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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.

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 ≤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, Elofson 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 ≥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 ≥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. KR, SK, SD, RC, AEE, AES, KGM, WMV, JvdH, JHo, and JvO have been offered financial compensation for meeting attendance and travelling expenses from the Health Council of The Netherlands. The Board of the Health Council consciously weighed the interests and conditions 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 ≥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 ≥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.

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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. Neuro-biological 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). 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.

**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 |
(19, 21, 53–127), including 17 studies on neuroimaging and
europhysiology (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 as-
seed 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.
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
available with sufficient quality based on ≥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

| Studies                                      | Sample                                      | n     | Exposure                                      | Follow-up time, y | Baseline alcohol consumption | Endpoints                                      | FDR correction | Risk of bias | Results                                                                 |
|----------------------------------------------|---------------------------------------------|-------|-----------------------------------------------|-------------------|-------------------------------|-----------------------------------------------|----------------|--------------|-------------------------------------------------------------------------|
| Cohort of Youth at Risk for Alcoholism, University of California, San Diego, USA          | Middle school students, 12–16 y             | 40    | Initiation of BD vs. minimal drinking         | 3                 | Limited (≤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 |
| Squeglia et al. (60)                         |                                             |       |                                               |                   |                               |                                               |                |              |                                                                          |
| Wetherill et al. (63)                        | Middle school students, 12–16 y             | 40    | Initiation of BD vs. minimal drinking         | 3                 | Limited (≤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 (≤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   | AF D (earlier; scale), AW DO (earlier; scale) | 6                 | Limited (≤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; AW DO: Visual working memory task: no associations; 2 ROIs: no associations; higher activation (less negative) in 5 regions (WB) |

(Continued)
| Studies                                      | Sample                                      | n   | Exposure                              | Follow-up time, y | Baseline alcohol consumption | Endpoints                                              | FDR correction | Risk of bias² | 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 ± SD alcohol units/wk: 20 ± 19 in BDs and 14 ± 29 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 ± SD drinks per episode: 17 ± 13 in controls and 5.6 ± 2.6 in BDs | ERP “attention, working memory”                       | Yes, for post hoc analyses | 7            | Visual oddball task: no differences; ERP: no group x time interaction |
| López-Caneda et al. (55)                    | University students, 18–19 y                | 57  | Sustained BD vs no BD                  | 2                 | Mean ± SD g alcohol/Wk: 40.6 ± 62.9 in controls and 373.5 ± 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 ± SD doses/Wk: 32.1 ± 21.2 for BDs and 45.5 ± 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 ↓, P3 amplitude ↓ for non-alcohol-related stimuli only |
| “Ad Brain Study”, USA Wilson et al. (64)    | Twins, 14–17 y                              | 96  | Alcohol index³ (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)
| Studies | Sample | n | Exposure | Follow-up time, y | Baseline alcohol consumption | Endpoints | FDR correction | Risk of bias | 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 ± SD alcohol (g/wk) | 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 ± SD blood alcohol concentration, % | 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 ± SD 2 ± 5 drinks/mo; heavy drinkers: mean ± SD 48 ± 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 ± SD lifetime alcohol use: 28.7 ± 37.7 glasses; mean ± SD alcohol use in the last month: 6.4 ± 12.4 glasses | fMRI resting state FC | No, ROI approach | 5 | No associations with resting-state connectivity |

1. 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.

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

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

4. A blood alcohol concentration of 0.08% corresponds to an intake of ≥5 drinks (≥4 for females) on 1 occasion within a 2-h interval.
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,
| Studies                                      | Sample                                    | n   | Exposure                                                      | Follow-up time, y | Baseline alcohol consumption | Endpoints                                                                 | Multiple testing correction | Risk of bias | Results                                                                                     |
|---------------------------------------------|-------------------------------------------|-----|----------------------------------------------------------------|-------------------|------------------------------|--------------------------------------------------------------------------------|-------------------------------|--------------|--------------------------------------------------------------------------------------------|
| High school students                        |                                           |     |                                                                |                   |                              |                                                                                |                               |              |                                                                                            |
| Cohort from University of California, San Diego, USA | 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                                                                             |
| 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 (≤ 1 total lifetime drinks)            | Response inhibition                                                            | n.r.                        | 7            | No associations                                                                             |

(Continued)
| Studies                      | Sample                               | n   | Exposure                                                                 | Follow-up time, y | Baseline alcohol consumption                                                                 | Endpoints                                                                 | Multiple testing correction | Risk of bias | Results                                                                 |
|------------------------------|--------------------------------------|-----|---------------------------------------------------------------------------|-------------------|----------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|---------------------------|--------------|-------------------------------------------------------------------------|
| Nguyen-Louie et al. (76)     | Middle school students, 12–14 y      | 234 | More alcohol use (continuous)                                             | 1–9 (mean 4)      | Limited (≤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 (≤10 lifetime alcohol use occasions, never >2 drinks/wk)                                | 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 (≤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, 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 (≤10 lifetime alcohol use occasions, never >2 drinks/wk)                              | Visual working memory                                                                                                                                     | n.r.                       | 5            | No associations                                                                                                          |
| Studies | Sample | n | Exposure | Follow-up time, y | Baseline alcohol consumption | Endpoints | Multiple testing correction | Risk of bias | 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 naïve 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 ± SD alcohol, g/wk: ♂ 14 y: 2.5 ± 5.0; ♂ 16 y: 37.7 ± 564; ♂ 18 y: 13.0 ± 179; ♂ 18 y: 7.7 ± 309 | 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 ± SD drinks per episode: 1.7 ± 1.3 in controls and 5.6 ± 2.6 in BDs | Visual attention | n.r. | 7 | No differences |
| 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 (≥6 alcoholic drinks on the same occasion weekly/monthly and ≥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 ± SD non-BDs: 40.6 ± 62.9 g alcohol/wk; BDs: 373.5 ± 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 ± SD non-BDs: 42.19 ± 52.79 g alcohol/wk; BDs: 302.46 ± 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 ± SD non-BDs: 42.19 ± 52.79 g alcohol/wk; BDs: 312.41 ± 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 ± SD non-BDs: 42.19 ± 52.79 g alcohol/wk; BDs: 302.46 ± 251.13 g alcohol/wk | Decision making                | n.r.                     | 6         | No differences |
| Cohort of University of Brussels, Belgium | University students, 22 y                  | 30  | BD vs. non-BD | 1                 | Varying, mean ± SD controls: 4.5 ± 3.3 doses/wk; BDs: 32.1 ± 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.
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, 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 naive 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 use 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)\(^1\)

