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Twenty years of participation of racialised groups in type 2 diabetes randomised clinical trials: a meta-epidemiological review

Rabeeyah Ahmed^{1,2} · Russell J. de Souza^{2,3} · Vincent Li¹ · Laura Banfield⁴ · Sonia S. Anand^{1,2,3}

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Abstract

Aims/hypothesis Type 2 diabetes mellitus prevalence is increasing globally and the greatest burden is borne by racialised people. However, there are concerns that the enrolment of racialised people into RCTs is limited, resulting in a lack of ethnic and racial diversity. This may differ depending whether an RCT is government funded or industry funded. The aim of this study was to review the proportions of racialised and white participants included in large RCTs of type 2 diabetes pharma-cotherapies relative to the disease burden of type 2 diabetes in these groups.

Methods The Ovid MEDLINE database was searched from 1 January 2000 to 31 December 2020. English language reports of RCTs of type 2 diabetes pharmacotherapies published in select medical journals were included. Studies were included in this review if they had a sample size of at least 100 participants and all participants were adults with type 2 diabetes. Industry-funded trials must have recruited participants from at least two countries. Government-funded trials were not held to the same standard because they are typically conducted in a single country. Data including the numbers and proportions of participants by ethnicity and race were extracted from trial reports. The participants in each trial by the percentage of white and racialised participants with type 2 diabetes, respectively, for the regions of recruitment. A random-effects meta-analysis was used to generate the pooled PPRs and 95% CIs across study types. A PPR <0.80 indicates under-representation and a PPR >1.20 indicates over-representation. Risk of bias assessments were not conducted for this study as the objective was to examine recruitment of racialised and white participants rather than evaluate the trustworthiness of clinical trial outcomes.

Results A total of 83 trials were included, involving 283,122 participants, of which 15 were government-funded and 68 were industry-funded trials. In government-funded trials, the PPR for white participants was 1.11 (95% CI 0.99, 1.24) and the PPR for racialised participants was 0.72 (95% CI 0.60, 0.86). In industry-funded trials, the PPR for white participants was 1.95 (95% CI 1.74, 2.18) and the PPR for racialised participants was 0.36 (95% CI 0.32, 0.42). The limitations of this study include the reliance on investigator-reported ethnicity and race to classify participants as 'white' or 'racialised', the use of estimates for type 2 diabetes prevalence and demographic data, and the high levels of heterogeneity of pooled estimates. However, despite these limitations, the results were consistent with respect to direction.

Conclusions/interpretation Racialised participants are under-represented in government- and industry-funded type 2 diabetes trials. Strategies to improve recruitment and enrolment of racialised participants into RCTs should be developed.

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Extended author information available on the last page of the article

Research in context

What is already known about this subject?

 The burden of type 2 diabetes mellitus is disproportionately higher in racialised groups than in white individuals. However, racialised people are generally under-represented in type 2 diabetes RCTs

What is the key question?

What is the representation of racialised participants in type 2 diabetes RCTs relative to their disease burden?

What are the new findings?

- Racialised participants are under-represented in industry- and government-funded type 2 diabetes trials relative to their disease burden
- The greatest disparity in ethnic and racial diversity of participants is observed in industry-funded type 2 diabetes trials

How might this impact on clinical practice in the foreseeable future?

Our study suggests that deliberate strategies to improve the recruitment and enrolment of racialised participants
into industry- and government-funded RCTs should be developed to increase the generalisability of trial findings
and uptake of guideline recommendations among racialised groups with the highest disease burden

Abbreviations

DPP-4Dipeptidyl peptidase-4GLP-1Glucagon-like peptide-1NIHNational Institutes of HealthPPRParticipation-to-prevalence ratioSGLT-2Sodium-glucose co-transporter 2

Introduction

The burden of type 2 diabetes is disproportionately higher in non-white ethnic and racial groups than in white individuals [1]. However, individuals from non-white ethnic or racial groups, herein referred to as racialised people, are generally under-represented in RCTs, which by design produce the most reliable evidence regarding the efficacy and safety of medical therapies [1, 2]. As such, RCTs inform treatment recommendations in guidelines. Underrepresentation of racialised people in RCTs can limit the generalisability of the trial findings and uptake of guideline recommendations among racialised groups with the highest disease burden [3].

In the USA, the National Institutes of Health (NIH) provides guidelines for the inclusion of racialised groups in the clinical research they fund, a measure taken to improve the generalisability of research findings [4]. Industryfunded trials do not have the same requirements as the NIH, nor do many other government-established funding agencies [5–8]. For example, Canada and Australia do not have guidelines for the recruitment of racialised populations into clinical trials. The 'Guidance for industry: standards for clinical trials in type 2 diabetes in Canada' (2007) document does not mention the terms 'race' or 'ethnicity,' nor does it provide guidelines on participant recruitment [7]. Similarly, the Government of Australia's guidelines for clinical trials do not include any regulations pertaining to recruitment of racialised groups [8]. In the UK, there is also no requirement to record and report ethnicity or race in research studies [5].

The NIH requirements are guided by the Public Health Service Act sec. 492B, 42 U.S.C. sec. 289a-2 and are designed to enhance the inclusion of minority groups in NIH-funded research [4]. Efforts to increase representation of racialised groups in RCTs have been made internationally as well. For example, some research institutions in the UK are taking measures to address the lack of ethnic participant recruitment guidelines for clinical trials. In 2018, the UK's National Institute for Health and Care Research (NIHR) launched the INCLUDE project, designed to enhance the diversity of research participants in clinical studies [5].

In this study we conducted a meta-epidemiological review of Phase II–IV RCTs published between 1 January 2000 and 31 December 2020 that tested at least one type 2 diabetes pharmacotherapy and investigated (1) the participation of racialised individuals relative to the disease burden of type 2 diabetes in large RCTs in which type 2 diabetes therapies were evaluated and (2) the differences in participation of racialised and white individuals between industry- and government-funded trials.

Methods

This meta-epidemiological review was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines. This study was registered on Open Science Framework (registration no. f59mk; https://osf.io/f59mk).

Data sources and searches Guided by a clinical expert, a broad search strategy with keywords related to type 2 diabetes RCTs was developed (electronic supplementary material [ESM] Table 1). Initially, the search was limited to trials published in the New England Journal of Medicine, The Lancet, JAMA, The BMJ and Annals of Internal Medicine. These journals were selected because they have a history of being targeted for publication of large, high-impact, multicountry trials of type 2 diabetes drugs. This criterion was kept for industry-funded trials; however, it was expanded for government-funded trials to include publications from five specialty journals (Diabetes Care, Circulation, Lancet Diabetes and Endocrinology, JAMA Internal Medicine, JAMA Ophthal*mology*), as we recognise that discipline-specific journals are more likely to publish smaller-scale government-funded trials that recruit fewer participants and/or are conducted in a single country. A complete list of study selection criteria can be found in ESM Table 2. The Ovid MEDLINE database was searched from 1 January 2000 to 31 December 2020 to identify relevant studies. The year 2000 was selected as a starting point because most of the oral hypoglycaemic agents for diabetes (metformin, glimepiride, rosiglitazone) were approved in the mid to late 1990s. As such, their use in clinical trials became more widespread in 2000 and beyond. The endpoint of our time frame was selected to capture trends before the COVID-19 pandemic. The decade-by-decade analysis presents an opportunity to revisit the data and examine trends in 10-year increments. Ovid MEDLINE was used because the identified journals are all indexed in the database, which eliminated the need for multiple database searching. Full-text screening was completed by two reviewers (RA and RJdS) independently and in duplicate based on predetermined study selection criteria (ESM Fig. 1). Covidence (https://www. covidence.org/) was used for data management.

Data extraction Three reviewers (authors RA and VL, with JW) independently extracted the following information from published studies: title, year of publication, journal, primary funding source, pharmacotherapy intervention, total number of participants, country or region of greatest participant recruitment, and numbers of white and racialised participants. For this review, participants were categorised as 'racialised' if they belonged to any race or ethnicity that was not specifically described as 'white' or 'Caucasian' by the investigators.

Discrepancies were cross-checked and, where necessary, were resolved by discussion with the senior author (SSA). The resource ClinicalTrials.gov and other publicly available web resources were consulted to obtain any missing information that was not in the main articles or supplementary materials.

