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META-ANALYSIS

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# Meta-analysis of factors associated with antidiabetic drug prescribing for type 2 diabetes mellitus

**Fatema Mahmoud**[1] | **Alexander Mullen**[1] | **Chris Sainsbury**[2] | **Gordon F. Rushworth**[3] | **Haya Yasin**[1] | **Nouf Abutheraa**[4] | **Tanja Mueller**[1] | **Amanj Kurdi**[1,5,6,7]

[1]Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK

[2]Department of Diabetes, NHS Greater Glasgow & Clyde, Glasgow, UK

[3]Highland Pharmacy Education & Research Centre, NHS Highland, Inverness, UK

[4]The Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, UK

[5]Department of Pharmacology and Toxicology, College of Pharmacy, Hawler Medical University, Erbil, Iraq

[6]Centre of Research and Strategic Studies, Lebanese French University, Erbil, Iraq

[7]Division of Public Health Pharmacy and Management, School of Pharmacy, Sefako Makgatho Health Sciences University, Pretoria, South Africa

**Correspondence**
Fatema Mahmoud, University of Strathclyde, Strathclyde Institute of Pharmacy & Biomedical Sciences (SIPBS), 161 Cathedral St, G4 0RE, Glasgow, UK.
Email: fatema.mahmoud@strath.ac.uk

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Jordan University of Science and Technology

## Abstract

**Background:** There is a lack of consensus on prescribing alternatives to initial metformin therapy and intensification therapy for type 2 diabetes mellitus (T2DM) management. This review aimed to identify/quantify factors associated with prescribing of specific antidiabetic drug classes for T2DM.

**Methods:** Five databases (Medline/PubMed, Embase, Scopus, Web of Science) were searched using the synonyms of each concept (patients with T2DM, antidiabetic drugs and factors influencing prescribing) in both free text and Medical Subject Heading (MeSH) forms. Quantitative observational studies evaluating factors associated with antidiabetic prescribing of metformin, sulfonylurea, thiazolidinedione, Dipeptidyl-peptidase 4 inhibitors (DPP4-I), sodium glucose transporter 2 inhibitors (SGLT2-I), Glucagon-Like peptide receptor agonist (GLP1-RA) and insulin in outpatient settings and published from January 2009 to January 2021 were included. Quality assessment was performed using a Newcastle-Ottawa scale. The validation was done for 20% of identified studies. The pooled estimate was measured using a three-level random-effect meta-analysis model based on odds ratio [95% confidence interval]. Age, sex, body mass index (BMI), glycaemic control (HbA1c) and kidney-related problems were quantified.

**Results:** Of 2331 identified studies, 40 met the selection criteria. Of which, 36 and 31 studies included sex and age, respectively, while 20 studies examined baseline BMI, HbA1c and kidney-related problems. The majority of studies (77.5%, 31/40) were rated as good and despite that the overall heterogeneity for each studied factor was more than 75%, it is mostly related to within-study variance. Older age was significantly associated with higher sulfonylurea prescription (1.51 [1.29–1.76]), yet lower prescribing of metformin (0.70 [0.60–0.82]), SGLT2-I (0.57 [0.42–0.79]) and GLP1-RA (0.52 [0.40–0.69]); while higher baseline BMI showed opposite significant results (sulfonylurea: 0.76 [0.62–0.93], metformin: 1.22 [1.08–1.37], SGLT2-I: 1.88 [1.33–2.68], and GLP1-RA: 2.35 [1.54–3.59]). Both

higher baseline HbA1c and having kidney-related problems were significantly associated with lower metformin prescription (0.74 [0.57–0.97], 0.39 [0.25–0.61]), but more insulin prescriptions (2.41 [1.87–3.10], 1.52 [1.10–2.10]). Also, DPP4-I prescriptions were higher for patients with kidney-related problems (1.37 [1.06–1.79]) yet lower among patients with higher HbA1c (0.82 [0.68–0.99]). Sex was significantly associated with GLP1-RA and thiazolidinedione prescribing (F:M; 1.38 [1.19–1.60] and 0.91 [0.84–0.98]).

**Conclusion:** Several factors were identified as potential determinants of antidiabetic drug prescribing. The magnitude and significance of each factor differed by antidiabetic class. Patient's age and baseline BMI had the most significant association with the choice of four out of the seven studied antidiabetic drugs followed by the baseline HbA1c and kidney-related problems which had an impact on three studied antidiabetic drugs, whereas sex had the least impact on prescribing decision as it was associated with GLP1-RA and thiazolidinedione only.

**KEYWORDS**

antidiabetic drugs, meta-analysis, prescribing, prescribing criteria, type 2 diabetes

## 1 | INTRODUCTION

Diabetes mellitus (DM) is a chronic progressive disorder characterised primarily by persistent hyperglycaemia[1]; according to the International Diabetes Federation, in 2021, around 537 million adults were diagnosed with DM worldwide.[2] More than 90% of people with DM have type 2 DM (T2DM) which is characterised by chronic hyperglycaemia and insulin resistance, contributing to the development of diabetes-related life-threatening complications.[3] These complications can be prevented/attenuated by achieving adequate glycaemic control following an appropriate non-pharmacological and pharmacological care plan.[4,5]

Several groups of antidiabetic drugs (ADDs) with different effectiveness and safety profiles are currently available. The most commonly used ADDs are metformin, sulfonylurea (SU), thiazolidinedione (TZD), dipeptidyl-peptidase-4 inhibitors (DPP4-I), sodium glucose transporter-2 inhibitors (SGLT2-I), glucagon-like peptide receptor-1 agonists (GLP1-RA) and insulins.[4–6] All clinical guidelines have agreed on metformin as first-line therapy for patients newly diagnosed with T2DM.[7–9] However, the choice of intensifying therapy or alternative initial therapy in the presence of contraindications to metformin, is more variable, and prescribing decision could be influenced by several factors relevant to patients and drugs characteristics.[7–9]

Several observational studies have evaluated the association of multiple factors with ADD prescribing (ADP) in clinical practice, including, for example, patient's age, sex, ethnicity, socioeconomic status, body mass index (BMI), glycaemic control (HbA1c), renal function and history of microvascular/macrovascular complications.[10–14] Nevertheless, no previous studies extensively quantified the impact of these different factors on prescribing decisions of different ADDs, which would be of interest especially after the introduction of newer ADDs which provided prescribers not only with wider options for T2DM management, but with ADDs that may have independent cardiac and renal protection effects.[15–17]

Generally, factors associated with drug prescribing may indirectly reflect prescriber's adherence to guideline recommendations and specific drug features. This highlights the importance of studying these factors in a systematic way to assess the process of patient care by investigating which and how factors contribute to the decision-making in clinical practice.[18] Therefore, this systematic review (SR) and meta-analysis (MA) aimed to summarise and quantify factors associated with ADP at both the initiation and intensification stages.

## 2 | METHODS

This SR&MA is presented following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Appendix S1[19]). The protocol was registered in the international prospective register of systematic reviews (PROSPERO; registration number CRD42020173917).

## 2.1 | Data sources and search strategy

The search strategy was developed using three main concepts: participants (patients with T2DM), intervention (antidiabetic drugs) and outcome (factors associated with ADP). Medline/PubMed, Embase, Scopus and Web of Science were searched for studies published between January 2009 and January 2021 (the date of starting data synthesis). Additional searches were conducted to ensure literature saturation on ProQuest, Open Grey database and the reference lists of included articles. The search strategy was independently reviewed by experienced researchers and an academic librarian. As an example, the full Medline search strategy is available in the Appendix S2.

## 2.2 | Eligibility criteria

Only quantitative observational studies reporting factors associated with ADP among adults with T2DM in primary-care/outpatient settings and published in English were included (Table 1). Literature was searched from 2009 onwards to ensure the inclusion of newer ADDs (GLP1-RA, DPP4-I and SGLT2-I), which have been introduced into market since 2009. Only adults (≥18 years of age) were included to ensure that all people were subject to the same treatment recommendations since different treatments are recommended for children with T2DM.

## 2.3 | Study selection, data extraction and quality assessment

Two stages of study selection were conducted using Covidence[20]: title/abstract screening; and full-text screening. Relevant data was extracted from included studies using an MS Excel extraction form that was initially piloted on a random 10% of included studies to assess whether it captures all relevant data. All identified factors were mapped into four categories: 1 – demographic factors; 2 – clinical factors; 3 – socioeconomic factors; and 4 – prescriber-related factors, which were initially developed based on the literature around factors affecting physician's prescribing decision and modified as appropriate to fit the current research question.[21] Along with data extraction, the included studies were evaluated for the risk of bias using the Newcastle-Ottawa scale (NOS) for cohort studies[22] and the adapted NOS for cross-sectional studies.[23,24] More details on the quality assessment and study scoring are available in the Appendix S5. At each step of screening, extraction and quality assessment, a total of 20% of included studies were validated by two independent reviewers.

**TABLE 1** Study inclusion and exclusion criteria.

| Category | Inclusion criteria |
|---|---|
| Language | English |
| Publication year | January 2009–January 2021 |
| Publication type | Any studies reporting on factors associated with antidiabetic drugs' prescription or patients' characteristics prior or at the time of antidiabetic drugs' prescription |
| Methodology | Quantitative observational study designs |
| Diabetes type | Only type 2 diabetes mellitus |
| Patients | Adults (≥18 years old) patients who were prescribed any of the following: Biguanide (metformin), Sulfonylurea (SU), thiazolidinedione (TZD), dipeptidyl-peptidase 4 inhibitors (DPP4-I), sodium glucose transporter 2 inhibitors (SGLT2-I), glucagon-like peptide 1 receptor agonists (GLP1-RA), and insulins |
| Category | Exclusion criteria |
| Language | Other than English |
| Publication year | Published before January 2009 |
| Publication type | Reports, commentaries, editorials, book chapters, systematic reviews and meta-analysis |
| Patients | Studies on children, adolescents, pregnant or breastfeeding women |
| Outcome | Studies including type I DM, gestational diabetes |
| | Studies did not clearly state that factors were collected at baseline |
| | Studies with data on inpatient or admitted patients |
| | No relevant outcomes (e.g. switching medicine, discontinuation) |
| | Studies did not specify the type of antidiabetic groups being studied |

### 2.4 | Data synthesis and meta-analysis

All factors related to ADP were identified from included studies. However, only factors reported by more than two studies for their association with the individual antidiabetic class were eligible for MA. Accordingly, MA was applied on five of the identified factors: age, sex, HbA1c, BMI and kidney-related problems.

Three-level random-effect models were used to combine the pooled estimates (presented as odds ratio (OR) and 95% confidence intervals (CI)) measuring the association of each factor with ADP; a three-level MA approach was used to address the presence of dependency or correlation of effect sizes arising from reporting more than one effect size per study due to examining the outcomes of more than one antidiabetic group.[25,26] Subsequently, the pooled estimate measuring the association of the individual factor with each type of antidiabetic class was calculated using a two-level random effect model. Studies to be included in the MA had to report the effects of the identified factors as OR from either binary or continuous data; or provide primary baseline data required for OR calculation. Appendix S3 provides details on the method of effect size computation.

Study heterogeneity was measured by conducting Higgins &Thompson's ($I^2$) test over three levels to compute the overall heterogeneity as well as within-study (level-2) and between-studies (level-3) variance, with $I^2 > 75\%$ indicating high heterogeneity.[27] Furthermore, the usefulness and performance of the three-level model was evaluated by conducting log-likelihood-ratio test.[27–29]

Moderator (sub-group) analysis was performed to explore any source of heterogeneity including the potential effect of several variables related to study characteristics on the overall estimate, such as class of ADDs, stage of treatment at which the outcome was assessed (initiation, intensification or not specified stage), quality of study, type of analysis used (adjusted vs. un-adjusted), study design and year of publication.[28] A $p$-value of <.05 indicates a significant result. Some factors (age, BMI, HbA1c) were reported as a binary variable in some studies and as a continuous variable in other studies. The pooled estimate of those factors was initially computed including all studies presenting the outcome as binary or continuous data following the approach described by Cochrane guideline. Additional sub-group analysis based on the type of reported data was performed to assess whether there was a significant difference in the pooled estimates according to the data type.

Publication bias was assessed with the funnel plot and extended Eggers' test.[30,31] Moreover, the number of outliers was measured and plotted as histogram for each MA and a sensitivity analysis was conducted to explore the influence of outliers on the pooled estimate. An effect size was considered as an outlier when its CI does not overlap with the CI of the pooled estimate.[32] Cook's distance ($D$) test was also performed with the results presented as scatter plots to explore the influential impact of included studies.[32] A Cook's-$D$ value of $\geq 4/k$ ($k$: the number of effect sizes) indicated an influential impact of a study on the overall estimate.[33] All statistical tests were performed using RStudio; for full R-syntax, please refer to Appendix S4.

## 3 | RESULTS

### 3.1 | Study selection

Of the 2331 identified studies which had title/abstract screened, 96 underwent full text screening and 40 articles met all inclusion criteria (Figure 1). The percentage of agreement between the independent reviewers from title/abstract and full-text screening was high (93.8% and 85.7%, respectively).

