

Alcohol use disorder

No. 2018/23E, The Hague, December 17, 2018

Backgrounddocument to:

Alcohol en hersenontwikkeling bij jongeren [in Dutch]

No. 2018/23, The Hague, December 17, 2018

Health Council of the Netherlands



contents

01	Introduction	3	05	Discussion and conclusions	24
02	Methods	5	5.1	Limitations	25
2.1	Identification and quality appraisal of longitudinal studies	6	5.2	Final conclusions	25
2.2	Data extraction and data synthesis	6		Literature	26
03	Outcomes	8		Annex	30
04	Results	10	A	Search strategy	31
4.1	Summary of study characteristics	11			
4.2	Frequency or quantity of alcohol consumption and alcohol use disorder	14			
4.3	Conclusions for frequency or quantity of alcohol consumption and alcohol use disorder	18			
4.4	Age of onset of alcohol use and alcohol use disorder	18			
4.5	Conclusions for age of onset of alcohol use and alcohol use disorder	21			



01 introduction



This background document forms an integral part of the advisory report on Alcohol and Brain Development in Adolescents and Young Adults. In this document the peer-reviewed scientific evidence is described on the association between alcohol consumption during adolescence and young adulthood (age range 12-24 years) and alcohol use disorder later in life.

In scientific literature, there is much interest in the later life consequences of adolescent alcohol use.^{1,2} McCambridge et al. (2011) performed a systematic review (SR) of prospective cohort studies about the adult (≥ 20 years of age) consequences of late adolescent (15-19 years of age) alcohol use, with at least three years of follow-up, based on publications up to and including 2008.¹ The authors identified 54 publications, 35 of which were judged as vulnerable to bias, based on sample size ($n < 1,000$), the inadequacy of control for confounding, and follow-up of participants ($< 80\%$). There was a large overlap in study samples; the identified 54 publications were based on 17 study samples (cohorts). Meta-analyses of the findings were not performed as the authors judged this inappropriate because of the potentially misleading nature of such summary effect estimates in the context of uncontrolled bias and confounding, and the heterogeneity of the studies. The authors concluded that there is consistent evidence that higher alcohol consumption in late adolescence continues into adulthood and is also associated with alcohol problems, including dependence. The existing evidence for adult physical and

mental health and social consequences was of insufficient quality to warrant causal inferences.¹

Maimaris and McCambridge (2014) performed an SR on the association between the age of first drink in relation to adult alcohol problems.² The authors included studies conducted before January 2013. Studies which defined age of first drink (AFD) as the age at which a participant had a first drink of more than a few sips of alcohol were included, while studies which assessed only the age of first intoxication or the initiation of regular drinking were excluded. Only cohort studies comprising general population samples were included, with a requirement of at least three years follow-up between the initial measurement of AFD in adolescence and the assessment of alcohol-related outcomes. Based on five studies (four study samples), Maimaris and Cambridge² concluded that there is some evidence for an association between AFD and alcohol dependence (AD), but this disappears with more rigorous control for confounding. The authors also mention that overadjustment is a point of concern, because peer variables may lie on the causal pathway to adult outcomes as well as being implicated in earlier AFD.

The focus of this background document is to update the totality of evidence regarding the role of alcohol consumption in relation to the risk of adult alcohol use disorder (AUD). The committee, therefore, systematically searched for peer-reviewed longitudinal studies on the association between alcohol use during adolescence or young adulthood and alcohol use disorder in later life.



02 methods



2.1 Identification and quality appraisal of longitudinal studies

The background document 'Methodology for the evaluation of the evidence' provides an extensive description and explanation of the methodology. In short, this SR includes longitudinal studies of alcohol consumption by adolescents or young adults in relation to the risk of alcohol use disorder in later life (see Annex for search strategy).

Published articles (in English) up to and including May 2018, were retrieved from Pubmed and PsychINFO, complemented by hand searches of reference lists, correspondence with researchers in the field and two SRs about adolescent alcohol use and adult outcomes that covered the literature until 2013² and 2008¹ respectively.

Studies about the acute effects of alcohol were excluded. Study samples of specific subgroups (e.g. subjects with ADHD or speech and language impairment, patients in drug clinics, patients with bipolar disorder) were also excluded. To be included, the studies needed to have data on alcohol exposure (independent^a of other substance use). For example, the committee excluded studies in which only the combined use of marijuana and alcohol was studied. Studies based on retrospective data regarding alcohol consumption were similarly excluded.³⁻⁸

The committee excluded two studies^{9,10} because of overlapping data with a more recent and larger study.¹¹ The study by Mason et al. (2010)¹² was

^a With 'independent' we refer to a design and statistical analyses that were intended to study alcohol exposure not combined with the use of other substances. In addition, (residual) confounding by other factors related to alcohol exposure as well as the study outcomes can never be completely ruled out in observational studies.

excluded, because later studies based on the same cohort^{13,14} used a longer follow-up time and a larger number of participants. The committee excluded the study by Keyes 2007,¹⁵ because a more recent analysis of this cohort (Minnesota Twin Family Study) was available.¹⁶ The study completed by Trim et al., 2009⁵ was excluded because of overlapping data with the study by Schuckit and Smith 2011.¹⁷ In total, this resulted in 23 studies.

The risk of bias in the studies was assessed with the Newcastle Ottawa Scale. The NOS rating system scores studies from 0 (highest degree of bias) to 9 (lowest degree of bias). Scoring was based on consensus between researchers of a research bureau and one of the two scientific secretaries. The committee judged studies with an NOS score of 7 or higher, with at least adjustment for confounding, to be of sufficient quality.

2.2 Data extraction and data synthesis

Studies were extracted using structured extraction forms which included information on the study population, measurement and grouping of exposure and outcomes measures, statistical analysis (including covariates, stratification or matching factors, and correction for multiple testing), results, limitations and funding. All relevant exposure and outcome measures were extracted. The results reported in this background document were based on the most extensive statistical models, in terms of adjustment. First, studies were grouped according to the measure of alcohol consumption: amount or frequency of alcohol



consumption, and age of first drink and early drinking. Studies that were based on the same cohort were clustered as well.

All studies will be briefly discussed one by one in terms of study sample, NOS score, baseline drinking status, and baseline differences of the outcomes (which is part of the NOS). The studies of sufficient quality (see Section 2.1) as judged by the committee will be discussed first, followed by the remainder of the evidence. Conclusions are primarily based on the studies of sufficient quality, while the results of the studies with lower NOS scores are used as ancillary material.



03 outcomes



The outcome alcohol use disorder comprised studies with alcohol abuse, alcohol dependence (addiction), or alcohol use disorder (AUD) as outcomes. Symptoms of these outcomes are listed in figure 1.

