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# Alcohol and Brain Development in Adolescents and Young Adults: A Systematic Review of the Literature and Advisory Report of the Health Council of the Netherlands

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## ABSTRACT

Young people, whose brains are still developing, might entail a greater vulnerability to the effects of alcohol consumption on brain function and development. A committee of experts of the Health Council of the Netherlands evaluated the state of scientific knowledge regarding the question whether alcohol negatively influences brain development in young people. A systematic literature search for prospective studies was performed in PubMed and PsychINFO, for longitudinal studies of adolescents or young adults ranging between 12 and 24 y of age at baseline, investigating the relation between alcohol use and outcome measures of brain structure and activity, cognitive functioning, educational achievement, or alcohol use disorder (AUD), with measures at baseline and follow-up of the outcome of interest. Data were extracted from original articles and study quality was assessed using the Newcastle-Ottawa Scale. A total of 77 studies were included, 31 of which were of sufficient quality in relation to the study objectives. There were indications that the gray matter of the brain develops abnormally in young people who drink alcohol. In addition, the more often young people drink or the younger they start, the higher the risk of developing AUD later in life. The evidence on white matter volume or quality, brain activity, cognitive function, and educational achievement is still limited or unclear. The committee found indications that alcohol consumption can have a negative effect on brain development in adolescents and young adults and entails a risk of later AUD. The committee therefore considers it a wise choice for adolescents and young adults not to drink alcohol. *Adv Nutr* 2021;12:1379–1410.

**Keywords:** adolescents, young adults, alcohol, brain, epidemiology, ethanol, public policy

## Introduction

In 2014 the Dutch government changed the legal drinking age from 16 to 18 y in order to protect children and adolescents from the risks of alcohol consumption, based on experts' advice to do so. The reason for this policy change was the emerging literature indicating that underage drinking may have detrimental effects on brain development (1–4), besides the fact that acute effects of alcohol include a higher risk of accidents, violence, and other transgressive behavior (5–8), and that chronic alcohol consumption increases the

risk of many diseases and disorders (9–16). That is why the Dutch advice for the general population is not to drink alcohol, or at least  $\leq 1$  glass/d. Especially for young people, alcohol is harmful. For example, they become intoxicated more quickly than adults (7, 17). Furthermore, drinking at a young age is associated with drinking later in life (18, 19). Also, it is widely assumed that alcohol negatively affects brain development, which continues into the late 30s (20).

In 2016, the Dutch State Secretary for Health, Welfare and Sport asked the Health Council of the Netherlands

what, according to the latest scientific knowledge, is known about the effects of alcohol on the brain of young people between the ages of 12 and 24 y and whether such possible effects are reversible. One of the reasons for this request may have been that conflicting data concerning adverse effects were published since the policy change, including a large prospective study in the Netherlands (21) showing *no* adverse effects of adolescent binge drinking on a number of neuropsychological functions, which made it to the front page of a national newspaper (22). The State Secretary also asked for the consequences of alcohol consumption at a young age on the extent of use of alcohol in adulthood to be evaluated. A committee was formed from experts from different relevant areas of scientific expertise.

Over the past decade, a large number of scientific reviews have addressed the topic of alcohol consumption in relation to brain development in adolescents and young adults indicating detrimental effects of alcohol on brain development (1–4, 23–41). We briefly highlight the findings from some of these reviews. Feldstein Ewing et al. (41) concluded in their systematic review (SR) of 21 observational studies, of which most were cross-sectional, that alcohol consumption during adolescence is associated with differences in both brain structure and function during development. Furthermore, based on 7 observational studies in adolescents, of which 1 was longitudinal and 6 were cross-sectional, Eloffson et al. (4) concluded that alcohol consumption is associated with reduced white matter integrity, particularly in the superior longitudinal fasciculus. Based on a review of 38 observational, also mainly cross-sectional, studies in adolescents, Silveri et al. (34) concluded that differences in brain structure, white matter architecture, and brain function associated with alcohol consumption were mainly present in the frontal lobe (in 61% of the studies), followed by the temporal lobe (45% of the studies) and parietal lobe (32% of the studies). Alcohol consumption during adolescence or young adulthood may influence cognitive functions (2, 24, 30), such as attention, memory, decision-making, planning, and learning ability. In addition, alcohol consumption appears to be associated with automatically activated appetitive responses to alcohol cues, known as alcohol-related cognitive bias (“being hypersensitive for cues of alcohol in the environment”). Such

cognitive biases are likely to contribute to the development of problem use (37). Adverse effects on cognitive function may, in turn, influence educational achievement, an important determinant of vocational success, income, health, social status, and quality of life (42). However, alcohol consumption is likely to also affect educational achievement directly, for example as a result of hangovers or sleep deprivation (43). A 2011 SR, however, reported mixed findings on the relation between alcohol consumption and educational consequences based on 3 longitudinal studies (18). In 2011, McCambridge et al. (18) performed an SR of prospective cohort studies into the adult consequences of late-adolescent alcohol use, with  $\geq 3$  y of follow-up. 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 alcohol use disorder (AUD) or alcohol dependence (AD) (18). In 2014, Maimaris and McCambridge (44) performed an SR on the association between the age of first drink (AFD) and adult alcohol problems. Only cohort studies comprising general population samples were included, with a requirement of  $\geq 3$  y follow-up between the initial measurement of AFD in adolescence and the assessment of alcohol-related outcomes. Based on 5 studies (4 study samples), the authors concluded that there is some evidence for an association between AFD and AD, but this disappears with more rigorous control for confounding. The authors also mention that over-adjustment 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 aforementioned reviews of human research (2, 4, 18, 30, 34, 37, 41, 44–46) point out several limitations regarding the interpretation of the available evidence, such as small sample sizes (18, 41), the small number of longitudinal studies (4, 18, 30, 34, 41, 44), overlap in study samples (18), and vulnerability to bias (18). Neurobiological differences may exist before the initiation of alcohol use. In addition, confounding or effect modification by gender, concurrent marijuana use, or comorbid psychiatric disorders may play a large role. Observed differences could also reflect antecedents of alcohol use, such as age of first use, family history of addiction, childhood maltreatment, or comorbid psychiatric conditions (34).

The committee decided to limit the scope of the review to 1) human studies, 2) with a prospective design, 3) on the following outcomes: brain structure and activity, cognitive function, educational achievement, and AUD. These 3 decisions will be further explained in what follows. Many reviews of experimental animal studies on the effects of alcohol are available (24, 35, 47–49), yet the committee was not aware of any SR. In a recent review from Spear (47), human observational research and experimental animal research were presented together and compared. The review referred to 3 studies in which alcohol intake affected gray matter volume and white matter volume and quality in adolescent rats. Based on other experiments presented in the review, adolescent rats repeatedly exposed to ethanol vapors

This systematic review (SR) has been adapted from a Dutch advisory report to substantiate national public health policy. The report and SR have been prepared and funded by the Health Council of the Netherlands, an independent scientific advisory body whose legal task it is to advise ministers and Parliament in the field of public health/health care research. KPB, SIC, SD, RCMEE, AEG, KGM, WAMV, TjDv, RWW, and JO have been offered financial compensation for meeting attendance and travelling expenses from the Health Council of The Netherlands. Author disclosures: The Board of the Health Council consciously weighed the interests and decided that KPB, SIC, SD, RCMEE, AEG, KGM, WAMV, TjDv, and RWW could participate in the committee without restrictions. JO could participate with the restriction that he would withdraw from the discussion if a subject would touch on specific diagnostic questionnaires for psychopathology in children for which JO receives royalties (this did not occur during the course of the project). All other authors report no conflicts of interest.

Supplemental Methods 1–3, Supplemental Tables 1–4, and Supplemental Results 1–5 are available from the “Supplementary data” link in the online posting of the article and from the same link in the online table of contents at <https://academic.oup.com/advances/>.

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Abbreviations used: AA, alcohol abuse; AD, alcohol dependence; AFD, age of first drink; AUD, alcohol use disorder; FA, fractional anisotropy; NOS, Newcastle-Ottawa Scale; SR, systematic review.

**TABLE 1** Summary of the PICOS criteria used to identify studies for inclusion

Parameter	Description
Population	Adolescents and young adults within the age range of 12–24 y at baseline
Intervention	Alcohol consumption
Comparator	Less or no alcohol consumption
Outcome	Measures of brain structure and activity, cognitive functioning, educational achievement, or alcohol use disorder
Study design	Human prospective studies with measures at baseline and follow-up of the outcomes of interest

showed an aberrant electrophysiological pattern (decrease in P300 amplitude), consistent with a disruption in the development of the hippocampus, a brain area involved in memory. According to Spear, cognitive studies in rodents generally have revealed that repeated exposure to alcohol during adolescence has minimal effects on simple spatial learning tasks and on more challenging learning tasks like 5-choice serial reaction time tests. However, when the task demands require some degree of cognitive flexibility, deficits have often emerged. It was argued by the committee that, although animal studies have unique merit in delineating causal mechanisms in the effects of alcohol on the brain, they also have their limitations: studied dosages (sometimes unrealistically high) as well as studied outcomes in animal studies limit extrapolation to humans.

The main drawback of cross-sectional studies is that they cannot disentangle causes and consequences. Neurobiological differences may have existed before the initiation of alcohol use and they could even be the cause of early drinking. Therefore, the committee focused on prospective studies with repeated measurements of the outcome in order to identify whether or not outcome differences were already present at baseline to get insight into reverse causation.

Because the committee hypothesized that changes in brain structure or activity could translate into changes of cognitive function and eventually educational performance, the committee decided to focus not only on measures of brain structure and brain activity, but also on the association between alcohol consumption and both cognitive function and educational achievement. For the question about the influence of alcohol consumption at a young age on the use of alcohol in adulthood, the committee focused on AUD, previously divided into 2 types of problematic drinking: alcohol abuse (AA) and AD. In AUD someone's activities, behavior, or relationships suffer from the use of alcohol and the person has difficulty stopping or cutting back alcohol use, or is addicted to alcohol.

Existing reviews either included both cross-sectional research and prospective studies, or were not *systematic* reviews, or were not sufficiently recent or specific. Therefore, the completeness of selection and judgment of the literature in existing reviews were uncertain. The committee therefore performed an SR of human prospective studies on alcohol consumption and both brain function and development and AUD in adolescents or young adults, including a quality assessment of the included studies.

