Trends in baseline HbA1c and body-mass index in randomised placebo-controlled trials of type 2 diabetes from 1987 to 2022: a systematic review and meta-analysis

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Summary

Background Curbing or reversing high glycated hemoglobin (HbA1c) and body mass index (BMI) are two essential parts in the clinical management of type 2 diabetes (T2D). We delineated the changing patterns of the baseline HbA1c and BMI in patients with T2D from placebo-controlled randomised trials to reflect the unmet clinical needs.

Methods PubMed, Medline, Embase and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched from inception to December 19, 2022. Placebo-controlled trials of T2D with reports of baseline HbA1c and BMI were included, of which summary data from published reports were extracted. Pooled effect sizes of baseline HbA1c and BMI of from studies published in the same year were computed in Random-effects model due to the high level of heterogeneity among studies. The main outcome was correlations between the pooled baseline HbA1c, the pooled baseline BMI, and study years. This study was registered in PROSPERO as CRD42022350482.

Findings We identified 6102 studies, of which 427 placebo-controlled trials with 261, 462 participants were finally included in the study. Baseline HbA1c level declined with time (Rs = −0.665, P < 0.0001, I^2 = 99.4%). Baseline BMI increased over the past 35 years (R = 0.464, P = 0.0074, I^2 = 99.4%), rising by around 0.70 kg/m^2 per decade. Patients with BMI ≤25.0 kg/m^2 dropped substantially from the half in 1996 to none in 2022. Patients with BMI ranging from 25 kg/m^2 to 30 kg/m^2 stabilized at 30–40% since 2000.

Interpretation A substantial decline in baseline HbA1c levels and a constant increase in baseline BMI levels was found in placebo-controlled trials through the past 35 years, which indicated the improvement in glycemic control and the urgency for the management of obesity in T2D.

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Keywords: HbA1c; Body mass index; Glycemic control; Obesity; Type 2 diabetes

Introduction

Prevalence of overweight and obesity has been increasing remarkably worldwide.[1] As a major global public health concern, the epidemic of overweight and obesity is strongly associated with the increased risk of type 2 diabetes (T2D).[2,3]

The intricate relationship between obesity and diabetes led to the term "diabesity", which was first proposed by Sims et al., in 1973.[4] "Diabesity" underlined the problem that the majority of individuals with diabetes had overweight or obesity.[5] Thus, it is quite necessary to improve the body weight control to halt the rises in obesity and diabetes. Actually, lifestyle interventions have been demonstrated to be effective in clinical trials and also have been implemented in various national and local diabetes prevention programs.[6,7] Body mass index (BMI) and body

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Translation: For the Chinese translation of the abstract see Supplementary Materials section.

Research in context

Evidence before this study

Prior to conducting our systematic review, we searched PubMed, Medline, Embase and Cochrane Central Register of Controlled Trials (CENTRAL) databases from inception to December 19, 2022 without language restrictions to identify previous studies summarising data about glycemic and weight control from placebo-controlled trials of T2D over years. The following medical subject heading terms were used: type 2 diabetes, placebo-controlled, randomized controlled trials, HbA1c, BMI, metformin, biguanides, sulfonylureas (SUs), thiazolidinediones (TZDs), alpha-glucosidase inhibitors (AGIs), dipeptidyl peptidase-IV inhibitors (DPP-4is), sodium-glucose co-transporter-2 inhibitors (SGLT-2is), glucagon like peptide 1 receptor agonists (GLP-1RAs), dual and triple receptor agonist/antagonists, and insulin. We found that no representative studies have comprehensively investigated the topic of interest. Besides, the separated trends of glycated hemoglobin (HbA1c) and BMI stratified by associated factors such as sex, age, races and treatment types in patients with T2D have not been adequately characterised. In this context, we conducted this meta-analysis to delineate the changing patterns of the baseline HbA1c and BMI in patients with T2D from placebo-controlled randomised trials.

Added value of this study

Our findings showed a substantial decline in HbA1c levels and a constant increase in BMI levels in patients from randomized placebo-controlled trials of T2D over the past 35 years, which suggested the improvement in glycemic control and the urgency to enhance the management of obesity in T2D.

Implications of all the available evidence

The increasing trends of BMI indicated an inadequate management of obesity despite novel antidiabetic therapies with weight-reducing effects have been developed. In addition to lifestyle modifications, appropriate application of novel agents with weight-reducing effects based on the individual evaluation should be encouraged, to promote an improved coverage of novel agents for patients in needs of enhanced management of obesity. It is time for a revolution in the management of diabesity.

weight are increasingly being used as the secondary endpoint for the management of T2D.[8] Curbing or reversing high BMI and body weight is becoming an essential part of the clinical management for diabetes.

With the thriving development of placebo-controlled clinical trials of T2D, it is possible to examine the transitions in the trends of global "diabesity" in the perspective of randomized controlled trials. To our knowledge, no representative studies with consistent study design have comprehensively investigated the changes in glycemic and weight control status over the time among patients with T2D from placebo-controlled randomized trials. Besides, the separated trends of glycated hemoglobin (HbA1c) and BMI stratified by associated factors such as sex, age, races and treatment types in patients with T2D have not been adequately characterised.

Therefore, we aimed to delineate the trends of baseline HbA1c and BMI among patients with T2D by using the data from placebo-controlled randomized trials. This study would provide with new insights for the future designs of randomized controlled trials (RCTs) with investigational hypoglycemic agents and might inspire the innovations in the interventional strategies and research approaches for the management of T2D.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis was conducted based on the criteria of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) protocol. Registration was completed on International Prospective Register of Systematic Reviews (PROSPERO) platform with the number of CRD 42022350482.

According to the guidelines from the Cochrane Handbook for Systematic Reviews for meta-analysis, we searched PubMed, Medline, Embase and Cochrane Central Register of Controlled Trials (CENTRAL) databases from inception to December 19, 2022. Following medical subject headings and free-text search terms were used: type 2 diabetes, placebo-controlled, randomized controlled trials, HbA1c, BMI, metformin, biguanides, sulfonylureas (SUs), thiazolidinediones (TZDs), alpha-glucosidase inhibitors (AGIs), dipeptidyl peptidase-IV inhibitors (DPP-4is), sodium-glucose co-transporter-2 inhibitors (SGLT-2is), glucagon like peptide 1 receptor agonists (GLP-1RAs), dual and triple receptor agonist/antagonists, and insulin. To identify every possibly eligible study, we also screened the references of existing reviews in this field.

The inclusion criteria were as following: (a) placebo-controlled RCTs conducted in patients with T2D; (b) placebo-controlled RCTs with available data on baseline HbA1c and BMI levels; (c) studies published in English. There were no restrictions on the length of follow-up. Two reviewers (ZL and SH) independently browsed the titles, abstracts, full texts and Supplementary materials of potentially eligible studies. Any disagreements were resolved by consultation with a third reviewer (CL).

Data analysis

Two reviewers (ZL and SH) used predefined forms to extract data from eligible studies, including the study characteristics (first author, publication year, sample size, and mean duration of follow-up), participant characteristics (age, sex, race, duration of diabetes, baseline HbA1c and BMI levels), and therapeutic interventions (drug type and dosage). Two reviewers (ZL and SH) worked independently and double checked the extracted data for validation purposes, and independently evaluated the quality of the included studies using the Cochrane risk-of-bias tool. Publication bias was assessed by Begg's test. Any disagreement among reviewers was resolved by consensus.

