Efficacy of Modern Diabetes Treatments DPP-4i, SGLT-2i, and GLP-1RA in White and Asian Patients With Diabetes

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Abstract

Background and Purpose:The pathophysiology of Type 2 diabetes differs markedly by ethnicity. A systematic review and meta-analysis was conducted to assess the impact of ethnicity on the glucose lowering efficacy of the newer oral agents, SGLT-2is, GLP-1RAs and DPP-4is, using evidence from randomized clinical trials (RCTs).

Data Sources:A literature search was conducted in PubMed of all randomized, placebo-controlled trials of DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1RA. The search strategy was developed based on medical subject sub-headings (MeSH) terms and keywords.

Study selection : 64 studies qualified for meta-analysis after full-text review based on pre-defined inclusion and exclusion criteria. RCTs with at least 50 patients in each arm; >70% of population from Asian or White group; duration>=24 weeks; published up to March 2019 were selected for systematic review and meta-analysis.

Data extraction:Data extraction was done for aggregated study-level data , by two independent researchers. Absolute changes in HbA1c (%) from baseline to 24 weeks between the drug and placebo was considered as the primary endpoint of the study.

Data synthesis: Change in HbA1c was evaluated by computing mean differences (MDs) and 95% confidence intervals (CI) between treatment and placebo arms.

Limitations: Study is based on summarized data and could not be separated based on East Asians and South Asians.

Conclusion : The glucose lowering efficacy of SGLT-2i, and to a lesser extent DPP-4i, was greater in studies of predominantly Asian ethnicity compared to studies of predominantly white ethnicity. There was no difference seen by ethnicity for GLP-1RA.

PROSPERO registration [CRD42019133587].

INTRODUCTION

Type 2 diabetes presents a global threat to health. According to the International Diabetes Federation (IDF) 2017 report China has the highest number of people (114.4 million) with diabetes in the age group 20-79. This is closely followed by India (72.9 million) which is projected to have the highest number of people with diabetes by 2045 (134.3 million)[1]. Yet most studies of diabetes are undertaken in western populations[2] and treatment guidelines do not take ethnicity into account. The latest consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommends the use of relatively newer drugs such as SGLT-2 inhibitors, GLP-1RA, and DPP-4 inhibitors in combination with metformin and lifestyle adjustments[3], unless cost is an issue. Nearly half of the subjects with diabetes fail to achieve the recommended treatment target and the reasons for this are multifactorial[4,5].

The pathophysiology and metabolic phenotype of type 2 diabetes differs markedly by ethnicity. For example, South east Asians and South Asians develop type 2 diabetes at younger age and lower BMI than whites[6,7,8]; and beta-cell deficiency has been reported to be a feature of Asian diabetes[6]. These pathophysiological differences may impact on treatment efficacy as most diabetes therapies largely target the underlying pathophysiological defects.

Even though a large number of studies have been carried out to measure safety and efficacy of anti-diabetic agents, only a few report on these measures in those of different ethnicity. Previous meta-analysis on DPP-4 inhibitors (reported in 2013) and GLP-1RAs (reported in 2014) based on ethnicity have reported that Asians responded better than non-Asians[9,10,11]. These studies defined a population as Asian if it was >50% Asian and White if the population

was <50% Asian; and included studies of short duration. There are no previous studies reporting efficacy of SGLT-2 inhibitors based on ethnicity. Thus, we performed a systematic review and meta-analysis to comprehensively assess the impact of ethnicity on the glucose lowering efficacy of relatively newer anti-diabetic agents; SGLT-2 inhibitors, GLP-1RAs and DPP-4 inhibitors using published evidence from randomized clinical trials reported up to 31 March 2019.

METHODS

Participants of three groups were considered for the study.

a) Receiving DPP-4 inhibitor alone or in combination with other drugs
b) Receiving SGLT-2 inhibitor alone or in combination with other drugs
c) Receiving GLP-1RA alone or in combination with other drugs

Data Sources and Searches

The meta-analysis was carried out using methods proposed in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement[12]. A literature search was conducted in PubMed for studies published up to March 31, 2019, by two independent investigators (SG, AYD) of all randomized, placebo-controlled trials of DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1RA. The search strategy was developed based on medical subject sub-headings (MeSH) terms and keywords. The search algorithm is presented in detail in the supplementary document.

Study selection

A title-based search was conducted followed by abstract screening. A full paper search of potentially eligible studies was also performed based on the pre-defined inclusion and exclusion criteria. Any discrepancies in selection was resolved by a third researcher (ERP).

Inclusion criteria

1. Randomized Controlled Trial (RCT) on adult, non-pregnant participants aged 18 or older with type 2 diabetes.
2. The efficacy of the drug was the primary outcome of the study.
3. Study reported the effect of drug versus placebo on the HbA1c in participants who were either drug naïve or on background therapy.
4. Study reported outcome by ethnicity and one ethnic group constituted at least 70% or more participants.
5. Studies were filtered on the basis of humans, clinical trials and age 19+.
6. Study written in English.

Exclusion criteria

1. Study duration was less than 24 weeks or more than 52 weeks.
2. The study had less than 50 participants in each study arm.
3. Participants were on insulin as background therapy.
4. Studies that were extensions of previous RCTs.
5. Studies that included participants under inpatients care.
6. Non RCT studies and reviews.

Data extraction

Data extraction was done for aggregated study-level data , by two independent researchers. Absolute changes in HbA1c (%) from baseline to 24 weeks between the drug and placebo was considered as the primary endpoint of the study. In case data was not available for 24 weeks, 52 weeks was considered. Studies with duration >52 weeks were excluded as these were open label extensions. A standardized pre-piloted form was used to extract data from the included studies for assessment of study quality and synthesis. Extracted information included: author, year of publication, sample sizes, participant demographics and baseline characteristics, interventions and HbA1c outcomes of the lowest dose(in case multiple doses were reported and placebo). Further, the studies were classified by their ethnicities provided percentage of participants in a particular ethnic group was more than 70%. A hierarchical approach was adopted to decide the relevance of studies based on title, abstract and full manuscript. If a study had more than two relevant arms, each arm was treated separately. Selection process of relevant studies retrieved from databases was shown in a PRISMA compliant flowchart.

We have used the classification of 'Asian' or 'White' of each study as it was reported in the manuscript. Where studies were conducted in relatively homogenous populations in Asian countries (eg Korea, China, Japan and Taiwan), we have considered the participants to be in the 'Asian' group. We have also followed the definitions of 'East Asians' (China, Japan, Mongolia, North Korea and South Korea) and 'South Asians'(Afganistan, Bangladesh, Bhutan, India, Maldives, Mauritius, Nepal, Pakistan, and Sri Lanka) from previous reports[13,14].

To ensure more robust ethnicity specific outcomes we required >70% of the population to be Asian or White for the study to be allocated to that ethnic group; and to ensure more robust treatment effects we limited our studies to those where the study duration was >=24 weeks and where there were more than 50 participants in the intervention and comparison arms.

Quality assessment

The quality of eligible studies were evaluated by two independent researchers using the Cochrane Collaboration's risk of bias tool[15] for assessing the design, execution and reporting of the included RCTs. Risk of bias was assessed in random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias). The risk of bias was classified as high, low or unclear. Funnel plot and Egger's test was carried out to assess the publication bias of the overall studies for each drug.

Data synthesis and analysis

For each drug group, meta-analysis was performed with the combined data and stratified analysis by ethnic group using meta package in R Studio (version 1.0.153). Change in HbA1c was evaluated by computing mean differences (MDs) and 95% confidence intervals (CI) between treatment and placebo arms. The MDs were calculated as the change from baseline to end point. When standard deviation was not reported, it was estimated by the formula provided by the Cochrane Handbook for Systematic Reviews of Interventions[16]. Forest plots for White and Asian dominant groups were constructed using RStudio. Higgins I^2 statistics was used to evaluate between study heterogeneity and classified as low (<25%), moderate (25-75%) or high (>75%)[16]. The Q statistic was used as a test of heterogeneity. τ^2 was estimated by Der-Simonian Laird Estimation Method[17]. A random effects model was used to estimate the pooled effect. Statistical significance was considered as p value<0.05. Tests for subgroup differences were carried out to check if there were any significant differences between ethnic groups. Meta-regression analyses were performed to determine whether estimates of treatment effects were associated with prespecified clinical characteristics such as: age, duration of disease,

percentage of specific ethnic group, percentage of men, baseline BMI and baseline HbA1c. A sensitivity analysis was conducted considering study duration from 12 weeks to 52 weeks for all the three drug groups, with all other criteria kept the same.

This review is registered with PROSPERO[CRD42019133587].

RESULTS

DPP-4inhibitors

Search results and study characteristics: Initially, 1411 articles were identified from the database, 12 articles were identified from references of other articles, 26 articles were included in the meta-analysis. A total of 26 comparison pairs were retrieved which satisfied the selection criteria (Fig S1a). The total number of study participants were 8531 of which 4728 were randomised to treatment arms and 3803 to the placebo arms. The White dominant group (17 studies) consisted of 5185 participants of which 3051 participants were randomised in the treatment group and 2134 participants in the placebo group. The Asian dominant group (9 studies) consisted of 3346 participants of which 1677 participants were randomised in the treatment group and 1669 participants in the placebo group (Fig 1). The summary of included studies are shown in Supplementary Table S1.

Quality of included studies and publication bias assessments: For the adequacy of sequence generation, 13 studies were categorised as unclear and 13 studies were categorised as low risk. All the included studies achieved the double blinding for the participants and the personnel. The allocation concealment was unclear in 16 studies and 10 studies were at low risk. There

was no particular indication of incomplete data, selective reporting or other biases in any of the included studies (Table S1a and Fig S1b). The Egger's Test and funnel plot suggested that there was no asymmetric pattern and no particular concern regarding publication bias (p=0.626) (Fig S1c and S1d).

Efficacy Outcomes: HbA1c data were pooled from the 26 comparison pairs from 26 studies. Overall, the difference between the treatment and placebo groups was -0.53[CI -0.62,-0.44 ; I^2=78%]favouring treatment (Fig 1). In the White dominant group, the difference between treatment and placebo groups was -0.49[CI -0.59,-0.38 ; I^2=74%] favouring treatment. In the Asian dominant group the difference between treatment and comparison group was -0.62[CI -0.80,-0.45 ; I^2=84%] favouring treatment (Fig 1). The test for sub-group differences (random effects model) showed no difference (p=0.1919) between the two groups (Table S2a).

Exploratory Analysis: The median (range) duration of diabetes was 6.1 (2.9-12.2) in the White dominant group and 6.4 (0.97-8.15) for the Asian dominant group. The median(range) HbA1c at baseline was 8.065(7.8-8.6) in the White dominant group and 8.5(7.9-9.4) in the Asian dominant group. The median (range) BMI at baseline was 31.7 (28.1-32.90) in the White dominant group and 25.9(25.30-27.90) in the Asian dominant group.

Meta-regression: The univariate meta-regression analysis showed age (p=0.33), percentage of white participants (p=0.12), HbA1c at baseline (p=0.98), duration of diabetes (p=0.22), percentage of men (p=0.60), BMI at baseline (p=0.38) were not associated with the change in HbA1c from baseline (Table S3 and Fig S4).

Sensitivity Analysis: Here we included additional studies with a shorter duration (from 12 weeks to 52 weeks). Out of the 1411 articles identified from the database, an additional 7 studies were identified, totalling 33 studies included in the sensitivity analysis. Overall, the difference between the treatment group and comparison group was -0.59[CI -0.70, -0.48; I^2=94%] favouring treatment (Fig S1e). In the White dominant group, the difference between treatment group and comparison group was -0.49[CI -0.59,-0.39 ; I^2=73%] favouring treatment. In the Asian dominant group the difference between treatment and comparison group was -0.73[CI -0.88,-0.57 ; I^2=94%] favouring treatment (Fig S1e). Test for sub-group differences (random effects model) showed a greater response in the Asians compared to the White predominant group (p=0.0098) (Table S2b).

SGLT-2inhibitors

Search results and study characteristics: 16 articles were included in the study from the 555 articles that were identified from the database(Fig S2a). The total number of study participants were 4189 of which 2178 were randomised in the treatment group and 2011 were from placebo group. The White dominant group (9 studies) consisted of 3015 participants of which 1515 participants were randomised in the treatment group and 1500 participants in the placebo group. The Asian dominant group (7 studies) consisted of 1174 participants of which 663 participants were randomised in the treatment group and 511 participants in the placebo group. The summary of included studies is shown in Supplementary Table 1.

Quality of included studies and publication bias assessments: All the studies were double blind for the participants and personnel. For the adequacy of sequence generation, 5 studies were categorised as unclear, 8 studies were categorised as low risk and 3 studies were categorised as high risk. The allocation concealment was unclear in 4 studies, 11 studies were at low risk and 2 studies were at high risk. There was no particular indication of incomplete data, selective reporting or other biases in any of the included studies (Table S1b and Fig S2b). The Egger's Test and funnel plot suggested that there was no asymmetric pattern and no particular concern regarding a publication bias (Fig S2b and S2c).

Efficacy Outcomes: HbA1c data was pooled from the 16 comparison pairs from 16 studies. Overall, the difference between the treatment group and comparison group was -0.79[CI -0.91, -0.66; I^2=80%] favouring treatment (Fig 2). In the White dominant group, the difference between treatment group and comparison group was -0.64[CI -0.74, -0.53; I^2=44%] favouring treatment. In the Asian dominant group, the difference between treatment and comparison group was -0.96[CI -1.10, -0.82; I^2=66%] favouring treatment. Test for sub-group differences (random effects model) showed a significant difference (p=0.0003) between the two groups (Table S2a).

Exploratory Analysis: The median(range) duration of diabetes was 8.3(5.64-12.3) in the White dominant group and 7.49(4.72-11.6) for the Asian dominant group. The median(range) HbA1c at baseline was 8.17(7.8-9.3) in the White dominant group and 8.18(7.9-8.45) in the Asian dominant group. The median(range) BMI at baseline was 31.9(31.2-33.3) in the White dominant group and 25.59(25.07-26.0) among the Asian dominant group.

Meta-regression: The univariate meta-regression analysis showed percentage of white participants (p<0.01), BMI at baseline (p=0.01) are associated with the change in HbA1c from baseline. On the other hand, age (p=0.38), HbA1c at baseline (p=0.80), duration of diabetes (p=0.85), and percentage of men (p=0.1) were not associated with the change in HbA1c from baseline (Table S3 and Fig S5).

Sensitivity Analysis: Including 5 additional studies between 12 and 24 week duration, HbA1c data were pooled from 21 comparison pairs from 21 studies. Overall, the difference between the treatment group and comparison group was -0.70[CI -0.82, -0.58; I^2=84%] favouring treatment (Fig S2e). In the White dominant group, the difference between treatment group and comparison group was -0.57[CI -0.69, -0.44; I^2=69%] favouring treatment. In the Asian dominant group the difference between treatment and comparison group was -0.85[CI -1.03, -0.66; I^2=87%] favouring treatment (Fig S2e). Test for sub-group differences (random effects model) showed a difference (p=0.0182) between the two groups (Table S2b).

