Investigating the Relationship between Anxiety and Alcohol Use: Observational and Experimental Evidence

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Abstract

The nature of the relationship between anxiety and alcohol use is unclear. Moderating factors, which influence the strength and direction of a relationship, may help to explain inconsistent findings in the literature.

By triangulating evidence from observational and experimental methods, the studies reported in this thesis aimed to investigate the strength of evidence for (a) a positive relationship between anxiety and alcohol use, and (b) a stronger positive relationship between anxiety and alcohol use among individuals with high (versus low) drinking to cope (DTC) motives (i.e., moderation by DTC).

I conducted four studies: a systematic review of 51 cohort studies from 11 countries including a meta-analysis of three studies, a cohort study using cross-sectional and prospective data from the Avon Longitudinal Study of Parents and Children (ALSPAC), an online cross-sectional study, and an experimental study using the 7.5% carbon dioxide model of anxiety induction.

There was some evidence to suggest that anxiety is positively related to more problematic alcohol use, supporting the first hypothesis. However, evidence for a relationship between anxiety and general levels of alcohol consumption and motivation for alcohol was less clear. Contrary to the second hypothesis, the observational data indicated there was no clear evidence that DTC motives moderated associations between anxiety and alcohol use, although there was some experimental evidence that DTC moderated the effect of state anxiety on alcohol choice.

Although these findings are suggestive of a positive relationship between anxiety and problematic alcohol use, this evidence is not sufficient to support strong conclusions regarding causality. Further research using novel methods is needed to examine the complexities of the relationship between anxiety and alcohol use. In addition, identification of reliable moderating factors would help to determine which individuals with anxiety may benefit most from an intervention to reduce the risk of problem drinking.

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I would like to dedicate this thesis to my parents, Cathy and Richard, who have always supported me, and been proud of my achievements.

Author’s Declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

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Chapter 1: Introduction

1.1. Thesis Overview

The relationship between anxiety and alcohol use is complex, and there are competing explanations. First, there is debate about whether anxiety precedes or follows alcohol use (i.e., what the temporal sequence is). Second, it is unclear whether anxiety is a risk or protective factor for alcohol use (i.e., whether the association is causal, and if so in what direction). Anxiety may be associated with higher or lower levels of alcohol use (positive or negative association, respectively). Third, it is possible that shared risk factors increase both anxiety and alcohol use, therefore there may be no direct causal relationship between the two (issue of confounding).

One explanation for the relationship between anxiety and alcohol use is the self-medication hypothesis (Khantzian, 1990), and related tension-reduction (Cappell & Herman, 1972), and stress response dampening (Sher & Levenson, 1982) theories. These negative reinforcement theories suggest that anxiety is associated with higher subsequent alcohol use. It is argued that individuals with anxiety consume more alcohol in order to cope with their symptoms, because they learn that alcohol can have anxiolytic effects.

My thesis is focused on the strength of evidence for a positive relationship between anxiety and alcohol use, in line with the self-medication hypothesis and previous experimental research from the Tobacco and Alcohol Research Group (TARG). Although important, the following areas of research were beyond the scope of this thesis: examination of the reverse causal pathway (i.e., the relationship between alcohol use and subsequent anxiety), possible explanatory mechanisms behind a relationship between anxiety and alcohol use (e.g., biological, psychological, or social mediators), and the relationship between depression and alcohol use.

Using observational and experimental methods, I conducted four studies: a systematic review and meta-analysis, a cohort study, an online cross-sectional study, and an experimental study.

My research questions were:

(a) Is anxiety positively related to alcohol use?

(b) Do drinking to cope (DTC) motives moderate the relationship between anxiety and alcohol use?

My hypotheses were:

(a) Anxiety phenotypes will be positively related to alcohol use phenotypes.

(b) The relationship between anxiety phenotypes and alcohol use phenotypes will be stronger among individuals with high (versus low) DTC motives.

Anxiety and alcohol problems are common and costly (Kessler et al., 2009; NICE, 2011). They can cause huge suffering to individuals and their families, by impacting work, relationships, and health (Whiteford et al., 2015; WHO, 2018). Anxiety and alcohol problems are also costly to society more widely, for example through loss of productivity, and the economic burden on health and social care services (Gustavsson et al., 2011). Determining the nature of the relationship between anxiety and alcohol use is therefore vital. In addition, establishing whether the relationship is influenced by moderating variables is important for understanding whether anxiety is only or differently related to alcohol use among certain individuals. This could help to determine which individuals with anxiety may benefit most or at all from a future intervention. We need to understand what we should change, and where financial and human resources are best placed, in order to improve population health and wellbeing.

1.2. Anxiety

1.2.1. Types and Symptoms

Anxiety is a heterogeneous construct; it refers to a range of psychological and physiological phenomena (Evans et al., 2012). Anxiety includes cognitive, emotional, and behavioural characteristics, for example unreasonable or excessive worry about potential future threats, fear of current threats, and hypervigilance towards perceived threats, respectively (NIH, 2019b).

Anxiety can be broadly categorised into three types: state anxiety, trait anxiety, and anxiety disorders (Eysenck, 1997). State anxiety refers to transient feelings of anxiety elicited by an environmental stressor (Sung et al., 2011). Once the stressor (situation or condition) has passed, the state anxiety should dissipate. Anxious states can be adaptive, facilitating threat detection and processing (Raymond et al., 2017).

Trait anxiety is a more stable personality characteristic which refers to dispositional differences in feelings of anxiety (Sung et al., 2011). Some individuals may have more frequent or intense feelings of anxiety compared to others. People with high levels of trait anxiety experience anxiety across novel and everyday situations (Spielberger et al., 1983). One example of trait anxiety is anxiety sensitivity, the dispositional tendency to catastrophize anxiety symptoms (e.g., blushing, elevated heart rate) and misattribute them to harmful consequences (e.g., social rejection, heart attack) (McNally, 2002). High trait anxiety is a risk factor for anxiety disorders (Chambers et al., 2004).

Anxiety disorders are psychiatric disorders characterised by excessive fear, maladaptive manifestations of anxiety and related behavioural disturbances (DSM-5, 2019; Raymond et al., 2017). There are 11 types of anxiety disorder that feature in the Diagnostic and Statistical Manual of Mental Disorders (5th Edition): generalised anxiety disorder (GAD), social anxiety disorder (previously social phobia), panic disorder, separation anxiety disorder, specific phobia, selective mutism, agoraphobia, substance/medication-induced anxiety disorder, anxiety disorder due to another medical condition, other specified anxiety disorder, and unspecified anxiety disorder (DSM-5, 2019). Key diagnostic criteria for GAD, for example, are excessive anxiety and uncontrollable worry on most days for a period of six months, about several events and activities, and at least three somatic symptoms such as restlessness, muscle tension, and sleep disturbance (Reynolds & Kamphaus, 2013). There is debate about this categorical classification system; others have advocated a dimensional approach (Insel et al., 2010). If state anxiety, trait anxiety, and each anxiety disorder are considered distinct, their associations with alcohol outcomes may be different.

1.2.2. Prevalence

Anxiety disorders are common. Prevalence estimates vary according to country, gender, type of anxiety, and duration over which symptoms are counted (Evans et al., 2012). Lifetime and 12-month worldwide prevalence estimates of anxiety disorders range between 5-25% and 3-20%, respectively (Kessler et al., 2009). One systematic review estimated the global average prevalence of anxiety disorders at 7% (5-11%), when adjusting for methodological differences (Baxter et al., 2013). The authors also reported that prevalence estimates were lowest in African cultures at 5% (4-8%) and highest in Euro/Anglo cultures (typically Western European, North American and Australasian populations) at 10% (7-16%) (Baxter et al., 2013).

According to the most recent Adult Psychiatric Morbidity Survey in 2014, around one in six adults surveyed in England (17%) met the criteria for a common mental disorder (CMD) (McManus et al., 2016). CMDs include GAD, depression, specific phobias, social phobia, obsessive compulsive disorder, panic disorder, and CMD not otherwise specified. Prevalence rates were higher in women (one in five) compared to men (one in eight). These rates have increased in women but have remained stable in men, since 2000 (McManus et al., 2016).

1.2.3. Harms

Because of their high prevalence and chronicity, anxiety disorders are costly to the individual and society more widely. In 2010, the estimated costs of anxiety disorders were €74.4 billion for 30 European Union countries, which related to treatment and lack of earnings (Gustavsson et al., 2011). Anxiety disorders account for 15% of disability adjusted life years (DALYs) and years lived with a disability caused by mental and substance use disorders, second only to depression (Whiteford et al., 2013). Anxiety disorders also account for 1.1% of the global burden of disease worldwide (26.8 million DALYs) (Whiteford et al., 2015).

1.3. Alcohol Use

1.3.1. Types and Symptoms

Alcohol use is also heterogeneous. It can be broadly categorised into three types: level of use, binge drinking, and alcohol use disorders (AUDs). Level of use includes constructs related to frequency and quantity of alcohol use (e.g., units per week). Binge drinking refers to high consumption in a single episode that raises an individual's risk of harm on that occasion (NHS, 2019). In the UK, binge drinking is classed as more than eight units for men and more than six units for women (NHS,

2019). AUD is a chronic, medically diagnosed, severe form of problem drinking (NIH, 2019a). Key diagnostic criteria for AUD include compulsive alcohol consumption, loss of control over drinking, and a negative emotional state when not drinking (NIH, 2019a).

1.3.2. Prevalence

Alcohol is one of the world's most ubiquitous drugs (WHO, 2018). As with anxiety, prevalence estimates vary according to country, gender, age, type of alcohol use, and duration over which symptoms are counted. Globally, one in five adults report heavy episodic drinking (≥7 units) in any month (Peacock et al., 2018). Europe has the highest rates of heavy alcohol consumption (46%), whereas North Africa and the Middle East (15%) have the lowest rates of heavy alcohol consumption (Peacock et al., 2018).

On average, women drink less than men, and have fewer problems with alcohol (Nolen-Hoeksema, 2004). In England, around 24% of people (33% of men and 16% of women) drink hazardous or harmful levels of alcohol, and around 4% of people between ages 16-64 experience alcohol dependence (6% of men and 2% of women) (NICE, 2011). Since 2000, hazardous drinking has declined in males but remains higher than in women, and rates of harmful or dependent drinking have remained stable (McManus et al., 2016). The prevalence of alcohol consumption has declined in the last 10 years in England. Reported alcohol use in the previous week has dropped from 65% in 2007 to 58% in 2017 (NHS digital, 2018). Binge drinking rates have dropped from 20% in 2007 to 15% in 2017, a change seen in 16-24 and 25-44 year olds but not in older age groups (45-64 year olds and the over 65s) (NHS digital, 2018).

1.3.3. Harms

There are health, social, and economic costs associated with problematic alcohol use. Harmful alcohol consumption contributes to over 200 chronic and acute health conditions (WHO, 2018), for example, cancer, cardiovascular diseases, gastrointestinal and liver diseases, psychiatric disorders, and injuries (Rehm et al., 2010). In 2017/18, nearly 1.2 million hospital admissions were related to alcohol in England (Public Health England, 2019). Each year, alcohol consumption is responsible for around 24,000 deaths in England (Public Health England, 2019) and 3 million deaths worldwide (5.3% of deaths) (WHO, 2018). AUDs are associated with social problems such as domestic violence, poorer parenting, neglect, abuse (Adamson & Templeton, 2012; Delargy et al., 2010), relationship breakdown, anti-social behaviour, and homelessness (Prime Minister's Strategy Unit, 2004). Each year, NHS England spends up to £2.7 billion treating alcohol related injuries and conditions, 17 million working days are lost through staff absenteeism caused by alcohol use (Prime Minister's Strategy Unit, 2004) and around 500,000 crimes are linked to alcohol use (NICE, 2010). There is therefore considerable clinical and research interest in identifying risk factors for problematic alcohol use.

1.3.4. Psychopharmacological Effects of Alcohol

Alcohol has different psychopharmacological effects. According to learning theory, these effects can be broadly categorised as positively reinforcing, negatively reinforcing, and punishing effects (Sher & Grekin, 2015). Effects depend on several factors such as quantity, experience, genetics (Sher & Grekin, 2015), and the nature of the situation in which alcohol is consumed (Carrigan & Randall, 2003).

Alcohol has stimulating, euphoric, and arousing effects at lower doses, which are positively reinforcing. Dopamine is implicated in the pleasurable euphoric effects of alcohol, as there are ethanol sensitive neurons in the nucleus accumbens (DiChiara, 1997). Alcohol increases noradrenaline in the locus coeruleus, improving alertness and arousal (Fromme & D'Amico, 1999). Endogenous opioids are also released in the nucleus accumbens and orbitofrontal cortex (Sher & Grekin, 2015), which increases alcohol craving through their analgesic and rewarding effects (Froehlich, 1997).

Alcohol also has negatively reinforcing effects. Alcohol can act as a beta-blocker, reducing physiological arousal and anxiety symptoms (e.g., heart palpitations, shaking) in stressful situations (Sher & Levenson, 1982). Alcohol has anxiolytic and tension reducing effects because it binds to the receptors of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter which leads to sedation and muscle relaxation, and alcohol depresses the prefrontal cortex, reducing self-consciousness and inhibition (Sher & Grekin, 2015). These effects form the basis of the self-medication, tension reduction, and other negative reinforcement theories of the relationship between anxiety and alcohol use, which I will discuss later in this chapter.

Alcohol has biphasic effects; it has stimulating effects at low doses and depressant effects at high doses (Hendler et al., 2013; Holdstock & de Wit, 1998). By impacting on several brain areas such as the frontal lobes, limbic system, cerebellum, and hypothalamus, heavy alcohol use causes cognitive, sensory and motor impairments (Oscar-Berman & Marinkovic, 2007). These aversive punishing effects are normally experienced by heavy drinkers (Sher & Grekin, 2015).

1.3.5. Drinking Motives

Understanding the psychopharmacological effects of alcohol can help to explain why people consume alcohol. Cooper (1994) originally proposed four drinking motives: social, conformity, enhancement, and coping, and the underlying four-factor structure of her questionnaire has been supported by evidence from other studies (Kuntsche et al., 2006; Sun et al., 2015). Cooper also categorised the drinking motives based on valence (type of reinforcement) and source (where the reward originates) (Collins et al., 2018). Social and enhancement motives relate to the positively reinforcing effects of alcohol (to gain social rewards, and to enhance positive affect, respectively), whereas coping and conformity motives relate to the negatively reinforcing effects of alcohol (to reduce anxiety and depression, and to avoid peer rejection and criticism, respectively) (Cooper, 1994). Social and conformity motives are also externally motivated (relate to other people), whereas enhancement and coping motives are internally motivated (relate to the self) (Cooper, 1994). For the purpose of this thesis, I have focused on coping motives for drinking (otherwise referred to as DTC motives). This is because DTC is linked to anxiety (e.g., trait anxiety) (Comeau et al., 2001) and greater alcohol use and alcohol problems (Kuntsche et al., 2005), which I will explain in more detail at the end of this chapter.

1.4. What is the Relationship between Anxiety and Alcohol Use?

1.4.1. Comorbidity

Comorbidity refers to the co-occurrence of two or more disorders in the same individual that exist simultaneously (because another factor causes both), or they are causally related (Kessler, 1995; Ollendick & King, 1994). However, there is debate about this definition. Some researchers argue that anxiety disorders should not be defined as comorbid if they are substance induced or withdrawal related,

and suggest that comorbidity should be tested after a period of abstinence (Gallagher et al., 2017). A related term, dual diagnosis, has also been criticised for not doing justice to the multiple additional health and social problems affecting these individuals (Marshall & Farrell, 2004). Psychiatric disorders are currently classified as either 'substance-independent' or 'substance-induced' because different treatments are required (Marshall & Farrell, 2004).

Research suggests anxiety disorders and AUDs are comorbid. People with comorbid internalising and AUDs experience more severe behavioural problems (Salom et al., 2014), greater levels of impairment, and use services at a higher rate (Prior et al., 2017), compared to people with only one disorder. Comorbidity tends to be higher in clinical studies with treatment-seeking samples than in epidemiological studies with community-based samples. For example, research with clinical samples suggests that 16-25% of patients with anxiety disorders also have comorbid alcohol problems, and 30-44% of patients with AUDs experience anxiety or mixed anxiety/depression symptoms (Kushner et al., 2000a). In the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), 33% of individuals who had sought treatment for AUD had at least one independent anxiety disorder, and 15-22% of individuals who had sought treatment for an independent anxiety disorder had a comorbid substance use disorder, primarily AUD (Grant et al., 2004).

Researchers examining psychiatric comorbidity in general population samples have found lower rates of comorbidity. Among individuals not seeking treatment, the 12-month prevalence of any anxiety disorder among those with alcohol dependence was 23%, and the 12-month prevalence of any AUD among those with any anxiety disorder was 13% (Grant et al., 2004). Another study found the prevalence rates of mixed anxiety disorder, GAD, and panic disorder among

alcohol dependent populations were 10%, 5%, and 3%, respectively (Farrell et al., 2003). This study also highlights variation depending on the type of anxiety disorder.

One explanation for the discrepancy between results with clinical and community samples is that anxiety needs to be severe for it to be associated with alcohol problems (or vice versa) (Sher & Grekin, 2015). Alternatively, there may be limitations associated with treatment-seeking samples such as lack of generalisability to the wider population (Turner et al., 2018), and treatment-seeking biases. Berkson's bias, for example, is a type of selection bias that induces spurious or distorted associations between factors that influence being in a treatment setting (Hall & Farrell, 1997).

The nature of the relationship between anxiety and alcohol use is complex. Although some research suggests anxiety disorders and AUDs are comorbid, other studies have found a negative association (i.e., anxiety is associated with a decreased risk of AUDs), or no clear evidence of an association. Being cross-sectional, comorbidity associations also provide little insight into the nature of the co-occurrence between anxiety disorders and AUDs (i.e., which disorder is primary and secondary, and whether other factors or processes explain the association) (Department of Health, 2003). It has been suggested that the aetiology of any comorbidity is likely multidimensional, due to an interaction between biological (e.g., genetic), psychological, and social factors (e.g., abuse, trauma, poverty, or lack of social capital) (Marshall & Farrell, 2004). There are several plausible mechanisms, and they are not mutually exclusive (Kushner et al., 2000a). Note that I am only testing the temporal direction of anxiety and subsequent alcohol use.

- Anxiety increases alcohol use
- Alcohol use increases anxiety
- Bi-directional relationship between anxiety and alcohol use
- Shared risk factors increase anxiety and alcohol use
- Anxiety decreases alcohol use
- No clear evidence of a relationship between anxiety and alcohol use

1.4.2. Anxiety Increases Alcohol Use

Some researchers suggest that anxiety is a risk factor for greater alcohol use, because alcohol use has been shown to reduce anxiety. Administration of alcohol reduces fear and avoidance behaviours in animals (Masserman & Yum, 1946). Alcohol consumption also reduces startle potentiation during the threat of unpredictable shocks (anxiety) but not predictable shocks (fear) in humans (Moberg & Curtin, 2009), and reduces laboratory-induced panic and state anxiety (Kushner et al., 1996). As mentioned above, this anxiolytic effect of alcohol could explain why alcohol is negatively reinforcing for people with anxiety. According to several theories, these negatively reinforcing effects of alcohol (alleviation of anxiety symptoms, dampening of physiological arousal), could explain the positive associations (comorbidity) between anxiety and alcohol use and the development and maintenance of alcohol problems.

The drive-reduction theory suggests that alcohol reduces emotional-physiological states (drives) associated with avoidance (Conger, 1956). This theory was later called the tension-reduction hypothesis, and it referred to tension and life stress more generally (Cappell & Herman, 1972). The self-medication hypothesis suggests that people consume alcohol to cope with their depression and anxiety (Khantzian, 1990). The stress response dampening hypothesis suggests that

people with anxiety may develop alcohol problems as they learn that alcohol dampens the fight or flight stress response in anxiety-provoking situations (Sher & Levenson, 1982). The affective processing model of negative reinforcement suggests continued alcohol use among individuals with addiction is predominately maintained by reduction of negative affect rather than just reduction of withdrawal symptoms (Baker et al., 2004).

There are also cognitive theories which offer explanations for why anxiety is associated with greater alcohol use. Cognitive theories suggest there may be an indirect effect of anxiety leading to increased alcohol use because alcohol impairs cognitive processes and thus reduces the cognitive symptoms of anxiety. These cognitive processes include increasing distractibility (reducing attention to the stressor) or decreasing the perceived level of threat (Levenson et al., 1980). The self-awareness model suggests alcohol interferes with encoding processes involved with self-awareness, which in turn reduces an individual's sensitivity to information about the self (anxiogenic cues) (Hull, 1981). For example, alcohol decreases self-awareness and thus negative affect following a failure (Hull, 1981). According to the attention-allocation model, alcohol reduces stress and anxiety indirectly, through cognitive and perceptual impairment (Steele & Josephs, 1988).

Alcohol reduces attention to threatening visual and emotional cues, (Curtin et al., 2001) negative bias towards threatening social stimuli (Stevens et al., 2009), and hypervigilance towards potential scrutiny (Abrams et al., 2001), which attenuate anxiety. Abrams and colleagues (2018) have suggested that alcohol may reduce anxiety by impairing interoceptive sensitivity - the conscious awareness of and sensitivity to somatic sensations (Cameron, 2001). There is evidence that people with trait anxiety and anxiety disorders have more accurate perception of autonomic arousal symptoms such as changes in heart rate (Abrams et al., 2018).

There was some evidence that alcohol reduces cardioceptive accuracy in men (Abrams et al., 2018). This reduction of anxiety via cognitive processes is also proposed to lead to greater alcohol use via negative reinforcement.

Anxiety may also directly lead to increased alcohol use and AUDs via biological mechanisms. For example, there is evidence that chronic stress causes neurobiological abnormalities, including for example dysregulation of the hypothalamic-pituitary-adrenal axis, and these changes play a part in the development of alcohol dependence (Dervaux & Laqueille, 2018).

There is some observational evidence from prospective cohort studies that suggests anxiety is associated with later alcohol use. For example, Fröjd and colleagues (2011) found generalised anxiety was associated with a higher incidence of frequent alcohol use. One study found the odds of AUD in adulthood were higher among individuals who had experienced panic attacks in adolescence (Asselmann et al., 2014a). Using the same cohort, another study found specific phobias and social phobia were associated with later alcohol dependence (Behrendt et al., 2011). Some studies have found social anxiety disorder is positively associated with later alcohol dependence (Buckner et al., 2008) and AUD (Torvik et al., 2019). Furthermore, one meta-analysis found social anxiety was positively associated with alcohol-related problems (Schry & White, 2013). There is also experimental evidence to support the theory that anxiety is related to greater alcohol use. Acute stress increases alcohol craving and alcohol self-administration in non-dependent binge drinkers (Ramchandani et al., 2018).

Interventions that reduce anxiety have been shown to reduce alcohol consumption. For example, cognitive behavioural therapy (CBT) for anxiety sensitivity reduced anxiety as well as alcohol related problems, supporting the idea that anxiety is

related to greater alcohol use (Olthuis et al., 2015). A brief CBT program for anxiety for patients with comorbid anxiety and substance use disorders in addition to usual care was superior to usual care alone in reducing anxiety symptoms and alcohol use (Wolitzky-Taylor et al., 2018). The researchers also found that decreases in anxiety sensitivity mediated the effect of treatment group on alcohol use (Wolitzky-Taylor et al., 2018). There is also evidence that anxiety is a risk factor for alcohol relapse among patients with AUD (Oliva et al., 2018).

1.4.3. Alcohol Use Increases Anxiety

The opposite causal pathway is also possible. Although alcohol may reduce anxiety in some circumstances, alcohol use can paradoxically increase anxiety in the short term and over the long term, via biological, psychological, or social mechanisms.

In the short term, alcohol intoxication, alcohol hangover, and alcohol withdrawal can have anxiogenic effects (Kushner et al., 2008; Marshall & Farrell, 2004). Within several hours after the cessation of binge drinking, people can experience a hangover. Symptoms of a hangover include unpleasant physical and mental symptoms which are analogous to anxiety, such as sympathetic hyperactivity (e.g., tremor, sweating, and elevated heart rate and blood pressure), and cognitive and mood disturbances (e.g., worrying about what one did or said while intoxicated) (Swift & Davidson, 1998). Symptoms of anxiety are also experienced during alcohol withdrawal (after multiple binge drinking sessions over several days) (Marshall & Farrell, 2004).

In the longer term, there is observational evidence that chronic alcohol use or AUDs are a risk factor for anxiety disorders (Kushner et al., 1999). Alcohol-induced anxiety disorders are characterised by the onset of anxiety soon after, and

consequent upon, alcohol use, and reduction of anxiety symptoms with alcohol abstinence (Marshall & Farrell, 2004). Anxiety symptoms can decrease after reduction of alcohol use (Charlet & Heinz, 2017) and treatment for alcohol problems (Gallagher et al., 2017), supporting the theory that alcohol use induces anxiety. However, other research has found anxiety does not remit after cessation of drinking (Olgiati et al., 2007).

Chronic alcohol use can cause neurobiological changes in the brain, for example reduction in GABAergic, dopaminergic, and opioid activity, which promotes anxiety and depression (Dervaux & Laqueille, 2018; Fromme & D'Amico, 1999). Interestingly, these changes are opposite to the rewarding psychopharmacological effects of low doses of alcohol, described earlier in this chapter. AUDs could also indirectly lead to anxiety via social and psychological mechanisms, such as job loss, relationship breakdown, health problems, social rejection, and shame (Sher & Grekin, 2015).

There is experimental evidence that administration of alcohol increases state anxiety in humans (Monteiro et al., 1990). There is also support from animal studies. Adolescent alcohol exposure in rats increased the risk of anxiety in adulthood due to abnormal epigenetic programming in the amygdala, a region involved in emotional regulation and anxiety (Kyzar et al., 2019). However experimental research in this area has limited scope. Although researchers can experimentally investigate the short-term effects of acute alcohol consumption on subsequent anxiety, it is ethically and practically infeasible to experimentally investigate the effects of chronic alcohol use over time on subsequent anxiety in humans.

1.4.4. Bi-Directional Relationship between Anxiety and Alcohol Use

The relationship between anxiety and alcohol use could be bi-directional (Crum et al., 2013). As suggested by Foster and colleagues (2018), there could be a vicious cycle in which anxiety and alcohol use exacerbate each other over time (Kushner et al., 2000a). This is supported by some longitudinal evidence. For example, Parrish and colleagues (2016) found alcohol use at age 14 prospectively predicted anxious arousal symptoms, and vice versa. However, the authors reported that these bi-directional effects were not consistent for cognitive symptoms of anxiety. People with anxiety may initially consume alcohol to self-medicate their anxiety symptoms. However, over time, excessive and regular problematic drinking may aggravate their anxiety or induce new internalising symptoms, via intoxication and withdrawal of alcohol (Dervaux & Laqueille, 2018).

1.4.5. Shared Risk Factors Increase Anxiety and Alcohol Use

Alternatively, comorbid anxiety disorders and AUDs may have shared common causes. The common-factor model suggests that third variables (genetic or environmental factors) account for the comorbidity between these disorders (Smith & Randall, 2012).

Biological factors may increase the risk of both anxiety and alcohol problems. For example, the amygdala, a brain region involved in assigning emotional salience to internal and external stimuli, is thought to be involved in the aetiology of anxiety disorders and AUDs (Agoglia & Herman, 2018). A genome wide association study found that variation in the SEMA3A gene was associated with comorbid alcohol dependence and depression (a related internalising disorder), in African American participants (Zhou et al., 2017). There is evidence from twin studies for a shared genetic contribution to problem drinking and neuroticism (de Moor et al., 2011), a personality dimension which is a risk factor for anxiety symptoms and disorders

(Clark et al., 1994). Another twin study suggested social anxiety disorder and alcohol dependence have some shared genetic risk factors (Nelson et al., 2000), although a more recent twin study found shared genetic risk factors explained the associations between anxiety disorders and AUD, but not social anxiety disorder (Torvik et al., 2019).

There may also been shared environmental or psychological vulnerabilities. One systematic review found that factors associated with social anxiety and alcohol use included female gender, peer approval, confrontation situations and/or compliance reasons, and secondary comorbidities, such as depression and generalised anxiety (da Cruz et al., 2017). Jones and colleagues (2018) found that family tobacco use and behavioural disinhibition predicted comorbid substance use and internalising problems in adolescence, and family history of depression predicted adult comorbidity. Chow and colleagues (2018) found AUD and social anxiety symptoms were associated with co-occurring interpretation (meaning of ambiguous situations) and expectancy (predictions of events) biases. However, as this study was cross-sectional, the cognitive biases may be a consequence rather than a cause of comorbidity.

Some researchers have suggested that the influence of shared risk factors may depend on developmental period. For example, environmental effects may be salient in adolescence, and genetic effects may be more important in adulthood (Pagan et al., 2006). Environmental effects may influence general level of consumption, whereas genetic effects may play a more important role in the development of alcohol problems. For example, using twins, Pagan and colleagues (2006) found that shared environmental factors contributed to initiation and frequency of alcohol use, whereas there was no clear evidence that shared

environmental factors influenced alcohol problems in early adulthood. Instead, genetic factors played a role in alcohol problems.

1.4.6. Anxiety Decreases Alcohol Use

Other studies have found negative associations between anxiety and alcohol use, (i.e., higher anxiety associated with lower alcohol use), which do not support the comorbidity statistics outlined earlier. For example, one study found social phobia was associated with a lower incidence of frequent drinking and frequent drunkenness (Fröjd et al., 2011) and lower alcohol use among college students (Schry & White, 2013). Childhood internalising symptoms were negatively associated with early adolescent alcohol use (Edwards et al., 2014), and early adolescent internalising symptoms were associated with less frequent alcohol use two years later (Strandheim et al., 2011). One study with male juvenile offenders found that symptoms of worry were negatively associated with quantity of alcohol use, frequency of binge drinking and alcohol dependence (Nichter & Chassin, 2015). In addition, another study found that adolescent anxiety was protective against alcohol dependence in early adulthood (Pardini et al., 2007).

Researchers have suggested that anxiety may be protective due to social withdrawal and avoidance (Pardini et al., 2007). Adolescents with severe anxiety may not be exposed to social drinking contexts, as they may avoid social events where alcohol is available, or avoid joining peer groups that support drinking (Fite et al., 2006). However, this explanation does not account for drinking alone. People who experience anxiety may also be concerned about the potential negative consequences of drinking alcohol such as cognitive or behavioural impairment, which is suggested to decrease the risk of alcohol use (Eggleston et al., 2004; Schry & White, 2013). People with social anxiety may avoid alcohol due to fear of

being out of control and disinhibited, which may cause embarrassment (Keough et al., 2016).

