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Appraisal

Research Note: Deriving latent trajectories in health research

Longitudinal data from repeated measures obtained from an individual at successive time points is essential for understanding changes in health phenomena. Longitudinal data can reflect fluctuations over time (such as variations in symptoms of a long-term health condition) or more systematic changes (such as response to a treatment). The time frame for collection of longitudinal data can range from short-term (such as heart rate change during exercise testing) to long-term (such as age-related growth or development). A pattern of change over time is often termed a trajectory.

Individual level longitudinal data are increasingly becoming available across biological, psychosocial and behavioural domains. Many techniques are available for longitudinal data analysis; choosing between them depends on the research questions alongside underlying theories about patterns of change in the reference population. An appreciation of the distinction between 'within-person' and 'between-person' variation is essential for formulating research questions and analysing longitudinal data. Fundamentally, most research questions pertain to the estimation of within-person change ('How do people change over time?') or between-person variation in within-person change ('Are there differences between people in how they change over time?').

Latent trajectory analysis has increasingly become popular in health research, including physiotherapy. A previous Research Note reviewed cross-sectional latent class analysis and is a helpful accompaniment to this one.[1] Latent class analysis estimates distinct patterns of within-person variability in a population. In latent class analysis, people are classified into distinct subgroups (classes) according to their profiles on multiple variables. In the context of longitudinal data, people are classified into subgroups based on repeated measures over time, and it is the patterns of change over time that are the 'latent' construct estimated. In health research, latent trajectory analysis has helped to identify distinct patterns of clinical course of various health conditions,[2,3] described the development or evolution of health conditions over the life-course[4] and described patterns of change in health-related behaviours.[5] Furthermore, latent trajectory subgroups that are identified can be: profiled on various factors of interest,[5] considered as risk factors for future outcomes,[6] outcomes themselves[7] or related to trajectories of other health outcomes.[8] Latent trajectory analysis encompasses a range of techniques and can be implemented in several software packages. This Research Note gives a non-technical review of latent trajectory analysis methods, provides guidance on key considerations for their use and discusses clinical implications of latent class trajectory models.

Approaches to estimating latent trajectories

Three common approaches to estimating latent trajectories within a population are latent class growth analysis (LCGA), latent growth mixture modelling (LGMM) and longitudinal latent class analysis (L-LCA). However, another widely used approach to modelling changes in a health factor over time is the mixed model approach. An understanding of the mixed model approach is helpful for understanding latent class approaches, as LCGA and LGMM can be seen as extensions of this approach. Box 1 outlines the key elements of each approach and Figure 1 provides a graphical description of each. The critical assumption pertaining to the choice of a mixed model approach is that individual variations (random effects) arise from a multivariate, normal distribution. Therefore, if it is reasonable to assume that all individuals within a population follow a similar underlying trajectory (eg, increase in height over childhood), with variation between individuals sufficiently captured by normally distributed random effects, then mixed models are an appropriate choice. However, if there is potential for very different trajectory shapes to exist within the population (eg, clinical course of musculoskeletal pain), then latent trajectory approaches may be more appropriate, as these allow estimation of trajectories unconstrained by assumptions of normally distributed variation in change over time.

Both LCGA and LGMM are approaches whereby subgroups are identified from the data by performing a latent class classification on individuals' 'growth' parameters (ie, the coefficients for time, such as initial value, slope and curvature). While both approaches subgroup individuals according to similar patterns of change over time, LCGA does not model further variability within each subgroup. This is somewhat analogous to collapsing a continuous variable, such as age, whereby all people aged 18 to 25 years might be categorised by one value representing 'young adults' for analysis. In contrast, LGMMs estimate further individual variance around the mean growth parameters within each subgroup. The relative appropriateness of the two methods is widely debated.[9] The term 'mixture' in LGMM arises from the assumption that the observed growth parameters arise from a mixture of two or more truly discrete subgroups.[10] On the other hand, LCGA is described as summarising a non-normal continuous population distribution of trajectories, such that a subgroup is a collection of individuals following approximately the same trajectory, like contour lines on a topographic map, rather than assuming that the subgroups represent distinct populations.[11] LCGA is often preferred purely due to the extra computational difficulties of LGMM.[12] Because LGMM allows variation within trajectory subgroups and LCGA does not, the optimal number of identified subgroups is usually fewer when using LGMM compared with LCGA. Ideally, both LCGA and LGMM models should be fitted to the data and compared using the methods described in the next section.[9] Lastly, the third type of latent trajectory analysis – L-LCA (also called repeated measures latent class analysis) – performs subgrouping using the repeated measures of the health phenomenon themselves, treating the data as if it were collected cross-sectionally rather than analysing it as longitudinal data accounting for time ordering. Although the time ordering of data is ignored, L-LCA has the advantage of not forcing any parametric relationship between the repeated measures and time.[13] This approach is useful when there may be complex patterns of change, such as the clinical course of long-term conditions,[2] or there are repeated measures over time pertaining to a number of different facets of a construct, such as pain impacts.[14]