<u>*GLP-1RA*</u>

Search results and study characteristics: 1481 articles were identified from the database and 4 articles were identified from references of other articles from which 22 articles were included in the meta-analysis (Fig S3a). A total of 23 comparison pairs were retrieved which satisfied the selection criteria. The total number of study participants were 6559 of which 3608 were randomised in the treatment group and 2951 were from placebo group. The White dominant group (19 studies, 20 arms) consisted of 5682 participants of which 3608 participants were randomised in the treatment group and 2951 participants in the placebo group. The Asian

dominant group (3 studies) consisted of 877 participants of which 438 participants were randomised in the treatment group and 439 participants in the placebo group. The summary of included studies are shown in Supplementary Table S1.

Quality of included studies and publication bias assessments: All the 22 of the studies achieved the double blindness for the participants and the personnel. For the adequacy of sequence generation, 14 studies were categorised as unclear and 8 studies were categorised as low risk. The allocation concealment was unclear in 6 studies and 16 studies were at low risk. There was no particular indication of incomplete data, selective reporting or other biases in any of the included studies (Table S1c and Fig S3b). The Egger's Test and funnel plot suggested that there was no asymmetric pattern and no particular concern regarding a publication bias (Fig S3c and S3d).

Efficacy Outcomes: HbA1c data were pooled from the 23 comparison pairs from 22 studies. Overall, the difference between the treatment group and comparison group was -0.78[CI -0.88,-0.69 ; I^2=79%] favouring treatment (Fig 3). In White dominant group, the difference between treatment group and comparison group was -0.79[CI -0.89,-0.69 ; I^2=77%] favouring treatment. In the Asian dominant group the difference between treatment and comparison group was -0.76[CI -1.19,-0.33 ; I^2=90%] favouring treatment (Fig 3). Test for sub-group differences (random effects model) showed no statistically significant difference (p=0.8957) between the two groups(Table S2a).

Exploratory Analysis: The median (range) duration of diabetes was 7.6(2.8-13.6) in the White dominant group and 9.3(4.0-13.7) for the Asian dominant group. The median(range) HbA1c at baseline was 8.1(7.5-9.3) in the White dominant group and 8.54(7.95-8.6) in the Asian dominant group. The median(range) BMI at baseline was 32.94(29.9-36.9) in the White dominant group and 25.4(25.3-26.8).

Meta-regression : The univariate meta-regression analysis showed age (p=0.98), percentage of white participants (p=0.99), HbA1c at baseline (p=0.99), duration of diabetes (p=0.54), percentage of men (p=0.59), BMI at baseline (p=0.94) were not significantly associated with the change in HbA1c from baseline (Table S3 and Fig S6).

Sensitivity Analysis : Including 4 additional studies that were identified between 12 and 24 week duration, HbA1c data were pooled from 27 comparison pairs from 26 studies. Overall, the difference between the treatment group and comparison group was -0.79[CI -0.88,-0.70 ; I^2=76%] favouring treatment (Fig S3e). In the White dominant group, the difference between treatment group and comparison group was -0.79[CI -0.89,-0.70 ; I^2=75.1%] favouring treatment. In the Asian dominant group the difference between treatment and comparison group was -0.79[CI -1.03,-0.54 ; I^2=82%] favouring treatment (Fig S3e). Test for sub-group differences (random effects model) showed no statistically significant difference (p=0.9657) between the two groups (Table S2b).

DISCUSSION

The current systematic review and meta-analysis focuses on the HbA1c-lowering efficacy of DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1RAs in ethnically White and Asian participants. Compared to Whites, Asians respond better to SGLT-2is. Even though the primary analysis of DPP-4 inhibitors showed no difference in response to DPP-4 inhibitors between the two groups, the sensitivity analysis including shorter duration studies did show that Asians respond better to DPP-4 inhibitors than Whites in keeping with previous reports. No difference was found in the response to GLP-1RAs between Asians and Whites.

This is the first meta-analysis which reports glycemic response to SGLT-2 inhibitors by ethnicity. Our results showed that the Asians respond better to SGLT-2 inhibitors as compared to the White dominant group. In the meta-regression, the percentage of White in the population and BMI at baseline were associated with the HbA1c reduction, whereas baseline HbA1c was not correlated. A recent meta-analysis showed that efficacy and safety of SGLT-2 inhibitors were favourable in East Asian patients with Type 2 diabetes[13]. It is interesting to know that SGLT-2 inhibitors also show greater, albeit non-significant, cardiovascular risk reduction in Asians compared to other ethnic groups[18].

Although, no significant difference was found between the two groups for DPP-4 inhibitors, the reduction in HbA1c levels at study endpoint was greater for the Asian dominant studies (between group difference p=0.1919). However, our sensitivity analysis that included studies of shorter duration (from 12 weeks) did show a -0.11% significantly greater reduction in HbA1c in the predominantly Asian group compared to the predominantly white population. A previous meta-analysis by Kim et al reported DPP-4 inhibitors showed greater HbA1c lowering effect in Asian-dominant studies than the non-Asian dominant studies (between group

difference : -0.18%, p=0.006)[9]. In another review, Ito et. al hypothesized that DPP-4 inhibitors had greater efficacy among East-Asian participants than their White counterparts due to the different pathophysiology of type 2 diabetes between the two ethnic groups[19]. Interestingly these two meta-analyses also included studies of 12 weeks or longer. Finally, in an individual level analysis of TECOS, Davis et al showed that the greatest initial reduction of HbA1c was observed in East Asians on Sitagliptin.[20] It is not clear why our primary analysis based upon studies of at least 24 weeks showed a smaller difference between ethnic groups; there was no obvious difference or bias introduced in the shorter duration studies but the results would suggest the difference seen at 12 weeks does not persist to 24 weeks or longer. Previous studies on sitagliptin and vildagliptin have reported that the clinical pharmacokinetic characteristics of DPP-4 inhibitors were not different among Asian, Black, Hispanics and Whites, suggesting that differences in response are more likely to reflect phenotypic or pathophysiological differences[21,22]. Lower BMI has been reported to be associated with a better glycemic response[23], yet in the present study, the meta-regression showed no correlation between age, BMI at baseline, percentage of White, HbA1c at baseline, duration of diabetes, percentage of men and HbA1c reduction. This meta-regression suggests that the greater HbA1c reduction seen in Asians in our meta-analysis is not driven by the higher HBA1c at recruitment in the Asian populations. There may, however, be other differences between ethnic groups that are not captured in the recorded baseline characteristics, such as adherence, that could have contributed to differences in results. The use of other glucose lowering agents in the trials were quite similar between Asian and White dominant studies and hence are unlikely to explain ethnic differences in treatment efficacy (Table S4).

In the present meta-analysis, no difference in efficacy was found between the White and Asian dominant groups (p=0.8957) among the studies of GLP-1RA. In a previous meta-analysis,

conducted on GLP 1 analogues by Kim et al, it was found that HbA1c reduction from baseline was greater in Asian dominant groups than in non-Asian dominant groups[10]. The fact that we show no evidence of difference in response between Asians and Whites is at odds with this previous report. However, unlike for DPP-4 inhibitors, for GLP-1RA, including shorter duration studies in our analysis, similar to that of Kim et al, did not make any difference to the estimate of efficacy difference. Even though our study had only three Asian studies included these differed from that of the three Asian studies included by Kim et al in their meta-analysis. Thus our lack of replication of the previous meta-analysis may reflect this small number of studies and heterogeneity between studies in the Asian population.

The only remaining differences were that in our study design, to ensure separation between studies reporting efficacy in Whites vs Asians we defined a population cut off of 70%, whereas Kim et al. used a 50% cut off, and we only included studies that have 50 patients per treatment arm.

There are some limitations to this study. First, this systematic review and meta-analysis is based on summarized data of RCT studies. Further investigation of individual level trial data based on ethnicity is required to confirm the reported differences for SGLT2i and DPP4i. Second, due to lack of enough studies that satisfied our inclusion and exclusion criteria, studies could not be separated based on South Asians and East Asians. It is known from previous reports that South Asians and East Asians are ethnically heterogeneous and this demands for more studies to be conducted in the South Asian region[14].

In conclusion, the glucose lowering efficacy of SGLT-2 inhibitors and DPP-4 inhibitors was higher in Asian dominant group as compared to the White dominant group but not for and GLP-1 analogues. Our data suggest that, if our results are replicated by individual-level patient analyses from clinical trials, ethnicity should be incorporated into the treatment guidelines. Further studies would also be warranted as to the physiological or pharmacological basis of these differences, given the reported beta-cell deficiency and visceral adiposity in Asians.

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Prof. Ewan R Pearson is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

S.G. researched data and wrote the manuscript. A.D. researched data and reviewed/edited manuscript. L.D. contributed to the discussion and reviewed/edited manuscript. A.N. researched data and reviewed the manuscript. C.P. reviewed the manuscript. V.M. reviewed/edited the manuscript. E.P. researched data and reviewed/edited the manuscript.

CONFLICT OF INTEREST

No

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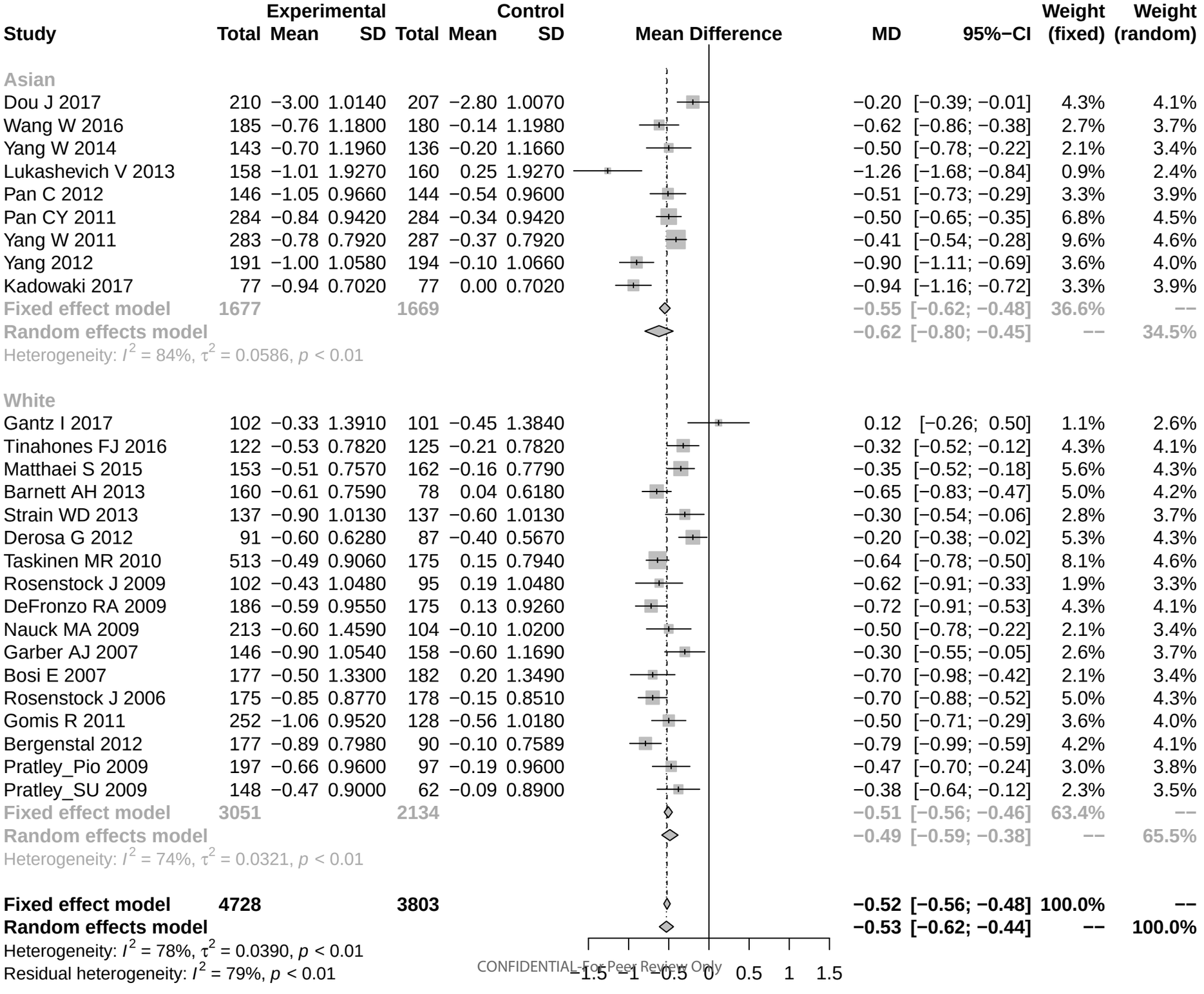
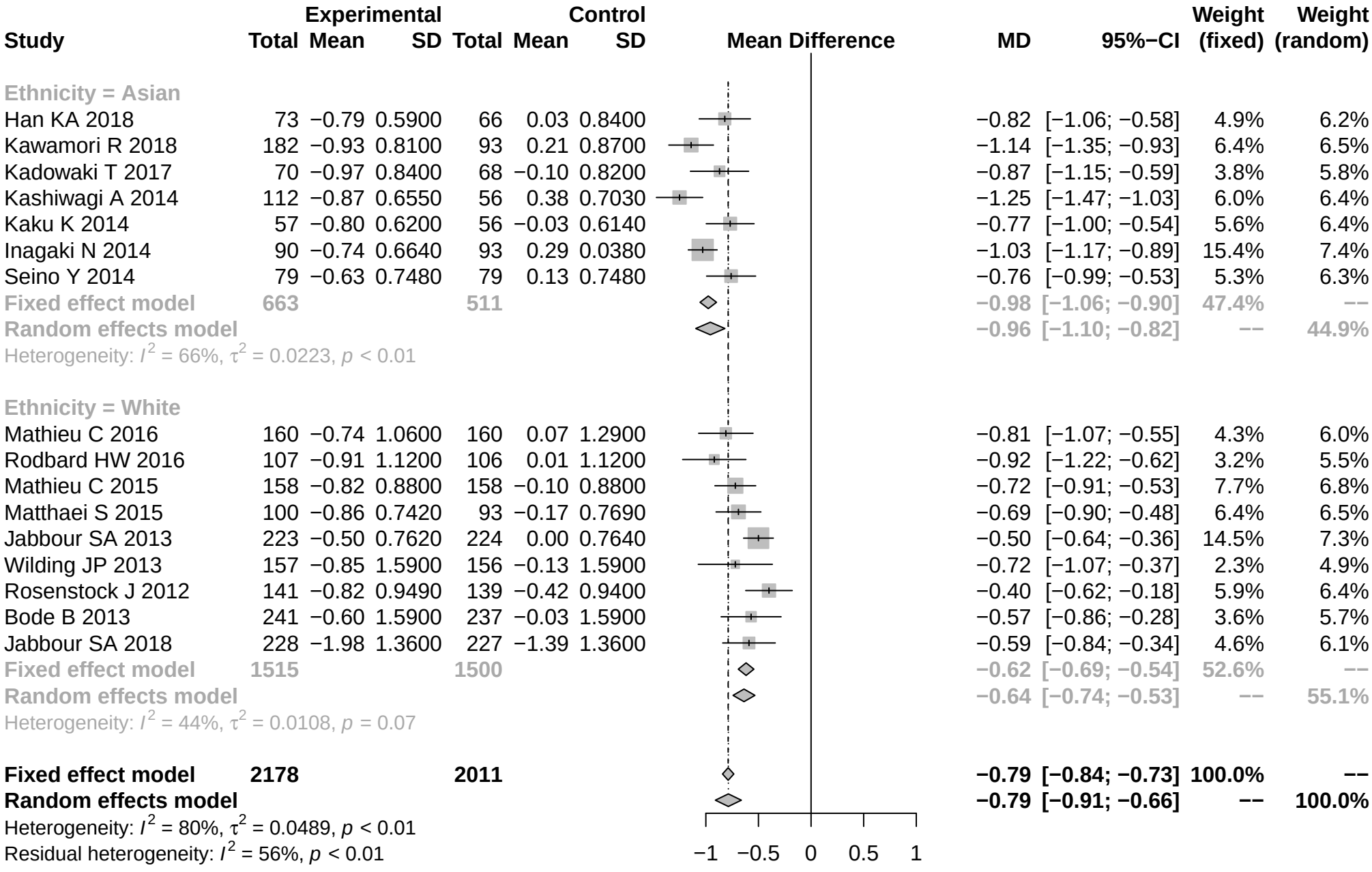
Figure Legends :

