Group-Based Trajectory Modelling (GBTM) To Assess the Effect of Medication Adherence on Health-Related Outcomes: A Protocol for A Systematic Review

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Protocol

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Abstract

Background: The Group-based trajectory modelling (GBTM) method is increasingly used in pharmacoepidemiologic studies to describe medication adherence trajectories over time. However, assessing the effects of these medication adherence trajectories on health-related outcomes remains challenging. The purpose of this review is to describe studies assessing the effects of medication adherence trajectories estimated by the GBTM method on health-related outcomes.

Methods: We will conduct a systematic review according to the recommendations of the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines. We will search in the following databases: PubMed, Embase, PsycINFO, Web of Science, CINAHL, and Cochrane database up to April 1st, 2021. Two reviewers will independently select articles and extract data. Discrepancies at every step will be resolved through discussion, and consensus will be reached for all disagreed articles. A third reviewer will act as a referee if needed. We will use tables to synthesize the modalities used to estimate medication adherence trajectories and the effect of adherence trajectories on health-related outcomes. We will identify the types of health-related outcomes studied and how they are defined, the statistical models used, the effect measure yield, and how medication adherence trajectories have been incorporated in the model. We will also review the limitations and biases reported by the authors and their attempts to mitigate them. We will provide a narrative synthesis.

Discussion: This review will provide a clear view of the strategies and methods used in medication adherence research to estimate the effects of adherence trajectories on different health-related outcomes. A thorough exploration of how GBTM is used for this specific purpose could represent the first crucial steps towards optimizing the utilization of this method in adherence studies.

Systematic review registration: Prospero CRD42021213503.

Background

Medication adherence is a real challenge for healthcare professionals and patients. Sub-optimal adherence may be associated with poorer health-related outcomes and higher healthcare costs, depending on the disease.[1–3] Numerous adherence studies have been conducted to identify patients' characteristics with suboptimal adherence and the impact of non-adherence on health-related outcomes.[4] Several measures of adherence exist. When using medico-administrative databases as the source of drug information, researchers often use the proportion of days covered (PDC) or medication possession ratio (MPR), usually dichotomized with an 80% cut-off to distinguish adherent from non-adherent individuals.[4–6] Other adherence measures include self-reported questionnaires (e.g., Medication Adherence Report Scale (MARS)), tablet counts, electronic devices for vial caps) and more direct methods such as directly observing medication administration or dosage of drug metabolites in blood.[7–10] Most of these measures allow summarizing adherence over a definite period, ranging from few weeks to years. However, an individual’s drug adherence may vary considerably over time, and a given summarized measure may recover situations drastically different from each other.

Studying adherence dynamics over time in a population may reflect patient’s adherence behaviors more accurately than summarizing adherence as a single average measure over time. The Group-based trajectory modelling (GBTM) is increasingly used to describe the dynamic and mutable nature of medication adherence behaviors.[11–14] It is a statistical method for modelling a variable of interest throughout time or age by identifying groups of individuals with similar profiles.[15] The method was initially developed by Nagin et al. to characterize developmental trajectories of criminal activities[16] and became prevalent for studying developmental trajectories in criminology, social science, and psychology.[17] GBTM is also increasingly used in medicine and clinical research to study the development of different mental health disorders, such as depression, attention deficit hyperactivity disorder, post-traumatic stress, or addiction,[17–20] and to capture heterogeneity in treatment response in clinical trials.[21] The GBTM method is part of the latent class growth analysis (LCGA) family and is a specialized application of the finite mixture models.[22–24] [15]As described by Nagin et al., the basic model yields two results: first, it identifies individuals with similar trajectories (i.e., a group), and second, it estimates the individuals' probability of being part of each group.[25] For example, in medication adherence, the model allows to identify several adherence trajectories, each of them defining a specific adherence group (e.g., optimal adherence for the entire duration of the treatment, early discontinuation, suboptimal adherence throughout the treatment course, etc.). Each individual is then allocated to the trajectory that he/she has the highest probability to belong to. Once groups are identified, trajectories are plotted and presented in graphical form. Trajectories can also be used as the dependent variable to estimate characteristics associated with trajectory membership. Extensions of the classical GBTM model have been made, such as the possibility to account for risk and protective factors (e.g., age, sex, gender).[17] These analyses are relatively widespread as they are well described in the literature and benefit from software macros to help and guide researchers.[25, 26]