Outcome measures There were two outcomes of interest for this meta-analysis: the proportion of white participants in government- and industry-funded trials relative to the type 2 diabetes disease burden in the population, and the proportion of racialised participants in government- and industry-funded trials relative to the type 2 diabetes disease burden in the population.

Statistical analysis The participation-to-prevalence ratio (PPR) metric was used to estimate the representation of white participants and the representation of racialised participants compared with their respective disease burden, separately in industry- and government-funded trials. The PPR for white participants and racialised participants in each trial was calculated using the respective formulas below.

PPR =	Percentage of white participants in the trial (%)
11K –	Percentage of white people among the diseased population (%)

 $PPR = \frac{Percentage of racialised participants in the trial (%)}{Percentage of racialised people among the diseased population (%)}$

A PPR of 1 suggests that racialised or white people make up the same proportion of participants in the trial as the proportion of racialised or white people, respectively, among the diseased population in the countries from which a trial recruited. For example, if 80% of participants in a trial are racialised and 80% of the cases of diabetes in the country or region occur in racialised groups, the PPR would be 1. The underlying goal for equity should be for the proportion of participants recruited by ethnicity or race to be similar to the disease burden faced by those ethnic or racial groups in that country or region. For this review, a group was considered to be under-represented when the PPR was <0.80 and overrepresented when the PPR was >1.20. These decision points are consistent with a 2020 study evaluating the participation of women in cardiovascular RCTs [9].

The numerator for the PPR was known for each trial. The denominator, however, was calculated for each trial using prevalence and demographic data. A detailed explanation of PPR calculations is provided in ESM Methods. A list of estimates used for the PPR calculations is provided in ESM Table 3.

Once the PPRs for white and racialised people were calculated for each trial, a random-effects meta-analysis was used to pool the individual-study PPRs and compute the overall 95% CIs for the pooled PPRs. A randomeffects model was used for this analysis because it provides appropriately wider CIs and study weights in the presence of heterogeneity, which we expected to see across varying recruitment approaches, trial conditions and countries of conduct. Under this model, it can be assumed that the true PPR may differ according to the setting, country or type of trial.

We conducted a sensitivity analysis by varying our worldwide population proportion estimates (11.7% white and 88.3% racialised). These estimates were used when a trial that recruited from three or more regions did not provide data on how many participants were recruited from each country/region. We systematically altered the proportion of racialised people to values from 80% to 90% in increments of 2.5%, and of white participants from 10% to 20% in increments of 2.5%.

All study-specific PPR estimates were calculated in Microsoft Excel and the pooled PPRs across studies and 95% CIs were calculated using Review Manager version 5.4 (RevMan; The Cochrane Collaboration, London, UK).

Results

Of the 512 records that were assessed for eligibility, 83 RCTs with either industry funding or government funding with a total of 283,122 participants were included (ESM Fig. 1). Three other studies with dual funding were included in a sensitivity analysis. The RCTs that were excluded after full-text review are listed in ESM Table 4. Of the 83 trials included in the review, 15 (18.1%) were government-funded [10–24], 68 (81.9%) were sponsored by industry [25-92] and 49 (59.0%) were published between the years 2011 and 2020. The proportion of racialised participants in this set of trials increased significantly from 10.7% in 2000-2005 to 23.6% in 2006–2010 and remained relatively constant between 2006 and 2020. Over one-third of the studies in the review (42.2%) recruited the greatest number of participants from the USA. The most common pharmacotherapy interventions were from the glucagon-like peptide-1 (GLP-1) receptor agonist, sodium-glucose co-transporter 2 (SGLT-2) inhibitor and dipeptidyl peptidase-4 (DPP-4) inhibitor classes. The percentage of racialised participants across all trials was 23.8%. Government-funded trials had a higher overall percentage of racialised participants (26.0%) than industry-funded studies (23.4%) (Table 1). The list of included RCTs is provided in Table 2.

The pooled PPR for white participants was 1.11 (95% CI 0.99, 1.24) for government-funded trials, consistent with proportional representation, and 1.95 (95% CI 1.74, 2.18) for industry-funded trials, consistent with over-representation. The PPR for racialised people was 0.72 (95% CI 0.60,

0.86) for government-funded trials and 0.36 (95% CI 0.32, 0.42) for industry-funded trials, both of which are consistent with under-representation (Fig. 1). Figures 2, 3, 4 and 5 show detailed breakdowns of the pooled PPRs.

The pooled meta-analytic estimates had high levels of heterogeneity ($l^2>90\%$). However, despite this, the results were directionally consistent. Only seven of 68 industry-funded trials had a PPR <1 for white people and a PPR >1 for racialised people [29, 53, 57, 60, 78, 79, 89], and these carried approximately 11.1% of the weight in the pooled estimates. Similarly, only four of 15 government-funded trials had a PPR <1 for white people and a PPR >1 for racialised people [18–20, 23], and these carried approximately 20.6% of the weight in the pooled estimates.

Sensitivity analysis Twelve industry-funded trials that recruited from three or more regions did not provide data on how many participants were recruited from each country or region (indicated by 'Worldwide' in Table 2). For these trials, worldwide estimates of the proportions of white and racialised people were used (11.7% and 88.3%, respectively) (ESM Methods). A series of sensitivity analyses were conducted in which the estimated proportions of white and racialised people were varied for these trials. The proportion of white participants was varied from 80% to 90% and of racialised participants from 10% to 20%. This did not result in appreciably different estimates from the main analyses. The full data for these sensitivity analyses are provided in ESM Appendix 1 (ESM Figs 2–5).

In addition to the 83 trials that were included in the main analysis, three trials that were funded by both government and industry sources were included in a separate sensitivity analysis [93–95]. Because a primary source of funding for these trials could not be determined with confidence, a sensitivity analysis was conducted to determine the effect that the trials would have on the pooled PPRs had they been included and categorised as industry or government funded. In one analysis both trials were included as industry-funded studies and in a second analysis both were included as government-funded trials. The results were not appreciably different from the main analyses (see ESM Appendix 2, ESM Figs 6 and 7).

Discussion

Type 2 diabetes disproportionately affects racialised people worldwide [96]. This meta-epidemiological review shows that white individuals are over-enrolled and racialised individuals are under-enrolled in type 2 diabetes RCTs. Government-funded type 2 diabetes trials tend to have better representation of racialised participants than industry-funded trials.

Table 1 Baseline characteristics of the 83 RCTs included in the meta-epidemiological review

