






ORIGINAL ARTICLE

WILEY

Patient-reported outcomes in adults with type 1 diabetes in global real-world clinical practice: The SAGE study

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Funding information

This study was funded by Sanofi. Editorial assistance was provided by Arthur Holland, PhD, of Fishawack Communications Ltd, part of Fishawack Health, and was funded by Sanofi

Abstract

Aims: To conduct a secondary analysis of the SAGE study to evaluate the association between glycaemic control and patient-reported outcomes (PROs), in adults with type 1 diabetes (T1DM) across different age groups and regions.

Materials and methods: SAGE was a multinational, cross-sectional, observational study in adults with T1DM. Data were collected at a single visit, analysed according to predefined age groups (26-44, 45-64, and ≥65 years), and reported across different regions. PRO questionnaires were applied to assess hypoglycaemia fear (Hypoglycemia Fear Survey-II), diabetes-related distress (Problem Areas In Diabetes questionnaire), insulin treatment satisfaction (Insulin Treatment Satisfaction Questionnaire), and diabetes-specific quality of life (QoL; Audit of Diabetes-Dependent Quality of Life). Multivariable analysis was performed to evaluate the relationship between glycated haemoglobin (HbA1c) target achievement (<7% and individualised targets) with PRO scores.

Results: The PRO scores showed relatively low levels of diabetes-related emotional distress and fear of hypoglycaemia, moderate to high treatment satisfaction, and low diabetes-related impact on QoL. Results were generally comparable across age groups with some regional variability. Achievement of the HbA1c <7% target was associated with less worry about hypoglycaemia, lower diabetes-related emotional distress, higher insulin treatment satisfaction, and higher QoL. Achievement of individualised HbA1c targets was associated with lower diabetes-related emotional distress and higher insulin treatment satisfaction.

Conclusions: Better glycaemic control was most closely associated with low emotional distress due to diabetes and high patient-reported insulin treatment satisfaction.

KEYWORDS

glycaemic control, hypoglycaemia, observational study, type 1 diabetes

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1 | INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a chronic disease, largely self-managed, affecting both physical health and quality of life (QoL).^{1,2} The QoL of people living with T1DM is somewhat different from that of other populations, due to the burden of disease and treatment self-management, and the associated frequent decision-making required.¹ Indeed, QoL in those with T1DM also includes satisfaction, and psychological and health-related well-being, and thus measuring these patient-reported outcomes (PROs) requires diabetes-specific instruments.¹ Such PRO data from people with T1DM across different global regions and healthcare systems are sparse.

SAGE (Study of Adults' Glycemia in T1DM) was a multinational, observational study undertaken to describe glycaemic control and QoL in adults aged ≥ 26 years with T1DM, by predefined age groups and across 17 countries in five regions outside the United States, with the aim of improving the understanding of T1DM over a person's lifespan. The results for the glycaemic endpoints have previously been published and highlight that glycaemic control remains poor in adults with T1DM.³ Briefly, 24.3% of participants achieved a glycated haemoglobin (HbA1c) level of $< 7\%$, the recommended target for most non-pregnant adults with diabetes, with a higher proportion of achievement in those aged 26 to 44 years (27.6%) than those aged 45 to 64 years (21.0%) and 65 years or above (22.8%).³ However, American Diabetes Association guidelines recommend glycaemic targets should be individualised based on several factors, including patient preference, hypoglycaemia risk, comorbidities, life expectancy and age.⁴ In SAGE, all participants were set individualised HbA1c targets by the treating physician; targets were between 7.0% and 7.5% in the majority of participants (55.9%) and were achieved by 20.9% of participants overall.³ Compared with the younger age groups, a higher proportion of those aged 65 years or above (26.2%) achieved individualised targets, although more people in this age group were set HbA1c targets of $\geq 7.5\%$. The incidence of symptomatic hypoglycaemia (≤ 3.9 mmol/L [70 mg/dL]) in the previous 3 months in SAGE was similar across all age groups (65.7% to 69.6%), while the incidence of one or more severe hypoglycaemia events in the previous 6 months increased modestly with age. Across the different regions analysed, rates of HbA1c target achievement and incidence of hypoglycaemia varied considerably.

An individual's experience of living with and managing T1DM may impact glycaemic and hypoglycaemic outcomes. Diabetes-related emotional distress is an increasingly recognised barrier to the achievement of optimal glucose control.⁵ Health-related QoL (HRQoL) has also been inversely associated with HbA1c levels in people with T1DM^{2,6}; however, the correlation between HbA1c levels and the results of the 36-item Short-Form (SF-36), a generic HRQoL questionnaire, is weak at best.^{2,7} In contrast, diabetes-specific QoL, as measured by the Audit of Diabetes-Dependent Quality of Life (ADDQoL) questionnaire, was independently associated with glycaemic control.⁷ Fear of hypoglycaemia (itself associated with an increase in incident severe hypoglycaemia and the frequency of symptomatic hypoglycaemia), and increased body mass index (BMI) have also both