Medication adherence trajectories issued from GBTM could be beneficial for studying the associations between adherence and health-related outcomes, such as hospitalizations, death, or any critical clinical event. However, the GBTM literature does not provide specific instructions for assessing these associations. To our knowledge, there is no software macro developed to perform analyses combining trajectories and the outcome in a joint model. Researchers generally proceed in two steps; identifying the adherence trajectories with GBTM and then using these trajectories as an observed variable in any suitable model to infer health-related outcomes.

Nonetheless, this approach presents statistical challenges, such as the uncertainty associated with group membership. The groups identified with the GBTM method are probabilistic. The group assignment may be considered a 100% imputation, possibly resulting in a not-quantifiable uncertainty when inference about these groups is made through regression. Another concern is non-identifiability since GBTM imputes group membership on a not sufficiently general model, resulting in attenuated estimates of the relationship between trajectories and health-related outcomes. All these problems are not specific to the GBTM method but all latent class modeling.[27] These challenges have been described in particular by Bakk et al.[28] and Nylund-Gibson et al.[29], who have tried to find solutions to limit these biases.

The lack of guidance on the modelling of adherence trajectories to estimate their effect on health-related outcomes may result in heterogeneity of the methods used. Thus, it is critical to investigate the different approaches existing in the literature, the biases, and the difficulties encountered when applying adherence trajectory models to the study of distal outcomes. To our knowledge, there is no systematic review of studies that have used the GBTM method to measure the effects of medication adherence trajectories on health-related outcomes.

The purpose of this review is to identify and describe the studies assessing the effect of medication adherence trajectories, estimated by GBTM methods, on health-related outcomes. We will document the different types of study designs used, methods used to identify adherence trajectories, health-related outcomes studied, statistic modelling and parameters used, and limitations acknowledged by the studies' authors and how they were addressed.

Methods/design

This review will be conducted according to the recommendations of the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines.[30] For this protocol, we followed the recommendations of PRISMA-p.[31] The filled checklist is available in Appendix A.

Eligibility criteria

This systematic review will include all studies estimating medication adherence trajectories with the GBTM method [25] and evaluating the effects of these trajectories on specified health-related outcomes. We will not include studies on adherence to recommendations other than drug therapy (e.g., diet or exercise). Inclusion criteria are summarized in Table 1, available in Appendix B.

Table 1
Study selection criteria

Inclusion	
Medication adherence	Any study about medication adherence, estimated with any kind of method whether direct (e.g., pill count or plasmatic measurement) or indirect (e.g., questionnaire, adherence measure using medication database such as the proportion of days' covered medication possessing ratio, medication gap).
Group-based trajectory	The group-based trajectory modeling a statistical methodology for modeling the evolution of medication adherence over time. This includes the based method described by Nagin et al. [19] and all its extensions.
Adherence trajectory	Adherence trajectory estimated with group-based trajectory as defined by Nagin et al. and considered as an **independent variable** in any statistic modeling.
Health related outcomes	Health-related outcomes any health results measured following an intervention or behavior (e.g., surgery, treatment etc.) that describe a consequence of disease, treatment, or event for an individual. These health-related outcomes can be symptoms, hospitalizations, death, patient's quality of life, participation in activities, and social roles
Domain	Health
Type of document	Original article, Excluded: Conference abstract, commentaries, letter to editors, review. They will be nevertheless checked for references
Timeline	No restriction
Language	No restriction, document in other languages than English will be translated and extracted
Population	No restriction
Inclusion Criteria	

Population:

We will not apply restrictions to the population: all studies measuring medication adherence trajectories in any human population will be considered. We will not apply restrictions based on age, race, sex or gender.