### 3.2 | Study characteristics

Table 2 shows the characteristics of included studies. More than two thirds of eligible studies ($n = 33$, 82.5%) were published from 2013 onwards.[10,13,14,35,37–39,41,43,44,46,48–67,69,70] The majority ($n = 36$, 90%) were of cohort study design[10,13,14,34–42,44,45,47–53,55–62,64–70] and more than one third ($n = 15$; 37.5%) originated from the United States.[14,36,40,42,46,47,54,56,57,59,60,64,65,67,68] The total number of participants from the included studies was 5,327,502 people with T2DM, excluding one study which provided the number of visits rather than the number of patients.[46] Oral antidiabetics were examined in 90% of studies ($n = 36/40$) whereas injectable drugs were evaluated in about half of included studies ($n = 21$, 52.5%). The most frequently investigated ADDs were SU ($n = 21$, 52.5%), metformin ($n = 20$, 50%) and DPP4-I ($n = 19$, 47.5%) while SGLT2-I was the least studied group ($n = 11$, 27.5%). Only 29 (72.5%) studies stated at which stage of treatment the outcome was observed; whether at initiation ($n = 14$) or intensification ($n = 15$). The quality assessment score of cohort studies ranged from 5 to 9 with the majority of studies ($n = 29/37$, 78.4%) rated as good. Of the three cross-sectional studies, two were rated as very good and one as satisfactory (Appendix S5).

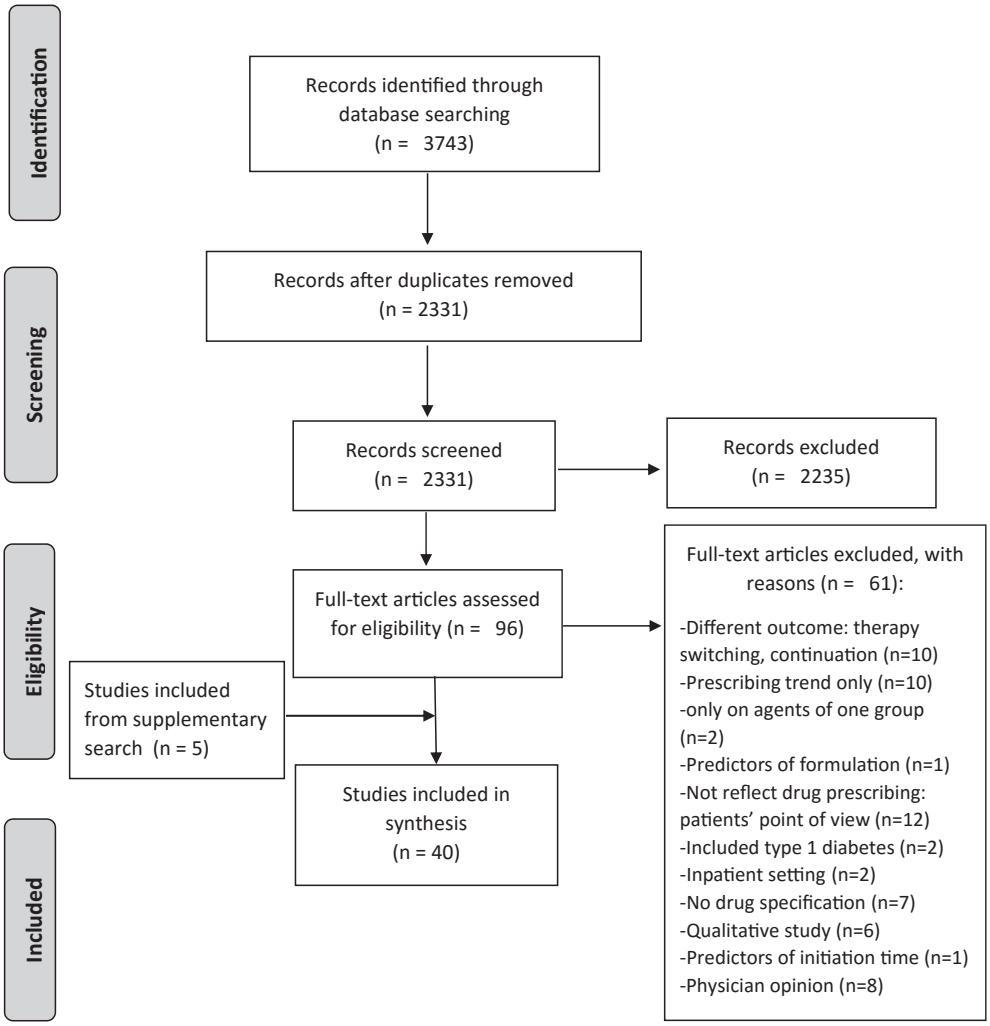


**FIGURE 1** PRISMA flow chart of screening process to identify relevant studies (January 2009–January 2021).

## 3.3 | Meta-analysis results

The following factors were identified in the included studies as factors associated with ADP (Table 3): demographic factors (patients' age, sex, ethnicity, smoking status, family history of diabetes and educational level), clinical factors (obesity, glycaemic status (HbA1c), kidney function, having macrovascular/microvascular complications or other comorbidities and diabetes duration), socioeconomic factors (deprivation level, income level, employment status, having insurance, area of living and type of medical facility) and prescriber-related factors (prescriber age, sex, speciality and practice experience).

However, it was possible to perform the MA on only five factors: age, sex, HbA1c, BMI and kidney-related problems.

## 3.4 | Sex

Out of the 40 eligible studies, 36 (90%) reported on sex association with ADP and all except one[50] were included in the MA, contributing to a total of 96 effect sizes. Heintjes et al.[50] was excluded since the outcome was not reported as OR and insufficient data was available for OR computation. The three-level MA showed that overall, sex had no association with ADP (OR [95% CI]: 1.00 [0.86–1.16]), Figures 2A, 2B. However, subgroup analysis showed that the effect of sex varied significantly by the class of ADDs ($p = .001$), with the most significant influence on GLP1-RA and TZD prescription. Female patients were significantly more likely to be prescribed GLP1-RA compared to male patients (OR [95%CI]: 1.38 [1.19–1.60]), yet less likely to get TZD prescription (OR [95% CI]: 0.91 [0.84–0.98]).

## 3.5 | Age

Age was evaluated in a total of 38 studies; 31 studies were included in the MA, contributing to a total of 88 effect sizes. Seven studies were excluded since they did not present the outcome as OR and did not provide the required data for OR computation.[37,40,46,50,52,58,62]

**TABLE 2** Characteristics of the 40 studies which were eligible for inclusion.

| Author, year, country | Study design | Study duration | # Of Participants/Age/Sex | Antidiabetic drug studied | Stage of treatment | Analysis method |
|---|---|---|---|---|---|---|
| Winkelmayer et al. (2010), Austria[34] | Retrospective cohort | 1/2007–6/2008 | 39,077 patients/19–100 years; mean 63.4 years/F: 50.4% | Metformin vs. Other oral hypoglycaemic | Initiation | Multivariable logistic regression |
| Abdelmoneim et al. (2013), Canada[35] | Retrospective cohort | January 1998–December 2010 | 31,421 patients/≥65 years; mean: 74.8 years/F: 49%. | Metformin vs. SU monotherapy | Initiation | Multivariable logistic regression models |
| Brouwer et al. (2012), United States[36] | Retrospective cohort | January 1998–December 2009 | 1972 patients/>21 years; median: 54 years/F: 52.5% | Metformin vs. SU, TZD, combination. SU vs. combination | Initiation | Multinomial regression model |
| Liu et al. (2017), Taiwan[37] | Retrospective cohort | January 2006–December 2010 | 28,640 patients/≥20 years; mean: 57.4/F: 47.3% | Non-metformin vs. metformin | Initiation | Logistic regression |
| Wang et al. (2013), Quebec, Canada[38] | Dynamic historical cohort study | January 2003–December 2011 | 1279 patients/≥18 years, 53.4% ≥65 years/F: 50.8% | Metformin vs. non metformin | Initiation | Multivariate generalised estimating equation analysis |
| Geier et al. (2014), Germany[13] | Retrospective cohort | June 2003–December 2009 | 10,657 patients/40–79 years; mean for both: 61.47 years/F:51% | Metformin vs. SU | Initiation | Multiple logistic regression |
| Fujihara et al. (2017), Japan[39] | Retrospective cohort | December 2009–March 2015 | 2666 patients/≥20 years; overall mean: 60.9 years/F: 35.9% | Metformin, DPP-4Is vs. SU | Initiation | Multinomial logistic regression analysis |
| Desai et al. (2012), United States[40] | Retrospective cohort | January 2006–December 2008 | 254,973 patients/18–100 years; mean: 58.2 years/F: 47.3% | Metformin | Initiation | Multivariable logistic models |
| Grimes et al. (2015), Ireland[41] | Retrospective cohort | January 2008–December 2009 | 20,947 incident users of antidiabetic agents/≥40 years/F:42.1% | Metformin vs. SU | Initiation | Adjusted logistic regression |
| Cai et al. (2010), United States[42] | Retrospective cohort | January 2006–June 2008 | 240,426 patients/26–88 years; mean: 54.4/F: 44.8% | Sitagliptin vs. non- Sitagliptin | Not specified | Chi-square statistics |
| Saine et al. (2015), United States and United Kingdom[43] | Cross-sectional/ | THIN: October 2009–September 2012, US Medicare: August 2009–December 2011, HIRD: August 2009–July 2012 | UK: 43,466, US: 631,273/Mean: UK: 58.8, US:67.6 years/F: UK: 42.4%, US:55% | Saxagliptin vs. other OAD | Not specified | Conditional logistic regression |
| Wilkinson et al. (2018), United Kingdom[10] | Retrospective cohort | January 2014–July 2017 | 14,149 individuals/≥18 years; Mean: 60 years/F: 40.3% | SGLT2-I, DPP 4-I vs. SU | 1st intensification | Multinomial logistic regression, Sensitivity analyses |
| Grabner et al. (2015), United States[14] | Retrospective cohort | January 2011–September 2013 | Overall: 27790 patients/≥18 years; mean overall: 55.03 years/F:39.4% | Canagliflozine vs. DPP 4-I | Intensification not specified level of intensification | Multivariable logistic regression |
| OU et al. (2016), Taiwan[44] | Retrospective cohort | 2011–2012 | 32,724 patients/≥20 years | DPP-4 I vs. other antidiabetics | Intensification, 1st, and 2nd | Multiple logistic regression |
| Stargardt et al. (2009), Finland, France, Germany, Norway, Poland, Spain, UK[45] | Retrospective cohort | June 2006 and February 2007 | 1218 patients: 891; added SU 327 added TZD/≥30 years; Mean: SU, TZD: 61.0, 57.8 years | TZD vs. SU | 1st intensification | Probit regression analysis |

TABLE 2 (Continued)

| Author, year, country | Study design | Study duration | # Of Participants/Age/Sex | Antidiabetic drug studied | Stage of treatment | Analysis method |
|---|---|---|---|---|---|---|
| Payk et al. (2015), United States[46] | Cross-sectional study | 2003 to 2004 and 2007 to 2010 | 7042 visits/≥18 years; Mean: 61.6 years/F: 52% | SU | Not specified | Weighted sampling, A multivariate logistic regression model |
| Zhang et al. (2010), United States[47] | Retrospective cohort | October 2006 – June 2008 | 41,836 patients/≥30 years; Mean overall: 60.08 | Sitagliptin vs. Non-Sitagliptin | Not specified | Adjusted logistic regression analysis |
| Morita et al. (2019), Japan[48] | Retrospective cohort | October 2012–September 2016 | Metformin and DPP4i users only: 74935.658 | DPP4i vs. metformin | Initiation | Univariate logistic regression |
| Kim et al. (2019), Korea[49] | Retrospective cohort | 2014–2016 | 3609 patients/≥20 years/F:48.9% | Newer (SGLT2I and DPP4I) vs. older (SU and TZD) | 1st Intensification | Logistic regression analysis |
| Heintjes et al. (2017), Netherlands, Italy, Spain, United Kingdom[50] | Retrospective cohort | 5 years: 2007 to 2011 (ES, IT, and NL) or 2008 to 2012 (UK) | 485,570 patients/≥18 years | Metformin, SU, TZD, DPP4i, GLP-1ra, insulin. | Initiation and intensification; 1st line, 2nd line, 3rd line, 4th line | Poisson Regression |
| Nicolucci et al. (2019), 38 Countries[51] | Prospective cohort | December 2014–June 2016 | 14,668 patients/≥18 years; mean: overall: 57.5 years/F: 46.1% | DPP4i, SGLT2-I, GLP1-RA vs. SU | 1st intensification (second line) | Firth logistic regression |
| Hartmann et al. (2019), Germany, Austria, Switzerland, Luxemburg[52] | Retrospective cohort | 2000–2017 | 4770 patients/>18 years; median: BOT initiated, OAD w/o insulin, GLP w/o insulin: 64.0, 62.6, 55.3 years/F: overall:45.7% | GLP1-RA, basal insulin, OAD | 1st Intensification | Multivariable linear and logistic regression models |
| Longato et al. (2020), Italy[53] | Retrospective cohort | | 12,996 patients/calculated mean for both groups: 62.84 years/F: 36.8% | SGLT2-I vs. GLP1-RA | Not specified | Chi-square, standardised mean difference, or many Whitney test |
| Ackermann et al. (2017), United States[54] | Multiple case-comparative study design | January 2011–June 2015 | 77,744 patients/≥18 years, 25.7% ≥65 years/F: 43.1% | DPP4-I, GLP1-RA, SGLT2-I, SU, TZD | 1st intensification | Multinomial logistic regression |
| Whyte et al. (2019), England[55] | Retrospective cohort | January 2012–December 2016 | 49,380 patients/≥ 18 years; Mean: 68.7 years/F: 43.9% | SGLT2-I, GLP1-RA, metformin, insulin, SU, DPP-4-I, TZD | Not specified | Logistic regression, mixed effects model |
| Arnold et al. (2018), United States[56] | Retrospective cohort | Not stated | 157,551 patients/≥18 years; Mean: 68.1 years/F:42.8 | SGLT2-I, GLP1-RA, metformin, insulin, SU, DPP-4-I, TZD | Not specified | Possion regression |
| Arnold et al. (2018), United States[57] | Retrospective cohort | 2013–2016 | 456,106 patients/Mean: 67.6 years | SGLT2-I, GLP1-RA, metformin, insulin, SU, DPP-4-I, TZD | Not specified | Possion regression |

