



**Developmental trajectories of body mass index
throughout the life course:
An application of latent class growth (mixture)
modelling**

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Abstract

The aims of this study are 1) to analyse developmental trajectories of body fatness from adolescence into adulthood, hereby determining the number and characteristics of distinct body fatness trajectories, and 2) to relate these distinct subgroups to indicators of cardiovascular disease risk, revealing subgroups specifically at risk.

Furthermore, this paper will illustrate in more detail the application of latent class growth (mixture) modelling (LCGMM) on longitudinal, observational data.

Data were obtained from the Amsterdam Growth and Health Longitudinal Study, an ongoing observational study of apparently healthy participants (N=336). Participants were followed up from 13-42 years of age. Body mass index was used as a marker for body fatness and CVD-risk factors included Mean Arterial Pressure and HDL-Cholesterol. LCGMM were used for the identification of developmental trajectories of body fatness and linear regression analyses were used for the associations between the trajectories and CVD-risk. Analyses revealed three distinct trajectories; a “normative” trajectory (88.4%); a progressively overweight trajectory (4.5%); and a progressively overweight but stabilising trajectory (7.1%). Statistically significant differences in CVD-risk between these trajectories appeared.

These results show that body fatness development throughout life is heterogeneous, showing differences in CVD-risk. This paper also demonstrates that LCGMM is a promising technique to distinguish between subjects with different developmental trajectories.

Introduction

Studying developmental patterns throughout the life course has gained interest over the recent years in the fields of epidemiology, psychology and beyond [73]. More often, longitudinal studies take a life course approach when collecting and analysing data, which offers, through its interdisciplinary framework, (new) opportunities to understand the natural history of chronic disorders such as diabetes, depression or low back pain [74]. Especially when studying disease aetiology, a life course approach offers valuable insights in the natural course of a risk factor and subsequent consequences for the chronic disease [73, 74]. Various statistical techniques are available when taking a life course approach [73, 75]. Most techniques take a so-called variable-centred approach [42] which focuses on relationships among variables in principle; the goal is to predict outcomes or to study the influence of certain risk factors on disease outcomes. Examples are regression models and structural equation models. Often, a different approach, namely a person-centred approach can offer more insight than a variable-centred approach when wanting to account for population heterogeneity within the sample. Person-centred techniques focus on relationships among individuals, aiming to group similar individuals based on their characteristics [42]. Latent class models, specifically latent class growth (mixture) models (LCGMM) are good examples of such a technique [5, 6, 18, 33, 41–43]. This paper will apply these techniques, following a rise in interest within life course research [74]. As an example, we will use data from a relevant field of research; we will study the course of body fatness in relation to cardiovascular diseases (CVD). As it is well known that the prevalence of cardiovascular diseases (CVD) is increasing rapidly across all age groups over the world [76], a range of attempts have been undertaken to prevent the onset of CVD. Examples of such attempts are mainly weight loss- and weight management programmes [77], but few have shown effectiveness. Application of LCGMM can give more insight in the heterogeneity of the (natural) development of obesity throughout the life course. Assessing cardiovascular disease consequences of distinct developmental patterns can provide opportunities for more targeted prevention of cardiovascular diseases to increase (long-term) effectiveness. Moreover, the limited papers available utilising these techniques highlight the need for more papers as it is becoming increasingly clear that in many fields of research (amongst others, in the field of cardiovascular diseases), multiple pathways to developing (chronic) diseases exist [14, 78–82] justifying taking into account this heterogeneity when analysing such data.

The aim of the current study is threefold. Our first aim is to analyse developmental patterns of body fatness from adolescence into adulthood, hereby determining the number and characteristics of distinct body fatness trajectories. Second, we aim to relate these distinct subgroups to indicators of cardiovascular disease risk (namely high-density lipoprotein (HDL)-cholesterol and mean arterial pressure, MAP) later in life, revealing subgroups specifically at risk. Overall, this paper will illustrate in more detail the application of LCGMM on longitudinal, observational data.

