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A new definition of early age at onset in alcohol dependence

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Abstract

Objective—The accurate cut-off of an early onset of alcohol dependence is unknown. The objectives of this analysis are (1) to confirm that ages at onset variability in alcohol dependence is best described as a two sub-groups entity, (2) to define the most appropriate cut-off, and (3) to test the relevancy of such distinction.

Method—Data were drawn the Epidemiologic Survey on Alcohol and Related Conditions (NESARC). This study focused on the 4,782 adults with lifetime alcohol dependence.

Results—The best-fit model distinguished two subgroups of age at onset of alcohol dependence, with a cut-off point at 22 years. Subjects with an earlier onset of alcohol dependence (< 22 years old) reported higher lifetime rates of specific phobia, antisocial behaviors and nearly all addictive disorders.

Conclusions—The early onset of alcohol dependence is best defined as beginning before the age of 22 years.

Keywords

NESARC; alcohol dependence; admixture test; DSM-V; age at onset

1. Introduction

Alcohol dependence and excess drinking are leading causes of morbidity and premature death (Di Castelnuovo et al., 2006), affecting 5.4% of the general population lifetime (Kessler et al., 2005). The age at onset of alcohol dependence varies widely, with a consistent peak at age 18–19 years old and then a rapid decline of onset after 25 years old (Li et al., 2004; Reich et al., 1998). The age at onset is an important characteristic of alcohol

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dependence in most of the existing typologies. These typologies diverge in the number of types as well as in the clinical variables included in their models, co-morbid addictive disorders or antisocial personality disorder being sometimes excluded. Despite this high variability and the lack of scientific validation of the definition of a specific threshold, age at onset of alcohol dependence continues to be included in most of alcohol dependence typologies. Indeed, early onset of alcohol dependence is associated with a family history of alcohol use disorders (Limosin et al., 2001), and some genetic markers may particularly (Edenberg et al., 2008) or specifically (Dahmen et al., 2005) contribute to an earlier onset of the disease. Furthermore, an early age at onset of alcohol dependence is associated with greater impulsivity, more severe dependence (Hingson et al., 2006b), and more severe and frequent alcohol withdrawal complications (Le Strat et al., 2008a). Finally, antisocial behaviors are the most consistent co-morbidity associated with an early onset of alcohol dependence (Kuperman et al., 2005; McGue et al., 2001). These studies have several limitations. For example, they use an arbitrary cut-off, often defined on the basis of clinical rather than epidemiological sample. They also rely on a single distribution model, which might not be appropriate for age-at-onset data (Mayberg et al., 2005). Moreover, some of these studies are based on the age at onset of usual alcohol consumption whereas the onset of alcohol dependence might be clinically more relevant.

The aim of our study is to discover the appropriate model for age at onset distribution by using data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Particularly, we examine whether there is a mixture of overlapping age at onset distribution that defines more homogenous sub-groups of alcohol dependent patients. An additional goal of this study is to examine sociodemographic and mental disorders associated with an early onset of alcohol dependence.

2. Methods

2.1 Participants

Subjects were participants in NESARC, a nationally representative face-to-face survey of 43,093 respondents aged 18 years and older (response rate, 81%), conducted by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in 2001–2002. The NESARC assessed the civilian non-institutionalized population residing in the United States. African-Americans and Hispanics were oversampled, as were young adults. The research protocol, including informed consent procedures, received full ethical review and approval from the US Census Bureau and the Office of Management and Budget.

2.2 Measures

The NESARC used the National Institute on Alcohol Abuse and Alcoholism's Alcohol Use Disorder and Associated Disabilities Interview Schedule DSM-IV version (AUDADIS-IV), a structured diagnostic interview made for non-clinician interviewers (Gorwood, 2003). Algorithms were designed to produce diagnoses of alcohol dependence consistent with the final DSM-IV criteria. Several studies have documented good to excellent retest reliability (Grant et al., 1995).