Intervention, exposure:

We will consider any study in which medication adherence trajectories, defined by the GBTM method,[25] are used as an exposure variable to explore or estimate the effect of adherence on any specified health-related outcome.

Comparators:

Depending on the study design, no comparator may be required. We will not exclude any of the studies based on the comparator.

Outcomes:

We will allow for any health-related measure described in the study as an endpoint outcome (dependent variable) in relation to adherence trajectories.

Study types:

We will include all original studies, observational studies, randomized trials, quasi-experimental studies, cohort or case-control studies. Conference abstracts, commentaries, letters to editors, and reviews will be excluded but retrieved to identify potentially eligible references.

Setting and time frame

No limit will be set for the study setting or time frame. We will retain all the original studies, including those conducted in clinical settings or those part of an intervention or a trial. Selected articles will enter the initial screening stage without a time limit for execution or publication.

Keys definitions

Medication adherence:

Medication adherence is defined as "the extent to which patients follow the instructions given to them for prescribed treatments."[32] It is composed of three main concepts: 1) initiation (representing the extent to which a newly prescribed treatment is undertaken); 2) persistence (representing to what extent the treatment is taken for the recommended duration); and 3) implementation (representing to what extent the treatment is taken at the recommended doses and according to the recommended schedule).[33] We will consider all studies on medication adherence, whatever the type of adherence concept is measured.

Adherence trajectory:

Adherence trajectories are defined as descriptive longitudinal patterns of adherence over a defined time set. Defined adherence metrics measured over a short time set are allowed to vary over a longer predefined time horizon. Trajectories help to distinguish differences in patterns of adherence for individuals or groups of individuals over time.[11] Adherence trajectories model the evolution of adherence measures (for example, monthly PDC) over time and make it possible to identify people with similar adherence behaviours.[14]

Health-related outcome

[34]

Health-related outcomes are results measured following an intervention or behavior (e.g., surgery, treatment) and describe a consequence of disease, treatment, or event for an individual. These health-related outcomes can be symptoms, hospitalizations, death, patient's quality of life, participation in activities, and social roles. In medication adherence, these outcomes allow us to measure the effect and consequences of different adherence profiles on individuals.

Information sources

We will search for relevant article references in the following databases: PubMed, Embase, PsycINFO, Web of Science, CINAHL, and Cochrane database up to April 1st, 2021. The search strategy has been developed and adapted for each database using the most sensible approach validated by a specialized librarian at Laval University. A complete description of the applied search strategies is described in Table 2 in Appendix B. Duplicate citations will be removed using EndNote and Covidence Solution software.[35] A final manual revision of the database will be conducted to check for remaining duplicates.