| Studies | Sample | Sample size | Exposure | Follow-up time, y | Baseline alcohol consumption | Risk of bias\(^2\) | Results for educational attainment and dropout | Results for school marks |
|---------|--------|-------------|----------|-------------------|-----------------------------|------------------|---------------------------------|-------------------------|
| **High school students** | | | | | | | | |
| Cohort from Technion-Israel Institute of Technology, Israel | 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 |
| 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 | High school seniors, 17–18 y | 752 | Number of drinks/wk | ~6 | Varying; mean ± SD drinks in the past wk: 2.6 ± 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 | Frequent BD vs. nonfrequent BD and frequent BD vs. non-BD | ~26 | Varying; 17% reported frequent BD, 40% nonfrequent BD, and 43% non-BD/abstinence | 8 | No association with number of completed years of schooling |
| RAND Adolescent Panel Survey, USA | 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)
| Studies | Sample | n | Exposure | Follow-up time, y | Baseline alcohol consumption | Risk of bias | 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) | 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) | ∼8 | n.r. | More senior 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. | 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 | |
| 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 ≥ 1 drink in the last month (yes/no), heavy drinking ≥ 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 ≥ 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 (≥ 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)
| 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        | Adolescents, 16 y                                 | 9107 | Heavy alcohol use (yes/no)                  | 26                | Varying; 13% of males and 25% of females 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 | 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 30d (yes/no); BD past 2 wk (yes/no); frequent drinking ≥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     |                          |

(Continued)
| Studies | Sample | n   | Exposure | Follow-up time, y | Baseline alcohol consumption | Risk of bias | Results for educational attainment and dropout | Results for school marks |
|---------|--------|-----|----------|------------------|-----------------------------|-------------|-----------------------------------------------|----------------------------|
| Icelandic cohort of adolescents, Iceland | Adolescents, 15 y | 201 | Alcohol consumption (yes/no) | 8 | n.r. | 5 | Higher likelihood of secondary school dropout |  |
| Pooling study of 3 UK cohorts | 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 | High school students, 18 y | 10,020 | BD on ≥ 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 | 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 | 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 | 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 | College students, ≥ 18 y | 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 |  |
| Studies | Sample | n | Exposure | Follow-up time, y | Baseline alcohol consumption | Risk of bias 2 | 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 4 | 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 enrollment of ≥1 semesters), no association with university discontinuity in the first 2 y of university |  |

1 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.

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

3 Cohort included in Green et al. (89).

4 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...
| Studies | Sample | n | Exposure: quantity or frequency of drinking | Exposure: AFD/early drinking | Follow-up time, y | Baseline alcohol consumption | Endpoints | Risk of bias | 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 (≥3 times/wk), 14–15 y | 1601 | Frequent drinking (≥3 d in <7 d), yes vs. no | | 6 | | AD | 6 | Higher risk |
| Minneapolis, USA, low-income birth cohort Englund et al. (111) | Adolescents, 16 y | 178 | Alcohol use (drinks per occasion: 0, 1, 2, 3, 4, ≥5), increasing scale | | 12 (birth to 28 y) | | 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 | | 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 |

