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At the heart of the problem - A person-centred, developmental perspective on the link between alcohol consumption and cardio-vascular events

Valéria Lima Passos *, Sven Klijn, Kevin van Zandvoort, Latifa Abidi, Paul Lemmens

Maastricht University, Department of Methodology and Statistics, Peter Debyeplein 1, 6229HA, Maastricht, Limburg, Netherlands

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ABSTRACT

Introduction: The cardio-protective effect of alcohol has been the subject of a long-standing scientific controversy. Emerging evidence remains equivocal, as the validity of the dose-dependent J-shape association is tainted by conceptual, theoretical and methodological problems. A major impediment for a resolution on the matter is the lack of a life-long developmental approach to pinpoint alcohol's specific impact on the risk for cardio-vascular events (CVE).
Objective: Using retrospective and prospective individual-level data of alcohol consumption (AC) we applied a model-based clustering technique to uncover life-course trajectories of AC and explored their links to CVE.
Methods: Data stemmed from a random sub-cohort of a large-scale, longitudinal study conducted in the Netherlands ($N = 2288$). Group Based Trajectory Model (GBTM) was applied to extract distinct progressions of AC over time. Stratified by sex, the association between the developmental trajectories and CVE was examined with multiple logistic regression models, with adjustment for traditional risk factors.
Results: GBTM analysis laid bare the heterogeneity of AC dynamics over the life-course, reiterating sex differences in drinking habits and CVE risk. AC temporal behaviors during adolescence and adulthood were diverse, but showed relative stability in in middle-age and elderly years. For males, adjusted odds for CVE differed among the uncovered developmental classes.
Conclusions: The findings elicited supportive evidence for a J-shape, but with a new twist. Besides moderation the results indicate that onset, timing, duration and stability of AC over the life-course are major aspects to be accounted for when attempting to elucidate alcohol's cardio-vascular role.

1. Introduction

Epidemiologic research assessing the cardio-vascular risks associated with alcohol consumption (AC) has produced a variety of shapes for risk curves across major cardio-vascular entities [1]. Among them, the J-shaped function has been consistently used to convey this association, mainly when the endpoint is coronary heart disease (CHD) [2–8]. The curve's lower point of inflection, corresponding to light-to-moderate AC is mapped to the smallest CHD risk estimate. Conversely, both the lower and upper-ends of the J-curve, representing abstention and heavy AC levels, respectively, are linked to higher CHD risks. The harmful effects of chronic heavy alcohol exposure and associated cardiomyopathy are well documented [9–11]. It is the beneficial effect of AC, in particular, that has aroused controversy [12–15], even though research on biological mechanisms underlying the cardio-protection is available. Several pathways have been proposed, and the current consensus is that different mechanisms may be operative. Alcohol increases high-density lipoprotein (HDL) concentration, decreasing endothelial damage, and reduced blood platelet aggregation (reducing the risk of occlusion). It has also been suggested that it affects, among others, glucose metabolism, insulin sensitivity, and lipid action, and has an anti-inflammatory effect [13,16–18]. However, these beneficial effects have often been challenged, largely on methodological grounds.

Methodological fallacies suggested are: [5,19–22] bias in self-reported AC measurement [23], publication bias [19], confounding bias, AC being irrefutably linked to certain socio-economic and lifestyle characteristics known to affect cardio-vascular events (CVE) [21,24]; systematic misclassification error, known also as abstainers'/sick quitters' fallacy [12,25], leading to a reverse causality bias [20]; and residual confounding bias that is often a result of dodgy AC operationalization [2,26,27].

Quantifying alcohol exposure is nothing short of challenging [27]. For this purpose the short-hand term 'drinking pattern' has been often employed. Drinking pattern can convey different aspects of AC, and accordingly has become an ambiguous catch-up word being applied in an inconsistent and non-uniform manner across studies. For example, beverage type and the frequency, quality, quantity and period of time of

* Corresponding author.
E-mail address: valeria.limapassos@maastrichtuniversity.nl (V. Lima Passos).

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consumption, have all been considered as elements of drinking pattern but not necessarily concurrently [28]. The quantity of AC expressed in ethanol g/day (100% ethanol) has become a standardised and widely used measure. Yet, even this continuum has been categorised and used to describe drinking patterns [29–31]. Moderate consumption, for instance, is around 30 g/day for men and 15 g/day for women [32]. Moderate-use is in itself an inaccurate term but is frequently considered to be up to 1 drink per day for women and up to 2 drinks per day for men [33,34].

The lack of a consistent operationalization of alcohol consumption hampers the comparison of AC studies [27]. Dissimilarities aside, most current AC categories share a common denominator in that they are ex-ante classifications. In being a priori defined groupings, they may exhibit a few non-negligible weaknesses: the existence of categories is assumed and cannot be tested; cut-off points are often arbitrary; the assignment of a subject to a certain category is deterministic (absolute certainty) instead of probabilistic; and they create fixed group boundaries that fail to capture gradual or rapid AC changes over time.

In addition to the ex-ante drawback, the inability to account for within-person variability of AC, especially throughout life, presents a major impediment to identifying its potential cardio-protective role. In most studies AC is measured over short time frames [20]. Longitudinal studies are scarce and usually do not take into account changes over time, using baseline measures as predictors of future CVE risk [5,31]. Recently, there have been efforts to measure longitudinal AC but they tend to resort to ex-ante groupings, e.g. categories of the ethanol g/day continuum, or to summary measures, e.g. an index for lifetime alcohol intake [35]. Either way, devising such constructs attenuates heterogeneity of individual AC courses over time. Moreover, because AC classes/categories are often too broad, residual confounding can be introduced. As a result, efforts to unravel exposure and health outcomes associations and to recognise factors associated with different AC temporal patterns become more difficult. For instance, over-simplified AC trends overlook developmental nuances, like timing and nature of AC changes, e.g. early/late onset, gradual or sudden, and duration of drinking behaviour that may affect subsequent health outcomes.

In an attempt to capture distinct patterns of AC over time and simultaneously avoid the ex-ante trap, we apply a model-based clustering technique for the analysis of longitudinal data, the Group-Based Trajectory Model (GBTM) [36,37]. As a person-centred approach GBTM capitalizes on the underlying heterogeneity of individual longitudinal behaviours, identifying distinct temporal patterns of changes in an outcome. In this process, subjects are clustered into more homogeneous (latent) subgroups or classes of developmental trajectories.

Our AC data stem from a random sub-cohort from a large-scale, longitudinal study conducted in the Netherlands [38], LEGO, which is a Dutch abbreviation of Lifestyle and Health Study (*Leefstijl en Gezondheid Onderzoek*). The analysis of the LEGO data with GBTM is unprecedented. Our main objective was to uncover life-course trajectories of AC and to explore their links to CVE, which herein encompass specifically coronary heart disease (CHD), heart failure and stroke.

2. Methods

LEGO was a prospective cohort study that took place in the Netherlands, whose design was approved by the review committee of the Registration Network Family Practices of Maastricht University. Its target population was middle-aged/elderly adults with no clinical manifestation of cardiac problems. The focus on this age group was grounded on the hypothesis that a cardio-protective effect, if existent, is manifest during late adulthood [31,39]. One of LEGO's original aims was to investigate potential moderating effects of life-events and social support on the AC-CVE association. It started in 1996 and ran for five follow-up years with annual questionnaires. 16,210 participants between the ages of forty-five and seventy years old were sampled from general practitioners' databases, excluding patients who were unable to fill out the questionnaire or were expected to drop out at short term due to a terminal illness [38].

Our data stem from a nested case-control study involving a random sub-cohort of 3253 participants. Fig. 1 presents the flowchart with subjects considered for data analysis and the reasons for their exclusion. The final sample consists of 2288 individuals (1188 men; 1100 women) with a mean age of 55.2 years at baseline, of whom 149 experienced a CVE (105 were men and 44 women). 83.4% of the 145 life time abstainers were female (121). The follow-up of patients stopped after detection of a CVE (also non-fatal).