Category	Number of trials, N (%)	White participants, N (%)	Racialised participants, N (%)		
Overall	83	215,840	67,282		
Sponsor					
Government	15 (18.1)	25,721 (74.0)	9059 (26.0)		
Industry	68 (81.9)	190,119 (76.6)	58,223 (23.4)		
Publication years					
2000–2005	11 (13.3)	21,323 (89.3)	2562 (10.7)		
2006–2010	23 (27.7)	28,210 (76.4)	8738 (23.6)		
2011–2015	26 (31.3)	61,157 (72.9)	22,763 (27.1)		
2016–2020	23 (27.7)	105,150 (76.0)	33,219 (24.0)		
Trial size					
Quartile 1 (100-500)	20 (24.1)	3987 (69.5)	1747 (30.5)		
Quartile 2 (501-1500)	24 (28.9)	14,802 (81.7)	3313 (18.3)		
Quartile 3 (1501-5000)	18 (21.7)	39,433 (77.8)	11,251 (22.2)		
Quartile 4 (>5000)	21 (25.3)	157,618 (75.6)	50,971 (24.4)		
Region of greatest recruitment					
Global	12 (14.5)	7887 (80.8)	1872 (19.2)		
Europe	13 (15.7)	45,004 (80.4)	10,976 (19.6)		
North America	5 (6.0)	5333 (75.4)	1743 (24.6)		
North America and Europe	4 (4.8)	2057 (88.5)	266 (11.5)		
North America and South America	1 (1.2)	480 (87.9)	66 (12.1)		
USA	35 (42.2)	129,911 (73.5)	46,769 (26.5)		
UK	2 (2.4)	3329 (90.9)	335 (9.1)		
Australia	1 (1.2)	9093 (92.8)	702 (7.2)		
China	1 (1.2)	0 (0)	304 (100)		
Argentina	1 (1.2)	7498 (75.7)	2403 (24.3)		
Qatar	1 (1.2)	16 (6.9)	215 (93.1)		
Greece	1 (1.2)	100 (100)	0 (0)		
Canada	1 (1.2)	152 (30.3)	350 (69.7)		
Europe and USA	1 (1.2)	426 (91.8)	38 (8.2)		
Bulgaria	1 (1.2)	691 (84.2)	130 (15.8)		
Russian Federation	1 (1.2)	527 (94.6)	30 (5.4)		
Serbia	1 (1.2)	2119 (87.6)	299 (12.4)		
Slovakia	1 (1.2)	1217 (60.8)	784 (39.2)		
Pharmacotherapy intervention					
GLP-1 receptor agonists	16 (19.3)	45,137 (20.9)	12,834 (19.1)		
SGLT-2 inhibitors	7 (8.4)	38,089 (17.7)	10,226 (15.2)		
DPP-4 inhibitors	6 (7.2)	32,371 (15.0)	11,670 (17.3)		
Aliskiren	1 (1.2)	4850 (2.2)	3711 (5.5)		
Bardoxolone methyl	1 (1.2)	1694 (0.8)	491 (0.7)		
Ticagrelor	1 (1.2)	13,696 (6.4)	5524 (8.2)		
Aleglitazar	1 (1.2)	4818 (2.2)	2408 (3.6)		
Atrasentan	1 (1.2)	2110 (1.0)	1558 (2.3)		
Apabetalone	1 (1.2)	2119 (1.0)	299 (0.4)		
Finerenone	1 (1.2)	691 (0.3)	130 (0.2)		
Darbepoetin alfa	1 (1.2)	2570 (1.2)	1468 (2.2)		
Rimonabant	1 (1.2)	925 (0.4)	120 (0.2)		
Angiotensin receptor blockers	4 (4.8)	7587 (3.5)	868 (1.3)		
Fibrates	2 (2.4)	9493 (4.4)	720 (1.1)		
Atorvastatin	1 (1.2)	2676 (1.2)	162 (0.2)		
Salicylates	2 (2.4)	206 (0.1)	188 (0.3)		
Metformin and glipizide	2 (2.4) 1 (1.2)	0 (0)	304 (0.5)		
Insulin	7 (8.4)	8555 (4.0)	2559 (3.8)		
Thiazolidinediones	2 (2.4)	5264 (2.4)	74 (0.1)		
Metformin					
wiedomini	1 (1.2)	152 (0.1)	350 (0.5)		

The finding that government-funded trials recruit more racialised participants may reflect adherence to the more stringent conditions associated with funding from government bodies. For example, the NIH emphasises the inclusion and appropriate representation of minority groups in clinical research [4]. This measure attempts to ensure that racialised populations are proportionately represented in NIH-funded clinical research and that research findings are generalisable across all ethnic groups. Industry-funded trials do not have the same requirements as some government bodies and therefore decisions regarding who to enrol and in what proportion (i.e. by ethnicity, race and sex) are influenced entirely by the trial sponsors, steering committees and research staff. The under-representation of racialised participants limits the ability to generalise efficacy and safety outcomes to racialised people and may limit the uptake of this evidence by racialised communities, which adds to the disadvantages they may face.

For industry-funded trials, white participants were over-represented relative to their disease burden (Fig. 4). However, the pooled PPR estimate was heterogeneous. For example, some studies had PPR values that were notably higher than the others [35, 37, 54, 55, 62, 64, 66, 70, 80, 82, 84, 92]. This is because worldwide estimates were used for both type 2 diabetes prevalence and demographic data for these trials. Prevalence estimates were obtained from Saeedi et al [97] and are listed in ESM Table 3. Although the PPRs for white participants in industry-funded trials may be overestimates, the results of our sensitivity analyses do not suggest any substantial overestimation (ESM Appendix 1). This is because the proportion of racialised participants in these trials was relatively small and therefore varying the worldwide proportion estimates for racialised participants did not greatly affect the pooled PPR. Greater variance was observed among the different proportions of white participants in the trials. Overall, the effects of varying worldwide proportions of both white and racialised people on the PPRs were limited. This is because worldwide estimates were needed for only 12 of the 68 industry-funded trials and the participants in all 12 trials comprised only 3.8% of the total participants across the industry-funded trials in this review.

Racialised participants were under-represented in industry-funded trials relative to their disease burden (Fig. 5). Seven trials [29, 53, 57, 60, 78, 79, 89], however, had a PPR >1, with racialised PPRs of 1.85, 1.47, 1.18, 1.04, 1.15, 1.06, 1.67, respectively. Six of these trials recruited over 1500 participants from at least 24 countries including regions of North America, Europe, South America, Asia and Africa. Future industry-funded trials should consider enrolling participants from diverse communities and regions of the world, especially when the disease burden is higher than in white European-origin individuals.

There are several potential explanations for the patterns of over-representation of white participants and under-representation of racialised participants in government- and industryfunded RCTs. First, inclusion and exclusion criteria for RCTs may favour enrolling white over racialised participants. For example, in the USA, the ability to read and speak English is often an inclusion criterion for clinical trials, which can disproportionately impact the participation of racialised groups. Second, recruitment processes can affect the overall diversity of participants in RCTs. For instance, specialty clinics and hospitals where research is taking place may be located in areas with lower proportions of racialised people. Third, limited screening of racialised people for enrolment may occur because of implicit biases and/or social or medical reasons that make participation difficult for these groups. Fourth, mistrust and fear of medical institutions because of historical mistreatment of racialised groups may result in a lack of willingness of racialised people to participate in clinical trials. Fifth, racialised groups may not enrol because of language barriers, cultural practices or related contextual factors that limit their participation, including socioeconomic disadvantages. Finally, logistical barriers may exist such as inflexible work schedules and additional costs associated with participating in research studies, such as transport costs for attending study visits [98].

Furthermore, a lack of diversity among principal investigators, local investigators and study staff in some RCTs may also be related to lower enrolment rates for racialised participants [98]. For example, in an NIH study on the diversity of the NIHfunded workforce, it was found that 71.9% of principal investigators on NIH-funded research project grants were white [99]. Ethnically or racially diverse representation among study staff might increase the trust of participants from racialised communities and improve communication [98]. Additionally, industryfunded trials might benefit from having racialised participant recruitment guidelines similar to those that exist for the NIH. Regulatory bodies could indicate that proportional representation of participants affected by the disease of interest by ethnicity is strongly recommended or mandatory so that industry trial leaders more carefully consider who and from where to recruit within a given country or region. In future work, reviews of the recruitment of racialised groups should be carried out for trials conducted within single countries to assess countryspecific trends. These reviews could guide clinical practice and be used to establish recruitment standards that are reasonable given the prevalence of type 2 diabetes and demographics in a given country. Future studies should also be conducted to analyse racialised participant recruitment trends in RCTs on other health conditions such as hypertension and stroke, which are known to be common in racialised communities.