1.4.7. No Clear Evidence of a Relationship between Anxiety and Alcohol Use

Some studies have found no clear evidence of an association between anxiety and later alcohol use. For example, Abram and colleagues (2015) found GAD in adolescence did not increase the odds of AUD five years later. One study found panic attacks, generalised anxiety, and social phobia did not predict later alcohol dependence (Zimmermann et al., 2003). Another study found no clear evidence of an association between adolescent anxiety sensitivity and alcohol use 20 months later (Malmberg et al., 2012). Finally, a recent meta-analysis using data from the NESARC and the National Comorbidity Survey found no clear evidence of a prospective association between social anxiety disorder and incident AUD (Miloyan & Van Doorn, 2019).

Chao and colleagues (2017) used Mendelian randomisation, a genetic epidemiological method, to examine the causal role of alcohol use on anxiety in Chinese adolescents. They used the aldehyde dehydrogenase 2 (ALDH2) rs671 single nucleotide polymorphism as an instrumental variable for alcohol use phenotypes because of its strong association with alcohol consumption (Luczak et al., 2006). They found no clear evidence of an association between the ALDH2 gene and anxiety, suggesting alcohol use does not cause anxiety. To the best of my knowledge, no study has used Mendelian randomisation to investigate the reverse causal pathway – the effect of anxiety on alcohol use, using genetic variants associated with anxiety as an instrumental variable.

1.5. Why is the Relationship between Anxiety and Alcohol Use Unclear?

As I have demonstrated, extensive research on the relationship between anxiety and alcohol use has produced inconsistent findings. There are several possible reasons why there are mixed findings even when narrowing the question to one temporal direction: heterogeneity of anxiety and alcohol use, sample differences (e.g., gender, ethnicity, age/developmental period), study quality and biases (e.g., representativeness of cohort, confounding, reverse causation, misclassification of exposure and outcome measures, statistical power), and moderating factors (other biological, psychological, or social influences).

1.5.1. Heterogeneity of Anxiety

Elucidating the relationship between anxiety and alcohol use has been complicated by the heterogeneous nature of anxiety. Anxiety is a multi-dimensional construct and is operationalised differently across studies. Associations may vary according to type of anxiety (e.g., state anxiety, trait anxiety, anxiety disorders), type of symptoms (e.g., cognitive, emotional, physiological, behavioural), type of fears (e.g., social interaction, performance) and severity of impairment.

Certain anxiety disorders may be a risk factor for alcohol use and disorders, whereas others may be a protective factor. For example, Fröjd and colleagues (2011) found that general anxiety was associated with a higher incidence of frequent alcohol use; however, social phobia was associated with a lower incidence. One study found higher odds of AUD among people who experienced panic attacks (Asselmann et al., 2014b), whereas another study found a lower risk of alcohol dependence among individuals who were anxious and withdrawn (Pardini et al., 2007).

There is some evidence to suggest physiological anxiety symptoms are a risk factor for alcohol use, whereas cognitive symptoms are a protective factor. For example, Nichter and Chassin (2015) found physiological anxiety increased the risk of binge drinking and alcohol dependence, whereas worry was associated with a decreased risk, in a sample of male juvenile offenders. This is supported by another study which found reciprocal effects of anxious arousal and alcohol use, but not cognitive aspects of anxiety (Parrish et al., 2016). Other studies suggest associations vary according to anxiety symptoms. For example, Chassin and colleagues (2004) found the heavy drinking group showed more negative emotionality but lower inhibition/constraint, whereas the moderate drinking group showed less negative emotionality but higher inhibition/constraint.

Some researchers have suggested that because different fears could contribute to the diagnosis of an anxiety disorder, associations with drinking behaviours may vary depending on the nature of the fear (Miloyan & Van Doorn, 2019). For example, fear of missing out is also associated with greater intentions for heavy drinking over and above clinical anxiety and test anxiety (Scalzo & Martinez, 2017). There is some evidence that individuals with social anxiety report greater alcohol use to cope with social interaction fears compared to social performance fears (Thomas et al., 2003), and are more likely to avoid social situations if alcohol is unavailable (Buckner & Heimberg, 2010). Students with interaction but not performance fears also reported more alcohol-related negative consequences (Villarosa-Hurlocker et al., 2018). This may be due to different alcohol expectancies in different contexts - positive or enhancing in social situations, versus negative or impairing in performance situations. However, students with more interaction social anxiety who additionally reported more fear of negative evaluation had fewer alcohol-related negative consequences, through their use of

harm-reducing protective behavioural strategies to manage people's impressions of them (Villarosa-Hurlocker et al., 2018). This highlights the nuances of anxiety.

1.5.2. Heterogeneity of Alcohol Use

There is also considerable heterogeneity in how alcohol use is defined and assessed across studies. Alcohol use is a broad term that covers a wide range of behaviours for example, frequency of drinking, quantity of alcohol use, binge drinking, and problem drinking or AUDs. Therefore, anxiety may be differentially associated with different alcohol phenotypes.

There is evidence that comorbidity statistics vary according to type of alcohol disorder. Anxiety is more consistently related to dependence than abuse. For example, Kessler and colleagues (1996) found the one-year rate of anxiety disorders in those with alcohol abuse was 29.1% (OR 1.7, $p < .05$), whereas for alcohol dependence it was 36.9% (OR 2.6, $p < .05$; confidence intervals [CI] not reported). This is supported by more recent studies which have found alcohol dependence is higher in people with pure anxiety disorder (no depression; OR 2.4, 95% CI 1.52 to 3.83), whereas there was no association for alcohol abuse (Boschloo et al., 2011). In another study, having an anxiety disorder was positively associated with later alcohol dependence but there was no clear evidence of an association with alcohol abuse (Behrendt et al., 2011).

Some research suggests anxiety may be more strongly related to alcohol problems than level of use. For example in one meta-analysis, social anxiety was a risk factor for alcohol related problems, but it was negatively associated with alcohol consumption (Schry & White, 2013). Other studies have found no clear evidence of an association between social anxiety and quantity and frequency of drinking but it was positively associated with alcohol related problems (Buckner et al., 2006).

1.5.3. Sample Differences

One study indicated that the relationship between anxiety and alcohol use may differ by gender and ethnicity. Higher separation anxiety was protective against alcohol use among Caucasian girls, although there was no clear evidence of an association between anxiety disorders and alcohol use for African American or Hispanic girls (Ohannessian, 2014). Higher social anxiety predicted less alcohol use among Caucasian and African American boys, but higher generalised anxiety and panic disorder symptoms predicted more frequent alcohol use in African American boys only. Another study found anxiety in childhood was positively associated with problem drinking in adulthood among females, but it was negatively associated among males (Pulkkinen & Pitkanen, 1994). Other studies have found no gender differences. For example, Abram and colleagues (2015) found no clear evidence of an association between generalised anxiety in adolescence and later AUD in both males and females.

Some researchers have hypothesised that internalising symptoms may become more positively associated with alcohol use and problems with increasing age (Colder et al., 2017a). For example, one study found adolescent anxiety, but not childhood anxiety, was positively associated with AUDs in adulthood (Essau et al., 2014). This is supported by other studies which found adolescent anxiety symptoms were a risk factor for later alcohol problems (Goodwin et al., 2004; McKenzie et al., 2011). On the contrary, childhood internalising symptoms were negatively associated with early adolescent alcohol use in one study (Edwards et al., 2014), and did not appear to be associated with alcohol use in adulthood (Englund et al., 2008). Adolescence is a developmental risk period for the initiation of alcohol use (Johnston et al., 2018) and alcohol problems (Kushner et al., 2000a). Colder and colleagues (2013) suggest that anxiety symptoms may protect children

from the initiation of alcohol use (due to social withdrawal), but then act as a risk factor in adolescence (due to increased access to alcohol, drinking norms, modelling of peer behaviour, and subsequent coping functions).

Some researchers have suggested the self-medication hypothesis may be more relevant in adulthood (Hussong et al., 2011; Virtanen et al., 2015). By adulthood, people with anxiety may have learned to use alcohol as a coping strategy or they may be more likely to have the insight that they are using alcohol for coping reasons compared to adolescents. This may explain the fewer positive associations between anxiety and alcohol use observed in young samples. However, another study found social anxiety became more protective at older ages (Colder et al., 2017b). The likelihood of alcohol use leading to anxiety may also depend on age. For example, there is some evidence that earlier initiation of substance use is more likely to lead to mental disorders (Jordan & Andersen, 2017).

1.5.4. Study Quality and Biases

Differences in study quality and biases could explain inconsistent findings (Wells et al., 2019). First, an unrepresentative sample may lead to distorted results. As mentioned above, comorbidity statistics tend to be higher among treatment-seeking samples compared to general population samples (Grant et al., 2004; Kushner et al., 2000a). Second, studies which fail to adjust for confounders could have biased conclusions. Third, certain study designs are weaker, such as cross-sectional studies, as they cannot rule out the possibility of reverse causality. Prospective cohort studies, which measure anxiety at time one, an alcohol outcome at time two, and demonstrate that the alcohol outcome was not present at time one, are more likely to give valid results (Wells et al., 2019). Fourth, if participant attrition from longitudinal studies is systematic, this may lead to selection biases and thus erroneous conclusions (Wolke et al., 2009). Fifth,

misclassification, when individuals are incorrectly assigned to a category, can lead to an increase or decrease in an observed association (Spencer et al., 2018). It is therefore important that researchers use accurate measures of anxiety and alcohol use, and ensure individuals are correctly categorised (Spencer et al., 2018). Finally, it is essential that studies are adequately powered to accurately detect a true association or effect (Button et al., 2013).

1.5.5. Moderating Factors

The mixed findings could be explained by moderating variables influencing the strength and direction of associations between anxiety and alcohol use. Moderators are third variables for which the exposure has a different association with the outcome at different values of the moderating variable (MacKinnon, 2011). These differ from mediators - third variables that describe the process by which the exposure is associated with the outcome, and confounders - third variables that cause the exposure and outcome that lead to distorted associations between the exposure and outcome if not adjusted for (MacKinnon, 2011).

Anxiety could act as a risk factor or a protective factor depending on other internal (e.g., demographic, personality, genetic), or external (e.g., environmental, contextual) factors. For example, Colder and colleagues (2017b) found externalising symptoms and age moderated associations between internalising symptoms and alcohol involvement. Internalising symptoms were protective against alcohol use and problems at high levels of externalising symptoms, and internalising symptoms increased the risk of drinking at low levels of externalising symptoms. They also found that drinking was highest among youths with high levels of externalising symptoms and low levels of internalising symptoms, particularly at younger ages (Colder et al., 2017b). Another study investigated the role of underlying physiological and personality traits on the effects of social

stress/anxiety on alcohol craving and alcohol consumption. Clay and Parker (2018) found that risky decision making and physiological stress-reactivity following social stress/anxiety were the strongest predictors of alcohol consumption.

The possible moderating variable that I focus on in my thesis is DTC. In the original scale, DTC items related to the tendency to drink alcohol to relax, forget worries, cheer up, cope with depression or nervousness, or to feel more self-confident (Cooper et al., 1992). Subsequent research has suggested that a five-factor model which separates coping with anxiety motives and coping with depression motives, has better utility (Grant et al., 2007). DTC with anxiety and DTC with depression may have distinct antecedents and consequences. For example, one study found DTC with anxiety directly predicted alcohol problems, whereas DTC with depression was indirectly associated with alcohol problems, mediated via alcohol consumption (Grant et al., 2007).

1.6. Drinking to Cope

1.6.1. What is the Relationship between Anxiety and Drinking to Cope?

Several studies have shown that DTC is higher among individuals with anxiety. For example, Stapinski and colleagues (2016) found a strong association between internalising disorders and a high-risk profile of coping-motivated drinking. Adolescents with anxiety or depression were six times more likely to drink to cope with negative emotions (Stapinski et al., 2016). Other studies have found state and trait anxiety were associated with DTC in low-, moderate-, and high-risk drinkers (Fitzgerald & Long, 2012), and high trait anxiety predicted DTC motives (Comeau et al., 2001). Some studies have narrowed associations to specific symptoms of anxiety. For example, fear of negative evaluation and social avoidance were positively related to DTC (Stewart et al., 2006), and social interaction anxiety was

positively associated with DTC (Lyvers et al., 2018). In addition to anxiety, personality traits such as neuroticism have been associated with greater DTC (Stewart & Devine, 2000). Furthermore, Colder and colleagues (2019) recently found that both between-person differences and within-person fluctuations in social anxiety symptoms were positively associated with DTC.

The relationship between anxiety and DTC may depend on the type of anxiety-provoking situation. For example, there is evidence that students with social anxiety disorder report more DTC in social interaction situations compared to performance situations (Buckner & Heimberg, 2010; Thomas et al., 2003), which highlights the importance of context. Genetic influences may also predispose adolescents (Mackie et al., 2011b) and adults (Agrawal et al., 2008; Prescott et al., 2004) to drink to cope with anxiety and negative affect. There is also some evidence that treating anxiety sensitivity reduces DTC motives and alcohol related problems (Olthuis et al., 2015), supporting the theory that anxiety is positively related to DTC and alcohol use.

1.6.2. What is the Relationship between DTC and Alcohol Use?

Several studies have shown that DTC motives are associated with later alcohol problems (Armeli et al., 2018; Cooper et al., 1995; Kuntsche et al., 2005). They are also a risk factor for alcohol dependence (Crum et al., 2013). DTC is more strongly associated with alcohol-related problems compared to other drinking motives, even when adjusting for the other drinking motives (Cooper et al., 2016). DTC motives are also implicated in the maintenance of alcohol problems and disorders (Cooper et al., 2016).

There is evidence that associations depend on the alcohol outcome. DTC motives are typically more strongly associated with problem drinking than level of use

(Kuntsche et al., 2005). One study found coping motives predicted negative alcohol consequences (i.e., impaired control, diminished self-perception, poor self-care, risky behaviours, academic/occupational, and physiological dependence), and these associations were not mediated by alcohol consumption (Merrill et al., 2014). DTC motives and enhancement motives are individual strategies whereas social and conformity motives relate to drinking confined to social situations (Cooper, 1994). As solitary drinking increases the risk for alcohol related problems (Keough et al., 2016), this may explain why DTC is a greater risk for problem drinking.

1.6.3. DTC as a Moderator of the Relationship between Anxiety and Alcohol Use

There is some evidence that DTC motives moderate prospective associations between anxiety and alcohol problems in adult samples. For example, Menary and colleagues (2011) found that people with an anxiety disorder who self-medicated with alcohol (used alcohol to manage their anxiety disorder symptoms) were more likely to have an additional AUD three years later compared to individuals with an anxiety disorder who did not self-medicate. There is also cross-sectional evidence for an interaction between anxiety and DTC motives in an adolescent sample. Higher anxiety symptoms were associated with greater alcohol problems among individuals with high DTC motives but not those with low DTC motives (Goldstein et al., 2012), although this study was conducted with a high-risk sample (adolescents involved with child welfare). Furthermore, moderate fear and shyness predicted drinking among individuals high in DTC but not those low in DTC (Hussong et al., 2005). To the best of my knowledge, no study has investigated DTC as a moderator of prospective associations between anxiety and later alcohol use in an adolescent sample.

1.7. Thesis Focus

1.7.1. Methods

I have used observational (non-experimental) and experimental methods to investigate whether anxiety is associated with alcohol use. By triangulating results from observational and experimental studies that rely on different assumptions, and have different and unrelated sources of potential bias (discussed below) (Lawlor et al., 2016), I aimed to improve the strength of evidence for my research questions. When results of two or more approaches are qualitatively similar (i.e., same direction of effect or association), this improves the reliability of the evidence, because the likelihood of bias is small (Lawlor et al., 2016).

In observational studies, researchers measure anxiety (exposure) and alcohol use (outcome), without experimental manipulation or intervention. There are different types of observational epidemiological studies for instance, ecological, cross sectional, case control, and cohort studies (Mann, 2003). Observational studies are useful when it is not ethically or practically possible to manipulate the exposure variable (e.g., an anxiety disorder) in a randomised control trial or experiment (Mann, 2003). Prospective cohort studies are superior to cross-sectional studies as one can better determine the temporal sequence of associations, given that the exposure and outcome variables are measured at different time points. However, unlike cross-sectional studies, longitudinal studies can suffer from attrition, which can lead to bias (Mann, 2003). The common weakness of all observational epidemiological studies is the inability to establish cause and effect relationships, because of the absence of randomisation to conditions. Confounding, residual confounding, and reverse causation, could instead explain the observed associations.

In experimental studies, researchers manipulate anxiety (independent variable) by creating high and low anxiety conditions, and then they measure alcohol use (dependent variable). The main advantage of experimental research over observational, is the ability to determine a cause and effect relationship between anxiety and alcohol use, by systematically manipulating and isolating the independent variables (Lumen, 2019). Experiments also eliminate confounding, as each experimental condition is randomly assigned, so confounding variables should be equally present in both groups (Mann, 2003). Limitations of experimental studies include the potential lack of external validity (generalisation of findings to other people and settings) because of the artificiality of a laboratory environment or tasks, or a less representative sample.

1.7.2. Purpose and Original Contribution

This thesis comprises four studies: a systematic review and meta-analysis of published cohort studies (Study 1; Chapter 2), a cohort study using secondary data from an established longitudinal study (Study 2; Chapter 3), an online cross-sectional study (Study 3; Chapter 4), and an experimental study (Study 4; Chapter 5). I have used different methods in order to triangulate findings and improve the reliability of the evidence. My thesis objectives were to investigate whether: (a) anxiety is positively related to alcohol use (Studies 1-4), and (b) DTC motives moderate the relationship between anxiety and alcohol use (Studies 2-4), which may explain some of the inconsistent findings in the literature.

Study 1 covers several anxiety disorders. It is novel because it is largest systematic review of longitudinal studies investigating prospective associations between a range of anxiety exposures and a range of subsequent alcohol use outcomes. Study 2 focuses on one anxiety disorder - GAD. It is more reliable than some comparable cohort studies in the field because of its large sample size, prospective

associations, adjustment of several confounders, and sensitivity analyses examining the robustness of the results. Study 3 builds on previous observational studies that have predominantly used measures of trait anxiety and anxiety disorders, by instead focusing on state anxiety. Study 4 used the 7.5% carbon dioxide (CO_2) model to investigate the effects of experimentally-manipulated state anxiety on several alcohol use outcomes, which builds on previous anxiety-induction experiments that have used other physical, psychological, and pharmacological methods to induce anxiety. The CO_2 model is also considered to be an experimental model of GAD (Bailey et al., 2011a), which connects Study 4 to Study 2. Finally, Studies 2-4 are original as I have considered the influence of a theoretically relevant moderator, DTC, on the relationship between anxiety phenotypes and alcohol use phenotypes.

In Chapters 2-5, I will outline and evaluate each study (introduction, aims, methods, results, discussion, and conclusions). In Chapter 6, I will summarise the main findings from each study in relation to my thesis questions, discuss similarities and differences between my study findings and the previous literature, evaluate their originality and strengths and weakness, and finally I will suggest possible directions for future research. See Table 1.1 for a summary of my research questions and variables of interest in each of my four thesis studies.

Table 1.1. Summary of thesis studies.

Chapter	Main Research Questions	Exposure Variables	Outcome Variables	Moderator Variables
Chapter 2: Systematic Review and Meta-Analysis	(a) Is child and adolescent anxiety positively associated with later alcohol use outcomes?	Generalised Anxiety Disorder Internalising Disorders Miscellaneous Anxiety Obsessive Compulsive Disorder Panic Disorder Separation Anxiety Disorder Social Anxiety Disorder Specific Phobias	Drinking Frequency/Quantity Binge Drinking Alcohol Use Disorders	None
Chapter 3: Cohort Study	(a) Is adolescent generalised anxiety disorder positively associated with alcohol use outcomes in late adolescence and early adulthood? (b) Do drinking to cope motives moderate these associations?	Generalised Anxiety Disorder	Frequent Drinking Frequent Bingeing Hazardous Drinking Harmful Drinking	Drinking to Cope
Chapter 4: Online Cross-Sectional Study	(a) Is naturally-occurring state anxiety positively associated with alcohol use outcomes (b) Do drinking to cope motives moderate these associations?	State Anxiety Trait Anxiety Drinking to Cope	Alcohol Choice Alcohol Craving Frequent Drinking Frequent Bingeing Hazardous Drinking Harmful Drinking	Drinking to Cope State Anxiety Trait Anxiety
Chapter 5: Experimental Study	(a) Does experimentally-induced state anxiety affect alcohol use outcomes? (b) Do drinking to cope motives moderate these effects?	State Anxiety	Alcohol Choice Alcohol Craving Alcohol Approach Tendencies Frequent Drinking Frequent Bingeing Hazardous Drinking Harmful Drinking	Drinking to Cope

Chapter 2: Systematic Review and Meta-Analysis

2.1. Overview

In Chapter 1, I introduced the complexities of the relationship between anxiety and alcohol use. There are several plausible causal pathways which are not mutually exclusive. Even when narrowing the focus to one temporal direction, anxiety and subsequent alcohol use, evidence remains inconsistent. Some studies have found a positive association (i.e., higher anxiety associated with higher alcohol use), whereas other studies have found a negative association (i.e., higher anxiety associated with lower alcohol use), or no clear evidence of an association. In this chapter, I will discuss my systematic review and meta-analysis which examined whether child and adolescent anxiety is positively or negatively associated with later alcohol use and alcohol use disorders (AUDs). By synthesising the published literature, I hoped to provide clearer findings.

This was a logical first PhD study, giving me a solid grounding of the observational epidemiology literature. I focused on childhood and adolescence as they are key developmental periods when anxiety disorders tend to emerge (Anxiety UK, 2018; The Department of Health, 2003). If childhood and adolescence are identified as developmental risk periods for later alcohol use and AUDs, this would help to identify prevention targets.

The chapter is based on the published paper: ‘Associations of child and adolescent anxiety with later alcohol use and disorders: a systematic review and meta-analysis of prospective cohort studies’ (Dyer et al., 2019a). I designed the study in collaboration with two of my supervisors (Marcus Munafò and Matthew Hickman). I identified the published studies and extracted the data, with quality control checks performed by a co-author (Kayleigh Easey). I classified and synthesised the data,

performed the meta-analysis, and wrote the manuscript, with advice and input from all authors.

The aims were to:

- Systematically review published prospective cohort studies that investigated associations between child and adolescent anxiety and later alcohol use outcomes.
- Synthesise the results of studies that are sufficiently similar in a meta-analysis.
- Explore whether study characteristics, such as type of anxiety disorder, explain any inconsistences in findings.

2.2. Introduction

2.2.1. Background

There is considerable clinical and research interest in determining the nature of associations between anxiety and alcohol disorders, including their strength and direction, given the substantial health, social and economic costs associated with both conditions (Bouchery et al., 2013; Hoffman et al., 2008; Public Health England, 2016). However, despite a wealth of observational evidence, the relationship between anxiety and alcohol use remains unclear.

Different theories exist regarding the temporal sequence and directionality of the relationship, and evidence is inconsistent (Kushner et al., 2000a). First, the self-medication hypothesis suggests anxious individuals consume alcohol to alleviate their physiological and emotional reactivity (Khantzian, 1990; Sher & Levenson, 1982). Second, anxiety may be protective due to social withdrawal, fear of negative

consequences associated with drinking (Pardini et al., 2007), and concerns about cognitive or behavioural impairment (Eggleston et al., 2004; Schry & White, 2013). Third, chronic alcohol use may cause anxiety, via biological or psycho-social mechanisms (George et al., 1990). Finally, there may be no causal relationship between anxiety and alcohol use; any associations found may be a product of confounding.

There are several possible explanations as to why the literature is conflicting. First, anxiety is heterogeneous; different anxiety disorders or symptoms may be associated with unique patterns of drinking. For example, Fröjd and colleagues (2011) found that general anxiety was associated with a higher incidence of frequent alcohol use; however, social phobia was associated with a lower incidence. Furthermore, Nichter and Chassin (2015) found adolescent physiological anxiety increased the risk of binge drinking and alcohol dependence, whereas worry was associated with a decreased risk. Second, variability in alcohol-related phenotypes may explain inconsistent findings. For example, adolescent social anxiety disorder and panic disorder predicted alcohol dependence in early adulthood but not alcohol abuse (Buckner et al., 2008). It is therefore important to consider how authors operationalise both anxiety and alcohol use. Third, the relationship may be age dependent. For instance, there is some evidence that childhood internalising symptoms are negatively associated with adolescent alcohol use (Edwards et al., 2014), whereas adolescent anxiety is positively associated with alcohol use in young adulthood (Goodwin et al., 2004). Some researchers have suggested that the self-medication pathway may only develop in late adolescence/early adulthood (Hussong et al., 2011) which may explain these differences. Fourth, authors may not have adequately adjusted for confounders, or other sources of bias may have caused spurious findings. Finally, other variables could influence the strength and direction of the anxiety-alcohol relationship;

anxiety may act as a risk or protective factor if there are moderating influences (Gorka et al., 2014).

Although there have been numerous critical reviews on the relationship between anxiety disorders and alcohol use (Allan, 1995; Carrigan & Randall, 2003; DeMartini & Carey, 2011; Jane-Llopis & Matytsina, 2006; Kushner et al., 2000a; Morris et al., 2005; Schuckit & Hesselbrock, 1994), only a few systematic reviews and meta-analyses have been conducted. In one meta-analysis, social anxiety among college students was negatively associated with alcohol use but positively associated with alcohol-related problems (Schry & White, 2013). This reinforces the importance of examining the relationship separately for different alcohol use phenotypes, although direction of effect could not be inferred as this was a review of cross-sectional studies. Another systematic review distinguished between anxiety phenotypes. Lemyre and colleagues (2019) found a tendency towards negative associations between social anxiety and alcohol use in adolescence, but associations between social anxiety *disorder* and alcohol use were inconclusive (direction unclear). This suggests findings may depend on anxiety symptom severity. A recent meta-analysis found early internalising symptoms increased the risk of AUD in young adulthood (Meque et al., 2019). However, in a subgroup analysis of four papers that distinguished anxiety symptoms (i.e., not depression or mixed anxiety-depression), the authors found no clear evidence of an association between anxiety and AUD (Meque et al., 2019).

In a systematic review of longitudinal studies which adjusted for co-occurring externalising symptoms, Hussong and colleagues (2017) also found no clear evidence of an association between anxiety and internalising symptoms with subsequent adolescent alcohol use. A limitation of this review was that authors counted individual (non-independent) tests of association despite many studies

contributing more than one test, which may have biased the results. Groenman and colleagues (2017) found childhood anxiety disorders did not increase the risk for later alcohol related disorders. However, the authors acknowledged findings from individual studies were highly heterogeneous, and only five studies examining the relationship between anxiety and alcohol use were included. Finally, another recent meta-analysis found no clear evidence of a longitudinal relationship between anxiety sensitivity and frequency of alcohol consumption, frequency of binge drinking, quantity of alcohol consumption, or alcohol-related problems, while adjusting for baseline alcohol outcomes (Bartel et al., 2018).

It is important to consider whether studies account for confounders, including other psychiatric problems (e.g., externalising disorders), and other factors such as gender, as these may be a source of bias. For example, externalising disorders and being female are positively associated with anxiety (Angold et al., 1999; McLean et al., 2011), and externalising disorders and being male are positively associated with alcohol use (Farmer et al., 2016; Nolen-Hoeksema, 2004). Therefore, if externalising disorders and gender are not adjusted for, this may result in spurious associations between anxiety and alcohol use.

2.2.2. Aims and Hypotheses

In the current systematic review, I synthesised evidence from cohort studies investigating prospective associations between child and adolescent anxiety with later alcohol use outcomes. I examined whether (a) anxiety is positively or negatively associated with later alcohol use, and (b) study characteristics explain any inconsistences in findings (i.e., type and developmental period of anxiety, type of alcohol use, length of follow-up, sample size, and confounders adjusted for). I hypothesised that most of the evidence would be in a positive direction (i.e., higher anxiety associated with greater alcohol use). I also performed a meta-analysis on

a small subgroup of comparable studies. By detecting patterns across multiple study characteristics, I aimed to identify which individuals may be more at risk of greater alcohol use, binge drinking, and AUDs. Currently, the discrepant evidence prevents the development of tailored prevention and intervention programs.

I carefully considered how broad or narrow the scope of the review should be, as there are advantages and disadvantages to both approaches, and decisions depend on how extensive the literature is. Compared to narrow reviews, broad reviews provide a comprehensive summary of the evidence, improving the generalisability of findings (The Cochrane Collaboration, 2011). However, they increase the likelihood of heterogeneity, and analysis and interpretation may be difficult (The Cochrane Collaboration, 2011).

Initial scoping exercises to test the effectiveness of my search strategy indicated that the literature on this topic was vast. I decided to keep the review broad and comprehensive in some ways by encompassing a range of anxiety exposure variables, a range of alcohol outcome variables, and including anxiety across two developmental periods (childhood and adolescence). As there was great variation in how studies operationalised anxiety and alcohol use, being inclusive allowed me to explore differences in associations based on the type and developmental period of anxiety and the type of alcohol use. For example, anxiety may be a protective factor for level of alcohol consumption (e.g., frequency and quantity of use), whereas it may be a risk factor for alcohol problems (e.g., AUDs).

I restricted the review in some ways too. For example, I included prospective studies but excluded cross-sectional studies to improve inferences about the chronology of anxiety and alcohol use. I also focused on one temporal direction – associations between anxiety and later alcohol use. Associations between alcohol

use and subsequent anxiety were not examined for several theoretical and practical reasons. First, I was primarily interested in whether anxiety disorders were a risk factor for later alcohol use and disorders, in line with the self-medication hypothesis and other negative reinforcement theories of alcohol use. Second, this temporal direction was selected to match the experimental approach described in Chapter 5, in which I used the 7.5% carbon dioxide (CO_2) model of anxiety induction to examine the effects of state anxiety on alcohol outcomes. Finally, I narrowed the review to one temporal direction, to prevent the project from becoming unwieldy. Alternative explanations (e.g., reverse causation, confounding) will be addressed in the discussion section of this chapter.

2.3. Methods

The protocol for this review was pre-registered on the Open Science Framework (https://osf.io/vg39k/) and all applicable PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and MOOSE (Meta-analyses Of Observational Studies in Epidemiology) guidelines were followed.

2.3.1. Selection Criteria

Studies were included if they met the following criteria: English language peer-reviewed publication, human participants, anxiety exposure in childhood (< 10 years) or adolescence (≥ 10 and < 18 years), alcohol outcome(s) distinct from general substance use, alcohol outcome(s) measured at least six months later than exposure, longitudinal design, and association(s) between anxiety and alcohol use reported. Anxiety exposure refers to any anxiety measure used as a predictor variable (i.e., it preceded the alcohol use outcome variable by at least six months). If an anxiety exposure range extended beyond age 18 years but included adolescence (e.g., 14-24 years), I still included the study. However, if the study sample range was solely or predominantly above 18 years, I excluded the study. I

did not have the resources to translate non-English language publications and locate unpublished studies. In this review, ‘studies’ refer to published journal articles.

