Longitudinal trends in HbA1c patterns and association with outcomes: A systematic review

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Abstract

Background: This study aimed to review studies that identified patterns of longitudinal HbA1c trends in patients with diabetes and to summarize factors and outcomes associated with distinct trajectory patterns.

Methods: PubMed and Web of Science were systematically searched for studies examining HbA1c trends among patients with diabetes from database inception through September 2017. Articles were included if they met the following inclusion criteria: (a) longitudinal study of subjects with diabetes only, (b) use of serial measurements of HbA1c, and (c) analysis of the trend of HbA1c using group‐based trajectory approaches.

Results: Twenty studies were included, 11 on type 1 diabetes and 9 on type 2 diabetes. These studies identified 2 to 6 HbA1c trajectory patterns. The most commonly identified patterns included stable HbA1c around 7.0% and at levels between 8.0% and 9.9%, which usually captured the HbA1c pattern among the majority of subjects in the study population. Unstable patterns identified included increasing HbA1c trend, decreasing HbA1c trend, and non‐linear patterns. These patterns were associated with differential risk of disease outcomes, over and beyond single‐point HbA1c measures. Age, gender, ethnicity, diabetes duration, disease management frequency, cardiovascular risk factors, insulin treatment, family environment, and psychosocial factors were the most frequently reported factors associated with membership of specific HbA1c pattern groups.

Conclusion: Common patterns of longitudinal HbA1c trends were identified despite heterogeneity among the studies. A better understanding of what underlies these different patterns may provide opportunities to tailor therapies and care for these patients to reduce adverse outcomes.

KEYWORDS
diabetes‐related outcomes, glycaemic control, group‐based trajectory analysis, HbA1c, longitudinal trends

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1 | INTRODUCTION

Glycaemic control is one of the primary goals of clinical management for most patients with diabetes. Poor glycaemic control has been causally associated with increased risk of diabetes-related complications and mortality risk, and glycaemic control is the main way to improve disease outcomes in clinical practice. Most studies examining the relationship between HbA1c and outcomes have used HbA1c measured at a single time point or derived summary measures that include average HbA1c during follow-up, change in HbA1c over time, or HbA1c variability. However, these analytical approaches may not be able to completely capture the information available in serial HbA1c measurements. Specifically, they fail to capture the trajectory of change over time. Existing data suggest that patients with diabetes in the population may have heterogeneous HbA1c trajectories, and these trajectories may not be correlated to baseline or average HbA1c levels; i.e., patients with the same baseline or average HbA1c may exhibit different patterns of change over time, or patients may exhibit the same pattern of change over time but have this change occur at different levels of average HbA1c. Previous studies have largely omitted these considerations in their analyses of the relationship between glycaemic control and diabetic outcomes.

In recent years, some studies have specifically examined if populations of patients with diabetes can be clustered to distinct groups based on the pattern of HbA1c control over time. This has been made possible by the use of group-based trajectory analysis, a relatively new statistical method that clusters individuals based on the trajectories of outcomes. In addition to diabetes, this technique has been applied to various areas of clinical research including physical aggression, cortisol levels, internet usage, obesity, anxiety, depression, crime trends, and psychological disorders. Use of this analytical approach to identify distinct patterns may provide us with new insights into the diabetes disease process. Also, comparing characteristics between patients with different HbA1c trajectories could help to identify modifiable factors underlying different HbA1c patterns, which may be used for targeted intervention in diabetes management.

In this article, we aim to systematically review the existing literature on patterns of HbA1c trajectories in patient populations with diabetes, to summarize (a) distinct HbA1c patterns and prevalence of different patterns in the diabetes population, (b) factors associated with different HbA1c patterns, and (c) outcomes associated with different patterns of HbA1c.

2 | METHODS

2.1 | Literature search

The protocol for this systematic review was registered on PROSPERO, the international prospective register of systematic reviews (unique identification number: CRD 42015019692) and is available in full on the National Institute for Health Research website. This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.

PubMed and Web of Science databases were searched for potentially relevant articles from inception of database to September 2017. The search terms “HbA1c” or all the Medical Subject Headings terms of HbA1c combined with “Trajectory” OR tracking OR longitudinal profile OR longitudinal data OR longitudinal level” OR secular trend” were used with no restriction on publication date or languages. The last search was performed in September 2017. Hand searching of citations in included articles for references to other relevant studies was also conducted.

2.2 | Study selection and eligibility criteria

Title and abstracts were evaluated to shortlist articles for this review and the eligibility of these articles were confirmed by a full-text review using the following inclusion criteria: (a) longitudinal study of subjects with diabetes only, (b) use of serial measurements of HbA1c, and (c) analysis of the trend of HbA1c using at least one of the group-based trajectory modelling and clustering approaches, including latent class growth analysis, latent class growth mixture model, 2-stage clustering method, k-means cluster analysis, and hierarchical cluster analysis.

Studies that did not meet the inclusion criteria were excluded. Ineligible studies were excluded based on one or more of the following: irrelevant to the topic (eg, not evaluating glycaemic control); inappropriate study population (eg, nondiabetes population or a mixture of diabetes population and nondiabetes population); inappropriate study types (eg, cross-sectional studies or case-control studies); and inappropriate analysis methods (eg, not identifying clusters of patients with distinct HbA1c trajectories).

Study selection was conducted independently by 2 authors. In the event of uncertainty, full text was examined, and discrepancies between authors were resolved by consultation between the 2 authors; if unable to reconcile, a third author was asked to review the title and abstract, or full text.