been associated with significant reductions in QoL in people living with T1DM.⁸

In the present study, we aimed to evaluate the association between diabetes-specific PROs and glycaemic control in adults aged ≥ 26 years with T1DM participating in SAGE, according to age group and across five world regions.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This report presents the results of a secondary analysis of the SAGE study. SAGE was a multinational, cross-sectional, observational study conducted in 17 countries across Asia (India, Japan and Thailand), Eastern Europe (Bulgaria, Croatia, Serbia and Ukraine), Latin America (Argentina, Brazil, Chile and Colombia), the Middle East (Iran and Saudi Arabia) and Western Europe (France, Germany, Italy and the United Kingdom). The study methods have been described previously in detail.³ Briefly, adults aged ≥ 26 years who had T1DM for ≥ 1 year, were being treated with insulin, and had an HbA1c value available were enrolled at one of 230 centres, which were each expected to see ≥ 100 people with T1DM each year. Between January and December 2018, data were collected from patient medical records and interviews during a single physician visit (endocrinologist, general practitioner and other physicians familiar with the management of people with T1DM). Participants were asked to complete paper PRO questionnaires during this visit, with translated and linguistically validated versions of the questionnaires used in each country. No interventions or investigations were performed for the purposes of this study. All participants provided written informed consent. The study was undertaken according to local regulatory requirements, including Institutional Review Board and Independent Ethics Committee approval where appropriate, and was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization guidelines for Good Clinical Practice.

2.2 | Outcomes

The primary endpoint of the SAGE study was to evaluate the percentage of participants achieving HbA1c $< 7\%$ in each predefined age group (26-44, 45-64 and ≥ 65 years). Secondary endpoints included PRO evaluations, which are the focus of the present analysis. The association between PRO scores and glycaemic control, based on the achievement of both a general HbA1c target of $< 7\%$ and individualised HbA1c targets as defined by the treating physician, were also analysed.

2.2.1 | PRO questionnaires

The PROs were assessed using a series of questionnaires, described below. Specific details of the scoring and interpretation of these questionnaires is provided in **Table S1**.

1. Hypoglycemia Fear Survey-II (HFS-II). This is used to assess fear of hypoglycaemia with the behaviour subscale (HFS-B), which measures hypoglycaemia avoidance behaviours, and the worry subscale (HFS-W), which measures worry about hypoglycaemia. Higher scores indicate a greater tendency to avoid hypoglycaemia and greater worry regarding hypoglycaemia, respectively. The sum of the two subscale scores provides the HFS-II total score.
2. Problem Areas In Diabetes (PAID) questionnaire. This is used to assess emotional status. This questionnaire describes negative emotions commonly experienced by those with diabetes, with higher scores indicating a higher level of diabetes-related emotional distress.
3. Insulin Treatment Satisfaction Questionnaire (ITSQ). This was used to assess satisfaction with current insulin treatment and how it affects patients' daily lives. It comprises five subscales (inconvenience of regimen, lifestyle flexibility, hypoglycaemic control, glycaemic control, insulin delivery device satisfaction). Higher scores indicate better treatment satisfaction.
4. Audit of Diabetes-Dependent Quality of Life (ADDQoL) questionnaire. This is used to assess diabetes-specific QoL, whereby the participant's perceptions of the impact of diabetes on their QoL is assessed. The questionnaire comprises 19 items, which measures participant perceptions of the impact of diabetes on specific aspects of their life, and the importance of these aspects on their QoL (higher scores reflecting greater positive impact of diabetes). A further two overview items measure both present QoL (overview item 1) and how QoL would be without diabetes (overview item 2). Higher scores on overview item 1 indicate greater present QoL; lower scores on overview item 2 indicate better potential QoL without diabetes.

2.3 | Data analysis and statistics

Statistical analyses were performed using SAS version 9.4. All analyses were conducted using data from the eligible population; that is, participants meeting the inclusion criteria and none of the exclusion criteria, using descriptive statistics for the overall population and participants within each predefined age group. The definition of eligible participants was extended to include those with an HbA1c value within the previous 45 days (previously 30 days) or with an HbA1c assessment that was due as part of routine practice in the following 15 days (previously 7 days).

The relationship between glycaemic control and PRO scores (HFS-W subscale score [to assess the impact of worry about hypoglycaemia], PAID total score, ITSQ total and five subscale scores, ADDQoL total and two overview item scores) were analysed in the overall population and by age group. Multivariable logistic regression models were performed with glycaemic control (proportion of participants achieving general HbA1c target <7% and individualized HbA1c targets) as a dependant variable, and with each PRO score considered independently as a covariate. Models were first adjusted by region and predefined age groups, then by the interaction between each

PRO score and age group. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were determined for an increase of 10 points in the HFS-W, PAID, and ITSQ scores, and an increase of 1 point in the three ADDQoL scores. Then, independent multivariable analyses were conducted to identify possible confounding factors in the relationship between glycaemic control and each PRO score, including variables related to sociodemographic factors, diabetes complications and comorbidities, T1DM treatment or treatment impacting glycaemia, and structure and process of medical care. Factors identified as significant confounders were used to adjust the multivariable analysis for the relationship between glycaemic control and each PRO score. The significance level was 5% using two-sided tests or CIs. *P* values are provided for descriptive purposes only, due to the descriptive nature of this study. No adjustments for multiple comparisons were undertaken.

3 | RESULTS

3.1 | Participants

Overall, 3903 patients were included in SAGE. The eligible population comprised 3858 patients, of whom 1724 (44.7%) were aged 26 to 44 years, 1512 (39.2%) were aged 45 to 64 years, and 622 (16.1%) were aged 65 years or above. Participants were enrolled in 17 countries across five regions: Asia (*n* = 780), Eastern Europe (*n* = 996), Latin America (*n* = 488), the Middle East (*n* = 444) and Western Europe (*n* = 1150).

