



Exploring ethnic representativeness in diabetes clinical trial enrolment from 2000 to 2020: a chronological survey

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Abstract

Aims/hypothesis Ethnic representativeness of participant enrolment in diabetes RCTs involving multiple ethnicities remains unknown. The aims of this study were to evaluate the status and temporal trend of ethnic representativeness in enrolment to diabetes RCTs, and to assess under-enrolment of non-white ethnic groups and explore trial characteristics associated with under-enrolment. **Methods** We conducted a chronological survey by systematically searching the literature to include eligible RCTs published between January 2000 and December 2020. We assessed temporal trends in enrolment of ethnic groups in the included trials. Univariable logistic regression was used to explore the association between trial characteristics and under-enrolment of non-white groups, using a participant to prevalence ratio of <0.8 to define under-enrolment. This study was registered in PROSPERO (CRD42021229100). **Results** We included 405 RCTs for analysis (327 multi-country trials, 69 conducted in the USA and nine conducted in the UK). The median enrolment rate of all non-white groups was 24.0% in the overall RCTs. Trials conducted in the USA and the UK had median enrolment rates of 29.0% and 12.0% for all non-white groups, respectively. There was a temporal trend towards increased participation of non-white ethnic groups in the overall RCTs; however, no significant improvement over time was found in the US or UK trials. Non-white groups were under-enrolled in most included trials: 62.3% (43/69) in US trials and 77.8% (7/9) in UK trials. The US trials with a high female proportion were associated with lower odds of under-enrolment of all non-white groups (OR 0.22; 95% CI 0.07, 0.65), while trials receiving funding from industry showed increased odds of under-enrolment (OR 4.64; 95% CI 1.50, 14.35). Outpatient enrolment and intervention duration were significantly associated with under-enrolment of Black participants. Only a small proportion of trials reported subgroup results or explored the effect modification by ethnicity. **Conclusions/interpretation** A temporal trend towards increased non-white ethnic enrolment was found in diabetes RCTs globally, but not in the USA or the UK. Non-white ethnic groups were under-represented in the majority of diabetes trials conducted in the USA and the UK. Some trial characteristics may be associated with non-white under-enrolment in diabetes trials. These findings provide some evidence for non-white ethnic representativeness in diabetes trials over the past two decades, and highlight the need for more effective strategies and endeavours to alleviate under-enrolment of non-white ethnic groups.

Keywords Clinical trial · Diabetes · Enrolment · Ethnicity · Representativeness

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Research in context

What is already known about this subject?

- Concerns have been raised recently about whether participants of different ethnicities are enrolled proportionately to disease prevalence in clinical trials
- Many non-white ethnic groups have a higher diabetes prevalence than white ethnic groups, and so would stand to benefit more from the results of diabetes trials

What is the key question?

- What is the temporal trend of ethnic enrolment in diabetes trials, and is there under-enrolment of non-white ethnic groups?

What are the new findings?

- A temporal trend towards increased non-white ethnic enrolment was found in diabetes trials globally, but not in the USA or the UK
- Non-white ethnic groups are under-represented in the majority of diabetes trials conducted in the USA and the UK

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

- Our study highlights the need for joint endeavours to alleviate the non-white ethnic under-representativeness in diabetes trials

Introduction

In light of the increasing prevalence of diabetes mellitus worldwide, various RCTs have been performed to provide high-quality evidence for the prevention, treatment and management of diabetes. Nevertheless, concerns have been raised about whether participants are enrolled into RCTs proportionately to disease prevalence in the population. For instance, in a systematic review, women were found to be under-represented in cardiovascular outcome trials on heart failure [1]. Ethnic under-representativeness is also a concern in health research because health inequities have been reported among non-white populations in terms of the management of digestive diseases, coronavirus disease-2019 (COVID-19)-related deaths, cardiovascular mortality and respiratory outcomes, and some of the under-representativeness may be related to socioeconomic factors and structural racism [2–5].

It has been reported that participants in RCTs have typically reached a higher educational level, demonstrate greater adherence to therapy, and have a higher socioeconomic status than patients in clinical practice [6]. Fewer adverse effects and reduced mortality rates are also observed in trial participants compared with those who are eligible for inclusion but are not enrolled in trials [7]. However it is unclear whether participant enrolment in diabetes RCTs is representative of disease distribution among those living with diabetes. Many non-white ethnic groups have a higher diabetes prevalence than white groups worldwide, and so would stand to benefit more from results of diabetes trials. For instance, one recent systematic review found that the glucose-lowering efficacy of sodium–

glucose cotransporter 2 inhibitors and dipeptidyl peptidase 4 inhibitors was more potent in trials comprising participants of predominantly Asian ethnicity than in trials comprising participants of predominantly white ethnicity [8]. As inadequate proportional representativeness of ethnic groups in trials would lead to an evidence gap in terms of treatment or management recommendations tailored to a specific non-white group [9], improving the representativeness of non-white ethnic groups in diabetes RCTs may be an important route to addressing the significant inter-ethnic health inequities. Therefore, the aims of this study were to evaluate the status and temporal trend of ethnic representativeness in diabetes RCT enrolment (objective I), and to assess under-enrolment of non-white ethnic groups and explore trial characteristics associated with under-enrolment (objective II). This study was registered on PROSPERO (Prospective Register of Ongoing Systematic Reviews; identifier: CRD42021229100).

Methods

Search strategy We conducted a chronological survey by systematically searching MEDLINE, EMBASE, CINAHL and the Cochrane Library for eligible RCTs from 1 January 2000 to 31 December 2020. Descriptors including synonyms for trials and diabetes were used for the search (see electronic supplementary material [ESM] Table 1 for the search strategy used in MEDLINE). Only trials published in English were included due to lack of language translation resources for non-English studies. The reference lists of included trials,

reviews, commentaries or editorials were also checked for potentially relevant trials.

Trial selection Four reviewers working in two pairs independently screened titles and abstracts. We included full-text RCTs involving multiple ethnicity that assessed the effects of interventions on treatment or management of diabetes and prevention of complications compared with standard care or placebo. We limited participants to those aged ≥ 18 years old and with type 1 or type 2 diabetes. Trials that did not have an RCT design, did not exclusively include diabetic patients at baseline, did not include two or more ethnicities, or did not aim to explore the effect of interventions were excluded. Trials with a predefined focus on a specific non-white group were excluded; for instance, a trial targeting the Black population only was not eligible. We also excluded trials that focused on gestational diabetes, which is a temporary form of diabetes in most cases. To ensure that we included only RCTs with the potential to impact clinical practice, a threshold for trial sample size of ≥ 400 patients was used for inclusion, on the assumption that trials with smaller sample sizes were mostly early-phase and single-centre studies [10, 11]. We only used trial data from original publications reporting primary outcomes and main results, i.e. secondary, exploratory or subgroup analyses were not included for analyses. However, some trials do not present information on non-white enrolment in the original publications. Instead, they publish ethnicity-related data in subsequent publications; these studies with data on ethnicity were eligible for inclusion. Over one-third of the studies considered were excluded during the full-text assessment process due to lack of ethnicity data in both original and subsequent publications (Fig. 1). Studies with insufficient information for extraction were also excluded, including protocols, short reports, commentaries and letters to editors.