Mood and anxiety disorders included in the survey were panic disorder, agoraphobia, specific phobia, social phobia, generalized anxiety disorder, major depressive episode and manic episode. All mood and anxiety diagnoses were primary or independent, e.g they excluded disorders that were substance-induced or due to a general medical condition. Lifetime history of suicide attempt, antisocial personality disorder (ASPD) and conduct disorder, as well as lifetime addiction - including pathological gambling, nicotine dependence, cannabis, cocaine, opioid, amphetamine, solvent, tranquilizer, sedative, hallucinogen and heroin abuse or dependence - were all assessed through the AUDADIS-IV and defined by DSM-IV criteria. Sex, age, race/ethnicity, educational level, marital status, income, urbanicity and region were used as covariates in the analyses. Age at interview was categorized into 4 groups: (1) 18–29 years, (2) 30–44 years, (3) 45–64 years and (4) 65 years and older. Race/ethnicity was categorized into 5 groups: (1) white, (2) black, (3) American Indian/Alaska Native, (4) Asian Native Hawaiian/Pacific Islander and (5) Hispanic/Latino. Educational level distinguished 3 groups: (1) less than high school, (2) high school graduate and (3) some college or higher. Marital status was classified in 4 groups (1) married or living common-law, (2) widowed, (3) divorced or separated and (4) never married. Household income was between (1) \$0–\$19,999, (2) \$20,000–\$34,999, (3) \$35,000–\$59,999 and (4) \$60,000 or greater.

Information on family history of first and second degree relatives was elicited for each relative separately by asking whether any of the relatives had been an alcoholic or problem drinker, defined as a person who has physical or emotional problems because of drinking, problems at work of school because of drinking, problems with the police because of drinking-like drunk driving, or a person who seems to spend a lot of time drinking or being hungover.

2.3 Data analysis

The age at onset distribution was investigated with the maximum likelihood estimation of the finite normal mixture (Kolenikov). We tested multiple mixture models with increasing number of theoretical components and assessed whether this increase improve the fit by using Akaike's information criterion (AIC) of parsimony. We also computed the Log likelihood value (LLH) for each model, with $AIC = -2 * \log\text{-likelihood} + 2 * k$, where k is the number of estimated parameters. We then defined age at onset cut-off points by adding or subtracting one standard deviation from the estimated mean of the theoretical component distribution, following a method described elsewhere (Lin et al., 2006).

According to these results, we divided the sample into subgroups of homogeneous ages at onset. Distributions of sociodemographic and clinical correlates of the subgroups were compared using chi-square. The odds ratio and confident intervals were estimated through a logistic regression. Sociodemographic covariates in the regressions included age at interview, race, marital status, educational level, household income, level of urbanicity and region. The appropriate statistical weight was employed when mentioned to ensure the data were representative of the population.

3. Results

At some point in their lives, 4782 participants of the NESARC sample met DSM-IV alcohol dependence criteria. Of these, age at onset was available for 4697 (99.6%). Admixture analysis decompounded the observed distribution of age at onset into a mixture of several normal theoretical distributions. The best-fitting model in terms of AIC had two components with a mean (SD) of 19.6 (S.D= 2.7) and 32.9 (S.D= 10.2) years (Table 1).

Since patients with ASPD have a highly specific pattern of disorder and co-morbidity, and typically have a very young age at onset, antisocial personality disorder could be a confounding factor. Therefore, we performed another admixture analysis excluding subjects with ASPD. No significant difference was detected, either for the number of clusters or the threshold distinguishing them (Table 4).

We obtained one cut-off point at 22 years, corresponding to the mean age at onset of the younger group plus one standard deviation as well as to the mean age at onset of the late onset group minus one standard deviation. The early onset group, comprising subjects with age at onset 22 years or less, represents 58% of the sample, whereas the late onset group represents 42% of the sample (Figure 1).

The sociodemographic correlates of early onset of alcohol dependence are presented in Table 2. Alcohol dependent men exhibit a higher proportion of early onset alcohol dependence. Black ethnic group had decreased odds of early onset of alcohol dependence. Being widowed, divorced or separated was associated with significantly decreased odds of early onset, whereas being never married was associated with significantly increased odds of early onset when compared with married /common-law individuals.

Panic disorder, major depressive episode and pathological gambling were associated with later onset of alcohol dependence when sociodemographic factors were not controlled for (Table 3), but were not significantly involved anymore when corrected for sociodemographic factors. Conversely, ASPD and conduct disorders, cannabis, amphetamine, solvent, tranquilizer, sedative and hallucinogen use disorders were more frequent in subjects with an earlier onset of alcohol dependence, the crude odds-ratio being close to the ones adjusted for socio-demographic factors.

