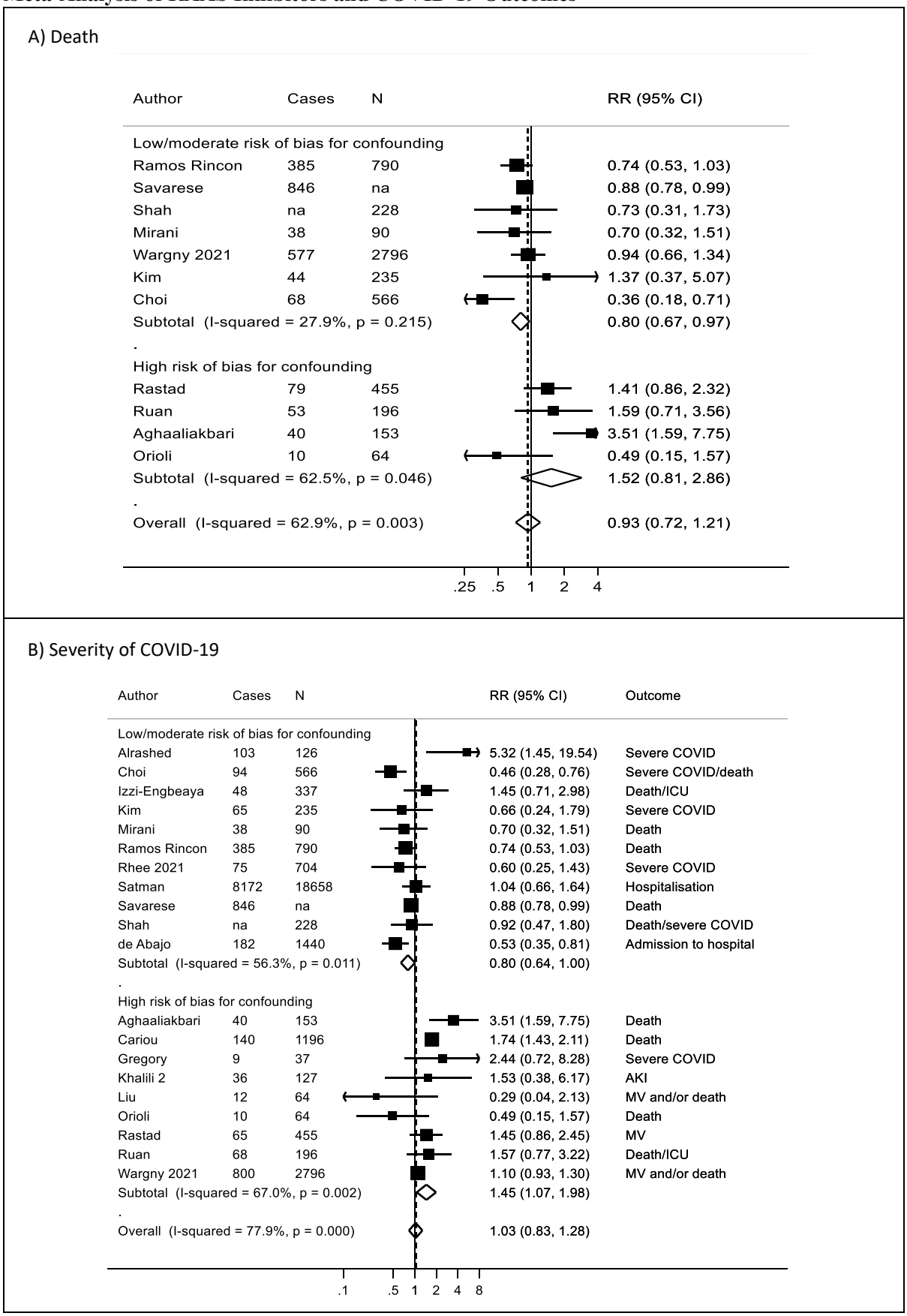
*Appendix Fig. 25: Meta-analysis on **obstructive sleep apnea (OSA)** and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (80)*