Table 2 List of RCTs included in the meta-epidemiological review

Publication			Pharmacotherapy intervention	Number of participants	White participants N (%)	Racialised participants N (%)	Country/region of greatest participant recruitment		
ACCORD [10]	2008	NEJM	Intense (HbA _{1c} <6%, <42 mmol/mol) vs standard therapy	10,251	6604 (64.4)	3647 (35.6)	USA		
BARI 2D [11]	2009	NEJM	Insulin-providing drugs vs insulin-sensitising drugs	2368	1561 (65.9)	807 (34.1)	USA		
CARDS [12]	2004	Lancet	Atorvastatin	2838	2676 (94.3)	162 (5.7)	UK		
FIELD [13]	2005	Lancet	Fenofibrate	9795	9093 (92.8)	702 (7.2)	Australia		
GRADE [14]	2019	Diabetes Care	Glimepiride, sitagliptin, liraglutide, insulin glargine	5047	3314 (65.7)	1733 (34.3)	USA		
Kadoglou et al [15]	2007	Diabetes Care	Rosiglitazone	100	100 (100)	0 (0)	Greece		
Levin et al [16]	2000	Diabetes Care	Intensive vs standard treatment (insulin)	153	99 (64.7)	54 (35.3)	USA		
Meyer et al [17]	2010	Diabetes Care	Gliusine vs insulin	180	136 (75.6)	44 (24.4)	USA		
MiTy [18]	2020	Lancet Diabetes and Endocrinology	Metformin	502	152 (30.3)	350 (69.7)	Canada		
SPREAD-DIMCAD [19]	2013	Diabetes Care	Glizipide plus metformin placebo or metformin plus glipizide placebo	304	0 (0)	304 (100)	China		
The Qatar Study [20]	2017	Diabetes Care	Exenatide, pioglita- zone, insulin therapy	231 ^a	16 (6.9) ^b	215 (93.1)	Qatar		
TINSAL-T2D [21]	2010	Annals of Internal Medicine	Salsalate	108	55 (50.9)	53 (49.1)	USA		
FINSAL-T2D II [22]	2013	Annals of Internal Medicine	Salsalate	286	151 (52.8)	135 (47.2)	USA		
UKPDS 57 [23]	2002	Diabetes Care	Insulin vs diet control	826	653 (79.1)	173 (20.9)	UK		
VADT [24]	2009	NEJM	Insulin, glimepiride, rosiglitazone, met- formin	1791	1111 (62)	680 (38)	USA		
1860-LIRA-DPP-4 [25]	2010	Lancet	Liraglutide vs sitag- liptin	665	576 (86.6)	89 (13.4)	North America and Europe		
4-T Study Group [26]	2007	NEJM	Biphasic vs prandial vs basal insulin	708	653 (92.2)	55 (7.8)	Europe		
ADOPT [27]	2006	NEJM	Rosiglitazone vs met- formin vs glyburide (glibenclamide)	4351°	3847 (88.4)	504 (11.6)	North America		
AleCardio [28]	2014	JAMA	Aleglitazar	7226	4818 (66.7)	2408 (33.3)	USA		
ALTITUDE [29]	2012	NEJM	Aliskiren	8561	4850 (56.7)	3711 (43.3)	Europe		
ARTS-DN [30]	2015	JAMA	Finerenone	821	691 (84.2)	130 (15.8)	Bulgaria		
AVOID [31]	2008	NEJM	Aliskiren, losartan	599	520 (86.8)	79 (13.2)	North America and Europe		
AWARD-4 [32]	2015	Lancet	Dutaglutide, glargine	884	697 (78.8)	187 (21.2)	USA		
AWARD-6 [33]	2014	Lancet	Dulaglutide vs lira- glutide	599	515 (86)	84 (14)	USA		
Bailey et al [34]	2010	Lancet	Dapagliflozin	546	480 (87.9)	66 (12.1)	North America and South America		
Barnett et al [35]	2013	Lancet	Linagliptin	241	233 (96.7)	8 (3.3)	Worldwide		
BEACON [36]	2013	NEJM	Bardoxolone methyl	2185	1694 (77.5)	491 (22.5)	USA		
BEGIN Basal-Bolus Type 2 [37]	2012	Lancet	Insulin degludec vs insulin glargine	992	822 (82.9)	170 (17.1)	Worldwide		
Burant et al [38]	2012	Lancet	TAK-875, glimepiride, placebo	426	352 (82.6)	74 (17.4)	North America		
Buse et al [39]	2011	Annals of Internal Medicine	Exenatide	259	201 (77.6)	58 (22.4)	North America and Europe		
CANTATA-SU [40]	2013	Lancet	Canagliflozin, glime- piride	1450	978 (67.4)	472 (32.6)	USA		
CANVAS [41]	2017	NEJM	Canagliflozin	10,142	7944 (78.3)	2198 (21.7)	USA		
CARMELINA [42]	2019	JAMA	Linagliptin	6979	5596 (80.2)	1383 (19.8)	Europe		
CREDENCE [43]	2019	NEJM	Canagliflozin	4401	2931 (66.6)	1470 (33.4)	USA		

Table 2 (continued)

Publication Year Journal		Pharmacotherapy intervention	Number of participants	White participants N (%)	Racialised participants N (%)	Country/region of greatest participant recruitment		
DAIS [44]	2001	Lancet	Fenofibrate	418	400 (95.7)	18 (4.3)	Europe	
Dapagliflozin 006 [45]	2012	Annals of Internal Medicine	Dapagliflozin	800 ^d	760 (95)	40 (5)	North America and Europe	
Davies et al [46]	2017	JAMA	Semaglutide	630	523 (83)	107 (17)	USA	
DECLARE-TIMI 58 [47]	2019	NEJM	Dapagliflozin, placebo	17,160	13,653 (79.6)	3507 (20.4)	USA	
DETAIL [48]	2004	NEJM	Telmisartan vs enalapril	250	246 (98.4)	4 (1.6)	Europe	
DEVOTE [49]	2017	NEJM	Insulin degludec, insulin glargine	7637	5775 (75.6)	1862 (24.4)	USA	
DIRECT-Protect 2 [50]	2008	Lancet	Candesartan	1905	1830 (96.1)	75 (3.9)	Europe	
DUAL V [51]	2016	JAMA	Insulin glargine, liraglutide	557	527 (94.6)	30 (5.4)	Russian Federation	
DURATION-1 [52]	2008	Lancet	Exenatide	295	230 (78)	65 (22)	North America	
DURATION-2 [53]	2010	Lancet	Exenatide, sitagliptin, pioglitazone	491 ^e	168 (34.2)	323 (65.8)	North America	
DURATION-3 [54]	2010	Lancet	Exenatide vs insulin glargine	456	379 (83.1)	77 (16.9)	Worldwide	
DURATION-6 [55]	2013	Lancet	Exenatide vs liraglutide	911	753 (82.7)	158 (17.3)	Worldwide	
ELIXA [56]	2015	NEJM	Lixisenatide	6068	4576 (75.4)	1492 (24.6)	USA	
EMPA-REG Outcome [57]	2015	NEJM	Empagliflozin	7020	5081 (72.4)	1939 (27.6)	Europe	
EUREXA [58]	2012	Lancet	Exenatide vs glime- piride	977	894 (91.5)	83 (8.5)	Europe	
EXAMINE [59]	2013	NEJM	Alogliptin	5380	3909 (72.7)	1471 (27.3)	USA	
EXSCEL [60]	2017	NEJM	Exenatide	14,752	11,175 (75.8)	3577 (24.2)	Europe	
Frias et al [61]	2018	Lancet	LY3298176	316 ^f	253 (80.1)	63 (19.9)	USA	
Gallwitz et al [62]	2012	Lancet	Linagliptin, glimepiride	1551 ^g	1319 (85)	232 (15)	Worldwide	
Harmony Outcomes [63]	2018	Lancet	Albiglutide	9463	8030 (84.9)	1433 (15.1)	USA	
Heine et al [64]	2005	Annals of Internal Medicine	Exenatide, insulin glargine	549 ^h	440 (80.1)	109 (19.9)	Worldwide	
INTERVAL [65]	2013	Lancet	Vildagliptin	278	269 (96.8)	9 (3.2)	Europe	
IRMA-2 [66]	2001	NEJM	Irbesartan	590 ⁱ	574 (97.3)	16 (2.7)	Worldwide	
LEAD-3 Mono [67]	2009	Lancet	Liraglutide vs glime- piride	746	583 (78.2)	163 (21.8)	USA	
LEAD-6 [68]	2009	Lancet	Liraglutide vs exenatide		426 (91.8)	38 (8.2)	Europe and USA	
LEADER [69]	2016	NEJM	Liraglutide	9340	7238 (77.5)	2102 (22.5)	USA	
Lewis et al [70]	2001	NEJM	Irbesartan, amlodipine	1715	1242 (72.4)	473 (27.6)	Worldwide	
PERISCOPE [71]	2008	JAMA	Pioglitazone, glime- piride	543	445 (82)	98 (18)	USA	
PIONEER 3 [72]	2019	JAMA	Semaglutide, sitagliptin	1864	1324 (71)	540 (29)	USA	
PIONEER 4 [73]	2019	Lancet	Semaglutide, liraglutide	711	519 (73)	192 (27)	USA	
PIONEER 6 [74]	2019	NEJM	Semaglutide	3183	2300 (72.3)	883 (27.7)	USA	
PROactive [75]	2005	Lancet	Pioglitazone	5238	5164 (98.6)	74 (1.4)	Europe	
Ray et al [76]	2020	JAMA	Apabetalone	2418 ^j	2119 (87.6)	299 (12.4)	Serbia	
RECORD [77]	2009	Lancet	Rosiglitazone vs metformin plus sulfonylurea	4447	4399 (98.9)	48 (1.1)	Europe	
RENAAL [78]	2001	NEJM	Losartan	1513	736 (48.6)	777 (51.4)	North America	
REWIND [79]	2019	Lancet	Dulaglutide	9901	7498 (75.7)	2403 (24.3)	Argentina	
RIO-Diabetes [80]	2006	Lancet	Rimonabant	1045	925 (88.5)	120 (11.5)	Worldwide	
ROADMAP [81]	2011	NEJM	Olmesartan	4447	4447 (100)	0(0)	Europe	
Rosenstock et al [82]	2010	Lancet	Inhaled insulin, glargine vs biaspart insulin	618 ^k	417 (67.5)	201 (32.5)	Worldwide	
SAVOR-TIMI 53 [83]	2013	NEJM	Saxagliptin	16,492	12,407 (75.2)	4085 (24.8)	USA	
SCALE [84]	2015	JAMA	Liraglutide	846	705 (83.3)	141 (16.7)	Worldwide	