Patient characteristics by age and region have been published previously. Briefly, the mean (standard deviation [SD]) participant age was 47.4 (14.0) years, and the mean (SD) BMI was 25.2 (4.5) kg/m² and was similar across the age groups. The mean (SD) duration of diabetes was 20.7 (12.6) years, ranging from 15.9 (9.1) years in those aged 26 to 44 years to 28.8 (15.1) years in those aged 65 years or above. Overall, 20.6% of participants had a family history of T1DM, which was similar across the age groups. The mean (SD) BMI was lowest in Asia (23.3 [4.0] kg/m²) and highest in the Middle East (26.3 [4.8] kg/m²). The mean duration of diabetes was lowest in Asia (16.8 [11.6] years) and highest in Western Europe (23.0 [13.3] years), while the proportion of participants with a family history of T1DM was highest in the Middle East (28.1%), Western Europe (25.0%) and Latin America (24.3%). The use of diabetes technologies was greatest in Western Europe (insulin pump 42.3%, continuous glucose monitoring 46.4%) and lowest in the Middle East (insulin pump 2.7%, continuous glucose monitoring 2.5%; **Table S2**).

3.2 | Patient-reported outcomes

Overall, PRO questionnaires were completed by >99.0% of participants for the HFS-II total and subscales, 99.5% for the PAID questionnaire, >97.0% for the ITSQ total and subscales, and >99.0% for the ADDQoL total questionnaire and overview items.

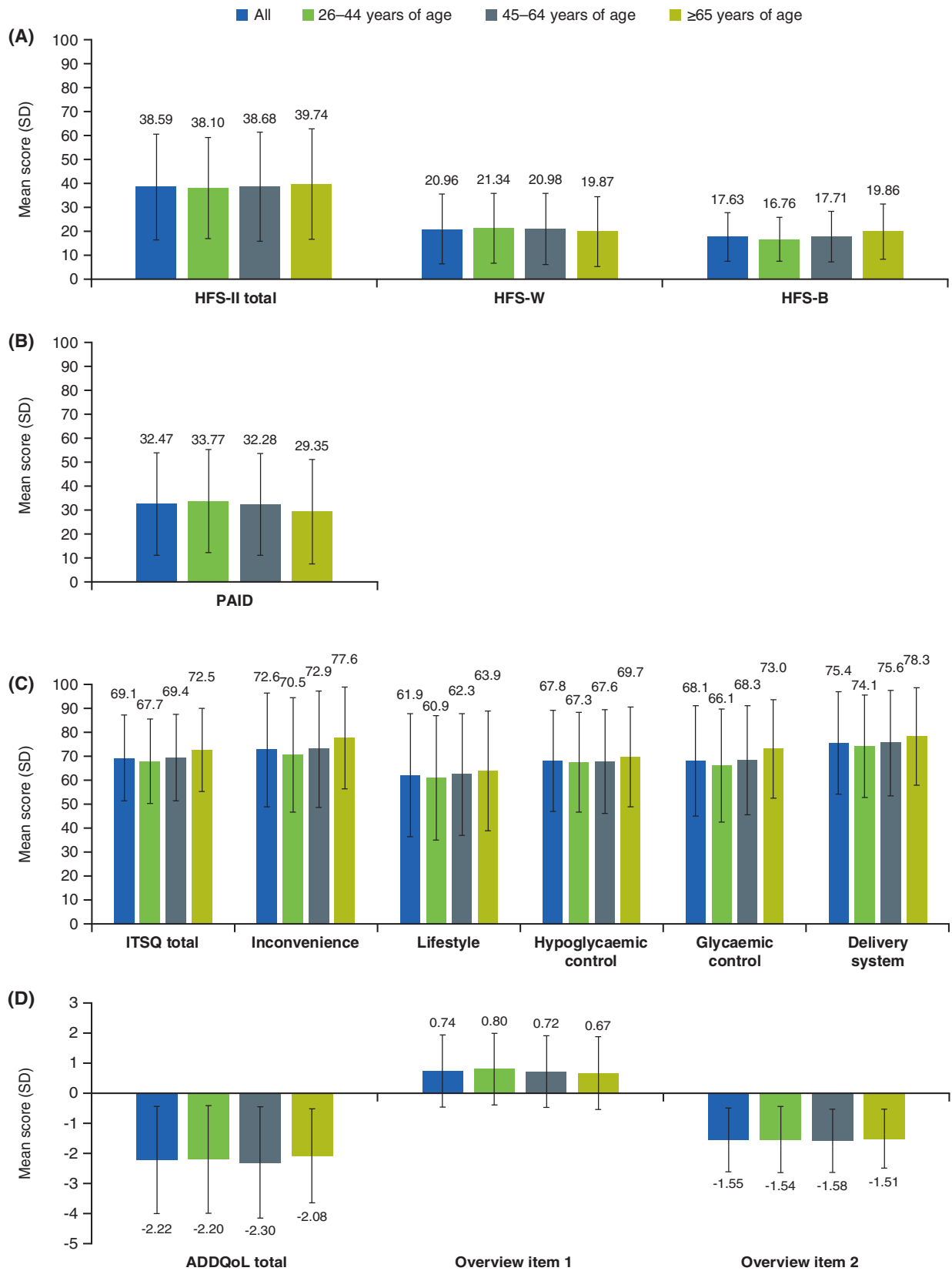


FIGURE 1 Patient-reported outcome scores by age group (eligible population). A) Hypoglycaemia Fear Survey II (HFS-II), B) Problem Areas in Diabetes questionnaire (PAID), C) Insulin Treatment Satisfaction Questionnaire (ITSQ), and D) Audit of Diabetes-Dependent Quality of Life (ADDQoL). HFS-B, Hypoglycaemia Fear Survey II behaviour subscale; HFS-W, Hypoglycaemia Fear Survey II worry subscale; SD, standard deviation