Table 2
Search strategy

Strategy	Pubmed	Embase	Psyinfo
Treatment adherence	"treatment adherence and compliance"[MeSH Terms] OR "adheren*"[Title/Abstract] OR "adheren*"[Other Term] OR "complian*"[Title/Abstract] OR "complian*"[Other Term] OR "persisten*"[Title/Abstract] OR "persisten*"[Other Term] OR "nonadheren*"[Title/Abstract] OR "nonadheren*"[Other Term]	**'patient compliance'**/exp OR **adheren***:ab,ti,kw OR non**adheren***:ab,ti,kw OR **complian***:ab,ti,kw OR non**complian***:ab,ti,kw	Treatment Compliance/ OR complian*.ti,ab,id OR noncomplian*.ti,ab,idOR persisten*.ti,ab,idOR
Compliance			
Adherence	OR "noncomplian*"[Title/Abstract] OR "noncomplian*"[Other Term] OR "nonpersisten*"[Title/Abstract] OR "nonpersisten*" [Other Term]	OR **persisten***:ab,ti,kw OR non**persisten***:ab,ti,kw OR **'persistence':de**	nonpersisten*.ti,ab,id OR adherenc*.ti,ab,id OR nonadherenc*.ti,ab,id
And			
Group based trajectory modelling	Trajectories[TIAB] OR Trajectory[TIAB] OR GBTM[OT] OR GBTM[TIAB]	'trajectory analysis':de OR 'trajector* near/3 model*':ab,ti,kw OR 'gbtm':ab,ti,kw	Trajector*.ti,ab,id OR GBTM .ti,ab,id
Trajectory modelling			
Strategy	**Web of science**	**CINAHL**	**Cochrane database**
Treatment adherence	ts=(adheren* or complian* or persisten* OR nonadheren* or noncomplian* or nonpersisten*)	MH medication compliance OR AB (complian* or adheren* or persisten*) OR AB (noncomplian* or nonadheren* or nonpersisten*) OR TI (complian* or adheren* or persisten*) OR TI (noncomplian* or nonadheren* or nonpersisten*)	[mh "Treatment Adherence and Compliance"] OR(adheren*):ti,ab,kw OR (nonadheren*):ti,ab,kw OR (complian*):ti,ab,kw OR (noncomplian*):ti,ab,kw OR (persisten*):ti,ab,kw OR (nonpersisten*):ti,ab,kw
Compliance			
Adherence			
And			
Group based trajectory modelling	ts= (trajector* NEAR/3 model*) OR ts=(gbtm)	TI (trajector* N3 model*) or AB (trajector* N3 model*) OR TI gbtm OR AB GBTM	(trajector*):ti,ab,kw OR (GBTM):ti,ab,kw
Trajectory modelling			
Search strategy			

We will consider and include any additional articles not identified by our search strategy and brought to our attention by screening references of selected articles or relevant systematic reviews if they meet the inclusion criteria.

All identified studies will be compiled and kept with the full text (when needed) in a shared reference management software (i.e., EndNote)[36] and with Covidence, a web-based solution for systematic reviews.[35]

Study selection

Article selection will be performed using Covidence solution.[35] First, two reviewers will screen titles and abstracts independently, and articles will either be included, excluded, or categorized as unsure. Articles excluded by both reviewers will not be selected. Second, reviewers will discuss discrepancies to reach a consensus for every disagreed article. A pilot screening test will be conducted on a sample of a randomly selected 10% of the articles.

Likewise, the full text of selected articles will be reviewed independently by two reviewers, and articles will be included or excluded. The reason for exclusion will be documented. Discrepancies between the two reviewers will be resolved by discussion until an agreement is reached. A third reviewer will act as a referee if needed.

Data extraction

We will develop an extraction form using the Cochrane checklist of items to consider in data extraction.[37] The form will include the following elements:

- Study identification, including title, corresponding author's name and contact details, country, language, and publication date;

- Study design and objectives;
- Health domain, including diseases and medications of interest;
- Sample size;
- Medication adherence measure used, including description of data source, adherence measure (e.g., adherence questionnaire, adherence measured from health database, medication electronic monitoring system), and a full definition of the variable and its operationalization (e.g., continuous, or dichotomized, threshold, scale, time frame);
- GBTM model software used, parameters, selection, and adequacy: link function, order, number of trajectories, statistics, and clinical criteria considered for the model selection.
- Health-related outcome definition: data source, variable definitions and their operationalization (e.g., continuous, dichotomized, time frame);
- Approach used in modelling the health-related outcomes (one step, two steps, or three steps) and the rationale;
- Model used to assess the effect of medication adherence trajectories on health-related outcomes and its description (e.g., linear regression, logistic regression, Cox modelling) and methods to take into account missing data, lost to follow-up, and censoring;
- Exposure variable: how trajectories were introduced in the model (e.g., group membership, inverse probability weighting);
- Limitations and biases identified by the authors;
- How authors tried to mitigate identified biases.