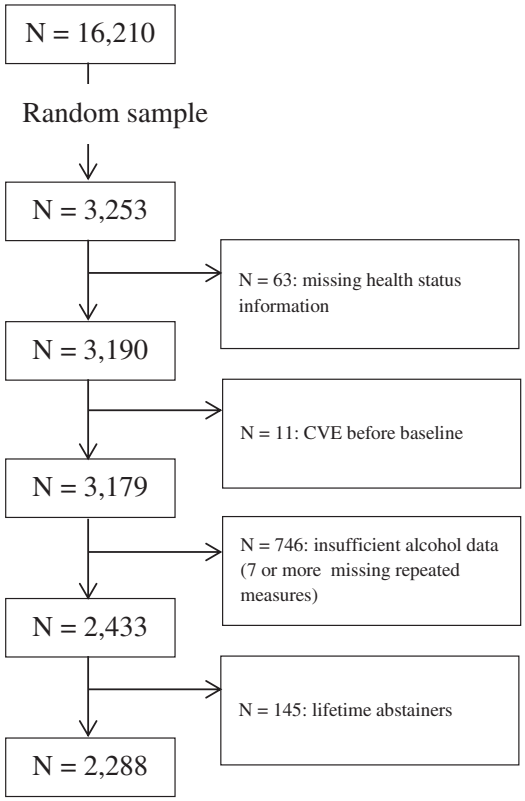

Fig. 1. Flow charts of subjects.

2.1. Variables

All variables of interest, including retrospective early life AC, were self-reported measures obtained at baseline, with exception of late life AC (also self-reported) and CVE.

2.1.1. Alcohol consumption (AC)

Longitudinal measures of AC were acquired both retro- and prospectively: measures of AC life-exposure between adolescence and early middle-age (*youth*, aged 12 to 18 years; *young adult*, aged 19 to 27 years; *adult*, aged 28 to 44 years and *middle-age*, aged 45 to 60 years) were obtained at baseline. The total AC volume expresses the weekly consumption (in glasses) including binge drinking. Middle-age/elderly AC was measured on an annual basis for 5 follow-up years.

For the annual AC measurements, a distinction was made between three different categories of drinks: beer, wine and liquor. Beer includes all types of beer, with the exception of alcohol free beer. Wine comprises all types of wine, as well as sherry, Martini, port, and fruit wine. Liquor includes mixed drinks, cocktails, liqueur with an alcohol percentage of 20% or higher and all distilled drinks such as gin, whiskey, and brandy. Participants were informed of these classifications prior to reporting their AC for the past twelve months.

AC was reported as a quantity and frequency measure for each drink type. Frequency was measured on a categorical scale, ranging from daily to never with six intermediate steps. These frequency data were converted to an average number of drinking occasions per week. Quantity is reported as the number of glasses drunk on a typical day at which the specific beverage was consumed. Based on the reported frequency and quantity measures the variable Total weekly AC volume was computed (quantity x frequency).

2.1.2. Cardiovascular events (CVE)

Cardiovascular events were operationalised as coronary heart disease (CHD), heart failure and stroke. The corresponding International Classification of Primary Care codes are K74, K75 and K76; K77; K89 and K90 [40]. A detailed description of the data collection procedure is provided elsewhere [41].

2.1.3. Risk factors for CVE and covariates (Potential confounders)

An overview of potential confounders available for data analysis is presented in Table 1. Region denotes the recruitment centre, either in the Southeast or the West of the Netherlands. Living together identifies whether or not participants are living together with a partner. Physical activity was calculated using several measures, such as weekly

Table 1
Operationalization of available covariates and risk factors for CVE.

Categorical		Continuous	
Variable	Categories	Variable	Unit or range of scale
Sex	2	Age	Years
Region	2	BMI	kg/m^2
Education	3	Physical activity	kcal/week
Income	3	Smoking status	pack years
Living together	2	Alcohol expectancies	16–64; 19–76
		Coping style	0–28; 0–40; 0–44
		Fat intake	0–56
		Actual Social support	3–12

number of hours of intensive sporting. Smoking status was operationalized as pack years, which is a measure of lifetime tobacco exposure based on the number of years a participant had smoked and the average number of smokes per day. Alcohol expectancies, i.e. the cognitive, affective, and behavioural outcomes an individual expects to incur due to drinking, were rated on a positive and negative scale as proposed by Leigh and Stacy [42]. Coping style was measured with a translation of the Bern Coping Forms. Fat intake was based on a questionnaire of eating habits for the past three months. Social support was measured using the Inventory for Social Reliance, a questionnaire with focus on the actual received support scale [43].

2.2. Statistical analysis

2.2.1. GBTM – Analysis strategy

2.2.1.1. Model selection. GBTM was used to identify developmental trajectories of AC outcomes with the *proc. traj*, SAS® software version 9.4. For model selection the number of latent trajectories was first established (class-enumeration) using a supportive R-code that compiles fit-indices for several models with different number of latent classes into graphical displays (Fit-criteria Assessment Plots – F-CAP) [44]. F-CAPs for all fitted GBTM models are available in the supplemental material (appendices I and II). Subsequently the order of the polynomials affecting the trajectories' level and shape was determined. Data were log transformed previous to model fitting and *proc. traj* was run with the censored normal link function. Separate models were considered for the AC total volume (aggregate over the beverage types, available for both life stages) and for individual beverages (available for late-stage time points only). In either case, linking early and late life AC, i.e. retrospective and prospective data, was achieved by applying the multi-trajectory version of GBTM. Multi-trajectory GBTM is an extension of the univariate model for a multivariate setting [45]. It is a model-based clustering used to uncover different temporal patterns of interdependences across multiple outcomes. In the multi-GBTM each extracted latent class is characterised by a set of developmental trajectories. With this model we aimed to explore the heterogeneity of linkage between the early and late AC courses both on composite as well on beverages-specific outcomes and to identify their progressions in terms of stability, change as well as their patterns of co-dependencies.

Latent class extraction was also conducted in the univariate setting, i.e. for the AC volume per life-period separately, early and late. For the sake of parsimony, these results are presented as supplemental material (appendix II and III).

2.2.1.2. Model validation. GBTM analyses proceeded with the full sample. Trajectory comparisons/profiling and their links to CVE were explored separately for men and women. Stratification was selected on the grounds of well-known sex differences both in AC, CVE risk, as well as accruing evidence of sex's pivotal role as a potential mediator in the AC-CVE causal link. In addition to men having a higher average AC, there is resounding evidence that women are more susceptible than men to the cardio-toxic effects of alcohol [46–49].

Latent groups' comparisons for continuous variables were carried out with one-way ANOVA/Kruskal-Wallis tests, when appropriate, using post-hoc Bonferroni correction. Pearson's Chi-square (χ^2) tests were performed for categorical variables at a 5% significance level. The uncovered latent classes were linked to CVE with a multivariable logistic regression model weighted by subjects' maximum posterior probability of assignment that is an output parameter estimated by GBTM. This last step was introduced to account for the uncertainty of cluster membership in the association between AC latent trajectories and CVE. Due to the decrease in statistical power induced by stratification, as well as accompanying cell sparseness, adjustment occurred only for those risk factors showing significant crude associations with the outcome (forward variables' selection at 10% significance level).

2.2.1.3. AC Missing values. Intermittent missingness of the outcome variable was assumed to be at random. We used a naive approach to handle potential non-random attrition in the multi-trajectory GBTM, by determining the proportion of subjects with ≥3 missing values in the final and immediate preceding time points.

3. Results

3.1. Model fitting – Total volume model (retrospective and prospective data)

Seven AC latent multi-trajectory groups were identified based on the acceptability of the available fit-criteria indices, model parsimony, distinctiveness of temporal patterns via visual inspection and cluster size (1% rule applied - see F-CAPs with changes in model adequacy criteria in appendix I). The final trajectories plot is presented in Fig. 2.

