Received: 16 October 2017 | Revised: 3 February 2018 | Accepted: 5 April 2018

DOI: 10.1002/dmrr.3015

RESEARCH ARTICLE

WILEY

Longitudinal trends in HbA_{1c} patterns and association with outcomes: A systematic review

Miyang Luo[1] | Kristin Hui Xian Tan[1] | Chuen Seng Tan[1] | Wei Yen Lim[1] | E-Shyong Tai[1,2] | Kavita Venkataraman[1]

[1] Saw Swee Hock School of Public Health, National University of Singapore, Singapore

[2] Division of Endocrinology, National University Hospital, Singapore

Correspondence
Kavita Venkataraman, Saw Swee Hock School of Public Health, National University of Singapore, Tahir Foundation Building, 12 Science Drive 2, Level 10, #10-03J, Singapore 117549.
Email: kavita_v@nus.edu.sg

Abstract

Background: This study aimed to review studies that identified patterns of longitudinal HbA_{1c} 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 HbA_{1c} 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 HbA_{1c}, and (*c*) analysis of the trend of HbA_{1c} 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 HbA_{1c} trajectory patterns. The most commonly identified patterns included stable HbA_{1c} around 7.0% and at levels between 8.0% and 9.9%, which usually captured the HbA_{1c} pattern among the majority of subjects in the study population. Unstable patterns identified included increasing HbA_{1c} trend, decreasing HbA_{1c} trend, and non-linear patterns. These patterns were associated with differential risk of disease outcomes, over and beyond single-point HbA_{1c} 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 HbA_{1c} pattern groups.

Conclusion: Common patterns of longitudinal HbA_{1c} 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, HbA_{1c}, longitudinal trends

1 | INTRODUCTION

Glycaemic control is one of the primary goals of clinical management for most patients with diabetes.[1] Poor glycaemic control has been causally associated with increased risk of diabetes-related complications and mortality risk,[2,3] and glycaemic control is the main way to improve disease outcomes in clinical practice. Most studies examining the relationship between HbA_{1c} and outcomes have used HbA_{1c} measured at a single time point or derived summary measures that include average HbA_{1c} during follow-up, change in HbA_{1c} over time, or HbA_{1c} variability.[4-7] However, these analytical approaches may not be able to completely capture the information available in serial HbA_{1c} 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 HbA_{1c} trajectories,[8] and these trajectories may not be correlated to baseline or average HbA_{1c} levels; ie, patients with the same baseline or average HbA_{1c} 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 HbA_{1c}. 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 HbA_{1c} 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.[9,10] 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,[11] crime trends,[12] and psychological disorders.[9] 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 HbA_{1c} trajectories could help to identify modifiable factors underlying different HbA_{1c} 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 HbA_{1c} trajectories in patient populations with diabetes, to summarize (*a*) distinct HbA_{1c} patterns and prevalence of different patterns in the diabetes population, (*b*) factors associated with different HbA_{1c} patterns, and (*c*) outcomes associated with different patterns of HbA_{1c}.

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.[13] This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.[14]

PubMed and Web of Science databases were searched for potentially relevant articles from inception of database to September 2017. The search terms "HbA_{1c}" or all the Medical Subject Headings terms of HbA_{1c} combined with "Trajector* 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 HbA_{1c}, and (*c*) analysis of the trend of HbA_{1c} using at least one of the group-based trajectory modelling and clustering approaches,[10] 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 HbA_{1c} 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 HbA_{1c} data, and source of HbA_{1c} measures; subject characteristics included type of diabetes, age, diabetes duration, and baseline HbA_{1c} 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 HbA_{1c} trajectories identified and reported factors/outcomes associated with different patterns of trajectories.

Patterns of HbA_{1c} trajectories identified in each article were renamed and categorized based on baseline HbA_{1c} and trend of change. We used 5 categories to classify the baseline HbA_{1c} 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 HbA_{1c} levels for type 1 diabetes and type 2 diabetes recommended in international guidelines.[15] The HbA_{1c} cut-off values were $\leq$7.0%, 7.1% to 7.5%, 7.6% to 9.0%, 9.1% to 11.0%, and >11.0% for the 5 type 1 diabetes categories and $\leq$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 HbA_{1c} less than 1.0% during follow-up as compared with baseline; deteriorating and improving trends were increasing or decreasing HbA_{1c} 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 HbA_{1c} or trend of change was not given in numbers, estimates were extracted from the plot of HbA_{1c} trajectories.

Quality of the studies was assessed using the Newcastle-Ottawa quality assessment scale[16,17] and Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statements[18] 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 HbA_{1c} 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 diagram[19] 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 HbA_{1c} values from medical records, while the rest obtained HbA_{1c} values by direct measurement. Half of the studies used the National Glycohemoglobin Standardization Program–certified method for the measurement of HbA_{1c} (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 HbA_{1c} measurement methods or standardization processes (n = 9). The number of HbA_{1c} points for each subject ranged from 4 to 18. Twelve of these studies used structured time points in the HbA_{1c} trajectory analysis, and the time points in the remaining 8 studies were unstructured.