Outcomes The primary outcomes were the enrolment percentages of non-white groups extracted from the included RCTs (for objective I) and the under-enrolment as defined below (for objective II). Secondary outcomes included under-enrolment of Black, Asian, Hispanic and/or other non-white groups. We extracted data about percentages of enrolment of non-white groups from both multi-country and single-country trials, but could only evaluate under-enrolment in single-country trials or when data on multi-country trials were available by ethnicity and study country. Some trials only report data for all non-white groups, rather than data for each individual non-white group; therefore, the number of included trials for analyses of primary outcomes differed from the number of included trials for secondary outcomes.

To define under-enrolment in individual countries/regions, we used the participation to prevalence ratio from cardiovascular trials, in which a participation to prevalence ratio < 0.8

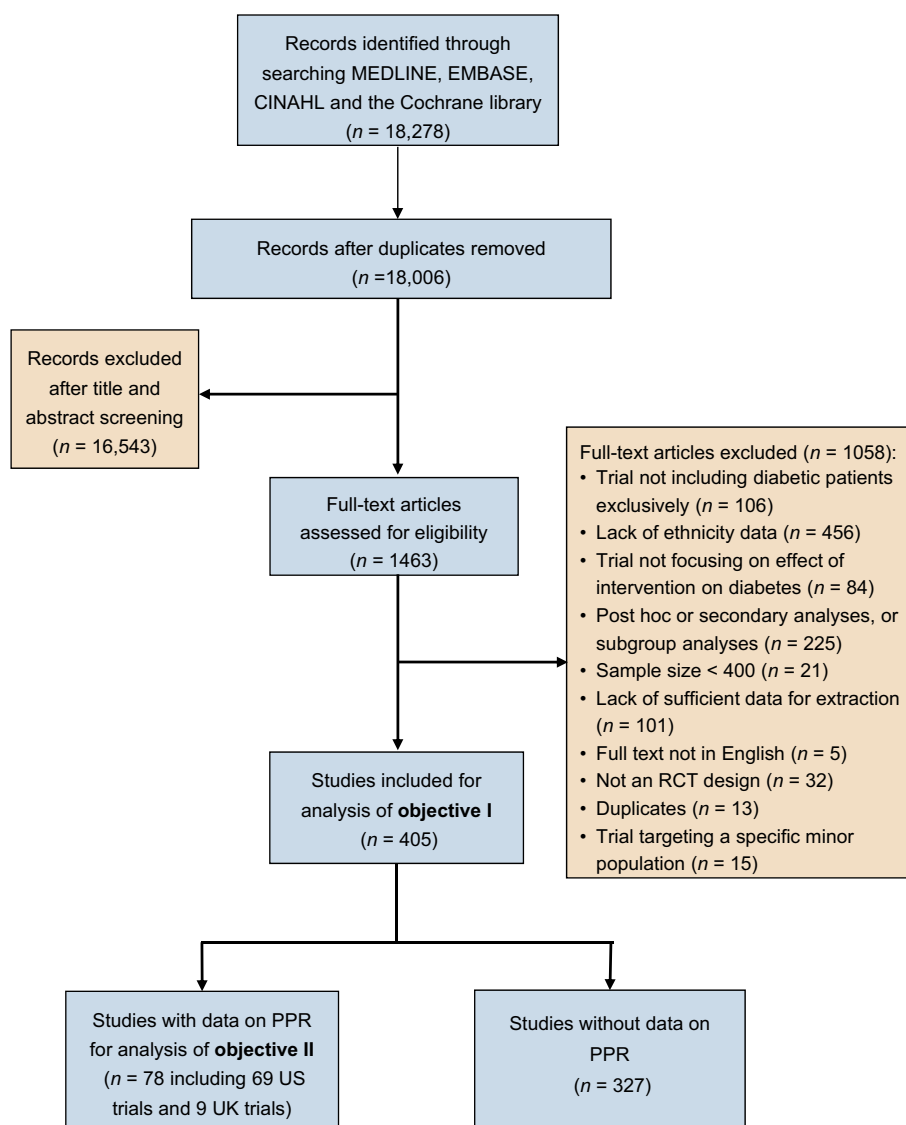
indicated under-enrolment [1, 12]. The participation to prevalence ratio is calculated as the percentage of non-white people among trial participants divided by the percentage of non-white people in the diabetic population. The percentages of non-white groups in the diabetes population were obtained from national census reports available in the literature or calculated by dividing the estimated number of participants with diabetes among the non-white group by the total estimated number of all the participants with diabetes (regardless of their race/ethnicity) (ESM Table 2). For instance, the Black group was considered as under-enrolled in the USA if the trial included $< 12.2\%$ Black patients with diabetes, given the percentage of Black adults with diabetes among the US diabetes population is 15.2% . However, if no data on non-white enrolment for individual countries/regions could be extracted from multi-country trials, we could not define under-enrolment for them due to no global participation to prevalence ratio being available for the global diabetes population stratified by ethnicity.

Data extraction Two reviewers (JZ and YW) independently extracted data from the included RCTs. Information collected included first, senior and corresponding authors, year of publication, sample size, mean age of the participants, sex proportion, inclusion and exclusion criteria related to ethnicity, enrolment by ethnicity, country/region of the trial coordination office (for multi-country trials), enrolment location, type of intervention, type of randomisation, trial reimbursement for participants, type, frequency and duration of follow-up, treatment effect modification by ethnicity, and funding source. The two reviewers discussed and resolved disagreements in data extraction, and consulted a third reviewer (GL) for a decision if no consensus was reached.

We compared the enrolment performed in a specific country/region with the corresponding ethnic distribution. If the trial was conducted in multiple countries/regions, we tried to extract enrolment proportions by ethnicity in each specific country/region. Many of the multi-country trials did not report detailed non-white enrolment proportions stratified by study country. For these trials, we contacted the corresponding authors via email to seek detailed data.

Statistical analyses Continuous variables are described using median and upper and lower quartiles (Q1 and Q3), and categorical variables are described using counts and percentages. Results are shown separately for the overall included trials (for objective I) and single-country trials (for objective II) because data from single-country trials could be used to assess the relationship between non-white ethnic under-enrolment and trial characteristics. The non-parametric Kolmogorov–Smirnov test was used as a test for goodness of fit to compare an observed sample distribution with a reference probability distribution to determine whether the

Fig. 1 Flow diagram showing the trial selection process. PPR, participation to prevalence ratio



enrolment rates by ethnicity significantly differed from the ethnic distribution in the diabetes population. We used the kernel-weighted local polynomial smoothing curve to display enrolment of non-white groups by ascending year of publication. The Jonckheere–Terpstra proportion trend test was used to test whether there was a temporal trend in enrolment of non-white ethnic groups.

