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Target journal: Diabetic medicine

Title: Changes in HbA1c and diabetes-specific quality of life following structured type 1 diabetes education: exploratory latent profile analysis of outcomes in the DAFNE*plus* trial

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Key-words: DAFNE, DAFNEplus, quality of life, HbA1c, diabetes education, type 1 diabetes

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Conflict of interest:

US has previously been employed by Novo Nordisk A/S. EHT has undertaken research funded by an unrestricted educational grant from Abbott Diabetes Care, AstraZeneca, and Sanofi, Australia; received speaker fees (to her research group) from Novo Nordisk and Roche; and has served on an advisory board for AstraZeneca. SH has contributed with advisory work with pharmaceutical companies (Novo Nordisk, Eli Lilly, Zealand, Zucara, Medtronic) for which his university received remuneration. JSp has served on advisory boards for Janssen, Medtronic, Omnipod, Roche Diabetes Care, and Sanofi Diabetes; received unrestricted educational grants and in-kind support from Abbott Diabetes Care, AstraZeneca, Medtronic, Roche Diabetes Care, and Sanofi Diabetes; received sponsorship to attend educational meetings from Medtronic, Roche Diabetes Care and Sanofi Diabetes, and consultancy income or speaker fees from Abbott Diabetes Care, AstraZeneca, Insulet, Medtronic, Novo Nordisk, Roche Diabetes Care, Sanofi Diabetes and Vertex. In all cases, JSp's research group (ACBRD) has been the beneficiary.

Novelty statement: (max 100 words)

What is already known?

- The DAFNEplus trial showed no significant between-group differences, at 12 months, in HbA1c or diabetes-specific quality of life when comparing DAFNE, a type 1 diabetes structured education program, and the updated DAFNEplus.

What this study has found?

- Latent profile analysis revealed two participant clusters with distinct baseline outcomes.
- One cluster experienced significant added benefit from DAFNEplus (compared to DAFNE) on diabetes-specific quality of life at 12 months, but not HbA1c.

What are the implications of the study?

- DAFNEplus may have quality of life benefits for subgroups of adults with type 1 diabetes, which should be considered for the real-world implementation of the programme.

Acknowledgments

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Data availability statement:

Deidentified data are available on reasonable request.

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Abstract

Aims: To identify meaningful clusters of participants with shared baseline characteristics (demographic, clinical and psychological) from a sample of adults with type 1 diabetes (T1D) completing Dose Adjustment For Normal Eating (DAFNE) structured T1D education, or the updated DAFNEplus program. Further, to determine whether those clusters respond differently, at 6- and 12 months, to DAFNE and DAFNEplus on core outcomes: HbA1c and diabetes-specific quality of life (QoL).

Methods: Latent profile analysis was conducted on the DAFNEplus randomised control trial dataset using relevant indicator variables (age; HbA1c; hypoglycaemia awareness; diabetes-specific QoL, distress, and positive well-being; fear of hypoglycaemia; satisfaction with diabetes management). Model fit indices were used to select the optimal number of clusters and multilevel linear regression models to estimate the effect of DAFNEplus (compared with DAFNE) on HbA1c and diabetes-specific QoL in each cluster.

Results: A total of n=363 participants were included in the analysis (n=147, 40% randomised to DAFNEplus). The final model included two clusters: the first was consistently worse off on clinical and psychological indicator variables. The multilevel analysis showed a significant adjusted mean difference, at 12 months (first cluster only), between DAFNE and DAFNEplus in diabetes-specific QoL (0.81; 95% CI 0.19 to 1.43; *p*=0.01), but not at other timepoints or in HbA1c.

Conclusions: This study suggests that DAFNEplus has significant added benefits in reducing the negative impact of diabetes on QoL for a subgroup of adults with T1D, but not for their HbA1c. This provides important insights for the future real-world implementation of the DAFNEplus programme.

Introduction

The structured diabetes education program "Dose Adjustment For Normal Eating" (DAFNE) is designed to support adults with type 1 diabetes (T1D) to enhance self-management, by training them in flexible intensive insulin therapy [1]. More than 60,000 adults with T1D have attended the five-day training program globally – which improves overall glycaemic management (HbA1c), diabetes-specific quality of life (QoL) and reduces hospital visits [1, 2], with such benefits maintained for the longer term [3]. Real-world evidence shows that, on average, recommended HbA1c targets have not been reached [4] and DAFNE 'graduates' have described finding it challenging to implement the skills needed to sustain such benefits [2, 5]. Consequently, this led to an extensive update of the programme in recent years [6].

Updated DAFNE (DAFNEplus), includes stronger focus on behaviour change, integrating diabetes technologies into self-management and pro-active follow-up by health professionals with training led by a clinical psychologist [6][7]. A cluster randomised controlled trial (RCT) compared DAFNEplus to DAFNE, showing no significant between-group differences at 12 months in the primary biomedical outcome (HbA1c) or diabetes-specific QoL, suggesting non-inferiority [8]. Interviews with a subgroup of study participants revealed that various elements of DAFNEplus, including behaviour change techniques, were perceived positively [9]. As the RCT findings represent group averages across potentially heterogenous study participants, there is a need to explore whether subgroups or clusters of participants have differential experiences.

Traditional statistical methods, such as regression analysis have several limitations, including being vulnerable to type 1 error (false positive) rates, and may not represent "real" individuals in the sample, but rather a theoretical relationship or interaction between variables assessed [10]. Latent profile analysis (LPA), a type of mixed modelling, is used across disciplines to identify subgroups ('latent profiles' or 'clusters') within an overall heterogenous sample [11-15]. More specifically, LPA clusters participants based on data patterns (e.g., participant characteristics, symptoms or questionnaire responses), and provides a classification probability of cluster membership [16, 17]. This enables insights into how particular variables may interact and can be used to identify certain phenotypes of participants in the data [17]. Furthermore, this can help highlight who derives most benefit from different interventions.

The DAFNEplus RCT dataset enables novel insights into whether meaningful clusters of participants exist with shared characteristics (demographic, clinical and psychological), and whether these clusters respond differently to the educational programs (DAFNE versus DAFNEplus). Therefore, the aim of this secondary analysis of the DAFNEplus RCT dataset was to apply LPA to explore whether meaningful clusters exist at baseline and subsequently see whether clusters respond differently to the DAFNE and DAFNEplus programs, at 6- and 12 months, in terms of HbA1c and diabetes-specific QoL.

Methods

The DAFNEplus RCT protocol is summarised below, with full details published elsewhere [6]. Ethics approval was granted by South West-Exeter Research Ethics Committee (REC ref: 18/SW/0100).

Participants and procedures

Participants were eligible for the RCT if they were adults (aged ≥18 years) living with diagnosed T1D for ≥6 months, prepared to undertake multiple daily insulin injections and frequent glucose self-monitoring and attend programme sessions.