Specific phobia was the only mental disorder still associated with an early onset of alcohol dependence among alcohol dependent subjects, when controlled for sociodemographic factors (Table 3). Opioid use disorder and pathological gambling were the sole addictions that were not associated with an early onset of alcohol dependence when adjusting for sociodemographics factors. A positive history of alcohol related problems was also associated with an early onset of alcohol dependence.

4. Discussion

This study ascertains the validity of a two solution factor of age at onset in alcohol dependence. Particularly, the age at onset of alcohol dependence can be decomposed by admixture analysis into two normal distributions, with a cut-off at 22 years. Our finding is in

line with previous researches, which suggest that the cut-off between early and late onset groups should range between 19 and 25 years (Buydens-Branchey et al., 1989; Hingson et al., 2006a). This is the first study to examine whether the age at onset distribution in alcohol dependence is a mixture of several normal distributions. This approach was previously used successfully in bipolar type I affective disorder, in schizophrenia (Schurhoff et al., 2004), as well as in obsessive compulsive disorder (Delorme et al., 2005) and suicide attempt (Slama et al., 2009). The size of the epidemiological sample studied herein is large, and even more important, the NESARC is a national representative sample using a well validated interview, whereas previous studies using admixture test to examine the distribution of age at onset relied on relatively small and clinical samples.

The relationships between socioeconomic status, educational levels and alcohol consumption are complex. Particularly, while lower socioeconomic status is associated with a higher risk of alcohol dependence, our findings suggest that, among alcohol dependent subjects, individuals with the highest income have a younger age at onset of dependence. Others found no difference in socioeconomic status between subjects with early versus late onset substance use disorder (Clark et al., 1998). Considering the educational level, the literature raised contradictory findings, since a 10 years prospective follow-up study found that subjects with the highest educational level have the lowest risk of alcohol dependence (Harford et al., 2006), while another 5 years prospective work, men with the highest educational level exhibit the greatest increase in at-risk drinking from grade 12 to adulthood (Bingham et al., 2005). In the NESARC, we found that educational level is associated with an early age at onset among alcohol dependent subjects. Taken together, these findings suggest that socioeconomic and educational achievement may have protective effects against the development of alcohol dependence in general and in particular against the late onset form.

The main clinical correlates of the early onset class of alcohol dependence were specific phobia, antisocial behaviors and most of substance use disorders. The finding that specific phobia is the only mental disorder associated with an early onset of dependence among alcohol dependent subjects is unexpected. Nevertheless, specific phobia was associated with an increased risk of alcohol lifetime alcohol dependence (adjusted O.R 2.7, CI: 2.41–3.02) (Stinson et al., 2007), this risk being highly comparable with the one associated with social phobia (adjusted OR: 2.7, CI:2.36–3.20) (Stinson et al., 2007) or generalized anxiety disorder (adjusted OR: 2.8, CI:2.46–3.24) (Grant et al., 2005). The association of specific phobia with an early onset of alcohol dependence may also be related to the early age at onset of specific phobia in the NESARC (mean 9.1 years) (Stinson et al., 2007). Indeed, the age at onset of the comorbid disorder is a plausible confounding factor, since individuals with an early onset of mental disorders exhibit early alcohol consumption and usually have an early age at interview. Therefore, the fact that social phobia is the sole mental disorder associated with an early alcohol dependence could be related to the observation that specific phobia is the mental disorder with the earliest age at onset. Furthermore, the temporal sequencing of specific phobia and alcohol dependence is unusual among anxiety and mood disorders, since specific phobia, like social phobia, often precedes alcohol dependence whereas alcohol dependence is temporally primary to all other disorders, including panic disorder, general anxiety disorder, dysthymia, major depression, and mania/hypomania.

Other axis I disorders, including mood and anxiety disorders were not associated with an early age at onset of alcohol dependence. This finding is consistent with the fact that most historical and contemporary classifications of alcohol dependence do not include psychiatric disorders.