(Continues)

TABLE 2 (Continued)

| Author, year, country | Study design | Study duration | # Of Participants/Age/Sex | Antidiabetic drug studied | Stage of treatment | Analysis method |
|---|---|---|---|---|---|---|
| Zaharan et al. (2013), Ireland[58] | Retrospective cohort | 2008–2012 | 524,305 | Metformin, SU, TZD, GLP1-RA, DPP4-I | Not specified | Adjusted logistic regression |
| Zoberi et al. (2017), United States[59] | Retrospective cohort | July 2008–July 2013 | Patients; Overall: 1952/≥18 years Mean:59.3 years. F: 60.76% | Metformin, Insulin | Not specified | Chi-square and independent sample t-tests |
| Montvida et al. (2017), United States[60] | Retrospective cohort | 2005–2016 | 1st line: 1,023,340 patients 2nd line: 357482 patients | GLP-1RA, SGLT2-I, MET, INS, TZD, DPP-4i, SU | Initiation and intensification | Descriptive only |
| Katakami et al. (2020), Japan[61] | Prospective cohort | September 2014–December 2015 | 1806 patients/mean:61.7 years/F;38.4% | Metformin, SU, TZD, glinides, DPP4i, SGLT2-I, GLP1-RA, insulin | Intensification | Firth logistic regression models |
| Kostev et al. (2014), Germany[62] | Retrospective cohort | January 2003–December 2012 | 10, 223 patients/>40 years; Mean for both groups: 65.69 years/F for both groups: 49.7% | Insulin | Initiation intensification | A multivariate Cox regression model for insulin |
| Dhanaraj et al. (2013), India[63] | Cross-sectional | June 2007–March 2009 | 1185 patients/mean age: 55 years/F: 49% | Metformin, SU, insulin, pioglitazone | Not specified | Univariate logistic regression |
| Yu et al. (2017), United States[64] | Retrospective cohort | November 2014–February 2016 | 11,053 patients/≥18 years; Mean overall: 61.26 years/F: 51.5% | GLP-1-RA vs. basal insulin | Intensification; Not specified intensification level | Boosted regression models (GBM), logistic regression model |
| Levin et al. (2014), United States[65] | Retrospective cohort | January 2000–March 2011 | 51,771 patients/≥18 years; Mean overall: 55.6 years/F:40.2% | Insulin, GLP1-R vs. 3OHA | Intensification; Not specified intensification level | t-test or chi square |
| Gentile et al. (2018), Italy[66] | Retrospective cohort | 2004–2011 | Sample size included in the model 4 ($n = 44,611$)/≥18 years; mean: Overall: 65 years/F: 44.2% | Insulin vs. Non-insulin | Intensification; Not specified level of intensification | Cox proportional hazard model |
| Korytkowski et al. (2014), United States[67] | Retrospective cohort | June 2005–November 2011 | 1892 patients/calculated mean age for all groups: 54.78 years/F: 48.95% | Insulin, GLP1-RA vs. OHA | Intensification | t-test or chi square |
| Hirsch et al. (2011), United States[68] | Retrospective cohort | October 1,2005, — January 2008 | 190, 444 patients; Sample size for multivariable model 51,048/≥18 years; mean: 62.4 years/F:51.9% | Exenatide vs. Non-exenatide | Not specified | Cox proportional hazard regression |
| Boom et al. (2020), Germany[69] | Retrospective cohort | January 2014–December 2018 | 10,497 patients/18-90 years, mean overall:63.6 years/F overall: 45.9% | Insulin vs. oral antidiabetic | Initiation | Multivariable logistic regression model |
| Moreno Juste et al. (2019), Italy[70] | Retrospective cohort | January 1 and December 31, 2016 | 12,753 patients/mean age for all groups: 63.9 years/F: 45.76% | Metformin, SU, DPP4-I | Initiation | t-test or chi square |

**TABLE 3** Description of the outcome of the 40 studies which were eligible for inclusion.

| Author | Outcome definition | Patients-related | Clinical-related | Socioeconomic | Prescriber-related | Reported as |
|---|---|---|---|---|---|---|
| Winkelmayer et al.[34] | Associations of metformin initiation vs. any other oral hypoglycaemic medication. | Patients age, sex | | Socioeconomic status | Age, sex, speciality | OR, 95% CI |
| Abdelmoneimet al.[35] | Predictors of new monotherapy users | Age, sex | Microvascular (neuropathy, retinopathy, nephropathy) and macrovascular complications (as ischemic heart disease (IHD), cerebrovascular disease, heart failure (hf), peripheral vascular disease (PVD)), comorbidities (as hypertension (HTN) and dyslipidaemia) | | | OR, 95% CI |
| Brouwer et al.[36] | Factors influencing selection of initial oral hypoglycaemic medication | Age, sex, race | Glycaemic status (HbA1c), Serum creatinine | | | Probability ratio, 95% CI |
| Liu et al.[37] | Factors associated with non-metformin prescription as initial antidiabetic therapy. | Sex, age | | Income level, medical facility features; accreditation level, ownership, location | Age, sex, speciality | OR, 95% CI |
| Wang et al.[38] | Predictors of starting metformin and the influence of guideline adherence on starting of oral hypoglycaemic agents | Age, sex | Comorbidities (renal and cardiovascular disease (CVD)) | | Sex, practice experience | OR, 95% CI |
| Longato et al.[53] | Difference in the baseline characteristics between patients newly initiated SGLT2-I vs. GLP1-RA | Age, sex | HTN, dyslipidaemia, microvascular and macrovascular complications, comorbidities | | | %/mean, *p* value |
| Geier et al.[13] | Predictors of Metformin vs. SU initiators | Age, sex, smoking status | Obesity, glycaemic status (HbA1c), diabetes duration | | | OR, 95% CI |
| Fujihara et al.[39] | Factors that influence the choice of each of three hypoglycaemic agents prescribed as initial monotherapy | Age, sex | Diabetes duration, body mass index (BMI), HTN, HbA1c | | | OR, 95% CI |
| Desai et al.[40] | Predictors of receiving metformin as initial oral hypoglycaemic therapy | Age, sex | Comorbidity | Income, Drug insurance cover | | OR, 95% CI |
| Grimes et al.[41] | Socio-demographic factors association with initiation of metformin or SU | Age, sex | | | | OR, 95% CI |
| Cai et al.[42] | Characteristics of patients prescribed Sitagliptin vs. other oral antidiabetics | Age, sex | Retinopathy, neuropathy, nephropathy, CVD (as HF, stroke, myocardial infarction (MI), PVD), other comorbid diseases (HTN), obesity | | | %, *p* value |
| Saine et al.[43] | Determinants of saxagliptin use | Age, sex, Smoking | HbA1c, obesity, nephropathy, neuropathy, retinopathy, CVD, PVD, cerebrovascular disease | | | OR, 95% CI *N*, % for age and sex |

(Continues)

**TABLE 3** (Continued)

| Author | Outcome definition | Patients-related | Clinical-related | Socioeconomic | Prescriber-related | Reported as |
|---|---|---|---|---|---|---|
| Wilkinson et al.[10] | Patient characteristics associated with the class of antidiabetic drug prescribed | Age, sex, Ethnicity, smoking | HbA1c, BMI, Kidney function (eGFR), CVD, retinopathy | SES | | OR, 95% CI |
| Grabner et al.[14] | Baseline Characteristics with Initiation of Canagliflozin vs. DPP4-I | | HbA1c, microvascular complications, dyslipidaemia, Obesity | | | OR, 95% CI |
| OU et al.[44] | Factors associated with the choice of DPP4-I rather than other antidiabetics | Age, sex | Comorbidities (HTN, dyslipidaemia, stroke, coronary artery disease (CAD), heart failure (HF)) | | | Estimates, SE |
| Stargardt et al.[45] | Predicted probabilities of adding glitazone or sulfonylurea to metformin | Age, history of diabetes in family | History of macrovascular complication, HbA1c, weight | | Speciality, years of experience | Predicted probability, *p* value |
| Payk et al.[46] | Predictors of SU use | Age, sex, race | | Payment type | Speciality | OR, 95% CI |
| Zhang et al.[47] | Baseline characteristics of initiating Sitagliptin monotherapy compared to non-Sitagliptin monotherapy | Age | HbA1c, obesity, Microvascular conditions, Chronic renal disease, CVD | | | OR, 95% CI |
| Morita et al.[48] | Patient characteristics associated with the selection of DPP4-I vs. metformin | Age, sex | Renal disease, HbA1c, obesity, microvascular complications, CAD, and stroke | | | OR, 95% CI |
| Kim et al.[49] | The influencing factors in the selection of second oral antidiabetics added to metformin | Age, sex | CVD, renal failure, HF, dyslipidaemia | Insurance, institution | Speciality | OR, 95% CI |
| Heintjes et al.[50] | Factors associated with the choice of treatment at intensification | Age, sex, smoking status | Macrovascular complication, renal function, HbA1c, obesity | | | RR, 95% CI |
| Nicolucci et al.[51] | Factors associated with second-line treatment choices in patients prescribed metformin | Age, sex, Education, Health | Obesity, microvascular/macrovascular complications, diabetes duration, HbA1c, chronic kidney disease | Insurance coverage, employment status | Physician speciality | OR, 95% CI |
| Hartmann et al.[52] | Predictors of treatment escalation after metformin monotherapy failure | Age, sex | HbA1c, diabetes duration, microvascular/ macrovascular disease, chronic kidney disease, obesity | | | OR, 95% CI |
| Ackermann et al.[54] | Correlates of type 2 diabetes second line medication selection | Age, sex, race/ ethnicity | HbA1c, obesity | Insurance | Speciality | Probability%, 95% C.I |
| Whyte et al.[55] | Disparity exists in drug prescribing | Ethnicity, sex | | Socioeconomic status | | OR, 95% CI |
| Arnold et al.[56] | The association of the variable of interest with the likelihood of being prescribed a glucose-lowering medication | Age | Obesity, Kidney function, CAD | | | Relative Risk/5years, 95% CI |
| Arnold et al.[57] | Glucose-Lowering Medication Use in T2D and HF | | Heart failure | | | Relative risk, 95% CI |
| Zaharan et al.[58] | Variations in the prescribing of oral antidiabetic therapies | Age, sex | | | | OR, 95% CI |

**TABLE 3** (Continued)

| Author | Outcome definition | Patients-related | Clinical-related | Socioeconomic | Prescriber-related | Reported as |
|---|---|---|---|---|---|---|
| Zoberi et al.[59] | Characteristics of patients with diabetes by non-metformin prescription and by insulin prescription | Age, sex, Race, Smoking | HbA1c, obesity, Microvascular complications, CVD, Cerebrovascular disease, comorbidities (Hyperlipidaemia, HTN) | | | %, *p* value |
| Montvida et al.[60] | Patient characteristics according to antidiabetic therapy prescribed | Age, sex, ethnicity | HbA1c, obesity, CVD, chronic kidney disease | | | *N*, % |
| Katakami et al.[61] | Factors associated with the selection of second-line treatment | Age, sex | HbA1c, obesity, renal function (eGFR), CVD | | | OR, 95% CI |
| Kostev et al.[62] | Predictors of Insulin Initiation in Metformin and Sulfonylurea Users | Age, sex | Kidney function (eGFR), comorbidities (HTN, stroke, HF, Hyperlipidaemia) | | Diabetologist care | HR, 95% CI; insulin |
| Dhanaraj et al.[63] | Choice of antidiabetic drug therapy and influencing factors | Age, sex, family history of diabetes | Obesity, HbA1c, microvascular complications, comorbidities, diabetes duration, serum creatinine. | | | OR, 95% CI |
| Yu et al.[64] | Factors that may predict choice of first injectable therapy. | Age, sex, ethnicity, smoking status | HbA1c, obesity, cardiovascular disease, chronic kidney disease, dyslipidaemia, hypertension | | | OR, 95% CI %, p value for some variables |
| Levin et al.[65] | Baseline Characteristics of patients with T2DM who added OAD, insulin, or GLP-1 | Age, sex | HbA1c, HTN, Dyslipidaemia, HF, Microvascular complications (neuropathy, nephropathy, retinopathy), MI, PVD. | | | %, *p* value |
| Gentile et al.[66] | Predictors of initiating insulin therapy | Age, sex | Diabetes duration, HbA1c, obesity, retinopathy, kidney function (eGFR) | | | HR, *p* value |
| Korytkowski et al.[67] | Baseline characteristics of T2DM patients according to intensifying drugs | Sex, age, race | Obesity, HbA1c | | | Mean or %, *p* value |
| Hirsch et al.[68] | Predictors of exenatide use | Age, sex | Obesity, HbA1c, diabetes duration | Payer type | | HR, 95% CI |
| Boom et al.[69] | Factors associated with the probability of receiving insulin | Age, sex | HbA1c, PAD, stroke, MI | | Practice specialty | OR, 95% CI |
| Moreno Juste et al.[70] | Difference in the baseline characteristics among antidiabetics new users | Age, sex | microvascular/macrovascular complications | Area of living | | Mean or %, *p* value |