(Continued)
| Studies                          | Sample                                                                 | n     | Exposure: AFD/early drinking | Follow-up time, y | Baseline alcohol consumption | Endpoints                                      | Risk of bias | Results                                                                 |
|--------------------------------|------------------------------------------------------------------------|-------|------------------------------|-------------------|------------------------------|-----------------------------------------------|--------------|--------------------------------------------------------------------------|
| Guttmannova 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 |
| Hil et al. (106)                | Adolescents from high-crime areas, 10 y                                | 808   | Binge trajectories (early highs, increasers, late onsetters, non-BDs) (13–18 y) | 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                 | Adolescents with oversampling of families with alcoholism, 11–16 y     | 185, 210 | Early alcohol use (≤13 y) (yes/no) | 10                | n.r.     | AD (20–29 y, 22 y)                           | 6            | No association                                                                 |
| King and Chassin (117)          | Adolescents with oversampling of families with alcoholism, 11–16 y     | 185, 210 | Frequency of BD (≥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                                                                 |
| Haller et al. (105)             | Adolescents from families with alcoholism and controls, 14 y           | 405   | Early (14 y) alcohol use     | 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 |
| Minnesota Twin Family Study, USA, birth cohort                         | Twins, 11 y                                                            | 1512  | 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)
| Studies                                                                 | Sample                                                                 | n     | Exposure: quantity or frequency of drinking | Follow-up time, y | Baseline alcohol consumption | Endpoints | Risk of bias | Results                                |
|------------------------------------------------------------------------|------------------------------------------------------------------------|-------|---------------------------------------------|-------------------|------------------------------|-----------|-------------|-----------------------------------------|
| Cohort from Pittsburgh, USA                                           | 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                | 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 Zealand³       | Birth cohorts and cohort of adolescents (including CHDS, MUSP, 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               | Adolescents and young adults, 18 y                                     | 957   | Frequency of alcohol use                     | Birth to age 32 y | n.r.                         | AD (21–32 y) | 5           | Developmentally limited AD: increased risk; persistent AD: no association |
|                                                                        | Daily use (yes/no)                                                     |       |                                             |                   |                              |            |             | Developmentally limited AD: increased risk; persistent AD: increased risk |
| 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           | No associations                          |
| CHDS, New Zealand                                                    | Adolescents, 11–13 y                                                   | 1056  | AFD (continuous)                            | Birth to age 33 y | n.r.                         | AUD (33 y) | 6           | No association                          |
| Newton-Howes and Boden (122)                                          |                                                                      |       |                                             |                   |                              |            |             |                                        |
| Colorado Community Twin Study, USA                                    | 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)
| 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 |
|---------|--------|---|---------------------------------------------|-------------------------------|------------------|-----------------------------|------------|-------------------------|---------|
| Oslo (no name), Norway Pedersen and Skrondal (124) | Adolescents, 12–15 y | 522 | AFD (continuous) | 6 | Mean ± SD starting drinking age: 14.8 ± 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 ± SD usual drinking frequency in recent 6 mo: 7.6 ± 6.1 to 12.4 ± 6.2; mean ± SD usual drinking quantity: 2.4 ± 1.3 to 3.6 ± 1.6 | AUD trajectories | 7 | Higher risk |
| British Birth Cohort Study, UK Viner and Taylor (93) | Adolescents, 16 y | 11,622 | Frequency of habitual drinking (7 categories), increasing scale; BD (≥4 drinks on ≥2 occasions during previous 2 wk) | 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 | 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 Feeling drunk at first use (yes/no) | | | Mean AFD: 14.2 y outside family setting | 18% | No association | 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, Mater 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 uncertain, 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 is. 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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References