The outcomes measured in our meta-analysis were pooled effect sizes of baseline HbA1c and BMI of participants from studies published in the same year. We used the random-effects model for analysis due to the high level of heterogeneity among studies.

Subgroup analyses were conducted based on participants' characteristics, including age group (<65 or ≥ 65 years old), sex (male predominant or female predominant), race (Caucasian- or Asians-predominant) and diabetes duration (<10 or ≥ 10 years); study characteristics, including follow-up period (<52 or ≥ 52 weeks) and study design (efficacy and safety evaluation studies or event-driven outcome trials); treatment characteristics, including treatment type (monotherapy or combination therapy), the use of insulin (insulin treatment or non-insulin treatment), the use of particular group of agents (users or non-users) and treatment stages (treatment naïve or non-naïve). Since studies on dual and triple receptor agonist/antagonists were concentrated in the last 5 years, we conducted analyses combining them with GLP-1RAs.

We checked the linearity of the data by visual assessments on the Residual versus Fitted plots (Fig. S1). If the plots had no pattern, and the lowess smoother lines were approximately horizontal at zero, linearity was validated. In this case, Pearson's test and linear regression analysis were performed. If linearity was not confirmed but monotonicity was shown by the scatter plots, Spearman's test was performed to assess the correlations. For the comparative analyses of baseline HbA1c and baseline BMI between the prespecified subgroups, the Wilcoxon test were performed. Statistical analyses were performed by STATA, version 11.0 (STATA, College Station, TX, USA) and SPSS version 27.0. P value < 0.05 was considered as statistically significant.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. XC and LJ had access to dataset and had final responsibility for the decision to submit for publication.

Results

In all, we identified 6102 studies by the literature search, of which 427 placebo-controlled RCTs with 261,462 participants were included in our analysis (Fig. 1). The investigational hypoglycemic agents in the enrolled RCTs covered 10 types of glucose-lowering treatments in our analyses, including biguanides, SUs, TZDs, AGIs, DPP-4is, SGLT-2is, GLP-1RAs, dual and triple receptor agonist/antagonists, and insulin. Among them, 68.04% of the participants were investigated with the combination treatment while 27.49% of the participants adopted monotherapy. Insulin had already been initiated in 33.63% of the participants at baseline while insulin-independent treatment arms were designed in 65.67% of the participants. For HbA1c, I^2 of the synthesized data from the same year ranged from 65.1% to 99.8%. And for BMI, I^2 of the synthesized data from the same year ranged from 62.0% to 99.4%. Baseline characteristics of included studies were summarized in Table S1. The quality assessment by the Cochrane risk-of-bias tool indicated low risk of selective reporting (Table S2). The Begg's funnel plots indicated potential publication bias in the analyses of baseline HbA1c level while no sign of publication bias was revealed in the analyses of baseline BMI level (Fig. S2).

Trends in baseline HbA1c and BMI

Generally, the mean baseline HbA1c level declined with time ($Rs = -0.665$, $P < 0.0001$, $I^2 = 99.4\%$) (Fig. 2A). Mean baseline HbA1c decreased from 10.60% (92.35 mmol/mol) (1987) to 7.92% (63.05 mmol/mol) (2022), with a peak in the early 1990s (more than 11.00%, 96.72 mmol/mol) and a nadir occurring in 2006 (7.56%, 59.12 mmol/mol).

As for the distribution pattern of HbA1c, patients in categories of HbA1c $\geq$ 9.00% (74.86 mmol/mol) decreased from 100% to nearly none during 1987–2022, while patients in categories of HbA1c 7–9% (53.00–74.86 mmol/mol) increased to over 85% (Fig. 3A and B).

Concurrently, the mean baseline BMI increased gradually over the past 30 years ($R = 0.464$, $P = 0.0074$, $I^2 = 99.4\%$), rising by around 0.70 kg/m^2 per decade in placebo-controlled trials of T2D throughout the world (Fig. 2B). Baseline BMI levels were relatively lower in the first 10 years, ranging from 25.99 kg/m^2 to 30.10 kg/m^2, while BMI stabilized at a high level (more than 29.00 kg/m^2) since 1998.

When it comes to degree of obesity, patients with BMI below 25 kg/m^2 dropped substantially from 50% in 1996 to none in 2022. Patients with BMI ranging from 25 to 30 kg/m^2 stabilized at about 30–40% from 2000. Apart from early 1990s, patients with BMI ranging from and 30 kg/m^2 to 35 kg/m^2 increased from 16.67% in 1994 to more than a half in 2010 and ever after. The proportion of patients with BMI over 35 kg/m^2 remained less than 10.00% in most study years, except for a proportion of 25.00% in 1996, a proportion of 20.00% in 2002 and a proportion of 11.43% in 2021 (Fig. 3C and D).