3.3 | Statistical methods used in group-based HbA_{1c} trajectory analysis

The statistical models used for analysing HbA_{1c} 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

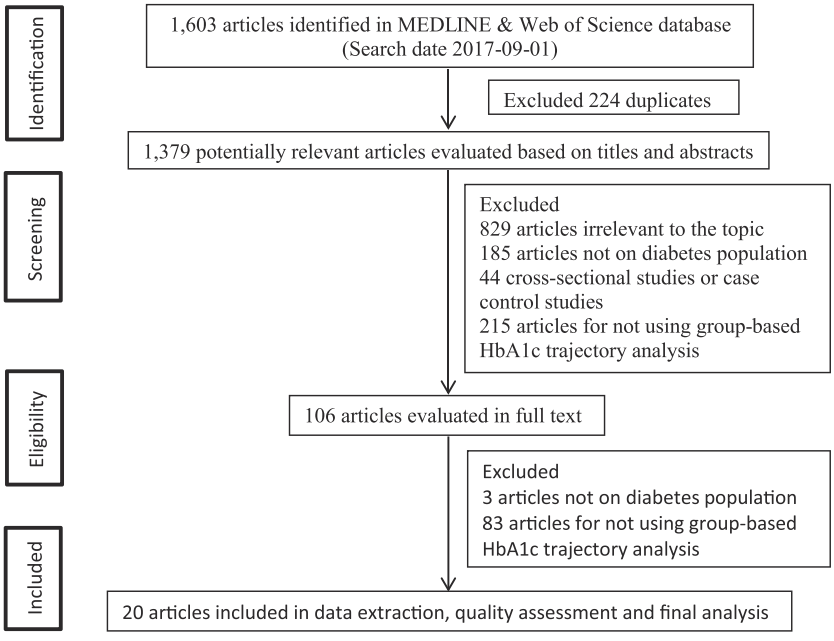

FIGURE 1 Flowchart of study selection process

TABLE 1 Summary of studies conducting group-based HbA_{1c} trajectory analysis

Study	Country	Study design	Sample size	Mean age (bl)	Mean diabetes duration (bl)	Length of follow-up	No./type of time points[a]	HbA_{1c} data source/ measurement method	HbA_{1c} trajectories identified
T1D									
Luyckx and Seiffge-Krenke[55]	Germany	Prospective cohort	72	14 y	4.8 y	11 y	8/structured	Medical records/—	Very low stable (13.9%, bl HbA_{1c} 6.3%) Moderate stable (70.8%, bl HbA_{1c} 7.6%) Very low deteriorating (15.3%, bl HbA_{1c} 6.6%)
Helgeson et al[58]	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 al[23]	United States	Prospective cohort	252	12 y	4.7 y	2 y	8/unstructured	Medical records/—	Moderate stable (92%, average HbA_{1c} 8.18%) Moderate-high deteriorating (8%, average HbA_{1c} 12.09%)
Hilliard et al[56]	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 HbA_{1c} 7.4%) Moderate-high stable (39.7%, bl HbA_{1c} 9.2%) High stable (20.5%, bl HbA_{1c} 11.2%)
Lawes et al[60]	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 al[21]	United States	Retrospective cohort	1449	11 y	—	3 y	9/unstructured	Medical records/ DCA Vantage (Siemens)	Moderate stable (58.1%, bl HbA_{1c} 8.0%) Moderate improving (25.5%, bl HbA_{1c} 8.8%) Moderate deteriorating (16.4%, bl HbA_{1c} 8.3%)
Rohan et al[20]	United States	Prospective cohort	239	11 y	4.4 y	3 y	7/structured	Direct assessment/ TOSOH-G7	Low stable (42.9%, bl HbA_{1c} 7.3%) Moderate deteriorating (44.6%, bl HbA_{1c} 8.6%) Moderate-high deteriorating (12.1%, bl HbA_{1c} 10.0%)
Marshall et al[30]	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 HbA_{1c} 6.5%) Moderate deteriorating (8.4%, average HbA_{1c} 8.6%) Moderate-high improving (26.9%, average HbA_{1c} 10.7%) High improving (31.8%, average HbA_{1c} 12.9%) High stable (24.9%, average HbA_{1c} 13.5%)
Monaghan et al[22]	United States	Retrospective cohort	74	18 y	9.0 y	2 y	5/structured	Medical records/—	Low stable (69%, bl HbA_{1c} 7.4%) Moderate-high improving (31%, bl HbA_{1c} 10.5%)
Viner et al[44]	United Kingdom	Prospective cohort	384	13 y	—	From age 9 to 17 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 al[45]	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 HbA_{1c} 6.6%) Low stable (40%, bl HbA_{1c} 7.4%) Moderate stable (16. 6%, bl HbA_{1c} 8.4%) Low deteriorating (13.0%, bl HbA_{1c} 7.4%) Moderate deteriorating (5.4%, bl HbA_{1c} 8.5%)

(Continues)

TABLE 1 (Continued)