1. Courtney KE, Polich J. Binge drinking in young adults: data, definitions, and determinants. Psychol Bull 2009;135(1):142–56.
2. Bava S, Tapert SF. Adolescent brain development and the risk for alcohol and other drug problems. Neuropsych Rev 2010;20(4):398–413.
3. Maldonado-Devincci AM, Badanich KA, Kirstein CL. Alcohol during adolescence selectively alters immediate and long-term behavior and neurochemistry. Alcohol 2010;44(1):57–66.
4. Elsoun J, Gongvatanaw W, Carey KB. Alcohol use and cerebral white matter compromise in adolescence. Addict Behav 2013;38(7):2295–305.
5. van Amsterdam JGC, Ramaekers JG, Verkes RJ, Kuypers KPC, Goudriaan AE, van den Brink W. Alcohol- and drug-related public violence in Europe, European Journal of Criminology. 2020;17(6):806–25.
6. Trimbos Instituut/WODC. Nationale Drug Monitor, Jaarbericht 2017 [Internet]. [Cited 2018 Oct 30]. Utrecht: Trimbos Instituut; 2017. Available from: https://assets.trimbos.nl/docs/0502344-4a38-4a87-9740-bc408805c26a.pdf.
7. National Institute on Alcohol Abuse and Alcoholism (NIAAA). Alcohol overdose: the dangers of drinking too much. [Internet]. Bethesda (MD): NIAAA; 2015. [Cited 2018 Oct 30]. Available from: https://pubs.niaaa.nih.gov/publications/AlcoholOverdoseFactsheet/Overdosefact.htm.
8. Paton A. Alcohol in the body. BMJ 2005;330(7482):85–7.
9. Poznyak V, Rekev D, editors. Global status report on alcohol and health 2014. [Internet]. Geneva (Switzerland): WHO; 2014. [Cited 2018 Oct 30]. Available from: https://www.who.int/substance Abuse/publications/alcohol_2014/en/.
10. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Amann M, Anderson HR, Andrews KG, Arrey M, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380(9859):2223–60.
11. Global Burden of Disease Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388(10053):1659–724.
12. Global Burden of Disease Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;386(10010):2287–323.
13. Rehm J, Gmel GE, Sr, Gmel G, Hasan OSM, Imtiaz S, Popova S, Probst C, Roerecke M, Room R, Samokhvalov AV, et al. The relationship between different dimensions of alcohol use and the burden of disease—an update. Addiction 2017;112(6):968–1001.
14. Global Burden of Disease 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2018;392(10152):1015–35.
15. Wood AM, Kaptego S, Butterworth AS, Willett P, Warnakula S, Bolton T, Paige E, Paul DS, Sweeting M, Burgess S, et al. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. Lancet 2018;391(10129):1513–23.
16. World Cancer Research Fund/American Institute for Cancer Research. Diet, nutrition, physical activity and cancer: a global perspective. Continuous update project expert report 2018. London: World Cancer Research Fund; 2018.
17. Zeigler DW, Wang CC, Yoast RA, Dickinson BD, McCaffree MA, Robinowitz CB, Sterling ML, Council on Scientific Affairs, American Medical Association. The neurocognitive effects of alcohol on adolescents and college students. Prev Med 2005;40(1):23–32.
18. McCambridge J, McAlaney J, Rowe R. Adult consequences of late adolescent alcohol consumption: a systematic review of cohort studies. PLoS Med 2011;8(2):e1000413.
19. Silins E, Horwood LJ, Najman JM, Patton GC, Toubourou JW, Olsson CA, Hutchinson DM, Degenhardt L, Ferguson D, Becker D, et al. Adverse adult consequences of different alcohol use patterns in adolescence: an integrative analysis of data to age 30 years from four Australasian cohorts. Addiction 2018;113(10):1811–25.
20. Giedd JN. Normal development. Child Adolesc Psychiatr Clin N Am 1997;6(2):265–82.
21. Boelema SR, Harakeh Z, van Zandvoort MJ, Reijneveld SA, Verhulst FC, Ormel J, Vollebergh WA. Adolescent heavy drinking does not affect maturation of basic executive functioning: longitudinal findings from the TRAILS Study. PLoS One 2015;10(10):e0139186.
22. Vermeulen M. Paar bierjassen niet per se slecht voor het puberbeen. Amsterdam: Volksrant; 3 December 2014.
23. Casey BJ, Jones RM. Neurobiology of the adolescent brain and behavior: implications for substance use disorders. J Am Acad Child Adolesc Psychiatry 2010;49(12):1189–201; quiz 1285.
24. Crews FT, Vetreno RP, Broadwater MA, Robinson DL. Adolescent alcohol exposure persistently impacts adult neurobiology and behavior. PharmacoL Rev 2016;68(4):1074–109.
25. Degenhardt L, Stockings E, Patton G, Hall WD, Lysnkey M. The increasing global health priority of substance use in young people. Lancet Psychiatry 2016;3(3):251–64.
26. Hermens DF, Lagopoulo J, Tobias-Webb J, De Regt T, Dore G, Juckes L, Latt N, Hickie IB. Pathways to alcohol-induced brain impairment in young people: a review. Cortex 2013;49(1):3–17.
27. Hill SY. Trajectories of alcohol use and electrophysiological and morphological indices of brain development: distinguishing causes from consequences. Annu N Y Acad Sci 2004;1021:245–59.
28. Jacobus J, Tapert SF. Neurotoxic effects of alcohol in adolescence. Annu Rev Clin Psychol 2013;9:703–21.
29. Lisdahl KM, Gilbart ER, Wright NF, Shollenberger S. Dare to delay? The impacts of adolescent alcohol and marijuana use onset on cognition, brain structure, and function. Front Psychiatry 2013;4:53.
30. López-Caneda E, Rodríguez Holguín S, Cadaveira F, Corral M, Doola S. Impact of alcohol use on inhibitory control (and vice versa) during adolescence and young adulthood: a review. Alcohol Alcohol 2014;49(2):173–81.
31. Nixon SJ. Executive functioning among young people in relation to alcohol use. Curr Opin Psychiatry 2013;26(4):305–9.
32. Peeters M, Vollebergh WA, Wiers RW, Field M. Psychological changes and cognitive impairments in adolescent heavy drinkers. Alcohol Alcohol 2014;49(2):182–6.
33. Petit G, Maupur P, Kornejch C, Verbanck P, Campanella S. Binge drinking in adolescents: a review of neurophysiological and neuroimaging research. Alcohol Alcohol 2014;49(2):198–206.
34. Silveri MM, Dager AD, Cohen-Gilbert JE, Sleeider JT. Neurobiological signatures associated with alcohol and drug use in the human adolescent brain. Neurosci Biobehav Rev 2016;70:244–59.
35. Spear LP, Swartwelder HS. Adolescent alcohol exposure and persistence of adolescent-typical phenotypes into adulthood: a mini-review. Neurosci Biobehav Rev 2014;45:1–8.
36. Squegal MM, Boissoneault J, Van Skile CE, Nixon SJ, Matthews DR. Age-related effects of alcohol from adolescent, adult, and aged populations using human and animal models. Alcohol Clin Exp Res 2014;38(10):2509–16.
37. Wiers RW, Boleema SR, Nikolau K, Gladwin TE. On the development of implicit and control processes in relation to substance use in adolescence. Curr Addict Rep 2015;2(2):141–55.