Materials and Methods

Study design

The Amsterdam Growth and Health Longitudinal Study (AGAHLS) is an observational longitudinal cohort study which started in 1976. Approximately 650 boys and girls (mean age of 13 years) from the first two grades of two secondary schools in the Netherlands were included in the study. The initial goals of the study were to describe the natural development of growth, health and lifestyle and further to investigate associations between health and lifestyle. During the adolescence period, participants were measured annually, and thereafter, six more examinations took place, of which the most recent took place in 2006 (mean age of 42 years).

Medical ethical approval was obtained from the Medical Ethics Committee of the VU University Medical Centre, and written informed consent was obtained from each participant, as well as from the parent or guardian (during adolescence).

More detailed information on study design and specific measurements at each examination has been published elsewhere [72, 83].

Inclusion and exclusion criteria

For the current study participants from whom valid measurements of the cardiovascular disease risk factors were available *and* who had at least one measurement of body fatness over the previous 30 years were included. If women were pregnant during a particular round of measurement, that measurement (for body fatness) was not included in the analyses. In total, 176 women (52.4%) and 160 men were included in the study (total N=336).

Body fatness measurements

Body fatness was quantified by the body mass index (BMI). BMI was calculated by dividing body mass (kilograms) by body height squared (meters squared).

Indicators of cardiovascular disease risk

Fasting HDL cholesterol values were determined from blood drawn from the antecubital vein (Roche diagnostics, Mannheim, Germany). Blood pressure was measured every 5 minutes for 60 minutes using an automated device (Dinamap Procare 100). Subsequently, mean arterial pressure (MAP) was calculated as $((2 \times \text{diastolic blood pressure} + \text{systolic blood pressure}) / 3)$ [84].

Lifestyle covariates

Habitual energy intake was measured using a detailed cross-check dietary history face-to-face interview method, based on Beal [85] and Marr [86], and expressed in kilojoules per day. The interview was adapted for the AGAHLs. For the analyses, mean life course food intake was calculated in kilojoules per day.

Physical activity in minutes per week was measured using a detailed questionnaire, especially designed and validated for the AGAHLs [87]. For the analyses, mean life course physical activity was calculated in minutes per week. Smoking behaviour was measured with a separate questionnaire [88], from which participants were categorised in either of three categories; never smoked, ever smoked (but not a current smoker) or current smoker.

Alcohol consumption was also measured with a short questionnaire [89], determining whether participants were alcohol drinkers or not (at the last time point).

Statistical analyses

Statistical analyses were conducted using the Mplus 6.1 [34, 43] and the PASW 17.0 software packages. The analyses for the current study consisted of two steps, described in detail below.

Step 1: (Piecewise) latent class growth (mixture) modelling

Heterogeneity in longitudinal development of body fatness was analysed with (piecewise (defined in Procedures below) latent class growth (mixture) modelling (LCGMM) [6, 33, 42, 43]. LCGMM is a contemporary longitudinal technique based on structural equation modelling, incorporating both continuous and categorical latent (unobserved) variables. The technique is an extension of conventional growth modelling. In conventional analyses, the assumption that all individuals in the study sample come from a single population should hold; meaning that one (average) trajectory will adequately

describe the developmental pattern of the sample. This assumption is relaxed in LCGMM, meaning that individuals in the sample need not come from one single underlying population, but can come from multiple, underlying (or latent) subpopulations. Identifying the number, and characteristics, of these underlying subpopulations is the main aim of LCGMM. This is done by identifying k number of distinct latent classes (i.e. subgroups) of, in the present study, trajectories of body fatness. Each identified class has its own specific growth parameters (intercept, slope), which are also assumed to be unobserved, or latent. Furthermore, LCGMM can also account for within-class variation in either, or both, of the growth factors, implying within-class heterogeneity on top of the between-class heterogeneity in initial status (intercept) or growth (slope).