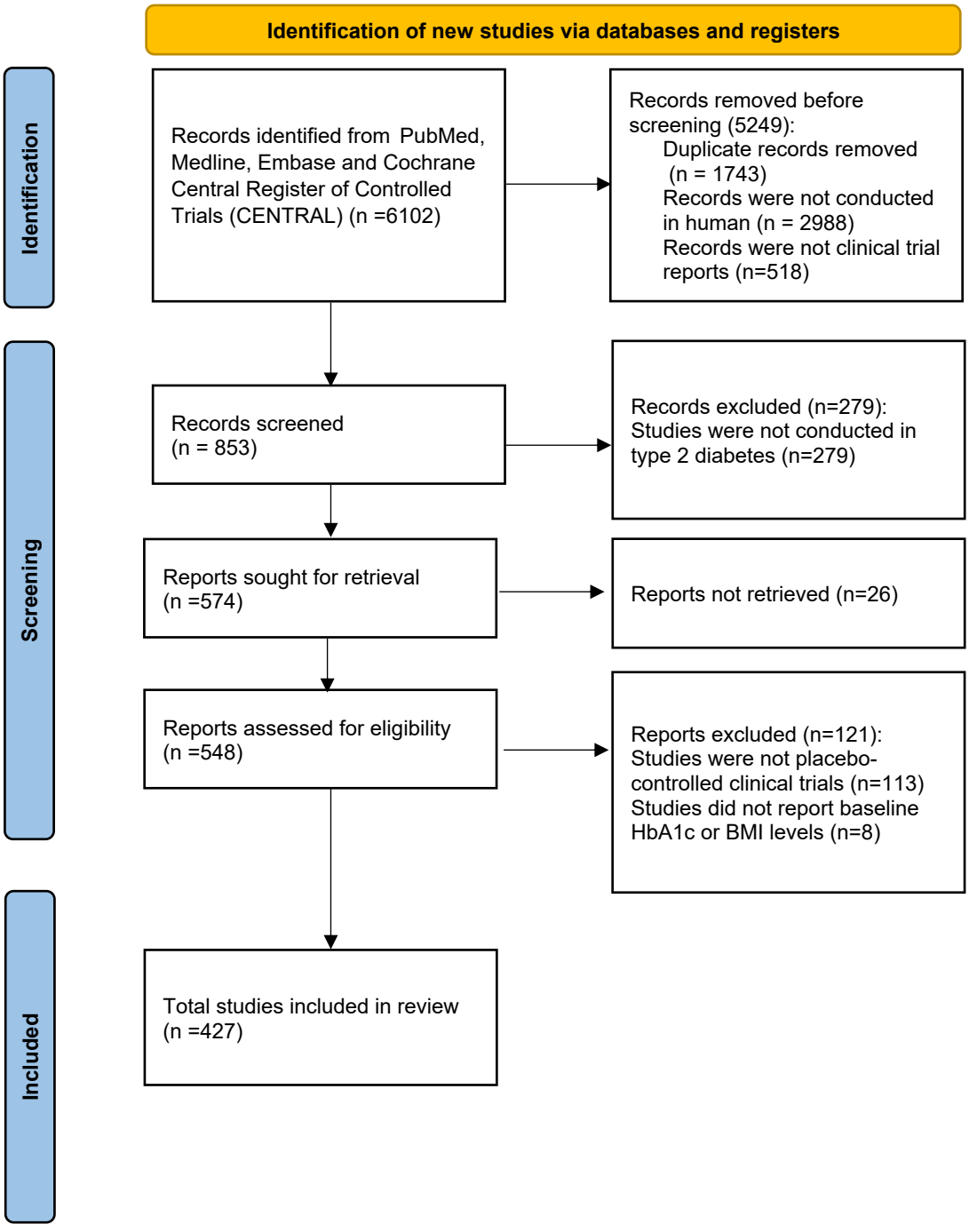

Fig. 1: **The flowchart of the included studies.**

Trends in baseline HbA1c and BMI categorized by variables

Age

Negative correlation between the mean baseline HbA1c and study year was seen in non-elderly patients (non-elderly population: Rs = –0.512, P = 0.0023, I^2 = 98.9%; elderly population: Rs = –0.136, P = 0.63, I^2 = 99.5%, Fig. 4A). HbA1c level was much higher in non-elderly patients than that in elderly population (Z = –3.045, P = 0.0023, Table S3).

In non-elderly population, the mean baseline BMI level had a rise by nearly 0.65 kg/m^2 per decade. While

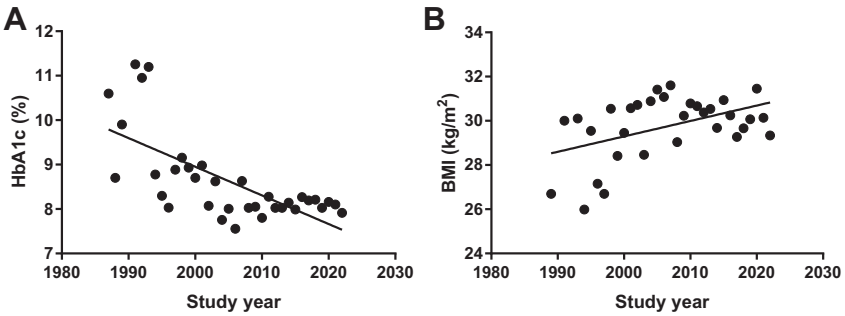

***Fig. 2:* Trends of baseline HbA1c and BMI among patients with T2D in placebo controlled RCTs from 1987 to 2022.** (A) Trends of baseline HbA1c: Rs = −0.665 (P < 0.0001). (B) Trends of baseline BMI: R = 0.464, Y = 0.070X-110.184 (P = 0.0074) *HbA1c, glycated hemoglobin; BMI, body mass index; T2D, type 2 diabetes; RCT, randomized controlled trial.*

in elderly population, no obvious correlation was observed between BMI and time (non-elderly population: R = 0.424, P = 0.020, I^2 = 99.0%; elderly population: Rs = 0.134, P = 0.65, I^2 = 98.4%, Fig. 4B). No statistically significant difference in mean BMI level was found between the two subgroups (Z = 0.105, P = 0.92, Table S3).

Sex

We observed reduction in the trends of HbA1c by year in male predominant studies (male predominant: Rs = –0.382, P = 0.037, I^2 = 99.4%; female predominant: Rs = –0.383, P = 0.053, I^2 = 99.4%, Fig. 4C). Though there was no significant difference on the magnitude of HbA1c level between males and females (Z = 1.600, P = 0.11, Table S3), female patients seemed to have a slightly higher baseline HbA1c level than male patients over the entire observation period.

As for BMI, in female predominant studies, the overall trend of BMI increased with time at nearly 1.40 kg/m^2 per decade (R = 0.611, P = 0.0012, I^2 = 99.0%, Fig. 4D). However, sex-stratified analysis did

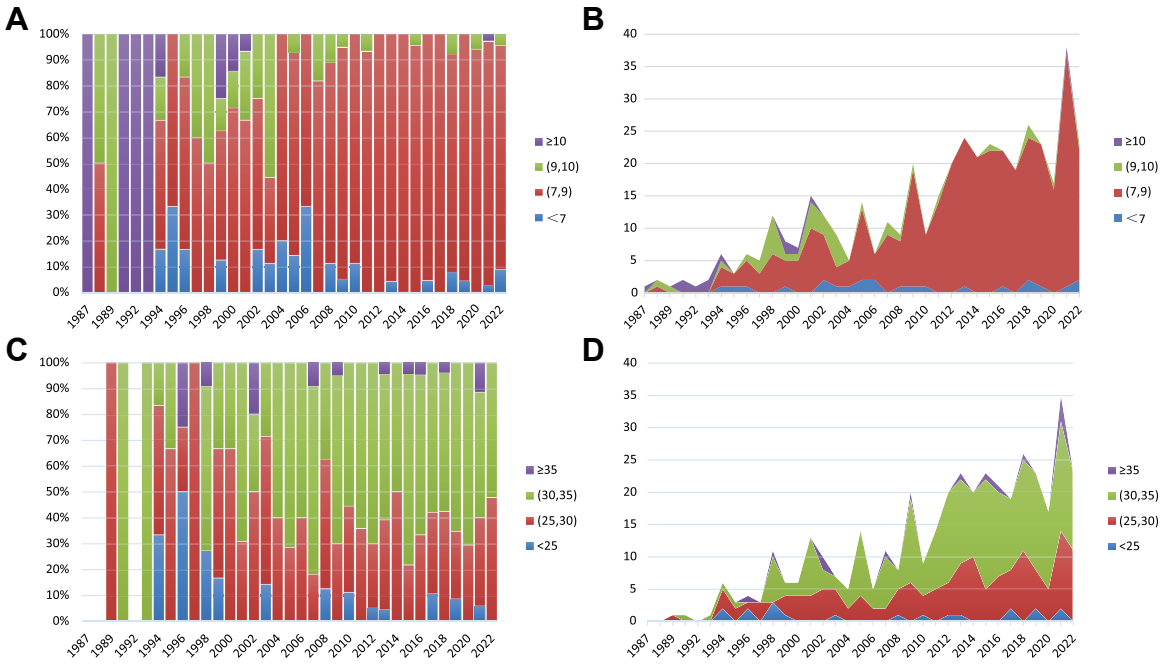

***Fig. 3:* Trial number and its proportion of different baseline HbA1c and BMI categories for patients with T2D in placebo controlled RCTs from 1987 to 2022.** (A) Trial proportions of different baseline HbA1c categories (B) Trial number of different baseline HbA1c categories (C) Trial proportions of different baseline BMI categories (D) Trial number of different baseline BMI categories *HbA1c, glycated hemoglobin; BMI, body mass index; T2D, type 2 diabetes; RCT, randomized controlled trial.*