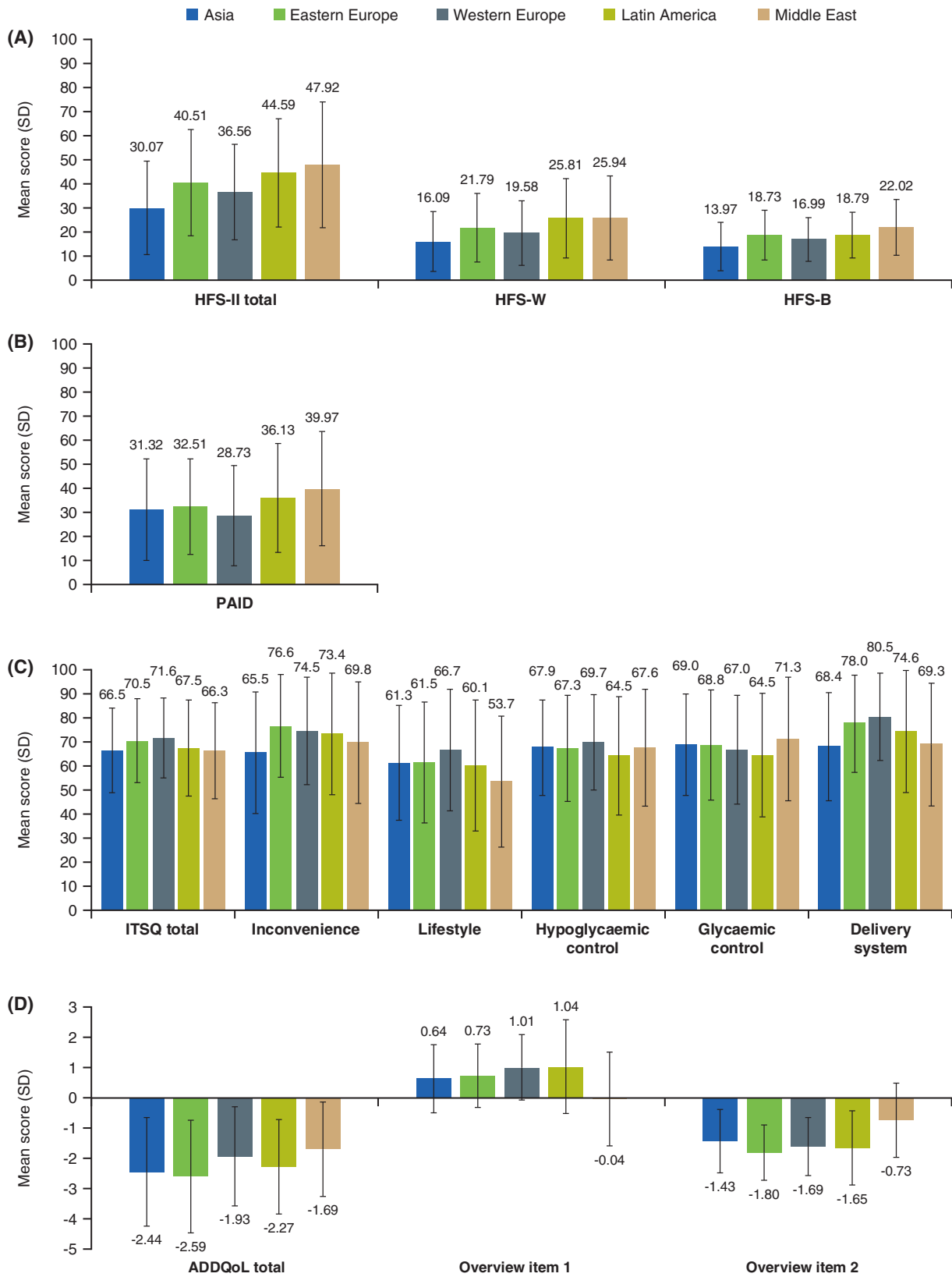


FIGURE 2 Patient-reported outcome scores by region (eligible population). A) Hypoglycaemia Fear Survey II (HFS-II), B) Problem Areas in Diabetes questionnaire (PAID), C) Insulin Treatment Satisfaction Questionnaire (ITSQ), and D) Audit of Diabetes-Dependent Quality of Life (ADDQoL). HFS-B, Hypoglycaemia Fear Survey II behaviour subscale; HFS-W, Hypoglycaemia Fear Survey II worry subscale; SD, standard deviation

3.2.1 | Hypoglycaemia fear

The mean [SD] HFS-II total score, (38.59 [22.11]), HFS-W score (20.96 [14.73]) and HFS-B score (17.63 [10.23]) were similar across the age groups (Figure 1). HFS-II total and subscale scores were lowest in Asia (Figure 2).

3.2.2 | Diabetes distress

The mean (SD) PAID total score was 32.47 (21.48). Similar results were observed in the 26 to 44 years (33.77 [21.45]) and 45 to 64 years (32.28 [21.29]) age groups, while participants aged 65 years or above had the lowest score (29.35 [21.72]; Figure 1). Across the regions, PAID scores were lowest in Western Europe (28.73 [20.76]), and highest in the Middle East (39.97 [23.73]; Figure 2).

3.2.3 | Treatment satisfaction

For insulin treatment satisfaction, the mean (SD) ITSQ total score was 69.14 (17.86). High levels of satisfaction were observed across all ITSQ subscales, with the highest score in the delivery system subscale (75.35 [21.47]), while the lowest score was in the lifestyle subscale (61.91 [25.64]), in the overall population. For all ITSQ scores, there was a slight trend for increasing level of satisfaction with increasing age (Figure 1). When considering the regions, ITSQ total scores were the highest in Eastern and Western Europe (70.46 [17.47] and 71.64 [16.51]) compared with other regions (Figure 2).