Meta-Analysis of Beta-Blockers and COVID-19 Outcomes



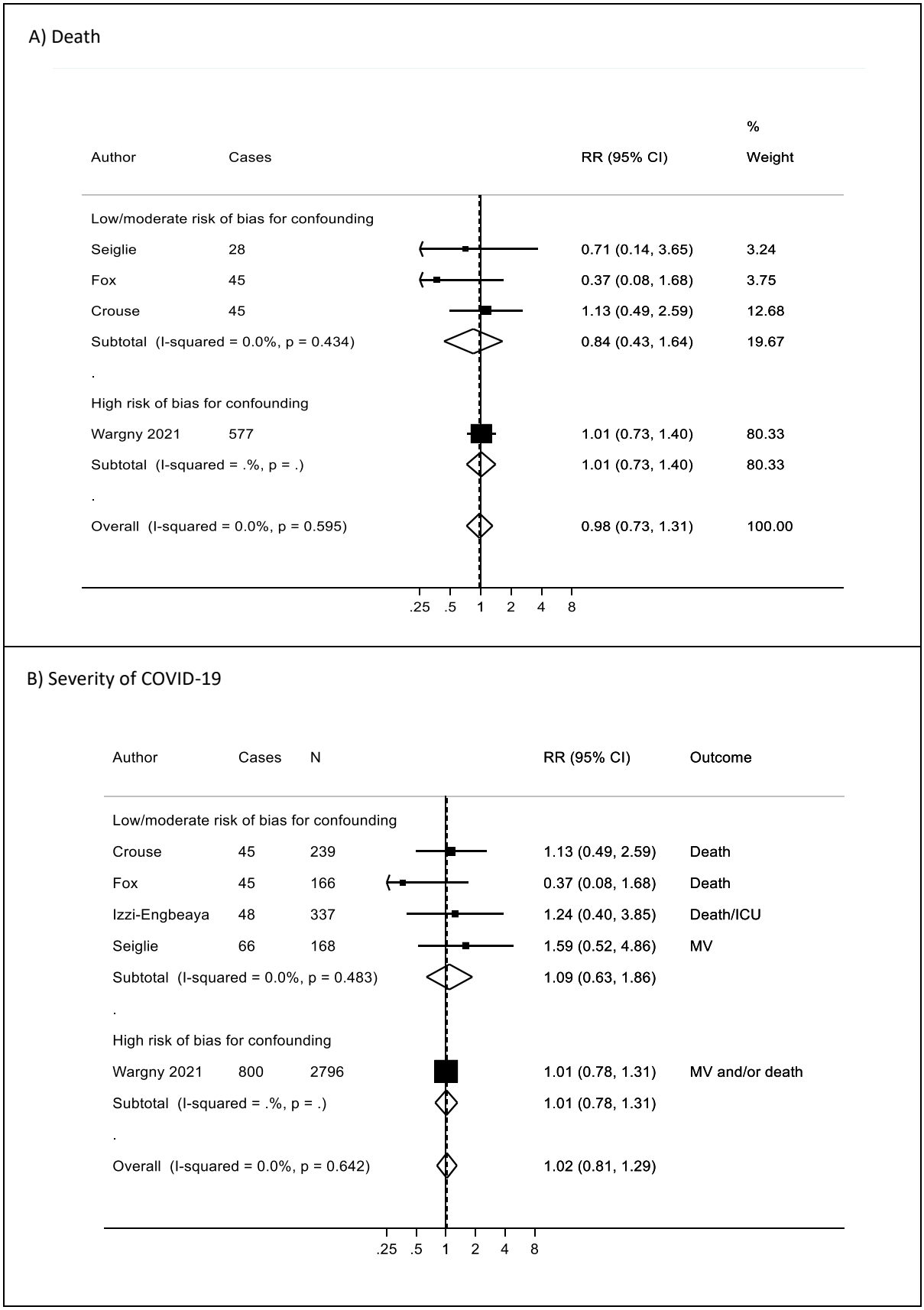
*Appendix Fig. 26: Meta-analysis on **beta-blockers** and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