2.3.2. Identification of Studies

I searched PubMed, Scopus, Web of Science and PsycINFO electronic databases until February 2017, using the following terms: anxi*, internali?ing, phobi*, *phobia, panic, obsessive-compulsive, OCD, post-traumatic stress disorder, PTSD, alcohol*, drink*, ethanol, longitudinal, prospective, cohort, trajector*, wave. Animal terms (rodent*, mice, mouse, rat, rats) were specified for exclusion. Boolean operators and truncations were modified depending on database conventions. An example of the full electronic search strategy in Scopus can be found below.

(TITLE-ABS-KEY ("anxi*" OR "internali?ing" OR "phobi*" OR "*phobia" OR "panic" OR "OCD" OR "obsessive-compulsive" OR "PTSD" OR "post-traumatic stress disorder") AND TITLE-ABS-KEY ("alcohol*" OR "ethanol" OR "drink*") AND TITLE-ABS-KEY ("longitudinal" OR "prospective" OR" cohort" OR "trajector*" OR "wave*") AND NOT TITLE-ABS-KEY ("rodent*" OR "mice" OR "mouse" OR "rat" OR “rats”)).

I first screened electronic titles, abstracts and keywords, then full-text articles were screened. Reasons for exclusion at the second phase were documented. A 10% check was independently completed by a second author at each screening phase as a quality control procedure. Any disagreements were resolved by consensus. I also hand searched reference lists of included articles. A 100% screening check may have identified additional discrepancies, and thus minimised errors. However due to the time constraints of my PhD, I decided that a 10% check would be an appropriate compromise. The checks did not yield many discrepancies, which supported my decision to stop at 10%.

I later decided to exclude post-traumatic stress disorder (PTSD), because it has been reclassified in the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) from an anxiety disorder to a trauma- and stressor-related disorder (DSM-5, 2019). Studies were excluded if alcohol initiation was the only outcome since I was primarily interested in level rather than commencement of use. Finally, studies were excluded if statistical analyses violated my inclusion criteria (e.g., concurrent or retrospective analyses). See Appendix 2.1 for studies excluded after the full-text phase with reasons.

2.3.3. Data Extraction

I extracted the following information (if available) from each included study: sample, country, percentage male, anxiety exposure (measure used, age, respondent), alcohol use outcome (measure used, age, respondent), follow-up time, statistical test, results summary, confounders adjusted for, and sample size. Full data extraction was independently checked by a second author to help minimise errors. Differences were resolved by consensus.

2.3.4. Quality Assessment

I originally planned to assess the risk of bias of included studies, using the Newcastle Ottawa Scale for cohort studies, as stated in my protocol. I later decided not to perform a formal risk of bias assessment, as this is typically used to explore heterogeneity in a meta-analysis. For example, sensitivity analyses may be used to see if between-study heterogeneity is due to outlier studies such as those with a high risk of bias. However, since only three studies contributed to my meta-analysis, this was not practical. Instead I assessed the methodological quality of included studies by focusing on whether authors adjusted for important potential confounders, and whether the study had a large sample (statistical power). All

studies had an appropriate follow-up period as I pre-specified this in my search strategy.

2.3.5. Classification and Synthesis of Study Findings

As anticipated, there was considerable heterogeneity between studies in terms of type and age of anxiety exposure and alcohol outcome, length of follow-up, statistical methods, and confounders adjusted for. This diversity precluded a statistical synthesis of findings from all 51 studies. I therefore present a narrative summary of results.

2.3.5.1. Narrative Synthesis. I coded associations between an anxiety exposure and an alcohol outcome in six categories according to strength of evidence (Gogtay et al., 2016): 'negative' (negative point estimate and $p < .05$ or 95% confidence interval (CI) excludes the null), 'weak negative' (negative point estimate and $p < .1$ or > 70% of the 95% CI is in the negative direction), 'equivocal' ($p > .1$ or < 70% of the 95% CI is in a positive or negative direction), 'weak positive' (positive point estimate and $p < .1$ or > 70% of the 95% CI is in a positive direction, 'positive' (positive point estimate and $p < .05$ or 95% CI excludes null), and 'unclassifiable' (required statistical information was not reported). If the exact p-value was reported, that was used together with the point estimate to determine how the result should be categorised. If the p-value was not reported, I used the CI. To determine what percentage of a CI is in a positive or negative direction, I first took the natural log (ln) of the lower CI and the upper CI, before calculating the proportion of the CI in a positive or negative direction.

Anxiety exposures and alcohol outcomes were grouped based on behavioural and clinical similarity. I organised associations based on three alcohol use categories: 'drinking frequency/quantity' (hazardous drinking, heavy drinking, drinking

frequency, alcohol quantity, and alcohol use), 'binge drinking' (binge drinking, heavy episodic drinking, and intoxication/drunkenness), and 'alcohol use disorders' (alcohol dependence, alcoholism, harmful drinking, AUDs, alcohol problems, and alcohol abuse). Within each alcohol category, I subcategorised by eight anxiety categories: generalised anxiety disorder (GAD) (including overanxious disorder and general worry), internalising disorders (including anxiety/depression combined), obsessive compulsive disorder (OCD), panic disorder (including panic attacks), separation anxiety disorder, social anxiety disorder (including social phobia), and specific phobias. I also had a miscellaneous anxiety category that included trait measures of anxiety (behavioural inhibition, trait anxiety, and anxiety sensitivity) and combined measures of several anxiety disorders. I counted the number of positive, negative, equivocal, and unclassifiable associations according to type of anxiety exposure and alcohol outcome.

As many studies reported several associations, I devised rules to avoid counting non-independent associations. Counting non-independent associations would give an inaccurate picture of the literature. These rules were not arbitrary, they were based on my research question. For each study, and for each anxiety exposure, only one drinking frequency/quantity association, one binge drinking association, and one AUD outcome association were counted. If several alcohol outcomes were reported from the same alcohol category, I selected based on the order they are listed above (e.g., alcohol dependence instead of alcohol use disorder). I also counted associations based on the following rules:

- Most adjusted result (versus unadjusted or partially adjusted) as it is important to account for confounding.
- Unstandardised betas (versus standardised) to see the magnitude of the association based on the scale used.

- Main effects (versus interactions) as I made no hypotheses about the interactions of anxiety with other factors on alcohol use.
- More complex model (versus simpler model), for example regression rather than correlation.
- Male and female results separately if total score were not reported as these associations are independent.
- Adolescent report (versus parent versus teacher), parent report (versus teacher versus child). It was difficult to decide which type of respondent was likely to be most accurate. There is some evidence that anxiety symptoms may be reported more accurately by the young person themselves (Ederer, 2004) compared to, for example, externalising symptoms, which are more noticeable to parents and teachers. However young children may lack the vocabulary and insight to fully articulate their feelings, compared to adolescents and adults.
- Adolescent anxiety (versus child anxiety) as it was consistent with the developmental period used in my cohort study which I will discuss in Chapter 3, and measurement bias was less likely.
- Anxiety in the prior year (versus baseline), anxiety experienced on >2 waves (versus 1-2 waves), and total anxiety score (versus subscales).
- Alcohol use in early adulthood (versus other developmental periods) as that was the key developmental period for the synthesis, and it was consistent with the developmental period used in my cohort study which I will discuss in Chapter 3. Measures of alcohol use before the legal drinking age, might also result in more biased reporting.
- Greatest length of follow-up (if several relevant time-points reported), as having a wider gap between exposure and outcome gives more certainty of the temporal precedence.

- Greatest class comparison (e.g., heavy use versus abstainers), and trajectories closest to my research question.

2.3.5.2. Meta-Analysis. Finally, I performed a meta-analysis on three studies investigating associations between GAD and alcohol use disorder/alcohol dependence, because I considered them to be combinable (similarity of exposure, outcome, and statistical method). Studies were not included if they measured worry only, a different anxiety disorder to GAD, drinking frequency/quantity, or binge drinking. One study that met my selection criteria was dropped as the corresponding author did not respond to my request for additional statistical information. I judged the suitability of results for inclusion in the meta-analysis after discussion with co-authors. Statistical analyses were conducted in Stata version 15 using the *metan* command (Harris et al., 2008). Between-study heterogeneity was assessed using I^2. I^2 assesses the proportion of total variation in study estimates due to heterogeneity (Higgins & Thompson, 2002). I used the DerSimonian and Laird method for fitting the random effects meta-analysis model.

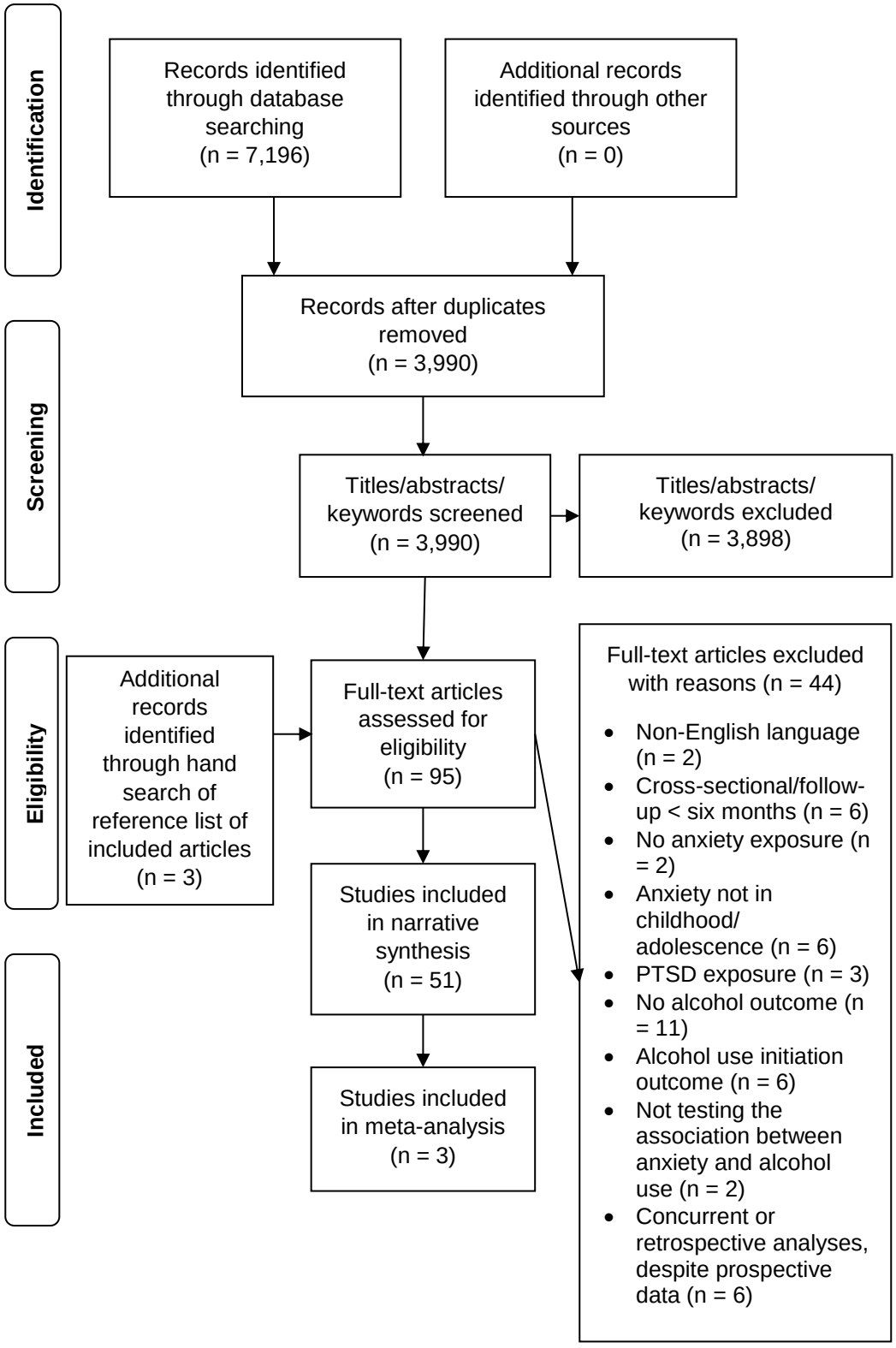
I aspired to do a meta-analysis on more studies but results from the other seven anxiety categories were judged to be too heterogeneous. When faced with heterogeneity, researchers have four options: to not conduct a meta-analysis, to perform a random effects meta-analysis, to conduct a subgroup analysis to explore heterogeneity for discrete characteristics, or to conduct a meta-regression to explore heterogeneity for continuous study level characteristics. Given that I had already classified the different anxiety exposures and alcohol outcomes into distinct categories for the narrative synthesis, I decided it was not appropriate to then combine associations across those categories for a meta-analysis.

2.4. Results

2.4.1. Results of the Literature Search

A total of 3,990 articles were screened by title, abstract and keywords, of which 3,898 were excluded. Ninety-two full-text articles were assessed for eligibility, of which 44 were excluded. Three further articles were identified following a hand search of reference lists of the 48 articles which met the inclusion criteria, leaving a total of 51 studies in the systematic review. Of these, three studies contributed to the meta-analysis. Full details of the literature search and reasons for exclusion can be found in Figure 2.1.

Figure 2.1. PRISMA flow diagram of the literature search.



2.4.2. Characteristics of Included Studies

There were 27 studies from the USA, five from Germany, five from Finland, four from the UK, three from the Netherlands, two from Australia, one from Taiwan, one from Canada, one from New Zealand, one from Sweden, and one from Norway. Forty-six studies included males and females, four had an all-male sample, and one had an all-female sample. Thirty different measures were used to assess anxiety and 40 were used to assess alcohol use. Nine studies reported results for GAD, 19 for internalising disorders, 19 for miscellaneous anxiety, two for OCD, six for panic disorder, three for separation anxiety disorder, 10 for social anxiety disorder, and three for specific phobias. Twenty-seven studies reported results for drinking frequency/quantity, nine for binge drinking, and 26 for AUDs. Length of follow-up ranged from six months to 26 years and sample sizes ranged from 110 to 11,157 participants. Age of anxiety ranged from three to 24 years, and age of alcohol use ranged from 11 to 42 years. Full data extraction information can be found in Appendix 2.2 and see Table 2.1 for a pared-down version.

Table 2.1. Characteristics of included studies.

Study	Sample & Country	Sample Size	% Male	Anxiety Type (Measure)	Age of Anxiety	Alcohol Use Type (Measure)	Age of Alcohol Use
1. (Abram et al., 2015)	Youth at a juvenile detention centre, USA	1504	64	Generalised anxiety disorder (DISC-2.3)	10-19 (median 15)	Alcohol use disorder (DISC-IV)	15-25 (median 20)
2. (Asselmann et al., 2014b)	Early Developmental Stages of Psychopathology Study, Germany	122	33	Panic attacks (DSM-IV-TR M-CIDI)	14-24 (median 19)	Alcohol use disorder (DIA-X/M-CIDI)	21-34
3. (Behrendt et al., 2011)	Early Developmental Stages of Psychopathology Study, Germany	2929	51	Specific phobias (DIA-X/M-CIDI)	14-24	Alcohol use, alcohol abuse, alcohol dependence (DIA-X/M-CIDI)	1.6, 3.5, and 8.2 years later
4. (Bruckl et al., 2007)	Early Developmental Stages of Psychopathology Study, Germany	1090	49	Separation anxiety disorder: subthreshold, threshold (M-CIDI)	14-17	Alcohol abuse, alcohol dependence (M-CIDI)	20 and 42 months later
5. (Buckner et al., 2008)	Oregon Adolescent Depression Project, USA	816	41	Social, generalised, and separation anxiety, panic, obsessive-compulsive and overanxious disorder, specific phobia (K-SADS, K-SADS-P)	16	Alcohol abuse, alcohol dependence (LIFE, SCID-4)	30
6. (Cerda et al., 2016)	Pittsburgh Youth Study, USA	487	100	Anxiety problems (CBCL, TRF, YSR, YASR)	13-19 (annual or semi-annual)	Alcohol frequency, alcohol quantity (Substance Use Scale from NYS)	13–19 (semi-annual)
7. (Cheng et al., 2004)	Taiwan Aboriginal Study Project, Taiwan	164	30	Anxiety disorders (Chinese version of the CIS)	15-24	Time to onset of alcoholism (Chinese version of the CIS)	4 years later
8. (Colder et al., 2013)	From a longitudinal study of adolescent substance use, USA	367	45	Internalising problems (YSR)	11-13	Alcohol use (NYS)	12-16
9. (Dahne et al., 2014)	From a longitudinal study of HIV-related risk behaviours, USA	277	56	Social phobia (RCADS)	11, 12, 13, 14, 15	Alcohol use (modified version of YRBSS)	11, 12, 13, 14, 15
10. (Edwards et al., 2014)	Avon Longitudinal Study of Parents and Children, UK	11157	51	Internalising symptom trajectories (SDQ)	3, 6, 8, 9, 11	Whole drink, drank without parental permission, ever binge, number of whole drinks in past 6 months	13
11. (Englund et al., 2008)	Minnesota Longitudinal Study of Parents and Children, USA	158-170	53	Internalising behaviour (TRF of Child Behavior Checklist)	9	Abstainers, moderate drinkers, heavy drinkers, and alcohol use disorder (Adult Health Survey)	19, 23, 26, 28
12. (Englund & Siebenbruner, 2012)	Minnesota Longitudinal Study of Parents and Children, USA	191	55	Internalising symptoms (TRF, YSR)	7, 9, 12, 16	Frequency and quantity of alcohol use (Adolescent Health Survey)	16
13. (Essau et al., 2014)	Oregon Adolescent Depression Project, USA	816	41	Anxiety disorders (K-SADS, LIFE, SCID)	16, 17, 24, 30	Alcohol use disorder (K-SADS, LIFE, SCID)	24, 30

14. (Farmer et al., 2016)	Oregon Adolescent Depression Project, USA	641	No info	Anxiety disorders (K-SADS, LIFE, SCID-NP)	16, 17, 24, 30	Alcohol use disorder (DSM III-R, DSM-IV, K-SADS, LIFE, SCID-NP)	16, 17, 24, 30
15. (Fröjd et al., 2011)	Adolescent Mental Health Cohort Study, Finland	2070	44	General anxiety (1 item), social phobia (SPIN)	15-16	Frequent alcohol use, frequent drunkenness	17-18
16. (Goodman, 2010)	The British Child and Adolescent Mental Health Surveys, UK	3607	52	Internalising symptoms (SDQ, DAWBA), internalising disorder (clinical diagnosis)	11-12, 13-14, 15-16	Frequent alcohol consumption (different item for each group)	3 years later
17. (Goodwin et al., 2004)	Early Developmental Stages of Psychopathology Study, Germany	2548	No info	Panic attacks (M-CIDI)	14-24	Alcohol use disorder (M-CIDI)	14-25 and 34-50 months later
18. (Gorka et al., 2014)	Oregon Adolescent Depression Project, USA	817	No info	Anxiety disorders (K-SADS)	16	Alcohol use disorder (K-SADS, LIFE)	16, 17, 24, 30
19. (Haller & Chassin, 2013)	From a longitudinal study of familial alcoholism, USA	166	62	Internalising symptoms (CBCL, CDIS-III-R)	11-15	Alcohol problems (from Sher's 1987 questionnaire)	25
20. (Hill et al., 2010)	Seattle Social Development Project, USA	640	50	Behavioural inhibition/trait anxiety (CBCL)	14-15	Alcohol abuse and alcohol dependence (DISC)	27
21. (Jester et al., 2015)	Michigan Longitudinal Study, USA	1064	69	Distress/internalising symptoms (YSR of CBCL)	12-14	Maximum number of drinks, heavy episodic drinking frequency (Drinking and Drug History questionnaire)	18-20
22. (Jun et al., 2015)	Project on Human Development in Chicago Neighbourhoods, USA	724	51	Internalising symptoms (YSR of CBCL)	12, 15, 18	Alcohol Use (number of days drunk alcohol in the past month)	12, 15, 18
23. (King et al., 2004)	Minnesota Twin Family Study, USA	699	0	Separation anxiety disorder, overanxious disorder (DICA-R)	10-12 (mean 11)	Regular use, ever drunk, heavy drinking (DICA-R)	14
24. (Mackie et al., 2011a)	From 24 secondary schools in London with personality risk for substance misuse, UK	393	No info	Anxiety (BSI)	13, 13.5, 14, 14.5	Alcohol use (quantity x frequency)	13, 13.5, 14, 14.5
25. (Maggs et al., 2008)	National Child Development Study, UK	4756-12772	52	Internalising behaviours (Health and Behaviour Checklists)	7, 11	Weekly quantity & harmful drinking (CAGE)	16, 23, 33
26. (Malmberg et al., 2013)	Healthy Schools and Drugs prevention program, Netherlands	853-979	48	Anxiety sensitivity (SURPS)	12-13, and 8, 20, 32 months later	Alcohol use and binge drinking	12-13, and 8, 20, and 32 months later
27. (Malmberg et al., 2012)	Healthy Schools and Drugs prevention program, Netherlands	648-758	48	Anxiety sensitivity (SURPS)	12-13	Lifetime prevalence of alcohol use	20 months later
28. (Marmorstein et al., 2010)	Pittsburgh Youth Study, USA	503	100	Generalised anxiety and social anxiety (CBCL, YSR, TRF)	6	First alcohol problem (DIS)	20

29. (Marmorstein, 2015)	Camden Youth Development Study, USA	134	50	Social and generalized anxiety symptoms (SCARED)	11	Frequency of drinking alcohol	Every 4 months for 16 months
30. (McKenzie et al., 2011)	From secondary schools in the state of Victoria, Australia	1758	No info	Anxiety/depression symptoms (CIS)	14-17 (6 waves every 6 months)	Alcohol abuse or dependence (CIDI)	24
31. (Miettunen et al., 2014)	Northern Finland Birth Cohort 1986 Study, Finland	6349	49	Internalising problems (Rutter Scales)	8	Often drunk	15-16
32. (Nichter & Chassin, 2015)	The pathways to desistance project, juvenile offenders, USA	818	100	Worry, physiological anxiety (RCMAS)	14-19	Typical quantity of drinking, frequency of binge drinking, dependence	6 months later
33. (Pardini et al., 2007)	Pittsburgh Youth Study, USA	506	100	Anxiety/withdrawal (YSR, TRF, CBCL)	13	Alcohol abuse and dependence (DIS)	20, 25
34. (Parrish et al., 2016)	California Families Project, USA	620	50	Internalising symptoms (MASQ)	14, 16	Frequency of alcohol use	14, 16
35. (Peeters et al., 2014)	From secondary special education schools, Netherlands	378	88	Anxiety sensitivity (SURPS)	13	Alcohol use (quantity x frequency) and problems (trajectories)	2 year follow up (6-8 months between waves)
36. (Pitkanen et al., 2008)	Jyväskylä Longitudinal Study of Personality and Social Development, Finland	290-347	53	Anxiety (1 item)	8, 14	Heavy use, frequency of drinking, binge drinking, problem drinking (LSQ and interview questions)	20, 27, 42
37. (Pulkkinen & Pitkanen, 1994)	Jyväskylä Longitudinal Study of Personality and Social Development, Finland	242-311	53	Anxiety (3 items)	8, 14	Social drinking, problem drinking, controlled drinking (CAGE)	26
38. (Savage et al., 2016)	Finn Twin12 study, Finland	1225-1906	51	Social anxiety (MPNI)	12	Drinking frequency, alcohol dependence (SSAGA)	14, 17, 22
39. (Scalco et al., 2014)	Community sample, USA	387	45	Internalising problems (YSR)	11-12	Alcohol use (YSR of Achenbach Assessment)	12-13, 13-14
40. (Schmidt et al., 2007)	From a primary prevention study, USA	295	39	Anxiety sensitivity (ASI), trait anxiety (STPI)	16-24	Alcohol use disorder (SCID-NP)	18-26
41. (Stanley et al., 2014)	American Indian Research data, USA	281	No info	Internalising behaviours (CBCL)	11	Alcohol use disorder (SSAGA-II)	19-20
42. (Steele et al., 1995)	Community sample, USA	185-187	47	Internalising behaviour problems (RBPC)	11-15	Alcohol use (MAST, NYS)	17-22
43. (Stice et al., 1998)	Longitudinal community sample (1/2 parental alcoholism), USA	216	52	Internalising symptoms (CBCL)	12-16	Quantity and frequency of alcohol use, problem alcohol use	13-17
44. (Strandheim et al., 2011)	Young-HUNT 1, and Young-HUNT 2, Norway	2399	46	Anxiety/depression (SCL 90-R, SCL-5)	13-15	Frequent alcohol use	17-19

45. (Swift et al., 2016)	Random sample from secondary schools, Australia	1203	50	Anxiety/depression symptoms (CIS-R)	14/15–17 (2 waves every 6 months)	Alcohol use disorder symptom classes (CIDI)	24
46. (Thompson et al., 2015)	Victoria Healthy Youth Survey, Canada	657-662	49	Internalising symptoms (BCFPI)	12/13, 14/15, 16/17	Heavy episodic drinking, alcohol related harms (Harmful Effects of Alcohol Scale)	12/13, 14/15, 16/17, 18/19
47. (Virtanen et al., 2015)	The Northern Swedish Cohort Study, Sweden	1010	52	Anxiousness (DSM-5)	16	Drinking trajectories (frequency, consumption)	16, 18, 21, 30, 42
48. (Weekes et al., 2011)	Black adolescents with asthma, USA	110	34	Anxiety symptoms (MASC-10)	11-19	Alcohol use frequency (from Adolescent Risk Behavior Survey)	12-20
49. (Wolitzky-Taylor et al., 2012)	Northwestern-UCLA Youth Emotion Project, USA	420-627	31	Anxiety disorders (SCID-I/NP)	16	Alcohol use disorder (SCID-I/NP)	1-4 years later
50. (Woodward & Fergusson, 2001)	Christchurch Health and Development Study, New Zealand	964	50	Anxiety disorders (DISC supplemented by DSM-III-R)	15-16	Alcohol abuse/dependence (CIDI)	Between 16 and 21, annually
51. (Zimmermann et al., 2003)	Early Developmental Stages of Psychopathology Study, Germany	2548	No info	Anxiety disorders (DIA-X/M-CIDI)	14-24	Regular use, hazardous use, abuse, dependence, alcohol use disorder (M-CIDI)	20 and 42 months later

Anxiety Measures: Diagnostic Interview Schedule for Children (DISC): 3; Munich-Composite International Diagnostic Interview (M-CIDI): 5; Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS): 4; Achenbach System of Empirically Based Assessment (ASEBA), Child Behaviour Checklist (CBCL)/Youth Self-Report (YSR)/Teacher's Report Form (TRF)/Young Adult Self-Report (YASR): 13; Clinical Interview Schedule (CIS)/Clinical Interview Schedule-Revised (CIS-R): 3; Revised Child Anxiety and Depression Scale (RCADS): 1; Strengths and Difficulties Questionnaire (SDQ): 1; Longitudinal Interval Follow-up Evaluation (LIFE): 2; Structured Clinical Interview for DSM (SCID)/Structured Clinical Interview for DSM Non Patient (SCID-NP): 3; Social Phobia Inventory (SPIN): 1; Clinician rated diagnosis: 1; Diagnostic Interview Schedule III Revised (DIS-III-R): 2; Diagnostic Interview for Children and Adolescents-Revised (DICA-R): 1; Brief Symptom Inventory (BSI): 1; Health and Behaviour Checklists: 1; Substance Use Risk Profile Scale (SURPS): 3; Screen for Child Anxiety Related Disorders (SCARED): 1; Rutter Scales: 1; Revised Children's Manifest Anxiety Scale (RCMAS): 1; Mini-Mood and Anxiety Symptom Questionnaire (MASQ): 1; Multidimensional Peer Nomination Inventory (MPNI): 1; Anxiety Sensitivity Index (ASI): 1; Revised Behaviour Problem Checklist (RBPC): 1; Symptom Check List (SCL-5): 1; Brief Child and Family Phone Interview (BCFPI): 1; Anxiousness (based on the symptom clusters in DSM-5): 1; Multidimensional Anxiety Scale for Children (MASC- 10): 1; State-Trait Personality Inventory(STPI): 1; and 2 researcher constructed measures.

Alcohol Measures: Diagnostic Interview Schedule for Children (DISC): 2; Diagnostic Interview Schedule (DIS): 2; Munich-Composite International Diagnostic Interview (M-CIDI): 5; Longitudinal Interval Follow-up Evaluation (LIFE): 4; Structured Clinical Interview for DSM (SCID)/Structured Clinical Interview for DSM Non Patient (SCID-NP): 5; National Youth Survey (NYS): 3; Clinical Interview Schedule (CIS): 1; Youth Risk Behavior Surveillance System (YRBSS): 1; Adult Heath Survey: 1; Adolescent Health Survey: 1; Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS): 3; Measures adapted from Questionnaire for the Alcohol, Health, and Behavior study: 1; Drinking and Drug History Questionnaire: 1; Diagnostic Interview for Children and Adolescents-Revised (DICA-R): 1; Composite International Diagnostic Interview: 3; CAGE Questionnaire (cut-annoyed-guilty-eye): 1; Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA): 2; Youth Self-Report (YSR): 1; Michigan Alcohol Screening Test (MAST): 1; Harmful Effects of Alcohol Scale: 1; Adolescent risk behaviour survey: 1; and 19 researcher constructed measures.

2.4.3. Narrative Synthesis

Below I present a summary of results organised by alcohol outcome. Totals refer to number of associations rather than number of studies, and I included 97 associations across 51 studies (see Tables 2.2-2.4).

2.4.3.1. Alcohol Consumption (Collectively). Across all alcohol outcome groups, there were 32 (33%) positive associations, 17 (18%) negative associations, 25 (26%) equivocal associations, and 23 (24%) unclassifiable associations. There were more positive than negative associations for AUDs (20 versus 5), compared to drinking frequency/quantity (9 versus 8) and binge drinking (3 versus 4). Findings were robust to the removal of the 24 internalising associations (where anxiety and depression could not be distinguished): 28 (38%) positive associations, 11 (15%) negative associations, 19 (26%) equivocal associations, and 15 (21%) unclassifiable associations.

I explored whether the mixed findings were due to heterogeneity of anxiety. There were only positive associations (not negative) for OCD (1), panic disorder (5), separation anxiety disorder (3), and specific phobias (2). There were more positive than negative associations for miscellaneous anxiety (9 versus 3) and social anxiety disorder (6 versus 5). There were more negative than positive associations for generalised anxiety (3 versus 2), and internalising disorders (6 versus 4). No anxiety disorder had only negative associations. There were equivocal results for all anxiety disorders, except OCD (generalised anxiety [8], internalising disorders [6], miscellaneous anxiety [5], panic disorder [1], separation anxiety disorder [1], social anxiety disorder [2], and specific phobias [2]).