2.3 | Data extraction and quality assessment

General information, study and subject characteristics, statistical methods to determine trajectories, and key findings were extracted for all the included articles. General information included authorship details, publication year, and country where the study was performed; study characteristics included study design, sample size, follow-up duration, number and type of time points for HbA1c data, and source of HbA1c measures; subject characteristics included type of diabetes, age, diabetes duration, and baseline HbA1c levels; statistical methods included the statistical model used for group-based trajectory analysis, software used, approaches to determine the optimal number of subgroups, and number of clusters identified and attempted; key findings included HbA1c trajectories identified and reported factors/outcomes associated with different patterns of trajectories.

Patterns of HbA1c trajectories identified in each article were renamed and categorized based on baseline HbA1c and trend of change. We used 5 categories to classify the baseline HbA1c for both type 1 diabetes and type 2 diabetes: very low, low, moderate, moderate-high, and high. However, the cut-off values used to define these categories were different, considering the different target HbA1c levels for type 1 diabetes and type 2 diabetes recommended in international guidelines. The HbA1c cut-off values were ≤7.0%, 7.1% to 7.5%, 7.6% to 9.0%, 9.1% to 11.0%, and >11.0% for the type 1 diabetes categories and ≤6.5%, 6.6% to 7.0%, 7.1% to 8.0%, 8.1% to 10.0%, and >10.0% for type 2 diabetes. Trends of change were categorized into stable, deteriorating, improving, and other non-linear trends. Stable trends were trajectories with a change of HbA1c less than 1.0% during follow-up as compared with baseline; deteriorating and improving trends were increasing or decreasing HbA1c with a change of more than 1.0% as compared with baseline during follow-
up; non-linear trends included patterns that had more than 1 trend during follow-up, eg, increasing first and then decreasing. If baseline HbA1c or trend of change was not given in numbers, estimates were extracted from the plot of HbA1c trajectories.

Quality of the studies was assessed using the Newcastle-Ottawa quality assessment scale16,17 and Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statements18 for cohort studies. Nine items of the Newcastle-Ottawa quality assessment scale of cohort studies and 22 items of STROBE statements were evaluated for each article. Studies that fulfilled ≥8 items in the Newcastle-Ottawa scale and ≥15 items in the STROBE statement were considered of good quality. Two studies with a randomized controlled trial design were also evaluated in the same manner as described earlier as such studies can be viewed as a prospective cohort design in terms of the HbA1c trajectory analysis. Data extraction and quality assessment were conducted by 2 authors independently.

3 | RESULTS

3.1 | Study selection

The search identified 1379 nonduplicated articles. After the review of titles and abstracts, we excluded articles with irrelevant topics (n = 829), nondiabetic population (n = 185), cross-sectional or case-control study design (n = 44), and irrelevant analysis methods (n = 215). Of the 106 articles included for full-text review, we further excluded 3 articles with nondiabetic population and 83 articles with irrelevant analysis methods. In total, 20 articles were included for data extraction. The Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram19 is displayed in Figure 1.

3.2 | Study characteristics

The general information and study characteristics of the 20 included articles are summarized in Table 1. The studies were ordered by type of diabetes, year of publication, and first author’s last name.

All 20 included studies were published in international journals within the recent decade (from 2009 to 2017). The majority of the studies were conducted in the United States (n = 10), followed by Europe (n = 6) and Asia (n = 3), and one study was conducted in Africa. Fourteen of these studies were prospective cohort studies, 3 were retrospective cohort studies, 1 was an ambispective cohort study, and 2 were randomized controlled trials. Eleven of the studies were conducted among type 1 diabetes patients (mean age at baseline 8-18 y), and 9 studies were conducted among type 2 diabetes patients (mean age at baseline 56-76 y). The sample size for the 20 studies ranged from 72 to 28,016 subjects, and follow-up duration ranged from 2 to 13.6 years. Thirteen studies acquired HbA1c values from medical records, while the rest obtained HbA1c values by direct measurement. Half of the studies used the National Glycohemoglobin Standardization Program–certified method for the measurement of HbA1c (n = 10). One study mathematically standardized their results to the reference range of the Diabetes Control and Complications Trial (n = 1), while the rest did not report their HbA1c measurement methods or standardization processes (n = 9). The number of HbA1c points for each subject ranged from 4 to 18. Twelve of these studies used structured time points in the HbA1c trajectory analysis, and the time points in the remaining 8 studies were unstructured.

