Early life mental health and alcohol use behaviours in adulthood: evidence from prospective data in the UK and the US

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I, Ke Ning, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Evidence on the association between early life mental health and alcohol use behaviours in adulthood is inconsistent. This thesis aims to summarise the available evidence in a systematic way, investigate the association from a developmental perspective and examine the co-development of alcohol use and stressful life events.

In the systematic review, positive associations between externalising problems and alcohol outcomes were consistently reported, while associations between the internalising domain and alcohol outcomes varied across subtypes. Internalising problems tended to be negatively associated with alcohol consumption but positively with severe outcomes. Depression tended to be positively associated with alcohol outcomes, while no clear association was evident for anxiety.

In two British birth cohorts, early life externalising and internalising problems were associated with problematic drinking in mid-adulthood, with externalising being a risk factor and internalising a protective factor. The strength of these associations did not differ by the developmental timing of externalising or internalising problems and cohort but was stronger in males. Mediation analysis indicated that in the UK context, the association between externalising problems and problematic drinking was not via educational attainment.

In Michigan Longitudinal Study, three classes of individuals with heterogeneous dual trajectories of alcohol use and stressful life events over adolescence and young adulthood were identified. Two classes were characterised by consistently low levels of stressful life events with one class having a normative increase in alcohol use, while the other had a rapid escalation from ages 14 to 23. The third class had consistently high levels of alcohol use and stressful life events.

Utilising prospective longitudinal data, the current thesis emphasises the interplay between externalising and internalising problems regarding their relationships with alcohol use, highlights potential sex differences in these and reveals the contextual role of stressful life events in the development of alcohol use.

Impact Statement

From a public health perspective, this thesis provides new insights on the links that externalising and internalising difficulties have with alcohol use in the UK and highlights the potential benefits of interventions to prevent and reduce childhood and adolescent mental health difficulties in decreasing the burden of alcohol in adulthood, especially in males. This continuity from externalising problems to problematic drinking may not be disrupted by improving one's educational attainment.

This thesis highlights the contextual role of stressful life events in the development of one's drinking behaviours and the role of several other alcohol-related time-varying risk factors. These findings further support the developmental cascade hypothesis using a person-centred approach and depict a holistic picture of the life led by individuals with heterogeneous drinking trajectories, which may offer implications for effective alcohol interventions. For example, one's involvement with deviant peers, smoking status and marijuana use are the main factors that covary with the trajectory of alcohol use during adolescence and young adulthood, rather than stressful life events and externalising and internalising problems, and thus could be targeted to alter one's drinking trajectory.

The findings also have several implications for future research. First, the findings of the systematic review and cross-cohort comparison stress the importance and necessity of exploring the aetiology of alcohol use from a developmental perspective. Second, the null mediating effect of educational attainment on the pathway from externalising problems to problematic drinking under the UK context warrants more population-level studies in other contexts. Third, the finding that stressful life events, externalising and internalising problems did not change systematically with one's alcohol use over time emphasises the necessity of exploring aetiology of alcohol use using person-centred approaches.

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It was the best four years; it was the worst four years.

This PhD journey was the best four years, during which I horned my academic skills, set foot in many countries, harvested lifetime friendships and matured as a person.

With the sole aim to indulge myself in the ocean of knowledge, especially in statistics, I started this journey. Despite a twist of fate which prevented me from conducting the original methodology-based research, I managed to cultivate my statistical ability with full and unconditional support from my supervisors: Professor George B. Ploubidis, Dr Praveetha Patalay and Professor Jennifer Maggs. Funded by an Economic and Social Research Council and Overseas Research Scholarship from UCL, I gained many opportunities to attend summer schools, international conferences and overseas institutional visit around the world and met great people in the field. With my greatest respect, I would also like to thank Professor Robert Zucker for his support and encouragement.

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With all my gratitude, I will continue pursuing my dream: To make the world a better place with all my trivial contributions.

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Abbreviations

EXT=externalising problems

INT=internalising problems

PD=problematic drinking

AUD=alcohol use disorder

AUDIT=alcohol use disorders identification test

AUDIT-PC= alcohol use disorders identification test for primary care

CAGE=Cut-down, Annoyed, Guilt, Eye-opener

SLE=stressful life events

NCDS58=1958 National Child Development Study

BCS70=1970 British Birth Cohort

MLS=Michigan Longitudinal Study

DAG=directed acyclic graph

MAR=missing at random

MI=multiple imputation

SD=standard deviation

NDE=natural direct effect

TE=total effect

TNIE=total natural indirect effect

CDE=controlled direct effect

1. Chapter 1 Introduction

Alcohol contributes substantially to the global burden of disease, not only through alcohol use disorders (AUD) but also via other disease consequences resulting from alcohol use, such as injuries and suicide, cardiovascular disease and cancer [1]. The worldwide prevalence of AUD has been increasing consistently over the last decades - from 3.6% in 2004 [2] to 4.1% in 2012 [3] and 5.1% in 2016 [4]. Measured by disability-adjusted life years (DALYs), the global burden of disease attributable to alcohol use is three times higher compared to other substance use [1]. It accounted for 4.5% of all DALYs in 2004, increased to 5.1% in 2010 and remained stable afterwards [4–6], ranking as the 7th leading risk factor in 2017 compared to 14th in 1990 [7,8]. In terms of mortality, the proportion of alcohol-attributable deaths increased from 3.8% in 2004 to 5.6% in 2010 and decreased slightly to 5.3% in 2017 [4–6]. Almost three quarters of alcohol-attributable premature deaths occur before age 70 [9]. Apart from the estimable burden of alcohol as highlighted above, other inestimable burdens such as the social burden on friends and families and economic burden [10,11], make alcohol use a priority for public health interventions.

1.1 Health consequences of different alcohol use behaviours

To alleviate alcohol burden, the foremost question to ask is which type of alcohol use behaviours to target. Alcohol consumption induces harm to health and has other consequences mainly through three related dimensions of drinking: the volume of alcohol consumed, the pattern of drinking and, on rare occasions, the quality of alcohol consumed [6].

Since the publication depicting a U-shape relationship between alcohol consumption and mortality in 1981 [12], there has been on-going discussion on potential beneficial effect of alcohol. A meta-analysis of 34 prospective studies in 2006 discovered a J-shape between alcohol dosing and total mortality after adjusting for other health conditions and indicated that 1-2 drinks (one drink is equivalent to 14 g pure alcohol) per day for women and 2-4 drinks for men present

the lowest risk of mortality [13]. However, a more recent meta-analysis of 87 studies found that the reverse association between low-consumption and mortality disappeared after adjusting for abstainer biases and quality-related study characteristics [14], which is in accordance with the flattened J-shape discovered by analysing individual-participant data in 83 prospective studies [15]. Moreover, one study shows that moderate drinking (14-21 units/week, one unit is equivalent to 8 g pure alcohol) had three times the odds of right sided hippocampal atrophy compared with abstainers, and no protective effect of light drinking (1-<7 units/week) over abstinence was found [16]. Thus, current evidence indicates no beneficial effect (flattened J-shape) of light or moderate alcohol consumption.

In contrast, less controversial is the harmful effect of heavy episodic drinking on various aspects of health, containing but not limiting to acute negative consequences, cardiovascular and metabolic diseases, psychological distress and mental disorders, neurological diseases, neuropsychological deficits [17] and its direct effect on accidents and related-injuries, and assaults [18–21].

Prevention of problematic alcohol use instead of banning all alcohol use may be the most pragmatic and effective way to reduce alcohol's social, economic and health burdens, especially when considering the fact that alcohol is an integral part of almost every culture [22].

1.2 Aetiology of alcohol use

Globally, initiatives to reduce alcohol-related harm have focused on affordability, availability and acceptability of alcohol [23]. However, individuals are not always rational beings who can make reasoned decisions about health, especially on alcohol, which can be perceived as desirable and whose health risks are not immediate [24,25]. In order to change individuals' drinking behaviour, it is important to understand the underlying aetiology to alcohol use.

Rarely is alcohol use initiated prior to or after the second decade of life [26], and much effort has been made to incorporate critical antecedents of alcohol use

initiation and escalation onto the developmental pathway [26,27]. Accumulating evidence has shown that a range of genetic and environmental factors could contribute to the development of drinking behaviour [28–30]. Numerous twin/adoption and genome-wide association studies (GWASs) document the importance of genetic influence on a range of alcohol use behaviours [31–33]. Namely, associations with alcohol-metabolizing genes are the most consistent and definitive ones; novel associations with other genes replicated by large-scale GWASs involve genes which are central to stress response or impulsive/risky behaviours [31]. Correspondingly, evidence from non-genetic research has mainly focused on the role of stress and externalising problems on the development of alcohol use behaviours, and much progress has been made over the past decades.

1.2.1 Stress and alcohol use

Whereas stress refers to internal biological effects, it is typically measured using external life stressors [34]. Four important categories of life stressors are general life events, fateful/catastrophic events, childhood maltreatment, and minority stress [35]. A summary of the relationship between each type of stressors and alcohol consumption and AUD can be found in Keyes et al.'s review [35,36].

Several mechanisms of action may explain the relationship between stress and alcohol use behaviours. Theories, such as tension-reduction, self-medication and drinking to cope, posit that people drink alcohol either to reduce the tension caused by stressors or to seek mood enhancement [37]. Such theories are perhaps best supported by alcohol expectancies research [38] and drinking motives research [39,40]. Specifically, research collecting daily data on stress and alcohol consumption contributed to the stress-drinking literature by capturing the temporary changes in hours or within one day: individuals consumed more alcohol on days when they encountered more stressors [41–44]. Other more complicated theories, including the stressor-vulnerability model [45] and the stress response dampening model [46], state that there are individual differences in the connection between stress and alcohol use. Empirical research generally supports these hypotheses by finding a moderation effect of gender [41,42,47,48],

coping mechanisms [49,50], alcohol expectancies [42], drinking motivations [51], negative emotionality [38], family and peer support [52], parental depression [47] and age at first drink [53,54].

In addition, stressors may also contribute to alcohol use through their non-specific risk for a variety of psychiatric problems, including negative emotions [55–57] and externalising features (e.g., impulsivity) [58–60]. Theorists from developmental psychology found that functioning in one domain can spill over to exert lasting influences on functioning in other domains over time. Applying this perspective to the longitudinal association between life stressors and alcohol use behaviours, one mechanism of action is that the occurrence of stressful events tends to increase one's negative emotions of anger and depressive symptoms, which further contributes to affiliations with deviant companions and involvement in risk behaviours, such as drinking [55,56]; another mechanism of action is that exposure to early stress could disrupt the development of childhood inhibitory control, which in turn leads to the development of problem behaviours and affiliations with peers who provide reinforcement of risk behaviours [59,60].

However, existing theories and empirical research have yet to view the association between stressors and alcohol use over a long-term span and on an individual level. Most research focused on the role of early life stress and found that a stressful environment prior to puberty, particularly in the first few years of life, was associated with early-onset problem drinking in adolescence [52,58,61] and AUD in early adulthood [52]. This continuity from early life stress to alcohol problems in young adulthood may be due to the permanent disruption in the brain circuits caused by early life stress and/or alcohol use [52]. Typically, these circuits involve stress response [52,62,63], inhibitory control [64] and reward [52,65,66]. Yet, not all individuals exposed to early life stressors go on to develop alcohol problems [52], indicating the necessity to examine the association over the long term. Long-term longitudinal data that examines the co-development between stressors and alcohol use over key developmental periods is limited, but essential for better understanding of the mechanisms of their association, especially when one's exposure to stressors and alcohol use behaviours is likely to be dynamic over time [67,68].

1.2.2 Externalising and internalising problems and alcohol use

Developmental psychologists have long attempted to classify types of AUD based on personal characteristics such as age-of-onset, childhood risk factors (e.g., family history of alcoholism, life stress) and comorbid psychopathology [69,70]. One dimension that has shown great potential is that of developmental course [71], which emphasises the origin of AUD in early life. Two types of AUD, used to be coined as antisocial alcoholism and negative affect alcoholism, have attracted the most attention. From a developmental perspective, they correspond to the externalising pathway and internalising pathway respectively [72,73].

The externalising pathway is the most articulated developmental pathway emanating from early childhood to alcohol use/disorder in adulthood. The emergence of this pathway can present as early as infancy as difficult temperament, followed by externalising problems in childhood and adolescence (accompanied by early onset of alcohol use in some cases), involvement in deviant peer affiliations which brings greater exposure to alcohol and eventual onset of alcohol use/disorder [27,73]. Under-control/disinhibition, that is, the "inability or unwillingness or failure to inhibit behaviour even in the face of anticipated or already received negative consequences", is deemed the underlying trait of the externalising domain (aggressive and delinquent behaviour) [74]. This vulnerability can render an individual to intake more alcohol when exposed and be exacerbated by social environmental factors which tend to be highly aggregated in high-risk families [74]. Longitudinal studies have identified a long list of factors associated with the externalising pathway from early or middle childhood to the mid-40s [27,71,74].

In contrast, the role of early life internalising origins of alcohol use behaviours has received less attention. In 2011, Hussong et al. articulated a life course model in which underlying internalising pathway contributes to alcohol use problems in adulthood [73]. It is posited to first emerge as inhibited temperament in infancy, followed by internalising symptoms through childhood and adolescence. Early onset internalising symptoms could in turn increase one's risk of social withdrawal and other interpersonal skill deficits (e.g., peer rejection and disengagement).

Entering adolescence, the development of coping expectancies and motives for alcohol use facilitates the initiation of alcohol use for the purpose of self-medication or peer acceptance, which eventually leads to escalation of alcohol use and onset of AUD. However, empirical studies present a much more complicated picture of the internalising pathway. A systematic review was conducted by Hussong et al. to examine the association of negative affect symptoms (anxiety, depression, and internalising symptoms more broadly) and adolescent substance use prospectively controlling for externalising symptoms. The most consistent associations were evident for depressive symptoms where only positive associations other than null associations were reported [75]. No clear pattern of associations between anxiety and alcohol use or between general internalising symptoms and alcohol use was evident, and as was concluded by the authors, “these associations were as often negative as positive”. The associations between the internalising domain and adulthood alcohol use behaviours have not been systematically summarised yet but also seem to be quite inconsistent: positive, negative or null associations were all detected for general internalising problems [76–80], depressive symptoms [81–85], and anxiety [86–89] regarding their relationships with alcohol use behaviours.

1.3 A developmental perspective

There is a lack of knowledge both conceptionally and empirically to view the association between mental health problems and alcohol use/disorders from a developmental perspective. Developmental science framework emphasises multi-dimensional and multi-directional developmental changes over time, revealing the possibility of both continuity and discontinuity across the life-span [90]. For example, with respect to the internalising pathway, continuity reflects the cumulative impact of early difficulties and limited opportunities on subsequent escalating and expanding difficulties in multiple domains [90]. In contrast, discontinuity highlights that early experiences do not always have long-lasting effects and the long-term distal effects can be reduced or even reversed by more proximal effects [90,91].

Consensus among developmental psychologists is that a life-span approach for

understanding the causes and course of alcohol use and abuse needs to consider the dimensions of developmental timing, sex, history and culture [90,92,93].

1.3.1 Developmental timing

Developmental timing of both alcohol use behaviour and mental health problems is an important factor to be considered when examining their associations.

Drinking behaviour follows a developmental pattern, which typically initiates in adolescence, escalates and peaks during early adulthood and then gradually declines thereafter [94–97]. More importantly, drinking may carry different meaning for individuals and be influenced by different factors across different life stages [25,98]. Youthful drinking tends to be more associated with aiming to get drunk quickly, while drinking in mid-life is featured as being relaxing, sociable and civilised [98,99]. Also, youthful drinking is more easily influenced by parenting and peer relationships [100,101], while drinking in mid-life is more of a self-decision [25,98]. Thus, the robust association between mental health and alcohol use in adolescence and young adulthood does not necessarily last into mid/late adulthood, and even if it does, direction or strength of the association between mental health and alcohol use behaviours in mid/late adulthood may differ from that in adolescence and young adulthood. For example, when alcohol use behaviours were measured in young adulthood, studies generally found positive associations for internalising problems [77,79,80,102], while when they were measured in mid/late adulthood, negative associations were found [76,103].

Similarly, mental health status may also change over the course of childhood and adolescence [104–106], and its onset timing and duration may have different implications for drinking. On one hand, early onset mental problems may have stronger predictive power that lasts longer than late onset problems: late childhood (age 8-11) is when children start to form their own identity, thus aversive experiences at this stage set the basis for later behaviours and decisions (critical period) [107]; early onset mental health problems may trigger a series of vulnerabilities (e.g., interpersonal skills) which in turn reinforce and escalate the risk of drinking (cumulative continuity) [73]; many problematic behaviours are

deemed normative during adolescence and thus may lose some long-term predictive power [90]. On the other hand, adolescent-onset problems may play a more important role: adolescence is a time accompanied with rapid physical, biological, and neurocognitive change and a prime period for alcohol use and escalation and thus, any disturbance from normative development may result in permanent change or act as a turning point in the life course [108,109]. Therefore, the developmental timing of early life mental health could be viewed from two dimensions: persistence and severity. Persistence refers to whether the stage when mental health problems happen affects its association with later alcohol use; severity refers to whether the strength of the association between mental health problems and alcohol use differs across stages.

Studies that derived trajectories of mental health problems and examined their association with later alcohol use behaviours offer insights from the dimension of persistence. Compared to those with a low level of externalising problems throughout early life, those with early-onset externalising problems that persist into adolescence or adolescent-onset externalising problems tend to have more alcohol use and alcohol-related problems [110–116]. In contrast, individuals with childhood-limited externalising problems do not show higher risk of excessive alcohol use [110–116]. The persistent association between early-onset-persistent externalising problems and later alcohol use and the null association between childhood-limited externalising problems and later alcohol use are good illustrations of continuity and discontinuity from mental health to alcohol use. Differences between early-onset-persistent externalising problems and adolescent-onset externalising problems regarding their association with alcohol outcomes are equivocal: the association tends to be stronger for early-onset-persistent externalising problems in some cases [110,113,115], weaker in some cases [112] or presents no differences in other cases [111,114]. To complicate the picture even more, the differences may be modified by gender [116] and their pathways to alcohol use may also be different [111]. Individuals with early-onset-persistent externalising problems are characterized with much higher level of social, family and neurodevelopmental risk factors than those with adolescent-onset externalising problems [116]. Thus, it seems that early-onset-persistent externalising problems accompanied by a disadvantaged environment contribute

to alcohol onset and escalation, which then cascades into other difficulties (continuity). In contrast, adolescence-onset externalising problems, exposed to much less severity of other risk factors, may contribute to excessive alcohol use mainly through peer influence [26,111].

There is a lack of evidence regarding the developmental timing of mental health from the dimension of severity. This might be due to two reasons: mental health problems were only assessed at one time point in the majority of available studies that explored the association into adulthood; among those that assessed mental health at several time points, the dimension of severity was taken over by persistence due to the theoretical and methodological ambiguity between these two dimensions.

1.3.2 Sex

Consumption of alcohol is lower in females than that in males in nearly all countries [9], and this divergence emerges in adolescence and persists across the life course [95], so is the prevalence of heavy drinking and alcohol-related problems [94,117]. For example, in the UK, the mean consumption level of alcohol, though changing with age, was almost 3 times higher in males [95]. Yet, lower than expected, prevalence of problematic drinking (assessed using CAGE questionnaire) was only 2 times higher in males [118]. Due to biological differences, it is indicated that women are more susceptive than men to experience alcohol-related problems (e.g., women were more likely to report drinking problems at the same consumption level, women had later onset of drinking but took less time to develop disorders), which is known as telescope effect - women initiate drinking later but progress faster to alcohol dependence or to treatment compared with men [118–120]. More recent study utilising general population found out otherwise: women had a later age at initiating but did not have a shorter time to dependence [121]. Therefore, sex differences in the development of problematic drinking warrant more examinations.

It is well-established that prevalence of mental health problems during childhood and adolescence varies between sexes, with externalising problems being more

common in boys and internalising problems being more common in girls [122–125]. However, sex differences regarding the association between mental health problems and problematic drinking are equivocal. Important differences in the typical experiences and social role transitions across the life-span between males and females could all render their pathway from mental health to alcohol use behaviours to differ [90,126]. Theoretically, it is hypothesised that high levels of early life externalising or internalising problems exert stronger effect on drinking in males than in females [27]. There is a trend that adolescent males are more susceptible to peer influences that encourage risk-taking behaviours than adolescent females, especially in terms of substance use, as females may be better at evaluating adverse consequences of drinking [126,127]. Also, males are more likely to self-mediate using alcohol when facing mood and anxiety disorders [126,128]. Empirical evidence, though, present an inconsistent picture. Some evidence has found that the association between mental health and alcohol outcomes varies as a function of sex [81,129–132], but they seem to conflict with each other. Many other studies did not find variation of the association across sex [72,84,93,102,133,134].

1.3.3 History and culture

There is no doubt that alcohol consumption at the population level tends to fluctuate historically and across countries [9,135]. There is no simple answer as to why there have been such fluctuations, as historical time period and culture represent the confluence of countless phenomena that can be related to alcohol use [136]. Knowing whether the association between mental health and alcohol outcomes persists over time in a specific context has important implications for studying alcohol use aetiology and prevention. If the relationship between the established factor and alcohol use is inconsistent across historical periods and cultures, using evidence from other contexts to inform interventions on the correlate to reduce later alcohol burden would be unreliable and of limited use, especially when applied to different generations.

In the UK, policies and public acceptance towards alcohol changed over time. Consumption of pure alcohol per capita per year almost doubled between 1950

to the mid-1970s, rising from 5.2 litres to 9.3 litres [137]. Afterward, it fluctuated slightly around 10 litres but saw an upward fluctuation in the first decade of new century [4,138]. Along with the surge of alcohol consumption came increasing cases of alcoholism and other issues, such as drink driving and associated health problems (e.g., liver cirrhosis) [139]. Gradually, these attracted attention to view alcohol as a public health problem. From the 1970s onwards, campaigns, academic committees and health education targeting alcohol problems became more common [137,140], resulting in the production of *Drinking Sensibly* (1981) which influenced the evolution of alcohol policy and alcohol health education in the UK until today [137]. In general, this shifted alcohol prevention from population-level strategies to individual-level strategies which focused on getting individuals to take responsibility for their own behaviours [137], and health education and identification and treatment of problematic drinking are the main strategic approaches to tackling alcohol-related problems [141]. On a practical level, the notion of sensible drinking set the foundation for the development of safe limits or sensible limits of drinking [137]. Since 1987, it was recommended that men should not drink more than 21 units of alcohol a week and women not more than 14 units a week (A unit of alcohol equals to 10ml or 8g of pure alcohol) [142]. In January 2016, the recommendation of weekly alcohol consumption of men was brought to 14 units, same as that of women [143].

How the association between mental health and alcohol outcomes might change over historical period is unknown, specifically under the UK context. A limited number of studies from the US reported the stability of psychosocial and behavioural factors in explaining alcohol use behaviours over a long-term span [93,136,144]. For example, analysing nationally representative samples of the US adolescents who were followed into mid-adulthood, Merline et al. found no significant cohort variations in the predictability of adolescent risk-taking, aggression and depressive affect on several alcohol outcomes (drinking frequency, heavy drinking and AUD) at age 22, 26 and 35 [93].

However, alcohol consumption in the US can be very different from that in the UK [9] with regard to the drinking cultures and alcohol regulations [145–147]. Compared with that in the UK, alcohol consumption in the US has been relatively

constant, averaging around 8-9 litres of pure alcohol per capita, since the end of the National Alcohol Prohibition in 1933 [4,9,148]. The type of alcoholic beverage was dominated by beer (47%), followed by spirits (35%) and wine (18%) for the past three decades, whereas wine gradually replaced the dominance of beer in the UK, constituting an equally important proportion (36%) as that of beer (35%) by 2016 [4]. In addition, prevalence of AUD in the US (Male: 17.6%; Female: 10.4%) is much higher than that in the UK (Male: 13%; Female: 4.7%). It appears that people in the UK seem to drink more sensibly compared to people in the US. In terms of public health policies, the US explicitly states its goal of reducing total alcohol consumption on population level and set many specific targets to identify the amount of improvement intended [141], whereas the UK contends that "there is no direct relationship between the amounts or patterns of consumption and types or levels of harm caused" and thus is more concerned about binge or heavy drinking [141]. Details regarding the public health policies between the US and the UK can be found in Crombie's review [141].

Therefore, examining how mental health are associated with alcohol use behaviours across historical periods under the UK context is still warranted to inform alcohol prevention programmes in the UK.

1.4 Potential mediating role of education

Other than answering the question of whether the pathway from early life mental health to alcohol use behaviours lasts into mid/ late adulthood, it is also important to understand the underlying mechanisms that account for this association. The hypothesis of continuity emphasizes that early life mental health problems could contribute to alcohol initiation and escalation, which then cascades into a series of other difficulties [26]. For example, both theoretical and empirical research have articulated how early life mental health could lead to alcohol use via its influence on parenting (e.g., parent monitoring, parent support) or deviant peer involvement [149–152]. However, they only pertain a short-term pathway into adolescence and young adulthood, which may not apply to alcohol drinking in mid/late adulthood. As discussed before, drinking behaviours during adolescence and young adulthood are different from that in mid/late adulthood in many ways.

For one, it is more easily influenced by families and peers [92]. Second, heavy or problematic drinking during adolescence and young adulthood tends to be developmentally limited for one-fifth of the adolescent and young adult population [71,97], and almost half of those who were diagnosed with a lifetime diagnosis of alcohol dependence fell into the category of onset during adolescence and young adulthood, but diminishing afterwards [153].

Therefore, if the pathway from early life mental health to alcohol use does last into mid/late adulthood, this continuity is likely to be mediated by factors that could have a long-lasting effect on one's behaviours. Education is one such factor that has far-reaching role on one's health behaviours [154,155]. Moreover, due to the well-established evidence between education and health [154,156], many countries which aim to reduce health inequalities specially target education or factors related with education [157,158]. Investigating the role of education on the links between mental health problems and alcohol use may help inform policies that aim to reduce alcohol burden in adulthood by targeting early life antecedents.

In general, current evidence indicates more "sensible drinking" behaviours among people with higher educational attainment. Less well-educated adults tend to drink more per occasion [159,160], engage in binge drinking (drinking 5/6 or more per occasion) [161,162] and have a higher risk of alcohol dependence [163–165]. Also, compared to those with a college degree, those without a college degree were more likely to progress from alcohol use to dependence [165]. However, evidence also shows that people with higher educational attainment tend to drink moderately as opposed to abstaining or light drinking [166–168]: they tended to drink more often [160,168] and more in total intake [168–170] and even had higher risk of heavy drinking (total volume exceeds certain threshold during certain period) [171,172]. It was hypothesized that more educated people tend to drink more often and in total volume due to their social and working environment [154], which could result in entering the realm of heavy drinking; however, they may be better at managing the behaviour before it escalates into more severe drinking behaviours such as problematic drinking, binge drinking and AUD [154].

From the perspective of discontinuity, education may be such a factor that could alter or change the pathway from early life mental health to drinking problems in adulthood. One study on gene-environment effects on alcohol use discovered that education did not moderate genetic risk for alcohol use but did moderate environmental variance in that under conditions of low education, environmental factors explained more variations in alcohol use outcomes [173]. Another study showed that the strong and consistent relationships between childhood disadvantages (measured by occupational economic position and house tenure status) and binge and problematic drinking behaviours in midlife could still be alleviated substantially by educational attainment by age 33 [167]. For instance, each additional report of manual occupational position across age 7, 11 and 16 (range 0-3) was linked to a 16% increase in odds for binge drinking, while each additional increase in level of education (no qualifications, below Ordinary levels, Ordinary levels, Advanced levels, Higher) could reduce odds of binge drinking by 18%.

1.5 Methodological issues in longitudinal data analysis

When measures are collected at multiple time points across the life course, the acquired data contains information about both between-person and within-person relationships. Take the dynamic relationship between stressors and alcohol use for example. The between-person relationships examine whether individuals exposed to higher level of stressors would consume a greater quantity of alcohol compared to those exposed to lower level of stressors, and whether individuals who report systematic increases in stressors over time are more likely to also report systematic increases in alcohol use; the within-person relationships investigate whether an individual who experiences higher level of stress *relative to his/her underlying level of stress* at one time point is more likely to consume greater quantity of alcohol *relative to his/her underlying level of alcohol use* at a *subsequent* point in time.

Unfortunately, the magnitude (if not direction) of between- and within-person relations typically turns out to be different from each other [174,175]. Generalizing between-person effects to within-person effects directly would usually result in

the so-called “ecological fallacy” [176,177]. For example, between-person effects may indicate that individuals experiencing high level of stress tend to consume more alcohol than those experiencing low level of stress [35], but an individual may decrease their alcohol consumption following a negative life event (i.e. hitting bottom experience which enacts positive life changes) [178]. Failure to disaggregate them both theoretically and empirically would result in uninterpretable estimates or misleading interpretations.

The availability of longitudinal studies and advances in statistical analysis provides great opportunities to examine the associations between stressors, mental health and alcohol problems dynamically. Considering the complexity of dynamic associations, it is important to understand the underlying assumptions of each statistical model and their similarities and differences. An overview of commonly used models in the field of alcohol research, broadly categorised into variable-based analysis and person-based analysis, is provided below.

1.5.1 Variable-based analysis

Variable-based analysis, namely regression-based models, might be the most common analysis strategy employed in longitudinal research. It models between-person relationships: the interpretation of parameters pertains to how much change of the outcome is associated with one unit change in the exposure while keeping other covariates constant in the population [177].

One advantage of a variable-based approach is that it returns population-specific results which may have implications for population level interventions. As discussed in section 1.3.1, compared with consistently low level of externalising problems over childhood and adolescence, early-onset-persistent and adolescent-onset externalising problems, but not childhood-limited externalising problems, were associated with more alcohol use in adulthood [110–113,116]. Thus, variable-based analysis examining the association between early life externalising problems and adulthood alcohol use may return null, positive or negative results depending on the proportions of individuals with different trajectories of externalising problems in the population. Results that detect

significant associations indicate the cascading continuity from early life antecedents to alcohol use behaviours in later life in the specific population, regardless of how proximal factors may have altered or influenced one's drinking. In contrast, failing to detect the association may indicate the discontinuity from the hypothesised antecedents to later alcohol use behaviours in the population. In other words, the association, if causal, offers a rough estimate of the potential benefits intervention programmes may bring by intervening the exposure at a certain time point in the specific population.

However, it is nearly impossible to interpret the associations derived using observational studies as causal. Unmeasured confounding is one of the biggest challenges when making causal inference using observational studies [179,180]. It is well-recognised that one can never be certain about unmeasured confounding factors in observational studies no matter how much data are available for confounding adjustment [180]. Fortunately, with advances in causal inference in the field of epidemiology [181–183], especially under the guidance of directed acyclic graph (DAG), it becomes clearer what conclusions we can and cannot draw from variable-based analysis. Conceptually, DAG forces researchers to be explicit about their causal goal instead of disguising it under the umbrella of associational estimates [180]. Practically, by drawing hypothesised structural relationships among relevant variables, DAG provides guidance on which variables should be adjusted for to minimize potential confounding, and which variables should not be adjusted to avoid selection bias (also known as collider bias) [181]. The combination of prospective data and DAG help establish the temporal order of exposure and outcome and alleviate bias of reverse causality. Moreover, it propels the progress in the field of causal mediation analysis and refines the definition of total effect, direct effect and indirect effect under a counterfactual framework [184–187]. More details on mediation analysis under counterfactual framework are introduced in Chapter 5.

It is mentioned previously that between-person effects typically do not equate to within-person effects. In most situations, this is due to failures to adjust for all possible confounding factors that cluster within individuals but differ across individuals in variable-based analysis. Otherwise, randomised control trials which

collect and analyse measures across individuals would not be taken as the gold standard for drawing causal relationships [188,189]. From this perspective, fixed effect model or person-based analysis could better deal with the time-fixed unmeasured confounding by focusing on changes within individuals over time, whereas variable-based analysis suffers from both time-fixed and time-varying unmeasured confounding.

1.5.2 Person-based analysis

Autoregressive cross-lagged panel model (e.g., Figure 1) might be one of the most well-known and commonly used models to study dynamic, reciprocal feedback process between variables [174]. Modelling the respective autoregressive relations of two (or more) variables that unfold over time and the time-lagged regression between them simultaneously, the autoregressive parameters are typically interpreted as reflecting the stability of respective variables, and the cross-lagged parameters as the between-person effect of the lagged variable (e.g., X_{t-1}) on current variable (e.g., Y_t), controlling for its lagged value (Y_{t-1}) (and vice versa). However, more recent research has shown that "it typically (a) fails to align with the theoretical processes that it is intended to test and (b) yields estimates that are difficult to interpret meaningfully" [174]. Simulation shows that the cross-lagged estimates reflect a weighted compound of between- and within-person associations which is uninterpretable [174].

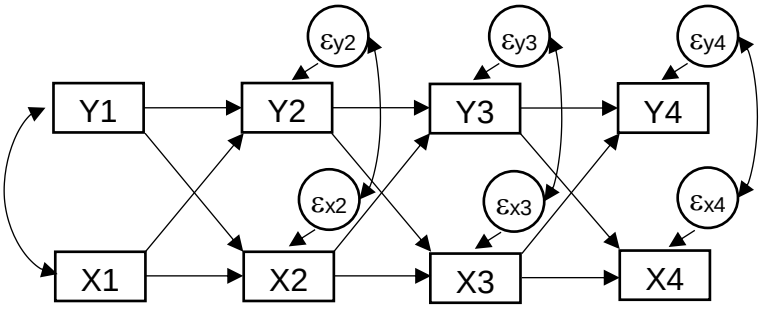


Figure 1 A prototypical autoregressive cross-lagged panel model for four repeated measures

Another well-known method to analyse repeated measures data is fixed effect model, which can reduce the confounding of time-invariant covariates by relying only on within-individual variations [190]. As shown in Figure 2, fixed effect model deals with time-invariant covariates by creating a time-invariant latent variable

(α_y), which represents both observed and unobserved characteristics on individual level [191]. Then, fixed effect model eliminates α_y by demeaning all the variable during the estimating process [192]. In other words, each variable is transformed by deducting their respective within-individual mean (time invariant latent variable will be eliminated, while values of time-varying variable represent within-individual variation), and then estimates of interest are obtained using an ordinary linear regression. Rarely mentioned, the underlying assumption is that there is no systematic time trend of both outcome and time-varying covariate. Intuitively, this assumption means that the underlying level of both outcome and time-varying covariate can be represented by their person-mean over several time points [177]. Unfortunately, it is almost certain that this assumption will be violated in the field of alcohol research, as robust heterogeneous trajectories of alcohol use have been derived across empirical studies [68]. As a result, the "within-individual" variation is actually a mixture of between-person and within-person variations.

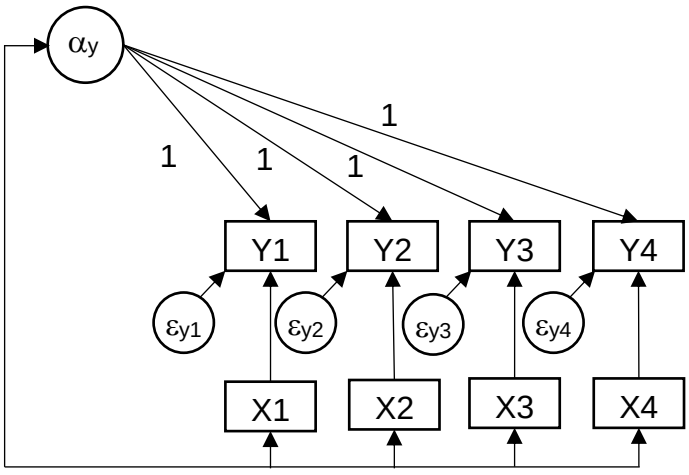


Figure 2 A prototypical fixed effect model for four repeated measures

In contrast, approaches under the framework of multilevel growth modelling might do a better job at separating between-person effects from within-person effects. One commonly used method is multilevel growth modelling with person-mean centring (e.g., Figure 3) [193,194]: deviations from person-mean at each time point represent within-person changes over time and person-means across individuals represent between-person differences. This method of estimation is proven to be valid under the assumption that there is no time trend of the time-varying covariate. However, this subtle assumption is seldom tested or mentioned in substantive research, and lack of discussion on differentiating those

effects in the substantive literature sometimes leads to the ambiguity or misinterpretation of the analytical models (e.g., not mentioning how the covariates are dealt with, covariates are wrongly centred at the grand-mean instead of person-mean) [195,196]. Moreover, between-person relationships are typically left out instead of being estimated in such models.

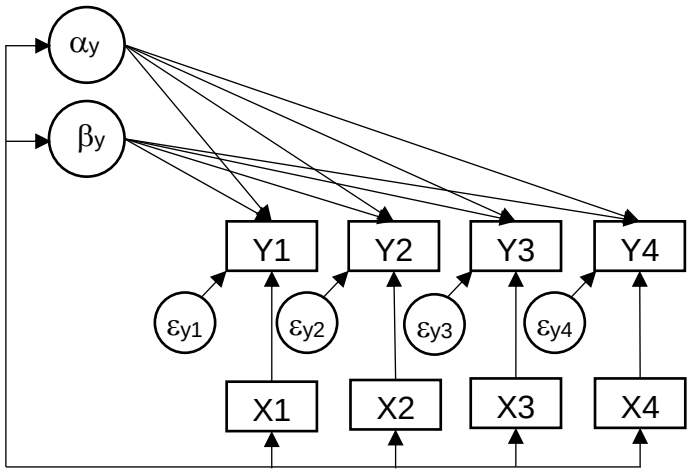


Figure 3 A prototypical multilevel growth model for four repeated measures*

*X1-X4 indicates values of X after person-mean centring

The emergence of the multivariate latent growth curve model (e.g., Figure 4) and auto-regressive latent trajectory models (e.g., Figure 5) was thought to overcome the above two limitations [176]. Instead of using the fixed person-mean, they estimate the underlying trajectory of time-varying covariate (typically depicted using intercept, slope and quadratic terms as in standard latent growth curve model). Then, between-person differences can be captured by investigating the covariance among trajectory parameters, and within-person differences can be calculated by regressing deviations from the underlying trajectory of outcome on deviations from the underlying trajectory of time-varying covariate at the corresponding time point. Though intuitively appealing, they still fail to disaggregate the between-person and within-person effect methodologically [176]. Just as the traditional framework of multilevel model with person-mean centring, the time-specific relations among the observed repeated measures are modelled at the level of manifest variable, which will directly influence the between-person estimates of the latent growth curve factors. In other words, just as in Figure 3 and Figure 5, the repeated measures of Y are regressed directly on repeated measures of X. As a result, those models only posit that the repeated measures of Y are a function of the joint contribution of the underlying latent

growth factor and the time-specific influences of X but do not provide a pure disaggregation of the between- and within-person relations over time [176].

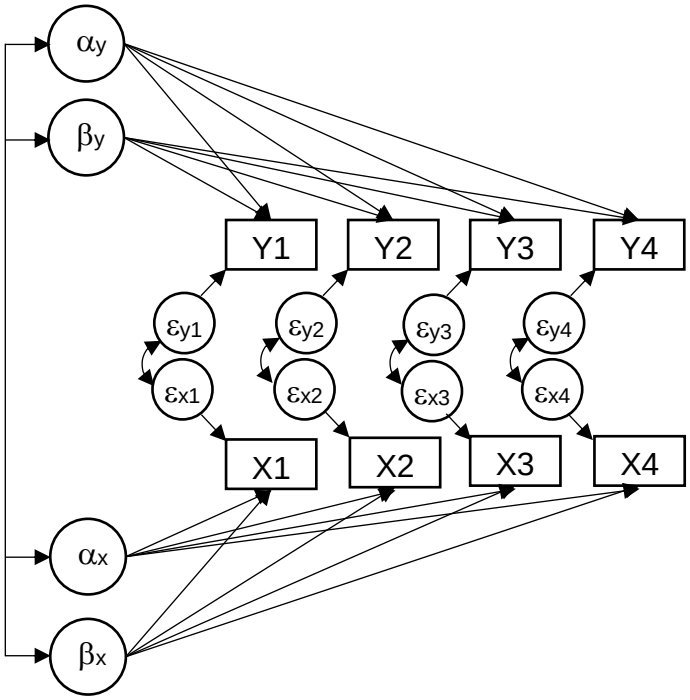


Figure 4 A prototypical multivariate latent growth curve model for four repeated measures

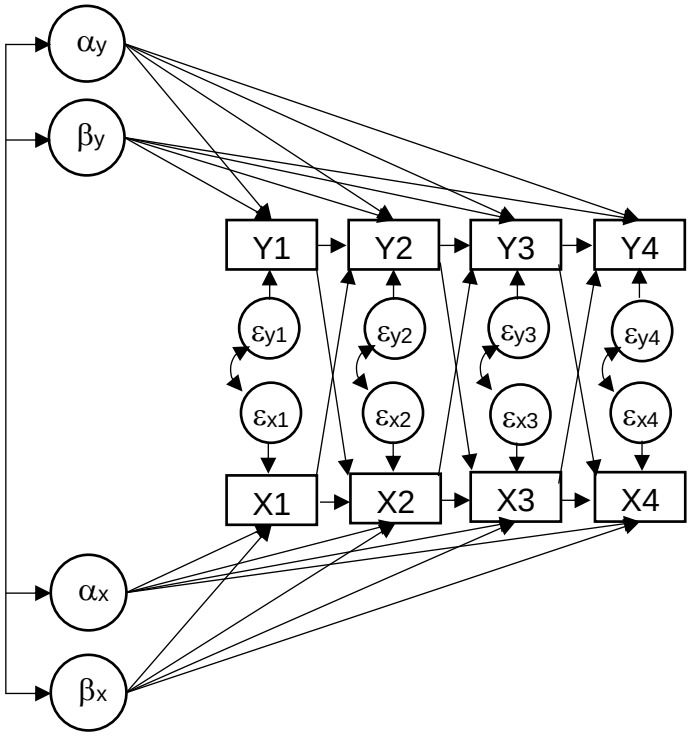


Figure 5 A prototypical auto-regressive latent trajectory model for four repeated measures

Latent curve model with structured residuals provides a better solution (e.g., Figure 6) [176]. By structuring the time-specific within-person changes explicitly on residuals, the underlying latent growth curve factors are not influenced, which enables the clean separation of time-specific and person-specific components. Even so, two implicit conditions still warrant one's attention. First, one needs to ensure that the direction is from the time-varying covariate to the outcome at each time point (at least chronologically) and if the time frame is appropriate for within-person effect to take place. Second, it assumes homogeneity of trajectories of both the outcome and time-varying covariate.

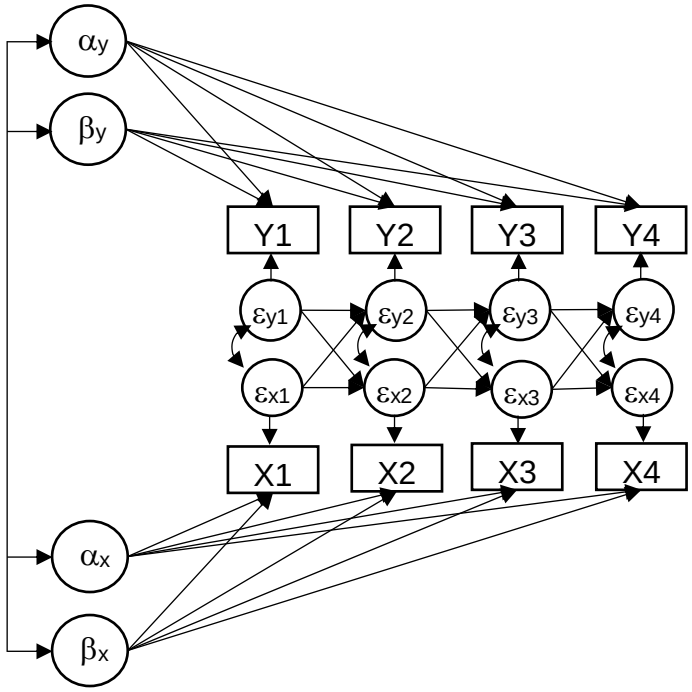


Figure 6 A prototypical latent curve model with structured residuals for four repeated measures

Unfortunately, in the case of alcohol research, both conditions are likely to be violated. First, one can hardly ensure the timing of alcohol use behaviours and covariate of interest (e.g., stressors). Typically, those measures are collected by recalling events in the past week/month/year, and thus it is impossible to know which happens first. Moreover, even if one can ensure the direction by collecting life stressors in the last six months and alcohol use in the last week, it is problematic to draw conclusions about within-person effects (do people drink more on stressful days?) from such data [42]. Second, empirical studies have derived heterogenous trajectories of alcohol use behaviours utilising samples

from various populations [68]. Four trajectories were usually detected: chronic high trajectory, increasing trajectory, decreasing trajectory, consistently low trajectory [68]. This means that individuals who share some of the trajectory parameters could be on totally different trajectories. For instance, two individuals who share zeros on slope could either be on chronic high trajectory or consistently low trajectory. Thus, covariation between the trajectory parameters could be hard to interpret, and the between-person effects regarding how two variables evolve over time are not examined directly.

Group-based multi-trajectory modelling offers a solution for the second concern mentioned above (e.g., Figure 7), as the first concern is more of a conceptual problem which could be better dealt with using appropriate study design (e.g., collecting daily data). By modelling the trajectory parameters simultaneously, group-based multi-trajectory modelling, a combination of latent class modelling and latent growth curve modelling, derives classes of individuals who share similar trajectories [197,198]. As a result, comparing across classes and within classes could offer a holistic view regarding the between-person effects: how the variables relate with each other on interindividual level and how they evolve over time.

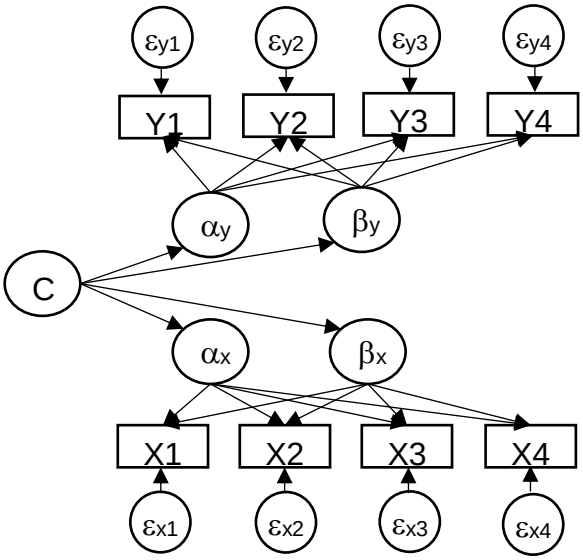


Figure 7 A prototypical group-based multi-trajectory model for four repeated measures

1.6 Overall structure of the thesis

This thesis aims to investigate the aetiology of adulthood alcohol use behaviours from a developmental perspective and is structured into seven chapters.

Chapter 1 gives a brief overview on the development of alcohol use behaviours from a developmental perspective and dissects the longitudinal relationships between two variables and their empirical implications from a methodological perspective.

Studies investigating the externalising and internalising pathways into adulthood are emerging, but present a mixed picture regarding the internalising pathway. Several factors could contribute to this inconsistency, including lack of a developmental perspective on associations, heterogeneous subtypes of mental health and drinking behaviours across studies and failure to consider the high occurrence between externalising and internalising problems. Chapter 2 sets out to summarise existing empirical evidence on the associations between externalising and internalising problems in early life and alcohol use behaviours in adulthood in a systematic way. In addition, Chapter 2 examines how these associations varied across the above-mentioned factors: subtypes of both mental health problems and alcohol use behaviours, developmental timing of both mental health problems and alcohol use behaviours, sex, historical periods, cultures and whether externalising and internalising problems were adjusted accordingly. This examination would strengthen our understanding of these developmental pathways from the different facets and identify factors that may contribute to the inconsistency of empirical evidence.

Built on Chapter 2, this thesis aims to extend existing evidence by analysing three prospective longitudinal datasets from the UK and the US and examining the longitudinal relationships utilising variable-based and person-based approaches. Chapter 3 introduces the three datasets for empirical analysis: the 1958 National Child Development Study (NCDS58), the 1970 British Cohort Study (BCS70) and the Michigan Longitudinal Study (MLS). NCDS58 and BCS70 were chosen due to their representativeness of the British population, rich measurements on

mental health and alcohol use behaviours (into mid-adulthood) and other early life confounding factors and adequate resemblance for cross-cohort comparisons. These merits make it possible to examine the long-term associations between mental health and alcohol use behaviours and how they vary across developmental timing of mental health, sex and historical periods in the UK (variable-based approach). MLS was chosen due to its intensive and abundant data collection (a comprehensive survey every three years and a brief one annually from age 11 to age 26) on life stressors, externalising/internalising problems, alcohol use behaviours and a series of alcohol-related factors from childhood to young adulthood. It provides opportunities to model trajectories of these constructs and see how they evolve over key developmental periods (person-based approach). Chapter 3 also gives details on the construction of exposure, outcome and confounding factors that will be used in later chapters.

Few studies have viewed the associations between early life externalising and internalising problems and alcohol use behaviours from a developmental perspective and done so well into mid-adulthood. Thus, built upon Chapter 2, Chapter 4 aims to explore whether these associations persist into mid-adulthood and if so, how they vary across developmental timing of externalising and internalising problems, sex and the two British birth cohorts. Examining these factors with one study would complement and strengthen the results found in Chapter 2, which are summarised based on heterogenous studies. Furthermore, this has implications for whether one can alleviate alcohol burden in mid-adulthood by intervening in early life mental health problems, and if this is viable, when and who should be targeted, and how this may change over generations in the UK context.

Studies examining the mechanism of the robust externalising pathway to alcohol use only pertain to short-term associations into adolescent or young adulthood, whereas long-term mechanisms into mid-adulthood have not been investigated. Built on Chapter 4, Chapter 5 aims to investigate the mediating role of educational attainment on the pathway from adolescent externalising problems to mid-adulthood problematic drinking across sex and cohorts. This would inform whether the long-term continuity from externalising problems to problematic

drinking in mid-adulthood can be blocked by improving educational attainment in the population.

Both mental health problems and drinking behaviours are not stable on an individual level over time; thus, examining how they evolve over key developmental periods would offer new insights on their mechanism of action. The long time lag among waves in the two British birth cohorts constrains one's ability to carry out person-based analysis. In contrast, MLS was designed to study the aetiology of substance use, and alcohol-related data were collected more intensively. As discussed in section 1.2.1, life stressors are likely to be on the upstream of the externalising and internalising pathway to alcohol problems. Chapter 6 aims to study the co-development of problematic drinking and stressful life events over adolescence and young adulthood and to describe the distribution of several other time-invariant and time-varying risk factors of alcohol use, which include externalising and internalising problems.

Chapter 7 closes the thesis by summarising and integrating the main findings, and their implications for future research and policy making is discussed.

2. Chapter 2 Early life mental health and alcohol use behaviours in adulthood: A systematic review

Associated publication: This chapter has been published as a paper:
Ning K, Gondek D, Patalay P, Ploubidis GB (2020) The association between early life mental health and alcohol use behaviours in adulthood: A systematic review. PloS ONE 5(2): e0228667.

2.1 Introduction

Although mixed findings exist on whether mental health during childhood and adolescence is deteriorating in recent generations, most evidence suggests an increasing trend for internalising problems and a stable if not increasing trend for externalising problems [199–204]. Understanding how externalising and internalising problems are associated with alcohol use behaviours in adulthood may help inform policy-making decisions on whether intervening on early life mental health may alleviate alcohol burden in adulthood.

The dominant pathway that links mental health problems to alcohol use behaviours is the externalising pathway [205,206]. An alternative mechanism, receiving more attention in recent years, involves the internalising pathway [207]. These pathways have been supported by accumulating empirical evidence, but not all studies have found the same links, with results on the internalising pathway being particularly ambiguous [27,75]. Some studies reported positive associations in which greater internalising problems, depression, and anxiety are related to greater subsequent alcohol use [208,209], while others found opposite associations [76,93,210,211], or no links at all [86]. Many factors may contribute to this inconsistency [75,207].

First, from a developmental point of view, developmental timing, sex, culture and history are all key considerations which may influence the association between externalising or internalising problems and alcohol use behaviours (see more discussions in section 1.3) [90,92]. Regarding developmental timing, it matters

when experiences occur and manifest in regard to their meaning, and this is true for both mental health and alcohol use behaviours. The stage when mental health problems develop or the duration of the problems may present different associations with later alcohol use [110]. Also, drinking behaviours during adolescence are largely influenced by social context (mainly peers and parents) [100,212–216], while drinking patterns in adulthood may be more established and stable [95]. With respect to sex, robust sex differences in the prevalence of both mental health problems and alcohol use behaviours were established [71,122,123,217]. However, how sex may play a role in the association between mental health and alcohol use is yet unclear. As a result, how sex is treated in the analysis (whether male and female subjects are analysed separately, or sex is adjusted for or added as an interaction term with mental health problems) varies across studies, which adds another layer of complexity. Historical period and context may also contribute to different levels of externalising and internalising problems and alcohol use, and more interestingly to the relationships between them [93]. Different from other drugs, alcohol is an integral part of almost all cultures and regulated by social norms about proper context of use and availability in society [29]. Thus, comparing associations without taking these factors into account may also contribute to inconsistent findings.

Second, from a methodological perspective, how mental health problems and alcohol use behaviours are constructed and analysed may also contribute to the inconsistency of results. For example, different forms of internalising problems (global indices, depression, anxiety) may represent different pathways to alcohol use [75], and the same form of internalising problems may have a different pathway to subtypes of alcohol use behaviours (drinking frequency and quantity, binge or heavy or problematic drinking, AUD) across studies [218]. The high and stable comorbidity between externalising and internalising problems in youth [104,106] may also confound the association of each with alcohol use when the other one is not well adjusted for in the model [219].

Due to the above challenges, few systematic reviews have summarised the evidence on the association between mental health and alcohol use until recent years. One systematic review conducted by Hussong et al. (2017) summarised

the association between negative affect symptoms (internalising problems [10 articles], depression [22 articles] and anxiety [9 articles]) and adolescent substance use, controlling for externalising problems [75]. No consistent results were found regarding alcohol use, but the review indicated varying associations between the internalising domain and alcohol use across their subtypes. Another systematic review conducted by Bevilacqua et al. studied the association between conduct problem trajectories and a series of psychosocial outcomes, and five articles on alcohol use were included. It was found that, compared to consistently low conduct problems, both early-onset and persistent (EOP) and adolescent-onset (AO) conduct problems were positively associated with later alcohol use (OR (95%CI): 1.85 (1.04, 3.28) for EOP and 1.72 (1.23, 2.41) for AO), but null association was reported for childhood-limited conduct problems [110]. A more recent review by Dyer et al. indicated that the association between childhood and adolescent anxiety and later alcohol use might vary with different alcohol subtypes but was generally inconsistent across studies [218]. This study also found that the type and developmental period of anxiety, the length of follow-up, the sample size, and the confounders adjusted for did not seem to explain the discrepant findings [218]. The above reviews focused on limited aspects of the association between early life mental health and alcohol use behaviours. For example, Hussong et al.'s paper did not differentiate among different subtypes of alcohol use behaviours and stages of internalising problems [75]. Dyer et al.'s study differentiated among different subtypes of alcohol use behaviours, developmental periods of anxiety, and other potential factors, but did not investigate developmental periods of alcohol use and role of externalising problems [218].

This systematic review aims to summarise current evidence on the association between early life mental health and alcohol use behaviours in adulthood while taking into consideration potential factors that may affect their association. Alcohol use behaviours are confined to those behaviours measured in adulthood, at or after age 18, for three reasons: alcohol use behaviours in adolescence were summarised by Hussong et al.'s review; how early life mental health problems are associated with alcohol use in adulthood, when drinking patterns have been established, may be different from that in adolescence, but no review has

summarised the association pattern systematically; and 18 years old is the minimum legal drinking age in most countries (116 out of 190 countries) [220]. Correspondingly, only studies which measured mental health before age 18 were eligible to ensure temporality and avoid reverse causality with alcohol use.

To summarise, the association between early life mental health problems and alcohol use behaviours in adulthood was examined by considering a) subtypes of early life mental health problems (externalising problems, internalising problems, depression, anxiety), b) subtypes of alcohol use behaviours (alcohol consumption [frequency/volume], heavy/problematic drinking and AUD), c) whether externalising and internalising problems were adjusted for accordingly, d) the developmental timing in which mental health problems occurred (childhood [before age 11 years], early-adolescence [11 to 15 years], late-adolescence [16 to 17.9 years]) [92], and alcohol use behaviours occurred (transition to adulthood [18 to 25 years], early-adulthood [26 to 40 years]), midlife and beyond [41 years old onwards]), e) whether the association varies across sex, history, and culture.

2.2 Methods

2.2.1 Search strategy and selection criteria

Initial searches were conducted on 4 April 2017 with an update search conducted on 31 October 2018. Four databases (EMBASE, Medline, PsycINFO, and the ISI Web of Science) were searched for publications (see Appendix 1 for the search strategy used for the ISI Web of Science). Results were merged and imported into Eppi-reviewer 4 for the first-round search and then EndNote X9 for the second round.

2.2.2 Inclusion and exclusion criteria

Population and study type

Studies were restricted to prospective longitudinal designs that recruited samples from general community populations and collected information prospectively instead of retrospectively. Clinical and high-risk samples recruiting people diagnosed with specific mental/physical diseases and children of alcoholics were excluded. Experimental, clinical, cross-sectional, case-control, and time-series or econometric studies were excluded.

Exposure

Mental health problems were categorised into externalising domain and internalizing domain (internalising problems, depression, and anxiety). The externalising domain focused on general measures of externalising problems and did not include attention deficit hyperactivity disorder, which is under the externalising domain but does not contain features that contribute to the externalising pathway [74]. Studies using specific behaviour of mental health as exposure, such as stealing or fighting, were excluded. Studies with a wide age range population over age 18 were included only if the upper age boundary (two standard deviations above the mean age) was below age 18 to ensure mental health problems were measured below age 18 for the majority of the population. Studies that derived trajectories for mental health problems beyond age 18 were included only if the derived trajectories mainly reflected mental health status across childhood or adolescent (i.e., more than half of the measurement occasions occurred before age 18).

Outcome

All alcohol-specific outcomes were included, but substance use outcomes that did not explicitly represent alcohol use were excluded. For clarity, alcohol use behaviours were further categorized into three broad categories: alcohol

consumption including drinking frequency/volumes; heavy/problematic drinking, including binge drinking, heavy drinking, and problematic drinking identified through well-known scales (e.g., CAGE [221,222], Alcohol Use Disorder Identification Test (AUDIT) [223]); AUD diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) [224]. As mentioned above, the included studies all measured alcohol use behaviour at or after age 18; studies with a wide age range population under age 18 were included only if the lower age boundary (two standard deviations below the mean age) was at or above age 18. Studies that derived trajectories for alcohol use below age 18 were included only if the derived trajectories mainly reflected alcohol use in adulthood (i.e., more than half of the measurement occasions occurred after age 18). In addition, all studies included in this review had alcohol outcomes that were measured at least one year after the mental health measurements were taken to reflect the long-term prospective association between them.

2.2.3 Screening and data extraction

Guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were followed to ensure transparency [225], and the protocol for this systematic review was published on PROSPERO (registration number: CRD42018115502).

After excluding 5833 duplicates, 17,259 articles were screened for inclusion, and 15% of them were independently screened by a colleague. The agreement rate was 97.9% and Cohen's kappa was 0.71 at this stage. Disagreements were discussed and consensus was reached before screening the rest of the articles. After excluding 16,768 articles based on the titles and abstracts, 495 articles were retrieved and assessed for eligibility. Ten percent of the full texts were screened by a colleague, and the agreement rate and Cohen's kappa at this stage were 92.3% and 0.75, respectively. The final sample constituted 36 articles, comprising 33 articles that met the eligibility criteria as well as three articles obtained through screening the references of eligible articles and relevant publications [75,218]. See more details in Figure 8 and Table 1.

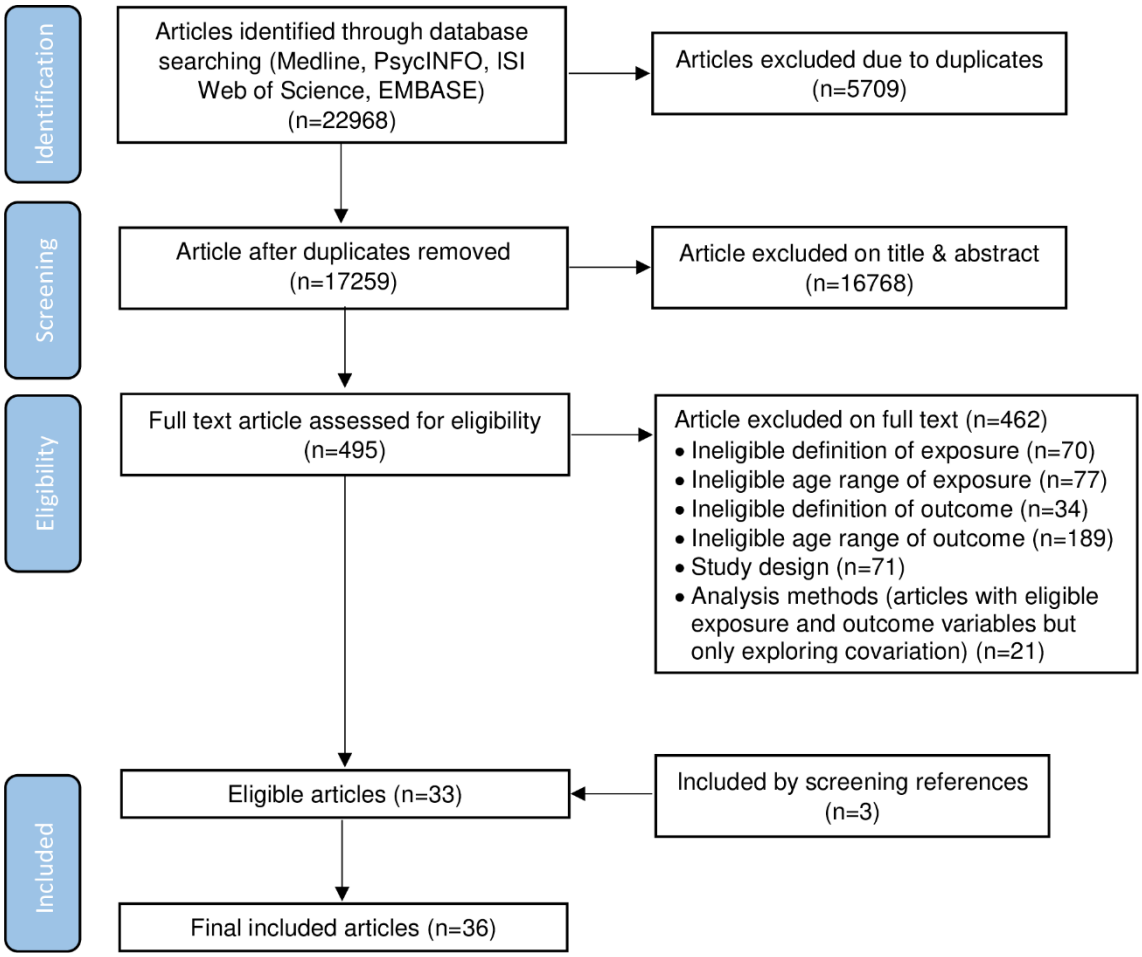


Figure 8 Flow chart of the screening process

Table 1 Summary of studies included in the review

Study	Sample and country	Birth year	Sample size (% Male)	Exposure (measure) *	Exposure age (years)&	Outcome (measure) #	Outcome age (years)&
Berg et al. (2018)[102]	Ninth-grade pupils attending comprehensive school in Tampere, Finland	1967	2194 (NR)	Psychological symptoms (a checklist of 17 physical and psychological complaints)	15.9 (SD 0.3)	Frequency of intoxication (3 categories)	22
Kendler et al. (2018)[226]	All births due between April 1, 1991 and December 31, 1992 in the Avon district, UK	1991~1992	7168 (49.1%)	Ext (sum score of antisocial behaviours)	13.5 and 15.5	Heavy episodic use weekly (AUIDT, binary)	20
						Alcohol problems (AUDIT, binary)	
Soloski et al. (2018)[85]	National representative sample of high-school adolescents (Add Health), USA	1976~1983	9330 (45.2%)	Depression (6 questions assessing depressive symptoms)	14.9 (11~18)	Binge drinking (Days of 5+ drinks in a row over past 12 months, 6 categories)	21.6 (18~26)
Hoyland et al. (2017)[82]	National representative sample of high-school adolescents (Add Health), USA	1976~1983	2610 (44.5%)	Depression (9 items from CES-D scale)	15.6 (11~18)	Derived latent classes (ever had a drink, drinking frequency, drunk frequency, binge drinking frequency, drinking quantity, negative consequences)	29.6 (24-32)
Squeglia et al. (2017)[227]	Selective sample of students from local middle school, USA	NR	137 (56%)	Conduct disorder (DSM-IV)	12~14	Alcohol initiation	18 (16~19)
Edwards et al. (2016)[72]	All births due between April 1, 1991 and December 31, 1992 in the Avon district, UK	1991~1992	4534~6598 (NR)	Conduct problems (SDQ)	11.8	Alcohol problems (20 questions from AUDIT, DSM-IV, and other negative consequences)	20
				Conduct problems (22 types of delinquent or anti-social behaviour)	15.6		
				Major Depression (SMFQ)	16.6		
Quinn et al. (2016)[228]	Nine-year-old twins identified in the Swedish Twin Registry, Sweden	1992~1995	15602 (51%)	Conduct problems (SDQ)	15	Alcohol problems (AUDIT)	18

Table 1 (Continued)

Study	Sample and country	Birth year	Sample size (% Male)	Exposure (measure) *	Exposure age (years)	Outcome (measure) #	Outcome age (years)
Savage et al. (2016)[229]	Twins born from 1983 to 1987 in FinTwin12 study, Finland	1983~ 1987	1906 (51.2%)	Social anxiety (MPNI)	12	Frequency of drinking alcohol	22
Swift et al. (2016)[79]	Representative sample of the Victorian population of school pupils, Australia	1977~ 1979	1268 (50.9%)	Antisocial behaviour (self-report early delinquency scale)	Onset of antisocial behaviour from age 14/15 to 17	AUD (DSM-V)	24
				Anxiety and depression (revised CIS)	Persistence of depression /anxiety from age 14/15 to 17		
Thompson et al. (2016)[80]	Youth recruited by random digit dialing from a medium-sized Canadian city, Canada	1985~ 1991	622 (49%)	EXT (DSM-IV)	16~17	Frequency of 5+ drinks (binary)	18~19
				INT (DSM-IV)		Alcohol related harm (six items from the Harmful Effects of Alcohol Scale)	
Cook et al. (2015)[129]	National representative sample of high-school adolescents (Add Health), USA	1976~ 1983	5422 (46.1%)	Latent class of antisocial behaviour across time (adapted Health Behaviour Questionnaire)	Baseline 13.96 (SD 1.06), follow-up one year later	Problematic alcohol use (6-item alcohol related problems scale)	20.32 (SD 1.09)
Jun et al. (2015)[230]	Community-based sample from 80 neighbourhood clusters, USA	1982~ 1985	724 (51.0%)	EXT (YSR) INT (YSR)	15	Drink or not in the past month	18
Pesola et al. (2015)[84]	All birth due between April 1, 1991 and December 31, 1992 in the Avon district, UK	1991~ 1992	2964 (36%)	Depression (SMFQ)	13.9 (SD 0.21)	Harmful drinking (AUDIT)	18.7 (SD 0.49)
Virtanen et	All pupils who	1965	1001	Depression (DSM-V)	16	Trajectory of average	5 waves

Study	Sample and country	Birth year	Sample size (% Male)	Exposure (measure) *	Exposure age (years)	Outcome (measure) #	Outcome age (years)
al.(2015)[231]	attended the last year of compulsory school (age 16) in all nine schools in a middle-sized municipality in Northern Sweden		(51.8%)	Anxiety (DSM-V)		alcohol intake (multiply drinking frequency with drinking quantity per occasion)	from 16~45
Edwards et al. (2014)[81]	All birth due between April 1, 1991 and December 31, 1992 in the Avon district, UK	1991~1992	1637 (37.8%)	Trajectory of depression (SMFQ)	4 waves from 12~17	Binary harmful drinking (AUDIT) Latent alcohol use (AUDIT)	18.5
Kretschmer et al. (2014)[232]	All births due between April 1, 1991 and December 31, 1992 in the Avon district, UK	1991~1992	7218 (NR, 52% in initial sample)	Trajectory of conduct problems (SDQ)	6 waves from age 4 to age 13	Binary harmful drinking (AUDIT)	17.9 (IQR17.7~17.11)
Pesola et al. (2014)[134]	All births due between April 1, 1991 and December 31, 1992 in the Avon district, UK	1991~1992	3710 (44%)	Depression (SMFQ)	16	Alcohol problems (AUDIT)	18
Stanley et al. (2014)[78]	Community sample of urban Indian youths in the Seattle area, USA	1976~1978	281 (~48.3%)	EXT(CBCL) INT (CBCL)	11.7 (11~12)	AUD (DSM-IV)	19.7
Meier et al. (2013)[233]	Birth cohort of consecutive births between April 1, 1972, and March 31, 1973, in Dunedin, New Zealand	1972~1973	957 (~52%)	EXT (DSM-IV)	Average of 4 waves at age 5,7,9,11 Onset at age 11,13,15,18	AUD (DSM-IV)	3 waves from age 18 to age 32
				Anxiety (DSM-III)	Onset at age 11,13,15,18		
				Depression (DSM-III)	Onset at age 11,13,15,18		
				INT (RBQ)	Average of 4 waves at age 5,7,9,11		

Study	Sample and country	Birth year	Sample size (% Male)	Exposure (measure) *	Exposure age (years)	Outcome (measure) #	Outcome age (years)
Naicker et al. (2013)[234]	A representative sample of general population randomly selected by stratified two-stage design, Canada	1977~ 1983	1027 (53.8%)	Depression (Short Form for Major Depression)	12~17 at baseline, depression assessed at age 16~17	Heavy drinking (consumption of >16 drinks/wk for males and >11 drinks/wk for females), and/or consuming 5+ drinks in one sitting at a frequency greater than once a month)	Measured every two years from age 18/19 to 26/27
Green et al. (2012)[131]	Essentially all first grade students of Urban African Americans in the Woodlawn community area of Chicago, USA	1959~ 1960	1242 (48.8%)	Psychological distress (How I feel scale on anxiety and depression)	15~16	Drinking quantity when they were drinking the most in last year	32~33
McKenzie et al. (2011)[77]	Two-stage cluster sample selecting random class from 44 secondary schools in the state of Victoria, Australia	~1977	1758 (NR)	Number of waves when depression and anxiety symptoms over a threshold (revised CIS)	5 waves from age 15.5 to age 17.4	AUD (Composite International Diagnostic Interview (CIDI))	24
Stumm et al. (2011)[235]	Primary school students aged 6 to 12 in Aberdeen, Scotland in 1962, UK	1950~ 1956	12500 (~52.3%)	EXT (RBQ) INT (RBQ)	9.7 (SD 1.5)	Frequency of alcohol consumption, weekly alcohol units (category), number of hangovers last year and how often they consumed 4+ drink per occasion (category)	46~51
Bor et al. (2010)[236]	Pregnant women attending clinic visit at one hospital in Brisbane, Australia	1981~ 1984	3173 (~51.9%)	Anti-social behaviour (CBCL)	2waves at age 5 and age 14	Binge drinking (non-drinkers, 1~6 drinks, 6+drinking per occasion)	21
Hill et al. (2010)[86]	Youths recruited from 18 elementary schools	1975	640 (NR)	EXT (5 items, “How many times have you done the	Average score at age	AUD (DSM-IV)	27

Study	Sample and country	Birth year	Sample size (% Male)	Exposure (measure) *	Exposure age (years)	Outcome (measure) #	Outcome age (years)
	in urban Seattle, USA			following things?" Done what feels good, no matter what?; Gone to a wild, out-of-control party?; Upset or annoyed adults just for the fun of it?; Done something dangerous because someone dared you to do it?; Done crazy things even if they are a little dangerous?	14 and15		
				Anxiety (CBCL)			
Huurre et al. (2010)[237]	Ninth-grade pupils attending comprehensive school in Tampere, Finland	~1967	1387 (44.2%)	Depression (seven items indicative of depression (lack of energy; sleeping difficulties; nightmares; fatigue; irritability; loss of appetite; and nervousness/anxiety))	15.9 (SD 0.3)	Excessive alcohol use (AUDIT)	32
Colman et al. (2009)[238]	A stratified sample of every child born in England, Scotland, or Wales during 1 week in March 1946, UK	1946	3652 (51.9%)	EXT (RBQ)	2 waves at age 13 and 15	Alcohol abuse (CAGE) (number of waves with alcohol abuse)	2 waves at age 43 & 53
Maggs et al. (2008)[76]	all children born in Great Britain between 3 and 9 March 1958, UK	1958	4758~12772 (~50.8%)	EXT (RBQ) INT (RBQ)	At age 7 and 11	Weekly alcohol units Harmful drinking (CAGE)	At age 23, 33, 42
Pitkanen et al. (2008)[88]	Twelve complete (the initial participation level was 100%) school classes of second-grade pupils in the town of Jyväskylä, Finland	1959	347 (53.0%)	Anxiety (easily starts crying if others treat him/her nastily, afraid of other children; and cries easily at age 8; fearful and helpless in other's company, target of teasing, unable to defend at age 14)	At age 8 and 14	Heavy drinking (police records, annual drinking etc.) by age 20 (4 categories) Annual frequency of drinking at age 27, 42 (days)	At age 20, 27, 42

Study	Sample and country	Birth year	Sample size (% Male)	Exposure (measure) *	Exposure age (years)	Outcome (measure) #	Outcome age (years)
						Frequency of binge drinking at 27, 42 (6 categories) Harmful drinking (CAGE score) Problem drinking by 27, by 42 (whether experienced any difficulties, 6 categories)	
Timmermans et al. (2008)[239]	Randomly from the Dutch province of Zuid Holland, using inoculation registers and the municipal population register of Rotterdam in 1989, Netherland	1986~1987	309 (48.9%)	Trajectory of EXT (CBCL)	3 waves at 4/5, 10/11, 18	Alcohol use (combination of drinking frequency and drunkenness, 7 categories)	18.19 (SD 0.7[239][216])
Pardini et al. (2007)[83]	Randomly selected from a list of names and addresses of all seventh-grade boys in participating Pittsburgh public schools during 1987–1988, USA	~1973	506 (100%)	Conduct disorder (DSM3, SRD, YSR)	13.9 SD NR	AUD symptoms, AUD onset (DSM III/IV)	20.4-25.4
				Anxiety (YSR, Teacher Report Form and CBCL)			
				Depression (Recent Moods and Feeling Questionnaire)			
Niemela et al. (2006)[211]	10% of all births in 1981, a representative sample of communities, Finland	1981	1967 (100%)	EXT (RBQ)	8	Frequency of drunkenness (4 categories)	18
				INT (RBQ)			
Moffit et al. (2002)[240]	Consecutive births between April 1972 and March 1973 in Dunedin, New Zealand	1972~1973	457 (100%)	Antisocial behaviour (RBQ/SRD)	6 waves at age 5, 7, 9, 11, 15, 18	AUD (DSM-IV)	26

Study	Sample and country	Birth year	Sample size (% Male)	Exposure (measure) *	Exposure age (years)	Outcome (measure) #	Outcome age (years)
Moffitt et al. (1996)[241]	Consecutive births between April 1972 and March 1973 in Dunedin New Zealand	1972~ 1973	457 (100%)	Antisocial behaviour (RBQ/SRD)	6 waves at age 5, 7, 9, 11, 15, 18	AUD (DSM-III)	18
Steele et al. (1995)[242]	An urban community sample of Caucasian adolescents in the southeastern region, USA	NR	187 (47.1%)	Conduct problems (Revised Behaviour Problem Checklist)	13.5 (11.1-15.8)	Potential alcohol dependence (MAST)	19.75 (17.8,22.4)
				Anxiety (Revised Behaviour Problem Checklist)			
Pulkkinen et al.(1994) [243]	Second-grade pupils (8~9 years old) in the town of Jyvaskyla, Finland	1959~ 1960	369 (53.1%)	Conduct problems (teacher ratings on punishments at school, truancy, smoking, drinking and contacts with the police)	14	Problematic drinking (CAGE)	26-27
				Anxiety (Peer nomination, "Who is fearful, helpless in others' company, a target of teasing, unable to defend himself or herself?)			