A pragmatic cluster RCT design was used [6], with centres randomised 1:1 to either control (standard DAFNE) or intervention (DAFNEplus) arms.

Measures and outcomes

The RCT's primary outcome was the between-arm difference in HbA1c at 12 months; with difference at 6 months among the secondary endpoints. The primary psychological outcome was the between-arm difference at 12 months in diabetes-specific QoL, as assessed by the 15-item Audit of Diabetes-Dependent Quality of Life (ADDQoL-15) [18]. The outcome from the current analysis was to identify meaningful clusters at baseline. If identified, we then used the same outcomes as for the main trial, i.e. between arm differences at 6- and 12-months in HbA1c and ADDQoL within each cluster.

Indicator variables (i.e. of interest to define otherwise unobserved clusters in a dataset) for the LPA, were selected based on the following criteria: 1) continuous variables (a criterion for LPA), 2) potential relevance for explaining differences in the outcomes (HbA1c and/or diabetes-specific QoL), 3) potential relevance for explaining differences in responses to DAFNEplus versus DAFNE programme content, 4) no missing data at baseline (to minimise bias), and 5) variable based on brief measures (increasing their potential for future clinical use). Based on these criteria, the core author group (US, ST, EHT and JS) agreed upon inclusion of baseline data from indicator variables listed in Table 1. The results from the primary and secondary study objectives, as well as the process evaluation, supported authors in identifying variables (particularly psychological variables) with significant associations to the two outcomes of interest. A few additional variables were also used to characterise clusters (but not included in the LPA as they are not continuous variables), including gender and means of glucose monitoring.

Table 1: Latent profile analysis indicator variables

1. Demographic variables: *a. Age:* collected via clinical proforma at baseline.
2. Clinical variables: *a. HbA1c (mmol/mol and %):* assessed using a centralised assay at baseline, 6 and 12 months. *b. Severe hypoglycaemia:* Number of severe episodes in the past year *c. Diabetes-related ketoacidosis (DKA):* Number of episodes in the past year requiring hospitalisation d. *Awareness of hypoglycaemia* (Gold score): single item rating from 'always aware' (1) to 'never aware' (7) [19].
3. Psychological variables were collected via self-completed questionnaires (postal or online) at baseline, 6 and 12 months: a. *Diabetes-specific QoL* (15-item Audit of Diabetes-Dependent Quality of Life; ADDQoL-15): Two overview items (present QoL and the impact of diabetes on QoL) and 15 items (domains of life) rated in terms of the impact of diabetes on the domain and its importance for QoL [18]. The impact and importance ratings are multiplied to provide a weighted impact score for each domain (with -9 representing the maximum negative impact and +3 the maximum positive impact). The average weighted impact (AWI) score is calculated as the mean of the applicable weighted impact scores scores. b. *Diabetes-specific distress* (11-item Problem Areas in Diabetes; PAID-11): 11 items rated on a 5-point scale (0=no problem to 4=a serious problem) [20]. The 11 scores are summed, forming a total score ranging from 0-44, with higher scores indicating greater diabetes distress, and scores ≥18 indicating severe diabetes distress. c. *Diabetes-specific positive well-being* (W-BQ28): Four items rated on a 4-point scale (0=not at all to 3=all the time) [21]. The 4 scores are summed, forming a total score ranging from 0-12, with higher scores representing greater diabetes-specific positive well-being. d. *Fear of hypoglycaemia* (Hypoglycaemia Fear Survey-II short-form; HFS-SF): The short-form includes 11 items rated on a 5-point scale (0=never to 4=almost always) [22]. Five

behavioural items reflect avoidance of hypoglycaemia or situations in which its negative consequences would be problematic and maintaining high glucose levels to avoid hypoglycaemia); and six items reflect worries related to hypoglycaemia. Subscale scores are calculated by summing the item scores, with higher scores indicating greater fear of hypoglycaemia.

e. *Satisfaction with diabetes management* (Diabetes Management Experiences-Questionnaire; DME-Q): 22 items rated on a 5-point scale (1=strongly disagree to 5=strongly agree) [23]. A composite score, ranging from 1-5, is calculated as the average of the item scores (with item 2 scores reversed). Higher scores indicate greater satisfaction with diabetes management. Three subscales can be calculated (effectiveness, convenience and intrusiveness) but to minimise number of variables we opted for only using the total score.

Statistical Analyses

Analyses were conducted using R (version 4.4.1) and Rstudio (version 2024.12.0.467) [24]. Descriptive statistics were used to summarise participant characteristics at baseline. Continuous measures were summarised using means and standard deviations, with skewed data summarised using medians and interquartile ranges. Counts and percentages were used to summarise categorical data. Latent profile analysis (LPA) was used to identify clusters in the DAFNEplus dataset based on participants' responses to continuous baseline indicator variables described above, applying complete cases (i.e. excluding participants with missing data) [25, 26]. LPA was conducted using the TidyLPA package in R [27]. In addition to assessing and finding optimal number of clusters, the TidyLPA package furthers allows for iteratively exploring whether cluster-specific variances and covariances of the indicator variables should be fixed or vary between and within clusters [25]. The optimal number of clusters was determined using model fit indices. An analytic hierarchy process, based on several fit indices including 'Bayesian information criterion' (BIC) and 'Alkaike information criterion' (AIC), where lower values indicate more optimal model, were used to guide model selection [16, 28]. Elbow plots were used to assess at which level these model fit values plateau (i.e., where adding further clusters is only leading to minor model fit improvement), and used in combination with model interpretability to guide final model selection. [16]. Additionally, the 'Bootstrapped likelihood ratio test' (BLRT), assessing whether the addition of another cluster significantly improve model fit (as indicated by test p-values), was used [25]. Classification accuracy (i.e., reliability of the assigned cluster membership) was evaluated using the entropy value (where a minimum of ≥0.60 is needed, but ≥0.80 desirable) [16]. We hypothesized that at least two and a maximum of five clusters would emerge from the LPA analysis.

Resulting clusters were characterised and statistical difference between clusters explored using Wilcoxon rank sum test or Pearson's Chi-squared test (for categorical data). Cluster classification was included as a fixed (independent) variable in two separate multilevel linear regression models with HbA1c and diabetes-specific QoL as outcomes using the Lme4 package in R [29]. An interaction between cluster classification, time (baseline, 6-months and 12-months) and intervention arm (DAFNEplus vs. DAFNE) was included to explore treatment effects within each cluster. Models were adjusted for age, gender and baseline continuous glucose monitor (CGM) use as per the primary RCT analysis [8]. Adjusted mean difference in HbA1c and QoL between DAFNEplus and DAFNE at 6- and 12-months within clusters were assessed, with $p<0.05$ considered statistically significant. Standardised effect sizes (Cohen's d) were reported for significant mean differences.