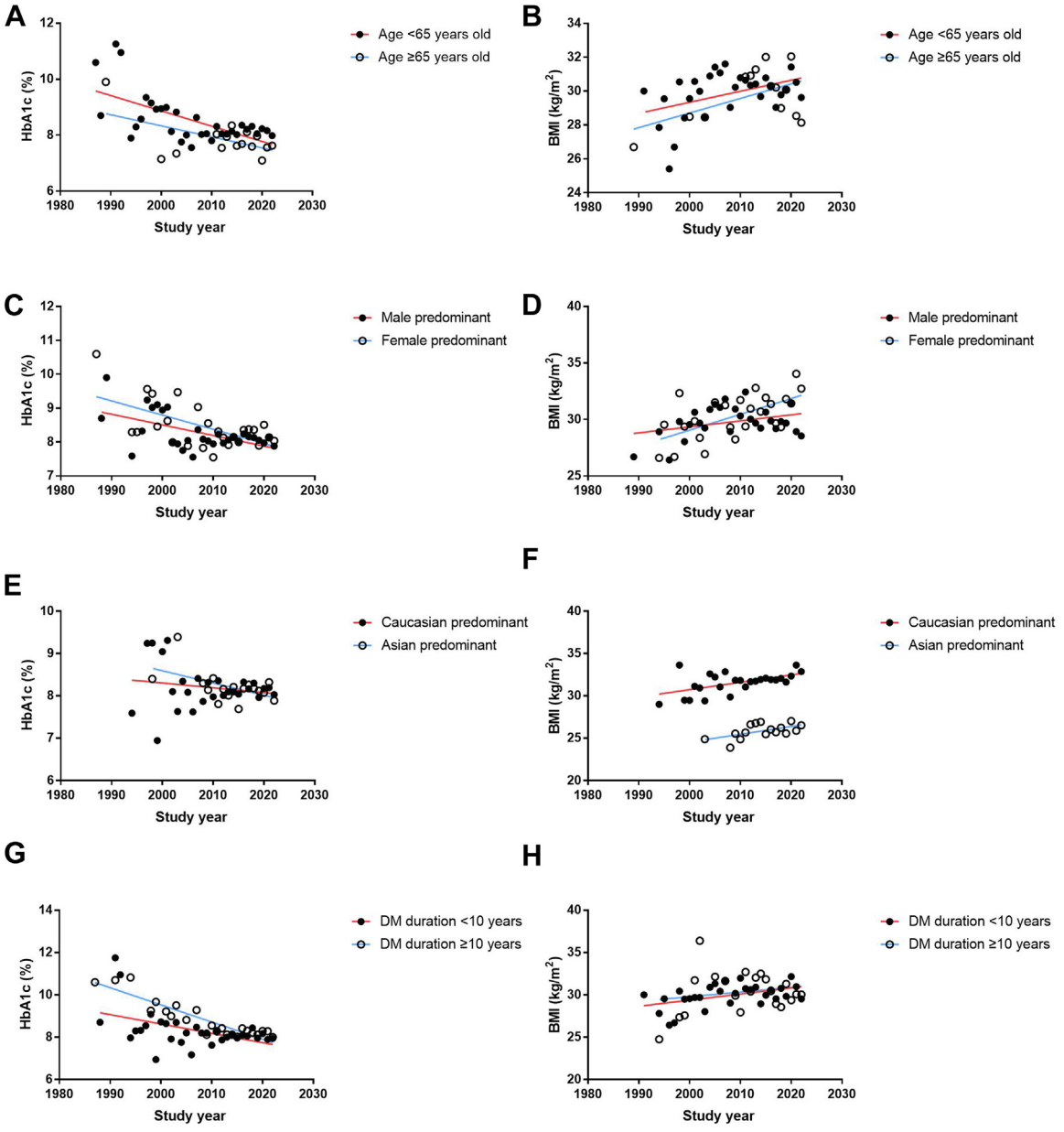

Fig. 4: **Baseline HbA1c and BMI trends categorized by participants' characteristics.** (A) Baseline HbA1c trends categorized by age <65 years old and ≥65 years old: <65 years old: Rs = −0.512 (P = 0.0023); ≥65 years old: Rs = −0.136 (P = 0.63) (B) Baseline BMI trends categorized by age <65 years old and ≥65 years old: <65 years old: R = 0.424, Y = 0.065X-100.951 (P = 0.020); ≥65 years old: Rs = 0.134 (P = 0.65). (C) Baseline HbA1c trends categorized by male and female predominant studies: male predominant: Rs = −0.382 (P = 0.037); female predominant: R = −0.383 (P = 0.053) (D) Baseline BMI trends categorized by male and female predominant studies: male predominant: Rs = 0.194 (P = 0.32); female predominant: R = 0.611, Y = 0.140X-251.220 (P = 0.0012) (E) Baseline HbA1c trends categorized by Caucasian and Asian predominant studies: Caucasian predominant: Rs = −0.097 (P = 0.63); Asian predominant: Rs = −0.404 (P = 0.11) (F) Baseline BMI trends categorized by Caucasian and Asian predominant studies: Caucasian predominant: Rs = 0.487 (P = 0.012); Asian predominant: Rs = 0.553 (P = 0.026) (G) Baseline HbA1c trends categorized by diabetes duration <10 years and ≥10 years: <10 years: Rs = −0.494 (P = 0.0040); ≥10 years: Rs = −0.820 (P < 0.0001) (H) Baseline BMI trends categorized by diabetes duration <10 years and ≥10 years: <10 years: R = 0.477, Y = 0.072X-115.471 (P = 0.0077); ≥10 years: Rs = 0.074 (P = 0.75) *HbA1c, glycated hemoglobin; BMI, body mass index.*

not reveal obvious trend of BMI in male predominant studies (Rs = 0.194, P = 0.32, I^2 = 99.0%). The BMI levels of women over last 35 years were generally comparable with that of men (Z = 1.156, P = 0.25, Table S3).

Races

Baseline HbA1c did not show significant trend through time in Caucasians or Asians (Caucasian predominant: Rs = –0.097, P = 0.63, I^2 = 99.6%; Asian predominant: Rs = –0.404, P = 0.11, I^2 = 99.6%, Fig. 4E). No significant difference was found in HbA1c levels between Caucasians and Asians (Z = –0.047, P = 0.96, Table S3).

We observed both positive correlations between BMI and time in Caucasians and Asians (Caucasians: Rs = 0.487, P = 0.012, I^2 = 97.5%; Asians: Rs = 0.553, P = 0.026, I^2 = 94.4%, Fig. 4F). The mean BMI level was appreciably higher among Caucasians than that in Asians (Z = –3.516, P = 0.0004, Table S3).

Duration of diabetes

Baseline HbA1c levels were negatively related with study year regardless of T2D duration (long duration: Rs = –0.820, P < 0.0001, I^2 = 99.8%; short duration: Rs = –0.494, P = 0.0040, I^2 = 99.1%, Fig. 4G). Baseline HbA1c was constantly higher in patients with T2D duration longer than 10 years compared to those with duration less than 10 years (Z = 3.041, P = 0.0024, Table S3).

When stratified by diabetes duration, no association between baseline BMI and time was found in patients with diabetes duration more than 10 years, while baseline BMI was positively correlated with time in patients with short disease duration, increasing by 0.72 kg/m^2 per decade (long duration: Rs = 0.074, P = 0.75, I^2 = 99.8%; short duration: R = 0.477, P = 0.0077, I^2 = 98.9%, Fig. 4H). Levels of baseline BMI between diabetes duration groups were not significantly different (Z = –0.191, P = 0.85, Table S3).