Table 2 (continued)

Publication	Year	Journal	Pharmacotherapy intervention	Number of participants	White participants N (%)	Racialised participants N (%)	Country/region of greatest participant recruitment
SONAR [85]	2019	Lancet	Atrasentan	3668	2110 (57.5)	1558 (42.5)	USA
TECOS [86]	2015	NEJM	Sitagliptin	14,671	9957 (67.9)	4714 (32.1)	USA
THEMIS [87]	2019	NEJM	Ticagrelor	19,220	13,696 (71.3)	5524 (28.7)	USA
TREAT [88]	2009	NEJM	Darbepoetin alfa	4038	2570 (63.6)	1468 (36.4)	USA
VERIFY [89]	2019	Lancet	Vildagliptin, metformin	2001	1217 (60.8)	784 (39.2)	Slovakia
VERTIS CV [90]	2020	NEJM	Ertugliflozin	8246	7240 (87.8)	1006 (12.2)	USA
Zinman et al [91]	2007	Annals of Internal Medicine	Exenatide	233	195 (83.7)	38 (16.3)	USA
Zinman et al [92]	2011	Lancet	Insulin degludec, insulin glargine, metformin	245	78 (31.8)	167 (68.2)	Worldwide
Fayfman et al [93] ¹	2019	Diabetes Care	Exenatide	150	41 (27.3)	109 (72.7)	USA
Dailey et al [94] ¹	2004	Diabetes Care	Insulin glulisine	876	748 (85.4)	128 (14.6)	North America and Australia
Zhu et al [95] ¹	2018	Lancet Diabetes and Endocrinology	Dorzagliatin	255	0 (0)	255 (100)	China

^a251 participants were randomised but baseline characteristics are available for only 231 participants

^bEthnic breakdown was categorised as Qatari, Non-Qatari Arab, Asian Indian and Other. As a conservative assumption, it was assumed that the participants categorised as 'Other' were white, resulting in 16 white and 215 racialised participants

^c4360 participants were randomised but nine of these participants did not receive the study medication

^d808 participants were randomised but baseline characteristics are available for only 800 participants

e514 participants were randomised but baseline characteristics are available for only 491 participants who were included in the final analysis

^f318 participants were randomised but demographic information is provided for only 316 participants

^g1552 participants were randomised. One participant was untreated but demographic information for the untreated participant is not provided

^h551 participants were randomised. Two participants were lost to follow-up after receiving the study drug and it is not known if they took at least one dose of the drug. For the purposes of data analysis, these participants were classified as untreated

ⁱ611 participants were randomised but 21 participants were excluded

^j2425 participants were randomised but efficacy analyses and baseline characteristics are available for only 2418 participants

^k677 participants were randomised but baseline characteristics are available for only 618 participants

¹These trials were included only in the sensitivity analysis (ESM Appendix 2)

NEJM, New England Journal of Medicine

Our study has several strengths. The meta-analysis included trials that were published in top-tier medical journals and that are likely to be highly cited and used to inform clinical guidelines. Analysing racialised participant recruitment in these studies allows for a finer assessment of the generalisability of the results to certain practice settings. The calculation and presentation of PPRs improves the summary of the findings of over-representation of white participants and underrepresentation of racialised participants (Figs 2, 3, 4 and 5).

Our study also has certain limitations. First, this analysis relied on investigator-reported ethnicity or race. Participants belonging to any ethnicity or race that was not explicitly defined by trial investigators as 'white' were categorised as 'racialised'. We recognise, however, that the understanding of the terms 'white' and 'racialised' may vary between countries and trial investigators. Inconsistent interpretations of the term 'white' could influence the overall PPR estimates. Second, the PPR denominator calculations were based on prevalence and demographic data for white and racialised participants in different countries and regions of the world. While type 2 diabetes prevalence and demographic data are typically documented for specific countries, limited data exist for type 2 diabetes prevalence and demographics in larger regions of the world. When specific data were not available, these values were estimated (ESM Methods and ESM Table 3). Third, this meta-epidemiological review included studies that were published between 1 January 2000 and 31 December 2020. However, our estimates of type 2 diabetes prevalence and demographic data did not correspond exactly to the prevalence of type 2 diabetes in white and racialised people and the ethnic breakdown of countries or regions at the time that each trial was conducted, although we attempted to match them as closely as possible. Fourth, our pooled meta-analytic estimates had high levels of heterogeneity ($I^2 > 90\%$). This heterogeneity may stem from many factors, including the study design used, country or region of conduct, study size and period of enrolment. Despite the high levels of heterogeneity, our

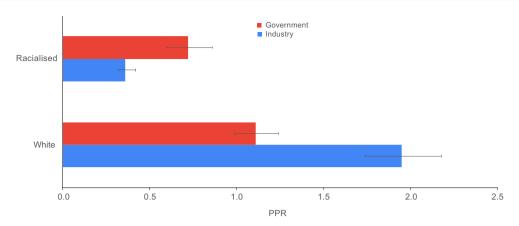
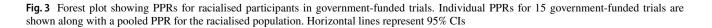


Fig. 1 Representation of racialised and white participants in industry- and government-funded trials. Error bars represent 95% CIs

			White	Racialise	ed	PPR			PPR			
Study or Subgroup	log[PPR]	SE	Total	Total	Weight	IV, Random, 95% CI		IV, Rano	dom, 95%	CI		
ACCORD 2008 [10]	0.284088	0.02063059	6604	3647	10.1%	1.33 [1.28, 1.38]						
BARI 2D 2009 [11]	0.30706866	0.04335634	1561	807	9.7%	1.36 [1.25, 1.48]			-			
CARDS 2004 [12]	0.13977786	0.08091064	2676	162	8.5%	1.15 [0.98, 1.35]			-			
FIELD 2005 [13]	0.11145231	0.03917239	9093	702	9.8%	1.12 [1.04, 1.21]			-			
GRADE 2019 [14]	0.30314965	0.02964429	3314	1733	10.0%	1.35 [1.28, 1.44]			-			
Kadoglou et al 2007 [15]	0.1793224	1.41774469	100	0	0.2%	1.20 [0.07, 19.26]	•		-			→
Levin et al 2000 [16]	0.28846966	0.16917307	99	54	5.4%	1.33 [0.96, 1.86]						
Meyer et al 2010 [17]	0.44348577	0.17343648	136	44	5.2%	1.56 [1.11, 2.19]				_		
MiTy 2020 [18]	-0.72539254	0.09713954	152	350	7.9%	0.48 [0.40, 0.59]						
SPREAD-DIMCAD 2013 [19]	-2.17712989	1.41537609	0	304	0.2%	0.11 [0.01, 1.82]	+-		<u> </u>			
The Qatar Study 2017 [20]	-0.54756745	0.25913541	16	215	3.3%	0.58 [0.35, 0.96]			-			
TINSAL-T2D 2010 [21]	0.04898969	0.1924831	55	53	4.7%	1.05 [0.72, 1.53]		-				
TINSAL-T2D-II 2013 [22]	0.08507576	0.11844798	151	135	7.1%	1.09 [0.86, 1.37]			+			
UKPDS 57 2002 [23]	-0.03646335	0.08550871	653	173	8.3%	0.96 [0.82, 1.14]			+			
VADT 2009 [24]	0.24627412	0.04868961	1111	680	9.6%	1.28 [1.16, 1.41]			-			
Total (95% CI)			25,721	9059	100.0%	1.11 [0.99, 1.24]			•			
Heterogeneity: $T^{2} = 0.03$;	$\times ^{2} = 148.97$, df	= 14 (p < 0.0)	0001); / ² =	= 91%						1	<u> </u>	
Test for overall effect: $Z = 1.7$							0.1 0.2	0.5	1	2	5	10
	• •						Under-rep	resented		Over-rep	oresente	ed .