For objective II, we used univariable logistic regression models to perform exploratory analyses of the association between trial characteristics and under-enrolment of non-white groups. Associations were quantified as ORs and corresponding 95% CIs. An OR >1 indicated an association between the trial characteristic and increased odds of under-enrolling non-white groups. No multivariable logistic regression analysis was performed due to the small number of included trials and insufficient statistical power. We did perform a post hoc exploratory analysis using a multivariable linear regression model to assess the relationship between trial

characteristics and non-white enrolment percentages in the US trials, where the model included all trial characteristics except for those with a variance inflation factor >4. A negative β coefficient implied a relationship between the trial characteristic and a lower enrolment rate of non-white ethnic groups. No regression analysis was performed for the UK trials due to the limited number of trials; instead, we performed a post hoc analysis comparing the proportions of trial characteristics between the UK trials with and without under-enrolment.

All statistical tests were two-sided, with a p value <0.05 taken to indicate statistical significance. We performed all data analyses using STATA software, version 13.0.

Results

A total of 18,006 records were included for title and abstract screening. After assessing a total of 1463 full-text articles for

eligibility, we included 405 RCTs for analysis. There were 78 single-country trials (69 in the USA and nine in the UK) and 327 multi-country trials for which data on non-white ethnic groups by specific country could not be extracted (Fig. 1).

Status and temporal trend of non-white ethnic representativeness in diabetes RCTs Among the overall 405 included trials, the median enrolment rate of non-white ethnic groups was 24.0% (6.4% for Black, 11.2% for Hispanic and 8.5% for Asian groups, respectively). Only 26 of the trials (6.4%) provided subgroup results or explored effect modification by ethnicity, of which seven trials (10.1%) were from the USA and one trial (11.1%) was from the UK. Only one trial specifically mentioned a significant effect modification by ethnicity ($p < 0.01$) [13], and all the remaining trials showed no significant differences in efficacy, effectiveness and/or safety outcomes between ethnicities. However, it is unknown whether these trials did not show significant subgroup effects because of insufficient statistical power or the true absence of effect modification, because most of the trials (20/26, 76.9%) performed exploratory post hoc subgroup analyses by ethnicity without a predefined hypothesis or sample size consideration.

The temporal change in non-white ethnic enrolment is shown in Fig. 2 and ESM Fig. 1. A significant trend towards increased non-white group enrolment rate was found

chronologically across the last two decades for the overall trials ($p = 0.04$).

Under-enrolment of non-white ethnic groups in the US and UK trials, and trial characteristics related to under-enrolment

Table 1 summarises the trial characteristics for the US and UK trials. Approximately half of the trials were published after 2010 (50.7% for the USA and 44.4% for the UK). The trials had a median female proportion and patient age of 46% and 58 years, respectively, for the USA and 41% and 63 years, respectively, for the UK. The trials mainly focused on type 2 diabetes (63.8% for the USA and 55.6% for the UK) and enrolled outpatients (47.8% for the USA and 55.6% for the UK). No trials reported inclusion criteria specifically related to ethnicity or whether patients received reimbursement for compensation. Approximately half of the US trials (47.8%) and three-quarters of the UK trials (77.8%) were funded by industry. The multi-country trials generally had similar characteristics to the US and UK trials (ESM Table 3). As shown in Table 2, the US trials had a median enrolment rate of 29.0% (Q1–Q3: 22.5–37.9%) for all non-white ethnicities ($n = 69$ trials): 13.5% for Black participants ($n = 62$), 11.6% for Hispanic participants ($n = 38$), 2.6% for Asian participants ($n = 34$) and 3.3% for other non-white ethnicities ($n = 63$). The UK trials had a median enrolment rate of 12.0% (Q1–Q3: 9.4–21.0%) for all non-white ethnicities ($n = 9$ trials): 5.0% for

Fig. 2 Enrolment percentages of all non-white ethnic groups in all included diabetes trials published between 2000 and 2020 ($n = 405$), and in the US trials ($n = 69$) and UK trials ($n = 9$) trials

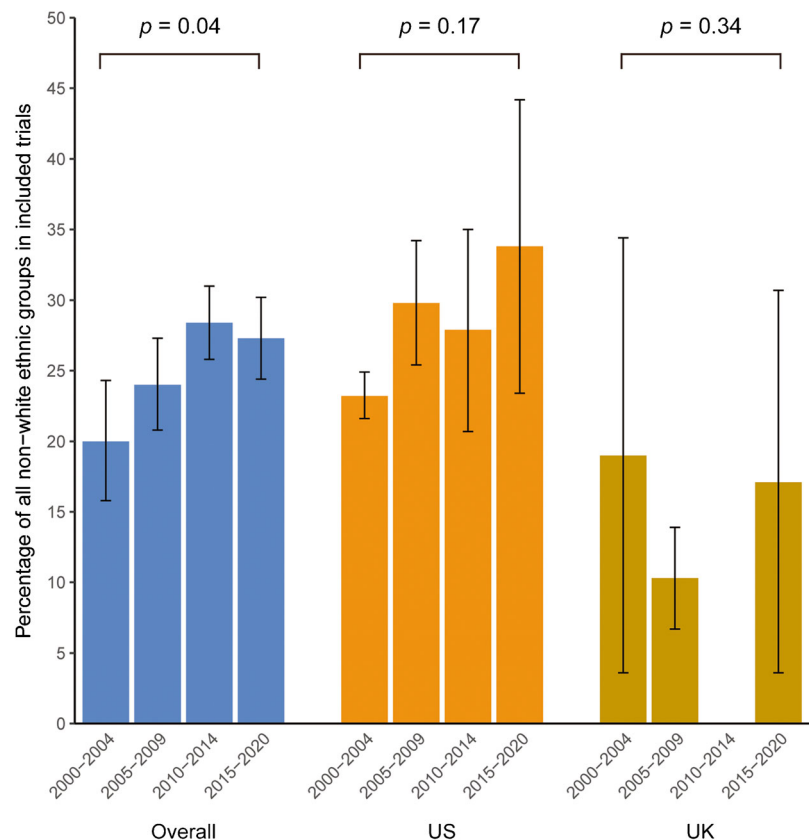


Table 1 Summary of trial characteristics for the included US and UK trials published between 2000 and 2020