Study	Country	Study design	Sample size	Mean age (bl)	Mean diabetes duration (bl)	Length of follow-up	No./type of time points[a]	HbA_{1c} data source/ measurement method	HbA_{1c} trajectories identified
T2D									
Bayliss et al[28]	United States	3 subcohorts from a prospective cohort	582 (cancer)	66 y	—	4.7 y	9/unstructured	Medical records/—	Very low stable (37.7%) Moderate stable (41.0%) Moderate-high deteriorating (7.4%) High improving (10.6%) High stable (3.2%)
			2959 (depression)	62 y	—	5.0 y	8/unstructured		Low stable (49.7%) Moderate-high stable (32.5%) Moderate-high deteriorating (8.4%) High improving (6.2%) High stable (3.2%)
			2322 (pulmonary disease)	63 y	—	5.0 y	9/unstructured		Very low stable (48.2%) Moderate stable (31.8%); Moderate-high stable (12.6%) High U shape (1.4%) High N shape (5.9%)
Wang and Hazuda[57]	United States	Prospective cohort	119	76 y	12.5 y	3.0 y	7/structured	Direct assessment/—	Very low stable (44.7%) Moderate stable (55.3%)
Chang et al[24]	Taiwan	RCT	1091	56 y	10.0 y	4.5 y	9/structured	Direct assessment/ Variant II (Bio-Rad Laboratories)	Low stable (47.2%) Moderate-high stable (38.3%) High stable (14.5%)
Ravona-Springer et al[62]	Israel	Prospective cohort	835	73 y	—	8.7 y	18/unstructured	Medical records/—	Very low stable (27.1%, bl HbA_{1c} 6.0%) Low stable (43.6%, bl HbA_{1c} 6.8%) Moderate stable (14.7%, bl HbA_{1c} 7.3%) Moderate deteriorating (5.5%, bl HbA_{1c} 7.8%) Moderate-high improving (7.1%, bl HbA_{1c} 9.2%) High improving (1.8%, bl HbA_{1c} 10.7%)
Migliore et al[59]	United States	RCT	109	—	—	2 y	6/structured	Direct assessment/ Glyc-affin Ghd column method	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	5.7 y	9/structured	Direct assessment/ HA-8160 analyser, Menarini	Low stable (83.1%, bl HbA_{1c} 6.9%) Moderate deteriorating (3.4%, bl HbA_{1c} 7.9%) Moderate-high improving (5.2%, bl HbA_{1c} 9.1%) High improving (L shape) (8.2%, bl HbA_{1c} 11.9%)
Mast et al[61]	The Netherlands	Prospective cohort	1203	65 y	8.3 y	5.6 y	12/structured	Direct assessment/ HA-8160 analyser, Menarini	Moderate stable (88.7%, bl HbA_{1c} 7.4%) Moderate-high N shape (3.0%, bl HbA_{1c} 8.1%) Moderate-high improving slow (3.9%, bl HbA_{1c} 10.0%) High improving fast (4.4%, bl HbA_{1c} 10.9%)
Laiteerapong et al[25]	United States	Prospective cohort	28 016	—	Newly diagnosed	13.6 y	10/structured	Medical records/HPLC	Moderate stable (82.5%, bl HbA_{1c} 7.2%) Moderate-high deteriorating (5.1%, bl HbA_{1c} 8.3%) Moderate-high peaking late (N shape) (4.1%, bl HbA_{1c} 8.5%)

(Continues)

TABLE 1 (Continued)

Study	Country	Study design	Sample size	Mean age (bl)	Mean diabetes duration (bl)	Length of follow-up	No./type of time points[a]	HbA_{1c} data source/ measurement method	HbA_{1c} trajectories identified
									Moderate-high peaking early (N shape) (3.3%, bl HbA_{1c} 9.3%) High improving (4.9%, bl HbA_{1c} 11.9%)
Luo et al[27]	Singapore	Ambispective cohort	6079	59 y	4.5 y	4.1 y	−/unstructured	Medical records/−	Moderate stable (72.2%, bl HbA_{1c} 7.2%) Moderate-high stable (22.0%, bl HbA_{1c} 8.9%) High deteriorating (2.9%, bl HbA_{1c} 10.4%) High improving (2.8%, bl HbA_{1c} 12.1%)

Abbreviations: −, not mentioned; bl, baseline; HPLC, high-performance liquid chromatography; RCT, randomized control trial.

Patterns of HbA_{1c} trajectories were renamed and categorized based on baseline HbA_{1c} and trend of change. Baseline HbA_{1c} were 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 patients.

[a]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. For studies with unstructured time points, the number of time points refers to the average number of HbA_{1c} measurements for each participant.

determining the optimal number of subgroups (n = 15), and it was often used in combination with other statistics, which included Akaike information criterion, entropy, average posterior probabilities, bootstrapped likelihood ratio test, Lo-Mendell-Rubin likelihood ratio test, sufficient subject in each group, clinical plausibility, and other model diagnostics.

3.4 | Summary of HbA_{1c} trajectories identified

As summarized in Table 1, different HbA_{1c} 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 HbA_{1c} (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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} (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%-7.0%), and another 3 studies identified a cluster with continuously poor control with HbA_{1c} maintained at a moderate high (9.1%-11.0%) or very high baseline level (higher than 11.0%), and each pattern usually contained less than one-third of the sample. Groups with deteriorating HbA_{1c}, from very low (n = 1), low (n = 1), moderate (n = 7), and moderate-high (n = 3) baseline HbA_{1c}, 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} levels over time. Groups with deteriorating glycaemic control starting from moderate (n = 2) or moderate-high (n = 4) HbA_{1c} 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 HbA_{1c} level were identified in 6 studies, with group percentage ranging from 2% to 11%. Other non-linear patterns, including U

TABLE 2 Statistical methods used by studies conducting group-based HbA_{1c} trajectory analysis