Fig 1: Forest plot for White and Asian dominant groups for DPP-4 inhibitors

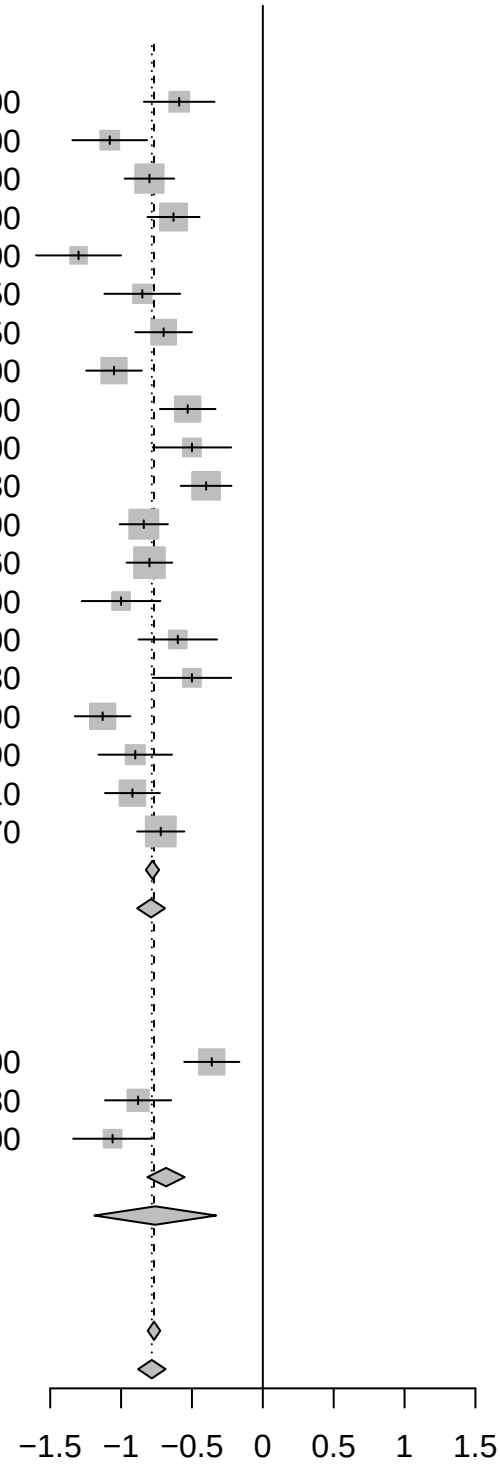
Fig 2 : Forest plot for White and Asian dominant groups for SGLT-2 inhibitors

Fig 3 : Forest plot for White and Asian dominant groups for GLP-1RA




Study
Experimental
Total Mean SD
Control
Total Mean SD
Mean Difference
MD 95%−CI
Weight (fixed)
Weight (random)
Ethnicity = Asian
Han KA 2018 73 −0.79 0.5900 66 0.03 0.8400 −0.82 [−1.06; −0.58] 4.9% 6.2%
Kawamori R 2018 182 −0.93 0.8100 93 0.21 0.8700 −1.14 [−1.35; −0.93] 6.4% 6.5%
Kadowaki T 2017 70 −0.97 0.8400 68 −0.10 0.8200 −0.87 [−1.15; −0.59] 3.8% 5.8%
Kashiwagi A 2014 112 −0.87 0.6550 56 0.38 0.7030 −1.25 [−1.47; −1.03] 6.0% 6.4%
Kaku K 2014 57 −0.80 0.6200 56 −0.03 0.6140 −0.77 [−1.00; −0.54] 5.6% 6.4%
Inagaki N 2014 90 −0.74 0.6640 93 0.29 0.0380 −1.03 [−1.17; −0.89] 15.4% 7.4%
Seino Y 2014 79 −0.63 0.7480 79 0.13 0.7480 −0.76 [−0.99; −0.53] 5.3% 6.3%
Fixed effect model 663 511 −0.98 [−1.06; −0.90] 47.4% ––
Random effects model −0.96 [−1.10; −0.82] –– 44.9%
Heterogeneity: I^2 = 66%, τ^2 = 0.0223, p < 0.01
Ethnicity = White
Mathieu C 2016 160 −0.74 1.0600 160 0.07 1.2900 −0.81 [−1.07; −0.55] 4.3% 6.0%
Rodbard HW 2016 107 −0.91 1.1200 106 0.01 1.1200 −0.92 [−1.22; −0.62] 3.2% 5.5%
Mathieu C 2015 158 −0.82 0.8800 158 −0.10 0.8800 −0.72 [−0.91; −0.53] 7.7% 6.8%
Matthaei S 2015 100 −0.86 0.7420 93 −0.17 0.7690 −0.69 [−0.90; −0.48] 6.4% 6.5%
Jabbour SA 2013 223 −0.50 0.7620 224 0.00 0.7640 −0.50 [−0.64; −0.36] 14.5% 7.3%
Wilding JP 2013 157 −0.85 1.5900 156 −0.13 1.5900 −0.72 [−1.07; −0.37] 2.3% 4.9%
Rosenstock J 2012 141 −0.82 0.9490 139 −0.42 0.9400 −0.40 [−0.62; −0.18] 5.9% 6.4%
Bode B 2013 241 −0.60 1.5900 237 −0.03 1.5900 −0.57 [−0.86; −0.28] 3.6% 5.7%
Jabbour SA 2018 228 −1.98 1.3600 227 −1.39 1.3600 −0.59 [−0.84; −0.34] 4.6% 6.1%
Fixed effect model 1515 1500 −0.62 [−0.69; −0.54] 52.6% ––
Random effects model −0.64 [−0.74; −0.53] –– 55.1%
Heterogeneity: I^2 = 44%, τ^2 = 0.0108, p = 0.07
Fixed effect model 2178 2011 −0.79 [−0.84; −0.73] 100.0% ––
Random effects model −0.79 [−0.91; −0.66] –– 100.0%
Heterogeneity: I^2 = 80%, τ^2 = 0.0489, p < 0.01
Residual heterogeneity: I^2 = 56%, p < 0.01
−1 −0.5 0 0.5 1

Study	Experimental Total	Mean	SD	Control Total	Mean	SD	MD	95%−CI	Weight (fixed)	Weight (random)
White										
Jabbour SA 2018	228	−1.98	1.3600	230	−1.39	1.3600	−0.59	[−0.84; −0.34]	3.1%	4.1%
Lingvay I 2018	64	−1.10	0.8800	129	−0.02	0.8800	−1.08	[−1.34; −0.82]	2.8%	4.0%
Ludvik B 2018	142	−1.34	0.7150	140	−0.54	0.7800	−0.80	[−0.97; −0.63]	6.4%	4.8%
Meneilly GS 2017	176	−0.57	0.9550	174	0.06	0.7900	−0.63	[−0.81; −0.45]	5.8%	4.7%
Dungan KM 2016	239	−1.40	1.0600	60	−0.10	1.0600	−1.30	[−1.60; −1.00]	2.2%	3.7%
Nauck MA 2015	101	−0.70	0.9650	101	0.15	0.9750	−0.85	[−1.12; −0.58]	2.7%	4.0%
Reusch J 2014	150	−0.80	0.8850	151	−0.10	0.8850	−0.70	[−0.90; −0.50]	4.9%	4.6%
Wysham C 2014	279	−1.51	1.0000	141	−0.46	0.9500	−1.05	[−1.25; −0.85]	5.1%	4.6%
Wysham C 2014	276	−0.99	0.9970	141	−0.46	0.9500	−0.53	[−0.73; −0.33]	5.1%	4.6%
Bolli GB 2013	161	−0.90	1.2700	160	−0.40	1.2600	−0.50	[−0.78; −0.22]	2.5%	3.9%
Derosa G 2013	86	−0.60	0.6340	84	−0.20	0.5530	−0.40	[−0.58; −0.22]	6.1%	4.8%
Pinget M 2013	323	−1.16	0.8990	161	−0.32	0.8990	−0.84	[−1.01; −0.67]	6.7%	4.8%
Derosa G 2012	86	−1.20	0.5910	85	−0.40	0.4760	−0.80	[−0.96; −0.64]	7.5%	4.9%
Zinman B 2009	100	−1.50	1.0000	100	−0.50	1.0000	−1.00	[−1.28; −0.72]	2.5%	3.9%
Nauck M 2008	100	−0.70	1.0000	100	−0.10	1.0000	−0.60	[−0.88; −0.32]	2.5%	3.9%
DeFronzo RA 2005	110	−0.40	1.0500	113	0.10	1.0630	−0.50	[−0.78; −0.22]	2.5%	3.9%
Bergenstal 2012	182	−1.23	0.8090	90	−0.10	0.7590	−1.13	[−1.33; −0.93]	5.1%	4.6%
Henry 2012	106	−1.35	0.9270	94	−0.45	0.9390	−0.90	[−1.16; −0.64]	2.9%	4.0%
Raz 2012	112	−1.01	0.7400	115	−0.09	0.7510	−0.92	[−1.11; −0.73]	5.2%	4.6%
Hollander 2013	149	−0.81	0.7300	143	−0.09	0.7170	−0.72	[−0.89; −0.55]	7.1%	4.9%
Fixed effect model	**3170**			**2512**			**−0.78**	**[−0.83; −0.73]**	**88.7%**	**––**
Random effects model							**−0.79**	**[−0.89; −0.69]**	**––**	**87.2%**
Heterogeneity: I^2 = 77%, τ^2 = 0.0377, p < 0.01										
Asian										
Yu Pan C 2014	196	−0.83	0.9800	194	−0.47	0.9800	−0.36	[−0.55; −0.17]	5.1%	4.6%
Seino Y 2012	154	−0.77	1.0480	157	0.11	1.0480	−0.88	[−1.11; −0.65]	3.6%	4.3%
Kaku K 2010	88	−1.46	0.9500	88	−0.40	0.9300	−1.06	[−1.34; −0.78]	2.5%	3.9%
Fixed effect model	**438**			**439**			**−0.68**	**[−0.81; −0.55]**	**11.3%**	**––**
Random effects model							**−0.76**	**[−1.19; −0.33]**	**––**	**12.8%**
Heterogeneity: I^2 = 90%, τ^2 = 0.1297, p < 0.01										
Fixed effect model	**3608**			**2951**			**−0.77**	**[−0.81; −0.72]**	**100.0%**	**––**
Random effects model							**−0.78**	**[−0.88; −0.69]**	**––**	**100.0%**
Heterogeneity: I^2 = 79%, τ^2 = 0.0434, p < 0.01										
Residual heterogeneity: I^2 = 79%, p < 0.01										



DPP-4 inhibitors

Author	Year	Ethnicity	White (%)	Duration of Treatment (weeks)
Dou J[1]	2017	Asian	0	24
Wang W[2]	2016	Asian	10.5	24
Yang W[3]	2014	Asian	0	24
Lukashevich V[4]	2013	Asian	21.5	24
Pan C[5]	2012	Asian	0	24
Pan CY[6]	2011	Asian	0	24
Yang W[7]	2011	Asian	0	24
Yang[8]	2012	Asian	0	24
Kadowaki[9]	2017	Asian	0	24
Gantz I[9]	2017	White	82.4	24
Tinahones FJ[10]	2016	White	98.4	24
Matthaei S[11]	2015	White	88.9	24
Barnett AH[12]	2013	White	96.9	24
Strain WD[13]	2013	White	97.1	24
Derosa G[14]	2012	White	100	24
Taskinen MR[15]	2010	White	75	24
Rosenstock J[16]	2009	White	87.3	24
DeFronzo RA[17]	2009	White	79.7	24
Nauck MA[18]	2009	White	80	26
Garber AJ[19]	2007	White	83.9	24
Bosi E[20]	2007	White	74.1	24
Rosenstock J[21]	2006	White	72.6	24
Gomis R[22]	2011	White	74.5	24
Bergenstal[23]	2012	White	76	24
Pratley_Pio[24]	2009	White	72.6	26
Pratley_SU[25]	2009	White	100	26

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5 Pan, C. *et al.* Efficacy and tolerability of vildagliptin as add-on therapy to

6 Pan, C. Y., Yang, W., Tou, C., Gause-Nilsson, I. & Zhao, J. Efficacy and saf
7 Yang, W., Pan, C. Y., Tou, C., Zhao, J. & Gause-Nilsson, I. Efficacy and saf
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9 Kadowaki, T. *et al.* Efficacy and safety of teneligliptin added to canagliflo
10 Tinahones, F. J. *et al.* Linagliptin as add-on to empagliflozin and metforn
11 Matthaei, S. *et al.* Randomized, Double-Blind trial of triple therapy with
12 Barnett, A. H. *et al.* Linagliptin for patients aged 70 years or older with t
13 Strain, W. D., Lukashevich, V., Kothny, W., Hoellinger, M. J. & Paldánius,
14 Derosa, G. *et al.* Effects of a combination of sitagliptin plus metformin v
15 Taskinen, M.-R. *et al.* Safety and efficacy of linagliptin as add-on therapy
16 Rosenstock, J. *et al.* Effect of saxagliptin monotherapy in treatment-naïv
17 DeFronzo, R. A. *et al.* The Efficacy and Safety of Saxagliptin When Added
18 Nauck, M. A., Ellis, G. C., Fleck, P. R., Wilson, C. A. & Mekki, Q. Efficacy a
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20 Bosi, E., Camisasca, R. P., Collober, C., Rochotte, E. & Garber, A. J. Effect
21 Rosenstock, J. *et al.* Efficacy and Safety of the Dipeptidyl Peptidase-4 Inh
22 Gomis, R., Espadero, R.-M., Jones, R., Woerle, H. J. & Dugi, K. A. Efficacy
23 Bergenstal, R. M. *et al.* Efficacy and safety of taspoglutide versus sitaglip
24 Pratley, R. E., Reusch, J. E.-B., Fleck, P. R., Wilson, C. A. & Mekki, Q. Effic
25 Pratley, R. E. *et al.* Efficacy and safety of the dipeptidyl peptidase-4 inhib