A Comparison Between DSM-IV and DSM-5

DSM-IV		DSM-5	
In the past year, have you:		In the past year, have you:	
Any 1 = ALCOHOL ABUSE	Found that drinking—or being sick from drinking—often interfered with taking care of your home or family? Or caused job troubles? Or school problems?	1	Had times when you ended up drinking more, or longer, than you intended?
	More than once gotten into situations while or after drinking that increased your chances of getting hurt (such as driving, swimming, using machinery, walking in a dangerous area, or having unsafe sex)?	2	More than once wanted to cut down or stop drinking, or tried to, but couldn't?
	More than once gotten arrested, been held at a police station, or had other legal problems because of your drinking? **This is not included in DSM-5**	3	Spent a lot of time drinking? Or being sick or getting over other aftereffects?
	Continued to drink even though it was causing trouble with your family or friends?	4	Wanted a drink so badly you couldn't think of anything else? **This is new to DSM-5**
Any 3 = ALCOHOL DEPENDENCE	Had to drink much more than you once did to get the effect you want? Or found that your usual number of drinks had much less effect than before?	5	Found that drinking—or being sick from drinking—often interfered with taking care of your home or family? Or caused job troubles? Or school problems?
	Found that when the effects of alcohol were wearing off, you had withdrawal symptoms, such as trouble sleeping, shakiness, restlessness, nausea, sweating, a racing heart, or a seizure? Or sensed things that were not there?	6	Continued to drink even though it was causing trouble with your family or friends?
	Had times when you ended up drinking more, or longer, than you intended?	7	Given up or cut back on activities that were important or interesting to you, or gave you pleasure, in order to drink?
	More than once wanted to cut down or stop drinking, or tried to, but couldn't?	8	More than once gotten into situations while or after drinking that increased your chances of getting hurt (such as driving, swimming, using machinery, walking in a dangerous area, or having unsafe sex)?
	Spent a lot of time drinking? Or being sick or getting over other aftereffects?	9	Continued to drink even though it was making you feel depressed or anxious or adding to another health problem? Or after having had a memory blackout?
	Given up or cut back on activities that were important or interesting to you, or gave you pleasure, in order to drink?	10	Had to drink much more than you once did to get the effect you want? Or found that your usual number of drinks had much less effect than before?
Continued to drink even though it was making you feel depressed or anxious or adding to another health problem? Or after having had a memory blackout?	11	Found that when the effects of alcohol were wearing off, you had withdrawal symptoms, such as trouble sleeping, shakiness, restlessness, nausea, sweating, a racing heart, or a seizure? Or sensed things that were not there?	

The presence of at least 2 of these symptoms indicates an **Alcohol Use Disorder (AUD)**.

The severity of the AUD is defined as:

Mild: The presence of 2 to 3 symptoms

Moderate: The presence of 4 to 5 symptoms

Severe: The presence of 6 or more symptoms

Figure 1. Symptoms and definitions of alcohol abuse, alcohol dependence, and alcohol use disorder¹⁸



04 results



4.1 Summary of study characteristics

The committee identified 23 studies (see Table 1) based on 18 cohorts published between 1998 and 2018 that reported on the association of adolescent alcohol consumption and later life alcohol use disorder (AUD) including alcohol abuse (AA), and alcohol dependence (AD).^{5,11,13,14,16,17,19-36} Studies were performed in the USA (n=13), Australia and New Zealand (n=5), Norway (n=2), the United Kingdom (n=2), and Switzerland (n=1). The number of participants ranged between 141 and 4,352. Study samples varied between adolescents and high school students from

various backgrounds. The follow-up time varied between 1 and 28 years. Studies were generally funded by governmental grants or, in a minority of the studies, funding details were not reported. Fifteen studies focussed on frequency or amount of alcohol drinking,^{9-11,17,19,20,22-25,28-30,32,35} and nine on age of first drinking or early drinking.^{13,14,16,26,27,31,33,34,36} NOS scores (see Table 2) ranged between 3 and 9 (out of 9). Seven studies were vulnerable to attrition bias (NOS item 8). In thirteen studies, confounding was not sufficiently adjusted for (i.e. 0 points were scored, NOS item 5).

Table 1. General characteristics of longitudinal studies (in alphabetical order and clustered by cohort)

Studies	Sample	N	Exposure	Follow-up time (years)	Baseline alcohol consumption	Endpoints	Risk of bias ^a
Cohort on Substance Use Risk Factors (C-SURF), Switzerland							
Baggio 2015 ¹⁹	Young adult males, 20y old	4,352	Alcohol use	1.25	n.r.	AUD	5
Cohort study of adolescent health, Australia							
Bonomo 2004 ²⁰	High school student, subgroup of frequent drinkers (≥3 times/week), 14-15y old	1,601	Frequent drinking	6	58% non-drinking; 29% not drinking last week; 10% 1-2 glasses last week; 2% ≥3 glasses last week	AD	6
ALSPAC, UK, birth cohort							
Heron 2012 ²⁴	13-15y old	4,100	Alcohol use	3-4	At 13y: 79% non-drinkers, 15% <weekly, 5% weekly drinkers.	Hazardous use, harmful use (AUDIT) at 16y	5
Minneapolis, USA, low income birth cohort							
Englund 2008 ²¹	16y old adolescents	178	Alcohol use	12 (birth to age 28)	At 16y: 52% abstainers, 40% moderate drinkers; 7% heavy drinkers	AUD (28y of age)	5
Seattle Social Development Program, USA							
Guo 2001 ²²	Adolescents from high crime areas, 13y old	808	Alcohol use	11	n.r.	AA, AD	5
Guttmanova 2012 ¹⁴	Adolescents from high crime areas, 10y old	706	Early alcohol use (<11y) initiation	~23	n.r.	AD problems	7



Studies	Sample	N	Exposure	Follow-up time (years)	Baseline alcohol consumption	Endpoints	Risk of bias ^a
Guttmanova 2011 ¹³	Adolescents from high crime areas, 10y old	706	AFD, any use	~23	n.r.	Alcohol misuse, AD (33y of age)	7
Hill 2000 ²⁵	Adolescents from high crime areas, 10y old	808	Binge trajectories (13-18y)	11	n.r.	AA+AD (21y old)	4
Longitudinal study of familial alcoholism, Arizona, USA							
King 2007 ²⁶	Adolescents with oversampling of families with alcoholism, 11-16y old	185, 210	Early alcohol use (≤13y)	10	n.r.	AD (20-29y old, 22y old)	6
Haller 2010 ²³	Adolescents from families with alcoholism and controls, 14y old	405	Binge drinking	18	n.r.	Adult AD	6
Minnesota Twin Family Study, USA, birth cohort							
Irons 2015 ¹⁶	Twins, 11y old	1,512	Early (14y) alcohol use, early (14y) alcohol intoxication	10	At 14y: 36% ever had alcohol; 15% had ever been intoxicated	AUD	8
Cohort from Pittsburgh, USA							
Kirisci 2013 ²⁷	High school students, 10-12y old	261	AFD	10-12	Mean AFD: 14.8y	AUD 22y old	5
Collaborative Study on the Genetics of Alcoholism, USA							
Kramer 2008 ²⁸	Adolescents; oversampling of alcohol-dependent adolescents, 15y old	141	Alcohol use	5	n.r.	Problematic alcohol use	3
Pooling study of 3 Australasian cohorts, Australia, New Zealand							
Silins, 2018 ¹¹	Birth cohorts and adolescents (including CHDS, MUSP and VAHCS), 14-16y old	1,643 up to 3,864	Frequency of alcohol use, quantity of alcohol use	8-10, 14-16	n.r.	AD	8
Dunedin Multidisciplinary Health and Development Study							
Meier 2013 ²⁹	Adolescents and young adults, 18y old	957	Alcohol use	Birth to age 32	n.r.	AD (21-32y)	5
Meier 2016 ³⁰	Adolescents and young adults, 18y old	1,037	Frequent alcohol use	Birth to age 38	n.r.	AD (21-38y)	5
Christchurch Health and Development Study (CHDS), New Zealand							
Newton-Howes 2016 ³¹	Adolescents, 11-13y old	1,056	AFD	Birth to age 33	n.r.	AUD (33y)	6
Colorado Community Twin Study, USA							
Palmer 2009 ³²	Adolescent twins, 11.5-18.5y old	1,733	Alcohol use	5	Ever used: 53%, repeated use: 22%	AA, AD (16.5-25y)	5
Oslo (no name), Norway							