Consistent with the existing literature, early onset of alcohol dependence was associated with antisocial disorders. Schuckit and Irwin indeed proposed that one type of alcohol dependence (Cloninger's type II) is characterized mainly by antisocial behaviours more than by alcohol related symptoms (Schuckit and Irwin, 1989). Alcohol dependent patients with an early onset of dependence are more likely to have impaired decision making, higher impulsivity, even when controlled for comorbid drug abuse and age at interview (Dom et al., 2006). These characteristics are partially underlied by genetic factors (for a more complete review, see (Kreek et al., 2005)). The fact that the bimodal distribution of ages at onset of alcohol dependence is maintained, with a non significantly different cut-off, when excluding all patients with antisocial personality disorder, is pleading against the hypothesis that Cloninger's type II is mainly explained by antisocial personality disorder. Furthermore, the direct evidence (e.g. without correcting for confounding factors) of early versus late onset of alcohol dependence reinforce these two classifications regarding co-morbidity, with more anxious and mood disorders in the later onset group, and more ASPD, familial history of alcohol dependence and addictive disorder's co-morbidity in the younger age at onset group. Our study has several limitations.

First of all, the method used to choose a cut-off is somehow arbitrary. We followed a methodology described by Lin et al., using points of rarity in the observed age at-onset distribution (Lin et al., 2006), but the use of another methodology could have led to another result. An important point is that our cut-off at 22 years separates the sample into two groups of identical distribution, and correctly classify two third of each group, thus reducing the risk of misclassification in each group. Moreover, the exclusion of subjects with ASPD did not modify our results, thus arguing that the two groups do not differ solely on the presence or absence of an ASPD.

A second restriction is the use of a retrospective measure to assess age at onset of alcohol dependence, which raises concern about the accuracy of these data. In that view, a replication of our findings in a prospective sample is required. Noteworthy, we also used the age at interview as a confounding variable in the logistic regression analyses, thus controlling for its effects.

A third limitation is that AUD assessed family history with information elicited from the respondent, rather than by direct interview. However, methodological research has shown that alcohol dependence can be as validly measured from information from family members as from the relatives directly (Andreasen et al., 1986).

Several studies used age at onset of alcohol dependence as a putative biological marker (Apprey et al., 2005; Le Strat et al., 2008a; Tayo et al., 2005; Zhong and Zhang, 2005). Particularly, age at onset could be genetically mediated, since genetic factors account for 49% of the variation in the age at onset of alcohol dependence (Liu et al., 2004). Moreover,

the relationships between alcohol dependence and other addictive disorders are complex and involve several biological and clinical interactions (Funk et al., 2006; Ribeiro-Carvalho et al., 2008). Addictive disorder probably have in common neurobiological pathway (Ribeiro-Carvalho et al., 2008), and share part of the involved genetic and environmental influences to initiation (Xian et al., 2008), the development of a dependence (Kendler et al., 2008; Le Strat et al., 2008b) as well as the cessation of the disorders (McKee et al., 2008).

Accordingly, the consideration of a more genetically homogenous subgroup of patients defined by the age at onset of alcohol dependence earlier than 22 years old, and characterized by a higher rate of addictive comorbidities could be meaningful.

The clinical relevance of this cut-off must be assessed. In absence of prospective study, we may only hypothesize that patients with an early onset of alcohol dependence (earlier than 22 years old) will have a worst prognosis. In the literature, as mentioned, retrospective studies found that an early age at onset of alcohol dependence is associated with greater impulsivity, a more severe dependence (Hingson et al., 2006b), and more severe and frequent alcohol withdrawal complications (Le Strat et al., 2008a). This prognosis is even worsened by more frequent addictive comorbidities. Clinicians usually perform screening tests for other addictions when treating a patient with alcohol dependence. This assessment may be particularly relevant if the patient has an early onset disorder.

In summary, we found that the distribution of age at onset in alcohol dependence revealed two subgroups of patients. The optimal cut-off of age at onset of alcohol dependence in this sample is 22 years, which correctly classified two thirds of each group. Future typologies, including DSM-V, could take this cut-off into account in order to improve their accuracy, when efficacy and specificity rather than sensitivity is the priority, for examples in order to matched treatment or in the analysis of complex markers.

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Figure 1. Observed single normal distribution (—) and theoretical two component mixture distribution (.....) of age at onset of alcohol dependence in the 4697 alcohol-dependent participants of the NESARC sample.