Fig. 2 Forest plot showing PPRs for white participants in government-funded trials. Individual PPRs for 15 government-funded trials are shown along with a pooled PPR for the white population. Horizontal lines represent 95% CIs

			Racialised	l White		PPR				PPR			
Study or Subgroup	log[PPR]	SE	Total	Total	Weight	IV, Random, 95% CI			IV, Ra		95% CI		
ACCORD 2008 [10]	-0.37005273	0.02063059	3647	6604	8.7%	0.69 [0.66, 0.72]			1	•			
BARI 2D 2009 [11]	-0.4130597	0.04335634	807	1561	8.6%	0.66 [0.61, 0.72]			-	-			
CARDS 2004 [12]	-1.1489308	0.08091064	162	2676	8.2%	0.32 [0.27, 0.37]		-	-				
FIELD 2005 [13]	-0.8612428	0.03917239	702	9093	8.6%	0.42 [0.39, 0.46]			-				
GRADE 2019 [14]	-0.40552237	0.02964429	1733	3314	8.7%	0.67 [0.63, 0.71]				.			
Kadoglou et al 2007 [15]	-3.52142848	1.41774469	0	100	0.4%	0.03 [0.00, 0.48]	←						
Levin et al 2000 [16]	-0.37803625	0.16917307	54	99	6.6%	0.69 [0.49, 0.95]							
Meyer et al 2010 [17]	-0.74534959	0.17343648	44	136	6.6%	0.47 [0.34, 0.67]							
MiTy 2020 [18]	0.62129093	0.09713954	350	152	7.9%	1.86 [1.54, 2.25]							
SPREAD-DIMCAD 2013 [19]	0.01294686	1.41537609	304	0	0.4%	1.01 [0.06, 16.23]	←			_			\longrightarrow
The Qatar Study 2017 [20]	0.05578154	0.25913541	215	16	5.0%	1.06 [0.64, 1.76]			-				
TINSAL-T2D 2010 [21]	-0.04842169	0.1924831	53	55	6.2%	0.95 [0.65, 1.39]			-		_		
TINSAL-T2D-II 2013 [22]	-0.0872994	0.11844798	135	151	7.6%	0.92 [0.73, 1.16]							
UKPDS 57 2002 [23]	0.15102455	0.08550871	173	653	8.1%	1.16 [0.98, 1.38]				- -	-		
VADT 2009 [24]	-0.30501898	0.04868961	680	1111	8.5%	0.74 [0.67, 0.81]				-			
Total (95% CI)			9059	25721	100.0%	0.72 [0.60, 0.86]							
Heterogeneity: $T^2 = 0.09$; X	$^{2} = 402.69$, df =	14 (p < 0.000)	$(01): l^2 = 979$	%			H						
Test for overall effect: $Z = 3.70$							0.1	0.2	0.5	1	2	5	10
	- (p =)						ι	nder-rep	resented		Over	-represent	ed



Study or Subgroup	log[PPR]	SE	White Total	Racialis Total	ed Weight	PPR IV, Random, 95% CI	PPR IV, Random, 95% CI
1860-LIRA-DPP-4 2010 [25]	0.28605035	0.11389498	576	89	1.5%	1.33 [1.06, 1.66]	
4-T Study Group 2007 [26]		0.14040374	653	55	1.5%	1.20 [0.91, 1.59]	+
ADOPT 2006 [27]	0.47110518		3847	504	1.6%	1.60 [1.46, 1.76]	-
AleCardio 2014 [28]		0.02495671	4818	2408	1.6%	1.38 [1.31, 1.44]	
ALTITUDE 2012 [29] ARTS-DN 2015 [30]		0.02180951 0.09560066	4850 691	3711 130	1.6% 1.5%	0.74 [0.71, 0.77] 1.10 [0.91, 1.33]	•
AVOID 2008 [31]		0.12075307	520	79	1.5%	1.33 [1.05, 1.69]	
AWARD-4 2015 [32]	0.48611608	0.0823548	697	187	1.5%	1.63 [1.38, 1.91]	
AWARD-6 2014 [33]	0.57269304	0.11767119	515	84	1.5%	1.77 [1.41, 2.23]	
Bailey et al 2010 [34]		0.13128156	480	66	1.5%	1.33 [1.03, 1.72]	
Barnett et al 2013 [35]		0.35957175	233	8	1.0%	14.85 [7.34, 30.05]	F F
BEACON 2013 [36] BEGIN–Basal–Bolus Type 2 2012 [37]		0.05125406 0.08425496	1694 822	491 170	1.6% 1.5%	1.60 [1.45, 1.77] 12.73 [10.79, 15.02]	
Burant et al 2012 [38]	0.40340909		352	74	1.5%	1.50 [1.17, 1.92]	,, ,
Buse et al 2011 [39]		0.14905202	201	58	1.4%	1.19 [0.89, 1.60]	
CANTATA-SU 2013 [40]	0.329979	0.05604587	978	472	1.6%	1.39 [1.25, 1.55]	
CANVAS 2017 [41]	0.479519	0.02410063	7944	2198	1.6%	1.62 [1.54, 1.69]	-
CARMELINA 2019 [42]	0.045846	0.0300294	5596	1383	1.6%	1.05 [0.99, 1.11]	-
CREDENCE 2019 [43]		0.03196017	2931	1470	1.6%	1.37 [1.29, 1.46]	
DAIS 2001 [44] Dapagliflozin 006 2012 [45]	0.22268246 0.37843644	0.2409472	400 760	18 40	1.3% 1.4%	1.25 [0.78, 2.00] 1.46 [1.06, 2.01]	
Davies et al 2017 [46]	0.53764938		523	107	1.5%	1.71 [1.39, 2.11]	
DECLARE-TIMI 58 2019 [47]		0.01893114	13,653	3507	1.6%	1.64 [1.58, 1.70]	
DETAIL 2004 [48]	0.25056997		246	4	0.7%	1.28 [0.48, 3.45]	
DEVOTE 2017 [49]	0.444321	0.0266499	5775	1862	1.6%	1.56 [1.48, 1.64]	-
DIRECT-Protect2 2008 [50]		0.11781248	1830	75	1.5%	1.25 [1.00, 1.58]	
DUAL V 2016 [51]	0.21133466		527	30	1.4%	1.24 [0.86, 1.78]	
DURATION-1 2008 [52] DURATION 2 2010 [53]	0.34532121		230	65	1.5%	1.41 [1.07, 1.86]	
DURATION 2 2010 [55] DURATION-3 2010 [54]		0.09512285 0.12500214	168 379	323 77	1.5% 1.5%	0.62 [0.51, 0.75] 12.77 [9.99, 16.31]	-
DURATION-6 2013 [55]		0.08750506	753	158	1.5%	12.70 [10.70, 15.07]	
ELIXA 2015 [56]		0.02981229	4576	1492	1.6%	1.56 [1.47, 1.65]	-
EMPA-REG OUTCOME 2015 [57]		0.02669347	5081	1939	1.6%	0.95 [0.90, 1.00]	-
EUREXA 2012 [58]	0.17791847	0.11474651	894	83	1.5%	1.19 [0.95, 1.50]	
EXAMINE 2013 [59]		0.03058806	3909	1471	1.6%	1.50 [1.41, 1.59]	÷
EXSCEL 2017 [60]		0.01921066	11,175	3577	1.6%	0.99 [0.95, 1.03]	Ť
Frias et al 2018 [61]		0.14080336 0.07119336	253 1319	63 232	1.5% 1.5%	1.65 [1.25, 2.18]	,
Gallwitz et al 2012 [62] Harmony Outcomes 2018 [63]		0.02867699	8030	1433	1.5%	13.07 [11.36, 15.02] 1.75 [1.65, 1.85]	
Heine et al 2005 [64]		0.10699084	440	109	1.5%	12.31 [9.98, 15.19]	•
INTERVAL 2013 [65]	0.23378961		269	9	1.0%	1.26 [0.65, 2.45]	
IRMA-2 2001 [66]	2.70451193		574	16	1.2%	14.95 [9.10, 24.56]	•
LEAD-3 Mono 2009 [67]		0.08860155	583	163	1.5%	1.61 [1.35, 1.92]	
LEAD-6 2009 [68]	0.40359079		426	38	1.4%	1.50 [1.07, 2.09]	
LEADER 2016 [69] Lewis et al 2001 [70]	2.40931498	0.02477695	7238 1242	2102 473	1.6% 1.6%	1.60 [1.52, 1.68] 11.13 [10.01, 12.37]	-
PERISCOPE 2008 [71]		0.11158527	445	98	1.5%	1.69 [1.36, 2.10]	·
PIONEER 3 2019 [72]	0.38172048		1324	540	1.6%	1.46 [1.33, 1.62]	
PIONEER 4 2019 [73]	0.40901919	0.08446961	519	192	1.5%	1.51 [1.28, 1.78]	
PIONEER 6 2019 [74]		0.03958896	2300	883	1.6%	1.49 [1.38, 1.61]	-
PROactive 2005 [75]	0.25247107		5164	74	1.5%	1.29 [1.02, 1.62]	
Ray et al 2020 [76]		0.06177704	2119	299	1.6%	1.14 [1.01, 1.29]	
RECORD 2009 [77] RENAAL 2001 [78]	0.25584688		4399 736	48 777	1.4% 1.6%	1.29 [0.97, 1.72] 0.88 [0.80, 0.97]	
REWIND 2019 [79]		0.02344174	7498	2403	1.6%	0.98 [0.94, 1.03]	· · · · ·
RIO-Diabetes 2006 [80]	2.61002665	0.0970279	925	120	1.5%	13.60 [11.24, 16.45]	•
ROADMAP 2011 [81]	0.26658692		4447	0	0.2%	1.31 [0.08, 20.87]	· · · · · · · · · · · · · · · · · · ·
Rosenstock et al 2010 [82]	2.33860284	0.08586737	417	201	1.5%	10.37 [8.76, 12.27]	•
SAVOR-TIMI 53 2013 [83]		0.01803878	12,407	4085	1.6%	1.55 [1.50, 1.61]	· ·
SCALE 2015 [84]		0.09225312	705	141	1.5%	12.80 [10.69, 15.34]	
SONAR 2019 [85]	0.17082913		2110	1558	1.6%	1.19 [1.11, 1.27]	 ⁺
TECOS 2015 [86] THEMIS 2019 [87]	0.336191 0.38494	0.01767953 0.0159387	9957 13696	4714 5524	1.6% 1.6%	1.40 [1.35, 1.45] 1.47 [1.42, 1.52]	
TREAT 2009 [88]		0.0159587	2570	5524 1468	1.6%	1.31 [1.23, 1.40]	
VERIFY 2019 [89]	-0.23055889		1217	784	1.6%	0.79 [0.73, 0.87]	-
VERTIS CV 2020 [90]		0.03364755	7240	1006	1.6%	1.81 [1.70, 1.93]	-
Zinman et al 2007 [91]	0.54574884	0.17732455	195	38	1.4%	1.73 [1.22, 2.44]	——————————————————————————————————————
Zinman et al 2011 [92]	1.58745569	0.13714422	78	167	1.5%	4.89 [3.74, 6.40]	
Total (95% CI)			190,119	58223	100.0%	1.95 [1.74, 2.18]	•
Heterogeneity: $T^{2} = 0.22$; $X^{2} = 8819$		0.00001 ; $l^2 =$	99%				
Test for overall effect: $Z = 11.34$ ($p < 0.0$	00001)						Under-represented Over-represented
							onaci representeu over-representeu