3.3 | Statistical methods used in group-based HbA1c trajectory analysis

The statistical models used for analysing HbA1c trajectories included latent class growth analysis (n = 14), latent class growth mixture model (n = 3), 2-stage clustering method (n = 1), k-means cluster analysis (n = 1), and hierarchical cluster analysis (n = 1) (Table 2). The maximum number of clusters evaluated during the model selection was less or equal to 7 in all the studies, and the number of clusters identified in the final model ranged from 2 to 6 (final model: 2 clusters, n = 5; 3 clusters, n = 5; 4 clusters, n = 5; 5 clusters, n = 4; 6 clusters, n = 1). Bayesian information criterion was the most commonly used tool for
| Study                  | Country            | Study design     | Sample size | Mean age (bl) | Mean diabetes duration (bl) | Length of follow-up | No./type of time points | HbA1c data source/measurement method | HbA1c trajectories identified                                                                 |
|-----------------------|--------------------|------------------|-------------|---------------|-----------------------------|---------------------|------------------------|--------------------------------------|------------------------------------------------------------------------------------------|
| Luyckx and Seiffge-Krenke55 | Germany           | Prospective cohort | 72          | 14 y          | 4.8 y                       | 11 y                | 8/structured          | Medical records/ —                | Very low stable (13.9%, bl HbA1c 6.3%) Moderate stable (70.8%, bl HbA1c 7.6%) Very low deteriorating (15.3%, bl HbA1c 6.6%) |
| Helgeson et al58      | United States      | Prospective cohort | 132         | 12 y          | 4.9 y                       | 5 y                 | 13/unstructured       | Medical records/ HPLC (Tosoh)     | Moderate stable (63.7%) Moderate deteriorating (36.3%)                                    |
| King et al23          | United States      | Prospective cohort | 252         | 12 y          | 4.7 y                       | 2 y                 | 8/unstructured        | Medical records/ —                | Moderate stable (92%, average HbA1c 8.18%) Moderate-high deteriorating (8%, average HbA1c 12.09%) |
| Hilliard et al56      | United States      | Prospective cohort | 150         | 16 y          | 6.0 y                       | 1.5-2 y             | 4/structured          | Medical records/ DCA+ 2000 (Bayer) | Low stable (39.8%, bl HbA1c 7.4%) Moderate-high stable (39.7%, bl HbA1c 9.2%) High stable (20.5%, bl HbA1c 11.2%) |
| Lawes et al60         | Scotland           | Retrospective cohort | 155         | 8 y (at recruitment) | Newly diagnosed               | 4.8 y               | —/unstructured        | Medical records/ DCA 2000 (Bayer) | Low stable (21%) Moderate stable (33%) Moderate deteriorating (34%) Moderate-high deteriorating (2%) |
| Phan et al21          | United States      | Retrospective cohort | 1449        | 11 y          | —                           | 3 y                 | 9/unstructured        | Medical records/ DCA Vantage (Siemens) | Moderate stable (58.1%, bl HbA1c 8.0%) Moderate improving (25.5%, bl HbA1c 8.8%) Moderate deteriorating (16.4%, bl HbA1c 8.3%) |
| Rohan et al20         | United States      | Prospective cohort | 239         | 11 y          | 4.4 y                       | 3 y                 | 7/structured          | Direct assessment/ TOSOH-G7       | Low stable (42.9%, bl HbA1c 7.3%) Moderate deteriorating (44.6%, bl HbA1c 8.6%) Moderate-high deteriorating (12.1%, bl HbA1c 10.0%) |
| Marshall et al30      | Rwanda              | Prospective cohort | 214         | 18 y          | 3.4 y                       | 1-2 y               | 9/structured          | Direct assessment/ DCA Vantage (Siemens) | Very low stable (8.0%, average HbA1c 6.5%) Moderate deteriorating (8.4%, average HbA1c 8.6%) Moderate-high improving (26.9%, average HbA1c 10.7%) High improving (31.8%, average HbA1c 12.9%) High stable (24.9%, average HbA1c 13.5%) |
| Monaghan et al22      | United States      | Retrospective cohort | 74          | 18 y          | 9.0 y                       | 2 y                 | 5/structured          | Medical records/ —                | Low stable (69%, bl HbA1c 7.4%) Moderate-high improving (31%, bl HbA1c 10.5%) |
| Viner et al44         | United Kingdom     | Prospective cohort | 384         | 13 y          | —                           | 6.7/unstructured    | Medical records/ DCA 2000+ (Siemens) | Low stable (45.1%) Moderate deteriorating (39.6%) Moderate deteriorating fast (6.5%) High stable (8.8%) |
| Schwandt et al45      | Germany and Austria | Prospective cohort | 6443        | 9 y           | 4.1 y                       | From age 8 to 19 y | —/unstructured        | Medical records/ National Glycohemoglobin Standardization Program standardized | Very low stable (26.9%, bl HbA1c 6.6%) Low stable (40%, bl HbA1c 7.4%) Moderate stable (16.6%, bl HbA1c 8.4%) Low deteriorating (13.0%, bl HbA1c 7.4%) Moderate deteriorating (5.4%, bl HbA1c 8.5%) |

(Continues)
| Study                  | Country          | Study design                  | Sample size | Mean age (bl) | Mean diabetes duration (bl) | Length of follow-up | No./type of time points | HbA1c data source/measurement method | HbA1c trajectories identified |
|------------------------|------------------|-------------------------------|-------------|--------------|----------------------------|---------------------|-------------------------|--------------------------------------|---------------------------------|
| **T2D**                |                  |                               |             |              |                            |                     |                         |                                      |                                 |
| Bayliss et al\(^{28}\) | United States    | 3 subcohorts from a prospective cohort | 582 (cancer) | 66 y         | 4.7 y                      | 9/unstructured       | Very low stable (37.7%) Moderate stable (41.0%) Moderate-high deteriorating (7.4%) High improving (10.6%) High stable (3.2%) Low stable (49.7%) Moderate-high stable (32.5%) Moderate-high deteriorating (8.4%) High improving (6.2%) High stable (3.2%) Very low stable (48.2%) Moderate stable (31.8%); Moderate-high stable (12.6%) High U shape (1.4%) High N shape (5.9%) |
|                        |                  |                               | 2959 (depression) | 62 y         | 5.0 y                      | 8/unstructured       |                          |                                      |                                 |
|                        |                  |                               | 2322 (pulmonary disease) | 63 y         | 5.0 y                      | 9/unstructured       |                          |                                      |                                 |
| Wang and Hazuda\(^{57}\) | United States    | Prospective cohort            | 119         | 76 y         | 12.5 y                     | 7/structured         | Very low stable (44.7%) Moderate stable (55.3%) Low stable (47.2%) Moderate-high stable (38.3%) High stable (14.5%) |
| Chang et al\(^{24}\)  | Taiwan           | RCT                           | 1091        | 56 y         | 10.0 y                     | 9/structured         | Low stable (47.2%) Moderate stable (55.3%) Low stable (47.2%) Moderate-high stable (38.3%) High stable (14.5%) |
| Ravona-Springer et al\(^{62}\) | Israel          | Prospective cohort            | 835         | 73 y         | —                          | 18/unstructured      | Very low stable (27.1%, bl HbA1c 6.0%) Low stable (43.6%, bl HbA1c 6.8%) Moderate stable (14.7%, bl HbA1c 7.2%) Moderate deteriorating (5.5%, bl HbA1c 7.8%) Moderate-high improving (7.1%, bl HbA1c 9.2%) High improving (1.8%, bl HbA1c 10.7%) |
| Migliore et al\(^{59}\) | United States    | RCT                           | 109         | —            | 2 y                        | 6/structured         | Moderate non-linear (74.3%) Moderate-high non-linear (22.0%) |
| Walraven et al\(^{26}\) | The Netherlands  | Prospective cohort            | 5432        | 61 y         | 1.0 y                      | 9/structured         | Low stable (83.1%, bl HbA1c 6.9%) Moderate deteriorating (3.4%, bl HbA1c 7.9%) Moderate-high improving (5.2%, bl HbA1c 9.1%) High improving (L shape) (8.2%, bl HbA1c 11.9%) |
| Mast et al\(^{61}\)   | The Netherlands  | Prospective cohort            | 1203        | 65 y         | 8.3 y                      | 12/structured        | Moderate stable (88.7%, bl HbA1c 7.4%) Moderate-high N shape (3.0%, bl HbA1c 8.1%) Moderate-high improving slow (3.9%, bl HbA1c 10.0%) High improving fast (4.4%, bl HbA1c 10.9%) |
| Laiteerapong et al\(^{25}\) | United States   | Prospective cohort            | 28 016      | —            | Newly diagnosed            | 10/structured        | Moderate stable (82.5%, bl HbA1c 7.2%) Moderate-high deteriorating (5.1%, bl HbA1c 8.3%) Moderate-high peaking late (N shape) (4.1%, bl HbA1c 8.5%) |
### TABLE 1 (Continued)