The AC developmental behaviours of uncovered clusters, estimated by using retrospective and prospective AC data simultaneously, showed relative stability of AC during and beyond middle-ages within the 5-years of follow-up. In this period, differences were observed in their average levels but less so in their shapes. Conversely, AC courses were substantially more diverse during earlier life-stages. In youth the majority of subjects clustered around lower levels of AC (small intercept of trajectories 1, 3 5 and 7), but branching was already firmly established in young adulthood. Most clusters, except the lowest one (1) were risers between the first two time points, some of them substantial (trajectory 6), others less so (trajectory 3). Two latent classes were transient, reaching a peak in early adulthood, before declining (trajectories 4 and more so for cluster 2); others showed minor increases but stabilized relatively early, except for trajectory 7, showing a steady and substantial increase up to the middle-age years. Based on onset level/patterns of change in early life/and level of AC during middle age and beyond trajectories were labelled: **(1)** *Low onset/persistent low/stable light AC* - **28.25%; (2)** *Low onset/transient/light AC* - **10.73%; (3)** *Low onset/low riser/light to moderate* AC **19.24%; (4)** *Moderate onset/transient/persistent moderate AC* **12.39%; (5)** *Low onset/moderate riser/persistent moderate to high AC* **14.92%; (6)** *Moderate to high onset/fast riser/persistent heavy* AC **11.28%** and **(7)** *Low onset/gradual but sizeable riser/persistent heavy AC* **3.16%.**

The sex distribution (in % of males) across the trajectories from 1 to 7 was: 1–20%, 2–62.6%, 3–40.3%, 4–86.2%, 5–56.8%, 6–94.6% and 7–68.6%). Women were over-represented in the lowest trajectory but their proportion decreased towards the higher ones, with men making up almost 95% of trajectory 6. Fig. 3 shows the CVE counts across the trajectories per sex (accompanied by their respective proportions).

Variability in AC developmental progression was substantially larger for men than for women (Fig. 3). In both strata the trajectory characterized by the most elevated AC during late-life had the highest CVE prevalence (Fig. 3, trajectory 7). Otherwise, sex differences were striking with respect to both CVE risk, men being much more susceptible, and to CVE distribution across trajectories. For instance, CVE prevalence estimate was smallest for males in trajectory 4 (4.8%), whereas the same trajectory had second highest CVE prevalence for females (5%). The numbers of CVE events did not differ across the 5 follow-up years, being (in N/%): year 1–23/15.4%, year 2–29/19.5%, year 3–30/20.1%, year 4–36/24.2% and year 5–31/20.8% ($p = 0.573$).

There were 145 life abstainers (not displayed) of which 121 were females ($N = 121$). CVE prevalence was 12.4% for women in this group, which was substantially larger than the crude prevalence of the other AC latent classes (Fig. 3), and only 1 case was observed in men (out of 24, i.e. 4.2%).

3.2. Trajectories profiling

Tables 2 and 3 display summary statistics of background variables and risk factors of the extracted developmental classes. Results of the trajectories' comparisons are also given. Both males and females of the lowest AC latent class (trajectory 1) were on average older and of lower educational/income levels, having also the lowest values for pack years. Trajectory 6 (heavy middle-age AC), by contrast, had the largest proportion of high income, also for both sexes. Compared to trajectory 6, the intermediary trajectories

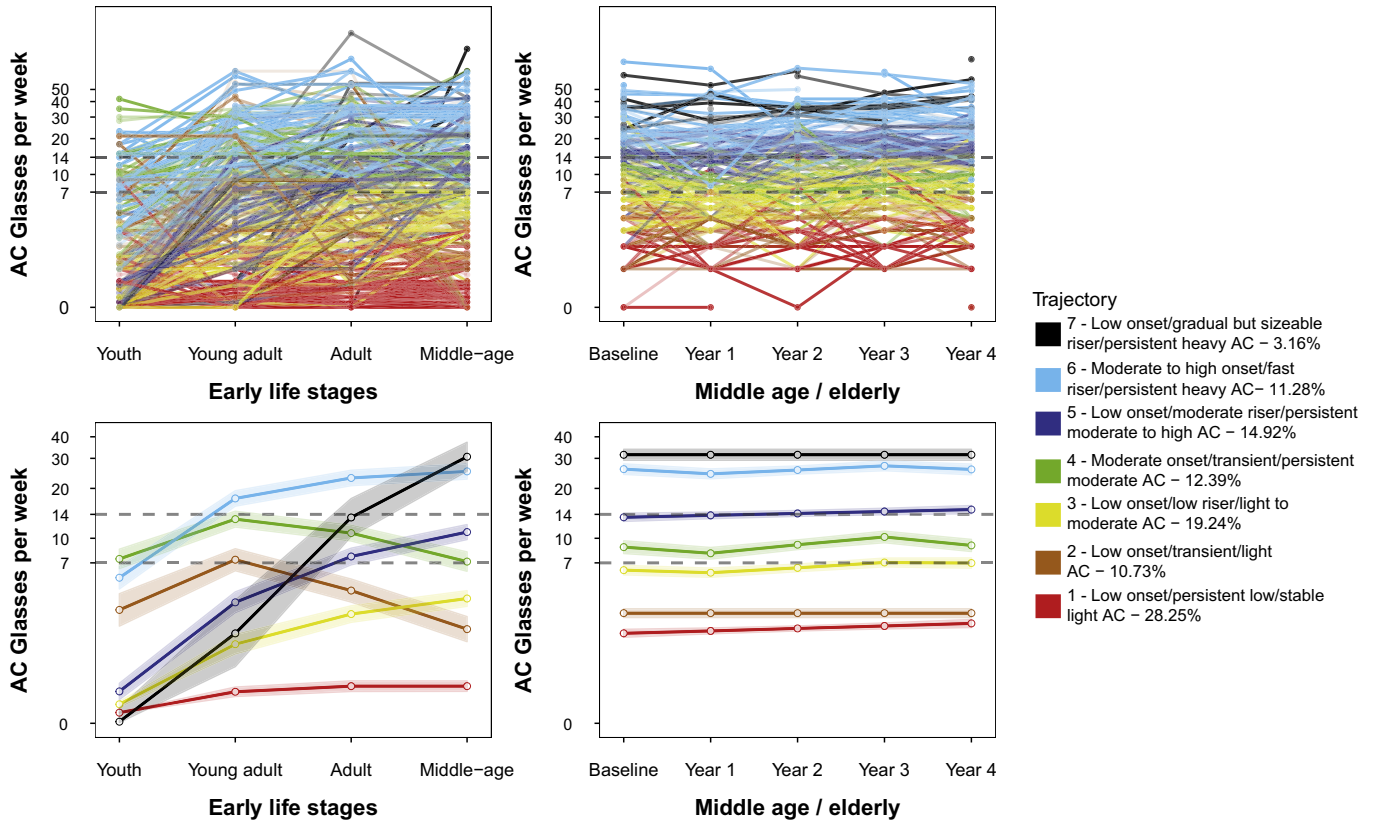

Fig. 2. Spaghetti plots based on a random sample of 500 subjects (top row) and estimated mean trajectories plots with 95% confidence bands (bottom row). Horizontal dashed lines represent the lower and upper boundaries of the ex-ante moderate drinking class (7/8 to 14 glasses a week). Baseline prevalence (trajectories' size in %) is also given.

2 and 4 did not fare well (significantly lower income and education), but were not different from trajectory 1.

For both sexes heavy smokers were observed in trajectories 6 and 7 (both heavy drinkers during middle-ages). Fat intake was higher for trajectories 2, 4 and 6 for males (4 for females), although the heaviest AC, trajectory 7, had the lowest fat consumption for both sexes. Trajectories were also differently distributed across geographical regions. A larger representation of residents from southern part of the Netherlands, notorious for its Bourgognian influence, was observed in the moderate class, trajectory 4 for men. Other known CVE-risk factors, e.g. partnership, physical activity and BMI were neither markedly nor significantly different among the extracted latent classes.