Follow-up period

323 of all RCTs were with short-term follow-up less than 52 weeks and 100 of all RCTs were with medium/long-term follow-up over 52 weeks. 4 RCTs did not report the specific follow-up duration in the original articles, which were excluded in the sensitivity analysis of follow-up period. Baseline HbA1c levels were negatively associated with study year in population with short follow-up period, while in patients with long follow-up period, no association between baseline HbA1c and time was found (long follow-up period: Rs = –0.412, P = 0.071, I^2 = 99.8%; short follow-up period: Rs = –0.607, P = 0.0001, I^2 = 98.0%, Fig. 5A). No significant differences for the mean HbA1c levels were found between groups (Z = –0.037, P = 0.97, Table S3).

When looking specifically at subgroups with different follow-up time, the increase in BMI was not pronounced regardless of follow-up period (long follow-up period: Rs = 0.261, P = 0.27, I^2 = 99.8%; short follow-up period: Rs = 0.300, P = 0.096, I^2 = 98.6%, Fig. 5B). No significant differences were found in BMI levels between these two groups (Z = 0.805, P = 0.42, Table S3).

Study type

The mean baseline HbA1c was negatively correlated with time in efficacy trials (Rs = –0.776, P < 0.0001, I^2 = 98.9%). Contrary to that in efficacy trials, we observed a positive correlation between the mean baseline HbA1c and time with a rising rate of 0.87% per decade in event-driven outcome trials (R = 0.773, P = 0.0003, I^2 = 99.9%, Fig. 5C).

However, no obvious correlations between the mean baseline BMI level and study year were observed in efficacy trials, while BMI was found to correlate positively with study year in event-driven outcome trials (event-driven outcome trials: Rs = 0.515, P = 0.041, I^2 = 99.3%; efficacy trials: Rs = 0.269, P = 0.14, I^2 = 99.2%, Fig. 5D). No statistically significant difference in mean baseline BMI level was found between the two subgroups (Z = –1.086, P = 0.28, Table S3).

Medications

Monotherapy versus combination therapy

Downward trends in baseline HbA1c with time were observed in combination therapy (monotherapy: Rs = –0.194, P = 0.30, I^2 = 98.4%; combination: Rs = –0.685, P < 0.0001, I^2 = 99.6%, Fig. 6A). Moreover, baseline HbA1c level in patients with combination therapy was higher than that with monotherapy (Z = 2.854, P = 0.0043, Table S3).

No correlation was observed between baseline BMI level and time in monotherapy or combination therapy (monotherapy: Rs = 0.159, P = 0.39, I^2 = 99.0%; combination therapy: Rs = 0.274, P = 0.16, I^2 = 99.0%, Fig. 6B). No significant difference in baseline BMI levels between these two groups was found (Z = –0.216, P = 0.83, Table S3).

Treatment naïve or not

Downward trends in baseline HbA1c with study year were observed in non-naïve patients (treatment naïve: Rs = –0.333, P = 0.096, I^2 = 96.5%; non-naïve: Rs = –0.634, P < 0.0001, I^2 = 99.5%, Fig. 6C). In all, HbA1c level in non-naïve patients was much higher than that in treatment naïve patients (Z = 2.486, P = 0.013, Table S3).

No obvious correlations between the mean baseline BMI level and study year were observed in treatment naïve or non-treatment naïve patients (treatment naïve: Rs = 0.224, P = 0.30, I^2 = 98.5%; non-naïve: Rs = 0.318, P = 0.099, I^2 = 99.4%, Fig. 6D). As for BMI levels, no significant difference was observed between two groups (Z = 1.207, P = 0.23, Table S3).

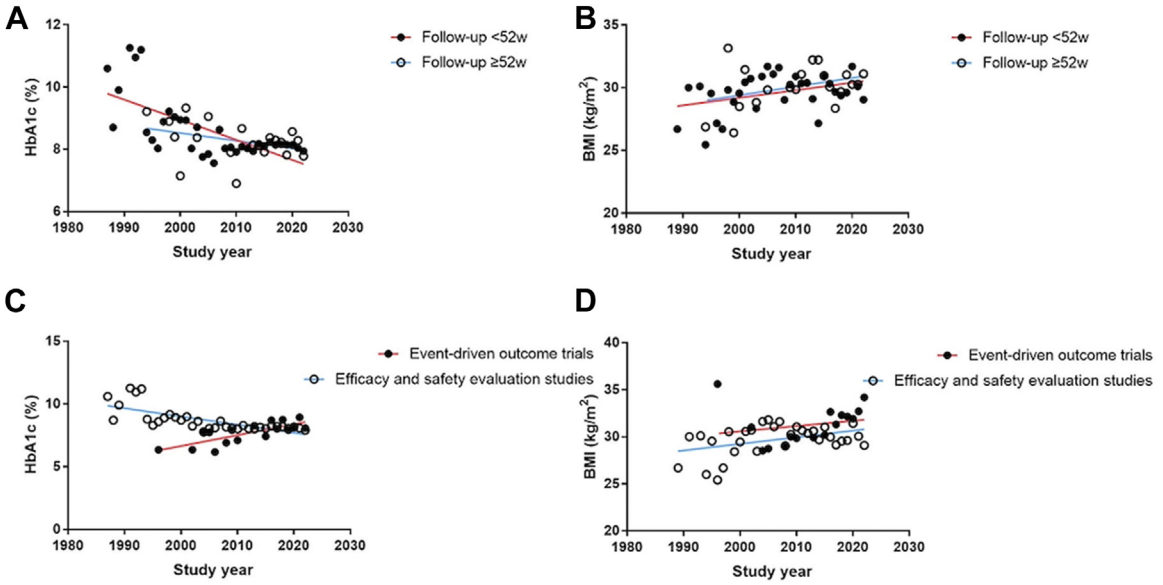

Fig. 5: **Baseline HbA1c and BMI trends categorized by trial characteristics.** (A) Baseline HbA1c trends categorized by follow-up period <52 weeks and ≥52 weeks: Follow-up: <52 weeks: Rs = −0.607 (P = 0.0001); ≥52 weeks: Rs = −0.412 (P = 0.071) (B) Baseline BMI trends categorized by follow-up period <52 weeks and ≥52 weeks: Follow-up: <52 weeks: Rs = 0.300 (P = 0.096); ≥52 weeks: Rs = 0.261 (P = 0.27) (C) Baseline HbA1c trends categorized by event-driven outcome trials and efficacy and safety evaluation studies: event-driven outcome trials: R = 0.773, Y = 0.087X-167.194 (P = 0.0003); efficacy and safety evaluation studies: Rs = −0.776 (P < 0.0001) (D) Baseline BMI trends categorized by event-driven outcome trials and efficacy and safety evaluation studies: event-driven outcome trials: Rs = 0.515 (P = 0.041); efficacy and safety evaluation studies: Rs = 0.269 (P = 0.14) *HbA1c, glycated hemoglobin; BMI, body mass index.*