*EXT: externalising problems; INT: internalising problems; CES-D: Center for Epidemiologic Studies - Depression Scale; SDQ: Strengths and Difficulties Questionnaire; SMFQ: Short Mood and Feelings Questionnaire; MPNI: Multidimensional Peer Nomination Inventory; YSR: Youth Self-report scale; RBQ: Rutter Behaviour Questionnaire; CBCL: Childhood Behaviour Check List; SRD: Self-Reported Delinquency Scale.
& SD: standard deviation; NR: not reported; IQR: interquartile range.
#AUD: alcohol use disorder; CIS: Clinical Interview Schedule; AUDIT: Alcohol Use Disorder Identification Test; DSM: diagnostic and statistical manual; MAST: Michigan Alcohol Screening Test; NR: not reported.

An extraction form was developed, and 10% of the selected articles were extracted by a colleague. The information extracted included author, year of publication, country (proxy for culture) and sampling strategy, sample size (proportion of male) and their birth year (proxy for history), measurement scale of exposure and outcome, age when exposure and outcome were measured, direction and size of the association, sex differences of the association, covariates adjusted for, statistical models, assessment of attrition bias, and methods for dealing with missing data. Associations were extracted if they reflected the total association of the relationship. For example, if depression at age 7 and depression at age 16 were adjusted for in the model simultaneously (e.g., alcohol outcome = a + b1*depression at age 7 + b2*depression at age 16), then the coefficient b2 can be interpreted as the total association between depression at age 16 and alcohol, which was not confounded by previous depression status (and thus was extracted), while the coefficient b1 was the controlled direct association between depression at age 7 and the outcome not through later depression status (and thus was not extracted). See more definitions in Pearl (2001) [244]. In addition, some studies reported several associations for the same exposure-outcome set, so other rules were devised to avoid duplicate associations: continuous measures (over categorical), self-report (over parent or teacher report), most properly adjusted result, unstandardized betas (over standardised), whole population (over sub-population). Discrepancies were discussed and agreed upon before extracting information from all included articles.

2.2.4 Data synthesis

As shown by previous research [75], there was a high heterogeneity in studies that were included in this review in terms of sample characteristics (a wide age range of participants at baseline of studies), subtype and developmental timing of mental health problems and alcohol use behaviours (binary/continuous, trajectory/one-time-point, measurement scales), length of follow-up, and confounders adjusted for. Approaches exist to overcome heterogeneity due to analytical approaches [245], with the exception of exposure heterogeneity. Particularly, for continuous exposures, it was not possible to standardise or

transform them to the same metric required by meta-analysis [246]. In addition, the number of articles was too low to be pooled after taking into account the potential factors [247]. Thus, results were reported narratively, and extracted associations were displayed in detail in Appendix 2.

To minimize potential bias caused by different ways of reporting the results (e.g., different exposure and outcome categories, reporting separately by sex/age), or by articles using the same population, data were synthesised in the following three ways:

a) the proportion of tests that were significant (*P* value equal or less than 0.05) out of all tests that reported specific exposure-outcome sets regardless of studies/articles, as done by Hussong et al. [75]. For example, for the internalising problems and alcohol consumption set, article A reported 4 tests of this association (mild internalising problems vs. no internalising problems in males, severe internalising problems vs. no internalising problems in males, mild internalising problems vs. no internalising problems in females, severe internalising problems vs. no internalising problems in females), and only association for severe internalising problems vs. no internalising problems in males was significant negative; article B reported 2 tests (one in males, one in females), and neither of them was significant. Then, the proportion of negative association would be 1 / (4+2) =16.7%.

b) the proportion of studies that reported a significant association for each exposure-outcome set. For each study (using the same dataset) and for each exposure and outcome pair, no matter how many tests were reported, the association was counted as significant as long as one test was significant. For instance, in the example above, article A would be counted as reporting a significant negative association between internalising problems and alcohol consumption, and article B would be counted as reporting no association between internalising problems and alcohol consumption. Then the proportion would be 1 / (1+1) = 50%.

c) The method outlined in point a) was repeated in high-quality studies as defined below. Results synthesised using the first method were reported in the main article, and other results in Appendix 3 and Appendix 4.

To maximize the use of available information and informed by the albatross plot [248], the distribution of *P*-values for each association test against its sample size was plotted in Figure 9-Figure 13. In addition, distribution of average *P*-value across subtypes and developmental timing of both exposure and outcome is presented in Appendix 5-Appendix 8.

2.2.5 Quality assessment

An adapted version of the Critical Appraisal Skills Programme (CASP) Cohort Study Checklist [249], which was shortened to 8 questions, was employed as shown in Appendix 9. Mainly four aspects of each cohort study were assessed: sample selection, measurement error, core confounder adjustment, and the handling of missing data, which are key issues that can cause bias in observational studies [250,251].

A quality score (QS) was assigned for each question. The scores were then summed, with total scores ranging from 0 to 8. Studies with scores ranging from 0-4 were considered as poor quality, and studies with score 5-8 as good quality. Quality assessment was done for all 36 selected articles by me and the same colleague who participated in the screening stage separately, and disagreements were discussed to reach a final consensus.

The results were organized by four subtypes of mental health problems: externalising problems, internalising problems, depression and anxiety. Within each domain, the findings were further structured for three subtypes of alcohol use behaviours. Where appropriate, it was examined whether the results were affected by adjusting for externalising and internalising accordingly, the developmental timing of exposure and outcome, and country origin or birth cohort; evidence for potential sex differences was also summarised.

2.3 Results

2.3.1 Search results

Of the 36 articles included in this review, eleven studies were carried out in the US and nine in the UK, followed by six in Finland. The data used were from over 20 longitudinal studies, but six articles used data from the Avon Longitudinal Study of Parents and Children (ALSPAC). The sample size in 22 articles was over 1000.

Fifteen of the 36 articles were rated as high quality due to their large sample size, representativeness of the population, inclusion of core confounding factors and advanced principles to deal with missing data. By comparison, 21 of the 36 studies were rated as poor quality due to their failure to control for potential confounding factors, small sample sizes, and improper strategies for missing data (mainly complete case analysis). The frequency of the potential confounders that were adjusted for in the 36 articles was summarised in Appendix 10 to give a more comprehensive picture.

Twelve out of 36 articles focused on the internalising domain as the exposure, 9 articles focused on the externalising domain, and 14 articles explored both domains. This resulted in 26 articles on the internalising domain (INT: n=9, depression: n=13, anxiety: n=8) and 23 articles on the externalising domain. With regard to alcohol use behaviours, the distribution was as following (see more details in Appendix 11): alcohol consumption (n=9), heavy/problematic drinking (n=22) and AUD (n=8).

Most articles measured mental health problems at one time point: four in childhood, 17 in early adolescence, seven in late-adolescence, and 6 with a wide age range. Six articles derived mental health trajectories. Alcohol use behaviours were measured during early adulthood in 26 articles, mid-adulthood in eight articles, late adulthood in four articles and modelled as trajectories across adulthood in two articles.

2.3.2 Association between externalising problems and alcohol use behaviours

This review identified 103 tests of the association between externalising problems and alcohol use behaviours in 23 articles, and higher early life externalising was significantly associated with more alcohol-related issues later in 37 tests (35.9%).

With respect to the association between externalising and different alcohol subtypes, a higher number of positive associations was found with more severe alcohol outcomes (See the distribution of *P*-value across subtypes of alcohol use behaviours in Figure 9). Unique associations between externalising and alcohol consumption were examined in 37 tests. Six (16.2%) tests reported positive associations, one test found a negative association, and the rest reported no association. 42 tests in 13 articles examined heavy/problematic drinking as an outcome, and 22 (52.4%) tests reported positive associations. For AUD, 24 tests in seven articles were extracted, and nine (37.5%) tests reported positive associations. Results are presented in Table 2.

Table 2 Distribution of associations across subtypes of mental health problems and alcohol use behaviours

	Alcohol consumption			Heavy/problematic drinking			AUD		
	positive	negative	no	positive	negative	no	positive	negative	no
Externalising problems	6/37	1/37	30/37	22/42	0/42	20/40	9/24	0/24	15/24
	16.2%	2.7%	81.1%	52.4%	0%	47.6%	37.5%	0%	62.5%
Internalising problems	0/26	9/26	17/26	3/14	5/14	6/14	4/9	0/9	5/9
	0%	34.6%	65.4%	21.4%	35.7%	42.9%	44.4%	0%	55.6%
Depression	3/5	0/5	2/5	9/24	2/24	13/24	2/5	0/5	3/5
	60%	0%	40%	37.5%	8.3%	54.2%	40%	0%	60%
Anxiety	4/13	2/13	7/13	0/31	2/31	29/31	2/7	1/7	4/7
	30.8%	15.4%	53.8%	0%	6.4%	93.6%	28.6%	14.3%	57.1%

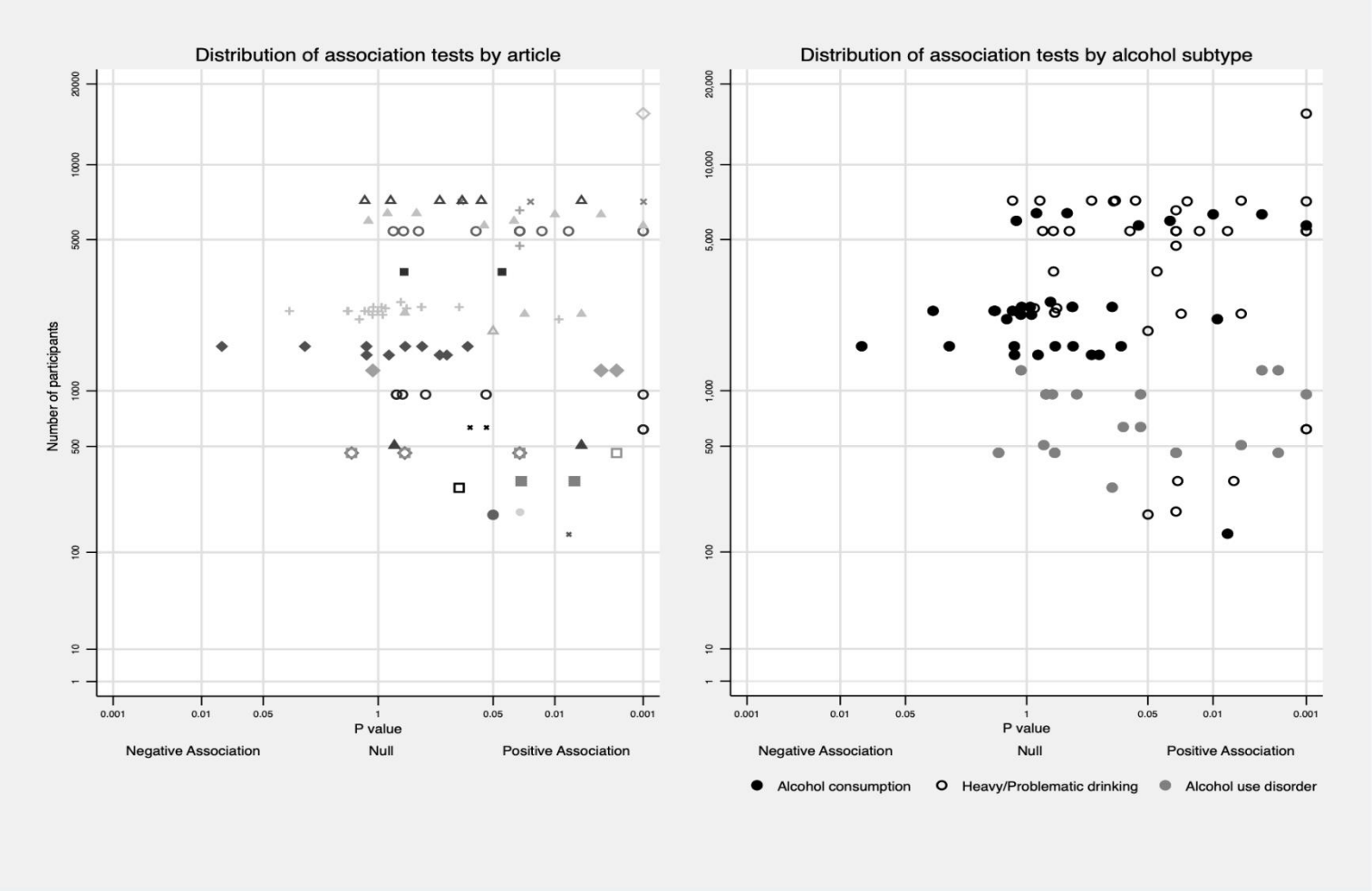


Figure 9 Distribution of association tests between externalising problems and subtypes of alcohol use behaviours*

*Distribution of association tests clustering in one article was plotted on the left to show the non-independence among tests.

Then, the variation of association according to the developmental timing excluding alcohol consumption outcomes was explored. Two out of seven (28.6%) tests measuring externalising problems in childhood reported positive associations with later alcohol use behaviours, 10 out of 19 (52.6%) tests measuring externalising problems in early adolescence showed positive associations, and two tests measuring externalising problems in late adolescence both reported positive associations. Results from four papers using externalising problems trajectories indicated that externalising problems in late adolescence might be more strongly related to alcohol outcomes, especially the persistence of externalising problems from childhood to adolescence [232,239–241] with the exception of Bor et al.'s study [204]. This association pattern was also reflected in papers that measured externalising problems at several time points [72,226,233] with the exception of Maggs et al.'s study [76]. Out of 41 tests measuring alcohol use in transition to adulthood, 23 (56.1%) presented positive associations between externalising problems and alcohol outcomes. Four out of nine (44.4%) tests measuring alcohol use in early adulthood presented positive associations; however, alcohol use was measured at around 26/27 years old in these studies [86,240,243]. By comparison, three out of ten tests (30%) measuring alcohol use in midlife and above showed positive associations [76,235,238]. Besides, 13 out of 23 (56.5%) tests adjusting for internalising problems simultaneously reported positive associations, while 18 out of 43 (41.9%) tests not adjusting for internalising problems reported positive associations. More information is in Figure 10.

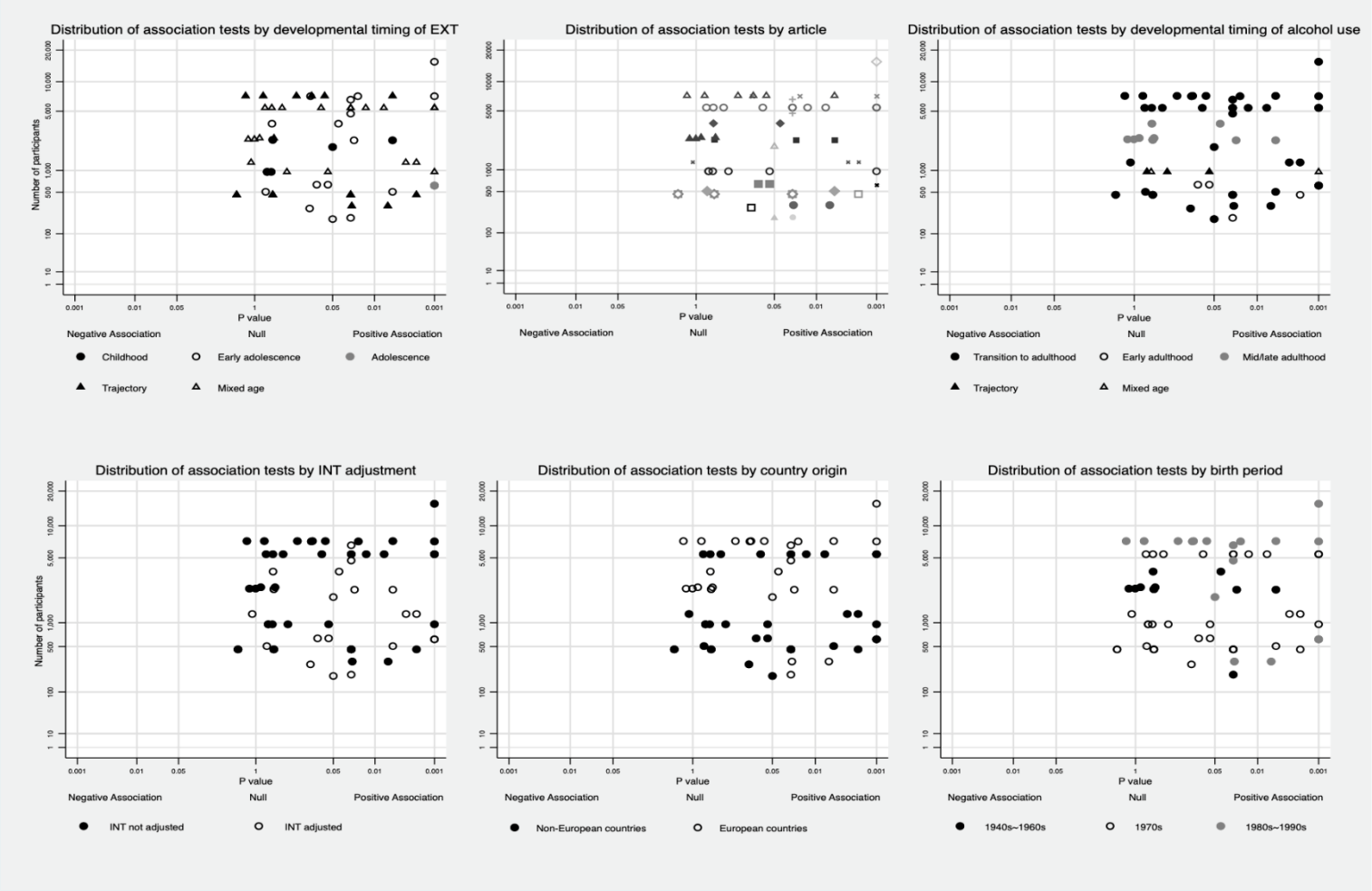


Figure 10 Distribution of association tests between externalising problems and alcohol problems among various subgroups*

*Association tests were limited to those using heavy/problematic drinking, AUD as the outcome, and distribution of association tests nested in one article was plotted in the upper middle for easy comparison.

Among the 23 articles, 19 included both males and females in their samples, and four explored associations only among males [83,211,240,241]. Eleven of the 19 articles that included both sexes did not explore whether there was an interaction between sex and externalising problems in the association with later alcohol use. Only two of the remaining articles reported a significant sex interaction with the association being stronger in males [129], while the other six articles found no statistically significant interaction [72,80,230,238,239,242]. Among tests reporting the association separately in male and female, 15 out of 42 (35.7%) in male were significantly positive; 6 out of 28 (21.4%) in female were significantly positive. To explore the role of culture and history, country origin was categorized into two groups (Europe versus non-Europe), and birth year into three cohorts (born in or before 1960s, born in 1970s, born in or after 1980s). Proportion of positive results were similar across continents (Europe 44.8% versus non-Europe 48.6%) (See Figure 10); four out of twelve tests (33.3%) among those born in or before 1960s reported positive associations, 15 out of 34 tests (44.1%) among those born in 1970s reported positive associations, and 11 out of 19 tests (57.9%) among those born in or after 1980s reported positive associations (See Figure 10). To tease out age effect from cohort effect, analysis was further limited to those born in 1970s and had their alcohol measured during transition to adulthood, 11 out 21 tests (52.4%) found positive results.

Summary

Externalising problems were positively associated with later alcohol use and this association varied across subtypes of alcohol use behaviours with a higher proportion of positive associations for more severe outcomes. More positive associations were detected when externalising problems were measured in adolescence and alcohol use in transition to adulthood. The probability of detecting significant positive associations between externalising problems and later alcohol use behaviours was higher when adjusting for internalising problems simultaneously. Most of the studies that tested sex differences in the associations detected no significant interactions, however, a higher proportion of positive results were reported in males. The probability of detecting a positive association

between externalising problems and alcohol use behaviours appeared to be consistent across countries and cohorts.

2.3.3 Association between the internalising domain and alcohol use behaviours

In the 26 articles exploring the association between the internalising domain and alcohol use behaviours, 135 tests were extracted, including 49 tests in 11 articles investigating internalising problems as the exposure, 34 tests in 11 articles using depression and 52 tests in 8 articles assessing anxiety.

Internalising problems and alcohol use

Among 49 tests investigating the association between internalising problems and alcohol use behaviours, seven tests found a positive association, 14 produced a negative association, and 28 found no association.

With respect to subtypes of alcohol use behaviours (See Figure 11), 9 out of 26 (34.6%) tests found negative associations with alcohol consumption while the rest reported no association. 14 tests in five articles used heavy/problematic drinking as an outcome; three (21.4%) of them found a positive association [80,102], and five (35.7%) tests indicated negative association. Out of nine tests in four articles with AUD as an outcome, four (44.4%) tests reported a positive association and 5 found no association.

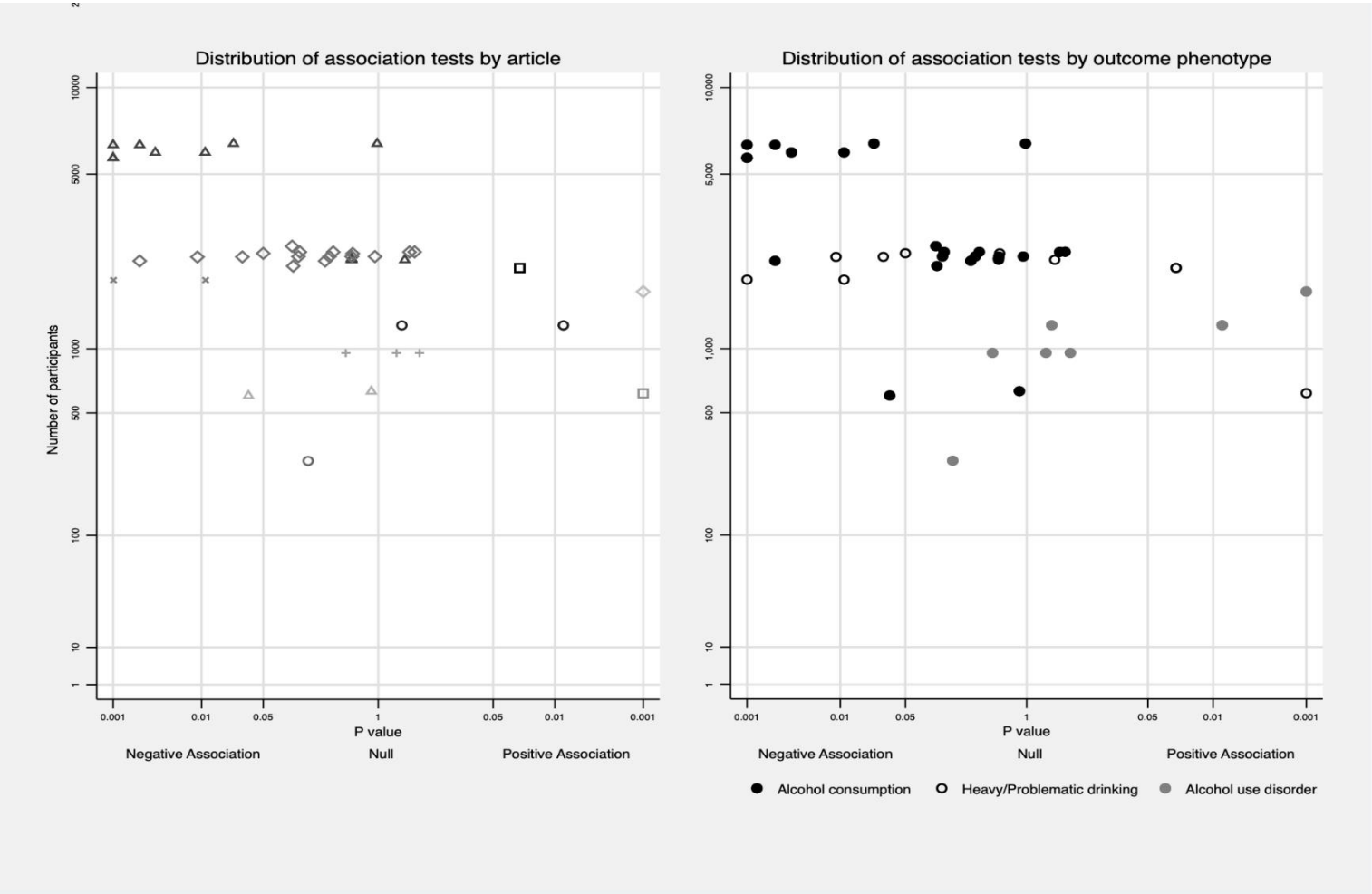


Figure 11 Distribution of association tests between internalising problems and subtypes of alcohol use behaviours*

*Distribution of association tests clustering in one article was plotted on the left to show the non-independence among tests.

Due to the divergent directions of the associations, analysis was done with respect to each subtype of alcohol outcome and summarised as following: for alcohol consumption, a higher proportion of negative associations was detected when externalising problems were simultaneously adjusted (7 out of 8 tests vs. 5 out of 27 tests); for heavy/problematic drinking, it was more likely to detect positive associations when internalising problems were measured at late adolescence; for AUD, which was mainly measured during transition to adulthood, significant positive associations were reported when internalising problems were measured during adolescence and when externalising problems were simultaneously adjusted. There was no country-source heterogeneity within subtype of alcohol outcomes, but none of the studies using AUD as an outcome was from European countries. Cohort effect cannot be explored as the majority of the tests on alcohol consumption were from participants born in or before the 1960s, and all tests on AUD were from participants born in the 1970s.

Depression *and alcohol use*

14 out of 34 (41.2%) tests using depression as the exposure showed positive associations, while three tests showed negative associations [82,85] and 17 tests showed no association. Within sub-categories of alcohol use behaviours (more information in Figure 12), three out of five tests reported a positive association between depression and alcohol consumption [231]; among 24 tests in eight articles using heavy/problematic drinking as an outcome, nine (37.5%) tests reported a positive association and three (12.5%) presented negative associations [82,85]; two out of five (40%) tests indicated positive associations between depression and AUD [233] and no association was found by the remaining tests [83,233].

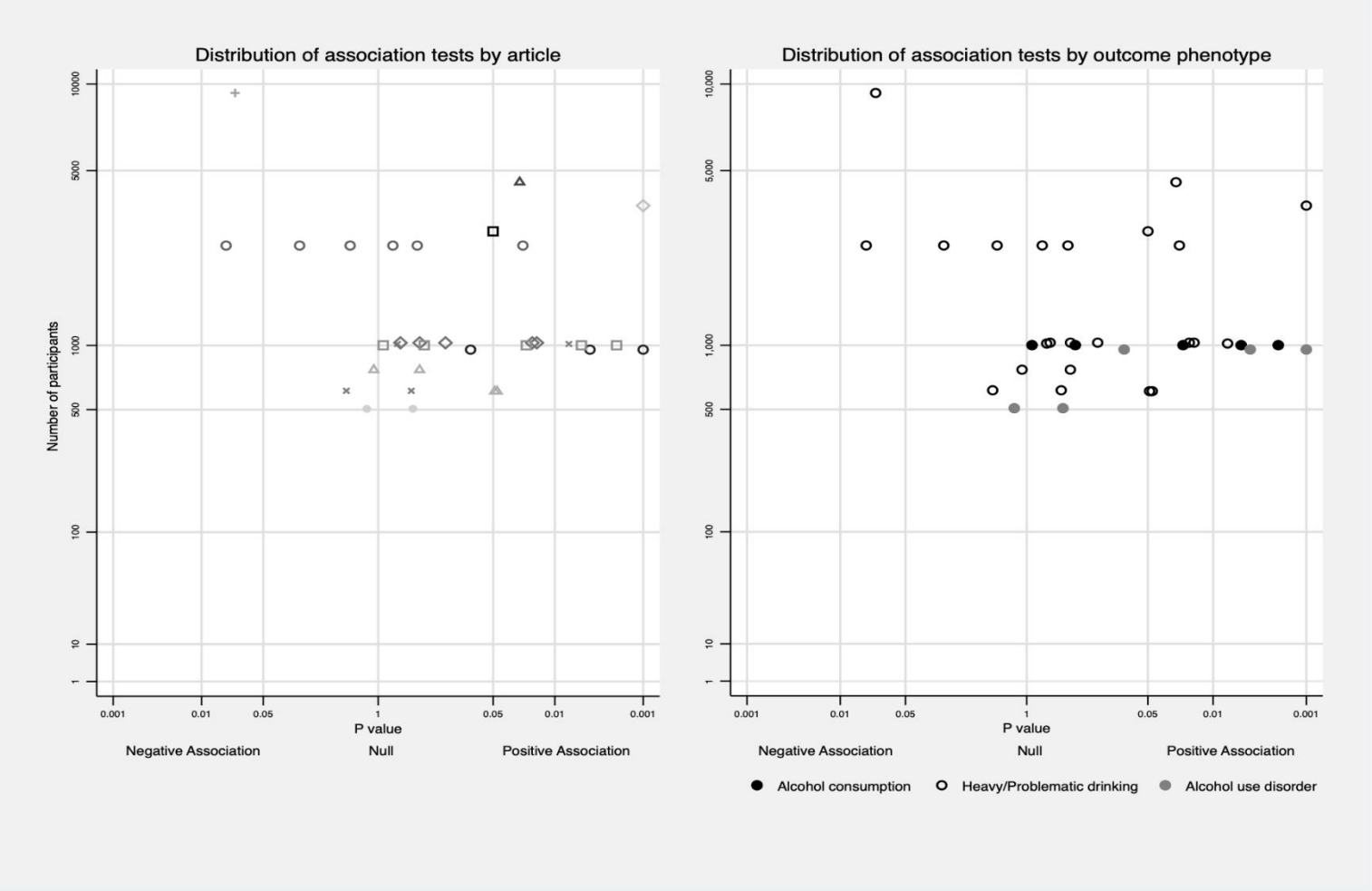


Figure 12 Distribution of association tests between depression and subtypes of alcohol use behaviours*

*Distribution of association tests clustering in one article was plotted on the left to show the non-independence among tests.

No further exploration was carried out due to the limited number of tests for alcohol consumption and AUD. With respect to heavy/problematic drinking, among 12 tests that adjusted for externalising problems, four (33.3%) tests reported positive associations while two (16.7%) tests reported negative associations; among 12 tests that did not adjust for externalising problems, five (41.7%) found positive associations while one (8.3%) found negative associations. No conclusion can be drawn regarding the development period for depression as depression was mainly measured during late adolescence. As for country and cohort differences, negative associations were only detected in one national study in the US [82,85].

Anxiety and alcohol use

There were 52 tests for the association between anxiety and alcohol use, one of which measured social anxiety [229]. Six out of 51 tests measuring general anxiety indicated positive associations [231,233] and five produced negative associations [83,88,243]. A negative association between social anxiety and alcohol consumption was reported in the one paper examining this [229].

For alcohol consumption, two out of 13 tests in one article showed negative associations [88] and four tests found positive associations [231]. For heavy/problematic drinking, two out of 31 tests in two articles showed negative association [88,243], and no statistically significant association was detected for the remaining tests [88,242]. Out of seven tests identified from three articles with AUD as an outcome [83,86,233], two tests found positive associations [233] and one test reported negative associations [83]. The distribution of *P*-values against sample size for anxiety and alcohol use behaviours is shown in Figure 13, and no systematic pattern of the association can be observed.

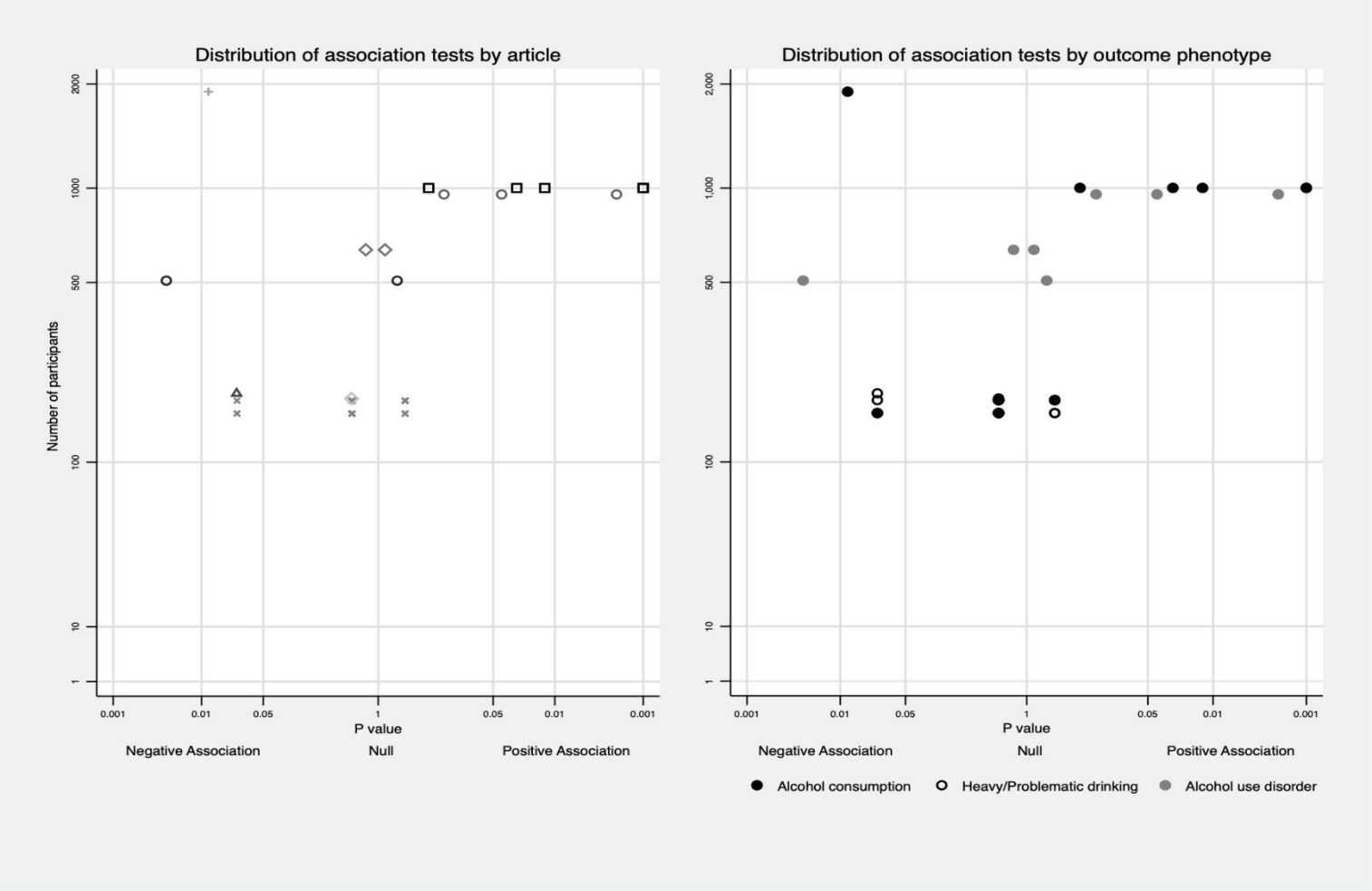


Figure 13 Distribution of association tests between anxiety and subtypes of alcohol use behaviours*

*Distribution of association tests clustering in one article was plotted on the left to show the non-independence among tests.

It should be noted that when anxiety was measured during early adolescence, only negative associations were found [83,88], while positive associations were only reported when anxiety was measured during late adolescence [233,252]. No significant associations were reported when anxiety was measured during childhood. Two out of seven (28.6%) tests that adjusted for externalising problems reported negative associations, while three out of 44 (6.8%) tests found negative associations and six out of 44 (13.6%) tests reported positive associations when externalising problems were not adjusted for. No exploration for country or cohort effect can be done after taking into account the influence of developmental timing of anxiety.

Summary

Evidence for the association between internalising domain and alcohol use behaviours was inconsistent and somewhat varied across subtypes of the internalising domain and alcohol use behaviours. The relationship between internalising problems and alcohol use behaviours tended to be negative for mild alcohol behaviour, especially when externalising problems were adjusted for, and positive for more severe alcohol outcomes. The association between depression and alcohol outcomes seemed to be positive across subtypes. The association between anxiety and alcohol use behaviour was equivocal, and the reason might be that anxiety at different developmental timing was associated with later alcohol use behaviours in a different way.

24 out of 26 articles about the internalising domain had both males and females in their studies, and 11 of them did not explore sex differences in the associations between internalising domain and alcohol outcomes [76–79,82,84,86,233–235,237]. Among the 13 studies that explored sex differences, two articles found stronger association in males and one in females [81,131,243], while the remaining reported no sex differences [72,80,85,88,102,134,229,230,242,253]. More studies are needed to draw conclusion on the potential influence of country and cohort on the association between internalising domain and alcohol use behaviours.

2.3.4 Sensitivity Analysis

For externalising problems, 19 out of 36 (52.8%) tests from high-quality studies reported positive associations with alcohol use behaviours, while 18 out of 67 (26.9%) tests from poor-quality studies reported positive associations. With respect to the internalising domain, ten out of 36 (27.8%) tests from good-quality studies reported positive associations and ten tests (27.8%) reported negative associations, while 17 out of 99 (17.2%) outcomes from poor quality studies reported positive associations and 12 out of 99 (12.1%) found negative associations.

Results synthesised with subtype of alcohol use behaviours among high-quality studies are presented in Appendix 4. There are some discrepancies with the main results: the trend that the proportion of positive associations between externalising problems and alcohol use increases with the severity of the outcome became less obvious (alcohol consumption: 50%; heavy/problematic drinking: 60%; AUD: 37.5%); only negative associations were found between internalising problems and alcohol consumption and only positive associations were detected between internalising problems and more severe alcohol outcomes (heavy/problematic drinking, AUD); no significant association in either direction was found between depression and AUD; only two high-quality studies examined the association between anxiety and AUD, and one of them reported negative association.

The analysis done by extracting one association item from studies using the same dataset did not change the main conclusion.

2.4 Discussion

This systematic review investigated the association between early life mental health and alcohol use behaviours in adulthood. The evidence indicates positive associations between externalising problems and later alcohol use behaviours, but this association tends to vary with subtypes of alcohol use behaviours, with

externalising problems being more consistently linked with more severe outcomes. Externalising problems measured during adolescence are more likely to be associated with alcohol outcomes compared to externalising problems measured during childhood. The association between the internalising domain and alcohol use behaviours is inconclusive with both positive and negative associations presented for the same subtype of alcohol use behaviours.

2.4.1 Association between externalising problems and alcohol use behaviours

This review points to a positive association between early life externalising problems and various alcohol use behaviours with more consistent positive associations being observed for more severe outcomes (ranging from alcohol consumption to problem drinking to AUD). This trend can also be seen from the distribution of *P* values across subtypes in Figure 9. Publication bias may underlie this finding since papers reporting no/negative associations are less likely to be published, but this pattern can also be seen when looking at different alcohol use behaviours within one study [211,232,233,235,254].

Whether the strength of the association between externalising problems and alcohol use behaviours varied across developmental timing of externalising problems could not be explored in current study due to the exposure heterogeneity. However, results show that it was more likely to detect a positive association when externalising problems were assessed in adolescence. This supports the developmental timing of externalising problems from the dimension of persistence (see section 1.3.1). Existing evidence all indicates that compared to those with a low level of externalising problems throughout childhood and adolescence, those with early-onset externalising problems that persist into adolescence or adolescent-onset externalising problems tend to have more alcohol use and alcohol-related problems [110–116], while those with childhood-limited externalising problems did not show higher risk of excessive alcohol [110–116]. Based on these findings, the association between childhood externalising problems and alcohol outcomes derived in regression-based analysis would migrate towards the null: some of those who have high level of externalising

problems in childhood would end up with less alcohol use and alcohol-related problems (childhood-limited externalising problems), and some of those who have a low level of externalising problems in childhood would end up with more alcohol use and alcohol-related problems (adolescent-onset externalising problems). In contrast, the association between adolescent externalising problems and alcohol outcomes is more likely to be detected.

2.4.2 Association between internalising problems and alcohol use behaviours

Compared to externalising problems, the associations between the subtypes of internalising problems and alcohol use behaviours are less consistent. Inconsistency may arise from the co-occurrence of externalising problems, which were not adjusted for in more than half of the included studies. The proportion of positive/negative associations differed between tests adjusting for externalising problems and those not adjusting for it, especially for internalising problems (negative association for alcohol consumption: 87.5% vs. 18.5%). More effort needs to be made to understand how externalising and internalising problems operate in tandem in children's lives to increase or decrease the risk for alcohol use/problems in adulthood, as externalising problems is quite prevalent across different levels of internalising problems [104]. For example, a positive association between depression and AUD was found only in participants with high levels of conduct problems and not in those with low and moderate conduct problems [83]. Moreover, one small sample size study found that pure externalising problems (without internalising problems) had the strongest positive association with adolescent alcohol use, but this association became weaker when externalising problems co-occurred with internalising problems [219]. Meanwhile, pure internalising problems (without externalising problems) presented a negative association, though it was statistically non-significant [219]. Colder et al. also found that the highest probability of alcohol use was observed in those with high externalising problems and low internalising problems, and a negative association between internalising problems and alcohol use was strongest for youth with no externalising problems [255].

Opposite associations with alcohol use were also detected across subtypes of internalising domain (positive between depression and alcohol use [83] but negative between internalising problems and alcohol use [219,255]), as is indicated by the review (See Figure 11-Figure 13). A further implication would be that heterogeneity in measurement tools/instruments may underlie these inconsistencies in the literature as well. In 36 articles, five different scales were used to assess externalising problems, whereas more than ten scales were used for the internalising domain. It may be the case that these various tools measure different aspects of internalising problems that exhibit different associations with alcohol use behaviours. A good illustration would be the differences between general anxiety and social anxiety. Articles that used social anxiety as exposure found negative associations with later alcohol use behaviours [229,256,257], while articles measuring general anxiety but using a scale that tended to reflect symptoms of social anxiety (“too dependent on adults,” “afraid of going to school,” “self-conscious or easily embarrassed,” “shy or timid,” “keeps from getting involved with others” [83], “fearful and helpless in other’s company, target of teasing, unable to defend” [88]) also reported negative associations. Thus, it could be argued that these scales measure different aspects of anxiety, and consequently, the effect of these aspects of anxiety on alcohol behaviour may differ. For example, a person who has social anxiety might be at lower risk for getting involved with alcohol because he/she may be less exposed to other adolescents who drink, or may not have the skills to obtain alcohol if he/she is below legal drinking age [229]; however, a person with other types of anxiety may have a higher risk for later alcohol use [256].

Another finding worth our attention is how the direction of the association between the internalising domain and alcohol use behaviours flipped across the subtypes of alcohol outcomes, especially for internalising problems. One possible explanation for this might be the U or J shaped association reported in cross-sectional studies [258–260]. Studies that reported negative association between internalising problems and alcohol consumption were either large sample-size studies or measured alcohol consumption in mid-adulthood [76,131,235]. Under this situation, the majority of the participants would be light-to-moderate drinkers, and a negative association would be found when the relationship was modelled

as linear. By comparison, for more severe outcomes, which were mainly measured at transition to adulthood [77–80,102] when alcohol use reaches its peak, the results may reflect a positive association. Interestingly, a U-shaped pattern was also observed in a recent prospective study, which discovered that adolescents with more symptoms of depression were more likely to be either abstainers or to demonstrate problematic use [82]. Researchers should take into account the potential non-linear relationship in the future.

Even though differences were observed in some studies between males and females [76,235], sex does not appear to be a substantial factor that caused the inconsistencies in the review. However, more attention should be paid to the role sex plays in the association between early mental health and later alcohol use behaviours due to the profound sex differences in the development of mental health, physiological vulnerability to alcohol, alcohol consumption patterns, and social norms and expectations about drinking [27]. No obvious country or history differences were discovered after taking other factors into account. This may indicate that the association between early life mental health and alcohol use behaviours in adulthood reflect general developmental trends rather than specific historically bounded ones or culture specific ones [93]. However, studies comparing the historical differences or cross-countries comparison (especially in non-Western countries) are needed, as none of the included studies tried to answer this question directly.

2.4.3 Other implications for future studies

There are several implications for future studies. Future work should examine whether the association between early life externalising and internalising problems and alcohol use in adulthood can be interpreted as causal. Although causality in observational data is not easy to infer, a range of techniques such as cross-contextual comparisons, negative controls, sensitivity analysis for unmeasured confounders, instrumental variable analysis or Mendelian Randomization [261,262], and fixed-effect models that eliminate time-invariant confounders [263] can be used for more robust causal inference. To the best of my knowledge, only two articles in this area have applied fixed-effect models

[264,265]. However, their exposure and outcome were measured within the same period and the direction of the association they found could be from alcohol use behaviours to mental health problems [264,266].

Moreover, the fact that almost half of the selected articles were rated as poor quality, and the fact that many high-quality studies did not account for missing data, raise more concern. Principled techniques to deal with missing data, such as inverse probability weighting, multiple imputations, full information maximum likelihood, or even combinations of these techniques [267–269] have been shown to return valid estimates under the missing at random assumption [270] and should be applied more often in the future.

2.4.4 Strengths and limitations

This systematic review built on previous reviews that focused on alcohol use in adolescent [75] and extended alcohol use behaviours into adulthood. Also, both domains of mental health problems (externalising and internalising problems) and subtypes of alcohol use behaviours according to their level of severity were investigated, which provided new insights into these associations. Furthermore, evidence for a potential age effect and sex differences was summarised, although no conclusive findings can be drawn. Several limitations need to be considered when interpreting the results. First, based on current theory, this review focused on broad categories of mental health problems, which resulted in missing studies on Attention Deficit Hyperactivity Disorder and specific anxiety subtypes. Recent studies have shown that Attention Deficit Hyperactivity Disorder is also positively associated with later alcohol use [271,272], and it is very likely that a particular trait within the domain of the disorder is the driver for later alcohol use [273]. Future studies should compare how the associations may change when focusing on different symptoms within a certain disorder, such as aggression, impulsivity, sensation seeking under externalising domain, and social withdrawal under internalising domain. Second, though alternative ways of data synthesis were tried to avoid the risk of bias, it was difficult to explain the discrepancies discovered and only one set of the results was reported in detail as Hussong et al. did [75]. Results using alternative data synthesis methods are attached in

Appendix 3 and Appendix 4. Third, due to the large number of articles retrieved (over 17,000), only a subset of the articles was reviewed by the second author. Fourth, studies were restricted to articles published in English, and as a result, results may not be generalizable to other populations and may suffer from publication bias. However, publication bias may exaggerate the proportion of positive associations for externalising problems to a limited extend and would not affect the results for internalising problems much, as the reported associations were already quite mixed.

2.5 Conclusion

This review evaluated the evidence on the association between early life externalising and internalising problems and alcohol use behaviours in adulthood. For externalising problems, consistent positive associations were found across studies, and positive associations were more likely to be detected with more severe alcohol outcomes, such as heavy/problematic drinking and AUD. Externalising problems in adolescence seem to be more consistently associated with alcohol outcomes than externalising problems in childhood. The evidence on associations between internalising problems and alcohol use behaviours is inconclusive, and the results suggested that different domains of internalising problems may differ in their associations with later alcohol use.

By summarising evidence from heterogenous studies, this review uncovers a few association patterns that warrant further exploration. First, there may be a critical period of mental health problems that is associated with higher risk of later alcohol use; second, externalising and internalising problems may influence each other's relationship with alcohol use; third, there is a lack of evidence to examine how the associations between externalising and internalising problems and alcohol use are conditioned on sex and historical period. These help inform the design of Chapter 4, which extends the associations of externalising problems and internalising problems with problematic drinking into mid-adulthood and examines how these associations vary across developmental timing of mental health, sex and historical periods.

3. Chapter 3 Introduction to the datasets, data availability and descriptive results

Three prospective longitudinal studies were utilised in the thesis: the 1958 British birth cohort (National Child Development Study, NCDS58), the 1970 British birth cohort (BCS70) and the Michigan Longitudinal Study (MLS).

The two British birth cohorts were employed to explore the associations between early life externalising and internalising problems and problematic drinking in adulthood and how they varied across developmental timing, sex and cohorts, and to investigate the mediating role of educational attainment on the pathway from adolescent externalising problems to adulthood problematic drinking across sex and cohorts. MLS was employed to study the co-development of problematic drinking and stressful life events and other time-varying risk factors from adolescence to young adulthood.

3.1 Overview of NCDS58 and BCS70: Comparison between two British birth cohorts

NCDS58 is an ongoing, multidisciplinary, longitudinal study that follows the lives of all those currently living in Great Britain who were born in a single week in March 1958 [274]. It started as the Perinatal Mortality Survey which aimed to identify the social and obstetric factors associated with stillbirth and neonatal death and initially recruited over 17,000 births. Since then, ten waves of data have been collected respectively in 1965 (age 7), 1969 (age 11), 1974 (age 16), 1981 (age 23), 1991 (age 33), 1999/2000 (age 41/42), 2002/2003 (age 44/45), 2004/2005 (age 46/47), 2008 (age 50), and 2013 (age 55).

BCS70 was designed along similar lines to NCDS58, surveying over 17,000 babies born in Great Britain in a single week in April 1970 [275]. Not including the original birth survey, there have been nine waves of the study collected respectively in 1975 (age 5), 1980 (age 10), 1986 (age 16), 1996 (age 26),

1999/2000 (age 29/30), 2004 (age 34), 2008 (age 38), 2012 (age 42), and 2016/2018 (age 46/48).

The target population for both cohorts were those who were born in the Great Britain and were still alive by the time the outcomes were assessed. Thus, the analytic sample size in NCDS58 is 16600 (M=8511, F=8089) by age 33, 16336 (M=8349, F=7987) by age 44/45. Similarly, in BCS70 it is 16655 (M=8601, F=8054) by age 34, 16593 (M=8586, F=8007) by age 46 in BCS70. It should be noted that the two British cohorts were mainly constituted with European/Caucasian people (NCDS58: 98.6%; BCS70: 96.0%) and thus may only be representative of people of this origin.

3.1.1 Availability of early life mental health variables

Several scales were used to collect information on early life mental health problems in NCDS58 and BCS70, such as the Bristol Social Adjustment Guide [276], Rutter Behaviour Questionnaire (RBQ) (Parent version) [277], RBQ (Teacher version) [278] as listed in Appendix 12. Only items from Rutter Behaviour Questionnaire reported by parents were consistently collected across ages and cohorts, and thus were utilised in this thesis.

In NCDS58, cohort members were assessed using 14 items at ages 7, 11, and 18 items at age 16, while the 19-item version was collected at ages 5, 10, 16 in BCS70 (Appendix 12). Exploratory factor analysis was carried out to establish items which represent externalising and internalising problems (Appendix 15 & Appendix 16). Eventually, four items (fights, disobedient, destructive, and irritable) were used for externalising problems and four items (being worried, solitary, fearful and miserable) for internalising problems. Originally item responses were “does not apply”, “apply sometimes”, and “certainly apply” and coded as 0, 1 and 2 respectively. Distribution of the sum score of externalising and internalising problems among complete cases is shown in Table 3.

Table 3 Sum of externalising and internalising score across sex and cohort

	NCDS58		
Male	Age 5/7 (n=7319)	Age 10/11 (n=6821)	Age 16 (5692)
Externalising score	2.3 ± 1.5	2.1 ± 1.5	0.9 ± 1.3
Internalising score	2.2 ± 1.6	2.5 ± 1.6	1.4 ± 1.5
Female	Age 5/7 (n=6933)	Age 10/11 (n=6480)	Age 16 (n=5432)
Externalising score	1.8 ± 1.5	1.6 ± 1.4	0.9 ± 1.2
Internalising score	2.3 ± 1.6	2.6 ± 1.6	1.5 ± 1.5
	BCS70		
Male	Age 5/7 (n=6698)	Age 10/11 (n=6750)	Age 16 (4123)
Externalising score	2.3 ± 1.7	1.5 ± 1.9	1.1 ± 1.4
Internalising score	1.6 ± 1.5	1.7 ± 1.9	1.3 ± 1.4
Female	Age 5/7 (n=6232)	Age 10/11 (n=6373)	Age 16 (n=4320)
Externalising score	1.7 ± 1.5	1.0 ± 1.5	1.1 ± 1.3
Internalising score	1.6 ± 1.5	1.8 ± 2.0	1.5 ± 1.6

3.1.2 Availability of alcohol use behaviours in adulthood

The CAGE questionnaire [222] and Alcohol Use Disorder Identification Test (AUDIT) [223], both well-known for detecting problematic drinking, were utilised in both cohorts as shown in Appendix 13. For cross-cohort comparisons, CAGE at age 33 in NCDS58 and age 34 in BCS70 and a shortened version of the AUDIT at age 44/45 in NCDS58 and age 46 in BCS70 were employed.

The CAGE questionnaire is a screening instrument for detecting alcoholism [279], which contains 4 questions: have you ever a. felt the need to Cut down your drinking; b. felt Annoyed by criticism of your drinking; c. had Guilty feelings about drinking and d. taken a morning Eye opener? A score of 2 or more indicates a propensity for AUD [222,279]. Prevalence of problematic drinking across sex and cohort is shown in Table 3.

The shortened version (AUDIT primary care, AUDIT-PC) contains five items scored 0-4 points: How often do you have a drink containing alcohol? (drinking frequency); How many units of alcohol do you drinking on a typical day when you are drinking? (drinking quantity); How often during the last year have you found that you were not able to stop drinking once you had started? (can't stop); How often during the last year have you failed to do what was normally expected from you because of your drinking? (fail to work); Has a relative or friend, doctor or other health worker been concerned about your drinking or suggested that you cut down? (cause concerns). A sum score of 5 or over indicated problematic drinking [223,280]. Prevalence of problematic drinking across sex and cohort is shown in Table 4.

Table 4 Prevalence of problematic drinking across sex and cohort

	NCDS58				BCS70			
	Age	N	Male	Female	Age	N	Male	Female
CAGE	33	10902	924 (17.2%)	437 (7.9%)	34	9193	1031 (23.4%)	650 (13.6%)
AUDIT-PC	44/45	8953	1933 (43.6%)	901 (20.0%)	46	8265	1217 (30.5%)	719 (16.7%)

Questions about drinking frequency and drinking amount vary across age and cohort (Appendix 14) but were directly comparable at age 33 in NCDS58 and age 34 in BCS70. Information on drinking frequency and drinking amount of different kinds of alcohol (mainly beer, wine, spirits and mixed drinks) in the past 7 days was collected across adulthood, but survey methods and questions were not identical across waves and cohorts. To ensure comparability, weekly alcohol use at age 34 in NCDS58 and at age 33 in BCS70 were retained. The number of drinks consumed was converted into UK weekly alcohol units (one unit equals 10ml or 8g of pure alcohol, which is around the average amount of alcohol one adult can process in an hour) using the following conversion: one pint of beer=two units, one pint of strong beer=three units, one pint of low alcohol beer=one unit, one glass of low alcohol wine=0.5 unit, 125ml glass of wine=one unit, 175ml glass of wine=two units, 225ml glass of wine=three units, one single measure of spirit=one unit, one glass of mixed drink=one unit [95]. For those who reported never or drank monthly or less, alcohol units were aligned to 0 units per week [281]. Distribution of drinking frequency and weekly drinking units across sex and cohorts is presented in Table 5.

3.1.3 Availability of potential confounding factors

Both cohorts collected a wide range of data covering health, physical, educational, social development and economic circumstances, providing a unique opportunity for cross-cohort comparisons. Based on previous literature [29,282], a series of potential confounding factors that were comparable across cohorts were selected. Information regarding how the variables were derived can be found in Table 6.

Table 5 Distribution of drinking frequency and weekly drinking units across sex and cohorts

	NCDS58 at age 34		BCS70 at age 33	
	Male	Female	Male	Female
Drinking frequency				
4+ times per week	952 (17.7%)	393 (7.1%)	999 (22.2%)	576 (11.7%)
1-3 times per week	2906 (54.1%)	2265 (40.6%)	2484 (55.2%)	2391 (48.6%)
2-3 times per month	814 (15.2%)	1342 (24.1%)	466 (10.4%)	692 (14.0%)
non-/occasional drinkers	700 (13.0%)	1574 (28.2%)	548 (12.2%)	1265 (25.7%)
Weekly drinking units				
5^{th} percentile	0	0	0	0
25^{th} percentile	3	0	3	0
50^{th} percentile	11	2	11	3
75^{th} percentile	24	7	22	8
95^{th} percentile	57	18	51	20
Mean $\pm$ SD	17.1 $\pm$ 20.8	5.0 $\pm$ 8.0	16.2 $\pm$ 19.4	5.8 $\pm$ 8.6

Table 6 Derivation of confounding factors

Variable	Age	Description
Maternal age at birth	0 in both NCDS58 and BCS70	In both NCDS58 and BCS70, maternal age at birth was collected
Breast-feeding or not	0 in both NCDS58 and BCS70	In both NCDS58 and BCS70, data were collected on whether the mother breastfed the infant or not
Pregnancy smoke	0 in both NCDS58 and BCS70	In NCDS58, mothers were asked how much they smoked per day before pregnancy and whether this behaviour changed during pregnancy. In BCS70, detailed question on whether the mother smoked during pregnancy and how much they smoked per day was collected. Binary variable indicating whether the mother smoked more than 1 cigarette on a daily basis was created.
Gestational days	0 in both NCDS58 and BCS70	Gestational days in both cohorts
Birthweight	0 in both NCDS58 and BCS70	In NCDS58, birthweight was recorded in ounces and transformed into grams; In BCS70, birthweight was recorded in grams
Social Class	0, 7, 11, 16 in NCDS58; 0, 5, 10, 16 in BCS70	Occupation of the father was coded according to the Registrar General's classification. Participant's current or most recent jobs were classified as: I (professional), II (managerial and technical), III (skilled non-manual/manual), IV (partly-skilled), and V (unskilled). Family with no male head or unemployed were coded as missing.
Parental education	0 in both NCDS58 and BCS70	In NCDS58, questions were asked on whether the mother and father continued to stay at school after minimum school leaving age (Yes/No); In BCS70, questions were collected on age when the mother and

		father left school. Because minimum school leaving age was raised to 16 in 1974, a cut-off point of age was applied.
Marital status	0, 7, 11, 16 in NCDS58; 0, 5, 10, 16 in BCS70	In both NCDS58 and BCS70, marital status of the mother was recorded. Married/stable union/twice married were coded into one category, and unmarried/widow/separated/divorce were coded into another category. Marital status at later ages mainly reflects whether the participants lived together with their natural parents at the moment. In NCDS58, when participants became 33 years old, they were asked to recall whether their parents had ever permanently separated or divorced, if so, how old they were when it happened. Marital status at age 7, 11 and 16 was then derived based on the above two questions. In BCS70, when participants were age 16, they were also asked to recall whether they lived with their natural parents at age 5, 10 and 16.
Read to child every week	7 in NCDS58 and 5 in BCS70	In NCDS58, how often mother and father read to the child was recorded (every week/occasionally/hardly ever). Those family where either mother or father read to the child every week were coded into one category (read to every week) and the rest into another category. In BCS70, questions on who read to the child most often and how many days the child was read to last week were collected. Those family where mother or father read to the child most often and days read to last week were greater than zero were coded into one category (read to every week) and the rest into another category.
House tenure	7 in NCDS58 and 5 in BCS70	In NCDS58, information on tenure of the accommodation was collected (owner occupied, council rented, private rented, rent free and other). In BCS70, similar information was also recorded (owned outright, being bought, council rented, private rented but unfurnished, private rented but furnished, tied to occupation and other). Thus, a binary variable indicates whether the accommodation is tenure was created (1=tenure, 0=non-tenure).
House amenity access	7 & 16 in NCDS58 and 5 & 16 in BCS70	In NCDS58, access (sole use, shared use, no facility) to household amenities (bathroom, indoor WC, outdoor WC, kitchen, hot water) was collected at age 7, 11, 16. In BCS70, access to household amenities (bathroom, indoor WC, outdoor WC, hot water, kitchen) at age 5 and access to household amenities (bathroom, indoor WC, hot water, kitchen) at age 16 were collected. Thus, binary variable indicating whether household had sole use of a bathroom, indoor WC, kitchen and hot water was created at age 7&16 in NCDS58 and at age 5&16 in BCS70.

Crowdness in the household	7, 11, 16 in NCDS58; 5, 10, 16 in BCS70	In NCDS58 and BCS70, number of people in the household and number of rooms (excluding kitchen, toilet, bathroom and any room used for business/trade) in the household was asked. Number of persons per room (up to 1, over 1 to 1.5, over 1.5) was then created. In BCS70, at age 16, total number of people in the household was calculated using number of people younger than the target, exactly same age with the target, older than the target but below age 21, older than 21, and number of room in the household was calculated using number of bedroom and number of other rooms.
Whether mother worked before child went to school	7 in NCDS58 and 5 in BCS70	In NCDS58, information on whether mother went to paid work outside the home since child's birth and before child started school (Part-time/temporary, full-time, has not worked); In BCS70, has mother had a regular full-time or part-time job out of the home since the time of N's birth which she subsequently gave up (full-time job, part-time job, both full and part-time job, never had a job out of the home, other). A binary variable indicating whether the mother had worked outside the home was created.
Separated with the child for more than one month	7 in NCDS58 and 5 in BCS70	In both NCDS58 and BCS70, question on whether the mother and the child were separated for more than one month was asked.
Interested in Education	11 in NCDS58 and 10 in BCS70	In NCDS58, level of mother and father's interest (over-concerned, very interested, some interest, little interest) in child's education was asked at age 7, 11 & 16. Same information was collected at age 10 in BCS70. Thus, those family where either mother or father showed great interest (over-concerned, very interested) in the child's education was coded as very interested, and those where both of the parents showed little interest were coded as little interest and the rest were coded as some interest. Variable was created for age 11 in NCDS58 and for age 10 in BCS70.
Times of family moves	7 in NCDS58 and 5 in BCS70	In both NCDS58 and BCS70, how many times has the family moved houses since child's birth. A three-category variable was created (no moves, 1-2 moves, 3+ moves)
BMI	11 & 16 in NCDS58 and 10 & 16 in BCS70	Height and weight were measured by trained medical personnel using standard protocols at age 7, 11 & 16 in NCDS58 and at age 10 & 16 in BCS70. Thus, BMI was created for both cohorts and were harmonised by the CLOSER consortium to facilitate comparisons across cohorts [283].

Cognitive ability	7, 11 in NCDS58 and 5, 10 in BCS70	In NCDS58, copy and design test, drawing a man, Southgate Group Reading Test, Problem arithmetic test was carried out at age 7; Copy and design, reading comprehension, mathematics test and general ability test was carried out at age 11; Reading comprehension and mathematic comprehension was done at age 16. In BCS70, copy and design test, drawing a man, English Picture Vocabulary test, Profile test, Reading test was done at age 5; tests carried out at age 10 includes Shortened Edinburgh Reading test, British Ability Scales, the CHES Pictorial Language Comprehension test, the CHES Friendly math test, Social Judgement scale, Diagnostic Measures; only Vocabulary and spelling test was done at age 16. Thus, for cross-cohort comparison, copy and design test and drawing a man were used at age 7 in NCDS58 and at age 5 in BCS70 (variables were transformed to be on the same scale); general ability test which contains verbal and non-verbal domain at age 11 in NCDS58 and British Ability Scales which contains four subsets (word definition and word similarity for verbal skills, recall of digits and matrices for non-verbal skills) at age 10 in BCS70 were used. For both cohorts, Principle Component Analysis was conducted to extract the common variance across verbal and non-verbal scales [284]. Specifically, for BCS70, items within each subset were first summed up, and Principle Component Analysis was applied to extract score for verbal and non-verbal scales separately. Then a general ability score was calculated by applying Principle Component Analysis to verbal and non-verbal scales. All variables were standardised to a mean of 0 and a SD of 1.
Medical conditions	7, 11 in NCDS58 and 5, 10 in BCS70	Whether a series of comparable medical conditions (eczema, hay fever and sneezing, ear discharge, sore throats, bronchitis, pneumonia, hearing difficulty) had ever happened were both collected at age 7 in NCDS58 and at age 5 in BCS70. Whether a series of medical conditions (recurrent sore throat/ear infection, eczema, hay fever, pathological heart condition, recurrent abdominal pain) happened last year was collected at age 11 in NCDS58 and at age 10 in BCS70. A series of medical conditions (Hay fever or allergic rhinitis, recurrent vomiting or bilious attacks, dysmenorrhoea, travel sickness, recurrent abdominal pains, recurrent throat and/or ear infections requiring treatment by a doctor, severe acne, eczematous rashes, psoriasis) were recorded at age 16 in both cohorts. Medical conditions were recoded into two categories (had >=2 medical conditions versus <=1 medical conditions)
Wet bed	7 in NCDS58 and 5 in BCS70	Whether child wet bed since age 5 was asked in NCDS58 and whether child wet bed at 5 years old was asked in BCS70

3.1.4 Analytic strategy

To explore the association between early life externalising and internalising problems and problematic drinking in adulthood, lagged logistic regression was carried out by adding early life externalising and internalising problems chronologically into the model [76]. To study how the association varied across developmental timing of externalising and internalising problems, post-hoc test was done to compare the coefficients of externalising/internalising problems across various ages [285]. To investigate how the association varied across sex and cohorts, interaction terms between externalising/internalising problems and sex and cohort were added [286]. A series of sensitivity analysis was performed to assess the robustness of the results. More details are presented in Chapter 4.

To investigate the mediating role of educational attainment on the pathway from adolescent externalising problems to adulthood problematic drinking across sex and cohorts, formal mediation analysis under the counterfactual framework was carried out [287]. More details are explained in Chapter 5.

3.2 Michigan Longitudinal Study (MLS)

MLS is a prospective longitudinal family study with participants at high risk for substance use disorder [288,289]. It was established in the mid-1980s with the primary aim of tracking and characterising childhood risk and protective factors for substance use disorders over the course of development.

3.2.1 Sample recruitment

The core group was preschool age children of alcoholics and a matched set of control children, and their biological parents. Families were initially ascertained through two methods. The first involved recruitment through all district courts in a four-county wide area surrounding Michigan’s capitol Lansing. Inclusion criteria were as follows: all men living in the area appearing in court for a drunk driving offense with a blood alcohol level of 0.15% if first arrest, or 0.12% if second or

more, who had a biological son between the ages of 3.0 and 5.11, and were living with the boy and his biological mother at time of contact. The second ascertainment was carried out through the neighbourhoods in which the court-recruited alcoholic men lived. Study entry was based on the same family demographics. Two subgroups were discovered in this process and recruited into the study: families where neither parent met a substance use disorder diagnosis were designated as controls, and families where fathers met diagnostic thresholds for an alcoholism diagnosis. Families where only mothers were diagnosed were not recruited. In addition to the original male participants and their biological parents (the original National Institutes of Health panel did not see a reason for including female participants because of the lower alcoholism base rate in them), all full biological siblings who were within eight years of age of the original male participants were recruited in later waves. In order to enrich the number of ethnic minority families in the sample, a 2nd phase of neighbourhood canvassing was carried out in those MLS recruitment neighbourhoods where minority families lived. Since this activity started later than the other sampling, the 6–8-year-old age range was selected as the starting point with males being the target children. Families where the parents separated during the study were still retained in the sample, and step-parents were surveyed where needed. As a result, the final sample involve 467 families (1050 target participants: 742 males, 308 females), 460 mothers, 450 fathers, as well as 84 stepparents. Compared to the British birth cohorts, the MLS has a higher proportion of minority groups (18.9%).

Assessment was carried out at 3-year intervals for all parents and children. In addition, a one-session assessment is carried out annually on all target participants between the ages of 11 and 26. A series of indicators of child, parent, family, peer group, school, and other environmental influences on risk and protective factors of alcohol use over the life course were collected. Scales that collected information related to stressful life events, drinking behaviours and other alcohol related time-varying risk factors are listed in Table 7.