3.2.4 | Impact of diabetes on QoL

The mean total score for ADDQoL was -2.22 (1.78), with comparable results across age groups (Figure 1). In the overall population, the score for overview item 1, which assessed present QoL was 0.74 (1.20), while the score for overview item 2, which specifically assessed how QoL would be without diabetes, was -1.55 (1.06). Similar patterns for ADDQoL scores were observed across all regions except the Middle East, where total and overview item 2 scores were highest, while overview item 1 score was lowest (Figure 2).

3.3 | Relationship between PRO scores and glycaemic target achievement

Relationships between the proportion of participants achieving HbA1c <7% and each PRO score, adjusted by region and age group, are presented in Figure 3A. In the overall population, achievement of HbA1c target <7% was significantly associated with lower HFS-W scores (OR 0.94 [95% CI 0.89 to 0.99]), lower PAID scores (OR 0.90 [95% CI 0.87 to 0.93]), and higher scores in the ITSQ total (OR 1.15 [95% CI 1.10 to 1.20]) and all subscales except for lifestyle. The

strongest association was observed between HbA1c target achievement and the ITSQ glycaemic control subscale (OR 1.25 [95% CI 1.20 to 1.29]). HbA1c <7% achievement was also associated with higher ADDQoL total (OR 1.05 [95% CI 1.01 to 1.10]) and overview item 1 (present QoL) scores (OR 1.13 [95% CI 1.06 to 1.21]), whereas there was no significant association with ADDQoL overview item 2 (potential QoL without diabetes) scores.

Relationships between the proportion of patients achieving physician-defined individualised HbA1c targets and each PRO score, adjusted by age and region, are presented in Figure 3B. In the overall population, individualised target achievement was significantly associated with lower PAID scores (OR 0.93 [95% CI 0.89 to 0.97]), and higher scores in the ITSQ total (OR 1.11 [95% CI 1.06 to 1.16]) and all subscales except for lifestyle. Similar to the result for general glycaemic control, the strongest relationship between ITSQ score and individualised target achievement was observed for the glycaemic control subscale (OR 1.21 [95% CI 1.16 to 1.25]). No association was observed between individualised target achievement with HFS-W and ADDQoL scores in the overall population.

After adjustment for the interaction between PRO scores and age group, there was no significant impact of age on the relationship between general glycaemic control and any of the PRO scores ($P > 0.05$; Figure 3A). However, for the relationship between individualised glycaemic control and PRO scores (Figure 3B), a significant impact of age was demonstrated for ITSQ inconvenience and delivery system subscales ($P = 0.045$ and $P = 0.030$, respectively) and ADDQoL overview item 2 ($P = 0.018$). With higher ITSQ inconvenience and delivery system scores, the likelihood of achieving individualised targets increased with age. Higher ADDQoL overview item 2 scores in the age group 26 to 44 years were more likely to be associated with individualised target achievement compared with older age groups (Figure 3B).

After adjustment for possible confounders (Table S3), the association between HbA1c <7% achievement and higher ITSQ total score remained significant. Similar results were observed for ITSQ inconvenience, hypoglycaemic control, glycaemic control, and delivery system scores (Figure 4A). The association between HbA1c <7% achievement and lower PAID scores also remained significant. After adjustment for possible confounders (Table S4), the associations between individualised target achievement with ITSQ total, inconvenience, and glycaemic control scores, as well as PAID scores remained significant (Figure 4B). However, associations between individualised target achievement with higher ITSQ hypoglycaemic control and delivery system subscale scores were no longer significant after adjustment for possible confounders.

4 | DISCUSSION

In this analysis of the global SAGE study, PRO scores showed relatively low levels of diabetes-related emotional distress and fear of hypoglycaemia, moderate to high treatment satisfaction, and low diabetes-related impact on QoL, across the study populations. When