Fig. 4 Forest plot showing PPRs for white participants in industry-funded trials. Individual PPRs for 68 industry-funded trials are shown along with a pooled PPR for the white population. Horizontal lines represent 95% CIs

results were consistent with respect to direction. Thus, statistical heterogeneity influenced the precision of our estimates but not the direction or magnitude to an extent that would cause concern. Finally, we did not conduct risk of bias assessments for the trials used in this review. This is because our goal was to examine recruitment of white and racialised participants as opposed to evaluating the clinical outcomes of included studies. Furthermore, our selection criteria were such that we only included large (n>100) RCTs (lowest risk of bias design) published in top-tier journals, which helped to ensure a comparable and low risk of bias across included studies.

Study or Subgroup bg/Peril SE Tot Tot Tot Tot Tot Tot Tot No No Automs 595 (C) ADDPT JOSE [27]				Racialise	ed White		PPR	PPR
4-T Study Cross 2007 [26] 1-10980887 0.14640974 55 656 1.58 0.28 0.24 0.24 0.44 AutTUDE CDI2 [29] 0.0510105 0.01490051 1071 485 106 108 108 118 108 118 108		log[PPR]	SE			-	IV, Random, 95% CI	IV, Random, 95% Cl
ALSOPT 2006 [27]								
Alccard 2014 [28] -0.3377445 0.2439571 2403 4485 1.68 0.51 [26] 0.68 AVIDD 2021 [29] -0.541001 0.0218051 71 455 1.68 0.18 [10, 7] 0.13 0.14 [10, 7] 0.13 0.14 [10, 7] 0.14								
Attribus 2012 [29] 0.010105 0.0219991 3711 455 1.06 1.8 [1.8 [1.7, 1.93]								
ARTS-D0215 [20] -0.3996/762 0.09500066 130 691 1.5% 0.08 (B.55.0.82)								
AV02.0206 [3] AV02.0206 [3] AV02.0206 [3] AV02.0206 [3] AV02.0207 [1] AV02.0207 [1] AV02.0								
AWARD 4 2015 [2] -0.6893082 0.082348 187 697 1.58 0.41 (0.35, 0.48) AWARD 6 2014 [33] -1.301027 0.112815 6.6 4.63 1.58 0.27 (0.25, 0.46) Balley et al 2010 [24] -1.5040073 0.112815 6.6 4.63 1.58 0.26 (0.25, 0.46) BEGM-Estal-Bolis Type 2.2012 [37] -1.6966211 0.0922456 170 128 1.58 0.46 (0.45, 0.56) BEGM-Estal-Bolis Type 2.2012 [37] -0.4972456 0.1788 128 704 158 0.46 (0.45, 0.56) BEGM-Estal-Bolis Type 2.2013 [37] -0.4972456 170 128 704 164 0.46 (0.46, 0.56) CAMMS 2017 [41] -0.6972 0.0241063 1183 5396 1.66 0.55 (0.80, 0.50) - CARDENA 2019 [42] -0.66653 0.3902491 133 5396 1.66 0.45 (0.80, 0.50) - CARDENA 2019 [42] -0.066653 0.3902491 133 5396 1.66 0.45 (0.80, 0.50) - CARDENA 2019 [42] -0.02440 0.1269127 128 0.40 (0.35, 0.41) - - DELA 2004 [
AWARD 2 2014 [3] -1.0012777 0.1172119 84 931 1.58 0.027 (0.22, 0.34) Barger et al 2013 [33] -3.04281 0.1212155 6 450 0.04 0.02, 0.04								<u> </u>
Lailey et al 2010 [24] -1.04940078 0.1312815 -1.04940078 0.1312815 -1.04940078 0.1312815 BACCM 2013 [36] -0.32951 0.0512540 +0.1 1.33 0.04 (0.13, 0.04) BACCM 2013 [36] -0.32951 0.0512540 +0.1 1.33 0.04 (0.13, 0.04) BACCM 2013 [36] -0.4494246 0.01495022 53 203 1.55 0.04 (0.04, 0.05) Buse et al 2011 [30] -0.444246 0.01495022 53 203 1.55 0.64 (0.04, 0.06)								
Immeter al 2013 [35] -3.33801382 0.332 0.33297175 6 2.233 1.1% 0.04 (0.02, 0.07) EGN: Board Doils 240 D012 240 D012 240 D012 240 D012 240 EGN: Board D012 240 D012 240 D012 240 D012 240 D012 240 D012 240 EGN: Board D042 201 297 -1.06662 D012 200 D012 240								(
EACON 2013 [6] -0.82251 0.63225406 491 1694 1.5% 0.816.6.0.22								•
$ \begin{array}{c} \mbox{scale} at 2012 [18] & -0.94742456 & 0.127844 & 74 & 352 & 1.5% & 0.64 [0.48, 0.68] & \\ \mbox{scale} at 2011 [19] & -0.44560 & 0.1490502 & 52 & 201 & 55 & 0.64 [0.48, 0.68] & \\ \mbox{cl} at 2011 [19] & -0.44560 & 0.039024 & 77 & 378 & 1.5\% & 0.64 [0.48, 0.68] & \\ \mbox{cl} at 2011 [19] & -0.44560 & 0.039024 & 178 & 203 & 1.6\% & 0.65 [0.61, 0.69] & \\ \mbox{cl} at 2011 [10] & -0.44560 & 0.039024 & 178 & 203 & 1.6\% & 0.65 [0.61, 0.69] & \\ \mbox{cl} at 2011 [10] & -0.44560 & 0.049472 & 18 & 400 & 138 & 0.18 [0.11, 0.29] & \\ \mbox{cl} at 2011 [10] & -1.64395129 & 0.1222142 & 40 & 700 & 1.4\% & 0.14 [0.10, 0.20] & \\ \mbox{cl} at 2011 [10] & -0.42440 & 0.249472 & 118 & 100 & 138 & 0.18 [0.13, 0.24] & \\ \mbox{cl} at 2011 [10] & -0.42440 & 0.049424 & 40 & 700 & 1.4\% & 0.14 [0.10, 0.20] & \\ \mbox{cl} at 2011 [10] & -0.42440 & 0.0250494 & 10.29 & 118 & 100 & 10.86 & 0.41 & \\ \mbox{cl} at 2001 [10] & -1.642444 & 0.0250506 & 142 & 753 & 10.80 & 0.77 [0.13, 0.21] & \\ \mbox{cl} at 2001 [10] & -1.712378 & 0.1170128 & 73 & 118 & 1.5\% & 0.19 [0.16, 0.22] & \\ \mbox{cl} at 1.7121389 & 0.1572285 & 123 & 168 & 1.4\% & 0.13 (0.14, 0.23) & \\ \mbox{cl} at 1.7121389 & 0.1012428 & 1.73 & 1.5\% & 0.18 [0.14, 0.23] & \\ \mbox{cl} at 2010 [13] & & & & & \\ \mbox{cl} at 2010 [13] & & & & & & & \\ \mbox{cl} at 2010 [13] &$	BEACON 2013 [36]	-0.82951	0.05125406	491	1694	1.5%		-
Buse et al 2011 [39] -0.44460406 0.1409202 S8 201 1.5% 0.64 [0.45, 0.65]	BEGIN-Basal-Bolus Type 2 2012 [37]	-1.6966211	0.08425496	170	822	1.5%	0.18 [0.16, 0.22]	