The form will be tested on a random sample of 10% of the included studies. We will contact study authors (three attempts, two weeks apart) to request any relevant missing information. Data extraction will be conducted independently by two reviewers, and discrepancies checked for accurate extraction.

The data form with item definitions is available in Table 3 in Appendix B.

Table 3
Extraction Grid

Variables	Definition	Format (or example)
Identification		
Id	Report the order number of the article assigned incrementally	1
Author	Report the name of the corresponding author as recorded in the article	name, surname
Mail	Report the corresponding author's mail	xxxx@xxxx.xx
Year	Report the publication year of the article	yyyy
Country	Report the country where the study has been conducted	
Title	Report the title of the article	
Study design	Report the design of the study (Randomised trial, cohort study, case-control, other)	
Objectives		
Objectives	Report the objectives of the article as stated in the paper (copy and paste)	
Medication, intervention, analysis object		
Intervention	Report whether the study included an intervention to improve adherence	yes no unclear
Medication class	Report the medication or class of medication of interest	antidiabetic drugs antihypertensive drugs cardiovascular drugs asthma drugs oncology drugs other, specify
Medication other	If other, specify the medication or class of medication of interest	
Medication's name	Report the name of all the medications mentioned	
Prevalent or incident user	Report whether the participants are new users or prevalent users of the medication	prevalent user incident user both unclear
Population disease	Report diseases of concern in the study	
Population age group	Specify whether there is any description of age group in the study	
Sample size	Report whether the sample size calculation was performed before the study	yes no unclear
Sample size calculation	Report whether the sample size calculation was performed considering the GBTM or the HRO	power for GBTM power for the HRO both other

Extraction Grid

Variables	Definition	Format (or example)
Sample size method	Report the method used to estimate the sample size	
Adherence		
Adherence measure: electronic monitoring caps (EMC) device	Report whether adherence is measured by an electronic device (EMC or similar device)	yes no
Adherence measure: adherence questionnaire	Report whether an adherence questionnaire measures adherence	yes no
Adherence measure: adherence questionnaire type	Report the adherence questionnaire used	
Adherence measure: visual analog scale	Report whether adherence is measured using a visual analog scale	yes no
Adherence measure: visual analog scale type	Report the visual analog scale used by the author	
Adherence measured by drug concentration/metabolite levels (in the blood)	Report whether the study has measured adherence using drug concentration/metabolite levels	yes no
Adherence measured by pill count	Report whether the study has measured adherence by pill count	yes no
Adherence measure: medico-administrative database	Report whether the study computed adherence from a medico-administrative database	yes no
Adherence measure: claims database	Report whether the study used a medico-administrative database from prescription claims	yes no unclear
Adherence measure: prescription database	Report whether the study used a medico-administrative database from physician prescriptions	yes no unclear
Adherence measure in database: type	Report adherence measure used in the medico-administrative database	PDC MPR medication gap other, specify
Adherence measure in database: other	If other, report the name of the adherence measure used in the database	
Adherence measure in database: definition	Report whether the study reports a clear description of the adherence measure used	yes no unclear
Adherence measure in database: definition	Report the definition of adherence measure as stated in the document (copy and paste)	
Adherence measure: time frame	Report whether the authors have indicated the period of measurement of adherence	yes no
Adherence measure: time frame definition	If yes, indicate the period of measurement of the adhesion (weekly, monthly, quarterly, etc.)	
GBTM		
GBTM: software	Report the software used for the GBTM	
GBTM: software package	Report the package used	