Alcohol expectancies differed among clusters. Females assigned to trajectory 1 (low AC) and 6/7 (heavy AC) had the lowest and highest positive expectancy scores, respectively. For males, trajectory 2

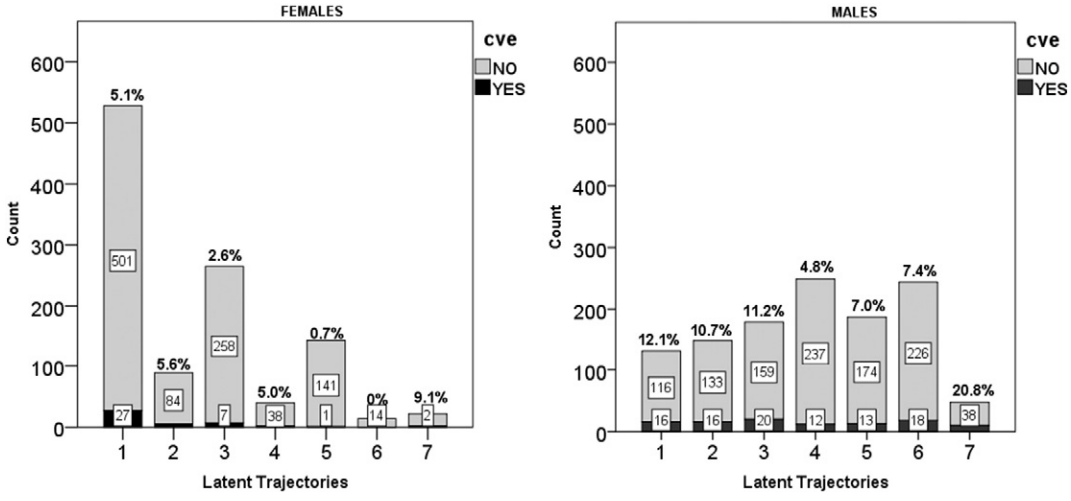

Fig. 3. Absolute counts of CVE and CVE-free subjects assigned to the extracted latent trajectories. Crude CVE prevalence per trajectory (%) is given.

Table 2
Trajectory profiling for females. Large (in bold) and small (underscored) values are highlighted. Trajectory labels reflect AC regarding *onset level*, *patterns of change in early life* and *level during late life*.

FEMALES	LATENT AC TRAJECTORIES							*p*-values
	1 *Low/persistent low/light*	**2** *Low/transient/light*	**3** *Low/low/light to moderate*	**4** *moderate/transient/moderate*	**5** *Low/riser/moderate*	**6** *moderate/riser/persistent high*	**7** *low/riser/persistent high*	
Age, years Mean (SD)	**56.64** (7.55)	51.96 (6.18)	55.05 (6.92)	52.30 (6.27)	54.56 (7.41)	*50.43* (3.92)	54.82 (6.22)	< 0.001*
BMI Mean (SD)	26.07 (4.63)	**26.08** (5.60)	25.41 (4.27)	24.87 (4.22)	24.66 (3.24)	25.67 (3.12)	25.43 (5.07)	0.03*
Smoking Pack Years MEDIAN (1st/3rd Quartiles)	0.0 (0.00–12.00)	10.50 (0.00–26.00)	3.60 (0.00–17.33)	8.10 (0.00–23.25)	8.33 (0.00–25.88)	**22.38** (8.50–38.25)	**25.00** (13.13–35.88)	< 0.001**
Positive Expectancy Total - Mean (SD)	32.22 (10.96)	**38.50** (11.39)	36.45 (11.58)	35.72 (10.65)	36.26 (11.24)	37.69 (11.25)	**38.50** (12.02)	< 0.001*
Negative Expectancy Total - Mean (SD)	30.15 (11.26)	**31.71** (10.10)	28.58 (9.31)	**30.36** (9.89)	28.02 (10.08)	28.85 (8.82)	28.85 (8.99)	0.153
Actual support (SD)	7.06 (2.11)	7.05 (2.06)	7.24 (2.15)	7.54 (2.41)	7.50 (2.11)	8.00 (2.51)	7.61 (2.41)	0.202
Action coping Mean (SD)	21.35 (4.31)	21.53 (4.59)	21.85 (4.34)	22.21 (5.27)	22.56 (4.38)	23.21 (3.28)	22.57 (5.12)	0.071
Cognitive coping - Mean (SD)	25.60 (4.77)	24.79 (5.18)	25.35 (4.51)	26.24 (5.23)	24.79 (4.32)	24.28 (3.62)	25.33 (4.89)	0.365
Emotional coping Mean (SD)	13.64 (3.31)	**14.43** (3.84)	12.99 (3.46)	13.56 (3.90)	13.17 (3.16)	13.14 (3.67)	13.85 (2.72)	0.027*
Region – N (%)								0.203
1 Southern	272 (51.5)	54(60.6)	134(50.5)	27(67.5)	75(52.8)	10(71.4)	12(54.5)	
2 Northern	256	35	131	13	67	4	10	
Education– N (%)								< 0.001*
1	322(**63.1**)	52(61.2)	117(46.1)	23(59)	56(40)	4(28.6)	11((55)	
2	154(30.2)	26(30.6)	102(40.2)	13(33.3)	65(46.4)	7(50)	7((35)	
3	34(6.7)	7(8.2)	35(13.8)	3(**21.4**)	19(13.6)	3(**21.4**)	2(10)	
Income- N (%)								< 0.001*
1	309(**69**)	45(60)	117(51.1)	20(60.6)	55(46.2)	4(30.8)	9(50)	
2	96 (21.4)	20(26.7)	68(30)	8(24.2)	31(26.1)	4(30.8)	6(33.3)	
3	43 (9.6)	10(13.3)	42(18.5)	5(15.1)	33(27.7)	5(**38.5**)	3(16.7)	
Living together (yes) - N (%)	318(77.6)	57(79.2)	171(80.3)	26(78.8)	88(76.5)	10(90.9)	11(68.8)	0.298
Physical activity MEDIAN (1st/3rd Quartiles)	2259 (1299–3171)	2141 (1326–3156)	2265 (1389–3519)	2151 (1635–3111)	2499 (1639–3480)	3111 (1563–3495)	2052 (1041–3279)	0.545
Fat intake - Mean (SD)	13.89 (4.73)	14.74 (5.12)	13.61 (5.11)	**14.82** (4.63)	12.99 (5.21)	12.10 (4.14)	11.54 (6.46)	0.026*
Attrition ≥ 3 missing final measures - N (%)	267(**50.6**)	28(31.5)	30(11.3)	6(15.0)	11(7.7)	0(0)	2(9.1)	< 0.001*

(decreasing over time) showed the lowest positive expectancy average, and similarly to females trajectories 4 and 6 the highest positive expectancy, whereas trajectory 1 had the largest negative expectancy.

The proportion of loss to follow-up was also significantly and substantially higher for lower AC trajectories for both men and women. It is possible that the higher average line of trajectory 1, compared to the early-life average line (Fig. 2), is attributable to this differential attrition.

3.3. AC Trajectories links to CVE

Of the variables listed in Tables 2 and 3, only those significantly associated with CVE in simple logistic models were considered in the subsequent multiple logistic regression linking AC trajectories to CVE. The results can be found in the forest plots for women and men (Figs. 4 and 5). The absolute number of individuals with CVE was relatively low, resulting in large confidence intervals. For females, links between AC developmental courses to CVE were inconclusive due to data sparseness. For males, significant associations were observed for traditional risk factors. Older men and smokers were evidently more at risk for CVE (2 to 5 fold increase in odds), but differences were also observed among the AC trajectories. All of them had a higher point estimate OR compared to trajectory 4 (taken as a reference), some reaching statistical significance (trajectories 1, 2, 3 and 7). Notably, the direction and magnitude of the trajectories' adjusted ORs were similar to those of established CVE risk factors (2 to 4 fold increase in odds). We also draw attention to the subtle 'J-shape' depicting the non-linear pattern of changes of ORs as one goes from trajectory 1 to 7 (note: log OR scale). This J-shape, however, needs to be cautiously interpreted. It is important to bear in mind that AC is ordered from lowest (trajectory 1) to highest (trajectory 7) value only with respect to late life consumption. For instance, subjects in trajectory 7 had the highest AC during middle-age years and beyond. However, this same trajectory had the lowest AC during adolescence and young adulthood. Thus, the developmental classes express much more than just AC volume; they convey distinct gradations of AC changes over a life-course. Consequently, the non-linearity of changes in risk does not follow straightforwardly from a linear increase in AC, as the extracted classes represent a composite measure of AC level, plus fluctuation and stability over a life time. In this regard, trajectory 4 was conveniently selected as a reference category, as it allowed for a J-shape to emerge (Fig. 5).