Studies	Sample	N	Exposure	Follow-up time (years)	Baseline alcohol consumption	Endpoints	Risk of bias ^a
Pedersen 1998 ³³	Adolescents, 12-15y old	522	AFD	6	Mean starting age: 14.8y	RAPI	7
Young in Norway Longitudinal Study, Norway							
Rossow 2013 ³⁴	High school students, 13-14y old	1,311	AFD	13	13-14y: 34% reported onset of drinking and 14% had drunk to intoxication	AUD	6
San Diego Prospective Study, USA							
Schuckit 2011 ¹⁷	University male students; oversampling of offspring of alcohol dependent fathers, 18-25y old	373	Alcohol use	25	Usual drinking frequency: 7.6-12.4. Usual drinking quantity: 2.4-3.6 (in recent 6 months)	AUD trajectories	7
British Birth Cohort Study, UK							
Viner and Taylor 2007 ³⁵	Adolescents, 16y old	11,622	Binge drinking, regular drinking	14	Habitual frequency (last year): every day: 2%; 4-5x per week: 4%; 2-3x week: 20%, once/week: 30%, once/month: 15%, occasionally: 21, never: 9	AD (age 30y)	6
Rutgers Health and Human Development Project, USA							
Warner 2003 ³⁶	Community based adolescents, 12y old	374	Early use <11y	18-19	AFD: 8.6y in family setting; AFD: 14.2 outside family setting, 18%	AD+AA (age 30-31y)	9

Abbreviations: n.r.: not reported, y: year, AA: alcohol abuse, AD: alcohol dependence, AFD: age of first drink, AUD: alcohol use disorder, VAHCS: Victorian Adolescent Health Cohort Study (Australia), MUSP: Mater Hospital and University of Queensland Study of Pregnancy, CHDS: Christchurch Health and Development Study (New Zealand), RAPI: Rutgers Alcohol Problem Index, AUDIT: Alcohol Use Disorders Identification Test.

^a Study quality / risk of bias was assessed with the Newcastle Ottawa Scale (0-9); see for clarification the document 'Methodology for the evaluation of the evidence'

Table 2. Detailed NOS scores for each outcome (in alphabetical order)

		Selection		Ascertainment of exposure	Outcome not present at start of study	Comparability	Outcome			Total score
		Representativeness of the exposed cohort	Selection of the non-exposed cohort			Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Baggio 2015 ¹⁹	AUD	1 (A)	1 (A)	1 (A)	0 (B)	0 (C)	1 (A)	1 (A)	0 (C)	5
Bonomo 2004 ²⁰	AD	1 (A)	1 (A)	1 (A)	1 (A)	0 (C)	1 (A)	1 (A)	0 (C)	6
Englund 2008 ²¹	AUD	0 (C)	1 (A)	0 (C)	1 (A)	0 (C)	1 (A)	1 (A)	1 (A)	5
Guo 2001 ²²	AA, AD	0 (C)	1 (A)	0 (C)	1 (A)	0 (C)	1 (A)	1 (A)	1 (A)	5
Guttmanova 2011 ¹³	AD - AFD	0 (C)	1 (A)	1 (A)	1 (A)	1 (A)	1 (A)	1 (A)	1 (A)	7
Guttmanova 2012 ¹⁴	AUD - AFD	0 (C)	1 (A)	0 (C)	1 (A)	2 (A B)	1 (A)	1 (A)	1 (A)	7
Haller 2010 ²³	AD	0 (C)	1 (A)	1 (B)	1 (A)	0 (C)	1 (A)	1 (A)	1 (A)	6



		Selection		Ascertainment of exposure	Outcome not present at start of study	Comparability	Outcome		Total score	
		Representativeness of the exposed cohort	Selection of the non-exposed cohort			Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow up long enough for outcomes to occur		Adequacy of follow-up of cohorts
Heron 2012 ²⁴	Hazardous use, harmful use	1 (A)	1 (A)	1 (A)	0 (B)	0 (C)	1 (A)	1 (A)	0 (C)	5
Hill 2000 ²⁵	AUD	0 (C)	1 (A)	0 (C)	0 (B)	0 (C)	1 (A)	1 (A)	1 (A)	4
Irons 2015 ¹⁶	AUD	1 (A)	1 (A)	0 (C)	1 (A)	2 (A B)	1 (A)	1 (A)	1 (A)	8
King 2007 ²⁶	AD	0 (C)	1 (A)	0 (C)	0 (B)	2 (A B)	1 (A)	1 (A)	1 (B)	6
Kirisci 2013 ²⁷	AUD	0 (C)	1 (A)	1 (A)	0 (B)	0 (C)	1 (A)	1 (A)	1 (B)	5
Kramer 2008 ²⁸	Problem use	0 (C)	1 (A)	0 (C)	0 (B)	0 (C)	1 (A)	1 (A)	0 (D)	3
Meier 2013 ²⁹	AD	1 (A)	1 (A)	0 (C)	0 (B)	0 (C)	1 (A)	1 (A)	1 (A)	5
Meier 2016 ³⁰	AD	1 (A)	1 (A)	0 (C)	0 (B)	0 (C)	1 (A)	1 (A)	1 (A)	5
Newton-Howes 2016 ³¹	AUD	1 (A)	1 (A)	0 (C)	0 (B)	2 (A B)	1 (A)	1 (A)	0 (C)	6
Palmer 2009 ³²	AA, AD	1 (B)	1 (A)	0 (C)	0 (B)	1 (A)	1 (A)	1 (A)	0 (D)	5
Pedersen 1998 ³³	AUD	1 (A)	1 (A)	1 (A)	1 (A)	0 (C)	1 (A)	1 (A)	1 (B)	7
Rossow 2013 ³⁴	AUD	1 (A)	1 (A)	0 (C)	1 (A)	1 (A)	1 (A)	1 (A)	0 (C)	6
Schuckit 2011 ¹⁷	AUD	0 (C)	1 (A)	0 (D)	1 (A)	2 (A B)	1 (A)	1 (A)	1 (A)	7
Silins 2018 ¹¹	AD	1 (A)	1 (A)	0 (C)	0 (B)	2 (A B)	1 (A)	1 (A)	1 (A)	7
Viner 2007 ³⁵	AD	1 (A)	1 (A)	0 (C)	1 (A)	0 (C)	1 (A)	1 (A)	1 (B)	6
Warner 2003 ³⁶	AUD	1 (A)	1 (A)	1 (A)	1 (A)	2 (A B)	1 (A)	1 (A)	1 (A)	9

AUD: alcohol use disorder; AD: alcohol dependence; AA: alcohol abuse; AFD: age of first drink. Letters A, B, A B, C, D reflect scoring categories within the NOS. Within each NOS domain letters have their own meaning. See

background document 'Methodology for the evaluation of the evidence' for further explanation.