Extraction Grid

Variables	Definition	Format (or example)
GBTM: time horizon	Report the time horizon used for adherence trajectories	
GBTM: form of the likelihood function - report	Report whether the form of the likelihood function has been reported	yes no
GBTM: form of the likelihood function	Specify the form of the likelihood function used	Poisson distribution censored normal distribution binary logit distribution other not applicable
GBTM: form of the likelihood function_other	If other, report the form of the likelihood function used	
GBTM: Link function order	Report whether the link function order has been reported	yes no
GBTM: Link function order – report	Report the link function order	
GBTM: Link function order justification	Report whether the authors justified the choice of the link function order	yes no
GBTM: number of groups tested	Report whether the author(s) has reported the number of groups tested	yes no
GBTM: number of groups tested	If yes, report the number of groups tested	
GBTM: number of groups selected	Report the number of groups selected	
GBTM: number of groups selected justification report	Report whether the authors have provided a rationale for the choice of the number of groups selected	yes no
GBTM: number of groups selected justification report	If yes, report the statement for the rationale behind the choice of the number of groups	
GBTM- Best fit parameters choice model in consideration		
GBTM: Best fit parameters AIC	Report whether the authors have considered the AIC in model choice	yes no
GBTM: Best fit parameters AIC_all_models	Report whether the authors have reported the AIC for all different models considered	yes no
GBTM: Best fit parameters AIC_best_model	Report whether the authors have reported the AIC for the model selected	yes no
GBTM: Best fit parameters BIC	Report whether or not the authors have considered the BIC in choice of the model	yes no
GBTM: Best fit parameters BIC_all models	Report whether the authors have reported the BIC for all different models considered	yes no
GBTM: Best fit parameters BIC_best model	Report whether the authors have reported the BIC for the model selected	yes no
GBTM: Minimum size per group	Report whether the authors have reported the minimum size per group in the choice of the model	yes no

Extraction Grid

Variables	Definition	Format (or example)
GBTM: Best-fit -Average Posterior Probability of Assignment (APPA)	Report whether the authors have considered the Average Posterior Probability of Assignment (APPA) in choice of the model	yes no
GBTM: Best-fit -APPA all models	Report whether the authors have reported the APPA for the different models in consideration	yes no
GBTM: Best-fit -APPA best model	Report whether the authors have reported the APPA for the model selected	yes no
GBTM: Best-fit -Odds of Correct Classification (OCC)	Report whether the authors have considered the Odds of Correct Classification (OCC) in choice of the model	yes no
GBTM: Best-fit -OCC- all models	Report whether the authors have reported the OCC for the different models in consideration	yes no
GBTM: Best-fit -Odds of Correct Classification-best model	Report whether the authors have reported the OCC for the model selected	yes no
GBTM: Estimated Group Probabilities versus the Proportion of the Sample Assigned to the Group	Report whether the authors have considered the Group Probabilities versus the Proportion of the Sample Assigned to the Group in the choice of the model	yes no
GBTM- Best-fit- Estimated Group Probabilities versus the Proportion of the Sample Assigned to the Group-all models	Report whether the authors have considered the Group Probabilities versus the Proportion of the Sample Assigned to the Group for the different models in consideration	yes no
GBTM- Best-fit- Estimated Group Probabilities versus the Proportion of the Sample Assigned to the Group-best model	Report whether the authors have considered the Group Probabilities versus the Proportion of the Sample Assigned to the Group for the model selected	yes no
GBTM Best fit: Confidence Intervals for Group Membership Probabilities	Report whether the authors report the confidence intervals for group membership probabilities	yes no
GBTM Best fit: Tool for fit criteria assessment	Report whether the authors have used a fit criteria assessment tool for model selection	yes no unclear
GBTM Best fit: tool for fit criteria assessment	If yes, report the name of the tool	
Analysis_Sensibility_GBTM	Report whether the authors have conducted any sensibility analysis for GBTM	yes no
Missing Data		
Missing Data	Report whether the authors considered missing data	yes no unclear
Missing data adherence	If yes, report how authors managed missing data in GBTM	exclusion imputation other
Missing data adherence_other	If other, specify	
Missing data HRO	If yes, report how authors managed missing data in HRO modeling	exclusion imputation other
Missing data HRO_other	If other, report how authors managed missing data in HRO modeling	