| Study | Sample size | Country | Study design | Mean age (y) | Mean diabetes duration (y) | Length of follow-up (y) | No. of time points | HbA1c data source/method | HbA1c data source/measurement method | HbA1c trajectories identified | Duration (%) |
|-------|-------------|---------|--------------|--------------|----------------------------|------------------------|------------------|--------------------------|-----------------------------------|-----------------------------------|---------------|
| Luo et al27 | 6079 | Singapore | Ambispective cohort | 59 | 4.5 | 4.5 | - | Medically recorded | - | Moderately high peaking early (N shape) (3.3%, bl HbA1c 9.3%) | Moderate-high stable (72.2%, bl HbA1c 7.9%) | High improving (4.9%, bl HbA1c 11.9%) |
| | | | | | | | | Structured time points: studies that used predesigned or reshaped measurement intervals in the trajectory model; unstructured time points: studies that used original measurement intervals as in clinical practice. | | |

Patterns of HbA1c trajectories were named and categorized based on the following cut-off points: ≤7.0% (very low), 7.1% to 7.5% (low), 7.6% to 9.0% (moderate), 9.1% to 11.0% (moderate-high), and >11.0% (high) for type 1 diabetes; ≤6.5% (very low), 6.6% to 7.0% (low), 7.1% to 8.0% (moderate), 8.1% to 10.0% (moderate-high), and >10.0% (high) for type 2 diabetes.

3.4 Summary of HbA1c trajectories identified

As summarized in Table 1, different HbA1c patterns were identified in each study. Although these patterns were named differently in each article, we have renamed and categorized these patterns based on baseline HbA1c (very low, low, moderate, moderate-high, and very high) and trend of change (stable, deteriorating, improving, and other non-linear trends) as described in the Section 2 above. The very low stable and low stable trajectories indicated optimal glycaemic control status, with stable control below the target HbA1c level maintained over the follow-up period. The other patterns indicated poorer glycaemic control status to different extents.

Among studies on type 1 diabetes (n = 11), most studies (n = 6) identified a group of patients that maintained stable HbA1c levels at a low baseline of 7.1% to 7.5%, containing 21% to 69% of the sample. Another stable trajectory pattern with moderate baseline levels of HbA1c (7.6%-9.0%) was also frequently observed (n = 6), with the proportion ranging from 17% to 92%. These 2 patterns were usually the largest subgroups in the study population. Three studies also identified a stable pattern at a very low baseline level (6.0% to 7.0%), and another 3 studies identified a cluster with continuously poor control with HbA1c level slightly above the 7.0% target level. This group was usually the third of the sample. Groups with deteriorating HbA1c, from very low (n = 1), low (n = 1), moderate (n = 7), and moderate-high (n = 3) baseline HbA1c, were also identified, with the proportion ranging from 2% to 45%. The group deteriorating from moderate baseline level was most commonly observed in studies. Three studies also identified groups with improving HbA1c over time, with the proportion ranging from 26% to 32%.