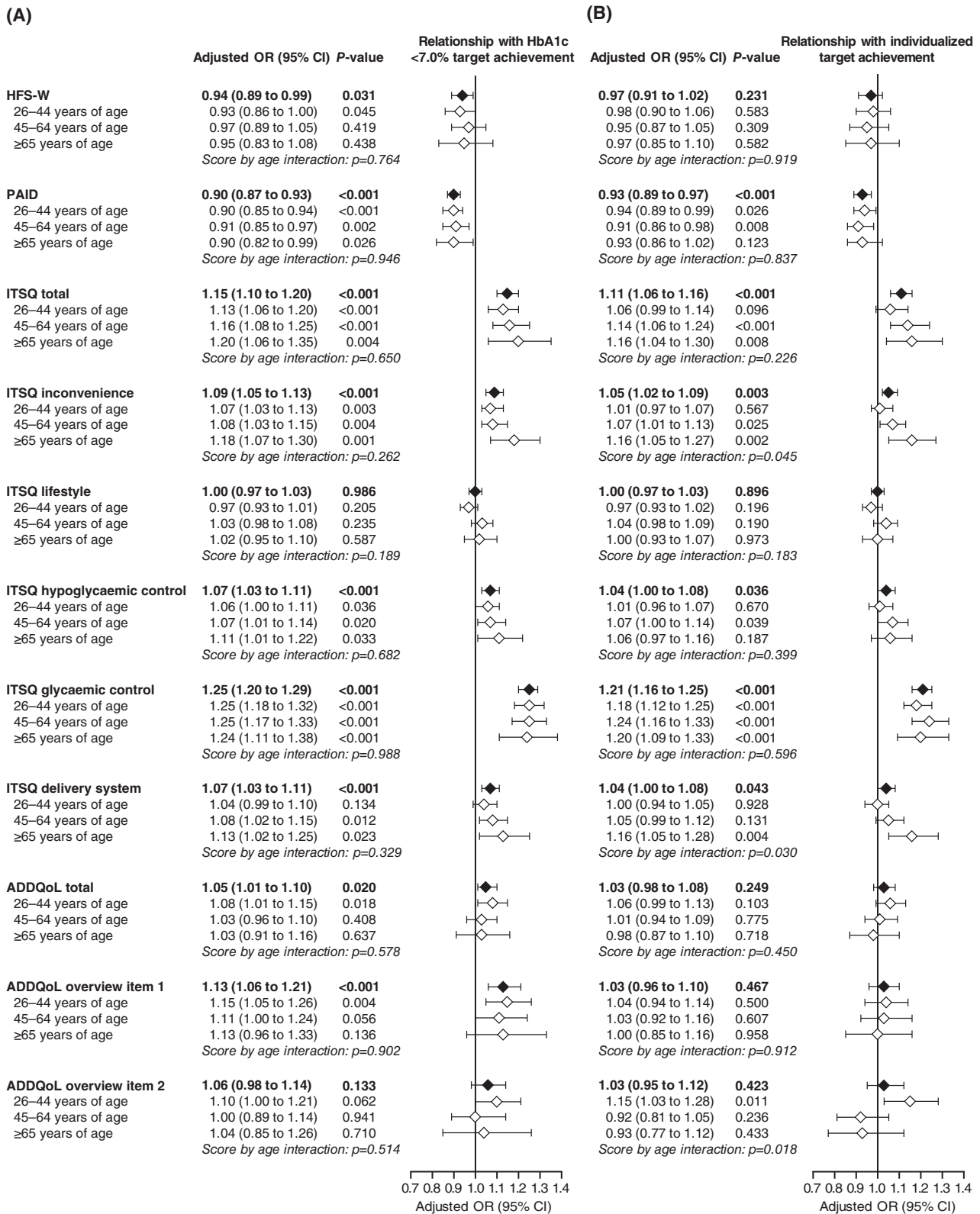


FIGURE 3 Relationship between glycaemic control (A, proportion of participants achieving glycated haemoglobin [HbA1c] <7% and B, proportion of participants achieving their individualised HbA1c target) and each patient-reported outcome score (eligible population). Adjusted odds ratios, 95% confidence intervals (CIs) and P values based on logistic regression with glycaemic control (proportion of patients achieving HbA1c <7%) as a dependent variable, with each score considered independently as a covariate, adjusted by region and predefined age groups. ADDQoL, Audit of Diabetes-Dependent Quality of Life; HFS-W, Hypoglycaemia Fear Survey II worry subscale; ITSQ, Insulin Treatment Satisfaction Questionnaire; PAID, Problem Areas in Diabetes questionnaire