Trial characteristic	RCTs performed in the USA (<i>n</i> =69)	RCTs performed in the UK (<i>n</i> =9)
Year of publication		
2000–2004	11 (15.9)	2 (22.2)
2005–2009	23 (33.3)	3 (33.3)
2010–2014	20 (29.0)	0
2015–2020	15 (21.7)	4 (44.4)
Sample size	685 (538, 1191)	2721 (826, 9597)
Patient age (years)	58 (55.0, 60.3)	63 (52.4, 64.0)
Female proportion	46 (40.9, 52.6)	41 (40.9, 43.0)
Trial primary objective		
Glycaemic control	22 (31.9)	4 (44.4)
Management	28 (40.6)	2 (22.2)
Complications	19 (27.5)	3 (33.3)
Mixed	0	0
Had criteria related to ethnicity	0	0
Trial reimbursement for patients	0	0
Outpatient enrolment	33 (47.8)	5 (55.6)
Type of diabetes		
Type 1	0	0
Type 2	44 (63.8)	5 (55.6)
Unspecified	25 (36.2)	4 (44.4)
Type of randomisation		
Individual	67 (97.1)	6 (66.7)
Cluster	2 (2.9)	3 (33.3)
Type of intervention		
Medication	42 (60.9)	2 (22.2)
Lifestyle or education	10 (14.5)	2 (22.2)
Device	5 (7.2)	2 (22.2)
Other	12 (17.4)	3 (33.3)
Frequency of intervention		
>1 time/week	45 (65.2)	4 (44.4)
1–4 times/month	3 (4.3)	1 (11.1)
Other	21 (30.4)	4 (44.4)
Duration of intervention (weeks)	8.6 (6.0, 14.0)	15.0 (6.0, 72.0)
Type of follow-up		
Face to face	23 (33.3)	4 (44.4)
Telephone	2 (2.9)	0
Other	44 (63.8)	5 (55.6)
Frequency of follow-up		
Weekly	1 (1.4)	0
Monthly	4 (5.8)	1 (11.1)
Yearly	4 (5.8)	1 (11.1)
Unknown	60 (87.0)	7 (77.8)
Duration of follow-up (months)	12 (6.0, 24.0)	18 (6.0, 84.0)
Subgroup analysis by ethnicity reported	7 (10.1)	1 (11.1)
Source of funding		
Public or institute	27 (39.1)	0
Industry	33 (47.8)	7 (77.8)
Combination	9 (13.0)	2 (22.2)

Values are *n* (%) or median (Q1, Q3)

Black participants (*n*=5), 12.0% for Asian participants (*n*=4) and 3.1% for other non-white ethnicities (*n*=6).

All distributions of non-white enrolment significantly differed from the ethnic distribution in the diabetes population in the US trials (*p* values <0.01) (ESM Table 4). Similarly, there were significant differences between non-white enrolment in the UK trials and the population distribution (*p* values <0.01). As shown in Fig. 2, no significant temporal change was observed in trials performed in the USA (*p*=0.17) or the UK (*p*=0.34). Figure 3 shows the trend in US trials by specific

ethnicity. A temporal trend was observed for increased enrolment of Black and Asian participants; however, the trend was not significant (ESM Table 4). Inclusion of Hispanic participants fluctuated over time, with a non-significant temporal trend. Likewise, no significant trend regarding enrolment of Black and Asian participants was observed in UK trials.

The under-enrolment rate for all non-white groups in the US trials was 62.3% (43/69), while for a specific non-white subgroup, the under-enrolment rate ranged from 33.3% for other non-white groups (21/63) to 82.4% for Asian

Table 2 Non-white ethnic enrolment percentages in the diabetes trials conducted in the USA and the UK

	All non-white groups	Black group	Hispanic group	Asian group	Other non-white groups
RCTs conducted in the USA					
Number of included trials	69	62	38	34	63
Trial enrolment percentage	29.0 (22.5, 37.9)	13.5 (9.6, 16.4)	11.6 (10.0, 19.5)	2.6 (1.4, 3.8)	3.3 (1.3, 6.5)
RCTs conducted in the UK					
Number of included trials	9	5	0	4	6
Trial enrolment percentage	12.0 (9.4, 21.0)	5.0 (3.4, 5.0)		12.0 (6.5, 38.9)	3.1 (1.1, 9.6)

Values are medians (Q1, Q3)

participants (28/34) (ESM Table 4). The results from univariable logistic regression models are shown in Table 3 and ESM Table 5. For all non-white ethnic groups, trials with a female proportion $\geq 46\%$ showed 78% lower odds of under-enrolment (OR 0.22; 95% CI 0.07, 0.65; $p < 0.01$). Funding from industry was significantly related to increased odds of under-enrolment in all non-white groups when compared with

funding from a public body or institute (OR 4.64; 95% CI 1.50, 14.35; $p < 0.01$). The results from the multivariable linear regression model also showed that funding from industry was significantly related to reduced non-white enrolment ($\beta = -15.44\%$, $p < 0.01$) (ESM Table 6). For Black participants, trials recruiting patients from outpatient settings were more likely to have under-enrolment compared with inpatient

