Cognitive functioning

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Backgrounddocument to:

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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 measures of cognitive functioning.

Adolescence is a period in which brain structures develop and when many people start to use alcohol. Maturational changes in the brain during adolescence are associated with, among others, significant improvements in complex cognitive functions, including so-called ‘executive functions’ such as working memory, inhibition and cognitive flexibility.[1,2] These higher level cognitive functions are mainly supported by functional networks involving fronto-striatal pathways and the prefrontal cortex.[3] These changes may be vulnerable to the harmful effects of alcohol.[4]

A systematic search was performed for peer-reviewed longitudinal studies on the association between alcohol use during adolescence and young adulthood and measures of cognitive functioning.

Apart from studies on general cognitive abilities, the committee also included studies on more specific alcohol-related cognitive biases. In a recent review of the literature, it was concluded that alcohol appears to be associated with automatically activated appetitive responses to substance cues (such as alcohol-related cognitive biases), and that these biases are likely to contribute to the development of problem use.[5]

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 systematic review includes longitudinal studies in adolescents and young adults from 12 up to 24 years of age at baseline (see Annex for search strategy). Published articles (in English) up to and including May 2018 were retrieved from Pubmed and PsychINFO, and complemented by hand searches of reference lists and correspondence with researchers in the field.

Studies about the acute effects of alcohol were excluded. Study samples of specific subgroups (i.e. 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.

The initial search resulted in 13 studies.[6-18] In addition, eight studies were identified via other routes,[18-26] resulting in 21 studies. Nine studies were primarily designed to explore brain imaging outcomes, but also reported on cognitive measures. The results of the brain imaging outcomes of these studies are described in the background document “Neuro imaging and neuro physiology”.[8,9,17,19-23,25] Because of overlap in study sample and lack of report of relevant results, two studies were excluded at a later stage.[8,26] These studies do not contribute to the totality of evidence but, for the sake of completeness, their results are described in this background document. Thus, in total we included 19 studies.

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

2.1 Data extraction and data synthesis

Data were extracted using structured extraction forms which included information on the study sample, 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 among high school students were grouped together, as well as studies among university/college students. Secondly, studies that were performed on the same cohort were clustered as well.

[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.

All studies are briefly discussed one by one in terms of sample, NOS score, baseline drinking status, baseline differences of the outcomes (which is part of the NOS), and the adjustment for multiple testing. 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
results

3.1 Summary of study characteristics

The Committee included 19 longitudinal studies, published between 2009 and 2018 (Table 1) on 7 cohorts.[6,7,9-25] Ten of these studies were conducted in Europe[6,7,9-13,17,19,20], of which 2 in the Netherlands[6,7] and 6 in Spain.[9-13,19] Nine studies originate from the USA.[14-16,18,21-25] The number of participants ranged between 30 and 2,230. The study samples included adolescents and young adults, or subgroups such as high-school students, college or university students.

In the description of the results, a distinction is made between high school students and college/university students, i.e. a rough distinction in groups that differ in age and social circumstances. Within each group, studies are listed by NOS score and cohort. Eight studies were based on samples with no or minimal alcohol use at baseline.[14-16,21-25] Thirteen studies focused on binge drinking.[6,9-14,16,18-22] Eight studies took adjustment for multiple testing into account.[6,10,14-18,24] The NOS scores ranged between 5 and 8 (Table 2). The committee judged 8 studies to be of sufficient quality based on NOS score.[6,9,11,14-16,21,24]

Table 1. General characteristics of the longitudinal studies (grouped by cohort and publication date)

Studies	Sample	N	Exposure	Follow-up time	Baseline alcohol consumption	Endpoints	Multiple testing correction	Risk of bias[a]
High school students								
Cohort of "Adolescent Cannabis Users", San Diego, USA								
Jacobus 2013[18]	Middle school students 16-19y	54	Sustained binge drinking	3y	Control group: 0 drinks/month, Binge drinkers: 10 drinks/month	Cognitive functioning (a composed measure of complex attention, processing speed, verbal memory, visuospatial functioning, and executive functioning)	Yes	5
Cohort of Youth at Risk for Alcoholism, University of California, San Diego, USA								
Squeglia 2009[14]	Middle school students 12-14y	76	Initiation moderate or heavy drinking	1-5y	Control group: 0 drinking days. Drinkers: female 1.15 drinking days; males 0.83 drinking days	Visuospatial functioning, attention and working memory, learning and memory, executive functioning / planning	Yes	7
Squeglia 2012[22]	Middle school students 12-16y	40	Initiation binge drinking	3y	Continuous non-drinkers: 0.05 lifetime alcohol occasions. Heavy drinking transitioners: 1.50 lifetime alcohol use occasions.	Visual working and memory	n.r.	6
Wetherill 2013[21]	Middle school students 12-16y	40	Initiation binge drinking	3y	Limited (≤ 1 total lifetime drinks)	Response inhibition	n.r.	7