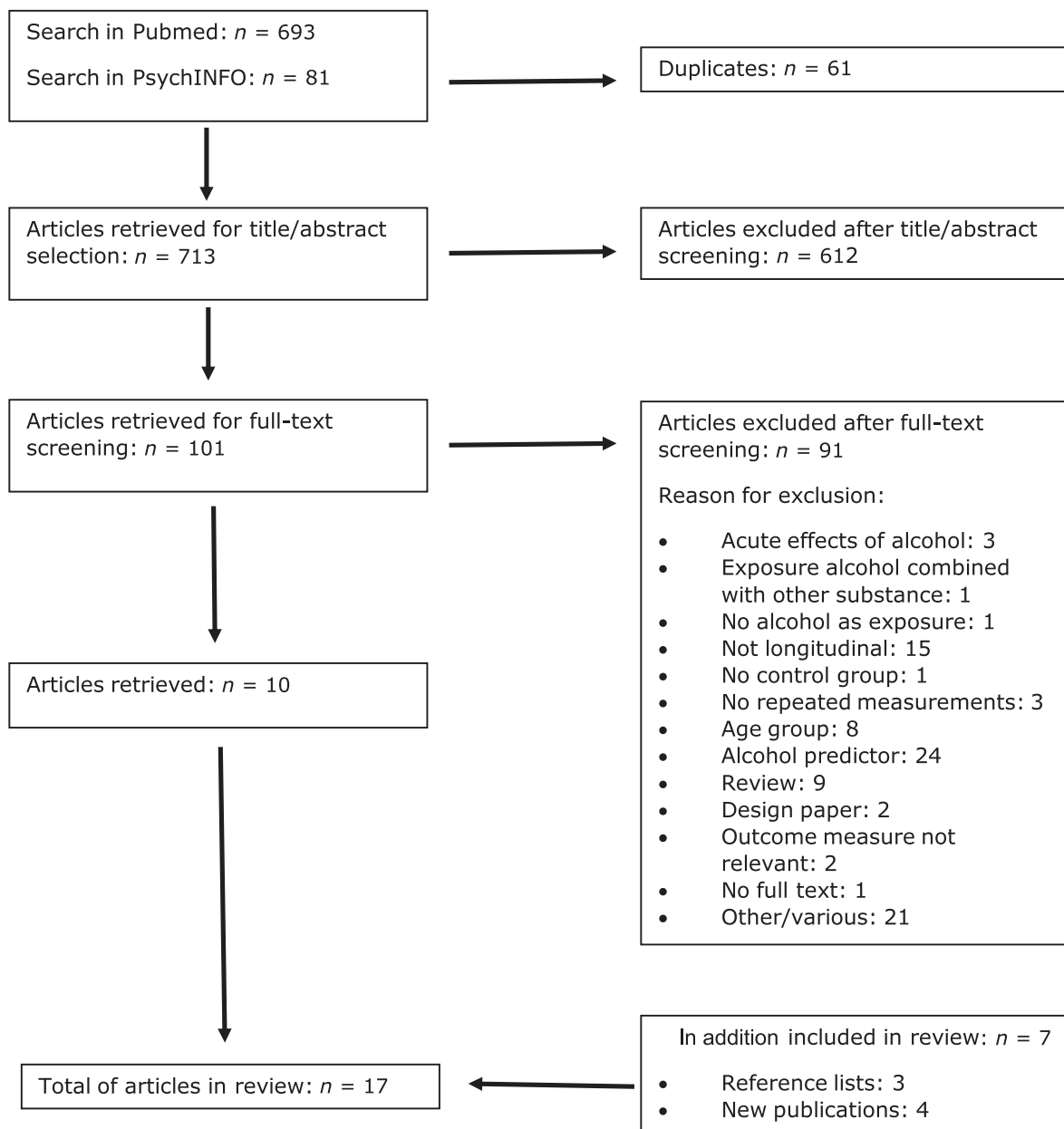
## Methods

The 10 committee members, covering the research fields of (alcohol) addiction, cognition, neurology, neuropsychology, neuroimaging, social sciences, epidemiology, and statistics, filled out declarations of interest, which were published (in Dutch) on the website of the Health Council ([www.gezondheidsraad.nl](http://www.gezondheidsraad.nl)). The committee performed an SR of peer-reviewed longitudinal studies of alcohol consumption by young people (adolescents and young adults) in relation to outcome measures of 1) brain structure and activity, 2) cognitive functioning including alcohol-related cognitive biases, 3) educational achievement, and 4) AUD. The SR was performed in accordance with the Meta-analysis and Systematic Reviews Of Observational Studies in Epidemiology (MOOSE) guidelines (see **Supplemental Methods 1**) (50).

### Identification and quality appraisal of longitudinal studies

Published articles (in English) up to and including May 2018 were retrieved by the committee and librarian from PubMed and PsychINFO, and complemented by hand searches of reference lists and correspondence with researchers in the field. Included were longitudinal studies of alcohol consumption by adolescents and young adults within the age range of 12–24 y at baseline with repeated measurements of any of the 4 outcomes of interest (**Table 1**). For the outcome educational achievement (mainly school dropout or highest attained degree), by definition, there are no differences yet at baseline. For reasons of consistency, within the topic of educational achievement, the committee also included studies with only 1 measurement of educational marks. For studies concerning AUD, we also included studies that lacked a baseline assessment of AUD for subjects aged 16 y or younger, because the committee regarded the risk of already existing AUD as low in this age group.

The committee excluded 1) studies on the acute effects of alcohol; 2) studies of specific subgroups, because findings could not be generalized to the general population (e.g., subjects with attention deficit hyperactivity disorder or speech and language impairment, patients in drug clinics, patients with bipolar disorder); 3) studies without a control group with no alcohol use; 4) studies with only combined use of alcohol and other substances (such as marijuana); and 5) studies in which the onset of alcohol consumption was assessed retrospectively, because of the risk of recall bias (51, 52). In total, the committee included 77 studies



**FIGURE 1** Flowchart of studies on neuroimaging and neurophysiology.

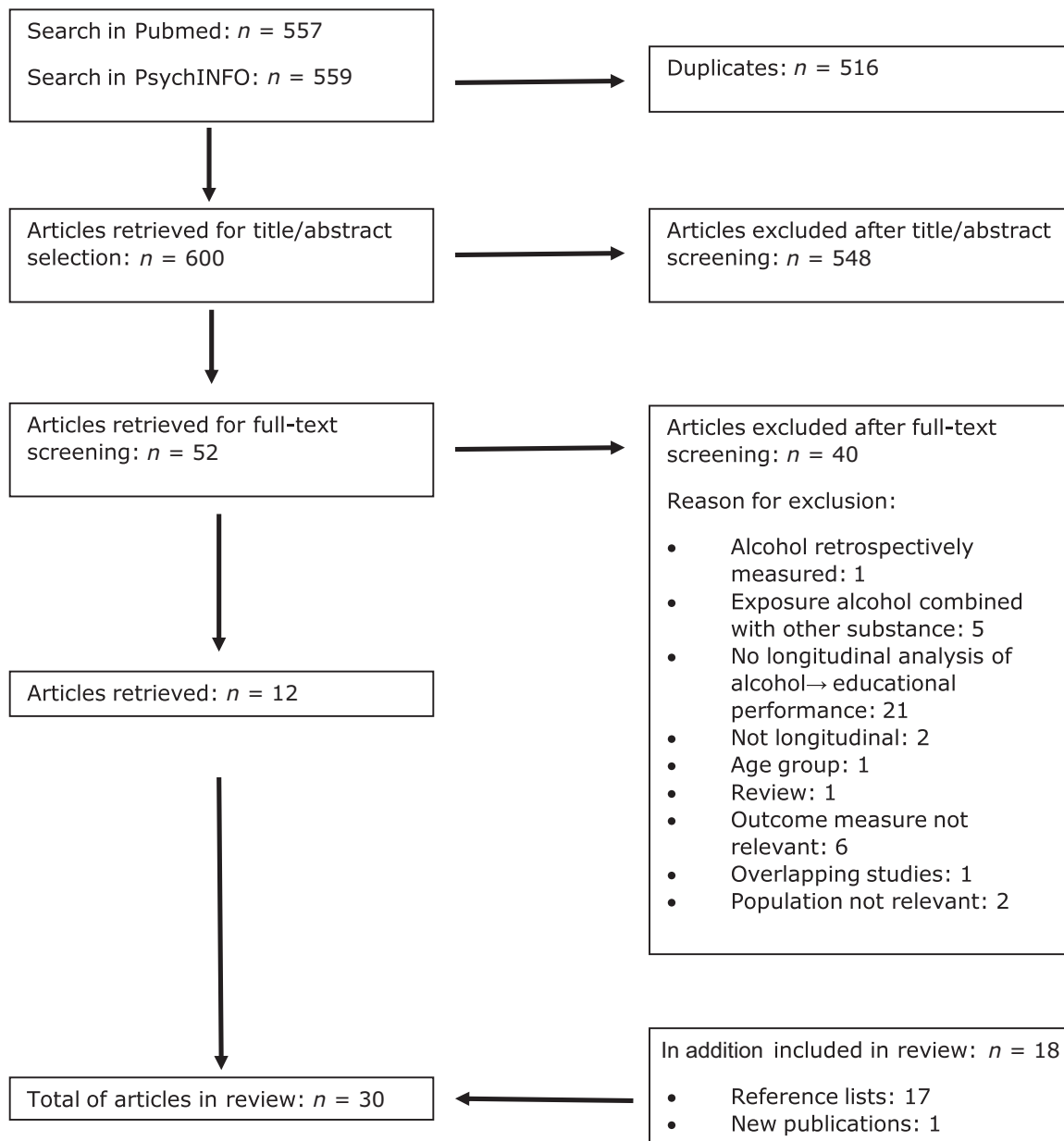
(19, 21, 53–127), including 17 studies on neuroimaging and neurophysiology (53–69), 19 studies on cognitive function (21, 53–55, 58, 60, 63, 67, 69–79), 30 studies on educational achievement (19, 80–108), and 23 studies on AUD (19, 93, 105, 106, 109–127) (see **Supplemental Methods 2** for search strategies and **Figures 1–3** for flowcharts).

### Study quality assessment and weighing of study quality

The risk of bias for each study was assessed with the Newcastle-Ottawa Scale (NOS) (128) (see **Supplemental Methods 3** for the scoring method and **Supplemental Table 1** for the scores per study), based on consensus between 2 independent judges (pairs of authors). The NOS rating

system scores studies from 0 (highest risk of bias) to 9 (lowest risk of bias) on the nature of the study sample, exposure and outcomes assessments, baseline differences in the assessed outcome, attrition bias, and potential confounding. The committee judged gender, age, use of other drugs or smoking, externalizing behavior, and family history of AUD as important potential confounders. The committee judged studies where the outcome was assessed before the *initiation* of alcohol consumption to be of high value for the research questions. In that situation, the baseline measurements cannot (yet) be affected by alcohol consumption. In cases of large study samples or many statistical comparisons within a study, the possibility of chance findings is relatively high.