Procedures

Various LCGMM models were run before choosing a final model. First, several linear LCGMM with fixed intercept- and slope variance within-classes were investigated. Next, quadratic slopes were added to the model allowing for curved developmental patterns. Third, we investigated piecewise models which allow for different phases in development. Models with three pieces were investigated, showing possibilities of different growth rates (and directions) during each phase. Phase one was defined as the adolescence phase (age 13-16), phase two was defined as the young adulthood phase (age 21-29) and phase three was defined as the adulthood phase (age 32-42).

For all models, a one to four class solution was modelled, starting with a one class solution (i.e. there are no subgroups within the data; all individuals follow the same trajectory over time), then adding classes one at a time.

After the choice for a final model was made, necessity for the estimation of within-class intercept- and slope variance was assessed. The assessment was made based on another stepwise procedure; step by step, intercept- and/or slope variances within classes were estimated in the model. After each step, model fit and clinical interpretation was assessed. Caution was taken when dealing with estimated slope variance, according to the current literature [17, 18, 42, 43].

Model selection (class identification)

To determine the optimal number of latent classes, we used two model fit indices; the Bayesian Information Criterion (BIC), and the Bootstrap

Likelihood Ratio Test (BLRT). The BIC (18) is commonly used within mixture modelling analyses, considering both the likelihood of the model as well as the number of parameters in the model; a lower BIC value indicates a better model fit (a decrease of at least 10 points shows a sufficient improvement [67]). The BLRT uses bootstrap samples to estimate the distribution of the log likelihood difference test statistic. The test provides a *P*-value, indicating that a model with one class less ($k-1$ class model) has to be rejected in favour of the k class model. The BLRT has been shown to be a very consistent indicator of the optimal number of classes (19). To further determine the optimal number of classes, we looked at the posterior probabilities for each individual in the sample (4). For each individual in the sample, the probability to belong to each of the k classes is estimated. The probability for the class to which the individual was assigned to, should be considerably higher than the other probability/probabilities. In this way, the classes clearly distinguish from each other. Third, we considered the usefulness of the separate classes in practice.

Technical issues

Missing data were handled according to the Expectation-Maximization Algorithm (EM-Algorithm) [61, 62]. An important assumption of this algorithm is that the data should be missing at random (MAR). Although this assumption is difficult to test [59], the included participants were compared with the excluded participants on the variables analysed. Regarding BMI at baseline (i.e. in 1976 at age 13), these two groups did not differ; the average BMI of the included participants was 17.39 (1.88), compared to 17.77 (2.23) for the excluded participants. Further, of the included participants, 52.4% was female compared to 52.8% of the excluded participants. In the Mplus program [43], it is in addition possible to extract missing data patterns to study the missing data in further detail. These assessments did not point to selective missing data either, corresponding to earlier research with data from the Amsterdam Growth and Health Longitudinal Study (see for example [90]).

LCGMM models are computationally-heavy models, often with convergence issues or hitting local maxima. Mplus incorporates random starts to avoid these issues as much as possible [18, 34, 43]. In the current paper, 750 random starting values were applied with 50 final optimisations. Only solutions with replicated log likelihoods were accepted, where the OPTSEED procedure can help in making a final decision [18, 43]. Because LCGMM are complicated models, often problems arise when estimating more than three classes [18,

43]. By taking into account this complexity, together with the sample size and the number of hypothesized trajectories from previous studies [91, 92], we modelled a maximum of four trajectories.

Step 2: Linear Regression

The first step of the analyses provided us with a classification of the study sample into distinct trajectory subgroups, coded as a categorical variable with k number of categories. To study the association between the distinct trajectories and CVD risk (i.e. mean arterial pressure- and HDL values) later in life (i.e. at 42 years of age), several linear regression analyses were performed. First, crude analyses were performed, in which class membership was related to the CVD risk indicators, correcting for gender. Second, adjusted analyses were carried out, adding the lifestyle covariates described above to the regression model.