Studies	Sample	N	Exposure	Follow-up time	Baseline alcohol consumption	Endpoints	Multiple testing correction	Risk of bias[a]
Nguyen-Louie 2015[15]	Middle school students 12-14y	234	More alcohol use	1-9y (mean 4y)	Limited (≤10 lifetime alcohol use occasions, never >2/week), 91% were alcohol naive	Verbal memory, visuospatial ability, psychomotor speed, processing speed, working memory	Yes	7
Nguyen-Louie 2016[16]	Middle school students 12-16y	112	Extreme binge drinking, binge drinking vs. moderate drinking	4-9y	Limited (≤10 lifetime alcohol use occasions, never >2/week)	Verbal learning and memory	Yes	8
Jacobus 2016[23]	Middle school students 12-14y	69	Alcohol initiation vs. no drinking	6-8y	Limited (both groups had a mean of 0.04 lifetime alcohol use days at baseline)	Complex attention, processing speed, verbal memory, visuospatial functioning, executive functioning	n.r.	6
Nguyen-Louie 2017[24]	Middle school students 12-15y	215	Age of first drinking onset, age of weekly drinking onset	Average 6.8y	Limited (≤10 lifetime alcohol use occasions), 90% were alcohol naive	Verbal learning and memory, cognitive inhibition, psychomotor speed, working memory, visual attention, visuospatial ability	Yes	7
Nguyen-Louie 2018[25]	Middle school students 12-15y	133	Weekly drinkers vs. non-weekly drinkers	6y	Limited (≤10 lifetime alcohol use occasions, never >2/week), 98% of the non-weekly drinkers were alcohol naive and 89% of the weekly drinkers	Visual working and memory	n.r.	5
TRAILS cohort, the Netherlands								
Boelema 2015[6]	Pre-adolescents 11y	2230	Chronic heavy, decreasing heavy, increasing heavy, infrequent heavy, light drinking vs. non drinking	8y	Varying (% alcohol naive per drinking group: chronic heavy drinking 77%; decreasing heavy drinking 79%; increasing heavy drinking 81%; infrequent heavy drinking 85%; light drinking 88%; non drinking 95%)	Executive functioning (inhibition, working memory, sustained attention, shift attention)	Yes	7
Health Behaviours in School-aged Children cohort, the Netherlands								
Janssen 2015[7]	Adolescents 12-18y	378	Average number of alcohol units consumed on each weekday	2y	Varying (23.2% used alcohol weekly)	Alcohol-related cognitive bias (approach bias and attention bias)	n.r.	6
Cohort from "The adolescent brain" project, Germany								
Jurk 2016[17]	Adolescents 14y	92	Alcohol (g/week)	4y	Varying (mean (SD) for males 2.5 (5.0) g/week; mean (SD) for females 2.7 (6.3) g/week.	Cognitive control abilities	Yes	6
College / University students								
Cohort University of Santiago de Compostela, Spain								
López-Caneda 2013[9]	University students 18-19y	57	Binge drinking vs. non-binge drinking	2y	Varying (drinks per episode: 1.7 (SD 1.3) in controls and 5.6 (SD 2.6) in binge drinkers)	Visual attention	n.r.	7
Mota 2013[10]	University students 18-19y	89	Binge drinking, ex-binge drinking vs. non-binge drinking and vs. each other	2y	Binge drinking (≥6 alcoholic drinks on the same occasion weekly/monthly and at least 3 drinks per hour) and non-binge drinking	Memory, executive abilities	Yes	6

Studies	Sample	N	Exposure	Follow-up time	Baseline alcohol consumption	Endpoints	Multiple testing correction	Risk of bias[a]
López-Caneda 2014[19]	University students 18-19y	57	Binge drinking and ex-binge drinking vs. Non-binge drinking	2y	Varying (non-binge drinkers: 40.6 (SD 62.9) g alcohol/week. Ex-binge drinkers 128.7 (SD 56.5) g alcohol/week. Binge drinkers 373.5 (SD 268) g alcohol/week	Response inhibition	n.r.	5
Carbia 2017[11]	University students 18-19y	155	Binge drinking, ex-binge drinking vs. non-binge drinking and vs. each other	6y	Varying (non-binge drinkers: 42.19 (SD 52.79) g alcohol/week. Binge drinkers 302.46 (SD 251.13) g alcohol/week)	Working memory	n.r.	7
Carbia 2017[12]	University students 18-19y	155	Binge drinking, ex-binge drinking vs. non-binge drinking and vs. each other	6y	Varying (non-binge drinkers: 42.19 (SD 52.79) g alcohol/week. Binge drinkers 312.41 (SD 262.84) g alcohol/week)	Verbal episodic memory	n.r.	6
Carbia 2017[13]	University students 18-19y	155	Binge drinking, discontinued binge drinking vs. non-binge drinking and vs. each other	4y	Varying (non-binge drinkers: 42.19 (SD 52.79) g alcohol/week. Binge drinkers 302.46 (SD 251.13) g alcohol/week)	Decision making	n.r.	6
Cohort of University of Brussels, Belgium								
Petit 2014[20]	University students 22y	30	Binge drinking vs. non-binge drinking	1y	Varying (controls 4.5 (SD 3.3) doses/week. binge drinkers 32.1 (SD 21.2) doses/week	Alcohol cue reactivity (cognitive bias)	n.r.	6

[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'

g: gram; n.r.: not reported; SD: standard deviation; y: year.