4.2 Frequency or quantity of alcohol consumption and alcohol use disorder

The committee identified 14 studies on the frequency or quantity of drinking in relation to later alcohol use disorder.^{11,17,19-25,28-30,32,35} The committee prioritised two studies based on the study quality.^{11,17}

Studies of sufficient quality

Pooling study of 3 Australasian cohorts, Australia and New Zealand
Silins et al. (2018; NOS=7) performed a pooling study based on two birth cohorts and one cohort of adolescents from New Zealand and Australia with in total ~1643 to 2958 participants.¹¹ Frequency of drinking and number of drinks per occasion, as measured prior to age 17 years (ages varied between cohorts) were associated with alcohol dependence at age



24 years with p-values (beta \pm SE) of 0.015 (0.28 \pm 0.12) for frequency of alcohol consumption and 0.07 (0.16 \pm 0.06) for amount of alcohol consumption. P-values (beta \pm SE) for alcohol dependency at 30 years of age (based on two of the three cohorts) were <0.001 (0.60 \pm 0.17) and 0.008 (0.24 \pm 0.09) for frequency and amount of alcohol consumption, respectively. A bonferroni-adjusted p-value ($P < 0.002$) was used to minimise false positive findings. Therefore only the findings for frequency of alcohol use in relation to alcohol dependence at age of 30 years reached statistical significance. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for alcohol dependence at the age of 30 years were 1.81 (1.30-2.54) for less than weekly use and 3.30 (1.69-6.47) for weekly use or more, compared to the reference group of no alcohol use.

San Diego Prospective Study, USA

Schuckit and Smith (2011; NOS=7)¹⁷ focused on onset and course of AUD over a follow-up of 25 years and four measurement rounds in 373 men (18-25y at baseline) in which men with an alcohol dependent father were overrepresented. The outcome was defined as 1: no AUD, 2: Early onset (no remission), 3: late onset (no remission), and 4: early onset and persistent remission. Compared with the group with no AUD, the three AUD groups had a significantly higher usual drinking frequency (OR=1.07, $p \leq 0.001$) and usual drinking quantity (OR=1.46; $p \leq 0.001$). Drinking frequency and quantity were no predictors for late onset vs. no AUD and late vs. early onset.

The remaining studies

Cohort study of adolescent health, Australia

In a seven wave cohort study conducted by Bonomo et al. (2004; NOS=6), 14-15 year old Australian adolescents (n=1601) were followed for the incidence of alcohol dependence over six years. Frequent drinking, defined as drinking on ≥ 3 days in the previous week, was associated with alcohol dependence at the age of 20 years with ORs (95%CI) of 2.0 (1.0-4.3) for frequent drinking assessed in one wave and 3.1 (1.2-7.7) for frequent drinking assessed in >1 wave. Binge drinking, defined as drinking 45 grams of ethanol or more (>5 standard drinks) in one or more waves, compared to no binge drinking was not associated with later alcohol dependence with ORs (95% CI) of 1.5 (0.62-3.6) and 1.4 (0.61-3.4) for binge drinking during one wave and more than one wave, respectively.²⁰

Cohort from Arizona, USA

Haller et al. (2010; NOS=6) studied bidirectional relations among alcohol use, affiliation with substance promoting peers, and academic achievement in adolescence (14y) and young adulthood (32y) to identify cascades ultimately resulting in alcohol dependence (n=405 Americans).²³ Higher levels of binge drinking (frequency of five drinks per occasion) during young adulthood (14-15y) significantly predicted greater likelihood of adult alcohol dependence (onset [$\beta=0.30$, $p < 0.05$] or relapse [$\beta=0.54$;



$p < 0.05$]). All continuity paths in the model were significant, indicating stability of binge drinking, peer use, and academic achievement.

British birth cohort, UK

In a British birth cohort ($n=11,622$), the frequency of regular alcohol consumption at baseline (when participants were 16 years of age) was associated with an increased risk of alcohol dependency at 30 years of age, with ORs (95%CI) of 1.5 (1.1-1.9) for weekly or less often and 1.6 (1.1-2.2) for two or more times per week, compared to rarely or never. The frequency of binge drinking at baseline, defined as drinking four or more drinks in a row for two or more episodes in the previous two weeks, was associated with alcohol dependency at 30 years of age, with an OR (95%CI) of 1.4 (1.1-1.9) for binge drinking compared to no binge drinking (Viner and Taylor, 2007; NOS=6).³⁵

C-SURF, Switzerland

Baggio et al. (2015; NOS=5)¹⁹ found that alcohol intake (number of drinks per week) of 4,352 Swiss men (20y) predicted alcohol use disorder 1.25 years later ($\beta=0.323$, $p < 0.001$).

Low income birth cohort, Minneapolis, USA

Englund et al. (2008; NOS=5) studied the association between the number of alcoholic drinks per occasion (0, 1, 2, 3, 4, 5 or more) at 16 years of age and alcohol use disorder at the age of 28 years.²¹ From the

178 participants, eleven developed AUD (nine men and two women). In men, the OR (95%CI) for not having an AUD was 0.61 (0.39-0.98), i.e. for every 1-unit increase in adolescent alcohol use the odds of having an alcohol use disorder increased by a factor of 1.64 ($=1/0.61$). No OR for AUD in women was provided (only two incident cases).

Dunedin Multidisciplinary Health and Development Study, New Zealand

Meier et al. (2013; NOS=5)²⁹ investigated adolescent alcohol use (18y) and adult (32y) alcohol dependence subtypes (developmentally-limited, persistent, or adult-onset) in 957 participants from a birth cohort from New Zealand. Alcohol use by the age of 18 years was significantly associated with an increased risk of a lifetime diagnosis of AD with ORs (95%CI) of 2.01 (1.66-2.44) for alcohol frequency and 2.48 (1.29-4.80) for daily alcohol use. Daily use of alcohol by age 18 years (but not alcohol frequency) significantly increased the odds of developing persistent AD compared to a developmentally-limited AD (OR: 95%CI: 6.41; 1.91-21.54). Relative to the never-diagnosed group, the odds of adult-onset alcohol dependence was not significantly higher based on alcohol frequency or daily alcohol use.