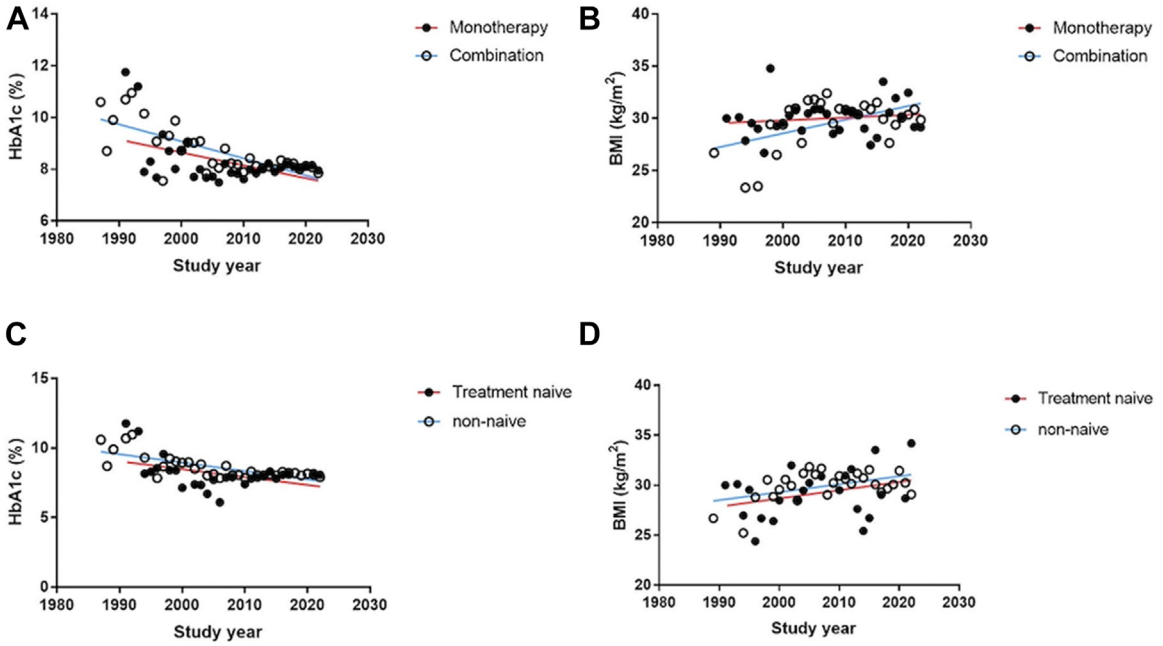

Fig. 6: **Baseline HbA1c and BMI trends categorized by treatment characteristics.** (A) Baseline HbA1c trends categorized by monotherapy and combination therapy: monotherapy: Rs = −0.194 (P = 0.30); combination therapy: Rs = −0.685 (P < 0.0001) (B) Baseline BMI trends categorized by monotherapy and combination therapy: monotherapy: Rs = 0.159 (P = 0.39); combination therapy: Rs = 0.274 (P = 0.16) (C) Baseline HbA1c trends categorized by treatment naïve and non-naïve: treatment naïve: Rs = −0.333 (P = 0.096); non-naïve: Rs = −0.634 (P < 0.0001) (D) Baseline BMI trends categorized by treatment naïve and non-naïve: treatment naïve: Rs = 0.224, P = 0.30); non-naïve: Rs = 0.318 (P = 0.099).

With or without the use of insulin

The mean baseline HbA1c level showed strong negative correlation with study year independent of insulin use (with insulin: Rs = –0.737, P < 0.0001, I^2 = 98.9%; without insulin: Rs = –0.523, P = 0.0026, I^2 = 99.4%, Fig. S3A). Meanwhile, patients with insulin use had a relatively higher baseline HbA1c than that without insulin use (Z = –2.743, P = 0.0061, Table S3).

The trends in BMI showed no correlation with study year no matter insulin was included in the treatment regimens or not (with insulin: Rs = –0.029, P = 0.90, I^2 = 99.7%; without insulin: R = 0.260, P = 0.16, I^2 = 99.0%, Fig. S3B). Nevertheless, patients who adopted insulin as their routine medical therapy seemed to have a higher baseline BMI level since year 2000 although there was no statistically significant difference in the overall comparison (Z = –1.651, P = 0.099, Table S3).

With or without the use of metformin

Similar downward trends in baseline HbA1c with study year were observed in metformin and non-metformin users (with metformin: Rs = –0.541, P = 0.0030, I^2 = 99.2%; without metformin: Rs = –0.500, P = 0.0030, I^2 = 98.8%, Fig. S3C). In all, the HbA1c levels were comparable between metformin and non-metformin users (Z = –0.140 P = 0.89, Table S3).

In metformin users, baseline BMI level showed significant positive correlation with time while no obvious correlations between the mean baseline BMI level and time were observed in non-metformin users (with metformin: Rs = 0.398, P = 0.044, I^2 = 98.9%; without metformin: R = 0.133, P = 0.50, I^2 = 99.4%, Fig. S3D). BMI levels were much higher in metformin users than those non-users, and the difference was statistically significant (Z = –2.372, P = 0.018, Table S3).

With or without the use of SUs

Strong negative correlation between HbA1c and time was found in non-SU users (Rs = –0.487, P = 0.0055, I^2 = 99.4%, Fig. S3E), but not in SU users (Rs = –0.555, P = 0.077, I^2 = 99.6%, Fig. S3E). No significant difference was found in HbA1c levels between SU users and non-users (Z = –0.169, P = 0.87, Table S3).

No obvious correlations between the mean baseline BMI level and study year were observed in SU or non-SU users (with SUs: Rs = 0.500, P = 0.39, I^2 = 99.0%; without SUs: Rs = 0.263, P = 0.15, I^2 = 99.3%, Fig. S3F). The BMI levels over last 35 years were generally comparable in two groups (Z = –0.730, P = 0.47, Table S3).

With or without the use of TZDs

Negative correlation between baseline HbA1c with study year were observed in both TZD and non-TZD users (with TZDs: Rs = –0.759, P = 0.0003, I^2 = 98.1%; without TZDs: Rs = –0.620, P < 0.0001, I^2 = 99.5%, Fig. S3G). In all, there was no statistical difference between two groups in HbA1c level (Z = 0.087, P = 0.93, Table S3).

No obvious correlations between the mean baseline BMI level and time were observed regardless of TZD treatment (with TZDs: Rs = 0.024, P = 0.93, I^2 = 98.0%; without TZDs: Rs = 0.259, P = 0.15, I^2 = 99.5%, Fig. S3H). No statistically significant difference was found in BMI levels between in TZD users and non-users (Z = 1.851, P = 0.064, Table S3).

With or without the use of AGIs

Strong negative correlation between HbA1c and time was found in non-AGI users (Rs = –0.748, P < 0.0001, I^2 = 99.5%, Fig. S4A), but not in AGI users (Rs = –0.098, P = 0.76, I^2 = 99.2%, Fig. S2A). The baseline HbA1c levels were lower in patients with AGI treatment versus those without AGI treatment (Z = 2.275, P = 0.023, Table S3).

No obvious correlations between the mean baseline BMI level and time were observed regardless of AGI treatment (with AGIs: Rs = –0.009, P = 0.98, I^2 = 99.2%; without AGIs: Rs = 0.207, P = 0.26, I^2 = 99.5%, Fig. S4B). The BMI levels over last 35 years were generally comparable in two groups (Z = 0.267, P = 0.79, Table S3).

With or without the use of GLP-1RAs

The mean baseline HbA1c level showed a negative correlation with study year in non-GLP-1RA users (with GLP-1RAs: Rs = –0.385, P = 0.12, I^2 = 98.6%; without GLP-1RAs: Rs = –0.634, P < 0.0001, I^2 = 99.5%, Fig. S4C). The baseline HbA1c levels were comparable between patients with GLP-1RA treatment versus those without GLP-1RA treatment (Z = –0.631, P = 0.53, Table S3).