I also explored whether there were differences in associations according to sample age. There were seven associations where the anxiety exposure was measured in

childhood. Of these, there was one positive association (14%), two negative associations (29%), and four equivocal associations (57%). There were 87 associations where the anxiety exposure was measured in adolescence. Of these, there were 31 positive associations (36%), 14 negative associations (16%), 19 equivocal associations (22%), and 23 unclassifiable associations (26%). For three associations, developmental period was unclear due to the analysis method.

2.4.3.2. Drinking Frequency/Quantity. Thirty-seven associations were reported on the relationship between anxiety and drinking frequency/quantity. Nine (24%) associations were positive, and eight (22%) were negative. There was no clear evidence of an association in either direction for nine (24%) associations, and 11 (30%) were unclassifiable (see Table 2.2).

The nine associations in a positive direction included generalised anxiety (1), internalising disorders (1), miscellaneous anxiety (3), panic disorder (1), separation anxiety disorder (1), and social anxiety disorder (2). For all nine (100%) associations, anxiety was measured in adolescence only (≥ 10 years), and for eight (89%), drinking frequency/quantity was assessed less than four years later. Seven (78%) associations were statistically adjusted for gender, and four (44%) were adjusted for other psychological disorders. Four (44%) were based on a sample size greater than 1,000.

The eight associations in a negative direction included generalised anxiety (1), internalising disorders (3), miscellaneous anxiety (2) and social anxiety (2). Five (63%) associations measured anxiety in adolescence only, and there was no pattern in length of follow-up. Two (25%) associations were adjusted for gender, and four (50%) were adjusted for other psychological disorders. Five (63%) were based on a sample size greater than 1,000.

The nine equivocal associations included generalised anxiety (2), internalising disorders (5), miscellaneous anxiety (1), and specific phobias (1). Five (56%) came from adolescent samples only, two (22%) came from a sample which also included young adults, and two (22%) came from sample which included children. For six (67%) associations, drinking frequency/quantity was assessed less than four years later. Six (67%) associations were adjusted for gender and two (22%) were adjusted for other psychological disorders. Three (33%) were based on a sample size greater than 1,000.

2.4.3.3. Binge Drinking. Fourteen associations were reported on the relationship between anxiety and binge drinking. Three (21%) associations were positive, and four (29%) were negative. There was no clear evidence of an association in either direction for two (14%) associations and five (36%) were unclassifiable (see Table 2.3).

The three associations in a positive direction included generalised anxiety, miscellaneous anxiety and separation anxiety. All three (100%) assessed anxiety in adolescence and measured alcohol use less than four years later. One (33%) adjusted for gender and another psychological disorder and one was based on a sample size greater than 1,000.

The four associations in a negative direction included generalised anxiety (1), internalising disorders (2) and social anxiety (1). Two (50%) assessed anxiety in adolescence and two (50%) in childhood. One (25%) adjusted for gender and one (25%) adjusted for another psychological disorder. Three (75%) were based on a sample size greater than 1,000. Two equivocal associations were found for

generalised anxiety and internalising disorders. Both involved maternal reported anxiety, and binge drinking was assessed in adolescence.

2.4.3.4. Alcohol Use Disorders. Forty-six associations were reported on the relationship between anxiety and AUDs. Twenty (43%) associations were positive, and five (11%) were negative. There was no clear evidence of an association in either direction for 14 (30%) associations, and seven (15%) were unclassifiable (see Table 2.4).

The 20 results in a positive direction included internalising disorders (3), miscellaneous anxiety (5), OCD (1), panic disorder (4), separation anxiety disorder (1), social phobia (4) and specific phobia (2). Nineteen (95%) associations related to anxiety in adolescence, and one (5%) related to anxiety in childhood. For 13 (65%) associations, AUD was assessed 10 or more years later than exposure. Sixteen (80%) associations were adjusted for gender and seven (35%) were adjusted for other psychological disorders. Eight (40%) associations were based on a sample size over 1,000. As previously described, I classified associations based on the strength of evidence (p-values and confidence intervals) and the direction of the associations (positive or negative point estimates). The magnitude of the associations (size of the point estimates) are also important and they can be found in Appendix 2.2 if they were reported by study authors. As an example, odds ratios ranged from 2.4 to 5.8 for associations between a panic disorder exposure and an alcohol use disorder outcome (Asselmann et al., 2014b; Buckner et al., 2008; Goodwin et al., 2004).

The five associations in a negative direction included GAD (1), internalising disorder (1), miscellaneous anxiety (1) and social anxiety disorder (2). All five (100%) assessed anxiety in adolescence, and AUD was assessed over 10 years

later for two (40%) associations. Two (40%) associations were adjusted for gender and one (20%) was adjusted for other psychological disorders. One (20%) association was based on a sample size over 1,000.

The 14 equivocal associations were for GAD (5), miscellaneous anxiety (4), panic disorder (1), separation anxiety disorder (1), specific phobia (1), and social anxiety disorder (2). Twelve (86%) associations related to anxiety in adolescence, and two (14%) in childhood. For eight (57%) associations, AUD was assessed over 10 years later. Eight (57%) associations were adjusted for gender, and five (36%) were adjusted for other psychological disorders. Four (29%) associations were based on sample sizes over 1,000.

2.4.4. Meta-Analysis

Four associations (from three studies) on generalised anxiety and later AUD/alcohol dependence contributed to a meta-analysis. There was no clear evidence that generalised anxiety is associated with later AUD (OR 0.94, 95% CI 0.47 to 1.87, I^2 0%). As between-study heterogeneity tends to zero, the random-effect model defaults to a fixed-effect model. Therefore, as heterogeneity was low, I report only the random effects model for simplicity. A forest plot summarising the individual study estimates and pooled estimate is shown in Figure 2.2.

Table 2.2. Number of positive, negative, equivocal, and unclassifiable associations between an anxiety exposure and a drinking frequency/quantity outcome.

Anxiety Phenotype	Number of Studies	Negative	Weak Negative	Equivocal	Weak Positive	Positive	Unclassifiable
Generalised Anxiety Disorder	5	1 (20%)	0 (0%)	2 (40%)	0 (0%)	1 (20%)	1 (20%)
Internalising Disorders	12	2 (14%)	1 (7%)	5 (36%)	0 (0%)	1 (7%)	5 (36%)
Miscellaneous Anxiety	9	1 (10%)	1 (10%)	1 (10%)	0 (0%)	3 (30%)	4 (40%)
Obsessive Compulsive Disorder	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Panic Disorder	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)
Separation Anxiety Disorder	1	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)
Social Anxiety Disorder	5	2 (40%)	0 (0%)	0 (0%)	0 (0%)	2 (40%)	1 (20%)
Specific Phobias	1	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)
Total	**27**	**6 (16%)**	**2 (5%)**	**9 (24%)**	**1 (3%)**	**8 (22%)**	**11 (30%)**

Drinking frequency/quantity outcomes: hazardous drinking, heavy drinking, drinking frequency, alcohol quantity, and alcohol use. Number of Studies Total = number of studies which reported an association between an anxiety exposure and a drinking frequency/quantity outcome. Note that some studies examined multiple anxiety disorders.

Table 2.3. Number of positive, negative, equivocal, and unclassifiable associations between an anxiety exposure and a binge drinking outcome.

Anxiety Phenotype	Number of Studies	Negative	Weak Negative	Equivocal	Weak Positive	Positive	Unclassifiable
Generalised Anxiety Disorder	3	1 (33%)	0 (0%)	1 (33%)	1 (33%)	0 (0%)	0 (0%)
Internalising Disorders	4	0 (0%)	2 (40%)	1 (20%)	0 (0%)	0 (0%)	2 (40%)
Miscellaneous Anxiety	3	0 (0%)	0 (0%)	0 (0%)	1 (25%)	0 (0%)	3 (75%)
Obsessive Compulsive Disorder	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Panic Disorder	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Separation Anxiety Disorder	1	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)
Social Anxiety Disorder	1	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Specific Phobias	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total	**9**	**2 (14%)**	**2 (14%)**	**2 (14%)**	**3 (21%)**	**0 (0%)**	**5 (36%)**

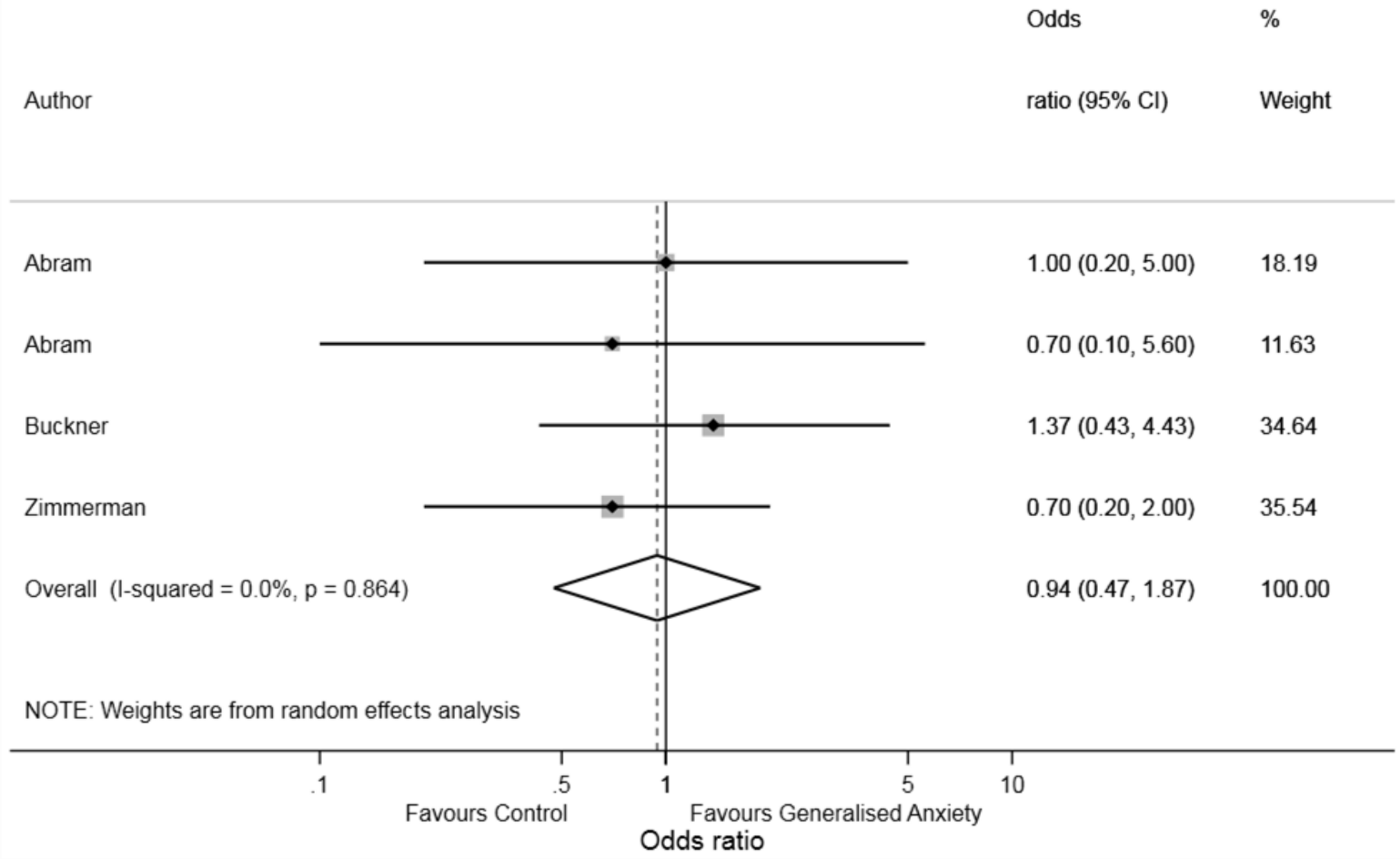
Binge drinking outcomes: binge drinking, heavy episodic drinking, and intoxication/drunkenness. Number of Studies Total = number of studies which reported an association between an anxiety exposure and a binge drinking outcome. Note that some studies examined multiple anxiety disorders.

Table 2.4. Number of positive, negative, equivocal, and unclassifiable associations between an anxiety exposure and an alcohol use disorder outcome.

Anxiety Phenotype	Number of Studies	Negative	Weak Negative	Equivocal	Weak Positive	Positive	Unclassifiable
Generalised Anxiety Disorder	6	1 (14%)	0 (0%)	5 (71%)	0 (0%)	0 (0%)	1 (14%)
Internalising Disorders	5	0 (0%)	1 (20%)	0 (0%)	0 (0%)	3 (60%)	1 (20%)
Miscellaneous Anxiety	12	1 (8%)	0 (0%)	4 (31%)	0 (0%)	5 (38%)	3 (23%)
Obsessive Compulsive Disorder	2	0 (0%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)	1 (50%)
Panic Disorder	6	0 (0%)	0 (0%)	1 (17%)	1 (17%)	3 (50%)	1 (17%)
Separation Anxiety Disorder	2	0 (0%)	0 (0%)	1 (50%)	0 (0%)	1 (50%)	0 (0%)
Social Anxiety Disorder	7	1 (13%)	1 (13%)	2 (25%)	1 (13%)	3 (38%)	0 (0%)
Specific Phobias	3	0 (0%)	0 (0%)	1 (33%)	1 (33%)	1 (33%)	0 (0%)
Total	**26**	**3 (7%)**	**2 (4%)**	**14 (30%)**	**4 (9%)**	**16 (35%)**	**7 (15%)**

Alcohol use disorder outcomes: alcohol dependence, alcoholism, harmful drinking, alcohol use disorders, alcohol problems, and alcohol abuse. Number of Studies Total = number of studies which reported an association between an anxiety exposure and an alcohol use disorder outcome. Note that some studies examined multiple anxiety disorders.

Figure 2.2. Forest plot of associations between generalised anxiety and alcohol use disorder.



2.5. Discussion

2.5.1. Summary of Findings

Overall one third of associations were in a positive direction (i.e., anxiety was prospectively associated with greater alcohol consumption), supporting my hypothesis. However, approximately one fifth of associations were in a negative direction (i.e., anxiety was prospectively associated with lower alcohol consumption), and a quarter of associations were equivocal (direction unclear). Few studies could contribute to the meta-analysis, which also showed no clear evidence of an association between generalised anxiety and AUD.

When separating associations by alcohol outcome, there was some evidence for a positive relationship between anxiety and AUDs. This was driven by all anxiety disorders except GAD, as shown by the narrative synthesis and the meta-analysis. Five associations between generalised anxiety and AUDs were equivocal, and zero were positive. Compared, for example, to panic disorder, where there was one equivocal association and four positive associations. These results may be explained by differences in symptoms. People with panic disorder experience higher sympathetic nervous system arousal (e.g., racing heart, shortness of breath), than people with GAD (Anderson et al., 1984; Mohlman et al., 2004). And there is some evidence that physiological anxiety symptoms are positively associated with alcohol dependence, whereas cognitive symptoms are negatively associated (Nichter & Chassin, 2015). Associations of anxiety with drinking frequency/quantity and binge drinking were unclear and inconsistent; there were a similar number of positive, negative and equivocal results. Across all alcohol consumption outcomes, there were no negative associations for OCD, panic disorder, separation anxiety disorder and specific phobias. There were positive and negative associations for miscellaneous anxiety, social anxiety disorder,

generalised anxiety, and internalising disorders. There were equivocal associations for all anxiety disorders, except OCD (however, there were very few associations for OCD in general).

Other sources of between-study heterogeneity including the developmental period that anxiety was measured in, length of follow-up, confounders adjusted for, and sample size, did not appear to account for the inconsistent findings. First, it was difficult to compare associations for child versus adolescent anxiety because of the imbalance in quantity (7 versus 87 associations, respectively). This imbalance arose because I avoided counting non-independent associations. If studies reported several associations at different ages, I selected adolescence because that was the key developmental period for my research question and measurement bias was less likely. Second, one might presume clearer evidence of an association with longer follow up, as this allows sufficient time to observe a problem drinking outcome. On the other hand, shorter time gaps between an exposure and outcome may reveal clearer evidence of an association, as self-medication theory suggests people drink alcohol in response to present rather than past anxiety. I also did not always include the longest follow up time-point as my question was focused on young adult alcohol use, for coherence with Chapter 3. Finally, I looked at confounders adjusted for and sample size as markers of study quality, but these factors may also cause mixed findings. For example, studies with small sample sizes and thus low statistical power can have a reduced chance of detecting a true association (Type II error), but they can also have an increased false positive rate (Type I error) (Button et al., 2013).

2.5.2. Original Research Contribution

This is the largest systematic review of longitudinal studies investigating prospective associations between different anxiety exposures and later alcohol use

outcomes. By conducting a systematic review with a meta-analytical component, my results are likely to be more objective and less biased, compared to unsystematic literature reviews. Overall, a clear association between anxiety and alcohol use was not evident, consistent with previous reviews (Groenman et al., 2017; Hussong et al., 2017; Lemyre et al., 2019) and meta-analyses (Bartel et al., 2018). It appears that Bartel and colleagues were able to meta-analyse a larger number of studies as they only focused on one type of anxiety, anxiety sensitivity, which was reportedly measured more consistently across studies. When distinguishing between different alcohol outcomes, anxiety was generally positively associated with AUDs, supporting a previous meta-analysis which found social anxiety was associated with alcohol-related problems (Schry & White, 2013). However, the authors also found that social anxiety was negatively associated with alcohol use variables, whereas I found a combination of positive, negative and equivocal associations between anxiety and drinking frequency/quantity. A new paper has subsequently been published that supports my findings to some extent. Meque and colleagues (2019) found child and adolescent internalising symptoms were positively associated with AUD in young adulthood. However, their subgroup analysis of anxiety disorders only (i.e., no depression) revealed no clear evidence of an association with AUD (Meque et al., 2019). Although only four studies contributed to this analysis.

2.5.3. Limitations

There are some limitations to this study. First, I only included English language publications which may have biased the review. Studies with significant positive results are more likely to be published in English language journals (Egger et al., 1997), therefore I may have missed relevant studies, particularly those with null findings. Second, my approach to coding the evidence resulted in several unclassifiable associations, as many studies did not report exact p-values or CIs.

However, coding associations by the strength of evidence was considered more accurate than using an arbitrary (e.g., $p < .05$) threshold, despite the loss of data. Third, some good studies with more sophisticated statistical models (e.g., multiple wave repeated measures analyses) were excluded as they did not report the prospective associations required, even though they may have had the data to do this. By excluding these studies, my results may have been potentially biased. Fourth, although I restricted to prospective studies to elucidate the temporal sequence of anxiety and alcohol use, I cannot infer causality from observational studies. For example, several studies did not adjust for important potential confounders (or did not report this information), and there still may be residual confounding. Fifth, some studies may have been underpowered to detect an association due to small sample sizes. This would not have been a problem if they could have been included in a meta-analysis, since meta-analyses improve power and precision by combining the evidence. Also, in some studies, associations between anxiety and alcohol use were one of many analyses explored without a specific *a priori* hypothesis which may have meant they were underpowered.

Finally, one limitation of my review, and the literature in general, may be the use of broad measures of internalising behaviour. I cannot determine what proportion of internalising measures are assessing depression rather than anxiety, without additional specific measures which were unavailable in some studies. For example, the Strengths and Difficulties Questionnaire (SDQ) contains a global measure of emotional symptoms, which does not distinguish between anxiety and depression or subtypes of anxiety (Heradstveit et al., 2018). Given that depression has been found to be a more consistent predictor of alcohol use than anxiety (Hussong et al., 2017), use of internalising measures as a proxy for anxiety may contribute to misclassification or measurement bias. I included internalising disorders in my search strategy to ensure comprehensiveness and because the term is often used

when referring to symptoms in children. The overall findings remained unchanged when I excluded the internalising associations.

2.5.4. Future Directions and Implications

There are different possible explanations for my findings. To assess the causality of my observed associations between anxiety and AUDs, future research should employ study designs which eliminate confounding and reverse causation, such as Mendelian randomisation (Lawlor et al., 2008). Alternatively, there may be no causal relationship between anxiety disorders and AUDs. The common-factor model suggests that third variables, for example genetic, environmental or personality factors, account for the comorbidity between these disorders (Smith & Randall, 2012). In addition, I did not include studies that investigated the reverse temporal associations; greater alcohol use may also increase susceptibility to anxiety disorders (George et al., 1990). These pathways are also important. Future systematic reviews that examine associations between alcohol use and subsequent anxiety are required to help elucidate temporal order and the validity of theoretical models.

I did not find compelling evidence of a relationship between anxiety and drinking frequency/quantity or binge drinking. However, absence of evidence is not evidence of absence. First, some studies had methodological limitations, which may have led to Type II errors. Better quality studies, which are adequately powered, adjust for relevant confounders, and test specific a priori hypotheses, would help to determine whether there is a genuine association. Second, the evidence may be equivocal, which suggests any association is likely to be weak or context dependent. Third, studies in the narrative synthesis may have been too heterogeneous to provide clear combined evidence, a concern also raised by other review authors (Hussong et al., 2017). Future meta-analyses with a greater

number of combinable studies would be informative, improving objectivity, power, and precision. However, this will not be possible unless future studies measure the relationship more consistently. Specifically, consistent types and measurements of anxiety and alcohol use, as well as full reporting of statistical information (e.g., exact p-values and CIs), would facilitate future quantitative syntheses and meta-analyses.

It may be important for future studies to distinguish between specific symptoms of anxiety. For example, Stewart and colleagues (2006) found fear of negative evaluation was positively associated with drinking problems, whereas social avoidance and distress were negatively associated with drinking frequency. This suggests anxiety disorders are complex and multidimensional, and different associations with alcohol use within anxiety disorders should be explored. Anxiety may also act as a risk or a protective factor depending on moderating influences (Gorka et al., 2014). Examination of potential moderating variables such as gender, age, alcohol expectancies, drinking motives, and stressful events may help to explain discrepant findings.

Large cohort studies which compare data at the between-participant and group level, cannot capture subtle dynamic differences in symptoms and behaviour, which may explain the lack of consistency in findings. Anxiety may be associated with more immediate alcohol use, rather than predicting alcohol use in the future (Colder et al., 2017b; Hussong et al., 2001). Therefore, prospective models may not be the right approach to capturing the relationship proposed by self-medication theory. Future research could therefore utilise more sensitive methodological approaches which account for these complexities. Ecological momentary assessment studies, with repeated real-time assessments of anxiety and alcohol use, may be a more nuanced approach to capturing the relationship and within-

participant variation (Bartel et al., 2018). Understanding individual differences in anxiety-alcohol comorbidity could lead to improvements in personalised interventions.

2.6. Chapter Conclusions

Evidence to date is suggestive but far from conclusive of a positive association between anxiety during childhood and adolescence and subsequent alcohol problems, supporting my hypothesis. However, associations of anxiety with drinking frequency/quantity and binge drinking were inconsistent. This suggests the self-medication hypothesis may be most relevant for problem drinkers. Separating results by anxiety type did not elucidate discrepancies. Other study characteristics also did not appear to account for the inconsistent findings. A lack of clear and consistent evidence may be due to between-study heterogeneity or weaknesses of individual studies. I discussed possible directions for future research to further investigate the relationship between anxiety and alcohol use. Early intervention for early signs and symptoms of anxiety disorders, may hold potential for reducing the risk of alcohol problems in later life. It is also important that future studies establish which anxious individuals consume more alcohol and develop AUDs, in order to develop targeted interventions.

Chapter 3: Cohort Study

3.1. Overview

In Chapter 2, I discussed my systematic review and meta-analysis of prospective cohort studies investigating associations between child and adolescent anxiety and later alcohol use and alcohol use disorders (AUDs). In this chapter, I will present my cohort study, which focused on one type of anxiety disorder - generalised anxiety disorder (GAD). Using data from the Avon Longitudinal Study of Parents and Children (ALSPAC), I investigated cross-sectional and prospective associations between GAD and four alcohol use outcomes (frequent drinking, frequent bingeing, hazardous drinking, and harmful drinking). I also extended my systematic review findings by exploring the role of drinking to cope (DTC) motives as a potential moderator of these associations. Moderating variables, which influence the strength and/or direction of associations between an exposure and outcome, may help to explain some of the mixed associations between anxiety and alcohol use in the literature.

As one of the most phenotypically rich cohorts in the world, ALSPAC is a valuable data resource hosted by the University of Bristol (Boyd et al., 2013; Fraser et al., 2013). With a large sample, measures of anxiety in adolescence, measures of alcohol use in adolescence and early adulthood, and a wealth of information on potential confounders, ALSPAC was an ideal birth cohort for answering my research questions.

This chapter is based on the published paper: ‘Alcohol use in late adolescence and early adulthood: the role of generalised anxiety disorder and drinking to cope motives’ (Dyer et al., 2019b). I designed the study in collaboration with my supervisors (Marcus Munafò, Matthew Hickman, and Jon Heron), and I analysed

the available data. Jon Heron (JH) produced and analysed the multiply-imputed datasets, while I wrote the manuscript, with advice and input from all authors.

The aims were to:

- Investigate whether GAD at age 18 is associated with frequent drinking, frequent bingeing, hazardous drinking, and harmful drinking at age 18 and age 21.
- Investigate whether DTC motives at age 18 moderate cross-sectional and prospective associations between GAD and frequent drinking, frequent bingeing, hazardous drinking, and harmful drinking at age 18 and age 21.

3.2. Introduction

3.2.1. Background

Substance use disorders, particularly alcohol abuse and dependence, are the most common psychiatric disorders in adolescence (12%), followed by anxiety disorders (11%) (Costello et al., 2011). Anxiety and alcohol disorders frequently co-occur (Smith & Randall, 2012), and this comorbidity is associated with poorer recovery compared to each condition individually (Bruce et al., 2005; Driessen et al., 2001). It is therefore important to determine the temporal sequence of associations between anxiety and alcohol use.

The self-medication hypothesis suggests anxious individuals may use alcohol to cope with their emotional distress and alleviate physical symptoms because of the drug's anxiolytic effects (Khantzian, 1990; Sher & Levenson, 1982). According to this hypothesis, anxiety is a risk factor for later alcohol problems (via negative reinforcement), which is supported by some longitudinal evidence from adolescent samples. For example, one study found generalised anxiety at age 15 was

associated with a higher incidence of frequent alcohol use two years later (Fröjd et al., 2011). However, other longitudinal studies have shown an inverse relationship. For example, Pardini and colleagues (2007) found adolescent boys with anxiety were less likely to develop AUD symptoms 12 years later. Possible explanations for a protective effect of anxiety include social withdrawal and fear of negative consequences associated with risky drinking (Pardini et al., 2007). Several studies also have found no clear evidence of a prospective relationship between generalised anxiety in adolescence and subsequent alcohol use (Marmorstein, 2015), or AUDs (Abram et al., 2015; Wolitzky-Taylor et al., 2012; Zimmermann et al., 2003).

This inconsistent evidence may be explained by other factors influencing the strength and direction of the anxiety-alcohol relationship; anxiety could act as a risk or protective factor if there are moderating influences. One factor that may moderate this relationship is DTC motives, the tendency to drink alcohol to relax, forget worries, cheer up, cope with depression or nervousness, or to feel more self-confident (Cooper et al., 1992). Higher anxiety is associated with greater DTC (Stapinski et al., 2016), and DTC motives are a risk factor for later alcohol problems (Kuntsche et al., 2005) and dependence (Crum et al., 2013). There is some evidence that DTC moderates the relationship between anxiety and alcohol problems in adult samples. For example, in one study, people with an anxiety disorder who self-medicated with alcohol were more likely to have an additional AUD three years later compared to anxious individuals who did not self-medicate (Menary et al., 2011). Other research has provided cross-sectional evidence for an interaction between anxiety and DTC motives in an adolescent sample. Higher anxiety symptoms were associated with greater alcohol problems among individuals with high DTC motives but not those with low DTC motives (Goldstein

et al., 2012), although this study was conducted with a high-risk sample (adolescents involved with child welfare).

The current study builds on these findings and other ongoing work from our research group. First, using the 7.5% carbon dioxide (CO_2) model of anxiety induction, experimentally-induced acute anxiety led to higher alcohol choice. The 7.5% CO_2 model is suggested to be an experimental model of GAD (Bailey et al., 2011a). Second, using latent class and latent transition analysis with ALSPAC, higher anxiety and DTC motives at age 18 were associated with an increased risk of being in the high-risk drinking class at age 21. DTC motives also influenced the transition from low-risk alcohol use at age 18 to binge drinking and high-risk alcohol use at age 21, while anxiety did not.

3.2.2. Aims and Hypotheses

In the current study, I investigated whether GAD at age 18 was associated with frequent drinking, frequent bingeing, hazardous drinking, and harmful drinking at baseline and longitudinally at age 21 and I tested whether adolescent DTC motives moderated these associations. In both the cross-sectional and longitudinal analyses, I hypothesised that: (a) GAD would be positively associated with all alcohol outcomes, and (b) the strength of associations would be greater among individuals who also endorse high (versus low) DTC motives.

I considered whether to examine several anxiety disorders, in accordance with the systematic review, or to focus on one. I chose to solely investigate GAD instead of other anxiety disorders primarily for consistency with the experimental work in our group. I considered whether to also include other anxiety disorders, such as social anxiety disorder, in secondary analyses. However, the other binary Clinical Interview Schedule – Revised (CISR) measures in ALSPAC at age 18 had small

sample sizes (for high anxiety) which would have made the adjusted analyses unfeasible. Another option was to use the Development and Well-Being Assessment (DAWBA) at age 15, but again the sample size was too small in some probability bands of the variable, preventing adjusted analyses. Because different types of anxiety may have distinct associations with alcohol use (Dyer et al., 2019a), I decided not to derive a single variable to denote presence versus absence of any anxiety disorder, as this amalgamation of anxiety variables may dilute any existing effects.

3.3. Methods

3.3.1. Participants

I used data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a prospective, population-based birth cohort study (Boyd et al., 2013; Fraser et al., 2013). A total of 14,541 pregnant women living in the former Avon Health Authority, with expected delivery dates between April 1st 1991 and December 31st 1992, were recruited into the study (http://www.bristol.ac.uk/alspac/). Data has been collected on the core participants, their mothers, fathers, grandparents, siblings, and now their offspring via questionnaires and focus clinics. Of the 13,978 singletons/twin offspring alive at one year, a small number of participants have since withdrawn consent (n = 24) leaving a starting sample of 13,954. In the late 1990's an attempt was made to bolster the sample by recruiting additional eligible participants. Ethics approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees.

ALSPAC has several strengths including its large sample size, general population base, and the breadth and frequency of data collection which allows repeated measures of the same participants over multiple time points (Boyd et al., 2013).

However, there are some limitations. Recruitment of eligible mothers to ALSPAC was incomplete, therefore there may be selection bias due to systematic differences between those recruited and not recruited (Boyd et al., 2013). The authors of the cohort profile suggest there may be an 'over-representation of more affluent groups and an under-representation of non-White minority ethnic groups compared with the national population' due to this original incomplete recruitment and subsequent differential attrition (Boyd et al., 2013). This could influence the external validity of ALSPAC and the ability to generalise findings to the national population.