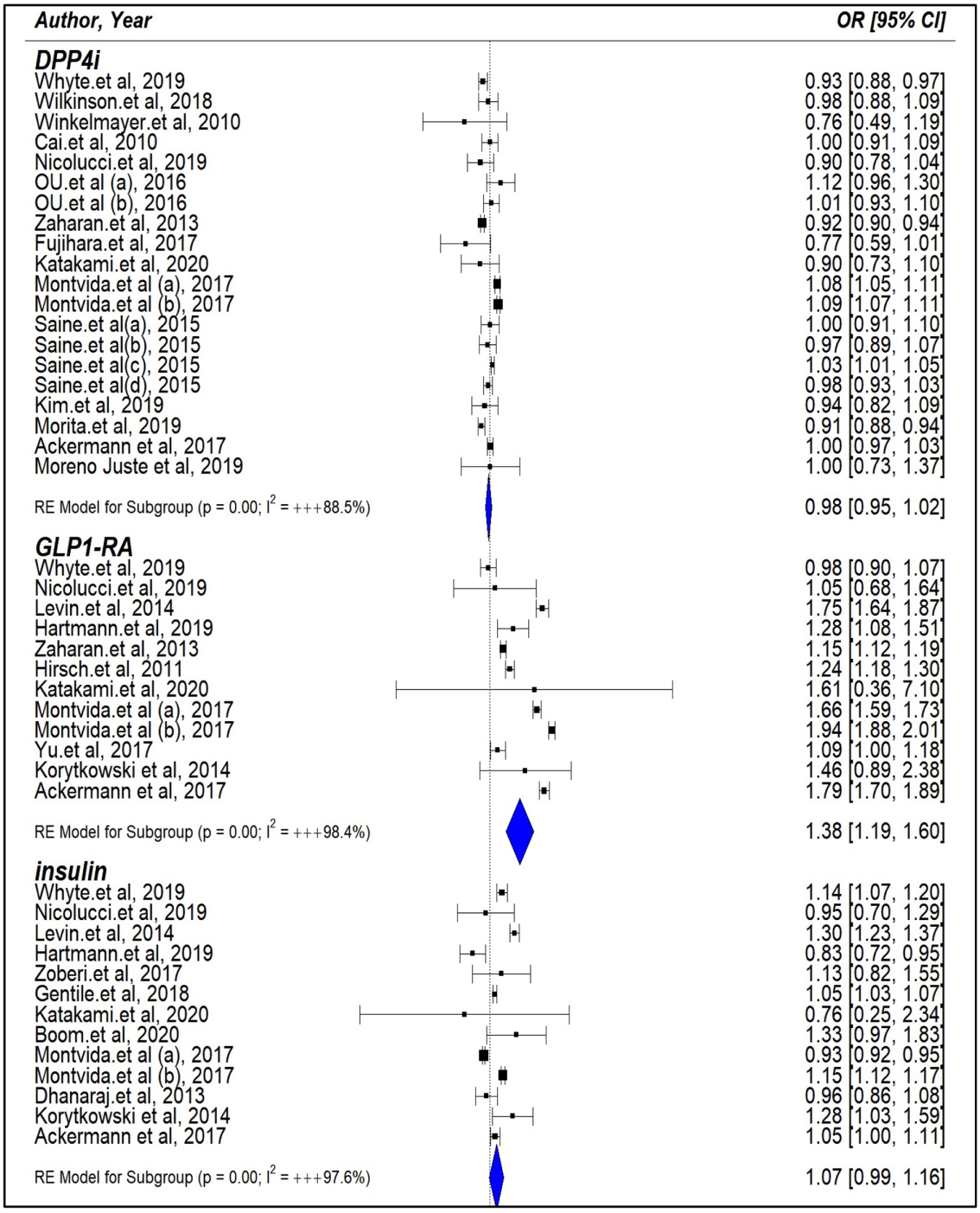


**FIGURE 2A** Forest plot of sex (female to male) association with antidiabetic drugs prescribing as overall and per antidiabetic group. CI, confidence interval; DPP4i, dipeptidyl peptidase 4 inhibitor ($N = 373{,}992$); GLP1-RA, glucagon-like peptide receptor agonist ($N = 107{,}128$); OR, odds ratio; insulin ($N = 390{,}711$). *N* represent all relevant studies except Whyte et al., Nicolucci et al. and Zaharan et al.

Despite that age showed an overall non-significant association with ADP (OR [95%CI]: 0.93 [0.66–1.32]), its effect varied significantly by class of ADDs ($p < .0001$). For instance, SU was 51% more likely to be prescribed for older patients (reported either as continuous or categorical) (OR [95%CI]: 1.51 [1.30–1.76]). Contrastingly, patients at older age were significantly less likely to be prescribed GLP1-RA (OR [95%CI]: 0.52 [0.40–0.69]), SGLT2-I (OR [95%CI]: 0.57 [0.42–0.79]) and metformin (OR [95%CI]: 0.70 [0.61–0.82]), Figures 3A, 3B.

## 3.6 | Baseline BMI

The influence of BMI on ADP was evaluated in 21 studies. All except one[50] were included in the MA,

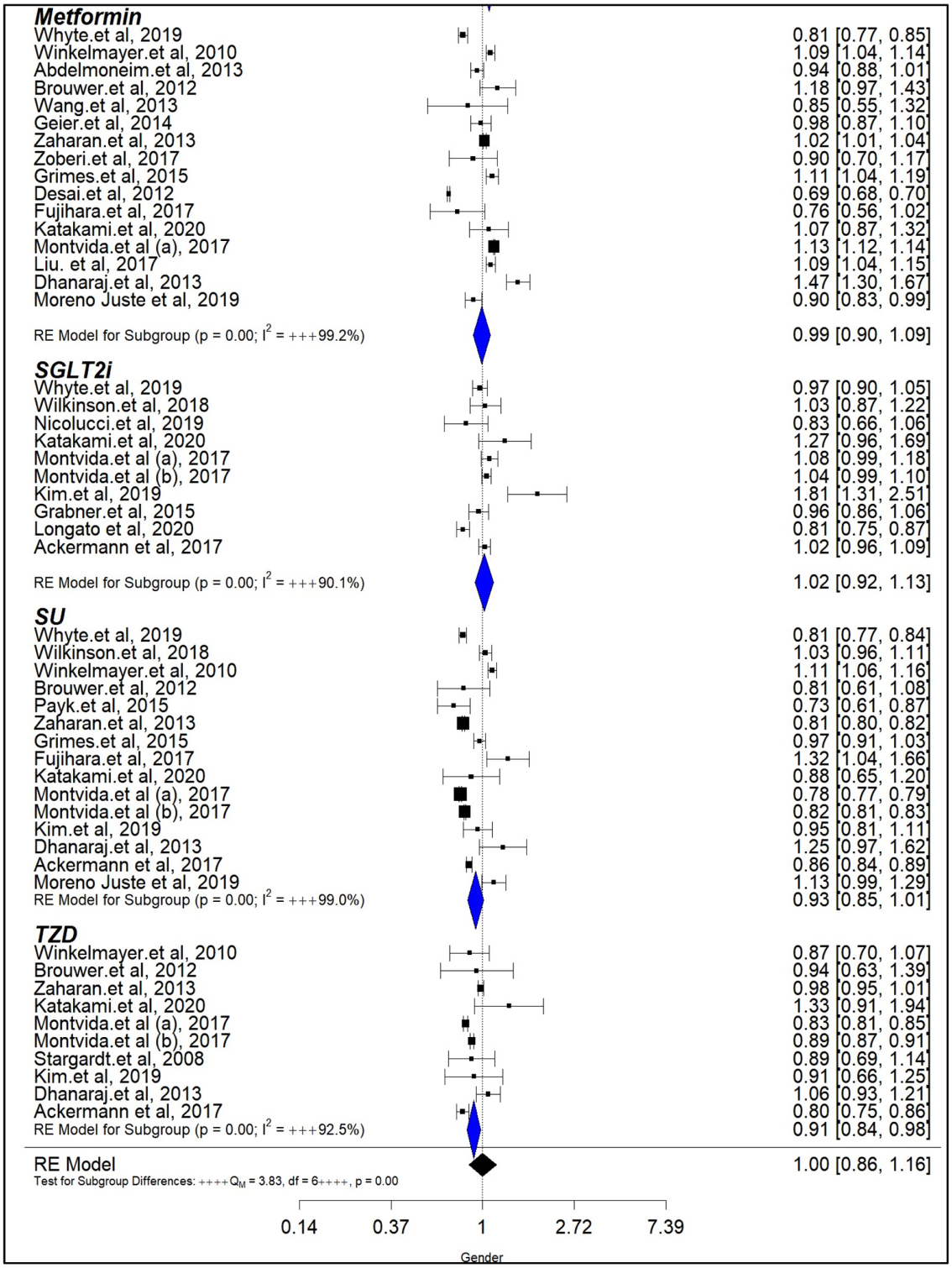


**FIGURE 2B** Continued on Figure 2A for the remaining antidiabetic groups and overall estimate. Metformin ($N = 1{,}186{,}718$); SGLT2-I, sodium glucose transporter 2 inhibitor ($N = 51{,}874$); SU, sulfonylurea ($N = 602{,}435$); TZD, thiazolidinedione ($N = 147{,}908$). *N* represent all relevant studies except Whyte et al., Nicolucci et al. and Zaharan et al.

contributing to a total of 66 effect sizes. Heintjes et al.[50] was excluded for the same reason stated previously. Despite that the overall MA showed no significant association of BMI with ADP (OR [95%CI]: 1.19 [0.85–1.67]), the result varied significantly by the investigated antidiabetic group ($p < .0001$). Figures 4A, 4B show that patients with higher BMI (reported either as a continuous or categorical) were more likely to be prescribed

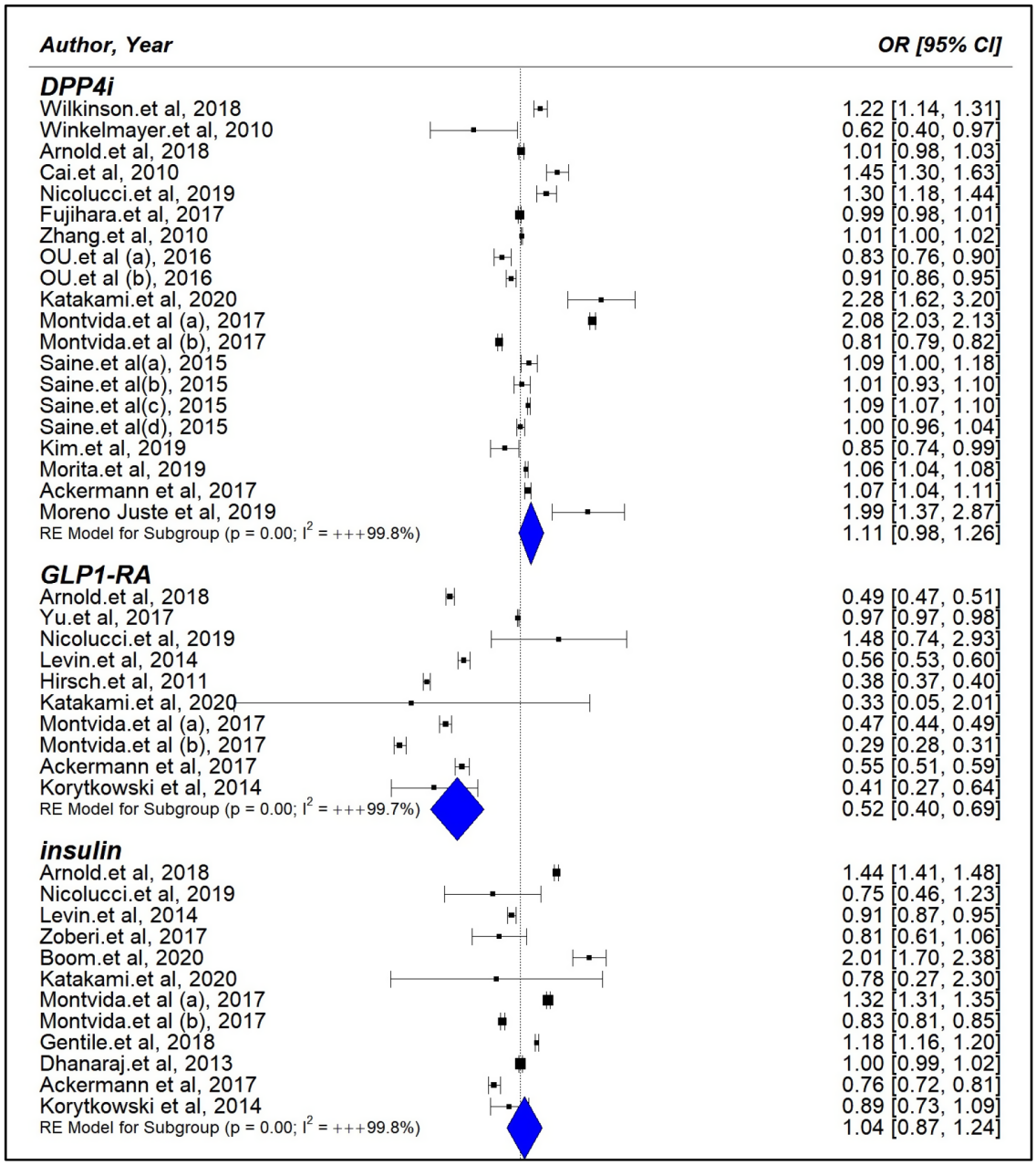


**FIGURE 3A** Forest plot of age association with antidiabetic drugs prescribing as overall and per antidiabetic group. CI, confidence interval; DPP4i, dipeptidyl peptidase 4 inhibitor ($N = 433,252$); GLP1-RA, glucagon-like peptide receptor agonist ($N = 104,870$); insulin ($N = 389,854$);OR, odds ratio. *N* represent all relevant studies except Arnold et al. and Nicolucci et al.