Results

Participants characteristics

The DAFNEplus trial included 423 participants. After exclusion of participants with missing data on indicator variables, the data of 363 participants (86% of full sample) were included in the current analysis: mean±SD age 43±15 years, 171 (47%) females, 147 (40%) randomised to DAFNEplus.

Table 2: Participants' demographic and clinical characteristics at baseline

	Total	By study arm	
	N = 363	DAFNE N = 216	DAFNEplus N = 147
Age, years	43.3±14.5	43.3±15.0	43.3±13.9
Gender, females	171 (47%)	109 (50%)	62 (42%)
Hba1c, mmol/mol	68.3±16.9	68.4±17.5	68.3±16.2
Hba1c, %	8.4±1.5	8.4±1.6	8.4±1.5
Awareness of hypoglycaemia: Gold score	2.0 [1.0, 3.0]	2.0 [1.0, 3.0]	2.0 [1.0, 3.0]
Glucose monitoring: CGM use 1 missing in DAFNE arm)	185 (51%)	100 (47%)	85 (58%)
Severe hypoglycaemic episodes in past year	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]
Diabetes-related ketoacidosis: number of episodes in the past year requiring hospitalisation	0.0 [0.0, 0.0]	0.0 [0.0, 1.0]	0.0 [0.0, 0.0]
Mean±SD; n (%); Median [Q1, Q3] Abbreviations: Continous glucose monitoring (CGM)			

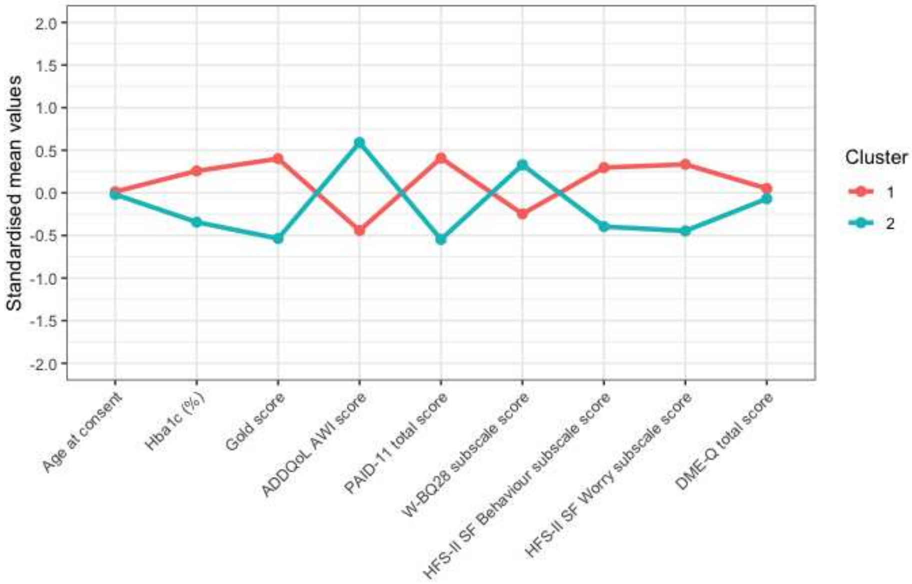
Model selection and classification accuracy

History of severe hypoglycaemia and DKA were included initially, but excluded later, as they were highly skewed which, despite transformations, caused warnings when running the LPA analysis (instead we included these when exploring characteristics of identified clusters; see below). With the remaining indicator variables, the analytic hierarchy process and model fit parameters suggested the two- cluster model with varying variance and covariance to be most optimal (Supplementary Table S1). Visual inspection of elbow plots with fit indices confirmed this (Supplementary Figure S1-4). In terms of classification accuracy, entropy values for the selected model were 0.79, suggesting appropriate reliability of the assigned cluster membership.

Characteristics of identified clusters

Indicator variables for the two clusters are presented visually in Figure 1. Table 3 summarises characteristics (baseline demographic, clinical and psychosocial variables) for each cluster and provides tests of statistical differences. On average, the first cluster was consistently worse off at baseline on clinical and psychological indicator variables compared to the second cluster – specifically, the first cluster had significantly lower diabetes-specific QoL, higher HbA1c, higher diabetes-specific distress, lower diabetes-specific positive well-being, more worries about and avoidant behaviours related to hypoglycaemia, and less awareness of their hypoglycaemia symptoms. Minimal differences were observed between clusters for age and satisfaction with diabetes management (DME-Q score). Of non-indicator variables, history of severe hypoglycaemia was statistically significant between clusters, while gender and glucose monitoring were not.

Figure 1: Cluster classifications across baseline indicator variables



ADDQoL-15 AWI: 15-item Audit of Diabetes-Dependent Quality of Life - average of weighted impact
PAID-11: 11-item Problem Areas in Diabetes
W-BQ28: Diabetes-specific positive well-being questionnaire
HFS-II: Hypoglycaemia Fear Survey-II short form
DME-Q: Diabetes Management Experiences - Questionnaire

Table 3: Characteristics of clusters

	First cluster n = 201[1]	**Second cluster n = 162[1]**	**p-value[2]**
Age, years	43.3±14.0	43.2±15.2	0.8
Gender, females	103 (51%)	68 (42%)	0.079
Randomisation, DAFNEplus	74 (37%)	73 (45%)	0.11
Hba1c, %	8.8±1.7	7.9±1.1	**<0.001**
Hba1c, mmol/mol	73.1±18.6	62.5±12.3	**<0.001**
Awareness of hypoglycaemia: Gold score	3.0 [2.0, 4.0]	2.0 [1.0, 2.0]	**<0.001**
Glucose monitoring: CGM use (1 missing)	105 (53%)	80 (49%)	0.6
Severe hypoglycaemic episodes in past year	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.018
Diabetes-specific QoL: ADDQoL-15 AWI score	-3.8±1.9	-1.8±1.0	**<0.001**
Diabetes-specific distress: PAID-11 score	23.7±10.5	12.9±8.1	**<0.001**
Diabetes-specific positive well-being: W-BQ28 positive well-being subscale score	5.1±2.6	6.7±2.5	**<0.001**
Fear of hypoglycaemia: (HFS-SF) – Worry subscale	9.8±5.1	6.0±3.2	**<0.001**
Fear of hypoglycaemia: (HFS-SF) – Behaviour subscale	6.9±4.4	4.1±2.9	**<0.001**
Satisfaction with diabetes management: DME-Q scale	3.1±0.4	3.0±0.3	0.2

[1] Mean±SD; n (%); Median [Q1, Q3]
[2] Wilcoxon rank sum test; Pearson's Chi-squared test