Among studies on type 2 diabetes (n = 9), the most commonly identified pattern was the moderate stable group (n = 7) with a HbA1c level slightly above the 7.0% target level. This group was usually the largest cluster, containing 15% to 89% of the sample. Two groups with a HbA1c level below the 7.0% target level and below a more stringent 6.5% level were also identified, ie, low stable (n = 4) and very low stable group (n = 4). The low stable group contained 44% to 83% of the sample, and the very low stable group contained 27% to 48% of the sample. Groups with stable HbA1c level at a moderately high level (7.1% to 8.0%) were found in 4 studies, with group percentages of 13% to 38%. Two studies identified a small proportion of patients (3% and 15%, respectively) that maintained high HbA1c levels over time. Groups with deteriorating glycaemic control starting from moderate (n = 2) or moderate-high (n = 4) HbA1c level were identified in 5 studies, which consisted of 3% to 8% of the sample. Groups with improving control starting from moderate-high (n = 3) or high (n = 6) baseline HbA1c level were identified in 6 studies, with group percentage ranging from 2% to 11%. Other non-linear patterns, including U-shaped and inverted U-shaped trajectories, were also identified in some studies.
| Study | Statistical method | Software | Dependent variable | Independent variable | Approach to determine number of clusters | Sufficient subjects in each cluster | Others | No. of clusters attempted | No. of clusters in the final model |
|-------|-------------------|----------|--------------------|----------------------|------------------------------------------|-----------------------------------|--------|-------------------------|----------------------------------|
| T1D   |                   |          |                    |                      | BIC | AIC | Entropy | Average posterior probabilities | Statistical tests | No. of clusters |                      |
| Luyckx and Seiffge-Krenke      | LCGA     | Mplus    | HbA1c              | Time from recruitment | ✓  |    |         | ✓ (E = 0.99)                    | Bootstrapped likelihood ratio test | ✓                | 2-4                   | 3                  |
| Helgeson et al                 | LCGA     | SAS Proc TRAJ | HbA1c              | Time from recruitment | ✓  |    |         | ✓                          |                            |                  | 2-4                   | 2                  |
| King et al                     | LCGA     | Mplus    | HbA1c              | Age                  | ✓  |    | ✓ (E = 0.92) |                            | Lo-Mendell-Rubin likelihood ratio test | ✓                | 1-3                   | 2                  |
| Hilliard et al                 | LCGA     | Mplus    | HbA1c, BGM frequency | Time from recruitment | ✓  |    |         |                            |                            | (10%) Nagin's diagnostics | 2-4                   | 3                  |
| Lawes et al                    | Two-stage clustering method | SPSS | HbA1c              | Time from diagnosis of diabetes | ✓  |    |         |                            |                            | Distant change | Maximum 6 4          |                    |
| Phan et al                     | Hierarchical cluster analysis | SAS and SPSS | HbA1c              | Time from study baseline | ✓  |    |         |                            |                            |                  | 3                    |                    |
| Rohan et al                    | LCGA     | SAS Proc TRAJ | HbA1c              | Time from recruitment | ✓  |    |         |                            |                            | (10%) Nagin's diagnostics | 2-6                   | 3                  |
| Marshall et al                 | LCGA     | SAS Proc TRAJ | HbA1c              | Time from recruitment | ✓  |    |         | ✓                           |                            |                  | 5                    |                    |
| Monaghan et al                 | LCGA     | SAS Proc TRAJ | HbA1c              | Time from college enrolment | ✓  |    |         | ✓                            |                            | ✓ (>5)                | 2                    |                    |
| Viner et al                    | LCGMM    | Mplus    | HbA1c              | Age                  | ✓  |    | ✓       | ✓                           |                            | Lo-Mendell-Rubin likelihood ratio test | Clinical plausibility | 1-4                   | 4                  |
| Schwandt et al                 | LCGA     | SAS Proc TRAJ | HbA1c              | Age                  | ✓  |    |         | ✓ (5%)                       | Clinical plausibility |                  | 1-6                   | 5                  |
| T2D   |                   |          |                    |                      | BIC | AIC | Entropy | Average posterior probabilities | Statistical tests | No. of clusters |                      |
| Bayliss et al                  | LCGA     | –        | HbA1c              | Time from diagnosis of incident co-morbidity | ✓  |    |         |                            |                            |                  | 5                    |                    |
| Wang and Hazuda                | LCGMM    | –        | HbA1c              | Time from recruitment | ✓  |    |         |                            |                            |                  | 2                    |                    |
| Chang et al                    | LCGA     | SAS Proc TRAJ | HbA1c              | Time from recruitment | ✓  |    |         |                            |                            |                  | 3                    |                    |
| Ravona-Springer et al          | LCGA     | SAS Proc TRAJ | HbA1c              | Time from entry to diabetes registry | ✓  |    |         |                            |                            |                  | 6                    |                    |
| Migliore et al                 | k-means cluster analysis | SPSS | HbA1c, blood pressure, BMI, triglycerides | Time from recruitment | ✓  |    |         |                            |                            | Hierarchical clustering: intervention |                  | 2                    |        | (Continues)
shaped (n = 1), N shaped (n = 3), and L shaped (n = 1), were also observed in a small number of studies.

3.5 | Factors and outcomes associated with HbA1c trajectories

Table 3 summarizes the reported factors associated with HbA1c trajectories in studies on patients with type 1 diabetes. Among demographic factors, older age, female gender, and ethnic minority status were associated with poor HbA1c trajectories. Disease-related factors associated with poor HbA1c trajectories included longer diabetes duration, less physical activity, fewer glucose monitoring frequencies, fewer or missed clinical appointments, and insulin treatment via injection versus insulin pump. Phan et al have shown that the association of age, ethnicity, and fewer or missed clinical appointments with deteriorating HbA1c trajectory was significant after adjustment for baseline HbA1c.21 Since the study population comprised mainly children and adolescents, family environment variables including poor family climate or family conflict and parental involvement in care were also found to be associated with poor glycaemic control. Psyhosocial variables, including negative emotions and poorer self-control, and onset of puberty were also associated with poorer control. In addition, Monaghan et al also found that 31% of adolescents showed deteriorating HbA1c upon college entry,22 and King et al reported that subjects with poorer HbA1c trajectories had more frequent diabetes-related emergency room visits and diabetes-related hospitalizations. Inconsistent findings were reported for body mass index (BMI), and Chang et al found that patients with poorer glycaemic control had lower BMI,24 while the other 3 studies found higher BMI was associated with poorer glycaemic control. Multiple studies also reported the association between higher estimated glomerular filtration rate and poorer glycaemic control.