**FIGURE 2** Flowchart of studies on educational achievement.

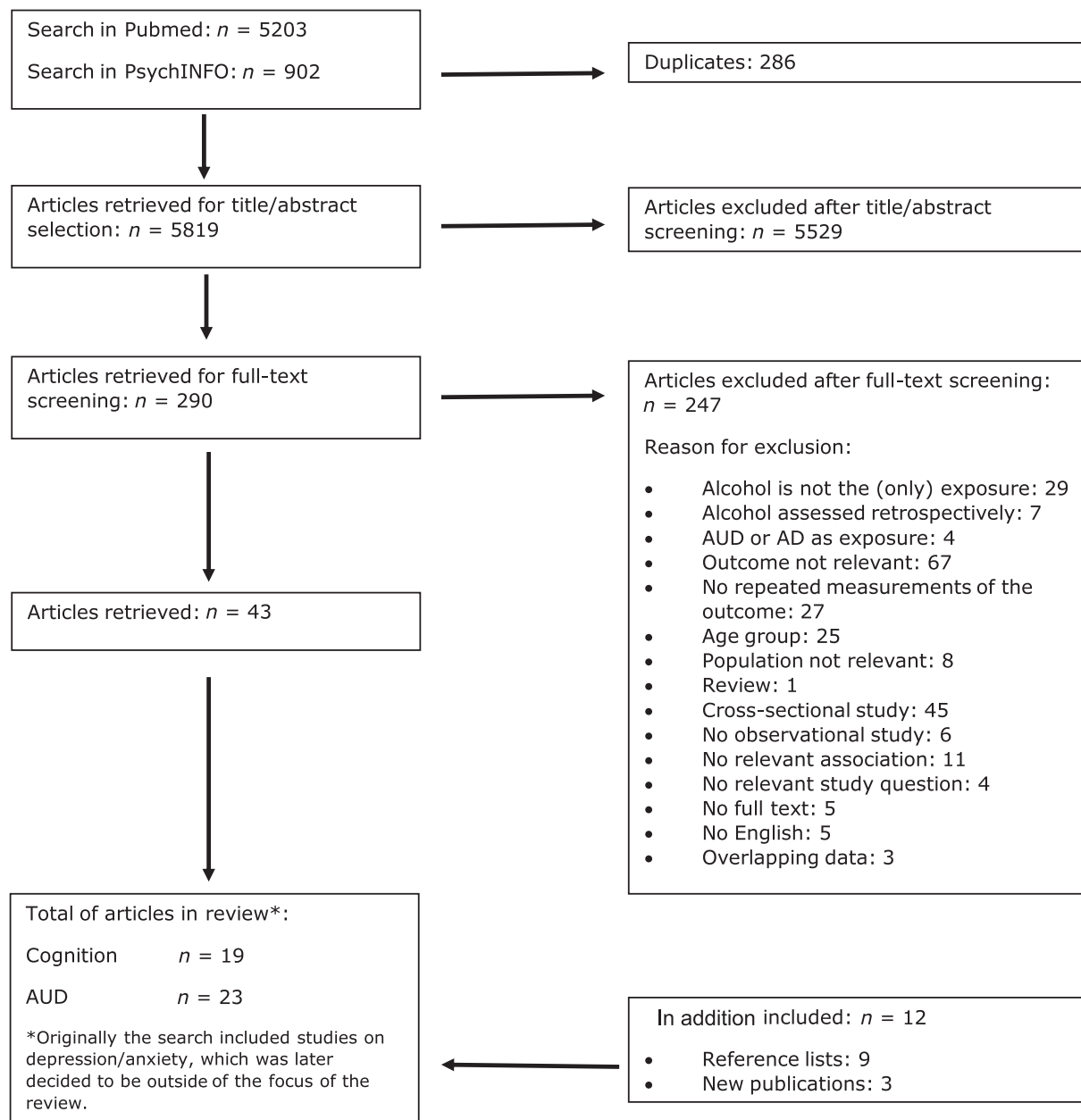
Therefore, the committee reported for each study whether results were based on a priori defined hypotheses (such as a priori defined brain “regions of interest”), or whether results were adjusted for multiple testing to limit chance findings. The committee also weighed whether results were based on independent data, i.e., different study populations.

### Data extraction and data synthesis

Data were extracted using structured extraction forms which included information on the study sample, measurement of exposure and outcomes measures, statistical analysis (including covariates, stratification or matching factors, and correction for multiple testing), results, and limitations. All relevant exposure and outcome measures were extracted,

based on the most extensive statistical models in terms of adjustment reported in the original studies.

The committee judged studies with an NOS score of  $\geq 7$ , with at least minimal adjustment for confounding, to be of sufficient quality and the remainder of the evidence of lower quality in relation to the study questions. In the description of the results, results were presented separately, if possible, for high school students and college/university students, i.e., providing a rough distinction between groups that differ in age, social circumstances, and drinking patterns. Conclusions of the committee were primarily based on the studies of sufficient quality, whereas the results of the studies with lower NOS scores were used as ancillary material. Conclusions were derived only if  $\geq 3$  studies were



**FIGURE 3** Flowchart of studies on cognitive function and AUD. AD, alcohol dependence; AUD, alcohol use disorder.

available with sufficient quality based on  $\geq 3$  different study populations. Regarding all outcomes, the large heterogeneity of studies did not allow quantitative conclusions.

## Results

### Neuroimaging and neurophysiology

The committee identified 17 longitudinal studies based on 11 cohorts (**Table 2, Supplemental Results 1**) (53–69), published between 2009 and 2018. Out of the 17 studies, 6 publications were from 1 study population by an (American) research group (53, 60–63, 69) and 2 from 1 Spanish study population (54, 55). In total, 10 studies were conducted

in the United States (53, 56, 59–65, 69) and 7 in Europe (54, 55, 57, 58, 66–68), of which 1 was in the Netherlands (66). The number of participants ranged between 30 and 483. The study populations included adolescents or young adults (56, 59, 66, 67), or subgroups such as middle-school students (53, 60–63, 69), college or university students (54, 55, 57, 58, 65, 68), or twins from a national twin registry (64). Most of the studies were focused on initiation of heavy or binge drinking or sustained heavy or binge drinking (54, 55, 57–63, 65, 68), and a few on regular drinking (64, 66, 67) or initiation of (regular) drinking (53, 56, 69). Outcomes included structural brain measures including volumes of gray matter (53, 56, 59, 61, 62, 64) and white matter (56, 59,

**TABLE 2** Longitudinal studies (grouped by study population and publication date) on the association between alcohol consumption and neuroimaging and neurophysiological outcomes<sup>1</sup>

Studies	Sample	n	Exposure	Follow-up time, y	Baseline alcohol consumption	Endpoints	FDR correction	Risk of bias <sup>2</sup>	Results
Cohort of Youth at Risk for Alcoholism, University of California, San Diego, USA									
Squeglia et al. (60)	Middle school students, 12–16 y	40	Initiation of BD vs. minimal drinking	3	Limited ( $\leq 10$ lifetime drinks, never $> 2$ drinks/wk)	fMRI “visual working memory”	Yes	6	Visual working memory task: no differences; lower activation in 2 of 5 ROIs at baseline, increased BOLD response after follow-up
Wetherill et al. (63)	Middle school students, 12–16 y	40	Initiation of BD vs. minimal drinking	3	Limited ( $\leq 1$ lifetime drinks)	fMRI “response inhibition”	Yes	7	Response inhibition task: no differences; lower activation at baseline, increased activation in 5 regions
Squeglia et al. (61)	Middle school students, 12–17 y	40	Initiation of BD vs. no drinking	3	Limited ( $\leq 10$ lifetime drinks, never $> 2$ drinks/wk)	Brain volume	Yes	6	Accelerated reductions
Squeglia et al. (62)	Middle school students, 12–19 y	134	Initiation of BD vs. no drinking	8	Limited (mean reported lifetime drinking occasions: 0.07 in nondrinkers and 16 in heavy drinkers)	Gray and white matter volume	No	5	Gray matter: more rapid volume decline; white matter: lower volume increase
Jacobus et al. (53)	Middle school students, 12–14 y	69	Initiation of drinking vs. no drinking	6	Limited (mean of 0.04 lifetime alcohol use days at baseline)	Cortical thickness	No	6	Pre-existing differences become smaller
Nguyen-Louie et al. (69)	Middle school students, 12–15 y	133	AFD (earlier, scale), AWDO (earlier, scale)	6	Limited ( $\leq 10$ lifetime alcohol use occasions, never $> 2$ drinks/wk),	Frontoparietal context-dependent FC during visual memory task (primary outcome based on ROIs; secondary outcome based on WB analysis)	Yes	6	AFD: visual working memory task: no associations; 2 ROIs: no associations AWDO: Visual working memory task: no associations; 2 ROIs: no associations; higher activation (less negative) in 5 regions (WB)

(Continued)



**TABLE 2** (Continued)

Studies	Sample	n	Exposure	Follow-up time, y	Baseline alcohol consumption	Endpoints	FDR correction	Risk of bias <sup>2</sup>	Results
Cohort of students of University of Louvain, Belgium Maurage et al. (57)	University students, 18 y	36	Initiation of BD vs. <3 units/wk	0.75	Mean $\pm$ SD alcohol units/wk: 2.0 $\pm$ 1.9 in BDs and 1.4 $\pm$ 2.9 in controls	ERP "emotion"	No, a priori selected ERPs	9	Emotional valence judgment task: no differences; delayed latencies of P1, N2, P3b
Cohort of University of Santiago de Compostela, Spain López-Caneda et al. (54)	University students, 18–19 y	57	Sustained BD vs. no BD	2	Mean $\pm$ SD drinks per episode: 1.7 $\pm$ 1.3 in controls and 5.6 $\pm$ 2.6 in BDs	ERP "attention, working memory"	Yes, for post hoc analyses	7	Visual oddball task: no differences; ERP: no group $\times$ time interaction
López-Caneda et al. (55)	University students, 18–19 y	57	Sustained BD vs. no BD	2	Mean $\pm$ SD g alcohol/wk: 40.6 $\pm$ 62.9 in controls and 373.5 $\pm$ 268 in BDs	ERP "response inhibition"	Yes, for post hoc analyses	6	Go/no go task: no differences; Go P3: no differences in amplitude; No go P3: larger amplitudes; Go and no go N2: no differences in amplitudes
Cohort on "Adolescent Brain Development", University of Minnesota, USA Luciana et al. (56)	Adolescents 14–19 y	55	Drinking (initiation) vs. no drinking	2	No alcohol use	Cortical thickness, white matter volume, white matter integrity	Yes	9	Decrease of cortical thickness; lower volume increase of white matter; lower increase of FA (DTI)
Cohort of University of Brussels, Belgium Petit et al. (58)	University students, 22 y	30	Sustained BD vs. no BD	1	Mean $\pm$ SD doses/wk: 32.1 $\pm$ 21.2 for BDs and 4.5 $\pm$ 3.3 for controls	ERP "alcohol dependence"	No, a priori ERPs were selected	7	Visual oddball task (alcohol cue reactivity, cognitive bias): no difference; P1 amplitude $\downarrow$ ; P3 amplitude $\downarrow$ for non-alcohol-related stimuli only
"Ad Brain Study", USA Wilson et al. (64)	Twins, 14–17 y	96	Alcohol index <sup>3</sup> (score; time varying)	1	Alcohol use (ever): 21%; BD (ever): 8%	Cortical and subcortical brain volume, cortical thickness	No	8	Brain volume: reduced within discordant twin pairs; cortical thickness: no differences within discordant twin pairs

(Continued)