Table 2. Detailed NOS scores sorted by first author

	Selection				Comparability	Outcome			Total score (maximum 9)
	Representa-tiveness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome not present at start	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow up long enough	Adequacy of follow-up	
Boelema 2015[6]	1 (A)	1 (A)	0 (D)	1 (A)	2 (AB)	1 (A)	1 (A)	0 (D)	7
Carbia 2017[11]	1 (B)	1 (A)	1 (A)	1 (A)	1 (A)	1 (A)	1 (A)	0 (C)	7
Carbia 2017[12]	1 (B)	1 (A)	1 (A)	1 (A)	0 (C)	1 (A)	1 (A)	0 (D)	6
Carbia 2017[13]	1 (B)	1 (A)	1 (A)	1 (A)	0 (C)	1 (A)	1 (A)	0 (C)	6
Jacobus 2013[18]	0 (C)	1 (A)	1 (A)	1 (A)	0 (C)	1 (A)	1 (A)	0 (D)	5
Jacobus 2016[23]	1 (A)	1 (A)	1 (A)	0 (B)	1 (A)	1 (A)	1 (A)	0 (D)	6
Janssen 2015[7]	1 (A)	1 (A)	1 (A)	1 (A)	0 (C)	1 (A)	1 (A)	0 (C)	6
Jurk 2016[17]	1 (A)	1 (A)	1 (A)	1 (A)	0 (C)	1 (A)	1 (A)	0 (D)	6

	Selection				Comparability	Outcome			Total score (maximum 9)
	Representa-tiveness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome not present at start	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow up long enough	Adequacy of follow-up	
López-Caneda 2013[9]	1 (B)	1 (A)	1 (A)	1 (A)	1 (A)	1 (A)	1 (A)	0 (D)	7
López-Caneda 2014[19]	1 (B)	1 (A)	1 (A)	1 (A)	0 (C)	0 (C)	1 (A)	0 (D)	5
Mota 2013[10]	1 (A)	1 (A)	1 (A)	1 (A)	0 (C)	1 (A)	1 (A)	0 (C)	6
Nguyen-Louie 2015[15]	1 (A)	1 (A)	1 (A)	0 (B)	2 (AB)	1 (A)	1 (A)	0 (D)	7
Nguyen-Louie 2016[16]	1 (A)	1 (A)	1 (A)	1 (A)	2 (AB)	1 (A)	1 (A)	0 (D)	8
Nguyen-Louie 2017[24]	1 (A)	1 (A)	1 (A)	0 (B)	2 (AB)	1 (A)	1 (A)	0 (D)	7
Nguyen-Louie 2018[25]	1 (A)	1 (A)	1 (A)	0 (B)	0 (C)	1 (A)	1 (A)	0 (D)	5
Petit 2014[20]	1 (B)	1 (A)	0 (D)	0 (B)	2 (AB)	1 (A)	1 (A)	0 (D)	6
Squeglia 2009[14]	1 (A)	1 (A)	1 (A)	0 (B)	1 (A)	1 (A)	1 (A)	1 (A)	7
Squeglia 2012[22]	0 (C)	1 (A)	1 (A)	0 (B)	2 (AB)	1 (A)	1 (A)	0 (D)	6
Wetherill 2013[21]	0 (C)	1 (A)	1 (A)	1 (A)	2 (AB)	1 (A)	1 (A)	0 (D)	7

Letters A, B, AB, 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.

3.1 High school students

The committee identified 12 studies on the association between alcohol use and cognitive functioning among high school students,[6,7,14-18,21-25] and prioritised six studies based on the study quality. For these studies two cohorts were used, one from the USA and one from the Netherlands.

Studies of sufficient quality

Cohort of "Youth at Risk for Alcoholism", San Diego, USA

Five studies of sufficient quality (NOS score 7 or 8) were based on an American cohort of middle school students who had no or minimal alcohol consumption at baseline. These five studies were performed by the same research group.