Table 7 Available information on stressful life events, mental health status and alcohol use behaviours

Name of Instrument	A*	1	2	3	4	5	6	7	8	9	Subject of Data	Source of Data
Age		3-5	6-8	9-11	12-14	15-17	18-20	21-23	24-26	27-29		
Stress-related measures												
Childhood Conflict Tactics Scale [290]								√			YA	YA
Coddington Life Stressors [291,292]		√	√	√	√						C	P
						√	√	√	√	√	YA	YA
Family Social Health Indicators [293,294]		√	√	√	√	√	√	√	√	√	P	P
							√	√	√	√	YA	YA
Oregon Social Learning Centre Family	√	√	√	√	√	√	√	√	√	√	P	P
Crisis List [295]							√	√	√	√	YA	YA
Moos Family Environment Scale [296,297]		√	√	√	√	√	√	√	√	√	P	P
				√	√	√	√	√	√	√	C/YA	C/YA
Hassles & Uplifts Scale [298]		√	√	√	√	√	√	√	√	√	P	P
							√	√	√	√	YA	YA
Parent Daily Reports [299]		√	√	√	√							
Mental health measures												
Achenbach Child Behaviour Check List [300]		√	√	√	√	√					C	P
Achenbach Adult Behaviour Check List [301]					√	√	√	√	√	√	YA	P
Achenbach Teacher Report Form [302]			√	√	√	√					C	T
Achenbach Youth Self Report [303]	√				√	√					C	C
Achenbach Adult Self Report [301]	√				√	√	√	√	√	√	YA	YA
Child Behaviour Rating Scale [304]		√	√	√	√	√					C	P
Alcohol use behaviours												
Drinking & Drug History [305]	√		√	√	√	√	√	√	√	√	C/YA	C/YA
Peer Behaviour Profile [306]	√					√	√	√	√	√		

* C = Target Child; YA = Target Child as a Young Adult (includes young adult's partner if present); P=Parent (includes stepparent, partner of parent); T=Teacher; E=Examiner. A indicates whether the scale was collected yearly from age 11 to age 26.

3.2.2 Availability of stressful life events (SLE)

Family Crisis List is a 40-item list of family-related troubles covering seven domains (family, household, economy, health, school, legal, social) [307]. Parents of the target participants reported whether a particular event had ever happened to their family and if “Yes”, they indicated when this event occurred (last 6 months, 6 months to 1-year ago, 2-years prior). The event was counted as happening as long as it was reported by either of the parents. Upon reaching adulthood (ages 18-20), the target participants completed the Family Crisis List. Twenty-one events that were considered as serious crises in the family (e.g., conflict with ex-partner, physical fight, do not have enough money, injured/non-injured accident, someone died) were utilised to construct parent-reported SLE, while 15 events (excluding 6 events that were school-related and reported only by parents) were used for self-reported SLE. Counts of total SLE across waves are described in Table 8.

Table 8 Counts of stressful life events across waves

Wave	Age	N	Mean ± SD
Wave 0	12-13	636	4.82 ± 3.21
Wave 1	14-15	520	4.82 ± 3.11
Wave 2	16-17	537	4.85 ± 3.26
Wave 3	18-19	508	4.54 ± 3.06
Wave 4	20-21	481	1.99 ± 1.77
Wave 5	22-23	561	2.17 ± 1.75
Wave 6	24-25	497	2.05 ± 1.55
Wave 7	26-27	414	2.09 ± 1.76
Wave 8	28-29	298	1.95 ± 1.73

*****Events was parent-reported before age 20 and self-reported thereafter.

3.2.3 Availability of alcohol use behaviours

The Drinking and Drug History Questionnaire was used to collect information on the participants’ alcohol and drug use [305]. Items covered quantity, frequency, age of onset, and consequences and problems related to alcohol and drug use. As done in prior studies [308,309], a composite measure of problematic drinking could be calculated using number of drinking days per month, typical drinking quantity per occasion, maximum number of drinks consumed in 24 hours, and

number of intoxications in the past 12 months. Values on the four measures were recoded into a 0 to 8 scale (Appendix 33), and the mean of these values was used for the composite score. Level of the composite score across waves is shown in Table 9.

Table 9 Descriptive statistics for composite score of problematic drinking across waves

Wave	Age	N	Mean ± SD
Wave 0	12-13	935	0.07 ± 0.38
Wave 1	14-15	906	0.37 ± 0.94
Wave 2	16-17	878	1.21 ± 1.72
Wave 3	18-19	659	1.83 ± 1.83
Wave 4	20-21	611	2.61 ± 1.85
Wave 5	22-23	575	2.9 ± 1.66
Wave 6	24-25	513	2.89 ± 1.63
Wave 7	26-27	435	2.67 ± 1.61
Wave 8	28-29	303	2.59 ± 1.6

3.2.4 Availability of other alcohol-related risk factors

Several covariates associated with alcohol use were also collected. Time-invariant variables included sex, family history of alcoholism, adverse childhood experiences (ACEs) before age 11, and age at first drink. Time-varying variables included externalising problems, internalising problems, smoking status in the past year and number of marijuana use occasions in the past year and peer substance use behaviours.

Family history of alcoholism was operationalized as either mother or father meeting criteria for AUD at baseline, which was assessed using the Diagnostic Interview Schedule [224].

ACEs before age 11 was derived by aggregating items across several questionnaires that are consistent with the most recent operationalisation of ACEs (Appendix 36) [310,311]. Five items were taken from the Oregon Social Learning Centre Family Crisis List [295] assessed at Waves 1-3. Eight items were taken from the Conflict Tactics Scale [290] assessed at Wave 1. These same items directed towards the parent and their spouse was used to assess the child's exposure to domestic violence. A retrospective self-report measure of the Conflict

Tactics Scale was used to assess whether the adolescent experienced sexual or physical abuse or domestic violence between parents prior to age 11 in cases where parents did not endorse items from the Conflict Tactics Scale. Five items were taken from a modified version of the Coddington Family Events Questionnaire [291,292] assessed at Waves 1-3. Lastly, one item was included that reflected presence of a parental AUD as assessed using the Diagnostic Interview Schedule - Version IV [224]. Accordingly, a total of 21 items were used to derive a measure of ACEs. All items were first dichotomized to reflect whether the event occurred or did not occur. If an event was endorsed during multiple time points, the event was coded as 1 (i.e., max value = 21) rather than “double counting” an event.

Age at first drink was assessed with the question: “How old were you the first time you ever took a drink? Do not count the times when you were given a “sip” by an adult”. To reduce recall bias and the effect of outliers, age at first drink was recoded into four categories (below age 11, 12-14, 15-17, over age 18).

Externalising and internalising problems were assessed using the Achenbach Youth Self-Report [303] for ages 11-18 and the Adult Self-Report [301] for ages 18-59, which was collected at each assessment. To ensure comparability of scores across waves, only items that were included at all-time points were used to calculate externalising and internalising problem scores (see Appendix 37 for the selected items for externalising and internalising problems).

Last year smoking status (Never, Occasionally, Regularly) and number of marijuana use occasions (None, 1-19, 20 or more) were also collected at each assessment.

Peer involvement in substance use was assessed using Peer Behaviour Profile [306] (see Appendix 38 for items used to construct peer involvement in substance use). Different questions were asked at different ages, and sum scores were calibrated to ensure comparability [105].

3.2.5 Analytic strategy

To study the co-development of problematic drinking and stressful life events, group-based dual trajectory analysis was employed [197]. Specifically, individuals who had similar trajectories of both problematic drinking and stressful life events were grouped into latent classes. Then, distributions of other alcohol-related risk factors were compared across classes as an external validation. See Chapter 6 for more details.

4. Chapter 4 Association between early life mental health and alcohol use behaviours across adulthood: evidence from two British birth cohorts

4.1 Introduction

As shown in Chapter 2, empirical evidence on the association between early life externalising and internalising problems and alcohol use behaviours, especially in mid-adulthood, is still quite limited. Moreover, how externalising and internalising problems interact with sex, historical period and contribute to the development of problematic drinking in the British context is not known. There is a need to enhance knowledge on the early life aetiological mechanisms underlying problematic alcohol use in adulthood.

From a developmental perspective, developmental timing, sex, history and culture are key factors to take into consideration to understand the causes and course of alcohol use and abuse [90,92,93]. Lack of consideration of these factors may contribute to the inconsistency in the literature regarding the associations between externalising and internalising problems and alcohol outcomes. As discovered in Chapter 2, externalising and internalising problems are typically measured at one-time point (mainly adolescence), which ignores their potential changes across childhood and adolescence [105,125,312]. In other words, the association between one-time-point externalising or internalising problems and alcohol outcomes, estimated using variable-based analysis, may be contaminated by the persistence of those mental problems. As a result, the direction of the association might depend on the proportions of individuals with heterogenous trajectories of externalising and internalising problems in the sample (see section 1.5.1). Similarly, alcohol use behaviours are mainly measured during adolescence and early adulthood, the years during which drinking is typically initiated and escalated [109] and more influenced by contextual factors (e.g., parenting and peers' drinking behaviours) [100,101]. In contrast, drinking in mid-adulthood stabilizes and is more of a self-decision [25,95,98]. Therefore, more empirical work is warranted to examine whether the

associations between externalising and internalising problems and alcohol use behaviours endure into mid-adulthood. And if they do, the question is whether there is a potential critical period of externalising and internalising problems, when high level of problems is linked to higher risk of problematic drinking. Such evidence would have some implications on policymaking regarding the utility of intervening on early life externalising and internalising problems to alleviate alcohol burden in mid-adulthood and when to intervene. In addition, as shown in Chapter 2, there is a lack of evidence on the potential interactions between externalising and internalising problems and sex/historical period. Evidence on this could help inform which population to target (male versus female) and the potential benefits of interventions targeted at different generations.

In NCDS58 and BCS70, scales on mental health problems were collected across childhood and adolescence, and scales on drinking behaviours were collected well into mid-adulthood. This provides a unique opportunity to examine the associations between externalising and internalising problems and drinking behaviours from a developmental perspective, including whether the associations lasted into mid-adulthood; whether there existed a time-point when manifestation of externalising and internalising problems were more strongly associated with later drinking behaviours; whether the strength of the associations differed between male and female; whether the associations changed over two generations born 12 years apart.

As the associations between early life externalising and internalising problems and adulthood drinking may vary across subtypes of alcohol use behaviours (as shown in Chapter 2), problematic drinking was used as the main drinking outcome, and weekly alcohol units as a secondary outcome.

To summarise, this chapter aims to investigate the associations between externalising and internalising problems across childhood and adolescence with problematic drinking in mid-adulthood in the UK and whether there is a potential historical effect in the form of secular changes and sex differences in the associations.

4.2 Methods

4.2.1 Sample

Two British birth cohorts born 12 years apart were utilised: the 1958 National Child Development Study (NCDS58) and the 1970 British Birth Cohort (BCS70). The NCDS58 recruited over 17,000 babies born in Great Britain during one week in March 1958, and 10 waves of data have been collected by 2013. BCS70 was designed along similar lines to NCDS58, surveying over 17,000 babies born in Great Britain in one week in April 1970 with 9 waves of data by 2016. Details about both cohorts are available elsewhere [274,275], and both NCDS58 and BCS70 can be accessed from the official website of the UK data archive (http://www.data-archive.ac.uk/).

4.2.2 Measures

Tools used to assess externalising and internalising problems, alcohol outcomes and potential confounding factors varied across waves and cohorts. To explore the potential cohort effect in the associations between externalising and internalising problems and problematic drinking, variables that were consistently collected across cohorts were retained and harmonised for analysis.

Early life mental health problems

Externalising and internalising problems were measured with the parent-rated Rutter Behaviour Questionnaire [277]. In NCDS58, cohort members were assessed using 14 items at ages 7 and 11, and 18 items at age 16, while the 19-item version was collected at ages 5, 10 and 16 in BCS70 (Appendix 12). Exploratory factor analysis was carried out to establish items that represent externalising and internalising problems (see Appendix 15 and Appendix 16 for factor loadings). Balancing the availability of items and their factor loadings for each latent domain, four items (fights, disobedient, destructive and irritable) were used to construct externalising problems (α=0.57, 0.55 and 0.57 for ages 7, 11 and 16, respectively, in NCDS58; α=0.64, 0.61 and 0.64 for ages 5, 10 and 16,

respectively, in BCS70) and four items (being worried, solitary, fearful and miserable) for internalising problems (α=0.44, 0.43 and 0.52 for ages 7, 11 and 16, respectively, in NCDS58; α=0.49, 0.54 and 0.60 for ages 5, 10 and 16, respectively, in BCS70). The internal reliabilities for mental health problems are comparable to previous studies [76,83,228].

Problematic drinking

The CAGE questionnaire is a screening instrument for detecting alcoholism [279], which contains 4 binary questions as describe in section 3.1.2. The questionnaire was collected at age 33 in NCDS58 and at age 34 in BCS70. A score of 2 or more indicates a propensity for AUD [222,279].

The AUDIT (Alcohol Use Disorder Identification Test) was developed by the World Health Organization (WHO) to identify those with hazardous and harmful patterns of alcohol consumption [313]. The full AUDIT with ten questions on drinking behaviours last year was collected at ages 44/45 in NCDS58, but only the primary-care AUDIT (AUDIT-PC) with five questions was collected at age 46 in BCS70 and thus was used in the current study (details on the five questions is described in section 3.1.2 and their distribution in Appendix 31). For simplicity, age 45 was used to refer to this timepoint throughout the thesis. A score of 5 or over indicated problematic drinking [223,280].

Potential confounders

As described in section 3.1.3, potential confounding factors include birth weight (grams), gestational age (days), maternal smoking during pregnancy, maternal age at birth (years), ever being breastfed, whether mom stayed at school after minimum school leaving age, whether father stayed at school after minimum school leaving age, parents' marital status (birth, ages 5/7, 10/11 and 16), father's social class (birth, ages 5/7, 10/11 and 16), whether parents read to child weekly (age 5/7), housing tenure (age 5/7), household amenities (bathroom, indoor toilet, kitchen and hot water) (ages 5/7 and 16), person room ratio in the house (ages 5/7, 10/11 and 16), whether mother worked before child went to school (age 5/7),

whether the mother was separated from the child for more than one month (age 5/7), parents' interest in child's education (age 10/11), how many times family has moved (age 5/7), body mass index (ages 10/11 and 16), cognitive ability (age 5/7 and 10/11), physical health conditions (ages 5/7 and 10/11), and bedwetting (age 5/7).

4.2.3 Statistical analysis

When estimating the association of childhood and adolescent externalising and internalising problems with problematic drinking in adulthood, three sources of bias commonly present in observational studies need to be taken into account: measurement error, residual confounding and missing data related selection bias [179,251].

With respect to measurement error, Item Response Theory models were applied to derive continuous latent scores at each wave in childhood and adolescence, allowing the externalising and internalising scores to be correlated [314] (Appendix 17). High latent scores indicate higher externalising or internalising problems, respectively.

The conceptual framework that guided the analysis is presented in Figure 14. Externalising and internalising problems were assumed to be associated with problematic drinking directly and indirectly through their later status. At the same time, time-invariant and time-varying confounding factors may bias the associations. More importantly, as confounding factors such as genes and family alcoholism history were not collected in the cohorts, the associations after adjusting for observed confounders may still be biased by residual/unmeasured confounding. Therefore, based on the findings that high co-occurrence between externalising and internalising problems is mainly due to a common cause [106,315–318], it could be argued that externalising and internalising problems at the same age should be adjusted simultaneously to minimise bias due to unmeasured/residual confounding. For example, by adjusting externalising problems at age 6, the spurious association between internalising problems at age 6 and problematic drinking due to unmeasured common causes of

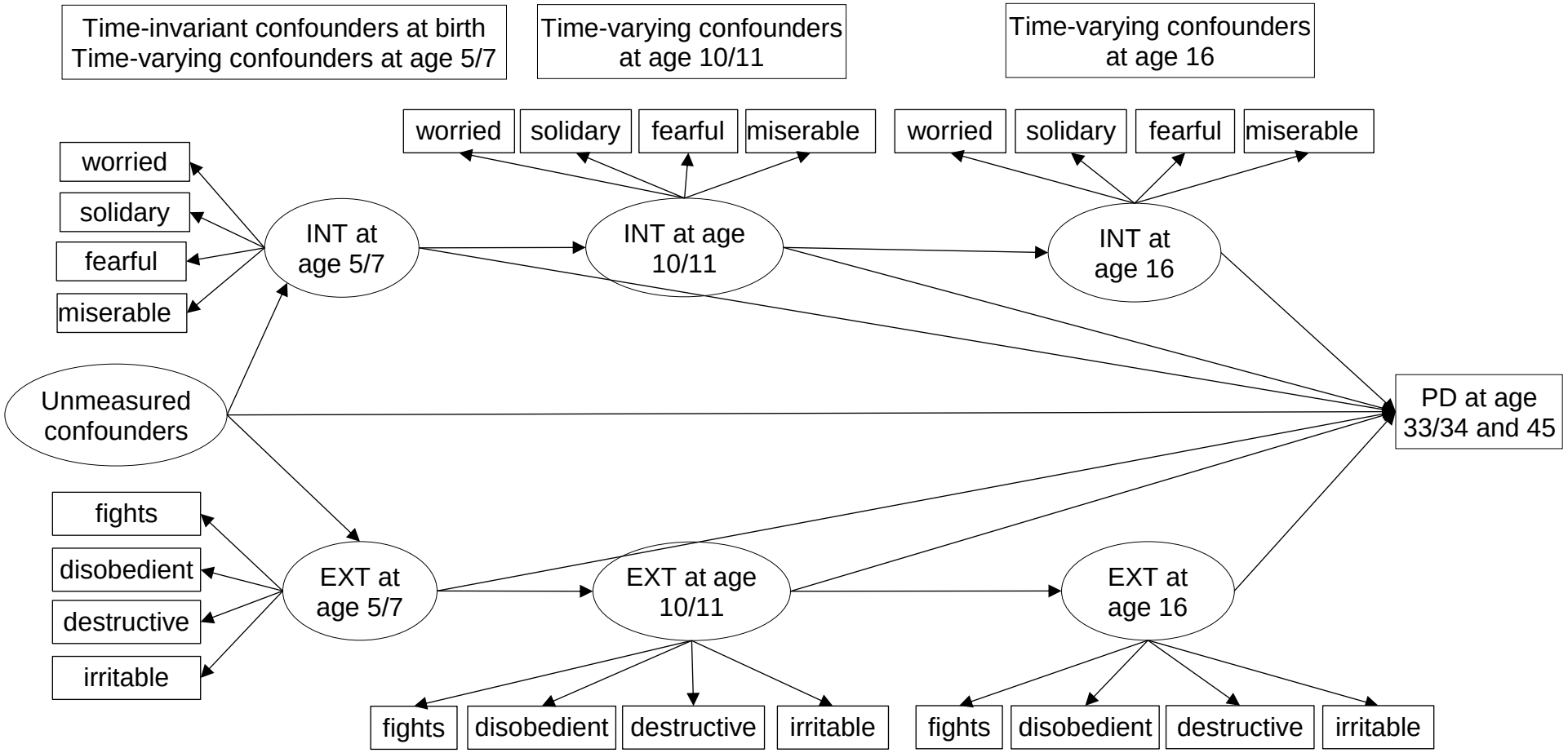


Figure 14 Conceptual framework*

*EXT = externalising problems; INT = internalising problems; PD = problematic drinking. For clarity, arrows from confounders to externalising and internalising problems at each age and alcohol behaviour are not shown.

externalising and internalising problems was blocked (internalising problems at age 6 ← unmeasured confounding factors → externalising problems at age 6 → alcohol behaviours) [181,182]. Similarly, the use of lags at ages 5/7 and 10/11 has the potential to block paths from unmeasured confounders in the associations between externalising and internalising problems at ages 10/11 and 16 with problematic drinking in mid-adulthood, respectively.

Both NCDS58 and BCS70 are nation-wide representative samples of British population. The target population for both cohorts was those who were born in the Great Britain and were still alive by the time the outcomes were assessed. Thus, the analytic sample size in NCDS58 is 16600 (Male=8511, Female=8089) by age 33, 16336 (Male=8349, Female=7987) by age 44/45. Similarly, in BCS70 it is 16655 (Male=8601, Female=8054) by age 34, 16593 (Male=8586, Female=8007) by age 46 in BCS70. Due to the attrition over four decades (Appendix 18), multiple imputation (MI), which can benefit from the rich information available in the cohorts, was used to deal with missing data [269,319]. Details on how MI was implemented were described in the next section.

The analysis was carried out in two stages. In the first stage, lagged logistic regression was carried out by adding externalising scores, internalising scores and corresponding confounders chronologically to explore the direction of the association and the potential critical period of externalising and internalising problems. For example, externalising and internalising scores at age 5/7 and confounders measured at birth and at age 5/7 were first included in Model 1 as in (1.1), and then externalising and internalising scores and time-varying confounders at age 10/11 were further added in Model 2 as in (1.2). Last, all potential confounders and previous externalising and internalising scores were included in Model 3 as in (1.3).

To test the potential critical period of experiencing externalising and internalising problems with respect to their association with later problematic drinking, post-hoc comparisons were conducted. By adjusting previous externalising and internalising problems, the associations between later externalising and internalising problems would not be influenced by the constitution of the

heterogeneous trajectories of externalizing and internalising problems in the population (see section 1.5.1 for more explanations). The strength of the association would represent the risk of problematic drinking between individuals with 1-unit difference in externalising or internalising problems assuming they had same level of prior externalising and internalising problems. For instance, comparisons were made to see whether the coefficient of externalizing scores at age 5/7 in Model 1, at age 10/11 in Model 2 and at age 16 in Model 3 were equivalent to each other. Increase in Type I error due to multiple comparisons was corrected using conservative Bonferroni correction [320], and a threshold of 0.017 (0.05/3) for *P* value was selected.

In the second stage, interactions of externalising and internalising problems at each age with sex and cohort were investigated. This was achieved by adding interaction terms into the previous models as in (2.1) - (2.3).

Weekly alcohol units at age 33 in NCDS58 and at age 34 in BCS70 were selected as a secondary outcome [321]. Since alcohol units per week were highly skewed, lagged quantile regression was carried out at 25%, 50%, 75% of the distribution [322].

Model 1:

$$\text{Logit (PD)} = \alpha+\text{INT1}+\text{EXT1}+\text{Sex}+\text{Cohort}+\text{C0}+\text{C1}+\varepsilon \quad (1.1)$$

Model 2:

$$\text{Logit (PD)} = \alpha+\text{INT1}+\text{INT2}+\text{EXT1}+\text{EXT2}+\text{Sex}+\text{Cohort}+\text{C0}+\text{C1}+\text{C2}+\varepsilon \quad (1.2)$$

Model 3:

$$\text{Logit (PD)} = \alpha+\text{INT1}+\text{INT2}+\text{INT3}+\text{EXT1}+\text{EXT2}+\text{EXT3}+\text{Sex}+\text{Cohort}+\text{C0}+\text{C1}+\text{C2}+\text{C3}+\varepsilon \quad (1.3)$$

Model 4:

$$\text{Logit (PD)} = \alpha+\text{INT1}+\text{EXT1}+\text{Sex}+\text{Cohort}+\text{Sex*Cohort}+\text{Sex*EXT1}+\text{Sex*INT1}+\text{Cohort*EXT1}+\text{Cohort*INT1}+\text{C0}+\text{C1}+\varepsilon \quad (2.1)$$

Model 5:

$$\text{Logit (PD)} = \alpha+\text{INT1}+\text{INT2}+\text{EXT1}+\text{EXT2}+\text{Sex}+\text{Cohort}+\text{Sex*Cohort}+\text{Sex*EXT2}+\text{Sex*INT2}+\text{Cohort*EXT2}+\text{Cohort*INT2}+\text{C0}+\text{C1}+\text{C2}+\varepsilon \quad (2.2)$$

Model 6:

$$\text{Logit (PD)} = \alpha+\text{INT1}+\text{INT2}+\text{INT3}+\text{EXT1}+\text{EXT2}+\text{EXT3}+\text{Sex}+\text{Cohort}+ \text{Sex*Cohort}+\text{Sex*EXT3}+\text{Sex*INT3}+\text{Cohort*EXT3}+\text{Cohort*INT3}+\text{C0}+\text{C1}+\text{C2}+\text{C3}+\varepsilon \quad (2.3)$$

* PD = problematic drinking (Yes/No); EXT1/EXT2/EXT3 = externalising problems at age 5/7, age 10/11 and age 16 respectively; INT1/INT2/INT3 = internalising problems at age 5/7, age 10/11 and age 16 respectively; C0/C1/C2/C3 = confounding factors at birth, age 5/7, age 10/11 and age 16 respectively.

4.2.4 Multiple Imputation with chained equations

Multiple imputation using chained equations (MICE) was implemented to impute attrition and item non-response mainly for two reasons. First, MICE has the flexibility to model each variable based on its respective distribution and release the multivariate normality assumption needed for multivariate normal imputation. With binary outcomes and many other categorical variables as in the current study, MICE was shown to have a better performance [323]. Second, the data-driven approach has shown MICE has the capability to restore representativeness of the original sample in the cohort study [324].

To increase the plausibility of the Missing At Random (MAR) assumption and improve imputation for the missingness of the outcome, auxiliary variables were incorporated in the imputation stage, including smoking habit (never, used to smoke, current smoker), drinking frequency (special occasion/never, 2~3 times per month, 1~3 times per week, 4+ times per week) and weekly alcohol units at ages 26, 33 and 42 in NCDS58 and at ages 23, 34 and 42 in BCS70 [324]. These auxiliary variables were all significant predictors of later problematic drinking (Appendix 19), and thus could help improve the imputation of missing outcomes and statistical efficiency [269,325,326].

As missing data in multi-item instruments were best handled by imputing at the item level [327,328], multi-item scales (CAGE/AUDIT-PC) were imputed at the item level. To avoid convergence problems, the sum score of each scale was used instead of item score as predictors in any imputation model [328]. In other words, for the imputation of non-scale variables, the sum score rather than each item was included in the imputation model, and for the imputation of each item, the sum score of all the other items within the scale was included instead of each item within the scale.

To ensure compatibility between the analytical model with interaction terms and the MI model, imputation was carried out separately for the four subgroups of interest (males/females in NCDS58/BCS70) [286]. The target population

consisted of those people who were still alive at the age when the outcome of interest was measured.

Binary variables were imputed using logistic regression; ordered categorical variables were imputed using ordinal logistic regression; un-ordered categorical variables were imputed using multi-nominal logistic regression; continuous and normal-distributed variables were imputed using linear regression; highly skewed variables including externalising and internalising problems at all ages, and weekly alcohol units across adulthood were imputed using the predictive mean match method [329].

One hundred and fifty datasets were imputed based on a two-stage calculation to ensure the precision of standard error estimates (how_many_imputations package in Stata) [330]. Distributions of complete and imputed variables were checked for abnormal imputation [331,332]. Standard MI with imputed outcome values was done in the analysis stage, as it is shown to provide robust parameter estimates in the presence of auxiliary variables associated with an incomplete outcome [326].

4.2.5 Sensitivity analysis

Several sets of sensitivity analysis were carried out to assess the robustness of the results.

First, though latent scores are deemed to better capture the latent trait behind externalising and internalising problems and are utilised in the main analysis, the sum scores of externalising and internalising items were calculated and entered in the model to examine whether the association pattern differed from that when utilising latent externalising and internalising score.

Second, latent scores of externalising and internalising problems were modelled simultaneously to minimise the confounding of unmeasured confounders, but the high correlation between them (Appendix 17) could cause the issue of potential multicollinearity and jeopardise the estimation of coefficients and standard error.

Therefore, they were added into the lagged logistic regression model separately to examine potential problems of multicollinearity. In addition, a general psychological factor, which captures covariation between externalising and internalising problems, was derived to further articulate their respective roles in each other's relationship with problematic drinking.

Third, the endorsement of items that reflect more on problematic drinking (such as can't stop, fail to work, cause concerns) was low in the population (Appendix 31). As a result, compared to the full AUDIT scale, participants classified as problematic drinkers based on AUDIT-PC were mainly those who scored high either on drinking frequency or drinking quantity, which may lead to false positives of problematic drinking (Appendix 32). Sensitivity analysis was carried out using both full and short versions of AUDIT at age 44/45 in NCDS58 to investigate potential bias due to misclassification.

Fourth, several well-established risk factors for alcohol use, such as alcohol-metabolising genes, parental alcohol use problems and peer's drinking behaviours were not available and thus not adjusted in the analysis. To assess the susceptibility of our results to potential unmeasured confounding factors, the E-Value was calculated and reported alongside the main results. The E-value evaluates the minimum strength, on risk ratio scale, that an unmeasured confounder would need to have with both exposure and the outcome in order to fully explain away the observed association, conditional on the measured confounding factors [333]. The larger an E-value is, the more strength an unmeasured confounding would need to have to explain away an effect estimate. Thus, E-value is particularly helpful in making causal inference using observational studies.

Fifth, analysis including observations with imputed outcomes may lead to bias if the model for imputing the missing outcomes was mis-specified [334]. Thus, the multiple imputation then deletion method was carried out as a sensitivity check [334].

4.3 Results

4.3.1 Association between externalising and internalising and problematic drinking

As is shown in Table 10, externalising and internalising problems at each age were associated in opposite directions with problematic drinking, and these associations persisted across mid-adulthood. Externalising problems acted as a risk factor for problematic drinking in mid-adulthood while internalising problems acted as a protective factor. Post hoc comparisons indicate that the strength of the association (absolute value of the coefficients) with problematic drinking did not differ significantly between externalising and internalising problems.

The size of the E-value ranged from 1.20 to 1.29, which means an unmeasured confounding factor would still need to be associated with both externalising or internalising problems and problematic drinking at a risk ratio of 1.20 to 1.29 to nullify the observed association between externalising or internalising problems and problematic drinking to 1. The strength needed to render the confidence interval to include 1 was smaller (1.08 to 1.22), as expected.

4.3.2 Critical period of early life mental health

Post hoc comparisons show that the strength of the associations between externalising problems measured at age 5/7, age 10/11 and age 16 and problematic drinking did not differ from each other, nor did the association between internalising problems at various ages and problematic drinking.

Table 10 Association between externalising and internalising problems and problematic drinking at age 33/34 and age 45 in two British birth cohorts[#]

	PD (CAGE) at age 33/34					
	Model 1	E-value[&]	Model 2	E-value	Model 3	E-value
EXT at age 5/7	1.10 (1.05,1.15)***	1.28 (1.18)	1.07 (1.02,1.12)**	NA	1.05 (1.00,1.10)	NA
INT at age 5/7	0.96 (0.92,1.00)	1.17 (1.00)	0.97 (0.93,1.02)	NA	0.98 (0.93,1.02)	NA
EXT at age 10/11			1.09 (1.04,1.15)***	1.26 (1.16)	1.05 (1.00,1.11)*	NA
INT at age 10/11			0.95 (0.92,0.99)*	1.19 (1.08)	0.97 (0.93,1.01)	NA
EXT at age 16					1.11 (1.06,1.16)***	1.29 (1.20)
INT at age 16					0.93 (0.87,0.99)*	1.23 (1.08)
N	33255		33255		33255	
	PD (AUDIT) at age 45					
EXT at age 5/7	1.06 (1.03,1.10)***	1.20 (1.14)	1.05 (1.01,1.09)*	NA	1.03 (0.99,1.08)	NA
INT at age 5/7	0.94 (0.91,0.98)***	1.21 (1.11)	0.96 (0.93,1.00)*	NA	0.97 (0.94,1.01)	NA
EXT at age 10/11			1.07 (1.03,1.11)**	1.22 (1.14)	1.03 (0.99,1.08)	NA
INT at age 10/11			0.94 (0.91,0.97)***	1.21 (1.14)	0.96 (0.93,0.99)*	NA
EXT at age 16					1.11 (1.07,1.15)***	1.29 (1.22)
INT at age 16					0.90 (0.86,0.94)***	1.29 (1.21)
N	32929		32929		32929	

[#]EXT = externalising problems; INT = internalising problems; PD = problematic drinking. Confounding factors were added chronologically as described in the method section. Logistic regression was run, and thus results are reported as OR (95%).

[&]NA refers to not applicable. The value outside the bracket is E-value for the point estimate, and the value in the bracket is E-value for the limit of the confidence interval closest to the null (the strength needed to move the confidence interval to include 1).

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

4.3.3 Interaction with sex and cohort

Evidence for an interaction between externalising and internalising problems and sex in predicting the probability of problematic drinking was only detected when they were measured at age 16, not at younger ages (Table 11). There was evidence for an interaction between externalising problems at age 16 and sex on its association with problematic drinking at age 33/34 (P=0.028) but not at age 45 (P=0.397). Specifically, the association between externalising problems at age 16 and problematic drinking at age 33/34 was observed only in males, while externalising problems were associated with problematic drinking at age 46 in both males and females. For internalising problems, an interaction with sex was detected for problematic drinking at both age 33/34 and age 45, and the association was stronger in males. These differences are illustrated in Figure 15.

No interaction between externalising and internalising problems at any age and cohort on its association with problematic drinking was found.

Table 11 Interaction between externalising and internalising problems and sex/cohort regarding their association with problematic drinking at age 33/34 and age 45 in two British birth cohorts*

	Main effect	P value	Interaction with sex	P value	Interaction with cohort	P value
	PD at age 33/34 (CAGE)					
EXT at age 5/7	1.14 (1.04,1.25)	0.004	0.93 (0.85,1.02)	0.136	1.02 (0.93,1.11)	0.688
INT at age 5/7	1.01 (0.94,1.1)	0.713	0.95 (0.88,1.04)	0.268	0.95 (0.88,1.02)	0.162
EXT at age 10/11	1.10 (1.01,1.21)	0.027	1.01 (0.93,1.10)	0.826	0.98 (0.90,1.06)	0.606
INT at age 10/11	0.98 (0.91,1.06)	0.616	0.96 (0.89,1.03)	0.256	1.00 (0.93,1.08)	0.990
EXT at age 16	1.06 (0.98,1.14)	0.166	1.10 (1.01,1.19)	0.028	0.99 (0.92,1.07)	0.833
INT at age 16	1.09 (0.98,1.20)	0.109	0.81 (0.73,0.90)	<0.001	0.95 (0.86,1.05)	0.290
	PD at age 45 (AUDIT-PC)					
EXT at age 5/7	1.12 (1.05,1.20)	0.001	0.9 (0.84,0.96)	0.003	1.03 (0.96,1.12)	0.379
INT at age 5/7	0.92 (0.87,0.98)	0.007	1.04 (0.97,1.11)	0.293	1.00 (0.94,1.07)	0.970
EXT at age 10/11	1.04 (0.97,1.11)	0.263	1.00 (0.93,1.08)	0.956	1.05 (0.98,1.13)	0.163
INT at age 10/11	0.96 (0.91,1.02)	0.183	0.98 (0.92,1.05)	0.612	0.97 (0.91,1.03)	0.349
EXT at age 16	1.07 (1.00,1.13)	0.037	1.03 (0.96,1.10)	0.397	1.05 (0.98,1.11)	0.164
INT at age 16	0.95 (0.88,1.03)	0.211	0.90 (0.83,0.99)	0.026	0.98 (0.9,1.07)	0.707

*EXT = externalising problems; INT = internalising problems; for the interaction term, female and NCDS58 were the reference groups; Confounding factors were added chronologically as described in the method section; Logistic regression was run, and thus results are reported as OR (95%CI).

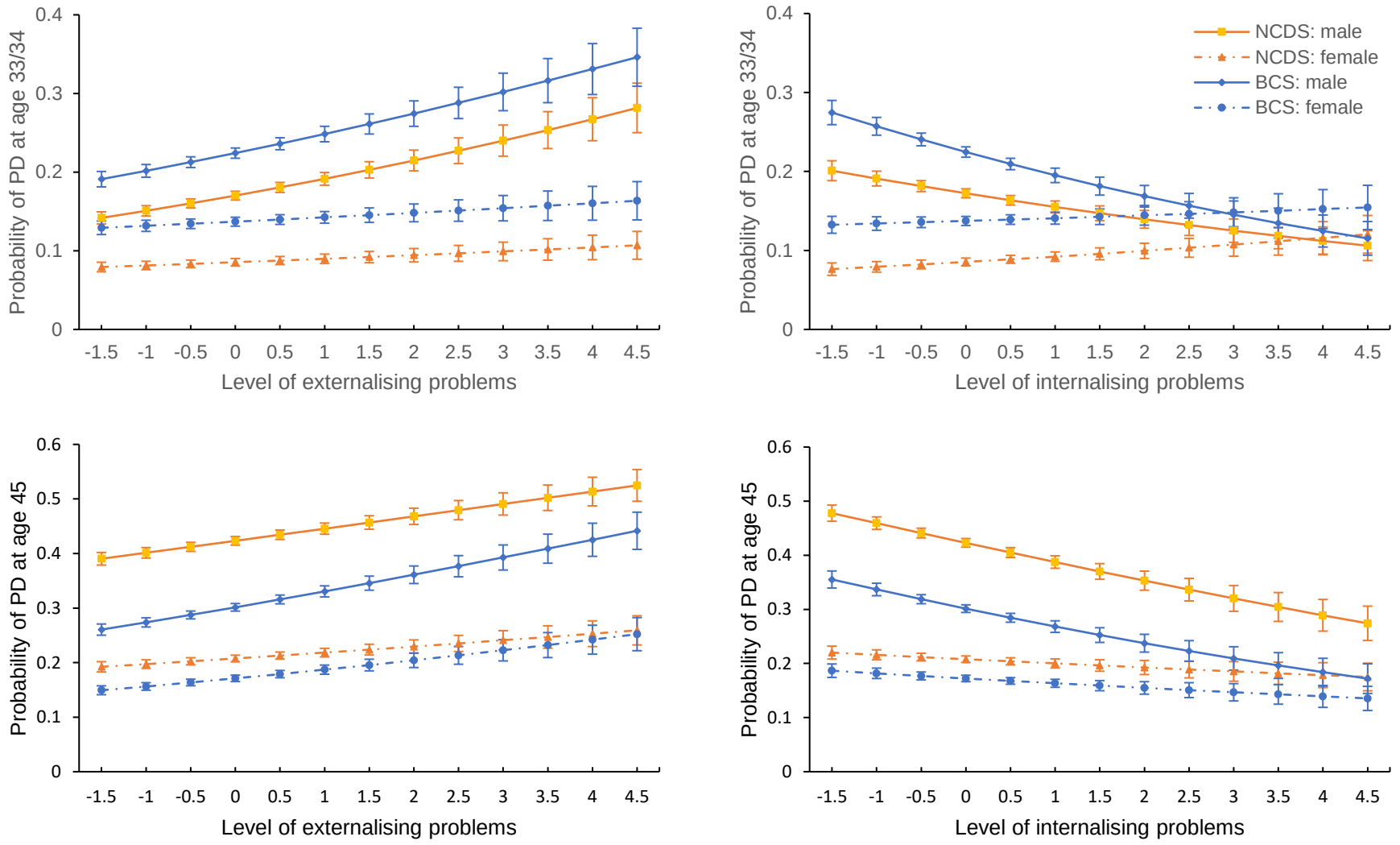


Figure 15 Probability of problematic drinking (PD) at different level of externalising and internalising problems at age 16

4.4 Discussion

4.4.1 Main findings

By analysing data from two population-based prospective British birth cohorts born in 1958 and 1970, externalising problems across childhood and adolescence act as a risk factor for problematic drinking in adulthood. In the British context, a negative association between internalising problems and problematic drinking was observed, which indicates that children and adolescents with greater internalising problems were less likely to engage in problematic drinking in adulthood than those who had fewer internalising problems. No critical period of externalising and internalising problems regarding their associations with problematic drinking was detected. Strength of the associations did not differ across cohorts but did so across sex, being stronger in males.

4.4.2 Externalising problems and problematic drinking

Consistent with prior research which found positive associations between early life externalising problems and drinking behaviours into mid-adulthood [27,235,238], the current study provides further evidence on this association using two national representative cohorts. Debates are still going on about the best characterization that encompasses the diverse behaviours in the externalising domain. Behavioural under-control/disinhibition, which refers to “a vulnerability of disinhibitory processes that involves the inability or unwillingness or failure to inhibit behaviour even in the face of anticipated or already received negative consequences”, seems to make the best sense [74,335]. The four items (fights, disobedient, destructive, and irritable) utilised to construct externalising behaviours in the current study fell into the domain of under-control/disinhibition [336], and they all contributed to the externalising construction equally (Appendix 17). This emphasizes the persistence and continuity of behavioural under-control/disinhibition and its potential influence on problematic drinking even after four decades of life changes.

4.4.3 Internalising problems and problematic drinking

Prior research is quite inconsistent regarding the association between early life internalising problems and alcohol use behaviours in adulthood [76,131,208,235,337–340]. This may be due to methodological differences, since studies that found positive associations either measured alcohol outcomes in adolescence or early adulthood (from age 16 to age 25) and did not adjust for externalising problems or were conducted in American/Australian settings [208,339]. By comparison, studies reporting negative associations either measured alcohol outcomes at mid/late adulthood (age 26 onwards) and adjusted for externalising problems [76,131,235] or were conducted in the UK [76,235]. Thus, the developmental stage at which alcohol behaviours were measured, whether externalising problems was adjusted for simultaneously as well as the context might explain part of the divergences among studies.

First, the association between childhood/adolescent internalising problems and alcohol use behaviours may vary with the developmental period of the latter, and childhood/adolescent internalising problems may act as a protective factor for drinking in mid/late adulthood. Adolescence is a period of changes physically, psychologically and socially when drinking alcohol is more affected by social norms, peer influences or parents' monitoring [100,212,341,342], whereas early adulthood is a period when individuals experience a series of role transitions which could also contribute to their drinking behaviours [91,343]. By comparison, people's drinking behaviour during mid/late adulthood is typically more stable [95,344]. Gene-environment studies discover that heritability for alcohol use increases from adolescence to young adulthood before stabilizing [345–347]. Evidence also show that childhood and adolescent antecedents and drinking by age 20 explained more variance of problematic drinking in mid-adulthood (43% in males, 31% in females) than that in young adulthood (31% in males, 19% in females) [88]. Therefore, drinking in mid/late adulthood may reflect more of its origins back in childhood and adolescence.

Second, the association between internalising problems and alcohol use behaviours may vary across populations. The proposed internalising pathway to

alcohol use/disorder, claiming that people with internalising problems might use alcohol to self-medicate or be accepted by peers [73], might not be the primary pathway in the British context. As discussed in section 2.4.2, how internalising problems were constructed may influence the direction of their association with drinking behaviours. In this study, internalising problems were featured as being solitary, fearful of new things, worried about many things and miserable/tearful. Consequently, in the UK context, where alcohol has mainly been used as a way of socializing since it became popular after World War II [348,349], people with internalising problems constructed as above may reduce their exposure to alcohol by avoiding going to pubs, bars or clubs. This aligns with the hypothesis that internalising tendencies towards social withdrawal and fear of negative consequences may decrease the risk of problematic drinking through reducing one's exposure to alcohol use [350], and does not support the hypothesis that social withdrawal may delay the onset of alcohol use but not necessarily decrease later alcohol involvement [73]. Current results indicate that the protective effect of social withdrawal persists into mid-adulthood in the UK context, and are consistent with another UK-based study [235].

Lastly, the results also support the possibility that not adjusting for externalising problems could introduce residual confounding in the association between internalising problems and alcohol outcomes [255,351,352]. This opposite direction of externalising and internalising problems regarding their associations with alcohol outcomes was also found in previous studies where externalising and internalising problems were included in the model simultaneously [76,83,211,243,350,352], and these findings were not limited to the UK setting or drinking behaviours in mid/late adulthood. In the current study, systematic attenuation of the association was observed when externalising and internalising problems were added into the model separately (Appendix 20, Appendix 21 and Table 10). To illustrate with DAG, when externalising problems were not adjusted for, the association between internalising problems and problematic drinking was a combination of two paths. One represented the path of interest (internalising problems→ problematic drinking) and the other one carried a spurious association (internalising problems ← unmeasured confounders → externalising

problems → problematic drinking) which was positive (Figure 16). Thus, when externalising problems were left out of the model, the true association of interest which was negative could be attenuated, cancelled out or even reversed depending on the strength of the association between externalising problems and alcohol outcomes in the population. [104,106]. The distribution of weekly alcohol units and prevalence of problematic drinking in mid-adulthood across different levels of externalising and internalising problems further supported this observation (Appendix 26 and Appendix 27). Individuals with high internalising problems and low externalising problems had the lowest level of weekly alcohol units and prevalence of problematic drinking, whereas individuals with low internalising problems and high externalising problems had the highest level of consumption. Furthermore, sensitivity analysis was carried out using a general psychopathological factor that captures the common variations of externalising and internalising problems as the predictor. It was found that the association between psychopathological factor and mid-adulthood problematic drinking was attenuated or became null (Appendix 22). This further supports the hypothesised DAG and the suppressing effect between externalising and internalising problems regarding their association with later problematic drinking.

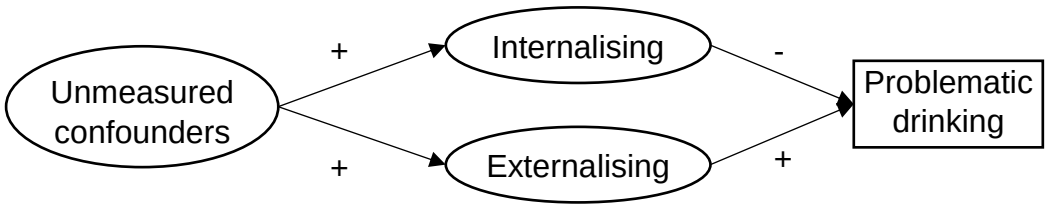


Figure 16 DAG illustration of the suppressing effect between externalising and internalising problems

4.4.4 Critical period of mental health problems

As discussed in section 1.5.1, the association between externalising problems at a specific time point and problematic drinking would be influenced by the proportions of heterogeneous trajectories of externalising problems in the population, if status of previous externalising problems is not taken into consideration. By adjusting previous externalising and internalising problems in the model, the association between later externalising and internalising problems

and problematic drinking explicitly represents the strength of the association at that specific time point, which offers the opportunity to test the developmental timing of externalising and internalising problems. That is, whether the strength of externalising and internalising problems with mid-adulthood problematic drinking differs across their ages. Results from post hoc comparisons indicate that there was not a critical period of early life mental health problems regarding the strength of their association with later problematic drinking. In other words, irrespective of the persistence of mental health problems, one-unit inter-individual difference of externalising and internalising problems in either childhood or adolescence was associated with similar change in the risk of problematic drinking on the population level. No previous studies have explored the developmental timing of externalising and internalising problems from the perspective of severity - whether the strength of the association between mental health problems and alcohol use differs across stages.

However, questions arise from current results regarding the respective implications and interpretations of the two perspectives in their approach to the developmental timing of mental health: persistence versus severity. Consistent evidence from person-based analysis has shown that those with early-onset-persistent and adolescent-onset externalising problems are more likely to become involved in alcohol use/misuse, compared to those with childhood-limited and consistently-low externalising problems [110–116]. This indicates that adolescence is the critical period to intervene. However, post hoc comparisons using variable-based analysis indicates no critical period of mental health problems as shown in the results. This contradictory interpretation exemplifies the importance of examining longitudinal relationships from multiple dimensions, both theoretically and empirically. As the above-mentioned trajectories cannot be derived from the two British birth cohorts empirically, reasons behind the discrepancies between person-based and variable-based approach are not further investigated. Future research would offer new insights if both approaches could be carried out within one study.

4.4.5 Interaction with sex and cohort

Another finding worth our attention is how the association between externalising and internalising problems and problematic drinking differed across sex but not cohorts.

In the UK, policies and public acceptance towards alcohol have changed over time. Alcohol consumption per capita per year almost doubled between 1950 to the mid-1970s [137] and then fluctuated slightly around 10 litres thereafter [138]. It's also from 1970s onwards that campaigns, academic committees and health education targeting on solving alcohol problems became more common [137,140], resulting in the production of *Drinking Sensibly* (1981) which influenced the evolution of alcohol policy and alcohol health education in the UK [137].

Born 12 years apart, participants from NCDS58 and BCS70 were raised under a different social environment towards alcohol. Though prevalence of problematic drinking at different ages differed significantly across cohorts, the strength of association between externalising and internalising problems and problematic drinking did not, which is consistent with previous findings [93]. This indicates that at least for these two generations the observed associations between early life mental health and later alcohol use reflect general developmental processes and there is no evidence that their association reflects historical changes in patterns and culture of alcohol use [93].

Modification by sex in the association between externalising and internalising problems and problematic drinking was found with associations being stronger in males, especially for internalising problems. For decades in the last century in the UK, even today, males are the main force who drank in the pub [349,353,354]. As explained previously, internalising problems featured as "fearful" and "solitary" in the current study may have a larger impact among males. Several studies reported significant but inconsistent interactions between mental health problems and sex on the pathway to alcohol use in adulthood [81,129,131,132]. Cook et al. discovered a stronger association between externalising problems and alcohol

problems in male [129], and Green et al. [131] found an association between general psychological health and drinking quantity in males but not females, which were consistent with current results. Two other studies using depression as the exposure returned conflicting results, with one study reporting a stronger association in females [81] and the other in males, but of minimal magnitude [132]. Many studies did not detect significant interactions between mental health problems and sex [72,84,85,102,238,338,340,355–358], though results took the form of slightly stronger associations among males in some situations [93,102,359]. In the UK, there is the trend that females are drinking more alike to their male counterpart [348,360,361], and as the participants were born in 1950s and 1970s, one could not rule out the possibility that variation of the association across sex reported here would disappear for younger generations in the UK.

4.4.6 Through the lens of causal inference

The biggest threat to claiming causality would be the potential unmeasured confounders in the current study. While efforts were made to minimise their influence by adjusting highly correlated externalising and internalising problems simultaneously, the calculation of the E-value brought more delicate thinking into the discussion.

On one hand, the size of the E-value (1.20 to 1.29) indicates that the association of the unmeasured confounder with both externalising or internalising problems and problematic drinking would need to be stronger than the observed associations between externalising or internalising problems and problematic drinking (1.06 to 1.11 for externalising problems and 1.05 [=1/0.95] to 1.11 [=1/0.90] for internalising problems) in our study, conditional on all the covariates included in the model. Thus, it could be argued that the observed associations were less likely to be fully nullified by unmeasured confounding factors, as the externalising pathway is, up to now, shown to be the most robust pathway [74].

On the other hand, the size of the E-value could also be seen to indicate that the observed associations were still susceptible to unmeasured confounding factors, including genetics [362,363], parental psychopathology and substance use and

peers' drinking behaviours [90]. However, the lack of studies examining the strengths of these potential confounders with problematic drinking into mid-adulthood while taking externalising and internalising problems into account constrains further speculations. Future studies would offer more insights if they could examine whether genetics and familial and social risk factors act as potential confounding factors for the pathway from externalising problems to problematic drinking or act as upstream factors, which are linked to problematic drinking only through externalising problems.

4.4.7 Strengths & limitations

There are several strengths of the current study in exploring the association between early life mental health and later alcohol problems. First, considering the high rate of co-occurrence between externalising and internalising problems in childhood and adolescence [104,106,315], the association of externalising and internalising problems with problematic drinking was investigated by not adjusting each other simultaneously in the sensitivity analysis. The result reveals their suppressing effect on each other, which has usually been overlooked in previous studies [85,102,131]. Second, latent scores for externalising and internalising problems on a continuum were developed as the exposure. Measurements for externalising and internalising problems are typically the sum of a Likert scale or dichotomised into "cases", which has been criticized due to its inaccuracy or the continuum nature of mental health problems [106,364]. For instance, the sum score of a Likert scale implicitly assumes equal contribution of each item to the total score which could conceal differences among individuals, as people with the same score could behave distinctively from each other. Third, apart from problematic drinking, weekly alcohol units were also explored as an outcome (Appendix 28). The fact that similar association patterns were found further assures the robustness of current results, as alternative alcohol indices may capture a different aspect of one's drinking behaviour [365] and lead to different association patterns [93,218]. Fourth, state-of-art techniques developed in the field of MI were applied to ensure robustness of the results. These include imputing adequate number of datasets (150 imputations) [330], imputing measurement scale on item-level [327,328], imputing datasets separately among

subgroups to ensure its compatibility with analytical model [286] and applying the multiple imputation then deletion method to assess potential bias due to imputed outcomes [334] (Appendix 23). Fifth, apart from the above-mentioned additional analysis, two other additional analyses were conducted: using the sum of the Likert scale to measure externalising and internalising problems (Appendix 24); using the full-scale AUDIT in NCDS58 to assess potential bias due to false positives. Results further validate the reported association patterns.

Several limitations should also be considered. First, as in many other longitudinal studies over decades, only half of the original sample was retained by age 46 in both cohorts which may result in selection bias. By making use of the abundant information collected in both longitudinal studies, 150 datasets were imputed, and sensitivity analysis with only cases with complete outcome was carried out. The results showed that the results were quite robust to attrition, but bias cannot be ruled out. Second, current measurement may not reflect the whole range of externalising and internalising problems. To ensure comparability across waves and cohorts, only four items were retained to construct externalising problems (fights, disobedient, destructive, irritable) and internalising problems (miserable, fearful, solitary, worried). Though the latent score derived utilising all externalising and internalising relevant items in each cohort was highly correlated with the latent score derived using four items ($r>0.95$ for NCDS58, $r>0.92$ for BCS70), Externalising and internalising problems in the current study should be interpreted keeping in mind the four items they were constructed with. Third, though the CAGE and AUDIT are considered to be valid tools for detecting hazardous or problematic alcohol use, they reflect different aspects of alcohol use behaviours and thus were not directly comparable. In the current study, the short version of AUDIT was used, and it mainly reflected individual's level of drinking frequency and drinking units instead of problems (can't stop once started, failed to work because of alcohol and caused concerns to others). Therefore, it would increase the rate of false positives in detecting problematic drinking and bias the results toward the null. This hypothesis was supported in the sensitivity analysis when full-AUDIT scale in NCDS58 was utilised (Appendix 25). Fourth, other potential confounders (e.g., family history of alcoholism, parenting strategy, peers' drinking behaviours, adolescent drinking) were not

adjusted for in the current study due to the unavailability of related information. However, one could argue that factors like peers' drinking behaviours [151] and adolescent drinking [265,366] are more likely to lie on the pathway from externalising and internalising problems to problematic drinking, thus should not be adjusted for in the model. Moreover, sensitivity analysis with the E-Value indicated that moderate confounding, stronger than the association between externalising and internalising and problematic drinking observed in our study, would be needed to fully account for our findings (see Table 10).

4.5 Conclusion

By utilising two British birth cohorts, I investigated how externalising problems and internalising problems in childhood and adolescence were associated with problematic drinking in mid-adulthood. Externalising problems were positively associated with problematic drinking across adulthood while internalising problems were negatively associated with problematic drinking, and the results were robust to a series of sensitivity analyses. There was no critical period of externalising or internalising problems detected regarding the strength of their association with problematic drinking. The stability of these associations across cohorts further indicates the developmental nature of the association between externalising and internalising problems with problematic drinking. Though the association was more prominent among male participants, the possibility of narrowing sex differences in more recent generations should be highlighted. As alcohol consumption is heavily affected by social norms and culture, current study provides new insights on the externalising and internalising pathway to alcohol use under the UK context. If causal, it lends support for the development of early life mental health programmes for reducing alcohol burden in adulthood.

5. Chapter 5 Does educational attainment mediate the association between early life externalising problems and problematic drinking in adulthood? Evidence from two British birth cohorts

5.1 Introduction

For the past two decades, theoretical and empirical research in developmental psychology has showcased the need to view alcohol use from a life course perspective [71,90–92,367,368]. Within this approach a range of factors across domains of individual, familial, social and societal contexts have been shown to be associated with alcohol use in adulthood [29,90]. The idea of incorporating early risk factors in the typology and treatment of AUD results in two widely discussed phenotypes: antisocial alcoholism and negative affect alcoholism [69,71,73]. These two phenotypes correspond to the association of early life externalising problems and internalising problems with adulthood problematic drinking, explored and presented in Chapter 4. The observation that internalising problems act as a protective factor with respect to problematic drinking in two British birth cohorts shifted the focus of the current chapter to externalising problems, which have been identified as a risk factor for problematic drinking.

5.1.1 Association between externalising problems and alcohol use

In contrast to internalising problems, more consistent and robust evidence supports externalising problems as a risk factor, which serves as the origin of antisocial alcoholism [71,74]. Recent theory posits that the core problem of this pathway typically reflects behavioural disinhibition, “an inability to inhibit socially undesirable or restricted actions” [369]. Thus, under a high-risk environment (e.g., parental drinking problems, deviant peer networks, lack of effective parenting), individuals with behavioural disinhibition are likely to end up with problematic behaviours [74]. Numerous empirical studies across various countries have validated the robustness of the association between externalising

problems and later alcohol use behaviours, some of which persist into mid-adulthood [72,76,79,110,129,228,238,340,370].

Studies that investigate the mediating role of multiple domains during childhood and adolescence (such as parenting style, peer involvement) provide evidence for the externalising pathway to alcohol use [149–152]. However, prior theories and evidence regarding the externalising pathway only pertain to a short-term pathway into adolescence and young adulthood during which drinking behaviours are easily influenced by family and peers [92]. Understanding the long-term pathway, through which the impact of early life externalising problems on problem drinking persists into mid-adulthood (when drinking behaviours are more stable) may provide a new perspective on the mechanism of action. Moreover, exploring how much of the association between early life externalising problems and problematic drinking in mid-adulthood could be mediated by other more malleable intervening factors may inform the development of prevention programmes to break this robust long-term pathway.

5.1.2 Association between education and alcohol use

Findings on the association between education and alcohol use vary across phenotypes of alcohol use behaviours. In general, current evidence indicates more “sensible drinking” behaviours among people with higher educational attainment. Less well-educated adults tend to drink less sensibly by drinking more per occasion [159,160], engaging in binge drinking (drinking 5/6 or more per occasion) [161,162] and having a higher risk of alcohol dependence [163–165]. In contrast, people with higher educational attainment are more likely to engage in any drinking [166–168], drink more often [160,168], and have greater total intake [168–170], but less likely to engage in binge drinking, heavy drinking or problematic drinking, and less likely to be diagnosed with AUD [154,163,169].

However, the evidence is not all as consistent as is shown above. Huerta et al. reported that compared to no qualifications, attainment of a degree (by age 34) was positively associated with problem drinking at age 34 in females and negatively associated with heavy drinking in males [168]. Two other studies

analysing three birth cohorts in the UK born in 1958, 1970 and 1971-2 showed that entering tertiary education (education beyond age 18) was positively associated with heavy drinking in young adulthood [172,371]. Apart from the heterogeneous definition of educational attainment and stage when alcohol use behaviours were measured across studies, the overlap in the definitions of binge, heavy and problematic drinking may contribute to this inconsistency. Caldwell et al. explored the association between educational attainment by age 33 and various exclusive drinking patterns [167]. Patterns were categorized as non-/occasional drinkers, low-risk drinkers, moderate-binge drinkers with low-problems scores and consuming within UK sensible weekly drinking guideline (21 units for men and 14 units for women) [372], low-problem heavy drinkers (regardless of binge) and problem drinkers (and heavy or binge). It was shown that people with higher educational attainment tend to be low-risk drinkers, are less likely to be moderate-binge drinkers and problem drinkers, but no association was found between educational attainment and low-problem heavy drinking [167]. Thus, it might be that college education could promote circumstances that favours alcohol drinking: a more intensive social life that encourages alcohol; a greater social acceptability of alcohol [168,373]. As a result, better educated people tend to drink more often and in total volume, which could result in entering the realm of heavy or problematic drinking. However, in most of the cases, they are better at managing the behaviour before it escalates into more severe drinking behaviours such as problematic drinking, binge drinking and AUD [154].

5.1.3 Association between mental health and educational attainment

Current research shows an association between mental health status and later educational attainment, and the direction being most likely from mental health problems to poor educational attainment [374,375]. Compared to physical impairment, mental health problems may have a larger impact on educational attainment [376].

It is well-established that childhood/adolescent conduct problems were related to a range of academic outcomes (such as grade repetition, early school leaving, low test score, failure to achieve high school qualifications) [377–381]. For

example, adolescents (age 13&15) with severe conduct problems are four times more likely to leave school without any qualifications compared to those without conduct problems [238].

5.1.4 A developmental perspective

From a developmental perspective, long-term connections are conditioned upon developmental timing, sex, history and culture, which should be considered when exploring the etiological pathway to problematic drinking [90,92]. Thus, externalising problems in adolescence, educational attainment in early adulthood and problematic drinking in mid-adulthood was chosen to be investigated for the following reasons.

Though results in Chapter 4 suggest no critical period of externalising problems regarding its strength with problematic drinking, other evidence suggests late adolescence as a critical period from the perspective of persistence [110,340,382]: early-onset externalising problems that persist into late adolescence can best predict later alcohol use, followed by adolescent-onset externalising problems and then childhood-limited externalising problems. In addition, externalising problems in late adolescence, rather than persistence per se, appear to be a key component in affecting leaving school age, qualifications at labour force entry and occupational social class [382]. This might be due to the temporal proximity of externalising problems in late adolescence with education and employments [383].

More advanced educational attainment, especially attainment of a college degree appeared to play a bigger role in later alcohol use behaviours [165,168]. A university/college degree shapes one's social position and opportunities in life, It is well known and documented that a college education significantly improves one's earnings and employment, in comparison to high school diploma [384], and the monetary benefits sustain throughout life time [385]. In addition, emerging evidence shows that a college education is also associated with a range of other benefits, including but not limited to better health, healthier health-related behaviours, longer life expectancy and more happiness [154,156,169]. According

to this literature, on one hand, higher education could cultivate healthier behaviours through facilitating the development of cognitive capacities which enable one to make more informed decisions about health, or through the accumulation of social ties that promote healthy behaviours and control unhealthy behaviour [154,386]. On the other hand, higher education may get one into those social positions or opportunities, which favour and promote drinking (e.g., they earn more wages to afford drinking more) [373,387]. It was observed that college-going increased the risk of risky drinking [386,388] which could last into mid-/late-adulthood [389].

As discussed in section 1.3.1 and 4.4.3, problematic drinking was assessed in middle adulthood when drinking behaviours are more stable and less affected by family, peers and neighbourhood environment [342,390] and thus may reflect more of the impact that mental problems and education have on alcohol use [88,345,346].

To summarise, the prior research suggests that higher externalising problems are associated with lower educational attainment, and higher educational attainment enables better management of risky drinking behaviours. Thus, this chapter aims to explore the mediating role of educational attainment in the association between adolescent externalising problems and mid-adulthood problematic drinking found in two British birth cohorts. It is hypothesised that the positive association between externalising problems and problematic drinking would be partially mediated by educational attainment, because higher externalising problems would decrease the likelihood of getting higher qualifications and then further increase the risk of problematic drinking.

It is well acknowledged that males and females differ in their exhibition of externalising problems and alcohol use [95,105]. Moreover, the association between externalising problems and alcohol use was shown to be stronger for males than that for females in the two British birth cohorts (see Chapter 4). In addition, they also experience social role transitions that differ in timing or meaning (e.g., spouse, parent, caregiver, part- and full-time worker) which in theory could also influence the pathway from early life mental health to alcohol

use [71,73,90,383]. For these reasons, analyses were carried out separately in males and females.

5.2 Methods

Operationalization of externalising problems and problematic drinking was the same as described in section 3.1.2 & 4.2.2, and thus not repeated here. This section mainly focuses on the issues encountered in modern formal mediation analysis and the operationalization of educational attainment.

5.2.1 Mediation analysis within the counterfactual framework

The traditional approach to mediation is based on standard regression analysis and typically referred to as the difference in coefficients approach and/or the product of coefficients approach [391,392]. While theoretically appealing and intuitively easy to understand, the traditional approach has several limitations regarding its applicability in models with interactions and non-linear relationships [393]. The application of the counterfactual framework in the field of mediation extended the definitions of direct and indirect effect to incorporate settings where interactions and non-linear relationships are presented [181,184,394]. Within the counterfactual framework, direct and indirect effect can be decomposed into various combinations [185,395]. The mostly widely acknowledged combination is natural direct effect (NDE) and total natural indirect effect (TNIE) as defined in Box 1[396]. In addition, the direct effect in traditional mediation analysis can be defined as controlled direct effect (CDE) under counterfactual framework (Box 1).

Box 1 Definitions of controlled direct, natural direct and total natural indirect effects under the counterfactual framework

Capital letters A/M/Y refers to exposure/mediator/outcome variable respectively; lower case letters a/m refers to a specific level of variable A/M.

Controlled direct effect (CDE): $Y_{a,m} - Y_{a^*,m}$

This effect is the contrast between the counterfactual outcome if individuals were exposed at A=a and the counterfactual outcome if the same individual were exposed at A=a*, with the mediator set to a fixed level M=m.

Natural direct effect (NDE): $Y_{a,M(a^*)} - Y_{a^*,M(a^*)}$

This effect is the contrast between the counterfactual outcome if individuals were exposed at A=a and the counterfactual outcome if the same individuals were exposed at A = a*, with the mediator assuming whatever value it would have taken at the reference value of the exposure A=a*.

Total Natural indirect effect (TNIE): $Y_{a,M(a)} - Y_{a,M(a^*)}$

This effect is the contrast of having set the exposure at level A=a, between the counterfactual outcome if the mediator assumed whatever value it would have taken at a value of the exposure A=a and the counterfactual outcome if the mediator assumed whatever value it would have taken at a reference value of the exposure A=a*.

Approaches to deal with exposure-mediator interaction, binary mediators or rare binary outcomes have been developed under the counterfactual framework [392] and can be implemented in mainstream statistical packages, such as SAS (Statistical Analysis System), Stata, SPSS (Statistical Package for the Social Sciences) [186] and Mplus [397]. However, most of these programs calculate NDE and TNIE by fixing the values of covariates to be the same for the whole sample (typically to mean level for continuous variables and to a reference group for categorical variables), which is equivalent to calculating the marginal effect at means [398]. This approach incurs two problems. First, by fixing the values of covariates, one is calculating NDE and TNIE for a population that does not exist in reality. As indicated by the derived formula of NDE and TNIE [392,397], the effect size also depends on the level of covariates. As a result, a combination of covariates at their mean level represents a population that does not exist; and thus, it would fail the aim to calculate NDE/TNIE for the target population where covariates differ across individuals. Second, to ensure the validity of the estimation based on the programs mentioned above, the rare outcome

assumption for binary outcomes is needed (typically prevalence of the outcome should be less than 10%) [392]. If the outcome is not rare and logistic regression is employed, the conditional odds ratio (OR) will be biased due to the non-collapsibility of OR [399], so will the NDE/TNIE calculated based on the OR.

This chapter takes an interest in how much of the effect from externalising problems in adolescence to problematic drinking in mid-adulthood was mediated through educational attainment in the British population. However, the prevalence of problematic drinking in mid-adulthood across sex and cohorts was much higher than 10% (see Table 4 in section 3.1.2). To avoid the two problems mentioned above, NDE/TNIE was calculated using the g-formula approach, which is originally proposed to overcome intermediate confounding bias in mediation analysis as well as bias due to time-varying confounders [400,401]. The estimation procedure of NDE/TNIE in g-formula is equivalent to calculating the average marginal effect where values of covariates are left as they were observed for each individual [287,398,402] and thus would help to avoid the above two problems [399].

5.2.2 Definition of educational attainment

Educational qualifications histories of the participants from NCDS58 and BCS70 were fully harmonized by Bukodi for cross-cohort comparisons [403] and are available from the UK Data Archive [404]. For the current study, cohort members' highest educational qualification attainment by age 23 was retained and categorized into four categories: No qualification, O-level or equivalent qualification, A-level or equivalent qualification and Diploma/degree or above. Proportion of each qualification across sex and cohort is displayed in Table 12.

Table 12 Proportion of educational achievement by age 23 across sex and cohorts

	Male	Female
	NCDS58	
No qualification	2550 (36.0%)	2142 (31.0%)
O-level or equivalent	3119 (44.1%)	3410 (49.3%)
A-level or equivalent	730 (10.3%)	834 (12.1%)
Diploma/degree or above	675 (9.5%)	529 (7.6%)
	BCS70	
No qualification	2103 (36.1%)	1897 (31.5%)
O-level or equivalent	2201 (37.7%)	2476 (41.1%)
A-level or equivalent	823 (14.1%)	940 (15.6%)
Diploma/degree or above	704 (12.1%)	711 (11.8%)

The DAG for the mediation analysis is shown in Figure 17. Educational attainment by age 23 was operationalized as the mediator instead of lifetime highest educational attainment for three main reasons:

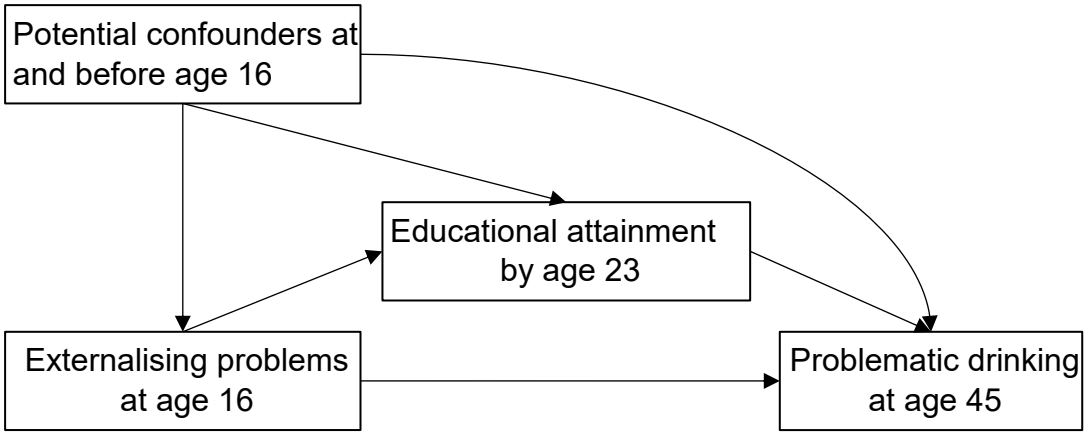


Figure 17 The conceptual model for mediation analysis

First, to minimise the influence of unmeasured confounding factors. Evidence shows that those who participate in education at later ages are different from those who achieve their higher qualifications at an early age in many aspects, such as higher level of autonomy, self-efficacy [405–409], which may also have an impact on their alcohol use [410–413] (Figure 18). Thus, those innate characteristics are likely to confound the association between highest educational attainment (e.g., by age 45) and problematic drinking at age 45. If education protects one from problematic drinking, this association would be overestimated if highest education attainment is utilised as the predictor.

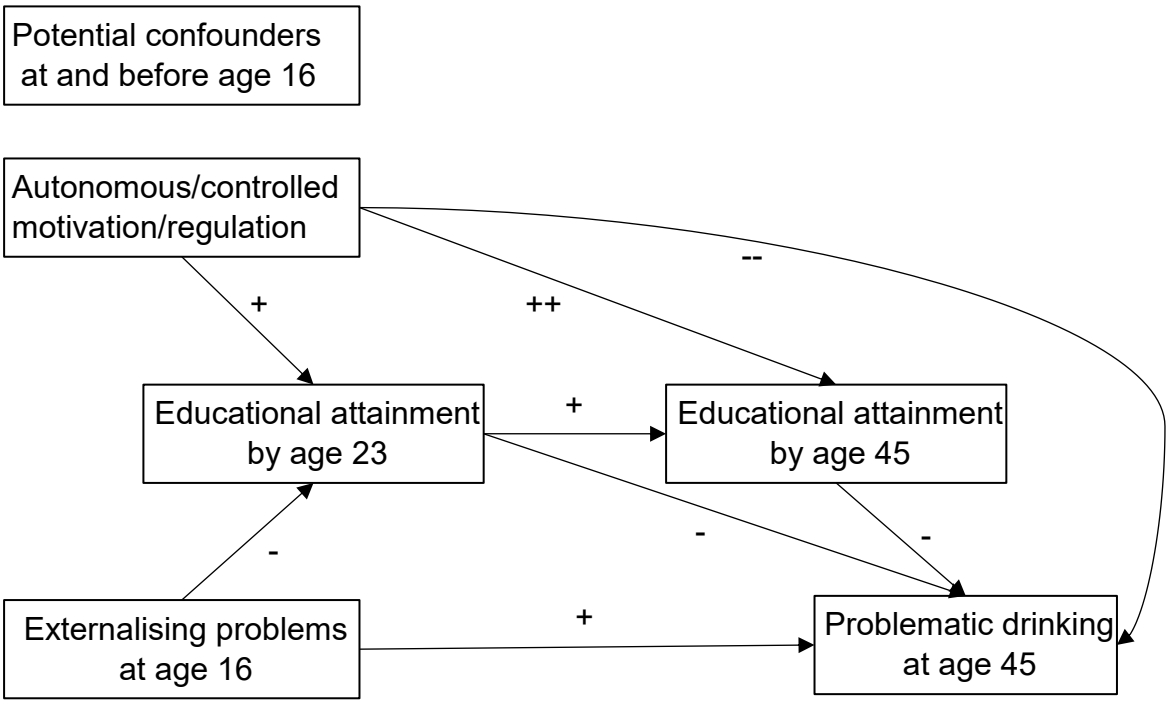


Figure 18 The framework for potential unmeasured confounders*
*Arrows from "Potential confounders at and before age 16" to exposure/mediator/outcome variable were deleted for clarity; +/- indicates the direction (positive/negative) of the potential causal effect between two variables and the number of +/- indicates relative strength.