GLP1-RA, SGLT2-I, and metformin (OR [95%CI]: 2.35 [1.54–3.59], 1.89 [1.33–2.68], and 1.22 [1.08–1.37], respectively), but they were 24% less likely to use SU (OR [95%CI]: 0.76 [0.62–0.93]).

## 3.7 | Baseline glycaemic status (HbA1c)

A total of 62 effect sizes from 22 studies were included in the MA of HbA1c. Two studies were not included because of insufficient baseline data needed for OR calculation.[50,62] Including all studies reporting HbA1c as continuous or binary, higher HbA1c value or category had no significant association with ADP (OR [95%CI]: 1.10 [0.81–1.49]). However, a significant difference in the pooled estimate per antidiabetic class was observed ($p = .029$). People with higher baseline HbA1C were 2.41 times more likely to be prescribed insulin (OR [95%CI]: 2.41 [1.87–3.10]) yet less likely to get prescriptions of metformin, TZD and DPP4-I (OR [95%CI]: 0.74 [0.57–0.97], 0.76 [0.59–0.98], and 0.82 [0.68–0.99], respectively), Figures 5A, 5B.

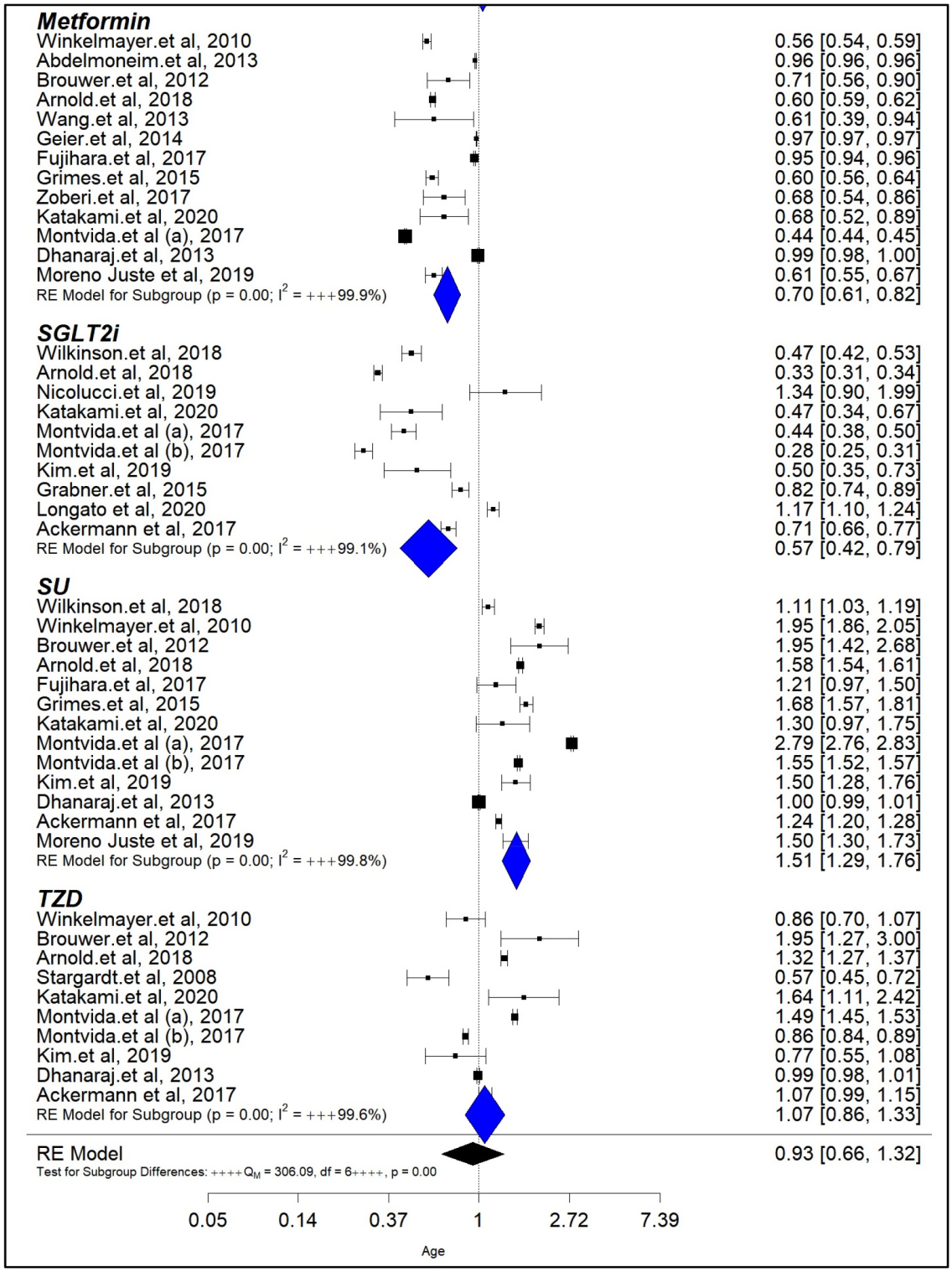


**FIGURE 3B** Continued on Figure 3A for the remaining antidiabetic groups and overall estimate. Metformin ($N = 903{,}101$); SGLT2-I, sodium glucose transporter 2 inhibitor ($N = 51{,}874$); SU, sulfonylurea ($N = 602{,}435$); TZD, thiazolidinedione ($N = 147{,}908$). *N* represent all relevant studies except Arnold et al. and Nicolucci et al.

## 3.8 | Kidney-related problems

A total of 21 studies examined the impact of kidney-related problems in terms of chronic renal disease (CRD), nephropathy or based on the estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 $m^2$. Only one study[50] was excluded due to insufficient data necessary for OR calculation, thus 20 studies were included in the MA,

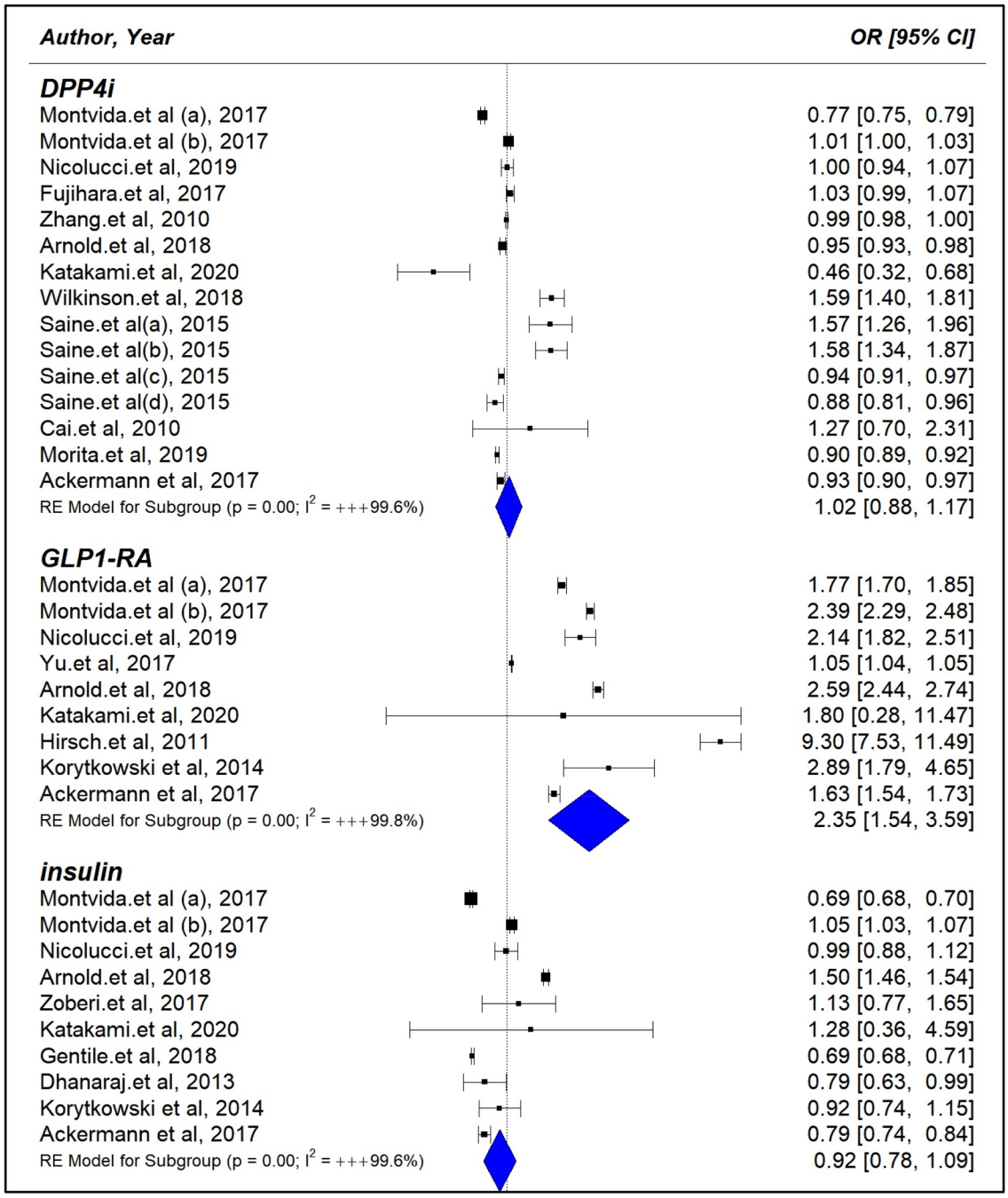


**FIGURE 4A** Forest plot of body mass index (BMI) association with antidiabetic drugs prescribing as overall and per antidiabetic groups. CI, confidence interval; DPP4i, dipeptidyl peptidase 4 inhibitor ($N = 393{,}433$); GLP1-RA, glucagon-like peptide receptor agonist ($N = 97{,}122$); insulin ($N = 380{,}937$); OR, odds ratio. *N* represent all relevant studies except Arnold et al. and Nicolucci et al.

contributing to a total of 61 effect sizes. Of the included studies, nine reported the outcome as CRD ($k = 28$) and six reported it as nephropathy ($k = 14$) while the remaining five studies examined the renal function based on eGFR value ($k = 19$).