**TABLE 2** (Continued)

Studies	Sample	n	Exposure	Follow-up time, y	Baseline alcohol consumption	Endpoints	FDR correction	Risk of bias <sup>2</sup>	Results
Cohort from "The Adolescent Brain" project, Germany Jurk et al. (67)	Adolescents, 14 y	92	Regular alcohol use (g/wk; continuous)	4	Varying; mean $\pm$ SD alcohol (g/wk): $\delta$ 14 y: 2.5 $\pm$ 5.0; $\delta$ 16 y: 2.7 $\pm$ 6.3; $\delta$ 16 y: 37.7 $\pm$ 56.4; $\delta$ 16 y: 13.0 $\pm$ 17.9; $\delta$ 18 y: 77.0 $\pm$ 79.7; $\delta$ 18 y: 30.9 $\pm$ 32.3	fMRI "inhibition, switching"	Yes	6	Incongruence and switching task: no association; no association with neural activation
Cohort of the University of Madrid, Spain Correas et al. (68)	University students, 18–19 y	39	Sustained BD vs. no BD	2	Mean $\pm$ SD blood alcohol concentration, % <sup>4</sup> : heavy drinkers: 0.17 $\pm$ 0.07 on a BD day; controls: 0.016 $\pm$ 0.02	DTI MEG resting state FC (DMN)	Yes	4	FA: no differences; increased FC
"Brain and Alcohol Research in College Students (BARCS)," USA Meda et al. (65)	First-year college students, 18–23 y	200	Sustained BD vs. light drinking	2	Sustained light users: mean $\pm$ SD 2 $\pm$ 5 drinks/mo; heavy drinkers: mean $\pm$ SD 48 $\pm$ 48 drinks/mo	Gray matter volume	Yes	5	Gray matter: more rapid and extensive decline
"National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA)," USA Pfefferbaum et al. (59)	Adolescents, 12–21 y	483	(Initiation of) moderate drinking, (initiation of) heavy drinking vs. no/low drinking	2	Limited; maximum number of lifetime drinks: <16 y: 5; 16–16.9 y: 11; 17–17.9 y: 23; > 18 y: 51	Gray and white matter volume	Yes	8	Gray matter: more rapid volume decline; white matter: similar volume increase
Cohort on "Cognitive and affective development," Netherlands Peters et al. (66)	Community-based adolescents, 12–27 y	193	Lifetime alcohol use (amount 11-point scale), recent (<30 d) alcohol use (amount 10-point scale)	2	Mean $\pm$ SD lifetime alcohol use: 28.7 $\pm$ 37.7 glasses; mean $\pm$ SD alcohol use in the last month: 6.4 $\pm$ 12.4 glasses	fMRI resting state FC	No, ROI approach	5	No associations with resting-state connectivity

<sup>1</sup> AFD, age of first drink; AWDO, age of weekly drinking onset; BD, binge drinking; BDs, binge drinkers; DMN, default mode network; DTI, diffusion tensor imaging; ERP, event-related potential; FA, fractional anisotropy; FC, functional connectivity;

FDR, false discovery rate; MEG, magnetoencephalography; ROI, region of interest; WB, whole brain approach.

<sup>2</sup> Study quality/risk of bias was assessed with the Newcastle-Ottawa Scale (0–9); for clarification see Supplemental Methods 3 and Supplemental Table 1.

<sup>3</sup> Alcohol index based on frequency of drinking, number of drinks per occasion, maximum number of drinks per occasion, and number of times intoxicated.

<sup>4</sup> A blood alcohol concentration of 0.08% corresponds to an intake of  $\geq$  5 drinks ( $\geq$  4 for females) on 1 occasion within a 2-h interval.

62) and white matter integrity (56, 59, 62), and functional measures including task-related fMRI (60, 63, 67), task-related event-related potential (33, 54, 55, 57), task-related connectivity (fMRI or magnetoencephalography) (69), and resting-state connectivity (66, 68). In 1 study, the study sample was selected for having no lifetime experience with alcohol (56). In 7 studies (of which 6 were from the same research group), baseline alcohol consumption was limited (53, 59–63, 69). NOS scores ranged between 4 and the maximum possible score of 9. In the majority of the studies ( $n = 12$ ), the extent of attrition bias could not be evaluated because limited information was available about the participants who were excluded from the analyses (see Supplemental Table 1) (53–55, 59–62, 65–69). In 11 studies, the groups already differed at baseline for the outcome measure of interest or baseline differences of the outcome were not reported (53, 58, 60–66, 68, 69). Eleven studies took adjustment for multiple testing into account (54–56, 59–61, 63, 65, 67–69). The committee judged 7 studies to be of sufficient quality based on NOS score (54, 56–59, 63, 64).

#### **Gray matter volume and cortical thickness.**

There were 7 studies (in secondary school students and university students) that reported on gray matter: 3 of sufficient quality. All 3 studies (based on 3 study populations) of sufficient quality on the association between alcohol consumption and gray matter volumes showed reduced gray matter volumes or cortical thickness for higher levels of alcohol consumption (56, 59, 64), with the most consistent findings for the frontal lobe. In 1 of these 3 studies (59), higher alcohol consumption was related to both reduced gray and white matter volumes, but not with differences in cortical thickness. In 2 of these 3 studies, baseline alcohol consumption was low or absent and baseline differences of the outcome measures were absent (56, 59). This strengthens the findings because reverse causation is unlikely. Three (61, 62, 65) out of the 4 (53, 61, 62, 65) lower-quality studies were consistent with a more rapid decline of gray matter volume, whereas 1 study of lower quality mainly suggested pre-existing gray matter volume differences, with groups (drinking initiators compared with nondrinkers) becoming more similar over time (53).

#### **White matter volume and integrity.**

Regarding white matter volume, 2 (56, 59) studies of sufficient quality in adolescents showed inconsistent results [a reduced increase of white matter volume over time (56) compared with no difference in relation to alcohol consumption (59)]. At baseline, outcome measures were similar between the alcohol groups in both studies (56, 59). A third study in adolescents, that had lower quality, suggested a lower increase of white matter volume in initiators of binge drinking than in nondrinkers. Baseline differences of the outcome were not reported (62). For white matter integrity, 1 study of sufficient quality showed a lower increase in fractional anisotropy (FA; a lower FA reflects disturbed integrity of white matter) in adolescent alcohol initiators than

in noninitiators. At baseline, the outcomes did not differ between the groups (56). In a study of lower quality in university students, no difference was found for FA between sustained binge drinkers and a reference group of non-binge drinkers. Baseline differences of the outcome were not reported (68).

#### **Brain activity.**

The 4 studies of sufficient quality on brain activity outcome measures all focused on binge drinking (54, 57, 58, 63). One of those 4 studies focused on cognitive bias as the outcome (58). In that study, there was no difference in the performance measure of cognitive bias between persistent binge-drinking students and nondrinking students (see also the section on “Cognitive functioning”). The brain activity measures linked to the behavioral measure, however, did differ between the groups (58). In the other 3 studies of sufficient quality (54, 57, 63), 1 in adolescents and 2 in students, the behavioral measures regarding the cognitive test did not differ between binge drinkers and non-binge drinkers. In 2 out of the 3 studies, differences in brain activity (electroencephalogram, fMRI), linked to the cognitive functions studied, were observed (57, 63). In 1 of the 2 studies in which binge drinkers showed different brain activity compared with non-binge drinkers, the participants did not drink yet or only drank limited amounts of alcohol at baseline (63). The diverse nature of the brain activity studies, however, limits drawing conclusions. In half of the studies of lower quality, based on 5 study populations, differences in brain activity were observed (60, 68, 69), whereas in the other half no differences were found according to alcohol consumption (55, 66, 67). Behavioral measures (regarding the cognitive tests used), if available, did not differ according to alcohol consumption (55, 60, 66–69).

#### **Cognitive functioning**

The committee included 19 longitudinal studies, published between 2009 and 2018 (Table 3, Supplemental Results 2), based on 7 study populations (21, 53–55, 58, 60, 63, 67, 69–79). Ten of these studies were conducted in Europe (21, 54, 55, 58, 67, 70–72, 74, 75), of which 2 were in the Netherlands (21, 74) and 6 in Spain (54, 55, 70–72, 75). Nine studies originated from the United States (53, 60, 63, 69, 73, 76–79). The number of participants ranged between 30 and 2230. The study samples included adolescents (21, 67, 74), middle-school students (53, 60, 63, 69, 73, 76–79), or university students (54, 55, 58, 70–72, 75). Thirteen studies focused on binge drinking (21, 54, 55, 58, 60, 63, 70–73, 75, 78, 79). Outcomes included global cognitive functioning (73), subtypes of cognitive functioning (21, 53–55, 60, 63, 67, 69–72, 75–79), or cognitive bias (58, 74). Eight studies were based on samples with no or minimal alcohol use at baseline (53, 60, 63, 69, 76–79). The NOS scores ranged between 5 and 8. In the majority of the studies ( $n = 14$ ), the extent of attrition bias could not be evaluated because limited information was available about the participants who were excluded from the analyses (see Supplemental Table 2) (21, 53–55, 58, 60, 63,

**TABLE 3** Longitudinal studies (grouped by cohort and publication date) on the association between alcohol consumption and cognitive function and cognitive bias<sup>1</sup>

Studies	Sample	n	Exposure	Follow-up time, y	Baseline alcohol consumption	Endpoints	Multiple testing correction	Risk of bias <sup>2</sup>	Results
High school students Cohort from University of California, San Diego, USA Jacobus et al. (73)	Middle school students, 16–19 y	54	Sustained BD vs. minimal drinking	3	Control group: 0 drinks/mo; BDs: 10 drinks/mo	Cognitive functioning (a composite measure of complex attention, processing speed, verbal memory, visuospatial functioning, and executive functioning)	Yes	5	No associations
Cohort of Youth at Risk for Alcoholism, University of California, San Diego, USA Squeglia et al. (79)	Middle school students, 12–14 y	76	Initiation of moderate or heavy drinking vs. nondrinking; number of drinking days	1–5	Control group: 0 drinking days. Drinkers: females, 1.15 drinking days; males, 0.83 drinking days	Visuospatial functioning, attention and working memory, learning and memory, executive functioning/planning	Yes	7	Relative decrease in visuospatial functioning among girls with more drinking days in the past (no association among boys); no association with attention and working memory, learning and memory, or executive functioning/planning (neither among boys nor among girls)
Squeglia et al. (60)	Middle school students, 12–16 y	40	Initiation of BD vs. nondrinkers	3	Continuous nondrinkers: 0.05 lifetime alcohol occasions. Heavy drinking transitioners: 1.50 lifetime alcohol use occasions	Visual working memory	n.r.	6	Groups become more comparable over time
Wetherill et al. (63)	Middle school students, 12–16 y	40	Initiation of BD vs. nondrinkers	3	Limited ( $\leq 1$ total lifetime drinks)	Response inhibition	n.r.	7	No associations

(Continued)