Results

Illustrating the study sample, **table 1** shows descriptive data for all subjects for body fatness (BMI) at each time point. Mean values seem to increase throughout the life course. Mean (standard deviation) HDL levels at age 42 for the total study population were 1.725 (0.423) mmol/l. Mean (standard deviation) MAP at age 42 was 84.970 (9.889). 57.9% of the study sample reported to have never smoked at age 42; whereas 26.6% did smoke in the past, but was not a current smoker. Only 8.8% did not drink alcohol at age 42.

Table 1 Descriptive information (mean (standard deviation)) regarding the development of body fatness

Age	Sample size (Females, Males)	BMI (kg/m ²)	BMI (kg/m ²)	BMI (kg/m ²)
		Females	Males	Study sample
13	168, 153	17.81 (2.14)	16.93 (1.42)	17.39 (1.88)
14	155, 124	18.66 (2.08)	17.68 (1.49)	18.23 (1.90)
15	151, 121	19.41 (2.14)	18.38 (1.66)	18.95 (2.01)
16	153, 122	20.01 (2.10)	19.21 (1.70)	19.66 (1.97)
21	74, 57	21.65 (2.48)	21.20 (1.67)	21.45 (2.17)
27	73, 60	22.03 (2.36)	22.46 (2.17)	22.22 (2.28)
29	64, 61	22.46 (2.58)	22.94 (2.22)	23.70 (2.41)
32	169, 145	22.85 (3.13)	23.79 (2.41)	23.28 (2.85)
36	157, 143	23.57 (3.47)	24.60 (2.68)	24.06 (3.16)
42	175, 160	24.09 (3.87)	25.20 (2.92)	24.62 (3.49)

(Piecewise) latent class growth (mixture) models

Table 2 shows the results of the (Piecewise) latent class growth (mixture) models (LCGMM). First, several linear models (one-four classes) were conducted and compared. These models are shown in the top four rows of the table, pointing towards a three- or four class solution. These four solutions were subsequently compared to the next four solutions which permit quadratic development in the class(es). However, the quadratic models with three and four classes are increasingly complex and lead to convergence problems. In our case, we had problems with the estimation of the standard errors due to a non-positive definite information matrix, and difficulties in estimating the quadratic slopes for some classes that appeared to include two or three individuals only. Therefore, for the quadratic models we had not four, but two models to compare. Next, four models with piecewise trajectories (piece one was defined by the ages 13-16, piece two by the ages 21-29 and piece three was defined by the ages 32-42) were conducted. It can be seen that the improvement of these models (specifically indicated by much lower BIC values) is clear.

Choosing the final model

Comparing the three sets of four models based in model fit alone was complicated, as often the different model fit indices are not in agreement with each other [17]. Based on the BIC, for example, the “best” model (i.e. the model with the lowest value) is the two class piecewise model, although the BIC of the three class piecewise model is almost the same (a difference of three points). Literature advices about “significant” improvement in the BIC-values; improvement of at least 10 points indicates a sufficient improvement of the model [67], indicating that based on the BIC, the two- and three class piecewise models have equivalent fit. Further, based on the BLRT, the “best” model is a four class model (indicated by a non-significant *P*-value). Both (BIC and BLRT) model fit indices therefore do not point consistently to one definite solution [17]. Hence, we also took the clinical interpretation of the trajectories into account. Based on this, our final model was a three class piecewise model, showing a “normative” BMI trajectory (N=297), a progressively overweight, but stabilising trajectory (N=24) and a progressively overweight (N=15) trajectory.