Abbreviations: Continous glucose monitoring (CGM), 15-item Audit of Diabetes-Dependent Quality of Life (ADDQoL-15), 11-item Problem Areas In Diabetes (PAID-11), 28-item Well-Being Questionnaire (W-BQ28), Hypoglycaemia Fear Survey – Short Form (HFS-SF), Diabetes Management Experiences Questionnaire (DME-Q)

Treatment effects within each clusters

Within cluster two, there were minimal differences in diabetes-specific QoL and HbA1c between intervention arms (DAFNEplus vs. DAFNE) at all timepoints (baseline, 6 and 12 months). In contrast, within cluster one there was a significant between-arm difference in diabetes-specific QoL (ADDQoL-15 AWI score: adjusted mean difference: 0.81; 95% CI 0.19 to 1.43; *p*=0.01, equivalent to a standardised effects size of d=0.91 , 95% CI 0.2 to 1.6) at 12 months, but not at other timepoints or in HbA1c. A sensitivity analysis on the QoL findings, retaining only participants with data at 12 months, produced the same significant findings (i.e. a significant, *p*=0.002, between-arm difference in diabetes-specific QoL at 12 months, but not at other timepoints). Findings are represented in Figures 2a and 2b, and Supplementary Table S2 and S3. At 12 months (compared to baseline) there was 28-42% missing data for the ADDQoL analyses, and 19-26% for the HbA1c analyses across clusters.

Figure 2a: Adjusted mean difference in diabetes-specific QoL for each cluster

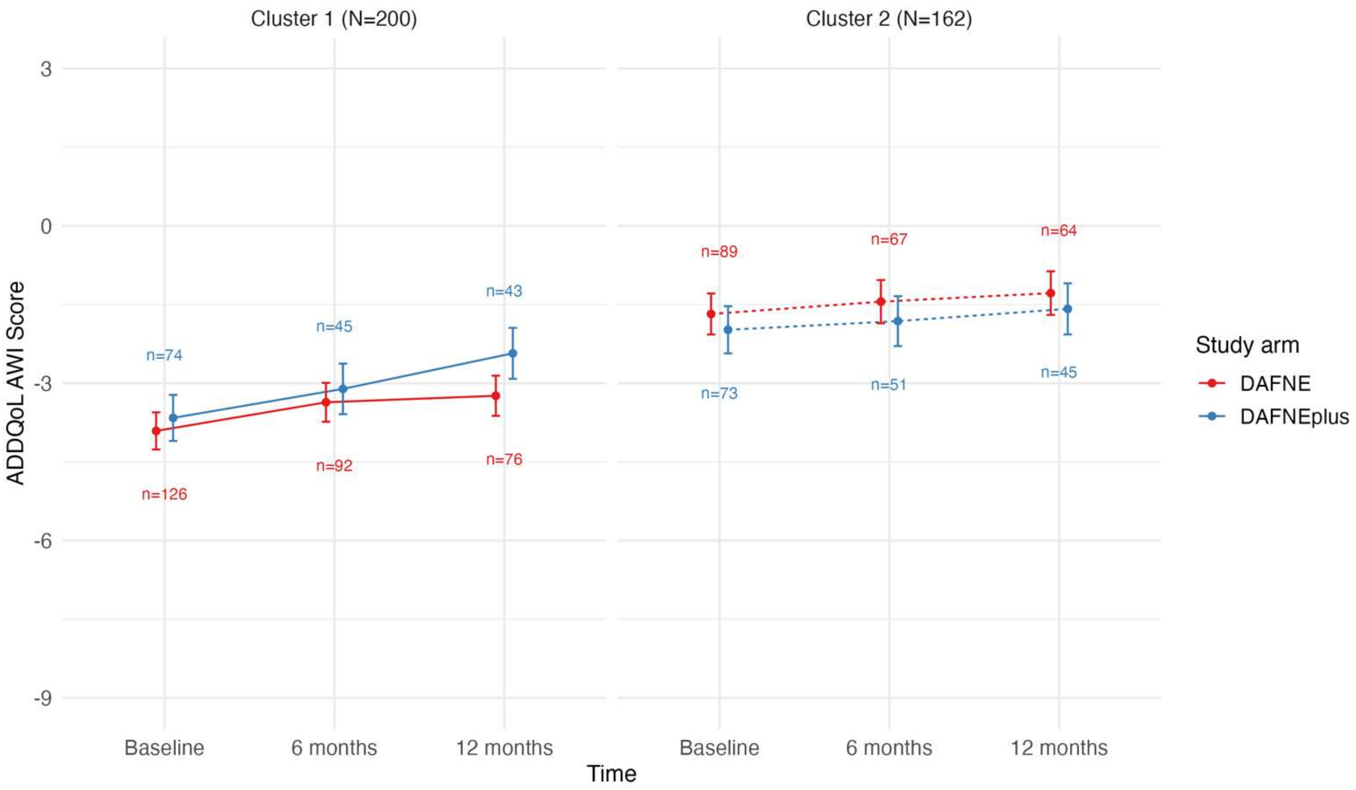


Figure elements: Points show estimated marginal means from multilevel models; error bars represent 95% confidence intervals.
Total N is the number of participants included in the model (may differ from earlier due to missing covariate data).
'n=' is the number of participants with available data at each time point.

ADDQoL Average Weighted Impact (AWI) score: average of weighted impact scores across 15 life domains.
Scores range from -9 (most negative impact of diabetes) to +3 (most positive impact of diabetes).