3.4. Beverage specific multi-trajectories and CVE (retrospective and prospective data)

Fig. 6a illustrates the beverage-specific multi-trajectories (6 in total, denoted A to F). Based on the displayed patterns of AC we labelled the beverage-specific multi-trajectories: **A** (25.91%) '*Light wine drinkers*', **B** (16.41%) '*Wine drinkers*', **C** (19.39%) '*Beer drinkers*', **D** (16.51%) '*Light wine/beer drinkers*', **E** (8.41%) '*Liquor drinkers*' and **F** (13.35%) '*Wine/beer drinkers*'. Just as in the results reported above, middle-age years and beyond were characterised by stability of AC for all beverages. The accompanying bar chart (Fig. 6b) shows the distribution in % of the total volume AC classes, contingent on their beverage-specific multi-trajectories counterparts.

Table 3
Trajectory profiling for males. Large (in bold) and small (underscored) values are highlighted. Trajectory labels reflect AC regarding *onset level*, *patterns of change in early life* and *level during late life*.

MALES	LATENT AC TRAJECTORIES							*p*-values
	1 *Low/persistent low/light*	**2** *Low/transient/light*	**3** *Low/low/light to moderate*	**4** *moderate/transient/moderate*	**5** *Low/riser/moderate*	**6** *moderate/riser/persistent high*	**7** *low/riser/persistent high*	
Age, years Mean (SD)	**57.52** (7.7)	55.33 (7.06)	57.27 (7.07)	53.43 (6.80)	56.21 (7.43)	52.72 (6.26)	**58.13** (7.09)	< 0.001*
BMI Mean (SD)	25.61 (3.02)	25.50 (2.79)	25.61 (2.86)	26.24 (3.95)	26.02 (4.49)	26.24 (3.23)	25.79 (2.85)	0.195
Smoking Pack years MEDIAN (1st/3rd Quartiles)	11.70 (0.23–23.21)	14.70 (4.40–27.75)	14.35 (0.30–25.80)	**16.80** (4.80–31.00)	16.75 (4.54–27.00)	**21.00** (8.75–37.00)	25.50 (10.25–44.13)	< 0.001**
Positive Expectancy Total - Mean (SD)	36.47 (11.73)	34.36 (11.05)	34.77 (12.15)	**40.35** (11.38)	37.45 (11.32)	**40.20** (10.77)	38.28 (11.64)	< 0.001*
Negative Expectancy Total - Mean (SD)	**33.53** (11.53)	29.94 (10.15)	29.41 (10.16)	30.63 (8.17)	28.01 (8.77)	29.39 (8.42)	28.77 (9.59)	< 0.001*
Actual support (SD)	6.28 (2.03)	6.62 (2.16)	6.43 (2.14)	6.81 (2.24)	6.71 (1.89)	6.85 (2.07)	6.71 (2.32)	0.179
Action coping Mean (SD)	19.81 (4.64)	19.58 (4.83)	20.64 (4.63)	20.16 (4.79)	20.32 (4.345)	20.70 (4.57)	21.00 (5.06)	0.217
Cognitive coping - Mean (SD)	24.05 (5.90)	23.87 (5.49)	25.23 (5.17)	24.22 (5.27)	24.15 (4.89)	24.46 (4.83)	25.33 (4.89)	0.207
Emotional coping Mean (SD)	12.55 (3.75)	13.00 (3.74)	13.34 (3.76)	13.02 (3.53)	12.60 (3.44)	13.19 (3.22)	13.02 (2.92)	0.385
Region – N (%)								< 0.001*
1 Southern	60 (45.4)	105(**70**)	84(46.9)	169(**67.8**)	90(48.1)	145(59.4)	25(52)	
2 Northern	72	44	95	80	97	99	23	
Education– N (%)								< 0.001*
1	65(**50.8**)	73(**50.7**)	76(44.2)	122(50)	63(34.8)	98(42.4)	21(46.7)	
2	48(37.5)	51(35.4)	62(36)	86(35.2)	71(39.2)	80(34.6)	12(26.7)	
3	15(11.7)	20(13.9)	34(19.8)	36(14.8)	47(26)	53(22.9)	12(**26.7**)	
Income- N (%)								< 0.001*
1	77**65.3**)	69(51.5)	78(48.8)	124(54.1)	64(37.6)	101(44.7)	24(53.3)	
2	29 (24.6)	44(32.8)	49(30.6)	75(32.8)	65(38.2)	63(27.9)	12(26.7)	
3	12 (10.2)	21(15.7)	33(20.6)	30(13.1)	41(24.1)	62(**27.4**)	9(20)	
Living together (yes) N (%)	94(87)	105(89.7)	126(88.7)	172(86.9)	146(90.1)	165(87.8)	33(91.7)	0.298
Physical activity MEDIAN (1st/3rd Quartiles)	2271 (1251–3279)	2499 (1389–3651)	2511 (1563–3759)	2289 (1299–3699)	2541(1644–3510)	2151 (1371–3519)	2499 (1587–3759)	0.497
Fat intake - Mean (SD)	16.99 (5.03)	18.25 (5.40)	16.84 (6.15)	17.72 (5.70)	17.06 (5.62)	18.03 (5.85)	15.86 (6.66)	0.055
Attrition ≥ 3 missing final measures - N (%)	45**(34.1)**	42(28.2)	15(8.4)	33(13.3)	8(4.3)	12(4.9)	4(8.3)	< 0.001*

Except for the considerable overlap between trajectories 1 and A (both lower total AC classes) and the fact that latent class 'D' (light wine/beer drinkers) is mainly composed of the lower total AC classes trajectories (1, 2 and 3), the conditional distributions of the total AC latent trajectories on the beverage-extracted show that the AC trajectories are relatively jumbled over the beverages-specific classes. Associations between these latter and CVE (males only) are shown in Fig. 7. ORs were attenuated relative to the ones displayed in Fig. 5– note however, the increased odds for CVE for class D (Light wine/beer drinkers) when compared to F (Wine beer drinkers). Interestingly, the majority of the subjects of the latent class with the lowest CVE prevalence based on AC volume, trajectory 4, were beer and/or wine drinkers (trajectories C and F).

3.5. Ex-ante classes and CVE (prospective data only)

For comparative purposes, AC-CVE association was further scrutinised using customary ex-ante classes (≤ 1 glass/week; >1 or ≤7 g/w; >7 or ≤14 g/w; >14 or ≤34 g/w and >34 g/w). After computing subject-specific averages over the 5 annual measurements of total AC (thus only late life prospective data), males were assigned into one of these a priori defined categories. Fig. 8 illustrates the link between them and CVE as estimated by the multivariable logistic regression. Of relevance are the relative attenuation of ORs and the loss of the J-shape. Nonetheless, low AC class (>1 or ≤7 g/w glasses a week) showed a higher risk of CVE when compared to the traditional moderate one.

4. Discussion

This study explored the link between (self-reported) data on life-long alcohol exposure and CVE. All subjects were free of cardiovascular problems at the outset, reducing the chance of reverse causality bias regarding cardiac endpoints. Moreover, identified AC classes were data-driven, taking into account within individual subjects' variability of AC over time. The emerging AC-classifications did not require cut-off points of AC to be stipulated in advance, thereby avoiding fixed typologies. The AC-CVE link was investigated using aggregate and beverage-related measures, accounting for the uncertainty of class-membership and with adjustment for traditional CVE risk factors.