In a follow-up publication based on the same cohort ($n=1,037$, followed to the age of 38 years), Meier et al. (2016; NOS=5)³⁰ identified adolescents at risk for adult persistent substance dependence. In supplemental tables



alcohol, tobacco, cannabis, and hard-drugs were separated. Based on a model with no covariates, frequent (>5 days/week) alcohol use at age 18 was not significantly associated with persistent alcohol dependence from age 21 to 38 years (RR: 2.35; 95%CI: 0.76-7.33).

Colorado Community Twin Study, USA

Based on a community sample of 11-18 year old American twin-pairs, Palmer et al. (2009; NOS=5) reported that lifetime alcohol use (one or more drinks) was associated with an increased risk of alcohol use disorder five years later.³² The committee decided not to use the reported ORs because the models seem to include interaction terms of age and sex with the exposure variable. In that situation, the ORs are not valid as estimators of a relative risk.

ALSPAC, birth cohort, UK

In the British ALSPAC (birth) cohort of 4,100 adolescents aged 13-15 years, Heron et al. (2012; NOS=5) investigated patterns of alcohol use (latent class analysis; drinking frequency and quantity classified as low, medium, or high) in early adolescence (three measurements at age 13, 14, and 15 years) in relation to problem use at age 16 years. At age 16 years, 29% of the participants were drinking hazardously (AUDIT=8-15) and a further 5.6% were assessed as harmful (AUDIT≥16) drinkers. Being in the high use class for either drinking frequency or quantity was associated with an 8 (OR: 8.63; 95%CI: 5.32-14) to 10-fold (OR: 9.87;

95%CI:6.52-14.9) increase in the odds of harmful alcohol use at age 16 years. ORs for the medium categories were lower, but also significantly different from the reference groups. Results were, however, unadjusted for other covariates.

Seattle Social Development Program, USA

In 808 American adolescents (13 years of age at baseline), trajectories of binge drinking (labelled as ‘non-bingers’ [70%], ‘early highs’ [3%], ‘increasers’ [4%], and ‘late onsetters’ [23%]) between 13-18 years of age were associated with alcohol abuse or dependence at the age of 21 years. ORs (CIs not provided) for ‘increasers’ and ‘late onsetters’ compared to the ‘non-bingers’ were 5.53 and 4.72 (p<0.05) whereas ‘early highs’ did not differ from the non-bingers (Hill 2000; NOS=4).²⁵

Guo et al. (2001; NOS=5) studied the frequency of alcohol consumption in the last month at the ages of 10, 14 and 16 years in relation to alcohol abuse (AA) and alcohol dependence (AD) in the same 808 American adolescents.²² The level of alcohol use at the age of 14 years, but not at the age of 10 years, predicted alcohol abuse and disorder at 21 years of age with ORs (p-value) of 1.40; (p<0.01) for AA+AD and 1.36 (p<0.05) for AD. The level of alcohol use at the age of 16 years predicted AA+AD (OR: 1.26, p<0.05) but not AD (OR: 1.23). Bonferroni adjustments were performed.



Collaborative Study on the Genetics of Alcoholism, USA

In American 15 year old adolescents (n=141), in which participants with alcohol dependent relatives were overrepresented, the association between alcohol consumption (quantity over past six months) and problematic alcohol use (SSAGA; problems associated with dependence and abuse) five years later was studied (Kramer et al., 2008; NOS=3)²⁸

The number of alcoholic drinks in a typical week did not predict problematic alcohol use, whereas baseline problematic alcohol use did.

4.3 Conclusions for frequency or quantity of alcohol consumption and alcohol use disorder

Main study findings are summarised in Table 3. It was not possible to quantitatively summarise the findings.

The committee identified two studies (based on three study populations) of sufficient quality. In both studies, a higher frequency of alcohol consumption was associated with a higher risk of later alcohol use disorder. A higher amount of alcohol consumption was associated with a higher risk of later alcohol use disorder in one of the two studies. In the second study, the association of a higher alcohol quantity with a higher risk of later alcohol use disorder disappeared after bonferroni corrections for multiple testing.

From the remaining 12 studies, based on 10 study populations, most of the studies (10 out of the 12) observed an association between a higher level of alcohol consumption and a higher risk of alcohol use disorder. The other two did not find an association between level of alcohol consumption and risk of later alcohol use disorder.

The cohorts generally comprised both boys and girls; yet sex differences were not reported nor investigated. All available studies, except for one, were comprised of adolescents. Therefore, the role of sex and age regarding the associations could not be evaluated.

4.4 Age of onset of alcohol use and alcohol use disorder

The committee identified nine studies^{13,14,16,26,27,31,33,34,36} of which five were included in an SR² on the relation between age of first drink (AFD) or early drinking and later life alcohol use disorder (AUD). Four additional studies were found that were not included in the SR²⁶ or were more recent.^{16,27,31}

The nine publications were based on cohorts from the USA (n=6), Norway (n=2) and New Zealand (n=1). The committee prioritised five studies based on the study quality,^{13,14,16,33,36} of which two were based on the same cohort.^{13,14}



Studies of sufficient quality

Rutgers Health and Human Development Project, USA

In American adolescents (n=447, 12y old), with a median AFD of 10 years of age, early AFD (before 11y) was not associated with the lifetime incidence of problem drinking (alcohol dependence or abuse incidence over 18-19 years) in the most stringent model with an adjusted beta of -0.06 (ns) for AFD < age 11 years (Warner et al., 2003; NOS=9).³⁶ The strongest predictor for adult problem drinking was whether one felt drunk at first episode and this was highly significant in all analyses, including the one with the most rigorous adjustment for confounders (adjusted beta=0.38, p<0.0001).

Minnesota Twin Family Study, USA

Irons et al. (2015; NOS=8)¹⁶ included 1,512 twins (mono and dizygotic twin pairs) to investigate adolescent early alcohol exposure (ever having had an alcoholic drink and ever having been intoxicated at age 14 years) and adult (age 24 years) outcomes including alcohol use disorder. The authors applied propensity scoring and co-twin control (CTC) analyses to adjust for confounding. The co-twin design controls for factors confounded with alcohol exposure and the outcome of interests that twins share (such as genetics and environmental factors). A between-twin pair difference captures the mean exposure effect, which is fully confounded with all shared factors that predispose towards alcohol use (comparable to a

singletons design). A within-twin pair difference represents effects of alcohol exposure unconfounded by these shared influences and therefore permits stronger inferences about the causal effect of alcohol exposure on the outcome. The beta coefficients of alcohol use disorder were 0.46 (p<0.001) for those exposed to alcohol early and 0.53 (p<0.001) for those who had ever been intoxicated at the age of 14 years. Adjustment for confounding by propensity scoring attenuated the findings, but results were still strongly significant. In CTC analyses, results for discordant dizygotic pairs were still significant (beta=0.34, p=0.04), but estimates attenuated and were non-statistically significant for discordant monozygotic pairs (beta=0.17, p=0.19). Results for early intoxication were generally similar to early alcohol consumption.