Study	Statistical method	Software	Dependent variable	Independent variable	Approach to determine number of clusters							No. of clusters attempted	No. of clusters in the final model
					BIC	AIC	Entropy	Average posterior probabilities	Statistical tests	Sufficient subjects in each cluster	Others		
T1D													
Luyckx and Seiffge-Krenke[55]	LCGA	Mplus	HbA_{1c}	Time from recruitment	✓	—	✓ (E = 0.99)	—	Bootstrapped likelihood ratio test	✓	—	2-4	3
Helgeson et al[58]	LCGA	SAS Proc TRAJ	HbA_{1c}	Time from recruitment	✓	—	—	—	—	—	—	2-4	2
King et al[23]	LCGA	Mplus	HbA_{1c}	Age	✓	—	✓ (E = 0.92)	✓	Lo-Mendell-Rubin likelihood ratio test	—	—	1-3	2
Hilliard et al[56]	LCGA	Mplus	HbA_{1c}, BGM frequency	Time from recruitment	✓	—	—	—	—	✓ (10%)	Nagin's diagnostics	2-4	3
Lawes et al[60]	Two-stage clustering method	SPSS	HbA_{1c}	Time from diagnosis of diabetes	✓	—	—	—	—	—	Distant change	Maximum 6	4
Phan et al[21]	Hierarchical cluster analysis	SAS and SPSS	HbA_{1c}	Time from study baseline	—	—	—	—	—	—	—	—	3
Rohan et al[20]	LCGA	SAS Proc TRAJ	HbA_{1c}	Time from recruitment	✓	—	—	—	—	✓ (10%)	Nagin's diagnostics	2-6	3
Marshall et al[30]	LCGA	SAS Proc TRAJ	HbA_{1c}	Time from recruitment	✓[a]	—	—	—	—	—	—	—	5
Monaghan et al[22]	LCGA	SAS Proc TRAJ	HbA_{1c}	Time from college enrolment	✓	—	—	—	—	✓ (>5)	—	—	2
Viner et al[44]	LCGMM	Mplus	HbA_{1c}	Age	✓[b]	✓	✓	—	Lo-Mendell-Rubin likelihood ratio test	—	Clinical plausibility	1-4	4
Schwandt et al[45]	LCGA	SAS Proc TRAJ	HbA_{1c}	Age	✓	—	—	—	—	✓ (5%)	Clinical plausibility	1-6	5
T2D													
Bayliss et al[28]	LCGA	—	HbA_{1c}	Time from diagnosis of incident co-morbidity	—	—	—	—	—	—	—	—	5
Wang and Hazuda[57]	LCGMM	—	HbA_{1c}	Time from recruitment	✓	✓	—	—	—	—	Residual diagnostics	—	2
Chang et al[24]	LCGA	SAS Proc TRAJ	HbA_{1c}	Time from recruitment	✓	—	—	—	—	—	—	—	3
Ravona-Springer et al[62]	LCGA	SAS Proc TRAJ	HbA_{1c}	Time from entry to diabetes registry	—	—	—	—	—	—	Nagin's diagnostics	—	6
Migliore et al[59]	k-means cluster analysis	SPSS	HbA_{1c}, blood pressure, BMI, triglycerides	Time from recruitment	—	—	—	—	—	—	Hierarchical clustering; intervention	—	2

(Continues)

TABLE 2 (Continued)

Study	Statistical method	Software	Dependent variable	Independent variable	Approach to determine number of clusters							No. of clusters attempted	No. of clusters in the final model
					BIC	AIC	Entropy	Average posterior probabilities	Statistical tests	Sufficient subjects in each cluster	Others		
Walraven et al[26]	LCGA	Mplus	HbA_{1c}	Time from recruitment	✓	–	–	✓ (0.8)	–	–	Clinical plausibility	1-5	4
Mast et al[61]	LCGA	Mplus	HbA_{1c}	Time from insulin initiation	✓	–	–	✓ (0.8)	–	✓ (1%)	Clinical plausibility	–	4
Laiteerapong et al[25]	LCGMM	Mplus	HbA_{1c}	Time from diagnosis of diabetes	–	–	–	–	Lo-Mendell-Rubin likelihood ratio test	✓ (1%)	–	–	5
Luo et al[27]	LCGA	R	HbA_{1c}	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.

[a]BIC log Bayes factor approximation was used: $2\log_e(B10) \cong 2(\Delta BIC)$.

[b]Sample adjusted BIC.

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 HbA_{1c} trajectories

Table 3 summarizes the reported factors associated with HbA_{1c} trajectories in studies on patients with type 1 diabetes. Among demographic factors, older age, female gender, and ethnic minority status were associated with poor HbA_{1c} trajectories. Disease-related factors associated with poor HbA_{1c} 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 HbA_{1c} trajectory was significant after adjustment for baseline HbA_{1c}.[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. Psychosocial 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 HbA_{1c} upon college entry,[22] and King et al reported that subjects with poorer HbA_{1c} trajectories had more frequent diabetes-related emergency room visits and diabetes-related hospitalizations.[23]