Second, the definition of highest educational attainment (by age 45) is ambiguous as it constitutes a range of individuals who achieved qualifications at various ages. For example, for those who achieved their highest degree at an early age, factors such as entering employment, starting cohabitation, having a first child, leaving parental house, lie on the pathway from educational attainment to later alcohol use (Figure 19) [172,414–418] and thus are part of the indirect effect of educational attainment of our interest. As the aim is to explore the total indirect effect through educational attainment in the target population regardless of the mechanisms from educational attainment to problematic drinking, one does not need to concern about the distribution of those factors in the population. However, for those who achieved their highest degree at older ages, the above factors may act as precursors for their education achievement chronologically [407] and should be treated and dealt with as intermediate confounders in order to obtain the unbiased indirect effect of interest [287,419]. In reality, the population is a combination of different event trajectories, and defining highest educational attainment as the mediator makes it impossible to delineate the mediating effect

of those factors from their effect as intermediate confounding factors. As a result, the indirect effect is very difficult to interpret from the perspective of causal inference.

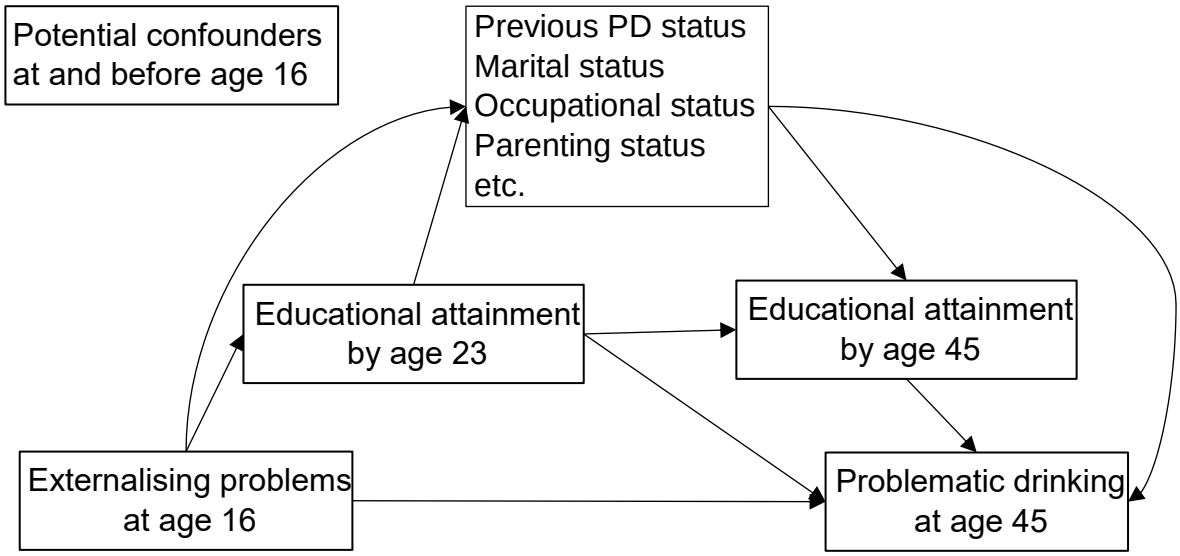


Figure 19 The framework of potential intermediate confounders*
*Arrows from "Potential confounders at and before age 16" to exposure, mediator and outcome variables were deleted for clarity.

Third, age 23 was selected as a cut-off point after tabulating educational attainment by age when it was achieved (Appendix 29 and Appendix 30). Under the UK context, there was a sharp decline in the number of people who achieved a degree in both NCDS58 and BCS70 after age 23. Therefore, age 23 could be considered as the youngest age when most people finished their full-time education, and defining educational attainment by age 23 as the mediator helps to mitigate the potential bias caused by unmeasured confounding factors, including intermediate confounding factors [185].

5.2.3 Interpretation of NDE/TNIE in current study

A continuous latent score was derived as an indicator of externalising problems, and it was standardised before the analysis to aid interpretation. Therefore, under the counterfactual framework, the definition of NDE, TNID in the current study could be present in formulas as in (3.1)-(3.4)*.

$$CDE = E\,[Pr\,(EXT, O\text{-}level) - Pr\,(-1SD, O\text{-}level)] \quad (3.1)$$

$$NDE = E\,[Pr\,(EXT, M(-1SD)) - Pr\,(-1SD, M(-1SD))] \quad (3.2)$$

$$TNIE = E\,[Pr\,(EXT, M(EXT)) - Pr\,(EXT, M(-1SD))] \quad (3.3)$$

$$TE = E\,[Pr\,(EXT, M(EXT)) - Pr\,(-1SD, M(-1SD))] = NDE+TNIE \quad (3.4)$$

*E=expectation, Pr=probability, EXT=observed distribution of externalising problems, -1SD=one standard deviation below average level of externalising problems, M()=distribution of mediator when externalising problems follow the condition listed in the bracket, TE=total effect

CDE is the difference between the marginal probability of problematic drinking of two populations, where the educational attainment for each individual is fixed to O-level, and the distribution of externalising problems in the first population is as observed and the distribution of externalising problems in the second population is set to 1 SD below the average for each individual.

NDE is the population-specific direct effect of externalising problems at age 16 on problematic drinking at age 45 not through educational attainment by age 23: the distribution of educational attainment by age 23 is set to the distribution it would have had if externalising problems of the whole population were set to 1 SD below the average; the distribution of externalising problems is set as observed in the first population whereas it is set to 1 SD below the average in the second population; all the other covariates are left as they were observed. In other words, the NDE is the proportion of problematic drinking that one could have reduced directly if one had intervened externalising problems of the whole population to 1 SD below the average while leaving other covariates as they were.

Similarly, TNIE is the indirect effect of externalising problems at age 16 on problematic drinking at age 45 through its influence on the distribution of educational attainment by age 23. In other words, TNID is the proportion of problematic drinking that could have been reduced indirectly due to the change of distribution of educational attainment by age 23 if we had intervened externalising problems of the whole population to 1 SD below the average while leaving other covariates as they were.

TE is the sum of NDE and TNID and can be interpreted as total proportion of problematic drinking that could have been reduced if we had intervened

externalising problems of the whole population to 1 SD below the average while leaving other covariates as they were.

5.2.4 Data imputation and estimating method

Selective drop-out and intermittent missingness (some participants missed a sweep but showed up at a subsequent sweep) are unavoidable in longitudinal surveys. In addition, a participant may have missing values for a subset of the variables at certain time point while others were observed, or some participants may have missingness in some baseline variables. Under the missing at random assumption (MAR) - missingness of the variable depends on the other observed variables, missingness can be dealt with via multiple imputation by chained equations [269,319,330]. Typically M imputed datasets are created, and the analysis is conducted on each of these datasets before combining the M results (M point estimates and M variance estimates) using Rubin's rules [420]. In the case of g-formula estimator, for which standard errors of the analysis model cannot be calculated directly, bootstrapping is used [287]. However, not enough studies have compared the validity and efficiency of the estimating methods for combining bootstrapping and multiple imputation.

Generally, these methods can be divided broadly into multiple imputation nested in bootstrapping (bootstrapping then impute) and bootstrapping nested in multiple imputation (impute then bootstrapping) [421,422]. Available studies indicate that single stochastic imputation nested in bootstrapping (a special case of multiple imputation nested in bootstrapping) can produce valid estimates [287,421,422], and thus it is employed in the available Stata package for g-formula estimator considering its superiority in terms of efficiency [287]. However, the imputation procedure in the g-formula package in Stata can only impute continuous variables using linear regression, and categorical variables using logistic regression, multinomial logistic regression or ordered logistic regression [287], which has two limitations in the case of the current research question. First, missingness in the outcome variable can only be imputed as a total scale instead of each item. However, evidence indicates that missing data in multi-item instruments could be better handled by imputing at item level than total scale level [327,328,423].

Second, highly skewed continuous variables, such as the latent score for internalising problems and externalising problems, weekly drinking units, can only be imputed using linear regression under the assumption of normal distribution of residual errors. In practice, they can be better handled by the approach of predictive mean matching [329]. In this instance, bootstrapping nested in multiple imputation could help avoid the above two limitations. Therefore, both methods were employed to assure the validity of the results in the current study.

Bootstrapping nested in multiple imputation

Indicated by its name, bootstrapping nested in multiple imputation first imputes complete datasets and then applies bootstrapping to each complete dataset to calculate standard errors for the estimates. Specifically, multiple imputation by chained equations was first employed to generate M completed datasets, and then the g-formula package in Stata was run on each of the completed datasets, and finally, the intermediate results (point estimate($\hat{\theta}_m$), variance ($\widehat{Var}(\hat{\theta}_m)$) for TE, NDE, TNIE, CDE) per completed datasets were pooled manually using Rubin's rule as below [420].

$$\hat{\bar{\theta}}_{MI} = \frac{1}{M}\sum_{m=1}^{M}\hat{\theta}_m \quad (4.1)$$

$$\widehat{Var}\left(\hat{\bar{\theta}}_{MI}\right) = \frac{1}{M}\sum_{m=1}^{M}\widehat{Var}(\hat{\theta}_m) + \frac{M+1}{M}\sum_{m=1}^{M}\left(\hat{\theta}_m - \hat{\bar{\theta}}_{MI}\right)^2 \quad (4.2)$$

As suggested by Graham et al. (Graham, 2007), 20 imputations would be sufficient at 30% missingness for a preventable power falloff less than 1%, and 40 imputations at 70% missingness for a preventable power falloff less than 1%. Thus, considering the computational intensity of 1000 bootstrapping for each imputed dataset, 40 imputations were generated instead of 150 imputations, as in Chapter 4. Other than number of imputations, the rest of the MI procedures followed the rules set out in Chapter 4 and imputed missing information using MICE in Stata 15.0. To repeat here. A set of auxiliary variables was added into the imputation model to improve the accuracy of imputed values and the efficiency of point estimates [324,325]. These include smoking (Never, used to smoke, current smoker), drinking frequency (special occasion/never, 2~3 times

per month, 1~3 times per week, 4+ times per week), weekly alcohol units at ages 26, 33, 42 in NCDS58 and at ages 23, 34, 42 in BCS70. Multi-item scales (CAGE/AUDIT-PC) was imputed at item level. To avoid convergence problems, when imputing specific item in scale variables, the sum score of all the other items within the scale was included instead of including each item separately [328]; and when imputing non-scale variables, the sum score of scale variables was included in the imputation model rather than each item. Binary variables were imputed using logistic regression; ordered categorical variables were imputed using ordinal logistic regression; un-ordered categorical variables were imputed using multinomial logistic regression; continuous and normally-distributed variables were imputed using linear regression; highly skewed continuous variables including externalising and internalising problems at all ages, and weekly alcohol units across adulthood were imputed using the approach of predictive mean match [329]. To incorporate interactions between externalising and internalising problems and sex/cohort properly, imputation was done separately in four subgroups (males/females in NCDS58/BCS70) [286]. Distributions of complete and imputed variables were checked in case of abnormal imputation during the imputation stage [331,332]. The target population was defined and imputed by excluding people who had died by the age 45.

Single stochastic imputation nested in bootstrapping

Opposite to bootstrapping nested in multiple imputation, single stochastic imputation nested in bootstrapping first bootstraps to generate an incomplete dataset, and then single stochastic imputation was employed to fill in missing values. Typically, 1000 bootstrapping replications are required [287], and this is also the default setting in the g-formula package in Stata. Bootstrapping 1000 times is computationally intense (each bootstrapping replication requires the imputation of a completed dataset, which means 1000 completed datasets are generated). After a trial run on computer clusters [424], each bootstrap replication is estimated to take up 10 minutes, which means that the whole analysis would consume 10*1000 minutes. To improve computational efficiency, 1000 bootstrapping replications were divided into 10 batches, and then intermediate results for each batch (point estimate ($\hat{\bar{\theta}}_1$, $\hat{\bar{\theta}}_2$,…, $\hat{\bar{\theta}}_{10}$), variance

($Var\left(\hat{\bar{\theta}}_1\right), Var\left(\hat{\bar{\theta}}_2\right), \ldots, Var\left(\hat{\bar{\theta}}_{10}\right)$) for TE, NDE, TNIE, CDE) were manually pooled according to the rule listed below (assuming normal distribution of the estimates $\hat{\theta}$).

For batch i (n=100):

$$\hat{\bar{\theta}}_i = \frac{1}{100}\sum_{j=1}^{100}\hat{\theta}_j \tag{5.1}$$

$$\begin{aligned} Var\left(\hat{\bar{\theta}}_i\right) &= \frac{1}{100}\sum_{j=1}^{100}\left(\hat{\theta}_j - \hat{\bar{\theta}}_i\right)^2 \\ &= \frac{1}{100}\sum_{j=1}^{100}\hat{\theta}_j{}^2 - \left(\frac{1}{100}\sum_{j=1}^{100}\hat{\theta}_j\right)^2 \\ &= \frac{1}{100}\sum_{j=1}^{100}\hat{\theta}_j{}^2 - \hat{\bar{\theta}}_i{}^2 \end{aligned} \tag{5.2}$$

For pooled estimate (N=1000):

$$\begin{aligned} \hat{\bar{\theta}} &= \frac{1}{1000}\sum_{j=1}^{1000}\hat{\theta}_j \\ &= \frac{1}{1000}\left(\sum_{j=1}^{100}\hat{\theta}_j + \sum_{j=101}^{200}\hat{\theta}_j + \cdots + \sum_{j=901}^{1000}\hat{\theta}_j\right) \\ &= \frac{1}{1000}\left(100 * \hat{\bar{\theta}}_1 + 100 * \hat{\bar{\theta}}_2 + \cdots + 100 * \hat{\bar{\theta}}_{10}\right) \end{aligned} \tag{5.3}$$

$$\begin{aligned} Var\left(\hat{\bar{\theta}}\right) &= \frac{1}{1000}\sum_{j=1}^{1000}\hat{\theta}_j{}^2 - \left(\frac{1}{1000}\sum_{j=1}^{1000}\hat{\theta}_j\right)^2 \\ &= \frac{1}{1000}\left(\sum_{j=1}^{100}\hat{\theta}_j{}^2 + \sum_{j=101}^{200}\hat{\theta}_j{}^2 + \cdots + \sum_{b=901}^{1000}\hat{\theta}_j{}^2\right) - \hat{\bar{\theta}}^2 \\ &= \frac{1}{1000}\Bigg(100 * \left(Var\left(\hat{\bar{\theta}}_1\right) + \hat{\bar{\theta}}_1{}^2\right) + 100 * \left(Var\left(\hat{\bar{\theta}}_2\right) + \hat{\bar{\theta}}_2{}^2\right) + \\ &\quad \ldots + 100 * \left(Var\left(\hat{\bar{\theta}}_{10}\right) + \hat{\bar{\theta}}_{10}{}^2\right)\Bigg) - \hat{\bar{\theta}}^2 \end{aligned} \tag{5.4}$$

5.2.5 Analytic strategy

Analyses were implemented in two stages. In the first stage, standard logistic regression (on the 40 imputed datasets) [425] was carried out to fully investigate how externalising problems at age 16, educational attainment by age 23 and problematic drinking at age 45 were associated with each other. Nominal logistic regression was carried out using educational attainment as an outcome to examine the association between externalising problems and educational attainment while adjusting for potential confounding factors. Binary logistic regression using problematic drinking as an outcome to examine the association between educational attainment and problematic drinking while adjusting for externalising problems and other confounding factors.

In the second stage, formal mediation analysis under counterfactual framework (explained in section 5.2.1) was carried out using the two estimating approaches introduced in section 5.2.4.

5.2.6 Sensitivity Analysis

Educational attainment was defined as the highest qualification achieved by age 23 as explained in section 5.2.2. As some participants (6.3% in NCDS58, 7.7% in BCS70) continued to achieve higher qualifications after age 23, which may affect the results, sensitivity analysis was carried out excluding those individuals.

As explained in section 4.2.2, problematic drinking identified using AUDIT-PC increased the risk of false positive compared to that identified using full AUDIT scale (Appendix 32), mainly because of the low endorsement on items that reflect more on problematic drinking (such as can’t stop, fail to work, cause concerns) in the population (Appendix 31). To assess the potential bias due to the misclassification, problematic drinking constructed using the full AUDIT scale (10 items, available only in NCDS58) was employed as an outcome.

As discussed in section 5.1.2, current evidence implies that the association of educational attainment with drinking behaviours may vary with phenotypes of

alcohol use behaviours: namely individuals with higher educational attainment tend to drink more often but drink less on each occasion. Hence, when problematic drinking was constructed using AUDIT-PC scale, which mainly reflects one's drinking frequency and drinking quantity per occasion, the association of educational attainment with problematic drinking might be cancelled out and rendered towards null. Sensitivity analysis exploring the association between educational attainment and each item in the AUDIT-PC scale was carried out to assess the potential bias. Item score was binarized (Yes/No) into five variables: drink on a daily basis, consume 5 or more units on a typical drinking day, ever can't stop drinking once started, ever fail to work because of drinking and ever cause concerns to others.

5.3 Results

5.3.1 Association between externalising problems and educational attainment

With all potential confounding factors at age 16 and before adjusted for (as in section 4.2.2), higher externalising problems at age 16 were negatively associated with educational attainment by age 23 (Table 13).

5.3.2 Association between educational attainment and problematic drinking (AUDIT-PC)

Table 14 displays the association between educational attainment and problematic drinking adjusting for externalising problems at age 16 and other potential confounding factors. No statistically significant association between educational attainment and problematic drinking was observed except that having no qualification was associated with a higher risk of problematic drinking at age 45 in females in NCDS58.

Table 13 Association between externalising problems at age 16 and educational attainment by age 23 across sex and cohorts

	NCDS58		BCS70	
	Male	Female	Male	Female
No qualification	1.03 (0.91, 1.15)	1.13 (1, 1.28)	1.11 (0.97, 1.28)	0.92 (0.79, 1.95)
O-level	Ref	Ref	Ref	Ref
A-level	0.82 (0.68, 0.98)	0.74 (0.61, 0.9)	0.94 (0.77, 1.14)	0.81 (0.66, 0.99)
Degree	0.7 (0.55, 0.88)	0.72 (0.55, 0.94)	0.69 (0.55, 0.86)	0.63 (0.49, 0.8)

*Nominal logistic regression was implemented, and thus results are reported as OR (95% CI)

Table 14 Association between educational attainment by age 23 and problematic drinking at age 45 across sex and cohorts

	NCDS58		BCS70	
	Male	Female	Male	Female
Externalising problems	1.21 (1.07, 1.37)	1.07 (0.92, 1.23)	1.26 (1.09, 1.46)	1.21 (1.02, 1.43)
Education				
No qualification	1.03 (0.89, 1.19)	1.24 (1.05, 1.47)	1.11 (0.94, 1.32)	0.92 (0.76, 1.13)
O-level	Ref	Ref	Ref	Ref
A-level	1.05 (0.86, 1.28)	0.85 (0.68, 1.06)	0.96 (0.76, 1.22)	0.81 (0.65, 1.02)
Degree	0.94 (0.75, 1.17)	0.89 (0.68, 1.17)	0.89 (0.7, 1.13)	0.78 (0.59, 1.04)

*Logistic regression was implemented, and thus results are reported as OR (95% CI)

5.3.3 TE, NDE, TNIE, CDE of counterfactual mediation analysis

Results from the two analytical approaches are displayed in Table 15. Contradictory to the hypothesis, no mediating effect of educational attainment was found with either approach. The size of total effect indicates that if we had intervened externalising problems of the male population to 1 standard deviation below the average, their prevalence of problematic drinking at age 45 would have been reduced by 4.3~4.5% in NCDS58 and by 5.0~6.8% in BCS70. The size of NDE and TNIE indicates that this reduction was mainly through direct effect (or other potential mediating pathways not through educational attainment by age 23) of externalising problems. In contrast, intervening externalising problems of the female population to 1 standard deviation below the average may not drive differences in their prevalence of problematic drinking by mid-adulthood.

Table 15 NDE, TNIE, CDE of externalising problems on problematic drinking through educational attainment in two British birth cohorts under two estimation methods*

	Bootstrapping nested in MI			Single stochastic imputation nested in Bootstrapping		
	Probability	SE	95% CI	Probability	SE	95% CI
NCDS58-male						
Total effect	0.045	0.016	(0.015,0.076)	0.043	0.021	(0.003,0.083)
NDE	0.039	0.021	(-0.002,0.080)	0.044	0.020	(0.005,0.083)
TNIE	0.006	0.013	(-0.020,0.032)	-0.001	0.011	(-0.023,0.021)
CDE	0.043	0.016	(0.012,0.074)	0.046	0.018	(0.012,0.080)
NCDS58-female						
Total effect	0.015	0.014	(-0.013,0.043)	0.014	0.019	(-0.022,0.051)
NDE	0.010	0.015	(-0.020,0.039)	0.013	0.019	(-0.024,0.050)
TNIE	0.005	0.009	(-0.012,0.023)	0.001	0.009	(-0.016,0.018)
CDE	0.012	0.014	(-0.015,0.040)	0.015	0.018	(-0.021,0.050)
BCS70-male						
Total effect	0.050	0.017	(0.018,0.083)	0.068	0.020	(0.029,0.108)
NDE	0.042	0.017	(0.009,0.076)	0.065	0.021	(0.025,0.105)
TNIE	0.008	0.015	(-0.021,0.037)	0.003	0.010	(-0.016,0.023)
CDE	0.046	0.015	(0.017,0.075)	0.070	0.021	(0.028,0.111)
BCS70-female						
Total effect	0.021	0.013	(-0.004,0.046)	0.036	0.018	(0.001,0.070)
NDE	0.021	0.013	(-0.005,0.047)	0.033	0.018	(-0.003,0.068)
TNIE	-0.000	0.008	(-0.016,0.016)	0.003	0.009	(-0.014,0.020)
CDE	0.029	0.014	(0.002,0.056)	0.034	0.019	(-0.002,0.071)

*NDE: natural direct effect; TNIE: total natural indirect effect; CDE: controlled direct effect.

5.3.4 Sensitivity analysis

Excluding those who achieved a higher level of qualification after age 23 and before age 45, the association between educational attainment and problematic drinking did not differ from that in the main analysis, and still, no mediating effect of educational attainment was detected (see Table 16).

When constructing problematic drinking using the full AUDIT scale from NCDS58, the imputation model did not converge for males. Thus, missingness in the outcome was imputed directly as binary variable instead of imputing at item level and then binarizing their sum score. The mediation analysis was estimated using single stochastic imputation nested in bootstrapping. As expected in section 5.2.6, the association of educational attainment with problematic drinking tended to be away from the null (see Table 17), compared with that in Table 14. Still, no mediating effect of educational attainment under the counterfactual framework was detected (see Table 17).

Associations of externalising problems and educational attainment with each item in the AUDIT-PC scale are shown in Table 18. Educational attainment was positively associated with daily drinking (mainly in NCDS58), while it was negatively associated with the risk of consuming 5 or more units on a typical drinking day. Higher educational attainment did not seem to protect individuals from other drinking-incurred behaviours (can’t stop drinking, fail to work, cause concern), but having no qualification did seem to increase the risk of getting into those behaviours. Employing drinking frequency and drinking quantity as the outcome, further mediation analysis under the counterfactual framework was carried out. Still, no mediating effect of educational attainment was detected for either outcome (see Table 19).

Table 16 Association between externalising problems/educational attainment by age 23 and problematic drinking at age 45 and their mediating effect across sex and cohort*

	NCDS58		BCS70	
	male	female	male	female
Problematic drinking (AUDIT-PC)		OR (95% CI)		
Externalising problems	1.21(1.08,1.36)	1.07(0.95,1.21)	1.26(1.10,1.44)	1.21(0.99,1.49)
Education				
No qualification	1.02(0.88,1.19)	1.26(1.06,1.50)	1.12(0.96,1.31)	0.96(0.78,1.18)
O-level	Ref	Ref	Ref	Ref
A-level	1.05(0.84,1.32)	0.81(0.63,1.04)	0.99(0.78,1.25)	0.80(0.60,1.06)
Degree	0.91(0.73,1.13)	0.91(0.69,1.20)	0.87(0.68,1.11)	0.79(0.59,1.05)
Mediation		Probability (95% CI)		
Total effect	0.036(0.011,0.062)	0.002(-0.018,0.022)	0.032(0.003,0.061)	0.014(-0.010,0.039)
NDE	0.032(0.008,0.056)	-0.001(-0.022,0.020)	0.029(-0.001,0.058)	0.014(-0.008,0.035)
TNIE	0.004(-0.013,0.021)	0.003(-0.008,0.015)	0.004(-0.011,0.018)	0.001(-0.014,0.015)
CDE	0.038(0.013,0.063)	-0.002(-0.021,0.017)	0.030(0.006,0.054)	0.017(-0.007,0.040)

*The population was limited to those who did not continue to achieve higher level of qualification after age 23.

Table 17 Association between externalising problems/educational attainment by age 23 and problematic drinking (AUDIT) at age 45 and their mediating effect in NCDS58*

	NCDS58	
	male	female
Problematic drinking (AUDIT)	OR (95% CI)	
Externalising problems	1.13(1.01,1.26)	1.15(0.99,1.33)
Education		
No qualification	1.02(0.88,1.18)	1.42(1.18,1.70)
O-level	ref	ref
A-level	0.96(0.78,1.20)	0.80(0.61,1.04)
Degree	0.81(0.62,1.05)	0.80(0.58,1.09)
Mediation	Probability (95% CI)	
Total effect	0.035 (-0.001,0.071)	0.025 (-0.007,0.056)
NDE	0.036 (-0.001,0.072)	0.025 (-0.005,0.055)
TNIE	-0.001 (-0.019,0.018)	0 (-0.015,0.015)
CDE	0.035 (0.000,0.070)	0.019 (-0.011,0.050)

*Full AUDIT scale was only collected in NCDS58.

Table 18 Association of externalising problems and educational attainment by age 23 with various drinking indices at age 45 across sex and cohort

	NCDS58		BCS70	
	male	female	male	female
Drinking frequency				
Externalising problems	1.23 (1.08, 1.39)	1.07 (0.92, 1.24)	1.19 (1, 1.41)	1.16 (0.97, 1.38)
Education				
No qualification	1.05 (0.89, 1.23)	0.95 (0.8, 1.13)	1.2 (1, 1.44)	0.91 (0.71, 1.16)
O-level	ref	ref	ref	ref
A-level	1.21 (0.99, 1.47)	1.12 (0.91, 1.38)	1.15 (0.91, 1.45)	0.92 (0.71, 1.2)
Degree	1.28 (1.01, 1.62)	1.23 (0.96, 1.58)	1.06 (0.81, 1.38)	1.03 (0.77, 1.39)
Drinking quantity				
Externalising problems	1.2 (1.07, 1.36)	1.07 (0.91, 1.28)	1.25 (1.06, 1.47)	1.14 (0.95, 1.38)
Education				
No qualification	1.01 (0.87, 1.17)	1.41 (1.17, 1.69)	1.17 (0.98, 1.4)	0.9 (0.73, 1.11)
O-level	ref	ref	ref	ref
A-level	0.86 (0.7, 1.06)	0.67 (0.5, 0.91)	0.8 (0.61, 1.04)	0.69 (0.51, 0.94)
Degree	0.7 (0.56, 0.88)	0.55 (0.36, 0.84)	0.61 (0.45, 0.83)	0.41 (0.27, 0.62)
Can't stop drinking				
Externalising problems	1.41 (1.16, 1.71)	0.98 (0.79, 1.22)	1.18 (0.95, 1.46)	1.19 (0.97, 1.45)
Education				
No qualification	1.36 (1.05, 1.77)	1.78 (1.37, 2.31)	1.18 (0.94, 1.49)	0.95 (0.71, 1.26)
O-level	ref	ref	ref	ref
A-level	1.11 (0.75, 1.64)	1.08 (0.74, 1.58)	0.9 (0.66, 1.24)	0.76 (0.54, 1.07)
Degree	0.96 (0.59, 1.54)	0.83 (0.51, 1.35)	1.19 (0.89, 1.6)	0.74 (0.52, 1.06)
Fail to work				
Externalising problems	1.32 (1.07, 1.64)	0.95 (0.75, 1.21)	1.16 (0.92, 1.46)	1.11 (0.87, 1.42)
Education				
No qualification	1.03 (0.78, 1.37)	1.81 (1.3, 2.53)	1.19 (0.86, 1.66)	1.05 (0.77, 1.45)
O-level	ref	ref	ref	ref

A-level	1.11 (0.8, 1.55)	0.83 (0.51, 1.35)	1.07 (0.76, 1.5)	0.87 (0.6, 1.28)
Degree	0.81 (0.55, 1.21)	1.13 (0.67, 1.89)	0.72 (0.48, 1.1)	0.87 (0.56, 1.34)
Cause concern				
Externalising problems	1.15 (0.95, 1.4)	1 (0.78, 1.3)	1.32 (1.08, 1.61)	1.21 (0.95, 1.54)
Education				
No qualification	1.27 (1.01, 1.59)	1.58 (1.18, 2.13)	1.31 (1.04, 1.65)	1.08 (0.78, 1.5)
O-level	ref	ref	ref	ref
A-level	1.15 (0.85, 1.58)	0.94 (0.62, 1.41)	1.08 (0.79, 1.48)	0.86 (0.6, 1.23)
Degree	1.25 (0.9, 1.74)	0.65 (0.38, 1.13)	0.99 (0.71, 1.37)	0.84 (0.54, 1.31)

*Logistic regression was implemented, and thus results are reported as OR (95%).

Table 19 NDE, TNIE, CDE of externalising problems on daily drinking and drinking quantity through educational attainment

	Drinking frequency			Drinking quantity		
	Probability	SE	95% CI	Probability	SE	95% CI
NCDS58-male						
Total effect	0.039	0.014	(0.013,0.066)	0.041	0.015	(0.011,0.071)
NDE	0.037	0.018	(0.003,0.072)	0.034	0.020	(-0.005,0.073)
TNIE	0.002	0.013	(-0.023,0.028)	0.007	0.012	(-0.017,0.030)
CDE	0.035	0.013	(0.010,0.061)	0.039	0.015	(0.010,0.069)
NCDS58-female						
Total effect	0.012	0.015	(-0.016,0.041)	0.014	0.012	(-0.010,0.038)
NDE	0.010	0.015	(-0.020,0.039)	0.010	0.012	(-0.013,0.033)
TNIE	0.003	0.008	(-0.013,0.019)	0.004	0.008	(-0.012,0.021)
CDE	0.012	0.014	(-0.015,0.040)	0.010	0.011	(-0.012,0.032)
BCS70-male						
Total effect	0.025	0.013	(0.000,0.050)	0.039	0.013	(0.013,0.065)
NDE	0.019	0.013	(-0.007,0.045)	0.032	0.015	(0.002,0.062)
TNIE	0.006	0.010	(-0.013,0.026)	0.007	0.012	(-0.017,0.031)
CDE	0.024	0.012	(0.002,0.047)	0.038	0.014	(0.011,0.065)
BCS70-female						
Total effect	0.009	0.010	(-0.011,0.028)	0.012	0.011	(-0.009,0.033)
NDE	0.009	0.010	(-0.011,0.028)	0.009	0.011	(-0.013,0.032)
TNIE	-0.000	0.007	(-0.014,0.014)	0.002	0.007	(-0.012,0.017)
CDE	0.015	0.010	(-0.004,0.034)	0.018	0.013	(-0.008,0.044)

5.4 Discussion

To investigate how much of the association between adolescent externalising problems and mid-adulthood problematic drinking is mediated by educational attainment, formal mediation analysis under counterfactual framework was performed. In contrast to the hypothesis, there was no mediating effect of educational attainment by age 23 on the pathway from externalising problems at age 16 to problematic drinking in mid-adulthood. This finding was confirmed using two alternate analytical approaches: bootstrapping nested in multiple imputation and single stochastic imputation nested in bootstrapping. The fact that bootstrapping nested in multiple imputation approach provides a wider confidence interval is in accordance with the results from simulation studies [421,422], which offers further assurance of the validity of the results. A series of sensitivity analysis did shed further light on the null finding with respect to the role of education as a mediator.

First, the operationalization of educational attainment in the current study may influence the association between educational attainment and problematic drinking. As explained in the method section, education was defined as highest qualification achieved by age 23 to avoid unmeasured confounding factors and issues of intermediate confounding factors. However, some people who did not obtain a degree by age 23 would continue their education afterwards (Appendix 29 and Appendix 30), which would render the association between education and problematic drinking towards the null. In the literature where the association between educational attainment and alcohol use behaviours was established, highest qualification by midlife (around 35 year-old) was typically utilised [166–169,426]; or in other cases, educational attainment was vaguely defined either because of the cross-sectional design or oversimplification (e.g., binarizing attainment into obtaining high school qualification or not) [161,162,164,165,170]. Such definitions could easily overestimate the effect of educational attainment by disguising the underlying relationships [183]. However, sensitivity analysis excluding those individuals who continued to achieve higher qualifications after age 23 indicates that the operationalization of educational attainment in current study was less of an issue for the null findings.

Second, the null mediating effect might be due to the null association between educational attainment and problematic drinking in the current study (Table 14). Sensitivity analyses employing different drinking indices were carried out. When problematic drinking was constructed using the full AUDIT scale, the association between educational attainment and problematic drinking did tend to be away from null compared with that constructed using the shortened AUDIT-PC scale. However, this away-from-null bias was not large enough to explain the null mediating effect, because there was still no association between educational attainment and problematic drinking (constructed using the full AUDIT scale) and no mediating effect of educational attainment (see Table 17). When specific items of AUDIT-PC scale were employed as the outcome, in accordance with existing evidence [154,162,168,427], it was discovered that higher educational attainment was associated with higher probability of daily drinking but lower probability of 5 or more drinking units on a typical day (see Table 18). This helps explain the null findings on the association between educational attainment and problematic drinking: the associations of educational attainment with different phenotypes of alcohol use behaviours are opposite and thus cancel out when different phenotypes are used to construct the index for problematic drinking. Results in Table 13 and Table 18 show that higher externalising problems was associated with lower educational attainment and lower educational attainment was associated with lower probability of daily drinking and higher probability of 5 or more drinking units on a typical day. Thus, one would expect negative mediating effect of educational attainment between externalising problems and daily drinking and positive mediating effect of educational attainment between externalising problems and 5 or more units on a typical day (see Figure 20 for illustration). However, when using drinking frequency and drinking quantity as outcomes, still, no mediating effect of educational attainment was detected under any occasion (see Table 19).

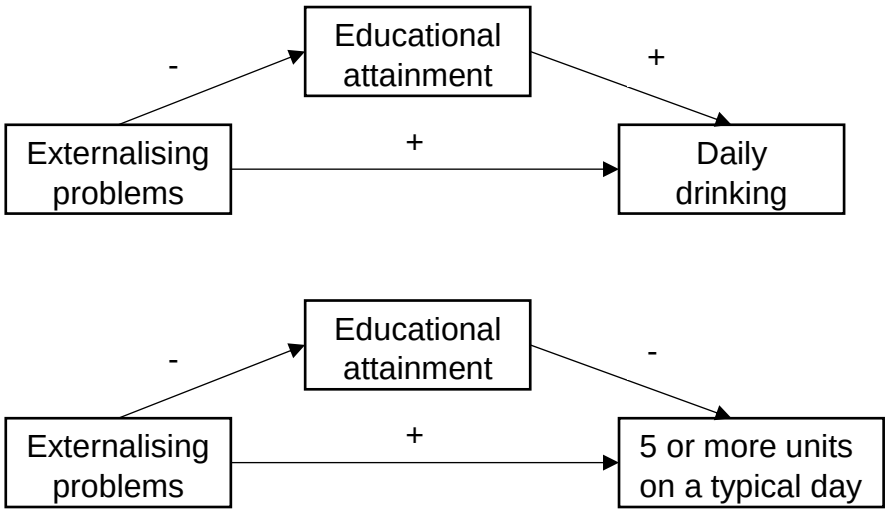


Figure 20 Simplified assumptions on the direction among externalising problems, educational attainment and drinking outcome

These findings bring up the population-specific interpretation of the mediating effects under counterfactual framework.

Theoretically and empirically, the effect of externalising problems on problematic drinking could be moderated by a series of factors [71,341], such as parenting style [86], religion [82], comorbidity of other mental disorders [82,83,219,351]. As illustrated by Hernan et al. [183], if the effect of the exposure is moderated by another variable but not modelled properly, the coefficient we get would be an average of the effect over different levels of the moderator and be null if the effect operates in the opposite direction. In practice, it is almost impossible to incorporate all the potential moderation effects in one model due to the finite statistical power to detect moderations in a real life dataset [428]. As a result, the estimate we get is typically an average effect of the exposure over all the potential moderators, which is seldomly interpreted as such in applied research. In contrast, the calculation of natural direct (indirect) effect is, by nature, equivalent to the marginal effect of the exposure (via the mediator) over the distribution of all the confounding factors in a specific population (it does not matter if one models the moderation effect properly in the model). Thus, they represent the natural direct and indirect of externalising problems on problematic drinking in the male or female British population born at a certain historical period. This means the alleviation of problematic drinking we could have achieved by intervening on

externalising problems to one standard deviation below the average was not through its effect on educational attainment by age 23 when other potential confounding factors were left unchanged; it does not indicate that there was no causal effect between externalising problems and educational attainment, or no causal effect between educational attainment and problematic drinking (causal effect among them could still exist at certain level of moderators, but it happens to cancel each other out in the marginal effect). In other words, intervening on educational attainment may still help alleviate alcohol burden in the population, but it would not alleviate the alcohol burden originating from early life externalising problems.

Furthermore, in observational studies, there is usually no clear, well-defined and binarized concepts of intervention/control as in experimental studies. As illustrated in section 5.2.3, under the counterfactual framework, the “experimental group” was defined as the population where externalising problems of each individual were intervened to one SD below the average; the “control group” was defined as the population where externalising problems of each individual were as they were observed. Thus, different from the interpretation of the results in traditional regression-based analysis-contrast between two artificial populations where everyone has the same level of all conditions except for externalising problems, the interpretation of current results under the counterfactual framework has more implications for intervention and policymaking. It indicates the percentage of problematic drinking we could have reduced on the population level if externalising problems had been reduced through intervention to one SD below the average back in 1974/1986 (when participants were at age 16), and how much of the alleviation was through the redistribution of educational attainment in the population because of the “intervention”. To be more specific, results (see Table 15) indicate that we could have reduced 4~7% of problematic drinking in males if their externalising problems had been reduced to one SD below the average, but any achieved reductions in externalising problems of females would not achieve any reduction in their prevalence of problematic drinking. In addition, the alleviation of problematic drinking among males was not through the redistribution of education.

5.4.1 Strengths and limitations

Strengths of the current study include the availability of two population-based prospective birth cohorts with a follow-up of alcohol use until mid-adulthood. To the best of my knowledge, this is the first attempt to apply formal mediation methods in the field of alcohol studies. However, applying formal mediation analysis does not make the estimates in current study causal in any sense. Factors that threaten the causal interpretation mediation analysis still exist as in all observational studies, such as unmeasured confounding factors—including intermediate confounding factors—and measurement error. However, efforts were made to minimize those threats by pointing them out explicitly, drawing DAG to understand the underlying relationships, adjusting for a series of confounding factors and defining the mediator meticulously. As pointed out by Hernan [180], "scientific euphemisms do not improve causal inference from observational data". Typically, in observational studies, researchers do not acknowledge the causal goal of a research project and use associational terms. However, they adjust a series of confounding factors in the model, which is a way of ensuring assumption of exchangeability in causal inference [183]. The conflict between claim and practise would not propel the progression of science but possibly impede it by presenting a mixed picture of associations which might be purely due to different analytic strategies. Claiming associational terms is a short-cut to explore the relationship between two variables by ignoring the assumptions behind causal inference [183], and thus should not be encouraged, especially for mediation analysis which aims to elaborate underlying mechanisms. By applying causal mediation analysis in a national representative sample, the current study has some implications for population-level alcohol prevention in the UK. Though no studies so far has explored how the association between externalising problems and problematic drinking vary across cultures, cultural norms and beliefs are strong predictors of alcohol use/misuse [147], and country-specific studies will help inform their own policy-making. For example, country-specific analysis on a national representative sample would provide evidence for cost-effectiveness analysis when developing an intervention or policy [429]. Third, by exploring potential reasons for the null results, this study reveals the importance of explicit definitions for both mediator and outcome, which is also a key component in

causal inference [183]. Fourth, rigorous analytic strategies are conducted to ensure the validity of the results. Not every analytic decision is supported by simulation studies and each strategy has its advantages and disadvantages in the applied scenario, thus they were all explored in the current study to avoid bias due to random choice of analytical strategies.

Several limitations need to be considered. First, the link between education and alcohol use can be in both directions depending on the phenotypes of the outcomes [373,430]. The AUDIT-PC scale used to detect problematic drinking in the current study increase the risk of false positive (Appendix 32). Though sensitivity analysis using AUDIT scale in NCDS58 returns similar results, caution should be taken when interpreting the null mediating effect of education. Second, other factors (e.g., employment, income, marital status) which are closely related to educational attainment may moderate the association between educational attainment and alcohol outcomes [431,432] but were not considered in the current study. Formal mediation analysis with multiple mediators could be carried out to articulate the mechanisms in the future [433,434].

5.5 Conclusion

No mediating role of educational attainment on the pathway from adolescent externalising problems to problematic drinking in mid-adulthood was detected. This was ascertained through two analytical approaches: bootstrapping nested in multiple imputation and single stochastic imputation nested in bootstrapping. In the UK population, leaving other confounding factors unchanged, the alleviation of alcohol burden we could have achieved by intervening early life externalising problems was not through educational attainment.

6. Chapter 6 Dual trajectories of problematic drinking and stressful life events from adolescence to young adulthood

6.1 Introduction

For several decades, alcohol researchers proposed typologies of pathological alcohol use based on personal characteristics such as sex, family history of alcoholism, onset of drinking, personality, and comorbid psychopathology [69–71]. These typologies have largely been supported by empirical approaches following the increased availability of long-term prospective studies and advances in analytic strategies for longitudinal data, such as hierarchical generalized linear models, growth mixture models, latent class growth models, and longitudinal latent class models [435,436]. Despite differences in various samples' mean age and age range, number of assessments and duration of the observation period, and indices for alcohol use behaviour, four trajectories of alcohol use have typically been identified across studies: a consistently low alcohol use group, a group whose alcohol use increases over time, a group whose alcohol use decreases over time and a consistently high alcohol use group [68]. These findings raised concerns that the trajectories may be an artefact of the statistical models used [68,437].

The identified alcohol use trajectory groups, however, have been shown to differ on a number of theoretically relevant variables, indicating these trajectory analyses can be useful in both establishing individual differences in alcohol over time and identifying developmental processes that contribute to differences in alcohol use problems. For example, the consistently high and low alcohol use groups differ with respect to sex [344,438,439], behavioural disinhibition, sensation seeking, risk taking [344,438,440–443], negative emotionality [344,440,442–444], conduct problems [441,442,444,445], alcohol expectancies [442,443], educational achievement [441,444,446], early-onset of alcohol use [444–447], parental alcohol use and other psychiatric problems [344,442,444–446], and family socio-economic-status [443,444]. However, differences among

the other identified classes are fewer, smaller, and less reliable [344,439,442,448]. Notably, the majority of previous studies used predictors observed only at baseline and ignored the developmental nature (continuity and discontinuity) of alcohol use behaviours [74,91,368] and predictors. This might be the reason why results are equivocal about the predictors that can differentiate between the decreasing/increasing and consistently high/low trajectories.

Apart from externalising and internalising problems, stress, which is typically measured using external life stressors, such as stressful life events (SLE), is another risk factor shown to be consistently related to alcohol use [35,57,449–452]. Several explanations—positing both direct and indirect mechanisms—have been proposed to account for their association. One is the tension reduction hypothesis which posits that individuals use alcohol to reduce stress [37]. This is directly supported by intensive longitudinal studies finding higher stress levels before drinking sessions and lower stress levels after drinking sessions [41,453], and by studies that utilized coping motives as an outcome [38,454]. SLE may also contribute to alcohol use/misuse indirectly by increasing risk for depressive symptoms [55–57], externalizing symptomatology (e.g., impulsivity) [58–60] and an earlier-onset of drinking [52,58,61,455]. Several models, such as the stressor vulnerability model [45] and stress response dampening theory [46], emphasize that the effects of SLE on alcohol use may differ across individuals. For example, the association could be moderated by genetic variants [47,455], biological sex [35,47,48], coping strategies [49,50], negative emotionality [38], occurrence of positive events [50], family and peer support [52], and personality disorder [450]. At the neurocognitive level, SLE may increase risk for drinking by disrupting circuits in the brain [52] that regulate stress response [62,63], inhibitory control [60,64] and reward [64–66].

However, the above-mentioned theories are mostly tested using variable-based analysis, which examines interindividual differences and ignores the intraindividual changes over time. As explained in section 1.5, two components must be differentiated when exploring longitudinal relationships: between-person effects and within-person effects [176]. As defined by Curran et al. [176], between-person effects address questions of whether individuals who experience

more SLE consume greater quantities of alcohol compared with those who experience less SLE, and whether individuals who report systematic changes in SLE over time are more likely to also report systematic changes in alcohol use over time. Effects summarising systematic changes (within-person trends) of two time-varying variables are seen as between-person effects, because “the overall levels and smoothed change over time are characteristics of the individual, and these individually-varying characteristics are thought to covary in. potentially meaningful ways” [176]. In contrast, within-person effects address questions of whether an individual who experiences higher levels of SLE *relative to his/her underlying level of SLE* at one point in time is more likely to consume more alcohol *relative to his/her underlying level of alcohol use* at a subsequent point in time. In other words, do individuals drink *more than usual* on days when they experience *more SLE than usual*?

Few attempts have been made to study the relationship between SLE and alcohol use longitudinally. Among those that did, more focus was put on time-specific, within-person effects rather than between-person effects over time [41,42,178,196,449,456]. For example, latent growth curve models with time-varying variables were typically applied to investigate the within-person effects of SLE on alcohol outcomes [42,176,196,456]. Conceptually, this analytic strategy is appropriate when data were collected daily or over the short term, whereby within-person effects can take place [42,456]. In other words, it is problematic to draw conclusions about within-person effects from data reflecting average levels of recalled stress and drinking behaviours [42]. Methodologically, such analysis implicitly blends the between- and within- person effects into one estimate and treats it as the within-person effect [176,177,457]. This could easily lead researchers to misinterpret their results and come to an inaccurate conclusion [176,457], such as trying to explain the between-person differences of drinking trajectories using the “within-person effects” (a mixture of between- and within-person effects) of SLE on drinking. Also, such analysis omits the latent growth process that may underlie SLE (see discussion in section 1.5.2) [176], and fails to examine how alcohol outcomes and SLE co-develop systematically over long the term.

Long-term longitudinal data that examine the co-development of alcohol use and SLE over many years is limited, but is essential for better understanding the mechanisms of their association [178,196,449]. Rather than being transient and random, longitudinal studies indicate that population-level SLE are relatively stable over time [195,458,459]. However, how level of SLE changes over time within individuals, and how SLE vary with concurrent alcohol use over the long-term has yet to be examined. Adolescence and young adulthood is a critical period for the onset and escalation of alcohol use, as well as numerous social context transitions (e.g., independence from family, socialization with peers) [26]. Understanding how alcohol use and SLE co-develop during this prime period is essential for better understanding the mechanisms underpinning their association.

Group-based dual trajectory modelling is designed to address such questions by identifying latent groups that follow similar trajectories across multiple variables [197]. It differs from conventional group-based trajectory model, because it allows for analysing the interrelationship between two variables over time and highlights the heterogeneity in the linkage between trajectories of distinct outcomes [197]. Comparing classes derived using one variable (alcohol index or SLE) to classes derived using two variables (both alcohol index and SLE) will offer new insights regarding their interdependence over time and the relative importance of each variable to adjustment. Several risk factors consistently associated with drinking behaviours can help validate alcohol and SLE class trajectories [29,341,460], such as parental alcoholism [461], cigarette and marijuana use [462], externalizing problems [74,367]; substance use of peers [463]. The time-varying nature of some risk factors will also provide a holistic picture of how those variables evolve over time.

To the best of my knowledge, no studies thus far have explored how alcohol use and SLE co-vary with each other across sub-groups undergoing developmental change from adolescence to young adulthood. This chapter aims to fill this gap by fitting a group-based dual trajectory model to alcohol use and SLE data in a longitudinal study of participants at elevated risk for substance use problems. As discussed before, within-person effects are better examined using data collected

daily, and thus are not investigated in the current study. In addition, as an external validation, the distribution of a series of theoretically relevant time-invariant and time-varying factors across derived classes was also examined [29,341].

6.2 Method

6.2.1 Sample

Participants were members of the Michigan Longitudinal Study (MLS), a prospective, high-risk community-based study designed to investigate the development of substance use disorders [288,289]. Three types of families were recruited. First, men were identified via arrest records for drunk driving in a four county-area in central Michigan. These men had to meet criteria for AUD and reside with a biological son aged 3-5 years-old and the child's mother at the baseline assessment. Second, control families were recruited by canvassing the same neighbourhoods as the court identified families. Control families had the same family-structure, but neither parents met criteria for a lifetime alcohol or drug use disorder diagnosis. A third, intermediate-risk family type was identified during the neighbourhood canvass; these families included a father who met criteria for AUD and a 3-5-year-old son but did not have a drunk driving or other alcohol-related arrest. For both father-AUD groups, mother diagnosis was free to vary. All siblings of the male targets within +/- 8 years of age were also added to the study in later waves. Final sample involves 467 families (1050 target participants: 742 males, 308 females), 460 mothers, 450 fathers, as well as 84 stepparents.

Extensive in-home assessments were conducted at 3-year intervals, and briefer annual assessments were conducted when the target participants were 11 to 26 years-old. All available data was organized into 2-year intervals based on participants' age at each assessment, which resulted in 9 waves from ages 12-13 to 28-29 years-old. As 92% of participants at ages 12-13 had yet to initiate alcohol use and the data sparseness at this wave resulted in model identification problems, this wave was dropped from the analysis, leaving 8 waves for longitudinal modelling. To ensure adequate reliability when modelling individual

trajectories of problematic drinking and SLE, only participants who had complete data for at least 3 assessments were retained in the current analyses. This yielded a sample of 714 participants (493 males, 221 females).

6.2.2 Measures

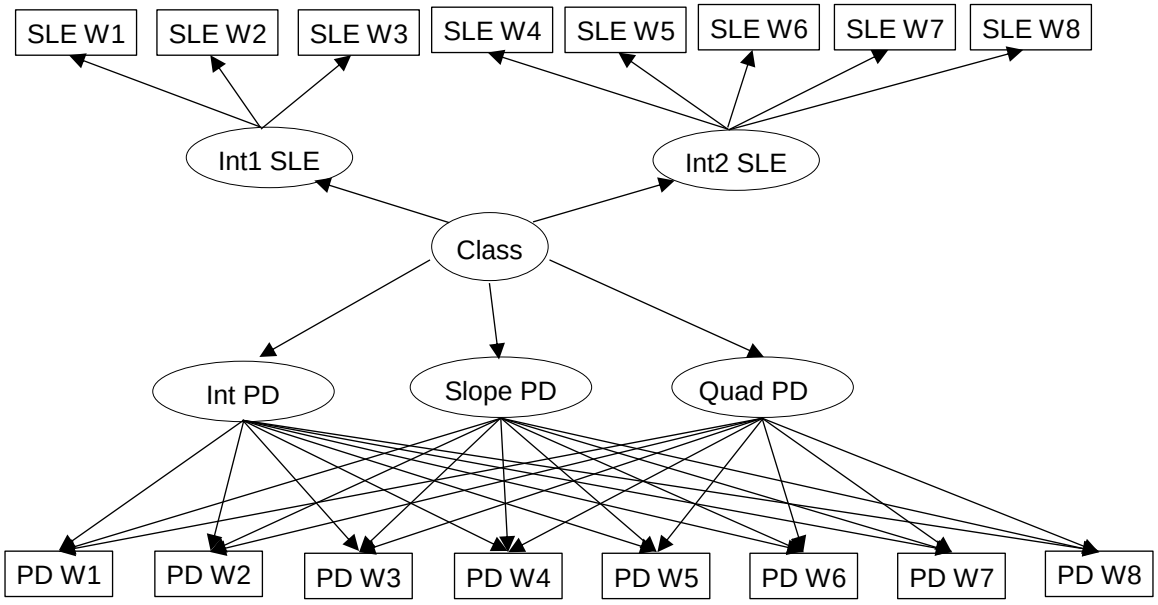
Problematic drinking

The Drinking and Drug History Questionnaire was used to collect information on the participants' alcohol and drug use [305]. Items covered quantity, frequency, age of onset, and consequences and problems related to alcohol and drug use. A composite measure of problematic drinking was calculated using number of drinking days per month, typical drinking quantity per occasion, maximum number of drinks consumed in 24 hours, and number of intoxications in the past 12 months, as done in prior research [308,309]. Values on the four measures were recoded into a 0 to 8 scale (Appendix *33*), and the mean of these values was used for the problematic drinking composite score.

Stressful life events (SLE)

Family Crisis List is a 40-item list of family-related troubles covering seven domains (family, household, economy, health, school, legal, social) [307]. Parents of the target participants reported whether a particular event had ever happened to their family, and if "Yes", they indicated when this event occurred (last 6 months, 6 months to 1-year ago, 2-years prior). The event was counted as having happened as long as it was reported by either of the parents. Upon reaching adulthood (ages 18-20), the target participants completed the Family Crisis List based on their personal experiences. Twenty-one events that were considered as a serious crisis in the family (e.g., conflict with ex-partner, physical fight, do not have enough money, injured/non-injured accident, someone died) were utilised to construct parent-reported SLE, while 15 events (excluding 6 events that were school-related and reported only by parents) were used for self-reported SLE. The incomparability of SLE across waves was dealt with by

modelling two separate trajectories as in Figure 21. The distribution of each item across waves is listed in Appendix 34.



Factor load for each latent variable from wave 1 to wave 8:
Int1 SLE: 1, 1, 1
Int2 SLE: 1, 1, 1, 1, 1
Int PD: 1, 1, 1, 1, 1, 1, 1, 1
Slope PD: 0, 2, 4, 6, 8, 10, 12, 14
Quad PD: 0, 4, 16, 36, 64, 100, 144, 196

Figure 21 Statistical framework for group-based dual trajectory analysis between problematic drinking and stressful life events

Note. W1-8 after SLE (stressful life events) and PD (problematic drinking) indicates each wave when SLE and PD were measured (from age 14-15 to age 28-29); Int = Intercept; Quad = Quadratic terms for latent curve model respectively; Term “class” represents the latent classes derived using the intercept, linear slope, and quadratic terms.

To ensure a sufficient sample size at each 2-year interval, the Family Crisis List was chosen to assess level of SLE, because it was the only scale collected at both 3-year and annual assessments. As some of the parent-reported SLE were not experienced by the target participants and thus may not reflect their stress level, distributions of other stress-related scales across derived classes over time, namely Coddington Life Stressors (as introduced in section 3.2.2), were depicted as a post hoc check.

Coddington Life Stressors inquiries about life events in the previous three years (past 6 months, the 6 months before that and the previous two years) of the child's

life [291,292]. This measure was reported mainly by mothers before the child was aged 15 and self-reported by the target participants thereafter. Events that were previously rated as negative life events and utilised to characterise the life stressors of children of alcoholic parents were selected [464] (Appendix 35). Notably, two versions of events questionnaires were used over time: the child form (30 negative events) and young adult form (27 negative events). In addition, at age 18~20, 37.7% of the target participants answered the child form and the rest answered the young adult form. To ensure comparability of the scale, the young adult form was calibrated to match the child form [105]. To be specific, a participant's score was summed across events from the young adult form and then was divided by 27, and finally multiplied by 30.

Time-invariant and time-varying risk factors

Several variables associated with AUP were used to validate the resulting trajectory classes. Time-invariant variables included biological sex, family history of alcoholism, adverse childhood experiences (ACEs) before age 11, and age at first drink. Time-varying variables included externalising problems, internalising problems, smoking status in the past year, number of marijuana use occasions in the past year and peer involvement in substance use. These additional variables were collected at both the 3-year interval and annual assessments. Details regarding how they were operationalised are in section 3.2.4.

6.2.3 Statistical analysis

First, latent growth curve models were fit to determine the appropriate curve function for problematic drinking and SLE [198,465]. This entailed fitting separate models for problematic drinking and SLE to determine the most appropriate descriptive shape for the mean trajectory (intercept only, linear slope, quadratic curve, etc.). Model fit was evaluated using several indices including the χ^2 test, Root Mean Square Error of Approximation (RMSEA), Comparative Fit Index (CFI), Tucker Lewis Index (TLI), Standardized Root Mean Square Residual (SRMR) [466].

Next, latent class growth models were fit to problematic drinking and SLE to explore the optimal number of latent classes for problematic drinking and SLE separately. Fit for these models was evaluated using the adjusted Bayesian Information Criteria (aBIC), Entropy, class probability, class interpretation and Lo-Mendell-Rubin adjusted Likelihood Ratio test (LMR-LRT) [467–469].

Finally, a group-based dual trajectory model was fit for problematic drinking and SLE simultaneously. Model fit was evaluated using the same indices for assessing latent class growth models. The statistical framework is presented in Figure 21. Growth parameters (intercept, slope, quadratic coefficients) of both problematic drinking and SLE were simultaneously estimated and used to derive classes of individuals that had similar characteristics in problematic drinking and SLE trajectories.

After identifying latent classes, the distribution of other risk factors across classes were compared for the purpose of external validation (ANOVA test for continuous variables and χ^2 test for trend for categorical variables [470]). Characteristics of time-varying variables were summarised using either latent score or latent classes depending on their respective model fit. After a series of exploratory analyses, a latent growth curve model was fit for externalizing and internalizing problems simultaneously [471,472], a latent class growth curve model for peer involvement in substance use and a longitudinal latent class analysis for categorical outcomes (smoking status and number of marijuana use occasions) [436,473,474]. See Appendix 44 for details on model fit indices of alternative models.

Data cleaning and analyses were carried out in Stata MP 14 and Mplus version 8.0. Models were fit using robust full information maximum likelihood estimation clustered by family to adjust standard errors for the non-independence of participants from the same family, to account for missing data, and to reduce bias due to the non-normal distributions of certain study variables [475,476].

6.3 Results

6.3.1 Descriptive results

Means and standard deviations for problematic drinking and SLE for the retained 714 participants across waves are reported in Table 20. There was an upward trend in participants' alcohol use over time, which peaked at age 22-23 then decreased slightly. By contrast, the trends for SLE were relatively stable, for both parent reports (ages 14-15 to 18-19) and self-reports (ages 20-21 to 28-29). Based on parent reports, the most common family-level SLE (35~50%) were having no money, death of relatives, having check bounced and non-injury-inducing accidents. Based on self-reports, the most common individual-level SLE (~50%) was family moving, followed by having no money, death of relatives and non-injurious accidents (15%~30%) (Appendix 34).

Table 20 Descriptive statistics for problematic drinking and stressful life events across waves*

		Wave1	Wave2	Wave3	Wave4	Wave5	Wave6	Wave7	Wave8
	Age	14-15	16-17	18-19	20-21	22-23	24-25	26-27	28-29
PD	Mean	0.44	1.30	2.00	2.67	2.92	2.91	2.65	2.58
	SD	1.03	1.73	1.87	1.84	1.65	1.61	1.60	1.54
	N	637	648	513	545	547	493	409	280
SLE	Mean	4.62	4.87	4.62	2.01	2.17	2.05	2.08	1.89
	SD	2.91	3.21	3.02	1.72	1.74	1.53	1.76	1.70
	N	376	407	422	437	539	478	390	275

*PD = problematic drinking; SLE = stressful life events.

6.3.2 Latent class analysis of univariate variable

Latent class analysis of problematic drinking

For problematic drinking, a model with an intercept factor, linear slope factor, and quadratic slope factor improved model fit over simpler models, and provided the best overall fit to the data, χ^2 (27) = 157.42, p < .001, RMSEA = .080, CFI = .904, TFI = .904, SRMR = .072. Next, it was examined whether the individual variation in growth curves for problematic drinking could be summarised by a small number

of latent classes. Though aBIC indicated that more classes improved model fit, other indices indicated that a 3 class-solution provided the best balance of overall fit and parsimony (see Table 21). Appendix 40 plots the within-class trajectory of problematic drinking under different solutions and also justifies the 3-class solution: the 3-class solution identified a class of individuals whose drinking was consistently high over the period which was not detected in a 2-classes solution, and a 4-class solution did not add new information.

In the 3-class solution, drinking behaviours of 303 (42.4%) individuals were normative, that is, low at the beginning and increasing slowly over time. Drinking behaviours of 348 (48.7%) individuals escalated rapidly during adolescence and stayed at a high level over their 20's. A small portion of individuals (63 [8.9%]) fell into the class whose drinking was consistently high over the whole period.

Latent class analysis of SLE

First, a growth curve model with two random intercepts (one for parent-reported SLE and one for self-reported SLE) was fit. The intercepts were allowed to be correlated (0.858). Model fit was good, χ^2 (31) =48.02, p = .03, RMSEA=0.028, CFI = 0.96, TFI = 0.96, SRMR = .065. Adding slopes did not yield a significant improvement in model fit; thus, a two intercept-only growth curve was retained for parent-reported and self-reported SLE (see Figure 21). The 3-class solution was judged to be the best for grouping SLE in the latent class growth modelling (Table 21 and Appendix 41).

In the 3-class solution, the majority of individuals (479 (67.1%)) were exposed to a low level of both parent-reported and self-reported SLE over time. 158 (22.1%) individuals were exposed to quite high level of parent reported SLE but low level of self-reported SLE. A small portion of individuals (77 (10.8%)) experienced high level of both parent-reported and self-reported SLE over time.

Table 21 Model fit for univariate and multivariate latent class growth curve analysis (n=714)

	aBIC	Entropy	Probability*	Proportions	LMR-LRT
	Problematic drinking				
2 classes	13965.8	.85	C1: .959	C1: 329 (46.1%)	< .001
			C2: .956	C2: 385 (53.9%)	
3 classes	13330.4	.86	C1: .937	C1: 303 (42.4%)	.01
			C2: .930	C2: 348 (48.7%)	
			C3: .938	C3: 63 (8.9%)	
4 classes	13060.4	.81	C1: .924	C1: 202 (28.3%)	.31
			C2: .873	C2: 294 (41.2%)	
			C3: .924	C3: 153 (21.4%)	
			C4: .878	C4: 65 (9.1%)	
5 classes	12828.1	.82	C1: .921	C1: 192 (26.9%)	.72
			C2: .849	C2: 274 (38.4%)	
			C3: .839	C3: 163 (22.8%)	
			C4: .914	C4: 54 (7.6%)	
			C5: .932	C5: 31 (4.3%)	
	Stressful life events				
2 classes	14021.8	.72	C1: .940	C1: 548 (76.8%)	.006
			C2: .848	C2: 166 (23.3%)	
3 classes	13879.2	.72	C1: .911	C1: 479 (67.1%)	.009
			C2: .792	C2: 158 (22.1%)	
			C3: .829	C3: 77 (10.8%)	
4 classes	13837.2	.73	C1: .891	C1: 461 (64.6%)	.30
			C2: .742	C2: 130 (18.2%)	
			C3: .800	C3: 104 (14.6%)	
			C4: .838	C4: 19 (2.7%)	
5 classes	13808.6	.73	C1: .875	C1: 422 (59.1%)	.08
			C2: .875	C2: 136 (19.0%)	
			C3: .749	C3: 121 (16.9%)	
			C4: .812	C4: 24 (3.4%)	
			C5: .900	C5: 11 (1.5%)	
	Problematic drinking and stressful life events				
2 classes	28326.5	.84	C1: .957	C1: 329 (46.1%)	<0.001
			C2: .956	C2: 385 (53.9%)	
3 classes	27624.3	.87	C1: .936	C1: 300 (42.0%)	<.001
			C2: .949	C2: 343 (48.0%)	
			C3: .912	C3: 71 (9.9%)	
4 classes	27356.5	.81	C1: .921	C1: 198 (27.7%)	.19
			C2: .868	C2: 278 (38.9%)	
			C3: .860	C3: 179 (25.1%)	
			C4: .912	C4: 59 (8.3%)	
5 classes	27127.4	.83	C1: .928	C1: 200 (28.0%)	.65
			C2: .864	C2: 285 (39.9%)	
			C3: .871	C3: 138 (19.3%)	
			C4: .898	C4: 50 (7.0%)	
			C5: .898	C5: 41 (5.7%)	

*The probability of belonging to the assigned class, averaged over individuals within the class.

6.3.3 Group-based dual trajectory analysis

Based on all available fit indices and class interpretability, the 3-class solution was judged to be the best model to summarise dual trajectories of problematic drinking and SLE (Table 21 and Appendix 42).

Parameters (intercept, slope, and quadratic terms) that characterized trajectories of problematic drinking and SLE within each class are shown in Figure 22. Class 1 included 300 (42.0%) participants that exhibited a normative increase of problematic drinking and low level of both parent-reported and self-reported SLE across adolescence and young adulthood (Normative alcohol, low stress [NA-LS]). Class 2 included 343 (48.0%) participants and was characterized by a rapid escalation of problematic drinking from ages 14-15 to ages 22-23 and a decline afterwards, and low level of both parent-reported and self-reported SLE (Escalating alcohol, low stress [EA-LS]). Class 3 included 71 (9.9%) participants and was characterized by consistently high levels of both problematic drinking and SLE trajectories (High alcohol, high stress [HA-HS]).

As an exploratory analysis, the distributions of single events are described in Figure 23 (exact numbers are presented in Appendix 43). In general, prevalence of parent-reported single events were higher in the HA-HS class compared with the other two classes, especially school-related events for the target participants (e.g., child sent home from school, suspended from school, skipped school) (see Figure 23). The divergence in prevalence of SLE between the HA-HS class and the other two classes was more apparent in terms of self-reported events, especially money-related (e.g., having no money, check bounced, applying for welfare) and interpersonal events (conflict with ex, physical fight, disagreement with friends).

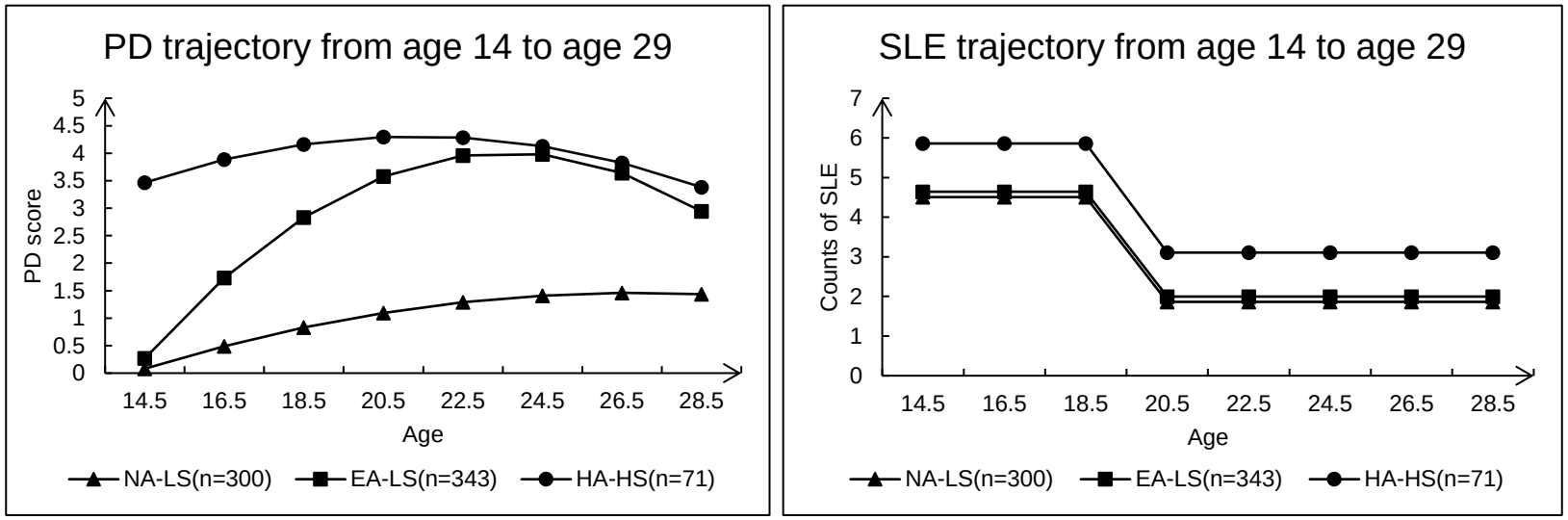


Figure 22 Group-based dual trajectory model for problematic drinking and stressful life events: 3-class solution*

*For each pair of problematic drinking (PD) and stressful life events (SLE) solution. Each class was constituted with the same participants; NA-LS refers to normative alcohol and low stress group; EA-LS refers to escalating alcohol and low stress group; HA-HS refers to high alcohol and high stress group.

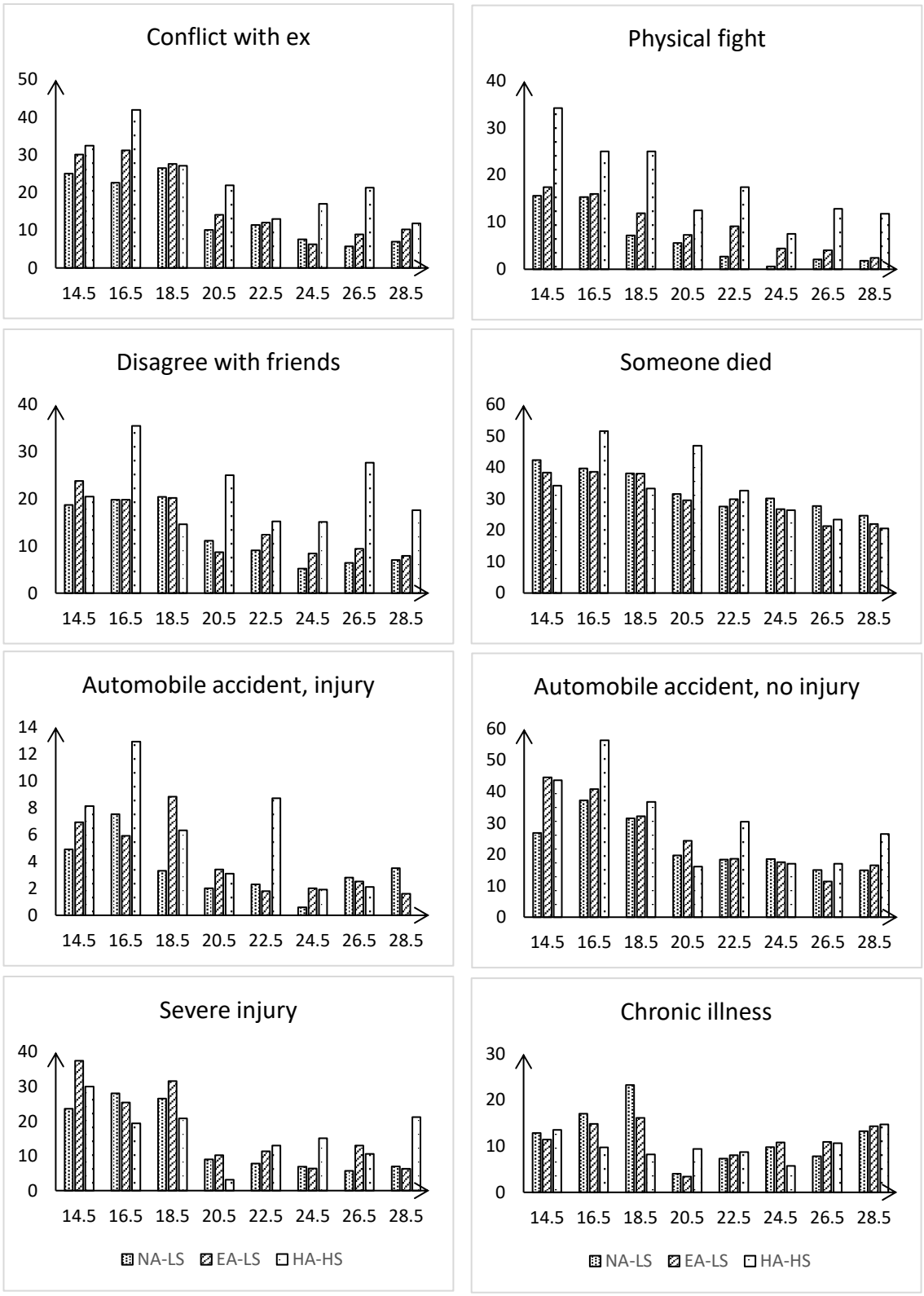


Figure 23 Occurrence of specific stressful life events across problematic drinking-stressful life events classes and waves (%)*

*NA-LS refers to normative alcohol and low stress group; EA-LS refers to escalating alcohol and low stress group; HA-HS refers to high alcohol and high stress group.