> **Box 1.** Common approaches to trajectory modelling in health research.
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> **Mixed Models**
> - also called multilevel, hierarchical, random-effects or random coefficient models
> - the repeated measures of the health outcome of interest is the dependent variable
> - one or more time parameters are included as independent variables, to capture average linear or nonlinear change as 'fixed effects' of time
> - 'random effects' for time parameters[a] can be added to allow individual variation around the average (fixed) effects for time
> - further variation between people can be captured by adding between-person factors and including interaction terms with time (eg, different trajectories for males versus females). For this reason, mixed models are considered a variable-centred approach, as opposed to latent class techniques below that do not rely on other measured variables, and are hence considered 'unsupervised', person-centred approaches (Figure 1A).
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> **Latent Growth Mixture Modelling (LGMM)**
> - extension to mixed models, where the assumption is that there is a 'mixture' of 'latent' populations
> - two or more latent subgroups are estimated with each latent subgroup having unique time parameters, representing different patterns of initial status and change over time
> - Within each latent subgroup, further variation in time parameters between individuals is estimated (ie, individuals in the same subgroup share similar, but not exactly the same, trajectory shapes) (Figure 1B).
>
> **Latent Class Growth Analysis (LCGA)**
> - also called group-based trajectory modelling
> - like LGMM, two or more latent subgroups are estimated, each having unique time parameters representing different patterns of initial status and change over time
> - No variation in time parameters between individuals within each latent subgroup is assumed (ie, individuals in the same subgroup follow exactly the same trajectory) (Figure 1C).
>
> **Longitudinal Latent Class Analysis (L-LCA)**
> - also called repeated-measures latent class analysis
> - The repeated measures of the health outcome of interest are the input variables that are subgrouped, rather than parameters for time (Figure 1D).
>
> [a] Footnote: One important distinction is that mixed models can be similarly estimated in a structural equation framework (then termed 'latent growth curve models' or 'latent curve analysis'). In this context, the random effects for the intercept, slope etc. are termed 'latent' (unobserved) variables, but these are not the same thing as the latent subgroups estimated in repeated-measures latent class analysis, latent class growth analysis, or latent growth mixture modelling. For a good review of how mixed (multilevel) models and structural equation latent growth curve models are equivalent, see Curran.[20]

Determining the latent trajectory shape and number

In addition to the choice of method, another challenge in estimating latent trajectories is deciding upon the number of trajectory subgroups and their shapes. Useful guides to the modelling strategies for LGMM, LCGA and L-LCA, along with code examples for software packages, are provided by Herle et al[13] and Lennon et al.[15] Typically, a series of models are fitted, starting with a single group model and increasing in number until certain thresholds are reached, in relation to measures of model fit and the size of the smallest subgroup. For LCGA and LGMMs, the optimal shape of the trajectories is usually evaluated by allowing for the most complex shape possible for each trajectory, given the number of time points. To avoid overfitting, at least three time points are needed for linear slopes and the minimum is four for quadratic terms (note: alternative shapes can be modelled by other functions of time such as piecewise linear functions). After the optimal number of trajectory subgroups has been tentatively decided, attention can be given to simplifying the time functions for each trajectory where possible (eg, first allowing for quadratic or cubic terms, then testing whether model fit substantially worsens by only including simple linear terms). The selection of the optimal latent class trajectory model is supported by statistical measures of model fit, including Akaike/Bayesian information criterion and various likelihood ratio tests, evaluated in combination with metrics based on each person's probability of membership for each trajectory. Both types of metrics are used in latent class techniques more generally and are well described in the previous Research Note on latent class analysis.[1]

Statistical indices do not always clearly indicate one optimal model and researchers often need to choose between models with different numbers of trajectory subgroups but comparable fit statistics. Therefore, evaluating the validity and utility of trajectories considering clinical and research knowledge is equally important.[11,15] This may involve evaluating potential models using fit statistics in conjunction with prior findings, pre-existing theory, patient experience or clinical observation. Plotting mean trajectory patterns in combination with observed individual trajectories within each subgroup is helpful to assess how well the trajectory groups capture individual variation. Meaningful differences between trajectory groups in terms of pre-existing characteristics, clinical examination findings, subsequent outcomes, response to treatment, or relationship between the trajectories and other outcomes provide support for the usefulness of identified latent trajectory groups.[11]