Table 4 presents the factors and outcomes associated with poorer HbA1c trajectories in patients with type 2 diabetes. Younger age, ethnic minority status, and lower educational level were reported demographic factors associated with poorer HbA1c trajectories. Disease-related factors reported included longer diabetes duration, higher glycated hemoglobin, poorer lipid profiles, insulin treatment, and complications like deteriorating kidney function (higher albumin-to-creatinine ratio, microalbuminuria), retinopathy, neuropathy, and peripheral arterial disease. Multiple studies also reported the association between higher estimated glomerular filtration rate and poorer glycaemic control. Poorest postulating factors associated with poorer HbA1c trajectories included diabetes-related complications and poor self-control. In addition, Monaghan et al also found that 31% of adolescents showed deteriorating HbA1c trajectories that had more frequent diabetes-related emergency room visits and diabetes-related hospitalizations. Inconsistent findings were reported for body mass index (BMI), and Chang et al found that patients with poorer glycaemic control had lower BMI,24 while the other 3 studies found higher BMI was associated with poorer glycaemic control. Multiple studies also reported the association between higher estimated glomerular filtration rate and poorer glycaemic control.

**Table 2** (Continued)

| Study | Statistical method | Software | Dependent variable | Independent variable | BIC | AIC | Entropy | Average posterior probabilities | Statistical tests | Sufficient subjects in each cluster | Others | No. of clusters in the final model | No. of clusters attempted |
|-------|--------------------|----------|--------------------|----------------------|-----|-----|---------|--------------------------------|------------------|-----------------------------------|--------|---------------------------------|------------------------|
| Walraven et al | LCGA | Mplus | HbA1c | Time from recruitment | ✓ | — | — | ✓ (0.8) | — | — | Clinical plausibility | 1-5 | 4 |
| Mast et al | LCGA | Mplus | HbA1c | Time from insulin initiation | ✓ | — | — | ✓ (0.8) | — | ✓ (1%) | Clinical plausibility | — | 4 |
| Laiteerapong et al | LCGMM | Mplus | HbA1c | Time from diagnosis of diabetes | — | — | — | Lo-Mendell-Rubin likelihood ratio test | ✓ (1%) | — | — | — | 5 |
| Luo et al | LCGA | R | HbA1c | Time from recruitment | ✓ | ✓ | ✓ (0.8) | — | — | — | — | 2-7 | 4 |

Abbreviations: —, not mentioned; AIC, Akaike information criterion; BIC, Bayesian information criterion; BMI, body mass index; LCGA, latent class growth analysis; LCGMM, latent class growth mixture model; T1D, type 1 diabetes; T2D, type 2 diabetes.

aBIC log Bayes factor approximation was used: $2 \log_e(B_{10}) = 2(\Delta \text{BIC})$.

bSample adjusted BIC.
| Studies            | Demographics | Disease related | Family environment | Psychosocial | Others                                      |
|-------------------|--------------|-----------------|--------------------|--------------|---------------------------------------------|
|                   | Older age    | Female          | Ethnic minority    | Poor family  | Negative emotions                          | Poorer self-control     |
|                   | (3/5)        | (3/5)           | status (3/5)       | climate/functional autonomy (4/5) | (3/3) | (4/5) |
|                   | Longer diabetes duration (1/5) | Fewer glucose monitoring frequency (4/4) | Fewer/missed clinical appointments (3/4) | Insulin delivery via injection versus insulin pump (3/7) | ns: Family composition, socio-economic status, and BMI score |
|                   | ns           | ns              | ns                 | ns           | ns after adjustment for bl HbA1c            |                                     |
| Luyckx and        | ✓            | —               | ✓                  | ✓            | —                                           | ns: Peer conflict, lower social status, higher pubertal status, higher BMI |
| Seiffge-Krenke55,a | –            | —               | ✓                  | —            | —                                           | —: Diabetes-related emergency room visit and hospitalizations |
| Helgeson et al56,b | ns           | ns              | —                  | ✓            | —                                           | —: Unmarried caregiver status |
| King et al23,c     | —            | —               | —                  | —            | —                                           | —: More frequent nonclinic health care contacts; higher rates of adverse psychosocial variables |
| Hilliard et al56,c| ✓            | —               | ✓                  | ✓            | —                                           | —: Medicaid vs commercial insurance |
| Lawes et al20,a    | ✓            | —               | —                  | ✓            | ns at 2 y after diagnosis                    | —: Increased daily insulin dose, less physical activity; lower BMI SD score, height SD score |
| Phan et al21,d     | ✓            | —               | ✓                  | —            | —                                           | —: Rates did not differ for bl microalbuminuria, neuropathy, and nephropathy; test not conducted owing to small sample size |
| Rohan et al30,e    | —            | ✓               | ns                 | —            | ns                                          | —: College entry |
| Marshall et al30,a | ns           | —               | ns                 | ✓            | —                                           | —: College entry |
| Monaghan et al22,a | —            | —               | ✓                  | —            | —                                           | —: Increased daily insulin dose, less physical activity; lower BMI SD score, height SD score |
| Viner et al46,e    | —            | ns              | ns                 | —            | ns                                          | —: Increased daily insulin dose, less physical activity; lower BMI SD score, height SD score |
| Schwandt et al45,e | ns           | ✓               | —                  | —            | ns                                          | —: Increased daily insulin dose, less physical activity; lower BMI SD score, height SD score |

Abbreviations: ✓, associated; —, not mentioned; bl, baseline; BMI, body mass index; ns, not significant; SD, standard deviation.