38. Windle M, Spear LP, Fuligini AJ, Angold A, Brown JD, Pine D, Smith GT, Giedd J, Dahl RE. Transitions into under age and problem drinking: developmental processes and mechanisms between 10 and 15 years of age. Pediatrics 2008;121:S273–89.
39. Squegal MM, Gray KM. Alcohol and drug use and the developing brain. Curr Psychiatry Rep 2016;18(5):46.
40. Wilson S, Bair JL, Thomas KM, Iacono WG. Problematic alcohol use and reduced hippocampal volume: a meta-analytic review. Psychol Med 2017;47(13):2288–301.
41. Feldstein Ewing SW, Sakhardande A, Blakemore SJ. The effect of alcohol consumption on the adolescent brain: a systematic review of MRI and fMRI studies of alcohol-using youth. Neuroimage Clin 2014;5:420–37.
42. Moffitt TE, Arseneault L, Belsky D, Dickson N, Hancox RJ, Harrington H, Houts R, Poulton R, Roberts BW, Ross S, et al. A gradient of childhood self-control predicts health, wealth, and public safety. Proc Natl Acad Sci U S A 2011;108(7):2693–8.
43. Singleton RA, Jr, Wolfson AR. Alcohol consumption, sleep, and academic performance among college students. J Stud Alcohol Drugs 2009;70(3):355–63.
44. Maimaris W, McCambridge J. Age of first drinking and adult alcohol problems: systematic review of prospective cohort studies. J Epidemiol Community Health 2014;68(3):268–74.
45. Rubia K, Linn L, Ecker C, Halari R, Gianpietro V, Simmons A, Brammer M, Smith A. Effects of age and gender on neural networks of motor response inhibition: from adolescence to mid-adulthood. Neuroimage 2013;83:690–703.
46. Diamond A. Executive functions. Annu Rev Psychol 2013;64:135–68.
47. Spear LP. Effects of adolescent alcohol consumption on the brain and behaviour. Nat Rev Neurosci 2018;19(4):197–214.
48. Spear LP. Consequences of adolescent use of alcohol and other drugs: studies using rodent models. Neurosci Biobehav Rev 2016;70:228–43.
49. Novier A, Diaz-Granados JL, Matthews DB. Alcohol use across the lifespan: an analysis of adolescent and aged rodents and humans. Pharmacol Biochem Behav 2015;133:65–82.
50. Stroup DF, Berlin JA, Morton SC, Olinin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA 2000;283(15):2008–12.
51. Neugebauer R, Ng S. Differential recall as a source of bias in epidemiologic research. J Clin Epidemiol 1990;43(12):1337–41.
52. Rosso I. Inferences of associations and implications for prevention: the case of early drinking onset. In: Elster J, Gjelvik E, Hylland A, Moene K, editors. Understanding choice, explaining behavior: essays in honour of Ole-Jørgen Skog. Oslo (Norway): UniPub; 2006. pp. 259–72.
53. Jacobus J, Castro N, Squegal LM, Meloy MJ, Brumback T, Huestis MA, Tapert SF. Adolescent cortical thickness pre- and post marijuana and alcohol initiation. Neurotoxol Teratol 2016;57:20–9.
54. López-Caneda E, Cadaveira F, Crego A, Dolaso S, Corral M, Gómez-Suárez A, Rodríguez Holguín S. Effects of a persistent binge drinking pattern of alcohol consumption in young people: a follow-up study using event-related potentials. Alcohol Alcohol 2013;48(4):464–71.
55. López-Caneda E, Rodríguez Holguín S, Corral M, Dolaso S, Cadaveira F. Evolution of the binge drinking pattern in college students: neurophysiological correlates. Alcohol 2014;48(5):407–18.
56. Luciana M, Collins PF, Muetzel RL, Lin KO. Effects of alcohol use initiation on brain structure in typically developing adolescents. Am J Drug Alcohol Abuse 2013;39(6):345–55.
57. Maupur P, Ponsenti M, Philippot P, Joassin F, Campanella S. Latent deleterious effects of binge drinking over a short period of time revealed only by electrophysiological measures. J Psychiatry Neurosci 2009;34(2):111–8.
58. Petit G, Kornejch C, Dan B, Verbanck P, Campanella S. Electrophysiological correlates of alcohol- and non-alcohol-related stimuli processing in binge drinkers: a follow-up study. J Psychopharmacol 2014;28(11):1041–52.
59. Pfefferbaum A, Kwon D, Brumback T, Thompson WK, Cummings K, Tapert SF, Brown SA, Colrain IM, Baker FC, Prouty D, et al. Altered brain developmental trajectories in adolescents after initiating drinking. Am J Psychiatry 2018;175(4):370–80.
60. Squegal MM, Pulido C, Wetherill RR, Jacobus J, Brown GG, Tapert SF. Brain response to working memory over three years of adolescence: influence of initiating heavy drinking. J Stud Alcohol Drugs 2012;73(5):749–60.
61. Squegal MM, Rinker DB, Bartsch H, Castro N, Chung Y, Dale AM, Jernigan TL, Tapert SF. Brain volume reductions in adolescent heavy drinkers. Dev Cogn Neurosci 2014;9:117–25.
62. Squegal MM, Tapert SF, Sullivan EV, Jacobus J, Meloy MJ, Rohlfing T, Pfefferbaum A. Brain development in heavy-drinking adolescents. Am J Psychiatry 2015;172(6):531–42.
63. Wetherell RR, Squegal LM, Yang TT, Tapert SF. A longitudinal examination of adolescent response inhibition: neural differences before and after the initiation of heavy drinking. Psychopharmacology (Berl) 2013;230(4):663–71.
64. Wilson S, Malone SM, Thomas KM, Iacono WG. Adolescent drinking and brain morphometry: a co-twin control analysis. Dev Cogn Neurosci 2015;16:130–8.
65. Meda SA, Dager AD, Hawkins KA, Tennent H, Raskin S, Wood RM, Austad CS, Fallahi CR, Pearson GD. Heavy drinking in college students is associated with accelerated gray matter volumetric decline over a 2 year period. Front Behav Neurosci 2017;11:176.
66. Peters S, Peper JS, Van Duijvenvoorde ACK, Braams BR, Crane EA. Amygdala-orbitofrontal connectivity predicts alcohol use two years later: a longitudinal neuroimaging study on alcohol use in adolescence. Dev Sci 2017;20(4):e12448.
67. Jurk S, Mennigen E, Goschke T, Smolka MN. Low-level alcohol consumption during adolescence and its impact on cognitive control development. Addict Biol 2018;23(1):313–26.
68. Correas A, Cuesta P, López-Caneda E, Rodríguez Holguín S, García-Moreno LM, Pineda-Pardo JA, Cadaveira F, Maestú F. Functional and structural brain connectivity of young binge drinkers: a follow-up study. Sci Rep 2016;6:31293.
69. Nguyen-Louie TT, Simmons AN, Squeglia LM, Alexandra Infante M, Schacht JP, Tapert SF. Earlier alcohol use onset prospectively predicts changes in functional connectivity. Psychopharmacology (Berl) 2018;235(4):1041–54.
70. Carbia C, Cadaveira F, Caamaño-Isorna F, Rodríguez Holguín S, Corral M. Binge drinking trajectory and decision-making during late adolescence: gender and developmental differences. Front Psychol 2017;8:783.