Table 4 presents the factors and outcomes associated with poorer HbA_{1c} trajectories in patients with type 2 diabetes. Younger age, ethnic minority status, and lower educational level were reported demographic factors associated with poorer HbA_{1c} trajectories. Disease-related factors reported included longer diabetes duration, higher baseline HbA_{1c} levels, 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 trajectories. 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.[25-27] In addition, Bayliss et al reported that the HbA_{1c} trajectories did not change significantly before and after the incident co-morbidity of cancer, depression, and pulmonary disease.[28] In terms of outcomes, poor HbA_{1c} trajectories were associated with risk of microvascular and macrovascular events and mortality, poorer cognitive function, and poorer lower-extremity function. Laiteerapong et al reported higher incidence of microvascular complications in all the nonstable trajectories and increased all-cause mortality risk for groups with high improving trajectory as compared with the low stable group, after adjustment for mean HbA_{1c}.[25] Luo et al reported increased risk of stroke, end-stage renal disease, and all-cause mortality in moderate-increase and high-decrease trajectories as compared with the low stable group, after adjustment for baseline HbA_{1c}.[27]

TABLE 3 Factors associated with poorer glycaemic control trajectories in patients with type 1 diabetes

	Demographics			Disease related				Family environment	Psychosocial		
Studies	Older age (3/5)	Female (3/5)	Ethnic minority status (3/5)	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)	Poor family climate/family conflict/less family monitoring and help (4/4)	Negative emotions (3/3)	Poorer self-control/functional autonomy (4/5)	Others
Luyckx and Seiffge-Krenke[55,a]	—	✓	—	ns	—	—	—	✓	✓	✓	ns: Family composition, socio-economic status, and BMI score
Helgeson et al[58,b]	ns	ns	—	—	✓	✓	ns after adjustment for bl HbA_{1c}	—	✓	✓	✓: Peer conflict, lower social status, higher pubertal status, higher BMI
King et al[23,c]	—	—	—	—	—	—	—	✓	—	✓	✓: Diabetes-related emergency room visit and hospitalizations
Hilliard et al[56,c]	✓	—	✓	✓	—	—	✓	✓	✓	✓	✓: Unmarried caregiver status
Lawes et al[60,a]	✓	—	—	—	—	✓	ns at 2 y after diagnosis	—	—	—	✓: More frequent nonclinic health care contacts; higher rates of adverse psychosocial variables
Phan et al[21,d]	✓	—	✓	—	—	✓	—	—	—	—	✓: Medicaid vs commercial insurance
Rohan et al[20,e]	—	✓	ns	ns	✓	—	ns	✓	—	ns	—
Marshall et al[30,a]	ns	—	—	ns	✓	—	—	—	—	—	ns: Rates did not differ for bl microalbuminuria, neuropathy, and nephropathy; test not conducted owing to small sample size
Monaghan et al[22,a]	—	—	✓	—	—	—	✓	—	—	—	✓: College entry
Viner et al[44,e]	—	ns	ns	ns	—	ns	✓	—	—	—	—
Schwandt et al[45,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.

[a]Unadjusted.

[b]Adjusted for social status, pubertal status, BMI, and household structure. Results for other variables were unadjusted.

[c]Adjusted for variables of the same categories (or with shared variance or in the same block).

[d]Adjusted for baseline HbA_{1c} and all variables in the model.

[e]Adjusted for all variables in the model.

TABLE 4 Factors and outcomes associated with poorer glycaemic control trajectories in patients with type 2 diabetes

	Factors									Outcomes		
	Demographics			Disease related								
Studies	Younger age (7/7)	Ethnic minority status (2/2)	Lower educational level (2/3)	Longer diabetes duration (5/6)	Higher bl HbA_{1c} (5/5)	Poorer lipid profiles (6/6)	Higher eGFR (4/5)	BMI	Others	Complications	Higher mortality (3/3)	Others
Bayliss et al[28]	—	—	—	—	—	—	—	—	ns: Incident co-morbidity	—	—	—
Wang and Hazuda[57,a,b]	✓	—	✓	✓	—	—	—	—	✓: Higher peripheral arterial disease prevalence	—	—	✓: Poorer lower extremity function
Chang et al[24,b,c]	✓	—	✓	✓	—	✓ (bl)	✓ (bl)	Lower (bl)	✓: Less physical activity; higher ACR; higher neuropathy; higher family history of diabetes at bl	✓: Higher incidence of retinopathy, nephropathy, stroke, hypoglycaemia, and ketoacidosis	—	✓: Higher use of oral anti-hyperglycaemic medications and insulin
Ravona-Springer et al[62,b,d]	✓	—	ns	✓	✓	✓	ns	—	✓: Insulin treatment	—	—	✓: Poorer cognitive function
Migliore et al[59,b]	—	—	—	—	—	—	—	—	✓: Self-management and coping skills training intervention	—	—	—
Walraven et al[26,e]	✓	—	—	✓	✓	✓ (bl)	—	Higher (bl)	✓: Higher urinary ACR, microalbuminuria, and retinopathy; higher insulin use (bl)	✓: Higher prevalence of retinopathy, microalbuminuria	—	—
Mast et al[61,b]	✓[e]	—	—	ns	✓[e]	✓	✓	ns	✓: Higher SU use; ns: retinopathy, ns: microalbuminuria	—	✓	—
Laiteerapong et al[25,b,f]	✓	✓	—	—	✓	✓	✓	Higher	✓: Less macrovascular diseases; more microvascular disease; smoking; higher blood pressure	✓: Higher incidence of retinopathy, end-stage renal disease, lower-extremity amputation, and macrovascular events[g]	✓	—
Luo et al[27,b,h]	✓	✓	—	✓	✓	✓	✓	Higher	✓: Insulin treatment; bl co-morbidities; managed in hospital outpatient clinics vs primary care clinics	✓: Higher incidence of end-stage renal disease, acute myocardial infarction, and stroke	✓	—

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

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

[b]Factors reported from comparisons without adjustment.