Both adverse and beneficial AC effects were observed for male drinkers. Those assigned to the cluster with the smallest CVE prevalence were characterized by stable and light to moderate life-long AC, from adolescence on. They were also beer and/or wine consumers, as in another recent study showing no differential effect of beverage type on heart failure risk [50]. Although they did not differ significantly from the high-prevalence CVE/low AC class in terms of educational level, they had a slightly higher average income. In general, the persistent low AC class with high CVE prevalence had a less advantageous socio-economic profile.

4.1. Caveats

The distinctiveness of the latent classes' profiles underscores the complex nature of the AC-CVE link. Interdependencies among risk factors impede a sifting out of alcohol's specific role. Despite

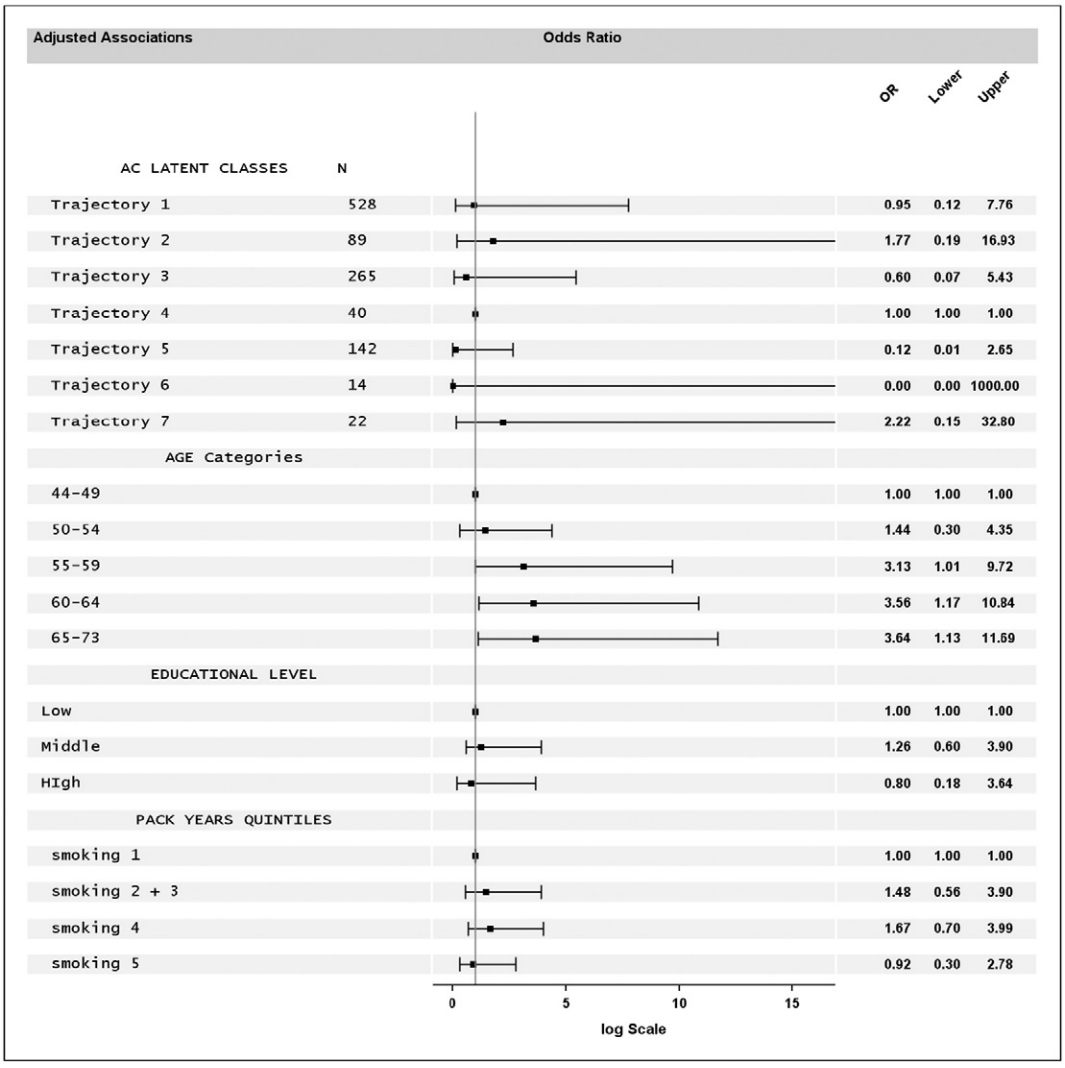

Fig. 4. Odds Ratios (OR) for CVE and 95% confidence intervals estimated by the multivariable logistic regression model weighted by subjects posterior probability of assignment – Females.

adjustment for important coronary risk factors in the multivariable model, we cannot rule out the possibility of residual confounding, especially concerning variables reflecting the wellness, mental health, self-perceived health and life-style behaviors. Alas, information on other clinically established CVE risk-factors (hypertension, cholesterol and diabetes) was not available. Therefore, the AC-CVE link could not be adjusted for them. However, because hypertension and hyperglycaemia are likely to be mediators in the causal paths between AC and CVE, correction for the latter risk factors is not uncontended. This could lead to over-adjustment in either direction. As for diabetes, the situation is different. However, research seems to indicate that, although absolute risk for CVE is higher among diabetics, the relative risks associated with AC are not different [51–52]. Further investigation of this is beyond the scope of this study, yet deserves attention in subsequent analyses.

Moreover, the observed AC changes failed to depict nuances or degrees of underlying AC fluctuations, for instance, the 4 early AC measures spanned over a period of ca. 4 decades. As such they were a coarse approximation of longitudinal alcohol exposure. Additionally, since the questionnaires are retrospective, recall bias cannot be ruled-out. More importantly, our findings reveal little about specific processes or mechanisms underlying the different patterns observed, i.e. which factors or sequences of events are associated with stability or change of AC over time. The higher average negative health expectancies observed in the lower latent class, together with its higher drop-out rate are coherent with the idea of Health selection, i.e. that reducing or ceasing AC is linked to a decline of perceived general health status [53]. Finally, the vast majority of the subjects were of Caucasian origin. In light of the ethnical differences in susceptibility to alcohol-induced heart damage, the external validity of our results is limited.

Regarding the statistics, data sparseness posed a problem, in particular for females. For a similar reason, we refrained from adding the class life-time abstainers to the males' multivariable models. Noticeably, however, the crude CVE prevalence was larger for female abstainers. Furthermore, GBTM fitting is a strenuous and lengthy procedure guided as much by formal criteria as by theoretical considerations and conceptual plausibility of the model. Despite the existence of statistical criteria to assist the process, there is no infallible rule to determine the ever evading 'right' model. Moreover, identified latent clusters are neither immutable nor fixed, true entities, but rather latent features of the data [36,44,54]. Readers should thus refrain from reifying these classes.