Meta-Analysis of RAAS Inhibitors and COVID-19 Outcomes



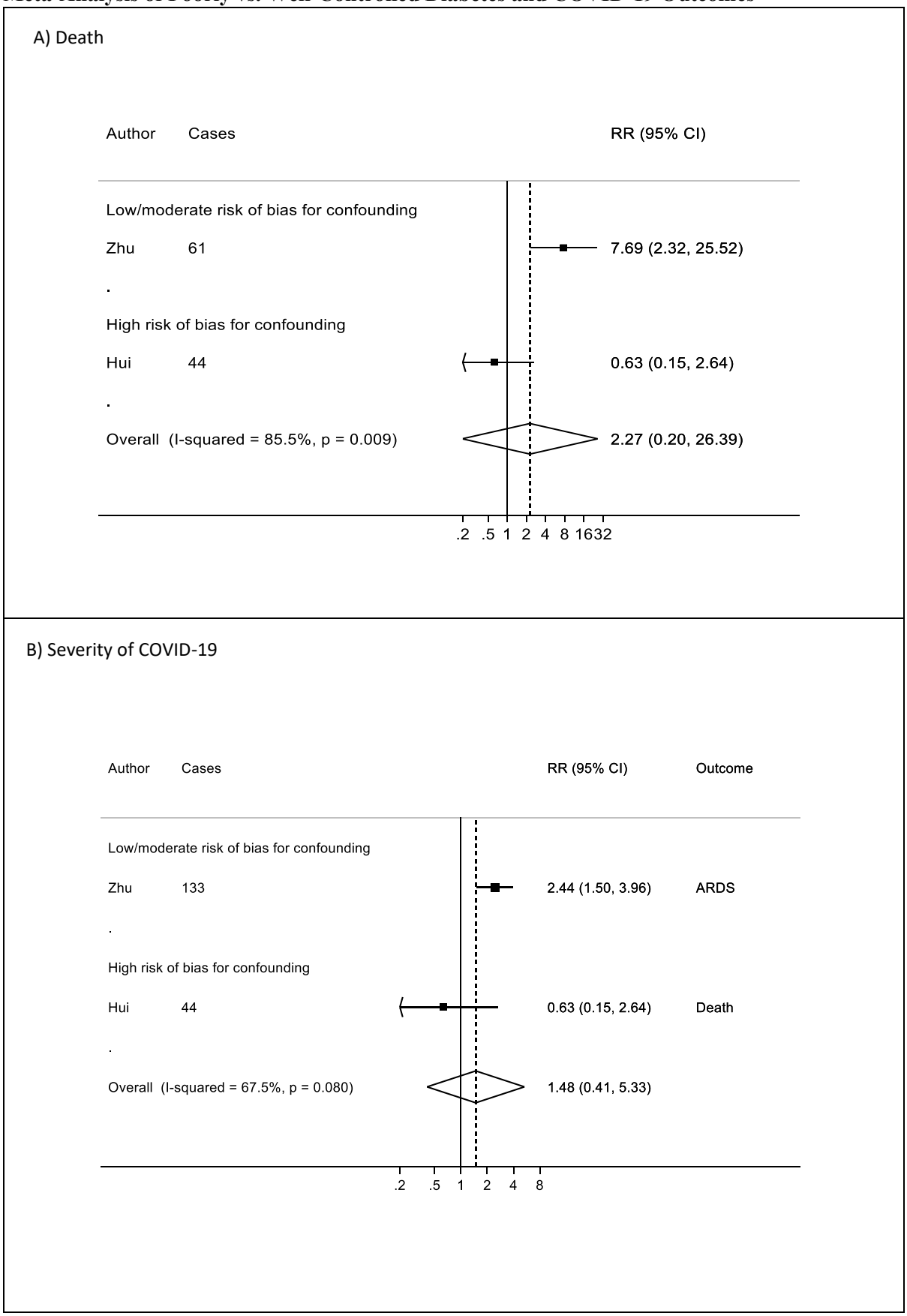
*Appendix Fig. 27: Meta-analysis on use of **RAAS inhibitors** compared to non-use and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 (1)*

Meta-Analysis of Ethnicity (African American vs. Non-Hispanic white) and COVID-19 Outcomes



*Appendix Fig. 28: Meta-analysis on **ethnicity (African American vs. Non-Hispanic white**) and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