[c]Outcomes were analysed by proportional hazards model with adjustment for age and BMI.

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

[e]Factors reported from comparisons with adjustment.

[f]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 HbA_{1c}.

[g]The association of macrovascular events was insignificant after adjustment for mean HbA_{1c}.

[h]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 HbA_{1c} at baseline.

4 | DISCUSSION

In this study, 20 articles reporting long-term HbA_{1c} trajectories were included. All but 2 were cohort studies with varying follow-up durations. These studies identified 2 to 6 HbA_{1c} trajectory subgroups and also reported several factors and outcomes associated with trajectory groups.

The review showed that there was heterogeneity in HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} over time. However, the actual HbA_{1c} 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 HbA_{1c}, while some also found patients with extremely high but stable HbA_{1c} levels. In contrast, some studies observed groups with unstable levels of HbA_{1c}, 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 larger proportion of patients in the trajectory with low and stable HbA_{1c} levels.[22,26,30] 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} levels[31-38] 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 HbA_{1c} trajectories. Associations with several family environment and psychosocial variables reported in cross-sectional studies[33,7,39-43] were also demonstrated in the longitudinal trajectory studies. However, we also noticed that 4 studies reported nonsignificant associations of poor HbA_{1c} trajectories and some of the variables mentioned above[20,30,44,45] 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} trajectories were mainly demographic or disease related. Younger age, ethnic minority status, lower educational level, longer diabetes duration, higher baseline HbA_{1c}, poorer lipid profiles, and higher baseline microvascular complications were reported to be associated with poorer HbA_{1c} trajectories, which were consistent with findings from previous analysis.[46-49] However, inconsistent with previous studies that observed increasing HbA_{1c} levels after incident co-rmorbidities,[50-52] Bayliss et al reported that patients' HbA_{1c} 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 HbA_{1c} trajectories, with Chang et al[24] reporting that low BMI was associated with worse trajectories while Walraven et al,[26] Laiteerapong et al,[25] and Luo et al[27] 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 control[53]; 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 HbA_{1c} trajectories were found to be associated with incident microvascular events and mortality, which was independent of average HbA_{1c} levels during follow-up[25] or baseline HbA_{1c} level.[27] Numerous studies have reported the association between elevated HbA_{1c} level and increased risk of diabetes-related complications and death,[2,3,54] and this finding further suggests that patterns of HbA_{1c} 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 multiple-group–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 HbA_{1c} 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 HbA_{1c} 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 adulthood[55] and college enrolment[22] 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.

ACKNOWLEDGEMENTS

The authors are grateful to the Saw Swee Hock School of Public Health, National University of Singapore, for their support.

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.

ORCID

Kavita Venkataraman http://orcid.org/0000-0002-3139-6998

REFERENCES

1. American Diabetes Association. 5. Glycemic Targets. Standards of medical care in diabetes. *Diabetes Care*. 2016;S39-S46.
2. Group UKPDS. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *The Lancet*. 1998;352(9131):837-853.
3. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358(24):2560-2572.
4. Svoren BM, Volkening LK, Butler DA, Moreland EC, Anderson BJ, Laffel LMB. Temporal trends in the treatment of pediatric type 1 diabetes and impact on acute outcomes. *J Pediatr*. 2007;150(3):279-285.
5. Hsu CC, Chang HY, Huang MC, et al. HbA_{1c} variability is associated with microalbuminuria development in type 2 diabetes: a 7-year prospective cohort study. *Diabetologia*. 2012;55(12):3163-3172.
6. Gorst C, Kwok CS, Aslam S, et al. Long-term glycemic variability and risk of adverse outcomes: a systematic review and meta-analysis. *Diabetes Care*. 2015;38(12):2354-2369.
7. Nichols GA, Joshua-Gotlib S, Parasuraman S. Glycemic control and risk of cardiovascular disease hospitalization and all-cause mortality. *J Am Coll Cardiol*. 2013;62(2):121-127.
8. Gebregziabher M, Egede LE, Lynch CP, Echols C, Zhao Y. Effect of trajectories of glycemic control on mortality in type 2 diabetes: a semiparametric joint modeling approach. *Am J Epidemiol*. 2010;171(10):1090-1098.
9. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. *Annu Rev Clin Psychol*. 2010;6(1):109-138.
10. Twisk J, Hoekstra T. Classifying developmental trajectories over time should be done with great caution: a comparison between methods. *J Clin Epidemiol*. 2012;65(10):1078-1087.
11. Musliner KL, Munk-Olsen T, Eaton WW, Zandi PP. Heterogeneity in long-term trajectories of depressive symptoms: patterns, predictors and outcomes. *J Affect Disord*. 2016;192:199-211.
12. Piquero AR. Taking stock of developmental trajectories of criminal activity over the life course. In: Liberman AM, ed. *The Long View of Crime: A Synthesis of Longitudinal Research*. New York, NY: Springer; 2008:23-78.
13. Luo M, Tan H, Lim W. HbA_{1c} trajectories and outcome among diabetes patients. Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015019692
14. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ (Clinical Research Ed)*. 2009;b2700:339.