Other considerations for latent class trajectory methods

Trajectory subgroups identified by latent class trajectory analysis are frequently related to individual or social factors, or outcomes that occur at a later point in time; such relationships can be quantified using one-step or three-step approaches. In the one-step approach, the latent class model used to estimate the trajectory groups is extended to incorporate covariates of interest. In contrast, the three-step approach involves estimating the trajectory groups, allocating individuals to the trajectory groups for which they have the highest probability of membership based on their observed data, then using the trajectory groups in further analyses either as a predictor or an outcome. Ideally, further analyses account for uncertainty of subgroup membership when the three-step method is used (as it is highly unlikely that a person will have a probability of 1 for a particular trajectory subgroup and 0 for others). However, if class membership is well predicted, the influence of this uncertainty on results will be minor.[9] van der Schoot discusses advantages and disadvantages of one-step and three-step approaches.[9] Trajectory groups can also be related to other time-varying covariates, for example: latent trajectory groups for two different outcomes can be estimated separately, then resultant subgroups associated via linking membership probabilities (dual trajectory analysis) or trajectory subgroups can be estimated based on repeated measures of multiple outcomes rather than a single outcome (multi-trajectory analysis).[11]

Sample size is an important, but complex, consideration for latent class trajectory studies. Simulation studies suggest that samples of at least 200 and preferably > 500 individuals are warranted, with model
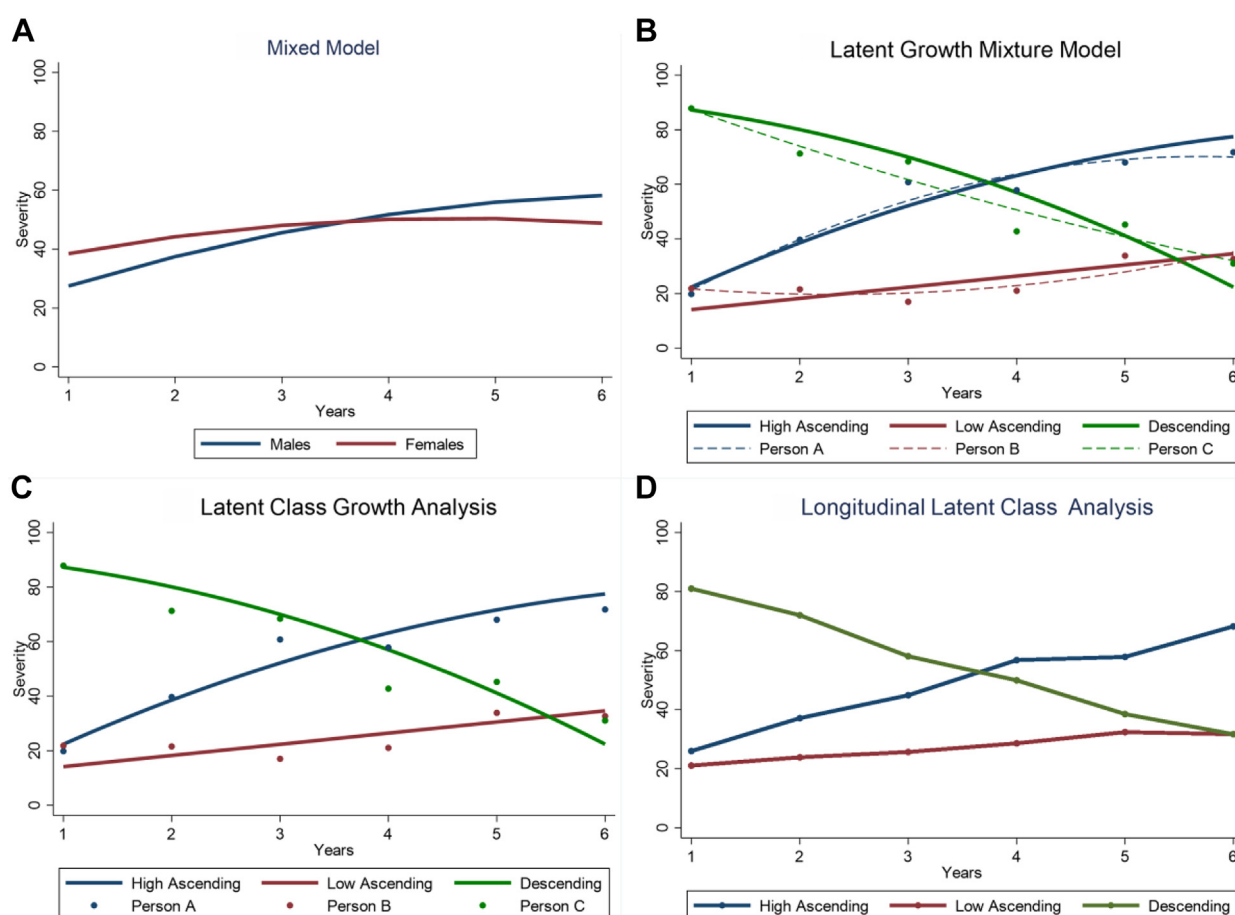
Figure 1. Illustration of four approaches to trajectory modelling in health research, using hypothetical simulated data. A. Illustrates how a mixed model approach can use other measured variables (in this case sex) to model between-person variation in within-person change over time. B. The latent growth mixture model estimates 'latent' subgroups based on parameters for time. Within each latent subgroup, further variation in time parameters between individuals is estimated. Everyone in the same subgroup shares similar, but not exactly the same, trajectory shapes. To demonstrate this, added dots represent simulated observed values for one individual within each subgroup, and the added dashed lines represent that person's corresponding estimated trajectory. C. Latent class growth analysis also estimates 'latent' subgroups based on parameters for time, but every person assigned to a particular trajectory subgroup is assumed to have exactly the same trajectory shape, and deviations of their observations from the overall subgroup trajectory are considered random error. To demonstrate this, added dots represent simulated observed values for one individual within each subgroup; that person's corresponding estimated trajectory is the subgroup mean. D. Longitudinal latent class analysis estimates subgroups of people by using the repeated measures of the health outcome of interest directly (in this case severity score), rather than 'growth' parameters for change over time (ie, the coefficients for time, such as initial value, slope and curvature). Subgrouping uses the repeated measures of the health phenomenon themselves, treating the data as if it were collected cross-sectionally, rather than analysing it as longitudinal data accounting for time ordering. Dots represent the mean value at each time point for each subgroup.