**TABLE 3** (Continued)

Studies	Sample	n	Exposure	Follow-up time, y	Baseline alcohol consumption	Endpoints	Multiple testing correction	Risk of bias <sup>2</sup>	Results
Nguyen-Louie et al. (76)	Middle school students, 12–14 y	234	More alcohol use (continuous)	1–9 (mean 4)	Limited ( $\leq 10$ lifetime alcohol use occasions, never > 2 drinks/wk), 91% were alcohol naïve	Verbal memory, visuospatial ability, psychomotor speed, processing speed, working memory	Yes	7	Relative decrease in verbal memory and visual memory; relative increase in working memory; no association with processing and psychomotor speed
Nguyen-Louie et al. (78)	Middle school students, 12–16 y	112	BD vs. moderate drinking; extreme BD vs. moderate drinking	4–9	Limited ( $\leq 10$ lifetime alcohol use occasions, never > 2 drinks/wk)	Verbal learning and memory	Yes	8	BD: no association with verbal learning and memory; extreme BD: relative decrease in verbal learning and memory
Jacobus et al. (53)	Middle school students, 12–14 y	69	Alcohol initiation vs. no drinking	6–8	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	No associations
Nguyen-Louie et al. (77)	Middle school students, 12–15 y	215	AFD, AWDO (continuous)	Mean 6.8	Limited ( $\leq 10$ lifetime alcohol use occasions), 90% were alcohol naïve	Verbal learning and memory, cognitive inhibition, psychomotor speed, working memory, visual attention, visuospatial ability	Yes	7	Younger AFD: relative decrease in psychomotor speed and visual attention; no association with verbal learning and memory, cognitive inhibition, working memory, or visuospatial ability; younger AWDO: relative decrease in cognitive inhibition and working memory; no association with verbal learning and memory, psychomotor speed, visual attention, or visuospatial ability
Nguyen-Louie et al. (69)	Middle school students, 12–15 y	133	Weekly drinkers vs. non-weekly drinkers	6	Limited ( $\leq 10$ lifetime alcohol use occasions, never > 2 drinks/wk)	Visual working memory	n.r.	5	No associations

(Continued)

**TABLE 3** (Continued)

Studies	Sample	n	Exposure	Follow-up time, y	Baseline alcohol consumption	Endpoints	Multiple testing correction	Risk of bias <sup>2</sup>	Results
TRAILS (TRacking Adolescents' Individual Lives Survey) cohort, Netherlands Boelema et al. (21)	Preadolescents, 11 y	2230	Chronic heavy drinking, decreasing heavy drinking, increasing heavy drinking, infrequent heavy drinking, light drinking vs. nondrinking	8	Varying (percentage alcohol naive per drinking group: chronic heavy drinking, 77%; decreasing heavy drinking, 79%; increasing heavy drinking, 81%; infrequent heavy drinking, 85%; light drinking, 88%; nondrinking, 95%)	Four measures of executive functioning: inhibition, working memory, sustained attention, and shift attention	Yes	7	No associations
Health Behaviours in School-aged Children cohort, Netherlands Janssen et al. (74)	Adolescents, 12–18 y	378	Mean number of alcohol units consumed on a weekday	2	Varying (23.2% used alcohol weekly)	Alcohol-related cognitive bias (approach bias and attention bias)	n.r.	6	No associations
Cohort from "The adolescent brain" project, Germany Jurk et al. (67)	Adolescents, 14 y	92	Alcohol (g/wk)	4	Varying, mean $\pm$ SD alcohol, g/wk: ♂ 14 y: 2.5 $\pm$ 5.0; ♀ 14 y: 2.7 $\pm$ 6.3; ♂ 16 y: 37.7 $\pm$ 56.4; ♀ 16 y: 13.0 $\pm$ 17.9; ♂ 18 y: 77.0 $\pm$ 79.7; ♀ 18 y: 30.9 $\pm$ 32.3	Cognitive control abilities	Yes	6	No associations
College/university students Cohort of University of Santiago de Compostela, Spain López-Caneda et al. (54)	University students, 18–19 y	57	BD vs. non-BD	2	Varying, mean $\pm$ SD drinks per episode: 1.7 $\pm$ 1.3 in controls and 5.6 $\pm$ 2.6 in BDs	Visual attention	n.r.	7	No differences

(Continued)



**TABLE 3** (Continued)

Studies	Sample	n	Exposure	Follow-up time, y	Baseline alcohol consumption	Endpoints	Multiple testing correction	Risk of bias <sup>2</sup>	Results
Mota et al. (75)	University students, 18–19 y	89	BD vs. non-BD	2	BD ( $\geq 6$ alcoholic drinks on the same occasion weekly/monthly and $\geq 3$ drinks/h); 1 drink = 10 g ethanol; baseline intake n.r.	Memory, executive functioning	Yes	6	No differences
López-Caneda et al. (55)	University students, 18–19 y	57	BD vs. non-BD	2	Varying; mean $\pm$ SD non-BDs: 40.6 $\pm$ 62.9 g alcohol/wk; BDs: 373.5 $\pm$ 268 g alcohol/wk	Response inhibition	n.r.	5	No differences
Carbia et al. (72)	University students, 18–19 y	155	BD vs. non-BD	6	Varying; mean $\pm$ SD non-BDs: 42.19 $\pm$ 52.79 g alcohol/wk; BDs: 302.46 $\pm$ 251.13 g alcohol/wk	Working memory	n.r.	7	Relative decrease
Carbia et al. (71)	University students, 18–19 y	155	BD vs. non-BD	6	Varying; mean $\pm$ SD non-BDs: 42.19 $\pm$ 52.79 g alcohol/wk; BDs: 312.41 $\pm$ 262.84 g alcohol/wk	Verbal episodic memory	n.r.	6	Relative decrease
Carbia et al. (70)	University students, 18–19 y	155	BD vs. non-BD	4	Varying; mean $\pm$ SD non-BDs: 42.19 $\pm$ 52.79 g alcohol/wk; BDs: 302.46 $\pm$ 251.13 g alcohol/wk	Decision making	n.r.	6	No differences
Cohort of University of Brussels, Belgium Petit et al. (58)	University students, 22 y	30	BD vs. non-BD	1	Varying; mean $\pm$ SD controls: 4.5 $\pm$ 3.3 doses/wk; BDs: 32.1 $\pm$ 21.2 doses/wk	Alcohol cue reactivity (cognitive bias)	n.r.	6	No differences

<sup>1</sup>AFD, age of first drink; AWDO, age of weekly drinking onset; BD, binge drinking; BDs, binge drinkers; n.r., not reported.

<sup>2</sup>Study quality/risk of bias was assessed with the Newcastle-Ottawa Scale (0–9); for clarification see Supplemental Methods 3 and Supplemental Table 2.

67, 69, 72, 73, 76–78). Seven studies differed at baseline for the outcome measure of interest or baseline differences of the outcome were not reported (53, 58, 60, 69, 76, 77, 79). In 8 studies no adjustment for relevant confounders was made (55, 67, 69–71, 73–75). Eight studies took adjustment for multiple testing into account (21, 67, 73, 75–79). The committee judged 8 studies to be of sufficient quality based on NOS score (21, 54, 63, 72, 76–79).

In total, 12 studies on high school students were found (21, 53, 60, 63, 67, 69, 73, 74, 76–79), 6 of which were of sufficient quality (21, 63, 76–79). Five of them were based on 1 American cohort (63, 76–79). Participants from this cohort were alcohol naïve or had a very low level of alcohol consumption at baseline. In 1 of these American studies, no difference was found in cognitive functions between those who initiated binge drinking and nondrinkers (78). In the other 4, differences were found on several cognitive functions between alcohol consumers and nondrinkers, 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 (63, 76, 77, 79). One of the American studies found an association between higher alcohol consumption and improvements in working memory (76). In the sixth study of high quality (a Dutch cohort, with 77%–95% alcohol-naïve participants at baseline and no initial differences of the outcome), no associations were found between alcohol consumption (including binge drinking) and cognitive functioning (21). In the remaining 6 studies of lower quality (53, 60, 67, 69, 73, 74), based on 4 cohorts, no associations were found between alcohol consumption and cognitive functioning or cognitive biases [only 1 study (74) was available on this outcome].

All 7 studies that were conducted among college/university students focused on sustained binge drinking (54, 55, 58, 70–72, 75). Two of these studies were of high quality; they used data from the same Spanish cohort (54, 72). No differences between sustained binge drinkers and non-binge drinkers with regard to visual attention were found (54), whereas an association between sustained binge drinking and relatively poor working memory was observed (72). The outcome measures of interest did not differ at baseline (54, 72). Four (55, 70, 71, 75) out of the 5 (55, 58, 70, 71, 75) studies of lower quality were from the same Spanish cohort. One of these studies found an association between higher alcohol consumption and relatively poor cognitive functioning (71). The other 3 Spanish studies did not find any differences (55, 70, 75). The last study, based on Belgian students, focused on cognitive biases and found no differences between binge drinkers and non-binge drinkers (58).

### Educational achievement

The committee identified 30 longitudinal studies (Table 4, Supplemental Results 3) (19, 80–108) based on 29 cohorts, published between 1984 and 2018. Studies were conducted in Europe (80, 85, 92–94, 104, 108), North America (82–84, 86–91, 95–98, 100–103, 105, 106), Australasia (19, 107),

the United States and Australia (81), and Israel (99). The number of participants ranged between 172 and 19,764. The study populations included adolescents (19, 80–87, 89, 90, 92–94, 97–102, 105–107), adolescent twins (108), or college or university students (88, 91, 95, 96, 103, 104). About half of the studies focused on heavy or binge drinking (81–83, 85–93, 95, 101, 105, 106), whereas others analyzed increasing levels of alcohol use (19, 80, 86, 87, 90, 92, 93, 96–98, 100, 101, 103, 104, 108), drinking initiation (102), or drinking (yes/no) at baseline (81, 84, 94, 99, 107). None of the studies was based on an alcohol-naïve population at baseline. Outcomes included school marks (81, 83, 90, 97, 105, 108) and level of educational attainment or dropout (19, 80, 82, 84–89, 91–96, 98–108). The NOS scores ranged between 4 and 9. In 16 studies the extent of the attrition bias could not be evaluated, because limited information was available about the participants who were excluded from the analyses (Supplemental Table 3) (82–84, 86, 89, 92, 94–96, 99–104, 107). In 16 studies no adjustment for relevant confounders was made (80, 84, 86, 88, 91–97, 99, 101, 103–105). The committee judged 13 studies to be of sufficient quality based on NOS score (19, 81, 82, 85, 87, 89, 90, 95, 98, 100, 106–108).

### Level of education.

The committee identified 10 studies of sufficient quality on the association between alcohol use and level of educational attainment in high school students (19, 82, 85, 87, 89, 98, 100, 106–108). In 5 of these higher alcohol consumption was associated with a higher risk of achieving a lower level of education (85, 87, 106–108). In 1 of the studies an association in the opposite direction was observed: i.e., higher alcohol used was associated with a lower likelihood of dropout (89). In the other 4 studies of sufficient quality no differences were observed between drinkers and nondrinkers (19, 82, 85, 100). Associations were found in studies that focused on increasing levels of alcohol use as well as in studies that focused specifically on binge drinking. Of the remaining 10 studies of lower quality on educational attainment (80, 84, 86, 92–94, 99, 101, 102, 105), 6 found an association with a lower level of education in drinkers (86, 92–94, 99, 101), 3 did not find a significant association (84, 102, 105), and in 1 study those who used more alcohol were more likely to attain a tertiary education (80).