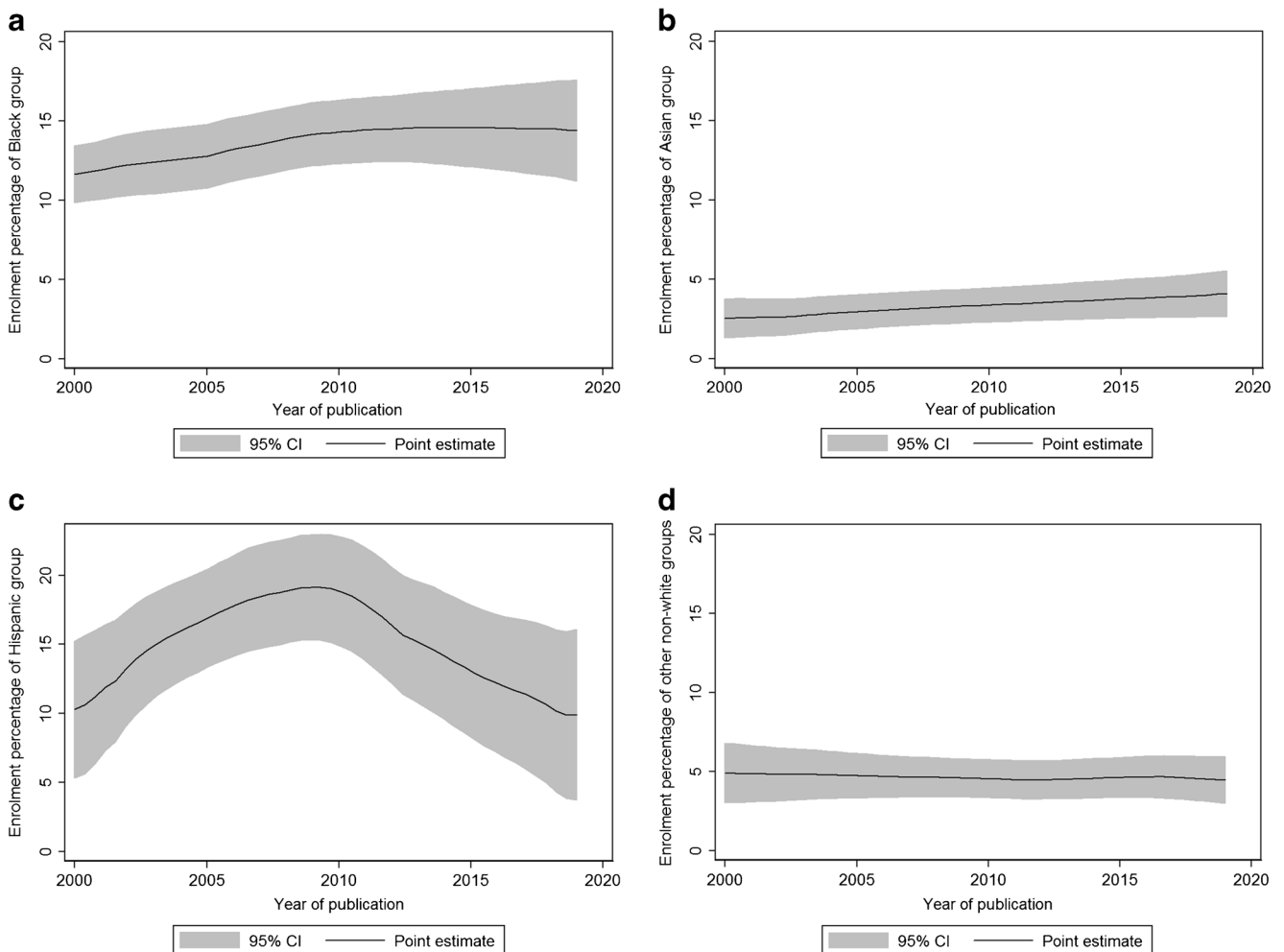


Fig. 3 Temporal trend of enrolment by specific non-white ethnic group in the US trials published between 2000 and 2020. (a) Black participants; (b) Asian participants; (c) Hispanic participants; (d) other non-white participants

Table 3 Relationship between trial characteristics and under-enrolment of non-white ethnic groups based on a univariable logistic regression model in the US trials published between 2000 and 2020

Trial characteristic	Under-enrolment of non-white ethnic groups ^a	
	OR (95% CI)	<i>p</i> value
All non-white groups (<i>n</i> =69)		
Year of publication ≥ 2010	0.38 (0.14, 1.05)	0.06
Female proportion $\geq 46\%$ ^b	0.22 (0.07, 0.65)	<0.01
Source of funding		
Public or institute	Reference	-
Industry	4.64 (1.50, 14.35)	<0.01
Combination	1.56 (0.34, 7.13)	0.57
Black group (<i>n</i> =62)		
Year of publication ≥ 2010	0.37 (0.11, 1.19)	0.10
Female proportion $\geq 46\%$ ^b	0.36 (0.13, 1.03)	0.06
Outpatient enrolment	2.92 (1.02, 8.37)	0.04
Duration of intervention >8 weeks ^b	0.13 (0.04, 0.40)	<0.01
Hispanic group (<i>n</i> =38)		
Year of publication ≥ 2010	1.83 (0.48, 7.07)	0.38
Duration of intervention >8 weeks ^b	3.43 (0.88, 13.39)	0.08
Asian group (<i>n</i> =34)		
Year of publication ≥ 2010	0.20 (0.03, 1.32)	0.09
Duration of follow-up >12 months ^b	5.00 (0.76, 32.93)	0.09
Other non-white group (<i>n</i> =63)		
Year of publication ≥ 2010	0.92 (0.83, 1.02)	0.12

Results shown for year of publication and other factors with a *p* value <0.1; an OR >1 indicates that the trial characteristic was related to increased odds of under-enrolment; results for the full list of factors are shown in ESM Table 5

^a Number (percentage) of included trials with under-enrolment: 43 (62.3%) for all non-white groups, 25 (40.3%) for Black people, 23 (60.5%) for Hispanic people, 28 (82.4%) for Asian people, 21 (33.3%) for other minority groups

^b The cut-off point used was the median value

settings (OR 2.92; 95% CI 1.02, 8.37), while a duration of intervention >8 weeks showed 87% lower odds of under-enrolment (OR 0.13; 95% CI 0.04, 0.40). No significant relationship was found between year of publication and under-enrolment of any specific non-white ethnic group.

Of the UK trials, 77.8% (7/9), 80.0% (4/5) and 75.0% (3/4) showed under-enrolment of all non-white groups, Black participants and Asian participants, respectively. No significant differences in trial characteristics were found between the UK trials with and without under-enrolment of all non-white groups (ESM Table 7).

Discussion

In this chronological survey, we assessed the enrolment of non-white ethnic groups in diabetes RCTs involving multiple ethnicities in the past two decades. There was a trend towards increased participation of non-white ethnic groups in the overall RCTs chronologically, but not in the US or UK trials.

There were significant differences in the non-white group distributions between the trial and diabetes populations, with non-white under-enrolment of 62.3% and 77.8% for the US and UK trials, respectively. The US trials with a high female proportion were significantly associated with lower odds of under-enrolment of all non-white groups, while trials receiving funding from industry had increased odds of under-enrolment.

Although non-white ethnic enrolment appeared to improve over time in the multi-country RCTs, no further explorations could be specifically performed by their study country. Only 12 trial authors indicated that they could not provide the data we requested or had no more data access in our email communications. By contrast, the US and UK trials failed to show a significant temporal trend. Moreover, while all non-white groups accounted for 42.8% and 35.4% of the US and UK diabetes populations, respectively (ESM Table 2), the included trials only had a median percentage of 29.1% in the USA and 12.0% in the UK for non-white enrolment. The non-white under-representativeness of patient enrolment in diabetes

trials thus remained an issue of concern in current practice, in line with a guideline indicating that reductions in health disparities among ethnic groups requires more urgent attention and endeavours [14]. Whether the lack of a temporal trend in non-white enrolment in the USA and the UK would remain robust after incorporating information from the multi-country trials is unknown due to the limited data on specific countries extracted from the multi-country RCTs.

Some authorities or guidelines have advocated the incorporation of ethnicity information into diabetes research [15, 16]. In our study, the enrolment of non-white participants indicated some improvement, but such participants remain largely under-represented in diabetes trials. Previous evidence suggested reasons for non-white under-enrolment in clinical trials, e.g. patients' lack of transportation and childcare, limited access to healthcare and adequate insurance, not being aware of their eligibility, and mistrust of physicians and research [17–19]. More importantly, implicit biased perception from physicians or research of non-white candidates deterred effective communication and clinical interactions with patients, thereby discouraging candidates from participating [20, 21]. Nevertheless, research has found that non-white groups are at least as likely as white groups to participate in trials if they are offered a trial with adequate details provided [22, 23]. Female patients were reported to consent less frequently to participation in trials than men, partly due to fear of adverse health events and negative experiences of research engagement [24, 25]. Enhanced female enrolment may therefore reflect a low level of implicit bias against sex and a better interaction between research personnel and trial candidates. Thus, a high female proportion in trials may be related to increased enrolment of non-white groups for similar reasons during the trial recruitment process. While US federal law and National Institutes of Health guidelines require proportional ethnic representativeness in research funded by the National Institutes of Health [26], industry-funded trials were less likely to recruit non-white groups, yielding an OR for under-enrolment of 4.64 for all non-white groups. Implicit bias against non-white groups may lead research personnel to believe that non-white groups would be poor candidates, with compromised mutual trust and low compliance [27, 28]. The impulse to identify favourable effects of intervention and/or potential conflicts of interest for researchers in industry-funded trials may also consciously or unconsciously discourage them from effectively communicating with non-white candidates. Potential factors related to specific under-enrolment of Black participants included outpatient settings and long intervention durations. Referral bias and/or logistical difficulties in outpatient settings may be important barriers for Black participants in particular [29]. The inverse association between long intervention duration and under-enrolment