I was not involved in participant recruitment or data collection for ALSPAC. The study described in this chapter involved secondary data analysis on a subset of the sample. I focused on data collected when the participants were age 18 years (median 17.8 years, inter-quartile range 17.6 to 17.9) and age 21 years (median 20.9 years, inter-quartile range 20.5 to 21.4). The age 18 baseline data were obtained from a subsample of the ALSPAC cohort who attended the 'Teen Focus 4' research clinic (n = 4,878), while the age 21 follow-up data were collected via questionnaires which were administered either online or through the post (n = 3,772). I decided to only include the 'core' cases from phase 1 recruitment and exclude the later enrollers due to the latter's lack of early background (e.g., sociodemographic) data. This early data is important as it is used in the adjusted models to examine the influence of potential confounding, and in the multiple imputation models to help inform the missing data at later ages. I also only included core cases to avoid possible selection bias; there may be differences between people who opt into a study at the beginning versus those who decide to participate later after initially declining.

3.3.2. Measures

3.3.2.1. Generalised Anxiety Disorder. GAD was assessed at the 18-year research clinic. Participants completed a self-administered computerised version of the Clinical Interview Schedule-Revised (CIS-R) (Lewis et al., 1992), which uses computer algorithms to identify psychiatric disorders according to DSM-IV and ICD-10 criteria. A binary variable indicating presence of GAD versus no diagnosis was taken as the primary exposure measure with sensitivity analyses examining a variable in which participants with depression or other forms of anxiety (panic disorder, agoraphobia, social phobia, specific phobia) were excluded from the reference group.

3.3.2.2. Drinking to Cope Motives. DTC motives were also assessed at the 18-year clinic. Participants completed a modified version of the original Drinking Motives Questionnaire (Cooper et al., 1992), which has good internal consistency (Cronbach's α = 0.79) and has previously been used by other ALSPAC researchers (Stapinski et al., 2016). The five original 'coping' items measured how often participants use alcohol to relax, forget worries, cheer up, cope with depression or nervousness, or feel more self-confident, over the past two years. This adapted scale separates the 'cope with depression or nervousness' item into two items, and an additional item was created to assess mood fluctuations ('drinking to help when your mood changes a lot'). For each of the seven items, participants rated on a four-point ordinal scale how frequently they drink alcohol for that reason: 0 'almost never', 1 'sometimes', 2 'often', 3 'almost always'. The seven ordinal items were then summed, and the resulting scale was dichotomised at the top quartile (score of 5). Other researchers have dichotomised DTC in other ways, for example using a median split, or using the mean +/- one standard deviation. I decided not to use the median, as this was quite low in this sample (score of 3), and I decided not to

use the latter method as this would exclude 50% of the sample and thus reduce power.

One reviewer questioned why I made changes to the original Drinking Motives Questionnaire. They suggested a sensitivity analysis with DTC scored in a more traditional manner. As only four out of the five original coping items were available in ALSPAC (forget worries, relax, cheer up, feel more confident), a sensitivity analysis would mean dropping the new item, and taking an average between the two items that were separated from a single measure. I considered whether a sensitivity analysis would be helpful, by deriving a polychoric correlation matrix for the seven DTC items in ALSPAC. As shown in Table 3.1, the four original items do not appear to correlate with each other any better than with the new items; they are all strongly positively correlated with a similar magnitude. This suggests the sensitivity analyses would not change my results and supports my decision to use all the data available (seven items). To justify this decision, I created a new DTC total score variable by combining the 'help when feeling nervous' and 'help when feeling depressed' items, and dropping the 'help when mood changes' item, as suggested. The upper quartile score on this new measure was 5 (matching my original binary measure), which confirmed that the proposed sensitivity analyses would make no difference to the results.

Table 3.1. Polychoric correlation matrix for the seven drinking to cope items.

		1	2	3	4	5	6	7
1.	Forget worries	1						
2.	Relax	.49	1					
3.	Cheer up	.69	.55	1				
4.	Feel more confident	.51	.52	.54	1			
5.	Help when feeling depressed	.75	.46	.80	.48	1		
6.	Help when feeling nervous	.57	.50	.56	.67	.58	1	
7.	Help when mood changes	.62	.46	.67	.56	.71	.66	1

Original items from the scale by Cooper are 1, 2, 3, and 4.

3.3.2.3. Alcohol Use. Alcohol use was assessed at age 18 and age 21 using the Alcohol Use Disorders Identification Test (AUDIT) (World Health Organisation, 2001). For each age, I derived four binary alcohol outcome variables: frequent drinking, frequent bingeing, hazardous drinking and harmful drinking. The frequent drinking measure came from the first item of the AUDIT. Drinking alcohol '2 to 4 times a month', 'monthly or less', or 'never', was coded as infrequent drinking. Drinking alcohol '2 to 3 times a week', or '4 or more times a week' was coded as frequent drinking. The frequent bingeing measure came from the third item of the AUDIT. Individuals who consume six or more units on one occasion 'monthly', 'less than monthly' or 'never' were coded as infrequent binge drinkers, and those who consume six or more units 'weekly' or 'daily or almost daily' were coded as frequent binge drinkers. Individuals who scored ≥ 8 on the AUDIT were classified as hazardous drinkers, and scores of ≥ 16 indicated harmful drinking (World Health Organisation, 2001).

I derived two single-item measures of alcohol use because I was interested in frequent drinking and frequent bingeing as separate constructs. These variables were originally five-level ordinal variables. To determine whether these variables met the proportional odds assumption of ordered logistic regressions, I used the *gologit2* user written Stata command. The proportional odds assumption (otherwise known as the parallel regression assumption) stipulates that 'the coefficients that describe the relationship between, for example, the lowest versus all higher categories of the response variable are the same as those that describe the relationship between the next lowest category and all higher categories', and so on (UCLA: Statistical Consulting Group, 2019). These tests suggested the assumption was met; there was evidence of a linear increase between each level of the categorical variables. However, there were small ns for some levels of the ordinal variables, which reduced the sample size. Given that results with binary outcomes are easier to interpret than results with ordinal outcomes, and my other two outcomes were also binary, I converted the original 'drinking frequency' and 'bingeing frequency' items to binary variables, for consistency with the other two alcohol outcomes and for ease of interpretation.

The AUDIT is only administered clinically to people reporting recent alcohol use. Many of the questions would be skipped if the person reported not drinking during the last 12 months (however this does not mean that a score assigned to non-drinkers would be invalid). As being a non-drinker precludes DTC, I excluded individuals who had either never consumed alcohol or not consumed alcohol in the last 12 months from all main analyses, for consistency. As a sensitivity analysis, models which did not include DTC (i.e., those relating GAD to alcohol) were re-estimated whilst retaining the non-drinkers, with these participants assigned a value of zero for each binary alcohol measure. I performed this sensitivity analysis

as it plausible that anxiety may predict avoidance of alcohol, contrary to my hypothesis. Non-drinkers were included for 21-year alcohol outcomes, but there were only a few participants in this instance.

3.3.2.4. Potential Confounders. The following variables were included as potential confounders: sociodemographic variables (gender, maternal education, family income, housing tenure, and social class), parental variables (parental depression, anxiety, alcohol use, and tobacco use), and adolescent variables (tobacco use, cannabis use, drinking frequency and bingeing frequency four years earlier than the baseline alcohol outcomes, conduct problems, and emotional symptoms). Previous studies on this topic have not consistently adjusted for potentially relevant confounders, as shown in Chapter 2. Choice of confounders was therefore an important decision for us when designing the study, to reduce the likelihood of bias.

Confounders were selected based on their associations with both anxiety and alcohol use in the literature, the time points where they were considered most relevant, and based on the data (biggest sample size). Sociodemographic confounders are typically included in epidemiology studies. I included four variables to represent socioeconomic status (SES), rather than including only one, as this helps reduce residual confounding. As SES does not tend to vary over time, I took the baseline ALSPAC measures as there were more complete data compared to later ages. Choice of parental and adolescent confounders were based on their associations with anxiety and alcohol use in the literature. For example, children of parents with internalising disorders, are more likely to experience internalising symptoms in adolescence and adulthood (Mars et al., 2012) and children of parents who drink alcohol are more likely to drink alcohol in adolescence and adulthood (Merline et al., 2008). In addition, externalising

disorders are positively associated with anxiety (Angold et al., 1999) and alcohol use (Farmer et al., 2016). I adjusted for earlier alcohol use to reduce the chance of reverse causation (i.e., alcohol use predicting subsequent anxiety).

Some variables are measured at several time points in ALSPAC, so I had to decide which time point was most appropriate for each variable. It is generally better to select confounders at earlier time-points as there is more likely to be complete data. However, it is important to select an age when the confounder is likely to have the most influence. For example, parental substance use confounders arguably should be selected at a time when the child starts drinking (i.e., around age 13). Where the same measures were available at several relevant time-points, I chose the measure with the biggest sample size, as measures typically correlate over time.

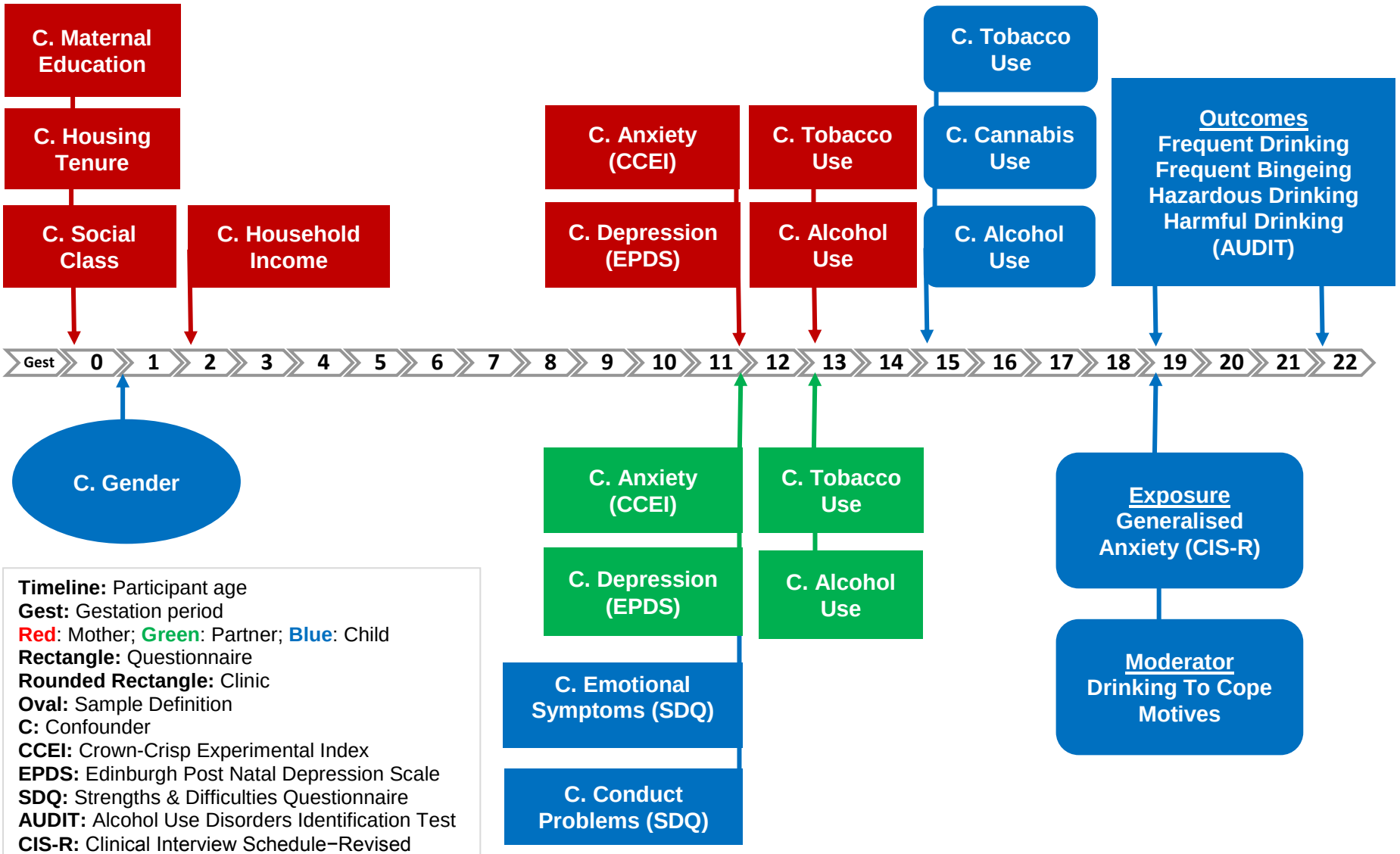
I did not include adolescent depression as a potential confounder as its comorbidity with anxiety may have resulted in model over-adjustment. I made all the confounders binary to improve sample size. I separated the confounders into three models instead of grouping them together in one model, as the more models there are, the easier it is to tell which confounders are affecting the associations. Table 3.2 provides more details of the confounding variables, and Figure 3.1 shows a timeline of all study variables.

Table 3.2. Confounding variables.

Variable	Variable Information
Gender	1 = male; 2 = female.
Maternal Education	0 = CSE, vocational, O-level; 1 = A-level, degree.
Household Income	Per week (£): 0 = <100, 100 – 199, 200 – 299; 1 = 300 – 399, >400.
Housing Tenure	0 = mortgaged, owned; 1 = council rented, private rented, housing association rented.
Social Class	Highest social class out of mother and mother's partner based on occupation: 0 = non-manual

	(professional, managerial and technical, skilled non-manual); 1 = manual (skilled manual, partly skilled, unskilled).
Parental Depression	First made the Edinburgh Post Natal Depression Scale (EPDS) binary based on the established cut-off: 0 = no depression (total score <13); 1 = depression (total score >12). Then combined parents: 0 = no parent with depression; 1 = either parent or both parents with depression.
Parental Anxiety	First made the anxiety subscale of the Crown Crisp Experiential Index (CCEI) binary based on the 85th percentile: 0 = no anxiety (total score 0-8 for mother, 0-5 for partner); 1 = anxiety (total score 9-16 for mother, 6-16 for partner). Then combined parents: 0 = no parent with anxiety; 1 = either parent or both parents with anxiety.
Mother Binge Drinking	Evidence of binge drinking (derived by JH for a different study) from a detailed record of beers, wines and spirits consumed in the previous week. First calculated binge drinking for each day of the week: binge drinking = >4 units. Then created an any binge drinking variable: 0 = no binge drinking on any day of the week; 1 = binge drinking on 1-7 days of the week.
Mother Alcohol Use	Evidence of high weekly consumption derived by JH from a detailed record of beers, wines and spirits consumed in the previous week: 0 = 0-13 units; 1 = 14 or more units.
Partner Alcohol Use	Drinking frequency: 0 = never, < once a week, ≥ once a week; 1 = nearly every day, every day.
Mother Tobacco Use	0 = no cigarettes per day; 1 = ≥1 cigarette per day.
Partner Tobacco Use	0 = no cigarettes per day; 1 = ≥1 cigarette per day.
Adolescent Tobacco Use	Smoking frequency: 0 = never; 1 = less than weekly, weekly or more.
Adolescent Cannabis Use	Cannabis use frequency: 0 = never; 1 = less than weekly, weekly or more.
Adolescent Ever Use of Alcohol	Ever consumed a whole drink in the past six months: 0 = no; 1 = yes.
Adolescent Binge Drinking	Maximum drinks in a 24-hour period based on an established cut-off for this age group: 0 = no binge drinking (0-2 drinks); 1 = binge drinking (>2 drinks).
Adolescent Conduct Problems	Conduct problems subscale of the Strengths and Difficulties Questionnaire (SDQ): 0 = low (total score 0-1); 1 = medium or high (total score 2-10).
Adolescent Emotional Symptoms	Emotional symptoms subscale of the Strengths and Difficulties Questionnaire (SDQ): 0 = low (total score 0-1); 1 = medium or high (total score 2-10).

Figure 3.1. Timeline of study variables.



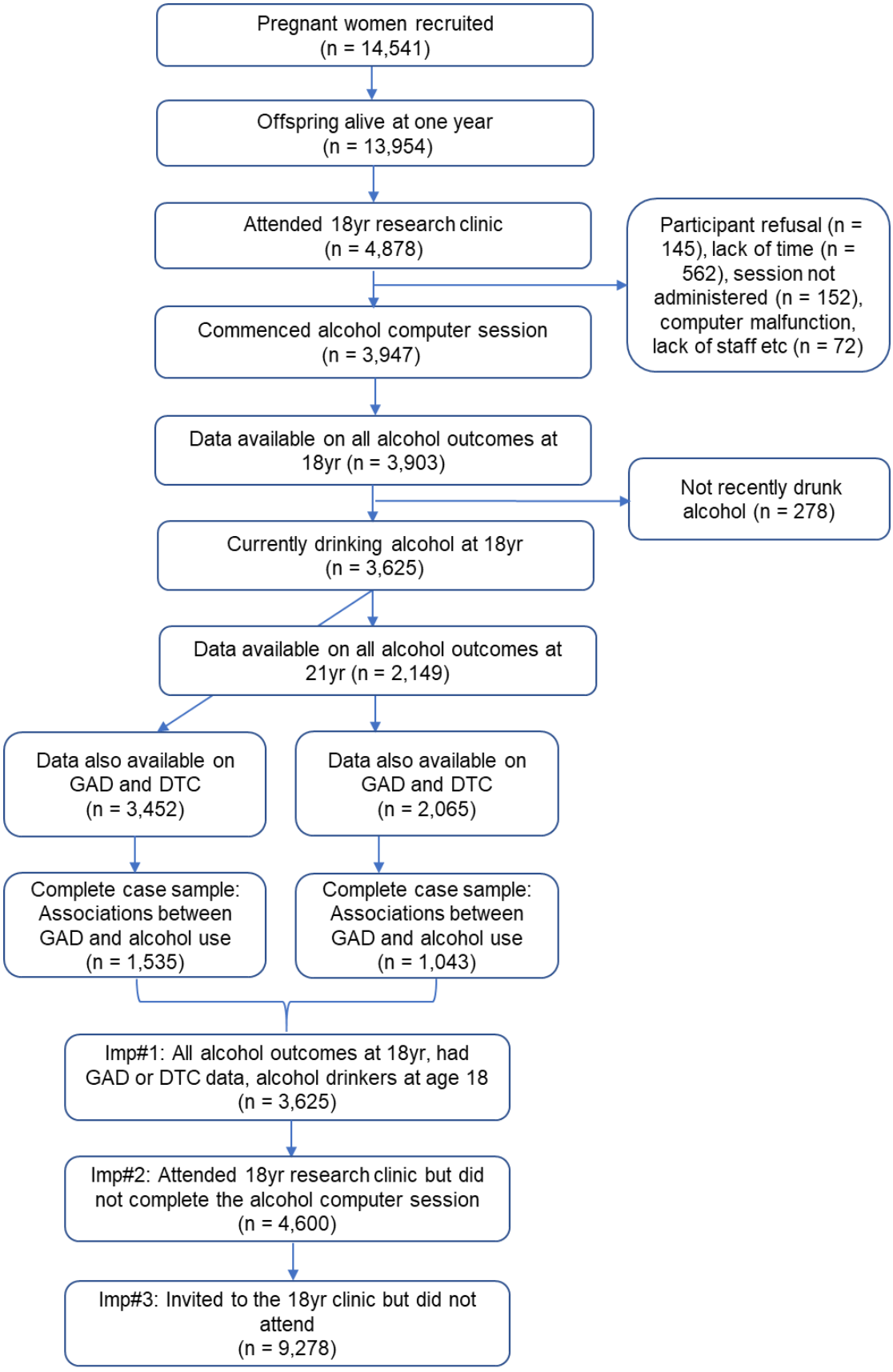
3.3.3. Statistical Analyses

3.3.3.1. Available Data. All analyses were conducted in Stata version 14. I used logistic regressions to examine associations between GAD at age 18 and frequent drinking, frequent bingeing, hazardous drinking and harmful drinking at ages 18 and 21. I assessed the impact of potential confounding by comparing unadjusted results (model 1) with results incrementally adjusted for sociodemographic confounders (model 2), parental confounders (model 3), and adolescent confounders (model 4). In the prospective analyses, I did not adjust for baseline alcohol use as I thought this would result in model over-adjustment.

I examined evidence of moderation by conducting interaction tests (i.e., including a GAD × DTC interaction term), and then stratifying analyses by DTC motives (high versus low). I also performed likelihood ratio tests by estimating and comparing models with and without an interaction term. The interaction analyses tested the null hypotheses of no interaction between GAD and DTC on the alcohol outcomes (i.e., no clear evidence that DTC moderates associations between GAD and alcohol use). The odds ratio for an interaction term is a ratio of odds ratios. For example, an odds ratio of 2 means the odds of harmful drinking among people with GAD is twice as high among people with high DTC motives versus people with low DTC motives. Corresponding stratified analyses show the odds of harmful drinking among people with GAD (versus no GAD), separately among people with high and low DTC motives. Regardless of the results of the interaction tests, I present all interaction analyses stratified for completeness.

3.3.3.2. Missing Data. A breakdown of how the final analysis samples were determined is shown in Figure 3.2.

Figure 3.2. Study sample size flow diagram.



Although 4,878 people attended the 18-year clinic, only 3,947 started the computer session which included questions on alcohol use, other substances and antisocial behaviour. Of the participants who started the computer session, 3,903 provided responses to the 10 AUDIT questions, with 278 reporting that they had never or not recently drunk alcohol. This left a sample of 3,625 who had all four baseline alcohol measures, had GAD or DTC measures, were core cases, and were alcohol drinkers at age 18.

Missing data can be classified into three types: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR). Data are MCAR when there are no systematic differences between the missing values and the observed values (Sterne et al., 2009). For example, anxiety data from a computer task may be missing if the computer broke down that day. Data are MAR when any systematic difference between the missing values and the observed values can be explained by differences in observed data (Sterne et al., 2009). For example, missing anxiety data may be higher than measured anxiety data, if females were more likely to have missing anxiety data. Data are MNAR if systematic differences remain between the missing values and the observed values, even after the observed data are taken into account (Sterne et al., 2009). For example, if people with anxiety were more likely to miss the ALSPAC research clinic appointments.

I initially conducted the analyses using only the available data (complete case). However, 3,625 participants represent a small proportion of the original ALSPAC sample. Furthermore, the inclusion of multiple confounders from a wide range of time-points, respondents, questionnaires, and clinics, meant that the proportion of missing data increased from model 1 (unadjusted) to model 4 (fully adjusted). When analysing only the available data, unadjusted and adjusted models are

difficult to compare. Any differences between point estimates across models may either be due to the adjustment of confounders, or the reduction of sample size and subsequent loss of power, as both are occurring. A co-author (JH) therefore used multiple imputation to examine the robustness of the available-data results. I did not do the multiple imputation analyses because my PhD is in psychology rather than epidemiology, and the training course was only available a year later, which would have delayed the submission of the paper.

Multiple imputation 'aims to allow for the uncertainty about the missing data by creating several different plausible imputed data sets and appropriately combining results obtained from each of them' (Sterne et al., 2009). With imputed data, sample size remains constant across unadjusted and adjusted models. Therefore, any changes in point estimates must be explained by confounding. Multiple imputation is also preferable to complete case analyses because it prevents the loss of statistical power. JH used multiple imputation to examine the potential for non-random attrition leading to distorted conclusions. The use of multiple imputation increases the likelihood that an MAR assumption can be made, as auxiliary variables that predict missingness can be included (Graham, 2009). In this study he used additional data in ALSPAC to try to break any link between the model variables and the missingness mechanism, and thus reduce potential bias.

First, 21-year alcohol and confounder information were predicted among the 3,625 participants with baseline alcohol data (imp#1). Following this, the imputation sample was boosted to 4,600 (imp#2) and then to 9,278 (imp#3) to include those who attended the 18-year research clinic but did not complete the alcohol session, and those who were invited to the clinic but did not attend, respectively. For these imputations, he made the simplifying assumption that these additional participants

would have been eligible to complete the whole AUDIT, as being a non-drinker is rare in this group.

JH performed the multiple imputation using multivariate imputation by chained equations, implemented using the -ice- command in Stata (Royston & White, 2011). Multiple datasets were created with missing values replaced by plausible imputed values, based on the original model variables (default approach), as well as auxiliary variables used to predict missingness (tailored prediction equations). Multiple imputation adds variability into imputed values to account for the uncertainty; it is impossible to know the true values of the missing data (Sterne et al., 2009). Twenty cycles of regression switching were used for all imputation models. Both the quantity of auxiliary data and the number of datasets were increased as the sample size increased, the latter being guided by the Monte Carlo errors (White et al., 2011). Imp#1 and imp#2 had 100 imputations, and imp#3 had 200 imputations. I present the results from the available data and imp#1 in this chapter, and results from all imputation models can be found in the appendices section.

3.4. Results

Frequencies and percentages of alcohol use according to GAD and DTC motives, are presented in Table 3.3 (available data) and Appendices 3.1 and 3.2 (available data and multiply-imputed data). Results from the regression models are presented in Tables 3.4, 3.5, and 3.6 (available data and imputation 1), and Appendices 3.3, 3.4, 3.5, and 3.6 (available data and imputations 1, 2, and 3).

Table 3.3. Frequencies and percentages for the main variables (available data).

		Frequent Drinking		Frequent Bingeing		Hazardous Drinking		Harmful Drinking	
		Age 18	**Age 21**	**Age 18**	**Age 21**	**Age 18**	**Age 21**	**Age 18**	**Age 21**
Whole sample		939 25.9%	845 40.9%	516 14.2%	706 32.6%	1551 42.8%	1246 57.6%	209 5.8%	280 12.9%
GAD	**No**	826 25.3%	786 40.3%	460 14.1%	635 32.6%	1382 42.3%	1118 57.3%	180 5.5%	247 12.7%
	Yes	62 32.1%	58 46.4%	36 18.7%	41 32.8%	99 51.3%	79 63.2%	20 10.4%	25 20.0%
DTC	**Low**	565 20.4%	658 39.0%	272 9.8%	516 30.6%	934 33.7%	907 53.8%	63 2.3%	172 10.2%
	High	373 44.3%	223 47.9%	241 28.6%	185 39.7%	614 72.8%	333 71.5%	146 17.3%	105 22.5%
GAD (Low DTC)	**No**	520 20.3%	598 38.5%	257 10.0%	470 30.3%	866 33.8%	830 53.4%	59 2.3%	156 10.1%
	Yes	16 15.8%	29 42.7%	7 6.93%	19 27.9%	33 32.7%	38 55.9%	<5 <5%	10 14.7%
GAD (High DTC)	**No**	305 43.5%	184 47.4%	201 28.7%	161 41.5%	514 73.3%	283 72.9%	121 17.3%	89 22.9%
	Yes	46 50.6%	29 51.8%	28 30.8%	21 37.5%	65 71.4%	40 71.4%	17 18.7%	14 25.0%

GAD = generalised anxiety disorder; DTC = drinking to cope

3.4.1. Associations between GAD and Alcohol Use

At age 18, there was evidence of a positive association between GAD and all four alcohol outcomes. In unadjusted analyses with the available data, GAD was associated with more frequent drinking (OR 1.40, 95% CI 1.02 to 1.91, p = .036), hazardous drinking (OR 1.44, 95% CI 1.08 to 1.92, p = .014) and harmful drinking (OR 1.98, 95% CI 1.22 to 3.23, p = .006). There was only very weak evidence that GAD was associated with more frequent bingeing (OR 1.40, 95% CI 0.96 to 2.04, p = .079). For hazardous and harmful drinking, the associations were robust to adjustment for sociodemographic, parental and adolescent confounders, whereas for frequent drinking and frequent bingeing the associations were attenuated (Table 3.4). Following imputation, it was clear that sample reduction was driving the instability in point estimates for the more problematic alcohol outcomes. Imputed results show confounders to have a more modest impact on the

associations between GAD and alcohol outcomes (Appendix 3.3). For harmful drinking, the odds ratios did not change as dramatically from model 1 (unadjusted) to model 4 (full adjusted) in the models with imputed data compared to the models with available data.

Table 3.4 shows the associations between adolescent GAD and alcohol use three years later were weaker than the cross-sectional associations. GAD increased the odds of harmful drinking at age 21 (available data unadjusted OR 1.72, 95% CI 1.09 to 2.73, p = .020), but there was no clear evidence of a longitudinal relationship between GAD and the other alcohol use outcomes. Imputed results showed little attenuation due to confounding (fully adjusted imputation 1 OR 1.68, 95% CI 1.09 to 2.60, p = .020). See Appendix 3.3 for all multiply-imputed results.

Table 3.4. Logistic regressions examining the associations of generalised anxiety disorder at age 18 with alcohol use at age 18 and 21.

		Age 18 Available data (n as shown)			Age 18 Imp#1 (n = 3625)		Age 21 Available data (n as shown)			Age 21 Imp#1 (n = 3625)	
	Model	**N**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**	**N**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**
Frequent Drinking	Model 1	3462	1.40 [1.02, 1.91]	.036	1.41 [1.03, 1.93]	.030	2076	1.28 [0.89, 1.84]	.178	1.26 [0.88, 1.80]	.204
	Model 2	2603	1.71 [1.19, 2.45]	.004	1.61 [1.17, 2.21]	.003	1611	1.34 [0.88, 2.06]	.176	1.38 [0.95, 2.00]	.091
	Model 3	1832	1.76 [1.13, 2.76]	.013	1.57 [1.13, 2.16]	.007	1213	1.77 [1.05, 3.00]	.033	1.38 [0.94, 2.03]	.097
	Model 4	1535	1.67 [0.99, 2.82]	.055	1.50 [1.07, 2.09]	.017	1043	1.44 [0.79, 2.63]	.232	1.34 [0.91, 1.99]	.138
Frequent Bingeing	Model 1	3462	1.40 [0.96, 2.04]	.079	1.39 [0.96, 2.02]	.083	2076	1.01 [0.69, 1.49]	.953	1.01 [0.69, 1.47]	.968
	Model 2	2603	1.66 [1.08, 2.57]	.021	1.54 [1.06, 2.26]	.025	1611	0.94 [0.60, 1.49]	.799	1.10 [0.75, 1.62]	.618
	Model 3	1832	1.81 [1.06, 3.09]	.031	1.51 [1.03, 2.22]	.034	1213	1.03 [0.60, 1.78]	.913	1.07 [0.72, 1.60]	.724
	Model 4	1535	1.67 [0.88, 3.18]	.120	1.45 [0.97, 2.15]	.068	1043	0.75 [0.40, 1.43]	.390	1.06 [0.71, 1.58]	.789
Hazardous Drinking	Model 1	3462	1.44 [1.08, 1.92]	.014	1.44 [1.08, 1.93]	.014	2076	1.28 [0.88, 1.86]	.197	1.23 [0.85, 1.79]	.279
	Model 2	2603	1.64 [1.17, 2.30]	.004	1.52 [1.13, 2.03]	.005	1611	1.31 [0.85, 2.01]	.226	1.30 [0.89, 1.90]	.174
	Model 3	1832	2.10 [1.37, 3.22]	.001	1.47 [1.09, 1.98]	.011	1213	2.16 [1.21, 3.84]	.009	1.29 [0.88, 1.89]	.200
	Model 4	1535	1.98 [1.21, 3.25]	.007	1.41 [1.03, 1.92]	.030	1043	1.86 [0.99, 3.49]	.054	1.26 [0.85, 1.87]	.256
Harmful Drinking	Model 1	3462	1.98 [1.22, 3.23]	.006	1.99 [1.22, 3.23]	.006	2076	1.72 [1.09, 2.73]	.020	1.67 [1.11, 2.51]	.014
	Model 2	2603	2.48 [1.42, 4.33]	.001	2.05 [1.25, 3.34]	.004	1611	1.51 [0.86, 2.67]	.152	1.79 [1.18, 2.71]	.006
	Model 3	1832	3.55 [1.90, 6.63]	<.001	1.97 [1.20, 3.25]	.008	1213	1.47 [0.75, 2.88]	.258	1.77 [1.16, 2.70]	.008
	Model 4	1535	4.10 [1.88, 8.93]	<.001	1.87 [1.12, 3.12]	.017	1043	1.29 [0.57, 2.91]	.536	1.68 [1.09, 2.60]	.020

Model 1 = unadjusted; model 2 = adjusted for sociodemographic confounders: gender, maternal education, family income, housing tenure, and social class; model 3 = additionally adjusted for parental confounders: parental depression, anxiety, alcohol use, and tobacco use; model 4 = additionally adjusted for adolescent confounders: tobacco use, cannabis use, drinking frequency, binge drinking, conduct problems, and emotional symptoms.