Meta-Analysis of Poorly vs. Well-Controlled Diabetes and COVID-19 Outcomes



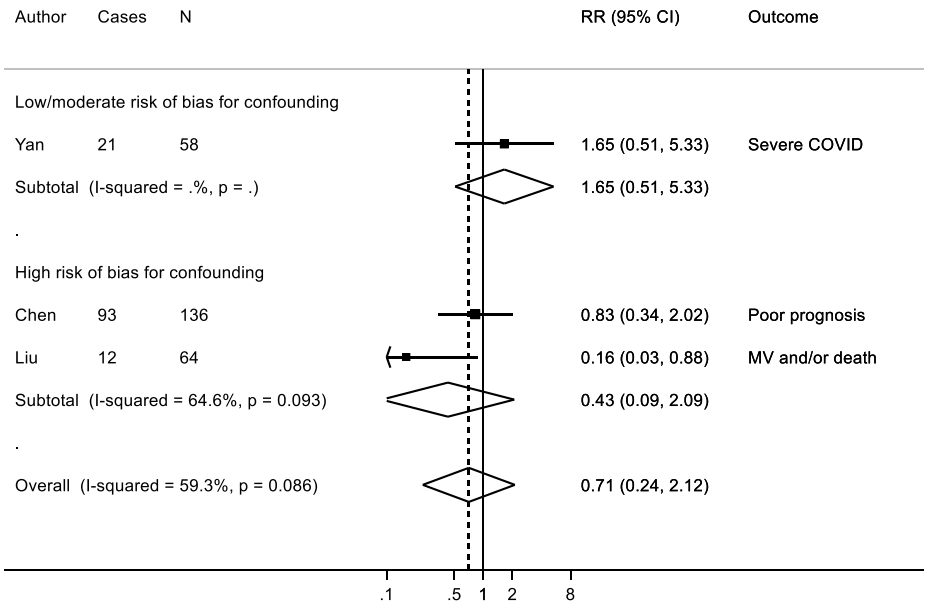
*Appendix Fig. 29: Meta-analysis for **poorly vs. well-controlled** at admission and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (80)*

Meta-Analysis of Alpha-Glucosidase Inhibitors and COVID-19 Outcomes

A) Death

No data

B) Severity of COVID-19



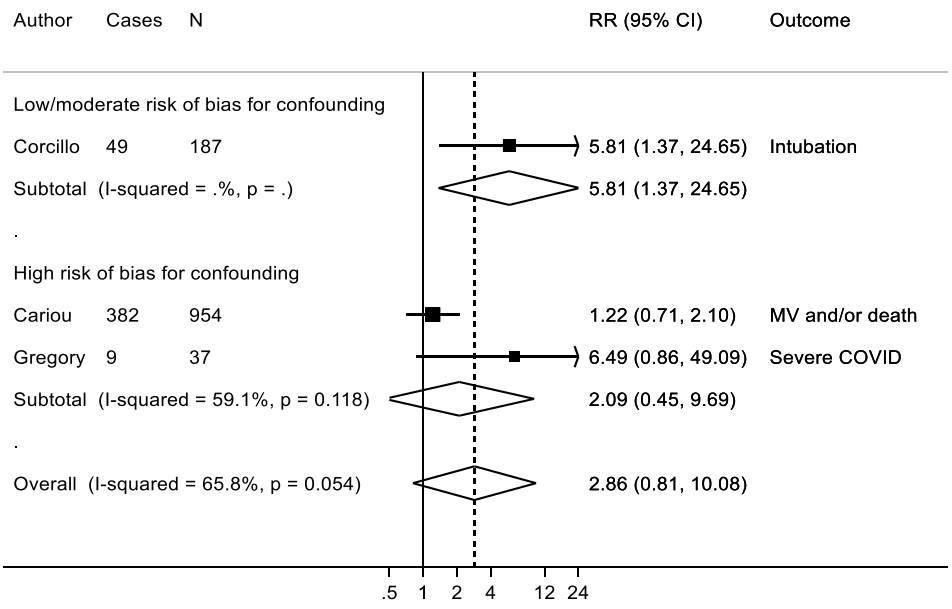
*Appendix Fig. 30: Meta-analysis on use of **alpha-glucosidase inhibitors** compared to non-use and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (1)*

Meta-Analysis of Retinopathy and COVID-19 Outcomes

A) Death

no data

B) Severity of COVID-19



*Appendix Fig. 31: Meta-analysis on pre-existing **retinopathy** compared to no diabetic foot and A) death and B) severity of COVID-19 in individuals with diabetes and COVID-19 - modified by Schlesinger et al (80)*

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