In the first study (Squeglia et al., 2009;[14] NOS score: 7), researchers selected 76 participants aged 12-14 years at baseline for their analyses; 25 adolescents who transitioned into heavy drinking during the 1-5 years of follow-up, 11 who transitioned into moderate drinking, and 40 demographically-matched controls who remained non-users throughout the follow-up. Relative reduction of visuospatial functioning over time was observed in girls with more drinking days in the past year as measured at follow-up ($\beta = -0.33$; $p<0.05$). No association between more drinking days

and visuospatial functioning was found for boys. Furthermore, no associations were found on attention and working memory, learning and memory, and executive functioning/planning in either girls or boys. Authors did not state whether or not differences in cognitive functioning were present at baseline. By creating composite scores for cognitive domain groups, and thus reducing the number of dependent variables, they adjusted for multiple testing.

In a second study (Wetherill et al., 2013;[21] NOS score: 7) the investigators performed their analyses on a selection of 40 participants aged 12-16 years at baseline who were matched on demographics: 20 who had transitioned into heavy drinkers at approximately 3 years of follow-up and 20 who were continuous non-drinkers. No baseline differences in response inhibition were present. The authors found no association between heavy drinking and response inhibition in this study.

In a later study with a larger sample (n=234) of adolescents aged 12 to 14 years at baseline and a follow-up of 1-9 years (Nguyen-Louie et al., 2015;[15] NOS score: 7), a higher level of alcohol use was associated with a relative reduction in verbal memory (β = -0.15) and visuospatial ability (β = -0.19), and an unexpected relative improvement of working memory (β = 0.12). No significant associations were found for psychomotor and processing speed. It was not reported whether or not baseline differences in cognitive functioning were present. The authors reduced the number of variables in the analyses by grouping the 19 neuropsychological test variables into five cognitive domains.

A comparison between those who started moderate (non-binge) drinking, binge drinking and extreme binge drinking was performed in a fourth study (Nguyen-Louie et al., 2016;[16] NOS score: 8). In a sample of 112 adolescents aged 12 to 16 years at baseline, extreme binge drinking predicted relatively poor scores on verbal learning and memory (in three out of ten measures of verbal learning and memory in the most comprehensive model) after a follow-up time of 4-9 years. Group comparisons used Bonferroni corrected tests. No association was found on any of the measures of verbal learning and memory when comparing 'normal' binge drinkers with either extreme binge drinkers or moderate (non-binge) drinkers. No significant baseline differences were present between the drinking groups for the measures of cognitive functioning.

In a fifth study, Nguyen-Louie et al. (2017)[24] (NOS score: 7) included 215 adolescents aged 12-15 years at baseline who started drinking alcohol during the (on average) 7 years after the first assessment. The authors used 26 neuropsychological test variables that were clustered into six domains to reduce potential type I error and redundancy among outcome measures: verbal learning and memory, cognitive inhibition, psychomotor speed, working memory, visual attention, and visuospatial ability. They found that an earlier age of onset for alcohol use was associated with a

relative decrease in visual attention (β = 0.106, T_{214} = 2.0, p = 0.048) and psychomotor speed (β = 0.137, T_{214} = 2.6, p = 0.042). Age of first drink was not a significant predictor for the other outcomes of interest (verbal learning and memory, cognitive inhibition, working memory, and visuospatial ability). In a subset of 127 participants who started weekly drinking during follow-up, the authors found that an earlier age of onset for weekly drinking was associated with decreased working memory (β = 0.304, T_{126} = 2.59, p = 0.014) and decreased cognitive inhibition (β = 0.313, T_{126} = 2.26, p = 0.030). Age of weekly drinking onset was not significantly associated with verbal learning and memory, psychomotor speed, visual attention and visuospatial ability. It was not clear whether or not baseline differences in cognitive functioning were present.

"TRAILS" cohort, the Netherlands

In a study in the Netherlands (Boelema et al., 2015;[6] NOS score: 7) the focus was on the association between alcohol use and executive functioning in 2,230 participants who were 11 years old at baseline and were followed up for approximately eight years. The authors created 6 drinking pattern groups based on follow-up drinking behaviour: chronic heavy drinkers, heavy drinkers who decreased their use over time, heavy drinkers who increased drinking, infrequent heavy drinkers, light drinkers, and non-drinkers. Within these groups 77-95% was alcohol naive at baseline. No significant associations were observed between the type of drinker and the development of the executive functions (inhibition, working memory, shift attention, and sustained attention). To reduce type I error the authors set the α at < 0.01. Furthermore, no baseline differences were present for cognitive measures between the drinking groups.

The remaining studies

Cohort of "Adolescent Cannabis Users", San Diego, USA

Jacobus et al. (2013)[18] (NOS score: 5) selected binge drinkers (n=17), binge drinkers with current marijuana use (n=21), and controls with no alcohol use (n=16) between 16-20 years of age from a larger American ongoing longitudinal study (n=168) to report on cognitive functioning. The committee was only interested in the differences between the binge drinkers and the controls. Controls were alcohol naive at baseline, binge drinkers had an average alcohol use of 10 drinks per month at baseline. The authors measured five neuropsychological domains (complex attention, processing speed, verbal memory, visuospatial functioning, and executive functioning) and composed a global neurocognitive functioning score for baseline, 1.5 years and 3 years of follow-up. No differences were observed between the groups at baseline cognitive functioning. They observed a significant group x time interaction, but this was driven by a difference between the binge drinking group and the group who combined binge drinking and marijuana use. No difference was observed between the binge drinkers and the control group with respect to cognitive functioning.