aUnadjusted.
bAdjusted for social status, pubertal status, BMI, and household structure. Results for other variables were unadjusted.
cAdjusted for variables of the same categories (or with shared variance or in the same block).
dAdjusted for baseline HbA1c and all variables in the model.
eAdjusted for all variables in the model.
| Studies          | Factors                                      | Outcomes                                                                 |
|-----------------|----------------------------------------------|---------------------------------------------------------------------------|
|                 | Demographics                                | Disease related                                                           | Outcomes                  | Complications | Higher mortality |
|                 | Younger age (7/7)                           | Ethnic minority status (2/2)                                               |                            |               | (3/3) Others     |
|                 | Lower educational level (2/3)                | Longer diabetes duration (5/6)                                             | Higher bl HbA1c (5/5)      |               |                |
|                 | Lower lipid profiles (6/6)                   | Poorer eGFR (4/5)                                                         | BMI                        |               |                |
|                 | Others                                       | ns: Incident co-morbidity                                                   |                            |               |                |
| Bayliss et al   | —                                            | —                                                                         | —                          | —             |                |
| Wang and Hazuda | ✓                                            | —                                                                         | —                          | —             |                |
| Chang et al     | ✓                                            | —                                                                         | ✓ (bl)                     | —             |                |
| Bayliss et al   | —                                            | —                                                                         | —                          | —             |                |
| Wang and Hazuda | —                                            | —                                                                         | —                          | —             |                |
| Chang et al     | ✓                                            | ✓ (bl)                                                                   | —                          | —             |                |
| Ravona-Springer | ✓                                            | —                                                                         | ns                         | —             |                |
| Migliore et a   | —                                            | —                                                                         | —                          | —             |                |
| Walraven et a   | ✓                                            | —                                                                         | —                          | —             |                |
| Mast et al      | ✓                                            | —                                                                         | —                          | —             |                |
| Laiteerapong et | ✓                                            | —                                                                         | —                          | —             |                |
| Luo et al       | ✓                                            | —                                                                         | —                          | —             |                |

Abbreviations: ✓, associated; –, not mentioned; ACR, albumin-to-creatinine ratio; bl, baseline; BMI, body mass index; eGFR, estimated glomerular filtration rate; ns, not significant.

*Outcomes were analysed by path analysis with adjustment for age, education, ethnicity, BMI, angina, stroke, and pulmonary function.

*Factors reported from comparisons without adjustment.

*Outcomes were analysed by proportional hazards model with adjustment for age and BMI.

*Outcomes were analysed by analysis of covariance with adjustment of sociodemographic, cardiovascular, diabetes-related covariates, and geriatric depression scale score.

*Factors reported from comparisons with adjustment.

*Outcomes were analysed by Cox proportional hazards models with adjustment for age, gender, ethnicity, BMI, blood pressure, cholesterol, smoking, haemoglobin, eGFR, history of microvascular and macrovascular complications, co-morbidity, and mean HbA1c.

*The association of macrovascular events was insignificant after adjustment for mean HbA1c.

*Outcomes were analysed by Cox proportional hazards models with adjustment for age, gender, ethnicity, BMI, blood pressure, cholesterol, eGFR, smoking, diabetes duration, insulin treatment, place receiving medical care, and HbA1c at baseline.
4 | DISCUSSION

In this study, 20 articles reporting long-term HbA1c trajectories were included. All but 2 were cohort studies with varying follow-up durations. These studies identified 2 to 6 HbA1c trajectory subgroups and also reported several factors and outcomes associated with trajectory groups.

The review showed that there was heterogeneity in HbA1c trajectories within and between study populations. In type 1 diabetes, we found that studies commonly reported patients with 2 major trends of glycaemic control, one with stable control and one with unstable control. The stable group was usually considered the better control group with HbA1c at an acceptable level (close to the 7.5% target), while the unstable group had either a deteriorating or improving trend. Although more than half of patients were grouped in the stable group in most of the studies, it is also worth noting that the proportions of patients with unstable trends were much higher in studies on type 1 diabetes (2%-40%) compared with studies on type 2 diabetes (2%-11%). These higher proportions may reflect the greater challenges in achieving glycaemic control in type 1 diabetes compared with type 2 diabetes.29

In type 2 diabetes, most studies reported a group, usually the largest one, with relatively low and stable HbA1c over time. However, the actual HbA1c levels of the low stable group and the percentage of patients in this group varied substantially between different studies. There was greater heterogeneity among studies in relation to groups with less than optimal control over time. Many studies reported another stable group of patients albeit with higher levels of HbA1c, while some also found patients with extremely high but stable HbA1c levels. In contrast, some studies observed groups with unstable levels of HbA1c, including patterns with improving control, deteriorating control, and other non-linear trends. These differences might be due to the country where the study was conducted, patient characteristics, follow-up duration, and the use of different statistical models. We observed that studies conducted in countries with well-developed health care systems, ie, the United States and the Netherlands, generally had a higher proportion of patients in the trajectory with low and stable HbA1c levels.22,24,30 Patient characteristics, including diabetes duration, place receiving diabetes management, and length of follow-up, may have also influenced the patterns of trajectories identified and proportions of patients in each cluster. For example, more patterns were likely to emerge with longer duration of follow-up. Identifying patterns of trajectories could help to map the glycaemic control in the population, which could be used for comparing across health care settings and populations. Knowing the distribution of HbA1c patterns in the population could also be used contextually to help allocate medical resources in the health system efficiently and establish tailored policies and programmes to improve the glycaemic control in the given population. In addition, these patterns can also be useful in clinical settings, if membership of specific groups can be predicted early, to provide targeted intensification of therapies and additional diabetes management support to patients likely to have poorer glycaemic control trajectories. Such personalization of care can lead to substantial improvements in outcomes and reduced health care costs for these patients in the long run.