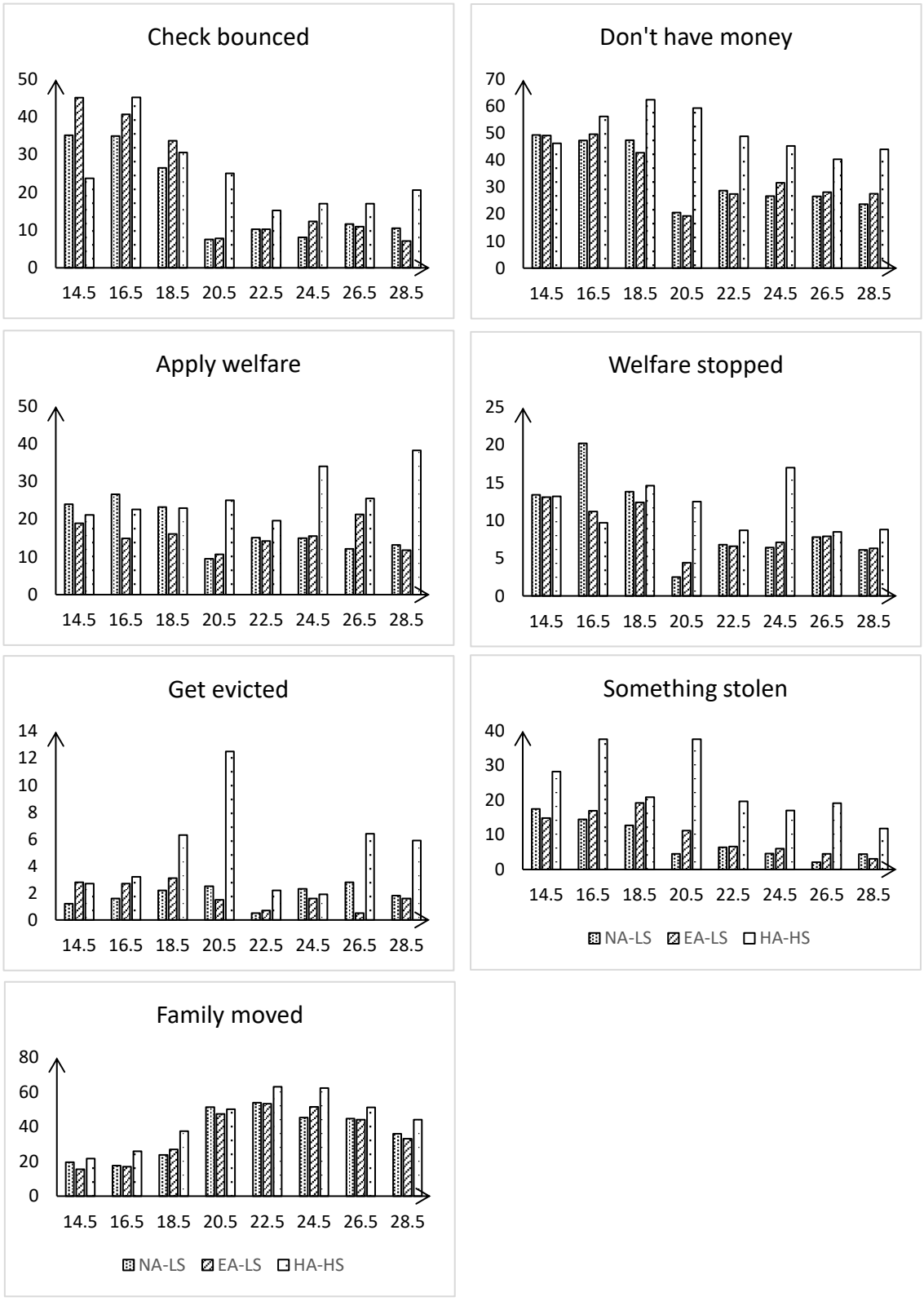


Figure 23 Continued.

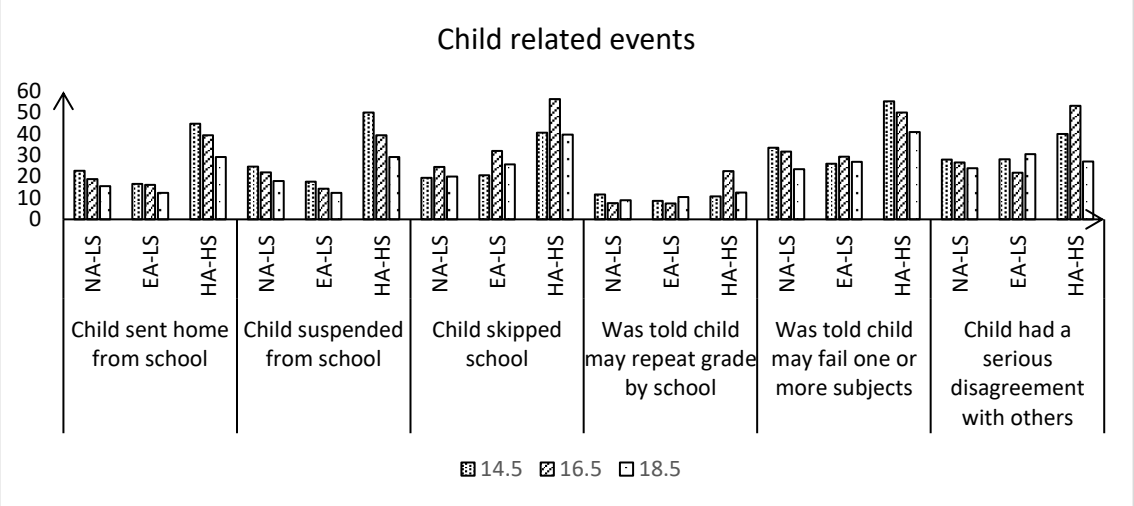


Figure 23 Continued.

6.3.4 Class differences on time-invariant and time-varying risk factors

Class differences on external risk factors are reported in Table 22. The proportion of males was highest in the EA-LS class. Rates of family history of alcoholism showed a statistically significant gradient across classes (NA-LS < EA-LS < HA-HS) as did age of first drink (HA-HS < EA-LS < NA-LS). Participants in the EA-LS and HA-HS classes reported significantly more ACEs than the NA-LS group.

Table 22 Distribution of external variables across classes

	Normative Alcohol-Low Stress	Escalating Alcohol-Low Stress	High Alcohol-High Stress	*P* value
N	300 (42.0%)	343 (48.0%)	71 (10.0%)	
Sex				
Male	176 (58.7%)[a]	271 (79.0%)[b]	46 (64.8%)[a]	< .001
Family History of Alcoholism				
Yes	166 (56.1%)[a]	238 (70.0%)[b]	61 (85.9%)[c]	< .001
First drinking age (years old)[#]				
<=11	10 (3.6%)	31 (9.6%)	12 (20.0%)	< .001
12-14	40 (14.6%)	118 (36.4%)	46 (76.7%)	
15-17	36 (13.1%)	75 (23.2%)	2(3.3%)	
>=18	188 (68.6%)	100 (30.9%)	0 (0.0%)	
ACEs before age 11	3.7 (2.2)[a]	4.4 (2.5)[b]	4.3 (2.3)[ab]	.001
Externalising problems				
Intercept	9.6[a]	11.3[b]	15.9[c]	< .001
Slope	-2.68[a]	-2.78[a]	-4.47[b]	< .001
Internalising problems				
Intercept	9.1[a]	9.0[a]	12.7[b]	< .001
Slope	0.25	0.06	-0.68	.33
Last year smoking status				
Non-user	200 (76.6%)	112 (35.8%)	8 (14.0%)	< .001
Adolescent-limited	32 (12.3%)	111 (35.5%)	16 (28.1%)	
Heavy user	29 (11.1%)	90 (28.8.3%)	33 (57.9%)	
Last year marijuana use occasions[#]				
Non-user	203 (77.8%)	126 (40.3%)	6 (10.5%)	< .001
Adolescent-limited	34 (13.0%)	91 (29.1%)	19 (35.1%)	
Heavy user	24 (9.2%)	96 (30.7%)	29 (54.4%)	
Peer substance use status				
Normative	229 (76.3%)	76 (22.2%)	2 (2.8%)	< .001
Escalating	68 (22.7%)	249 (72.6%)	31 (43.7%)	
Deviant	3 (1%)	38 (5.2%)	38 (53.5%)	

The latent curve model with a linear trajectory (an intercept and a slope term) had adequate fit for both externalising and internalising problems (Appendix 44). All classes differed on the initial level of externalising problems (NA-LS < EA-LS < HA-HS), but the differences became narrower over time with the level of externalising problems declining over time. For internalising problems, the HA-HS class had a higher initial level than the NA-LS and EA-LS classes, and the differences persisted over time with the level of internalising problems staying stable over time (see Appendix 47 for visual illustration).

Longitudinal latent class model with three classes was judged to best describe smoking status and marijuana use over time (Appendix 44 and Appendix 45) and was labelled as non-users, adolescent-limited users, and heavy users respectively. Over half of the participants in the HA-HS class were heavy cigarette (55.6%) and marijuana (53.7%) users, while the majority of participants in NA-LS class were non-users of cigarettes (76%) and marijuana (78%) (see Table 22).

Latent class growth curve analysis (see statistical framework in Appendix 43) indicates that the three-class solution also best described heterogeneity for peer involvement in substance use (Appendix 44): a class with a normative increase but relatively low level of substance use (48.7%; Normative peers); a class with a rapid escalation in substance use by age 22-23 before decreasing slightly (43.8%; Escalating peers); and a class with consistently high levels of substance use (7.6%; Deviant peers). The respective trajectories are depicted in Figure 24. Comparing across problematic drinking-SLE classes (see Table 22), 76.3% of the participants in NA-LS class were in the Normative class, 72.6% in the EA-LS class were in the Escalating class, and 53.5% in the HA-HS class were in the Deviant class.

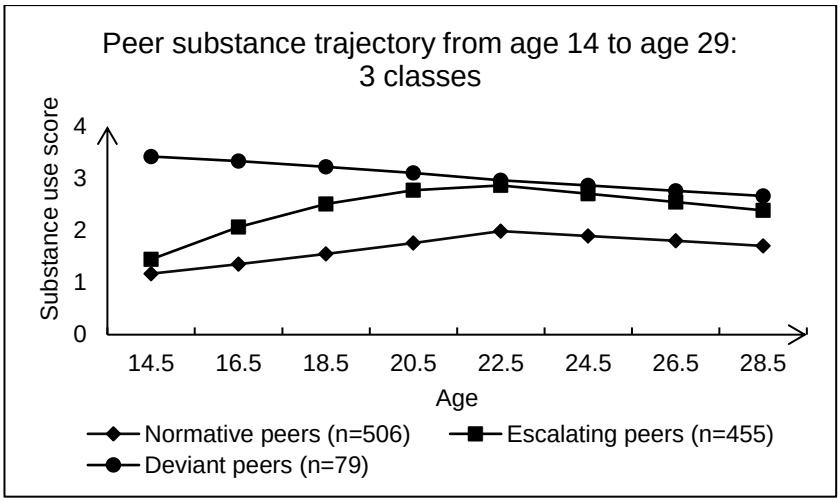


Figure 24 Classes of peer substance use trajectory

6.3.5 Post-hoc check

As shown in Figure 25, the mean levels of SLE measured by the Coddington Life Stressors exhibited a similar trajectory as SLE measured using the Family Crisis List across problematic drinking-SLE classes. This suggests that the level of parent reported SLE could reflect the level of SLE experienced by their children.

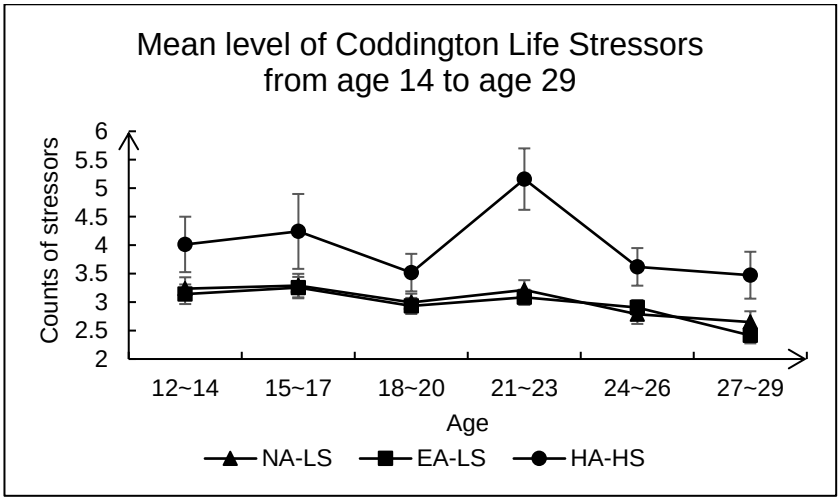


Figure 25 Mean level of Coddington Life Stressors over time across problematic drinking-SLE classes (n=714)*

* NA-LS refers to normative alcohol and low stress group; EA-LS refers to escalating alcohol and low stress group; HA-HS refers to high alcohol and high stress group.

6.4 Discussion

This chapter sought to investigate how problematic drinking and SLE co-develop over adolescence and young adulthood. Using a group-based dual trajectory model, three classes were identified: two classes were characterized by low levels of SLE over time with one class having a normative increase in problematic drinking over time, while the other had a rapid escalation in problematic drinking from ages 14 to 23. The third class had consistently high levels of problematic drinking and SLE over time. These classes also differed on a number of other alcohol-related risk factors. The results indicate that SLE act as a contextual but not determinative risk factor in driving the escalation of problematic drinking.

6.4.1 Trajectory of problematic drinking

By creating a composite score that captures participants' alcohol drinking behaviour from multiple aspects (drinking frequency, drinking quantity, max drinking and intoxication occasions), three heterogeneous classes of alcohol drinking trajectory across adolescence and young adulthood were identified in current sample, which differs from those reported by Sher and colleagues (2011) [68]. No linearly increasing and decreasing classes were detected, but a class of individuals whose alcohol use escalated quickly from age 14 to age 23 before declining. Several factors, including sample characteristics, time and duration of measurements and how alcohol use behaviour was defined, may lead to the inconsistency.

When comparing the results to studies with participants from a similar background, there was more consistency regarding the number of classes and the shape of alcohol trajectories within each class. Studying alcohol use of children from economically disadvantaged areas annually from age 11 to age 16, Wanner et al (2006) [477] derived three classes of individuals very similar to those shown in the current study. Capaldi et al (2013)'s study recruited participants from higher crime neighbourhood and assessed their alcohol use (alcohol volume, heavy episode drinking and alcohol problems) annually from age 18/19 to age 28/29 [478]. For both alcohol volume and heavy episode drinking, three classes

were identified as low/moderate, moderate/high desisting, high chronic, which matched the normative increase, rapid escalation and consistently high classes observed in the present analyses, respectively. The trajectory of alcohol use in the moderate/high desisting class was very similar to the problematic drinking trajectory in the rapid escalation class: increasing until age 23 before declining afterwards. Another study deriving alcohol trajectories of children of alcoholics also reported no decreasing group but three increasing/escalating groups from age 11-14 to age 27-30 [344]. In contrast, it is more typical to observe the cat's cradle depicted in Sher et al (2011)'s study [68] in community or college samples when alcohol use trajectories are modelled from age 18 and onward [68,437–439,442–444,479]. However, the alcohol trajectory from age 10/11 to age 18 of community sample also tended to present an increasing trend in general [87,436,441,441,480–484].

Those heterogeneities raise concerns on how one should interpret the latent classes of individuals derived within a limited timeframe, especially when researchers attempt to predict classes using previous risk factors, as it is very likely to misclassify one's drinking pattern based on short term observations. Another implication is the importance of studying trajectories of other time-varying factors that evolve contemporaneously with alcohol use, which can help us understand the development of alcohol use while avoiding the above concern.

6.4.2 Co-development of problematic drinking and SLE

The results indicate that SLE act as a contextual but not determinative risk factor in driving the escalation of problematic drinking. Classes identified using group-based dual trajectory modelling generally overlaid with classes identified using univariate trajectory analysis of problematic drinking, but not with classes identified using SLE. Moreover, classes identified solely based on SLE could not differentiate heterogeneous trajectories of AUP. In other words, the mean level of AUP within each SLE-class followed a similar trajectory, as shown in Appendix 48. The contextual role of SLE on alcohol use also lies in the fact that it stayed relatively stable over time at the individual level, and individuals exposed to

similar levels of SLE developed two distinct problematic drinking trajectories (NA-LS versus EA-LS).

However, level of SLE in the HA-HS class was generally higher than that in the other two classes. As presented in Figure 23, this difference was mainly driven by school-related events for the target participants during adolescence and by money-related and interpersonal conflicts during young adulthood, which reflects both a shift of developmental tasks over adolescence and young adulthood [57,195,451] and SLE that are strongly tied to a person's behaviour and trait characteristics such as impulsivity and antisocial behaviour [91,92]. In addition, several parent-experienced events were also higher in HA-HS class, which may act as a non-specific risk factor for drinking of their off-springs. Stress faced by parents may amplify pathological family processes that subsequently lead to problematic developmental outcomes of offspring [485]. For instance, parents who experience more SLE may exhibit more depressive symptoms [67,485–488], may parent in a more hostile/inconsistent way [56,489–492], or may drink more alcohol themselves [56,451,491,493], all of which would foster an adverse environment for the development of problematic behaviours for their offspring -- including alcohol use. This may also explain the clustering of other vulnerabilities in the HA-HS class, such as family history of alcoholism, early onset drinking, high externalising and internalising problems, regular use of other substance and involvement with deviant peers.

6.4.3 Class differences

Consistent with existing evidence [462,463,494–496], several well-established risk factors for alcohol use displayed gradient differences across problematic drinking-SLE classes, especially for family history of alcoholism, first drinking age, externalizing problems, concurrent smoking and marijuana use and peer involvement in substance use. Though the direction among those risk factors and alcohol use is uncertain, chronologically speaking, the clustering of risk factors among the participants in the HA-HS class is consistent with the concept of developmental cascades. Exposure to contextual risk factors (e.g., SLE, family history of alcoholism, ACEs, externalizing and internalizing problems) increases

the likelihood of exposure to another (deviant peers, early drinking, smoking and marijuana use) and eventually leads to persistently high levels of problematic drinking [60,367].

In contrast, participants in the EA-LS class were exposed to fewer contextual risk factors (low levels of SLE, internalizing problems, but moderate levels of family history of alcoholism, ACEs and externalizing problems), and thus may delay their escalation of alcohol use. Notably, trajectories of peer involvement in substance use closely corresponded to the problematic drinking-SLE classes. Specifically, peer involvement in substance use for the majority (72.6%) in the EA-LS class escalated quickly before ages 22-23 and declined slightly afterwards. Either through peer selection where people choose friends with similar behaviours, peer groups creating contexts that cause increases in substance use, or peer projection where one overestimates substance use of their peers [497,498], these findings emphasize the significance of peers in the development of drinking trajectories over adolescence and young adulthood.

6.4.4 Strengths and Limitations

By utilizing group-based dual trajectory analysis, this study explored the dynamic between-person relationships between SLE and problematic drinking from adolescence into young adulthood. The intensive assessment on abundant alcohol-related measures provide a unique opportunity to examine the co-development of alcohol use with SLE over critical developmental periods and depict the distribution of several other time-varying risk factors. To the best of my knowledge, this is the first paper that investigates heterogeneous classes of drinking trajectories by taking into considerations of other time-varying risk factors. The results provide support for the theoretical hypothesis that SLE act as a contextual but not determinative risk factor in driving the escalation of alcohol use.

Several limitations should be noted. First, the current sample was ascertained through a high-risk recruitment strategy, so the findings may not directly generalise to the general population and identify all potential co-developmental

trajectories between SLE and problematic drinking. Studies recruiting from the general population with larger sample sizes are needed to replicate the results. Second, group-based dual trajectory analysis cannot disentangle the direction of the association between SLE and problematic drinking. Current results should by no means be interpreted as the proof for a causal relationship between SLE and problematic drinking. A high level of SLE in the HA-HS class could also be the result of problematic drinking behaviours [499]. As mentioned previously, the difference of parent-reported SLE among classes was mainly driven by school-related events of the participants, and this difference was not as consistent over time for other parent-reported SLE, except for physical fights. Similarly, in young adulthood, class differences were not as evident for events that were less likely to occur as consequences of drinking (e.g. someone in the family died, someone in the family got diagnosed with chronic disease). Thus, the results should be seen as depicting how problematic drinking and SLE were co-varying on an individual level over key developmental periods. Third, self-reported SLE during adolescence and one's perception toward certain SLE were not available in the MLS dataset, which may limit our ability to investigate how self-perceived SLE co-develops with problematic drinking during adolescence [500].

6.5 Conclusion

Individuals who experience high levels of stressful life events are embedded in a matrix with a high level of other risk factors, which tends to maintain high levels of alcohol use across adolescence and young adulthood. On the individual level, stressful life events act as a contextual risk factor for alcohol use and add little value in differentiating individuals of heterogeneous alcohol trajectories over a long-term span.

7. Summary of main findings, implications, strengths and limitations

7.1 Summary of main findings

This thesis systematically summarised the existing evidence on the association between early life mental health and adulthood alcohol use behaviours (Chapter 2), explored whether the association persisted into mid-adulthood and varied across developmental timing, sex and cohorts (Chapter 4), investigated how much of the association was mediated through educational attainment using two British birth cohorts (NCDS58 & BCS70) (Chapter 5), and lastly, how problematic drinking and stressful life events co-developed across adolescence and young adulthood using a longitudinal survey (MLS) from the US (Chapter 6).

In Chapter 2, a systematic review concluded that the association between externalising problems and alcohol use behaviours persisted into mid-adulthood, and the likelihood of observing positive associations was higher for more severe alcohol use outcomes, but this trend was not observed among high-quality studies. In addition, more positive associations were found when externalising problems were measured during adolescence and alcohol use behaviours in young adulthood. The probability of detecting significant positive associations between externalising problems and later alcohol use behaviours was higher when adjusting for internalising problems simultaneously. The probability of detecting a positive association between externalising problems and alcohol use behaviours appeared to be consistent across countries and cohorts. Findings on associations between the internalising domain and alcohol use behaviours varied across their subtypes. Internalising problems tended to be negatively associated with alcohol consumption, especially when externalising problems were simultaneously adjusted for, but positively associated with more severe outcomes (heavy/problematic drinking, AUD). Depression tended to be positively associated with alcohol outcomes, while no clear association between anxiety and alcohol outcomes was evident. The moderating role of sex in the association between mental health problems and alcohol use behaviours was equivocal: half

of the studies did not explore the potential interaction; among those that did, the results were mixed with most of them not finding significant results.

In Chapter 4, a lagged logistic regression analysis of two national, longitudinal British birth cohorts (NCDS58&BCS70) found that externalising and internalising problems across childhood and adolescence were associated with problematic drinking in mid-adulthood, with externalising problems being a risk factor and internalising problems a protective factor. No critical period of externalising and internalising problems was observed during which the strength of their associations with problematic drinking was stronger or weaker. The strength of the associations between externalising and internalising problems and problematic drinking did not differ across cohorts, but associations were stronger in males. In addition, sensitivity analysis revealed the suppressing effect between externalising problems and internalising problems regarding their associations with problematic drinking, where the associations were alleviated or disappeared when they were not adjusted simultaneously. This point was illustrated using DAG in detail in section 4.4.3.

In Chapter 5, formal mediation analysis under counterfactual framework was carried out using the two British birth cohorts. Traditional regression analysis found that higher externalising problems were associated with lower educational attainment, but educational attainment was not associated with later problematic drinking. No mediating effect of educational attainment was detected under the counterfactual framework, and this was ascertained using two analytical approaches: bootstrapping nested in multiple imputation and single stochastic imputation nested in bootstrapping. Sensitivity analysis revealed that the effect of educational attainment on different phenotypes of alcohol use behaviours may be opposite (positive with drinking frequency but negative with drinking quantity), and thus they may cancel each other out when different phenotypes were used to construct the index for problematic drinking. However, there were still no mediating effects of educational attainment when using drinking frequency and drinking quantity as an outcome.

In Chapter 6, a group-based dual trajectory analysis utilising a high-risk sample (MLS) found three classes of individuals who had heterogeneous dual trajectory of problematic drinking and stressful life events over the period of adolescence and young adulthood. One class was characterized with a normative increase of problematic drinking and consistently low level of stressful life events across adolescence and young adulthood (300, 42%); one class was characterized with quick escalation of problematic drinking until age 23 and consistently low level of stressful life events across adolescence and young adulthood (343, 48%); one class was characterized with consistently high levels of both problematic drinking and stressful life events (71, 9.9%). Family history of alcoholism and age at first drink presented monotonically gradient distributions across classes. Externalising and internalising problems did not change within individuals over time but differed by their levels across classes. Smoking status, marijuana occasions and peer's involvement of substance covaried in accordance with the trajectory of problematic drinking within each class over time.

7.2 Implications of findings

Chapter 2 systematically evaluates existing evidence to investigate how the associations between externalising and internalising problems and alcohol use behaviours vary across a series of factors: subtypes of mental health and alcohol use behaviours, developmental timing, sex, culture, historical period and adjustment of externalising or internalising problems correspondingly. Chapter 4 provides empirical evidence on these questions by analysing two British birth cohorts. Several implications can be drawn from those results.

From the perspective of informing future research, further work that aims to articulate the association between mental health and alcohol use behaviours should pay more attention to interactions within the domain of mental health, especially between externalising problems and internalising problems. Besides the suppressing effect between them, they may also interact with each other to influence alcohol outcomes [83,351]. Moreover, Chapter 2 provides a preliminary picture of how the associations may vary across a series of factors. No definitive conclusions can be drawn, as the observed variation across certain factor might

be caused by the imbalance of other factors across studies. Though results from Chapter 4 support some findings in Chapter 2 (e.g. the suppressing effect between externalising and internalising problems), more studies that investigate how the associations vary across the above listed factors within the same population are warranted.

From the perspective of public health, early life externalising problems and depression are shown to be a promising phenotype to target to alleviate alcohol burden in adulthood. Compared with internalising problems or anxiety, more consistent positive associations with alcohol use behaviours were found for these two phenotypes. In addition, results regarding the developmental timing of externalising problems from Chapter 2 and Chapter 4 have different implications for public health interventions. As discussed in section 1.3.1, compared to individuals with consistently low level of externalising problems, individuals with early-onset-persistent or adolescent-onset externalising problems, but not those with childhood-limited externalising problems, tend to exhibit more alcohol use and alcohol-related problems [110–113,115,116]. As a result, when previous externalising problems are not taken into account, it is more likely to detect a positive association between externalising problems and alcohol use behaviours when externalising problems are measured in adolescence. This is in accordance with the results reported in Chapter 2 (more positive associations were found when externalising problems were measured during adolescence). In contrast, the results from Chapter 4 indicate that after adjusting for previous externalising problems, elevated levels of externalising problems either in childhood or adolescence were associated with a similar increased risk of problematic drinking. Last but not least, results from both the systematic review (Chapter 2) and the longitudinal analysis (Chapter 4) showed that the association between mental health and alcohol outcomes did not vary across generations. This indicates that there exists an underlying developmental pathway from early life mental health to adulthood alcohol use rather than specific historically bounded ones, and intervention programs developed to disrupt the pathway could be applied across generations.

Chapter 5 built on Chapter 4 to explore the extent to which educational attainment may mediate the continuity from early life externalising problems to mid-adulthood problematic drinking. Unexpectedly, no mediating effect of educational attainment was detected. This is most likely due to the population-specific interpretation of the mediating effect under the counterfactual framework. The null findings indicate that the alleviation of problematic drinking we could have achieved by intervening the observed distribution of externalising problems to one SD below the population average (leaving other potential confounding factors as they were) was not through its effect on one's educational attainment by age 23. Due to the population-specific interpretation of the results, this should be not seen as evidence against the hypothesis of cascading effect which posits that the continuity of early difficulties is due to their impact on other difficulties (such as educational attainment). However, as no other studies have attempted to examine the above mediating hypothesis in other populations, more empirical studies are needed to confirm current findings and examine other potential mediators. Chapter 5 further emphasizes how the associations between educational attainment and alcohol use vary across phenotypes of alcohol use behaviours. The findings call for more caution when using composite measures of alcohol use behaviours to study their relationships with educational attainment.

As discussed in section 1.5, person-based analysis might be better at handling unmeasured time-fixed confounding factors clustered within individuals and can provide results that are in accordance with most, if not all, theories in psychology. Due to the long interval among waves in the British birth cohorts, Michigan Longitudinal Study from the US, which collected data at shorter intervals from adolescence to young adulthood, was employed to explore the co-development between problematic drinking and stressful life events from an individual perspective. Chapter 6 focused on answering whether the systematic increase in one's alcohol use comes with a systematic increase in one's stressful life events. Results did not support the co-varying between problematic drinking and stressful life events due to the stability of the latter in participants' lives: the same was true for externalising and internalising problems. This indicates that factors (such as stressful life events, externalising and internalising problems) that are stable over time, may act as consistent contextual risk-factors for alcohol use across the life

course within individual. In contrast, individual drinking trajectories were more linked with smoking, marijuana use, and peer involvement in substance use correspondingly. The findings in the current study emphasize the necessity of dissecting different aspects (between-person and within-person effects) of dynamic associations between drinking behaviours and time-varying variables in future studies. Differentiating various effects would help facilitate the development of relevant theories and further inform the design of effective interventions. For instance, our results prove that the hypothesis that higher level of stressful life events is linked to higher level of alcohol consumption does not necessarily apply on individual level over time. Interventions that only target on lowering level of stressful life events may not prevent the escalation of alcohol use during adolescence, because other time-varying risk factors play a more important role at later stages.

7.3 Strengths and limitations

The specific strengths and limitations of each analysis are discussed within each chapter. To avoid repetition, only the overarching strengths and limitations of this thesis will be described below.

7.3.1 Strengths

This thesis is the first to systematically summarise the association between early life mental health and alcohol use behaviours across adulthood by taking into account several factors that could influence it, including subtypes of both mental health and alcohol use behaviours, whether adjusting for externalising problems or internalising problems simultaneously, developmental timing, sex, history and culture. The roles of developmental timing, sex, cohort and adjusting for externalising problems or internalising problems simultaneously were further explored in empirical studies extending the longitudinal associations into mid-adulthood.

National representative datasets with advanced data analytic strategies ensure the robustness of the results. The concept of directed acyclic graph was utilised

in the empirical studies to illustrate and guide the statistical analysis [181,182]. Multiple imputation was carried out using the most up-to-date techniques to deal with potential interactions, multiple-item scales and number of imputations [286,327,330]. Causal mediation analysis under the counterfactual framework was utilised to improve causal inference using observational studies and to deal with the problems of common outcomes [392]. Group-based dual trajectory analysis was done to better illustrate the dynamic associations between two time-varying variables [197].

7.3.2 Limitations

Long intervals between waves in the British cohorts makes it impossible to derive precise trajectories of either mental health in early life or alcohol use behaviours in adulthood, which limits the ability to examine the association over long period on individual level. Though annually collected data from MLS makes up for this limitation, the sample size is small and limited to individuals from at-risk families, reducing generalisability.

To make cross-cohort comparisons possible, measurements for mental health problems and alcohol use problems were shortened to four and five questions respectively, which may reduce the validity of the scale. Though latent scores derived using item response theory may help improve the validity, the latent scores were hard to interpret from a practical perspective.

Though externalising problems and internalising problems were adjusted to minimize unobserved confounding factors, there may still exist residual confounding from genetic influence, parenting style or peer drinking behaviours, which were not collected in the British cohorts.

7.4 Conclusion

Utilising prospective longitudinal datasets from the UK and the US and applying a series of advanced analytic strategies, the current thesis investigated associations between mental health and alcohol use behaviours over the life course.

These associations persist over four decades and may vary across a series of factors, including subtypes of mental health and alcohol use behaviours, developmental timing, sex, culture, historical period and adjustment of externalising or internalising problems correspondingly.

Ascertained through two analytical approaches (bootstrapping nested in multiple imputation and single stochastic imputation nested in bootstrapping), the continuity from adolescent externalising problems to problematic drinking in mid-adulthood was found not to be mediated by educational attainment in young adulthood under the UK context. Future work, under counterfactual framework, could examine other potential mediators that may contribute to this long-term relationship.

From an individual perspective, high levels of stressful life events, together with a high level of other risk factors, contribute to the maintenance of high alcohol use across adolescence and young adulthood. Stressful life events act as a contextual risk factor for alcohol use and add little value in differentiating individuals of heterogeneous alcohol trajectories. Other time-varying risk factors that exhibit more variations over time could be examined in future studies.

Investigating the mechanisms that underlie the long-term associations between early life mental health and adulthood alcohol use behaviours has important implications for interventions. It helps to answer whether alcohol burden in adulthood could be alleviated by targeting early life difficulties.

References

[1] Degenhardt L, Charlson F, Ferrari A, Santomauro D, Erskine H, Mantilla-Herrara A, et al. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. The Lancet Psychiatry 2018;5:987–1012. https://doi.org/10.1016/S2215-0366(18)30337-7.

[2] Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol use disorders. The Lancet 2009;373:2223–33. https://doi.org/10.1016/S0140-6736(09)60746-7.

[3] World Health Organization. Management of substance abuse unit. Geneva: World Health Organization; 2014.

[4] World Health Organization. Global status report on alcohol and health 2018. 2018.

[5] World Health Organization. Global health risks: mortality and burden of disease attributable to selected major risks. Geneva, Switzerland: World Health Organization; 2009.

[6] World Health Organization. Global status report on alcohol and health 2014. 2014.

[7] Ritchie H, Roser M. Causes of death. Our World in Data 2020. https://ourworldindata.org/causes-of-death (accessed March 4, 2020).

[8] Stanaway JD, Afshin A, Gakidou E, Lim SS, Abate D, Abate KH, et al. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet 2018;392:1923–94. https://doi.org/10.1016/S0140-6736(18)32225-6.

[9] Ritchie H, Roser M. Alcohol consumption. Our World in Data 2020. https://ourworldindata.org/alcohol-consumption (accessed March 6, 2020).

[10] Alcohol and Public Policy Group. Alcohol: no ordinary commodity - A summary of the second edition. Addiction 2010;105:769–79. https://doi.org/10.1111/j.1360-0443.2010.02945.x.

[11] Verhaeghe N, Lievens D, Annemans L, Vander Laenen F, Putman K. The health-related social costs of alcohol in Belgium. BMC Public Health 2017;17. https://doi.org/10.1186/s12889-017-4974-4.

[12] Marmot MG, Shipley MJ, Rose G, Thomas BrionyJ. Alcohol and mortality: A u-shaped curve. The Lancet 1981;317:580–3. https://doi.org/10.1016/S0140-6736(81)92032-8.

[13] Castelnuovo AD, Costanzo S, Bagnardi V, Donati MB, Iacoviello L, Gaetano G de. Alcohol dosing and total mortality in men and women: An updated meta-analysis of 34 prospective studies. Arch Intern Med 2006;166:2437–45. https://doi.org/10.1001/archinte.166.22.2437.

[14] Stockwell T, Zhao J, Panwar S, Roemer A, Naimi T, Chikritzhs T. Do “moderate” drinkers have reduced mortality risk? A systematic review and meta-analysis of alcohol consumption and all-cause mortality. J Stud Alcohol Drugs 2016;77:185–98. https://doi.org/10.15288/jsad.2016.77.185.

[15] Wood AM, Kaptoge S, Butterworth AS, Willeit P, Warnakula S, Bolton T, et al. Risk thresholds for alcohol consumption: Combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective

studies. The Lancet 2018;391:1513–23. https://doi.org/10.1016/S0140-6736(18)30134-X.
[16] Topiwala A, Allan CL, Valkanova V, Zsoldos E, Filippini N, Sexton C, et al. Moderate alcohol consumption as risk factor for adverse brain outcomes and cognitive decline: Longitudinal cohort study. BMJ 2017;357:j2353. https://doi.org/10.1136/bmj.j2353.
[17] Adan A, Benaiges I, Forero DA. Heavy episodic drinking or binge drinking. Neuropathology of Drug Addictions and Substance Misuse, Elsevier; 2016, p. 389–97. https://doi.org/10.1016/B978-0-12-800213-1.00036-5.
[18] Gilmore AK, Bountress KE. Reducing drinking to cope among heavy episodic drinking college women: Secondary outcomes of a web-based combined alcohol use and sexual assault risk reduction intervention. Addict Behav 2016;61:104–11. https://doi.org/10.1016/j.addbeh.2016.05.007.
[19] Lightowlers C, Elliot M, Tranmer M. The dynamic risk of heavy episodic drinking on interpersonal assault in young adolescence and early adulthood. Br J Criminol 2014;54:1207–27.
[20] Caamaño-Isorna F, Moure-Rodríguez L, Doallo S, Corral M, Rodriguez Holguín S, Cadaveira F. Heavy episodic drinking and alcohol-related injuries: An open cohort study among college students. Accid Anal Prev 2017;100:23–9. https://doi.org/10.1016/j.aap.2016.12.012.
[21] Rossow I, Bogstrand ST, Ekeberg Ø, Normann PT. Associations between heavy episodic drinking and alcohol related injuries: A case control study. BMC Public Health 2013;13:1076. https://doi.org/10.1186/1471-2458-13-1076.
[22] McGovern PE. Uncorking the past: the quest for wine, beer, and other alcoholic beverages. Berkeley ; London: University of California Press; 2009.
[23] Burton R, Henn C, Lavoie D, O'Connor R, Perkins C, Sweeney K, et al. A rapid evidence review of the effectiveness and cost-effectiveness of alcohol control policies: an English perspective. The Lancet 2017;389:1558–80. https://doi.org/10.1016/S0140-6736(16)32420-5.
[24] Frankel S, Davison C, Smith GD. Lay epidemiology and the rationality of responses to health education. Br J Gen Pract 1991;41:428–30.
[25] Parke H, Michalska M, Russell A, Moss AC, Holdsworth C, Ling J, et al. Understanding drinking among midlife men in the United Kingdom: A systematic review of qualitative studies. Addict Behav Rep 2018;8:85–94. https://doi.org/10.1016/j.abrep.2018.08.001.
[26] Schulenberg JE, Maslowsky J, Patrick ME, Martz M. Substance use in the context of adolescent development. In: Zucker RA, Brown SA, editors. The Oxford Handbook of Adolescent Substance Abuse, Oxford University Press; 2019, p. 18–36. https://doi.org/10.1093/oxfordhb/9780199735662.013.38.
[27] Zucker RA. Anticipating problem alcohol use developmentally from childhood into middle adulthood: What have we learned? Addiction 2008;103:100–8. https://doi.org/10.1111/j.1360-0443.2008.02179.x.
[28] Jessor R. Problem behavior theory over the years. The Origins and Development of Problem Behavior Theory, 2016, p. 15–42. https://doi.org/10.1007/978-3-319-40886-6_2.
[29] Stone AL, Becker LG, Huber AM, Catalano RF. Review of risk and protective factors of substance use and problem use in emerging

adulthood. Addict Behav 2012;37:747–75. https://doi.org/10.1016/j.addbeh.2012.02.014.
[30] Zucker RA, Wong MM, Clark DB, Leonard KE, Schulenberg JE, Cornelius JR, et al. Predicting risky drinking outcomes longitudinally: What kind of advance notice can we get? Alcohol Clin Exp Res 2006;30:243–52. https://doi.org/10.1111/j.1530-0277.2006.00033.x.
[31] Sanchez-Roige S, Palmer AA, Clarke T-K. Recent efforts to dissect the genetic basis of alcohol use and abuse. Biol Psychiatry 2020;87:609–18. https://doi.org/10.1016/j.biopsych.2019.09.011.
[32] Tawa EA, Hall SD, Lohoff FW. Overview of the genetics of alcohol use disorder. Alcohol Alcohol 2016;51:507–14. https://doi.org/10.1093/alcalc/agw046.
[33] Verhulst B, Neale MC, Kendler KS. The heritability of alcohol use disorders: a meta-analysis of twin and adoption studies. Psychol Med 2015;45:1061–72. https://doi.org/10.1017/S0033291714002165.
[34] Slavich GM. Life stress and health: A review of conceptual issues and recent findings. Teach Psychol 2016;43:346–55. https://doi.org/10.1177/0098628316662768.
[35] Keyes KM, Hatzenbuehler ML, Hasin DS. Stressful life experiences, alcohol consumption, and alcohol use disorders: The epidemiologic evidence for four main types of stressors. Psychopharmacology (Berl) 2011;218:1–17. https://doi.org/10.1007/s00213-011-2236-1.
[36] Keyes KM, Hatzenbuehler ML, Grant BF, Hasin DS. Stress and alcohol. Alcohol Res 2012;34:391–400.
[37] Cappell H, Herman CP. Alcohol and tension reduction. A review. Q J Stud Alcohol 1972;33:33–64.
[38] Colder CR. Life stress, physiological and subjective indexes of negative emotionality, and coping reasons for drinking: Is there evidence for a self-medication model of alcohol use? Psychol Addict Behav 2001;15:237–45. https://doi.org/10.1037/0893-164X.15.3.237.
[39] Kuntsche E, Knibbe R, Gmel G, Engels R. Why do young people drink? A review of drinking motives. Clin Psychol Rev 2005;25:841–61. https://doi.org/10.1016/j.cpr.2005.06.002.
[40] Kuntsche E, Knibbe R, Gmel G, Engels R. Who drinks and why? A review of socio-demographic, personality, and contextual issues behind the drinking motives in young people. Addict Behav 2006;31:1844–57. https://doi.org/10.1016/j.addbeh.2005.12.028.
[41] Ayer LA, Harder VS, Rose GL, Helzer JE. Drinking and stress: An examination of sex and stressor differences using IVR-based daily data. Drug Alcohol Depend 2011;115:205–12. https://doi.org/10.1016/j.drugalcdep.2010.10.022.
[42] Armeli S, Carney MA, Tennen H, Affleck G, O'Neil TP. Stress and alcohol use: A daily process examination of the stressor–vulnerability model. J Pers Soc Psychol 2000;78:979–94. https://doi.org/10.1037/0022-3514.78.5.979.
[43] Grzywacz JG, Almeida DM. Stress and binge drinking: A daily process examination of stressor pile-up and socioeconomic status in affect regulation. Int J Stress Manag 2008;15:364–80.
[44] Andersson C, Gordh AHVS, Berglund M. Use of real-time interactive voice response in a study of stress and alcohol consumption. Alcohol Clin Exp Res 2007;31:1908–12. https://doi.org/10.1111/j.1530-0277.2007.00520.x.

[45] Cooper ML, Russell M, Skinner JB, Frone MR, Mudar P. Stress and alcohol use: moderating effects of gender, coping, and alcohol expectancies. J Abnorm Psychol 1992;101:139–52. https://doi.org/10.1037//0021-843x.101.1.139.
[46] Sher KJ, Levenson RW. Risk for alcoholism and individual differences in the stress-response-dampening effect of alcohol. J Abnorm Psychol 1982;91:350–67. https://doi.org/10.1037//0021-843x.91.5.350.
[47] Bouma EMC, Ormel J, Verhulst FC, Oldehinkel AJ. Stressful life events and depressive problems in early adolescent boys and girls: The influence of parental depression, temperament and family environment. J Affect Disord 2008;105:185–93. https://doi.org/10.1016/j.jad.2007.05.007.
[48] Dawson DA, Grant BF, Ruan WJ. The association between stress and drinking: modifying effects of gender and vulnerability. Alcohol Alcohol 2005;40:453–60. https://doi.org/10.1093/alcalc/agh176.
[49] Veenstra MY, Lemmens PHHM, Friesema IHM, Tan FES, Garretsen HFL, Knottnerus JA, et al. Coping style mediates impact of stress on alcohol use: A prospective population-based study. Addiction 2007;102:1890–8. https://doi.org/10.1111/j.1360-0443.2007.02026.x.
[50] Wills TA. Stress and coping in early adolescence: Relationships to substance use in urban school samples. Health Psychology 1986;5:503–29. https://doi.org/10.1037/0278-6133.5.6.503.
[51] Armeli S, O'Hara RE, Covault J, Scott DM, Tennen H. Episode-specific drinking-to-cope motivation and next-day stress-reactivity. Anxiety Stress Coping 2016;29:673–84. https://doi.org/10.1080/10615806.2015.1134787.
[52] Enoch M-A. The role of early life stress as a predictor for alcohol and drug dependence. Psychopharmacology 2011;214:17–31. https://doi.org/10.1007/s00213-010-1916-6.
[53] Blomeyer D, Buchmann AF, Schmid B, Jennen-Steinmetz C, Schmidt MH, Banaschewski T, et al. Age at first drink moderates the impact of current stressful life events on drinking behavior in young adults. Alcohol Clin Exp Res 2011;35:1142–8. https://doi.org/10.1111/j.1530-0277.2011.01447.x.
[54] Dawson DA, Grant BF, Li T-K. Impact of age at first drink on stress-reactive drinking. Alcohol Clin Exp Res 2007;31:69–77. https://doi.org/10.1111/j.1530-0277.2006.00265.x.
[55] Brody GH, Chen Y-F, Kogan SM. A cascade model connecting life stress to risk behavior among rural African American emerging adults. Dev Psychopathol 2010;22:667–78. https://doi.org/10.1017/S0954579410000350.
[56] Chassin L, Pillow DR, Curran PJ, Molina BSG, Barrera M. Relation of parental alcoholism to early adolescent substance use: A test of three mediating mechanisms. J Abnorm Psychol 1993;102:3–19. https://doi.org/10.1037/0021-843X.102.1.3.
[57] Low NC, Dugas E, O'Loughlin E, Rodriguez D, Contreras G, Chaiton M, et al. Common stressful life events and difficulties are associated with mental health symptoms and substance use in young adolescents. BMC Psychiatry 2012;12:116. https://doi.org/10.1186/1471-244X-12-116.
[58] Cheadle JE, Whitbeck LB. Alcohol use trajectories and problem drinking over the course of adolescence: A study of North American indigenous youth and their caretakers. J Health Soc Behav 2011;52:228–45. https://doi.org/10.1177/0022146510393973.

[59] Kim ST, Hwang SS, Kim HW, Hwang EH, Cho J, Kang JI, et al. Multidimensional impulsivity as a mediator of early life stress and alcohol dependence. Sci Rep 2018;8:4104. https://doi.org/10.1038/s41598-018-22474-8.
[60] Otten R, Mun CJ, Shaw DS, Wilson MN, Dishion TJ. A developmental cascade model for early adolescent-onset substance use: The role of early childhood stress. Addiction 2019;114:326–34. https://doi.org/10.1111/add.14452.
[61] Elsayed NM, Kim MJ, Fields KM, Olvera RL, Hariri AR, Williamson DE. Trajectories of alcohol initiation and use during adolescence: The role of stress and amygdala reactivity. J Am Acad Child Adolesc Psychiatry 2018;57:550–60. https://doi.org/10.1016/j.jaac.2018.05.011.
[62] Diaz MR, Przybysz KR, Rouzer SK. Age as a factor in stress and alcohol interactions: A critical role for the kappa opioid system. Alcohol 2018;72:9–18. https://doi.org/10.1016/j.alcohol.2017.10.002.
[63] Yang H, Spence JS, Briggs RW, Rao U, North C, Devous MD, et al. Interaction between early life stress and alcohol dependence on neural stress reactivity. Addict Biol 2015;20:523–33. https://doi.org/10.1111/adb.12135.
[64] Pechtel P, Pizzagalli DA. Effects of early life stress on cognitive and affective function: an integrated review of human literature. Psychopharmacology (Berl) 2011;214:55–70. https://doi.org/10.1007/s00213-010-2009-2.
[65] Casement MD, Shaw DS, Sitnick SL, Musselman SC, Forbes EE. Life stress in adolescence predicts early adult reward-related brain function and alcohol dependence. Soc Cogn Affect Neurosci 2015;10:416–23. https://doi.org/10.1093/scan/nsu061.
[66] Holgate JY, Bartlett SE. Early life stress, nicotinic acetylcholine receptors and alcohol use disorders. Brain Sci 2015;5:258–74. https://doi.org/10.3390/brainsci5030258.
[67] Cohen S, Murphy MLM, Prather AA. Ten surprising facts about stressful life events and disease risk. Annu Rev Psychol 2019;70:577–97. https://doi.org/10.1146/annurev-psych-010418-102857.
[68] Sher KJ, Jackson KM, Steinley D. Alcohol use trajectories and the ubiquitous cat's cradle: Cause for concern? J Abnorm Psychol 2011;120:322–35. https://doi.org/10.1037/a0021813.
[69] Babor TF. The classification of alcoholics: Typology theories from the 19th century to the present. Alcohol Health Res World 1996;20:6–17.
[70] Babor TF, Hofmann M, DelBoca FK, Hesselbrock V, Meyer RE, Dolinsky ZS, et al. Types of alcoholics, I. Evidence for an empirically derived typology based on indicators of vulnerability and severity. Arch Gen Psychiatry 1992;49:599–608.
[71] Zucker RA. Alcohol use and the alcohol use disorders: A developmental-biopsychosocial systems formulation covering the life course. In: Cicchetti D, Cohen DJ, editors. Developmental Psychopathology, John Wiley & Sons, Inc.; 2015, p. 620–56. https://doi.org/10.1002/9780470939406.ch17.
[72] Edwards AC, Gardner CO, Hickman M, Kendler KS. A prospective longitudinal model predicting early adult alcohol problems: Evidence for a robust externalizing pathway. Psychol Med 2016;46:957–68.

[73] Hussong A M, Jones D J, Stein G L, Baucom D H, Boeding S. An internalizing pathway to alcohol use and disorder. Psychol Addict Behav 2011;25:390–404.
[74] Zucker RA, Heitzeg MM, Nigg JT. Parsing the undercontrol/disinhibition pathway to substance use disorders: A multilevel developmental problem. Child Dev Perspect 2011;5:248–55. https://doi.org/10.1111/j.1750-8606.2011.00172.x.
[75] Hussong AM, Ennett ST, Cox MJ, Haroon M. A systematic review of the unique prospective association of negative affect symptoms and adolescent substance use controlling for externalizing symptoms. Psychol Addict Behav 2017;31:137–47. https://doi.org/10.1037/adb0000247.
[76] Maggs JL, Patrick ME, Feinstein L. Childhood and adolescent predictors of alcohol use and problems in adolescence and adulthood in the National Child Development Study. Addiction 2008;103:7–22.
[77] McKenzie M, Jorm AF, Romaniuk H, Olsson CA, Patton GC. Association of adolescent symptoms of depression and anxiety with alcohol use disorders in young adulthood: Findings from the Victorian Adolescent Health Cohort Study. Med J Aust 2011;195:27.
[78] Stanley LR, Kimberly MA, Beauvais F, Walker PS, Walker RD. Predicting an alcohol use disorder in urban American Indian youths. J Child Adolesc Subst Abuse 2014;23:101–8.
[79] Swift W, Slade T, Carragher N, Coffey C, Degenhardt L, Hall W, et al. Adolescent predictors of a typology of dsm-5 alcohol use disorder symptoms in young adults derived by latent class analysis using data from an australian cohort study. J Stud Alcohol Drugs 2016;77:757–65. https://doi.org/10.15288/jsad.2016.77.757.
[80] Thompson KD, Leadbeater BJ, Ames ME. Reciprocal effects of internalizing and oppositional defiance symptoms on heavy drinking and alcohol-related harms in young adulthood. Subst Abuse 2016;9:21–31. https://doi.org/10.4137/SART.S33928.
[81] Edwards A C, Joinson C, Dick D M, Kendler K S, Macleod J, Munafo M, et al. The association between depressive symptoms from early to late adolescence and later use and harmful use of alcohol. Eur Child Adolesc Psychiatry 2014;23:1219–30.
[82] Hoyland MA, Rowatt WC, Latendresse SJ. Prior delinquency and depression differentially predict conditional associations between discrete patterns of adolescent religiosity and adult alcohol use patterns. Subst Abuse 2017;10. https://doi.org/10.1177/1178221816686060.
[83] Pardini D, White HR, Stouthamer-Loeber M. Early adolescent psychopathology as a predictor of alcohol use disorders by young adulthood. Drug Alcohol Depend 2007;88:S38–49.
[84] Pesola F, Shelton KH, Heron J, Munafò M, Hickman M, Van Den Bree MBM. The developmental relationship between depressive symptoms in adolescence and harmful drinking in emerging adulthood: The role of peers and parents. J Youth Adolesc 2015;44:1752–66.
[85] Soloski KL. Self-medication hypothesis and family socialization theory: Examining independent and common mechanisms responsible for binge drinking. Fam Process 2018;x. https://doi.org/10.1111/famp.12403.
[86] Hill KG, Hawkins JD, Bailey JA, Catalano RF, Abbott RD, Shapiro VB. Person–environment interaction in the prediction of alcohol abuse and

alcohol dependence in adulthood. Drug Alcohol Depend 2010;110:62–9. https://doi.org/10.1016/j.drugalcdep.2010.02.005.

[87] Meier MH, Caspi A, Houts R, Slutske WS, Harrington H, Jackson KM, et al. Prospective developmental subtypes of alcohol dependence from age 18 to 32 years: Implications for nosology, etiology, and intervention. Dev Psychopathol 2013;25:785–800. https://doi.org/10.1017/S0954579413000175.

[88] Pitkanen Tuuli, Kokko Katja, Lyyra Anna-Liisa, Pulkkinen Lea. A developmental approach to alcohol drinking behaviour in adulthood: A follow-up study from age 8 to age 42. Addiction 2008;103:48–68.

[89] Virtanen P, Nummi T, Lintonen T, Westerlund H, Hägglöf B, Hammarström A. Mental health in adolescence as determinant of alcohol consumption trajectories in the Northern Swedish Cohort. Int J Public Health 2015;60:335–42. https://doi.org/10.1007/s00038-015-0651-5.

[90] Schulenberg JE, Maggs JL. Destiny matters: Distal developmental influences on adult alcohol use and abuse. Addiction 2008;103:1–6. https://doi.org/10.1111/j.1360-0443.2008.02172.x.

[91] Schulenberg JE, Maggs JL. A developmental perspective on alcohol use and heavy drinking during adolescence and the transition to young adulthood. J Stud Alcohol 2002:54–70.

[92] Masten AS, Faden VB, Zucker RA, Spear LP. Underage drinking: A developmental framework. Pediatrics 2008;121:S235–51. https://doi.org/10.1542/peds.2007-2243A.

[93] Merline A, Jager J, Schulenberg JE. Adolescent risk factors for adult alcohol use and abuse: Stability and change of predictive value across early and middle adulthood. Addiction 2008;103:84–99. https://doi.org/10.1111/j.1360-0443.2008.02178.x.

[94] Berg N, Kiviruusu O, Karvonen S, Kestilä L, Lintonen T, Rahkonen O, et al. A 26-year follow-up study of heavy drinking trajectories from adolescence to mid-adulthood and adult disadvantage. Alcohol Alcohol 2013;48:452–457. https://doi.org/10.1093/alcalc/agt026.

[95] Britton A, Ben-Shlomo Y, Benzeval M, Kuh D, Bell S. Life course trajectories of alcohol consumption in the United Kingdom using longitudinal data from nine cohort studies. BMC Medicine 2015;13. https://doi.org/10.1186/s12916-015-0273-z.

[96] Chaiyasong S, Huckle T, Mackintosh A-M, Meier P, Parry CDH, Callinan S, et al. Drinking patterns vary by gender, age and country-level income: Cross-country analysis of the International Alcohol Control Study. Drug Alcohol Rev 2018;37:S53–62. https://doi.org/10.1111/dar.12820.

[97] Maggs JL, Schulenberg JE. Trajectories of alcohol use during the transition to adulthood. Alcohol Res Health 2004;28:195–201.

[98] Emslie C, Hunt K, Lyons A. Older and wiser? Men's and women's accounts of drinking in early mid-life. Sociol Health Illn 2012;34:481–96. https://doi.org/10.1111/j.1467-9566.2011.01424.x.

[99] Patrick ME, Schulenberg JE, O'Malley PM, Maggs JL, Kloska DD, Johnston LD, et al. Age-related changes in reasons for using alcohol and marijuana from ages 18 to 30 in a national sample. Psychol Addict Behav 2011;25:330–9. https://doi.org/10.1037/a0022445.

[100] Deutsch AR, Wood PK, Slutske WS. Developmental etiologies of alcohol use and their relations to parent and peer influences over adolescence and

young adulthood: A genetically informed approach. Alcohol Clin Exp Res 2017;41:2151–62. https://doi.org/10.1111/acer.13506.
[101] Dick DM. The genetics of addiction: Where do we go from here? J Stud Alcohol Drugs 2016;77:673–5. https://doi.org/10.15288/jsad.2016.77.673.
[102] Berg NJ, Kiviruusu OH, Lintonen TP, Huurre TM. Longitudinal prospective associations between psychological symptoms and heavy episodic drinking from adolescence to midlife. Scand J Public Health 2018. https://doi.org/10.1177/1403494818769174.
[103] von Stumm S, Deary IJ, Kivimaeki M, Jokela M, Clark H, Batty GD. Childhood behavior problems and health at midlife: 35-year follow-up of a Scottish birth cohort. J Child Psychol Psychiatry 2011;52:992–1001.
[104] Fanti KA, Henrich CC. Trajectories of pure and co-occurring internalizing and externalizing problems from age 2 to age 12: Findings from the national institute of child health and human development study of early child care. Dev Psychol 2010;46:1159–1175. https://doi.org/10.1037/a0020659.
[105] Petersen IT, Bates JE, Dodge KA, Lansford JE, Pettit GS. Describing and predicting developmental profiles of externalizing problems from childhood to adulthood. Dev Psychopathol 2015;27:791–818. https://doi.org/10.1017/S0954579414000789.
[106] Willner CJ, Gatzke-Kopp LM, Bray BC. The dynamics of internalizing and externalizing comorbidity across the early school years. Dev Psychopathol 2016;28:1033–52. https://doi.org/10.1017/S0954579416000687.
[107] Gibbons FX, Yeh H-C, Gerrard M, Cleveland MJ, Cutrona C, Simons RL, et al. Early experience with racial discrimination and conduct disorder as predictors of subsequent drug use: A critical period hypothesis. Drug Alcohol Depend 2007;88:S27–37. https://doi.org/10.1016/j.drugalcdep.2006.12.015.
[108] Cicchetti D, Rogosch FA. A developmental psychopathology perspective on adolescence. J Consult Clin Psychol 2002;70:6–20. https://doi.org/10.1037//0022-006x.70.1.6.
[109] Schulenberg JE, Maslowsky J, Patrick ME, Martz M. Substance use in the context of adolescent development. The Oxford Handbook of Adolescent Substance Abuse 2015. https://doi.org/10.1093/oxfordhb/9780199735662.013.38.
[110] Bevilacqua L, Hale D, Barker ED, Viner R. Conduct problems trajectories and psychosocial outcomes: A systematic review and meta-analysis. Eur Child Adolesc Psych 2018;27:1239–60. https://doi.org/10.1007/s00787-017-1053-4.
[111] Hammerton G, Edwards AC, Mahedy L, Murray J, Maughan B, Kendler KS, et al. Externalising pathways to alcohol-related problems in emerging adulthood. J Child Psychol Psychiatry 2019;n/a. https://doi.org/10.1111/jcpp.13167.
[112] Heron J, Maughan B, Dick DM, Kendler KS, Lewis G, Macleod J, et al. Conduct problem trajectories and alcohol use and misuse in mid to late adolescence. Drug Alcohol Depend 2013;133:100–7. https://doi.org/10.1016/j.drugalcdep.2013.05.025.
[113] Kretschmer T, Hickman M, Doerner R, Emond A, Lewis G, Macleod J, et al. Outcomes of childhood conduct problem trajectories in early adulthood: Findings from the ALSPAC study. Eur Child Adolesc Psychiatry 2014;23:539–49. https://doi.org/10.1007/s00787-013-0488-5.

[114] Moffit TE, Caspi A, Dickson N, Silva P, Stanton W. Childhood-onset versus adolescent-onset antisocial conduct problems in males: Natural history from ages 3 to 18 years. Dev Psychopathol 1996;8:399–424. https://doi.org/10.1017/S0954579400007161.
[115] Moffitt TE, Caspi A, Harrington H, Milne BJ. Males on the life-course-persistent and adolescence-limited antisocial pathways: Follow-up at age 26 years. Dev Psychopathol 2002;14:179–207. https://doi.org/10.1017/S0954579402001104.
[116] Odgers CL, Moffitt TE, Broadbent JM, Dickson N, Hancox RJ, Harrington H, et al. Female and male antisocial trajectories: From childhood origins to adult outcomes. Dev Psychopathol 2008;20:673–716. https://doi.org/10.1017/S0954579408000333.
[117] Harford TC, Grant BF, Yi H, Chen CM. Patterns of DSM-IV alcohol abuse and dependence criteria among adolescents and adults: Results from the 2001 national household survey on drug abuse. Alcohol Clin Exp Res 2005;29:810–28. https://doi.org/10.1097/01.ALC.0000164381.67723.76.
[118] Ely M, Hardy R, Longford NT, Wadsworth MEJ. Gender differences in the relationship between alcohol consumption and drink problems are largely accounted for by body water. Alcohol Alcohol 1999;34:894–902. https://doi.org/10.1093/alcalc/34.6.894.
[119] Frezza M, di Padova C, Pozzato G, Terpin M, Baraona E, Lieber CS. High blood alcohol levels in women. N Engl J Med 1990;322:95–9. https://doi.org/10.1056/NEJM199001113220205.
[120] Piazza NJ, Vrbka JL, Yeager RD. Telescoping of alcoholism in women alcoholics. Int J Addict 1989;24:19–28. https://doi.org/10.3109/10826088909047272.
[121] Keyes KM, Martins SS, Blanco C, Hasin DS. Telescoping and gender differences in alcohol dependence: New evidence from two national surveys. Am J Psychiatry 2010;167:969–76. https://doi.org/10.1176/appi.ajp.2009.09081161.
[122] Fernandez Castelao C, Kröner-Herwig B. Different trajectories of depressive symptoms in children and adolescents: Predictors and differences in girls and boys. J Youth Adolescence 2013;42:1169–82. https://doi.org/10.1007/s10964-012-9858-4.
[123] Hicks BM, Blonigen DM, Kramer MD, Krueger RF, Patrick CJ, Iacono WG, et al. Gender differences and developmental change in externalizing disorders from late adolescence to early adulthood: A longitudinal twin study. J Abnorm Psychol 2007;116:433–47. https://doi.org/10.1037/0021-843X.116.3.433.
[124] Leadbeater BJ, Kuperminc GP, Blatt SJ, Hertzog C. A multivariate model of gender differences in adolescents' internalizing and externalizing problems. Dev Psychol 1999;35:1268–1282. https://doi.org/10.1037/0012-1649.35.5.1268.
[125] Shanahan L, Calkins SD, Keane SP, Kelleher R, Suffness R. Trajectories of internalizing symptoms across childhood: The roles of biological self-regulation and maternal psychopathology. Dev Psychopathol 2014;26:1353–68. https://doi.org/10.1017/S0954579414001072.
[126] Schulte MT, Ramo D, Brown SA. Gender differences in factors influencing alcohol use and drinking progression among adolescents. Clin Psychol Rev 2009;29:535–47. https://doi.org/10.1016/j.cpr.2009.06.003.

[127] McCoy SS, Dimler LM, Samuels DV, Natsuaki MN. Adolescent susceptibility to deviant peer pressure: Does gender matter? Adolescent Res Rev 2019;4:59–71. https://doi.org/10.1007/s40894-017-0071-2.
[128] Turner S, Mota N, Bolton J, Sareen J. Self-medication with alcohol or drugs for mood and anxiety disorders: A narrative review of the epidemiological literature. Depress Anxiety 2018;35:851–60. https://doi.org/10.1002/da.22771.
[129] Cook EC, Pflieger JC, Connell AM, Connell CM. Do specific transitional patterns of antisocial behavior during adolescence increase risk for problems in young adulthood? J Abnorm Child Psychol 2015;43:95–106. https://doi.org/10.1007/s10802-014-9880-y.
[130] Dawson DA, Goldstein RB, Moss HB, Li T-K, Grant BF. Gender differences in the relationship of internalizing and externalizing psychopathology to alcohol dependence: Likelihood, expression and course. Drug Alcohol Depend 2010;112:9–17. https://doi.org/10.1016/j.drugalcdep.2010.04.019.
[131] Green KM, Zebrak KA, Robertson JA, Fothergill KE, Ensminger ME. Interrelationship of substance use and psychological distress over the life course among a cohort of urban African Americans. Drug Alcohol Depend 2012;123:239–48.
[132] Ohannessian C M, Flannery K M, Simpson E, Russell B S. Family functioning and adolescent alcohol use: A moderated mediation analysis. J Adolesc 2016;49:19–27.
[133] Colman I, Murray J, Abbott RA, Maughan B, Kuh D, Croudace TJ, et al. Outcomes of conduct problems in adolescence: 40 year follow-up of national cohort. BMJ 2009;338:a2981. https://doi.org/10.1136/bmj.a2981.
[134] Pesola F, Shelton KH, Van Den Bree MBM. Sexual orientation and alcohol problem use among U.K. adolescents: An indirect link through depressed mood. Addiction 2014;109:1072–80.
[135] Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE, Miech RA. Monitoring the Future national survey results on drug use, 1975–2014: Vol 2, College stu- dents and adults ages 19–55. Ann Arbor: Institute for Social Research, The University of Michigan; 2015.
[136] Brown TN, Schulenberg J, Bachman JG, O'Malley PM, Johnston LD. Are risk and protective factors for substance use consistent across historical time?: National data from the high school classes of 1976 through 1997. Prev Sci 2001:15.
[137] Mold A. 'Everybody Likes a Drink. Nobody Likes a Drunk'. Alcohol, health education and the public in 1970s Britain. Soc Hist Med 2017;30:612–36. https://doi.org/10.1093/shm/hkw094.
[138] World Health Organization. Management of substance abuse. Country Profiles 2014 2014. http://www.who.int/substance_abuse/publications/global_alcohol_report/profiles/en/ (accessed February 27, 2018).
[139] Mold A. Framing drug and alcohol use as a public health problem in Britain: Past and present. Nordisk Alkohol Nark 2018;35:93–9. https://doi.org/10.1177/1455072518765836.
[140] Baggott R. Alcohol, politics and social policy. J Soc Policy 1986;15:467–88. https://doi.org/10.1017/S0047279400015506.

[141] Crombie IK, Irvine L, Elliott L, Wallace H. How do public health policies tackle alcohol-related harm: a review of 12 developed countries. Alcohol Alcohol 2007;42:492–9. https://doi.org/10.1093/alcalc/agm001.
[142] Royal College of Physicians, Royal College of General Practitioners. Alcohol: A balanced view. London: Royal College of General Practitioners; 1987.
[143] Department of Health. Alcohol guidelines review - Report from the guidelines development group to the UK Chief Medical Officers. London: Department of Health; 2016.
[144] Donovan JE, Jessor R, Costa FM. Adolescent problem drinking: Stability of psychosocial and behavioral correlates across a generation. J Stud Alcohol 1999;60:352–61. https://doi.org/10.15288/jsa.1999.60.352.
[145] Brand DA, Saisana M, Rynn LA, Pennoni F, Lowenfels AB. Comparative analysis of alcohol control policies in 30 countries. PLoS Med 2007;4. https://doi.org/10.1371/journal.pmed.0040151.
[146] Savic M, Room R, Mugavin J, Pennay A, Livingston M. Defining “drinking culture”: A critical review of its meaning and connotation in social research on alcohol problems. Drugs (Abingdon Engl) 2016;23:270–82. https://doi.org/10.3109/09687637.2016.1153602.
[147] Sudhinaraset M, Wigglesworth C, Takeuchi DT. Social and cultural contexts of alcohol use. Alcohol Res 2016;38:35–45.
[148] Walsh DC. The shifting boundaries of alcohol policy. Health Aff 1990;9:47–62. https://doi.org/10.1377/hlthaff.9.2.47.
[149] Otten R, Mun CJ, Shaw DS, Wilson MN, Dishion TJ. A developmental cascade model for early adolescent-onset substance use: The role of early childhood stress. Addiction 2019;114:326–34. https://doi.org/10.1111/add.14452.
[150] Eiden RD, Lessard J, Colder CR, Livingston J, Casey M, Leonard KE. Developmental cascade model for adolescent substance use from infancy to late adolescence. Dev Psychol 2016;52:1619–33. https://doi.org/10.1037/dev0000199.
[151] Dodge KA, Malone PS, Lansford JE, Miller S, Pettit GS, Bates JE. A dynamic cascade model of the development of substance-use onset. Monogr Soc Res Child Dev 2009;74:vii–119. https://doi.org/10.1111/j.1540-5834.2009.00528.x.
[152] Scalco MD, Colder CR, Hawk Jr. LW, Read JP, Wieczorek WF, Lengua LJ. Internalizing and externalizing problem behavior and early adolescent substance use: A test of a latent variable interaction and conditional indirect effects. Psychol Addict Behav 2014;28:828–40. https://doi.org/10.1037/a0035805.
[153] Jacob T, Bucholz KK, Sartor CE, Howell DN, Wood PK. Drinking trajectories from adolescence to the mid-forties among alcohol dependent males. J Stud Alcohol 2005;66:745–55. https://doi.org/10.15288/jsa.2005.66.745.
[154] Cutler DM, Lleras-Muney A. Education and health: Evaluating theories and evidence. National Bureau of Economic Research; 2006. https://doi.org/10.3386/w12352.
[155] Shankar A, McMunn A, Steptoe A. Health-related behaviors in older adults: relationships with socioeconomic status. Am J Prev Med 2010;38:39–46. https://doi.org/10.1016/j.amepre.2009.08.026.