71. Carbia C, Cadaveira F, Caamaño-Isorna F, Rodriguez-Holguín S, Corral M. Binge drinking during adolescence and young adulthood is associated with deficits in verbal episodic memory. PLoS One 2017;12(2):e0171393.
72. Carbia C, Cadaveira F, López-Caneda E, Caamaño-Isorna F, Rodríguez Holguín S, Corral M. Working memory over a six-year period in young binge drinkers. Alcohol 2017;61:17–23.
73. Jacobs J, Squeglia LM, Bava S, Tapert SF. White matter characterization of adolescent binge drinking with and without co-occurring marijuana use: a 3-year investigation. Psychiatry Res 2013;214(3):374–81.
74. Janssen T, Larsen H, Vollebergh WA, Wiers RW. Longitudinal relations between cognitive bias and adolescent alcohol use. Addict Behav 2015;44:51–7.
75. Mota N, Parada M, Crego A, Doallo S, Caamaño-Isorna F, Rodríguez Holguín S, Cadaveira F, Corral M. Binge drinking trajectory and neuropsychological functioning among university students: a longitudinal study. Drug Alcohol Depend 2013;133(1):108–14.
76. Nguyen-Louie TT, Castro N, Matt GE, Squeglia LM, Brumbach T, Tapert SF. Effects of emerging alcohol and marijuana use behaviors on adolescents’ neuropsychological functioning over four years. J Stud Alcohol Drugs 2015;76(5):738–48.
77. Nguyen-Louie TT, Matt GE, Jacobus J, Li I, Cota C, Castro N, Tapert SF. Earlier alcohol use onset predicts poorer neuropsychological functioning in young adults. Alcohol Clin Exp Res 2017;41(12):2082–92.
78. Nguyen-Louie TT, Tracas A, Squeglia LM, Matt GE, Eberson-Shumate S, Tapert SF. Learning and memory in adolescent moderate, binge, and extreme-binge drinkers. Alcohol Clin Exp Res 2016;40(9):1895–904.
79. Squeglia LM, Spadoni AD, Infante MA, Myers MG, Tapert SF. Initiation moderate to heavy alcohol use predicts changes in neuropsychological functioning for adolescent girls and boys. Psychol Addict Behav 2009;23(4):715–22.
80. Green MI, Leyland AH, Sweeting H, Benzeval M. Adolescent smoking and tertiary education: opposing pathways linking socio-economic background to alcohol consumption. Addiction 2016;111(8):1457–65.
81. Hemphill SA, Heerde JA, Scholes-Balog KE, Herrenkohl TI, Toubourou JW, Catalano RF, Jr. Effects of early adolescent alcohol use on mid-adolescent school performance and connection: a longitudinal study of students in Victoria, Australia and Washington State, United States. J School Health 2014;84(11):706–15.
82. Sloan F, Grossman D, Platt A. Heavy episodic drinking in early adulthood and outcomes in midlife. J Stud Alcohol Drugs 2011;72(3):459–70.
83. Patte KA, Qian W, Leatherdale ST. Is binge drinking onset timing related to academic performance, engagement, and aspirations among youth in the COMPASS Study? Subst Use Misuse 2017;52(13):1795–800.
84. Kandel DB, Davies M, Karus D, Yamaguchi K. The consequences in young adulthood of adolescent drug involvement. Arch Gen Psychiatry 1986;43(8):746–54.
85. Staff J, Patrick ME, Loken E, Maggs JL. Teenage alcohol use and educational attainment. J Stud Alcohol Drugs 2008;69(6):848–58.
86. Cook PJ, Moore MJ. Drinking and schooling. J Health Econ 1993;12(4):411–29.
87. Chatterji P. Does alcohol use during high school affect educational attainment?: evidence from the National Education Longitudinal Study. Econ Educ Rev 2006;25:482–97.
88. Wood MD, Sher KJ, McGowan AK. Collegiate alcohol involvement and role attainment in early adulthood: findings from a prospective high-risk study. J Stud Alcohol 2000;61(2):278–89.
89. Patrick ME, Schulenberg JE, O’Malley PM. High school substance use as a predictor of college attendance, completion, and dropout: a national multi-cohort longitudinal study. Youth Soc 2016;48(3):425–47.
90. Crosnoe R. The connection between academic failure and adolescent drinking in secondary school. Socio Educ 2006;79(1):44–60.
91. Martinez JA, Sher KJ, Wood PK. Is heavy drinking really associated with attrition from college? The alcohol-attrition paradox. Psychol Addict Behav 2008;22(3):450–6.
92. Wichstrom L. Alcohol intoxication and school dropout. Drug Alcohol Rev 1998;17(4):413–21.
93. Viner RM, Taylor B. Adult outcomes of binge drinking in adolescence: findings from a UK national birth cohort. J Epidemiol Community Health 2007;61(10):902–7.
94. Svansdottir E, Arrngrimsson SA, Sveinsson T, Johannesson M. Importance of physical health and health-behaviors in adolescence for risk of dropout from secondary education in young adulthood: an 8-year prospective study. Int J Equity Health 2015;14:140.
95. Sloan FA, Malone PS, Kertesz SG, Wang Y, Costanzo PR. Racial differences in the relationship between alcohol consumption in early adulthood and occupational attainment at midlife. Am J Public Health 2009;99(12):2261–7.
96. McCarthy DM, Aarons GA, Brown SA. Educational and occupational attainment and drinking behavior: an expectancy model in young adulthood. Addiction 2002;97(6):717–26.
97. Mason WA, Windle M. Family, religious, school and peer influences on adolescent alcohol use: a longitudinal study. J Stud Alcohol 2001;62(1):44–53.
98. King KM, Meehan BT, Trim RS, Chassin L. Marker or mediator? The effects of adolescent substance use on young adult educational attainment. Addiction 2006;101(12):1730–40.
99. Epstein L, Tamir A. Health-related behavior of adolescents: change over time. J Adolesc Health Care 1984;3(2):91–5.
100. Ellickson P, Bui K, Bell R, McGuigan KA. Does early drug use increase the risk of dropping out of high school? J Drug Issues 1998;28(2):357–80.
101. Dee TS, Evans WN. Teen drinking and educational attainment: evidence from two-sample instrumental variables estimates. J Labor Econ 2003;21(1):178–209.
102. Bray JW, Zarkin GA, Ringwalt C, Qi J. The relationship between marijuana initiation and dropping out of high school. Health Econ 2000;9(1):9–18.
103. Arria AM, Caldeira KM, Vincent KB, Winick ER, Baron RA, O’Grady KE. Discontinuous college enrollment: associations with substance use and mental health. Psychiatr Serv 2013;64(2):165–72.
104. Andersson C, Johnson KO, Berglund M, Öjehagen A. Stress and hazardous alcohol use: associations with early dropout from university. Scand J Public Health 2009;37(7):713–9.
105. Haller M, Handley E, Chassin L, Bountress K. Developmental cascades: linking adolescent substance use, affiliation with substance use promoting peers, and academic achievement to adult substance use disorders. Dev Psychopathol 2010;22(4):899–916.
106. Hill KG, White HR, Chung I-J, Hawkins JD, Catalano RF. Early adult outcomes of adolescent binge drinking: person- and variable-centered analyses of binge drinking trajectories. Alcoholism Clin Exp Res 2000;24(6):892–901.