This review also summarized risk factors associated with different HbA1c trajectories. Several demographic, disease-related, family-related, and psychosocial variables have been reported among patients with type 1 diabetes. Most of the factors identified were consistent with previous studies that analysed average HbA1c levels31-38 and included older age, female gender, ethnic minority status, longer diabetes duration, lower glucose monitoring frequency, fewer or missed clinical appointments, and insulin delivery via injection versus insulin pump as associated with poorer HbA1c trajectories. Associations with several family environment and psychosocial variables reported in cross-sectional studies33,37,39-43 were also demonstrated in the longitudinal trajectory studies. However, we also noticed that 4 studies reported nonsignificant associations of poor HbA1c trajectories and some of the variables mentioned above20,30,44,45 including age, gender, ethnicity, disease duration, clinical appointment, insulin treatment, and self-control, although the direction of association effect was consistent with other studies. This nonsignificance in results may be due to the differences in study population and statistical analysis. The sample sizes for the studies conducted by Rohan et al, Marshall et al, and Viner et al were relatively small; thus, the results may have been attenuated when comparing among multiple groups.20,30,44 The study conducted by Schwandt et al only compared trajectories with similar initial HbA1c, but different trends, which may also have led to smaller differences between groups.45 Our review also highlights some associations that had not been reported in studies using average HbA1c levels, including college entrance and peer conflict. Helgeson et al reported that individuals in the poorer control group were characterized by higher peer conflict; Monaghan et al reported that although glycaemic control was relatively stable upon college entry, 31% of students had continuously poor glycaemic control during the follow-up period, suggesting the need for increased care during the transition from high school to college among these students.

It is worth noting that some factors influencing the HbA1c trajectories were only studied in type 1 diabetes but not in type 2 diabetes, including family environment, autonomy and self-control, peer conflict, and college entry. These factors were also significantly associated with glycaemic control patterns. As onset of disease in type 1 diabetes is predominantly during childhood and adolescence, it is logical that control may be dependent on family and social support. In addition, this is also a period of development and emotional maturation, which in itself is stressful without additional burdening by the responsibilities of diabetes management. Thus, interventions to improve diabetes management in patients with type 1 diabetes might need a comprehensive consideration of all these aspects.

For studies on patients with type 2 diabetes, the factors investigated in association with HbA1c trajectories were mainly demographic or disease related. Younger age, ethnic minority status, lower educational level, longer diabetes duration, higher baseline HbA1c, poorer lipid profiles, and higher baseline microvascular complications were reported to be associated with poorer HbA1c trajectories, which were consistent with findings from previous analysis.46-49 However, inconsistent with previous studies that observed increasing HbA1c levels after incident co-morbidities,50-52 Bayliss et al reported that patients’ HbA1c trajectories did not change after incident co-morbidities.28 It is possible that incident co-morbidities had no significant influence on
group trajectories because of the already high co-morbid burden in these patients, with patients having 4 to 5 co-morbid conditions at baseline. We also observed that inconsistent results were reported for the association between BMI and poorer HbA1c trajectories, with Chang et al24 reporting that low BMI was associated with worse trajectories while Walraven et al26 Laiterapong et al,25 and Luo et al27 reported the opposite associations. This inconsistency might be due to differences in study population, as the study by Chang et al was conducted among patients with 10-year diabetes duration while the other 3 studies were conducted among patients with newly diagnosed diabetes or patients with an average 4.5 years of diabetes. Obesity was an important risk factor for diabetes and glycaemic control53; however, persistent hyperglycaemia may lead to reduction in weight due to osmotic diuresis and muscle breakdown with excessive gluconeogenesis from amino acid, which might explain the result for the Chang et al study. For outcomes, poorer HbA1c trajectories were found to be associated with incident microvascular events and mortality, which was independent of average HbA1c levels during follow‐up25 or baseline HbA1c level.27 Numerous studies have reported the association between elevated HbA1c level and increased risk of diabetes‐related complications and death.2,3,54 and this finding further suggests that patterns of HbA1c might be an independent risk factor for diabetes‐related outcomes and emphasizes the importance of maintaining good glycaemic control over time.

This review has several limitations. Firstly, this review was only based on a qualitative comparison of studies. We are not aware of any current established method to combine results from multiplegroup‐based trajectory models quantitatively, given the heterogeneity between studies; thus, we could not combine studies to have estimates of effect sizes of various risk factors on glycaemic control trajectories. Also, since trajectory analysis is a relatively new method applied to HbA1c analysis, the number of articles available is limited. However, the current findings provide important information in terms of statistical methods and subgroup characteristics and will be useful for future research. Lastly, this review may be restricted by the selected databases, and studies published in some local journals and grey literature may have been omitted. Future studies searching on more databases may be beneficial to get a more comprehensive view of HbA1c trajectory analysis.

In summary, group‐based trajectory analysis identifies subgroups of patients with different natural history of disease. These groups have different characteristics in terms of sociodemographic and disease‐related factors. For instance, transition into adulthood55 and college enrolment22 have been found to represent vulnerable periods when patients will transition into a period of poor glycaemic control. They also have different outcomes. The groups are finite in number, and many seem to be common across populations studied, suggesting that the pattern of heterogeneity is generalizable to multiple different populations. A better understanding of the psychosocial and biological factors underlying the progression of disease in these groups could lead to the development of targeted strategies to improve outcomes in these patients.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

K.V. and E.S.T. were the guarantor for conducting the study and writing the manuscript. W.Y.L., C.S.T., and M.L. conceived and designed the study, M.L. and H.X.T. performed the systematic search, 2 rounds of study selection, data extraction, and quality assessment; K.V., C.S. T., and W.Y.L. reviewed and solved the discrepancies in data selection. M.L. summarized the results and drafted the manuscript. All authors critically revised the manuscript for important intellectual content.

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