No obvious correlations between the mean baseline BMI level and time were observed regardless of GLP-1RA treatment (with GLP-1RAs: Rs = –0.193, P = 0.44, I^2 = 99.0%; without GLP-1RAs: Rs = 0.090, P = 0.62, I^2 = 99.4%, Fig. S4D). BMI levels were much higher in GLP-1RA users than those non-users, and the difference was statistically significant (Z = –3.157, P = 0.0016, Table S3).

With or without the use of DPP-4is

Strong negative correlation between HbA1c and time was found in non-DPP-4i users (Rs = –0.641, P < 0.0001, I^2 = 98.6%, Fig. S4E), but not in DPP-4i users (Rs = –0.432, P = 0.094, I^2 = 99.7%, Fig. S4E). Baseline HbA1c level in patients with DPP-4i treatment was higher than that without DPP-4i treatment (Z = –1.965, P = 0.049, Table S3).

The mean baseline BMI was negatively correlated with time in DPP-4i users (Rs = –0.888, P < 0.0001, I^2 = 99.3%). On the contrary, we observed a positive

correlation between the mean baseline BMI and time in non-DPP-4i users (Rs = 0.532, P = 0.0017, I^2 = 99.5%, Fig. S4F).

With or without the use of SGLT-2is

Baseline HbA1c levels were negatively associated with study year in non-SGLT-2i users, but not in SGLT-2i users (with SGLT-2is: Rs = –0.341, P = 0.26, I^2 = 97.1%; without SGLT-2is: Rs = –0.682, P < 0.0001, I^2 = 99.5%, Fig. S4G). No significant differences for the mean HbA1c levels were found between groups (Z = 0.245, P = 0.81, Table S3).

BMI was found to correlate positively with study year in non-SGLT-2i users while negatively with study year in SGLT-2i users (with SGLT-2is: Rs = –0.555, P = 0.049, I^2 = 99.0%; without SGLT-2is: Rs = 0.359, P = 0.044, I^2 = 99.5%, Fig. S4H). There is no significant difference in BMI levels between two groups (Z = 0.734, P = 0.46, Table S3).

Discussion

According to our analysis, among participants with T2D in placebo-controlled randomized trials, baseline HbA1c level has shifted downwards in the past 35 years from 1987 to 2022, while the level of baseline BMI has elevated during the past three decades in this population, with increased proportion of patients with obesity. These findings were in line with data from developed countries before early 2010s,[9] indicating glycemic control has improved in patients with diabetes, while the pandemic of obesity has emerged and developed.[10]

It was well known that compared with the general population, individuals with diabetes were more likely to have cardiovascular disease,[11] renal disease,[12] cancer,[13,14] as well as increased risk of all-cause mortality.[15] At the same time, it was found that intensive glycemic-control policy substantially reduced the risk of multiple diabetes-related endpoints, especially microvascular endpoints.[16] Even the benefits of reduced risk of all-cause mortality were well preserved after 20 years of follow-up in United Kingdom Prospective Diabetes Study (UKPDS).[17] These landmark findings suggested that early detection and intensive treatment of T2D were of great clinical significance, which might be the main reason to explain the reason why baseline HbA1c level shifted downwards in the past 35 years.

As Non-communicable Disease (NCD) Risk Factor Collaboration indicated, the number of adults with diabetes was more than doubled over three decades.[18] Goodarz Danaei et al. also reported the global age-standardized mean fasting plasma glucose (FPG) having increased over years.[19] Diabetes has become an alarming health issue. Meanwhile, measures to promote early detection, prompt diagnosis, continuing care and regular monitoring of diabetes were also undertaken throughout the world, which were recommended by multiple guidelines. Our results indicated that baseline HbA1c level has shifted downwards in the past three decades in participants with T2D in placebo-controlled randomized trials, which might partly reflect the effects from the improvement in the management of diabetes worldwide. Of course, we should realize that there is still great room for improvement of the glycemic control globally.[9] In addition, with more concerns on participants' safety, therapeutic purposes and agent properties, certain restrictions towards the range of HbA1c were set on inclusion criteria in RCTs, which might also lead to an overall decline in HbA1c over the time.

On other hand, according to our study, we also found the continuing rapid increase in BMI among individuals with T2D in placebo-controlled randomized trials in the past three decades. It was supposed that the increasing rate of BMI has been slower in high-income countries since 2000 when compared with the increasing speed in the preceding decades.[10] However, the pandemic of obesity is still spreading over the low- and middle-income countries.[19,20] Hence, the global increase in BMI did not slow down due to the accelerations in the underdeveloped and developing regions. Different from previous studies in general populations, the level of baseline BMI in the placebo-controlled trials seemed to be much higher. Global age-standardized mean BMI from 1975 to 2014 ranged from 21·7 to 24·4 kg/m^2,[10] while the mean baseline BMI levels in our analyses were over 25 kg/m^2 constantly since 1987. Though baseline BMI followed a linear increasing trend generally, the increase in pre-2000 increase was steeper than that in post-2000.

Besides the trend of mean BMI, our study also included its unique scope of the distribution of all BMI categories in participants with T2D during the past three decades. These results might reveal the details of the transition from normal weight to overweight and obesity throughout the world in the perspective of clinical trials. Compared to previous studies in general populations,[10] we found that patients in the distribution of with BMI between 25 kg/m^2 and 30 kg/m^2 and between 30 kg/m^2 and 35 kg/m^2 occupied the majority in the placebo-controlled trials during the past three decades. By contrast, patients with normal weight or morbid obesity did not account for large percentages. This was quite different from that in general populations, where normal weight and overweight prevalence remained higher and underweight was still a public health concern in some poor regions.[10]

It was indicated that the management of obesity was highly beneficial in treating T2D, as weight loss may improve glycemic control[20–22] and cardiovascular outcomes,[23] and reduce the risk of mortality.[24] Thus, it was critical to address the concern of obesity in the treatment of T2D. Several evidence-based recommendations for weight control have been gradually generated for patients with T2D, including behavioral, pharmacologic,

and surgical interventions.[25] Therefore, it is time to consider substantial weight loss as a principal target for the treatment of T2D.[26,27]

However, present interventions and policies seemed to face big obstacles to stop the rise in BMI worldwide.[28–30] We have to admit that current approaches are insufficient achieve global NCD target to halt the rise in obesity.[31,32] Despite novel antidiabetic therapies with weight-reducing effects have developed, like SGLT-2is, GLP-1RAs as well as dual and triple receptor agonists/antagonists, the increasing trends of BMI according to our study indicated an inadequate management of obesity in patients with T2D. It might be associated with inadequate coverage of weight-reducing agents over patients in need of an enhanced weight management. Therefore, in addition to lifestyle modifications, based on the individual evaluations, appropriate application of novel agents that could substantially improve performance on the management of obesity should be encouraged.[33] The decrease trend in baseline HbA1c accompanied by an increase trend in BMI according to our study highlighted the urgency needed for the optimised management of obesity in patients with diabetes.

No difference of the trend of baseline HbA1c or baseline BMI was found between younger and older participants according to our analyses. However, the level of baseline HbA1c was significant higher in younger participants than that of elder ones. Previous investigations showed that patients with early-onset T2D (age at diagnosis ≤45 years) were more likely to present a poor glycemic control.[34,35] Interestingly, we found that the rising trend of baseline BMI in aged population surpassed that in younger population since 2010. It might be associated with a growing proportion of patients who were older and had obesity enrolled in the cardiovascular outcomes trials (CVOTs) or renal outcome trials (ROTs) in recent ten years.