107. Kelly AB, Evans-Whipp TJ, Smith R, Chan GC, Toubmourou JW, Patton GC, Hemphill SA, Hall WD, Catalano RF. A longitudinal study of the association of adolescent polydrug use, alcohol use and high school non-completion. Addiction 2015;110(4):627–35.

108. Latvala A, Rose RJ, Pulkkinen L, Dick DM, Korhonen T, Kaprio J. Drinking, smoking, and educational achievement: cross-lagged associations from adolescence to adulthood. Drug Alcohol Depend 2014;137:106–13.

109. Baggio S, Igleisas K, Studer J, Dupuis M, Daeen JP, Gmel G. Is the relationship between major depressive disorder and self-reported alcohol use disorder an artificial one? Alcohol Alcohol 2015;50(2):195–9.

110. Bonomo YA, Bowes G, Coffey C, Carlin JB, Patton GC. Teenage drinking and the onset of alcohol dependence: a cohort study over seven years. Addiction 2004;99(12):1520–8.

111. Englund MM, Egeland B, Oliva EM, Collins WA. Childhood and adolescent predictors of heavy drinking and alcohol use disorders in early adulthood: a longitudinal developmental analysis. Addiction 2008;103:23–35.

112. Guo J, Hawkins JD, Hill KG, Abbott RD. Childhood and adolescent predictors of alcohol abuse and dependence in young adulthood. J Stud Alcohol 2001;62(6):754–62.

113. Guttmannova K, Bailey JA, Hill KG, Lee JO, Hawkins JD, Woods ML, Catalano RF. Sensitive periods for adolescent alcohol use initiation: predicting the lifetime occurrence and chronicity of alcohol problems in adulthood. J Stud Alcohol Drugs 2011;72(2):221–31.

114. Guttmannova K, Hill KG, Bailey JA, Lee JO, Hartigan LA, Hawkins JD, Catalano RF. Examining explanatory mechanisms of the effects of early alcohol use on young adult alcohol dependence. J Stud Alcohol Drugs 2012;73(3):379–90.

115. Heron J, Macleod J, Munroe MR, Melotti R, Lewis G, Tilling K, Hickman M. Patterns of alcohol use in early adolescence predict problem use at age 16. Alcohol Alcohol 2012;47(2):169–77.

116. Irons DE, Iacono WG, McGue M. Tests of the effects of adolescent early alcohol exposures on adult outcomes. Addiction 2015;110(2):269–78.

117. King KM, Chassin L. A prospective study of the effects of initiation of alcohol and drug use on young adult substance dependence. J Stud Alcohol Drugs 2007;68(2):256–65.

118. Kirisci L, Tarter R, Ridenour T, Zhai ZW, Fishbein D, Reynolds M, Vanyukov M. Age of alcohol and cannabis use onset mediates the association of transmissible risk in childhood and development of alcohol and cannabis disorders: evidence for common liability. Exp Clin Psychopharmacol 2013;21(1):38–45.

119. Kramer JR, Chan G, Dick DM, Kuperman S, Bucholz KK, Edenberg HJ, Polgreen LA, Hesselbrock VM, Schuckit MA, Nurnberger JI, et al. Multiple-domain predictors of problematic alcohol use in young adulthood. J Stud Alcohol Drugs 2008;69(5):649–59.

120. Meier MH, Caspi A, Houts R, Slutsker WS, Harrington H, Jackson KM, Belsky DW, Poulton R, Moffitt TE. Prospective developmental subtypes of alcohol dependence from age 18 to 32 years: implications for nosology, etiology, and intervention. Dev Psychopathol 2013;25(3):785–800.

121. Meier MH, Hall W, Caspi A, Belsky DW, Cerda M, Harrington HL, Houts R, Poulton R, Moffitt TE. Which adolescents develop persistent substance dependence in adulthood? Using population-representative longitudinal data to inform universal risk assessment. Psychol Med 2016;46(4):877–89.

122. Newton-Howe S, Boden JM. Relation between age of first drinking and mental health and alcohol and drug disorders in adulthood: evidence from a 55-year cohort study. Addiction 2016;111(4):637–44.

123. Palmer RH, Young SE, Hopfer CJ, Corley RP, Stallings MC, Crowley TJ, Hewitt JK. Developmental epidemiology of drug use and abuse in adolescence and young adulthood: evidence of generalized risk. Drug Alcohol Depend 2009;102(1–3):78–87.