Cohort of "Youth at Risk for Alcoholism", San Diego, USA

A study (Squeglia et al., 2012;[22] NOS score: 6) was conducted among 40 participants aged 12-16 years of age at baseline. The continuous non-drinkers had 0.05 lifetime alcohol occasions at baseline, while the group who transitioned into heavy drinkers had 1.50 lifetime alcohol use occasions at baseline. The authors investigated the risk of transitioning into heavy drinking on visual working memory. They used four measures for visual working memory: 2 and 6-dot accuracy, and 2 and 6-dot reaction time. At baseline, the group who transitioned into heavy drinking performed significantly faster on the 2-dot condition than the continuous non-drinkers. On the other measures the two groups were statistically equivalent at baseline. The authors found significant group x time interactions for the 2 and 6-dot reaction time. Adolescents who transitioned into heavy drinking had attenuated decreases in reaction time compared to continuous non-drinkers. Specifically for the 2-dot condition, this means that that groups were more comparable after approximately 3 years of follow-up than at baseline. They adjusted for multiple testing.

Jacobus et al. (2016)[23] (NOS score: 6) assessed different domains of cognitive functioning (complex attention, processing speed, verbal memory, visuospatial functioning and executive functioning) from a battery of 23 tests in three groups which were demographically matched: alcohol initiators, alcohol and marijuana initiators and non-users at baseline and at the follow-up assessment 6 to 8 years later. For this report the committee was only interested in the differences between alcohol initiators and continuous non-users, decreasing the total number of participants from 69 to 46. Participants were 12 to 14 years old at baseline. No significant associations were found for any cognitive domain. The authors do not report whether or not there were significant differences in cognitive functioning between the drinking-groups.

In the final study of this series, Nguyen-Louie et al. (2018)[25] (NOS score: 5) included 133 adolescents aged 12 to 15 years at baseline. All participants transitioned into drinkers during the 6 years of follow-up. The authors made a distinction between non-weekly drinkers at follow-up and weekly drinkers at follow-up. They found no significant differences in visual working and memory (measured with 2 and 6-dot condition % correct and response time) between the two groups. No group x time interactions were reported. Based on visual inspection of the baseline values of the visual working and memory tests, there were no baseline differences between the groups. Since there were also no significant differences at follow-up, it is unlikely that a group x time interaction was present in this sample.

"Health Behaviours in School-aged Children" cohort, the Netherlands

A study conducted in the Netherlands followed a group of 378 adolescents aged 12 to 18 years at baseline for two years (Janssen et al. (2015);[7] NOS score: 6). Approximately 23% used alcohol on a weekly basis at

baseline. Among other aims they investigated whether drinking history predicted alcohol-related cognitive biases. Approach bias and attentional bias both assess the attractiveness of alcohol. At baseline no correlation was found between alcohol use and the measures for cognitive biases. No association was observed for the extent of alcohol use at baseline and approach and attentional bias at follow-up. The effect of (changes in) alcohol use during follow-up time on both biases was not assessed.

Cohort from "The adolescent brain" project, Germany

A study in Germany by Jurk et al. (2016)[17] (NOS score: 6) assessed the association and alcohol use during adolescence (from age 14 up to 18 years) and cognitive control parameters (inhibition and switching). The participants were already drinking at baseline, boys had a mean weekly alcohol use of 2.68 gram and girls 2.51 gram (range 0-31.21gram/week). At baseline no correlations were found between alcohol use and cognitive control parameters. Participants continued and increased drinking during the 4 year follow-up. The amount of alcohol use at the age of 14 years was not predictive for cognitive control parameters at the age of 16 years and the amount of alcohol use at the age of 16 years was not predictive for the parameters at the age of 18 years. This indicates that low alcohol consumption during mid-adolescence did not impair maturation of switching and inhibition. The authors corrected for multiple testing. The authors also report on cumulative alcohol exposure between 14 and 18 years of age which was analysed in relation to neural activation at 14, 16, and 18 years of age. However, this measure of cumulative alcohol exposure does not allow longitudinal analyses of alcohol exposure in relation to later life neural activation (for example: alcohol use at 18 years of age is part of the analysis at 14 years of age). Therefore, the committee did not include these findings in their review of the available literature.