### School marks.

Three studies of sufficient quality on alcohol use and school marks achieved were identified in high school students (81, 90, 108). One of them found an association between alcohol use at young age and lower school marks (108). The other 2 studies did not find evidence for an association (81, 90). Of the remaining 3 studies of lower quality (83, 97, 105), 2 found an association with lower school marks (83, 97). The other found no significant association (105). There were no studies of sufficient quality on the association between alcohol use and educational attainment in college/university students. Of the remaining 6 studies of lower quality (88, 91, 95, 96, 103, 104), 4 found an association of heavier alcohol use with a

**TABLE 4** Longitudinal studies on the association between alcohol consumption and educational achievement (grouped by high school and college/university students, cohort, and publication date)<sup>1</sup>

Studies	Sample	n	Exposure	Follow-up time, y	Baseline alcohol consumption	Risk of bias <sup>2</sup>	Results for educational attainment and dropout	Results for school marks
High school students Cohort from Technion-Israel Institute of Technology, Israel Epstein and Tamir (99)	High school students, 16 y	181	Drinking strong alcoholic beverages (yes/no)	2	Varying; 46% of males and 20% of females drank strong alcoholic beverages by age 16 y	6	Higher chance of high school dropout	
Cohort from New York State, USA Kandel et al. (84)	Secondary school and high school students, 15–16 y	1004	Ever alcohol use at baseline (yes/no)	9	n.r.	5	No association with highest educational level achieved	
National Longitudinal Survey of Youth, USA Cook and Moore (86)	High school seniors, 17–18 y	752	Number of drinks/wk	~6	Varying; mean $\pm$ SD drinks in the past wk: 2.6 $\pm$ 7.5	6	No association with number of years of completed schooling after high school Fewer years of college	
Sloan et al. (82)	Youth, 17–25 y	7757	Drinking $\geq$ 2 times in previous wk (yes/no) Drinking $\geq$ 4 times $\geq$ 6 drinks in the past mo (yes/no) Frequent BD vs. nonfrequent BD and frequent BD vs. non-BD	~26	Varying; mean $\pm$ SD frequency of 0.14 $\pm$ 0.34 % Varying; mean $\pm$ SD frequency: 0.10 $\pm$ 0.29% Varying; 17% reported frequent BD, 40% nonfrequent BD, and 43% non-BD/abstinence	8	No association with number of years of completed schooling after high school No association with number of completed years of schooling	
RAND Adolescent Panel Survey, USA Ellickson et al. (100)	High school students, 12–13 y	4390	More alcohol use	5	Varying; 74.4% ever used alcohol	8	No association with high school dropout	

(Continued)

**TABLE 4** (Continued)

Studies	Sample	n	Exposure	Follow-up time, y	Baseline alcohol consumption	Risk of bias <sup>2</sup>	Results for educational attainment and dropout	Results for school marks
Young in Norway, Norway Wichstrøm (92)	High school students, 12–20 y	5308	More alcohol (yes/no)	n.r.	Varying; mean alcohol consumption dropouts: 5.11 L/y; completers: 3.21 L/y	4	More senior high school dropout	
Cohort from south-eastern US public school system, USA Bray et al. (102)	High school students, 6th–8th grade (~11–13 y)	1392	Alcohol intoxication (yes/no) Alcohol initiation before age 16, 17, or 18 y (yes/no)	~8	n.r.	6	No association with high school dropout	
Seattle Social Development Program, USA Hill et al. (106)	Adolescents from high-crime areas, 10 y	808	BD trajectories vs. non-BD	~11	n.r.	7	Decreased chance of high school completion for 2 out of 3 binge trajectories (third trajectory same direction but n.s. different)	
Cohort from western New York, USA Mason and Windle (97)	High school students, 13–19 y	840	Drinking behavior: combination of beer and liquor use, and heavy beer drinking	1.5	Varying; no further interpretable figures reported	6		Decreased school rates for high school (cumulative grade point average on a 7-point Likert scale)
National Education Longitudinal Study of 1988, USA Dee and Evans (101)	High school students, ~13 y	7317	Drinking ≥ 1 drinks in the last month (yes/no); heavy drinking ≥ 5 drinks in a row at least once in the past 2 wk (yes/no)	2–4	Varying; 42% had had ≥ 1 drink in the last month of their sophomore year, and 52% had in their senior year	5	Both associated with a lower chance of high school completion and entering college	

(Continued)

TABLE 4 (Continued)

Studies	Sample	n	Exposure	Follow-up time, y	Baseline alcohol consumption	Risk of bias <sup>2</sup>	Results for educational attainment and dropout	Results for school marks
Chatterji (87)	High school students, ~15 y (10th and 12th grades)	7604	Drinking $\geq 1$ drink in the last month (yes/no); heavy drinking: $\geq 5$ drinks in a row at least once in the past 2 wk (yes/no)	8–10	Varying; 42% of males and 38% of females had had $\geq 1$ drink in the last month during 10th grade	8	No association with educational attainment for the 10th-grade cohort; reduction in the probability of entering college for the 12th-grade cohort	
Longitudinal study of familial alcoholism, Arizona, USA King et al. (98)	Children of alcoholics and matched controls, mean age 13.2 y	374	Levels of alcohol use and growth of alcohol use during adolescence	~11	n.r.	8	No association with college attendance and degree completion	
Haller et al. (105)	Children of alcoholics and matched controls, mean age 14.2 y	405	Frequency of BD ( $\geq 5$ drinks/occasion); from 0 (never) to 7 (every day) in 3 waves	18	n.r.	6	No association with college completion at age 25 y	No association with adolescent academic achievement (based on average grades)
National Longitudinal Study of Adolescent Health, USA Crosnoe (90)	Middle and high school students, 12–17 y	11,927	Past-year level of alcohol use; past-year frequency of BD (scale)	1	Varying; no further interpretable figures reported	9		No association with academic failure (based on reported grades in Math, Science, English, and Social Studies)
1970 British Birth Cohort Study, UK Viner and Taylor (93)	Adolescents, 16 y	4854	Frequency of regular drinking; BD (yes/no)	14	Varying; 17.7% reported BD	6	No association with leaving high school or college without qualifications Increased chance of leaving high school or college without any qualifications	

(Continued)

**TABLE 4** (Continued)

Studies	Sample	n	Exposure	Follow-up time, y	Baseline alcohol consumption	Risk of bias <sup>2</sup>	Results for educational attainment and dropout	Results for school marks
National Child Development Study, UK Staff et al. (85) <sup>3</sup>	Adolescents, 16 y	9107	Heavy alcohol use (yes/no)	26	Varying: 13% of females and 25% of males reported heavy drinking	8	Males: lower likelihood of attaining a postsecondary degree by age 42 y; females: no association at age 42 y	
International Youth Development Study, Australia and/or USA Hemphill et al. (81)	High school students in Australia and USA, 12–13 y	1858	Lifetime: ever more than a few sips (yes/no); current alcohol use: more than a few sips in the past 30 d (yes/no); BD past 2 wk (yes/no); frequent drinking: $\geq 3$ drinks in the past month (yes/no)	2	Varying: 46.7% of females and 51% of males reported lifetime (ever) drinking	9		No association with self-reported below-average marks in the past year
Kelly et al. (107); only Australia	Secondary school students; Australia, ~10–15 y	2287	Alcohol use vs. no use	8	n.r.	8	Higher likelihood of high school noncompletion	
FinnTwin12, Finland Latvala et al. (108)	Adolescents, 12 y; twins	4761	Drinking with friends at age 12 y (any alcohol use)	Max. 15	n.r.	9		Lower school performance (grade point average in the latest report) at age 14 y
			Drinking frequency at age 14 y Drinking frequency at age 17 y Intoxication frequency at age 14 y Intoxication frequency at age 17 y	Max. 15			Lower student status at age 17 y No association with educational attainment in young adulthood Lower student status at age 17 y No association with educational attainment in young adulthood	

(Continued)



**TABLE 4** (Continued)

Studies	Sample	n	Exposure	Follow-up time, y	Baseline alcohol consumption	Risk of bias <sup>2</sup>	Results for educational attainment and dropout	Results for school marks
Icelandic cohort of adolescents, Iceland Svansdottir et al. (94)	Adolescents, 15 y	201	Alcohol consumption (yes/no)	8	n.r.	5	Higher likelihood of secondary school dropout	
Pooling study of 3 UK cohorts Green et al. (80)	High school students, 15–16 y from 3 cohorts: NCDS, BCS, T07	NCDS: 15,672; BCS: 12,735; T07: 1181	Adolescent weekly drinking (yes/no)	6–10	Varying; prevalence (%) of weekly drinking: NCDS: 45.9; BCS: 52.2; T07: 5.7	6	Increased likelihood to attain tertiary education (i.e., education beyond 18 y)	
Monitoring the Future, USA Patrick et al. (89)	High school students, 18 y	10,020	BD on $\geq 1$ occasion in the past 2 wk (yes/no)	7	Varying; 29% reported BD	7	No association with college attendance; no association with shorter education (i.e., 2-y vs. 4-y college graduation); lower likelihood of dropping out of 4-y college	
COMPASS study, Canada Patte et al. (83)	High school students, 14–15 y	19,764	Early vs. late onset of BD	2	Non-BD	5		Associated with lower likelihood of high recent marks in Math and English
			Initiation of rarely BD, weekly BD, or monthly BD (all vs. non-BD)					Higher frequency of BD associated with lower likelihood of high recent marks in Math and English
Pooling study of 4 Australasian cohorts, Australia, New Zealand Sillins et al. (19)	High school students from 4 cohorts: ATP, CHDS, MUSP, VAHCS, 13–15 y	2615–3384	Frequency of alcohol use, quantity of alcohol use	Max. 17	n.r.	8	No association with high school completion or university degree attainment (both by age 30 y)	
College/university students Coronary Artery Risk Development in Young Adults, USA Sloan et al. (95)	College students, 18 $\geq$	1863	Frequent BD vs. non-BD; frequent BD vs. occasional BD	15	Varying; 13.6% of total sample (n = 3964) were nondrinkers	7	No association with years of schooling	

(Continued)

**TABLE 4** (Continued)

Studies	Sample	n	Exposure	Follow-up time, y	Baseline alcohol consumption	Risk of bias <sup>2</sup>	Results for educational attainment and dropout	Results for school marks
A Midwestern university cohort 87/88, USA Wood et al. (88)	College freshmen, 17–18 y	429	Frequency of BD	6	n.r.	6	Negative correlation with level of educational achievement (i.e., level of degree completion)	
A San Diego cohort, USA McCarthy et al. (96)	Young adults treated for alcohol and drug problems and matched controls, 22–24 y	172	Combined factor of quantity and frequency of alcohol use, proportion of time that drinking leads to drunkenness and alcohol use patterns	2	Varying; treated group: 55 drinks on 11 occasions per month; Controls: 25 drinks on 12 occasions per month	5	No association with educational attainment	
A Midwestern university cohort 2002, USA Martinez et al. (91)	First-time undergraduate students, assumed to be ~18 y	3290	Heavy drinking as a composite measure of BD occasions, felt high, got drunk on alcohol	4	n.r.	7 <sup>4</sup>	Higher likelihood of college dropout	
Lulea and Växjö University cohorts, Sweden Andersson et al. (104)	First-year university students at the start of the school year, mean age ~23 y	2032	Alcohol involvement on AUDIT scale (high vs. low); estimated blood alcohol concentration (high vs. low)	1	Varying; mean score on the AUDIT scale ranged between 7.2 and 7.6	6	No association with first-year university dropout	
College Life Study, USA Arria et al. (103)	First-year students, 17–20 y	1145	Typical number of drinks per day	4	Varying; mean ± SD typically consumed drinks: 4.4 ± 2.9/d	5	Higher likelihood of university discontinuity in the last 2 y of university (i.e., a gap in enrolment of ≥1 semesters); no association with university discontinuity in the first 2 y of university	

<sup>1</sup>ATP, Australian Temperament Project; AUDIT, Alcohol Use Disorders Identification Test; BCS, British Birth Cohort study; BD, binge drinking; CHDS, Christchurch Health and Development Study; MUSP, Mater Hospital and University of Queensland Study of Pregnancy; NCDS, National Child Development Study; n.r., not reported; n.s., not statistically significant; T07, West of Scotland Twenty-07; VAHCS, Victorian Adolescent Health Cohort Study.