Seattle Social Development Program, USA

In 808 American adolescents, Guttmanova et al. (2011; NOS=7), observed that any drinking before the age of 21 years was not associated with lifetime diagnosis of adult (assessed in five waves between ages 21 and 33 years) alcohol dependence. Any drinking before the age of 11 years was associated with a higher risk of chronicity of alcohol dependence (a diagnosis in >1 wave) with an OR of 1.68 (p<0.05) compared to those who starting drinking between ages 11-14 years. The age of regular use initiation was inversely associated with the risk of adult alcohol dependence. Compared to the reference group of initiators older than 21 years, ORs for a lifetime diagnosis of adult alcohol dependence



were 1.71, 1.76 for initiation between age 15-17 years and age 18-20 years, respectively. However, initiation at or before 14 years of age was not associated with ever diagnosed adult alcohol dependence. ORs for chronicity of alcohol dependence in relation to the age of onset of regular drinking were 1.67 (for <14y), 1.70 (for 15-17y), and 1.85 (for 18-20y) compared to the reference group of ≥ 21 years of age.¹³

Guttmanova's research (2012; NOS=7), was an extension of the previous study. The authors observed an association of early (<11y) onset of drinking and chronicity of alcohol dependence (present in >1 out of five waves between age 21 and 33). The magnitude of the association ($\beta=0.44$, $p<0.05$), adjusted for gender, ethnicity, poverty, parental drinking, family bonding and family management remained largely unaffected in four separate regression models, aiming to test hypotheses that the association is attributable to other predictive factors (peer factors: $\beta=0.53$; $p<0.01$), school factors ($\beta=0.46$, $p<0.05$), behavioural factors ($\beta=0.45$, $p<0.05$) and substance misuse factors ($\beta=0.46$, $p<0.05$).¹⁴

Cohort from Oslo, Norway

Pedersen and Skrandal (1998; NOS=7) reported that AFD (categorised into <13, 13, 14, 15-16, and 17-19 years of age) was inversely associated with the Rutgers Alcohol Problem Index (RAPI) with a structural equation coefficient of -13,828 ($p<0.0001$) six years later in $n=442$ Norwegian adolescents aged 12-15 years at baseline.³³ The mean RAPI score was

3.6 (out of the maximum of 23). The authors acknowledged that a more stringent control of confounding would weaken this association and that further studies were needed.

The remaining studies

Christchurch Health and Development Study, New Zealand

In a birth cohort from New Zealand (Newton-Howes et al., 2016; NOS=6), AFD of 1,056 adolescents (11-13 y old) was not associated with adult AUD between 15-35 years of age ($\beta=-0.08$; 95CI:-0.24-0.08).³¹

Young in Norway Longitudinal Study, Norway

In 1,311 Norwegian adolescents, early AFD (<13-14y) versus late AFD (>14 y) was associated with a higher risk of adult harmful alcohol use (AUDIT ≥ 8) 13 years later. Results were adjusted for sex only. After additional adjustment for baseline conduct problems, the association weakened and became non-significant (Rossow et al., 2013; NOS=6).³⁴

Longitudinal study of familial alcoholism, Arizona, USA

King et al. (2007; NOS=6) concluded, based on a nested case-control study of children (11-16 years old) of alcoholics and matched controls, that early onset ($\leq 13y$) of alcohol use is a marker of risk for later dependence (age 20-29 years) rather than a causal influence because the association (OR of 1.80; $p<0.01$) disappeared (OR of 1.41; $p>0.05$) after adjusting for



use of other substances and correlated family risk factors.²⁶ This study of children of alcoholics and matched controls was excluded by Maimaris and McCambridge because of the study sample.²

Cohort from Pittsburgh, USA

Kirisci (2013; NOS=5) studied a sample of American children (n=261) in which children (10-12 years old) of fathers with substance use disorder were oversampled. AFD (continuous) predicted AUD by the age of 22 years (OR, 0.78; 95% CI: 0.68-0.90). Adjustments were, however, not reported.²⁷

4.5 Conclusions for age of onset of alcohol use and alcohol use disorder

The main study findings are summarised in Table 3. It was not possible to quantitatively summarise the findings.

The committee identified four studies of sufficient quality that focused on the age of starting alcohol consumption (more than a sip). In all four study populations, drinking at a younger age or getting drunk after the first drinking episode was associated with later alcohol use disorder. In one of

the four studies the association was more pronounced for regular use initiation than for any drinking initiation. In the second of the four studies, the age of any drinking initiation was not associated with later alcohol use disorder, whereas getting drunk was the strongest predictor of later alcohol use disorder. In the third study, the risk of later alcohol use disorder for drinking before the age of 14 years was similar to the risk associated with getting drunk before the age of 14 years. The fourth study did not have information on the level of alcohol consumption in relation to drinking age.

From the remaining four studies, that were not of sufficient quality, based on four study populations, one study found an association between a younger starting age of alcohol consumption and an increased risk of later alcohol use disorder. The other three studies did not find an association.

In none of the studies was an earlier starting age of alcohol consumption associated with a lower risk of later alcohol use disorder.

The cohorts generally comprised both boys and girls; yet sex differences were not reported nor investigated.



Table 3. Overview of results of AUD studies (ordered by NOS-score)

Studies ^a	NOS	N	Exposure	Exposure AFD/early	Results for AUD
Studies of sufficient quality (NOS-score 7 to 9)					
Warner 2003 ³⁶	9	447		AFD at a family gathering; AFD outside family gathering; Feeling drunk at first use (y/n)	No association No association Higher risk for AUD
Irons 2015 ^{16b}	8	1,512		Early use (≤ 14 y) (y/n) Early intoxication (≤ 14 y) (y/n)	Higher risk for younger AFD Higher risk for intoxication at younger age
Silins 2018 ¹¹	7	2,937 (24y) 1,643 (30y)	Alcohol use, increasing frequency (never, <weekly, weekly+); Alcohol amount per occasion, increasing scale (≤ 2 , 3-4, 5-6, 7+)		No association with AD at 24y of age Higher risk for AD at 30y of age No association with AD at 24y No association with AD at 30y
Pedersen 1998 ³³	7	522		AFD (continuous)	Higher risk for younger AFD
Guttmanova 2012 ^{*14}	7	706		Early use (<11y)	Higher risk for early use
Guttmanova 2011 ^{*13}	7	706		AFD in 4 age categories (any alcohol use) Age of regular use initiation in 4 age categories (regular not specified)	No association for lifetime AUD, Higher risk for chronic AUD for AFD<11y compared to 11-14 y Higher risk for lifetime AUD for younger regular use Higher risk for chronic AUD for younger regular use
Schuckit 2011 ¹⁷	7	373	Usual frequency of alcohol use, increasing scale Usual drinking quantity, increasing scale		Higher risk Higher risk
Other studies (NOS-score 4 to 6)					
Newton-Howes 2016 ^{31c}	6	1,056		AFD (continuous)	No association
Bonomo 2004 ²⁰	6	1,601	Frequent drinking (≥ 3 days <7d); y/n BD (≥ 45 g ethanol; ≥ 5 drinks); y/n		Higher risk No association
Haller 2010 ^{#23}	6	405	Frequency of BD (≥ 5 drinks per occasion; from 0 (never) to 7 (every day), increasing scale, at three waves (path analyses)		Higher risk
King 2007 ^{#26}	6	185 / 211		Early alcohol use (≤ 13 y; y/n)	No association
Viner 2007 ³⁵	6	11,622	Frequency of habitual drinking (7 categories), increasing scale BD (≥ 4 drinks on ≥ 2 occasions during previous 2 weeks)		Higher risk
Rossow 2013 ³⁴	6	1,311		AFD (continuous)	No association
Baggio 2015 ¹⁹	5	4,352	Alcohol use (drinks/week), increasing scale		Higher risk
Englund 2008 ²¹	5	178	Alcohol use (drinks per occasion: 0, 1, 2, 3, 4, ≥ 5), increasing scale		Higher risk