3.4.2. Associations between GAD and DTC

The odds of DTC were three times higher in individuals with GAD compared to those without GAD (available data unadjusted OR 3.23, 95% CI 2.41 to 4.34, *p* <.001). This association remained after adjusting for sociodemographic, parental and adolescent confounders (Appendix 3.4).

3.4.3. Associations between DTC and Alcohol Use

DTC was strongly associated with all alcohol outcomes at both ages (Table 3.5). Similar to the relationship between GAD and the alcohol outcomes, associations between DTC and alcohol use at age 18 increased from frequent drinking (available data unadjusted OR 3.10, 95% CI 2.63 to 3.65, *p* <.001) to harmful drinking (available data unadjusted OR 9.01, 95% CI 6.63 to 12.25, *p* <.001). Associations were robust to adjustment for confounders. This pattern was also evident at age 21, but point estimates were smaller. Imputed results are shown in Appendix 3.5.

3.4.4. Interactions between GAD and DTC on Alcohol Use

I examined evidence that DTC motives moderated associations between GAD and alcohol use outcomes using stratified analyses (high versus low DTC) followed by interaction tests (Table 3.6). There was no clear evidence to support the hypothesis that associations between GAD and alcohol use outcomes would be stronger in people with high (versus low) DTC motives. Imputed results are shown in Appendix 3.6.

Table 3.5. Logistic regressions examining the associations of drinking to cope motives at age 18 with alcohol use at age 18 and 21.

		Age 18 Available data (n as shown)			Age 18 Imp#1 (n = 3625)		Age 21 Available data (n as shown)			Age 21 Imp#1 (n = 3625)	
	Model	**N**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**	**N**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**
Frequent Drinking	Model 1	3617	3.10 [2.63, 3.65]	<.001	3.10 [2.63, 3.65]	<.001	2152	1.43 [1.17, 1.76]	.001	1.43 [1.18, 1.74]	<.001
	Model 2	2730	3.15 [2.59, 3.82]	<.001	3.33 [2.82, 3.94]	<.001	1678	1.59 [1.24, 2.02]	<.001	1.50 [1.23, 1.84]	<.001
	Model 3	1915	2.84 [2.25, 3.59]	<.001	3.26 [2.75, 3.87]	<.001	1258	1.63 [1.22, 2.16]	.001	1.45 [1.18, 1.79]	<.001
	Model 4	1607	2.46 [1.88, 3.21]	<.001	3.00 [2.52, 3.57]	<.001	1084	1.50 [1.10, 2.06]	.012	1.37 [1.10, 1.69]	.005
Frequent Bingeing	Model 1	3617	3.68 [3.03, 4.47]	<.001	3.69 [3.03, 4.48]	<.001	2152	1.49 [1.21, 1.85]	<.001	1.51 [1.24, 1.84]	<.001
	Model 2	2730	3.65 [2.91, 4.60]	<.001	3.85 [3.16, 4.69]	<.001	1678	1.61 [1.26, 2.06]	<.001	1.58 [1.29, 1.93]	<.001
	Model 3	1915	3.34 [2.52, 4.43]	<.001	3.74 [3.06, 4.56]	<.001	1258	1.61 [1.21, 2.14]	.001	1.52 [1.23, 1.87]	<.001
	Model 4	1607	3.14 [2.27, 4.36]	<.001	3.44 [2.80, 4.23]	<.001	1084	1.48 [1.08, 2.03]	.015	1.45 [1.17, 1.80]	.001
Hazardous Drinking	Model 1	3617	5.28 [4.45, 6.27]	<.001	5.29 [4.46, 6.27]	<.001	2152	2.15 [1.72, 2.69]	<.001	2.19 [1.75, 2.74]	<.001
	Model 2	2730	4.81 [3.95, 5.86]	<.001	5.44 [4.58, 6.47]	<.001	1678	2.24 [1.73, 2.90]	<.001	2.28 [1.81, 2.86]	<.001
	Model 3	1915	4.81 [3.79, 6.10]	<.001	5.32 [4.47, 6.33]	<.001	1258	2.14 [1.58, 2.90]	<.001	2.21 [1.75, 2.79]	<.001
	Model 4	1607	4.34 [3.32, 5.68]	<.001	5.01 [4.19, 5.99]	<.001	1084	2.12 [1.52, 2.96]	<.001	2.12 [1.67, 2.69]	<.001
Harmful Drinking	Model 1	3617	9.01 [6.63, 12.25]	<.001	9.00 [6.62, 12.24]	<.001	2152	2.56 [1.96, 3.35]	<.001	2.73 [2.13, 3.51]	<.001
	Model 2	2730	8.62 [5.99, 12.41]	<.001	9.14 [6.71, 12.44]	<.001	1678	2.75 [2.02, 3.73]	<.001	2.83 [2.19, 3.65]	<.001
	Model 3	1915	8.02 [5.18, 12.42]	<.001	8.82 [6.45, 12.04]	<.001	1258	2.52 [1.76, 3.59]	<.001	2.70 [2.09, 3.50]	<.001
	Model 4	1607	7.06 [4.17, 11.96]	<.001	7.97 [5.81, 10.95]	<.001	1084	2.33 [1.56, 3.48]	<.001	2.46 [1.88, 3.22]	<.001

Model 1 = unadjusted; model 2 = adjusted for sociodemographic confounders: gender, maternal education, family income, housing tenure, and social class; model 3 = additionally adjusted for parental confounders: parental depression, anxiety, alcohol use, and tobacco use; model 4 = additionally adjusted for adolescent confounders: tobacco use, cannabis use, drinking frequency, binge drinking, conduct problems, and emotional symptoms.

Table 3.6. Logistic regressions examining the interactions between generalised anxiety disorder and drinking to cope motives at age 18 on alcohol use at age 18 and 21.

		Age 18 Available data (n as shown)			Age 18 Imp#1 (n = 3625)		Age 21 Available data (n as shown)			Age 21 Imp#1 (n = 3625)	
	Model	**N**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**	**N**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**
Frequent Drinking	*Stratum specific*										
	Low DTC	2660	0.74 [0.43, 1.27]	.270	0.76 [0.44, 1.30]	.315	1621	1.19 [0.73, 1.94]	.493	1.16 [0.71, 1.89]	.550
	High DTC	792	1.33 [0.86, 2.06]	.204	1.34 [0.87, 2.06]	.188	444	1.19 [0.68, 2.09]	.542	1.17 [0.68, 2.00]	.578
	Interaction	3452	1.80 [0.90, 3.62]	.098	1.77 [0.88, 3.54]	.108	2065	1.00 [0.48, 2.11]	.994	1.00 [0.49, 2.04]	.991
Frequent Bingeing	*Stratum specific*										
	Low DTC	2660	0.67 [0.31, 1.45]	.309	0.67 [0.31, 1.47]	.319	1621	0.89 [0.52, 1.53]	.683	0.89 [0.52, 1.50]	.651
	High DTC	792	1.11 [0.69, 1.78]	.678	1.15 [0.72, 1.84]	.557	444	0.85 [0.47, 1.51]	.570	0.91 [0.51, 1.61]	.736
	Interaction	3452	1.66 [0.67, 4.12]	.278	1.71 [0.69, 4.25]	.248	2065	0.95 [0.43, 2.09]	.892	1.02 [0.46, 2.27]	.955
Hazardous Drinking	*Stratum specific*										
	Low DTC	2660	0.95 [0.62, 1.45]	.810	0.96 [0.63, 1.47]	.850	1621	1.10 [0.68, 1.80]	.693	1.01 [0.64, 1.59]	.966
	High DTC	792	0.91 [0.56, 1.48]	.701	0.92 [0.57, 1.49]	.737	444	0.93 [0.50, 1.73]	.813	0.96 [0.53, 1.75]	.905
	Interaction	3452	0.96 [0.50, 1.82]	.896	0.96 [0.50, 1.82]	.899	2065	0.84 [0.38, 1.85]	.667	0.95 [0.45, 2.01]	.903
Harmful Drinking	*Stratum specific*										
	Low DTC	2660	1.30 [0.40, 4.21]	.664	1.30 [0.40, 4.23]	.659	1621	1.54 [0.77, 3.08]	.218	1.56 [0.78, 3.11]	.208
	High DTC	792	1.10 [0.63, 1.93]	.737	1.12 [0.64, 1.96]	.693	444	1.12 [0.58, 2.14]	.733	1.08 [0.59, 2.00]	.798
	Interaction	3452	0.85 [0.23, 3.13]	.805	0.86 [0.23, 3.17]	.820	2065	0.73 [0.28, 1.87]	.507	0.69 [0.28, 1.71]	.428

Unadjusted model. Stratified analysis: associations of generalised anxiety disorder (GAD) at age 18 with alcohol use outcomes at age 18 and 21 in each stratum of drinking to cope (DTC) motives. Interaction term: interaction of GAD x DTC at age 18 on alcohol use outcomes at age 18 and 21

3.4.5. Attrition

Analyses with the available data revealed that problem drinkers at age 18 were less likely to provide complete outcome data at age 21 (frequent drinkers OR 0.74, 95% CI 0.64 to 0.86, p <.001; frequent binge drinkers OR 0.63, 95% CI 0.52 to 0.76, p <.001; hazardous drinkers OR 0.74, 95% CI 0.65 to 0.84, p <.001; harmful drinkers OR 0.60, 95% CI 0.46 to 0.80, p <.001). However, there was no clear evidence of an association between GAD at age 18 and completeness of outcome data at age 21 (OR 1.07, 95% CI 0.82 to 1.39, p = .62).

3.4.6. Sensitivity Analyses

Results shown in Appendices 3.3 to 3.6 indicate my conclusions are consistent across the various imputed datasets. In addition, the inclusion of non-drinkers had little impact on the relationship between GAD and alcohol use at either age 18 or 21 years (Table 3.7). Conclusions were also seen to be robust to the removal of other internalising disorders from the GAD reference group (Table 3.8).

Table 3.7. Logistic regressions examining the associations of generalised anxiety disorder at age 18 with alcohol use at age 18 and 21, including non-drinkers at age 18 (available data only).

			Frequent Drinking		Frequent Bingeing		Hazardous Drinking		Harmful Drinking	
	Model	**N**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**
Age 18										
	Model 1	3727	1.40 [1.03, 1.91]	.031	1.41 [0.97, 2.05]	.071	1.43 [1.08, 1.90]	.012	2.00 [1.23, 3.24]	.005
	Model 2	2798	1.69 [1.19, 2.41]	.004	1.65 [1.08, 2.54]	.022	1.58 [1.14, 2.20]	.006	2.46 [1.41, 4.29]	.002
	Model 3	1957	1.73 [1.12, 2.69]	.014	1.78 [1.05, 3.03]	.033	1.95 [1.30, 2.94]	.001	3.48 [1.87, 6.48]	<.001
	Model 4	1641	1.62 [0.97, 2.72]	.065	1.64 [0.87, 3.11]	.129	1.82 [1.14, 2.92]	.013	3.96 [1.83, 8.58]	<.001
Age 21										
	Model 1	2511	1.24 [0.89, 1.73]	.205	0.94 [0.65, 1.35]	.724	1.13 [0.81, 1.58]	.467	1.68 [1.09, 2.58]	.018
	Model 2	1936	1.27 [0.85, 1.89]	.236	0.87 [0.56, 1.34]	.522	1.11 [0.75, 1.64]	.597	1.48 [0.87, 2.52]	.148
	Model 3	1445	1.67 [1.03, 2.70]	.039	0.94 [0.56, 1.57]	.817	1.59 [0.97, 2.60]	.065	1.49 [0.80, 2.78]	.208
	Model 4	1224	1.35 [0.77, 2.36]	.289	0.69 [0.37, 1.28]	.238	1.36 [0.79, 2.36]	.271	1.28 [0.60, 2.74]	.526

Model 1 = unadjusted; model 2 = adjusted for sociodemographic confounders: gender, maternal education, family income, housing tenure, and social class; model 3 = additionally adjusted for parental confounders: parental depression, anxiety, alcohol use, and tobacco use; model 4 = additionally adjusted for adolescent confounders: tobacco use, cannabis use, drinking frequency, binge drinking, conduct problems, and emotional symptoms.

Table 3.8. Logistic regressions examining the associations of generalised anxiety disorder at age 18 with alcohol use at age 18 and 21, with an alternative control group (available data only).

			Frequent Drinking		Frequent Bingeing		Hazardous Drinking		Harmful Drinking	
	Model	**N**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**
Age 18										
	Model 1	3407	1.42 [1.05, 1.94]	.025	1.44 [0.99, 2.09]	.057	1.49 [1.13, 1.98]	.005	2.17 [1.33, 3.54]	.002
	Model 2	2560	1.74 [1.22, 2.49]	.002	1.71 [1.11, 2.64]	.015	1.69 [1.21, 2.34]	.002	2.75 [1.57, 4.84]	<.001
	Model 3	1805	1.80 [1.16, 2.79]	.009	1.81 [1.06, 3.10]	.029	2.09 [1.39, 3.14]	<.001	3.82 [2.03, 7.19]	<.001
	Model 4	1525	1.71 [1.02, 2.87]	.043	1.70 [0.90, 3.25]	.105	1.94 [1.21, 3.12]	.006	4.35 [1.99, 9.52]	<.001
Age 21										
	Model 1	2306	1.20 [0.86, 1.68]	.288	0.92 [0.64, 1.32]	.645	1.15 [0.82, 1.60]	.429	1.69 [1.10, 2.60]	.017
	Model 2	1778	1.22 [0.82, 1.82]	.322	0.86 [0.55, 1.32]	.482	1.12 [0.75, 1.65]	.582	1.51 [0.88, 2.57]	.134
	Model 3	1333	1.61 [0.99, 2.62]	.053	0.94 [0.56, 1.58]	.821	1.63 [0.99, 2.67]	.054	1.50 [0.80, 2.80]	.207
	Model 4	1128	1.30 [0.74, 2.28]	.356	0.68 [0.37, 1.27]	.224	1.36 [0.78, 2.37]	.276	1.25 [0.58, 2.68]	.566

Alternative control group: individuals with no GAD or any other type of anxiety or depression. Model 1 = unadjusted; model 2 = adjusted for sociodemographic confounders: gender, maternal education, family income, housing tenure, and social class; model 3 = additionally adjusted for parental confounders: parental depression, anxiety, alcohol use, and tobacco use; model 4 = additionally adjusted for adolescent confounders: tobacco use, cannabis use, drinking frequency, binge drinking, conduct problems, and emotional symptoms.

3.5. Discussion

3.5.1. Summary of Findings

Consistent with self-medication theory, GAD at age 18 was positively associated with concurrent frequent drinking, frequent bingeing, hazardous drinking, and harmful drinking in this sample of late adolescent drinkers. Although the associations with hazardous and harmful drinking were robust to adjustment for all confounders, associations with frequent drinking and frequent bingeing were attenuated in later models. This suggests adolescent tobacco use, cannabis use, binge drinking, conduct problems, and emotional symptoms may be confounding these associations. GAD at age 18 was prospectively associated with more harmful drinking at age 21, consistent with self-medication theory. However, I found no clear evidence of a prospective relationship between GAD and frequent drinking, frequent bingeing, and hazardous drinking in early adulthood. I also predicted associations between GAD and alcohol outcomes would be stronger in individuals who endorse high (versus low) DTC motives. However, there was no clear evidence that DTC moderated associations between GAD and alcohol use outcomes. The findings were consistent across the three imputed datasets.

This same pattern has been observed with other anxiety disorders where anxiety is more strongly positively associated with alcohol problems/disorders than with alcohol consumption levels (Dyer et al., 2019a; Schry & White, 2013). This suggests the self-medication hypothesis and tension-reduction hypothesis may be most pertinent for problem drinkers. However, reverse causation is possible – problem drinking could lead to greater anxiety. Associations between anxiety and general consumption may be more context-dependent, which could explain the weaker associations. For example, there may be situational or individual difference variables which moderate the extent to which individuals with anxiety drink more

or more frequently. Perhaps at the most severe forms of drinking, there may be common biological (Agoglia & Herman, 2018), cognitive (Chow et al., 2018), and/or environmental vulnerabilities (Jones et al., 2018) that increase the risk of both anxiety disorders and alcohol problems.

The self-medication mechanism is perhaps more conceivable for cross-sectional than prospective associations. Like taking a painkiller to reduce current pain, drinking alcohol to reduce current anxiety would be immediate. GAD at age 18 may therefore be associated with harmful drinking at age 21, either through harmful drinking at age 18, or alternatively through anxiety at age 21. In support of the former proposed mechanism, other ongoing work from researchers in our group suggests there may be no prospective enduring association between adolescent anxiety and alcohol use in early adulthood; the effect of anxiety had already occurred through adolescent alcohol use.

3.5.2. Original Research Contribution

This is the largest study to investigate prospective associations between GAD in adolescence and alcohol use in early adulthood with a series of multiply-imputed datasets, other sensitivity analyses to examine the robustness of the available-data estimates, and statistical adjustment for a range of important confounders. I found adolescent GAD was positively associated with harmful drinking three years later, contrary to other prospective cohort studies that have found no clear evidence of a longitudinal relationship between adolescent GAD and later AUD or alcohol dependence (Abram et al., 2015; Wolitzky-Taylor et al., 2012; Zimmermann et al., 2003). These differences in findings may be due to differences in the outcome measures used, or differences in sample size. For example, my fully adjusted analyses with the available data indicated no clear evidence of an association between GAD and later harmful drinking. Whereas analyses with the

multiply-imputed data suggested there was evidence of a positive association between GAD and later harmful drinking, highlighting the importance of an adequate sample size. The previous studies which did not find clear evidence of a relationship between GAD and alcohol use had smaller sample sizes, and therefore may not have been adequately powered to detect an association if one exists (Type II error). My study is also unique because I investigated the interaction of GAD and DTC motives on alcohol use in a late adolescent sample, using cross-sectional and prospective data.

3.5.3. Limitations

The present study has several limitations. First, observational studies have inherent methodological limitations due to the absence of randomisation, which precludes causal inferences from the data. Reverse causation is a possibility in the cross-sectional data. I adjusted for several potential confounders, but there may still be residual confounding. A Mendelian randomisation study, using genetic variants associated with anxiety or neuroticism, would help to determine whether anxiety causes problem drinking by eliminating the impact of confounding and reverse causation (Chao et al., 2017; Lawlor et al., 2008). Second, self-report measures of alcohol consumption and motivations for drinking may be subject to recall or social desirability biases and thus measurement error. Third, a lack of clear evidence for prospective associations between GAD and frequent drinking and frequent bingeing may be due to the use of single-item measures for these outcomes. Converting these ordinal items to binary variables may have also resulted in reduced power. However, my results are consistent with other prospective cohort studies (Dyer et al., 2019a), which suggests these measures are valid. Fourth, there was evidence of differential attrition at follow up; problem drinkers at age 18 were more likely to have missing outcome data at age 21. A smaller sample of problem drinkers at age 21 may have biased my results with the

available data towards the null. However, when JH included auxiliary data in multiple imputation models there was stronger evidence of an association between GAD and harmful drinking. By using multiple imputation, we increased the likelihood that a Missing at Random assumption could be made, therefore reducing the likelihood of bias. Finally, as the UK has one of the highest alcohol consumption levels for adolescents in Europe (Hibell et al., 2012), the findings may not be generalisable to other countries.

3.5.4. Future Directions

The relationship between GAD and alcohol use may be qualitatively different in adolescence compared to emerging adulthood, as a result of biological or social context changes over time. Adolescence is a developmental period characterised by greater propensity for risk-taking, impulsivity (Arnett, 1992), sensation seeking and susceptibility to peer influences (Albert & Steinberg, 2011). Behavioural and neuroimaging research has also shown adolescents have increased reward sensitivity, and reduced cognitive control than adults (Albert & Steinberg, 2011). In addition, as the legal age for purchasing alcohol in the UK is 18, drinking at age 18 might be considered novel and exciting. Late adolescence may therefore be a vulnerable period where the relationship between anxiety and alcohol use is more pronounced. A replication study in a USA cohort, at comparable time points related to the legal minimum drinking age, (i.e., age 21 versus 24) would also test the changing social context interpretation. Researchers could also examine the importance of age by repeating the analyses in an older sample. When the ALSPAC 25-year clinic data is available, a repeated measures analysis with an outcome measure that captures longitudinal change in alcohol use, could be used to investigate these associations over time.

Changes in the relationship between GAD and alcohol use from age 18 to 21 could be explained by changes in alcohol expectancies - beliefs about the positive or negative behavioural, emotional and cognitive effects of alcohol intake (Baer, 2002). Individuals who have higher (versus lower) expectancies for alcohol to be anxiety reducing, display a stronger positive correlation between anxiety and alcohol use (Kushner et al., 1994) and are more likely to endorse a self-medicating style of drinking (Kushner et al., 2000b). GAD may initially lead to increased alcohol consumption in an attempt to self-medicate anxiety symptoms. After several years, individuals may notice alcohol exacerbates anxiety symptoms, which in turn could result in the reduction or cessation of drinking. Anxious individuals may also replace alcohol with prescription medication or psychological therapies to manage their symptoms. Future research examining changes in alcohol expectancies and treatments over time would be informative.

There are several possible explanations why DTC did not moderate the relationship between GAD and alcohol use. First, differences between high and low DTC individuals may have been undetected because of inadequate statistical power, a common criticism of interaction tests (Marshall, 2007). Second, since state elevations in anxiety increase alcohol choice (see Chapter 5), DTC may be more relevant to short term acute anxiety (e.g., drinking after a stressful day), than chronic anxiety such as GAD. Third, self-medicated drinking may be more greatly endorsed by adults than adolescents (Hussong et al., 2011). DTC was not common in my sample; the upper quartile total score was five out of a possible total of 21. DTC may arise after other motives (e.g., social, conformity, and enhancement), after repeated use of alcohol and learning there are anxiolytic effects. There is some evidence that DTC motivation peaks around age 22 (Cooper et al., 2008). Fourth, moderation effects of DTC may be masked in an adolescent sample as young people are motivated to drink for a variety of reasons (Kuntsche et al., 2005).

There may be meaningful differences between individuals who drink to cope only, and those who drink to cope *and* drink for social, conformity, and/or enhancement motives. Excluding the latter individuals from the DTC variable may have altered the results. It could also be that adolescents lack the insight to attribute their drinking to a form of coping and avoidance of negative emotion (misclassification or measurement error). Therefore, it would be useful to test whether these moderation results replicate in an older sample. Fifth, global/dispositional measures of DTC may not be sensitive enough as they fail to account for within-person variation in drinking motives (O'Hara et al., 2014). People who drink to cope also cope in other ways (Todd et al., 2004) and self-medication with alcohol may depend on situational variables (Arbeau et al., 2011). Finally, DTC motives may only occur in a subgroup of individuals with anxiety (Kushner et al., 2000b). Adolescents need exposure to alcohol for it to be used as a method of coping with anxiety. Possible factors affecting choice of alcohol as a method of coping include availability, modelling of parents' drinking behaviour, culture/religion, socioeconomic status, biological predisposition, and alcohol expectancies. Certain social situations could also act as a gateway. Follow up research examining how and why the relationship between GAD and alcohol use changes over time, reconsidering the role of DTC motives, is required.

3.6. Chapter Conclusions

There is considerable public health interest in identifying adolescent antecedents of drinking patterns and problems in adulthood. In this chapter, I found that GAD in adolescence predicted concurrent frequent drinking, frequent bingeing, hazardous drinking and harmful drinking, supporting my hypothesis. The relationship between GAD and harmful drinking at age 18 also persisted into early adulthood. DTC was strongly associated with all alcohol outcomes at both ages. However, there was no clear evidence that DTC moderated associations between

GAD and alcohol use outcomes in adolescence or early adulthood, contrary to my hypothesis. In Chapter 4 and Chapter 5, I examine whether DTC moderates associations between state anxiety and alcohol use outcomes. Helping adolescents to develop positive strategies for coping with anxiety, instead of drinking alcohol, may reduce the risk of future harmful drinking.

The evidence from this chapter adds to the evidence from Chapter 2. Both studies indicated that anxiety appears to be more strongly positively associated with alcohol problems/disorders than with alcohol consumption levels. However, there were some inconsistencies. For example, my meta-analysis of three other prospective cohort studies found no clear evidence of an association between GAD and AUD, whereas I found some evidence of a positive association between GAD and harmful drinking in this chapter. Possible reasons for this discrepancy will be discussed in the thesis discussion in Chapter 6.

Chapter 4: Online Cross-Sectional Study

4.1. Chapter Overview

In Chapter 3, I discussed a cohort study that investigated associations of adolescent generalised anxiety disorder (GAD) and drinking to cope (DTC) motives, with frequent drinking, frequent bingeing, hazardous drinking, and harmful drinking in adolescence and young adulthood. In this chapter, I will present my online cross-sectional study which investigated associations between state anxiety and alcohol outcomes. Previous observational studies have investigated associations of trait anxiety and anxiety disorders with alcohol outcomes, whereas fewer observational studies have examined associations of *state* anxiety with alcohol outcomes. As I mentioned in Chapter 1, if state anxiety, trait anxiety, and anxiety disorders are considered distinct, they may therefore have different associations with alcohol use outcomes.

This chapter is based on Study 3 from the following submitted paper: 'State anxiety and alcohol choice: evidence from experimental and online observational studies'. Previous research from our group showed that experimentally-induced state anxiety (7.5% carbon dioxide [CO_2] enriched air inhalation) led to higher alcohol choice compared to a control condition (medical air inhalation). The main aim of the study described in this chapter was to examine whether these experimental findings could be replicated in an observational study of naturally-occurring state anxiety. I designed the study in collaboration with my supervisors (Marcus Munafò, Matthew Hickman, and Jon Heron) and another co-author (Angela Attwood). Steph Suddell programmed the Concurrent Pictorial Choice Task, which was inherited from a collaborator – Lee Hogarth. I created the rest of the study on Gorilla, an online research platform (https://gorilla.sc/). I completed the ethics application, analysed the data, and wrote the manuscript, with advice and input from other authors.

The aims were to:

- Investigate whether naturally-occurring state anxiety is associated with alcohol choice and alcohol craving.
- Explore associations of, and interactions between, state anxiety, trait anxiety, and DTC motives, on alcohol choice, alcohol craving, and alcohol use.

4.2. Introduction

4.2.1. Background

The self-medication (Khantzian, 1990), tension-reduction (Conger, 1956), and stress response dampening (Sher & Levenson, 1982) models all suggest that individuals drink alcohol to cope with stress and anxiety because of alcohol's negatively reinforcing anxiolytic effects. Because alcohol reduces anxiety in some individuals, these positive effects can lead to continued use. This has negative health implications; coping-motivated drinking increases the risk of heavier alcohol consumption and the development of alcohol problems (Cooper et al., 1995), which in turn are major contributors to the global burden of disease (Rehm, 2011).

Many observational studies support these models, finding evidence of a positive relationship between trait anxiety and anxiety disorders with alcohol use outcomes, but others do not (Dyer et al., 2019a). Fewer observational studies have examined associations of state anxiety with alcohol outcomes. State anxiety refers to transitory feelings of anxiety elicited by an environmental stressor, whereas trait anxiety refers to dispositional differences in feelings of anxiety (Sung et al., 2011). Sung and colleagues (2011) found the odds of hazardous alcohol use were higher among females with high state anxiety compared to low state anxiety. However,

the authors found no clear evidence of an association in males. Drummond and colleagues (2002) found alcohol craving was positively correlated with state anxiety in an alcohol-dependent sample. Given that state and trait anxiety are distinct, their associations with alcohol outcomes may be different. For example, Fitzgerald and Long (2012) found that state anxiety, but not trait anxiety, was associated with coping motives for drinking in high-risk drinkers. Although Sung and colleagues (2011) found both state and trait anxiety were associated with more hazardous alcohol use.

These negative reinforcement models are also supported by some experimental findings. For example, research by our group has found that experimentally-induced state anxiety (7.5% CO_2 enriched air inhalation) led to higher alcohol (versus food) choice in social drinkers, compared to low state anxiety (medical air inhalation). Alcohol choice (preference to enlarge alcohol versus food images) is moderately positively correlated with alcohol dependence severity (Hardy et al., 2018). Alcohol choice increases following negative mood induction (Hardy & Hogarth, 2017), and it is also sensitive to individual differences in depression and DTC (Hogarth et al., 2018). Alcohol craving is associated with alcohol dependence severity (Glautier & Drummond, 1994). There is evidence that individuals with alcohol use disorder experience increased stress-induced alcohol craving (Sinha, 2001) and acute stress also increases craving and subsequent intravenous alcohol self-administration in non-dependent binge drinkers (Ramchandani et al., 2018).