Figure 2b: Adjusted mean difference in HbA1c for each cluster

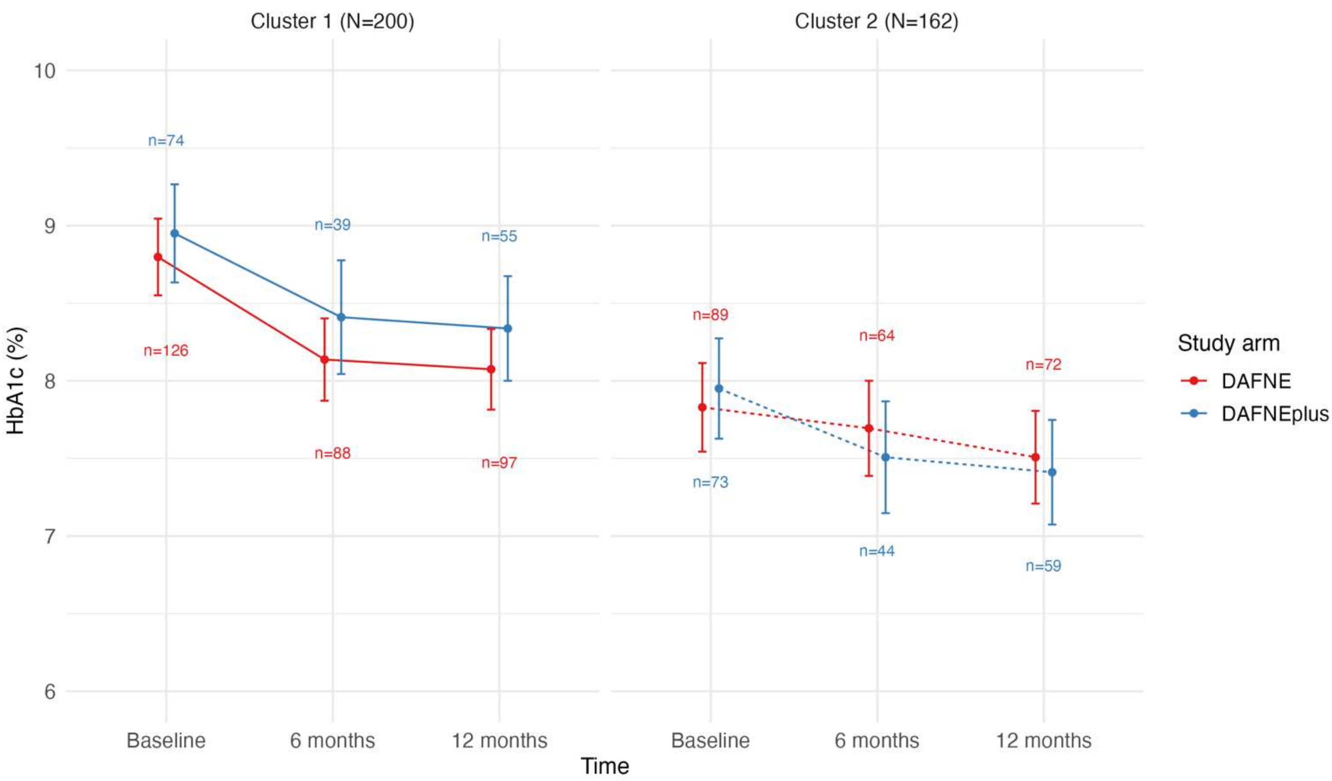


Figure elements: Points show estimated marginal means from multilevel models; error bars represent 95% confidence intervals.
Total N is the number of participants included in the model (may differ from earlier due to missing covariate data).
'n=' is the number of participants with available data at each time point.

Discussion

By using a data-driven approach, this study identified two meaningful clusters of participants with distinct baseline characteristics. The first and largest cluster (n=201) included participants who, compared to the second cluster (n=162), had, on average, worse clinical indicators (i.e. higher HbA1c and lower hypoglycaemia awareness) and greater psychological burden (i.e. greater negative impact of diabetes on QoL, greater diabetes distress, less diabetes-specific positive well-being, and greater worries about hypoglycaemia and avoidance of situations in which hypoglycaemia may occur or be problematic). Participants in the first cluster who were randomised to DAFNEplus, had significantly better diabetes-specific QoL at 12 months, compared to those randomised to DAFNE. No significant differences between arms were observed at other timepoints, or for HbA1c at any timepoint. These findings suggest that a subgroup of adults with T1D, and specifically those with most to gain, experienced added benefit from DAFNEplus (compared to DAFNE) on their diabetes-specific QoL over the 12-month study, but not on their HbA1c.

The observation that certain groups of participants experienced more positive effects from DAFNEplus than DAFNE, aligns with previously published qualitative research. Lawton et al. identified three groups of participants in their interviews: those with pessimistic, perfectionist and optimistic mindsets pre-course [9]. Compared to the latter group, those with pessimistic or perfectionist pre-course mindsets appeared to gain greater benefits – they emphasised several elements of DAFNEplus leading to meaningful changes in their mindsets, which supported their diabetes self-management. These benefits included normalising imperfect diabetes self-management and set-backs, increasing help-seeking and rethinking their risk of complications. In contrast, those with optimistic mindsets pre-course mainly highlighted the skills-based training and educational elements as beneficial. Although the number of groups do not match the number of clusters in the current study, the benefits experienced by those with previously pessimistic or perfectionist mindsets aligns well with the fact that those with greater psychological burden pre-course appear to benefit more in terms of diabetes-specific QoL from DAFNEplus. A recent cluster analysis from the HARPdoc psycho-educational trial (focussing on changing cognitive barriers to avoid hypoglycaemia) identified two clusters: one with cognitive barriers to hypoglycaemia avoidance but low fear of hypoglycaemia, and the other with reverse patterns [30]. Similarly to the current study, clusters differed in hypoglycaemia awareness, severe hypoglycaemia history and diabetes-specific distress, but not in age or technology use. Although the purpose and content of the HARPdoc and DAFNEplus programs differ, it is reassuring that several cluster characteristics align, and the focus on attitudes and cognitions in HARPdoc mirrors a similar emphasis in the recent development of DAFNEplus, compared to the earlier DAFNE.

When comparing the current study findings to the main DAFNEplus RCT, the observed improvements in HbA1c and diabetes-specific QoL from baseline to 12 months, in both intervention arms, aligns. Whether these changes can be attributed to the interventions alone cannot be answered with the current study, though similar changes were observed in the original DAFNE RCT, compared to wait-list control [1]. However, it is noticeable that the two clusters have substantial variation in starting points and extent of improvement over time. While all participants, across clusters, fulfilled the same inclusion criteria, what could be perceived as a generally homogenous group of adults with type 1 diabetes eligible for structured diabetes education, demonstrate substantial heterogeneity. The current findings emphasise the importance of exploring clusters to avoid averaging out effects at a group-level, and highlights the need for a more person-centric, or at least cluster-centric, approach to interventional designs and rollout of programs such as DAFNEplus. It is clear that optimal referral requires attention to both clinical factors (e.g. HbA1c) and psychological factors, which can be assessed with validated tools (such as those used here) or a truly person-centred clinical interview.

While added benefit from DAFNEplus was observed on diabetes-specific QoL, the effects on HbA1c were not significantly different between intervention arms in either of the two clusters. While it is encouraging that those in the second cluster had HbA1c, on average, approaching target recommendations (7.5%, as specified in the RCT protocol), the current findings also emphasise the need for further intervention to support all, particularly those in the first cluster, to optimise their HbA1c. Hybrid closed loop reduces HbA1c while simultaneously reducing diabetes distress [31]. Technological support, either alone or in combination with structured education, may benefit both clusters in reaching optimal HbA1c levels. Equally, it is important to consider any potential negative psychological consequences from technology (e.g. CGM alerts, cognitive burden, social stigma) [32, 33] and that some individuals may not experience adequate improvements for all outcomes that matter to them from technology alone [30]. Importantly, the two clusters in our study did not differ significantly on CGM use, which thereby does not explain observed differences.