4.2. Insights gained

Our findings reiterate a few well-established standpoints: the male/female divide in drinking habits and CVE risk, the decrease and relative

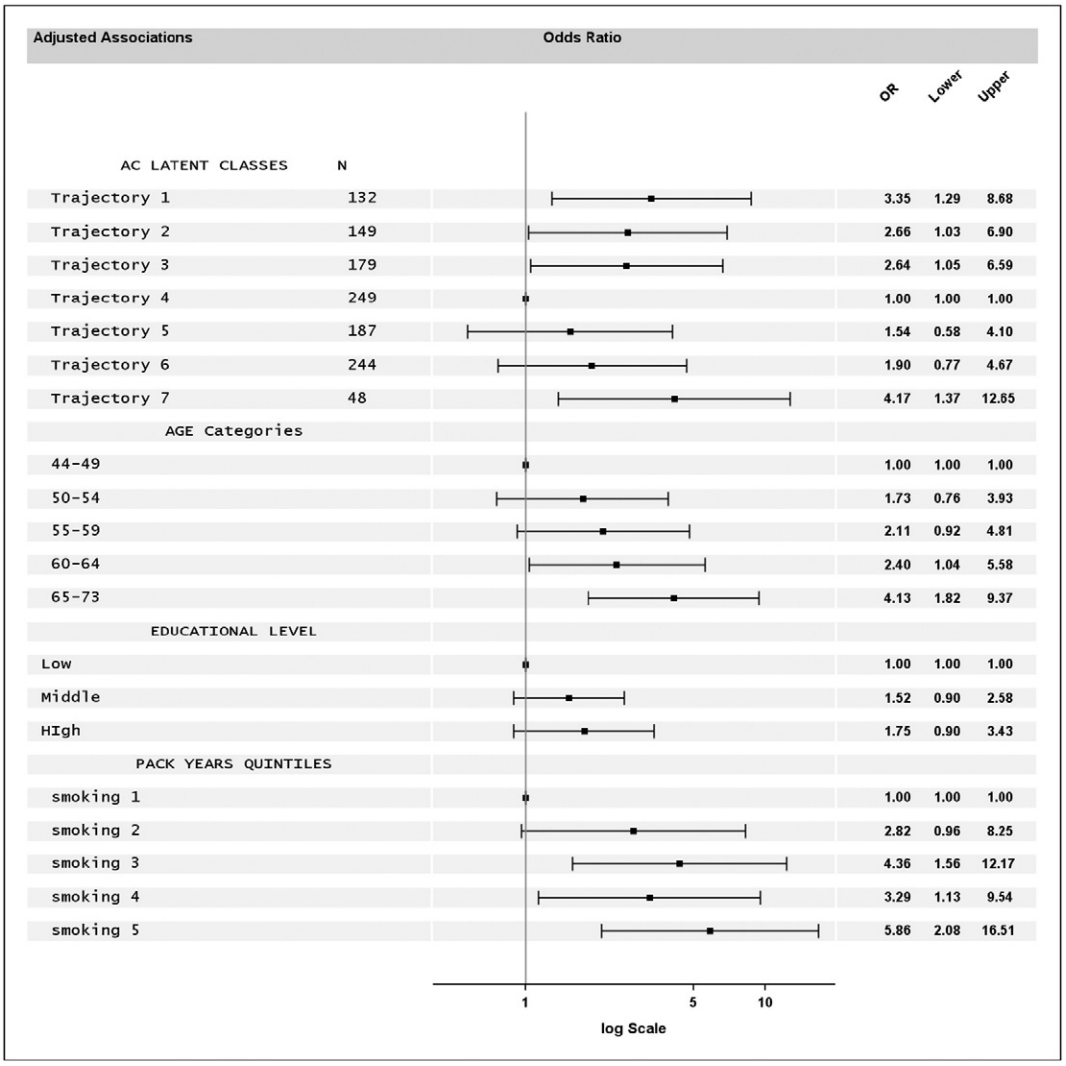

Fig. 5. Odds Ratios (OR) for CVE and 95% confidence intervals estimated by the multivariable logistic regression model weighted by subjects posterior probability of assignment – Males.

stability of AC in late years, contrasting with high diversity AC behavior during adolescence and young adulthood. Yet, despite the frailty of early-life AC operationalization, this developmental approach provided a fresh vantage point. Notably, GBTM analysis laid bare the heterogeneity of the inter-linkage between early and late-life AC. For ca. 40% of the sample, early onset levels directly reflected their AC in later life, consistent with previous findings [53,55]. However, for all other classes, the linkage between early and late life AC was less straightforward. Connections between the latent clusters based on composite/total AC and those based on the beverage types were also haphazard. Of note here was that beer and wine drinkers were assigned on equal measure to the lowest CVE prevalence category. Last but not least, analyses of the AC-CVE association per period separately (see supplemental material- appendix III) did not yield the same significant associations that were obtained when early and late AC were combined. It was only in the distinct patterns of interdependencies between the two life stages trajectories that differential links to CVE (for males) could be detected, underscoring the relevance of a life-long perspective.

Taken together, these curiosities reveal more than just a hint at AC cardio-protection. They also illustrate the perils of both proximal and static summary measures and of fixed a priori defined categories. For clarification: assigning subjects to ex-ante, deterministic AC classes led to an attenuation of the AC-CVE link. Similar attenuation was observed in the period-specific analyses. We go as far as to posit that the inconsistency between the ex-ante and period specific results on the one hand, and those of the life-course joint analyses, on the other, reflect to some extent the current state of affairs: the co-emergence of clashing empirical evidence, pro- [35,56,57] and contra-cardio-protection [58–61] that continue to feed the ongoing controversy. As we were able to show, such discrepancies may result from differences in AC operationalization.

The misgivings of AC classifications remain as relevant as ever, as shown by a recent paper on a dose-response meta-analysis of prospective studies on AC and risk of heart failure, and accompanying editorial [62–63]. Given the ex-ante and/or stationary nature of most current typologies, a problem that often surfaces is the misclassification bias, casting doubt on the use of the category abstainers or non-drinkers as the optimal reference group [63]. Nonetheless, because the links between AC and health outcomes are often captured by non-linear functions, Klatsky [63] underscores the importance of measuring AC categorically. The question of interest becomes then how to arrive at the AC classes that are neither static nor coarse as to mask the non-linearity or disregard temporal dependences of AC. We were able to show an alternative, data-driven and dynamic classification. The developmental categories herein described, though not immutable, may help to bypass a series of conceptual and methodological shortcomings of current AC labels.

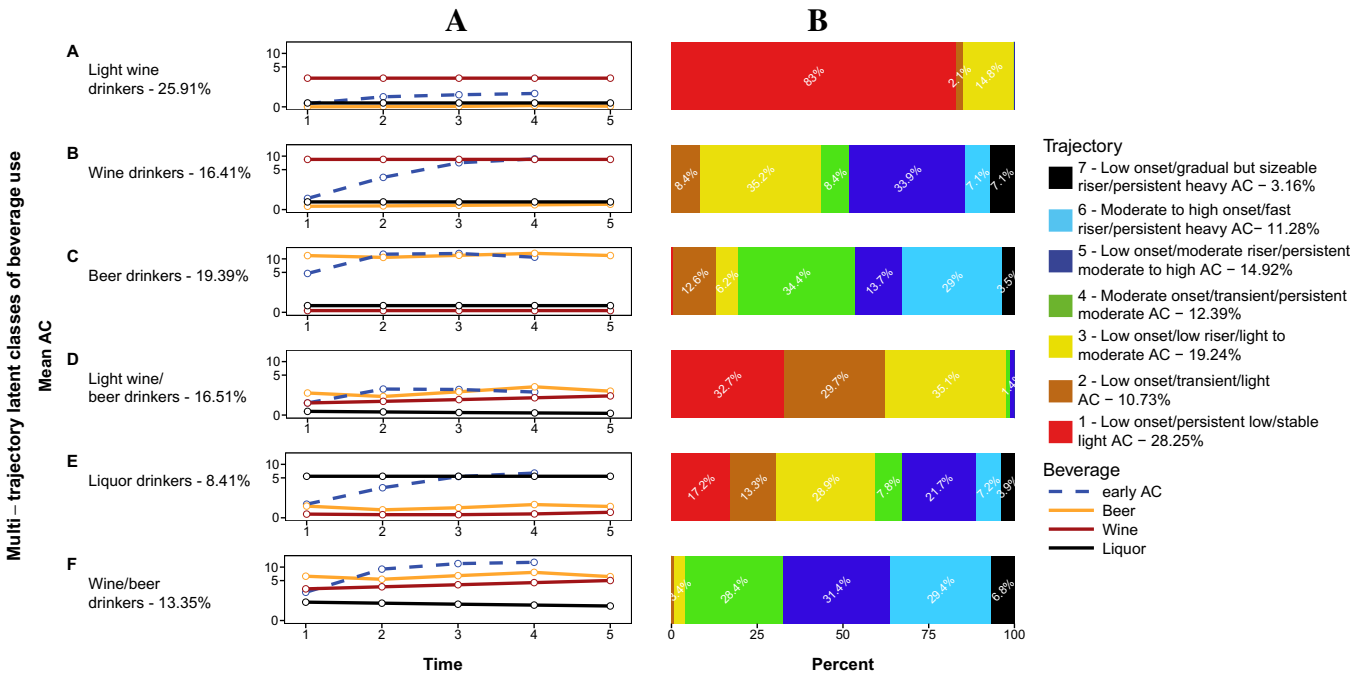

Fig. 6. A. Multi-trajectories latent classes (6 in total denoted A to F) showing interdependencies among beverage-specific AC in late life (solid lines) as well as their link to early total volume AC (dotted lines). AC is glasses/week. B. Conditional distributions of the total AC volume latent trajectories (1 to 7) within each extracted multi-trajectory class (A to F). The colours on the bar charts are the same as the AC trajectory colours displayed in Fig. 2.