Exploring the interactions of state anxiety, trait anxiety, and DTC, on alcohol outcomes, would be informative. A diathesis-stress model may better explain associations between anxiety and alcohol use (Bartel et al., 2018). For example, anxiety sensitivity, a dispositional fear of one's anxiety sensations, may only be associated with alcohol misuse (diathesis) during periods of elevated state anxiety

(stressor) (Stewart & Kushner, 2001). Observational and experimental studies have also found greater associations of anxiety and negative mood with alcohol seeking behaviour among individuals with high DTC motives (Menary et al., 2011; Rousseau et al., 2011). However, I found no clear evidence of an interaction between GAD and DTC on alcohol use outcomes in a large cohort study of adolescent drinkers (Dyer et al., 2019b) (see Chapter 3). DTC may instead be a moderator of associations between state anxiety and alcohol outcomes, for example drinking after a stressful day.

4.2.2. Aims and Hypotheses

The primary objective of the current study was to examine whether the finding that experimentally-induced state anxiety influences alcohol choice can be replicated in an observational study of naturally-occurring state anxiety. I tested the association between state anxiety and alcohol craving as a secondary outcome. I hypothesised that state anxiety would be positively associated with alcohol choice and alcohol craving. I also extended previous findings by exploring whether: (a) trait anxiety and DTC motives are associated with alcohol choice, craving, and use, (b) state anxiety and DTC motives interactively predict alcohol choice and craving (c) state anxiety and trait anxiety interactively predict alcohol choice and craving, and (d) trait anxiety and DTC motives interactively predict alcohol choice, craving and use. More specifically, for (b) and (d), I was interested in whether associations of state anxiety and trait anxiety with alcohol outcomes were moderated by DTC status (high versus low), in line with my secondary thesis aim. And I also wanted to explore whether associations between DTC and alcohol outcomes were moderated by state (and trait) anxiety.

By triangulating results from observational and experimental studies that have different and unrelated sources of potential bias (Lawlor et al., 2016), I aimed to

strengthen the inference I was able to draw from the data. Sources of bias in observational studies include confounding and reverse causation due to the absence of randomisation (Hammer et al., 2009). Online observational studies may also suffer from information biases; participants may be less attentive and honest without the presence of a researcher (Woods et al., 2015). Alternatively, experimental studies may suffer from selection bias, which arises when the study sample is not representative of the target population, and therefore reduces the generalisability of findings (Hammer et al., 2009). Many experimental psychology studies use student samples because of convenience and availability, but since students are younger and more educated than the general public, this may reduce the representativeness of experimental findings (Hanel & Vione, 2016).

As previously mentioned in Chapter 3, the self-medication mechanism may be more detectable in cross-sectional than prospective studies because, as a coping strategy, it implies immediacy. It is also therefore possible that state anxiety symptoms (which reflect how one feels at that moment in time) are more closely associated with alcohol use outcomes, than retrospective measures of anxiety.

4.3. Methods

4.3.1. Design

This was a cross-sectional observational study delivered online. The protocol for this study was pre-registered on the Open Science Framework (https://osf.io/wdm2y/). Ethics approval was obtained from the Faculty of Science Research Ethics Committee at the University of Bristol (reference 12071870461).

There were practical and ethical challenges relating to the Concurrent Pictorial Choice Task when I was designing the study. The task had previously been

programmed in E-Prime, for use in the laboratory experiment. However, it had to be re-programmed with different software for use on an online platform. Because of the time constraints of a PhD, I collaborated with a colleague, Steph Suddell, who had the necessary programming skills to do this.

We originally planned to program the task in JavaScript and host the study on Google Firebase, as other platforms used previously in the department (e.g., Bristol Online Survey, Qualtrics) were only suitable for questionnaires rather than behavioural tasks. However, our ethics committee rejected the use of Google Firebase as they stated that (a) it could potentially de-anonymise any data set and (b) personal data are recorded, which could cause data protection issues in relation to the EU General Data Protection Regulation (GDPR). We subsequently chose to program the task in Gorilla (https://gorilla.sc/). This was accepted by the ethics committee on the condition that the participant information sheet and consent form adequately informed participants that any content and personal data that they provide will be held by a third party (Gorilla), who may access it, and in turn share it with other third parties based overseas.

4.3.2. Participants

Sample size was calculated in G*Power. It was determined using data from the previous experimental study that investigated the effects of state anxiety on alcohol choice. State anxiety was positively correlated with alcohol choice during the CO_2 inhalation (r = .33). Because this was a moderate correlation in a discovery sample, I reduced the effect size by a third (r = .22), which required 219 participants to detect with 90% power at an alpha level of 5%. Associations between trait anxiety and DTC with alcohol choice, craving and use, and corresponding interaction analyses were therefore exploratory, as the study was not powered to detect these associations.

I used Prolific (https://www.prolific.ac/) to manage participant recruitment and screening because it was quicker and easier than doing this myself, (e.g., advertising the study on the Tobacco and Alcohol Research Group website, and directing participants to a Qualtrics screening questionnaire). Prolific have a large database of potential participants who have already signed up to take part in research, Gorilla has been designed for easy integration with Prolific, and Prolific handle participant reimbursement automatically. Participants were eligible if they met the following criteria: aged 18 years or over, UK national, fluent in English, and an alcohol drinker, for consistency with the experimental study. I added a new inclusion criterion of 'no dietary requirements' due to the nature of task stimuli. For example, if participants did not eat the types of foods presented in the task, this may have biased their responses towards selecting more alcohol images.

4.3.3. Measures

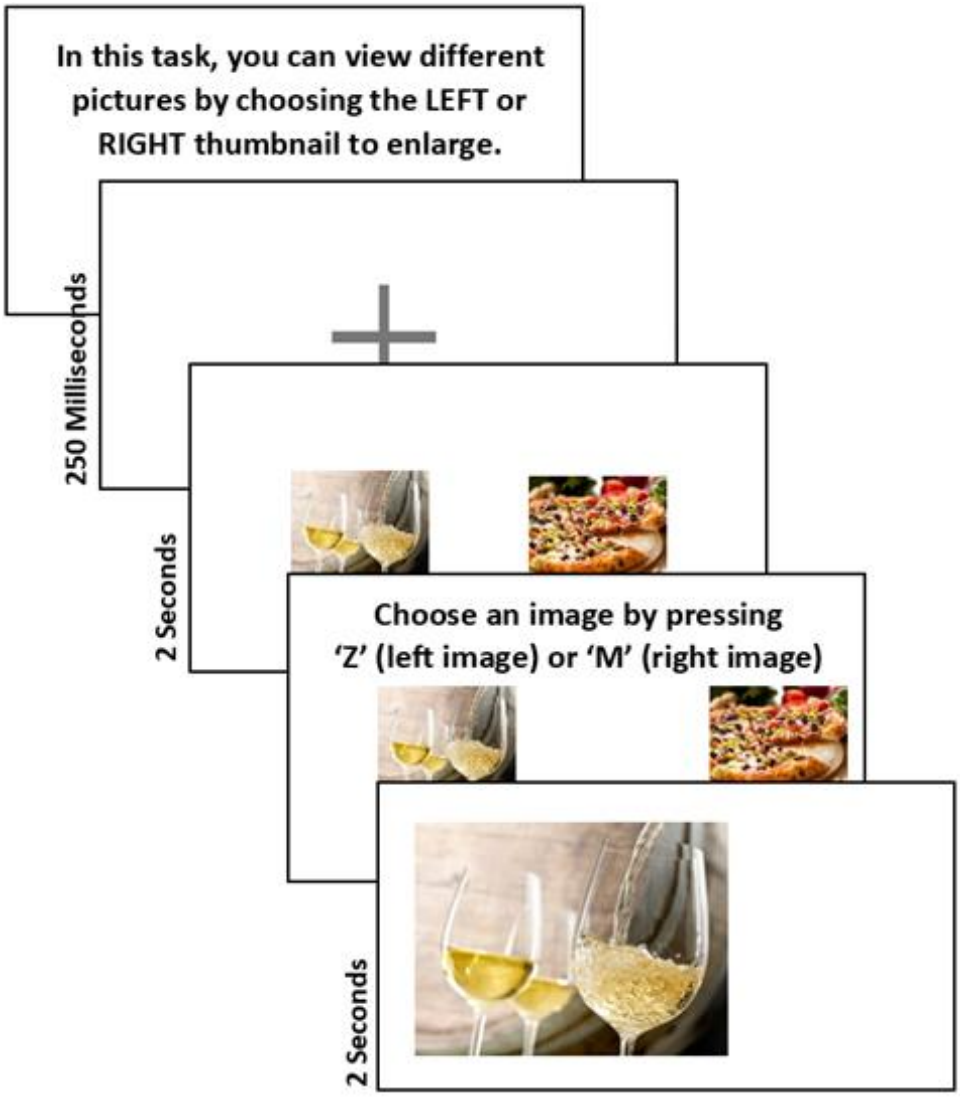
4.3.3.1. State Anxiety. State anxiety, the primary exposure, was measured using the 20-item Spielberger State-Trait Anxiety Inventory (state sub-scale; STAI-S) (Spielberger et al., 1983). Items included 'I am tense' and 'I feel nervous' and participants rated how they felt 'right now' on each item on a scale from 1 ('not at all') to 4 ('very much so'). State anxiety was used as a continuous exposure variable, where higher scores reflected greater state anxiety. I also derived a binary state anxiety variable (upper quartile split) for the exploratory interaction analyses. Scores of 20 to 41 were coded as low state anxiety and scores of 42 to 73 were coded as high state anxiety.

4.3.3.2. Alcohol Choice. Percentage alcohol choice, the primary outcome, was measured using the Concurrent Pictorial Choice Measure (Hardy & Hogarth, 2017)

(see Figure 4.1). Instructions said: ‘In this task, you can view different pictures by choosing the LEFT or RIGHT thumbnail to enlarge’. Each trial presented two images, alcohol and food, on either the left or right of the screen. After two seconds, the instructions appeared ‘Choose an image by pressing ‘Z’ (left image) or ‘M’ (right image)’, at which point pressing the ‘Z’ or ‘M’ key (which correspond to the left and right image, respectively) enlarged the selected image and removed the unselected image. The chosen image remained on screen for two seconds, before an inter-trial interval of between one and two seconds. There were 54 choice trials in total. Each trial randomly sampled from 27 alcohol (beer/cider, spirits, wine, to cover preferences) and 27 food (typical UK meals) images, each of which were shown twice. The left-right position of alcohol and food images was also randomised, except that runs on the same side were limited to four. Steph Suddell programmed this task, and I integrated it with the rest of the study questionnaires that I created in Gorilla.

The Concurrent Pictorial Choice Measure was originally created by a collaborator, and I inherited the task for this study. Food and alcohol images were matched in size and resolution, but there was no attempt to match the images based on other psychophysical properties because we were not concerned about eye tracking or pupil size that might be affected by this. Because the images were not matched, the random sampling of images on each trial could not break any matching. The key validation of the task is that alcohol choice correlates with self-reported alcohol dependence severity (Hardy & Hogarth, 2017). Studies that have used this task have shown that substance choice correlates with one or more indices of dependence severity across alcohol, tobacco, and opiates in both clinical and non-clinical samples (Hardy et al., 2018; Hogarth et al., 2019). Therefore, there is ample validation of the measure as an index of the relative value ascribed to the drug versus food.

Figure 4.1. Schematic of the concurrent pictorial choice measure.



4.3.3.3. Alcohol Craving. Alcohol craving, the secondary outcome, was measured using the eight-item Alcohol Urge Questionnaire (AUQ) (Bohn et al., 1995). Items included 'all I want to do now is have a drink,' and 'I crave a drink right now' and participants rated how they felt 'right now' on each item on a scale from 1 ('strongly disagree') to 7 ('strongly agree'). Higher scores reflected higher craving for alcohol.

4.3.3.4. Trait Anxiety. Trait anxiety, an exploratory exposure, was measured using the 20-item Spielberger State-Trait Anxiety Inventory (trait sub-scale; STAI-T) (Spielberger et al., 1983). Items included 'I worry too much over something that

doesn't really matter' and 'I lack self-confidence' and participants rated how they 'generally feel in life' on each item on a scale from 1 ('not at all') to 4 ('very much so'). Trait anxiety was used as a continuous exposure variable, where higher scores reflected greater trait anxiety. I also derived a binary trait anxiety variable (upper quartile split) for the exploratory interaction analyses. Scores of 20 to 55 were coded as low trait anxiety and scores of 56 to 79 were coded as high trait anxiety.

4.3.3.5. Drinking to Cope Motives. DTC with anxiety was measured using the coping-anxiety subscale of the 28-item Modified Drinking Motives Questionnaire - Revised (MDMQ-R) (Grant et al., 2007). I decided to use the MDMQ-R instead of the measure used in Chapter 3, because the MDMQ-R separates DTC with anxiety and DTC with depression. Participants rated how often they consumed alcohol for anxiety coping-motivated reasons on a scale from 1 ('never/almost never') to 5 ('always/almost always'). Items included 'to relax' and 'because it helps me when I am feeling nervous.' DTC was used as a continuous exposure variable, where higher scores reflected greater DTC. I also derived a binary DTC variable (upper quartile split), for the exploratory interaction analyses. Scores of 4 to 11 were coded as low DTC and scores of 12-20 were coded as high DTC. The upper quartile score on this DTC measure was higher in this sample 12 (range 4-20), compared to the upper quartile score of 5 on the DTC measure used in the Chapter 3 study sample (range 0-21). I also created a four-level categorical variable combining DTC and social motives for drinking, for use in a sensitivity analysis (0 = low DTC, low social motives; 1 = high DTC, low social motives; 2 = low DTC, high social motives; 3 = high DTC, high social motives).

4.3.3.6. Alcohol Use. Frequent drinking, frequent bingeing, hazardous drinking, and harmful drinking were measured using the Alcohol Use Disorders Identification

Test (AUDIT) (World Health Organisation, 2001). Drinking alcohol '2 to 4 times a month' or 'monthly or less' was coded as infrequent drinking. No participant reported drinking alcohol 'never,' in accordance with my inclusion criteria. Drinking alcohol '2 to 3 times a week', or '4 or more times a week' was coded as frequent drinking. Individuals who consumed six or more units on one occasion 'monthly', 'less than monthly' or 'never' were coded as infrequent binge drinkers, and those who consumed six or more units 'weekly' or 'daily or almost daily' were coded as frequent binge drinkers. Individuals who scored ≥ 8 on the AUDIT were classified as hazardous drinkers, and scores of ≥ 16 indicated harmful drinking (World Health Organisation, 2001). I included these four alcohol use outcomes for consistency with the cohort study described in Chapter 3. Despite the vastly discrepant sample sizes between the current study and the cohort study, I was interested to see whether the results on these variables were qualitatively similar.

4.3.3.7. Potential Confounders. The following confounders were assessed via self-report: sociodemographic confounders (age, gender, education, and income), mental health confounders (family history of anxiety or depression, family history of alcohol use disorders, personal history of externalising and internalising disorders, emotional eating, and experience of abuse), and substance use confounders (tobacco use and cannabis use). As described in Chapter 3, confounders were selected based on their associations with both anxiety and alcohol use in the literature. Emotional eating and experience of abuse were additional variables, which were not included in analysis models in Chapter 3. Table 4.1 provides more details of the confounding variables.

Table 4.1. Confounding variables.

Variable	Variable Information
Age	Participant age in years.
Gender	1 = male; 2 = female
Education	1 = no qualifications, entry level qualification, GCSE or equivalent, CSE or equivalent, A-Level or equivalent; 2 = certificate of higher education or equivalent, foundation degree, degree or equivalent, master's degree or equivalent, doctorate.
Income	Per week: 1 = £0 - £199, £200 - £399, £400 - £599; 2 = £600 - £799, £800 - £999, £1000 or more.
Family history of anxiety or depression	1 = no; 2 = yes.
Family history of alcohol use disorders	1 = no; 2 = yes.
Personal history of internalising disorders	1 = no; 2 = yes.
Personal history of externalising disorders	1 = no; 2 = yes.
Emotional eating	Total score on the Dutch Eating Behaviour Questionnaire (DEBQ) - Emotional Eating Subscale.
Experience of abuse	1 = no; 2 = yes.
Tobacco use	1 = never smoker; 2 = ex-smoker, occasional smoker, weekly smoker, daily smoker.
Cannabis use	1 = never; 2 = monthly or less, weekly, daily.

4.3.4. Procedure

The study was conducted online in a single session lasting approximately 30 minutes. Participants accessed the study through Prolific and data was collected and stored on Gorilla, hosted by Microsoft Azure. On Prolific, participants were invited to complete the study via a webpage on Gorilla. The study was advertised on Prolific under a different title: 'The Food, Drink, and Emotion Study', to avoid possible demand characteristics. After reading the study information sheet, participants were required to provide consent before being allowed to proceed to the next webpage. Participants were informed that they were able to withdraw from the study at any time by closing the study webpage. The alcohol choice task and questionnaires then followed, in the same order for all participants. All questions that did not feature in the original experimental study were included towards the

end of the study so that they would not affect the replication component. Participants then confirmed their consent (having participated), before submitting their data and being debriefed. On the final webpage, participants were redirected back to Prolific, which automatically recorded that they completed the study. Participants were reimbursed £2.50 through their prolific account, in line with Prolific's minimum hourly rate of £5. I had no access to participant payment details (participants entered these when they signed up for Prolific). Individuals who completed the study but failed the attention check question were still reimbursed, but their data were not included in the analyses.

4.3.5. Data Analyses

4.3.5.1. Main Analyses. After approximately 10% of data collection was complete, the data collection process was quality assessed by an independent researcher. All analyses were conducted in Stata version 15. I used linear regressions to investigate associations of state anxiety with alcohol choice and alcohol craving. I compared unadjusted results to results incrementally adjusted for sociodemographic, mental health, and substance use confounders. To match the task and sample used in the previous experimental study, I also performed a subgroup analysis restricted to wine drinkers and only using results from the wine stimuli (not beer and spirits) to investigate associations between state anxiety and alcohol choice. This subgroup analysis was necessary to ensure that any non-replicable results were not due to task differences across studies.

I did not investigate associations between state anxiety and alcohol use (e.g., hazardous drinking) as the STAI-S asks respondents to report their present feelings whereas the AUDIT includes questions about alcohol use in the past year. A previous study had also used the STAI-S and the Korean version of the AUDIT

to investigate the relationship between state anxiety and hazardous drinking (Sung et al., 2011), but since present feelings cannot predict past behaviour, their analyses may not have been appropriate.

4.3.5.2. Exploratory Analyses. I explored associations of trait anxiety and DTC with alcohol choice, alcohol craving, and alcohol use, using linear and logistic regressions. Interaction tests were used to explore moderating influences. For each interaction test, I also presented the four stratified analyses for completeness. For example, for interactions between state anxiety and DTC on alcohol choice, there were also separate associations between state anxiety and alcohol choice among high versus low DTC participants, and separate associations between DTC and alcohol choice among high versus low state anxiety participants. Finally, as a sensitivity analysis, individuals with high levels of DTC *and* high levels of social motives for drinking were compared to those who drink for either or neither reason.

I have presented both the unstandardised ('b') and standardised ('beta') beta coefficients in the tables for the linear regressions, to show the raw results and to allow direct comparisons between results that are using different scales, respectively. Beta coefficients are regression coefficients obtained by standardising variables to have a mean of zero and a standard deviation of one. For example, b = 0.5 means a 0.5 unit increase in the outcome with a one unit increase in the exposure variable, whereas beta = 0.5 means a 0.5 standard deviation increase in the outcome with a one standard deviation increase in the exposure variable.

4.4. Results

4.4.1. Participant Characteristics

I recruited 226 participants in total, to account for three participants who failed the attention check question (data were excluded), and four participants who experienced technical difficulties (no data was submitted). In order to adjust for gender, I excluded one participant who responded 'other/prefer not to say.' This resulted in a final sample size of 218 participants. In hindsight, I should not have recruited this participant if I could not use their data, as there is an ethical issue with this approach. I was faced with a dilemma as the faculty ethics committee requested that I included this response option, but it is not possible to know whether to group this participant with the male or female category for analysis purposes. In a future study, I could use the term 'gender assigned at birth' to overcome this issue and have an appropriate binary measure.

Participants (n = 218, 45% male) were aged between 18 and 66 years (*M* = 35.77; *SD* = 11.92). STAI-S anxiety scores and STAI-T anxiety scores ranged from 20 to 73 (*M* = 35.47; *SD* = 11.10) and 20 to 79 (*M* = 44.38; *SD* = 14.07), respectively. Percentage alcohol choice ranged from 0% to 98% (*M* = 34.72; *SD* = 18.93). AUQ craving scores ranged from 8 to 56 (*M* = 17.40; *SD* = 10.15). DTC scores ranged from 4 to 20 (*M* = 9.24; *SD* = 3.91). The alcohol use outcome frequencies were as follows: infrequent drinking 54%, frequent drinking 46%; infrequent bingeing 80%, frequent bingeing 20%; non-hazardous drinking 48%, hazardous drinking 52%; non-harmful drinking 89%, harmful drinking 11%.

4.4.2. Main Analyses

4.4.2.1. Associations between State Anxiety and Alcohol Choice. There was no clear evidence of an association between state anxiety and alcohol choice (unadjusted *b* 0.05, 95% CI -0.18 to 0.28, *p* = .654). Adjusting for sociodemographic, mental health, and substance use confounders had little impact on results (Table 4.2). There was also no clear evidence of an association between state anxiety and alcohol choice (unadjusted *b* 0.02, 95% CI -0.29 to 0.33, *p* = .894) in a subgroup analysis restricted to wine drinkers and wine stimuli to resemble the previous experimental study.

4.4.2.2. Associations between State Anxiety and Alcohol Craving. There was weak evidence of a positive association between state anxiety and alcohol craving (unadjusted *b* 0.14, 95% CI 0.02 to 0.26, *p* = .026). Associations were robust to adjustment of sociodemographic confounders, but associations attenuated when adjusting for mental health and substance use confounders (Table 4.2).

Table 4.2. Linear regressions examining associations of state anxiety, trait anxiety, and drinking to cope motives, with alcohol choice and alcohol craving.

		Alcohol Choice			Alcohol Craving		
	Model	**b [95% CI]**	**p-value**	**Beta**	**b [95% CI]**	**p-value**	**Beta**
State Anxiety	Model 1	0.05 [-0.18 to 0.28]	.654	0.03	0.14 [0.02 to 0.26]	.026	0.15
	Model 2	0.07 [-0.16 to 0.31]	.549	0.04	0.14 [0.01 to 0.26]	.031	0.15
	Model 3	0.01 [-0.26 to 0.28]	.934	0.01	0.13 [-0.01 to 0.27]	.075	0.14
	Model 4	-0.03 [-0.29 to 0.24]	.836	-0.02	0.11 [-0.04 to 0.25]	.142	0.12
Trait Anxiety	Model 1	0.11 [-0.07 to 0.29]	.214	0.08	0.15 [0.05 to 0.24]	.003	0.20
	Model 2	0.14 [-0.05 to 0.32]	.154	0.10	0.14 [0.04 to 0.24]	.007	0.19
	Model 3	0.15 [-0.08 to 0.39]	.205	0.11	0.15 [0.02 to 0.28]	.021	0.21
	Model 4	0.12 [-0.12 to 0.36]	.319	0.09	0.13 [-0.00 to 0.25]	.047	0.18
Drinking to Cope Motives	Model 1	1.12 [0.49 to 1.75]	.001	0.23	1.24 [0.93 to 1.54]	<.001	0.48
	Model 2	1.05 [0.41 to 1.69]	.001	0.22	1.19 [0.88 to 1.50]	<.001	0.46
	Model 3	1.10 [0.41 to 1.79]	.002	0.23	1.26 [0.92 to 1.60]	<.001	0.49
	Model 4	0.95 [0.26 to 1.65]	.007	0.20	1.19 [0.85 to 1.53]	<.001	0.46

Model 1 = unadjusted; model 2 = adjusted for age, gender, education, income; model 3 = additionally adjusted for family history of anxiety/depression and alcohol use disorder, personal history of externalising and internalising disorders, emotional eating, and experience of abuse; model 4 = additionally adjusted for tobacco use and cannabis use. N = 218; b = Unstandardised beta coefficients; Beta = Standardised beta coefficients.

4.4.3. Exploratory Analyses

4.4.3.1. Associations of Trait Anxiety with Alcohol Choice, Craving, and Use. There was no clear evidence of an association between trait anxiety and alcohol choice (unadjusted *b* 0.11, 95% CI -0.07 to 0.29, *p* = .214). However, there was evidence of a positive association between trait anxiety and alcohol craving (unadjusted *b* 0.15, 95% CI 0.05 to 0.24, *p* = .003) (Table 4.2).

There was no clear evidence of an association between trait anxiety and frequent drinking (unadjusted OR 1.00, 95% CI 0.98 to 1.02, *p* = .742) or frequent bingeing (unadjusted OR 1.00, 95% CI 0.98 to 1.03, *p* = .684). Trait anxiety was associated with more hazardous drinking (unadjusted OR 1.03, 95% CI 1.01 to 1.05, *p* = .005), although the effect estimates were small and the statistical evidence attenuated in the fully adjusted model (OR 1.02, 95% CI 0.99 to 1.05, *p* = .126). Trait anxiety was robustly associated with more harmful drinking, even after adjustment for all confounders (fully adjusted OR 1.07, 95% CI 1.02 to 1.12, *p* = .009) (Table 4.3). Therefore, the odds of harmful drinking were 7% higher among individuals with higher trait anxiety compared to those with lower trait anxiety.

4.4.3.2. Associations of DTC with Alcohol Choice, Craving, and Use. DTC was positively associated with alcohol choice (unadjusted *b* 1.12, 95% CI 0.49 to 1.75, *p* = .001) and alcohol craving (unadjusted *b* 1.24, 95% CI 0.93 to 1.54, *p* <.001), and associations remained after adjustment for confounders (Table 4.2). DTC was also robustly associated with more frequent drinking (unadjusted OR 1.16, 95% CI 1.07 to 1.25, *p* <.001), more frequent bingeing (unadjusted OR 1.23, 95% CI 1.13 to 1.34, *p* <.001), more hazardous drinking (unadjusted OR 1.33, 95% CI 1.20 to 1.47, *p* <.001), and more harmful drinking (unadjusted OR 1.31, 95% CI 1.17 to 1.46, *p* <.001) (Table 4.3).

Table 4.3. Logistic regressions examining associations of trait anxiety and drinking to cope motives, with alcohol use.

		Frequent Drinking		Frequent Bingeing		Hazardous Drinking		Harmful Drinking	
	Model	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**
Trait Anxiety	Model 1	1.00 [0.98 to 1.02]	.742	1.00 [0.98 to 1.03]	.684	1.03 [1.01 to 1.05]	.005	1.05 [1.02 to 1.08]	.004
	Model 2	1.02 [0.99 to 1.04]	.150	1.02 [1.00 to 1.05]	.091	1.04 [1.01 to 1.06]	.002	1.06 [1.02 to 1.10]	.001
	Model 3	1.01 [0.99 to 1.04]	.319	1.03 [1.00 to 1.06]	.111	1.03 [1.00 to 1.05]	.059	1.07 [1.02 to 1.12]	.005
	Model 4	1.01 [0.98 to 1.04]	.491	1.02 [0.98 to 1.06]	.290	1.02 [0.99 to 1.05]	.126	1.07 [1.02 to 1.12]	.009
Drinking to Cope Motives	Model 1	1.16 [1.07 to 1.25]	<.001	1.23 [1.13 to 1.34]	<.001	1.33 [1.20 to 1.47]	<.001	1.31 [1.17 to 1.46]	<.001
	Model 2	1.24 [1.14 to 1.36]	<.001	1.29 [1.16 to 1.42]	<.001	1.35 [1.22 to 1.50]	<.001	1.32 [1.18 to 1.48]	<.001
	Model 3	1.29 [1.16 to 1.43]	<.001	1.35 [1.20 to 1.52]	<.001	1.36 [1.22 to 1.52]	<.001	1.37 [1.19 to 1.57]	<.001
	Model 4	1.28 [1.15 to 1.42]	<.001	1.31 [1.17 to 1.47]	<.001	1.34 [1.20 to 1.50]	<.001	1.35 [1.17 to 1.54]	<.001

Model 1 = unadjusted; model 2 = adjusted for age, gender, education, income; model 3 = additionally adjusted for family history of anxiety/depression and alcohol use disorder, personal history of externalising and internalising disorders, emotional eating, and experience of abuse; model 4 = additionally adjusted for tobacco use and cannabis use. N = 218.

4.4.3.3. Interactions between State Anxiety and DTC on Alcohol Choice and Craving. There was no clear evidence of an interaction between state anxiety and DTC on alcohol choice (unadjusted *b* 6.66, 95% CI -6.28 to 19.60, *p* = .311) or alcohol craving (unadjusted *b* 5.32, 95% CI -1.25 to 11.90, *p* = .112) (Table 4.4). Stratified analyses revealed weak evidence of a positive association between DTC and alcohol choice among individuals with high state anxiety (unadjusted *b* 11.05 95% CI 0.78 to 21.31, *p* = .035), but there was no clear evidence of an association among individuals with low state anxiety.

4.4.3.4. Interactions between State Anxiety and Trait Anxiety on Alcohol Choice and Craving. There was no clear evidence of an interaction between state anxiety and trait anxiety on alcohol choice (unadjusted *b* -6.18, 95% CI -20.81 to 8.44, *p* = .406) or alcohol craving (unadjusted *b* -0.37, 95% CI -8.19 to 7.46, *p* = .926) (Table 4.4).

4.4.3.5. Interactions between Trait Anxiety and DTC on Alcohol Choice, Craving and Use. There was weak evidence of an interaction between trait anxiety and DTC on alcohol choice (unadjusted *b* 12.08, 95% CI -1.17 to 25.33, *p* = .074) and alcohol craving (unadjusted *b* 6.83, 95% CI 0.07 to 13.58, *p* = .048) (Table 4.4). Stratified analyses revealed evidence of a positive association between DTC and alcohol choice among individuals with high trait anxiety (unadjusted *b* 13.25, 95% CI 2.89 to 23.61, *p* = .013), but there was no clear evidence of an association among individuals with low trait anxiety. DTC was also more strongly positively associated with alcohol craving among individuals with high trait anxiety (unadjusted *b* 12.40, 95% CI 6.92 to 17.88, *p* < .001) versus individuals with low trait anxiety (unadjusted *b* 5.57, 95% CI 1.37 to 9.7, *p* = .010). There was no clear evidence of an interaction between trait anxiety and DTC on the four alcohol use outcomes (Table 4.5).

Table 4.4. Linear regressions examining the interactions between state anxiety (SA), trait anxiety (TA), and drinking to cope (DTC) motives, on alcohol choice and alcohol craving.