[156] Trostel P. It's not just the money: The benefits of college education to individuals and to society. Indianapolis, Indiana: Lumina Foundation: University of Maine; 2015.
[157] U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion. Healthy people 2030 2020. https://health.gov/healthypeople (accessed August 26, 2020).
[158] Public Health England. Local action on health inequalities: evidence papers. GOVUK 2020. https://www.gov.uk/government/publications/local-action-on-health-inequalities-evidence-papers (accessed August 26, 2020).
[159] Casswell S, Pledger M, Hooper R. Socioeconomic status and drinking patterns in young adults. Addiction 2003;98:601–10. https://doi.org/10.1046/j.1360-0443.2003.00331.x.
[160] Kendler KS, Gardner CO, Hickman M, Heron J, Macleod J, Lewis G, et al. Socioeconomic status and alcohol-related behaviors in mid- to late adolescence in the Avon Longitudinal Study of Parents and Children. J Stud Alcohol Drugs 2014;75:541–5.
[161] Karlamangla A, Zhou K, Reuben D, Greendale G, Moore A. Longitudinal trajectories of heavy drinking in adults in the United States of America. Addiction 2006;101:91–9. https://doi.org/10.1111/j.1360-0443.2005.01299.x.
[162] Monden CWS, van Lenthe F, De Graaf ND, Kraaykamp G. Partner's and own education: Does who you live with matter for self-assessed health, smoking and excessive alcohol consumption? Soc Sci Med 2003;57:1901–12. https://doi.org/10.1016/S0277-9536(03)00055-8.
[163] Crum R, Helzer J, Anthony J. Level of education and alcohol-abuse and dependence in adulthood - a further inquiry. Am J Public Health 1993;83:830–7. https://doi.org/10.2105/AJPH.83.6.830.
[164] Elliott M, Lowman J. Education, income and alcohol misuse: A stress process model. Soc Psychiatry Psychiatr Epidemiol 2015;50:19–26. https://doi.org/10.1007/s00127-014-0867-3.
[165] Gilman SE, Breslau J, Conron KJ, Koenen KC, Subramanian SV, Zaslavsky AM. Education and race-ethnicity differences in the lifetime risk of alcohol dependence. J Epidemiol Community Health 2008;62:224–30. https://doi.org/10.1136/jech.2006.059022.
[166] Assari S, Lankarani MM. Education and alcohol consumption among older Americans; Black–White differences. Front Public Health 2016;4. https://doi.org/10.3389/fpubh.2016.00067.
[167] Caldwell TM, Rodgers B, Clark C, Jefferis BJMH, Stansfeld SA, Power C. Lifecourse socioeconomic predictors of midlife drinking patterns, problems and abstention: Findings from the 1958 British Birth Cohort Study. Drug Alcohol Depend 2008;95:269–78. https://doi.org/10.1016/j.drugalcdep.2008.01.014.
[168] Huerta MC, Borgonovi F. Education, alcohol use and abuse among young adults in Britain. Soc Sci Med 2010;71:143–51. https://doi.org/10.1016/j.socscimed.2010.03.022.
[169] Bann D, Hamer M, Parsons S, Ploubidis GB, Sullivan A. Does an elite education benefit health? Findings from the 1970 British Cohort Study. Int J Epidemiol 2017;46:293–302.

[170] Moore AA, Gould R, Reuben DB, Greendale GA, Carter MK, Zhou K, et al. Longitudinal patterns and predictors of alcohol consumption in the United States. Am J Public Health 2005;95:458–64. https://doi.org/10.2105/AJPH.2003.019471.
[171] Green MJ, Leyland AH, Sweeting H, Benzeval M. Adolescent smoking and tertiary education: Opposing pathways linking socio-economic background to alcohol consumption. Addiction 2016;111:1457–65. https://doi.org/10.1111/add.13365.
[172] Green MJ, Leyland AH, Sweeting H, Benzeval M. Causal effects of transitions to adult roles on early adult smoking and drinking: Evidence from three cohorts. Soc Sci Med 2017;187:193–202. https://doi.org/10.1016/j.socscimed.2017.06.018.
[173] Barr PB, Salvatore JE, Maes H, Aliev F, Latvala A, Viken R, et al. Education and alcohol use: A study of gene-environment interaction in young adulthood. Soc Sci Med 2016;162:158–67. https://doi.org/10.1016/j.socscimed.2016.06.031.
[174] Berry D, Willoughby MT. On the practical interpretability of cross-lagged panel models: Rethinking a developmental workhorse. Child Dev 2017;88:1186–206. https://doi.org/10.1111/cdev.12660.
[175] Hoffman L. Longitudinal analysis: modeling within-person fluctuation and change. 1 edition. Routledge; 2015.
[176] Curran PJ, Howard AL, Bainter SA, Lane ST, McGinley JS. The separation of between-person and within-person components of individual change over time: a latent curve model with structured residuals. J Consult Clin Psychol 2014;82:879–94. https://doi.org/10.1037/a0035297.
[177] Curran PJ, Bauer DJ. The disaggregation of within-person and between-person effects in longitudinal models of change. Annu Rev Psychol 2011;62:583–619. https://doi.org/10.1146/annurev.psych.093008.100356.
[178] Hoyland MA, Latendresse SJ. Stressful life events influence transitions among latent classes of alcohol use. Psychol Addict Behav 2018;32:727–37. https://doi.org/10.1037/adb0000412.
[179] Sedgwick P. Bias in observational study designs: Prospective cohort studies. BMJ 2014;349:g7731. https://doi.org/10.1136/bmj.g7731.
[180] Hernán MA. The C-word: Scientific euphemisms do not improve causal inference from observational data. Am J Public Health 2018;108:616–9. https://doi.org/10.2105/AJPH.2018.304337.
[181] Pearl J, Mackenzie D. The book of why: The new science of cause and effect. Basic Books, Inc.; 2018.
[182] Pearl J, Glymour M, Jewell NP. Causal inference in statistics: A primer. 2016.
[183] Hernan MA, Robins JM. Causal inference: What if. Boca Raton: Chapman & Hall/CRC.; 2020.
[184] Pearl J. The causal mediation formula—A guide to the assessment of pathways and mechanisms. Prev Sci 2012;13:426–36. https://doi.org/10.1007/s11121-011-0270-1.
[185] De Stavola BL, Daniel RM, Ploubidis GB, Micali N. Mediation analysis with intermediate confounding: Structural equation modeling viewed through the causal inference lens. Am J Epidemiol 2015;181:64–80. https://doi.org/10.1093/aje/kwu239.

[186] Valeri L, Vanderweele TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: Theoretical assumptions and implementation with SAS and SPSS macros. Psychol Methods 2013;18:137–50. https://doi.org/10.1037/a0031034.
[187] Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. Psychol Methods 2010;15:309–34. https://doi.org/10.1037/a0020761.
[188] Hariton E, Locascio JJ. Randomised controlled trials—the gold standard for effectiveness research. BJOG 2018;125:1716. https://doi.org/10.1111/1471-0528.15199.
[189] Jones DS, Podolsky SH. The history and fate of the gold standard. The Lancet 2015;385:1502–3. https://doi.org/10.1016/S0140-6736(15)60742-5.
[190] Gunasekara FI, Richardson K, Carter K, Blakely T. Fixed effects analysis of repeated measures data. Int J Epidemiol 2014;43:264–9. https://doi.org/10.1093/ije/dyt221.
[191] Bollen KA, Brand JE. Fixed and random effects in panel data using structural equations models. Los Angeles: California Center for Population Research; 2008.
[192] Fixed effects model. Wikipedia 2020.
[193] Stawski RS, Sliwinski MJ, Hofer SM. Between-person and within-person associations among processing speed, attention switching and working memory in younger and older adults. Exp Aging Res 2013;39:194–214. https://doi.org/10.1080/0361073X.2013.761556.
[194] Buyukcan-Tetik A, Finkenauer C, Bleidorn W. Within-person variations and between-person differences in self-control and wellbeing. Pers Individ Dif 2018;122:72–8. https://doi.org/10.1016/j.paid.2017.10.013.
[195] Ge X, Natsuaki MN, Conger RD. Trajectories of depressive symptoms and stressful life events among male and female adolescents in divorced and nondivorced families. Dev Psychopathol 2006;18:253–73. https://doi.org/10.1017/S0954579406060147.
[196] Aseltine RH, Gore SL. The variable effects of stress on alcohol use from adolescence to early adulthood. Subst Use Misuse 2000;35:643–68. https://doi.org/10.3109/10826080009148415.
[197] Nagin DS, Jones BL, Passos VL, Tremblay RE. Group-based multi-trajectory modeling. Stat Methods Med Res 2018;27:2015–23. https://doi.org/10.1177/0962280216673085.
[198] Xie H, McHugo GJ, He X, Drake RE. Using the group-based dual trajectory model to analyze two related longitudinal outcomes. J Drug Issues 2010;40:45–61. https://doi.org/10.1177/002204261004000104.
[199] Collishaw S, Maughan B, Natarajan L, Pickles A. Trends in adolescent emotional problems in England: A comparison of two national cohorts twenty years apart. J Child Psychol Psychiatry 2010;51:885–94. https://doi.org/10.1111/j.1469-7610.2010.02252.x.
[200] Collishaw S, Maughan B, Goodman R, Pickles A. Time trends in adolescent mental health. J Child Psychol Psychiatry 2004;45:1350–62. https://doi.org/10.1111/j.1469-7610.2004.00335.x.
[201] Lu W. Adolescent depression: national trends, risk factors, and healthcare disparities. Am J Health Behav 2019;43:181–94. https://doi.org/10.5993/AJHB.43.1.15.

[202] Patalay P, Gage SH. Changes in millennial adolescent mental health and health-related behaviours over 10 years: A population cohort comparison study. Int J Epidemiol 2019. https://doi.org/10.1093/ije/dyz006.
[203] Potrebny T, Wiium N, Lundegard MM-I. Temporal trends in adolescents' self-reported psychosomatic health complaints from 1980-2016: A systematic review and meta-analysis. PLoS One 2017;12:e0188374. https://doi.org/10.1371/journal.pone.0188374.
[204] Bor W, Dean AJ, Najman J, Hayatbakhsh R. Are child and adolescent mental health problems increasing in the 21st century? A systematic review. Aust N Z J Psychiatry 2014;48:606–16. https://doi.org/10.1177/0004867414533834.
[205] Sher KJ. Children of alcoholics : a critical appraisal of theory and research. Chicago: University of Chicago Press; 1991.
[206] Sher KJ, Walitzer KS, Wood PK, Brent EE. Characteristics of children of alcoholics: Putative risk factors, substance use and abuse, and psychopathology. Journal of Abnormal Psychology 1991;100:427–48. https://doi.org/10.1037/0021-843X.100.4.427.
[207] Hussong AM, Jones DJ, Stein GL, Baucom DH, Boeding S. An internalizing pathway to alcohol use and disorder. Psychology of Addictive Behaviors 2011;25:390–404. https://doi.org/10.1037/a0024519.
[208] Delfabbro PH, Winefield HR, Winefield AH, Hammarstrom A. Mid-adolescent predictors of adult drinking levels in early adulthood and gender differences: Longitudinal analyses based on the south Australian school leavers study. J Addict 2016;2016:1489691–1489691. https://doi.org/10.1155/2016/1489691.
[209] Essau CA, Lewinsohn PM, Olaya B, Seeley JR. Anxiety disorders in adolescents and psychosocial outcomes at age 30. J Affect Disord 2014;163:125–32.
[210] Edwards AC, Latendresse SJ, Heron J, Bin Cho S, Hickman M, Lewis G, et al. Childhood internalizing symptoms are negatively associated with early adolescent alcohol use. Alcoholism (NY) 2014;38:1680–8. https://doi.org/10.1111/acer.12402.
[211] Niemela S, Sourander A, Poikolainen K, Helenius H, Sillanmaki L, Parkkola K, et al. Childhood predictors of drunkenness in late adolescence among males: A 10-year population-based follow-up study. Addiction 2006;101:512–21. https://doi.org/10.1111/j.1360-0443.2006.01381.x.
[212] Bucholz KK, McCutcheon VV, Agrawal A, Dick DM, Hesselbrock VM, Kramer JR, et al. Comparison of parent, peer, psychiatric, and cannabis use influences across stages of offspring alcohol involvement: Evidence from the COGA prospective study. Alcohol Clin Exp Res 2017;41:359–68. https://doi.org/10.1111/acer.13293.
[213] Cheng TC, Lo CC. Social risk and protective factors in adolescents' reduction and cessation of alcohol use. Subst Use Misuse 2017;52:916–28. https://doi.org/10.1080/10826084.2016.1267220.
[214] Colder CR, Shyhalla K, Frndak SE. Early alcohol use with parental permission: Psychosocial characteristics and drinking in late adolescence. Addict Behav 2018;76:82–7. https://doi.org/10.1016/j.addbeh.2017.07.030.
[215] Lutz HR, Mcclure K, Armstrong S. Social problem solving and adolescent alcohol use within the context of well-established risk factors for adolescent

alcohol use. J Child Adolesc Subst Abuse 2017;26:229–241. https://doi.org/10.1080/1067828X.2017.1292977.
[216] Trucco EM, Colder CR, Wieczorek WF, Lengua LJ, Hawk LW. Early adolescent alcohol use in context: How neighborhoods, parents and peers impact youth. Dev Psychopathol 2014;26:425–36. https://doi.org/10.1017/S0954579414000042.
[217] Deighton J, Lereya T, Patalay P, Casey P, Humphrey N, Wolpert M. Mental health problems in young people, age 11 to 14: Results from the first HeadStart annual survey of 30,000 children. London: CAMHS Press; 2018.
[218] Dyer ML, Easey KE, Heron J, Hickman M, Munafò MR. Associations of child and adolescent anxiety with later alcohol use and disorders: A systematic review and meta-analysis of prospective cohort studies. Addiction 2019;114:968–82. https://doi.org/10.1111/add.14575.
[219] Colder CR, Scalco M, Trucco EM, Read JP, Lengua LJ, Wieczorek WF, et al. Prospective associations of internalizing and externalizing problems and their co-occurrence with early adolescent substance use. J Abnorm Child Psychol 2013;41:667–677. https://doi.org/10.1007/s10802-012-9701-0.
[220] Minimum legal drinking age in 190 countries 2016. https://drinkingage.procon.org/view.resource.php?resourceID=004294 (accessed June 26, 2019).
[221] Ewing JA. The CAGE questionnaire for detection of alcoholism. JAMA 1984;252:1905–7.
[222] O'Brien CP. The CAGE questionnaire for detection of alcoholism. JAMA 2008;300:2054–6. https://doi.org/10.1001/jama.2008.570.
[223] Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The alcohol use disorders identification test: Guidelines for use in primary health care. Geneva 27, Switzerland: World Health Organization; 2001.
[224] Robins L, Cottler L, Bucholz K, Compton W. Diagnostic interview schedule for DSM-IV (DIS-IV). 1995.
[225] Moher D. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Ann Intern Med 2009;151:264. https://doi.org/10.7326/0003-4819-151-4-200908180-00135.
[226] Kendler KS, Gardner CO, Edwards AC, Dick DM, Hickman M, MacLeod J, et al. Childhood risk factors for heavy episodic alcohol use and alcohol problems in late adolescence: A Marginal Structural Model analysis. J Stud Alcohol Drugs 2018;79:370–9. https://doi.org/10.15288/jsad.2018.79.370.
[227] Squeglia L M, Ball T M, Jacobus J, Brumback T, McKenna B S, Nguyen-Louie T T, et al. Neural predictors of initiating alcohol use during adolescence. Am J Psychiatry 2017;174:172–85.
[228] Quinn PD, Pettersson E, Lundström S, Anckarsäter H, Långström N, Gumpert CH, et al. Childhood attention-deficit/hyperactivity disorder symptoms and the development of adolescent alcohol problems: A prospective, population-based study of Swedish twins. Am J Med Genet B Neuropsychiatr Genet 2016;171:958–70. https://doi.org/10.1002/ajmg.b.32412.
[229] Savage JE, Kaprio J, Korhonen T, Pulkkinen L, Rose RJ, Verhulst B, et al. The effects of social anxiety on alcohol and cigarette use across adolescence: Results from a longitudinal twin study in finland. Psychol Addict Behav 2016;30:462–74.

[230] Jun Hyun-Jin, Sacco Paul, Bright Charlotte Lyn, Camlin Elizabeth A. S. Relations among internalizing and externalizing symptoms and drinking frequency during adolescence. Substance Use & Misuse 2015;50:1814–25.
[231] Virtanen P, Nummi T, Lintonen T, Westerlund H, Hägglöf B, Hammarström A. Mental health in adolescence as determinant of alcohol consumption trajectories in the Northern Swedish Cohort. Int J Public Health 2015;60:335–42. https://doi.org/10.1007/s00038-015-0651-5.
[232] Kretschmer Tina, Hickman Matthew, Doerner Rita, Emond Alan, Lewis Glyn, Macleod John, et al. Outcomes of childhood conduct problem trajectories in early adulthood: Findings from the ALSPAC study. Eur Child Adolesc Psychiatry 2014;23:539–49.
[233] Meier M H, Caspi A, Houts R, Slutske W S, Harrington H, Jackson K M, et al. Prospective developmental subtypes of alcohol dependence from age 18 to 32 years: Implications for nosology, etiology, and intervention. Dev Psychopathol 2013;25:785–800.
[234] Naicker K, Galambos NL, Zeng Y, Senthilselvan A, Colman I. Social, demographic, and health outcomes in the 10 years following adolescent Depression. J Adolesc Health 2013;52:533–8.
[235] von Stumm S, Deary IJ, Kivimäki M, Jokela M, Clark H, Batty GD. Childhood behavior problems and health at midlife: 35-year follow-up of a Scottish birth cohort. J Child Psychol Psychiatry 2011;52:992–1001. https://doi.org/10.1111/j.1469-7610.2011.02373.x.
[236] Bor W, McGee TR, Hayatbakhsh R, Dean A, Najman JM. Do antisocial females exhibit poor outcomes in adulthood? An Australian cohort study. Aust N Z J Psychiatry 2010;44:648–57. https://doi.org/10.3109/00048671003631159.
[237] Huurre T, Lintonen T, Kaprio J, Pelkonen M, Marttunen M, Aro H. Adolescent risk factors for excessive alcohol use at age 32 years. A 16-year prospective follow-up study. Soc Psychiat Epidemiol 2010;45:125–34. https://doi.org/10.1007/s00127-009-0048-y.
[238] Colman I, Murray J, Abbott RA, Maughan B, Croudace TJ, Jones PB. Outcomes of conduct problems in adolescence: 40 year follow-up of national cohort. BMJ 2009;338:208–11.
[239] Timmermans M, van Lier PAC, Koot HM. Which forms of child/adolescent externalizing behaviors account for late adolescent risky sexual behavior and substance use? J Child Psychol Psychiatry 2008;49:386–94. https://doi.org/10.1111/j.1469-7610.2007.01842.x.
[240] Moffitt TE, Caspi A, Harrington H, Milne BJ. Males on the life-course-persistent and adolescence-limited antisocial pathways: Follow-up at age 26 years. Dev Psychopathol 2002;14:179–207.
[241] Moffitt TE, Caspi A, Dickson N, Silva P, Stanton W. Childhood-onset versus adolescent-onset antisocial conduct problems in males: Natural history from ages 3 to 18 years. Dev Psychopathol 1996;8:399–424. https://doi.org/10.1017/S0954579400007161.
[242] Steele RG, Forehand R, Armistead L, Brody G. Predicting alcohol and drug use in early adulthood: The role of internalizing and externalizing behavior problems in early adolescence. Am J Orthopsychiatry 1995;65:380–8. https://doi.org/10.1037/h0079694.

[243] Pulkkinen L, Pitkänen T. A prospective study of the precursors to problem drinking in young adulthood. J Stud Alcohol 1994;55:578–87. https://doi.org/10.15288/jsa.1994.55.578.
[244] Pearl J. Direct and indirect effects. Proceedings of the Seventeenth Conference on Uncertainty and Artificial Intelligence, San Francisco: Morgan Kaufmann: 2001, p. 411–420.
[245] Del Re A. Compute.es: compute effect sizes. 2013.
[246] Ryan R. Heterogeneity and subgroup analyses in Cochrane Consumers and communication Group reviews: Planning the analysis at protocol stage 2016.
[247] Gonnermann A, Framke T, Großhennig A, Koch A. No solution yet for combining two independent studies in the presence of heterogeneity. Stat Med 2015;34:2476–80. https://doi.org/10.1002/sim.6473.
[248] Harrison S, Jones HE, Martin RM, Lewis SJ, Higgins JPT. The albatross plot: A novel graphical tool for presenting results of diversely reported studies in a systematic review. Res Synth Methods 2017;8:281–9. https://doi.org/10.1002/jrsm.1239.
[249] CASP Cohort Study Checklist. Critical Appraisal Skills Programme (CASP) 2018. http://www.casp-uk.net (accessed February 27, 2018).
[250] Westreich D. Berkson's bias, selection bias, and missing data. Epidemiology 2012;23:159–64. https://doi.org/10.1097/EDE.0b013e31823b6296.
[251] Hammer GP, du Prel J-B, Blettner M. Avoiding bias in observational studies. Dtsch Arztebl Int 2009;106:664–8. https://doi.org/10.3238/arztebl.2009.0664.
[252] Gorka S M, Shankman S A, Olino T M, Seeley J R, Kosty D B, Lewinsohn P M. Anxiety disorders and risk for alcohol use disorders: The moderating effect of parental support. Drug and Alcohol Dependence 2014;140:191–7.
[253] Meisel SN, Colder CR, Bowker JC, Hussong AM. A longitudinal examination of mediational pathways linking chronic victimization and exclusion to adolescent alcohol use. Dev Psychol 2018;54:1795–1807. https://doi.org/10.1037/dev0000569.
[254] Hicks BM, Iacono WG, McGue M. Consequences of an adolescent onset and persistent course of alcohol dependence in men: Adolescent risk factors and adult outcomes. Alcohol Clin Exp Res 2010;34:819–33. https://doi.org/10.1111/j.1530-0277.2010.01154.x.
[255] Colder CR, Frndak S, Lengua LJ, Read JP, Hawk LW, Wieczorek WF. Internalizing and externalizing problem behavior: A test of a latent variable interaction predicting a two-part growth model of adolescent substance use. J Abnorm Child Psychol 2017;46:319–30. https://doi.org/10.1007/s10802-017-0277-6.
[256] Frojd S, Ranta K, Kaltiala-Heino R, Marttunen M. Associations of social phobia and general anxiety with alcohol and drug use in a community sample of adolescents. Alcohol Alcohol 2011;46:192–9.
[257] Clerkin EM, Barnett N. The separate and interactive effects of drinking motives and social anxiety symptoms in predicting drinking outcomes. Addict Behav 2012;37:674–7. https://doi.org/10.1016/j.addbeh.2012.01.005.
[258] Caldwell TM, Rodgers B, Jorm AF, Christensen H, Jacomb PA, Korten AE, et al. Patterns of association between alcohol consumption and symptoms

of depression and anxiety in young adults. Addiction 2002;97:583–94. https://doi.org/10.1046/j.1360-0443.2002.00092.x.
[259] O'Donnell K, Wardle J, Dantzer C, Steptoe A. Alcohol consumption and symptoms of depression in young adults from 20 countries. J Stud Alcohol 2006;67:837–40. https://doi.org/10.15288/jsa.2006.67.837.
[260] Skogen JC, Harvey SB, Henderson M, Stordal E, Mykletun A. Anxiety and depression among abstainers and low-level alcohol consumers: The Nord-Trøndelag Health Study. Addiction 2009;104:1519–29. https://doi.org/10.1111/j.1360-0443.2009.02659.x.
[261] Richmond RC, Al-Amin A, Smith GD, Relton CL. Approaches for drawing causal inferences from epidemiological birth cohorts: a review. Early Hum Dev 2014;90:769–80. https://doi.org/10.1016/j.earlhumdev.2014.08.023.
[262] Gage SH, Munafò MR, Smith GD. Causal inference in Developmental Origins of Health and Disease (DOHaD) research. Annu Rev Psychol 2016;67:567–85. https://doi.org/10.1146/annurev-psych-122414-033352.
[263] Gunasekara FI, Richardson K, Carter K, Blakely T. Fixed effects analysis of repeated measures data. International Journal of Epidemiology 2014;43:264–269. https://doi.org/10.1093/ije/dyt221.
[264] Fergusson DM, Boden JM, Horwood LJ. Tests of causal links between alcohol abuse or dependence and major depression. Arch Gen Psychiatry 2009;66:260–6. https://doi.org/10.1001/archgenpsychiatry.2008.543.
[265] Pape H, Norström T. Associations between emotional distress and heavy drinking among young people: A longitudinal study. Drug Alcohol Rev 2016;35:170–6. https://doi.org/10.1111/dar.12290.
[266] Wang J, Patten SB. Alcohol consumption and major depression: Findings from a follow-up study. Can J Psychiatry 2001;46:632–8. https://doi.org/10.1177/070674370104600708.
[267] Dong Y, Peng C-YJ. Principled missing data methods for researchers. Springerplus 2013;2. https://doi.org/10.1186/2193-1801-2-222.
[268] Little RJA, Rubin DB. Statistical analysis with missing data. Second Edition. Chichester: Willey; 2002.
[269] White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Statist Med 2011;30:377–99. https://doi.org/10.1002/sim.4067.
[270] Mostafa T, Wiggins R. The impact of attrition and non-response in birth cohort studies: A need to incorporate missingness strategies. Longit Life Course Stud 2015;6:131–46.
[271] Elkins IJ, McGue M, Iacono WG. Prospective effects of attention-deficit/hyperactivity disorder, conduct disorder, and sex on adolescent substance use and abuse. Arch Gen Psychiatry 2007;64:1145–52.
[272] Molina BSG, Howard AL, Swanson JM, Stehli A, Mitchell JT, Kennedy TM, et al. Substance use through adolescence into early adulthood after childhood-diagnosed ADHD: Findings from the MTA longitudinal study. J Child Psychol Psychiatry 2018;59:692–702. https://doi.org/10.1111/jcpp.12855.
[273] Lichtenstein P, Pettersson E, Lundstrom S, Cederlof M. Childhood aggression and adulthood adversities: General and specific associations. Behavior Genetics 2017;47:658–659.

[274] Power C, Elliott J. Cohort profile: 1958 British Birth Cohort (National Child Development Study). Int J Epidemiol 2006;35:34–41. https://doi.org/10.1093/ije/dyi183.
[275] Elliott J, Shepherd P. Cohort profile: 1970 British Birth Cohort (BCS70). Int J Epidemiol 2006;35:836–43. https://doi.org/10.1093/ije/dyl174.
[276] Shepherd P. 1958 National Child Development Study Bristol Social Adjustment Guides at 7 and 11 Years. London: Centre for Longitudinal Studies; 2013.
[277] Rutter M, Tizard J, Whitmore K. Education, health and behaviour. Longman; 1970.
[278] Rutter M. A children's behaviour questionnaire for completion by teachers: Preliminary findings. J Child Psychol Psychiatry 1967;8:1–11. https://doi.org/10.1111/j.1469-7610.1967.tb02175.x.
[279] Ewing JA. Detecting alcoholism. The CAGE questionnaire. JAMA 1984;252:1905–7.
[280] Guidance on the 5 alcohol use screening tests. GOVUK 2017. https://www.gov.uk/government/publications/alcohol-use-screening-tests/guidance-on-the-5-alcohol-use-screening-tests (accessed August 7, 2018).
[281] Caldwell TM, Rodgers B, Clark C, Jefferis BJMH, Stansfeld SA, Power C. Lifecourse socioeconomic predictors of midlife drinking patterns, problems and abstention: Findings from the 1958 British Birth Cohort Study. Drug Alcohol Depend 2008;95:269–78. https://doi.org/10.1016/j.drugalcdep.2008.01.014.
[282] Pinto ACS, Luna IT, Sivla A de A, Pinheiro PN da C, Braga VAB, Souza ÂMA e, et al. Risk factors associated with mental health issues in adolescents: An integrative review. Rev Esc Enferm USP 2014;48:555–64. https://doi.org/10.1590/S0080-623420140000300022.
[283] Bann D, Johnson W, Li L, Kuh D, Hardy R. Socioeconomic inequalities in body mass index across adulthood: Coordinated analyses of individual participant data from three british birth cohort studies initiated in 1946, 1958 and 1970. PLOS Med 2017;14:e1002214. https://doi.org/10.1371/journal.pmed.1002214.
[284] Schoon I. Childhood cognitive ability and adult academic attainment: evidence from three British cohort studies. Longit Life Course Stud 2010;1:241–158. https://doi.org/10.14301/llcs.v1i3.93.
[285] Canette I, Marchenko YV. Combining results other than coefficients in e(b) with multiply imputed data n.d. https://www.stata.com/support/faqs/statistics/combine-results-with-multiply-imputed-data/#suest (accessed September 19, 2019).
[286] Tilling K, Williamson EJ, Spratt M, Sterne JAC, Carpenter JR. Appropriate inclusion of interactions was needed to avoid bias in multiple imputation. J Clin Epidemiol 2016;80:107–15. https://doi.org/10.1016/j.jclinepi.2016.07.004.
[287] Daniel RM, Stavola BLD, Cousens SN. Gformula: Estimating causal effects in the presence of time-varying confounding or mediation using the g-computation formula. The Stata Journal 2011;4:479–517.
[288] Zucker RA, Ellis DA, Fitzgerald HE, Bingham CR, Sanford K. Other evidence for at least two alcoholisms II: Life course variation in antisociality

and heterogeneity of alcoholic outcome. Dev Psychopathol 1996;8:831–48. https://doi.org/10.1017/S0954579400007458.
[289] Zucker RA, Fitzgerald HE, Refior SK, Puttler LI, Pallas DM, Ellis DA. The clinical and social ecology of childhood for children of alcoholics: Description of a study and implications for a differentiated social policy. Children of Addiction, Routledge; 2002, p. 125–58. https://doi.org/10.4324/9780203904602-9.
[290] Straus MA. Measuring intrafamily conflict and violence: the Conflict Tactics (CT) scales. J Marriage Fam 1979;41:75–88. https://doi.org/10.2307/351733.
[291] Coddington RD. The significance of life events as etiologic factors in the diseases of children: I—A survey of professional workers. J Psychosom Res 1972;16:7–18. https://doi.org/10.1016/0022-3999(72)90018-9.
[292] Coddington RD. The significance of life events as etiologic factors in the diseases of children—II a study of a normal population. J Psychosom Res 1972;16:205–13. https://doi.org/10.1016/0022-3999(72)90045-1.
[293] Glenn S, Simpson A, McGuinness D, Drinnan D, Sandberg S. Reliability study of the PACE instrument: Measure of life events and experiences in childhood. Eur Child Adolesc Psych 1993;2:98–110.
[294] Sandberg S, Rutter M, Giles S, Owen A, Champion L, Nicholls J, et al. Assessment of psychosocial experiences in childhood: methodological issues and some illustrative findings. J Child Psychol Psychiatry 1993;34:879–97. https://doi.org/10.1111/j.1469-7610.1993.tb01096.x.
[295] Patterson GR. Coercive family process. Eugene, OR: Castalia; 1982.
[296] Moos RH, Moos BS. A typology of family social environments. Fam Process 1976;15:357–71. https://doi.org/10.1111/j.1545-5300.1976.00357.x.
[297] Moos RH, Insel PM, Humphrey B. Preliminary manual for family environment scale, work environment scale, group environment scale. Consulting Psychologists Press; 1974.
[298] Kanner AD, Coyne JC, Schaefer C, Lazarus RS. Comparison of two modes of stress measurement: daily hassles and uplifts versus major life events. J Behav Med 1981;4:1–39. https://doi.org/10.1007/BF00844845.
[299] Chamberlain P. A parent daily report measure. University of Oregon, 1980.
[300] Achenbach TM. Manual for the Child Behavior Checklist/4-18 and 1991 Profile. Department of Psychiatry, University of Vermont; 1991.
[301] Achenbach TM, Rescorla LA. Manual for the ASEBA Adult Forms and Profiles. Burlington, VT: University of Vermont: Research Center for Children, Youth, & Families; 2003.
[302] Achenbach TM. Manual for the Teacher's Report Form and 1991 Profile. Department of Psychiatry, University of Vermont; 1991.
[303] Achenbach TM. Manual for the Youth Self-report Form and 1991 Profile. Burlington, VT: University Associates in Psychiatry; 1991.
[304] Noll RB, Zucker RA. Child Behavior Rating Scale: School-Age Revision 1985.
[305] Zucker RA, Fitzgerald HE, Noll RB. Drinking and drug history. Michigan State University; 1990.
[306] Bingham CR, Fitzgerald HE, Zucker RA. Peer Behavior Profile/Peer Activities Questionnaire 1995.

[307] Patterson GR. Stress, coping and development in children. New York: McGraw-Hill: 1983.
[308] McGue M, Malone S, Keyes M, Iacono WG. Parent-offspring similarity for drinking: A longitudinal adoption study. Behav Genet 2014;44:620–8. https://doi.org/10.1007/s10519-014-9672-8.
[309] Johnson W, Hicks BM, McGue M, Iacono WG. How intelligence and education contribute to substance use: hints from the Minnesota Twin Family Study. Intelligence 2009;37:613–24. https://doi.org/10.1016/j.intell.2008.12.003.
[310] Finkelhor D, Shattuck A, Turner H, Hamby S. A revised inventory of adverse childhood experiences. Child Abuse Negl 2015;48:13–21. https://doi.org/10.1016/j.chiabu.2015.07.011.
[311] Fava NM, Trucco EM, Martz ME, Cope LM, Jester JM, Zucker RA, et al. Childhood adversity, externalizing behavior, and substance use in adolescence: Mediating effects of anterior cingulate cortex activation during inhibitory errors. Dev Psychopathol 2018:1–12. https://doi.org/10.1017/S0954579418001025.
[312] Melchior M, Touchette E, Prokofyeva E, Chollet A, Fombonne E, Elidemir G, et al. Negative events in childhood predict trajectories of internalizing symptoms up to young adulthood: An 18-year longitudinal study. PLoS One 2014;9:e114526. https://doi.org/10.1371/journal.pone.0114526.
[313] Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the alcohol use disorders identification test (AUDIT): Who collaborative project on early detection of persons with harmful alcohol consumption--ii. Addiction 1993;88:791–804.
[314] Ayala RJ de. The IRT tradition and its applications. The Oxford Handbook of Quantitative Methods in Psychology, Vol 1 2013. https://doi.org/10.1093/oxfordhb/9780199934874.013.0008.
[315] Cosgrove VE, Rhee SH, Gelhorn HL, Boeldt D, Corley RC, Ehringer MA, et al. Structure and etiology of co-occurring internalizing and externalizing disorders in adolescents. J Abnorm Child Psychol 2011;39:109–23. https://doi.org/10.1007/s10802-010-9444-8.
[316] Mesman J, Koot HM. Common and specific correlates of preadolescent internalizing and externalizing psychopathology. J Abnorm Psychol 2000;109:428–37. https://doi.org/10.1037//0021-843X.109.3.428.
[317] van Wijk-Herbrink MF, Bernstein DP, Broers NJ, Roelofs J, Rijkeboer MM, Arntz A. Internalizing and externalizing behaviors share a common predictor: The effects of early maladaptive schemas are mediated by coping responses and schema modes. J Abnorm Child Psychol 2018;46:907–20. https://doi.org/10.1007/s10802-017-0386-2.
[318] Symeou M, Georgiou S. Externalizing and internalizing behaviours in adolescence, and the importance of parental behavioural and psychological control practices. J Adolesc 2017;60:104–13. https://doi.org/10.1016/j.adolescence.2017.07.007.
[319] Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: What is it and how does it work? Int J Methods Psychiatr Res 2011;20:40–9. https://doi.org/10.1002/mpr.329.
[320] Mundfrom DJ, Perrett JJ, Schaffer J, Piccone A, Roozeboom M. Bonferroni adjustments in tests for regression coefficients. Multiple Linear Regression Viewpoints 2006;32:6.

[321] Elliott J, Dodgeon B, Elliott J. A descriptive analysis of the drinking behaviour of the 1958 cohort at age 33 and the 1970 cohort at age 34. London: Centre for Longitudinal Studies, Institute of Education, University of London; 2007.
[322] Koenker R. Quantile regression. Cambridge: Cambridge University Press; 2005. https://doi.org/10.1017/CBO9780511754098.
[323] Zaninotto P, Sacker A. Missing data in longitudinal surveys: a comparison of performance of modern techniques. J Mod App Stat Meth 2017;16:378–402. https://doi.org/10.22237/jmasm/1509495600.
[324] Mostafa T, Narayanan M, Pongiglione B, Dodgeon B, Goodman A, Silverwood RJ, et al. Improving the plausibility of the missing at random assumption in the 1958 British birth cohort: A pragmatic data driven approach. London: UCL Centre for Longitudinal Studies; 2020.
[325] von Hippel PT, Lynch J. Efficiency gains from using auxiliary variables in imputation. ArXiv:13115249 2013:10.
[326] Sullivan TR, Salter AB, Ryan P, Lee KJ. Bias and Precision of the “Multiple Imputation, Then Deletion” method for dealing with missing outcome data. Am J Epidemiol 2015;182:528–34. https://doi.org/10.1093/aje/kwv100.
[327] Eekhout I, de Vet HCW, Twisk JWR, Brand JPL, de Boer MR, Heymans MW. Missing data in a multi-item instrument were best handled by multiple imputation at the item score level. J Clin Epidemiol 2014;67:335–42. https://doi.org/10.1016/j.jclinepi.2013.09.009.
[328] Plumpton CO, Morris T, Hughes DA, White IR. Multiple imputation of multiple multi-item scales when a full imputation model is infeasible. BMC Res Notes 2016;9. https://doi.org/10.1186/s13104-016-1853-5.
[329] Morris TP, White IR, Royston P. Tuning multiple imputation by predictive mean matching and local residual draws. BMC Med Res Methodol 2014;14:75. https://doi.org/10.1186/1471-2288-14-75.
[330] von Hippel PT. How many imputations do you need? A two-stage calculation using a quadratic rule. Sociol Methods Res 2018:004912411774730. https://doi.org/10.1177/0049124117747303.
[331] Eddings W, Marchenko YV. Diagnostics for multiple imputation in Stata. The Stata Journal 2012;12:353–67.
[332] Marchenko YV, Eddings W. A note on how to perform multiple-imputation diagnostics in Stata n.d.:9.
[333] VanderWeele TJ, Ding P. Sensitivity analysis in observational research: Introducing the E-value. Ann Intern Med 2017;167:268. https://doi.org/10.7326/M16-2607.
[334] von Hippel PT. Regression with missing Ys: An improved strategy for analyzing multiply imputed data. Sociol Methodol 2007;37:83–117.
[335] McDowell YE, Vergés A, Sher KJ. Are some alcohol use disorder criteria more (or less) externalizing than others? Distinguishing alcohol use symptomatology from general externalizing psychopathology. Alcohol Clin Exp Res 2019;43:483–96. https://doi.org/10.1111/acer.13952.
[336] Clark DB, Vanyukov M, Cornelius J. Childhood antisocial behavior and adolescent alcohol use disorders. Alcohol Res Health 2002;26:109–15.
[337] Boyle Michael H, Offord David R, Racine Yvonne A, Szatmari Peter, Fleming Jan E, Links Paul S. Predicting substance use in late adolescence: Results from the Ontario Child Health Study follow-up. The American Journal of Psychiatry 1992;149:761–7.

[338] Jun H-J, Sacco P, Bright CL, Camlin EAS. Relations among internalizing and externalizing symptoms and drinking frequency during adolescence. Subst Use Misuse 2015;50:1814–25.
[339] Parrish K H, Atherton O E, Quintana A, Conger R D, Robins R W. Reciprocal relations between internalizing symptoms and frequency of alcohol use: Findings from a longitudinal study of mexican-origin youth. Psychology of Addictive Behaviors 2016;30:203–8.
[340] Farmer RF, Gau JM, Seeley JR, Kosty DB, Sher KJ, Lewinsohn PM. Internalizing and externalizing disorders as predictors of alcohol use disorder onset during three developmental periods. Drug & Alcohol Dependence 2016;164:38–46. https://doi.org/10.1016/j.drugalcdep.2016.04.021.
[341] Zucker RA, Hicks BM, Heitzeg MM. Alcohol use and the alcohol use disorders over the life course: A cross-level developmental review. Developmental Psychopathology, American Cancer Society; 2016, p. 1–40. https://doi.org/10.1002/9781119125556.devpsy318.
[342] Benţea C-C. Motivations for alcohol use in late adolescence and educational strategies of intervention. Procedia Soc Behav Sci 2014;128:186–91. https://doi.org/10.1016/j.sbspro.2014.03.141.
[343] Patrick ME, Rhew IC, Lewis MA, Abdallah DA, Larimer ME, Schulenberg JE, et al. Alcohol motivations and behaviors during months young adults experience social role transitions: Microtransitions in early adulthood. Psychology of Addictive Behaviors 2018;32:895–903. https://doi.org/10.1037/adb0000411.
[344] Chassin L, Flora DB, King KM. Trajectories of alcohol and drug use and dependence from adolescence to adulthood: The effects of familial alcoholism and personality. Journal of Abnormal Psychology 2004;113:483–98.
[345] Edwards AC, Kendler KS. Alcohol consumption in men is influenced by qualitatively different genetic factors in adolescence and adulthood. Psychol Med 2013;43:1857–68. https://doi.org/10.1017/S0033291712002917.
[346] Bergen SE, Gardner CO, Kendler KS. Age-related changes in heritability of behavioral phenotypes over adolescence and young adulthood: a meta-analysis. Twin Res Hum Genet 2007;10:423–33. https://doi.org/10.1375/twin.10.3.423.
[347] Rose RJ, Dick DM, Viken RJ, Kaprio J. Gene-environment interaction in patterns of adolescent drinking: regional residency moderates longitudinal influences on alcohol use. Alcohol Clin Exp Res 2001;25:637–43.
[348] Giles C. Why do the British drink so much? 2015. http://www.bbc.com/future/story/20151102-why-do-the-british-drink-so-much (accessed July 24, 2018).
[349] Mass Observation. The Pub and the people: A worktown study. Faber & Faber; 2011.
[350] Heradstveit O, Skogen JC, Bøe T, Hetland J, Pedersen MU, Hysing M. Prospective associations between childhood externalising and internalising problems and adolescent alcohol and drug use: The Bergen Child Study. Nordisk Alkohol Nark 2018;35:357–71. https://doi.org/10.1177/1455072518789852.

[351] Colder CR, Frndak S, Lengua LJ, Read JP, Hawk LW, Wieczorek WF. Internalizing and externalizing problem behavior: A test of a latent variable interaction predicting a two-part growth model of adolescent substance use. J Abnorm Child Psychol 2017:1–12. https://doi.org/10.1007/s10802-017-0277-6.
[352] Foster KT, Hicks BM, Zucker RA. Positive and negative effects of internalizing on alcohol use problems from childhood to young adulthood: The mediating and suppressing role of externalizing. J Abnorm Psychol 2018;127:394–403. https://doi.org/10.1037/abn0000337.
[353] Gutzke D. Women drinking out in Britain since the early twentieth century. Manchester University Press; 2016.
[354] Lader D, Steel M. Drinking: adults' behaviour and knowledge in 2009 : A report on research using the National Statistics Opinions (Omnibus) Survey produced on behalf of the NHS Information Centre for Health and Social Care. London: Office for National Statistics; 2010.
[355] Dubow E F, Boxer P, Huesmann L R. Childhood and adolescent predictors of early and middle adulthood alcohol use and problem drinking: The Columbia County Longitudinal Study. Addiction 2008;103:36–47.
[356] Mason W Alex, Hawkins J David, Kosterman Rick, Catalano Richard F. Alcohol use disorders and depression: Protective factors in the development of unique versus comorbid outcomes. J Child Adolesc Subst Abuse 2010;19:309–23. https://doi.org/10.1080/1067828x.2010.502491.
[357] Rhew IC, Fleming CB, Vander Stoep A, Nicodimos S, Zheng C, McCauley E. Examination of cumulative effects of early adolescent depression on cannabis and alcohol use disorder in late adolescence in a community-based cohort. Addiction 2017;112:1952–60.
[358] Thompson K D, Leadbeater B J, Ames M E. Reciprocal effects of internalizing and oppositional defiance symptoms on heavy drinking and alcohol-related harms in young adulthood. Substance Abuse: Research and Treatment 2015;9:21–31.
[359] Pitkänen T, Kokko K, Lyyra A-L, Pulkkinen L. A developmental approach to alcohol drinking behaviour in adulthood: A follow-up study from age 8 to age 42. Addiction 2008;103:48–68. https://doi.org/10.1111/j.1360-0443.2008.02176.x.
[360] Why are women drinking more? - IAS n.d. http://www.ias.org.uk/Alcohol-knowledge-centre/Alcohol-and-women/Factsheets/Why-are-women-drinking-more.aspx (accessed October 14, 2019).
[361] Davoren MP, Demant J, Shiely F, Perry IJ. Alcohol consumption among university students in Ireland and the United Kingdom from 2002 to 2014: A systematic review. BMC Public Health 2016;16. https://doi.org/10.1186/s12889-016-2843-1.
[362] Aliev F, Wetherill L, Bierut L, Bucholz KK, Edenberg H, Foroud T, et al. Genes associated with alcohol outcomes show enrichment of effects with broad externalizing and impulsivity phenotypes in an independent sample. J Stud Alcohol Drugs 2015;76:38–46.
[363] Dick DM. The genetics of alcohol and other drug dependence 2008;31:8.
[364] Hankin BL, Fraley RC, Lahey BB, Waldman ID. Is depression best viewed as a continuum or discrete category? A taxometric analysis of childhood and adolescent depression in a population-based sample. Journal of

Abnormal Psychology 2005;114:96–110. https://doi.org/10.1037/0021-843X.114.1.96.
[365] Thompson K, Stockwell T, Leadbeater B, Homel J. Association among different measures of alcohol use across adolescence and emerging adulthood. Addiction 2014;109:894–903. https://doi.org/10.1111/add.12499.
[366] Bell S, Orford J, Britton A. Heavy Drinking Days and Mental Health: An Exploration of the Dynamic 10-Year Longitudinal Relationship in a Prospective Cohort of Untreated Heavy Drinkers. Alcohol Clin Exp Res 2015;39:688–96. https://doi.org/10.1111/acer.12681.
[367] Hicks BM, Zucker RA. Alcoholism: A life span perspective on etiology and course. In: Lewis M, Rudolph KD, editors. Handbook of Developmental Psychopathology, Boston, MA: Springer US; 2014, p. 583–99. https://doi.org/10.1007/978-1-4614-9608-3_29.
[368] Schulenberg JE, Maggs JL, O'Malley PM. How and why the understanding of developmental continuity and discontinuity is important. In: Mortimer JT, Shanahan MJ, editors. Handbook of the Life Course, Boston, MA: Springer US; 2003, p. 413–36. https://doi.org/10.1007/978-0-306-48247-2_19.
[369] Iacono WG, Malone SM. Developmental endophenotypes: Indexing genetic risk for substance abuse with the P300 brain event-related potential. Child Dev Perspect 2011;5:239–47. https://doi.org/10.1111/j.1750-8606.2011.00205.x.
[370] Heron J, Maughan B, Dick DM, Kendler KS, Lewis G, Macleod J, et al. Conduct problem trajectories and alcohol use and misuse in mid to late adolescence. Drug Alcohol Depend 2013;133:100–7. https://doi.org/10.1016/j.drugalcdep.2013.05.025.
[371] Green MJ, Leyland AH, Sweeting H, Benzeval M. Adolescent smoking and tertiary education: Opposing pathways linking socio-economic background to alcohol consumption. Addiction 2016;111:1457–65. https://doi.org/10.1111/add.13365.
[372] Department of Health. Sensible drinking: the report of an interdepartmental Working Group. Department of Health; 1995.
[373] Zhou T, Sun D, Li X, Ma H, Heianza Y, Qi L. Educational attainment and drinking behaviors: Mendelian randomization study in UK Biobank. Mol Psychiatry 2019:1–12. https://doi.org/10.1038/s41380-019-0596-9.
[374] Baggio S, Iglesias K, Deline S, Studer J, Henchoz Y, Mohler-Kuo M, et al. Not in Education, Employment, or Training status among Young Swiss Men. Longitudinal associations with mental health and substance use. J Adolesc Health 2015;56:238–43. https://doi.org/10.1016/j.jadohealth.2014.09.006.
[375] Halpern-Manners A, Schnabel L, Hernandez EM, Silberg JL, Eaves LJ. The relationship between education and mental health: New evidence from a Discordant Twin Study. Soc Forces 2016;95:107–31. https://doi.org/10.1093/sf/sow035.
[376] Case A, Fertig A, Paxson C. The lasting impact of childhood health and circumstance. J Health Econ 2005;24:365–89. https://doi.org/10.1016/j.jhealeco.2004.09.008.
[377] Bardone AM, Moffitt TE, Caspi A, Dickson N, Silva PA. Adult mental health and social outcomes of adolescent girls with depression and conduct

disorder. Dev Psychopathol 1996;8:811–29. https://doi.org/10.1017/S0954579400007446.
[378] Currie J, Stabile M. Mental health in childhood and human capital. National Bureau of Economic Research; 2007. https://doi.org/10.3386/w13217.
[379] Fergusson DM, Lynskey MT. Conduct problems in childhood and psychosocial outcomes in young adulthood: A prospective study. J Emot Behav Disord 1998;6:2–18. https://doi.org/10.1177/106342669800600101.
[380] Sayal K, Washbrook E, Propper C. Childhood behavior problems and academic outcomes in adolescence: Longitudinal population-based study. J Am Acad Child Adolesc Psychiatry 2015;54:360-368.e2. https://doi.org/10.1016/j.jaac.2015.02.007.
[381] Washbrook E, Propper C, Sayal K. Pre-school hyperactivity/attention problems and educational outcomes in adolescence: Prospective longitudinal study. Br J Psychiatry 2013;203:265–71. https://doi.org/10.1192/bjp.bp.112.123562.
[382] Farmer EMZ. Extremity of Externalizing Behavior and Young Adult Outcomes. J Child Psychol Psychiatry 1995;36:617–32. https://doi.org/10.1111/j.1469-7610.1995.tb02317.x.
[383] Farmer EMZ. Extremity of externalizing behavior and young adult outcomes. J Child Psychol Psychiatry 1995;36:617–32. https://doi.org/10.1111/j.1469-7610.1995.tb02317.x.
[384] Abel JR, Deitz R. Do the benefits of college still outweigh the costs? Current Issues in Economics and Finance 2014;20:12.
[385] Waltmann B, van der Erve L, Dearden L, Britton J. The impact of undergraduate degrees on lifetime earnings. The IFS; 2020. https://doi.org/10.1920/re.ifs.2020.0167.
[386] Crosnoe R, Kendig S, Benner A. College-going and trajectories of drinking from adolescence into adulthood. J Health Soc Behav 2017;58:252–69. https://doi.org/10.1177/0022146517693050.
[387] Månsdotter A, Backhans M, Hallqvist J. The relationship between a less gender-stereotypical parenthood and alcohol-related care and death: A registry study of Swedish mothers and fathers. BMC Public Health 2008;8:312. https://doi.org/10.1186/1471-2458-8-312.
[388] Crosnoe R, Riegle-Crumb C. A life course model of education and alcohol use. J Health Soc Behav 2007;48:267–82. https://doi.org/10.1177/002214650704800305.
[389] Jennison KM. The short-term effects and unintended long-term consequences of binge drinking in college: a 10-year follow-up study. Am J Drug Alcohol Abuse 2004;30:659–84. https://doi.org/10.1081/ada-200032331.
[390] Kosterman R, Hill KG, Lee JO, Meacham MC, Abbott RD, Catalano RF, et al. Young adult social development as a mediator of alcohol use disorder symptoms from age 21 to 30. Psychol Addict Behav 2014;28:348–58. https://doi.org/10.1037/a0034970.
[391] MacKinnon DP, Kisbu-Sakarya Y, Gottschall AC. Developments in mediation analysis. The Oxford Handbook of Quantitative Methods in Psychology: Vol 2 2013. https://doi.org/10.1093/oxfordhb/9780199934898.013.0016.

[392] VanderWeele TJ. Mediation analysis: A practitioner's guide. Annu Rev Public Health 2016;37:17–32. https://doi.org/10.1146/annurev-publhealth-032315-021402.
[393] Robins JM, Greenland S. Identifiability and exchangeability for direct and indirect effects. Epidemiology 1992;3:143–55.
[394] Robins JM, Hernán MÁ, Brumback B. Marginal structural models and causal inference in Epidemiology. Epidemiology 2000;11:550–60.
[395] VanderWeele TJ. A unification of mediation and interaction: A four-way decomposition. Epidemiology 2014;25:749–61. https://doi.org/10.1097/EDE.0000000000000121.
[396] Richiardi L, Bellocco R, Zugna D. Mediation analysis in epidemiology: Methods, interpretation and bias. Int J Epidemiol 2013;42:1511–9. https://doi.org/10.1093/ije/dyt127.
[397] Muthén BO, Muthén LK, Asparouhov T. Regression and mediation analysis using Mplus. Muthén & Muthén; n.d.
[398] Williams R. Using the margins command to estimate and interpret adjusted predictions and marginal effects. The Stata Journal 2012;12:308–31. https://doi.org/10.1177/1536867X1201200209.
[399] Pang M, Kaufman JS, Platt RW. Studying noncollapsibility of the odds ratio with marginal structural and logistic regression models. Stat Methods Med Res 2013;25:1925–37. https://doi.org/10.1177/0962280213505804.
[400] Robins J, Hernan M. Estimation of the causal effects of time-varying exposures. Longitudinal Data Analysis, Chapman and Hall/CRC; 2008, p. 553–99.
[401] Naimi AI, Cole SR, Kennedy EH. An introduction to G methods. Int J Epidemiol 2016:dyw323. https://doi.org/10.1093/ije/dyw323.
[402] Daniel R m., Cousens S n., De Stavola B l., Kenward MG, Sterne J a. C. Methods for dealing with time-dependent confounding. Statist Med 2013;32:1584–618. https://doi.org/10.1002/sim.5686.
[403] Bukodi E. National Child Development Study and 1970 British Cohort Study educational qualifications histories, 1981-2009. University of London, Institute of Education, Centre for Longitudinal Studies; 2017.
[404] UK Data Service Home n.d. https://www.ukdataservice.ac.uk/ (accessed January 5, 2020).
[405] National Research Council. Improving adult literacy instruction: Supporting learning and motivation. 2012. https://doi.org/10.17226/13469.
[406] Rothes A, Lemos MS, Gonçalves T. Motives and beliefs of learners enrolled in adult education. Procedia Soc Behav Sci 2014;112:939–48. https://doi.org/10.1016/j.sbspro.2014.01.1252.
[407] Daiva T. The concept of nontraditional student. Vocational Training: Research And Realities 2017;28:40–60. https://doi.org/10.2478/vtrr-2018-0004.
[408] Obade MA. A model of nontraditional college student motivation and success. ProQuest LLC; 2013.
[409] Johnson ML, Taasoobshirazi G, Clark L, Howell L, Breen M. Motivations of traditional and nontraditional college students: From self-determination and attributions, to expectancy and values. The Journal of Continuing Higher Education 2016;64:3–15. https://doi.org/10.1080/07377363.2016.1132880.

[410] Connor JP, George SM, Gullo MJ, Kelly AB, Young RM. A prospective study of alcohol expectancies and self-efficacy as predictors of young adolescent alcohol misuse. Alcohol Alcohol 2011;46:161–9. https://doi.org/10.1093/alcalc/agr004.
[411] Sharma M, Smith L. Self determination theory and potential applications to alcohol and drug abuse behaviors. J Alcohol Drug Educ 2011;55:3.
[412] Benka J. Autonomous self-regulation and different motivations for alcohol use among university students. Ment Health Prev 2017;7:12–6. https://doi.org/10.1016/j.mhp.2017.06.002.
[413] Orosova O, Benka J. Autonomy in relation to alcohol use and motivation to alcohol use: A prevention perspective. Eur J Public Health 2017;27. https://doi.org/10.1093/eurpub/ckx189.144.
[414] Patrick ME, Rhew IC, Lewis MA, Abdallah DA, Larimer ME, Schulenberg JE, et al. Alcohol motivations and behaviors during months young adults experience social role transitions: Microtransitions in early adulthood. Psychology of Addictive Behaviors 2018;32:895–903. https://doi.org/10.1037/adb0000411.
[415] Reczek C, Pudrovska T, Carr D, Umberson D, Thomeer MB. Marital histories and heavy alcohol use among older adults. J Health Soc Behav 2016;57:77–96. https://doi.org/10.1177/0022146515628028.
[416] Windle M, Windle RC. A prospective study of alcohol use among middle-aged adults and marital partner influences on drinking. J Stud Alcohol Drugs 2014;75:546–56.
[417] Tavolacci M-P, Berthon Q, Cerasuolo D, Dechelotte P, Ladner J, Baguet A. Does binge drinking between the age of 18 and 25 years predict alcohol dependence in adulthood? A retrospective case–control study in France. BMJ Open 2019;9. https://doi.org/10.1136/bmjopen-2018-026375.
[418] Egerton GA, Read JP. Relationship role transitions and problem alcohol use in emerging adulthood. Emerging Adulthood 2019;7:291–303. https://doi.org/10.1177/2167696818772950.
[419] De Stavola BL, Daniel RM, Ploubidis GB, Micali N. Mediation analysis with intermediate confounding: structural equation modeling viewed through the causal inference lens. Am J Epidemiol 2015;181:64–80. https://doi.org/10.1093/aje/kwu239.
[420] Rubin DB. Multiple Imputation after 18+ Years. J Am Stat Assoc 1996;91:473–89. https://doi.org/10.1080/01621459.1996.10476908.
[421] Schomaker M, Heumann C. Bootstrap inference when using multiple imputation. Stat Med 2018;37:2252–66. https://doi.org/10.1002/sim.7654.
[422] Brand J, van Buuren S, le Cessie S, van den Hout W. Combining multiple imputation and bootstrap in the analysis of cost-effectiveness trial data. Stat Med 2019;38:210–20. https://doi.org/10.1002/sim.7956.
[423] Simons CL, Rivero-Arias O, Yu L-M, Simon J. Multiple imputation to deal with missing EQ-5D-3L data: Should we impute individual domains or the actual index? Qual Life Res 2015;24:805–15. https://doi.org/10.1007/s11136-014-0837-y.
[424] Cluster Computing - Research Computing Platforms Support n.d. https://wiki.rc.ucl.ac.uk/wiki/Cluster_Computing (accessed January 13, 2020).
[425] Marchenko YV. Multiple-imputation analysis using Stata's mi command 2010.

[426] Tarkiainen L, Martikainen P, Laaksonen M. The contribution of education, social class and economic activity to the income-mortality association in alcohol-related and other mortality in Finland in 1988-2012. Addiction 2016;111:456–64.
[427] Galea S, Ahern J, Tracy M, Rudenstine S, Vlahov D. Education inequality and use of cigarettes, alcohol, and marijuana. Drug Alcohol Depend 2007;90:S4–15. https://doi.org/10.1016/j.drugalcdep.2006.11.008.
[428] Leon AC, Heo M. Sample sizes required to detect interactions between two binary fixed-effects in a mixed-effects linear regression model. Comput Stat Data Anal 2009;53:603–8. https://doi.org/10.1016/j.csda.2008.06.010.
[429] WHO | Cost-effectiveness analysis for health interventions. WHO n.d. https://www.who.int/heli/economics/costeffanalysis/en/ (accessed January 15, 2020).
[430] Rosoff DB, Clarke T-K, Adams MJ, McIntosh AM, Davey Smith G, Jung J, et al. Educational attainment impacts drinking behaviors and risk for alcohol dependence: results from a two-sample Mendelian randomization study with ~780,000 participants. Mol Psychiatry 2019:1–14. https://doi.org/10.1038/s41380-019-0535-9.
[431] Murakami K, Hashimoto H. Associations of education and income with heavy drinking and problem drinking among men: evidence from a population-based study in Japan. BMC Public Health 2019;19:420. https://doi.org/10.1186/s12889-019-6790-5.
[432] Cerdá M, Johnson-Lawrence VD, Galea S. Lifetime income patterns and alcohol consumption: investigating the association between long- and short-term income trajectories and drinking. Soc Sci Med 2011;73:1178–85. https://doi.org/10.1016/j.socscimed.2011.07.025.
[433] VanderWeele TJ, Vansteelandt S. Mediation analysis with multiple mediators. Epidemiol Methods 2014;2:95–115. https://doi.org/10.1515/em-2012-0010.
[434] Vansteelandt S, Daniel RM. Interventional effects for mediation analysis with multiple mediators. Epidemiology 2017;28:258–65. https://doi.org/10.1097/EDE.0000000000000596.
[435] Berlin KS, Parra GR, Williams NA. An introduction to latent variable mixture modeling (part 2): Longitudinal latent class growth analysis and growth mixture models. J Pediatr Psychol 2014;39:188–203. https://doi.org/10.1093/jpepsy/jst085.
[436] Feldman BJ, Masyn KE, Conger RD. New approaches to studying problem behaviors: A comparison of methods for modeling longitudinal, categorical adolescent drinking data. Dev Psychol 2009;45:652–76. https://doi.org/10.1037/a0014851.
[437] Jackson KM, Sher KJ. Comparison of longitudinal phenotypes based on number and timing of assessments: A systematic comparison of trajectory approaches II. Psychol Addict Behav 2006;20:373–84. https://doi.org/10.1037/0893-164X.20.4.373.
[438] Bennett ME, McCrady BS, Johnson V, Pandina RJ. Problem drinking from young adulthood to adulthood: Patterns, predictors and outcomes. J Stud Alcohol 1999;60:605–14. https://doi.org/10.15288/jsa.1999.60.605.
[439] Greenbaum PE, Del Boca FK, Darkes J, Wang C-P, Goldman MS. Variation in the drinking trajectories of freshmen college students. J Consult

Clin Psychol 2005;73:229–38. https://doi.org/10.1037/0022-006X.73.2.229.
[440] Colder CR, Campbell RT, Ruel E, Richardson JL, Flay BR. A finite mixture model of growth trajectories of adolescent alcohol use: Predictors and consequences. J Consult Clin Psychol 2002;70:976–85.
[441] Flory K, Lynam D, Milich R, Leukefeld C, Clayton R. Early adolescent through young adult alcohol and marijuana use trajectories: Early predictors, young adult outcomes, and predictive utility. Dev Psychopathol 2004;16:193–213. https://doi.org/10.1017/S0954579404044475.
[442] Jackson KM, Sher KJ. Similarities and differences of longitudinal phenotypes across alternate indices of alcohol involvement: a methodologic comparison of trajectory approaches. Psychol Addict Behav 2005;19:339–51. https://doi.org/10.1037/0893-164X.19.4.339.
[443] Jackson KM, Sher KJ. Comparison of longitudinal phenotypes based on alternate heavy drinking cut scores: A systematic comparison of trajectory approaches III. Psychol Addict Behav 2008;22:198–209. https://doi.org/10.1037/0893-164X.22.2.198.
[444] Meier MH, Caspi A, Houts R, Slutske WS, Harrington H, Jackson KM, et al. Prospective developmental subtypes of alcohol dependence from age 18 to 32 years: Implications for nosology, etiology, and intervention. Dev Psychopathol 2013;25:785–800. https://doi.org/10.1017/S0954579413000175.
[445] Jester JM, Buu A, Zucker RA. Longitudinal phenotypes for alcoholism: Heterogeneity of course, early identifiers, and life course correlates. Dev Psychopathol 2016;28:1531–46. https://doi.org/10.1017/S0954579415001157.
[446] Casswell S, Pledger M, Pratap S. Trajectories of drinking from 18 to 26 years: Identification and prediction. Addiction 2002;97:1427–37. https://doi.org/10.1046/j.1360-0443.2002.00220.x.
[447] D'Amico EJ, Metrik J, McCarthy DM, Frissell KC, Applebaum M, Brown SA. Progression into and out of binge drinking among high school students. Psychol Addict Behav 2001;15:341–9. https://doi.org/10.1037/0893-164X.15.4.341.
[448] Warner LA, White HR, Johnson V. Alcohol initiation experiences and family history of alcoholism as predictors of problem-drinking trajectories. J Stud Alcohol Drugs 2007;68:56–65. https://doi.org/10.15288/jsad.2007.68.56.
[449] Boden JM, Fergusson DM, Horwood LJ. Associations between exposure to stressful life events and alcohol use disorder in a longitudinal birth cohort studied to age 30. Drug Alcohol Depend 2014;142:154–60. https://doi.org/10.1016/j.drugalcdep.2014.06.010.
[450] Reyes CD, Pagano ME, Ronis RJ. The impact of stressful life events on alcohol use relapse: Findings from the Collaborative Longitudinal Personality Disorders Study. J Dual Diagn 2009;5:226–32. https://doi.org/10.1080/15504260902886505.
[451] Tamers SL, Okechukwu C, Bohl AA, Guéguen A, Goldberg M, Zins M. The impact of stressful life events on excessive alcohol consumption in the French population: Findings from the GAZEL Cohort Study. PLOS ONE 2014;9:e87653. https://doi.org/10.1371/journal.pone.0087653.
[452] Veenstra MY, Lemmens PHHM, Friesema IHM, Garretsen HFL, Knottnerus JA, Zwietering PJ. A literature overview of the relationship between life-

events and alcohol use in the general population. Alcohol Alcohol 2006;41:455–63. https://doi.org/10.1093/alcalc/agl023.
[453] Orcutt JD, Harvey LK. The temporal patterning of tension reduction: stress and alcohol use on weekdays and weekends. J Stud Alcohol 1991;52:415–24. https://doi.org/10.15288/jsa.1991.52.415.
[454] Jester JM, Steinberg DB, Heitzeg MM, Zucker RA. Coping expectancies, not enhancement expectancies, mediate trauma experience effects on problem alcohol use: A prospective study from early childhood to adolescence. J Stud Alcohol Drugs 2015;76:781–9.
[455] Enoch M-A. The influence of gene–environment interactions on the development of alcoholism and drug dependence. Curr Psychiatry Rep 2012;14:150–8. https://doi.org/10.1007/s11920-011-0252-9.
[456] Armeli S, Tennen H, Todd M, Carney MA, Mohr C, Affleck G, et al. A daily process examination of the stress-response dampening effects of alcohol consumption. Psychol Addict Behav 2003;17:266–76. https://doi.org/10.1037/0893-164X.17.4.266.
[457] Bainter SA, Howard AL. Comparing within-person effects from multivariate longitudinal models. Dev Psychol 2016;52:1955–68. https://doi.org/10.1037/dev0000215.
[458] Johnson DP, Whisman MA, Corley RP, Hewitt JK, Rhee SH. Association between depressive symptoms and negative dependent life events from late childhood to adolescence. J Abnorm Child Psychol 2012;40:1385–400. https://doi.org/10.1007/s10802-012-9642-7.
[459] Kaczmarek M, Trambacz-Oleszak S. HRQoL impact of stressful life events in children beginning primary school: Results of a prospective study in Poland. Qual Life Res 2017;26:95–106. https://doi.org/10.1007/s11136-016-1371-x.
[460] Merline A, Jager J, Schulenberg J E. Adolescent risk factors for adult alcohol use and abuse: Stability and change of predictive value across early and middle adulthood. Addiction 2008;103:84–99.
[461] Chalder M, Elgar FJ, Bennett P. Drinking and motivations to drink among adolescent children of parents with alcohol problems. Alcohol Alcohol 2006;41:107–13. https://doi.org/10.1093/alcalc/agh215.
[462] Roche DJO, Bujarski S, Green R, Hartwell EE, Leventhal AM, Ray LA. Alcohol, tobacco, and marijuana consumption is associated with increased odds of same-day substance co- and tri-use. Drug Alcohol Depend 2019;200:40–9. https://doi.org/10.1016/j.drugalcdep.2019.02.035.
[463] Ivaniushina V, Titkova V, Alexandrov D. Peer influence in adolescent drinking behaviour: a protocol for systematic review and meta-analysis of stochastic actor-based modeling studies. BMJ Open 2019;9:e028709. https://doi.org/10.1136/bmjopen-2018-028709.
[464] Hussong AM, Bauer DJ, Huang W, Chassin L, Sher KJ, Zucker RA. Characterizing the life stressors of children of alcoholic parents. J Fam Psychol 2008;22:819–32. https://doi.org/10.1037/a0013704.
[465] Nagin DS, Tremblay RE. Analyzing developmental trajectories of distinct but related behaviors: A group-based method. Psychol Methods 2001;6:18–34. https://doi.org/10.1037/1082-989X.6.1.18.
[466] Hooper D, Coughlan J, Mullen MR. Structural equation modelling: Guidelines for determining model fit. Electronic Journal of Business Research Methods 2008;6:8.

[467] Asparouhov T, Muthen B. Using Mplus TECH11 and TECH14 to test the number of latent classes 2012.
[468] Jung T, Wickrama KAS. An introduction to latent class growth analysis and growth mixture modeling. Social Pers Psych Compass 2008;2:302–17. https://doi.org/10.1111/j.1751-9004.2007.00054.x.
[469] Nylund KL, Asparouhov T, Muthén BO. Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo simulation study. Struct Equ Modeling 2007;14:535–69. https://doi.org/10.1080/10705510701575396.
[470] Bigelow C. Stata for categorical data analysis 2016.
[471] Preacher KJ, Wichman AL, MacCallum RC, Briggs NE. Latent growth curve modeling. SAGE; 2008.
[472] Wu W, Selig JP, Little TD. Longitudinal data analysis. The Oxford Handbook of Quantitative Methods in Psychology: Vol 2 2013. https://doi.org/10.1093/oxfordhb/9780199934898.013.0018.
[473] Masyn KE, Petras H, Liu W. Growth curve models with categorical outcomes. Encyclopedia of Criminology and Criminal Justice, New York, NY: Springer New York; 2014, p. 2013–25. https://doi.org/10.1007/978-1-4614-5690-2_404.
[474] Lee TK, Wickrama K (K. AS), O'Neal CW. Application of latent growth curve analysis with categorical responses in social behavioral research. Struct Equ Modeling 2018;25:294–306. https://doi.org/10.1080/10705511.2017.1375858.
[475] Jia F. Methods for handling missing non-normal data in structural equation modeling. PhD. University of Kansas, 2016.
[476] Muthén LK, Muthén BO. Mplus User's Guide. Eighth Edition. Muthén & Muthén; 1998.
[477] Wanner B, Vitaro F, Ladouceur R, Brendgen M, Tremblay RE. Joint trajectories of gambling, alcohol and marijuana use during adolescence: A person- and variable-centered developmental approach. Addict Behav 2006;31:566–80. https://doi.org/10.1016/j.addbeh.2005.05.037.
[478] Capaldi DM, Feingold A, Kim HK, Yoerger K, Washburn IJ. Heterogeneity in growth and desistance of alcohol use for men in their 20s: Prediction from early risk factors and association with treatment. Alcohol Clin Exp Res 2013;37:E347–55. https://doi.org/10.1111/j.1530-0277.2012.01876.x.
[479] Johnsson KO, Leifman A, Berglund M. College students' drinking patterns: Trajectories of AUDIT scores during the first four years at university. Eur Addict Res 2008;14:11–8. https://doi.org/10.1159/000110406.
[480] Guo J, Chung I-J, Hill KG, Hawkins JD, Catalano RF, Abbott RD. Developmental relationships between adolescent substance use and risky sexual behavior in young adulthood. J Adolesc Health 2002;31:354–62. https://doi.org/10.1016/S1054-139X(02)00402-0.
[481] 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. Alcohol Clin Exp Res 2000;24:892–901. https://doi.org/10.1111/j.1530-0277.2000.tb02071.x.
[482] Mitchell CM, Beals J. The development of alcohol use and outcome expectancies among American Indian young adults: A growth mixture model. Addict Behav 2006;31:1–14. https://doi.org/10.1016/j.addbeh.2005.04.006.