15. Standards of medical care in diabetes—2017: summary of revisions. *Diabetes Care* 2017;40(Supplement 1):S4-S5.

16. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25(9):603-605.

17. Wells GA SB, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) For assessing the quality of nonrandomised studies in meta-analyses 2014 [8 June 2015]. Available from: main file with tracked change kv.docx.

18. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *International Journal of Surgery (London, England)*. 2014;12(12):1495-1499.

19. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6(7). e1000100

20. Rohan JM, Rausch JR, Pendley JS, et al. Identification and prediction of group-based glycemic control trajectories during the transition to adolescence. *Health Psychology : Official Journal of the Division of Health Psychology, American Psychological Association*. 2014;33(10):1143-1152.

21. Phan TL, Hossain J, Lawless S, Werk LN. Quarterly visits with glycated hemoglobin monitoring: the sweet spot for glycemic control in youth with type 1 diabetes. *Diabetes Care*. 2014;37(2):341-345.

22. Monaghan M, King MM, Alvarez V, Cogen FR, Wang J. Changes in type 1 diabetes health indicators from high school to college. *J Am Coll Health*. 2016;64(2):157-161.

23. King PS, Berg CA, Butner J, et al. Longitudinal trajectories of metabolic control across adolescence: associations with parental involvement, adolescents' psychosocial maturity, and health care utilization. *The Journal of Adolescent Health: Official Publication of the Society for Adolescent Medicine*. 2012;50(5):491-496.

24. Chang HY, Wahlqvist ML, Liu WL, et al. Management trajectories in the type 2 diabetes integrated delivery system project in Taiwan: accounting for behavioral therapy, nutrition education and therapeutics. *Asia Pac J Clin Nutr*. 2014;23(4):592-606.

25. Laiteerapong N, Karter AJ, Moffet HH, et al. Ten-year hemoglobin A_{1c} trajectories and outcomes in type 2 diabetes mellitus: the Diabetes & Aging Study. *J Diabetes Complications*. 2017;31(1):94-100.

26. Walraven I, Mast MR, Hoekstra T, et al. Distinct HbA_{1c} trajectories in a type 2 diabetes cohort. *Acta Diabetol*. 2015;52(2):267-275.

27. Luo M, Lim WY, Tan CS, et al. Longitudinal trends in HbA_{1c} and associations with comorbidity and all-cause mortality in Asian patients with type 2 diabetes: a cohort study. *Diabetes Res Clin Pract*. 2017;133:69-77.

28. Bayliss EA, Blatchford PJ, Newcomer SR, Steiner JF, Fairclough DL. The effect of incident cancer, depression and pulmonary disease exacerbations on type 2 diabetes control. *J Gen Intern Med*. 2011;26(6):575-581.

29. Control TD, Group CTR. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *New England Journal of Medicine*. 1993;329(14):977-986.

30. Marshall SL, Edidin DV, Arena VC, et al. Glucose control in Rwandan youth with type 1 diabetes following establishment of systematic, HbA_{1c} based, care and education. *Diabetes Res Clin Pract*. 2015;107(1):113-122.

31. Factors influencing glycemic control in young people with type 1 diabetes in Scotland: a population-based study (DIABAUD2). *Diabetes care*. 2001;24(2):239-244.

32. Levine BS, Anderson BJ, Butler DA, Antisdel JE, Brackett J, Laffel LM. Predictors of glycemic control and short-term adverse outcomes in youth with type 1 diabetes. *J Pediatr*. 2001;139(2):197-203.

33. Frey MA, Templin T, Ellis D, Gutai J, Podolski CL. Predicting metabolic control in the first 5 yr after diagnosis for youths with type 1 diabetes: the role of ethnicity and family structure. *Pediatr Diabetes*. 2007;8(4):220-227.

34. Petitti DB, Klingensmith GJ, Bell RA, et al. Glycemic control in youth with diabetes: the SEARCH for Diabetes in Youth Study. *The Journal of Pediatrics*. 2009;155(5):668-672.e661-663.

35. Ziegler R, Heidtmann B, Hilgard D, Hofer S, Rosenbauer J, Holl R. Frequency of SMBG correlates with HbA_{1c} and acute complications in children and adolescents with type 1 diabetes. *Pediatr Diabetes*. 2011;12(1):11-17.

36. Kim H, Elmi A, Henderson CL, Cogen FR, Kaplowitz PB. Characteristics of children with type 1 diabetes and persistent suboptimal glycemic control. *J Clin Res Pediatr Endocrinol*. 2012;4(2):82-88.

37. Zuijdwijk CS, Cuerden M, Mahmud FH. Social determinants of health on glycemic control in pediatric type 1 diabetes. *J Pediatr*. 2013;162(4):730-735.

38. Sherr JL, Hermann JM, Campbell F, et al. Use of insulin pump therapy in children and adolescents with type 1 diabetes and its impact on metabolic control: comparison of results from three large, transatlantic paediatric registries. *Diabetologia*. 2016;59(1):87-91.

39. Hassan K, Loar R, Anderson BJ, Heptulla RA. The role of socioeconomic status, depression, quality of life, and glycemic control in type 1 diabetes mellitus. *J Pediatr*. 2006;149(4):526-531.

40. Ellis DA, Podolski CL, Frey M, Naar-King S, Wang B, Moltz K. The role of parental monitoring in adolescent health outcomes: impact on regimen adherence in youth with type 1 diabetes. *J Pediatr Psychol*. 2007;32(8):907-917.