Table 1

Fit of mixture models with different components

Model	Number of the component	Characteristics of the model			AIC	LLH
		Mean	S.D	S.E		
One component	1	24.7	9.3	0.13	3.4*10 ⁴	-1.714*10 ⁴
Two components	1	19.6	2.7	0.06	3.1*10 ⁴	-1.567*10 ⁴
	2	32.9	10.2	0.35		
Three components	1	19.0	2.3	0.1	3.1*10 ⁴	-1.558*10 ⁴
	2	24.8	4.7	0.7		
	3	36.4	10.7	0.8		
Four components	1	18.7	2.1	0.11	3.1*10 ⁴	-1.555*10 ⁴
	2	22.4	4.0	0.7		
	3	33.5	8.3	1.0		
	4	55.3	8.7	5.5		

AIC: Akaike information criteria; LLH, Log likelihood value

Table 2

Sociodemographic correlates among people with alcohol dependence

Sociodemographic variables	Early onset class (≤ 22 years) ^a		Late onset class (>22 years) ^a		Odds ratio (95% CI) ^b
	N	%	N	%	
Sex					
Female	1007	32.5	783	35.3	1.00
Male	1709	67.5	1197	64.7	1.11 (0.98–1.25) *
Race/ethnicity					
White	1920	80.1	1249	75.6	1.00
Black	257	5.5	358	10.4	0.46 (0.39–0.55) ****
American Indian/Alaska native	81	3.5	51	3.1	1.03 (0.72–1.47)
Asian/Native Hawaiian/Pacific	59	2.4	28	1.7	1.37 (0.87–2.16)
Islander					
Hispanic/Latino	399	8.5	294	9.1	0.88 (0.75–1.04)
Age					
18–29	1126	43.2	202	10.2	1.00
30–44	1030	36.9	782	39.9	0.24 (0.20–0.28) ****
45–64	485	17.7	813	41.9	0.10 (0.09–0.13) ****
65+	75	2.1	183	7.9	0.07 (0.05–0.10) ****
Educational level					
Less than high school	61	2.3	107	4.4	1.00
High school graduate	962	35.4	794	40.9	2.12 (1.53–2.95) ****
Some college or higher	1693	62.3	1079	54.7	2.75 (1.99–3.80) ****
Marital status					
Married /common-law	1221	52.0	921	57.1	1.00
Widowed	36	0.7	106	4.0	0.26 (0.17–0.38) ****
Divorced or separated	380	10.1	578	22.9	0.50 (0.42–0.58) ****
Never married	1079	37.2	375	16.0	2.17 (1.88–2.51) ****
Income					

Sociodemographic variables	Early onset class (≤ 22 years) ^a		Late onset class (>22 years) ^a		Odds ratio (95% CI) ^b
	N	%	N	%	
\$0–\$19,999	644	19.4	497	20.1	1.00
\$20,000–\$34,999	573	19.9	445	21.0	0.99 (0.84–1.18)
\$35,000–\$59,999	680	26.3	509	27.0	1.03 (0.87–1.21)
\$60,000 or greater	819	34.4	529	31.9	1.19 (1.02–1.40)**
Urbanicity					
Urban	935	28.5	741	31.0	1.00
Rural	1781	71.5	1239	69.0	1.14 (1.01–1.28)**
Region					
Northeast	436	16.8	303	16.3	1.00
Midwest	765	29.8	465	24.7	1.14 (0.95–1.38)
South	764	28.0	638	30.5	0.83 (0.69–1.00)**
West	751	25.3	574	28.5	0.91 (0.76–1.10)

^a Numbers are unweighted values, percentages are weighted values.

^b Reference group is individuals with late onset (>22 years old) alcohol dependence. Boldface type indicates significance.

* $p < 0.1$.