The three-level MA showed that overall, kidney-related problems (either CRD, nephropathy or eGFR <60) had no significant association with ADP (OR [95%CI]: 0.89 [0.54–1.47]). Despite that the subgroup analysis showed a non-significant difference by class of ADDs ($p = .079$); patients with kidney-related problems were significantly more likely to receive insulin (OR [95%CI]: 1.52 [1.10–2.10]) and DPP4-I (OR [95%CI]: 1.37 [1.06–1.79]) yet 61% less likely to get metformin prescriptions (OR [95%CI]: 0.39 [0.25–0.61]), Figures 6A, 6B. Additionally, a non-significant difference was observed in the overall estimates according

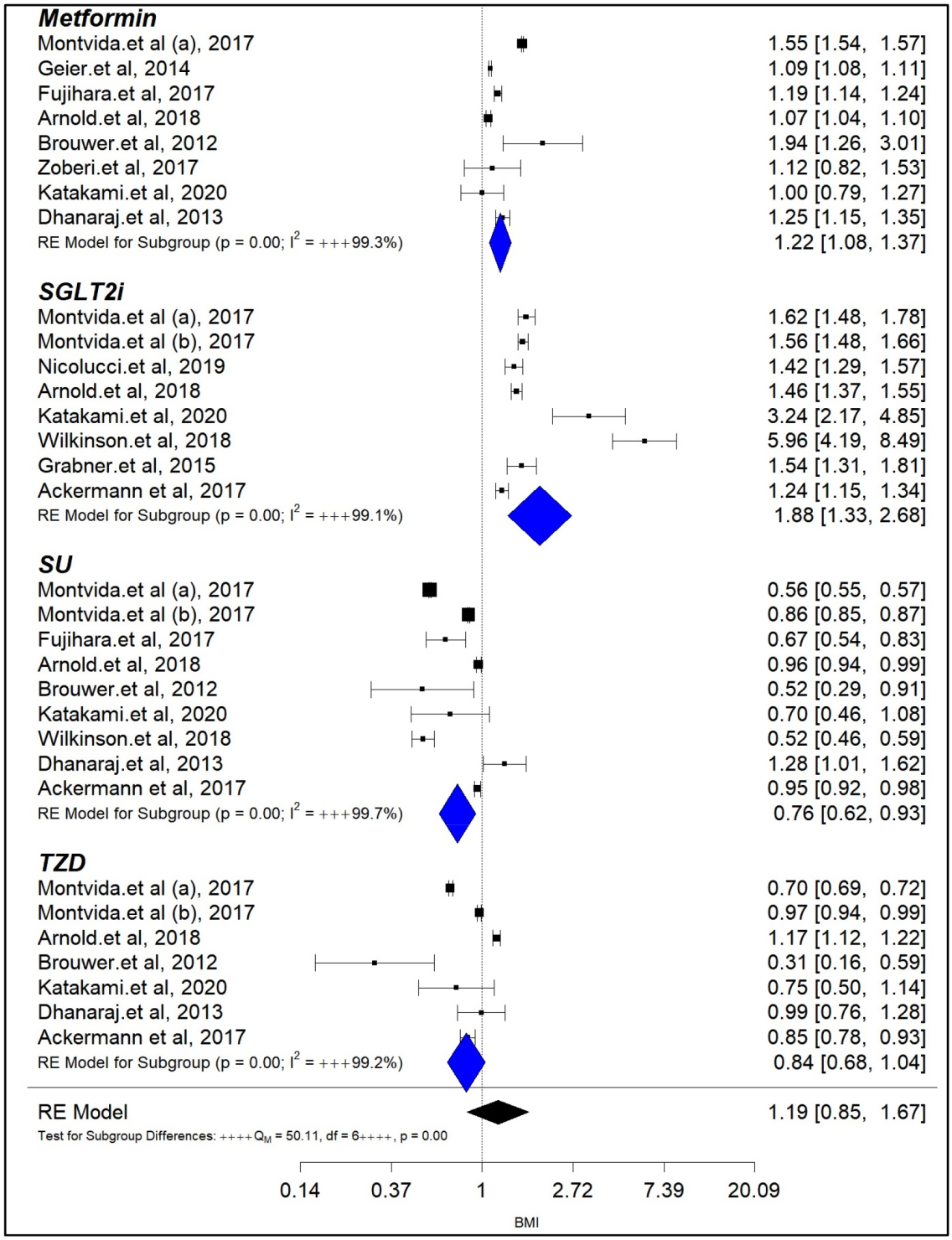


**FIGURE 4B** Continued on Figure 4A for the remaining antidiabetic groups and overall estimate. Metformin ($N = 821,416$); SGLT2-I, sodium glucose transporter 2 inhibitor ($N = 46,007$); SU, sulfonylurea ($N = 586,566$); TZD, thiazolidinedione ($N = 117,355$). *N* represent all relevant studies except Arnold et al. and Nicolucci et al.

to the type of kidney-related problems ($p = .286$). The overall estimate of studies defining kidney problems as CRD was 0.64 [0.32–1.28], while the pooled estimates of studies defined kidney problems as nephropathy and eGFR were 1.13 [0.66–1.96] and 1.33 [0.55–3.12], respectively.

### 3.8.1 | Heterogeneity and three-level model fitness

Despite that overall heterogeneity was high for all studied factors (>75%), most of the total heterogeneity was

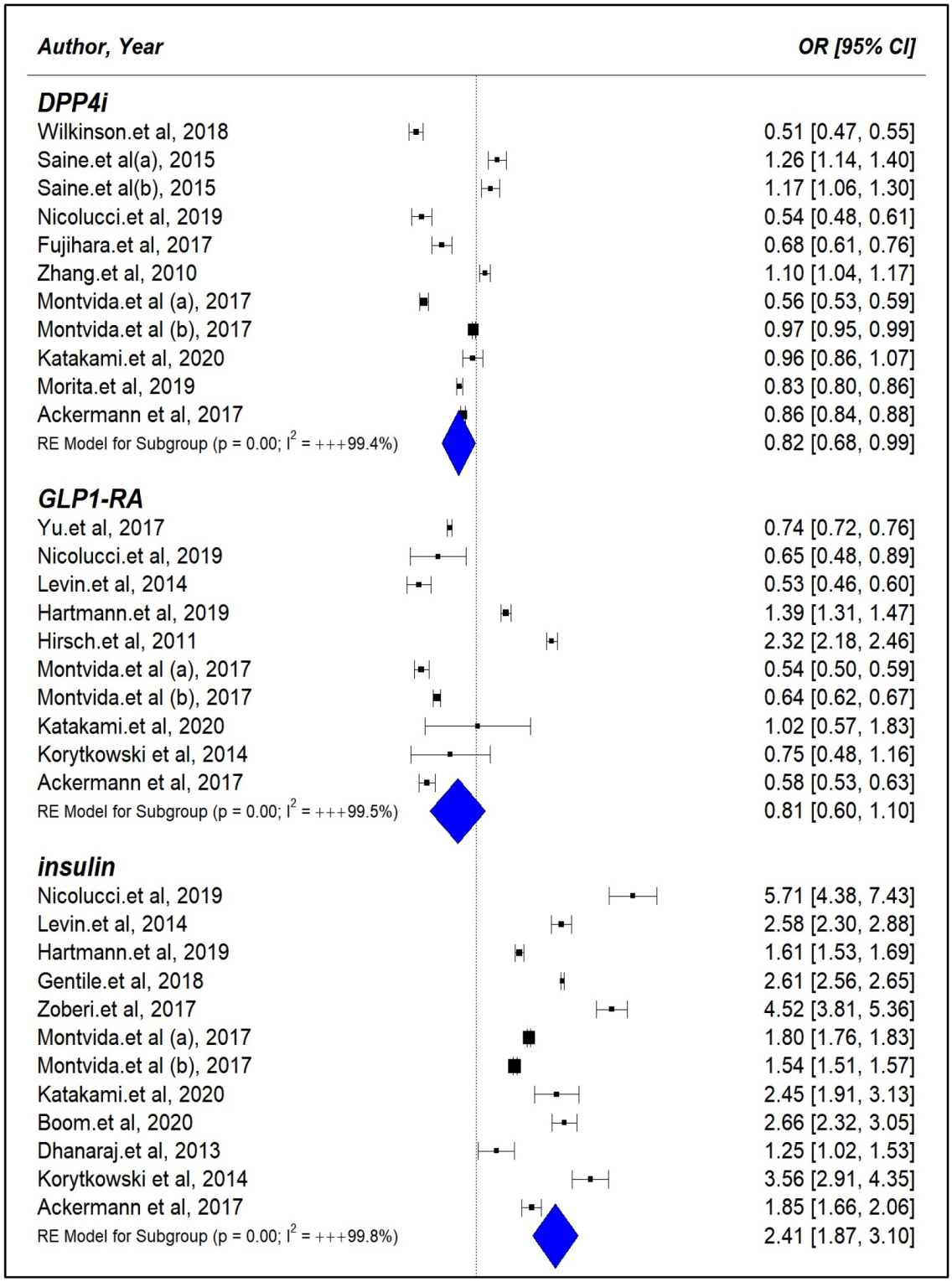


**FIGURE 5A** Forest plot of HbA1c association with antidiabetic drugs prescribing as overall and per antidiabetic groups. CI, confidence interval; DPP4-I, dipeptidyl peptidase 4 inhibitor ($N = 323,684$); GLP1-RA, glucagon-like peptide receptor agonist ($N = 95,944$); insulin ($N = 380,360$); OR, odds ratio. *N* represent all relevant studies except Nicolucci et al.

related to within-study variance while between-study variance for all studied factors were < 75% (Appendix S6). The results of the log likelihood ratio test (Appendix S6) indicated that the three-level model had a better fit for variability in data and better estimation of the pooled estimate.

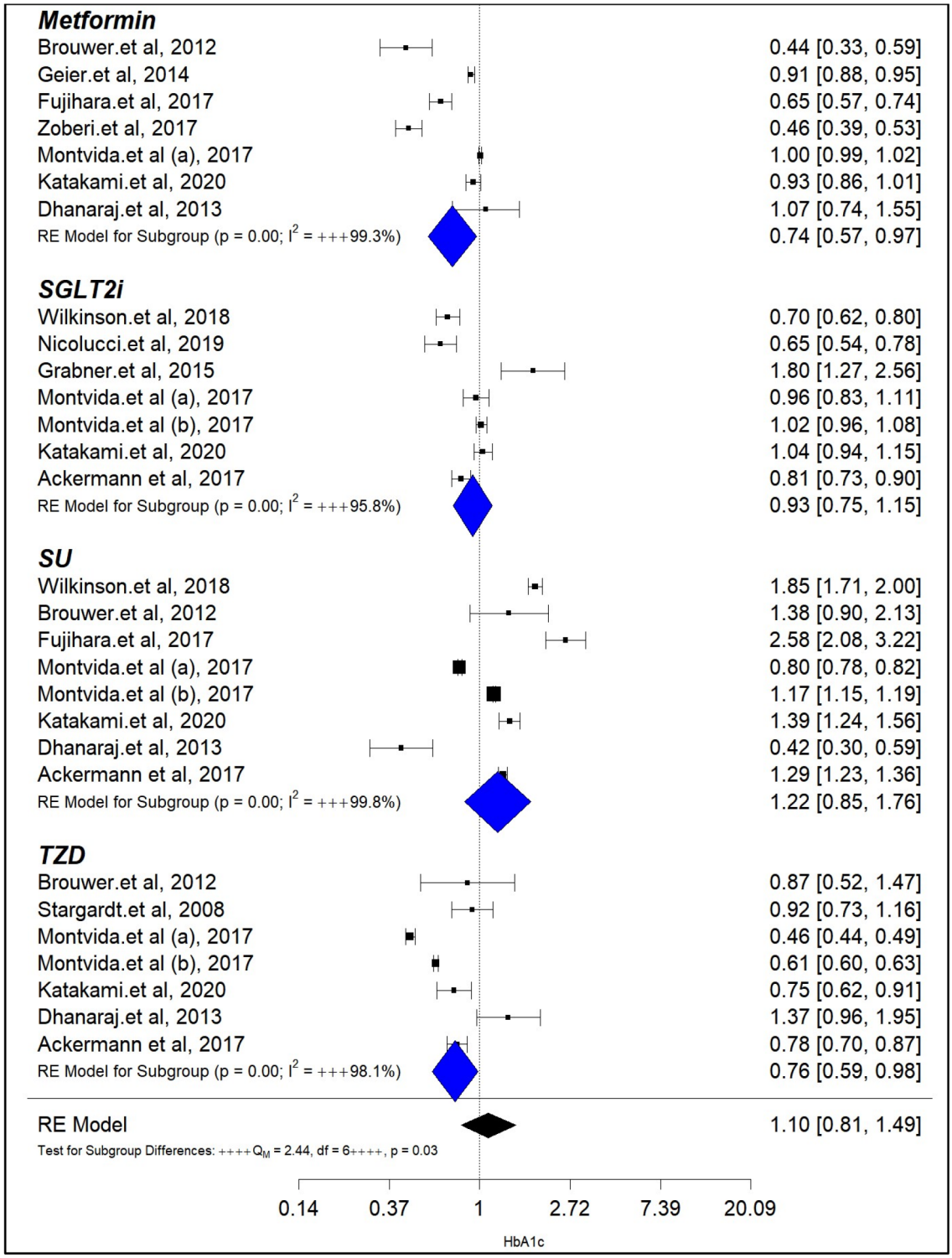


**FIGURE 5B** Continued on Figure 5A for the remaining antidiabetic groups and overall estimate. Metformin ($N = 821,416$); SGLT2-I, sodium glucose transporter 2 inhibitor ($N = 44,396$); SU, sulfonylurea ($N = 561,471$); TZD, thiazolidinedione ($N = 144,871$). *N* represent all relevant studies except Nicolucci et al.