<sup>2</sup>Study quality/risk of bias was assessed with the Newcastle-Ottawa Scale (0–9); for clarification see Supplemental Methods 3 and Supplemental Table 3.

<sup>3</sup>Cohort included in Green et al. (80).

<sup>4</sup>No sufficient adjustment for relevant confounders; therefore not qualified by the committee as a study of sufficient quality.

higher likelihood of relatively worse school performance (88, 91, 95, 103) and 2 found no significant association (96, 104).

## AUD

The committee identified 23 studies (Table 5, Supplemental Results 4) based on 18 cohorts, published between 1998 and 2018, that reported on the association of adolescent alcohol consumption and later-life AUD including AA, and AD (19, 93, 105, 106, 109–127). Studies were performed in the United States ( $n = 13$ ) (105, 106, 111–114, 116–119, 123, 126, 127), Australia and New Zealand ( $n = 5$ ) (19, 110, 120–122), Norway ( $n = 2$ ) (124, 125), the United Kingdom ( $n = 2$ ) (93, 115), and Switzerland ( $n = 1$ ) (109). The number of participants ranged between 141 and 4352. Study samples varied between adolescents (19, 93, 105, 106, 111–115, 117, 119, 122, 124, 126), adolescent twins (116, 123), high school students (110, 118, 125), young adults (109, 120, 121), and university students (127) from various backgrounds. Fourteen studies focused on frequency or amount of alcohol drinking (19, 93, 105, 106, 109–112, 115, 119–121, 123, 127) and 9 on age of first drinking or early drinking as the exposure. The follow-up time ranged from 1 to 28 y. NOS scores ranged between 4 and 8. Seven studies were vulnerable to attrition bias (Supplemental Table 4) (109, 110, 115, 119, 122, 123, 125). In 13 studies, confounding was not sufficiently adjusted for (93, 105, 106, 109–112, 115, 118–121, 124). The committee judged 7 studies to be of sufficient quality based on NOS score (19, 113, 114, 116, 124, 126, 127).

### *Amount or frequency of drinking.*

The committee identified 2 studies (based on 3 study populations of adolescents and university students) of sufficient quality regarding amount or frequency of alcohol consumption as exposures of interest (19, 127). In both studies, a higher frequency of alcohol consumption was associated with a higher risk of later AUD, whereas a higher amount of alcohol consumption was associated with a higher risk of later AUD in 1 of the 2 studies (127). In the second study, the association of a higher alcohol quantity with a higher risk of later AUD was no longer statistically significant after Bonferroni corrections for multiple testing (19). From the remaining 12 studies of lower quality (93, 105, 106, 109–112, 115, 119–121, 123), based on 10 study populations, 10 out of 12 (93, 105, 106, 109–112, 115, 120, 123) observed an association between a higher level of alcohol consumption and a higher risk of AUD. The other 2 (119, 121) did not find an association between level of alcohol consumption and risk of later AUD.

### *Age of onset of alcohol consumption.*

Regarding the age of onset of alcohol consumption, the committee identified 9 studies (113, 114, 116–118, 122, 124–126), of which 5 were included in a previous SR on the relation between AFD or early drinking and later-life AUD (44). Four additional studies were found by the committee that were not included (117) in the SR (44) or are more recent (116, 118, 122).

In all 4 studies of sufficient quality (all in adolescents) (113, 116, 124, 126), drinking at a younger age (113, 116, 124) or getting drunk after the first drinking episode (126) was associated with a higher risk of later AUD. In 1 of the 4 studies, the association was more pronounced for regular use initiation than for any drinking initiation (113). In the second of the 4 studies, the age of any drinking initiation was not associated with later AUD, whereas the age of first getting drunk was the strongest predictor of later AUD (126). In the third study, the size of the RR of later AUD for drinking before the age of 14 y was similar to the size of the RR associated with getting drunk before the age of 14 y (116). The fourth study did not have information on the level of alcohol consumption in relation to drinking age (124). From the remaining 4 studies (based on 4 study populations) that were not of sufficient quality (117, 118, 122, 125), 1 study (118) found an association between a younger starting age of alcohol consumption and an increased risk of later AUD. In the other 3 studies no such associations were observed (117, 122, 125).

## Discussion

The committee aimed to provide a systematic overview of human prospective studies on alcohol consumption and both brain function and development and AUD in adolescents and young adults. In the research results assessed, the committee found indications that alcohol consumption can have a negative influence on brain development in adolescents and young adults and entails a risk of later AUD.

### **Brain structure and function**

Regarding brain structure and function, the committee concluded that there are indications based on rather consistent findings across studies that the volume of gray matter in the brain shows an accelerated decline in young people who drink. The consequences of an accelerated decline of gray matter, however, are not yet clear. No judgment could be made on the relation between alcohol consumption and white matter volume or integrity because not enough studies of sufficient quality were available. For alcohol consumption and brain activity, the study designs were too diverse to make a judgment. Of note, in general, a difference in brain activity not paralleled by behavioral effects is difficult to interpret. A decrease in brain activity could be explained as impaired brain functioning, whereas the opposite (an increased brain function) could be explained as a compensatory mechanism of an affected brain to perform normally. Regarding the neuroimaging and neurophysiology outcome measures, the total number of studies was low and the study quality and study designs in terms of population, exposure, and outcome measures varied widely, limiting the possibility of drawing overall conclusions on the effect of alcohol on the brain. Furthermore, the available studies generally were not comprised of large groups of subjects and focused on groups that showed extreme differences in terms of their alcohol consumption. It may be that the majority of adolescents are part of the middle group, which was often not studied. In

**TABLE 5** Longitudinal studies on the association between alcohol consumption and AUD (in alphabetical order of first author and clustered by cohort)<sup>1</sup>

Studies	Sample	n	Exposure: quantity or frequency of drinking	Exposure: AFD/early drinking	Follow-up time, y	Baseline alcohol consumption	Endpoints	Risk of bias <sup>2</sup>	Results
C-SURF (Cohort on Substance Use Risk Factors), Switzerland Baggio et al. (109)	Young adult males, 20 y	4352	Alcohol use, drinks/wk		1.25	n.r.	AUD	5	Higher risk
Cohort study of adolescent health, Australia Bonomo et al. (110)	High school students, subgroup of frequent drinkers ( $\geq 3$ times/wk), 14–15 y	1601	Frequent drinking ( $\geq 3$ d in <7 d); yes vs. no		6	58% nondrinking; 29% not drinking last week; 10% drank 1–2 glasses last week; 2% drank $\geq 3$ glasses last week	AD	6	Higher risk
Minneapolis, USA, low-income birth cohort Englund et al. (111)	Adolescents, 16 y	178	BD ( $\geq 45$ g ethanol; $\geq 5$ drinks); yes vs. no		12 (birth to 28 y)	At 16 y: 52% abstainers, 40% moderate drinkers; 7% heavy drinkers	AUD (28 y of age)	5	Higher risk
ALSPAC (Avon Longitudinal Study of Parents and Children), UK, birth cohort Heron et al. (115)	13–15 y	4100	Frequency of alcohol use (low, medium, high), increasing scale Typical quantity (low, medium, high), increasing scale		3–4	At 13 y: 79% nondrinkers, 15% <weekly, 5% weekly drinkers	Hazardous use, harmful use (AUDIT) at 16 y	5	Higher risk
Seattle Social Development Program, USA Guo et al. (112)	Adolescents from high-crime areas, 13 y	808	Frequency of alcohol use in the previous month at 10 y Frequency of alcohol use in the previous month at 14 y Frequency of alcohol use in the previous month at 16 y		11	n.r.	AA, AD	5	No association with AUD or AD Higher risk of AUD and AD Higher risk of AUD; no association with AD

(Continued)

**TABLE 5** (Continued)

Studies	Sample	n	Exposure: quantity or frequency of drinking	Exposure: AFD/early drinking	Follow-up time, y	Baseline alcohol consumption	Endpoints	Risk of bias <sup>2</sup>	Results
Guttmanova et al. (113, 114)	Adolescents from high-crime areas, 10 y	706		AFD, any use, in 4 age categories (any alcohol use)	~23	n.r.	Alcohol misuse, AD (33 y of age)	7	No association for lifetime AUD, higher risk of chronic AUD for AFD < 11 y than for 11–14 y; higher risk of lifetime AUD for younger regular use Higher risk of chronic AUD for younger regular use
Hill et al. (106)	Adolescents from high-crime areas, 10 y	808	Binge trajectories (early highs, increasers, late onsetters, non-BDs) (13–18 y)	Age of regular use initiation in 4 age categories (regular not specified)	11	n.r.	AA + AD (21 y)	4	Higher risk of AUD (21 y) for “increasers” and “late onsetters” than for non-BDs; no association for AUD (21 y) for “early highs” compared with non-BDs
Longitudinal study of familial alcoholism, Arizona, USA King and Chassin (117)	Adolescents with oversampling of families with alcoholism, 11–16 y	185, 210		Early alcohol use ( $\leq 13$ y) (yes/no)	10	n.r.	AD (20–29 y, 22 y)	6	No association
Haller et al. (105)	Adolescents from families with alcoholism and controls, 14 y	405	Frequency of BD ( $\geq 5$ drinks/occasion); from 0 (never) to 7 (every day), increasing scale, at 3 waves (path analyses)		18	n.r.	Adult AD	6	Higher risk
Minnesota Twin Family Study, USA, birth cohort Irons et al. (116)	Twins, 11 y	1512		Early (14 y) alcohol use Early (14 y) alcohol intoxication	10	At 14 y: 36% ever drank alcohol; 15% had ever been intoxicated	AUD	8	Higher risk of younger AFD Higher risk of intoxication at younger age