Studies ^a	NOS	N	Exposure	Exposure AFD/early	Results for AUD
Kirisci 2013 ²⁷	5	261		AFD (continuous)	Higher risk for younger starting age
Meier 2013 ²⁹	5	957	Frequency of alcohol use Daily use (y/n)		Developmentally limited: ↑; persistent: - Developmentally limited ↑; persistent: ↑
Meier 2016 ³⁰	5	1,037	Frequent alcohol use (≥5 days/week; y/n)		No association
Palmer 2009 ³²	5	1,733	Lifetime alcohol use (≥1; y/n)		Higher risk
Heron 2012 ²⁴	5	4,100	Frequency of alcohol use (low, medium, high), increasing scale Typical quantity (low, medium, high), increasing scale		Higher risk Higher risk
Guo 2001 ²²	5	808	Level of alcohol use at 10y <30d Level of alcohol use at 14y <30d Level of alcohol use at 16y <30d		No association with AUD or AD Higher risk for AUD and AD Higher risk for AUD ↑ ; No association with AD
Hill 2000 ²⁵	4	808	BD trajectories (early highs, increasers, late onsetters, non-binge drinkers)		Higher risk for AUD (21y) for 'increasers' and 'late onsetters' vs. non-binge drinkers. No association for AUD (21y) for 'early highs' compared to non-binge drinkers.
Kramer 2008 ²⁸	3	141	Typical quantity (<6 months), increasing scale		No association

Abbreviations: AD: alcohol dependence, AFD: age of first drink, AUD: alcohol use disorder, BD: binge drinking, d: day, HED: heavy episodic drinking, NOS: Newcastle Ottawa Scale, y/n: yes/no, y: year

^a Corresponding signs mean corresponding cohort.

^b Estimates were significant for models based on propensity score adjustment and for discordant dizygotic twin pairs. Estimates attenuated and were non-statistically significant for discordant monozygotic twin pairs

^c Cohort included in Silins et al., 2018¹¹



05 discussion and conclusions



5.1 Limitations

In addition to some general limitations of the totality of evidence, such as self-reporting of alcohol consumption and publication bias, as also referred to in the background document ‘Methodology for the evaluation of the evidence’, the committee wants to address some limitations of the available evidence, specific for the outcome ‘alcohol use disorder’.

Although the majority of the studies suggested that an earlier age of onset plays a role for developing later AUD or dependence, several scientists doubt the usefulness of the concept of drinking onset.^{2,37,38} They argue that the focus should be shifted towards understanding the progression from infrequent, low quantity drinking to more detrimental drinking patterns and the prevention of associated acute and short-term harm.³⁷ In addition, some studies support the idea that the first experience with alcohol as such is not as strong a risk factor for later problems, as experiences of amounts of more than just a few sips.^{13,38}

Although the committee identified several studies of sufficient quality about the role of age of onset of drinking in relation to later alcohol use disorder, it was not possible to quantify these findings, because the studies generally did not provide confidence intervals. Furthermore, the measures of age of onset were different across the studies and the reference groups.

5.2 Final conclusions

Given the limitations, the committee concludes that there are indications that drinking at a young age, i.e. more frequent drinking or drinking at an earlier age, is associated with a risk of alcohol use disorder in later life. In all available studies of sufficient quality, adverse associations were observed. The committee, however, notes that starting age as a measure of exposure to alcohol has its limitations.^{2,37,38} The question is, whether the age of the first experience with drinking alcohol is as important a risk factor, as the starting age of regular alcohol consumption or the age of getting drunk for the first time.^{13,38}



literature



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annex



A search strategy

Pubmed search ‘Psychopathology and cognition’

July 2017

#1 Outcomes

“Psychopathology”[Mesh] OR psychopatholog*[tiab] OR “Anxiety”[Mesh] OR anxiet*[tiab] OR catastrophiz*[tiab] OR “Anxiety Disorders”[Mesh] OR agoraphob*[tiab] OR neurocirculatory asthenia[tiab] OR effort syndrome*[tiab] OR hyperkinetic heart syndrome*[tiab] OR neurotic disorder*[tiab] OR psychoneurosis[tiab] OR psychoneuroses[tiab] OR neurosis[tiab] OR neuroses[tiab] OR obsessive compulsive disorder*[tiab] OR obsessive compulsive personalit*[tiab] OR anankastic personalit*[tiab] OR hoarding[tiab] OR panic disorder*[tiab] OR panic attack*[tiab] OR phobic disorder*[tiab] OR phobia*[tiab] OR claustrophobia[tiab] OR “Cognition”[Mesh] or cogniti*[tiab] OR awareness*[tiab] brain reserve*[tiab] OR comprehension[tiab] OR understanding[tiab] OR consciousness*[tiab] OR imaginat*[tiab] OR intuiti*[tiab] OR metacogniti*[tiab] OR metamemor*[tiab] OR “Cognitive Dysfunction”[Mesh] OR neurocogniti*[tiab] OR mental deterioration*[tiab] OR “Executive Function”[Mesh] OR executive function*[tiab] OR executive control*[tiab] OR “Neuropsychology”[Mesh] OR neuropsycholog*[tiab] OR “Neurobiology”[Mesh] OR neurobiolog*[tiab] OR