When the choice for the number of classes in the final model has been made, the necessity of random intercept- or -slope variance within class was assessed. The results of these further analyses are not shown in the table, as none of the

Table 2 (Piecewise) latent class growth (mixture) model results

Number of classes	Intercept	Slopes ¹	BIC	BLRT	Prob.	Subjects per class
1, linear slope	class 1: 18.248	0.269	9899.165	Not calculated	1.000	336
2, linear slope	class 1: 18.081	0.261	9884.609	P<0.001	0.930	324/12
	class 2: 21.658	0.434				
3, linear slope	class 1: 17.950	0.258	9887.077	P<0.001	0.863	310/10/16
	class 2: 23.545	0.140				
	class 3: 19.734	0.479				
4, linear slope	class 1: 19.397	0.465	9894.435	P=0.034	0.829	31/286/3/16
	class 2: 17.757	0.259				
	class 3: 25.537	0.267				
	class 4: 21.344	0.119				
1, quadratic slope	class 1: 17.809	0.436/-0.007	8671.655	Not calculated	1.000	336
2, quadratic slope	class 1: 20.661	0.530/-0.003	8639.308	P<0.001	0.956	14/322
1, Piecewise, linear slope ²	class 2: 17.663	0.431/-0.007	88283.726	Not calculated	1.000	336
	class 1: 17.442	0.743/1.208/0.53				
	class 1: 17.292	0.752/1.159/0.497				
	class 2: 20.892	0.515/2.299/1.528				
3, Piecewise, linear slope²	class 1: 17.043	0.796/1.130/0.566	8265.720	P<0.001	0.867	297/24/15
	class 2: 20.160	0.551/1.514/-0.322				
	class 3: 20.924	0.517/2.313/1.502				
4, Piecewise, linear slope ²	class 1: 19.498	0.681/2.410/1.294	8274.552	P=0.05	0.910	16/2/294/24
	class 2: 25.892	0.184/0.824/2.080				
	class 3: 16.997	0.771/1.116/0.555				
	class 4: 20.238	0.525/1.431/-0.302				

¹. All values indicate linear slopes, except for the 1- and 2-class quadratic models where the second value indicates a quadratic slope². Piece one is defined by the ages 13-16, piece two is defined by the ages 21-29 and piece three is defined by the ages 32-42

additional models showed a sufficient increase in model indices. Based on existing literature [18], the ultimate final model was the most parsimonious model; a three class piecewise model without random intercept- and slope variance within classes (shown in bold in table 2). **Figure 3** shows mean trajectories of the final model and **table 3** provides descriptive information of the three trajectories regarding the confounders used in the regression models.

Linear Regressions

Table 4 summarises the results of the linear regression analyses investigating the associations between trajectory membership and MAP- and HDL values at the age of 42 years.

For MAP, both the overweight, but stabilising- and the progressively overweight classes were significantly different from the “normative” class. For HDL, the progressively overweight class showed significantly lower values compared to the two other classes. From the two adjusted models, it becomes clear that for both the analyses with MAP as well as HDL, gender is the most important confounder. After adding the lifestyle covariates, the effects in both models are much less affected.