41. Butler DA, Zuehlke JB, Tovar A, Volkening LK, Anderson BJ, Laffel LM. The impact of modifiable family factors on glycemic control among youth with type 1 diabetes. *Pediatr Diabetes*. 2008;9(4 Pt 2):373-381.

42. Duke DC, Geffken GR, Lewin AB, Williams LB, Storch EA, Silverstein JH. Glycemic control in youth with type 1 diabetes: family predictors and mediators. *J Pediatr Psychol*. 2008;33(7):719-727.

43. Helgeson VS, Palladino DK. Implications of psychosocial factors for diabetes outcomes among children with type 1 diabetes: a review. *Social and Personality Psychology Compass*. 2012;6(3):228-242.

44. Viner RM, White B, Amin R, et al. Impact of deprivation, ethnicity, and insulin pump therapy on developmental trajectories of diabetes control in COB type 1 diabetes. *Pediatr Diabetes*. 2016.

45. Schwandt A, Hermann JM, Rosenbauer J, et al. Longitudinal trajectories of metabolic control from childhood to young adulthood in type 1 diabetes from a large German/Austrian Registry: a group-based modeling approach. *Diabetes care*. 2017;40(3):309-316.

46. Misra R, Lager J. Ethnic and gender differences in psychosocial factors, glycemic control, and quality of life among adult type 2 diabetic patients. *J Diabetes Complications*. 2009;23(1):54-64.

47. Benoit SR, Fleming R, Philis-Tsimikas A, Ji M. Predictors of glycemic control among patients with type 2 diabetes: a longitudinal study. *BMC Public Health*. 2005;5(1):36.

48. de Rekeneire N, Rooks RN, Simonsick EM, et al. Racial differences in glycemic control in a well-functioning older diabetic population. *Findings from the Health, Aging and Body Composition study*. 2003;26(7):1986-1992.

49. Khattab M, Khader YS, Al-Khawaldeh A, Ajlouni K. Factors associated with poor glycemic control among patients with type 2 diabetes. *J Diabetes Complications*. 2010;24(2):84-89.

50. Richardson LK, Egede LE, Mueller M, Echols CL, Gebregziabher M. Longitudinal effects of depression on glycemic control in veterans with type 2 diabetes. *Gen Hosp Psychiatry*. 2008;30(6):509-514.

51. Davis WA, Knuiman M, Kendall P, Grange V, Davis TM. Glycemic exposure is associated with reduced pulmonary function in type 2 diabetes: the Fremantle Diabetes Study. *Diabetes Care*. 2004;27(3):752-757.

52. Keating NL, Zaslavsky AM, Herrinton LJ, Selby JV, Wolf RE, Ayanian JZ. Quality of diabetes care among cancer survivors with diabetes. *Med Care*. 2007;45(9):869-875.

53. Leong KS, Wilding JP. Obesity and diabetes. *Best Pract Res Clin Endocrinol Metab*. 1999;13(2):221-237.

54. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet (London, England)*. 1998;352(9131):837-853.

55. Luyckx K, Seiffge-Krenke I. Continuity and change in glycemic control trajectories from adolescence to emerging adulthood: relationships with family climate and self-concept in type 1 diabetes. *Diabetes Care*. 2009;32(5):797-801.

56. Hilliard ME, Wu YP, Rausch J, Dolan LM, Hood KK. Predictors of deteriorations in diabetes management and control in adolescents with type 1 diabetes. *The Journal of Adolescent Health : Official Publication of the Society for Adolescent Medicine*. 2013;52(1):28-34.

57. Wang CP, Hazuda HP. Better glycemic control is associated with maintenance of lower-extremity function over time in Mexican American and European American older adults with diabetes. *Diabetes Care*. 2011;34(2):268-273.

58. Helgeson VS, Snyder PR, Seltman H, Escobar O, Becker D, Siminerio L. Brief report: trajectories of glycemic control over early to middle adolescence. *J Pediatr Psychol*. 2010;35(10):1161-1167.

59. Migliore CL, Vorderstrasse A, Pan W, Melkus GD. Renal disease risk factors among risk groups comprised of African American women with type 2 diabetes: a secondary analysis. *Diabetes Educ*. 2015;41(5):569-581.

60. Lawes T, Franklin V, Farmer G. HbA_{1c} tracking and bio-psychosocial determinants of glycaemic control in children and adolescents with type 1 diabetes: retrospective cohort study and multilevel analysis. *Pediatr Diabetes*. 2014;15(5):372-383.

61. Mast MR, Walraven I, Hoekstra T, et al. Effectiveness of insulin therapy in people with type 2 diabetes in the Hoorn Diabetes Care System. *Diabetic Medicine : A Journal of the British Diabetic Association*. 2016;33(6):794-802.

62. Ravona-Springer R, Heymann A, Schmeidler J, et al. Trajectories in glycemic control over time are associated with cognitive performance in elderly subjects with type 2 diabetes. *PLoS One*. 2014;9(6):e97384.

How to cite this article: Luo M, Tan KHX, Tan CS, Lim WY, Tai E-S, Venkataraman K. Longitudinal trends in HbA_{1c} patterns and association with outcomes: A systematic review. *Diabetes Metab Res Rev*. 2018;34:e3015. https://doi.org/10.1002/dmrr.3015