CANTAS-SU 2013 [40]0.45852 0.05406437 472 978 1.5% 0.63 [0.57, 0.71] CARMAS 2017 [41]0.6663 0.0300394 1383 5366 1.6% 0.65 [0.5, 0.64] CARMAS 2017 [42]0.16663 0.0300394 1383 5366 1.6% 0.65 [0.5, 0.64] Dapagificatio 005 2012 [45] -1.04395129 0.15222142 40 760 1.4% 0.416 0.10 0.05 [0.7] Darkes et al 2017 [46] -1.104739129 0.10522142 40 760 1.4% 0.416 0.10 0.21 Darkes et al 2017 [46] -1.04395129 0.1522142 40 760 1.4% 0.416 0.10 0.21 Darkes et al 2017 [46] -1.04395129 0.1052027 107 523 1.5% 0.40 [0.8, 0.41] DECLARE-TIM 58 2013 [47] -0.9244 0.01895114 3507 13653 1.6% 0.4% 0.9% 0.410 [0.8, 0.3] DECLARE-TIM 58 2013 [47] -0.9244 0.01895114 3507 13653 1.6% 0.471 045, 0.31 DECLARE-TIM 58 2013 [47] -0.9244 0.01895114 3507 13653 1.6% 0.471 045, 0.31 DECLARE-TIM 58 2013 [47] -0.9244 0.01895114 3507 13653 1.6% 0.471 045, 0.31 DECLARE-TIM 58 2013 [47] -0.97493 0.056499 1862 5773 1.5% 0.471 045, 0.31 DECLARE-TIM 58 2013 [51] -1.4684464 0.18705887 30 1327 1.4% 0.23 [1.5% 0.31] DURATON-1 2008 [52] -0.70963839 0.14947221 65 230 158 for 31 1.5% 0.471 045, 0.23 DURATON-1 2008 [52] -0.70963839 0.14947221 65 139 7.31 1.5% 0.491 037, 0.561 DURATON-2 010 [54] -1.71138362 0.12500214 77 379 1.5% 0.31 0.14, 0.22] DURATON-2 010 [53] -1.684644 0.05750560 153 7.73 1.5% 0.31 0.14, 0.22] DURATON-2 010 [54] -1.71138362 0.12500214 73 129 508 1.4% 0.31 0.14, 0.22] DURATON-2 010 [54] -1.032501 0.1147681 83 894 1.5% 0.36 (0.2, 0.45] DURATON-2 010 [54] -1.032501 0.1147681 83 894 1.5% 0.36 (0.2, 0.45]	Burant et al 2012 [38]			74	352	1.5%	0.39 [0.30, 0.50]	
CAMMSLNA 2017 [41]0.68572 0.0240063 2198 7944 1.6K 0.42 [0.40, 0.44]		-0.44460406	0.14905202	58	201	1.5%	0.64 [0.48, 0.86]	
CAMPLINA 2019 [42] -0-01666 0.0300294 1383 5596 1.6K 0.68 [0.6.0.08]								-
CREDENCE 2019 [43] -0.43135 0.03196017 1470 2331 1.66 0.655 [0.61, 0.69] - Dapagifican: 002 2012 [45] -1.94393129 0.16222142 40 760 1.48 0.138 [0.11, 0.29] Deris et al 2017 [46] -1.063316 0.161 (0.22) 1.10 531 1.55 0.138 [0.11, 0.29] DETALL 2004 [48] -2.6831452 0.36401465 1.35 0.07 [0.03, 1.8] - DETALL 2004 [51] -1.07273 0.1781248 75 158 0.17 [0.13, 0.21] - DURATOR -1 2005 [51] -1.07096385 0.1497221 63 230 1.58 0.17 [0.15, 0.63] - DURATOR -1 2005 [51] -0.7096385 0.1497221 63 733 1.58 0.147 [0.15, 0.22] - DURATOR -2 100 [51] -0.63333 0.1266947 1393 5081 1.66 1.18 [1.1, 24] - DURATOR -2 100 [51] -1.664443 0.8750506 158 733 1.58 0.14 [0.61, 0.22] - - DURATOR -2 101 [51] -1.664443 0.8750506 158 733 1.58 0.14 [0.43, 0.53]								-
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Fig. 5 Forest plot showing PPRs for racialised participants in industry-funded trials. Individual PPRs for 68 industry-funded trials are shown along with a pooled PPR for the racialised population. Horizontal lines represent 95% CIs

Conclusion Racialised participants appear to be underrepresented in both government- and industry-funded type 2 diabetes RCTs relative to their disease burden, while white participants appear to be over-represented in industry-funded trials. This meta-epidemiological review shows that the greatest disparity in ethnic and racial diversity in RCTs occurs in industry-funded trials. Strategies to improve the recruitment and enrolment of racialised participants into industry- and government-funded RCTs should be developed. Supplementary Information The online version contains peer-reviewed but unedited supplementary material available at https://doi.org/10.1007/s00125-023-06052-w.

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Data availability The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials. Demographic and prevalence data sourced from resources in the public domain are referenced in the ESM.

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Contribution statement SSA, RJdS and RA were responsible for the conception and design of the study. LB developed the search strategy. RA and RJdS screened the articles and RA and VL carried out the data extraction. RA, RJdS, VL and SSA were responsible for the analysis and interpretation of the results. RA, RJdS and SSA drafted the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript to be published. RJdS and SSA are the guarantors 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.

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Authors and Affiliations

Rabeeyah Ahmed^{1,2} · Russell J. de Souza^{2,3} · Vincent Li¹ · Laura Banfield⁴ · Sonia S. Anand^{1,2,3}

Sonia S. Anand anands@mcmaster.ca

- ¹ Department of Medicine, Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada
- ² Chanchlani Research Centre, McMaster University, Hamilton, ON, Canada
- ³ Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada
- ⁴ Health Sciences Library, McMaster University, Hamilton, ON, Canada