“Psychophysiology”[Mesh] OR psychophysilog*[tiab] OR physiologic psycholog*[tiab] OR physiological psycholog*[tiab] OR mind body relation*[tiab] OR “Psychophysiologic Disorders”[Mesh] OR psychosomatic disorder*[tiab] OR appetite*[tiab] OR arousal*[tiab] OR cortical vigilance*[tiab] OR attention*[tiab] OR concentration*[tiab] OR conscious*[tiab] OR habituation*[tiab] OR orientation*[tiab] OR reaction time*[tiab] OR response time*[tiab] OR response latenc*[tiab] OR reflex*[tiab] OR satiation*[tiab] OR sensation*[tiab] OR sensory function*[tiab] OR sleep*[tiab] OR psychological stress*[tiab] OR psychologic stress*[tiab] OR emotional stress*[tiab] OR life stress*[tiab] OR mental suffering[tiab] OR anguish[tiab] OR “Learning”[Mesh] OR learn*[tiab] OR avoidance behavior*[tiab] OR avoidance behaviour*[tiab] OR conditioning*[tiab] OR generalization*[tiab] OR generalisation*[tiab] OR imprinting*[tiab] OR inhibition*[tiab] OR neuro-linguistic programming[tiab] OR neurolinguistic programming[tiab] OR overlearning[tiab] OR problem solving[tiab] OR “Memory”[Mesh] OR memor*[tiab] OR retention*[tiab] OR recall*[tiab] OR recognition*[tiab] OR repetition priming[tiab] OR “Memory Disorders”[Mesh] OR amnesia*[tiab] OR Korsakoff[tiab] OR “Volition”[Mesh] OR volition*[tiab] OR free will[tiab] OR “Perception”[Mesh] OR percept*[tiab] OR stereoscopic vision*[tiab] OR stereops*[tiab] OR stereognos*[tiab] OR interocepti*[tiab] OR alliesthesi*[tiab] OR nociception*[tiab] OR nociperception*[tiab] OR sensory deprivation*[tiab] OR sensory threshold*[tiab] OR auditory threshold*[tiab] OR differential threshold*[tiab] OR pain threshold*[tiab]



OR taste threshold*[tiab] OR subliminal stimulation*[tiab] OR visual disparit*[tiab] OR vision disparit*[tiab] OR fixation disparit*[tiab] OR ocular disparit*[tiab] OR ocular parallax[tiab] OR binocular disparit*[tiab] OR retinal disparit*[tiab] OR contrast sensitivit*[tiab] OR binocular vision*[tiab] OR monocular vision*[tiab] OR visual acuit*[tiab] OR “Perceptual Disorders”[Mesh] OR somatosensory discrimination disorder*[tiab] OR sensory neglect*[tiab] OR hemisensory neglect*[tiab] OR hemispatial neglect*[tiab] OR agnosia*[tiab] OR anosognosia*[tiab] OR visual disorientation syndrome*[tiab] OR Gerstmann syndrome[tiab] OR Syndrome de Gerstmann[tiab] OR Gerstmann Badal Syndrome[tiab] OR Gerstmann’s Syndrome[tiab] OR prosopagnosia*[tiab] OR Alice in Wonderland syndrome[tiab] OR allesthesia*[tiab] OR alloesthesia*[tiab] OR allachesthesia*[tiab] OR allochiria*[tiab] OR dyschiria*[tiab] OR hallucination*[tiab] OR illusion*[tiab] OR autokinetic effect*[tiab] OR “Disruptive, Impulse Control, and Conduct Disorders”[Mesh] OR disruptive disorder*[tiab] OR impulse control disorder*[tiab] OR conduct disorder*[tiab] OR intermittent explosive disorder*[tiab] OR kleptomania[tiab] OR firesetting behavior*[tiab] OR firesetting behaviour*[tiab] OR pyromania*[tiab] OR arson[tiab] OR arsons[tiab] OR trichotillomania*[tiab] OR “Mood Disorders”[Mesh] OR mood disorder*[tiab] OR affective disorder*[tiab] OR cyclothymic disorder*[tiab] OR cyclothymic personalit*[tiab] OR depressi*[tiab] OR melancholia*[tiab] OR involitional psychos*[tiab] OR involitional paraphrenia*[tiab] OR dysthymi*[tiab] OR premenstrual dysphoric syndrome*[tiab] OR

premenstrual dysphoric disorder*[tiab] OR seasonal affective disorder*[tiab] OR “Alcoholism”[Mesh] OR alcoholism[tiab] OR alcohol dependen*[tiab] OR alcoholic intoxication*[tiab] OR addict*[tiab] OR alcohol abuse[tiab] OR “Alcoholic Intoxication”[Mesh] OR “Alcohol-Induced Disorders, Nervous System”[Mesh] OR alcohol induced disorder*[tiab] OR ethanol induced nervous system disorder*[tiab] OR ethanol induced disorder*[tiab] OR amnestic disorder*[tiab] OR amnestic psychosis[tiab] OR amnestic psychoses[tiab] OR amnestic syndrome*[tiab] OR dysmnesic psychosis[tiab] OR dysmnesic psychoses[tiab] OR dysmnesic syndrome*[tiab] OR neuropath*[tiab] OR polyneuropath*[tiab] OR polyneuriti*[tiab] OR “Psychoses, Alcoholic”[Mesh] OR alcoholic psychoses[tiab] OR alcoholic psychosis[tiab] OR “Wernicke Encephalopathy”[Mesh] OR Wernicke encephalopath*[tiab] OR Wernicke’s encephalopathy*[tiab] OR cerebral beriberi[tiab] OR Wernicke Polioencephalitis[tiab] OR Wernicke’s Polioencephalitis[tiab] OR Wernicke superior hemorrhagic polioencephalitis[tiab] OR Wernicke’s superior hemorrhagic polioencephalitis[tiab] OR Wernicke syndrome[tiab] OR Wernicke’s syndrome[tiab] OR Wernicke’s disease[tiab] OR Wernicke disease[tiab].

N = 5,666,746.

N (published last 10 years) = 2,501,699.



#2 Exposure

“Alcoholic Beverages”[Mesh] OR alcohol*[tiab] OR absinthe*[tiab] OR beer*[tiab] OR wine*[tiab] OR “Drinking Behavior”[Mesh] OR drinking behavior*[tiab] OR drinking behaviour*[tiab] OR binge drink*[tiab] OR underage drink*[tiab] OR “Alcoholism”[Mesh] OR heavy drink*[tiab] OR age of first drink[tiab] OR age at first drink[tiab] OR (“Ethanol”[Mesh] NOT (“Ethamoxytriphetyl”[Mesh] OR “Ethanolamines”[Mesh] OR “Ethylene Chlorohydrin”[Mesh] OR “Mercaptoethanol”[Mesh] OR “Phenylethyl Alcohol”[Mesh] OR “Trifluoroethanol”[Mesh])) OR ethanol[tiab].

N (published last 10 years) = 172,746.

#3 Study design

“Prospective studies”[Mesh] OR “Retrospective Studies”[Mesh] OR “Follow-up studies”[Mesh] OR “Cohort studies”[Mesh] OR prospective*[tiab] OR retrospective*[tiab] OR longitudinal*[tiab] OR follow-up[tiab] OR followup[tiab] OR cohort*[tiab].

N (published last 10 years) = 1,360,443.

#4 Study population

“Students”[Mesh] OR student*[tiab] OR “Adolescent”[Mesh] OR adolescen*[tiab] OR teen*[tiab] OR youth*[tiab] OR “Young Adult”[Mesh] OR young adult*[tiab].

N (published last 10 years) = 1,009,633.

Total

#1 AND #2 AND #3 AND #4 published in the last 10 year = 5,185 hits.



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