Lastly, the current guideline for moderate consumption with its customarily applied cut-off points (7/8 to 14 glasses a week) may be in need of revision. Despite some overlap between the moderate ex-ante range of the late-life period and the estimated average AC for the cardio-protective trajectory, our data indicated that the upper boundary of 14 glasses could be on the high side.

4.3. Final remarks

The literature on the AC cardio-protection is vast and ever expanding. More recent takes on the issue strive to evade known methodological traps, e.g. a genetic approach (Mendelian randomization) [64] and randomized controlled trials (RCT). There is also a considerable effort to address the biological underpinnings of the cardio-protection, as given by an RCT on the effect of wine consumption on glucose and lipid profiles [65]; or by another recent RCT on the effect of moderate alcohol intake on cardiometabolic risk [66]. There can be little doubt that the thorny question remains which and how biological pathways triggered by moderate AC will ultimately induce (what kinds of) changes in cardiac geometry and function that are associated with favorable outcomes. Our current research design precludes the drawing of mechanistic explanations. General findings in epidemiological studies suggest that damage as well as protection by alcohol protection may be explained by two distinct mechanisms: one is an acute effect, occurring close to or immediately after ingestion; the other suggests additive effects of alcohol throughout the entire life. In the former case, lifelong exposure would matter very much. Damage or protection is independent of the time when exposure would occur. Example of the former is the known effect of alcohol on platelet aggregation, reducing the risk of an occlusion. Alternatively, when all alcohol use has an additive effect, the idea is that every

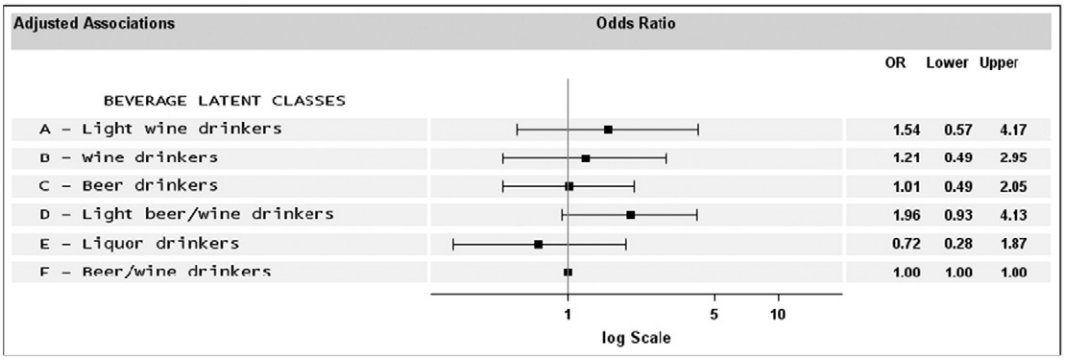

Fig. 7. Multi-trajectory latent classes odds Ratios (OR) for CVE with 95% confidence intervals. ORs were estimated by multivariable logistic regression models with adjustment for age, education and pack years, weighted by subjects' posterior probability of assignment – Males only.

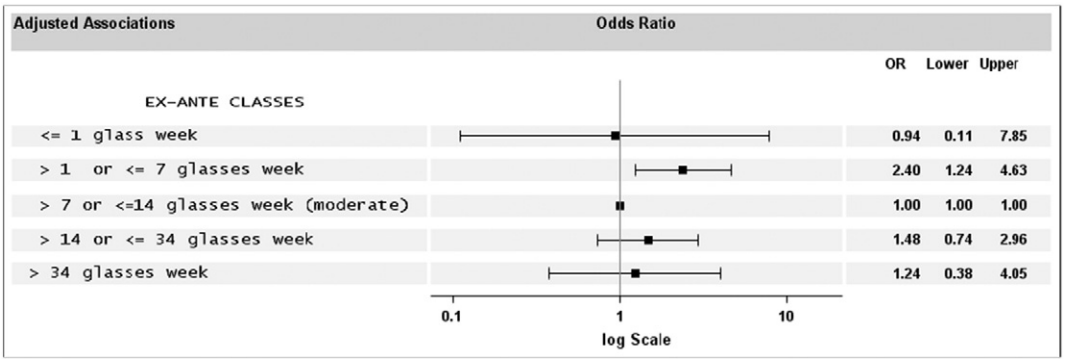

Fig. 8. Deterministic ex-ante classes odds Ratios (OR) for CVE with 95% confidence intervals. ORs were estimated by multivariable logistic regression models with adjustment for age, education and pack years – Males only.

drop has a noticeable effect on either risk or benefit, and overall exposure becomes relevant. An example would be the known effect of alcohol on cholesterol level (a higher' beneficial HDL, lower 'damaging' LDL). High cholesterol levels damage the arterial endothelium, and this is an additive process (atherosclerosis), already starting early in life, long before the person is faced with the grave consequences, and long before s/he is engaged in the cohort study.

Some of the trajectories that came up in this study (and population) can be typified as relatively flat throughout life, differing only in overall exposure. Others either rise or fall throughout life. This variation in trajectory opens the possibility to study the effects of alcohol beyond the two mechanisms described above. It is clear that in cohort studies the reference period over which alcohol consumption is assessed is usually rather short, leading to the assessment of the acute effects of alcohol. Retrospective measurement of lifetime exposure allows one to assess the additive effects of alcohol, yet independent of the time of exposure. Assessment of trajectories, as in this study, shows a much more varied assessment of risk. Multivariate longitudinal studies may enable one to tease out the time-dependency in risk due to AC and simultaneously investigate in more detail the induced changes in cardiac structure, function and associated biomarkers.

Irrespective of subclinical alterations in the heart's architecture that may underlie the assumed cardio-protection, the extracted patterns of AC progression suggest that moderation alone may not suffice. The results put a new spin on the elicited J-shape, drawing attention to the hitherto unsung facet of temporality, i.e. timing and duration, as well as relative steadiness of exposure.

This temporal dimension brings us to the DOHaD (developmental origins of health and disease), which conceptualizes health and disease through a life-course framework. DOHaD focus is on genetic predispositions, contextual changes and physiological processes operating in early development with consequences manifesting in later life [67]. Despite the lobby for DOHaD when tackling the AC-CVE link [68,69], the approach goes unheeded. The dynamics and heterogeneity of individual AC life-course are underexplored, partly because of the methodological and statistical challenges posed by life-long data. Accordingly, the DOHaD have been more readily entertained conceptually than applied in practice. The developmental paradigm is certainly ambitious. But it is also a viable option that will bring special attention to how time-varying health, social and economic conditions contribute to the dynamics of drinking behaviors [70–72]. The DOHaD could enable accounting for contextual and individual-level factors acting as potential shapers of AC developmental trajectories. Emerging statistical techniques can now be realistically aligned to this purpose. While they do not represent the solution for this conundrum, they do offer a methodological line of investigation meriting greater appreciation in the future.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2016.12.094.

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