[483] Wiesner M, Weichold K, Silbereisen RK. Trajectories of alcohol use among adolescent boys and girls: Identification, validation, and sociodemographic characteristics. Psychol Addict Behav 2007;21:62–75. https://doi.org/10.1037/0893-164X.21.1.62.
[484] Casswell S, Pledger M, Pratap S. Trajectories of drinking from 18 to 26 years: Identification and prediction. Addiction 2002;97:1427–37. https://doi.org/10.1046/j.1360-0443.2002.00220.x.
[485] Compas BE, Howell DC, Phares V, Williams RA, Ledoux N. Parent and child stress and symptoms: An integrative analysis. Dev Psychol 1989;25:550–9. https://doi.org/10.1037/0012-1649.25.4.550.
[486] Michl LC, McLaughlin KA, Shepherd K, Nolen-Hoeksema S. Rumination as a mechanism linking stressful life events to symptoms of depression and anxiety: Longitudinal evidence in early adolescents and adults. J Abnorm Psychol 2013;122:339–52. https://doi.org/10.1037/a0031994.
[487] Lieb R, Isensee B, Höfler M, Pfister H, Wittchen H-U. Parental major depression and the risk of depression and other mental disorders in offspring: A prospective-longitudinal community study. Arch Gen Psychiatry 2002;59:365–74. https://doi.org/10.1001/archpsyc.59.4.365.
[488] Ge X, Conger RD, Lorenz FO, Simons RL. Parents' stressful life events and adolescent depressed mood. J Health Soc Behav 1994;35:28–44.
[489] Čablová L, Pazderková K, Miovský M. Parenting styles and alcohol use among children and adolescents: A systematic review. Drugs (Abingdon Engl) 2014;21:1–13. https://doi.org/10.3109/09687637.2013.817536.
[490] Cwik MF, Rosenstock S, Tingey L, Redmond C, Goklish N, Larzelere-Hinton F, et al. Exploration of pathways to binge drinking among American Indian adolescents. Prev Sci 2017;18:545–54. https://doi.org/10.1007/s11121-017-0752-x.
[491] Fosco GM, Feinberg ME. Interparental conflict and long-term adolescent substance use trajectories: The role of adolescent threat appraisals. J Fam Psychol 2018;32:175–85. https://doi.org/10.1037/fam0000356.
[492] Lorence B, Hidalgo V, Pérez-Padilla J, Menéndez S. The role of parenting styles on behavior problem profiles of adolescents. Int J Environ Res Public Health 2019;16. https://doi.org/10.3390/ijerph16152767.
[493] Choi KW, Watt MH, MacFarlane JC, Sikkema KJ, Skinner D, Pieterse D, et al. Drinking in the context of life stressors: A multidimensional coping strategy among South African women. Subst Use Misuse 2014;49:66–76. https://doi.org/10.3109/10826084.2013.819365.
[494] Banks DE, Rowe AT, Mpofu P, Zapolski TCB. Trends in typologies of concurrent alcohol, marijuana, and cigarette use among US adolescents: An ecological examination by sex and race/ethnicity. Drug Alcohol Depend 2017;179:71–7. https://doi.org/10.1016/j.drugalcdep.2017.06.026.
[495] Maimaris Will, McCambridge Jim. Age of first drinking and adult alcohol problems: Systematic review of prospective cohort studies. J Epidemiol Community Health 2014;68:268–74. https://doi.org/10.1136/jech-2013-203402.
[496] Newton-Howes G, Boden JM. Relation between age of first drinking and mental health and alcohol and drug disorders in adulthood: Evidence from a 35-year cohort study. Addiction 2016;111:637–44. https://doi.org/10.1111/add.13230.

[497] Mundt MP, Mercken L, Zakletskaia L. Peer selection and influence effects on adolescent alcohol use: a stochastic actor-based model. BMC Pediatrics 2012;12:115. https://doi.org/10.1186/1471-2431-12-115.
[498] Bauman KE, Ennett' ST. On the importance of peer influence for adolescent drug use: Commonly neglected considerations. Addiction 1996:185–198.
[499] Hart DKE, Fazaa N. Life stress events and alcohol misuse: Distinguishing contributing stress events from consequential stress events. Subst Use Misuse 2004;39:1319–39. https://doi.org/10.1081/JA-120039390.
[500] Sutin AR, Costa PT, Wethington E, Eaton W. Perceptions of stressful life events as turning points are associated with self-rated health and psychological distress. Anxiety Stress Coping 2010;23:479–92. https://doi.org/10.1080/10615800903552015.

Appendices

Appendix 1 Key words for systematic review

	Domain	Key words
#1	Mental health	TS=(depression$ OR “depress* symptom$” OR “depress* disorder$” OR “emotional depression$” OR “mental health” OR “mental problem$” OR “mental disorder$” OR “mental illness” OR “mood disorder$” OR anxiety OR “problem* behavio$r” OR internali* OR externali* OR “conduct* problem$” OR “emotional symptom$” OR “emotional problem$” OR “emotional disorder$” OR “behavio* problem$” OR “behavio* symptom$” OR “psychological distress” OR “psychological symptom$” OR “psychological disorder$” OR “psychological health”)
#2	Alcohol consumption	TS=(“alcohol drinking” OR “alcohol* drink*” OR “alcohol intake” OR “alcohol consumption” OR “alcohol behavio$r” OR “alcohol use” OR alcoholism OR “alcohol* beverage$” OR “heavy alcohol use” OR “alcohol abuse” OR “alcohol misuse” OR “alcohol problem$” OR “alcohol-related problems” OR “alcohol use disorder$” OR “alcohol dependence” OR alcohol* OR “heavy NEAR/15 drink*” OR “drink* problem$” OR “problem drink*” OR “binge drink*” OR drinker$ OR “drinking behavio$r” OR “hazardous drink*” OR “harmful drink*” OR “extreme drinking” OR “high$intensity alcohol use” OR “high$intensity drink*” OR “drink* culture”)
#3	Limit Exposure Stage	TS=(“early mental health” OR child OR childhood OR child* OR adolescence OR adolescent OR adolescen* OR teen$ OR teenager$ OR youth$ OR “young people” OR “young person” OR “young adult” OR kid$ OR boy$ OR girl$ OR pupil$ OR schoolchild OR school$age OR minor$ OR “primary school” OR “secondary school” OR “elementary school” OR “high$school” OR student$ OR juvenil*)
#4	Limit Study type	TS=(“life$course” OR “life$span” OR longitudinal OR cohort$ OR prospective OR life$time OR temporal OR developmental OR trajector* OR “follow$up” OR sweep$ OR wave$ OR “panel study”)
#5	#1 AND #2 AND #3 AND #4	
#6	Exclusion	TI=(pregnant OR pregnancy OR rat$ OR animal$ OR HIV OR lesbian OR gay OR mice OR cancer OR “fetal alcohol NEAR/10 dis*” OR “fetal alcohol NEAR/10 syndrom$” OR “alcoholic NEAR/10 liver disease” OR “neonatal” OR “prenatal”)

Appendix 2 Extracted associations for each exposure-outcome set in 36 articles

Study	Exposure and outcome	Association (β,SE,95%CI,*P*-value)[#]	Sex dif[§]	Model[&]	Covariates	QA*
Berg et al. (2018)[102]	INT (15.9)-H/P Drinking (22)	Female: 0.07,NR,p<0.05 Male: 0.10,NR,p<0.01	No	Cross-lagged	Parental social economic position (16), basic education, marital and parental status, smoking, and unemployment (22, 32, 42)	6
Kendler et al. (2018)[226]	EXT (13.5)- H/P Drinking(HD) (20)	0.024 (-0.006,0.054)	NE	MSM	Sex, parental socioeconomic status before age 8, parental alcohol problems (from pregnancy to age 12), sensation seeking at age 13.5 and 18, peer group deviance at age 12.5 and 17.5, lack of parental monitoring at age 13.5 and 15.5	6
	EXT (15.5)- H/P Drinking(HD) (20)	0.042 (0.007,0.077)				
	EXT (13.5)- H/P Drinking(PD) (20)	0.000 (-0.028, 0.028)				
	EXT (15.5)- H/P Drinking(PD) (20)	0.078 (0.038, 0.118)				
Soloski et al. (2018)[85]	DEP (14.9)- H/P Drinking (21.6)	-0.09 (0.04)	No	Cross-lagged	Age, sex, race, ethnicity, number of parents living in the household with the adolescent, parent alcohol use, number of three closest friends who used alcohol	5
Hoyland et al. (2017)[82]	DEP (15.6)- H/P Drinking (29.6)	Problem vs low-intake: OR 1.139, p=0.361 Non-problem vs low-intake: OR 0.532, p=0.129 Abstainer vs low-intake: OR 0.929, p=0.482 Problem vs abstainers: OR 1.059, P=0.681 Nonproblem vs abstainers: OR 0.782, p=0.019 Problem vs nonproblem: OR 1.353, p=0.023	NE	Logistic reg	Age, race, and sex, wave one alcohol use and Catholic/Protestant identification, delinquency, delinquency*depression	3
Squeglia et al. (2017)[227]	EXT (13)-AC (18)	NR, positive, p=0.007	NE	Random forest analyses	A series of demographic, neuropsychological and neuroimaging variables, but not sex	4

Study	Exposure and outcome	Association (β,SE,95%CI,*P*-value)[#]	Sex dif[§]	Model[&]	Covariates	QA*
Edwards et al. (2016)[72]	EXT (11.8)- H/P Drinking (20)	0.031, NR, p<0.05	No	SEM	Sex, parental SES, paternal AP, maternal AP, good peer relationships 11.8, low parental monitoring12.8, peer group deviance12.8, extraversion13.6, low conscientiousness13.6, sensation seeking13.6, conduct disorder15.6, major depression symptoms16.6, peer group deviance17.6, stressful life events17.6, illicit substance use17.6 (alcohol problem17.6, sensation seeking18, illicit substance use18)	5
	EXT (15.6)- H/P Drinking (20)	0.146, NR, p<0.05				
	DEP (16.6)- H/P Drinking (20)	0.035, NR, p<0.05				
Quinn et al. (2016)[228]	EXT (15)- H/P Drinking (18)	0.25 (0.19,0.32)	NE	OLS	Sex	3
Savage et al. (2016)[229]	ANX (12)-AC(22)	-0.1 (0.04), p<0.05	No	Pearson Correlation	None	4
Swift et al. (2016)[79]	Onset of EXT (14.5~17)-AUD(24)	OR(95%) Moderate vs mild: 0.96 (0.60,1.6) Severe vs mild: 3.2 (1.5,6.8) Severe vs moderate: 3.3 (1.6,7.1)	NE	Multi-nomial logistic reg	Geographical location, sex, frequency of parental drinking, frequency of parental smoking, parental education, and parental divorce/separation, adolescent indices: age at alcohol use onset<15 years, frequent/binge alcohol use, alcohol use problems,daily cigarette smoking, weekly cannabis use, persisting symptoms of anxiety/depression, antisocial behaviours	6
	Onset of INT (14.5~17)-AUD(24)	Moderate vs mild: 1.9 (1.2,3.1) Severe vs mild: 2.5 (1.3,5.0) Severe vs moderate: 1.3 (0.6,3.2)				
Cook et al. (2015)[129]	EXT across time (13.9~14.9)- H/P Drinking (20.3)	Reference group: non-ASB, OR Agg Stable (female): 1.09(0.73,1.63) Theft Stable(female): 1.79(1.36,2.42) Serious Stable(female): 1.23(0.65,2.28) Escalators(female): 2.19(1.48,3.23) De-Escalators(female): 1.30(0.97,1.74) Agg Stable*male: 1.93(1.19,3.12) Theft Stable*male: 1.32(0.85,2.01) Serious Stable*male: 2.52(1.20,5.28)	Yes	Logistic reg	Sex, adolescents' age as indicated by grade, race/ethnicity (dummy coded with 'White' as the reference group), and poverty status	5

Study	Exposure and outcome	Association (β,SE,95%CI,*P*-value)[#]	Sex dif[§]	Model[&]	Covariates	QA*
		Escalators*male: 0.89(0.53,1.52) De-Escalators*male: 1.19(0.83,1.72)				
Jun et al. (2015)[230]	EXT(15)-AC(18)	No association for male, coefficient NR No association for female, coefficient NR	No	Cross-lagged	Race/ethnicity of subjects, and salary and educational level of primary caregivers	3
	INT(15)-AC(18)	No association for male, coefficient NR No association for female, coefficient NR				
Pesola et al. (2015)[84]	DEP(14)- H/P Drinking (19)	0.049 (0,0.098)	NE	SEM	Sex, financial difficulties, family education level, parents' alcohol consumption, and parents' depression, SDQ conducting problem, earlier deviant peers at 13, earlier alcohol use at 13	5
Thompson et al. (2016)[80]	EXT(16/17)- H/P Drinking(HD)(18/19)	0.08,p<0.001	No	Cross-lagged	Sex, mother's education	3
	EXT(16/17)- H/P Drinking (PD)(18/19)	0.10, p<0.001				
	INT(16/17)- H/P Drinking (HD)(18/19)	No association, NR				
	INT(16/17)- H/P Drinking (PD)(18/19)	0.10,p<0.001				
Virtanen et al.(2015)[231]	DEP(16)-AC(16~45)	Reference group: compliant group, OR(95%) Late onset low: 1.07(0.45,2.50) Ordinary:1.41(0.74,2.72) Early onset low:2.37(1.14,4.93) Early onset moderate:2.46(1.31,4.64) Early onset high:2.86(1.45,5.66)	No	Multi-nomial logistic reg	Sex, parental social class	4
	ANX(16)-AC(16~45)	Reference group: compliant group, OR(95%)				

Study	Exposure and outcome	Association (β,SE,95%CI,*P*-value)[#]	Sex dif[§]	Model[&]	Covariates	QA*
		Late onset low: 1.54(0.72,3.32) Ordinary:1.97(1.08,3.60) Early onset low:2.43(1.21,4.88) Early onset moderate:2.84(1.56,5.15) Early onset high:3.59(1.89,6.82)				
Edwards et al. (2014)[81]	DEP(12~17)- H/P Drinking (18.5)	Intercept 0.05(-0.07,0.16), p=0.426 for male 0.04(-0.05,0.13), p=0.610 for female Slope -0.03(-0.17,0.10),p=0.432 for male 0.15(0.04,0.25),p=0.007 for female	Yes	Growth Curve Model+ OLS	Maternal education, parity and tenure, smoking 12, alcohol 12, cannabis 9, EPDS 11, conduct problems11, bullying 13, smoking, cannabis and alcohol 13	5
Kretschmer et al. (2014)[232]	EXT(4~13)- H/P Drinking (18)	Reference group: low, OR(95%) Childhood-limited(CL): 0.86(0.39,1.86) Adolescence-onset(AO): 1.68(0.89,3.20) Early onset persistent(EOP):1.91(1.21,3.01) Reference group:CL EOP:2.22(0.95,5.26) AO:1.96(0.70,5.50) EOP vs AO: 1.14(0.55,2.33)	NE	Logistic reg	Socio-economic status, marital status/cohabitation, maternal education, and age of the mother when first pregnant, drinking during pregnancy and maternal family history of alcohol use, smoking during pregnancy, any maternal contact with the police during child's first 4 years of life, childbirth weight, gestational age, parity and a single indicator for any birth complications, language development, child temperament at 24 months postpartum, maternal depression, anxiety at 32 weeks antenatal and 8 weeks postnatal, harsh parenting at 24 months and partner emotional and/or physical cruelty to the mother during child's first 4 years of life. low emotional and practical support for the mother during child's first 4 years of life. Indication of child head injury during child's first 4 years of life. Maternal attitude toward the child at 33 months postpartum.	4
Pesola et al.	DEP(16)- H/P Drinking (18)	0.06, p=0.001	No	SEM	Family environment (i.e. parental drinking	5

Study	Exposure and outcome	Association (β,SE,95%CI,*P*-value)[#]	Sex dif[§]	Model[&]	Covariates	QA*
(2014)[134]					and depression, collected at 12 years) and socio-economic status, earlier depressed mood and earlier alcohol problem use at age 16	
Stanley et al. (2014)[78]	EXT(11.7)-AUD(19.7)	OR(95%) 1.05(0.99,1.12)	NE	Logistic reg	Sex, income, alcoholic mother, alcoholic father, family cohesion, family conflict, likes school, early alcohol initiation, and Internalising behaviours accordingly	5
	INT(11.7)-AUD(19.7)	OR(95%) 0.96(0.91,1.02)				
Meier et al. (2013)[233]	EXT(5-11)-AUD onset(18~32)	1.04(0.91,1.20),p=0.53	NE	Logistic reg	Sex	4
	INT(5-11)-AUD onset(18~32)	0.95(0.82,1.09),p=0.43				
	EXT(11-18)-AUD onset(18-32)	3.08(2.24,4.24),p<0.001				
	DEP(11-18)-AUD onset(18-32)	2.31(1.65,3.24),p<0.001				
	ANX(11-18)-AUD onset(18-32)	1.57(1.17,2.10),p=0.002				
	EXT(5-11)-AUD traj(18~32)	Persistent vs develop limited: 1.10(0.76,1.58),p=0.62				
	INT(5-11)-AUD traj (18~32)	1.21(0.82,1.81),p=0.34				
	EXT(11-18)-AUD traj (18-32)	2.11(0.96,4.64),p=0.06				
	DEP(11-18)-AUD traj (18-32)	3.49(1.48,8,25),p=0.004				
	ANX(11-18)-AUD traj (18-32)	2.30(1.02,5.22),p=0.04				
	EXT(5-11)-AUD traj(18~32)	Adult onset vs never diagnosed 1.08(0.81,1.45),p=0.59				
	INT(5-11)-AUD traj (18~32)	1.08(0.80,1.46),p=0.62				
	EXT(11-18)-AUD traj (18-32)	1.50(0.71,3.19),p=0.29				
	DEP(11-18)-AUD traj (18-32)	1.90(0.92,3.96),p=0.09				
	ANX(11-18)-AUD traj (18-32)	1.55(0.82,2.93),p=0.18				

Study	Exposure and outcome	Association (β,SE,95%CI,*P*-value)[#]	Sex dif[§]	Model[&]	Covariates	QA*
Naicker et al. (2013)[234]	DEP(16/17)-H/P Drinking (18/19)	2.70(1.20,6.07)	NE	Logistic reg	Sex and adolescent socioeconomic status	4
	DEP(16/17)-H/P Drinking (20/21)	1.47(0.67,3.25)				
	DEP(16/17)-H/P Drinking (22/23)	1.39(0.46,4.21)				
	DEP(16/17)-H/P Drinking (24/25)	2.14(0.72,6.44)				
	DEP(16/17)-H/P Drinking (26/27)	1(0.33,3.1)				
	DEP(16/17)-H/P Drinking (18-27)	1.78(1.10,2.87)		General ized Linear Mixed Model		
Green et al. (2012)[131]	INT(16)-AC(32/33)	-0.311(0.147),p<0.05 for male -0.023(0.111),p>0.05 for femaleAutomatic citation updates are disabled. To see the bibliography, click Refresh in the Zotero tab.	Yes	SEM	Mother's psychological distress at childhood and adolescence; low social economic status, mother's rating of psychological distress, teacher's rating of psychological distress, poor school performance, poor classroom behaviour, mother's substance use at adolescence, later psychological distress and marijuana/cocaine use	5
McKenzie et al. (2011)[77]	INT(15.5-17.4)-AUD(24)	Reference group: 0 waves OR(95%) 1-2 waves: 1.3(1.2-1.4),p<0.001 >2 waves: 1.9(1.7-2.0),p<0.001	NE	Logistic reg	Adolescent alcohol use, tobacco use, sex, school location, country of birth, parental education, marital status, parental tobacco and alcohol use	8
Stumm et al. (2011)[235]	EXT(9.7)-AC(46~52)	Drinking cessation(binary): 1.10(0.91,1.33) for male 1.08(0.84,1.40) for female Four or more drinks(continuous): -0.01(-0.09,0.05) for male	NE	OLS(continuous); Logistic reg(bina	Age, intelligence, social class of origin, and educational qualification	3

Study	Exposure and outcome	Association (β,SE,95%CI,*P*-value)[#]	Sex dif[§]	Model[&]	Covariates	QA*
		0.01(-0.08,0.10) for female Hangovers(continuous): -0.00(-0.05,0.04) for male 0.02(-0.03,0.08) for female Drinking frequency(categorical): Reference group: drinking on special occasions MALE Every day: 0.96(0.78,1.19) Most days: 0.85(0.70,1.03) Weekends: 0.94(0.80,1.11) <once a week: 0.93(0.77,1.12) FEMALE Every day: 1.27(0.94,1.72) Most days: 0.98(0.75,1.28) Weekends: 1.01(0.84,1.21) <once a week: 1.11(0.90,1.36) Alcohol amount(categorical): Reference group: light drinkers MALE Moderate drinker: 1.01(0.88,1.16) Extreme drinker: 0.99(0.88,1.11) FEMALE Moderate drinker: 0.95(0.78,1.16) Extreme drinker: 1.27(1.06,1.52)		ry); Multinomial logistic reg(categorical)		
	INT(9.7)-AC(46~52)	Drinking cessation(binary): 1.09(0.90,1.33) for male 1.00(0.84,1.19) for female Four or more drinks(continuous): -0.08(-0.18,-0.06) for male -0.06(-0.14,-0.02) for female Hangovers(continuous): -0.05(-0.10,-0.01) for male -0.01(-0.04,0.02) for female				

Study	Exposure and outcome	Association (β,SE,95%CI,*P*-value)[#]	Sex dif[§]	Model[&]	Covariates	QA*
		Reference group: drinking on special occasions MALE Every day: 0.99(0.82,1.21) Most days: 0.88(0.75,1.04) Weekends: 0.92(0.79,1.07) <once a week: 0.94(0.78,1.12) FEMALE Every day: 0.88(0.69,1.13) Most days: 1.00(0.88,1.15) Weekends: 0.92(0.83,1.03) <once a week: 1.05(0.92,1.18) Alcohol amount(categorical): Reference group: light drinkers MALE Moderate drinker: 0.80(0.69,0.92) Extreme drinker: 0.94(0.85,1.05) FEMALE Moderate drinker: 0.91(0.81,1.02) Extreme drinker: 0.90(0.79,1.02)				
Bor et al. (2010)[236]	EXT(5-14)-AC(21)	Reference group: Unclassified group for EXT Non-drinker for AC Male-1-6 drinks per occasion CL: 0.9(0.5,1.7) AL:1.0(0.5,2.2) LCP:1.0(0.2,4.5) Female-1-6 drinks per occasion CL: 1.9(0.9,4.1) AL:0.9(0.5,1.7) LCP:0.4(0.2,0.9) Male->6 drinks per occasion CL: 1.1(0.6,2.0) AL:1.7(0.8,3.6)	NE	Multinomial logistic reg	None	2

Study	Exposure and outcome	Association (β,SE,95%CI,*P*-value)[#]	Sex dif[§]	Model[&]	Covariates	QA*
		LCP:2.6(0.6,11.2) Female->6 drinks per occasion CL: 1.6(0.6,3.8) AL:1.3(0.6,2.7) LCP:0.4(0.1,1.2)				
Hill et al. (2010)[86]	EXT(14/15)-AUD(27)	Alcohol abuse:0.086,p=0.060 Alcohol dependence: 0.076,p=0.092	NE	OLS	Ethnicity, sex and poverty, past-month drinking at age 12, Family management—ages 11–14, Behavioural inhibition/anxiety (BI/A)—ages 14–15, Behavioural disinhibition/anxiety (BDI)—ages 14–15 accordingly	5
	ANX(14/15)-AUD(27)	Alcohol abuse: -0.015,p=0.723 Alcohol dependence: 0.008,p=0.837				
Huurre et al. (2010)[237]	DEP(16)-H/P Drinking (32)	Reference: Low depression Male Middle: 1.69(1.01,2.84),p=0.048 High: 1.77(1.01,3.11),p=0.045 Female Middle:1.34(0.73,2.46),p=0.34 High:0.96(0.49,1.86),p=0.892	NE	Logistic reg	Parental social class, school performance, parental divorce, relationship with mother, relationship with father, parental trust, self-esteem, impulsiveness, spent leisure-time daily among friends, dating experience, drinking habit, smoking habit, problems with the law.	4
Colman et al. (2009)[238]	EXT(13-15)-H/P Drinking (43-53)	Reference: no EXT group Mild: 1.4(1.0,1.9) Severe:1.2(0.7,2.1)	No	Ordinal logistic reg	Sex, father's social class, cognitive ability, and depression-anxiety in adolescence	3
Maggs et al. (2008)[76]	EXT(7)-AC(23)	2.17(0.84) for man, p<0.05 0.27(0.30) for woman, p>0.05	NE	OLS/Logistic reg	Social class and parents' educational level, parents reading with the child (at age 7), academic ability, academic test scores, Social maladjustment, Externalising behaviour (EB) at ages 7 and 11 accordingly, Internalising behaviour (IB) at ages 7 and 11 accordingly	5
	INT(7)-AC(23)	-3.66(0.76) for man, p<0.001 -0.59(0.26) for woman, p<0.05				
	EXT(11)-AC(23)	2.72(0.91) for man, p<0.01 0.09(0.33) for woman, p>0.05				
	INT(11)-AC(23)	-2.54(0.82) for man, p<0.01 -0.01(0.28) for woman, p>0.05				
	EXT(7)-AC(33)	2.41(0.75) for man, p<0.01 0.70(0.32) for woman, p<0.05				

Study	Exposure and outcome	Association (β,SE,95%CI,*P*-value)[#]	Sex dif[§]	Model[&]	Covariates	QA*
	INT(7)-AC(33)	-3.08(0.67) for man, p<0.001 -0.83(0.28) for woman, p<0.01				
	EXT(11)-AC(33)	1.49 (0.80) for man, p>0.05 -0.10(0.35) for woman, p>0.05				
	INT(11)-AC(33)	-2.77(0.72) for man, p<0.001 -0.76(0.30) for woman, p<0.05				
	EXT(7)-H/P Drinking (42)	1.10, NR for man, p>0.05 1.54 (1.14,2.09) for woman, p<0.01				
	INT(7)-H/P Drinking (42)	0.91, NR for man, p>0.05 0.89, NR for woman, p>0.05				
	EXT(11)-H/P Drinking (42)	1.30, NR for man, p>0.05 1.59 (1.07,2.36) for woman, p<0.05				
	INT(11)-H/P Drinking (42)	0.78, NR for man, , p>0.05 1.04, NR for woman, p>0.05				
Pitkanen et al. (2008)[88]	ANT(8)-H/P Drinking (20)	0.06 for male, p>0.05 0,04 for female, p>0.05	No	OLS	Age8 social behaviour accordingly: social activity, constructiveness, compliance, aggressiveness, low self-control, anxiety, school success; Age14 social behaviour accordingly: social behaviour, constructiveness, compliance, aggressiveness, low self-control, anxiety, school success	5
	ANT(8)-H/P Drinking(PD)(27)	-0.15 for male,p>0.05 0.09 for female,p>0.05				
	ANT(8)-H/P Drinking(PD)(42)	0.06 for male,p>0.05 -0.02 for female,p>0.05				
	ANT(14)-H/P Drinking(20)	-0.24 for male, p<0.01 -0.07 for female, p>0.05				
	ANT(14)-H/P Drinking(PD)(27)	0.01 for male,p>0.05 0.00 for female,p>0.05				
	ANT(14)-H/P Drinking(PD)(42)	-0.14 for male,p>0.05 -0.11 for female,p>0.05				
	ANT(8)-AC(27)	0.06 for male,p>0.05 -0.06 for female,p>0.05				
	ANT(8)-AC(42)	-0.03 for male,p>0.05 -0.08 for female,p>0.05				
	ANT(14)-AC(27)	-0.15 for male,p>0.05 -0.20 for female, p<0.05				

Study	Exposure and outcome	Association (β,SE,95%CI,*P*-value)[#]	Sex dif[§]	Model[&]	Covariates	QA*
	ANT(14)-AC(42)	-0.01 for male,p>0.05 -0.19 for female, p<0.05				
	ANT(8)-H/P Drinking(HD)(27)	0.15 for male,p>0.05 -0.07 for female,p>0.05				
	ANT(8)-H/P Drinking(HD)(42)	-0.03 for male,p>0.05 -0.06 for female,p>0.05				
	ANT(14)-H/P Drinking(HD)(27)	-0.16 for male,p>0.05 -0.13 for female, p<0.05				
	ANT(14)-H/P Drinking(HD)(42)	-0.16 for male,p>0.05 -0.13 for female, p<0.05				
	ANT(8)-H/P Drinking(CAGE)(27)	0.07 for male,p>0.05 0.09 for female, p>0.05				
	ANT(8)-H/P Drinking(CAGE)(42)	0.08 for male,p>0.05 0.00 for female, p>0.05				
	ANT(14)-H/P Drinking(CAGE)(27)	-0.09 for male,p>0.05 -0.03 for female,p>0.05				
	ANT(14)-H/P Drinking(CAGE)(42)	-0.03 for male,p>0.05 -0.12 for female, p>0.05				
Timmermans et al. (2008)[239]	EXT(4-18)-H/P Drinking(CAGE)(18)	Intercept: 0.11(0.04),p<0.01 Slope: 0.95(0.42),p<0.05	No	OLS	None	2
Pardini et al. (2007)[83]	EXT(13.9)-AUD(20.4-25.4)	Zero inflation: 1.065(0.808,1.402), p=0.656 Symptom count: 1.190(1.054,1.342), p=0.005	NA	Poisson reg	Age, minority status, family socioeconomic status, parent alcohol/drug problems, child's prior alcohol use, child's prior alcohol problems, CD symptoms, ADHA symptoms, depression, Anxiety/withdrawal	7
	DEP(13.9)-AUD(20.4-25.4)	Zero inflation: 0.956(0.736,1.241), p=0.736 Symptom count: 1.048(0.937,1.172), p=0.408				
	ANX(13.9)-AUD(20.4-25.4)	Zero inflation: 1.079(0.806,1.445), p=0.610 Symptom count: 0.858(0.774,0.952), p=0.004				

Study	Exposure and outcome	Association (β,SE,95%CI,*P*-value)[#]	Sex dif[§]	Model[&]	Covariates	QA*
Niemela et al. (2006)[211]	EXT(8)-H/P Drinking(18)	Reference: no drunkenness Drunkenness less than weekly: 1.0(0.94,1.16) Drunkenness once a week or more often: 1.1(1.0,1.31)	NA	Logistic reg	Non-intact family structure, hyperactive, conduct and emotional problems according to teacher's report	4
	INT(8)-H/P Drinking(18)	Drunkenness less than weekly: 0.8(0.71,0.90) Drunkenness once a week or more often: 0.8(0.68,0.96)				
Moffit et al. (2002)[240]	EXT(5-18)-AUD(26)	Reference: Unclassified group Abstainer: no, p>0.01 Recovery: no, p>0.01 Life-course Persistent path: positive, p<0.01 Adolescence-limited path: positive, p<0.01 LCP vs AL: positive, p=0.002	NA	ANOVA	None	3
Moffitt et al. (1996)[241]	EXT(5-18)-AUD(18)	Reference: Unclassified group Abstainer: no, p>0.01 Recovery: no, p>0.01 Life-course Persistent path: positive, p<0.01 Adolescence-limited path: positive, p<0.01 LCP vs AL: no, p>0.05	NA	ANOVA	None	3
Steele et al. (1995)[242]	EXT(13.5)-AUD(19.75)	0.087,p=0.05	No	OLS	Sex, anxiety/conduct problem accordingly, anxiety*sex, conduct problem*sex, anxiety*conduct problem, anxiety*conduct problem*sex	2
	ANX(13.5)-AUD(19.75)	-0.042,p>0.05				
Pulkkinen et	EXT(14)-H/P Drinking(26-27)	0.20 for male, p<0.05	Yes	Path	Anxiety at age 8, aggression at age 8,	3

Study	Exposure and outcome	Association (β,SE,95%CI,*P*-value)[#]	Sex dif[§]	Model[&]	Covariates	QA*
al.(1994) [243]		No for female,p>0.05		analysis	prosociality at age 8, school success at age 8, school success at age 14	
	ANX(14)-H/P Drinking(26-27)	-0,21 for male, p<0.01 No for female,p>0.05				

#Report in order whatever is available in the study

[§]Sex differences of the association; NE: not explored; NA: not appliable

[&]EXT: externalising problems; INT: internalising problems; DEP: depression/depressive symptoms; ANX; anxiety; AC: alcohol consumption; H/P drinking: heavy/problematic drinking; HD: heavy episode drinking/binge drinking; PD: problematic drinking; AUD: alcohol use disorder; OLS: ordinary least-square regression; reg: regression; ANOVA: analysis of variance; SEM: structural equation model; MSM: marginal structural model

*Quality assessment

!The acronym applied throughout the supplements.

Appendix 3 Proportion of reported associations across domain of mental health and alcohol use behaviours*

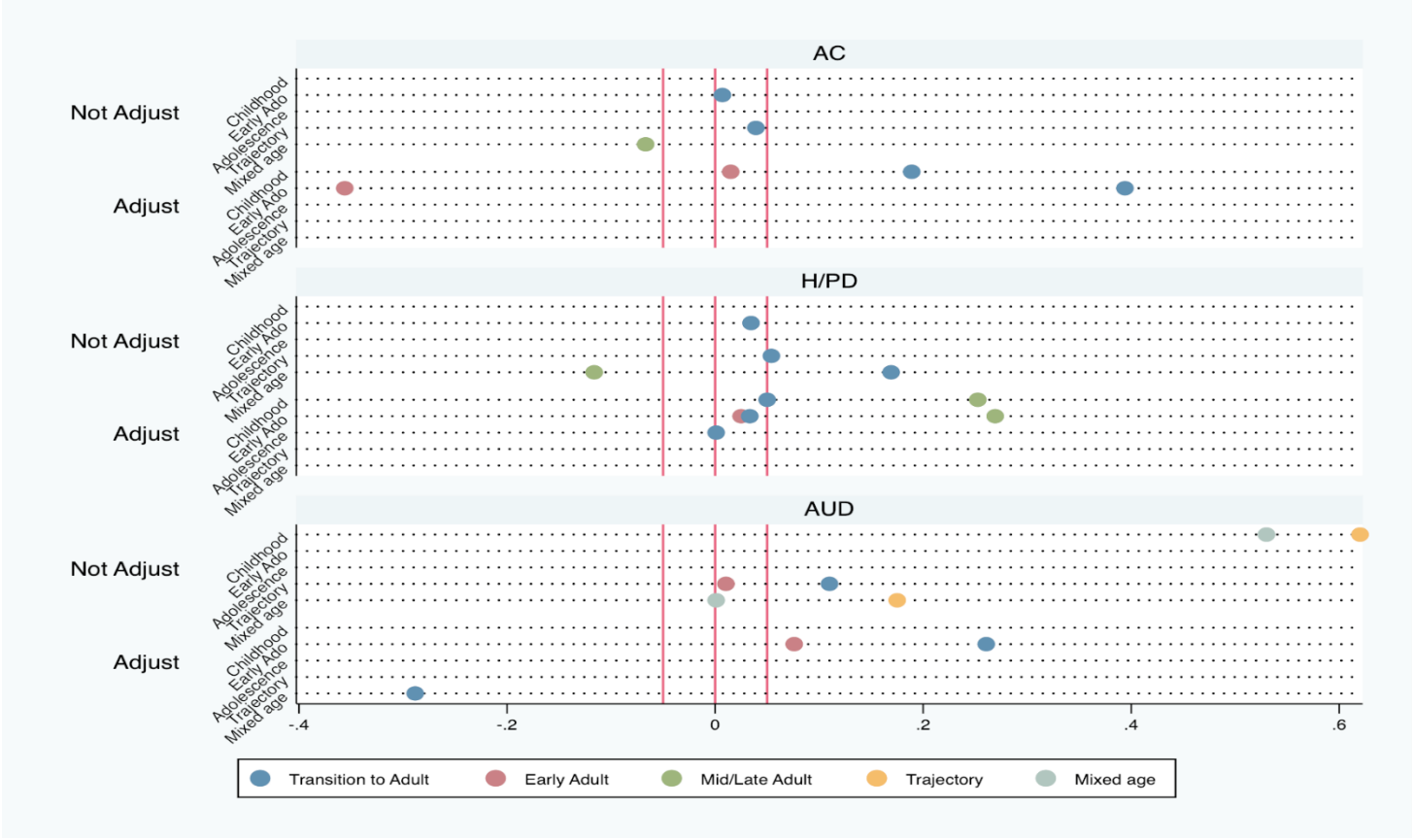
	positive	negative	no
	Alcohol consumption		
Externalising domain	3/5 (60%)	1/5 (20%)	1/5 (20%)
Internalising domain			
Internalising	0/4 (0%)	¾ (75%)	¼ (25%)
Depression#	1/1 (100%)	0/1 (0%)	0/1 (0%)
Anxiety	1/3(33.3%)	2/3 (66.7%)	0/3 (0%)
	Heavy/problematic drinking		
Externalising domain	10/11 (90.9%)	0/11 (0%)	1/11 (9.1%)
Internalising domain			
Internalising	2/5 (40%)	2/5 (40%)	1/5 (20%)
Depression#	¾ (75%)	¼ (25%)	0/4 (12.5%)
Anxiety	0/2 (0%)	½ (50%)	½ (50%)
	Alcohol use disorder		
Externalising domain	3/5 (60%)	0/5 (0%)	2/5 (40%)
Internalising domain			
Internalising	1/3 (33.3%)	0/3 (0%)	2/3 (66.7%)
Depression#	2/3 (66.7%)	0/3 (0%)	1/3 (33.3%)
Anxiety	1/3 (33.3%)	1/3 (33.3%)	1/3 (33.3%)

*for each exposure-outcome set, no matter how many items there were, the pair of association was counted as significant as long as one item is significant.

Appendix 4 Proportion of reported associations limited to high-quality studies

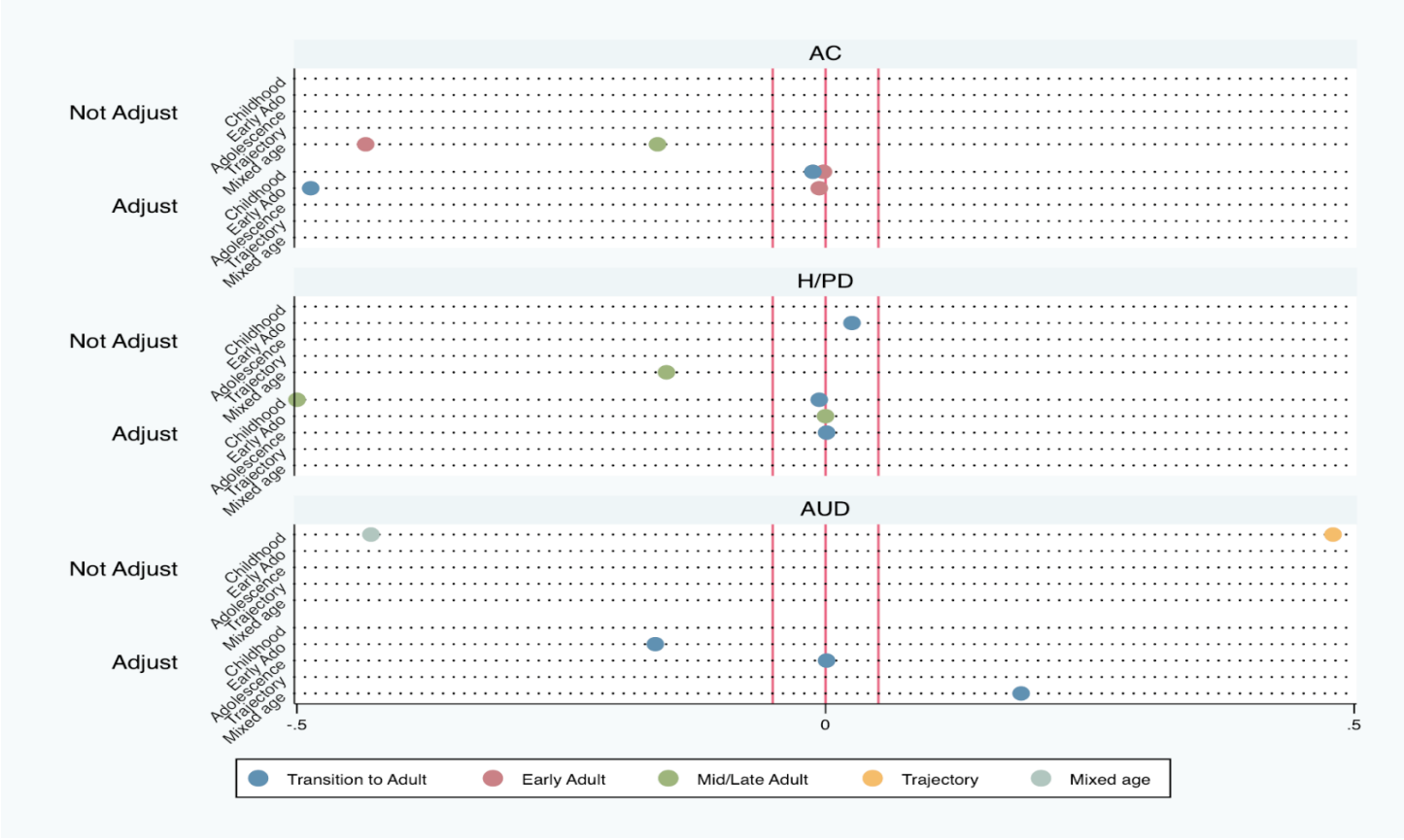
	positive	negative	no
	Alcohol consumption		
Externalising domain	4/8 (50%)	0/8 (0%)	4/8 (50%)
Internalising domain			
Internalising	0/10 (0%)	8/10 (80%)	2/10 (20%)
Depression	0/0 (0%)	0/0 (0%)	0/0 (0%)
Anxiety	0/0 (0%)	0/0 (0%)	0/0 (0%)
	Heavy/problematic drinking		
Externalising domain	12/20 (60%)	0/20 (0%)	8/20 (40%)
Internalising domain			
Internalising	2/6 (33.3%)	0/6 (0%)	4/6 (66.7%)
Depression	4/8 (50.0%)	1/8 (12.5%)	3/8 (37.5%)
Anxiety	0/0 (0%)	0/0 (0%)	0/0 (0%)
	Alcohol Use Disorder		
Externalising domain	3/8 (37.5%)	0/8 (0%)	5/8 (62.5%)
Internalising domain			
Internalising	4/6 (66.7%)	0/6 (0%)	2/6 (33.3%)
Depression	0/2 (0%)	0/2 (0%)	2/2 (100%)
Anxiety	0/4 (0%)	1/4 (25%)	0/4 (0%)

Appendix 5 Distribution of P-value between externalising problems and phenotype of alcohol use behaviours

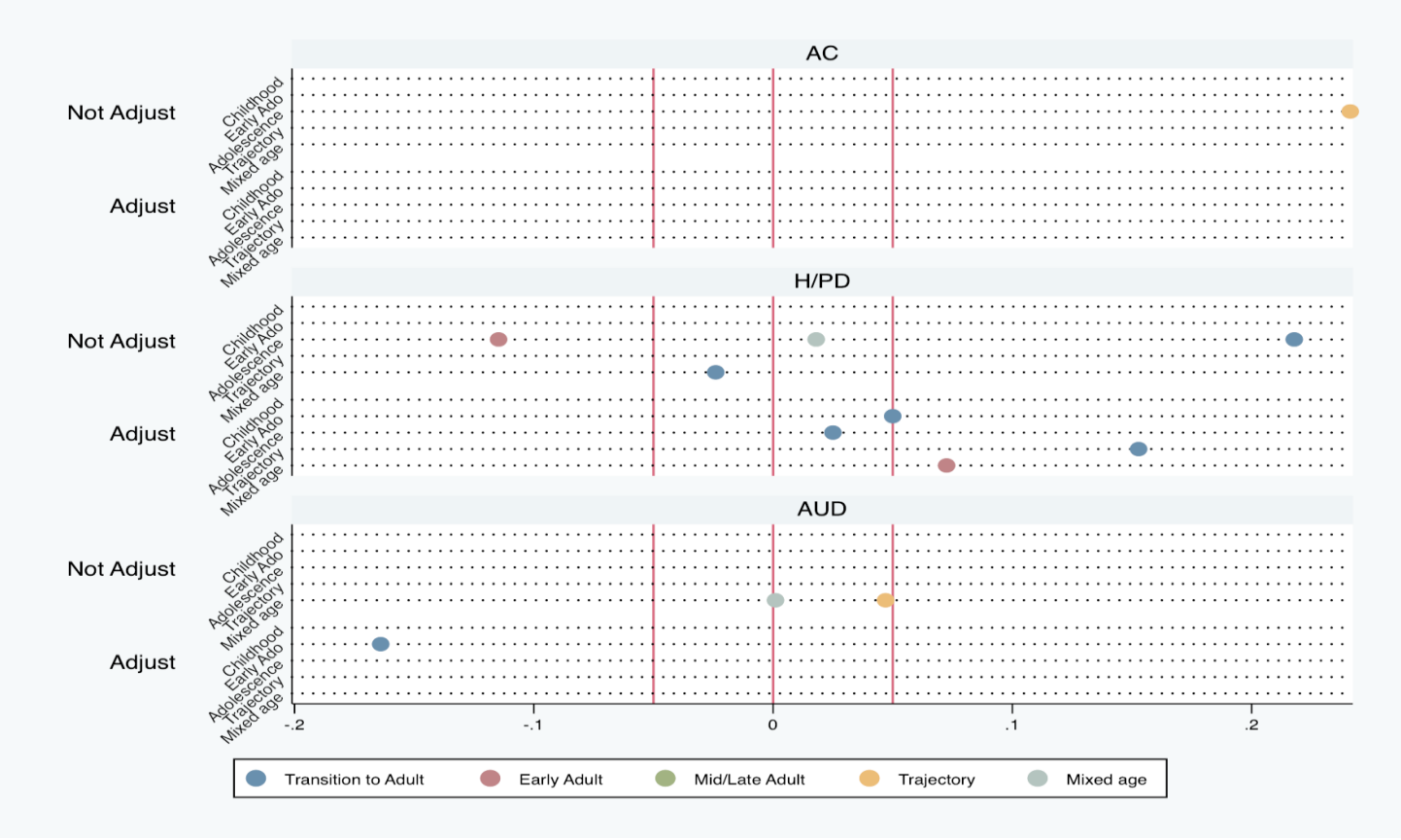


Each dot represents the mean of P-value for all items that measure the corresponding association. P-value was either extracted or calculated using available information and was coded as missing when not available. Dots on the right side of zero indicate size of P-values for positive associations, and dots on the left side of zero indicate size of P-value for negative associations. Two red lines represent a threshold of 0.05 respectively. “Adjust” means that INT(EXT) was adjusted simultaneously. This figure illustration applies to Appendix 6-Appendix 8.

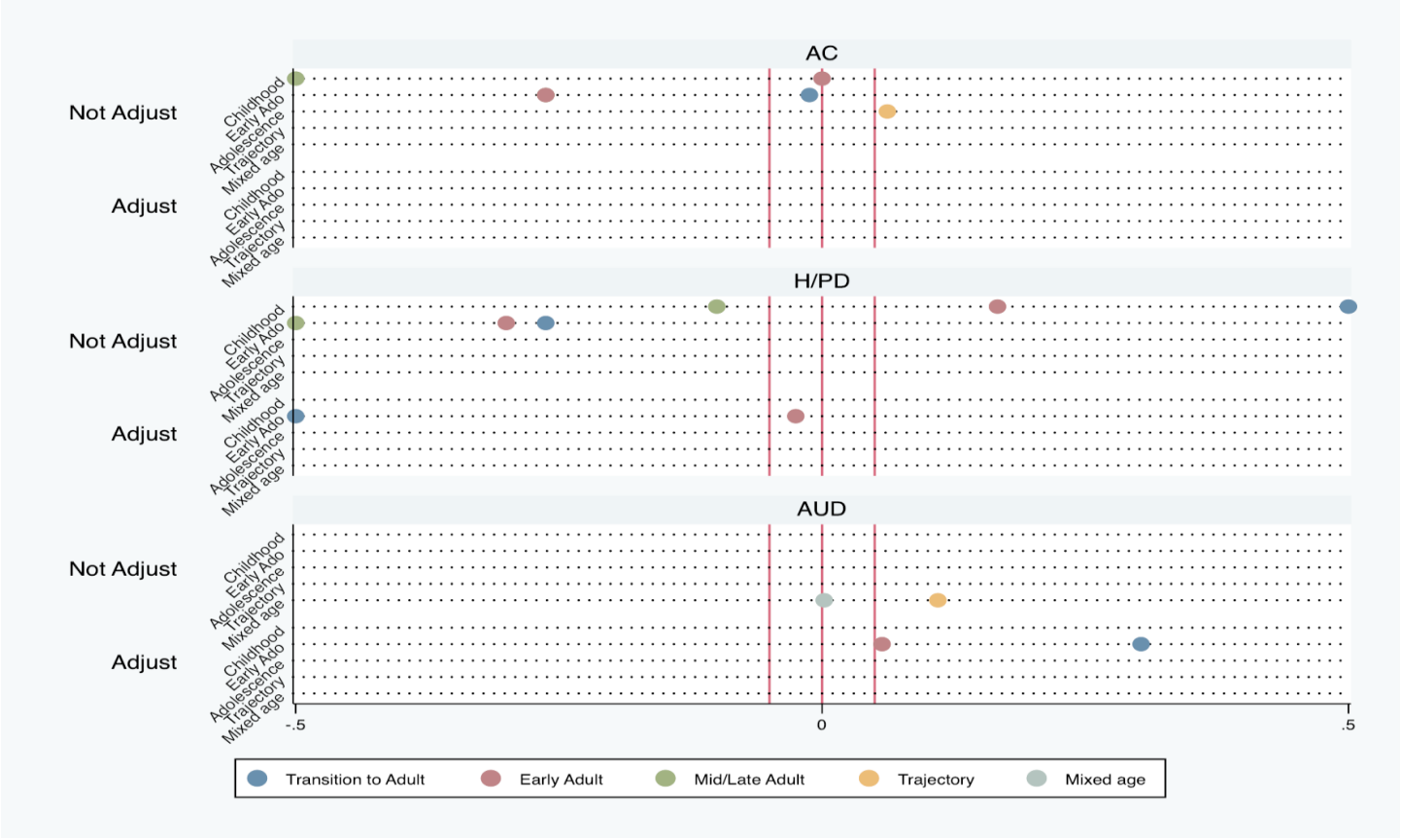
Appendix 6 Distribution of P-value between internalising problems and phenotype of alcohol use behaviours



Appendix 7 Distribution of P-value between Depression and phenotype of alcohol use behaviours



Appendix 8 Distribution of P-value between Anxiety and phenotype of alcohol use behaviours



Appendix 9 Quality assessment criteria

Sample
How is the representativeness of the sample? 1=not representative 2=representative of the local/whole population Is the sample size large enough? 1=No (below 1000) 2=Yes (over 1000)
Assessment
How is the exposure measured? 1= self-report/reported by others 2= clinical interview/record linkage How is the outcome measured? 1= self-report/reported by others 2= clinical interview/record linkage
Confounders
Has the author identified and control all important confounding factors? 1=No 2=Yes (Core confounding factors include: gender, family SES) Has the author controlled for other relevant confounders or other more advanced analysis? 1=No 2=Yes
Missing data
Was the follow up of subjects complete enough? 1=No (attrition rate >=20% or attrition analysis shows significant biases) 2=Yes (attrition rate<20% or attrition analysis shows no significant biases) Has the author taken account of the missing data? 1=No (complete case analysis or traditional missing data method) 2=Yes (advanced methods including Inverse Probability Weight, Multiple imputation, Maximum likelihood estimation)

Appendix 10 The frequency of corresponding factors controlled for in the selected 36 articles

Family-related factors	Individual-related factors
Family socioeconomic status (19)	Demographics (26)
Prenatal and post-natal indicators (2)	Intrinsic trait (Personality/IQ) (8)
Parental education (11)	Prior mental health status (15)
Parental marital status (7)	Prior substance use (13)
Parental mental health status(8)	History of abuse/neglect (0)
Parental substance use (12)	School performance (6)
Family function (3)	Transitional life events (3)
Social factors	Personal belief/moral order (1)
Peer relationship (4)	Physical health status (1)
Peer substance use (4)	Self-regulation ability (1)
	Victimization/bullying (2)
	Risky behaviour (4)

*demographics includes gender, race/ethnicity, religion and own financial status; family function refers to family relations, communication, management and family support et al; transitional life events include college attendance, involvement in a relationship/marriage, pregnancy or other major life events.

Appendix 11 Details on exposure and outcome of 36 included articles

Exposure included internalising problems (n=5), depression (n=13), anxiety (n=8) and other emotional and psychological statuses (n=4), as well as externalising problems (n=7), conduct problems (n=10) and anti-social behaviour (n=6). Outcomes included drinking frequency (how often the participants drank alcohol, n=5), drinking quantity (how much the participants drank, usually per occasion, n=2), total drinking volume (calculated by drinking frequency x quantity, n=3), drunkenness (frequency of drunkenness or number of drunkenness occasions during a certain time period, n=8), problem drinking (featured by being involved in accidents/fights/conflicts because of drinking, n=5), harmful drinking (assessed by the CAGE/AUDIT/Michigan Alcohol Screening Test which indicate the possibility of AUD, n=13), and AUD (as defined in Diagnostic and Statistical Manual III/IV which refers to either alcohol abuse (AA) or alcohol dependence (AD), n=10).

Appendix 12 Mental health related variables collected in NCDS58 and BCS70 in early life

Scale	Question	NCDS 58			BCS70		
		1965 Age 7	1969 Age 11	1974 Age 16	1975 Age 5	1980 Age 10	1986 Age 16
Rutter Behaviour Questionnaire(parent)	Is squirmy or fidgety	√	√	√	√	√	√
	Destroys own or others' belongings (e.g. tears or breaks)	√	√	√	√	√	√
	Fights with other children	√	√	√	√	√	√
	Worries about many things	√	√	√	√	√	√
	Prefers to do things on his/her own rather than with others	√	√	√	√	√	√
	Is irritable, quick to fly off the handle.	√	√	√	√	√	√
	Is miserable or tearful	√	√	√	√	√	√
	Has twitches or mannerisms of the face, eyes or body	√	√	√	√	√	√
	Sucks thumb or finger during the day	√	√	√	√	√	√
	Bites nails	√	√	√	√	√	√
	Is disobedient at home	√	√	√	√	√	√
	Has difficulty in settling to anything for more than a few moments	√	√	√	√	√	√
	Is upset by new situation, by things happening for first time	√	√	√	√	√	√
	Is bullied by other children	√	√	bully others	bully others	bully others	bully others
	Often tell lies	×	×	√	√	√	√
	Fussy or over-particular	×	×	√	√	√	√
	Not much liked by other children	×	×	√	√	√	√
	Very restless, has difficulty staying seated for long	×	×	√	√	√	√
	Sometimes takes things belonging to others	×	×	×	√	√	√
Rutter Behaviour Questionnaire(teacher)	Very restless, has difficulty staying seated for long	×	×	√	×	×	×
	Truants from school	×	×	√	×	×	×
	Squirmy, fidgety child	×	×	√	×	×	×
	Often destroys or damages own or others' property	×	×	√	×	×	×
	Frequently fights or is extremely quarrelsome with other children	×	×	√	×	×	×
	Not much liked by other children	×	×	√	×	×	×
	Often worries, worries about many things	×	×	√	×	×	×

	Tends to do things on his/her own – rather solitary	×	×	√	×	×	×
	Irritable, touchy, is quick to fly off the handle	×	×	√	×	×	×
	Often appears miserable, unhappy, tearful or distressed	×	×	√	×	×	×
	Has twitches, mannerisms or tics of the face or body	×	×	√	×	×	×
	Frequently sucks thumb or finger	×	×	√	×	×	×
	Frequently bites nails or fingers	×	×	√	×	×	×
	Tends to be absent from school for trivial reasons	×	×	√	×	×	×
	Is often disobedient	×	×	√	×	×	×
	Cannot settle to anything for more than a few moments	×	×	√	×	×	×
	Tends to be fearful or afraid of new things or new situations	×	×	√	×	×	×
	Fussy or over-particular	×	×	√	×	×	×
	Often tells lies	×	×	√	×	×	×
	has stolen things on one or more occasions in the past 12 months	×	×	√	×	×	×
	Unresponsive, inert or apathetic	×	×	√	×	×	×
	Often complains of aches or pains	×	×	√	×	×	×
	Has had tears on arrival at school or has refused to come into the building in the past 12 months	×	×	√	×	×	×
	Has a stutter or stammer	×	×	√	×	×	×
	Resentful or aggressive when corrected	×	×	√	×	×	×
	Bullies other children	×	×	√	×	×	×
	Unforthcomingness	√	√	×	×	×	×
	Withdrawal	√	√	×	×	×	×
	Depression	√	√	×	×	×	×
	Anxiety	√	√	×	×	×	×
	Hostility towards adults	√	√	×	×	×	×
Bristol Social Adjustment Guide	Writing off adults and adult standards	√	√	×	×	×	×
	Anxiety for acceptance by kids	√	√	×	×	×	×
	Hostility towards children	√	√	×	×	×	×
	Restlessness	√	√	×	×	×	×
	Inconsequential behaviour	√	√	×	×	×	×
	Miscellaneous symptoms	√	√	×	×	×	×
	Miscellaneous nervous symptoms	√	√	×	×	×	×
	Poor control of hands (e.g. in writing, drawing, handwork, or buttoning coat)	√	√	×	×	×	×

Teacher's assessment	Squirmy, fidgety child	√	√	×	×	×	×
	Poor physical coordination (e.g. in running, jumping, or throwing)	√	√	×	×	×	×
	Clumsy	√	×	×	×	×	×
	Often running or jumping about; hardly ever still	√	√	×	×	×	×
	Over-dependent upon mother	√	×	×	×	×	×
	Difficult to understand because of poor speech	√	√	×	×	×	×
	Imperfect grasp of English (i.e. when native language is other than English)	√	√	×	×	×	×
Parents' questionnaire	Is noticeably clumsy	×	×	×	×	√	√
	Trips or falls easily or bumps into objects or other children	×	×	×	×	√	√
	Inattentive, easily distracted	×	×	×	×	√	√
	Hums or makes other odd noises at inappropriate times	×	×	×	×	√	√
	Has difficulty picking up small objects	×	×	×	×	√	√
	Drops things which are being carried	×	×	×	×	√	√
	Becomes obsessional about unimportant things	×	×	×	×	√	√
	Requests must be met immediately easily frustrated	×	×	×	×	√	√
	Shows restless or over-active behaviour	×	×	×	×	√	√
	Is impulsive excitable	×	×	×	×	√	√
	Interferes with the activity of other children	×	×	×	×	√	√
	Is sullen or sulky	×	×	×	×	√	√
	Fails to finish things he/she starts, short attention span	×	×	×	×	√	√
	Given to rhythmic tapping or kicking	×	×	×	×	√	√
	Cries for little cause	×	×	×	×	√	√
	Changes mood quickly and drastically	×	×	×	×	√	√
	Displays outbursts of temper, explosive or unpredictable behaviour	×	×	×	×	√	√
	Has difficulty using scissors	×	×	×	×	√	√
	Has difficulty concentrating on any particular task though may return to it frequently	×	×	×	×	√	√

Appendix 13 Questions collected for CAGE and AUDIT in NCDS58 and BCS70 across waves

		NCDS58				BCS70			
	year	1991	2000	2002/2003	2008	2000	2004	2012	2016
Scale	age	33	42	44-45	50	30	34	42	46
CAGE	Have you ever felt you needed to Cut down on your drinking?	√	√			√	√		
	Have people Annoyed you by criticizing your drinking?	√	√			√	√		
	Have you ever felt Guilty about drinking?	√	√			√	√		
	Have you ever felt you needed a drink first thing in the morning (Eye-opener) to steady your nerves or to get rid of a hangover?	√	√			√	√		
AUDIT	How often do you have a drink containing alcohol?			√	√			√	√
	How many drinks containing alcohol do you have on a typical day when you are drinking?			√	√			√	√
	How often do you have six or more drinks on one occasion			√	√				
	How often during the last year have you found that you were not able to stop drinking once you had started			√	√			√	√
	How often during the last year have you failed to do what was normally expected from you because of drinking?			√	√			√	√
	How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?			√	√				
	How often during the last year have you had a feeling of guilt or remorse after drinking?			√	√				
	How often during the last year have you been unable to remember what happened the night before because you had been drinking?			√	√				
	Have you or someone else been injured as a result of your drinking?			√	√				
	Has a relative or friend or a doctor or other health worker been concerned about your drinking or suggested you cut down?			√	√			√	√

Appendix 14 Variables collected with information about drinking frequency and amount in NCDS58 and BCS70

	NCDS58							BCS70					
Year	1981	1991	2000	2002/2003	2004	2008	2013	1996	2000	2004	2008	2012	2016
Age	23	33	42	44/45	46	50	55	26	30	34	38	42	46
How often do you usually have an alcoholic drink of any kind?	√	√	√	√	√	√	√	√	√	√			
In the last week, I have drunk no alcohol at all								√					
Since this time last week, how much shandy have you drunk? Pints (assume that one small can=half a pint)								√					
In the last seven days, not counting today, how much beer stout lager or cider have you had?	√	√	√			√			√	√			
In the last seven days, how much normal strength beer stout lager stout ale or cider have you had?												√	√
In the last seven days, how much strong strength beer stout lager stout ale or cider have you had?												√	√
Since this time last week, how much beer (including lager) have you drunk? Pints								√					
In the last week, I have X pints of low alcohol beers/lagers								√					
Since this time last week, how much cider have you drunk? pints								√					
In the last week, I have X pints of Low alcohol of cider								√					
In the last 7 days, how many measures of spirits or liqueurs have you had, like gin, whisky, rum, brandy, vodka or advocat?	√	√	√			√		√	√	√		√	√

In the last seven days, how many glasses of wine have you had?	√	√	√			√		√	√	√			
In the last week, I have X glasses of Low alcohol wine								√					
In the last seven days, how much wine, including sparkling wine and champagne have you had?												√	√
In the last seven days, were the glasses of wine that you drank large (250ml), standard (175ml) or small (125ml) glasses?												√	√
In the last 7 days, how many large (250ml) glasses of wine did you have?												√	√
In the last 7 days, how many standard (175ml) glasses of wine did you have?												√	√
In the last 7 days, how many standard (125ml) glasses of wine did you have?												√	√
In the last seven days, how many glasses of martini, vermouth or similar drinks have you had?	√	√	√			√		√	√	√		√	√
In the last 7 days, how many bottles of alcopops have you had?			√						√	√		√	√
In the last 7 days, have you had any other alcoholic drinks?			√			√		√	√	√			√
As far as the amount you drink is concerned, would you say the last seven days were?	√												
In an average week, how many units do you drink?					√		√						
On the days when you do drink alcohol, on average how many units do you drink in a day?					√								

Appendix 15 Exploratory factor analysis for Rutter Behaviour Questionnaire in NCDS58

	Age 7			Age 11			Age 16		
	Conduct problems	Internalising problems	ADHD	Conduct problems	Internalising problems	ADHD	Conduct problems	Internalising problems	ADHD
Poor concentration	0.44	--	0.43	0.39	--	0.45	0.35	--	0.64
Fidgety	0.45	--	0.44	0.41	--	0.49	--	--	0.82
Sucks thumb	--	--	--	--	--	--	--	--	--
Twitches/tics	--	--	--	--	--	--	--	--	0.36
Bites nails	--	--	--	--	--	--	--	--	--
Restless	NC	NC	NC	NC	NC	NC	--	--	0.82
Solitary	--	--	--	--	--	--	--	0.41	--
Miserable	0.40	0.42	--	0.44	0.39	--	0.44	0.50	--
Worries	--	0.67	--	--	0.67	--	--	0.66	--
Fearful	--	0.55	--	--	0.57	--	--	0.60	--
Fussy	NC	NC	NC	NC	NC	NC	--	0.36	--
Destructive	0.55	--	--	0.62	--	--	0.66	--	0.37
Irritable	0.58	--	--	0.58	--	--	0.56	--	--
Fights	0.55	--	--	0.57	--	--	0.76	--	--
Disobedient	0.66	--	--	0.63	--	--	0.70	--	--
Not liked	NC	NC	NC	NC	NC	NC	0.48	0.37	--
Steals	NC	NC	NC	NC	NC	NC	NC	NC	NC
Lies	NC	NC	NC	NC	NC	NC	0.68	--	--
Bullies	NC	NC	NC	NC	NC	NC	0.75	--	--
Bullied	--	0.41	--	--	0.39	--	NC	NC	NC

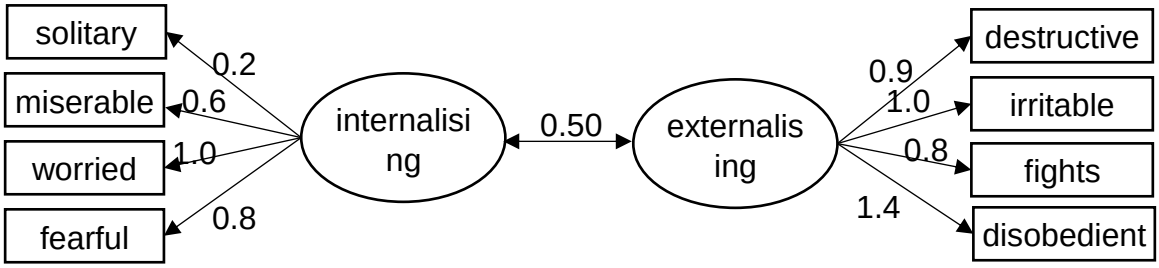
*NC=Not collected. Factor loadings below 0.3 are not displayed.

Appendix 16 Exploratory factor analysis for Rutter Behaviour Questionnaire in BCS70

	Age 5			Age 10			Age 16		
	Conduct problems	Internalising problems	ADHD	Conduct problems	Internalising problems	ADHD	Conduct problems	Internalising problems	ADHD
Poor concentration	0.33	--	0.57	0.36	--	0.57	0.49	--	0.51
Fidgety	--	--	0.69	--	--	0.72	0.30	--	0.74
Sucks thumb	--	--	--	--	--	--	--	--	--
Twitches/tics	--	--	--	0.40	--	--	--	--	0.42
Bites nails	--	--	--	--	--	--	--	--	--
Restless	--	--	0.70	--	--	0.78	0.30	--	0.67
Solitary	--	0.38	--	--	0.44	--	--	0.44	--
Miserable	--	0.51	--	0.40	0.51	--	0.47	0.58	--
Worries	--	0.66	--	--	0.72	--	--	0.72	--
Fearful	--	0.53	--	--	0.65	--	--	0.61	--
Fussy	--	0.46	--	--	0.45	--	--	0.45	--
Destructive	0.60	--	0.33	0.68	--	0.35	0.73	--	0.31
Irritable	0.42	0.32	0.30	0.40	0.36	0.38	0.55	0.43	--
Fights	0.69	--	--	0.62	--	0.31	0.74	--	--
Disobedient	0.58	--	0.38	0.59	--	0.43	0.76	--	--
Not liked	0.41	0.31	--	0.40	0.33	--	0.50	0.35	--
Steals	0.62	--	--	0.80	--	--	0.79	--	--
Lies	0.60	--	--	0.75	--	--	0.81	--	--
Bullies	0.68	--	--	0.69	--	--	0.78	--	--

*Factor loadings below 0.3 are not displayed.

Appendix 17 Factor loadings for latent internalising and externalising score in NCDS58 and BCS70



(one figure example of the IRT model built in Mplus)

	NCDS58			BCS70		
	Age 7	Age 11	Age 16	Age 5	Age 10	Age 16
Internalising items						
Solitary	0.2	0.2	0.4	0.4	0.4	0.5
Miserable	0.6	0.5	1.2	1.0	0.8	1.3
Worried	1.0	1	1.0	1.0	1.0	1.0
Fearful	0.8	0.7	0.8	0.7	0.7	0.8
Externalising items						
Destructive	0.9	1.1	0.8	1.0	1.1	0.8
Irritable	1.0	1.0	1.0	1.0	1.0	1.0
Fights	0.8	0.8	0.9	1.0	1.0	0.9
Disobedient	1.4	1.2	0.8	1.4	1.1	0.9
Cor (internalising, externalising)	0.50	0.55	0.71	0.56	0.70	0.82

Appendix 18 Missingness in NCDS58 (upper half) and BCS70 (lower half) across waves

	Mental Health			Alcohol outcomes	
Age	Age 7	Age 11	Age 16	Age 33	Age 44/45
Year	1965	1969	1974	1991	2002/04
Complete cases	13582	12354	11000	10902	8953
Missing due to incomplete scale*	1468	2402	2919	140	60
Missing due to non-participation	1762	2037	2842	5558	7323
Missing due to death	821	840	872	1033	1297
Total	17633	17633	17633	17633	17633
Age	Age 5	Age 10	Age 16	Age 34	Age 46
Year	1975	1980	1986	2004	2016
Complete cases	12620	13526	7871	9193	8265
Missing due to incomplete scale	1113	1230	3840	252	106
Missing due to non-participation	3250	2216	5226	7,210	8222
Missing due to death	585	596	631	913	975
Total	17568	17568	17568	17568	17568

*Refers to those who participated in the survey but didn't provide complete information for mental health or alcohol use

Appendix 19 Associations between auxiliary variables and the outcomes

CAGE at age 33/34			
At age 23/26	Smoking		
	Previous smokers	1.51 (1.3, 1.75)	<0.001
	Current smokers	1.98 (1.79, 2.2)	<0.001
	Drinking frequency		<0.001
	2-3 times per month	1.14 (0.89, 1.47)	0.31
	1-3 times per week	2.51 (2.03, 3.1)	<0.001
	4+ times per week	4.39 (3.5, 5.52)	<0.001
	Weekly drinking units	1.01 (1.01, 1.02)	<0.001
	Cohort		
	BCS70	1.64 (1.48, 1.8)	<0.001
	Sex		<0.001
	Male	1.29 (1.17, 1.44)	<0.001
AUDIT-PC at age 46			
At age 23/26	Smoking		
	Previous smokers	0.99 (0.78, 1.24)	0.903
	Current smokers	1 (0.8, 1.26)	0.978
	Drinking frequency		
	2-3 times per month	1.29 (1.01, 1.65)	0.038
	1-3 times per week	1.46 (1.18, 1.8)	0.001
	4+ times per week	1.46 (1.14, 1.86)	0.003
	Weekly drinking units	1.01 (1.01, 1.01)	<0.001
At age 33/34	Smoking		
	Previous smokers	1.25 (0.99, 1.58)	0.065
	Current smokers	1.52 (1.17, 1.97)	0.001
	Drinking frequency		
	2-3 times per month	1.34 (1.05, 1.7)	0.018
	1-3 times per week	1.75 (1.4, 2.18)	<0.001
	4+ times per week	1.97 (1.51, 2.56)	<0.001
	Weekly drinking units	1.02 (1.02, 1.02)	<0.001
At age 42	Smoking		
	Previous smokers	1.18 (0.96, 1.47)	0.120
	Current smokers	1.47 (1.15, 1.88)	0.002
	Drinking frequency		
	2-3 times per month	1.6 (1.22, 2.09)	0.001
	1-3 times per week	3.39 (2.67, 4.31)	<0.001
	4+ times per week	5.52 (4.23, 7.2)	<0.001
	Weekly drinking units	1.04 (1.03, 1.04)	
	Cohort		
	BCS70	0.78 (0.7, 0.88)	<0.001
	Sex		
	Male	1.15 (1.03, 1.3)	0.015

Appendix 20 Association between early life externalising and internalising problems and problematic drinking at age 33/34 (CAGE) in two British birth cohorts (n=33255) [#]

	Model 1	Model 2	Model 3
	Externalising and problematic drinking		
EXT at age 7	1.07 (1.03,1.11) ***	1.08 (1.03,1.13) **	1.06 (1.00,1.11) *
INT at age 7		0.96 (0.92,1.00) *	0.97 (0.93,1.01)
EXT at age 11		1.06 (1.02,1.10) **	1.07 (1.01,1.12) *
INT at age 11			0.95 (0.91,0.99) *
EXT at age 16			1.06 (1.03,1.10) ***
	Internalising and problematic drinking		
EXT at age 7		1.11 (1.06,1.16) ***	1.07 (1.01,1.12) *
INT at age 7	1.01 (0.97,1.04)	0.96 (0.92,1.00) *	0.97 (0.93,1.01)
EXT at age 11			1.09 (1.04,1.15) ***
INT at age 11		1.00 (0.97,1.03)	0.95 (0.91,0.99) *
INT at age 16			1.03 (0.99,1.07)

EXT = externalising problems; INT = internalising problems; PD = problematic drinking; EXT and INT at the same age were entered into the model separately; confounding factors were adjusted for correspondingly in each model.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix 21 Association between early life externalising and internalising problems and problematic drinking at age 45 (AUDIT-PC) in two British birth cohorts (n=32929) [#]

	Model 1	Model 2	Model 3
	Externalising and problematic drinking		
EXT at age 7	1.03 (1.00,1.06)	1.06 (1.02,1.11) **	1.04 (1.00,1.08)
INT at age 7		0.94 (0.91,0.97) ***	0.96 (0.93,1.00) *
EXT at age 11		1.02 (0.99,1.05)	1.05 (1.01,1.10) *
INT at age 11			0.94 (0.91,0.97) ***
EXT at age 16			1.04 (1.01,1.06) **
	Internalising and problematic drinking		
EXT at age 7		1.07 (1.04,1.12) ***	1.05 (1.01,1.09) *
INT at age 7	0.97 (0.95,1.00)	0.95 (0.92,0.99) **	0.96 (0.93,1.00)
EXT at age 11			1.07 (1.03,1.11) ***
INT at age 11		0.97 (0.95,1.00) *	0.94 (0.91,0.97) ***
INT at age 16			0.99 (0.96,1.02)

EXT = externalising problems; INT = internalising problems; PD = problematic drinking; EXT and INT at the same age were entered into the model separately; confounding factors were adjusted for correspondingly in each model.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix 22 Comparison of associations between early life psychopathology factor* and externalising/internalising problems at age 16 with problematic drinking at age 33/34 and age 45 in two British birth cohorts[#]

	PD at age 33/34 (CAGE) (n=33255)	PD at age 46 (AUDIT) (n=32929)
Externalising problems	1.11 (1.06, 1.16)	1.11 (1.07, 1.15)
Internalising problems	0.93 (0.87, 0.99)	0.90 (0.86, 0.94)
Psychopathology factor	1.05 (1.02, 1.09)	1.02 (0.99, 1.05)

*Psychopathology factor was derived using all 8 items (fights, disobedient, destructive, irritable, being worried, solitary, fearful and miserable) used to derive latent score for externalising and internalising problems. Thus, it captures the common variance of both externalising and internalising problems.