Our results revealed a visually more obvious reduction in mean baseline HbA1c in Asians than Caucasians. In fact, it was suggested that patients with T2D attaining glycemic control in western populations seemed to follow a quadratic trend, roughly rising from 1990s to 2010 but declining from 2010.[36–40] While in Asian populations, owing to several beneficial factors such as launches of multiple initiatives, increase of public awareness and access to novel antidiabetic medications, overall improvements in glycemic control were still observed since 2010.[41–43]

In our study, it was found that baseline HbA1c levels were negatively related with study year regardless of diabetes duration. Consistent with previous studies,[44–47] our analyses showed that the proportion of poor glycemic control increased with diabetes duration.

We observed totally opposite association between mean baseline HbA1c and the study year in event-driven outcome trials versus efficacy trials. Contrary to the negative correlation in efficacy trials, the mean baseline HbA1c increased with time in event-driven outcome trials. Nearly 2/3 of event-driven outcome trials included in our analyses were published after 2010. Participants enrolled in these studies were required to develop several complications like chronic kidney diseases or with additional cardiovascular risk factors. Thus, theses participants were more likely characterised by venerable age, relatively longer disease duration and follow-up period. These patients tended to present poor glycemic control, thus showing different changing pattern compared to those in efficacy trials.

We also performed additional analysis for each medication group to explore the possible correlation between a particular group of agents and the trends in glycemic control and weight control. It turned out that, the use of most agents did not change the declining trend of HbA1c and increasing trend of BMI through the past 35 years. However, our results showed that BMI appeared to decline with time in patients with DPP-4i or SGLT-2i treatment. So far, a variety of evidence indicated a neutral effect on body weight of DPP4is[48–51]. It was supposed that the study design for DPP-4is were becoming more focused on its hypoglycemic effects and cardiovascular safety rather than weight loss.[52,53] Therefore, the BMI criteria for DPP-4i trials might become relatively lower, showing a declining trend. Likewise, SGLT-2is gained extensive attention in recent years for their excellent cardiovascular and renal benefits.[54] Thus, it was supposed that in recent clinical trials, SGLT-2is were more targeted to patients with prior CV events, heart failure, or chronic kidney disease but not those with excessive body weight. However, since the number of studies for DPP-4is and SGLT-2is in this analysis was limited, further investigations with longer observation might contribute to a more comprehensive understanding.

However, our study had several limitations. First, participants from randomized controlled trials were a special selected population, the trends of baseline HbA1c were indeed influenced by the inclusion criteria on HbA1c. Therefore, it cannot fully represent the general population with diabetes. But the trends of HbA1c from participants in randomized controlled trials reflected the transformation in design ideas of trials in diabetes, which was influenced by the change of the general glycemic control status in patients with diabetes. Secondly, the impact of using HbA1c for the diagnosis of diabetes from 2010 may have reduced the amount of data available in trials, especially those who only used fasting plasma glucose or an oral glucose tolerance test. Begg's test also indicated potential publication bias in the analysis of baseline HbA1c. Thus, the results should be interpreted with caution. However, although HbA1c was added to the diagnostic criteria for diabetes after 2010, in those placebo-controlled clinical trials we

collected before 2010, HbA1c was set as one of the inclusion criteria for the trials. That is, although HbA1c was not used as the diagnostic criteria for diabetes at that time, HbA1c was standardly assessed and listed as one of the inclusion criteria for a well-conducted RCT of diabetes. Therefore, even if only fasting plasma glucose or an oral glucose tolerance test was used in some trials before 2010, as long as the HbA1c level as assessed and reported, these data would not be excluded from the study enrollment. Since this study was focused on the participants from RCTs only, we supposed the transition of diagnostic criteria for diabetes would not cause substantial impacts on our analysis. Thirdly, it is true that BMI is just one single surrogate measurement for obesity, it is hard to delineate visceral obesity or central obesity. Therefore, other practical indices that could enrich the dimensions of obesity evaluation such as waist circumference, waist-to-hip ratio, and total adipose tissue of the abdomen should be used in future investigations. Fourthly, a total of 427 studies were included in our analysis, which differed greatly in publication time, study design, treatment regimens, research procedure, leading to substantial heterogeneity among studies. Although we used random-effects model for analysis and conducted subgroup analyses to explore the sources of the high heterogeneity, the high level of heterogeneity of this meta-analysis is still a limitation. Fifthly, a certain race with more than half of the population in the study was considered as predominant. In all included studies, there were two groups of patients, Caucasians and Asians, who met the definition of predominant race. It is true that there were other races included in the trials, but their proportions were quite small. Therefore, due to the small numbers of participants from other ethnic groups (aside from Caucasian or Asian) included in the trials, we were unable to perform any subgroup analyses in other ethnic groups. Sixthly, we believed that a further analysis based on the detailed types of insulin would provide more information and clinical guidance. However, limited data made it difficult to obtain detailed information about the specific type of insulin at baseline and therefore a further analysis was not available. Furthermore, since there is no standard cut-off value to determine the sex predominance in previous literature, for the subgroup analysis of sex, we divided the enrolled studies into two subgroups with the cut-off value at 50% in terms of male percentage. In fact, the significant difference was hard to verify especially when the sex percentage was mildly above or below 50%. Actually, the number of studies with male percentage at 45%–55% is 145 (33.96%). Thus, it might influence the overall trend when stratified by sex. Therefore, the results of the sensitivity analysis on sex should also be interpreted with caution. Further explorations are needed to focus on the sex-difference on the changing pattern of HbA1c and BMI. In addition, several variables, including education level, dietary habit, economic status, and behavioral preference, were not available in most included RCTs. Further investigations are still needed to assess the influences from these factors. Last but not the least, the purpose of this paper is to assess the correlation between HbA1c, BMI and time in patients with T2D, and if possible, to quantify the changing rate over time. Thus, we checked the linearity of the data by visual assessments on the Residual versus Fitted plots. Pearson's test and linear regression analysis or Spearman's test were performed to assess the correlations. More accurate models to simulate these trends might be needed in the future.

In conclusion, trends of baseline HbA1c and BMI in placebo-controlled randomized trials of T2D have changed markedly in the past 35 years. A large decline in HbA1c levels and a constant increase in BMI levels were found, suggesting the improvement in glycemic control and the urgency for the management of obesity in T2D. Overall, it is time to further emphasize the dual strategy of glycemic control and weight control in patients with T2D.

Contributors

LJ and XC conceptualized this study and designed the systematic review protocol; SH, CL and ZL performed the study selection and data extraction; SH and CL performed the statistical analyses; SH, CL and XC prepared the outlines and wrote the manuscript. SH, CL and ZL have directly accessed and verified the underlying data reported in the manuscript. LJ and XC were responsible for the decision to submit the manuscript. All authors contributed to the critical revision of manuscript and approved to submit the manuscript.

Data sharing statement

All data relevant to the study are included in the article or uploaded as supplementary information.

Declaration of interests

Ji L has received fees for lecture presentations and for consulting from AstraZeneca, Merck, Metabasis, MSD, Novartis, Eli Lilly, Roche, Sanofi-Aventis and Takeda. No other support from any organization for the submitted work other than that described above. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101868.

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