The strengths of the present study include the use of a precision medicine approach to understand the nuances of the effects of DAFNE and DAFNEplus. More than half the included study participants (first cluster) were characterised by worse baseline outcomes on majority of indicator variables. This could suggest that a large proportion of adults with T1D being referred to DAFNE programs share similar characteristics and may experience added benefits from DAFNEplus on their QoL. However, further research is needed to confirm these findings given the amount of missing outcome data. The embedded classification uncertainty is, also, a key benefit of LPA that distinguishes it from traditional cluster analytic approaches [16]. LPA is becoming increasingly popular and used across a range of disciplines, including exploring mood dynamics in people with depression [34], determining cardiometabolic subgroups [15], and using self-management questionnaire data in combination with biomarkers to discover subgroups with greater risk for retinopathy [13]. The current study has further highlighted the potential of this methodology applied to structured diabetes education programs.

Several limitations are also important to consider. First, while CGM use at baseline did not differ between randomised groups, this study was conducted during the years when CGM was rolled out across England, and we did not consider CGM uptake over time, which may have important implications to the observed findings. Future work could consider adding blinded CGM to gain more nuanced insights into glucose management over time and including CGM metrics (such as time in range) as part of an updated LPA. Second, there is inherent subjectivity in the selection of indicator variables and optimal model(s). Considering previous findings on how certain personality types may benefit more or less from DAFNEplus [9], future studies could consider including personality questionnaires to assess if these constructs change the clustering of participants. Third, while significant differences were observed at 12 months, more work is needed to understand if these effects are sustained across several years. Fourth, age and satisfaction with diabetes management (DME-Q scores) did not differ significantly between clusters, and could be candidates for removal, and further sensitivity analysis could be considered to see if further reduction in indicator variables is possible, without compromising classification accuracy. Fifth, sample size was based on power calculations for the primary objective in the DAFNEplus RCT and not the current analyses, and there was substantial attrition at follow up for the primary DAFNEplus analyses. Further, in order to conduct the LPA, we could only include participants from the trial with available data at baseline, which further reduced the sample size. It is reassuring that the sensitivity analysis confirmed that findings overall did not change when only retaining those with data at 12 months. However, more work is needed to confirm findings, as those with complete data may represent a subgroup of participants more likely to respond positively to DAFNE*plus* (compared to those with missing data). Finally, the COVID-19 pandemic and introduction of telehealth may have led the DAFNE centres to be more responsive and flexible in their follow-up support, which was partly the intention behind the DAFNEplus centres. This may have unintentionally minimised the difference in overall trial outcomes.

In conclusion, this study suggests that adults with T1D and eligible for DAFNE or DAFNEplus can be grouped broadly into two clusters, with one cluster experiencing significant added benefit from DAFNEplus (compared to DAFNE) for their QoL (but not for HbA1c) at 12 months. Further research is required to validate these findings in a more complete dataset. This exploratory analysis provides important insights for the future rollout of the DAFNEplus program.

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Supplementary files:

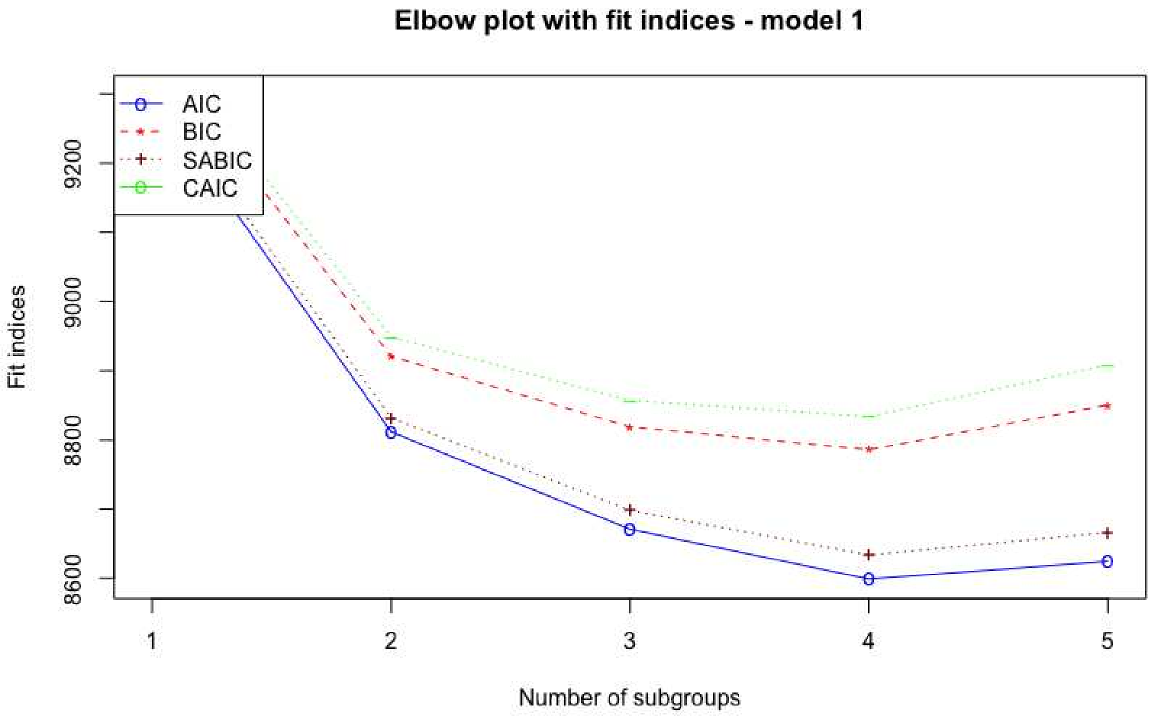
Supplementary Table S1 – model fit parameters:

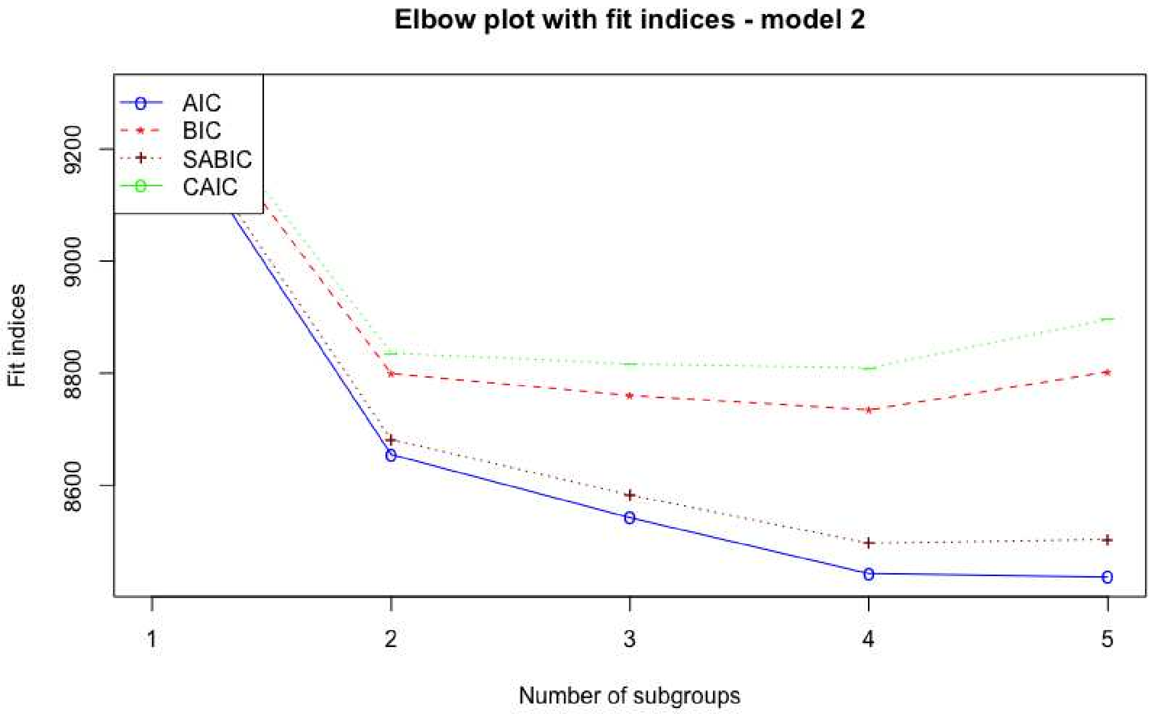
Model	Classes	AIC	BIC	CAIC	SABIC	Entropy	BLRT_val	BLRT_p
1	1	9298	9368	9386	9311	1.00	NA	NA
1	2	8812	8921	8949	8832	0.82	506.6	0.0099
1	3	8671	8819	8857	8698	0.85	160.8	0.0099
1	4	8599	8786	8834	8634	0.80	91.9	0.0099
1	5	8624	8850	8908	8666	0.78	-5.5	1.0000
2	1	9298	9368	9386	9311	1.00	NA	NA
2	2	8655	8799	8836	8682	0.87	681.0	0.0099
2	3	8542	8761	8817	8583	0.80	150.9	0.0099
2	4	8443	8735	8810	8497	0.78	137.7	0.0099
2	5	8436	8802	8896	8504	0.78	44.5	0.0990
3	1	8472	8682	8736	8511	1.00	NA	NA
3	2	8439	8688	8752	8485	0.77	52.6	0.0099
3	3	8415	8703	8777	8468	0.72	44.1	0.0099
3	4	8366	8693	8777	8427	0.79	68.6	0.0099
3	5	8297	8663	8757	8364	0.77	89.8	0.0099
6	1	8472	8682	8736	8511	1.00	NA	NA
6	2	8240	8664	8773	8319	0.79	341.8	0.0099
6	3	8205	8843	9007	8323	0.81	145.2	0.0099
6	4	8202	9055	9274	8360	0.87	113.0	0.2574
6	5	8197	9265	9539	8395	0.90	114.2	0.3762

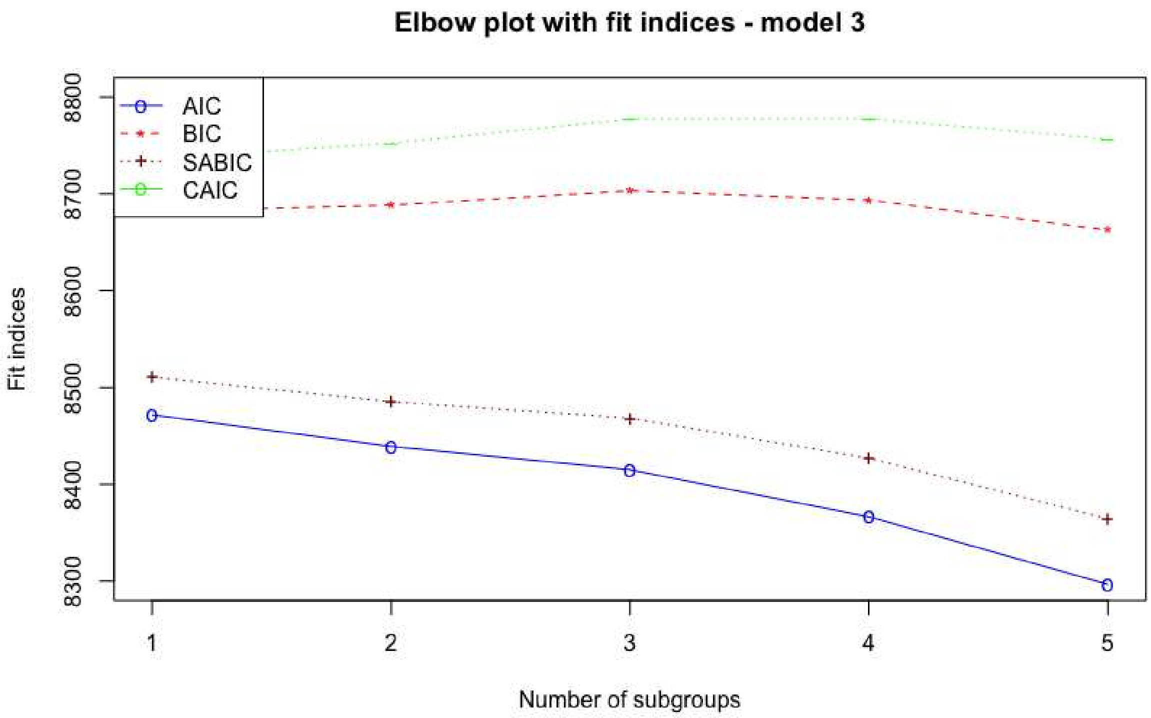
Best model according to AIC is Model 6 with 5 classes.
Best model according to BIC is Model 3 with 5 classes.
Best model according to SABIC is Model 6 with 2 classes.
Best model according to CAIC is Model 3 with 1 classes.