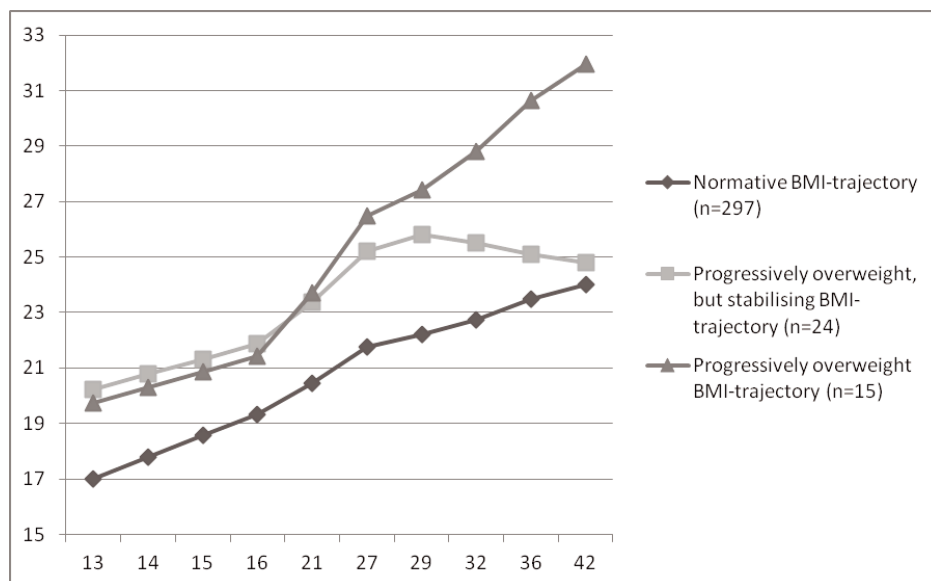


Figure 3 Estimated trajectories of body mass index (on the Y-axis) from the age of 13 to 42 years (on the x-axis)

Table 3 Descriptive information of the three estimated trajectories of body mass index

Variables of interest	“Normative” trajectory	Overweight, but stabilising trajectory	Progressively overweight trajectory
Gender (% Female)	49.2	79.2	73.3
Smoking:			
% Smoker at age 42	15.9	4.2	26.7
% Previous smoker	26.7	25.0	26.7
Alcohol intake (% drinkers at age 42)	92.2	95.8	66.7
Average total physical activity (SD) in min/week	559.33 (179.52)	472.28 (159.49)	424.73 (62.96)
Average nutritional intake (SD) in KJ/day	10,805.38 (2157.70)	9,083.25 (2140.79)	8,647.71 (2118.43)

Table 4 Linear regression analyses showing associations between class membership and indicators of CVD-risk

	Mean Arterial Pressure			HDL-Cholesterol		
	b	95% CI	P-value	b	95% CI	P-value
Crude:						
Overweight, stabilising ¹	1.629	-2.593 to 5.851	0.448	0.115	-0.064 to 0.294	0.206
Progressively overweight ¹	3.865	-1.465 to 9.195	0.155	-0.162	-0.380 to 0.057	0.146
Adjusted for gender:						
Overweight, stabilising ¹	3.909	-0.078 to 7.896	0.055	-0.008	-0.168 to 0.153	0.926
Progressively overweight ¹	6.168	1.158 to 11.177	0.016	-0.265	-0.460 to -0.070	0.008
Adjusted additionally for lifestyle:						
Overweight, stabilising ¹	3.373	-0.612 to 7.358	0.097	-0.034	-0.192 to 0.123	0.668
Progressively overweight ¹	5.013	-0.192 to 10.218	0.059	-0.212	-0.411 to -0.013	0.037

¹ The “normative” trajectory was set as reference

Discussion

The current study gave particular attention to the application of latent class growth (mixture) models on life course data. As an example, we investigated the possible existence of distinct life course trajectories of body fatness, in an apparently healthy sample. Developmental patterns of body mass index were studied from the age of 13 to 42 years, where three distinct trajectories emerged. Subsequently, class membership was related to CVD risk factors at the age of 42 years.

Researching heterogeneity in development of body fatness

The acknowledgement of the existence of heterogeneity within a study sample has gained interest over the past years. Especially within the field of alcohol research, recognising heterogeneity has led to theories of multiple developmental pathways of alcohol abuse [15, 93, 94]. Slowly, similar approaches are emerging in other fields of research [79, 80, 91]. Comparing the analysis of heterogeneity of body fatness development with existing studies shows that limited research has been conducted and methodologies differ a great deal. Studies with methods comparable to ours are for example the study by Li et al. [92]. They studied developmental trajectories of BMI focussing only on childhood (American children of age 2 to 12 years). The authors found a three class solution to be the best option, containing a “normative” group, a consistently overweight group and a late-onset overweight group. Another study, by Mustillo et al. [91], also studied developmental patterns of body fatness, but with a slightly different statistical technique implemented in the SAS software [41]. They studied American children from the age of 9 to 16 years, and found four distinct trajectories, where most children were classified in the group with a very low prevalence of obesity. A third study [95], following up adults from the age of 18-49, also conducted the analyses in the SAS program, and analysing continuous BMI-values in their models is worth mentioning in the light of our study. Their sample, more heterogeneous in terms of race and socioeconomic status and larger compared to our sample, revealed four trajectories, three of them comparable to our trajectories. The papers highlighted above show consistently that body fatness development is heterogeneous throughout the life course, in various study populations. This indicates that researchers should be aware of this when analysing their data. There are other noteworthy studies, which investigate differences in development of body fatness *retrospectively*, seeing differences in the development of body