Mean Age (years)	Baseline HbA1c level (%)	Duration of diabetes (Years)	Men (%)	BMI (kg/m2)
49.5	9.4	0.97	64.8	26.7
56.5	8.9	7.4	50.8	25.9
58.3	8.6	6.9	55.2	24.8
55.3	8.7	7.1	50.6	27.9
54.2	8.09	4.92	50	26.01
51.2	8.1	0.8	56.3	25.9
53.8	7.9	5.1	48.1	26.3
54.1	8.5	6.4	47	25.3
55.9	7.98	8.15	83.1	25.53
38.8	7.9	2.9	65.7	32.9
56.6	8.04	NR	56.6	31.3
54.7	7.97	8.1	47.7	31.4
74.9	7.8	NR	71.6	29.6
75.1	7.9	12.2	52.5	29.1
55.9	8.1	5.8	46.1	28.1
56.5	8.09	NR	57	30.05
53.27	7.9	3.1	45.9	31.9
54.7	8.1	6.7	43.2	31.7
55	7.9	6	47.4	32
54	8.6	4.7	54.8	32.6
54.3	8.4	6.8	57.3	32.1
55.6	8.1	6.1	53.1	32
57.7	8.6	NR	58.7	28.7
55.5	7.94	6	59	32.4
55.5	8.1	7.7	55.3	32.3
56.5	NR	7.6	50	30

ormin as initial therapy in Chinese patients with type 2 diabetes: Results from the START study, a multice
sitagliptin in patients with type 2 diabetes mellitus inadequately controlled by acarbose alone. *Curr. Mea*
ntrol without hypoglycemia and weight gain in Chinese patients with type 2 diabetes mellitus. *J. Diabetes*
of vildagliptin in patients with type 2 diabetes mellitus inadequately controlled with dual combination c
o metformin in Chinese patients with type 2 diabetes mellitus. *Diabetes. Obes. Metab.* **14**, 737–744 (201

ety of saxagliptin in drug-naive Asian patients with type 2 diabetes mellitus: a randomized controlled tri
ety of saxagliptin added to metformin in Asian people with type 2 diabetes mellitus: A randomized contr
significantly improves glycemic control in Chinese patients with type 2 diabetes. *J. Diabetes* **4**, 227–37 (
ozin monotherapy in Japanese patients with type 2 diabetes mellitus: A multicentre, randomized, double
nin in patients with type 2 diabetes: Two 24-week randomized, double-blind, double-dummy, parallel-gr
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agliptin in combination with pioglitazone improves glycaemic control in patients with type 2 diabetes fa
s of vildagliptin on glucose control over 24 weeks in patients with type 2 diabetes inadequately controlle
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bitor alogliptin in patients with type 2 diabetes inadequately controlled by glyburide monotherapy. *Diab*

Background Therapy	Drug	Participants (n)	Comparator	Participants (n)
Metformin	Saxagliptin	210	Placebo	207
	Sitagliptin	185	Placebo	180
SU	Vildagliptin	143	Placebo	136
Metformin+SU	Vildagliptin	158	Placebo	160
	Vildagliptin	146	Placebo	144
	Saxagliptin	284	Placebo	284
Metformin	Saxagliptin	283	Placebo	287
Metformin	Sitagliptin	191	Placebo	194
Canagliflozin	Tenegliptin	77	Placebo	77
	Omarigliptin	102	Placebo	101
Empa+ Met	Linagliptin	122	Placebo	125
Dapa+Met	Saxagliptin	153	Placebo	162
	Linagliptin	160	Placebo	78
	Vildagliptin	137	Placebo	137
Metformin	Sitagliptin	91	Placebo	87
Metformin	Linagliptin	513	Placebo	175
	Saxagliptin	102	Placebo	95
Metformin	Saxagliptin	186	Placebo	175
Metformin	Alogliptin	213	Placebo	104
Pioglitazone	Vildagliptin	146	Placebo	158
	Vildagliptin	177	Placebo	182
Pioglitazone	Sitalgliptin	175	Placebo	178
Pioglitazone	Linagliptin	252	Placebo	128
	Sitagliptin	177	Placebo	90
Pioglitazone	Alogliptin	197	Placebo	97
SU	Alogliptin	148	Placebo	62

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SGLT-2 inhibitors

Author	Year	Ethnicity	White (%)	ation of Treatm (weeks)	Mean Age (years)	seline HbA1c le (%)
Han KA[26]	2018	Asian	0	24	57.62	7.9
Kawamori R[27]	2018	Asian	0	24	60	8.27
Kadowaki T[28]	2017	Asian	0	24	58.4	8.18
Kashiwagi A[29]	2014	Asian	0	24	56.2	8.25
Kaku K[30]	2014	Asian	0	24	58.6	8.45
Inagaki N[31]	2014	Asian	0	24	58.4	7.98
Seino Y[32]	2014	Asian	0	24	58.9	8.14
Mathieu C[33]	2016	White	93.8	52	55.2	8.24
Rodbard HW[34]	2016	White	74.8	26	57.4	8.5
Mathieu C[35]	2015	White	93.8	24	55.2	8.24
Matthaei S[36]	2015	White	96.3	24	61.1	8.08
Jabbour SA[37]	2013	White	72.2	24	54.8	7.9
Wilding JP[38]	2013	White	84.1	26	57.4	8.1
Rosenstock J[39]	2012	White	72.3	24	53.2	8.4
Bode B[40]	2013	White	80.5	26	64.3	7.8
Jabbour SA[41]	2018	White	83.3	28	53.8	9.3

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39 Rosenstock, J. *et al.* Efficacy and safety of empagliflozin, a sodium glucose cotransporte
40 Bode, B., Stenlöf, K., Sullivan, D., Fung, A. & Usiskin, K. Efficacy and safety of canagliflo
41 Jabbour, S. A. *et al.* Safety and efficacy of exenatide once weekly plus dapagliflozin onc

ration of diabet (Years)	Men (%)	BMI (kg/m2)	ckground Thera	Drug	Participants (n)	Comparator
11.6	50.7	25.5		Ifragliflozin	73	Placebo
9	78	26	Linagliptin	Empagliflozin	182	Placebo
8.34	77.1	25.53	Tenegliptin	Canagliflozin	70	Placebo
7.49	58.9	25.96		Ipragliflozin	112	Placebo
6.3	66.7	25.07		Tofogliflozin	57	Placebo
4.72	65.6	25.59		Canagliflozin	90	Placebo
6.5	75.9	25.98		Luseogliflozin	79	Placebo
7.2	43.7	31.2	Saxa+Met	Dapagliflozin	160	Placebo
9.8	61.7	32.3		Canagliflozin	107	Placebo
7.2	43.7	31.2	Saxa+Met	Dapagliflozin	158	Placebo
9.3	42.6	31.9		Dapagliflozin	108	Placebo
5.7	57			Dapagliflozin	223	Placebo
9	48.4	33.3		Canagliflozin	157	Placebo
5.64	55.3			Dapagliflozin	141	Placebo
12.3	51.5	31.4		Canagliflozin	241	Placebo
7.6	51.1	32	Exenatide	Dapagliflozin	228	Placebo

nd metformin in Korean patients with inadequately controlled type 2 diabetes mellitus: A randomized contro
n Japanese patients with type 2 diabetes: Glycaemic efficacy and safety profile in a 52-week, randomized, pla
n in Japanese patients with type 2 diabetes mellitus: Results of a 24-week, randomized, double-blind, placeb
panese patients with type 2 diabetes: ILLUMINATE, a randomized, double-blind, placebo-controlled study. *D*
ansporter-2 inhibitor tofogliflozin in Japanese patients with type 2 diabetes mellitus: A combined Phase 2 an
with type 2 diabetes inadequately controlled with diet and exercise: a 24-week, randomized, double-blind, p
s with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled, phase 3 study. *Curr. Med. R*
agliptin plus metformin over 52 weeks in patients with type 2 diabetes. *Diabetes, Obes. Metab.* **18**, 1134–113
2 diabetes mellitus inadequately controlled on metformin and sitagliptin. *Diabetes, Obes. Metab.* **18**, 812–81
gliflozin Add-on to saxagliptin plus metformin in type 2 diabetes. *Diabetes Care* **38**, 2009–2017 (2015).
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oy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-cont
es mellitus inadequately controlled with metformin and sulphonylurea: A randomised trial. *Int. J. Clin. Pract.*
er 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. *Diabetes, Obes.*
zin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. *Hosp. Pract. (1995)* **41**, 72–
e daily versus exenatide or dapagliflozin alone in patients withtype2diabetesinadequately controlled with m

Participants (n)
66
93
68
56
56
93
79
160
106
158
108
224
156
139
237
227

olled trial. *Diabetes, Obes. Metab.* **20**, 2408–2415 (2018).
acebo-controlled trial. *Diabetes. Obes. Metab.* **20**, 2200–2209 (2018).
o-controlled trial. *Diabetes, Obes. Metab.* **19**, 874–882 (2017).
Diabetes, Obes. Metab. **17**, 304–308 (2015).
d 3 randomized, placebo-controlled, double-blind, parallel-group comparative . *Cardiovasc. Diabetol.* **13**, 1–
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Metab. **15**, 1154–1160 (2013).
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·15 (2014).

136–2146 (201

GLP 1RA

Author	Year	Ethnicity	White (%)	ation of Treatm (weeks)	Mean Age (years)	seline HbA1c le (%)
Yu Pan C[42]	2014	Asian	0	24	54.5	7.95
Seino Y[43]	2012	Asian	0	24	58.7	8.54
Kaku K[44]	2010	Asian	0	24	59.1	8.6
Jabbour SA[41]	2018	White	83.3	28	53.8	9.3
Lingvay I[45]	2018	White	76.6	26	57.5	7.9
Ludvik B[46]	2018	White	89	24	56.17	8.04
Meneilly GS[47]	2017	White	72.7	24	74	8.1
Dungan KM[48]	2016	White	84.5	24	57.7	8.4
Nauck MA[49]	2015	White	84.2	52	53.6	8
Reusch J[50]	2014	White	72.7	52	55.2	8.1
Wysham C[51]	2014	White	74	26	56	8.1
Wysham C[52]	2014	White	76	26	55	8.1
Bolli GB[53]	2013	White	87.13	24	55.4	8
Derosa G[54]	2013	White	100	24	57.3	8.1
Pinget M[55]	2013	White	85	24	56	8.1
Derosa G[56]	2012	White	100	52	57.3	8.1
Zinman B[57]	2009	White	81	26	55	8.5
Nauck M[58]	2008	White	84	26	56	8.4
DeFronzo RA[59]	2005	White	77.3	30	53	8.3
Bergenstal[60]	2012	White	79	24	55.3	7.95
Henry[61]	2012	White	75	24	52.5	8.2
Raz[62]	2012	White	86	24	53.4	7.5
Hollander[63]	2013	White	92	24	53	7.54

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43 Seino, Y. *et al.* Randomized, double-blind, placebo-controlled trial of the once-daily GLI
44 Kaku, K., Rasmussen, M. F., Clauson, P. & Seino, Y. Improved glycaemic control with mi
45 Lingvay, I. *et al.* A 26-week randomized controlled trial of semaglutide once daily versu
46 Ludvik, B. *et al.* Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inad
47 Meneilly, G. S. *et al.* Lixisenatide Therapy in Older Patients With Type 2 Diabetes Inade
48 Dungan, K. M. *et al.* A 24-week study to evaluate the efficacy and safety of once-weekl
49 Nauck, M. A. *et al.* Efficacy and safety of once-weekly GLP-1 receptor agonist albiglutid
50 Reusch, J. *et al.* Efficacy and safety of once-weekly glucagon-like peptide 1 receptor ag
51 Efficacy and safety of once-weekly glucagon-like peptide 1 receptor agonist albiglutide
52 Wysham, C. *et al.* Efficacy and safety of dulaglutide added onto pioglitazone and metfc
53 Bolli, G. B. *et al.* Efficacy and safety of lixisenatide once daily vs. placebo in people with

Derosa, G. *et al.* Variation in inflammatory markers and glycemic parameters after 12 r
Pinget, M. *et al.* Efficacy and safety of lixisenatide once daily versus placebo in type 2 d
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Zinman, B. Efficacy of Liraglutide in combination woth Pioglitazone and Metformin. Lea
Nauck, M. *et al.* Efficacy and safety comparison of liraglutide, glimepiride, and placebo,
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Bergenstal, R. M. *et al.* Efficacy and safety of taspoglutide versus sitagliptin for type 2 d
Henry, R. R., Mudaliar, S., Kanitra, L., Woloschak, M. & Balena, R. Efficacy and safety of
Raz, I. *et al.* Efficacy and safety of taspoglutide monotherapy in drug-naive type 2 diabe
Hollander, P. *et al.* Effects of taspoglutide on glycemic control and body weight in obes

ration of diabet (Years)	Men (%)	BMI (kg/m2)	ckground Thera	Drug	Participants(n)	Comparator
4	51.5	26.8		Lixisenatide	196	Placebo
13.7	44.8	25.4		Lixisenatide	154	Placebo
9.3	40	25.3		Liraglutide	88	Placebo
7.6	51.1	32	Dapagliflozin	Exenatide	228	Placebo
6.5	51.6	32.3		Semaglutide	64	Placebo
9.21	54	32.87		Dulaglutide	142	Placebo
13.6	52.3	29.9		Lixisenatide	176	Placebo
7.8	43.5	30.9		Dulaglutide	239	Placebo
3.4	57.4	33.7		Albiglutide	101	Placebo
8	61.3	33.6		Albiglutide	150	Placebo
9	58	33		Dulaglutide	279	Placebo
9	57	34		Exenatide	276	Placebo
5.8	44	33		Lixisenatide	161	Placebo
7.6	50	31.9	Metformin	Exenatide	86	Placebo
8.1	53	33.7		Lixisenatide	323	Placebo
7.6	50.6	31.9	Metformin	Exenatide	86	Placebo
9	57	33.2		Liraglutide	100	Placebo
7	62	30.5		Liraglutide	100	Placebo
6.2	51.8	34		Exenatide	110	Placebo
6.1	56	32.7		Taspoglutide	182	Placebo
7.3	59	32.8		Taspoglutide	106	Placebo
2.8	37	33.2		Taspoglutide	112	Placebo
5.2	42	36.9		Taspoglutide	149	Placebo

ith type 2 diabetes mellitus inadequately controlled on metformin with or without sulfonylurea: a randomiz
P-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insu
nimal hypoglycaemia and no weight change with the once-daily human glucagon-like peptide-1 analogue lir
s liraglutide and placebo in patients with type 2 diabetes suboptimally controlled on diet and exercise with
lequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled
quately Controlled on Their Current Antidiabetic Treatment: The GetGoal-O Randomized Trial. *Diabetes Car*
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le (HARMONY 2): 52 week primary endpoint results from a randomised, placebo-controlled trial in patients v
onist albiglutide (HARMONY 1 trial): 52-week primary endpoint results from a randomized, double-blind, pla
(HARMONY 1 trial): 52-week primary endpoint results from a randomized, double-blind, placebo-controllec
ormin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). *Diabetes Care* **37**, 215
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months of exenatide plus metformin treatment compared with metformin alone: a randomized placebo-con
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Participants (n)
194
157
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230
129
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with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetologia* **59**, 266–274 (201
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ıtrolled trial. *Pharmacotherapy* **33**, 817–826 (2013).

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ɂ study. *Diabetes Care* **32**, 84–90 (2009).

ɛr 24 weeks: T-Emerge 3 trial. *J. Clin. Endocrinol. Metab.* **97**, 2370–2379 (2012).