Cohort of Oregon Health and Science University, USA

The study by Jones et al. (2017)[26] (NOS score: 5) focused on impulsive choice in 116 adolescents aged 10-17 years at baseline. The cohort had minimal alcohol use at baseline (≤10 lifetime alcohol drinks). The authors were interested in the influence of drinking status and family history of alcohol use disorder on the association between age and impulsive choice. In their full multilevel model (including both family history, drinking status and their interaction) they found a significant interaction term ($b = 1.090$, $p < 0.05$, β 0.298). However, they did not present a subsequent stratified analysis for drinking status. Visual inspection of the figure in the paper suggests that those who initiated binge drinking during the study period (of up to 8 years) had worse outcomes if they had a family history of alcohol use disorder. But as the committee is not able to determine the influence of drinking status based on the presented data the study is not included in the advisory report and the summary table of this background document.

3.3 Conclusions on high school students

In total, 12 studies on high school students were found, six of which were of sufficient quality. Five of them were based on one American cohort. Participants from this cohort were alcohol naive or had a very low level of alcohol consumption at baseline. In one of these American studies, no difference was found in cognitive functions between those who initiated binge drinking compared to non-drinkers. In the other four, differences were found on several cognitive functions between alcohol consumers and non-drinkers, where alcohol consumers showed relatively poor outcomes compared with controls or where more drinks or starting at a younger age was associated with relatively poor cognitive outcomes. Of note is that one of the American studies found an association between higher alcohol consumption and improvements in working memory. In the sixth study of high quality (a Dutch cohort) no associations were found between alcohol consumption (including binge drinking) and cognitive functioning.

In the remaining studies, based on four cohorts, no associations were found between alcohol consumption and relatively poor cognitive functioning or cognitive biases (only one study available on this outcome).

Table 3 shows an overview of the results of studies focusing on the association between alcohol consumption and cognitive functioning among high school students.

Table 3. Overview of results of studies among high school students

Studies[a]	Alcohol consumption at baseline	Exposure	Results for measures of cognitive functioning and cognitive biases
Studies of sufficient quality (NOS-score 7 to 8)			
Boelema 2015[6] Netherlands	Varying	Different patterns of drinking (including heavy drinking) versus non-users	No association with four measures of executive functioning (inhibition, working memory, shifting attention, sustained attention)
Nguyen-Louie 2016[16] USA*	Limited	Binge drinking versus moderate drinking	No association with verbal learning and memory
		Extreme binge drinking versus moderate drinking	Relative decrease in verbal learning and memory
Nguyen-Louie 2015[15] USA*	Limited	More alcohol use	Relative decrease in verbal memory, visual memory
		More alcohol use	Relative increase in working memory
		More alcohol use	No association with processing and psychomotor speed

Studies[a]	Alcohol consumption at baseline	Exposure	Results for measures of cognitive functioning and cognitive biases
Nguyen-Louie 2017[24] USA*	Limited	Younger age of first drink	Relative decrease in psychomotor speed, visual attention No association with verbal learning and memory, cognitive inhibition, working memory or visuospatial ability
		Younger age of first weekly drinking	Relative decrease in cognitive inhibition, working memory No association with verbal learning and memory, psychomotor speed, visual attention or visuospatial ability
Squeglia 2009[14] USA*	Limited	More alcohol use	Relative decrease in visuospatial functioning among girls (no association among boys) No association with attention and working memory, learning and memory or executive functioning/planning (neither among boys or among girls)
Wetherill 2013[21] USA*	Limited	Binge drinking versus non-users	No association with response inhibition
Other studies (NOS-score 5 to 6)			
Squeglia 2012[22] USA*	Limited	Heavy drinking versus non-users	Groups become more comparable
Jacobus 2016[23] USA*	Limited	Drinking versus non-users	No association with complex attention, processing speed, verbal memory, visuospatial functioning or executive functioning
Nguyen-Louie 2018[25] USA*	Limited	Weekly drinking versus non-weekly drinking	No association with visual working memory
Jacobus 2013[18] USA	Varying	Binge drinking versus minimal drinking	No association with cognitive functioning
Janssen 2015[7] Netherlands	Varying	Number of alcoholic drinks	No association with alcohol-related cognitive biases (approach bias and attention bias)
Jurk 2016[17] Germany	Varying	More alcohol	No association with cognitive control abilities

[a] Corresponding signs mean corresponding cohort.

College/university students

The committee identified 7 studies on the association between alcohol use and cognitive functioning among college/university students,[9-13,19,20] and prioritised two studies based on the study quality. They originate from one cohort.

Studies of sufficient quality

University of Santiago de Compostela cohort, Spain

Several studies were conducted in this Spanish cohort of 18 to 19 year olds. Two were of sufficient quality: López-Caneda et al. 2013[9] (NOS score 7) and Carbia et al., 2017[11] (NOS score 7).