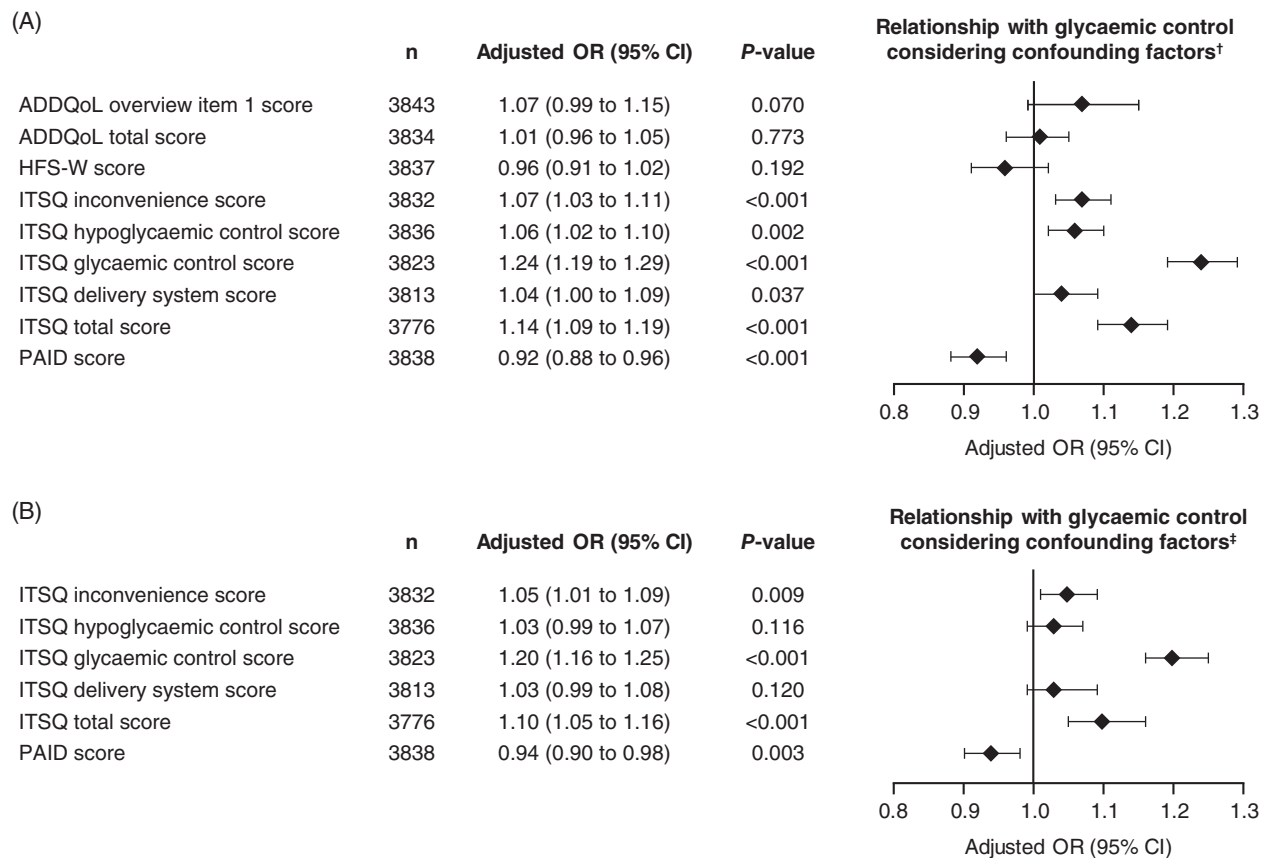


FIGURE 4 Relationship between glycaemic control (A, proportion of participants achieving glycated haemoglobin [HbA_{1c}] <7% and B, proportion of participants achieving individualised HbA_{1c} target) and patient-reported outcome (PRO) scores (eligible population), adjusted for confounding factors. Odds ratio (OR) for an increase of 10 points in the Hypoglycaemia Fear Survey II worry subscale (HFS-W), Problem Areas in Diabetes questionnaire (PAID) and Insulin Treatment Satisfaction Questionnaire (ITSQ) scores and OR for an increase of 1 point in the Audit of Diabetes-Dependent Quality of Life (ADDQoL) scores, based on multivariate logistic analysis with confounding factors considered in the model. [†]See Table S3 for confounding factors identified for relationship between glycaemic control (proportion of participants with T1DM achieving HbA_{1c} <7%) and PRO scores. [‡]See Table S4 for confounding factors identified for relationship between glycaemic control (proportion of people with T1DM achieving individualised HbA_{1c} target) and PRO scores. CI, confidence interval

considering present QoL specifically, the global score indicated a neutral impact of diabetes.

Multivariable analyses indicated that lower diabetes-related emotional distress and higher insulin treatment satisfaction reported by patients are associated with achievement of both general (HbA_{1c} <7%) and individualized HbA_{1c} targets. Relatively low levels of diabetes-related distress have previously been observed in adults with T1DM,⁹⁻¹¹ although a study including participants with T1DM and T2DM did identify 45% of participants as having “high distress” using a cut-off score of ≥ 40 on the PAID scale.¹² Similar to SAGE, other studies have reported a significant association between higher levels of distress and worse glycaemic control.^{10,11,13} For diabetes treatment satisfaction, high scores on the ITSQ assessment have been reported regardless of previous insulin delivery system used,¹⁴ although satisfaction has also been shown to improve with use of insulin pump versus multiple daily injections.¹⁵ Other analyses have shown poor diabetes-related satisfaction to be associated with higher HbA_{1c} levels in adults and adolescents,^{16,17} supporting the results from SAGE. Notably in SAGE, the association between target

achievement and treatment satisfaction was particularly strong for the ITSQ glycaemic control subscale, which specifically evaluates the patient's satisfaction with their insulin treatment to control glucose levels.

In contrast to the multivariable analysis of distress and treatment satisfaction, lower worry about hypoglycaemia and higher ADDQoL total scores (lower impact of diabetes on QoL) were only associated with achievement of the general HbA_{1c} target, but these relationships disappeared after adjusting for confounders. The lack of association between worry of hypoglycaemia and individualised target achievement could reflect the higher HbA_{1c} levels set as individualised targets (mostly 7.0%-7.5%), particularly in the older age groups. Experiencing severe hypoglycaemia has previously been shown to be associated with increased hypoglycaemia fear scores,^{8,18} and the relatively low fear of hypoglycaemia observed in SAGE could conceivably reflect the perception that less intensive HbA_{1c} targets reduce the risk of hypoglycaemia. However, the association between hypoglycaemia events and PROs was not assessed in SAGE, and it is important to note that the relationship between HbA_{1c} levels and

hypoglycaemia is nonlinear, with both particularly low and high levels having been linked with a greater risk of hypoglycaemia.¹⁹ Also reflecting results from SAGE, ADDQoL scores showing overall neutral general QoL, and a relatively low negative impact of diabetes, have been reported in adults with T1DM.²⁰ Although some gender differences on specific domains of the ADDQoL were observed, only the presence of diabetes complications was found to be a significant predictor of lower QoL in the study, whereas factors including age, BMI and HbA1c were not.²⁰ Similarly, this analysis of SAGE showed no association between ADDQoL and HbA1c target achievement after adjusting for potential confounders including age and BMI, therefore HbA1c control may not be relevant for how people living with diabetes perceive the impact of diabetes on their QoL. This lack of correlation between HbA1c and QoL has been reported elsewhere,²¹ but other studies provide conflicting results showing a significant inverse relationship between HbA1c and QoL, in both adults and children.^{1,2,6,22}

Patient-reported outcomes and their association with glycaemic control may be affected by age and regional differences in T1DM management as well as cultural perceptions and healthcare system-related factors, including access to newer therapies and technologies. Some differences across age groups and regions in participant education levels, employment, health insurance and technology use were described in the primary SAGE report.³ However, PRO scores were generally comparable across age groups, while more variability was observed among regions. Discrepancies between the actual experience of hypoglycaemia or target achievement, and the PROs related to these factors, could reflect differences in healthcare access and diabetes education,^{12,23} which may impact how individuals understand hypoglycaemia and treatment success. However, it is important to note that any regional differences reported in this study are purely descriptive.