Extraction Grid

Variables	Definition	Format (or example)
Censoring	Report whether the authors took into account censored data	yes no unclear
Censoring GBTM	If yes, report how authors managed censoring data in GBTM	
Censoring HRO	If yes, report how authors managed censoring data in HRO	
Health-related outcomes (HRO)		
HRO: definition	Report whether the study report a clear definition of the HRO	yes no
HRO: definition_report	Report the definition of the outcomes, including how they were measured	
HRO: outcomes data sources	Report the data source of the outcomes	
HRO: nature	Report whether the study report a clear definition of the HRO variable	continuous dichotomic categorial ordinal
HRO: time_related	Report whether the HRO defined in the article is time-related (e.g., number of hospitalizations per month), an instant screen shoot (e.g., cross-sectional), health measure (e.g., quality of life), or definitive (e.g., death)	time-related instant screenshot definitive
HRO: modelling	Report whether the authors have included the HRO variable in the modelling of GBTM	yes no
HRO: model	Report the statistical method used to estimate the association between adherence trajectories and HRO	modeled in GBTM cox modeling logistic regression linear regression dual trajectory modeling other
HRO: model_other	If other, report the model used to estimate the association between adherence trajectories and HRO	
HRO: model_rationale	Report whether the authors provide a rationale for the choice of the model	yes no
HRO: model_rationale_report	If yes, report the rationale of the model choice	
HRO: time_lag	Report whether the outcomes were measured immediately after the end of the trajectories or not (yes = distal time, dual = same time of trajectory, no = no time lag)	yes dual no unclear/not specified
HRO: time_lag_definition	Report the time lag (in months)	

Extraction Grid

Variables	Definition	Format (or example)
HRO: time_lag_rationale	Report whether the authors have provided a rationale for the definition of the time lag used	yes no
HRO: time_lag_rationale	If yes, report the rationale used	
HRO: Adherence trajectories used	Report how trajectories have been used in the model (e.g., trajectory groups as a variable, inverse probability weighting, e.tc)	
Analysis_Sensibility_HRO	Report whether the authors have conducted any sensibility analysis for the HRO modelling	yes no
Limitations		
Confounding by indication	Report whether the authors have reported confounding by indication as a possible limitation of the study	yes no
Time-dependent confounding	Report whether the authors have reported time-dependent confounding as a possible limitation of the study	yes no
Healthy user/adherer effect	Report whether the authors have reported healthy user/adherer effect as a possible limitation of the study	yes no
Protopathic bias	Report whether the authors have reported protopathic bias as a possible limitation of the study	yes no
Depletion of susceptible	Report whether the authors have reported depletion of susceptible as a possible limitation of the study	yes no
Time-related bias	Report whether the authors have reported time-related bias as a possible limitation of the study	yes no
Immortal time bias	Report whether the authors have reported immortal time bias as a possible limitation of the study	yes no
Immeasurable time bias	Report whether the authors have reported immeasurable time bias as a possible limitation of the study	yes no
Time-window bias	Report whether the authors have reported time-window bias as a possible limitation of the study	yes no
Time-lag bias	Report whether the authors have reported time-lag bias as a possible limitation of the study	yes no
Others		
Conflict of interest	Report whether the authors have reported conflict of interest	yes no
Extraction Grid		

Quality assessment

The risk of bias and the quality of each study will be assessed using two checklists. For randomized trials, the risk of bias will be assessed with the Cochrane RoB 2.0 Tool.[38] For observational studies, we will use the ROBINS-I tool.[39] As the review does not intend to estimate a global measure of effect, no studies will be excluded based on the quality assessment. Quality assessment will only serve for analysis purposes and discussion of findings. This assessment will follow the same procedure as the data collection process. The quality assessment of each study will be done independently by two reviewers. Disagreements will be resolved by discussion between the reviewers or with a third reviewer as a referee.