In a study with two years of follow-up López-Caneda et al. 2013[9] reported on the performance of a visual oddball task as a measure of visual attention in continuous binge drinkers (n=26) and non-binge drinkers (n=31). At baseline, the continuous binge drinkers drank on average 5.6 (SD 2.6) alcoholic consumptions per episode, whereas the non-binge drinkers drank on average 1.7 (SD 1.3) alcoholic consumptions. T-tests for independent samples revealed that there were no significant differences in visual attention performance between the two groups, neither at baseline nor at follow-up.

In a study with 6 years of follow-up (Carbia et al., 2017;[11] NOS score: 7), the authors studied the relationship between binge drinking trajectories and working memory in 155 university students. At baseline researches included a binge drinking group (consuming on average 302.5 g alcohol per week (SD 251.1)) and a non-binge drinking group (consuming on average 42.2 g alcohol per week [SD 52.8]). The groups did not differ in estimated intellectual level at baseline. Three out of the 16 measures of working memory showed significant relative risks that indicated relatively poor working memory in the binge drinking group when compared to the non-binge drinking group (perseverative errors, Relative Risk (RR) 1.45 95%CI 1.05-2.00; working memory span first trial of third block, RR 0.90 95%CI 0.82-0.99; working memory span third trial of fourth block, RR 0.92 95%CI 0.84-0.99). The other 13 measures were non-significant. Further, there were no significant differences in working memory between ex-binge drinkers and non-binge drinkers, and between binge drinkers and ex-binge drinkers.

The remaining studies

University of Santiago de Compostela cohort, Spain

Several studies were conducted in this Spanish cohort of 18 to 19 year olds. Two studies, both with 2 years of follow-up, explore the differences in response inhibition between drinking pattern groups (López-Caneda et al. 2012[8] [NOS score 5] and López-Caneda et al. 2014[19] [NOS score 5]). Both studies concluded that there is no significant difference between the drinking pattern groups regarding response inhibition. The 2012 study included 48 participants and made a distinction between continuous non-binge drinkers and continuous binge drinkers. The 2014 study included 57 participants, 46 of whom were also included in the 2012 study. They made a distinction between continuous non-binge drinkers, continuous binge drinkers and ex-binge drinkers. As the studies overlap substantially with regard to participants and research question regarding response inhibition, the committee only included the results of López-Caneda et al. 2014 in the advisory report and this background document as this is the most comprehensive study of the two. At baseline the participants had varying alcohol use. Those who had a continuous non-binge drinking pattern over time consumed on average 40.6 (SD 62.9) g alcohol per week at baseline, compared with 373.5 (SD 268) g

alcohol per week in the continuous binge drinking group and 128.7 (SD 56.5) g alcohol per week in the ex-binge drinking group. There were no baseline differences between the groups with respect to response inhibition.

In the study by Mota et al., 2013[10] (NOS score 6), the follow-up time was 2 years and the sample size 89. Researchers compared continuous binge drinkers, continuous non-binge drinkers and ex-binge drinkers with each other regarding memory and executive functions. At baseline there were no differences in estimated intellectual level. Twelve measures of memory were assessed. On one of these measures the authors reported a group x time interaction. However, they did not state between which groups the difference was found. Visual inspection of the data suggests that the ex-binge drinking group improved their retention score, while the other two groups showed almost no change between baseline and follow-up. The final scores at follow-up seemed similar for the three groups. Overall the committee judges that there is no difference over time in memory between the groups in this study. Furthermore, Mota et al. found no differences between the drinking pattern groups regarding executive functions (assessed with 6 measures). All post hoc pair comparisons were performed with Bonferroni adjustment for multiple comparisons.

A paper on this cohort published in PLOS One by Carbia et al., 2017[12] (NOS score: 6), reported on verbal episodic memory (a person's unique memory of a specific event) in 155 university students. At baseline, non-binge drinkers consumed on average 42.2 (SD 52.8) g alcohol per week and binge drinkers 312.2 (SD 262.8) g alcohol per week. At baseline there were no differences in estimated intellectual level. Over the 6-year follow-up period stable binge drinking and transitioning from binge drinking to non-binge drinking (versus stable non-binge drinking) were associated with a relative decreased verbal episodic memory; for stable binge drinkers on three of the thirteen measures for verbal episodic memory (RR Logical Memory I 0.94 95%CI 0.89-0.98; RR Logical Memory II 0.91 95%CI 0.87-0.97, and RR intrusion errors 1.65 95%CI 1.02-2.68), and for ex-binge drinkers on one of the thirteen measures (RR logical memory I 0.92 95%CI 0.86-0.98). No differences were found between ex-binge drinkers and stable binge drinkers. This study performed an additional analysis where they grouped the ex-binge drinkers into two categories: short-term ex-binge drinkers and long-term ex-binge drinkers and checked whether they differed from stable non-binge drinkers with regard to the three significant measures of verbal episodic memory. The authors found that short-term binge drinkers performed poorly on two of the three measures relative to the stable non-binge drinkers (RR Logical Memory I 0.94 95%CI 0.89-0.99; and RR Logical Memory II 0.91 95%CI 0.85-0.98), whereas long-term ex-binge drinkers performed similarly to the stable non-binge drinkers (RR Logical Memory I 0.96 95%CI 0.91-1.02; and RR Logical Memory II 0.93 95% 0.86-1.00).