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SUPPLEMENTARY DOCUMENT

CONTENTS

SEARCH TERMS FOR DPP-4inhibitors

"Diabetes Mellitus, Type 2/drug therapy*"[MeSH] OR "Diabetes Mellitus, Type 2/ethnology*"[MeSH] OR "Diabetes Mellitus, Type 2/blood* "[MeSH] OR "Diabetes Mellitus, Type 2/epidemiology"[MeSH] OR "Metabolic Syndrome/epidemiology* "[MeSH] OR "Metabolic Syndrome/therapy*"[MeSH]

AND

"Dipeptidyl-Peptidase IV Inhibitors/administration & dosage*"[MeSH] OR "Dipeptidyl-Peptidase IV Inhibitors/therapeutic use*" [MeSH] OR Sitagliptin OR Linagliptin OR Alogliptin OR Vildagliptin OR Saxagliptin

NOT

"Dipeptidyl-Peptidase IV Inhibitors /adverse effects"[MeSH] OR Retinopathy OR Nephropathy OR Cardiovascular OR renal

Filters: **Clinical Trial; Humans; Age 19+; English**

SEARCH TERMS FOR SGLT-2inhibitors

"Diabetes Mellitus, Type 2/drug therapy*"[MeSH] OR "Diabetes Mellitus, Type 2/ethnology*"[MeSH] OR "Diabetes Mellitus, Type 2/blood* "[MeSH] OR "Diabetes Mellitus, Type 2/epidemiology"[MeSH] OR "Metabolic Syndrome/epidemiology* "[MeSH] OR "Metabolic Syndrome/therapy*"[MeSH]

AND

"Sodium-Glucose Transporter 2/antagonists & inhibitors*"[MeSH] OR Empagliflozin OR Dapagliflozin OR Luseogliflozin OR Canagliflozin OR Ipragliflozin OR Tofogliflozin

NOT

"Sodium-Glucose Transporter 2/antagonists & inhibitors* /adverse effects"[MeSH] OR Retinopathy OR Nephropathy OR Cardiovascular OR Renal

Filters: **Clinical Trial; Humans; English, Age : 19 +**

SEARCH TERMS FOR GLP 1RA

"Diabetes Mellitus, Type 2/drug therapy*"[MeSH] OR "Diabetes Mellitus, Type 2/ethnology*"[MeSH] OR "Diabetes Mellitus, Type 2/blood* "[MeSH] OR "Diabetes Mellitus, Type 2/epidemiology"[MeSH] OR "Metabolic Syndrome/epidemiology* "[MeSH] OR "Metabolic Syndrome/therapy*"[MeSH]

AND

"glucagon-like peptide-1 receptor agonists"[MeSH] OR Exenatide OR Liraglutide OR Lixisenatide OR Dulaglutide OR Albiglutide

NOT

" glucagon-like peptide-1 receptor agonists /adverse effects"[MeSH] OR Retinopathy OR Nephropathy OR Cardiovascular OR renal

Filters: **Clinical Trial; Humans; Age 19+, English**

DPP-4inhibitors

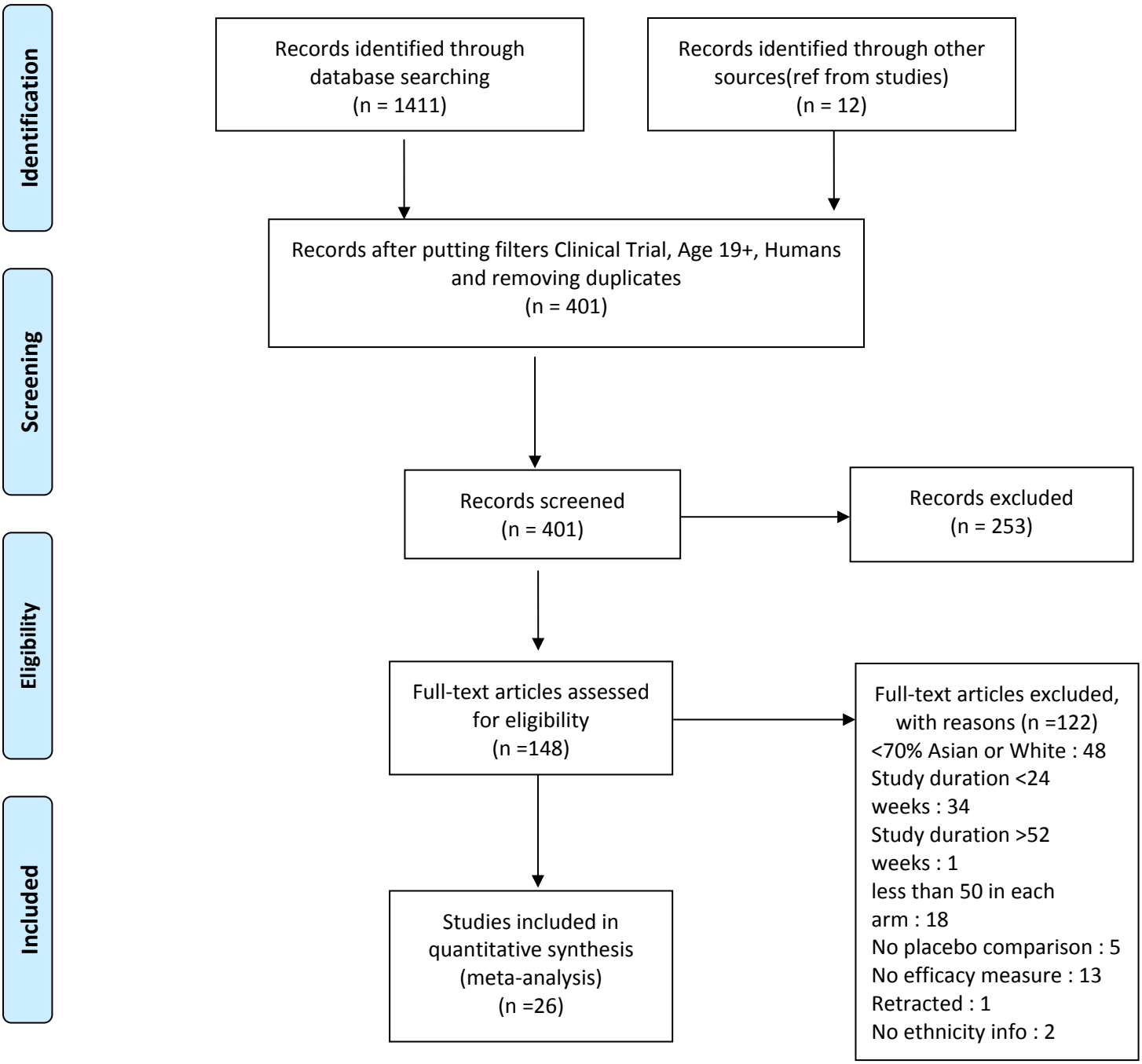


Figure S1a : Selection of DPP-4 inhibitor studies included in meta-analysis.

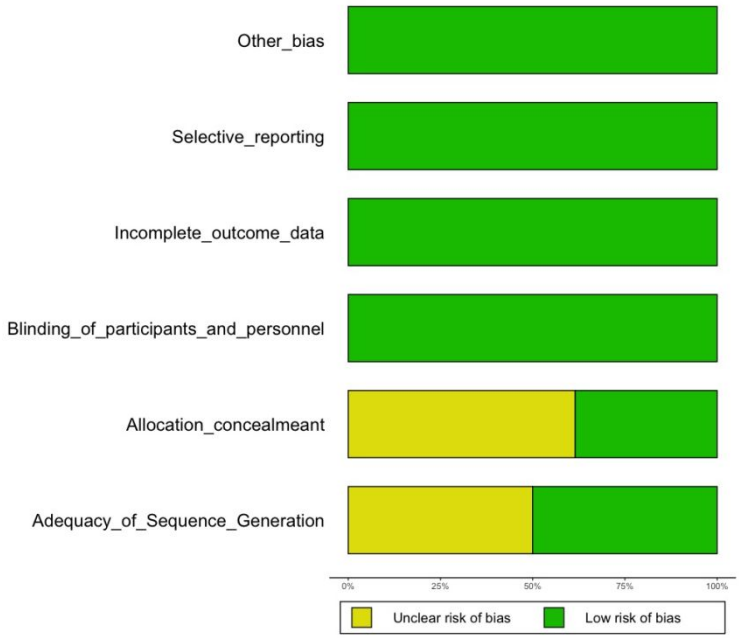


Figure S1b : Risk of Bias of DPP-4 inhibitor studies included in meta-analysis.

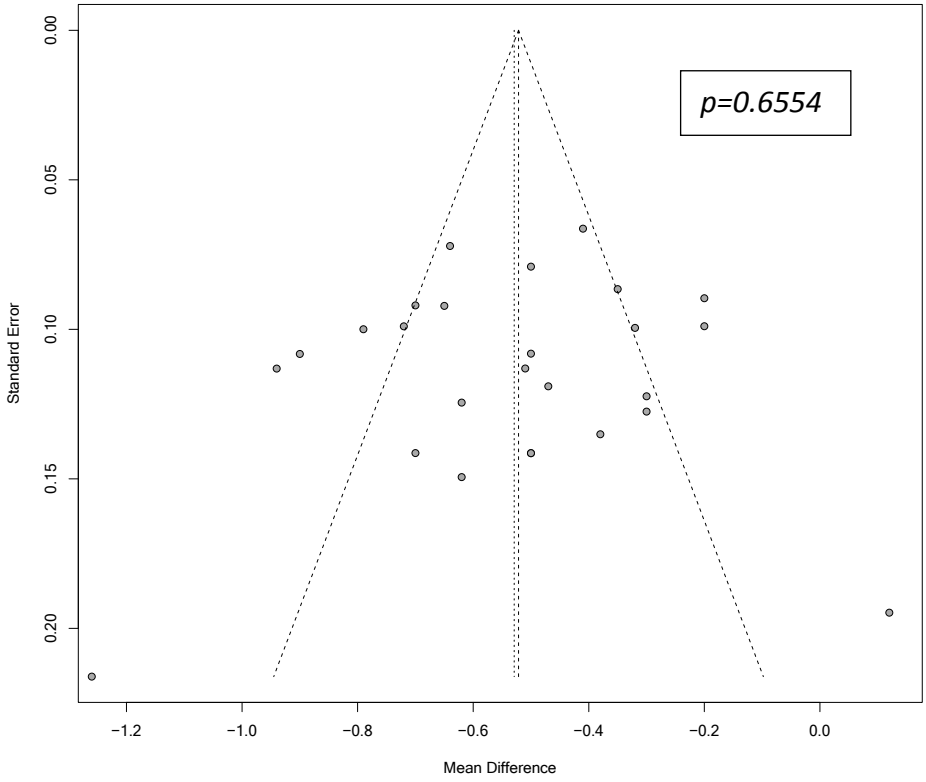


Fig S1c : Funnel plot of change in HbA1c in the studies used in the meta-analysis for DPP-4 inhibitors

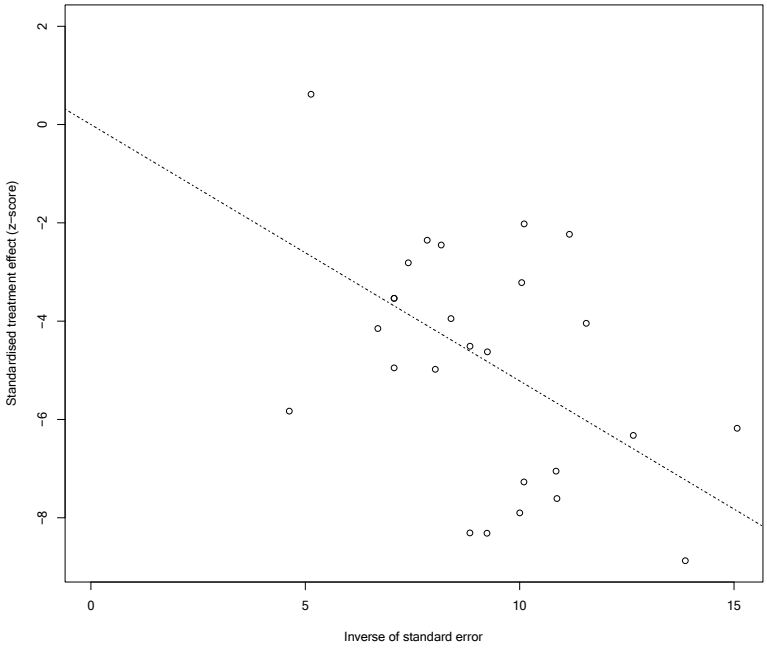


Fig S1d : Egger's test of change in HbA1c in the studies used in the meta-analysis for DPP-4 inhibitors

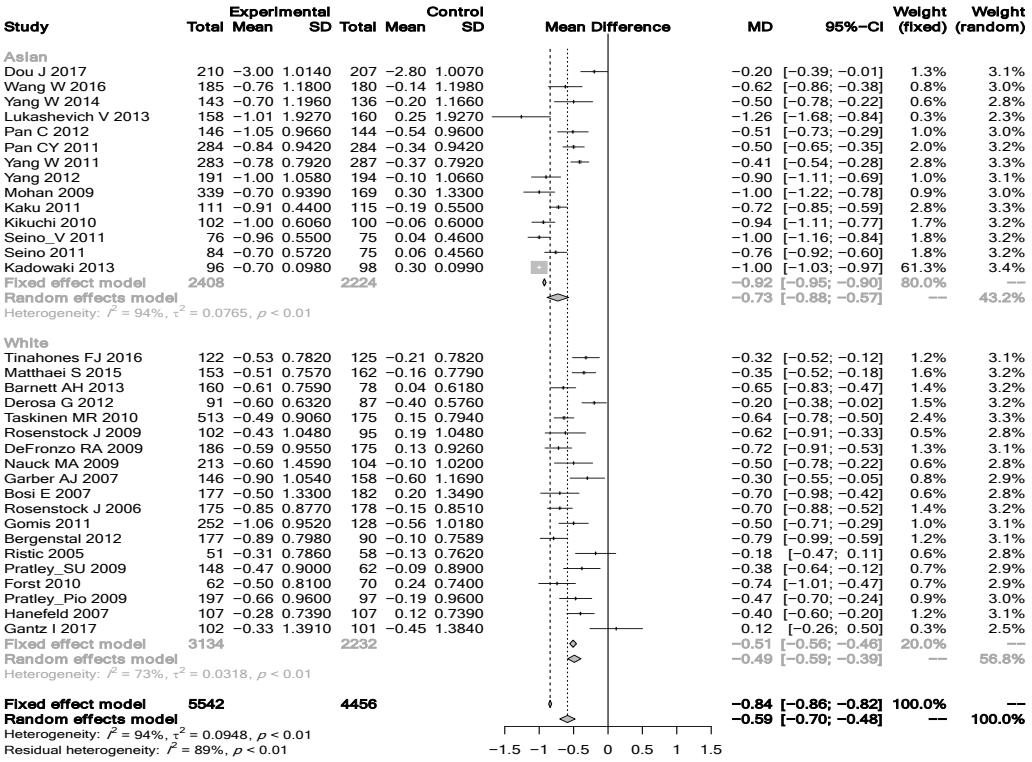


Fig S1e : Forest plot for White and Asian dominant groups for DPP-4 inhibitors for 12 weeks