### 3.8.2 | Moderator analysis

Tables 4 and 5 display the results of moderator analyses of all tested variables and the overall estimate within the levels of each variable for all synthesised factors. Of all examined variables, only the type of statistical model used to assess the outcome (adjusted vs. un-adjusted) had a significant influence on the pooled estimate resulting from the MA of sex, age and kidney-related problems ($p < .0001$). On the other hand, there was no

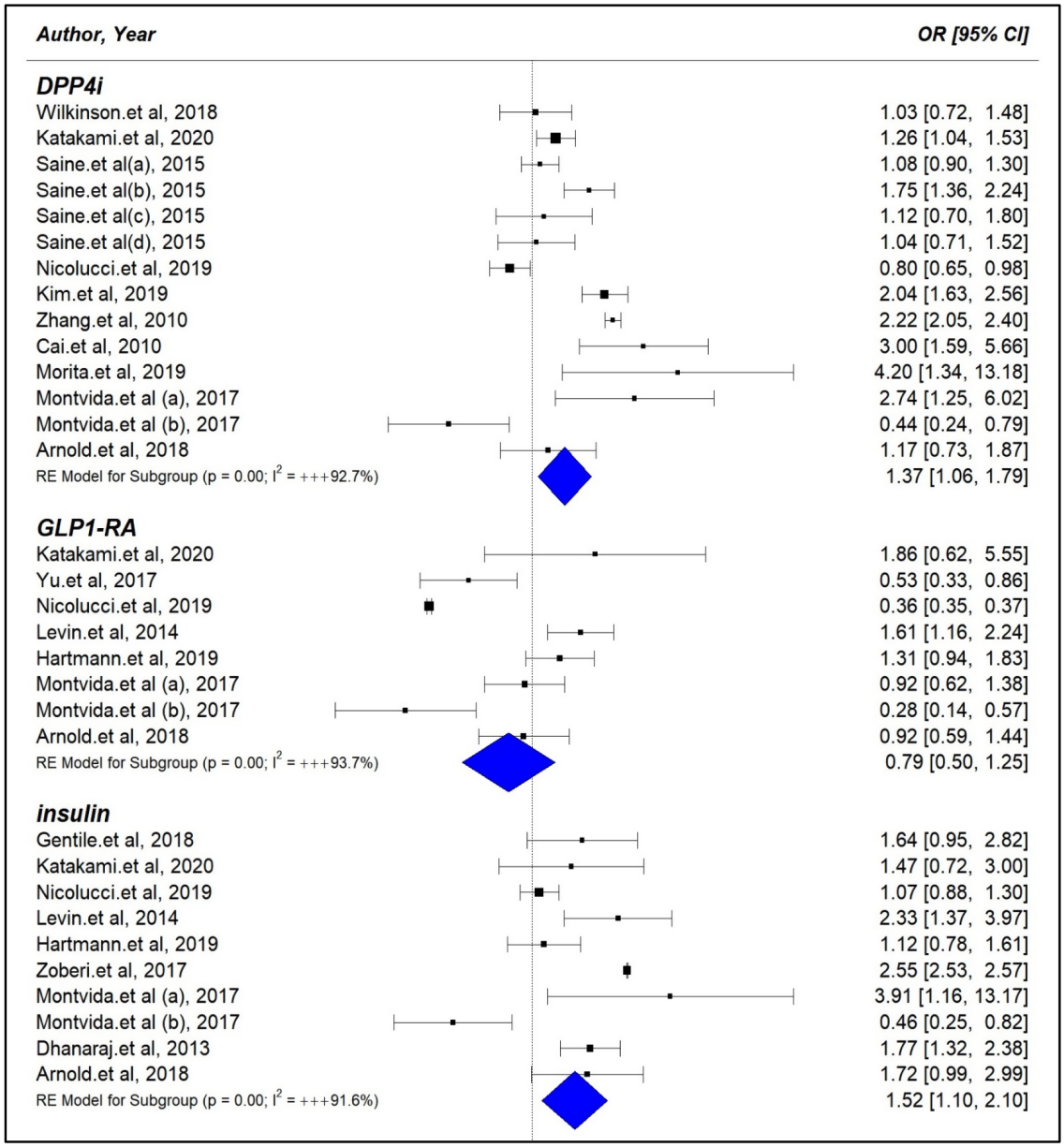


**FIGURE 6A** Forest plot of kidney problem association with antidiabetic drugs prescribing as overall and per antidiabetic groups. CI, confidence interval; DPP4i, dipeptidyl peptidase 4 inhibitor ($N = 378,170$); GLP1-RA, glucagon-like peptide receptor agonist ($N = 91,916$); insulin ($N = 383,203$); OR, odds ratio. *N* represent all relevant studies except Arnold et al.

significant difference in the pooled estimate by country of study, stage of treatment and the other studied variables.

### 3.8.3 | Outliers/influential studies

A total of 15 out of 96 effect sizes of sex data, 27 out of 88 effect sizes of age data, 18 out of 66 effect sizes of BMI data and 12 out of 61 effect sizes of renal data were detected as outliers; moreover, about half of the effect sizes of HbA1c data were detected as outliers (31/62). Histogram plots of all factors (Appendix S7) reflect that the potential outliers are not uniformly distributed around the pooled estimate. However, the results of the sensitivity analysis (Table 6) revealed a close overall OR and narrower but overlapped 95%CI of the pooled estimate after excluding the outliers compared to the one including the outliers. Nevertheless, it could not be determined whether the outliers did, in fact, bias the pooled estimate.

Cook's-D was measured for all factors (scatterplots in Appendix S7). None of the effect sizes included in the sex MA had a Cook's value exceeding 0.04(4/96), indicating that none had an influential effect on the pooled estimate.

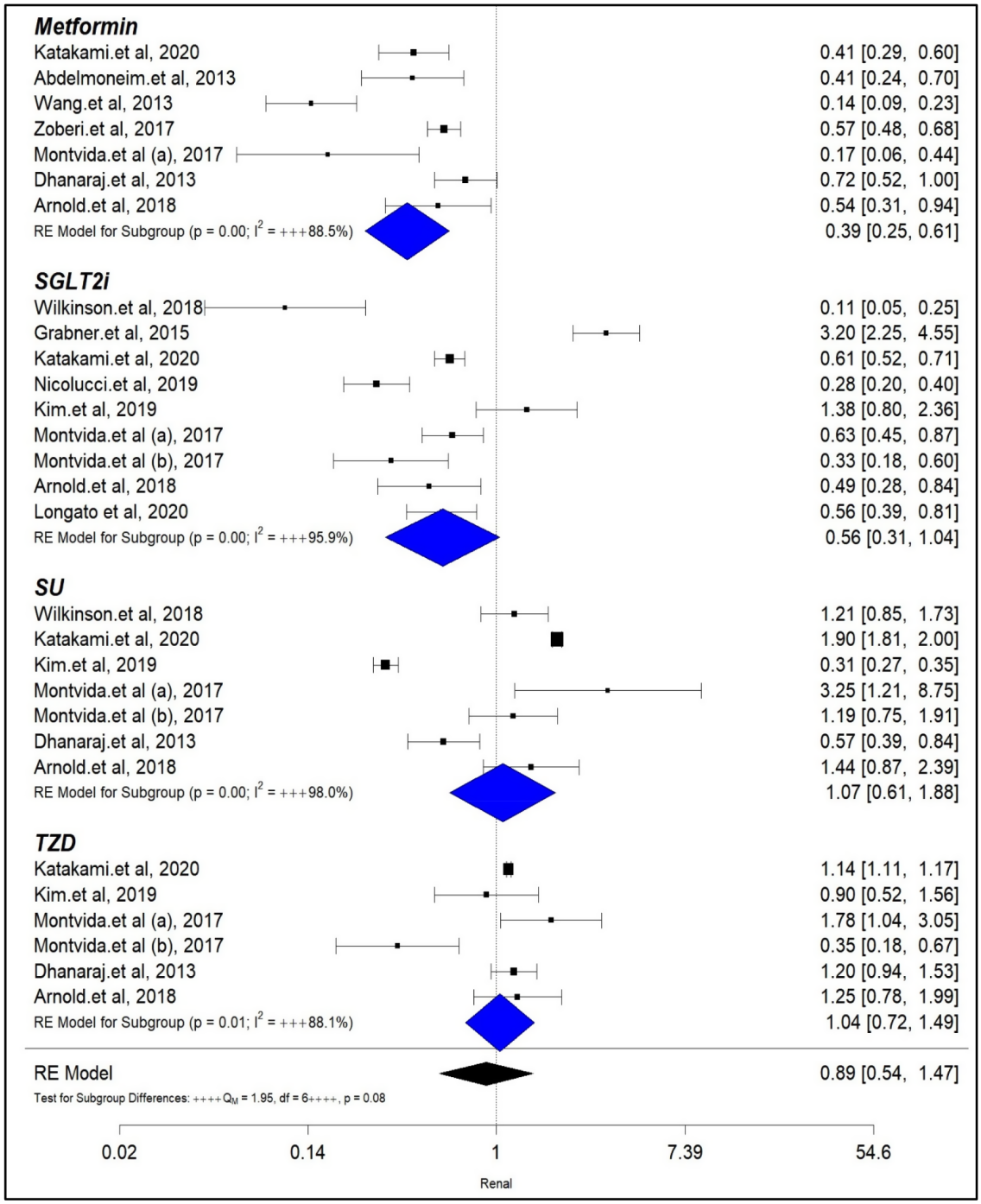


**FIGURE 6B** Continued on Figure 6A for the remaining antidiabetic groups and overall estimate. Metformin ($N = 837,850$); SGLT2-I, sodium glucose transporter 2 inhibitor ($N = 46,914$); SU, sulfonylurea ($N = 549,998$); TZD, thiazolidinedione ($N = 143,382$). *N* represent all relevant studies except Arnold et al. and Nicolucci et al.

In contrast, two effect sizes of age and HbA1c were considered as influential cases in the model as they have a distance value of >0.05(4/88) and >0.06(4/62), respectively.[59,60,63,68] For BMI MA, only one study presented a distance value larger than 0.06(4/66).[68] Lastly, three effect sizes included in the MA of kidney-related problems were considered to have influential effect in the model with a distance value of >0.07(4/61).[49,61]

### 3.8.4 | Publication bias

The funnel plots (Appendix S8) of all factors showed that all studies cluster at the top part of the plots, suggesting a possible presence of publication bias. Extended Eggers' test showed a significant possibility of asymmetry in the funnel plots of age, BMI and kidney-related problems ($p < .0001$, .0013 and <.0001, respectively), while the test

**TABLE 4** Results of the moderator analysis of tested variables on the pooled estimate of each quantified factors.

| Tested variable | Sex | Age | BMI | HbA1C | Kidney problem |
|---|---|---|---|---|---|
| Type of outcome variable | | | | | |
| Continuous | – | 29/0.89 [0.72–1.10] | 14/0.99 [0.67–1.45] | 28/1.05 [0.59–1.87] | – |
| Binary | | 59/0.89 [0.62–1.28] | 52/1.33 [0.92–1.94] | 34/1.12 [0.71–1.74] | |
| | | $p = .713$ | $p = .115$ | $p = .812$ | |
| Type of analysis test | | | | | |
| Unadjusted | 58/1.06 [0.86–1.31] | 70/0.86 [0.76–1.27] | 45/1.30 [0.88–1.93] | 42/1.13 [0.77–1.64] | 50/0.95 [0.59–1.52] |
| Adjusted | 38/0.97 [0.86–1.20] | 18/0.85 [0.64–1.13] | 21/1.04 [0.83–1.31] | 20/1.10 [0.87–1.40] | 11/0.81 [0.36–1.86] |
| | ***p* < .0001** | ***p* < .0001** | $p = .518$ | $p = .378$ | ***p* < .0001** |
| Stage of treatment | | | | | |
| Initiation | 30/0.98 [0.79–1.22] | 28/1.16 [0.66–2.04] | 15/0.93 [0.61–1.42] | 16/0.87 [0.57–1.34] | 11/1.35 [0.48–3.78] |
| Intensification | 42/1.02 [0.82–1.27] | 40/0.85 [0.58–1.25] | 31/1.02 [0.75–1.38] | 36/1.13 [0.84–1.51] | 31/0.87 [0.43–1.75] |
| Not specified stage | 24/1.00 [0.90–1.12] | 20/1.04 [0.75–1.45] | 20/1.57 [1.02–2.41] | 10/1.21 [0.57–2.57] | 19/1.05 [0.65–1.70] |
| | $p = .520$ | $p = .415$ | $p = .073$ | $p = .179$ | $p = .959$ |
| Study design | | | | | |
| Retrospective cohort | 70/0.99 [0.85–1.16] | 63/0.98 [0.60–1.59] | 41/1.17 [0.79–1.74] | 39/1.13 [0.82–1.57] | 42/0.97 [0.55–1.71] |
| Prospective cohort | 11/0.97 [0.83–1.13] | 11/1.04 [0.76–1.42] | 11/1.10 [0.80–1.52] | 11/1.00 [0.52–1.91] | 11/0.74 [0.33–1.66] |
| Cross-sectional | 9/0.99 [0.79–1.13] | 8/1.03 [0.98–1.09] | 8/1.14 [0.74–1.76] | 6/1.00 [0.58–1.71] | 8/1.06 [0.58–1.92] |
| Comparative multiple case | 6[a]/1.05 [0.78–1.41] | 6[a]/0.87 [0.63–1.20] | 6[a]/1.03 [0.78–1.37] | 6[a]/0.95 [0.62–1.47] | – |
| | $p = .9684$ | $p = .902$ | $p = .799$ | $p = .844$ | $p = .719$ |
| Country | | | | | |
| United States | 35/0.95 [0.76–1.20] | 40/0.92 [0.56–1.50] | 38/1.25 [0.81–1.93] | 32/1.18 [0.78–1.80] | 29/1.43 [0.72–2.85] |
| United Kingdom | 16/1.06 [0.91–1.24] | 5/0.87 [0.33–2.35] | 3[c]/1.69 [0.08–34.57] | 3[c]/0.87 [0.17–4.61] | 3[c]/0.53 [0.12–2.38] |
| Cross-national | 11/0.97 [0.82–1.14] | 9/0.89 [0.60–1.30] | 8/1.49 [0.89–2.51] | 9/1.39 [0.55–3.52] | 10/0.80 [0.38–1.65] |
| Austria | 4[b]/1.03 [0.85–1.26] | 4[b]/0.89 [0.53–2.23] | – | – | – |
| Canada | 2/0.94 [0.60–1.46] | 2/0.81 [0.52–1.25] | – | – | 2/0.24 [0.08–0.68] |
| Germany | 2/1.10 [0.17–7.20] | 2/1.39 [0.68–2.84] | 1/1.09 [1.08–1.11] | 2/1.55 [0.54–4.44] | – |
| Taiwan | 3/1.07 [0.96–1.20] | 2[c]/0.87 [0.50–1.54] | – | – | – |
| Italy | 5/0.07 [0.81–1.16] | 5/1.18 [0.69–2.01] | 1/0.70 [0.68–0.71] | 1[g]/2.61 [2.56–2.65] | 2/0.94 [0.33–2.69] |
| Japan | 10/1.05 [0.88–1.26] | 11/0.95 [0.64–1.40] | 11/1.16 [0.66–2.06] | 11/1.05 [0.72–1.54] | 7[d]/1.05 [0.61–1.80] |