fatness between individuals at high- and low risk of coronary artery disease [96], between people with and without the metabolic syndrome [97] and also between people with high- and low adult body fat [98]. Although the aim of these studies was also to investigate developmental patterns of risk factors, they were primarily interested in difference in development between patients and non-patients. This is an a-priori categorisation of the study participants into predefined groups on the basis of their disease status, whereas the categorisation with LCGMM is on the basis of the developmental trajectory of the risk factor per se. When choosing a statistical method incorporating a heterogeneity component, one should keep in mind the differences between the techniques available to allow for answering the research questions appropriately.

Methodological issues

In the current literature, there is discussion about the usage of latent class growth (mixture) models within epidemiology. Models are mathematically complicated and care should be taken when applying them as a wide range of possibilities are available for the specification of the model. The debate is mainly between the choice between a latent class growth model (LCGM) and a latent class growth mixture model (LCGMM). In short, the LCGM methodology was developed by Nagin and colleagues [40, 41, 44, 99, 100] and is implemented in the SAS software, whereas the LCGMM methodology was developed by Muthén and colleagues and implemented in the Mplus software (LCGM is also possible in this framework) [6, 33, 34, 42, 43]. The difference between the two methods is the assumptions both have about the underlying (latent) populations. LCGM assumes no within-class variation (the variance within each class is fixed to zero), whereas LCGMM relaxes this assumption by allowing the within class variance to be estimated. Hereby, LCGMM allows for additional heterogeneity in the model and thus being the more flexible technique. Because of this flexibility, however, models can have difficulty leading to a proper statistical solution. Although the underlying aims of both techniques are similar (namely, identifying distinct developmental trajectories), the approach can vary. It is important for researchers to clearly describe which approach they used to allow for objective comparison and interpretation of the results.

Another important point of discussion is the decision of the number of classes (or subgroups). Several model fit indices are available aiding the researcher with this decision. However, these fit indices are not always consistent [17].

Although an interesting simulation study has been published showing that the BLRT is the most consistent fit index, controversy remains. Therefore, in this paper, several indices are reported and all are used deciding on the final model.

General remarks

We have shown that LCGMM is a promising technique to distinguish between subjects with different developmental trajectories. It can help researchers in the field of obesity and cardiovascular disease risk specifically and epidemiology in general, amongst others, to gain insight in the relationships between developmental patterns of risk factors for chronic disease and provide interesting novel research opportunities. However, researchers should take caution when utilising these complex techniques as they still cope with technical issues that have not all been resolved. Careful application, with careful interpretation of the results, can, however, bring valuable insights in many fields of research and instigate new research ideas.

We have shown that elaborate comprehension of heterogeneity in the progress of risk factors for (preventable) chronic diseases is interesting for aetiology and prevention. Our results have shown that body fatness development from adolescence into adulthood is heterogeneous, consistent with previous studies [91, 92, 95]. Trajectory membership was associated with CVD risk later in later life, even if lifestyle variables are taken into account. This indicates that fatness trajectory shape matters for the magnitude of CVD risk in this study population. However, effects were small and our study sample is relatively healthy, making it difficult to generalise these findings to other study samples or the general population. The AGAHLs is one of few studies following up participants for over thirty years, throughout life, making these findings very valuable. Further research, studying the technical issues LCGMM are currently experiencing, should be conducted, but also continued application of these models on data from diverse fields of research is warranted to continue to explore the usability and applicability of these models.