Assessment of reporting

Included studies will be classified according to the quality of their reporting. The Detailed Guidelines for reporting on Latent Trajectory Studies (GRoLTS),[40] and the ESPACOMP Medication Adherence Reporting Guideline (EMERGE),[41] will be used to evaluate the studies. No study will be

excluded during this step; instead, the reporting quality will be used for discussion purposes.

Analysis

Data analysis will proceed in three phases. In the first phase, we will describe selected studies with simple descriptive statistics and classify them in a table under the health domain studied (e.g., cancer, cardiovascular disease), medications used, population, and the studies' stated objective. In the second phase, we will summarize data according to the studies' method to estimate adherence trajectories. Studies will also be classified according to the source of data for medication adherence, medication adherence measure, the parameters used in GBTM, including the rationale behind parameter choice (e.g., statistics, clinical characteristics, the minimal number of patients included, number of groups). In the third phase, we will perform classification and narrative synthesis. We will review the choice and modalities used to estimate the effect of adherence trajectories on health-related outcomes, including the source of data, nature, and definition of the health-related outcomes studied, the statistical model used, the effect measure yield, and how medication adherence measure has been incorporated in the model. We will also summarize limitations and biases reported by the authors and their attempt to mitigate them. Moreover, we will classify studies according to the quality of reporting and the study's overall quality in the synthesis. As the review does not aim to estimate a measured effect, we will not conduct a meta-analysis and assess studies' heterogeneity.

Discussion

GBTM method has grown in popularity in adherence research over the last 20 years.[17] The method and its applications, the macro-implementations in the software, are well established and developed in many disciplines, such as pharmacoepidemiology.[42] Most of the studies on GBTM in this field have primarily used trajectories to describe membership groups over time and associated factors.[43, 44] To our knowledge, there are two systematic reviews on Latent Class Modelling approaches, including the GBTM method.[24, 45] Nevertheless, they did not focus on the GBTM method to assess the association between adherence trajectories and health-related outcomes and related challenges. While the GBTM method provides a more refined measure of medication adherence over time by identifying adherence trajectories,[46] it remains essential to study the effect of these trajectories on health-related outcomes. Despite the growing use of GBTM in adherence research and the availability of statistical tools, there is still considerable heterogeneity in how researchers use this method to model health-related outcomes.[47, 48] This again leads to disparate and sometimes confusing ways of studying and reporting outcomes. However, modelling health outcomes according to pathway groups could help identify problematic groups and subsequently guide interventions and policies. It is, therefore, necessary to review how the method is used to model data and how results are reported.

The review will summarize the various strategies and methods used by authors to estimate the effect of adherence trajectories on health-related outcomes. Special attention will be paid to study designs, model parameter specifications, and limitations. It will also document biases that could arise while using GBTM as an independent variable and how authors attempted to mitigate them. We will discuss how authors constructed the model, how they interpreted the results, and consider the effect of latent trajectories on health-related outcomes. Moreover, the review will also describe the studies' reporting quality with the two reporting guidelines specific to latent class analysis and adherence studies. Therefore, this review could represent the first crucial step towards developing a guide for the use of GBTM in medication adherence studies to infer health-related outcomes.

List Of Abbreviations

EMERGE ESPACOMP Medication Adherence Reporting Guideline

GBTM Group-Based Trajectory Modelling

GRoLTS The Detailed Guidelines for reporting on Latent Trajectory Studies

MPR Medication possession ratio

PDC Proportion of days covered

PRISMA Preferred Reporting Items for Systematic Review and Meta-analysis

Prisma-p Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

RoB 2.0 A revised tool to assess the risk of bias in randomized trials

ROBINS-I Risk Of Bias in Non-randomized Studies - of Interventions

Declarations

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Not applicable

Consent for publication:

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Not applicable

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Authors' contributions:

GE and VM conceived, designed the study protocol, and wrote the manuscript. SL, LG, ADB and CL contributed substantially to the conception and design of the study protocol and contributed significantly to the manuscript through a critical evaluation of the content and assisted with drafting the manuscript.

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