of Black participants merits further investigation, with potential improvements such as enhanced community engagement, strategic and cultural motivations for minority involvement, and positive physician–patient relationships [30, 31]. However, these results should be interpreted with caution given the exploratory nature of our analyses, the small number of included trials, with potentially insufficient statistical power and wide imprecision, and potential confounding factors that we were unable to capture.

Non-white ethnic enrolment has been systematically explored in trials relating to cancer [32, 33], vaccines [34, 35], behaviour [36, 37] and cardiology [38, 39]. These analyses either focused on specific high-profile journals [39] or a specific country [35, 36], targeted trials of drugs for approval by the US Food and Drug Administration [38], or covered a short time span [32–34, 37]. However, similar findings were reported in these different areas, i.e. non-white groups were less likely to be enrolled and were under-represented in clinical trials relative to the disease distribution, highlighting the need for more effective strategies to enhance non-white group enrolment.

There are also some epidemiological studies exploring the differences in engagement, management and healthcare service usage between ethnicity in routine practice or some diabetes-related programmes [40–43]. However, we are not aware of any previous study systematically assessing the temporal trend of non-white enrolment in diabetes trials. A recent study has reported non-white ethnic under-representativeness in eight US trials of type 1 diabetes from 2015 and 2020, focusing on technologies approved by the Food and Drug Administration [44]. Unlike this previous work, our study comprehensively investigated non-white enrolment in diabetes RCTs in the past two decades. Another difference is our exploratory results regarding trial characteristics in relation to non-white enrolment, which may provide insights into current trial practices and potentially generate targeted recommendations for enhancing non-white ethnic enrolment.

Despite endeavours and policies aimed at overcoming the social and structural causes of healthcare inequities among ethnic groups, under-representativeness in trial enrolment undermines this goal. Under-enrolment of non-white participants deprives them of the benefits of trial participation [45]. More importantly, results from trials that lack ethnic diversity and representativeness may not be generalisable to non-white groups in clinical practice [46]. Thus, despite the disproportionately higher rates of diabetes in non-white ethnic populations, ethnic differences in effects of genes or gene–environment interactions, patients' responses to interventions, and pathophysiological processes remain largely unknown. Therefore, outcomes stratified by ethnicity are recommended to be reported in Phase III clinical trials, in order to explore the heterogeneity of

intervention effects and improve evidence-based decision-making. Unfortunately, we found that only a small proportion of trials (6.4%) published results stratified by ethnicity, and almost none of them showed a significant ethnic effect modification. Thus, it is not possible to assess the heterogeneity of intervention effects in trials without ethnic subgroup reporting or to evaluate whether selective outcome reporting exists [47]. Equitable selection and enrolment of eligible patients, in combination with predefined ethnicity-related hypotheses and transparent subgroup result reporting, are needed to enhance the credibility and generalisability of trial findings and to mitigate the current practice of ethnic under-representativeness. Furthermore, post hoc analyses of trials and meta-analyses on effect estimates among non-white groups [8, 48], real-world evidence studies [49] and transport studies [50] may be potential solutions in progressing towards improved ethnic representativeness in RCTs.

Strengths and limitations Our assessment may offer insights into improving non-white engagement in future diabetes trials. Another strength was the duplication of study processes, including literature search, screening, data extraction and statistical analyses, to increase the credibility of the study findings. However, some limitations exist in this study. We were unable to obtain data on non-white enrolment by specific country in multi-country trials; therefore, it was unknown to what extent the data from multi-country trials would impact our findings about trial enrolment in the UK and USA. Although we wished to assess non-white representativeness in specific countries, we could only evaluate under-enrolment in US and UK trials due to the lack of other single-country trials and lack of such data from multi-country trials. Likewise, under-enrolment could not be assessed in multi-country trials because no global participation to prevalence ratio is available for the global diabetes population stratified by ethnicity. Similar to previous studies, we assumed that the non-white ethnic distributions in the diabetes population were constant over time. It was not possible to collect data on detailed enrolment strategies, whether the research personnel were members of minority groups, or whether they had a conflict of interest with non-white groups, even though these data may be important factors influencing non-white representativeness. We only included trials in English language, which may omit some eligible studies from analyses and thus impair our study findings. Furthermore, only data on the US trials were used for regression analyses, and these associations between trial characteristics and non-white ethnic enrolment may not be generalisable to other countries or other research areas. Given the small number of included US trials and the occurrence of under-enrolment, no multivariable logistic regression analysis could be performed to adjust for other covariates in the model. Therefore, our exploratory results

regarding trial characteristics in relation to non-white under-representativeness were hypothesis-generating in nature and should be interpreted with caution. In addition, we only included trials of ≥ 400 patients for analysis, which limited further exploration and may compromise our results. Future research is recommended to increase the trial sample size for further analyses by including small-scale trials.

Conclusions In this chronological survey, we observed a temporal trend towards increased non-white ethnic enrolment in diabetes RCTs involving multiple ethnicities globally, but not in the USA or the UK specifically. Non-white ethnic groups were under-represented in most trials performed in the USA and the UK. Some trial characteristics were found to be associated with non-white enrolment, such as the proportion of women, and whether the study was industry-sponsored. These findings provide some evidence regarding non-white ethnic representativeness in diabetes trials over the past two decades, and show that more strategies and endeavours are required to alleviate the under-enrolment of non-white ethnic groups.

Supplementary Information The online version contains supplementary peer-reviewed but unedited material available at <https://doi.org/10.1007/s00125-022-05736-z>.

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Data availability The data used in this study are publicly available in the literature.

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Contribution statement GL, JZ, XS and LT conceived and designed the study. GL, JZ, YW and LT acquired data, performed statistical analyses and interpretation, and drafted the manuscript. HGCVS, PSD, XS and LT provided professional and statistical support, and made several critical revisions to the manuscript. All authors read and approved the final manuscript. GL acts as the guarantor of this work.