In another paper by Carbia et al., 2017[13] (NOS score: 6), the process of decision-making was investigated using the 4-year follow-up data of 155 participants. At baseline, non-binge drinkers consumed on average 42.2 (SD 52.8) g alcohol per week and binge drinkers 302.5 (SD 251.1) g alcohol per week. At baseline there were no differences in estimated intellectual level. No differences in decision-making were observed between stable binge drinkers, subjects who stopped binge drinking and stable non-binge drinkers.

University of Brussels cohort, Belgium

Researchers from Belgium (Petit et al., 2014,[20] NOS score: 6) compared a group of binge drinkers (n=15) with controls (n=15 drinkers who were not binge drinkers). At baseline, the non-binge drinkers drank on average 4.5 (SD 3.3) alcoholic consumptions per week, whereas binge drinks drank on average 32.1 (SD 21.2) alcoholic consumptions per week. Two measurements were done one year apart. In a 2x2x2x2 ANOVA, including group (control vs. binge), sex, time, and type of stimulus (alcohol-related vs. non-alcohol-related), no significant differences were observed between the control and binge drinking group. The authors did not report on possible baseline differences in alcohol cue reactivity between the drinking groups.

3.5 Conclusions on college/university students

All 7 studies that were conducted among college/university students focused on sustained binge drinking. Two of these studies were of high quality; they originate from the same Spanish cohort.[9,11] One high quality study found no differences between sustained binge drinkers and non-binge drinkers with regard to visual attention. In contrast, the other high quality study found an association between sustained binge drinking and relatively poor working memory when compared to non-binge drinkers.

Four out of the remaining five studies were from the same Spanish cohort as the studies of sufficient quality. One of these studies found an association between higher alcohol consumption and relatively poor cognitive functioning. The other three Spanish studies did not find any differences. The last study, based on Belgian students, focused on cognitive biases and found no differences between binge drinkers and non-binge drinkers.

Table 4 shows an overview of the results of college/university students.

Table 4. Overview of results of studies among college/university students

Studies[a]	Alcohol consumption at baseline	Exposure	Results for measures of cognitive functioning and cognitive biases
Studies of sufficient quality (NOS-score 7)			
Lopéz-Caneda 2013[9] Spain*	Binge drinking and non-binge drinking	Sustained binge drinking versus non-binge drinking	No differences in visual attention
Carbia 2017[11] Spain*	Binge drinking and non-binge drinking	Sustained binge drinking versus non-binge drinking	Relative decrease in working memory
Other studies (NOS-score 5 to 6)			
Carbia 2017[12] Spain*	Binge drinking and non-binge drinking	Sustained binge drinking versus non-binge drinking	Relative decrease in verbal episodic memory
Carbia 2017[13] Spain*	Binge drinking and non-binge drinking	Sustained binge drinking versus non-binge drinking	No differences in decision making
Lopéz-Caneda 2014[19] Spain*	Binge drinking and non-binge drinking	Sustained binge drinking versus non-binge drinking	No differences in response inhibition
Mota 2013[10] Spain*	Binge drinking and non-binge drinking	Sustained binge drinking versus non-binge drinking	No differences in memory No differences in executive functioning
Petit 2014[20] Belgium	Binge drinking and non-binge drinking	Binge drinking versus non-binge drinking	No differences in alcohol cue reactivity (cognitive biases)

[a] Corresponding signs mean corresponding cohort.

04 discussion and conclusions

4.1 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 ‘cognitive functioning’.

The studies of sufficient quality were performed on a limited number of study samples, hampering the interpretation of findings. Furthermore, a large variety of cognitive measures were used in the included studies, making the studies difficult to compare. Besides, in some studies a large number of comparisons were tested, increasing the possibility of chance findings.

4.2 Final conclusions

The studies of sufficient quality were performed on a limited number of study samples (i.e. 2 for high school students and 1 for college/university students). The committee therefore concludes that the association between alcohol consumption and cognitive functioning in adolescents and young adults is unclear.

literature

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annex

A search strategy

Pubmed search 'cognition'

July 2017

This was a combined search for psychopathology and cognition.

#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 psychophysiolog*[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 involutional psychos*[tiab] OR involutional 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 (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 ("Ethamoxytriphetol"[Mesh] OR "Ethanolamines"[Mesh] OR "Ethylene Chlorohydrin"[Mesh] OR "Mercaptoethanol"[Mesh] OR "Phenylethyl Alcohol"[Mesh] OR "Trifluoroethanol"[Mesh])) OR ethanol[tiab].

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

Total

#1 AND #2 AND #3 AND #4 + last 10 years = 5,185 hits.

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