Appendix 23 Association between early life externalising and internalising problems and problematic drinking at age 33/34 and age 45 in two British birth cohorts[#]

	Model 1	Model 2	Model 3
	PD at age 33/34 (CAGE) (n=20095)		
EXT at age 7	1.08 (1.03,1.14) ***	1.05 (1.00,1.11) *	1.04 (0.98,1.09)
INT at age 7	0.96 (0.92,1.00)	0.97 (0.93,1.02)	0.97 (0.93,1.02)
EXT at age 11		1.10 (1.04,1.15) ***	1.06 (1.00,1.12) *
INT at age 11		0.95 (0.91,1.00) *	0.96 (0.92,1.01)
EXT at age 16			1.10 (1.05,1.16) ***
INT at age 16			0.94 (0.88,1.00) *
	PD at age 46 (AUDIT) (n=17218)		
EXT at age 7	1.08 (1.03,1.12) ***	1.06 (1.01,1.11) *	1.04 (1.00,1.09)
INT at age 7	0.93 (0.90,0.97) ***	0.95 (0.91,0.99) *	0.96 (0.92,1.00)
EXT at age 11		1.07 (1.02,1.12) **	1.04 (0.99,1.08)
INT at age 11		0.94 (0.91,0.98) **	0.96 (0.92,1.00) *
EXT at age 16			1.11 (1.06,1.15) ***
INT at age 16			0.90 (0.85,0.95) ***

EXT = externalising problems; INT = internalising problems; PD = problematic drinking; Only cases with complete outcome were retained in the analysis; confounding factors were adjusted for correspondingly in each model.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix 24 Association between early life externalising and internalising problems and problematic drinking at age 33/34 and age 45 in two British birth cohorts[#]

	PD at age 33/34 (CAGE) (n=33255)		
	Model 1	Model 2	Model 3
EXT at age 7	1.23 (1.11,1.36) ***	1.16 (1.03,1.30) *	1.11 (0.99,1.25)
INT at age 7	0.91 (0.81,1.02)	0.94 (0.83,1.06)	0.95 (0.84,1.07)
EXT at age 11		1.24 (1.09,1.41) **	1.11 (0.97,1.28)
INT at age 11		0.92 (0.84,1.00)	0.94 (0.85,1.04)
EXT at age 16			1.48 (1.26,1.74) ***
INT at age 16			0.85* (0.75,0.98)
	PD at age 45 (AUDIT-PC) (n=32929)		
EXT at age 7	1.15 (1.05,1.25) **	1.11 (1.01,1.23) *	1.08 (0.98,1.20)
INT at age 7	0.84 (0.77,0.91) ***	0.89 (0.81,0.98) *	0.92 (0.83,1.01)
EXT at age 11		1.16 (1.05,1.28) **	1.08 (0.97,1.20)
INT at age 11		0.85 (0.78,0.92) ***	0.89 (0.82,0.97) *
EXT at age 16			1.36 (1.20,1.54) ***
INT at age 16			0.76 (0.69,0.85) ***

EXT = externalising problems; INT = internalising problems; PD = problematic drinking; EXT and INT were measured using the sum score of corresponding items; confounding factors were adjusted for correspondingly.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix 25 Association between early life externalising and internalising problems and problematic drinking at age 44/45 measured using different AUDIT scale in NCDS58 (n=16336)

	Model 1	Model 2	Model 3
	PD at age 46 (full AUDIT)		
EXT at age 7	1.06 (1.00,1.11) *	1.04 (0.98,1.10)	1.02 (0.96,1.08)
INT at age 7	0.96 (0.92,0.99) *	0.98 (0.94,1.02)	0.99 (0.95,1.04)
EXT at age 11		1.07 (1.01,1.14) *	1.04 (0.98,1.11)
INT at age 11		0.93 (0.89,0.98) **	0.95 (0.91,1.00)
EXT at age 16			1.10 (1.04,1.16) ***
INT at age 16			0.88 (0.83,0.94) ***
	PD at age 46 (AUDIT-PC)		
EXT at age 7	1.05 (1.00,1.10) *	1.04 (0.99,1.09)	1.02 (0.97,1.08)
INT at age 7	0.94 (0.90,0.98) **	0.96 (0.91,1.00)	0.97 (0.92,1.01)
EXT at age 11		1.05 (0.99,1.11)	1.02 (0.96,1.09)
INT at age 11		0.96 (0.91,1.00)	0.97 (0.93,1.02)
EXT at age 16			1.08 (1.03,1.14) **
INT at age 16			0.90 (0.85,0.96) **

* EXT = externalising problems; INT = internalising problems; PD = problematic drinking; $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; confounding factors were adjusted for correspondingly in each model.

Appendix 26 Distribution of weekly alcohol units and prevalence of problematic drinking across mid-adulthood in NCDS58

	Weekly alcohol units at age 33					PD at age 33*		PD at age 44/45*	
	N	Mean	Q25	Q50	Q75	N	Mean	N	Mean
Wave1									
Male	4809	17.1	3	11	24	4781	17.0%	3959	43.6%
HILE[&]	629	15.8	4	11	23	627	18.3%	542	41.1%
HIHE	1583	15.9	2	10	22	1571	16.4%	1274	42.7%
LILE	1386	18.0	4	12	24	1380	16.1%	1150	45.8%
LIHE	1211	18.4	3	12	25	1203	18.4%	993	43.5%
P value				0.103			0.301		0.202
Female	5000	5.0	0	2	7	4959	7.9%	4059	19.9%
HILE	902	4.7	0	2	6	897	8.0%	748	15.1%
HIHE	1434	4.6	0	2	7	1424	8.6%	1174	20.5%
LILE	1802	5.2	0	3	8	1786	6.8%	1450	21.2%
LIHE	862	5.4	0	2	7	852	8.7%	687	21.1%
P value				0.427			0.254		0.004
Wave2									
Male	4633	17.1	3	11	24	4605	16.9%	3844	43.3%
HILE	640	14.6	3	11	20	638	15.7%	554	39.4%
HIHE	1567	16.1	2	10	22	1555	16.4%	1264	41.6%
LILE	1389	17.9	4	12	24	1383	16.1%	1188	44.9%
LIHE	1037	19.3	4	12	28	1029	19.6%	838	46.3%
P value				0.004			0.068		0.583
Female	4781	5.1	0	2	7	4742	7.9%	3913	20.1%
HILE	907	4.7	0	2	7	899	7.8%	732	19.8%
HIHE	1376	4.8	0	2	7	1365	8.7%	1122	20.4%
LILE	1808	5.4	0	3	8	1790	7.4%	1479	19.6%
LIHE	690	5.5	0	2	8	688	8.0%	580	20.9%
P value				0.022			0.025		0.911
Wave3									
Male	3998	17.1	3	12	24	3978	16.8%	3344	44.6%
HILE	527	15.0	3	10	20	526	13.9%	438	39.5%
HIHE	1016	17.1	2	11	24	1008	18.8%	792	42.8%
LILE	1763	17.4	4	12	24	1754	16.3%	1517	45.9%
LIHE	692	18.3	2	12	24	690	17.1%	597	47.2%
P value				0.067			0.086		0.001
Female	4196	5.1	0	3	7	4165	7.8%	3452	20.0%
HILE	645	4.6	0	2	6	639	6.6%	535	19.4%
HIHE	1511	5.2	0	2	7	1501	10.1%	1219	19.8%
LILE	1463	5.3	0	3	8	1451	6.4%	1241	19.7%
LIHE	577	5.2	0	3	7	574	6.4%	457	22.1%
P value				0.021			0.038		0.693

*PD = problematic drinking measured by CAGE scale at age 33/34 and by AUDIT-PC scale at age 45; [&]HILE = high internalising and low externalising problems, and so on for HIHE, LILE, LIHE. Threshold for high and low is value 0 for latent score.

Appendix 27 Distribution of weekly alcohol units and prevalence of problematic drinking across mid-adulthood in BCS70

	Weekly alcohol units at age 34					PD at age 34*		PD at age 46*	
	N	Mean	Q25	Q50	Q75	N	Mean	N	Mean
Wave1									
Male	3773	16.3	3	11	23	3711	23.3%	3288	30.7%
HILE[&]	403	15.4	4	11	22	397	19.4%	340	30.0%
HIHE	1333	16.1	2	10	22	1310	24.1%	1159	31.9%
LILE	1195	16.2	3	11	23	1175	24.6%	1056	28.9%
LIHE	842	17.2	2	11	24	829	22.1%	733	31.8%
P value[#]				0.926			0.128		0.390
Female	4106	5.8	0	3	8	4001	13.3%	3568	16.6%
HILE	668	4.9	0	2	7	643	11.4%	567	13.6%
HIHE	1186	6.0	0	3	9	1165	13.7%	1059	18.4%
LILE	1676	5.8	0	3	8	1630	14.0%	1424	15.3%
LIHE	576	6.1	0	3	8	563	13.0%	518	20.1%
P value				0.041			0.401		0.006
Wave2									
Male	3885	16.3	3	11	22	3823	23.7%	3436	31.1%
HILE	480	14.0	3	10	20	471	20.6%	439	26.7%
HIHE	1247	17.2	3	12	24	1227	25.3%	1086	32.1%
LILE	1479	16.3	4	12	22	1459	23.0%	1324	28.9%
LIHE	679	16.0	2	10	22	666	24.2%	587	37.1%
P value				0.153			0.187		0.313
Female	4296	5.8	0	3	8	4176	13.4%	3728	16.9%
HILE	730	5.3	0	3	8	709	12.4%	619	14.9%
HIHE	1164	5.8	0	3	8	1131	14.2%	994	17.9%
LILE	1916	6.1	0	3	9	1866	12.7%	1674	17.3%
LIHE	486	5.9	0	3	9	470	15.3%	441	16.3%
P value				0.210			0.001		0.423
Wave3									
Male	2685	16.6	3	11	24	2653	23.3%	2327	30.0%
HILE	285	14.2	3	10	20	278	20.1%	240	22.1%
HIHE	807	16.6	2	10	23	798	23.6%	690	30.0%
LILE	1259	16.1	4	11	23	1248	22.2%	1115	29.6%
LIHE	334	20.6	4	13	32	329	29.2%	282	38.7%
P value				0.052			0.032		0.140
Female	3192	5.7	0	3	8	3106	13.6%	2756	15.8%
HILE	337	5.3	0	3	7	323	14.6%	295	13.2%
HIHE	1269	5.6	0	2	8	1232	15.1%	1094	17.5%
LILE	1307	5.7	0	3	8	1277	12.5%	1121	14.1%
LIHE	279	6.1	0	3	8	274	10.9%	246	19.1%
P value				0.170			0.001		0.042

*PD = problematic drinking measured by CAGE scale at age 33/34 and by AUDIT-PC scale at age 45; [&]HILE = high internalising and low externalising problems, and so on for HIHE, LILE, LIHE. Threshold for high and low is value 0 for latent score.

Appendix 28 Association between externalising and internalising problems and weekly alcohol units at age 33/34 in two British birth cohorts (n=33255)[#]

	Model 1	Model 2	Model 3
q50			
EXT at age 7	0.21 (0.05, 0.37) **	0.18 (0.01, 0.35) *	0.13 (-0.04, 0.30)
INT at age 7	-0.28 (-0.41, -0.15) ***	-0.17 (-0.31, -0.03) *	-0.14 (-0.27, 0.00)
EXT at age 11		0.19 (0.01, 0.37) *	0.10 (-0.08, 0.28)
INT at age 11		-0.26 (-0.40, -0.13) ***	-0.18 (-0.32, -0.04) *
EXT at age 16			0.33 (0.17, 0.49) ***
INT at age 16			-0.41 (-0.58, -0.24) ***
q75			
EXT at age 7	0.59 (0.31, 0.86) ***	0.47 (0.17,0.77) **	0.34 (0.04,0.64) *
INT at age 7	-0.59 (-0.82, -0.36) ***	-0.42 (-0.66,-0.17) ***	-0.35 (-0.60,-0.10) **
EXT at age 11		0.52 (0.22,0.83) ***	0.32 (-0.00,0.64)
INT at age 11		-0.50 (-0.73,-0.27) ***	-0.38 (-0.61,-0.14) **
EXT at age 16			0.71 (0.41,1.01) ***
INT at age 16			-0.72 (-1.05,-0.38) ***

EXT = externalising problems; INT = internalising problems; PD = problematic drinking; confounding factors were adjusted for correspondingly in each model.

Appendix 29 Distribution of educational attainment in NCDS58 from age 16 to age 30

	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Certificate of Secondary Education	1,999	80	34	2	3	2	1	7	2	0	1	2	4	1	2
Scottish standard grade 4-5	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Certificate of Secondary Education	74	8	6	2	0	0	1	0	1	0	3	7	6	2	19
General Certificate of Education O level	4,392	1,049	533	102	67	33	33	67	18	17	23	15	27	17	17
Scottish standard grade 1-3	35	1	1	1	0	0	0	0	0	0	0	0	1	0	0
Scottish lower qualification	7	12	5	3	0	2	2	5	0	0	0	0	0	0	0
Advanced Subsidiary level	0	20	55	8	1	2	0	1	0	1	1	2	0	3	3
General Certificate of Education A level	0	0	2,700	277	54	38	19	29	9	12	8	5	8	6	10
Scottish higher qualification	2	27	12	8	6	1	0	6	0	2	2	1	2	0	1
Scottish Certificate	1	0	2	0	0	0	0	0	0	0	0	0	0	0	0
Diploma of higher education	0	0	14	13	21	25	26	22	10	6	13	8	4	8	6
Other diploma	0	0	0	10	19	87	47	40	16	13	11	12	20	9	12
Degree	0	0	0	0	0	644	477	218	59	34	34	23	26	20	17
Higher Degree	0	0	0	0	0	0	22	34	31	30	20	12	17	12	7

Appendix 30 Distribution of educational attainment in BCS70 from age 16 to age 30

	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Scottish standard grade 4-5	50	6	1	0	0	1	0	0	0	0	1	0	2	0	0
Other Scottish qualification	2	7	4	0	1	0	0	0	0	0	0	0	0	0	0
General Certificate of Secondary Education	1,022	204	183	77	41	34	36	35	30	30	33	35	31	29	14
Certificate of Secondary Education	3,922	99	8	0	0	0	0	0	0	0	0	0	0	0	0
General Certificate of Education O level	4,705	1,035	137	21	9	10	5	4	6	16	51	26	15	9	4
Scottish standard grade 1-3	220	18	2	2	0	0	1	0	0	0	1	0	0	0	0
Scottish lower qualifications	30	4	0	0	0	0	0	0	0	0	0	0	0	0	0
Advanced Subsidiary level	0	243	284	59	5	7	10	10	8	6	6	10	9	5	5
General Certificate of Education A level	0	0	1,750	302	56	36	26	20	31	16	20	27	41	10	10
Scottish higher qualifications	4	185	32	6	2	2	2	1	0	2	1	1	3	0	1
Scottish Certificate of 6th year	0	3	31	0	0	0	0	0	0	0	0	0	1	0	0
Diploma of higher education	10	54	188	138	99	89	71	57	48	34	50	45	40	34	29
Other diploma	0	0	0	23	14	46	72	85	95	77	85	71	77	75	43
Degree	0	0	0	0	0	557	652	356	160	118	97	64	57	65	40
Higher degree	0	0	0	0	0	0	42	54	57	38	55	33	34	34	25

Appendix 31 Distribution of AUDIT-PC score at age 45 across two cohorts (count (%))*

Score	0	1	2	3	4
			NCDS58		
Drinking frequency	207 (4.7)	436 (9.8)	907 (20.4)	1481 (33.4)	1408 (31.7)
Drinking quantity	1769 (39.8)	1188 (26.8)	788 (17.8)	410 (9.2)	285 (6.4)
Can't stop	4081 (91.9)	167 (3.8)	76 (1.7)	93 (2.1)	23 (0.5)
Fail to work	4100 (92.3)	284 (6.4)	31 (0.7)	22 (0.5)	3 (0.1)
Cause concern	3936 (88.7)		241 (5.4)		263 (5.9)
			BCS70		
Drinking frequency	385 (9.6)	596 (14.9)	924 (23.1)	1314 (32.9)	775 (19.4)
Drinking quantity	1881 (47.2)	1205 (30.3)	602 (15.1)	201 (5.1)	93 (2.3)
Can't stop	3447 (86.4)	313 (7.9)	102 (2.6)	79 (2.0)	47 (1.2)
Fail to work	3632 (91)	288 (7.2)	36 (0.9)	18 (0.5)	16 (0.4)
Cause concern	3481 (87.2)		246 (6.2)		267 (6.7)

Appendix 32 Cross-tabulation of problematic drinking defined by AUDIT and AUDIT-PC scale across sex in NCDS58

	AUDIT-PC			
	Male		Female	
	Yes	No	Yes	No
AUDIT				
Yes	1534 (96.7)	53 (3.3)	607 (93.2)	44 (6.8)
No	399 (14.0)	2453 (86.0)	294 (7.6)	3569 (92.4)

Appendix 33 Variable coding for problematic drinking

Value	Average drinking days per month	Average drinking amount per occasion	Maximum drinking/24h	Intoxication times
0	Don't drink	Don't drink	Don't drink	Never
1	Once or less	1 drink	1~4 drinks	1~2 times
2	2~3 days	2 drinks	5~6 drinks	3~10 times
3	4~9 days	3 drinks	7~9 drinks	11~20 times
4	10~15 days	4 drinks	10~14 drinks	21~50 times
5	16~20 days	5 drinks	15~19 drinks	51~100 times
6	21~26 days	6 drinks	20~24 drinks	101~250 times
7	27~29 days	7~10 drinks	25~29 drinks	251~500 times
8	30 days	11 or more drinks	30+ drinks	500+ times

Appendix 34 Distribution of stressful life events across waves (Count (%))

	Wave1	Wave2	Wave3	Wave4	Wave5	Wave6	Wave7	Wave8
Conflict with ex	109(28.1)	115(28)	114(27.1)	56(12.8)	64(11.9)	38(8)	36(9.2)	25(9.1)
Physical fight	70(18.3)	67(16.3)	48(11.4)	30(6.9)	39(7.2)	16(3.4)	17(4.4)	9(3.3)
Don’t have money	199(49)	205(49.2)	199(47)	100(22.9)	159(29.8)	150(31.4)	113(29.1)	77(28)
Check bounced	150(38.7)	157(38.4)	128(30.3)	39(8.9)	57(10.6)	54(11.3)	46(11.9)	28(10.2)
Get evicted	8(2.1)	9(2.2)	13(3.1)	12(2.7)	4(0.7)	9(1.9)	8(2.1)	6(2.2)
Moved	67(17.8)	73(17.9)	113(26.8)	216(49.3)	292(54.4)	240(50.4)	176(45.1)	98(35.6)
Accident, no injury	143(36.8)	167(40.3)	137(32.4)	94(21.6)	105(19.5)	85(17.8)	52(13.4)	47(17.1)
Accident, injury	23(6.1)	29(7.1)	26(6.2)	12(2.7)	14(2.6)	7(1.5)	10(2.6)	6(2.2)
Apply welfare	82(21.3)	85(20.9)	84(19.9)	49(11.2)	81(15)	83(17.4)	72(18.5)	43(15.6)
Welfare stopped	50(13.2)	62(15.2)	56(13.3)	18(4.1)	37(6.9)	38(7.9)	31(7.9)	18(6.5)
Something stolen	66(17.3)	71(17.4)	70(16.6)	44(10.1)	41(7.6)	32(6.7)	21(5.4)	13(4.7)
Sever injury	118(30.7)	107(26.2)	119(28.2)	40(9.2)	54(10)	36(7.6)	39(10.1)	23(8.4)
Chronic illness	46(12.2)	63(15.4)	77(18.2)	18(4.1)	42(7.8)	47(9.9)	38(9.7)	38(13.9)
Someone died	154(39.6)	165(40.1)	158(37.5)	138(31.7)	157(29.2)	133(27.9)	93(23.8)	63(22.9)
Disagree with friends	82(21.2)	85(21)	83(19.7)	48(11)	61(11.3)	38(8)	41(10.5)	24(8.7)
Child sent home from school	61 (14.4)	56 (13.4)	44 (10.4)					
Child suspended from school	65 (15.3)	58 (13.8)	52 (12.3)					
Child skipped school	64 (15.1)	90 (21.4)	78 (18.5)					
Was told child may repeat grade by school	20 (4.7)	12 (2.9)	14 (3.3)					
Was told child may fail one or more subjects	86 (20.3)	85 (20.2)	75 (17.8)					
Child had a serious disagreement with others	85 (20)	80 (19.1)	79 (18.7)					

Appendix 35 Construction of the Coddington Life Stressors at different stages

Parent-reported/Self-reported (youth) Ages 12-14/15-20	Self-reported (adult) Ages 18-29
Family negative life events	**Family negative life events**
Grandparent ill or hospitalized	Grandparent ill or hospitalized
Grandparent died	---
Parent returned to school	---
Parent away more due to job	Away more often due to job
Increased arguments between parent and child	Increased arguments with parents
Increased arguments between parents	Increased arguments with wife/partner
Parent seriously ill	Parent seriously ill
Friend or relative moved in	Friend or relative moved in
Sibling seriously ill	Sibling seriously ill
Sibling involved with drugs or alcohol	Sibling involved with drugs or alcohol
---	Wife/partner seriously ill
---	A parent died
Family separation	**Family separation**
(Step) mother begins to work	Wife/partner began to work
New stepparent	New stepparent
(Step) parents separated or divorced	(Step) parents separated or divorced
Parent received jail sentence	Parent received jail sentence
Parent moved away	---
Financial	**Financial**
(Step) mother quit work	Wife/partner quit work
Financial condition worsened	Financial condition worsened
Family evicted	Family evicted
Parent lost job	Parent lost job
Family cut off welfare	Wife/partner funds cut off
Work/academics	**Work/academics**
Child repeated a grade	Lost or was fired from a job
Peers issues	**Peers issues**
Child changed schools	Changed jobs
Family moved	Family moved
Child picked on by mates	---
Child's friend died	Friend died
Loss or illness	**Loss or illness**
Sibling moved away	Sibling moved away
Child's pet died	---
Child seriously ill or hospitalized	Seriously ill or hospitalized
Child needed medical attention	Needed medical attention
Child in serious accident	Child in serious accident

Appendix 36 Construction of Adverse Childhood Experiences

Oregon Social Learning Centre Family Crisis List	**Conflict Tactics Scale**	**Coddington Family Events Questionnaire**
Didn't have enough money to pay the bills	Insulting or swearing	A brother or sister (step, half, or full) died
Didn't have any clean clothes	Threaten to hit or throw something at their child	A parent/stepparent received a minor jail sentence
Family member saw a psychiatrist, psychologist, counsellor or other	Throw or smash or hit or kick something, but not at their child	A parent/stepparent received a jail sentence of more than one year's duration
Something stolen from the house	Actually throw something at their child	A brother or sister (step, half, or full) of the child has become involved with drugs or alcohol
Went to apply for welfare or unemployment funds	Push, grab, or shove, slap, hit, or spank their child	the child has been picked on (teased, bullied) by classmates
	Used a belt on their child	
	Kick, bit, or beat their child	
	threatened/used knife/gun	

Appendix 37 Items used to assess externalising and internalising problems

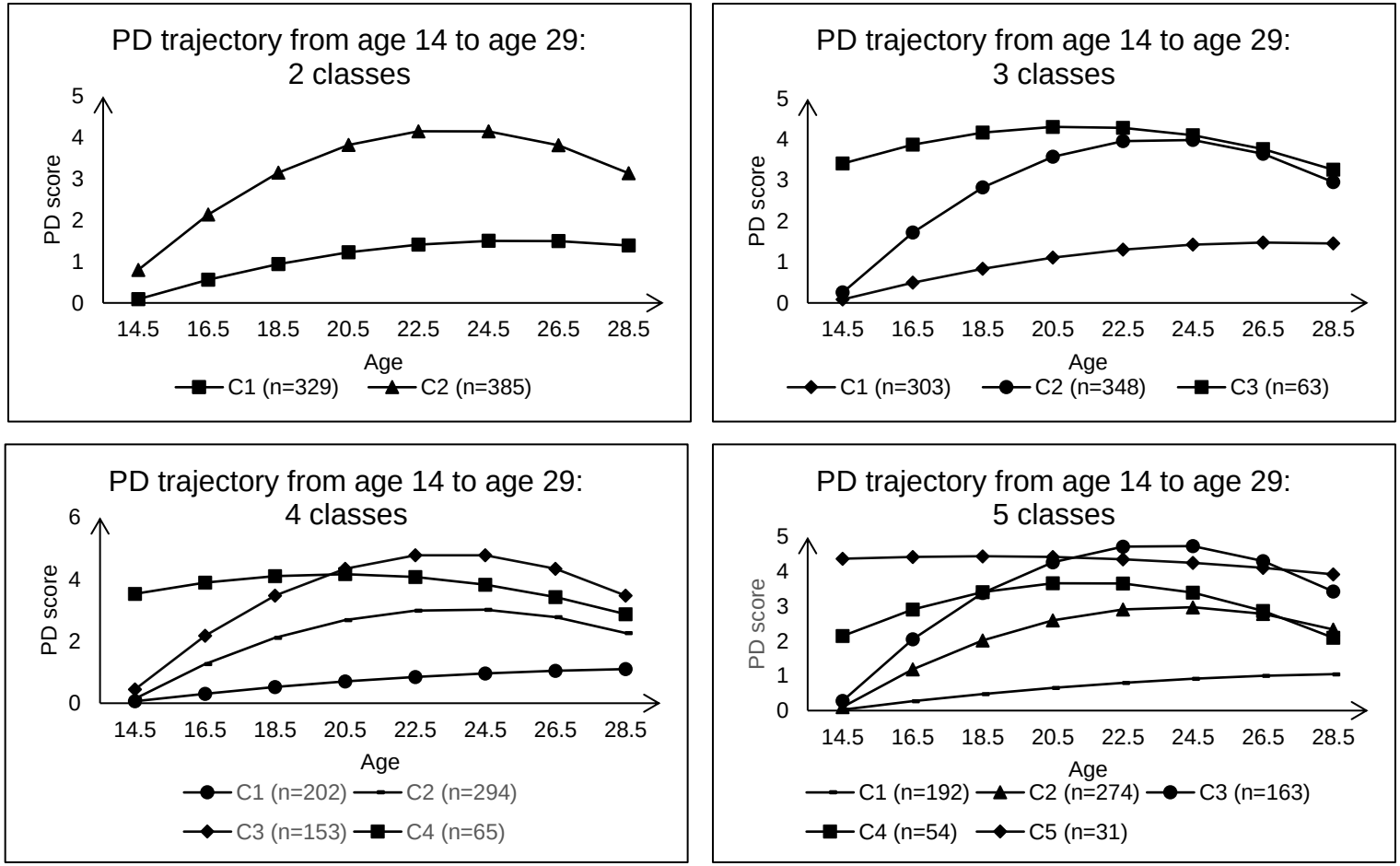
Externalising problems	Internalising problems
3.I argue a lot	12.I feel lonely
7.I brag	13.I feel confused or in a fog
16.I am mean to others	14.I cry a lot
19.I try to get a lot of attention	18.I deliberately try to hurt or kill myself
20.I destroy my own things	25.I don't get along with other kids
21.I destroy things belongs to others	29.I am afraid of certain animals, situations, or places, other than school
23.I disobey at school/I break rules at work or elsewhere	31.I am afraid I might think or do something bad
26.I don't feel guilty after doing something I shouldn't	32.I feel that I have to be perfect
27.I am jealous of others	33.I feel that no one loves me
37.I get in many fights	34.I feel that others are out to get me
39.I hang around with kids (people) who get in trouble	35.I feel worthless or inferior
41.I act without stopping to think/I am impulsive or act without thinking	42.I would rather be alone than with others
43.I lie or cheat	45.I am nervous or tense
57.I physically attack people	48.I am not liked by other kids
63.I would rather be with older kids (people) than with kids (people) my own age	50.I am too fearful or anxious
68.I scream a lot	51.I feel dizzy
74.I show off or clown	52.I feel too guilty
82.I steal	54.I feel overtired
86.I am stubborn	56a.Aches or pains (not stomach or headaches)
87.My moods or feelings change suddenly	56b.Headaches
93.I talk too much	56c.Nausea, feel sick
94.I tease others a lot	56d.Problems with eyes (not if corrected by glasses)
95.I have a hot temper	56e.Rashes or other skin problems
96.I think about sex too much	56f.Stomachaches or cramps
97.I threaten to hurt people	56g.Vomiting, throwing up
101.I cut classes or skip school/I stay away from my job even when I'm not sick or not on vacation	65.I refuse to talk
104.I am louder than other kids	69.I am secretive or keep things to myself
	71.I am self-conscious or easily embarrassed
	75.I am shy
	91.I think about killing myself
	100.I have trouble sleeping
	102.I don't have much energy
	103.I am unhappy, sad, or depressed
	111.I keep from getting involved with others
	112.I worry a lot

Appendix 38 Items used to construct peer involvement in substance use

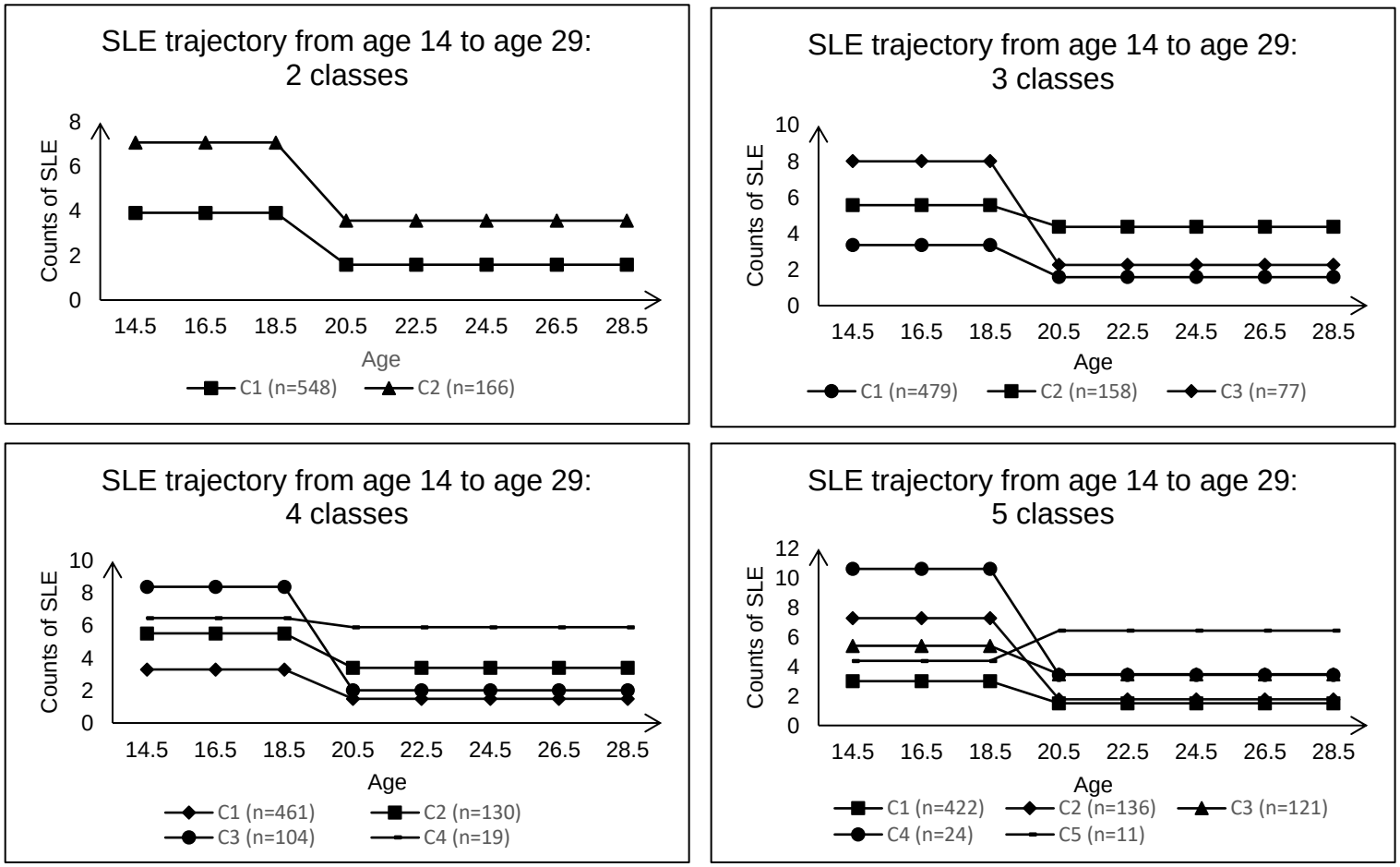
From age 12 to 18	From age 19 to age 24	From age 25 to age 30
Skip school and hang out and smoke	Hang out at bars	Hang out at bars (sports bar, club, neighbourhood bar)
Have ever been drunk	Have ever had 5 or more alcoholic drinks in a row	Have ever had 5 or more alcoholic drinks in a row
Have gotten drunk in past year	Have ever drank enough to feel drunk or high	Have ever drunk enough to feel drunk or very high
Get drunk once a month or more	5 or more alcoholic drinks in a row in last 2 weeks	Have had >=5 alcoholic drinks in a row in the last two weeks
Get drunk once a week or more	5 or more alcoholic drinks in a row in last year	Have had 5 or more alcoholic drinks in a row in the last year
Smoke cigarettes	Smoked cigarettes in the past year	Smoked cigarettes in the past year
Smoke at least one cigarette/week	Smoke cigarettes on a daily basis	Smoke cigarettes on a daily basis
Smoke at least one cigarette/day	Have ever smoked marijuana or hashish	Have ever smoked marijuana or hashish
Smoke at least 10 cigarettes/day	Use crack cocaine	Have smoked marijuana or hashish in the last year
Smoke at least a pack of cigarettes a day	Use club drugs (Ecstasy, Roofies)	Have used crack cocaine in the last year
Have gotten high on drugs	Sniff glue, gasses, or sprays	Have used club drugs (Ecstasy, Roofies) in the last year
Get high on drugs once a year or more	Use Heroin	Have used methamphetamines (meth) in the last year
Get high on drugs once a month or more	Get high on drugs once a week or more often	Have used Heroin in the last year
Get high on drugs once a week or more		Get high on drugs once a week or more often

* To ensure comparability of the scale across stages, mean score was calculated and utilised for trajectory analysis.

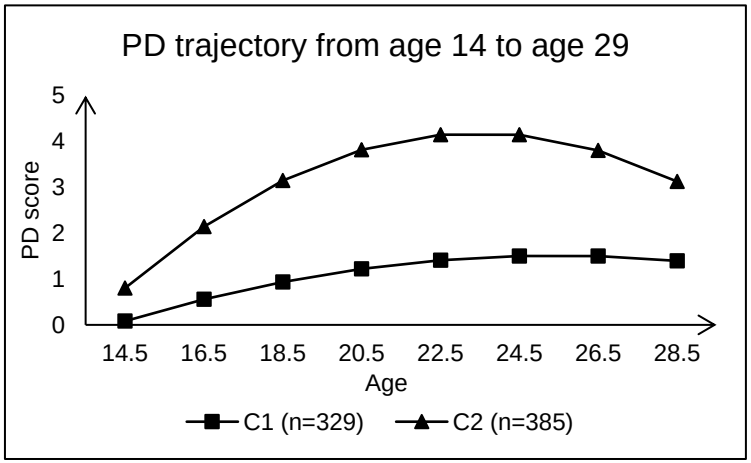
Appendix 39 Univariate latent class growth model for problematic drinking (PD) (n=714)

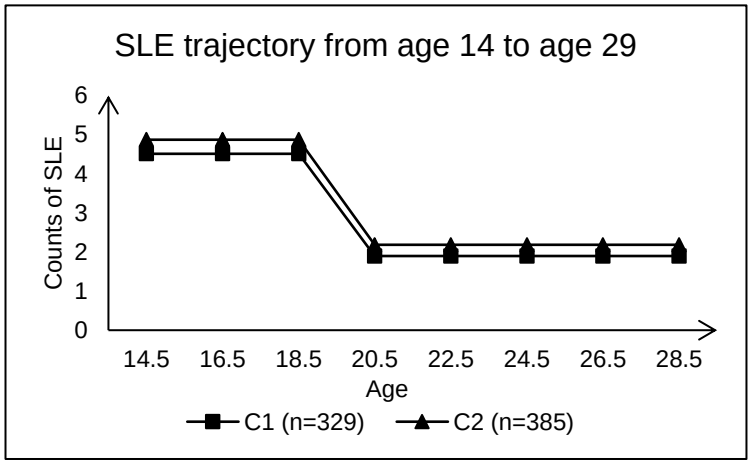


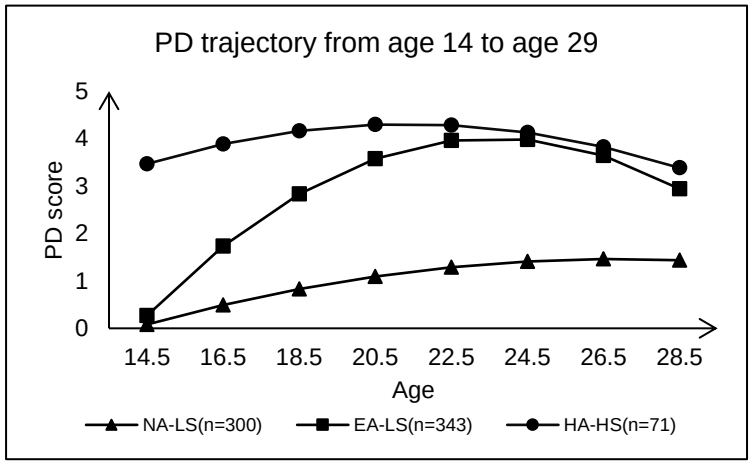
Appendix 40 Univariate latent class growth model for stressful life events (SLE) (n=714)

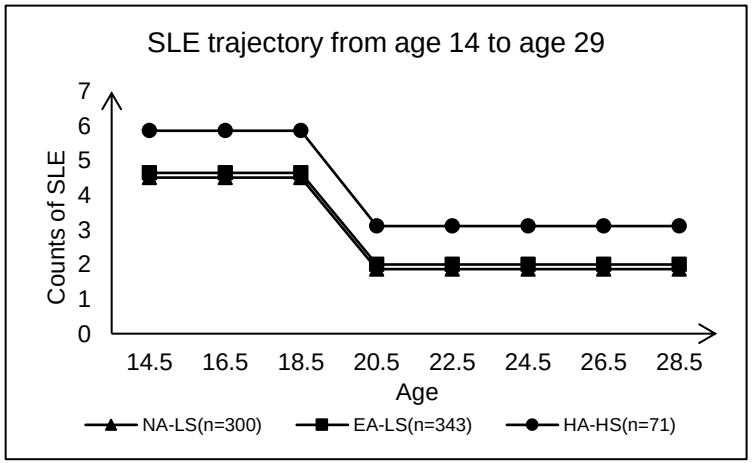


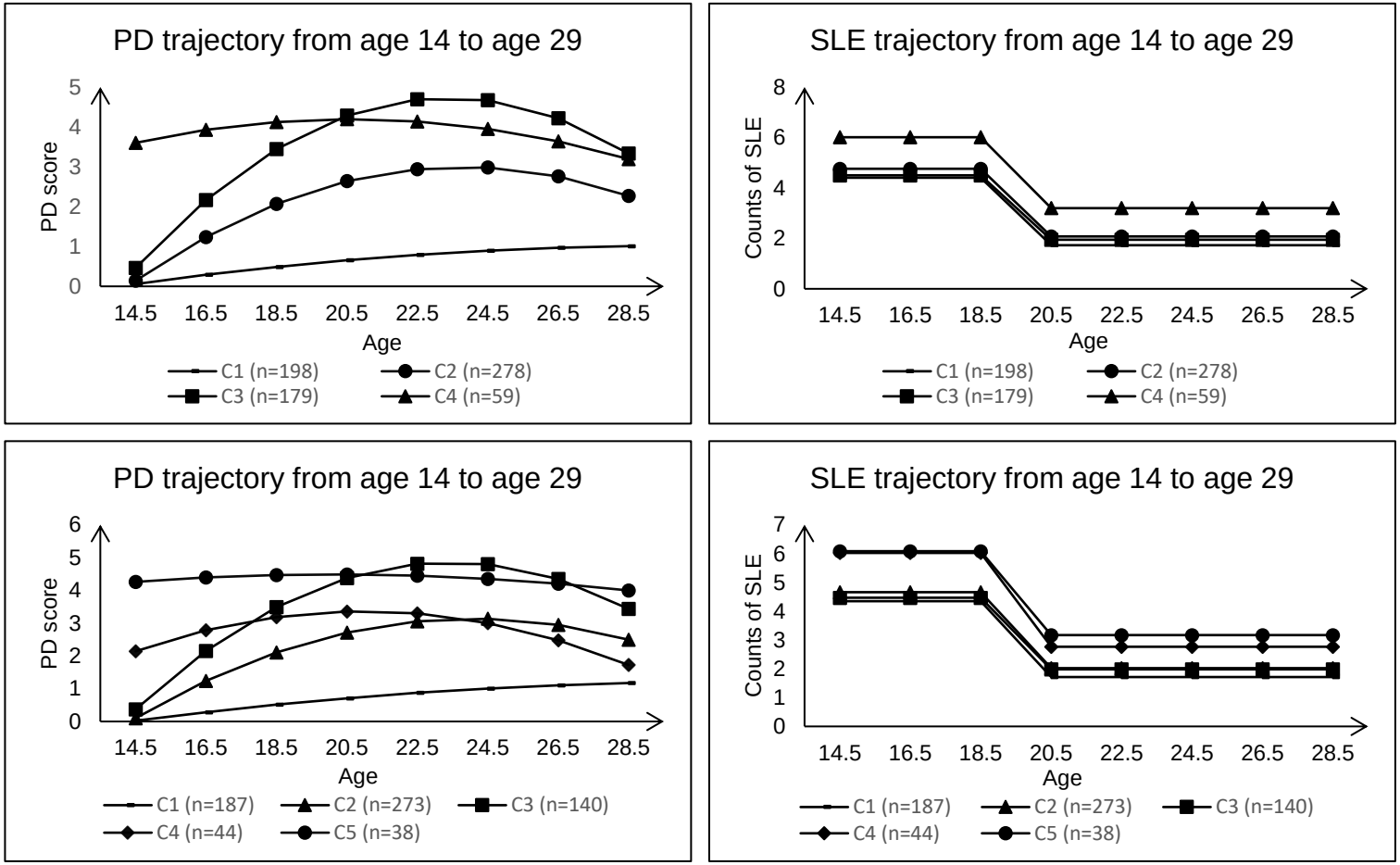
Appendix 41 Group-based dual trajectory model for problematic drinking and stressful life events (n=714)*











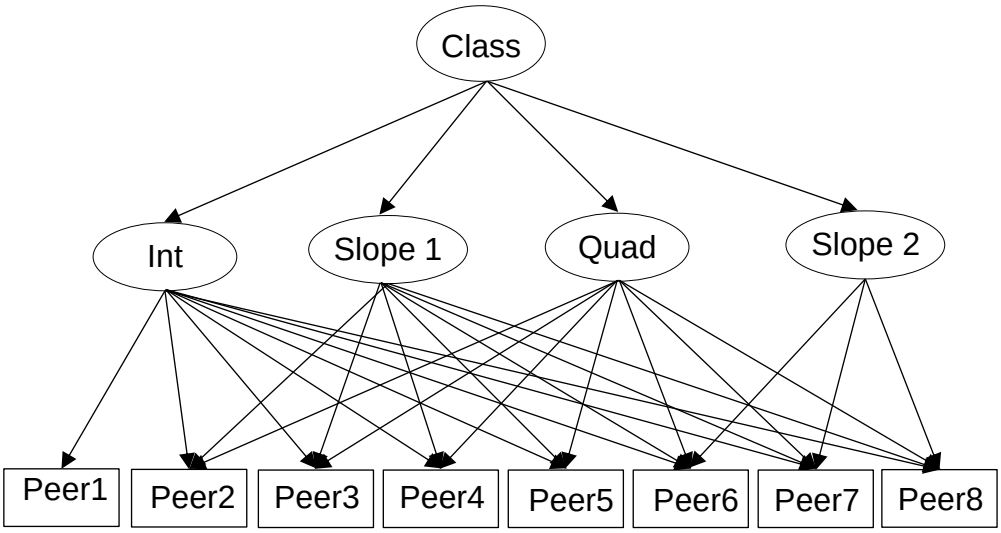
*For each pair of problematic drinking (PD) and stressful life events (SLE) solution, class with the same name constitutes the same participants; NA-LS refers to normative alcohol and low stress group; EA-LS refers to escalating alcohol and low stress group; HA-HS refers to high alcohol and high stress group.

Appendix 42 Distribution of stressful life events across problematic drinking-stressful life events classes and waves

		Wave1	Wave2	Wave3	Wave4	Wave5	Wave6	Wave7	Wave8
Conflict with ex	NA-LS	42 (25)	43 (22.6)	48 (26.5)	20 (10.1)	25 (11.4)	13 (7.6)	8 (5.7)	8 (7)
	EA-LS	55 (30.1)	59 (31.2)	53 (27.6)	29 (14.1)	33 (12)	16 (6.3)	18 (8.9)	13 (10.2)
	HA-HS	12 (32.4)	13 (41.9)	13 (27.1)	7 (21.9)	6 (13)	9 (17)	10 (21.3)	4 (11.8)
Physical fight	NA-LS	26 (15.6)	29 (15.3)	13 (7.2)	11 (5.6)	6 (2.7)	1 (0.6)	3 (2.1)	2 (1.8)
	EA-LS	31 (17.4)	30 (16)	23 (11.9)	15 (7.3)	25 (9.1)	11 (4.4)	8 (4)	3 (2.4)
	HA-HS	13 (34.2)	8 (25)	12 (25)	4 (12.5)	8 (17.4)	4 (7.5)	6 (12.8)	4 (11.8)
Don’t have money	NA-LS	87 (49.4)	92 (47.4)	86 (47.5)	41 (20.6)	62 (28.8)	46 (26.7)	37 (26.6)	27 (23.7)
	EA-LS	93 (49.2)	95 (49.7)	83 (42.8)	40 (19.4)	75 (27.5)	80 (31.7)	57 (28.2)	35 (27.6)
	HA-HS	19 (46.3)	18 (56.3)	30 (62.5)	19 (59.4)	22 (48.9)	24 (45.3)	19 (40.4)	15 (44.1)
Check bounced	NA-LS	59 (35.1)	66 (34.9)	48 (26.5)	15 (7.5)	22 (10.2)	14 (8.1)	16 (11.6)	12 (10.5)
	EA-LS	82 (45.1)	77 (40.7)	65 (33.7)	16 (7.8)	28 (10.2)	31 (12.3)	22 (10.9)	9 (7.1)
	HA-HS	9 (23.7)	14 (45.2)	15 (30.6)	8 (25)	7 (15.2)	9 (17)	8 (17)	7 (20.6)
Get evicted	NA-LS	2 (1.2)	3 (1.6)	4 (2.2)	5 (2.5)	1 (0.5)	4 (2.3)	4 (2.8)	2 (1.8)
	EA-LS	5 (2.8)	5 (2.7)	6 (3.1)	3 (1.5)	2 (0.7)	4 (1.6)	1 (0.5)	2 (1.6)
	HA-HS	1 (2.7)	1 (3.2)	3 (6.3)	4 (12.5)	1 (2.2)	1 (1.9)	3 (6.4)	2 (5.9)
Family moved	NA-LS	32 (19.5)	33 (17.6)	43 (23.8)	102 (51.3)	117 (53.9)	78 (45.3)	63 (44.7)	41 (36)
	EA-LS	27 (15.4)	32 (17)	52 (26.9)	98 (47.3)	146 (53.3)	129 (51.4)	89 (44.1)	42 (33.1)
	HA-HS	8 (21.6)	8 (25.8)	18 (37.5)	16 (50)	29 (63)	33 (62.3)	24 (51.1)	15 (44.1)
Accident, no injury	NA-LS	45 (26.8)	71 (37.2)	57 (31.5)	39 (19.7)	40 (18.3)	32 (18.5)	21 (15)	17 (14.9)
	EA-LS	81 (44.5)	78 (40.8)	62 (32.1)	50 (24.3)	51 (18.6)	44 (17.5)	23 (11.4)	21 (16.5)
	HA-HS	17 (43.6)	18 (56.3)	18 (36.7)	5 (16.1)	14 (30.4)	9 (17)	8 (17)	9 (26.5)
Accident, injury	NA-LS	8 (4.9)	14 (7.5)	6 (3.3)	4 (2)	5 (2.3)	1 (0.6)	4 (2.8)	4 (3.5)
	EA-LS	12 (6.9)	11 (5.9)	17 (8.8)	7 (3.4)	5 (1.8)	5 (2)	5 (2.5)	2 (1.6)
	HA-HS	3 (8.1)	4 (12.9)	3 (6.3)	1 (3.1)	4 (8.7)	1 (1.9)	1 (2.1)	0 (0)
Apply welfare	NA-LS	40 (24)	50 (26.6)	42 (23.2)	19 (9.5)	33 (15.1)	26 (15)	17 (12.1)	15 (13.2)
	EA-LS	34 (18.9)	28 (14.9)	31 (16.1)	22 (10.7)	39 (14.2)	39 (15.5)	43 (21.3)	15 (11.8)
	HA-HS	8 (21.1)	7 (22.6)	11 (22.9)	8 (25)	9 (19.6)	18 (34)	12 (25.5)	13 (38.2)
Welfare stopped	NA-LS	22 (13.4)	38 (20.2)	25 (13.8)	5 (2.5)	15 (6.8)	11 (6.4)	11 (7.8)	7 (6.1)
	EA-LS	23 (13.1)	21 (11.2)	24 (12.4)	9 (4.4)	18 (6.6)	18 (7.1)	16 (7.9)	8 (6.3)
	HA-HS	5 (13.2)	3 (9.7)	7 (14.6)	4 (12.5)	4 (8.7)	9 (17)	4 (8.5)	3 (8.8)
Something stolen	NA-LS	29 (17.4)	27 (14.4)	23 (12.7)	9 (4.5)	14 (6.4)	8 (4.6)	3 (2.1)	5 (4.4)

		Wave1	Wave2	Wave3	Wave4	Wave5	Wave6	Wave7	Wave8
	EA-LS	26 (14.8)	32 (16.9)	37 (19.2)	23 (11.2)	18 (6.6)	15 (6)	9 (4.5)	4 (3.1)
	HA-HS	11 (28.2)	12 (37.5)	10 (20.8)	12 (37.5)	9 (19.6)	9 (17)	9 (19.1)	4 (11.8)
Sever injury	NA-LS	39 (23.6)	53 (28)	48 (26.5)	18 (9)	17 (7.8)	12 (6.9)	8 (5.7)	8 (7)
	EA-LS	67 (37.4)	48 (25.4)	61 (31.6)	21 (10.2)	31 (11.3)	16 (6.4)	26 (13)	8 (6.3)
	HA-HS	12 (30)	6 (19.4)	10 (20.8)	1 (3.1)	6 (13)	8 (15.1)	5 (10.6)	7 (21.2)
Chronic illness	NA-LS	21 (12.8)	32 (17)	42 (23.2)	8 (4)	16 (7.3)	17 (9.8)	11 (7.8)	15 (13.2)
	EA-LS	20 (11.4)	28 (14.8)	31 (16.1)	7 (3.4)	22 (8)	27 (10.8)	22 (10.9)	18 (14.3)
	HA-HS	5 (13.5)	3 (9.7)	4 (8.2)	3 (9.4)	4 (8.7)	3 (5.7)	5 (10.6)	5 (14.7)
Someone died	NA-LS	71 (42.3)	75 (39.7)	69 (38.1)	62 (31.5)	60 (27.5)	52 (30.1)	39 (27.7)	28 (24.6)
	EA-LS	70 (38.3)	73 (38.6)	73 (38)	61 (29.5)	82 (29.9)	67 (26.7)	43 (21.3)	28 (22)
	HA-HS	13 (34.2)	17 (51.5)	16 (33.3)	15 (46.9)	15 (32.6)	14 (26.4)	11 (23.4)	7 (20.6)
Disagree with friends	NA-LS	31 (18.7)	37 (19.8)	37 (20.4)	22 (11.1)	20 (9.1)	9 (5.2)	9 (6.4)	8 (7)
	EA-LS	43 (23.8)	37 (19.8)	39 (20.2)	18 (8.7)	34 (12.4)	21 (8.4)	19 (9.4)	10 (7.9)
	HA-HS	8 (20.5)	11 (35.5)	7 (14.6)	8 (25)	7 (15.2)	8 (15.1)	13 (27.7)	6 (17.6)
Child sent home from	NA-LS	38 (22.8)	35 (18.8)	28 (15.6)	---	---	---	---	---
school	EA-LS	30 (16.6)	30 (16.1)	24 (12.4)	---	---	---	---	---
	HA-HS	17 (44.7)	13 (39.4)	14 (29.2)	---	---	---	---	---
Child suspended	NA-LS	41 (24.7)	41 (22)	32 (17.9)	---	---	---	---	---
from school	EA-LS	32 (17.7)	27 (14.4)	24 (12.4)	---	---	---	---	---
	HA-HS	19 (50)	13 (39.4)	14 (29.2)	---	---	---	---	---
Child skipped school	NA-LS	32 (19.4)	46 (24.5)	36 (20.1)	---	---	---	---	---
	EA-LS	37 (20.6)	61 (32.1)	50 (25.8)	---	---	---	---	---
	HA-HS	15 (40.5)	18 (56.3)	19 (39.6)	---	---	---	---	---
Was told child may	NA-LS	19 (11.6)	14 (7.6)	16 (8.9)	---	---	---	---	---
repeat grade by	EA-LS	15 (8.6)	14 (7.5)	20 (10.4)	---	---	---	---	---
school	HA-HS	4 (10.8)	7 (22.6)	6 (12.5)	---	---	---	---	---
Was told child may	NA-LS	55 (33.5)	59 (31.7)	42 (23.5)	---	---	---	---	---
fail one or more	EA-LS	47 (26.1)	55 (29.3)	52 (26.9)	---	---	---	---	---
subjects	HA-HS	21 (55.3)	16 (50)	20 (40.8)	---	---	---	---	---
Child had a serious	NA-LS	47 (28)	50 (26.6)	43 (24)	---	---	---	---	---
disagreement with	EA-LS	51 (28.2)	41 (21.9)	59 (30.6)	---	---	---	---	---
others	HA-HS	16 (40)	17 (53.1)	13 (27.1)	---	---	---	---	---

Appendix 43 Framework of latent class growth curve modelling for peer substance use



Factor load for each latent variable from wave 1 to wave 8:

Int: 1, 1, 1, 1, 1, 1, 1, 1

Slope1: 0, 2, 4, 6, 8, 8, 8, 8

Quad: 0, 4, 16, 36. 64, 64, 64, 64

Slope2: 0, 0, 0, 0, 0, 2, 4, 6

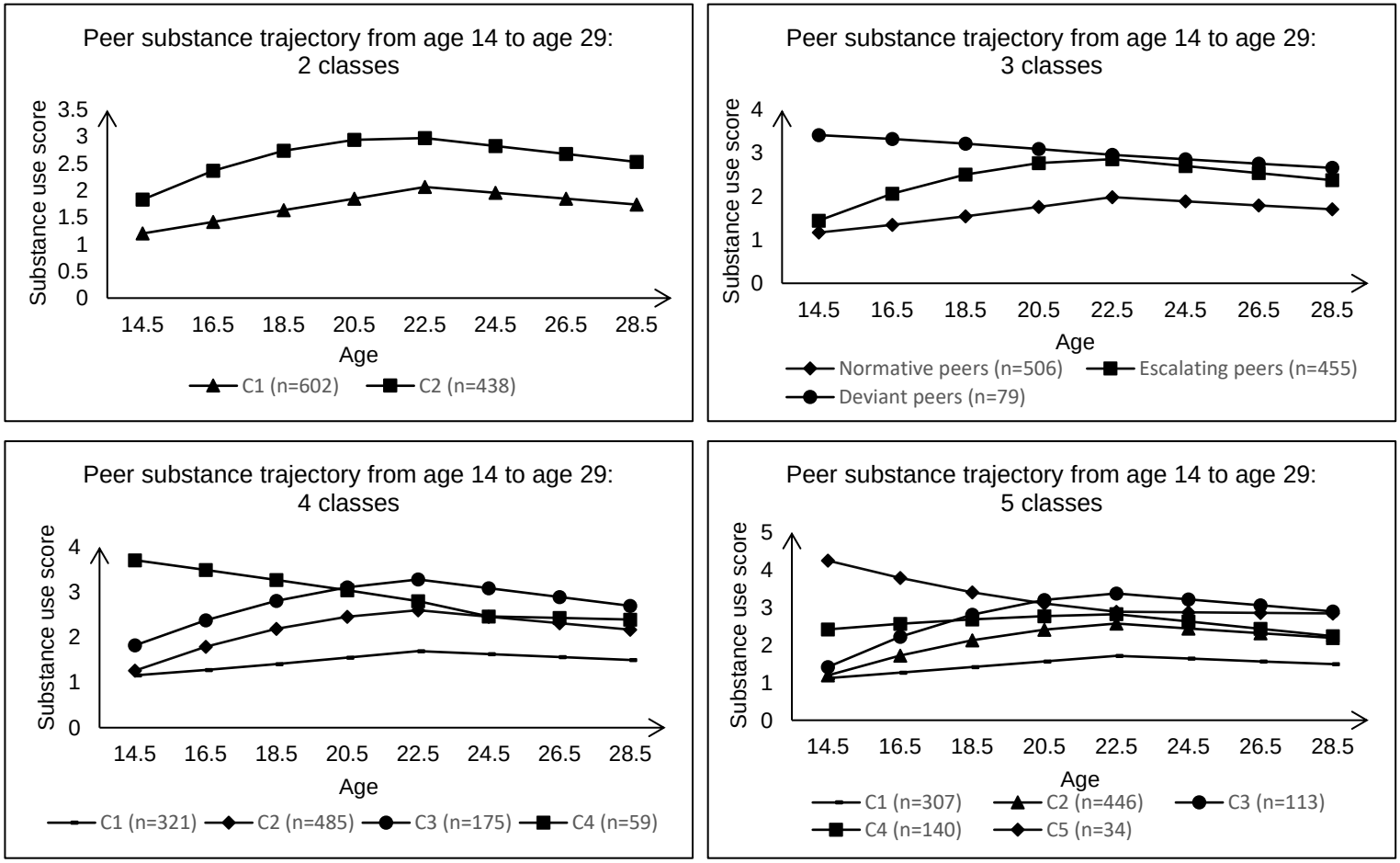
Appendix 44 Model fit index for time-varying covariates

	Externalising and internalising problems				
	χ^2 test	RMSEA	CFI	TLI	SRMR
Intercept-only	822.08(123), P<0.001	0.089	0.804	0.808	0.100
Linear curve	282.75(114), P<0.001	0.046	0.953	0.950	0.054
Quadratic curve	920.90(118), P<0.001	0.098	0.774	0.771	0.068
			Smoking		
	aBIC	Entropy	Probability	Count	LMR-LRT
2 classes	5225.67	0.909	C1: 0.980	C1: 405 (61.8%)	<0.001
			C2: 0.967	C2: 250 (38.2%)	
3 classes	4894.35	0.859	C1: 0.948	C1: 329 (50.2%)	<0.001
			C2: 0.904	C2: 165 (25.2%)	
			C3: 0.950	C3: 161 (24.6%)	
4 classes	4880.18	0.862	C1: 0.957	C1: 315 (48.1%)	0.013
			C2: 0.850	C2: 98 (15.0%)	
			C3: 0.801	C3: 86 (13.1%)	
			C4: 0.954	C4: 156 (23.8%)	
5 classes	5159.77	0.840	C1: 0.937	C1: 347 (53.0%)	0.103
			C2: 0.839	C2: 108 (16.5%)	
			C3: 0.805	C3: 81 (12.4%)	
			C4: 0.852	C4: 27 (4.1%)	
			C5: 0.912	C5: 92 (14.0%)	
			Marijuana		
	aBIC	Entropy	Probability	Count	LMR-LRT
2 classes	5310.00	0.863	C1: 0.968	C1: 397 (60.6%)	<0.001
			C2: 0.953	C2: 258 (39.4%)	
3 classes	5178.31	0.797	C1: 0.942	C1: 348 (53.1%)	0.092
			C2: 0.823	C2: 148 (22.6%)	
			C3: 0.925	C3: 159 (24.3%)	
4 classes	5145.81	0.823	C1: 0.938	C1: 348 (53.1%)	0.015
			C2: 0.825	C2: 114 (17.4%)	
			C3: 0.810	C3: 78 (11.9%)	
			C4: 0.938	C4: 115 (17.6%)	
5 classes	5159.77	0.840	C1: 0.937	C1: 347 (53.0%)	0.103
			C2: 0.839	C2: 108 (16.5%)	
			C3: 0.805	C3: 81 (12.4%)	
			C4: 0.852	C4: 27 (4.1%)	
			C5: 0.912	C5: 92 (14.0%)	
			Peer substance use		
	aBIC	Entropy	Probability	Count	LMR-LRT
2 classes	9268.20	0.687	C1: 0.910	C1: 602 (57.9%)	<0.001
			C2: 0.900	C2: (42.1%)	
3 classes	8740.41	0.739	C1: 0.871	C1: 506 (48.7%)	0.014
			C2: 0.867	C2: 455 (43.8%)	
			C3: 0.914	C3: 79 (7.6%)	
4 classes	8544.30	0.699	C1: 0.826	C1: 321 (30.9%)	0.54
			C2: 0.790	C2: 485 (46.6%)	
			C3: 0.821	C3: 175 (16.8%)	
			C4: 0.891	C4: 59 (5.7%)	
5 classes	8288.75	0.717	C1: 0.819	C1: 307 (29.5%)	0.003
			C2: 0.764	C2: 446 (42.9%)	
			C3: 0.779	C3: 113 (10.9%)	
			C4: 0.851	C4: 140 (13.5%)	
			C5: 0.916	C5: 34 (3.3%)	

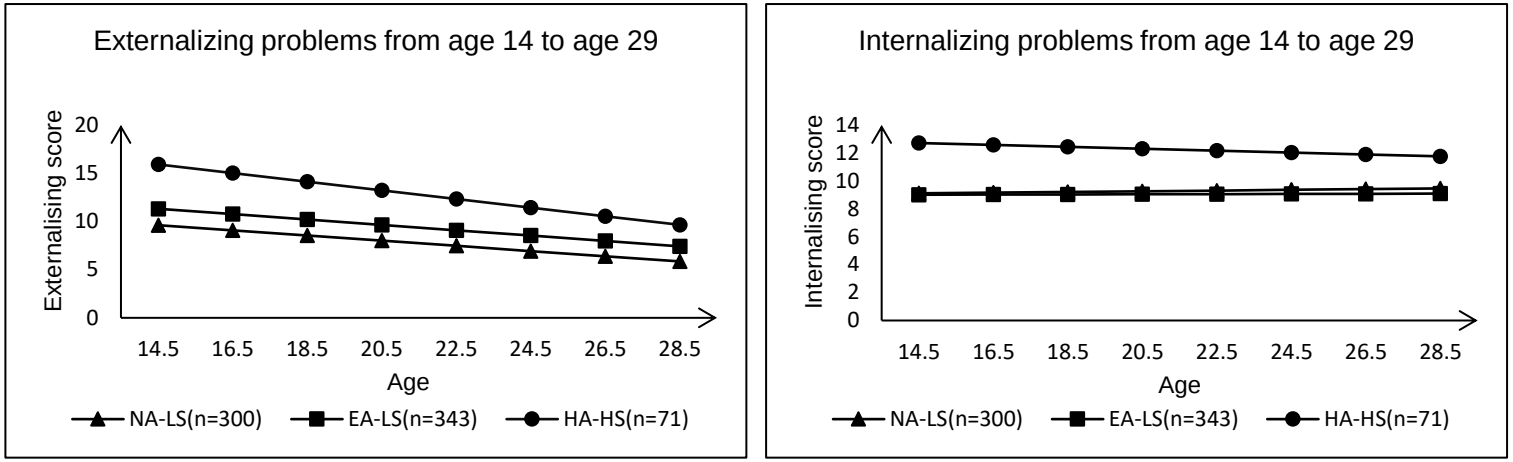
Appendix 45 Distribution of smoking status and marijuana occasions across waves and classes (count (%))

		Wave1	Wave2	Wave3	Wave4	Wave5	Wave6	Wave7	Wave8
Smoking status									
Nonuser	Never	269 (93.4)	287 (94.4)	223 (90.7)	238 (89.1)	214 (89.9)	205 (98.1)	171 (96.1)	117 (96.7)
	Occasionally	18 (6.3)	17 (5.6)	21 (8.5)	29 (10.9)	23 (9.7)	4 (1.9)	6 (3.4)	3 (2.5)
	Regularly	1 (0.3)	0 (0)	2 (0.8)	0 (0)	1 (0.4)	0 (0)	1 (0.6)	1 (0.8)
Adolescent-limited	Never	103 (79.8)	82 (58.6)	40 (36.4)	15 (12.2)	31 (24.4)	33 (28.4)	42 (42)	40 (52.6)
	Occasionally	22 (17.1)	46 (32.9)	44 (40)	76 (61.8)	67 (52.8)	56 (48.3)	45 (45)	26 (34.2)
	Regularly	4 (3.1)	12 (8.6)	26 (23.6)	32 (26)	29 (22.8)	27 (23.3)	13 (13)	10 (13.2)
Heavy user	Never	80 (58.8)	42 (30.4)	5 (4.7)	0 (0)	0 (0)	1 (0.9)	8 (8.4)	4 (6.2)
	Occasionally	28 (20.6)	29 (21)	11 (10.3)	0 (0)	0 (0)	7 (6.3)	5 (5.3)	5 (7.7)
	Regularly	28 (20.6)	67 (48.6)	91 (85)	103 (100)	112 (100)	104 (92.9)	82 (86.3)	56 (86.2)
Marijuana use (occasions)									
Nonuser	Never	292 (98.3)	285 (91.1)	235 (90.7)	244 (91.7)	249 (96.9)	217 (93.5)	182 (91.9)	128 (92.1)
	1-19 occ	5 (1.7)	21 (6.7)	20 (7.7)	22 (8.3)	8 (3.1)	14 (6)	12 (6.1)	10 (7.2)
	Over 20 occ	0 (0)	7 (2.2)	4 (1.5)	0 (0)	0 (0)	1 (0.4)	4 (2)	1 (0.7)
Adolescent-limited	Never	89 (73)	54 (41.2)	20 (20.4)	28 (24.3)	37 (35.6)	36 (35.6)	55 (58.5)	34 (53.1)
	1-19 occ	31 (25.4)	51 (38.9)	48 (49)	68 (59.1)	56 (53.8)	59 (58.4)	36 (38.3)	24 (37.5)
	Over 20 occ	2 (1.6)	26 (19.8)	30 (30.6)	19 (16.5)	11 (10.6)	6 (5.9)	3 (3.2)	6 (9.4)
Heavy user	Never	94 (71.2)	61 (44.2)	28 (26.4)	14 (12.5)	7 (6)	10 (9.6)	3 (3.7)	8 (13.8)
	1-19 occ	18 (13.6)	28 (20.3)	14 (13.2)	14 (12.5)	10 (8.6)	7 (6.7)	14 (17.3)	15 (25.9)
	Over 20 occ	20 (15.2)	49 (35.5)	64 (60.4)	84 (75)	99 (85.3)	87 (83.7)	64 (79)	35 (60.3)

Appendix 46 Univariate latent class growth model for peer substance use

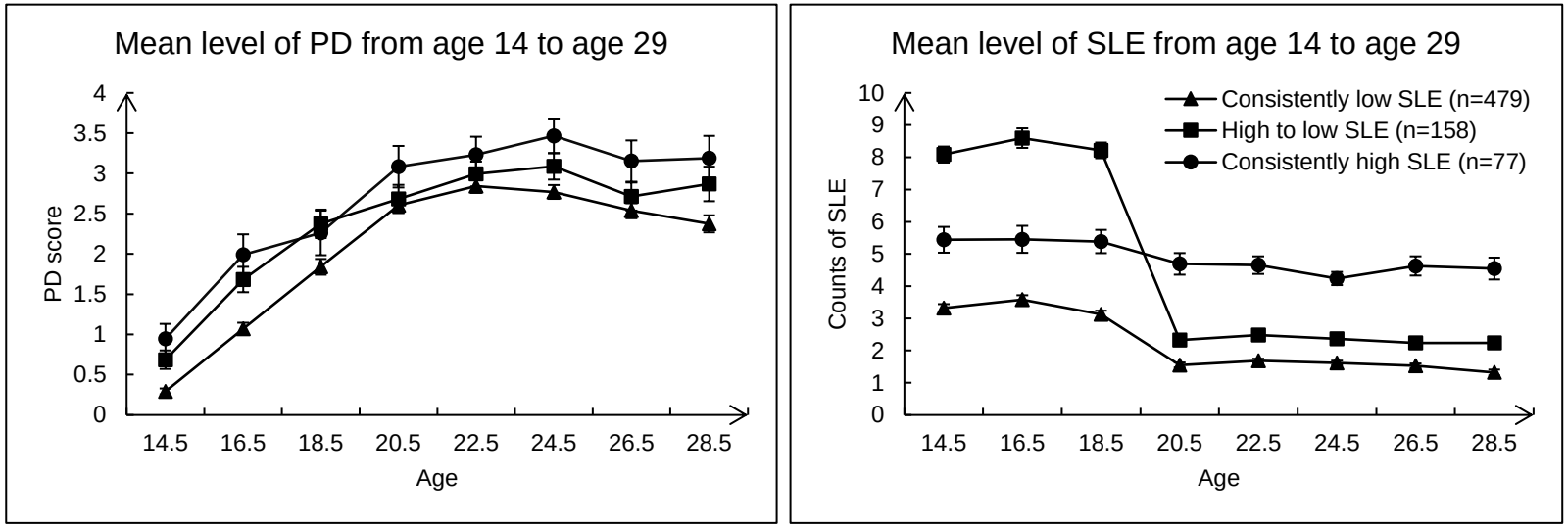


Appendix 47 Trajectory of externalising and internalising problems across problematic drinking-SLE classes (n=714)*



* NA-LS refers to normative alcohol and low stress group; EA-LS refers to escalating alcohol and low stress group; HA-HS refers to high alcohol and high stress group

Appendix 48 Mean level of problematic drinking and stressful life events across classes*



*Classes were derived using latent class growth curve model for stressful life events (SLE)