(Continued)

**TABLE 5** (Continued)

Studies	Sample	n	Exposure: quantity or frequency of drinking	Exposure: AFD/early drinking	Follow-up time, y	Baseline alcohol consumption	Endpoints	Risk of bias <sup>2</sup>	Results
Cohort from Pittsburgh, USA Kirisci et al. (118)	High school students, 10–12 y	261		AFD (continuous)	10–12	Mean ± SD AFD: 14.8 ± 2.1 y	AUD 22 y	5	Higher risk of younger starting age
Collaborative Study on the Genetics of Alcoholism, USA Kramer et al. (119)	Adolescents; oversampling of alcohol-dependent adolescents, 15 y	141	Alcohol use, typical quantity (<6 mo), increasing scale		5	n.r.	Problematic alcohol use	3	No association
Pooling study of Australasian cohorts, Australia, New Zealand <sup>3</sup> Silins et al. (19)	Birth cohorts and cohort of adolescents (including CHDS, M USP, and VAHCS), 14–16 y	2937 (24 y), 1643 (30 y)	Alcohol use, increasing frequency (never, < weekly, ≥ weekly)		8–10, 14–16	n.r.	AD	8	No association with AD at 24 y of age; higher risk of AD at 30 y of age
Dunedin Multidisciplinary Health and Development Study Meier et al. (120)	Adolescents and young adults, 18 y	957	Alcohol amount per occasion, increasing scale (≤2, 3–4, 5–6, ≥7)		Birth to age 32 y	n.r.	AD (21–32 y)	5	Developmentally limited AD: increased risk; persistent AD: no association
Meier et al. (121)	Adolescents and young adults, 18 y	1037	Frequent alcohol use (≥5 d/wk; yes/no)		Birth to age 38 y	n.r.	AD (21–38 y)	5	Developmentally limited AD: increased risk; persistent AD: increased risk
CHDS, New Zealand Newton-Howes and Boden (122) <sup>4</sup>	Adolescents, 11–13 y	1056	Daily use (yes/no)	AFD (continuous)	Birth to age 33 y	n.r.	AUD (33 y)	6	No association
Colorado Community Twin Study, USA Palmer et al. (123)	Adolescent twins, 11.5–18.5 y	1733	Lifetime alcohol use (≥1; yes vs. no)		5	Ever used alcohol: 53%; repeated use of alcohol: 22%	AA, AD (16.5–25 y)	5	Higher risk

(Continued)



**TABLE 5** (Continued)

Studies	Sample	n	Exposure: quantity or frequency of drinking	Exposure: AFD/early drinking	Follow-up time, y	Baseline alcohol consumption	Endpoints	Risk of bias <sup>2</sup>	Results
Oso (no name), Norway Pedersen and Skrandal (124)	Adolescents, 12–15 y	522		AFD (continuous)	6	Mean $\pm$ SD starting drinking age: 14.8 $\pm$ 2.9 y	RAPI	7	Higher risk of younger AFD
Young in Norway Longitudinal Study, Norway Rossow and Kuntsche (125)	High school students, 13–14 y	1311		AFD (continuous)	13	13–14 y: 34% reported onset of drinking; 14% had drunk to intoxication	AUD	6	No association
San Diego Prospective Study, USA Schuckit and Smith (127)	University male students; oversampling of offspring of alcohol-dependent fathers, 18–25 y	373	Usual frequency of alcohol use, increasing scale		25	Mean $\pm$ SD usual drinking frequency in recent 6 mo: 7.6 $\pm$ 6.1 to 12.4 $\pm$ 6.2; mean $\pm$ SD usual drinking quantity: 2.4 $\pm$ 1.3 to 3.6 $\pm$ 1.6	AUD trajectories	7	Higher risk
British Birth Cohort Study, UK Viner and Taylor (93)	Adolescents, 16 y	11,622	Usual drinking quantity, increasing scale		14	Habitual frequency (%) last year: every day: 2; 4–5 times/wk: 4; 2–3 times/wk: 20; once per week: 30; once per month: 15; occasionally: 21; never: 9	AD (30 y of age)	6	Higher risk
Rutgers Health and Human Development Project, USA Warner and White (126)	Community-based adolescents, 12 y	374	Frequency of habitual drinking (7 categories), increasing scale; BD ( $\geq$ 4 drinks on $\geq$ 2 occasions during previous 2 wk)	AFD at a family gathering	18–19	Mean AFD: 8.6 y in family setting	AD + AA (30–31 y of age)	9	No association
				AFD outside family gathering		Mean AFD: 14.2 y outside family setting			No association
				Feeling drunk at first use (yes/no)		18%			Higher risk of AUD

<sup>1</sup> AA, alcohol abuse; AD, alcohol dependence; AFD, age of first drink; AUD, alcohol use disorder; AUDIT, Alcohol Use Disorders Identification Test; BD, binge drinking; BDs, binge drinkers; CHDS, Christchurch Health and Development Study; MUSP, Matter Hospital and University of Queensland Study of Pregnancy; n.r., not reported; RAPI, Rutgers Alcohol Problem Index; VAHCS, Victorian Adolescent Health Cohort Study.

<sup>2</sup> Study quality/risk of bias was assessed with the Newcastle-Ottawa Scale (0–9); for clarification see Supplemental Methods 3 and Supplemental Table 4.

<sup>3</sup> For the outcome measure at 24 y of age 3 cohorts (CHDS, VAHCS, and MUSP) were included; for the outcome measure at 30 y of age 2 cohorts were included (CHDS and MUSP).

<sup>4</sup> Cohort included in Silins et al. (19).

addition, studying only extreme groups makes it impossible to study the shape of associations (i.e., dose-response or threshold effects).

### **Cognitive functioning**

Regarding cognitive functioning, the committee concluded that the relation between alcohol consumption and cognitive functioning in young people is still unclear, because the available studies of sufficient quality were largely based on data from only 2 study populations. Other caveats were that a variety of cognitive tests have been used, making the results difficult to compare, and that in some studies a large number of cognitive outcomes (test results) have been reported, which increases the possibility of chance findings.

### **Educational achievement**

Regarding educational achievement, in approximately half of the available studies, adolescents who drank alcohol performed worse at school than young people who did not drink: they achieved a lower level of education or left school without a diploma. In the analyzed studies, it is difficult, however, to establish the extent to which the risk of early school dropout at the start of the study already differed among the participants. As a result, it is possible that poorer educational achievement is not the *result* of alcohol consumption but the *cause*. It can also not be ruled out that the associations found were caused by a so-called “third factor” (129) associated with both alcohol consumption and educational achievement. For example, personality characteristics such as risk-seeking behavior may be related both to higher alcohol consumption and to skipping classes or problem behavior. Two of the included studies that found an association between higher alcohol use and lower school performance (1 of sufficient quality) doubted the causality of their findings and discussed alternative explanations for their findings (87, 101). Altogether, the committee therefore concluded that the connection between alcohol consumption and educational achievement is still unclear.

### **AUD**

Regarding AUD, the committee concluded that there are indications that starting drinking at a young age is associated with a higher risk of developing AUD later in life. The more often young people drink, or the younger they start, the higher this risk. In all available studies of sufficient quality, adverse associations were observed. It was, unfortunately, not possible to quantitatively summarize these findings because studies differed substantially in the figures reported, precluding the aggregation of findings. For example, the measures of age of onset were different across the studies and the reference groups. The committee in addition notes that starting age of drinking as a measure of exposure to alcohol has its limitations (44, 130, 131). 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 (113, 131). Several authors doubted the usefulness of the concept of drinking onset (44, 130, 131). In addition, some studies supported the idea that the first experience with alcohol, as such, is not as strong a risk factor for later problems as are experiences of amounts of more than just a few sips (113, 131). Also a “third factor” (129) could play a role here.

### **Limitations**

The committee wants to address some general limitations of this review. First, it is not possible to perfectly assess alcohol consumption in observational research, because the information on alcohol consumption is based on self-report by research participants, which is influenced, among other factors, by memory. In addition, alcohol consumption can vary over time. Based on extensive research it is known that the accuracy of self-reporting on alcohol is enhanced when 1) people are alcohol free when interviewed; 2) written assurances of confidentiality are provided to the participants; 3) people are interviewed in a setting that encourages honest reporting; and 4) participants are asked clearly worded objective questions (e.g., “Did you get drunk last night?”) (132). Depending on one’s personality, alcohol consumption may be underestimated (by providing socially acceptable answers) or overestimated on purpose (showing off) (18, 130). Although the committee weighed the quality of the alcohol exposure assessment using the NOS, it is not possible to judge to what extent self-reporting has affected the results. Second, although the committee evaluated other substance use and externalizing behavior as confounding factors (NOS), it is still difficult to disentangle the role of alcohol from other often clustered risk factors for the outcomes studied here: brain development or AUD. Third, the variability in measurements of alcohol consumption impaired drawing conclusions for the degree of alcohol consumption, e.g., binge drinking. In addition, comparison groups varied widely between studies, e.g., binge drinking was often compared with non-binge drinking and not with nondrinking. Fourth, the committee could also not answer the question whether the consequences of alcohol consumption are reversible because hardly any studies were available. Finally, publication or reporting bias may have played a role (18, 44, 133–136).

To improve the evidence base of the impact of alcohol consumption on the developing brain, additional population-based studies are urgently needed. These studies would need to include measurements of the outcomes of interest before the initiation of alcohol consumption in order to disentangle causes and consequences. Future studies should cover a wide range of measures of brain structure and function. That would, for example, enable studying functional consequences of aberrations of brain structure or activity in relation to cognitive function, or the impact of cognitive impairments after alcohol consumption in relation to educational achievements or AUD in later life. To this respect, a few ongoing initiatives should be mentioned (137, 138). Furthermore, data on the reversibility of findings are of importance. Finally, data of

non-Western countries are needed to enable extrapolations of the findings.

Because of the several potential limitations, which are largely inherent to this field of research, the committee has been cautious with drawing firm conclusions, first, by requesting a minimum of 3 comparable studies of sufficient quality based on nonoverlapping study populations and, second, by incorporating additional points of concern in the weighing for specific endpoints.

We identified 3 recent SRs (139–141) and 7 individual studies compliant with our inclusion criteria (142–148) that were published after finalizing the advisory report (search performed July 2020). These 7 additional cohort studies comprised 4 additional study populations: 3 regarding cognition and 1 regarding AUD. The results of the studies are in agreement with the findings of our advisory report [see **Supplemental Results 5** for further description of these 10 publications (139–148)].

## Conclusion

This SR suggested that alcohol consumption can have a negative influence on brain development of young people and entails a risk of later AUD. Moreover, based on previous research it is known that alcohol consumption leads to risky behavior, due to acute effects of alcohol, and health risks in the longer term. The committee therefore considers it a wise choice for adolescents and young adults not to drink alcohol.

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