SGLT-2inhibitors

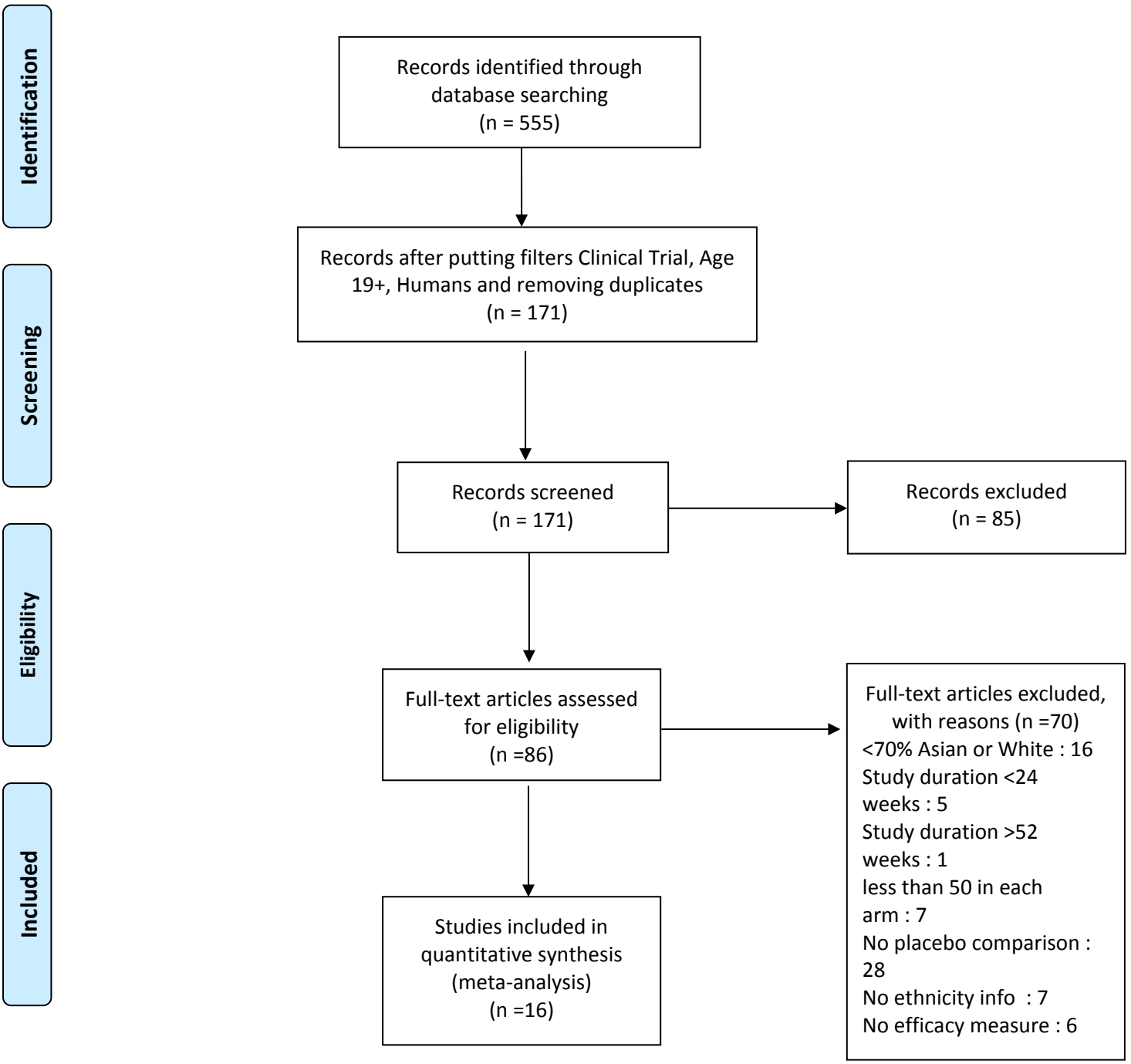


Figure S2a : Risk of Bias of SGLT-2 inhibitor studies included in meta-analysis.

Figure S2b : Risk of Bias of SGLT-2 inhibitor studies included in meta-analysis.

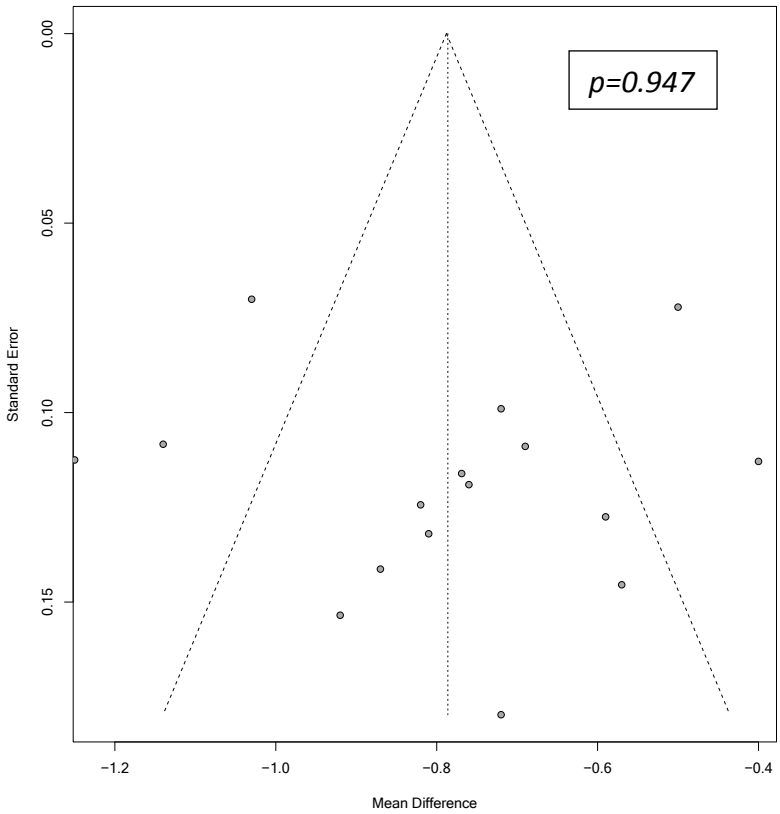


Fig S2c : Funnel plot of change in HbA1c in the studies used in the meta-analysis for SGLT-2 inhibitors

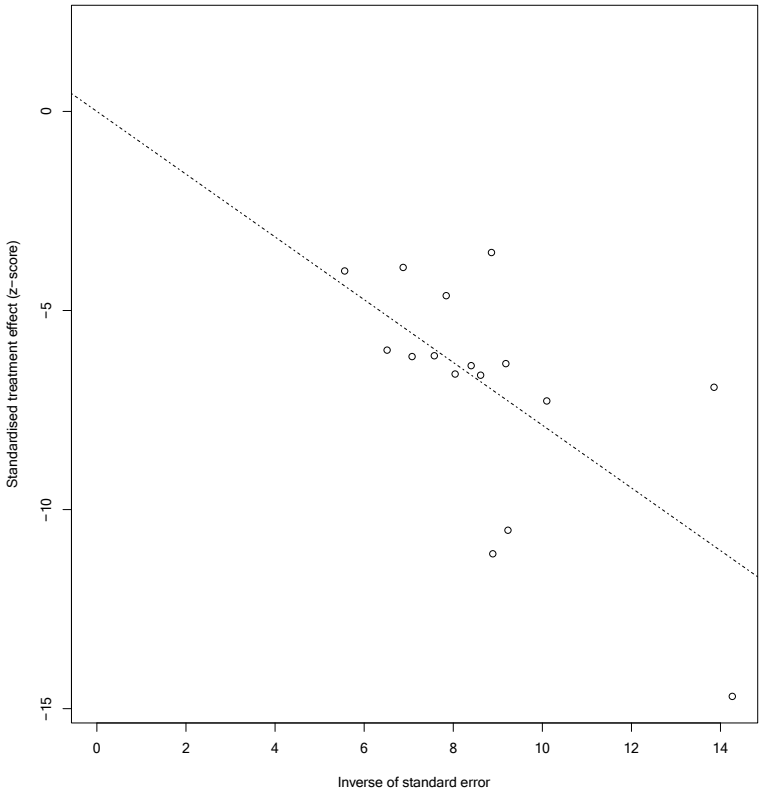


Fig S2d: Egger's test of change in HbA1c in the studies used in the meta-analysis for SGLT-2 inhibitors

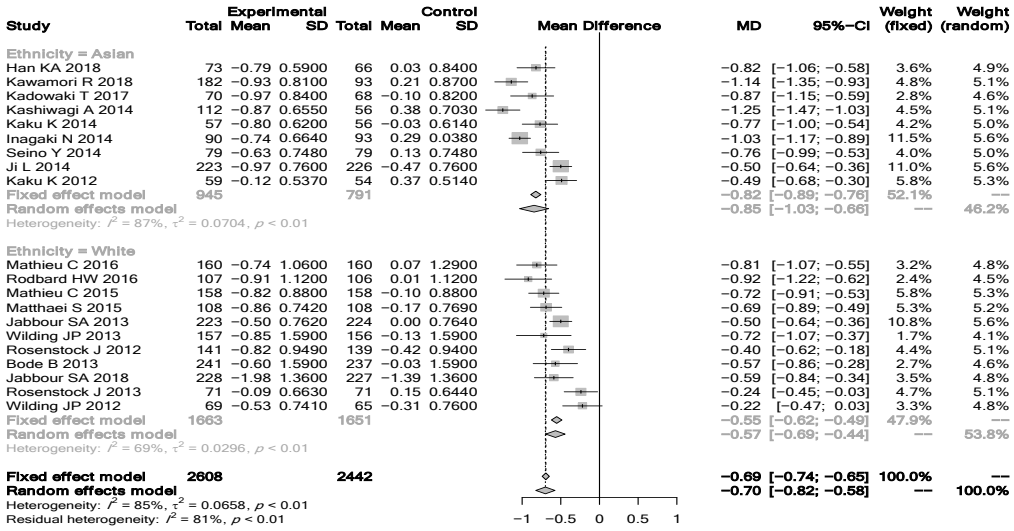


Fig S2e : Forest plot for White and Asian dominant groups for SGLT-2 inhibitors for 12 weeks

GLP-1RA

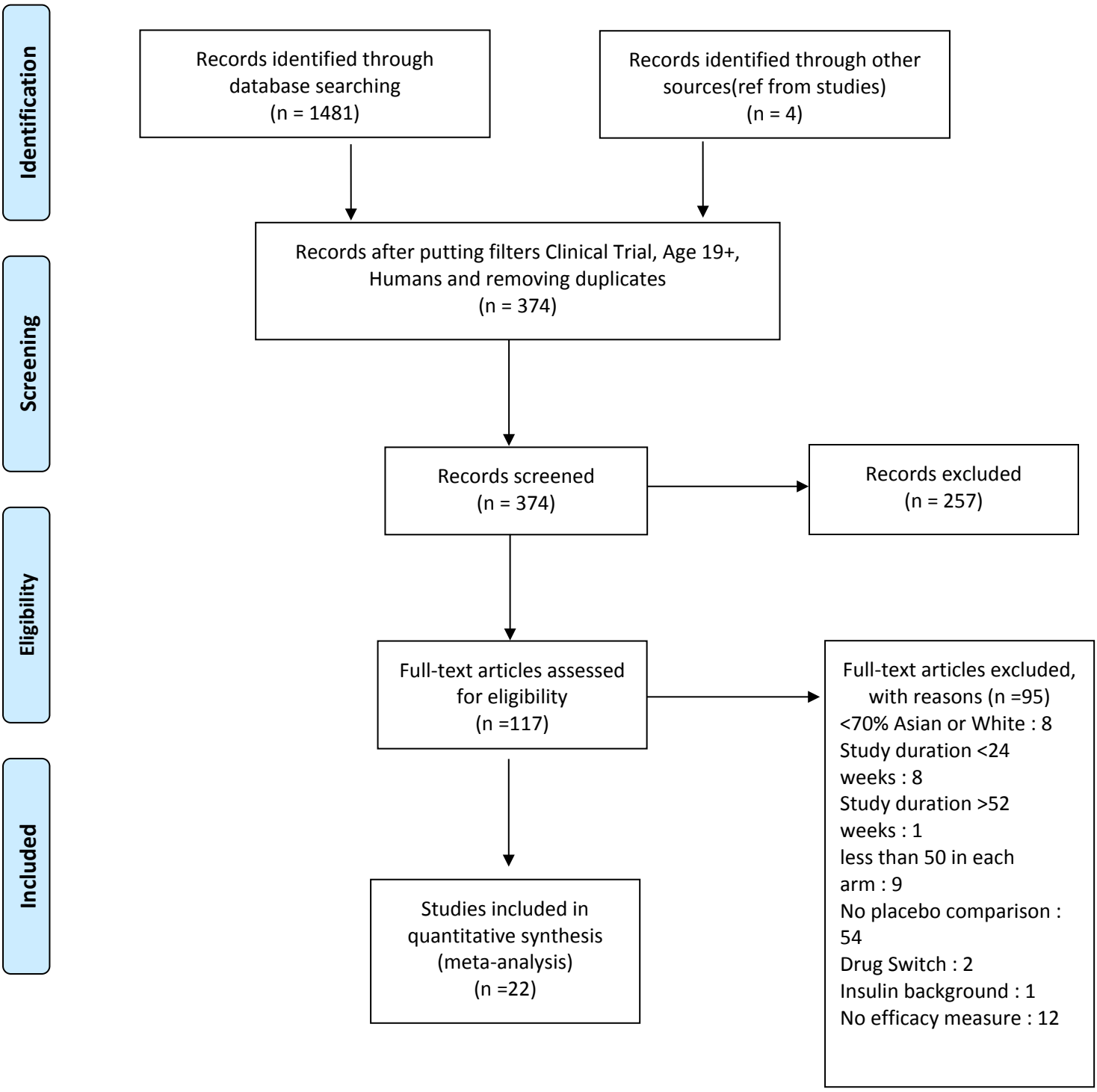


Figure S3a : Selection of GLP-1RA studies included in meta-analysis.

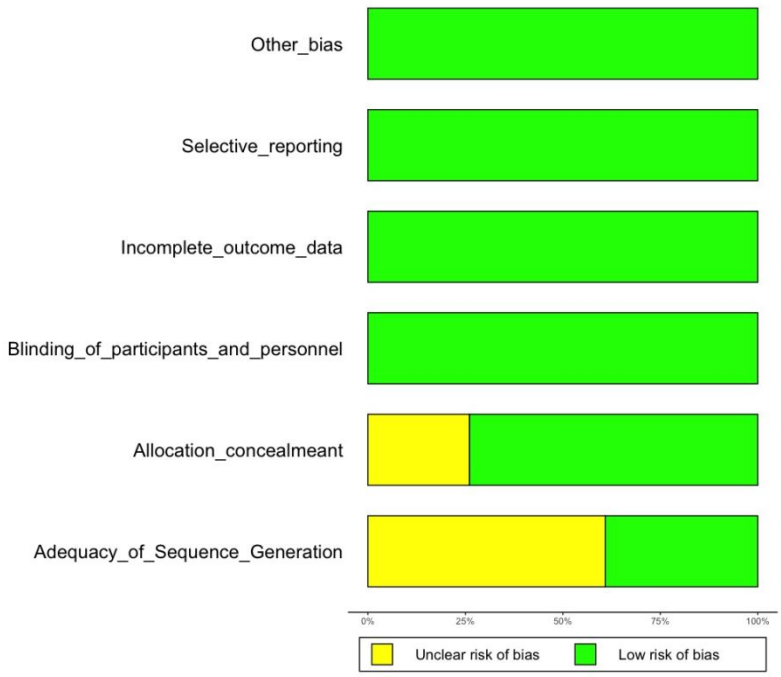


Figure S3b : Risk of Bias of GLP-1RA studies included in meta-analysis.