** $p < 0.05$.

*** $p < 0.01$.

Table 3

Clinical correlates among people with alcohol dependence

Mental disorder	Early onset class (≤22 years) ^a		Late onset class (>22 years) ^a		Crude Odds ratio (95% CI)	Adjusted Odds ratio (95% CI)
	N	%	N	%		
Lifetime Mental disorders						
Panic disorder	226	8.0	199	10.4	0.81 (0.66–0.99) **	0.98 (0.78–1.22)
Agoraphobia	10	0.4	10	0.7	0.73 (0.30–1.75)	1.22 (0.47–3.18)
Specific phobia	507	18.5	324	16.5	1.17 (1.00–1.36) **	1.26 (1.06–1.50) **
Social Phobia	280	10.6	202	11.5	1.01 (0.84–1.22)	1.13 (0.91–1.40)
Generalized anxiety disorder	238	8.2	204	10.0	0.84 (0.69–1.02)	1.06 (0.86–1.33)
Major depressive episode	906	30.7	722	35.9	0.87 (0.78–0.98) *	0.95 (0.82–1.10)
Manic disorder	319	10.4	210	11.5	1.22 (0.93–1.35)	1.03 (0.84–1.28)
Suicide attempt	214	13.4	156	14.6	0.93 (0.74–1.12)	0.90 (0.70–1.15)
Antisocial disorders						
ASPD	466	16.5	192	11.0	1.93 (1.61–2.30) **	1.86 (1.53–2.27) **
Conduct disorder without ASPD	58	1.9	20	1.0	2.14 (1.28–3.57) **	1.89 (1.09–3.29) *
Lifetime addiction						
Nicotine dependence	1324	48.8	924	49.6	1.09 (0.97–1.22)	1.22 (1.07–1.40) **
Cannabis use disorder	1032	37.9	489	26.2	1.87 (1.64–2.12) **	1.67 (1.45–1.93) **
Cocaine use disorder	405	13.5	264	14.2	1.14 (0.96–1.24)	1.26 (1.05–1.51) *
Opioid use disorder	27	1.2	24	1.0	0.82 (0.47–1.43)	0.84 (0.45–1.56)
Amphetamine use disorder	316	11.5	162	8.4	1.48 (1.21–1.80) **	1.72 (1.38–2.14) **
Solvent use disorder	70	2.2	17	1.1	3.05 (1.78–5.20) **	3.23 (1.82–5.73) **
Tranquilizer use disorder	160	5.6	75	4.3	1.59 (1.20–2.15) **	1.84 (1.35–2.50) **
Sedative use disorder	174	6.3	75	4.3	1.74 (1.32–2.30) **	2.11 (1.56–2.85) **
Hallucinogen use disorder	312	11.5	91	4.8	2.70 (2012–3.43) **	2.34 (1.80–3.04) **
Heroin use disorder	45	1.2	31	1.1	1.57 (0.93–2.65)	3.07 (1.73–5.44) **

Mental disorder	Early onset class (≤ 22 years) ^a		Late onset class (>22 years) ^a		Crude Odds ratio (95% CI)	Adjusted Odds ratio (95% CI) ^{b,c}
	N	%	N	%		
Pathological gambling	41	1.1	49	2.4	0.60 (0.40–0.92) *	0.78 (0.49–1.25)
Family history of alcohol problem						
Positive history	2054	75.8	1509	76.6	0.97 (0.84–1.11)	1.20 (1.02–1.40) *

ASPD, antisocial personality disorder.

* $p < 0.05$.

** $p < 0.01$

^a Numbers are unweighted values. Percentages are weighted values.

^b Reference group is individuals with late onset (>22 years old) alcohol dependence. Boldface type indicates significance.

^c Adjusted for sociodemographic variables (sex, race/ethnicity, age, educational level, marital status, income, urbanicity, region).

Table 4
Fit of mixture models with different components in alcohol dependent subjects without antisocial personality disorder.

Model	Number of the component	Characteristics of the model			AIC	LLH
		Mean	S.D	S.E		
One component	1	25.2	9.5	0.1	3.0*10 ⁴	-1.482*10 ⁴
Two components	1	21.9	5.5	0.1	2.8*10 ⁴	-1.411*10 ⁴
	2	43.2	5.5	0.3		
Three components	1	21.9	5.5	0.2	2.8*10 ⁴	-1.375*10 ⁴
	2	37.8	4.3	0.3		
	3	43.2	5.5	0.3		
Four components	1	20.2	3.3	0.1	2.8*10 ⁴	-1.375*10 ⁴
	2	31.9	3.3	0.3		
	3	42.9	3.3	0.3		
	4	59.3	3.3	0.5		

AIC, Akaike information criteria; LLH, Log likelihood value