**TABLE 4** (Continued)

| Tested variable | Sex | Age | BMI | HbA1C | Kidney problem |
|---|---|---|---|---|---|
| Korea | 4[e]/1.08 [0.67–1.76] | 4[e]/0.86 [0.42–1.75] | – | – | 4[e]/0.93 [0.24–3.59] |
| India | 4[f]/1.17 [0.85–1.60] | 4[f]/0.10 [0.99–1.01] | 4[f]/1.07 [0.75–1.53] | 4[f]/0.94 [0.40–2.22] | 4[f]/0.98 [0.438–2.18] |
| | $p = .079$ | $p = .763$ | $p = .701$ | $p = .853$ | $p = .242$ |
| Quality of study | | | | | |
| Poor | 25/1.02 [0.82–1.28] | 25/0.92 [0.49–1.75] | 19/1.15 [0.78–1.70] | 20/1.01 [0.69–1.48] | 20/1.27 [0.57–2.58] |
| Satisfactory | 4[f]/1.17 [0.85–1.60] | 4[f]/0.10 [0.99–1.01] | 4[f]/1.07 [0.75–1.53] | 4[f]/0.94 [0.40–2.22] | 4[f]/0.98 [0.44–2.18] |
| Good | 62/1.00 [0.90–1.12] | 55/0.99 [0.70–1.39] | 39/1.22 [0.58–1.75] | 36/1.18 [0.88–1.58] | 33/0.85 [0.45–1.60] |
| Very good | 5/0.87 [0.59–1.35] | 4[g]/1.05 [0.97–1.13] | 4[g]/1.18 [0.71–1.96] | 2[h]/1.21 [0.76–1.94] | 4[g]/1.24 [0.80–1.91] |
| | $p = .6812$ | $p = .976$ | $p = .649$ | $p = .685$ | $p = .647$ |
| Year of publication | 96/$p = .9537$ | 88/$p = .06$ | 66/$p = .080$ | 62/$p = .143$ | 61/$p = .409$ |

*Note*: The result presented as the number of effect sizes (K)/Overall estimate per level (OR [95% C.I])/*p* value.

Bold values indicate as $p < 0.0001$.

[a]Only one study.[70]

[b]4 effect sizes from one study.[34]

[c]3 effect sizes from one study.[10]

[d]7 effect sizes from one study.[61]

[e]4 effect size from one study.[49]

[f]4 effect sizes from one study.[63]

[g]4 effect sizes from one study.[43]

[h]2 effect sizes from one study.[43]

was non-significant for sex and HbA1c ($p = .101$ and .329, respectively).

## 4 | DISCUSSION

To our knowledge, no previous review either quantified the impact of several factors related to patients' characteristics on ADP; or compared their impact among different classes of ADDs. Age, baseline BMI and baseline HbA1c had the greatest impact on the selection of ADDs while patients' sex had the least impact.

The significant variability in the pooled estimate of sex by class of ADDs could be linked to the differences in the number of studies investigating each antidiabetic class, or to the differences in the pharmacological characteristics of ADDs (mainly their safety and tolerability profile). The observed higher prescriptions of GLP1-RA for female patients compared to male patients could be explained in part by previous findings that GLP1-RA was better tolerated and associated with a lower cardiovascular risk among female patients.[71] On the contrary, the significantly lower prescriptions of TZD for female patients could be explained by the findings that female patients have experienced more side effects from TZD including weight gain, fracture and oedema.[72,73] This suggests a possible consideration of the variability in the effectiveness and tolerability of ADDs between female and male patients when making a decision on the appropriate ADDs in clinical practice. However, because of the limited number of studies examined the majority of antidiabetic classes, more studies are required to have a better understanding regarding the impact of sex on the choice of ADDs.

Despite the risk of SU-related hypoglycaemia being higher among older people, the pooled estimate of SU showed that older people were significantly more likely to use SU. The low cost of SU and the current availability of short-acting second-generation SU (e.g. glipizide) with fewer side effects might be partially responsible for the observed impact of age on SU prescription.[74] This could also reflect the legacy availability of SU for T2DM management as none of the newer ADDs were available 10 years ago, and patients started on SU may have stayed on the same regimen unless they developed intolerable side effects or required additional drug therapy.

**TABLE 5** Results of moderator analysis of categorisation scheme of binary data of age, body mass index and HbA1c meta-analysis.

| Categorisation scheme of binary data | # Of effect sizes (Total k) | Pooled estimate (OR [95% CI]) | *p* value |
|---|---|---|---|
| Age | 59 | | |
| ≥60 vs. <60 years | 13 | 1.06 [0.61–1.83] | |
| ≥65 vs. <65 years | 29 | 1.01 [0.69–1.46] | $p = .942$ |
| ≥70 vs. <70 years | 13 | 0.75 [0.30–1.84] | |
| ≥55 vs. <55 years | 4[a] | 0.96 [0.98–1.01] | |
| Body mass index (BMI) | 52 | | |
| Obese (BMI ≥ 30 kg/m$^2$) vs. non-obese (BMI < 30 kg/m$^2$) | 32 | 1.175 [0.855–1.615] | |
| Overweight/obese (BMI ≥ 25 kg/m$^2$) vs. normal/underweight (BMI < 25 kg/m$^2$) | 13 | 1.545 [0.546–4.369] | $p = .067$ |
| BMI ≥25 vs. BMI 22–25 kg/m$^2$ | 7[b] | 1.018 [0.519–1.996] | |
| Glycaemic control (HbA1c) | | | |
| ≥7% (≥53 mmol/mol) vs. <7% (<53 mmol/mol) | 13 | 1.5 [0.34–6.75] | |
| ≥8% (≥63.9 mmol/mol) vs. <8% (<63.9 mmol/mol) | 21 | 1.05 [0.74–1.51] | $p = .916$ |

Abbreviations: CI, confidence interval; K, effect sizes; OR, odds ratio.

[a]All from one study.[63]

[b]All from one study.[61]

**TABLE 6** The pooled estimate of all quantified factors before and after excluding the outliers.

| Studied factor | Pooled estimate without outliers | Pooled estimate with outliers |
|---|---|---|
| Sex | 1.00 [0.86–1.16] | 0.99 [0.92–1.07] |
| Age | 0.93 [0.66–1.32] | 0.96 [0.83–1.10] |
| BMI | 1.19 [0.85–1.67] | 1.21 [1.00–1.47] |
| HbA1c | 1.10 [0.81–1.49] | 1.06 [0.88–1.29] |
| Kidney problem | 0.89 [0.54–1.47] | 0.94 [0.69–1.29] |

The safety of newer ADDs (GLP1-RA, SGLT2-I) in older adults was less studied thus prescribers might be less confident to prescribe the newer ADDs for older patients because of the higher concern that elderly patients are more susceptible to adverse reactions.[74–76] Furthermore, the higher cost of newer drugs, the cost of the required monitoring and the familiarity of prescribers with the update in clinical guidelines could contribute to the lower prescription of GLP1-RA and SGLT2-I for older patients. Therefore, further studies investigating prescribing quantity of newer ADDs for older patients are still required since older patients are more likely to have cardiovascular and renal diseases, the situations where the newer ADDs are recommended. The negative significant association between metformin prescription and age could be related to the fact that metformin is not recommended to be prescribed for patients with gastrointestinal complaints, functional impairment or with renal insufficiency, conditions that are increasingly present with increasing age.[75,77,78] This might positively reflect clinical practice adherence to drug characteristics when prescribing metformin to older patients with T2DM.

GLP1-RA and SGLT2-I were reported to have weight loss effect and metformin was accepted to have weight neutral or slight weight loss effects, while SU is associated with weight gain.[79–81] Thereby, the weight effect of ADDs might be responsible for our findings that overweight/obese people were more likely to get a medication with weight neutral/loss effect (GLP1-RA, SGLT2-I, and metformin) but less likely to be prescribed a medication with weight gain effect (SU). Overall, these findings might indirectly reflect a consistency of ADD selection in clinical practice considering patient weight against drug features.

Baseline HbA1c level had the strongest association with insulin prescription where patients with higher baseline HbA1C were more likely to receive insulin, whereas

higher baseline HbA1c had negative weak significant associations with metformin, TZD and DPP4-I prescriptions. All aforementioned associations were consistent with the known effectiveness of each antidiabetic class relevant to HbA1c reduction, which partially indicate clinicians' consideration of disease severity (indicated by HbA1c) when selecting the most appropriate ADDs for each patient. Insulin is known to have the greatest effect on the reduction of HbA1c and this might explain the greater likelihood of prescribing insulin for patients with higher baseline HbA1c.[82,83]

Lastly, the management of diabetes in patients with kidney-related problems is challenging as the impairment in kidney function might affect glucose metabolism and alter drug clearance.[84] This further complicates the selection of an appropriate ADD, considering the need for more frequent adjustment of doses and monitoring for the risk of hypo/hyperglycaemia.[84] Insulin has been considered as the best choice for patients with T2DM and kidney problems, yet still requires close monitoring and dose adjustment.[84] Also, DPP4-I is among the most acceptable option for patients with kidney problems considering dose adjustment based on the agent and degree of impairment.[84] In contrast, metformin is not recommended for patients with kidney disease, and it is contraindicated when eGFR is <30 mL/min/1.73 $m^2$, because of the higher risk of lactic acidosis.[84] Collectively, that could explain the observed associations of higher prescription of insulin and DPP4-I and lower prescription of metformin for patients with kidney-related problems.

Despite that the use of SGLT2-I and GLP1-RA has been recently encouraged by several guidelines especially for patients with established or high risk of cardiovascular or renal diseases because of their cardioprotective and renal protective effects,[9,85–88] the pooled estimates of studies investigating the prescription of SGLT2-I and GLP1-RA for patients with kidney-related problems were not in line with the previous recommendations. Nevertheless, those recommendations are relatively recent while the majority of included studies were conducted early after the introduction of GLP1-RA and SGLT2-I. Therefore, more studies are still required to further investigate prescribing of newer classes for patients with kidney problems in clinical practice considering different stages and types of kidney disease.

### 4.1 | Strength and limitations

To the best of our knowledge, this is the first SR/MA integrating the results of observational studies assessing the association of several factor with ADP to draw an overall estimate. This review provides a wide range of data by investigating each factor on seven different antidiabetic classes. Additionally, applying a three-level MA approach to account for the presence of dependency among effect sizes gave an opportunity to answer the research question without losing valuable data and to directly compare different antidiabetic groups.

Nevertheless, all previous results should be interpreted cautiously because of several limitations of the study. First, limited number of studies examined certain classes of ADDs, especially the newer ones; thus, more studies are required to draw a more robust conclusion. Second, the possible presence of publication bias especially for age, BMI and kidney-related problems may have affected the reliability of findings; however, there is no agreed-upon method available to adjust for publication bias in the three-level MA model. Third, bias could have been introduced by including all studies in the pooled estimate regardless the type of data presentation (categorical vs. continuous) and the type of categorisation scheme; yet, subgroup analyses were done and showed no significant impact, and the pooled estimate of each sub-group was reported separately. Lastly, other important factors, including socioeconomic and prescriber-related factors, were much less frequently studied and further investigations are needed.

## 5 | CONCLUSION

In conclusion, all identified factors are crucial to be considered when making a decision regarding the most appropriate ADDs for patients with T2DM. The magnitude, direction and significance of influence of the identified factors on ADP varied according to the type of antidiabetic group. Age, baseline BMI and baseline HbA1c had the greatest impact on the selection of ADDs in which they had statistically significant associations with prescribing of four out of the seven investigated antidiabetic classes. On the other hand, sex had the least impact on ADDs selection which had only a significant influence on GLP1-RA and TZD prescriptions. The findings of this SR&MA could be helpful in determining the need of improving prescribing practice of ADDs by reflecting the consistency of prescribing decision of ADDs with guidelines recommendations and specific drugs features.

### AUTHOR CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: Study concept and design: FM, AK, AM; Study screening, data collection and validation: FM, HY, NA; Data analysis: FM; interpretation of results: FM, AK, AM, TM, CS, GR; Draft manuscript preparation: FM, AK, TM, AM, CS, GR, HY, NA. All authors reviewed and revised the manuscript, and approved the final version.

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## CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to disclose.

## ORCID

*Fatema Mahmoud* https://orcid.org/0000-0003-2218-224X
*Amanj Kurdi* https://orcid.org/0000-0001-5036-1988

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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