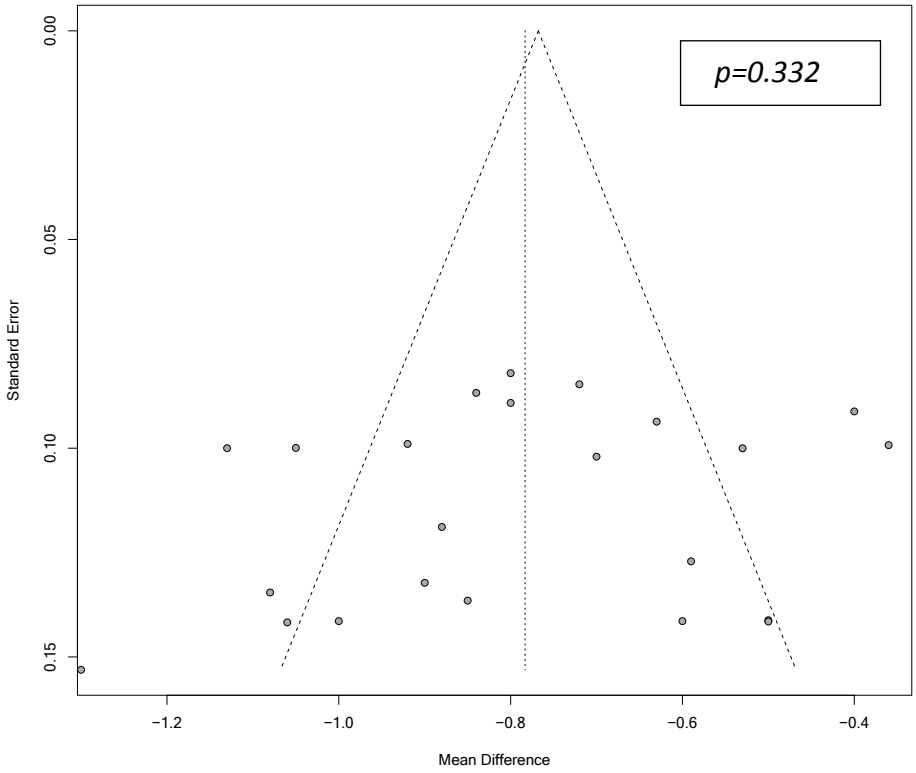


Fig S3c : Funnel plot of change in HbA1c in the studies used in the meta-analysis for GLP-1R

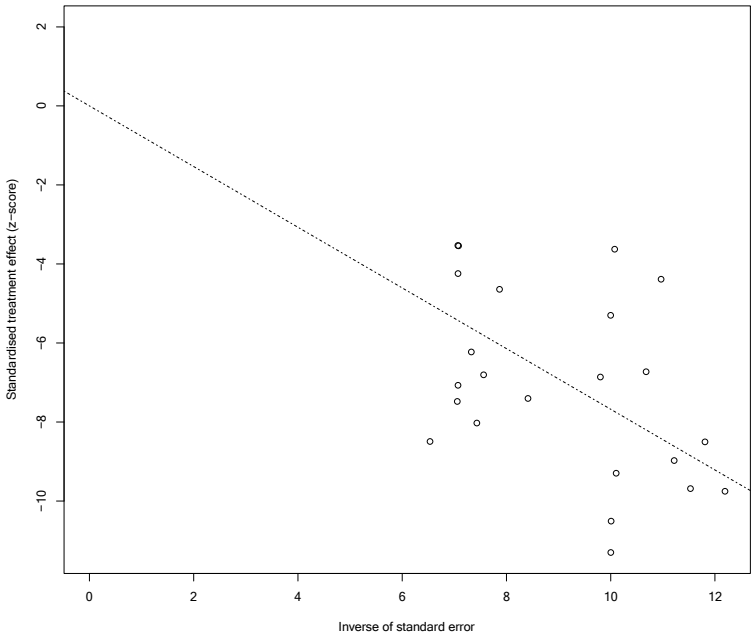


Fig S3d : Egger's test of change in HbA1c in the studies used in the meta-analysis for GLP-1RA

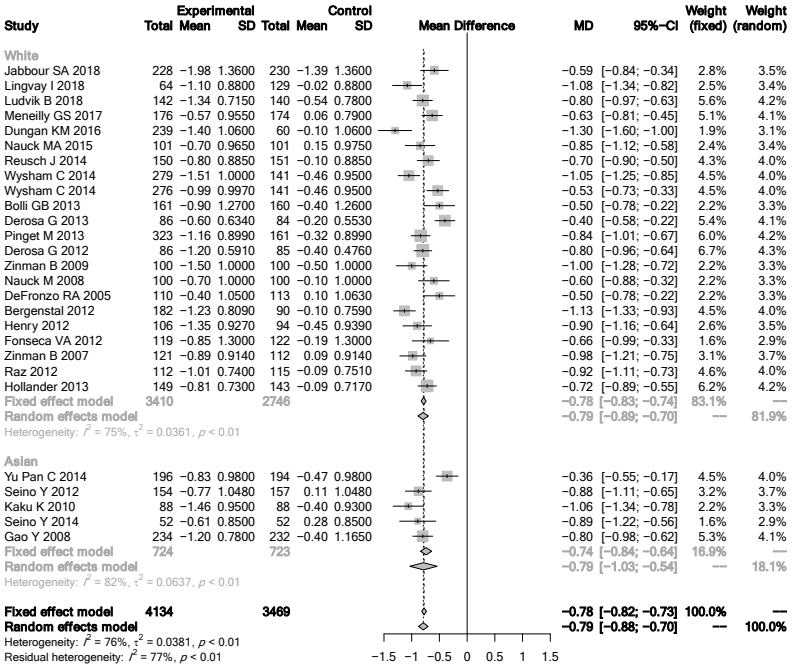
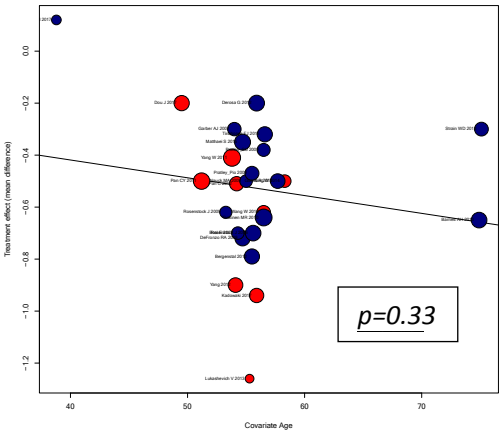


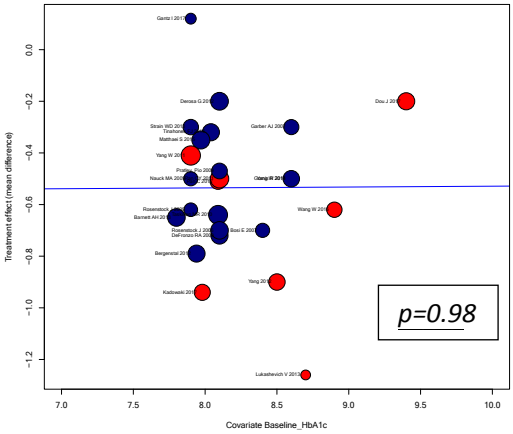
Fig S3e : Forest plot for White and Asian dominant groups for GLP 1RA for 12 weeks

Fig S4 : Univariate meta-regression analysis for HbA1c (DPP-4 inhibitors)

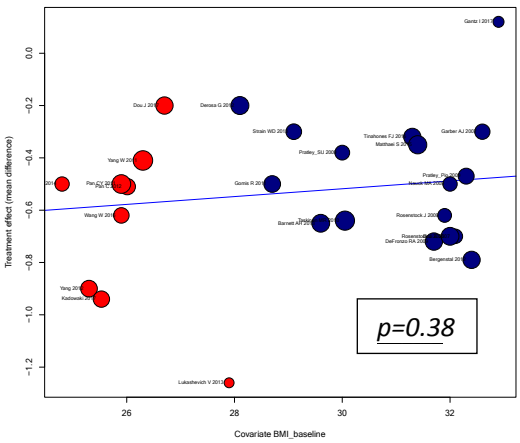
White
Asian



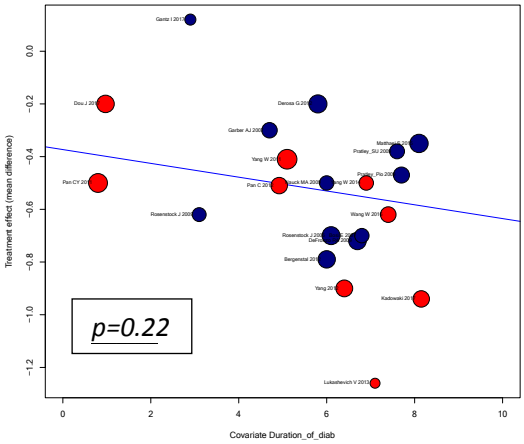
a : Age



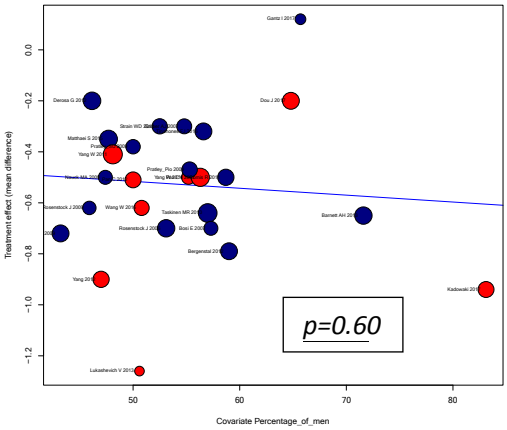
b : Baseline HbA1c



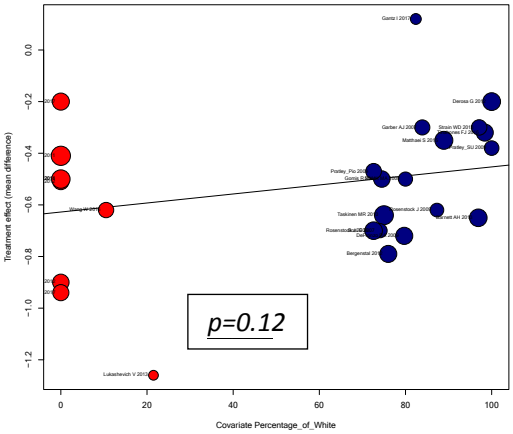
c : BMI baseline



d : Duration of diabetes

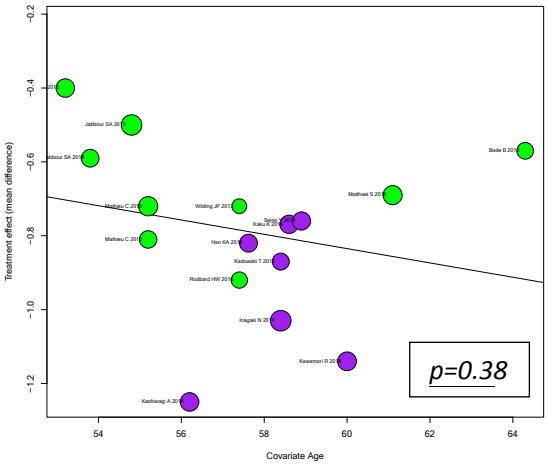


e : Percentage of Men.

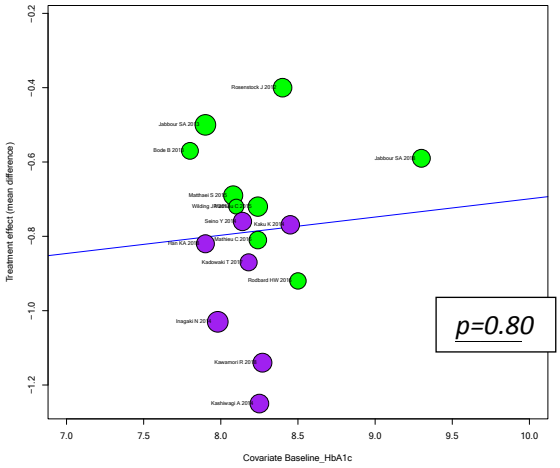


f : Percentage of White

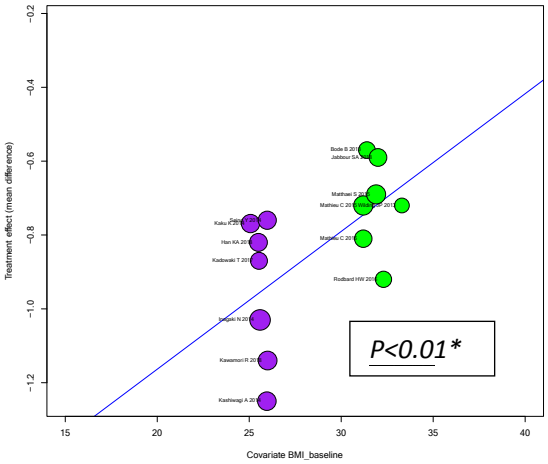
Fig S5 : Univariate meta-regression analysis for HbA1c (SGLT-2 inhibitors)



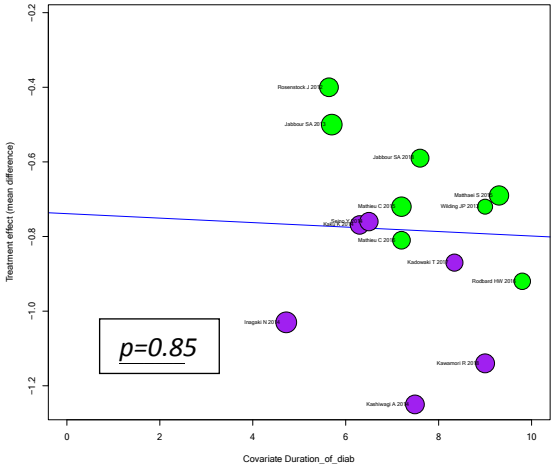
a : Age.