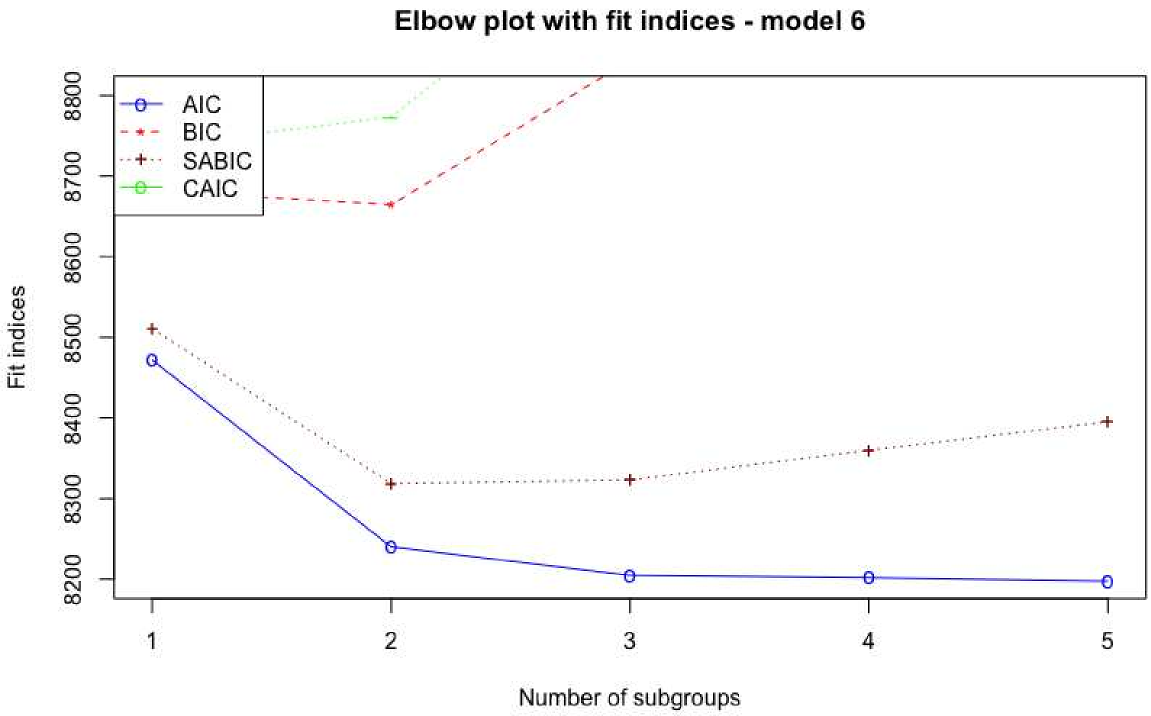
An analytic hierarchy process, based on the fit indices AIC, AWE, BIC, CLC, and KIC (Akogul & Erisoglu, 2017), suggests the best solution is Model 6 with 2 classes.

Supplementary Figure S1-S4 - elbow plots with fit indices:









Best fitting model: The TidyLPA package in R suggested that the best solution was Model 6 with 2 classes. Visual inspection of the Elbow plot confirms this. So we use Model 6 with 2 classes forward.

Supplementary Table S2: Estimated means and between-arm differences from multilevel model for ADDQo

Time	Cluster	DAFNEplus (N=147)[1]	DAFNE (N=215)[1]	Mean Difference[2]	SE[2]	95% CI[2]	P-value[3]
Baseline	Cluster 1	n=74, -3.66 (0.21) [-4.1, -3.22]	n=126, -3.91 (0.17) [-4.26, -3.56]	0.25	0.27	[-0.32, 0.81]	0.37
Baseline	Cluster 2	n=73, -1.98 (0.22) [-2.43, -1.53]	n=89, -1.68 (0.19) [-2.07, -1.29]	-0.30	0.29	[-0.9, 0.29]	0.31
6 months	Cluster 1	n=45, -3.11 (0.24) [-3.59, -2.63]	n=92, -3.36 (0.18) [-3.73, -2.99]	0.25	0.30	[-0.35, 0.86]	0.4
6 months	Cluster 2	n=51, -1.82 (0.23) [-2.29, -1.34]	n=67, -1.44 (0.2) [-1.86, -1.03]	-0.37	0.31	[-1, 0.26]	0.24
12 months	Cluster 1	n=43, -2.43 (0.24) [-2.92, -1.94]	n=76, -3.24 (0.19) [-3.62, -2.86]	0.81	0.31	[0.19, 1.43]	**0.01**
12 months	Cluster 2	n=45, -1.58 (0.24) [-2.07, -1.09]	n=64, -1.28 (0.21) [-1.7, -0.87]	-0.30	0.32	[-0.94, 0.34]	0.35

Model: Multilevel linear regression with:

- *Fixed effects for gender, CGM use, and cluster × time × randomisation interaction*
- *Random intercepts for site and participant (site_code/screening)*
- *Estimated marginal means and between-arm differences (DAFNEplus – DAFNE) using Satterthwaite approximation*
- *95% confidence intervals computed from the emmeans framework*

[1] Values are shown as n=sample size, Mean (Standard Error) [95% Confidence Interval]

[2] Mean difference between DAFNEplus and DAFNE; SE and 95% CI from the emmeans contrasts.

[3] P-value from pairwise comparison using Satterthwaite approximation. Bold indicates significance at P < 0.05.

Supplementary Table S3: Estimated means and between-arm differences from multilevel model for HbA1c (%)

Time	Cluster	DAFNEplus (N=147)[1]	DAFNE (N=215)[1]	Mean Difference[2]	SE[2]	95% CI[2]	P-value[3]
Baseline	Cluster 1	n=74, 8.95 (0.16) [8.63, 9.27]	n=126, 8.8 (0.12) [8.55, 9.04]	0.15	0.20	[-0.25, 0.55]	0.44
Baseline	Cluster 2	n=73, 7.95 (0.16) [7.63, 8.27]	n=89, 7.83 (0.14) [7.54, 8.11]	0.12	0.21	[-0.31, 0.55]	0.57
6 months	Cluster 1	n=39, 8.41 (0.18) [8.04, 8.78]	n=88, 8.14 (0.13) [7.87, 8.4]	0.27	0.23	[-0.18, 0.72]	0.23
6 months	Cluster 2	n=44, 7.51 (0.18) [7.15, 7.87]	n=64, 7.69 (0.15) [7.39, 8]	-0.19	0.24	[-0.66, 0.29]	0.43
12 months	Cluster 1	n=55, 8.34 (0.17) [8, 8.67]	n=97, 8.07 (0.13) [7.81, 8.33]	0.26	0.21	[-0.16, 0.69]	0.22
12 months	Cluster 2	n=59, 7.41 (0.17) [7.07, 7.75]	n=72, 7.51 (0.15) [7.21, 7.81]	-0.10	0.22	[-0.55, 0.35]	0.67

Model: Multilevel linear regression with:

- *Fixed effects for gender, CGM use, and cluster × time × randomisation interaction*
- *Random intercepts for site and participant (site_code/screening)*
- *Estimated marginal means and between-arm differences (DAFNEplus – DAFNE) using Satterthwaite approximation*
- *95% confidence intervals computed from the emmeans framework*

[1] Values are shown as n=sample size, Mean (Standard Error) [95% Confidence Interval].

[2] Mean difference between DAFNEplus and DAFNE; SE and 95% CI from the emmeans contrasts.

[3] P-value from pairwise comparison using Satterthwaite approximation. Bold indicates significance at P < 0.05.