References

1. Whitelaw S, Sullivan K, Eliya Y et al (2021) Trial characteristics associated with under-enrolment of females in randomized controlled trials of heart failure with reduced ejection fraction: a systematic review. *European Journal of Heart Failure* 23(1):15–24. <https://doi.org/10.1002/ehf.2034>

2. Mackey K, Ayers CK, Kondo KK et al (2021) Racial and ethnic disparities in COVID-19-related infections, hospitalizations, and deaths: a systematic review. *Annals of Internal Medicine* 174(3): 362–373. <https://doi.org/10.7326/m20-6306>
3. Ejike CO, Woo H, Galiatsatos P et al (2021) Contribution of individual and neighborhood factors to racial disparities in respiratory outcomes. *American Journal of Respiratory and Critical Care Medicine* 203(8):987–997. <https://doi.org/10.1164/rccm.202002-0253OC>
4. Barnes EL, Loftus EV Jr, Kappelman MD (2021) Effects of race and ethnicity on diagnosis and management of inflammatory bowel diseases. *Gastroenterology* 160(3):677–689. <https://doi.org/10.1053/j.gastro.2020.08.064>
5. Chastain DB, Henao-Martínez AF, Young HN (2020) Racial disproportionality in Covid clinical trials. Reply. *New England Journal of Medicine* 383(25):2488–2490. <https://doi.org/10.1056/NEJMc2029374>
6. Carls GS, Tuttle E, Tan RD et al (2017) Understanding the gap between efficacy in randomized controlled trials and effectiveness in real-world use of GLP-1 RA and DPP-4 therapies in patients with type 2 diabetes. *Diabetes Care* 40(11):1469–1478. <https://doi.org/10.2337/dc16-2725>
7. Fanaroff AC, Vora AN, Chen AY et al (2019) Hospital participation in clinical trials for patients with acute myocardial infarction: results from the National Cardiovascular Data Registry. *American Heart Journal* 214:184–193. <https://doi.org/10.1016/j.ahj.2019.05.011>
8. Gan S, Dawed AY, Donnelly LA et al (2020) Efficacy of modern diabetes treatments DPP-4i, SGLT-2i, and GLP-1RA in White and Asian patients with diabetes: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Care* 43(8):1948–1957. <https://doi.org/10.2337/dc19-2419>
9. Goonesekera SD, Yang MH, Hall SA, Fang SC, Piccolo RS, McKinlay JB (2015) Racial ethnic differences in type 2 diabetes treatment patterns and glycaemic control in the Boston Area Community Health Survey. *BMJ Open* 5(5):e007375. <https://doi.org/10.1136/bmjopen-2014-007375>
10. Tahhan AS, Vaduganathan M, Greene SJ et al (2018) Enrollment of older patients, women, and racial and ethnic minorities in contemporary heart failure clinical trials: a systematic review. *JAMA Cardiology* 3(10):1011–1019. <https://doi.org/10.1001/jamacardio.2018.2559>
11. Reza N, Tahhan AS, Mahmud N et al (2020) Representation of women authors in international heart failure guidelines and contemporary clinical trials. *Circulation Heart Failure*. 13(8):e006605. <https://doi.org/10.1161/circheartfailure.119.006605>
12. Scott PE, Unger EF, Jenkins MR et al (2018) Participation of women in clinical trials supporting FDA approval of cardiovascular drugs. *Journal of the American College of Cardiology* 71(18): 1960–1969. <https://doi.org/10.1016/j.jacc.2018.02.070>
13. Farmer AJ, Oke J, Stevens R, Holman RR (2011) Differences in insulin treatment satisfaction following randomized addition of biphasic, prandial or basal insulin to oral therapy in type 2 diabetes. *Diabetes, Obesity & Metabolism* 13(12):1136–1141. <https://doi.org/10.1111/j.1463-1326.2011.01475.x>
14. National Institute for Health and Care Excellence (2018) Promoting health and preventing premature mortality in Black, Asian and other minority ethnic groups. Available from <https://www.nice.org.uk/guidance/qs167>. Accessed 10 Aug 2021.
15. National Institute for Health and Care Excellence (2011) Type 2 diabetes prevention: population and community-level interventions. Available from <https://www.nice.org.uk/guidance/ph35/>. Accessed 20 Jul 2021.
16. Food and Drug Administration (2020) Fighting diabetes' deadly impact on minorities. Available from <https://www.fda.gov/consumers/consumer-updates/fighting-diabetes-deadly-impact-minorities>. Accessed 9 Aug 2021.
17. Rivers D, August EM, Sehovic I, Lee Green B, Quinn GP (2013) A systematic review of the factors influencing African Americans' participation in cancer clinical trials. *Contemporary Clinical Trials* 35(2):13–32. <https://doi.org/10.1016/j.cct.2013.03.007>
18. Hamel LM, Penner LA, Albrecht TL, Heath E, Gwede CK, Eggy S (2016) Barriers to clinical trial enrollment in racial and ethnic minority patients with cancer. *Cancer Control* 23(4):327–337. <https://doi.org/10.1177/107327481602300404>
19. Satcher D, Dawes DE (2021) Race and the patient-physician relationship in 2021. *JAMA* 326(7):595–596. <https://doi.org/10.1001/jama.2021.12454>
20. Hagiwara N, Penner LA, Gonzalez R et al (2013) Racial attitudes, physician–patient talk time ratio, and adherence in racially discordant medical interactions. *Social Science & Medicine* 87:123–131. <https://doi.org/10.1016/j.socscimed.2013.03.016>
21. Fisher JA, Kalbaugh CA (2011) Challenging assumptions about minority participation in US clinical research. *American Journal of Public Health* 101(12):2217–2222. <https://doi.org/10.2105/ajph.2011.300279>
22. Wendler D, Kington R, Madans J et al (2006) Are racial and ethnic minorities less willing to participate in health research? *PLoS Medicine*. 3(2):e19. <https://doi.org/10.1371/journal.pmed.0030019>
23. Svensson K, Ramírez OF, Peres F, Barnett M, Claudio L (2012) Socioeconomic determinants associated with willingness to participate in medical research among a diverse population. *Contemporary Clinical Trials* 33(6):1197–1205. <https://doi.org/10.1016/j.cct.2012.07.014>
24. Ding EL, Powe NR, Manson JE, Sherber NS, Braunstein JB (2007) Sex differences in perceived risks, distrust, and willingness to participate in clinical trials: a randomized study of cardiovascular prevention trials. *Archives of Internal Medicine* 167(9):905–912. <https://doi.org/10.1001/archinte.167.9.905>
25. Mather M, Lighthall NR (2012) Both risk and reward are processed differently in decisions made under stress. *Current Directions in Psychological Science* 21(2):36–41. <https://doi.org/10.1177/0963721411429452>
26. Freedman LS, Simon R, Foulkes MA et al (1995) Inclusion of women and minorities in clinical trials and the NIH Revitalization Act of 1993 – the perspective of NIH clinical trialists. *Controlled Clinical Trials* 16(5):277–285; discussion 286–289, 293–309. [https://doi.org/10.1016/0197-2456\(95\)00048-8](https://doi.org/10.1016/0197-2456(95)00048-8)
27. Sabin JA, Greenwald AG (2012) The influence of implicit bias on treatment recommendations for 4 common pediatric conditions: pain, urinary tract infection, attention deficit hyperactivity disorder, and asthma. *American Journal of Public Health* 102(5):988–995. <https://doi.org/10.2105/ajph.2011.300621>
28. Moskowitz GB, Stone J, Childs A (2012) Implicit stereotyping and medical decisions: unconscious stereotype activation in practitioners' thoughts about African Americans. *American Journal of Public Health* 102(5):996–1001. <https://doi.org/10.2105/ajph.2011.300591>
29. Adams M, Caffrey L, McKeivitt C (2015) Barriers and opportunities for enhancing patient recruitment and retention in clinical research: findings from an interview study in an NHS academic health science centre. *Health Research Policy and Systems* 13:8. <https://doi.org/10.1186/1478-4505-13-8>
30. George S, Duran N, Norris K (2014) A systematic review of barriers and facilitators to minority research participation among African Americans, Latinos, Asian Americans, and Pacific Islanders. *American Journal of Public Health* 104(2):e16–e31. <https://doi.org/10.2105/ajph.2013.301706>
31. Michos ED, Van Spall HGC (2021) Increasing representation and diversity in cardiovascular clinical trial populations. *Nature*