124. Pedersen W, Skrondal A. Alcohol consumption debut: predictors and consequences. J Stud Alcohol 1998;59(1):32–42.

125. Rossow I, Kuntsche E. Early onset of drinking and risk of heavy drinking in young adulthood—a 13-year prospective study. Alcohol Clin Exp Res 2013;37:E297–304.

126. Warner LA, White HR. Longitudinal effects of age at onset and first drinking situations on problem drinking. Subst Use Misuse 2003;38(14):1983–2016.

127. Schuckit MA, Smith TL. Onset and course of alcoholism over 25 years in middle class men. Drug Alcohol Depend 2011;113(1):21–8.

128. Wells GA, Shea B, O’Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [Internet]. Ottawa (Ontario): Ottawa Hospital Research Institute; [cited 2018 May 14]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/ oxford.asp.

129. Sher KJ. Children of alcoholics: a critical appraisal of theory and research. Chicago (IL): University of Chicago Press; 1991.

130. Kuntsche E, Rossow I, Engels R, Kuntsche S. Is ‘age at first drink’ a useful concept in alcohol research and prevention? We doubt that. Addiction 2016;111(6):957–65.

131. Kuntsche E, Rossow I, Simons-Morton B, Bogt TT, Kokkevi A, Godeau E. Not early drinking but early drunkenness is a risk factor for problem behaviors among adolescents from 38 European and North American countries. Alcohol Clin Exp Res 2013;37(2):308–14.

132. Sobell LC, Sobell MB. Alcohol consumption measures. [Internet]. In: Allen JP, Wilson VB, editors. Assessing alcohol problems: a guide for clinicians and researchers. Bethesda (MD): National Institute on Alcohol Abuse and Alcoholism; 2003. pp. 75–101. [Cited 2018 Sep 6]. Available from: https://pubs.niaaa.nih.gov/publications/assessingalcohol/index.pdf.

133. Ioannidis JP. Excess significance bias in the literature on brain volume abnormalities. Arch Gen Psychiatry 2011;68(8):773–80.

134. David SP, Ware JJ, Chu IM, Loftus PD, Fusan-Poli P, Radua J, Munroe MR, Ioannidis JP. Potential reporting bias in fMRI studies of the brain. PLoS One 2013;8(7):e70104.

135. McCambridge J. A case study of publication bias in an influential series of reviews of drug education. Drug Alcohol Rev 2007;26(5):463–8.

136. McCambridge J. A response to the commentaries: look away now or face up to the profound problem of publication bias in drug education research. Drug Alcohol Rev 2008;27(4):352–6.

137. Schumann G, Loth E, Banaschewski T, Barbot A, Barker G, Buchel C, Conrod PJ, Dalley JW, Flor H, Gainall J, et al. The IMAGEN study: reinforcement-related behaviour in normal brain function and psychopathology. Mol Psychiatry 2010;15(12):1128–39.

138. ABCD Research Consortium. The Adolescent Brain Cognitive Development study. [Internet]. San Diego (CA): ABCD Research Consortium; 2018[cited 25 October, 2018]. Available from: https://abcdstudy.org/.

139. Carbia C, López-Caneda E, Corral M, Cadaveira F. A systematic review of neuropsychological studies involving young binge drinkers. Neurosci Biobehav Rev 2018;90:332–49.

140. Lees B, Mewton L, Stapinski LA, Squeglia LM, Rae CD, Teesson M. Adolescent brain surface area pre- and post-cannabis and alcohol use in early adulthood among young adults: a systematic review of longitudinal studies. Alcohol Alcohol 2019;54(3):310–24.

141. McCambridge J. In: Allen JP, Wilson VB, editors. Assessing alcohol problems: a guide for clinicians and researchers. Bethesda (MD): National Institute on Alcohol Abuse and Alcoholism; 2003. pp. 75–101. [Cited 2018 Sep 6]. Available from: https://pubs.niaaa.nih.gov/publications/assessingalcohol/index.pdf.

142. Infante MA, Courtney KE, Castro N, Squeglia LM, Jacobus J. Adolescent brain surface area pre- and post-cannabis and alcohol dependence. J Stud Alcohol Drugs 2018;79(6):835–43.

143. Ruan H, Zhou Y, Luo Q, Robert GH, Desrivieres S, Quinlan EB, Liu Z, Banaschewski T, Bokde ALW, Bromberg U, et al. Adolescent binge drinking disrupts normal trajectories of brain functional organization and personality maturation. Neuroimage Clin 2019;22:101804.
144. Infante MA, Nguyen-Louie TT, Worley M, Courtney KE, Coronado C, Jacobus J. Neuropsychological trajectories associated with adolescent alcohol and cannabis use: a prospective 14-year study. J Int Neuropsychol Soc 2020;26(5):480–91.

145. Paz AL, Rosselli M, Conniff J. Identifying inhibitory subcomponents associated with changes in binge drinking behavior: a 6-month longitudinal design. Alcohol Clin Exp Res 2018;42(9):1815–22.

146. Morin JG, Afzali MH, Bourque J, Stewart SH, Seguin JR, O’Leary-Barrett M, Conrod PJ. A population-based analysis of the relationship between substance use and adolescent cognitive development. Am J Psychiatry 2019;176(2):98–106.

147. Meruelo AD, Castro N, Nguyen-Louie T, Tapert SF. Substance use initiation and the prediction of subsequent academic achievement. Brain Imaging Behav 2020;14(6):2679–91.

148. Waller R, Murray L, Shaw DS, Forbes EE, Hyde LW. Accelerated alcohol use across adolescence predicts early adult symptoms of alcohol use disorder via reward-related neural function. Psychol Med 2019;49(4):675–84.