This analysis of the SAGE study provides insights into PROs and their relationship with glycaemic control, in a large international population of adults with T1DM. The analysis shows surprisingly consistent PRO results, despite the large variability of healthcare systems across the regions. Nevertheless, there is a lack of representation from North America, Africa, and even certain countries within each analysed region. Another limitation is the cross-sectional design of the study, which does not allow for any temporal or directional association between PROs and glycaemic control to be determined. Furthermore, any interpretation of the results must consider the healthy survivor effect, particularly in the older age group. This selection bias may further limit how representative the study population is of patients in each region.

In conclusion, this analysis of the SAGE study indicates people with T1DM reported a relatively low impact of diabetes on hypoglycaemia fear, emotional distress and QoL, and a moderate to high insulin treatment satisfaction, despite suboptimal glycaemic control observed in populations across regions and age groups. Better glycaemic control was most closely associated with patient-reported insulin treatment satisfaction (especially satisfaction in the ability of their insulin treatment to control their blood glucose levels) and low emotional distress due to diabetes; therefore, better understanding of how PROs and levels of glycaemic control influence each other may help improve the management of adults with T1DM.

ACKNOWLEDGMENTS

This study was funded by Sanofi. Editorial assistance was provided by Arthur Holland, PhD, of Fishawack Communications Ltd, part of Fishawack Health, and was funded by Sanofi. Coordination of the development of this manuscript and assistance with the revision was provided by Sirisha Pedapudi, MSc, MS, at Sanofi.

CONFLICT OF INTEREST

Emma G. Wilmot reports personal fees from Abbott Diabetes Care, Dexcom, Eli Lilly, Insulet, Medtronic, Novo Nordisk and Sanofi. Kelly L. Close reports subscription fees, refer to closeconcerns.com, and nonprofit contributions, refer to diaTribe.org. Dubravka Jurišić-Eržen reports Consultancy fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Sanofi Aventis and Takeda. Daniela Bruttomesso has served as a consultant/speaker for Abbott, Eli Lilly, Movi, Novo Nordisk, Roche Diagnostics and Sanofi. F. Javier Ampudia-Blasco has served as a consultant/advisor for Abbott Diabetes Care, AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, LifeScan, MannKind Co., Medtronic, Menarini, Merck, Novartis, Novo Nordisk and Sanofi, and as a speaker for Abbott Diabetes Care, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, LifeScan, Eli Lilly, Madaus, Medtronic, Menarini, Merck, Novartis, Novo Nordisk and Sanofi, and has received grant support from Novo Nordisk and Sanofi. Zsolt Bosnyak was an employee of and holds stocks/shares in Sanofi (at the time when this work was conducted but has since left the company). Aude Roborel de Climens was an employee of and holds stocks/shares in Sanofi (at the time when this work was conducted but has since left the company). Gregory Bigot is an employee of Ividata Life Sciences, mandated by Sanofi. Anne Peters has served as a consultant/advisor for Abbott Diabetes Care, Bigfoot, Boehringer Ingelheim, Eli Lilly, Livongo, MannKind, Novo Nordisk, Sanofi and Whole Biome, has received research support from Dexcom and vTvTherapeutics, and has stock options in Mellitus Health, Omada Health, Stability Health and Pendulum Therapeutics. Eric Renard has served as a consultant/advisor for Abbott, Air Liquide, Cellnovo, Eli Lilly, Insulet, Johnson & Johnson (Animas, LifeScan), Medtronic, Novo Nordisk, Roche Diagnostics and Sanofi, and has received research grant/material support from Abbott, Dexcom, Insulet, Roche Diagnostics and Tandem Diabetes Care. Lori Berard has served a consultant for Abbott, AstraZeneca, Bayer, BD, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, MontMed, Novo Nordisk, Quanta, Sanofi and HLS Therapeutics. Luis Eduardo Calliari is an advisory board member of Abbott, Medtronic, NovoNordisk and Sanofi, and a consultant for Eli Lilly and Roche Diabetes. Jochen Seufert is an advisory board member of Abbott, AstraZeneca, Boehringer Ingelheim, GI Dynamics, Janssen, LifeScan Mundipharma, Novartis, Novo Nordisk and Sanofi, has been a speaker for Abbott, AstraZeneca, Bayer, Berlin Chemie, Boehringer Ingelheim, Bristol-Myers Squibb, Janssen, Eli Lilly, Merck Sharp & Dohme (MSD), MedScape, Novartis, Novo Nordisk, Omniamed and Sanofi, and has received research support from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, GI Dynamics, Intarcia, Ipsen, Janssen, Novartis, Novo Nordisk, Sanofi and Ypsomed.

AUTHOR CONTRIBUTIONS

Z.B, A.R.C, and G.B were involved in the concept and design of this analysis. E.W, D.J-E, D.B, E.R, and L.E.C contributed to the acquisition of data. All authors were involved in the interpretation of the data, writing and reviewing drafts of the manuscript and approved the final version for submission.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to patient level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan and dataset specifications. Patient level data will be anonymised, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies and process for requesting access can be found at: <https://www.clinicalstudydatarequest.com>.

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SUPPORTING INFORMATION

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

How to cite this article: Wilmot EG, Close KL, Jurišić-Eržen D, et al. Patient-reported outcomes in adults with type 1 diabetes in global real-world clinical practice: The SAGE study. *Diabetes Obes Metab*. 2021;1-10. <https://doi.org/10.1111/dom.14416>