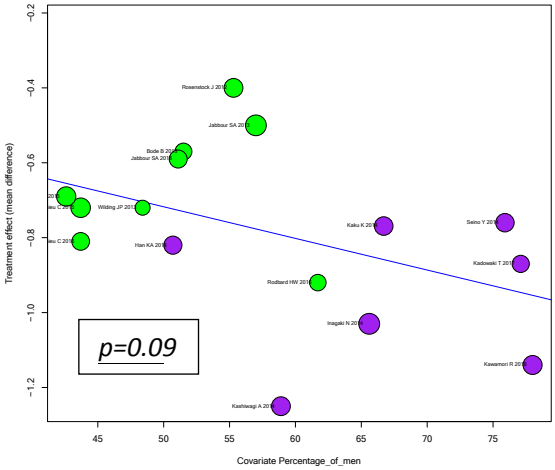
b : Baseline HbA1c



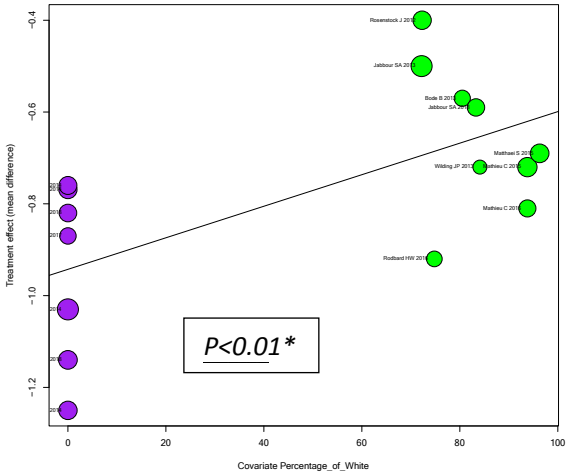
c : BMI baseline



d : Duration of diabetes

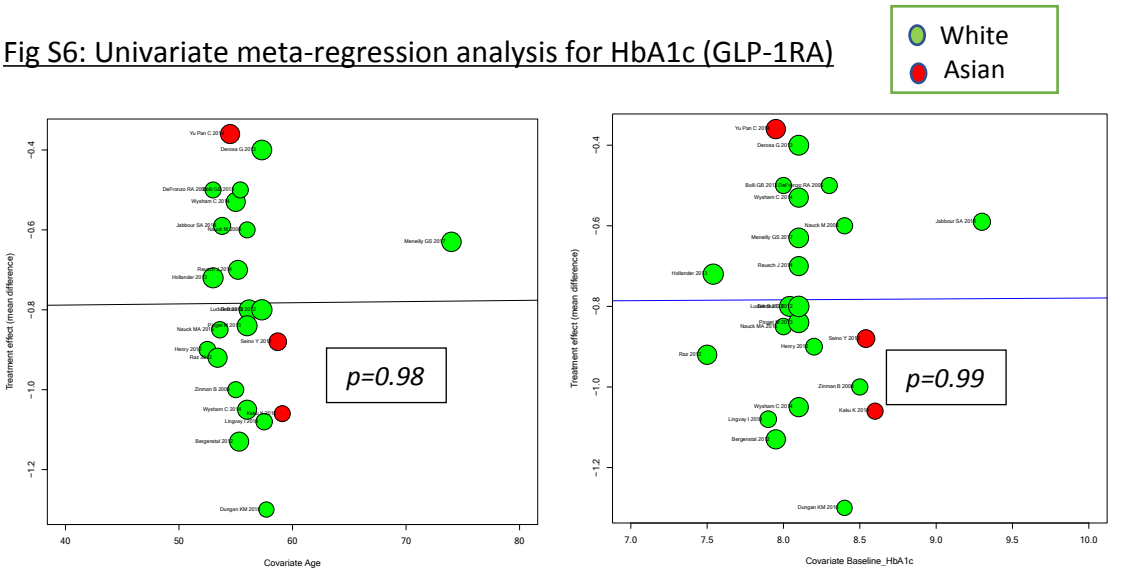


e : Percentage of Men.



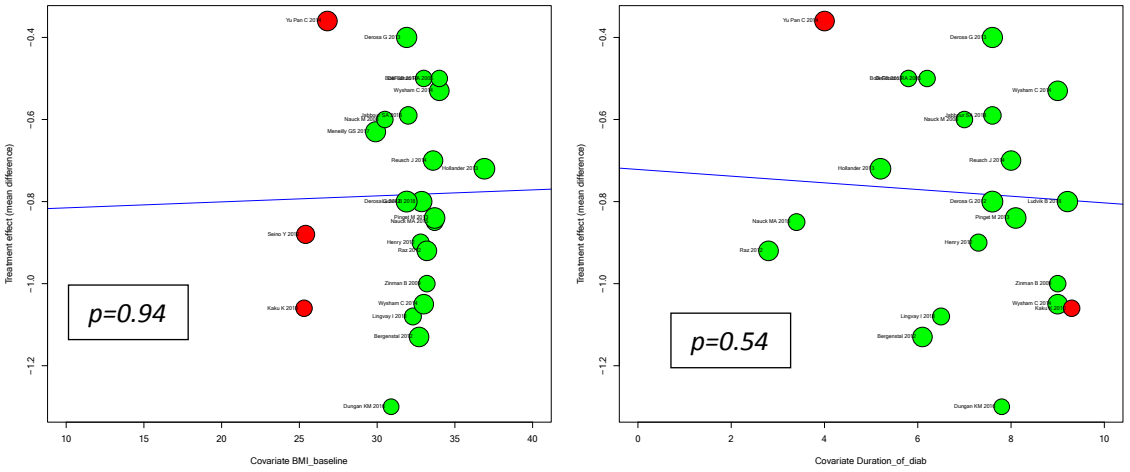
f : Percentage of White

Fig S6: Univariate meta-regression analysis for HbA1c (GLP-1RA)



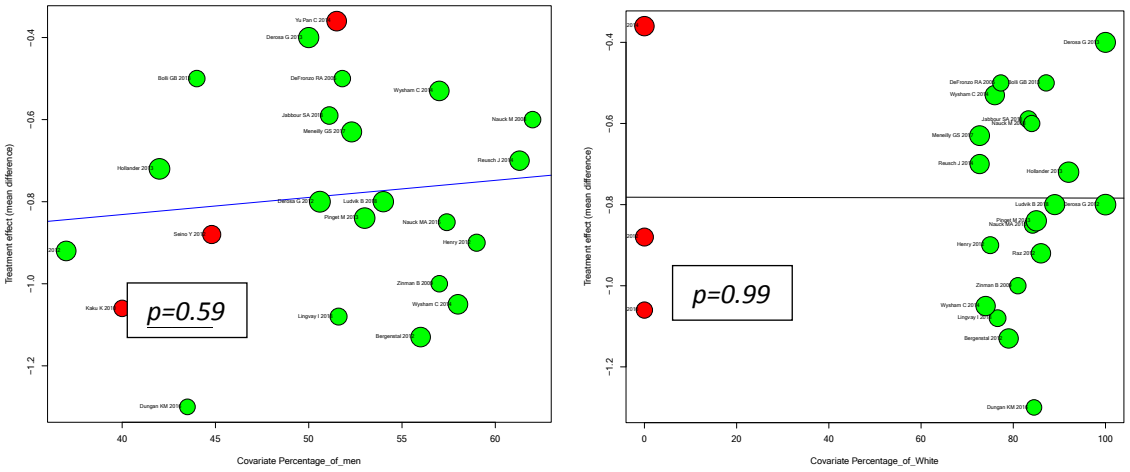
a : Age.

b : Baseline HbA1c



c : BMI baseline

d : Duration of diabetes



e : Percentage of Men.

f : Percentage of White

Author	Year	Adequacy of Sequence Generation	Allocation concealmeant	Blinding of participants and personnel	Incomplete outcome data	Selective reporting	Other bias
Dou J	2017	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Gantz I	2017	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Wang W	2016	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Tinahones FJ	2016	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Matthaei S	2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Yang W	2014	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Lukashevich V	2013	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Barnett AH	2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Strain WD	2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Derosa G	2012	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Pan C	2012	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Pan CY	2011	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Yang W	2011	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Taskinen MR	2010	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Rosenstock J	2009	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
DeFronzo RA	2009	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Nauck MA	2009	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Garber AJ	2007	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Bosi E	2007	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Rosenstock J	2006	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Gomis R	2011	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Yang	2012	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Bergenstal	2012	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Pratley_PG	2009	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Pratley_SU	2009	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Kadowaki	2017	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk

Table S1a : Risk of bias assessment for DPP-4 inhibitors for the included studies

Author	Year	Adequacy of Sequence Generation	Allocation concealmeant	Blinding of participants and personnel	Incomplete outcome data	Selective reporting	Other bias
Han KA	2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kawamori R	2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kadowaki T	2017	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Mathieu C	2016	Unclear	High risk	Low risk	Low risk	Low risk	Low risk
Rodbard HW	2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Mathieu C	2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Matthaei S	2015	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Kashiwagi A	2014	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Kaku K	2014	High risk	Low risk	Low risk	Low risk	Low risk	Low risk
Jabbour SA	2013	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Wilding JP	2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Rosenstock J	2012	High risk	Unclear	Low risk	Low risk	Low risk	Low risk
Inagaki N	2014	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Seino Y	2014	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Bode B	2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Jabbour SA	2018	High risk	Low risk	Low risk	Low risk	Low risk	Low risk

Table S1b : Risk of bias assessment for SGLT-2 inhibitors for the included studies

Author	Year	Adequacy of Sequence Generation	Allocation concealmeant	Blinding of participants and personnel	Incomplete outcome data	Selective reporting	Other bias
Jabbour SA	2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Lingvay I	2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ludvik B	2018	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Meneilly GS	2017	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Dungan KM	2016	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Nauck MA	2015	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Reusch J	2014	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Wysham C	2014	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Yu Pan C	2014	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Bolli GB	2013	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Derosa G	2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Pinget M	2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Seino Y	2012	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Derosa G	2012	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Kaku K	2010	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Zinman B	2009	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Nauck M	2008	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
DeFronzo RA	2005	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Bergenstal	2012	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Henry	2012	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Raz	2012	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Hollander	2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Table S1c : Risk of bias assessment for GLP-1RA for the included studies

DPP-4 inhibitors		
Ethnicity	***Number of studies***	***Mean difference (95% CI)***
Asian	*9*	*-0.62[-0.80,-0.45]*
White	*17*	*-0.49[-0.59,-0.38]*
Test for sub-group differences (p value)		*0.1919*
SGLT-2 inhibitors		
Ethnicity	***Number of studies***	***Mean difference (95% CI)***
Asian	*7*	*-0.96[-1.10,-0.82]*
White	*9*	*-0.64[-0.74,-0.53]*
Test for sub-group differences (p value)		*0.0003*
GLP-1RA		
Ethnicity	***Number of studies***	***Mean difference (95% CI)***
Asian	*3*	*-0.76[-1.19,-0.33]*
White	*20*	*-0.79[-0.89,-0.69]*
Test for sub-group differences (p value)		*0.8957*

Table S2a : Results of sub-group analysis for DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1RA for 24 weeks

DPP-4 inhibitors		
Ethnicity	***Number of studies***	***Mean difference (95% CI)***
Asian	*14*	*-0.73[-0.88,-0.57]*
White	*19*	*-0.49[-0.59,-0.39]*
Test for sub-group differences (p value)		*0.0098*
SGLT-2 inhibitors		
Ethnicity	***Number of studies***	***Mean difference (95% CI)***
Asian	*9*	*-0.85[-1.03,-0.66]*
White	*12*	*-0.57[-0.69,-0.44]*
Test for sub-group differences (p value)		*0.0182*
GLP-1RA		
Ethnicity	***Number of studies***	***Mean difference (95% CI)***
Asian	*5*	*-0.79[-1.03,-0.54]*
White	*22*	*-0.79[-0.89,-0.70]*
Test for sub-group differences (p value)		*0.9657*

Table S2b : Results of sub-group analysis for DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1RA for 12 weeks

DPP-4 inhibitor				
Variable	***Estimate***	***SE***	***CI***	***p value***
Intercept	*-0.15*	*0.40*	*[-0.93,0.64]*	*0.72*
Age	*-0.01*	*0.01*	*[-0.02,0.01]*	*0.33*
Intercept	*-0.63*	*0.08*	*[-0.78,-0.47]*	*<0.01*
Percentage of white	*0*	*0*	*[-0.00,0.00]*	*0.12*
Intercept	*-0.37*	*0.14*	*[-0.64,-0.10]*	*<0.01*
Duration of diabetes	*-0.03*	*0.02*	*[-0.07,0.02]*	*0.22*
Intercept	*-0.38*	*0.29*	*[-0.94,0.18]*	*0.19*
Percentage of men	*0*	*0.01*	*[-0.01,0.01]*	*0.60*
Intercept	*-0.97*	*0.5*	*[-1.95,-0.02]*	*0.05*
BMI baseline	*0.01*	*0.02*	*[-0.02,0.05]*	*0.38*
Intercept	*-0.56*	*1.01*	*[-2.55,1.42]*	*0.58*
HbA1c baseline	*0*	*0.12*	*[-0.24,0.24]*	*0.98*
SGLT-2 inhibitor				
Variable	***Estimate***	***SE***	***CI***	***p value***
Intercept	*0.34*	*1.27*	*[-2.15,2.83]*	*0.79*
Age	*-0.02*	*0.02*	*[-0.06,0.02]*	*0.38*
Intercept	*-0.94*	*0.07*	*[-1.08,-0.81]*	*<0.01*
Percentage of white	*0*	*0*	*[0.00,0.01]*	*<0.01*
Intercept	*-0.74*	*0.26*	*[-1.25,-0.23]*	*<0.01*
Duration of diabetes	*-0.01*	*0.03*	*[-0.07,0.06]*	*0.85*
Intercept	*-0.29*	*0.30*	*[-0.88,0.29]*	*0.33*
Percentage of men	*-0.01*	*0.01*	*[-0.02,0]*	*0.10*
Intercept	*-1.91*	*0.41*	*[-2.72,-1.09]*	*<0.01*
BMI baseline	*0.04*	*0.01*	*[0.01,0.07]*	*0.01*
Intercept	*-1.19*	*1.61*	*[-4.34,1.96]*	*0.46*
HbA1c baseline	*0.05*	*0.20*	*[-0.33,0.43]*	*0.80*
GLP-1RA inhibitor				

Variable	*Estimate*	*SE*	*CI*	*p value*
Intercept	*-0.80*	*0.67*	*[-2.12,0.52]*	*0.23*
Age	*0*	*0.01*	*[-0.02,0.02]*	*0.98*
Intercept	*-0.78*	*0.14*	*[-1.05,-0.51]*	*<0.01*
Percentage of white	*0*	*0*	*[0,0]*	*0.99*
Intercept	*-0.68*	*0.40*	*[-1.78,-0.22]*	*<0.01*
Duration of diabetes	*-0.01*	*0.01*	*[-0.01,0.02]*	*0.59*
Intercept	*-1.00*	*0.38*	*[-1.81,-0.32]*	*<0.01*
Percentage of men	*0.01*	*0.01*	*[-0.01,0.02]*	*0.43*
Intercept	*-0.83*	*0.60*	*[-2.00,0.34]*	*0.17*
BMI baseline	*0*	*0.02*	*[-0.04,0.04]*	*0.94*
Intercept	*-0.80*	*1.16*	*[-3.08,1.48]*	*0.49*
HbA1c baseline	*0*	*0.14*	*[-0.28,0.28]*	*0.99*

Table S3: Univariate meta-regression analysis.

Drug	*Ethnicity*	*Monotherapy*	*Dual therapy*	*Triple therapy*	*Total*
DPP-4i	*Asian*	*3*	*4*	*1*	*8*
	Percent(%)	*37.5*	*50*	*12.5*	
	White	*6*	*10*	*2*	*18*
	Percent(%)	*33.3*	*55.5*	*11.1*	
SGLT 2i	*Asian*	*5*	*2*	*0*	*7*
	Percent(%)	*71.4*	*28.6*	*-*	
	White	*6*	*1*	*2*	*9*
	Percent(%)	*66.6*	*11.1*	*22.2*	
GLP 1RA	*Asian*	*3*	*-*	*-*	*3*
	Percent(%)	*100*	*-*	*-*	
	White	*17*	*3*	*-*	*20*
	Percent(%)	*85*	*15*	*-*	

Table S4: Percentage of Asian or White studies in multiple therapy