- Reviews Cardiology. 18(8):537–538. <https://doi.org/10.1038/s41569-021-00583-8>
32. Duma N, Vera Aguilera J, Paludo J et al (2018) Representation of minorities and women in oncology clinical trials: review of the past 14 years. *Journal of Oncology Practice* 14(1):e1–e10. <https://doi.org/10.1200/jop.2017.025288>
 33. Loree JM, Anand S, Dasari A et al (2019) Disparity of race reporting and representation in clinical trials leading to cancer drug approvals from 2008 to 2018. *JAMA Oncology*. 5(10):e191870. <https://doi.org/10.1001/jamaoncol.2019.1870>
 34. Flores LE, Frontera WR, Andrasik MP et al (2021) Assessment of the inclusion of racial/ethnic minority, female, and older individuals in vaccine clinical trials. *JAMA Network Open* 4(2):e2037640. <https://doi.org/10.1001/jamanetworkopen.2020.37640>
 35. Huamani KF, Metch B, Broder G, Andrasik MJPHR (2019) A demographic analysis of racial/ethnic minority enrollment into HVTN preventive early phase HIV vaccine clinical trials conducted in the United States, 2002–2016. *Public Health Reports* 134(1):72–80. <https://doi.org/10.1177/0033354918814260>
 36. Houghton CF, Silfee VJ, Wang ML et al (2018) Racial/ethnic representation in lifestyle weight loss intervention studies in the United States: a systematic review. *Preventive Medicine Reports* 9:131–137. <https://doi.org/10.1016/j.pmedr.2018.01.012>
 37. Rosenbaum DL, Piers AD, Schumacher LM, Kase CA, Butryn ML (2017) Racial and ethnic minority enrollment in randomized clinical trials of behavioural weight loss utilizing technology: a systematic review. *Obesity Reviews* 18(7):808–817. <https://doi.org/10.1111/obr.12545>
 38. Chen S, Li J (2021) Participation of Black US residents in clinical trials of 24 cardiovascular drugs granted FDA approval, 2006–2020. *JAMA Network Open* 4(3):e212640. <https://doi.org/10.1001/jamanetworkopen.2021.2640>
 39. Wei S, Le N, Zhu J et al (2022) Factors associated with racial and ethnic diversity among heart failure trial participants: a systematic bibliometric review. *Circulation Heart Failure* 15(3):e008685. <https://doi.org/10.1161/CIRCHEARTFAILURE.121.008685>
 40. Brown AF, Gregg EW, Stevens MR et al (2005) Race, ethnicity, socioeconomic position, and quality of care for adults with diabetes enrolled in managed care: the Translating Research Into Action for Diabetes (TRIAD) study. *Diabetes Care* 28(12):2864–2870. <https://doi.org/10.2337/diacare.28.12.2864>
 41. Mathur R, Palla L, Farmer RE, Chaturvedi N, Smeeth L (2020) Ethnic differences in the severity and clinical management of type 2 diabetes at time of diagnosis: a cohort study in the UK Clinical Practice Research Datalink. *Diabetes Research and Clinical Practice* 160:108006. <https://doi.org/10.1016/j.diabres.2020.108006>
 42. Chandler RF, Monnat SM (2015) Racial/ethnic differences in use of health care services for diabetes management. *Health Education & Behavior* 42(6):783–792. <https://doi.org/10.1177/1090198115579416>
 43. Agarwal S, Schechter C, Gonzalez J, Long JA (2021) Racial–ethnic disparities in diabetes technology use among young adults with type 1 diabetes. *Diabetes Technology & Therapeutics* 23(4):306–313. <https://doi.org/10.1089/dia.2020.0338>
 44. Akturk HK, Agarwal S, Hoffecker L, Shah VN (2021) Inequity in racial-ethnic representation in randomized controlled trials of diabetes technologies in type 1 diabetes: critical need for new standards. *Diabetes Care* 44(6):e121–e123. <https://doi.org/10.2337/dc20-3063>
 45. Brauholtz DA, Edwards SJ, Lilford RJ (2001) Are randomized clinical trials good for us (in the short term)? Evidence for a ‘trial effect’. *Journal of Clinical Epidemiology* 54(3):217–224. [https://doi.org/10.1016/s0895-4356\(00\)00305-x](https://doi.org/10.1016/s0895-4356(00)00305-x)
 46. Clark LT, Watkins L, Piña IL et al (2019) Increasing diversity in clinical trials: overcoming critical barriers. *Current Problems in Cardiology* 44(5):148–172. <https://doi.org/10.1016/j.cpcardiol.2018.11.002>
 47. Chastain DB, Osae SP, Henao-Martínez AF, Franco-Paredes C, Chastain JS, Young HN (2020) Racial disproportionality in Covid clinical trials. *New England Journal of Medicine* 383(9):e59. <https://doi.org/10.1056/NEJMp2021971>
 48. Tang H, Kimmel SE, Hernandez I et al (2022) Are novel glucose-lowering agents’ cardiorenal benefits generalizable to individuals of Black race? A meta-trial sequential analysis to address disparities in cardiovascular and renal outcome trials enrolment. *Diabetes, Obesity & Metabolism* 24(1):154–159. <https://doi.org/10.1111/dom.14540>
 49. Schneeweiss S, Patomo E (2021) Conducting real-world evidence studies on the clinical outcomes of diabetes treatments. *Endocrine Reviews* 42(5):658–690. <https://doi.org/10.1210/endrev/bnab007>
 50. Webster-Clark M, Lund JL, Stürmer T, Poole C, Simpson RJ, Edwards JK (2020) Reweighting oranges to apples: transported RE-LY trial versus nonexperimental effect estimates of anticoagulation in atrial fibrillation. *Epidemiology* 31(5):605–613. <https://doi.org/10.1097/ede.0000000000001230>
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