performance also being a function of number of time points, and the number, relative size and distinctness of underlying population subgroups.[16] The main problems of insufficient sample size are the risk of over-fitting the data, which means that spurious subgroups might be identified as a result of sample variation or alternatively, small but important population subgroups fail to be identified. In addition, there are often problems with models failing to converge on a solution when there are too many parameters to estimate compared with the number of data points available. Latent class trajectory analysis uses maximum likelihood estimation, which accommodates missing time points when they are missing at random. This means that people missing some time points can still be included in, and be informative for, the analysis. Furthermore, as those with less data are allocated to a trajectory subgroup with less certainty, uncertainty due to missing data can be incorporated in subsequent analyses using trajectory groups by accounting for individuals' probability of membership. However, large amounts of missing data, insufficient sample size or limited number of time points can compromise validity and subgroup detection.[17]

Because there are so many choices involved in latent trajectory modelling, and the software used to implement them have different capabilities, the findings from latent class trajectory analyses can vary, sometimes greatly;[18] therefore, quality reporting of the methodological process is essential. The Guidelines for Reporting on Latent Trajectory Studies (GRoLTS) checklist is a useful and recommended 16-item reporting tool that can facilitate the transparency and robustness of latent trajectory findings.[9]

Discussion and Summary

One of the reasons why latent class trajectory methods have become so popular is because the resultant trajectories are intuitively easy to understand, and once estimated provide a helpful way to relate complex longitudinal patterns of change in a health outcome to other health variables. In addition, they are relatively easy to implement in various popular software packages. With the increasing availability and ease of collection of longitudinal data from mobile devices and sensors, it is likely that latent class trajectory methods will be even more commonly utilised. However, it is important that latent class trajectory methods are used judiciously, proficiently and in conjunction with substantive knowledge of the particular field of enquiry.[15] As inferences about the number and shape of latent trajectories can be heavily influenced by sample size, nature of the data and methodological choice, there have been strong calls for caution in the interpretation of findings, with researchers urged to consider latent trajectories as abstract rather than concrete, and an individual's assignment to a particular trajectory group as an approximation only.[17,18] An individual will be allocated to the subgroup for which they have the highest probability of membership, but they will have a probability of membership, albeit lower, for all trajectory subgroups

and their particular trajectory pattern will not exactly match that of the mean trajectory for their allocated subgroup.

Replication of latent class trajectory studies is important to understand commonalities and differences across populations, for example: in the field of low back pain, a large body of trajectory research across different settings and countries has shifted understanding of the condition away from a recovery/nonrecovery paradigm to a more subtle classification that includes patterns of long-term fluctuating or episodic pain, such that contemporary understanding is of a long-lasting condition with varying trajectories.[1,19] As further studies are unlikely to identify different trajectory patterns, focus could now shift to investigation of trajectory patterns as prognostic markers, patient communication aids, outcome measures or potential treatment effect modifiers (ie, particular trajectory subgroups as targets for specific treatments).[1]

In summary, latent class trajectory analysis is a valuable person-centred approach for longitudinal health data. Findings can potentially facilitate personalised approaches to health care, if researchers can identify and test ways to incorporate them into clinical practice. With the rapidly growing application of these techniques, there is a need to balance enthusiasm for use with caution. This involves both recognition that inferences regarding trajectory subgroups are affected by choice of methods, and the avoidance of overinterpretation of identified subgroups from a sample as real subpopulations versus useful summaries of complex longitudinal data.

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