			Alcohol Choice			Alcohol Craving		
		n	**b [95% CI]**	**p-value**	**Beta**	**b [95% CI]**	**p-value**	**Beta**
State Anxiety	Low DTC	168	-1.96 [-9.06 to 5.13]	.585	-0.04	-0.53 [-3.89 to 2.83]	.755	-0.02
	High DTC	50	4.70 [-6.54 to 15.94]	.405	0.12	4.79 [-2.03 to 11.62]	.165	0.20
DTC	Low SA	165	4.38 [-3.14 to 11.90]	.251	0.09	6.19 [2.52 to 9.86]	.001	0.25
	High SA	53	11.05 [0.78 to 21.31]	.035	0.29	11.51 [5.63 to 17.40]	<.001	0.48
	Interaction	218	6.66 [-6.28 to 19.60]	.311	0.10	5.32 [-1.25 to 11.90]	.112	0.15
State Anxiety	Low TA	167	0.89 [-8.38 to 10.15]	.850	0.01	1.31 [-3.45 to 6.08]	.587	0.04
	High TA	51	-5.30 [-17.07 to 6.48]	.370	-0.13	0.94 [-6.08 to 7.97]	.788	0.04
Trait Anxiety	Low SA	165	7.75 [-2.14 to 17.65]	.124	0.12	2.42 [-2.58 to 7.42]	.340	0.07
	High SA	53	1.57 [-9.28 to 12.42]	.773	0.04	2.05 [-4.72 to 8.83]	.546	0.08
	Interaction	218	-6.18 [-20.81 to 8.44]	.406	-0.12	-0.37 [-8.19 to 7.46]	.926	-0.01
Trait Anxiety	Low DTC	168	-2.83 [-10.97 to 5.31]	.493	-0.05	-2.87 [-6.70 to 0.97]	.142	-0.11
	High DTC	50	9.25 [-1.45 to 19.95]	.088	0.24	3.96 [-2.73 to 10.65]	.240	0.17
DTC	Low TA	167	1.17 [-7.17 to 9.50]	.783	0.02	5.57 [1.37 to 9.77]	.010	0.20
	High TA	51	13.25 [2.89 to 23.61]	.013	0.34	12.40 [6.92 to 17.88]	<.001	0.54
	Interaction	218	12.08 [-1.17 to 25.33]	.074	0.21	6.83 [0.07 to 13.58]	.048	0.22

Unadjusted models. Stratified analyses: associations of SA with alcohol choice and alcohol craving in each stratum of DTC and TA; associations of DTC with alcohol choice and alcohol craving in each stratum of SA and TA; associations of TA with alcohol choice and alcohol craving in each stratum of SA and DTC. Interaction terms: interaction of state anxiety x DTC, state anxiety x trait anxiety, and trait anxiety x DTC on alcohol choice and alcohol craving. N = 218; b = Unstandardised beta coefficients; Beta = Standardised beta coefficients. All exposure variables made binary based on the upper quartile.

Table 4.5. Logistic regressions examining the interactions between trait anxiety (TA) and drinking to cope (DTC) motives, on alcohol use.

			Frequent Drinking		Frequent Bingeing		Hazardous Drinking		Harmful Drinking	
	Model	**n**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**
Trait Anxiety	Low DTC	168	1.18 [0.50 to 2.82]	.702	0.53 [0.12 to 2.43]	.416	1.12 [0.47 to 2.67]	.799	0.74 [0.09 to 6.19]	.780
	High DTC	50	1.56 [0.50 to 4.83]	.442	1.50 [0.48 to 4.72]	.488	2.82 [0.62 to 12.89]	.180	0.80 [0.23 to 2.76]	.724
DTC	Low TA	167	1.53 [0.63 to 3.69]	.347	3.12 [1.18 to 8.28]	.022	3.75 [1.40 to 10.06]	.009	7.44 [2.38 to 23.23]	.001
	High TA	51	2.01 [0.66 to 6.16]	.222	8.80 [1.72 to 45.12]	.009	9.45 [2.23 to 40.07]	.002	8.05 [0.91 to 71.16]	.061
	Interaction	218	1.32 [0.32 to 5.48]	.706	2.82 [0.42 to 18.89]	.286	2.52 [0.44 to 14.51]	.300	1.08 [0.09 to 12.66]	.950

Unadjusted models. Stratified analyses: associations of trait anxiety with alcohol use outcomes in each stratum of drinking to cope motives, and vice versa. Interaction term: interaction of trait anxiety x DTC on alcohol use outcomes. N = 218.

Table 4.6. Linear regressions examining associations of a combined measure of drinking to cope (DTC) and social motives with alcohol choice and alcohol craving.

	Alcohol Choice			Alcohol Craving		
	b [95% CI]	**p-value**	**Beta**	**b [95% CI]**	**p-value**	**Beta**
High DTC Low Social	3.44 [-3.77 to 10.65]	.348	0.06	9.20 [5.54 to 12.85]	<.001	0.32
Low DTC High Social	8.60 [0.57 to 16.63]	.036	0.14	7.19 [3.12 to 11.26]	.001	0.22
High DTC High Social	14.90 [6.01 to 23.79	.001	0.22	9.07 [4.56 to 13.57]	<.001	0.25

Unadjusted models. Reference group = Low DTC Low Social; N = 218; b = Unstandardised beta coefficients; Beta = Standardised beta coefficients. Exposure variable made categorical by combining DTC and social motives variables made binary based on the upper quartile.

4.4.4. Sensitivity Analyses

Compared to individuals with low DTC and low social motives, alcohol choice was higher among individuals with high DTC and high social motives, than those who just have high social motives, and those who just have high DTC. Associations with alcohol craving were similar among individuals with high DTC and high social motives, those who just have high social motives, and those who just have high DTC (Table 4.6).

4.5. Discussion

4.5.1. Summary of Findings

Contrary to my first hypothesis and the results of the experimental study, there was no clear evidence of an association between naturally-occurring state anxiety and alcohol choice. In support of my second hypothesis, and the self-medication and negative reinforcement theories, state anxiety was associated with higher alcohol craving. However, associations attenuated when adjusting for substance use confounders, suggesting that tobacco and cannabis use confounded this association.

Exploratory analyses revealed DTC was robustly positively associated with all alcohol outcomes. Trait anxiety was positively associated with alcohol craving, hazardous drinking, and harmful drinking, although associations remained only for alcohol craving and harmful drinking in the fully adjusted models. There was no clear evidence of a state anxiety x DTC interaction or a state anxiety x trait anxiety interaction on alcohol choice or alcohol craving. Although stratified analyses revealed some evidence of a positive association between DTC and alcohol choice among individuals with high (but not low) state anxiety. There was weak evidence of a trait anxiety x DTC interaction on alcohol choice and alcohol craving. Stratified

analyses revealed some evidence of a positive association between DTC and alcohol choice among individuals with high (but not low) trait anxiety. Associations between DTC and alcohol craving were also greater among individuals with high (versus low) trait anxiety, and individuals with high (versus low) state anxiety.

4.5.2. Original Research Contribution

This study is novel as it attempted to replicate an earlier experimental study from our research group using an observational study design. In addition, by examining associations of state anxiety with alcohol choice and craving, this study builds on previous observational research which has used measures of trait anxiety and anxiety disorders to investigate the relationship between anxiety and alcohol use (Dyer et al., 2019a). Although I found only weak evidence of an association between state anxiety and alcohol craving, this supports some previous research which examined the relationship in a clinical sample (Drummond & Phillips, 2002).

My findings are consistent with previous research which suggests DTC positively predicts alcohol outcomes (Cooper et al., 2016). Although there was no clear evidence that DTC moderated associations of anxiety with alcohol choice and alcohol craving. This is contrary to previous research that found DTC moderated associations of fear and shyness with alcohol use (Hussong et al., 2005). State anxiety, trait anxiety, and DTC were all associated with higher alcohol craving (although state anxiety only weakly associated), which indicates that reducing anxiety and maladaptive coping strategies may reduce people's urge to drink alcohol. However, these associations do not show a causal relationship.

There are several possible explanations why the current study did not replicate the main experimental effect. First, the observational results may have been a false negative (Type II error). The lack of clear evidence may have been due to the low

levels of state anxiety among participants completing an online survey. Naturally-occurring fluctuations in state anxiety (STAI-S range 20-73, *M* = 35.47, *SD* = 11.10) were approximately 15 points lower than experimentally-manipulated state anxiety (STAI-S range 20-77, *M* = 50.74; *SD* = 11.79). In fact, state anxiety levels in the current study were comparable to levels observed in the control condition of the experiment (STAI-S range 20-52, *M* = 34.19, *SD* = 8.39). There therefore may be a floor effect, where higher anxiety is needed to see a signal with alcohol choice, compared to alcohol craving. Second, there may be no true association between state anxiety and alcohol choice; the experimental effect may have been a false positive (Type I error). Third, the experimental study may lack external validity. Compared to the current study, findings from the experimental study were based on a younger, predominantly student sample (age range 19-35, *M* = 23.21, *SD* = 3.34), which may not be generalisable to a wider, more diverse population. For example, there is evidence that the prevalence of binge drinking is higher among 16-24-year olds compared to 25-44- and 45-64-year olds (NHS digital, 2018), which may explain the inconsistent results. The artificial induction of state anxiety may also lack generalisability to more real-world experiences of state anxiety.

4.5.3. Limitations

The current study has some limitations. First, although a self-medication mechanism may be more detectable in cross-sectional (versus prospective) studies because, as a coping strategy, it implies immediacy, possible reverse causation is a limitation in cross-sectional studies. Second, results from the fully adjusted models suggest smoking and cannabis use may be confounding associations between state anxiety and alcohol outcomes, but there may also be further unmeasured and residual confounding (Fewell et al., 2007). Third, although I explored a range of theoretically relevant interactions and conducted sensitivity analyses, the study was not powered for these analyses. Results of the interaction,

stratified, and sensitivity analyses should therefore be interpreted with caution. Future studies with adequate sample sizes are required to assess their reliability. Fourth, although online studies have several strengths relative to laboratory studies, such as speed, lower costs, and access to a more representative sample of participants (Woods et al., 2015), they also have several weaknesses. Online participants may respond with less care, diligence, and honesty due to the absence of a researcher, which may impact internal validity (Woods et al., 2015). However, I excluded data from participants who failed our attention check question to improve data quality. Finally, there were limitations with the Concurrent Pictorial Choice Measure. Participants may have selected the alcohol images if the food images of typical UK meals did not reflect their preferences. However, I tried to avoid this issue by only recruiting UK nationals. I explored whether hunger and thirst levels during the study predicted responses on the task but there were only weak correlations between alcohol choice and hunger (r_s = -.13) and thirst levels (r_s = .10). Time of day may have also affected preferences, for example it is possible that participants may have been less likely to pick alcohol images if completing the study in the morning. However, any temporal effects should have been balanced out, as I staggered recruitment across the day.

4.5.4. Future Directions

A natural experiment could be an alternative method of investigating associations between state anxiety and alcohol related outcomes, without an experimental intervention. Individuals who are experiencing naturally-occurring high state anxiety could be compared on alcohol related variables to individuals who are experiencing low state anxiety. For example, comparing state anxiety and alcohol use among professionals with anxiety provoking jobs (e.g., emergency services workers), after a shift versus a day-off could be another naturalistic way to investigate this relationship.

4.6. Chapter Conclusions

I found no clear evidence of an association between state anxiety and alcohol choice, failing to support the findings of the previous experimental study and my hypothesis. However, state anxiety, trait anxiety, and DTC were associated with higher alcohol craving. This has potential health implications, given that alcohol craving predicts alcohol consumption (de Wit, 2000), and alcohol choice is correlated with alcohol dependence severity (Hardy & Hogarth, 2017).

Trait anxiety was positively associated with hazardous drinking and harmful drinking, although associations remained only for harmful drinking in the fully adjusted models. DTC was positively associated with all alcohol use outcomes (frequent drinking, frequent bingeing, hazardous drinking, and harmful drinking). These findings are qualitatively similar to the cohort study results presented in Chapter 3, with the strongest associations seen for harmful drinking. However, the point estimates were smaller in magnitude, particularly for the DTC associations. There was also no clear evidence of an interaction between trait anxiety and DTC on the four alcohol use outcomes, consistent with the cohort study. I will discuss possible reasons for the differences between my studies in the thesis discussion (Chapter 6).

Chapter 5: Experimental Study

5.1. Chapter Overview

In Chapter 4, I presented an online cross-sectional study that examined associations of naturally-occurring self-reported state anxiety with alcohol choice, alcohol craving, and alcohol use. In the current chapter, I discuss an experimental study that investigated the effects of experimentally-manipulated state anxiety on alcohol choice, alcohol craving, and alcohol approach-avoidance. I also explored whether these effects differed by drinking to cope (DTC) status. I used the 7.5% carbon dioxide (CO_2) model to induce anxiety, which has been found to increase symptoms of generalised anxiety disorder (GAD) (Bailey et al., 2011a).

Chapter 5 is based on Study 2 in the following submitted paper: 'State anxiety and alcohol choice: evidence from experimental and online observational studies'. Study 2 was a replication and extension of Study 1 in this paper, with an additional between-subjects factor of DTC. Study 2 was originally led by MSc students. However, the study was stopped as it was discovered that most of the participants were not completing the computer tasks within the inhalation block (allocated 20-minute time frame) and therefore they were not being manipulated.

I then joined the project, took control as lead investigator, and started the study again as an undergraduate dissertation project. I made several changes to the protocol after discussion with study co-authors (Marcus Munafò, Angela Attwood, Jon Heron, Matthew Hickman, and Lee Hogarth). Changes included different questionnaire measures, task stimuli and trials, analysis plan, and additional exploratory analyses. I revised all the study documents (protocol, participant information sheet, consent form, debrief form, and all case report forms), submitted the ethics amendment, and created the screening and participant surveys in Qualtrics (https://www.qualtrics.com/uk/). The computer tasks had been previously

created by colleagues for use in their own studies. I adapted an Approach-Avoidance Task (AAT) (stimuli, trials, timings) that had been created by Andy Eastwood, and the Concurrent Pictorial Choice Measure that had previously been created by Alex Board was left unchanged. Four undergraduate students (Daisy Macioccu, Alisha Mehta, Emily Jowett, and Isabel Mitchelson) handled participant recruitment and completed 85% of the data collection under my direction, and I finished the remaining 15%. I helped the students set up their study file, monitored their progress (projections and consorts), and performed quality control procedures (in session, study file, and data file). I analysed the data and wrote the manuscript with contributions from all authors.

The aims were to:

- Investigate whether experimentally-manipulated state anxiety affects alcohol choice, alcohol craving, and approach tendencies to alcohol.
- Explore whether these effects differ by DTC status.

5.2. Introduction

5.2.1. Background

Some observational studies have supported an anxiety-alcohol relationship, but many measure trait anxiety rather than state anxiety. Several experimental studies have investigated the effects of physical, psychological, and pharmacological stressors that induce state anxiety on alcohol outcomes (Thomas et al., 2012). Example psychological stressors used previously to investigate the effect of anxiety on alcohol use include social interaction tasks such as the Trier Social Stress Test (TSST) that involves an interview and a public mental arithmetic task (de Wit et al., 2003), and individualised guided imagery tasks that involve imagining a recent personal stressful situation (Fox et al., 2007).

The TSST has been found to increase alcohol consumption in social drinkers (de Wit et al., 2003; Magrys & Olmstead, 2015), and in combination with an alcohol cue reactivity procedure (smelling an alcoholic drink), the TSST increased alcohol craving in detoxified alcohol-dependent individuals with co-morbid post-traumatic stress disorder (Kwako et al., 2015). There is evidence that guided imagery tasks increase alcohol craving (Fox et al., 2007) and intravenous alcohol self-administration in non-dependent binge drinkers (Ramchandani et al., 2018). In addition, negative mood induction procedures increased alcohol choice (Hardy & Hogarth, 2017). A recent meta-analysis of laboratory studies found higher alcohol use and craving following a negative affect manipulation than following a control manipulation (Bresin et al., 2018). However, as the authors acknowledge, the methods of negative affect induction used in the reviewed studies likely target several different emotions (Bresin et al., 2018). Therefore, unique effects of state anxiety on alcohol use and alcohol craving cannot be deduced from these findings. Furthermore, there is evidence that anxiety-induction effects are greater in those who drink to cope. For example, negative mood induction increased alcohol seeking responses (Hogarth & Hardy, 2018), alcohol choice (Hogarth et al., 2018), and the reinforcing value of alcohol (Rousseau et al., 2011), among individuals who drink to cope.

Another experimental anxiogenic method is the 7.5% CO_2 model of anxiety induction. Previous research from our group has used this procedure to investigate the effects of state anxiety on alcohol choice and alcohol cognitive bias (using the modified pictorial Stroop task) in social drinkers. There was evidence of increased alcohol choice, but there was no clear evidence of increased cognitive bias during the 7.5% CO_2 inhalation. Furthermore, there was some evidence that self-reported DTC tendencies positively correlated with alcohol choice during both inhalations

(CO_2 and air), but this was not greater in the state anxiety (CO_2) condition. To the best of my knowledge, no other study has used the 7.5% CO_2 challenge to investigate its anxiogenic effects on alcohol-related outcomes.

The 7.5% CO_2 respiratory challenge is considered to be a reliable and safe human experimental model of anxiety that produces robust effects on subjective and objective measures of anxiety (Bailey et al., 2005). The inhalation has been shown to increase self-reported state anxiety, as well as autonomic physiological and psychological symptoms of GAD (Bailey et al., 2011a; Garner, 2015), including increased heart rate (HR), blood pressure (BP), and hypervigilance to threat (Garner et al., 2012). There is also evidence that anxiolytic medication such as the benzodiazepines lorazepam and alprazolam reduce some of the symptoms produced by the 7.5% CO_2 inhalation (Bailey et al., 2007; Bailey et al., 2009). This supports the idea that anxiety disorders and the 7.5% CO_2 inhalation have similar biological responses. The effects of the CO_2 appear to be dose dependent. Compared to lower concentrations, higher concentrations of CO_2 (35%) elicit panic symptoms (Verburg et al., 1998) and more pronounced subjective and autonomic effects (Colasanti et al., 2008). The 35% CO_2 model (single breath) also activates the hypothalamic-pituitary-adrenal axis, increasing adrenocorticotropic hormone and cortisol levels (Argyropoulos et al., 2002; Kaye et al., 2004), but the 7.5% CO_2 model does not reliably produce these effects (Bailey et al., 2003).

The amygdala has been hypothesised to play a role in anxiety responses to the CO_2 inhalation. It is sensitive to hypercapnia - elevated CO_2 in the bloodstream (Brannan et al., 2001). Inhalation of CO_2 lowers brain pH and acidifies the bloodstream, activating acid sensing ion channels in the amygdala (Ziemann et al., 2009). Researchers have therefore suggested that the amygdala is a chemosensor that detects acidosis and elicits fear and anxiety responses (Ziemann et al., 2009).

However, the 35% CO_2 challenge has been found to produce panic and anxiety in patients with bilateral amygdala damage (Feinstein et al., 2013), which highlights other brain structures may also be important (Taugher et al., 2014). Bailey and colleagues (2003) propose that chemoreceptors in the noradrenergic system, particularly the locus coeruleus, may mediate anxiety and panic responses to higher concentrations of CO_2 via noradrenaline release.

As well as alcohol choice and alcohol craving mentioned above, previous studies have also used AATs to measure automatic motivation for alcohol. In the AAT, participants are required to respond as quickly as possible to a stimulus presented on screen by pushing or pulling a joystick, as directed by a visual cue. The premise of the AAT is that approach and avoidance are 'basic responses associated with the primary motive systems of the brain that underlie complex emotional responding' (Klein et al., 2011). Research suggests that heavy drinkers are faster to pull than to push images of alcoholic drinks, which indicates an approach bias to alcohol (Wiers et al., 2009). Training variants of the AAT have also been used to reduce alcohol use in problem drinkers by repeatedly pairing alcohol stimuli with an avoidance joystick cue and movement (Sharbanee et al., 2014). For example, Wiers and colleagues (2010) showed that heavy drinkers trained with avoid-alcohol AAT cues later consumed less alcohol than those trained with approach-alcohol AAT cues.

There are advantages of including both direct and indirect outcome measures in a study. Direct measures, such as questionnaires, involve participants being explicitly asked about their drinking behaviour. Although questionnaires are quick and easy to administer, answers are controlled and deliberate so may be limited by social desirability biases, memory biases, and people's introspection abilities (Klein et al., 2011). Alternatively, indirect measures such as reaction time (RT) and

other cognitive tasks, can capture more fast, automatic cognitive processes (Klein et al., 2011). However, a limitation of these behavioural tasks is that they may lack validity, as they measure behaviour not directly related to drinking behaviour (e.g., joystick movement, pressing computer keys) (Klein et al., 2011). Because of these strengths and limitations of direct and indirect measures, I have included both questionnaires (for alcohol craving) and behavioural tasks (for alcohol choice and alcohol approach tendencies) to assess alcohol-related outcomes in this study.

5.2.2. Aims and Hypotheses

The main aim of the current study was to investigate the effects of state anxiety on alcohol choice, alcohol craving, and alcohol approach-avoidance tendencies in social drinkers, using the 7.5% CO_2 model to induce state anxiety (Bailey et al., 2011b). I hypothesised that inhalation of 7.5% CO_2 (compared to inhalation of medical air) would lead to increased: (a) alcohol choice, (b) alcohol craving, and (c) approach tendencies to alcohol stimuli (versus neutral stimuli). As an extension of the original experimental study, and a replication of my online cross-sectional study (Chapter 4), I explored whether these effects differed by DTC status (high versus low DTC). The cognitive bias measure used in the original experimental study (modified pictorial Stroop task) was replaced, as it has been reported to be unreliable (Adams et al., 2012; Ataya et al., 2012).

5.3. Methods

The protocol for this study was pre-registered on the Open Science Framework (https://osf.io/5q8gc/). Ethics approval was obtained from the Faculty of Science Research Ethics Committee at the University of Bristol (reference 25051752981).

5.3.1. Design

I used a mixed model design with one within-subjects factor of gas (medical air, 7.5% CO_2) and one between-subjects factor of DTC status (low, high). For the AAT analyses, there was an additional within-subjects factor of stimuli image type (alcohol, neutral). Alcohol choice, alcohol craving, and AAT bias scores were the outcome measures. Order of gas inhalation (medical air, CO_2) and computer tasks (alcohol choice, AAT) were fully counterbalanced across participants using a random number generator.

5.3.2. Participants

Sample size was calculated using G*Power. It was determined using an effect size estimate from our previous experimental study that investigated the effects of state anxiety on alcohol choice (manuscript in preparation). This study compared percentage alcohol choice during a 7.5% CO_2 enriched air inhalation (*M* = 43%, *SD* = 25) and a medical air inhalation (*M* = 33%, *SD* = 22). Correlation between conditions was .79, which is equivalent to dz = .65. Cohen's dz is the standardised mean difference effect size for within-subjects designs (Lakens, 2013). It is plausible that this effect size may be inflated as it was a discovery sample; I therefore reduced the effect size to dz = .43 (reduction by one third), which required 60 participants to detect with 90% power at an alpha level of 5%. I aimed to recruit 15 low DTC males, 15 low DTC females, 15 high DTC males, and 15 high DTC females.

Participants were recruited from staff and students at the University of Bristol and local population via existing email lists, poster and flyer advertisements around the University of Bristol and local pubs/bars, social media, word of mouth, and the School of Psychological Science website. Participants were eligible to take part if they met the following criteria: aged 18-50 years, in good physical and psychiatric

health, spoke English as first language or had an equivalent level of fluency, consumed alcohol at least weekly, consumed wine and/or beer as a drink of choice, had no dietary requirements (due to the nature of the task stimuli), and had low or high scores on the Modified Drinking Motives Questionnaire - Revised (MDMQ-R) (Grant et al., 2007). Exclusion criteria and their rationale (safety or scientific reasons) are listed in Table 5.1.

Table 5.1. Exclusion criteria and rationale.

Exclusion Criteria	Rationale
Alcohol consumption within 24 hours of the study session	Safety and scientific
Consumption of more than 35 alcoholic units per week (female) and 50 units per week (male) - 'higher risk' drinking	Safety and scientific
Current or past psychiatric disorders	Safety and scientific
Current or past alcohol or drug dependence	Safety and scientific
Strong family history of mood disorder including panic disorder	Safety and scientific
Medication use within the past eight weeks (except local treatment, aspirin or paracetamol, and contraceptive medication)	Safety and scientific (depending on the medication)
Illicit drug use in the past month (past week for cannabis, past year for heroin)	Safety and scientific
Systolic/diastolic blood pressure higher than 140/90 mmHg	Safety
Heart rate < 50 or > 90 beats per minute	Safety
Being pregnant or breastfeeding	Safety
Body mass index (BMI) < 17 kg/m^2 or > 30 kg/m^2	Safety
Current or past migraine headaches requiring treatment, other ongoing physical illnesses or abnormalities (e.g., history of cardiac or respiratory problems, and asthma)	Safety
Not being registered with a general practitioner	Safety
Consumption of more than eight caffeinated drinks per day	Scientific
Daily smoking	Scientific
Impaired or uncorrected vision and hearing	Scientific

Participants were initially recruited based on their DTC motivation. I selected total scores of 4-8 to represent the low DTC group as that reflected responses of 'almost never/never' or 'some of the time' on the four anxiety-coping items of the MDMQ-R (Grant et al., 2007). The items are: 'to relax', 'because I feel more confident or sure of myself', 'because it helps me when I am feeling nervous', and 'to reduce my anxiety'. I attempted to recruit high DTC participants based on total scores of 16-20 as that reflected responses of 'most of the time/often' or 'almost always/always' on the four anxiety-coping items. However, recruitment of these individuals was difficult, so after a few months I relaxed these criteria to 4-8 (low-DTC) and 12-20 (high DTC), as per the protocol. The DTC measure I used in the previous chapter also used scores of 12-20 to denote high DTC individuals, but the low DTC group included scores from 4-11. In Chapter 4, a continuous DTC measure was dichotomised after data collection at the upper quartile determining the cut-offs, whereas in this chapter, cut-offs were determined prior to data collection and I dropped middle scorers on the questionnaire to get a stronger DTC measure. There was one participant who completed the DTC screening questionnaire twice and scored in the low and high category each time. I asked her to complete the questionnaire again to determine which group to allocate her to.

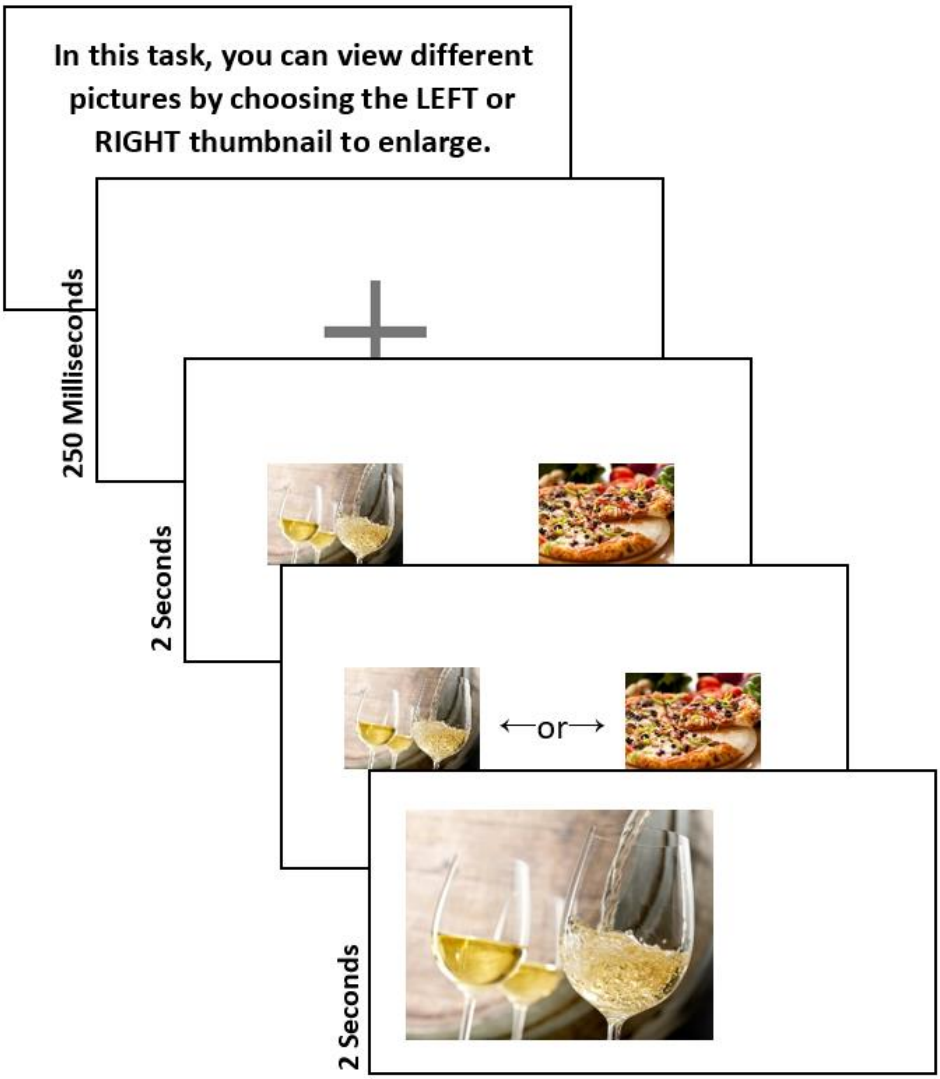
There were several barriers to recruiting high DTC individuals. First, DTC is associated with internalising disorders (Stapinski et al., 2016) and alcohol problems (Kuntsche et al., 2005), but there are strict safety/ethical criteria for participating in CO_2 studies which includes no personal history of a diagnosed psychiatric disorder or alcohol dependence. Second, due to the safety constraints of a CO_2 study, we could only test participants from 9am to 5pm Monday to Friday, which made it difficult for people who are employed full time to participate. Participant recruitment also became difficult in June, when the exam period started.

5.3.3. Measures and Materials

5.3.3.1. Gas Mixtures. The gas mixture for the CO_2 (high state anxiety) condition was 7.5% CO_2/21% Oxygen/71.5% Nitrogen and the gas mixture for the medical air (low state anxiety) condition was 21% O_2 (BOC Ltd.). Gases were administered using an oro-nasal mask (Hans Rudolph Inc., USA). For safety reasons, gas administration was single-blind.

5.3.3.2. Computer Tasks. I measured percentage alcohol choice using the computerised Concurrent Pictorial Choice Measure (Hardy & Hogarth, 2017) (see Figure 5.1). Instructions were: 'In this task, you can view different pictures by choosing the LEFT or RIGHT thumbnail to enlarge'. Each trial presented an alcohol image and a food image (typical UK meals) on either the left or right side of the screen. After 2000ms, the instructions '←or→' appeared, at which point pressing the corresponding arrow key enlarged the selected image and removed the unselected image. The enlarged image remained on screen for 2000ms, before an inter-trial interval of 1-2 seconds. Each of the 48 trials randomly selected from 12 alcohol and 12 food images, and the left-right position of food and alcohol images was also randomised (maximum four trials in either position). The percentage choice of alcohol images was the primary outcome measure.

Figure 5.1. Schematic of the concurrent pictorial choice measure.

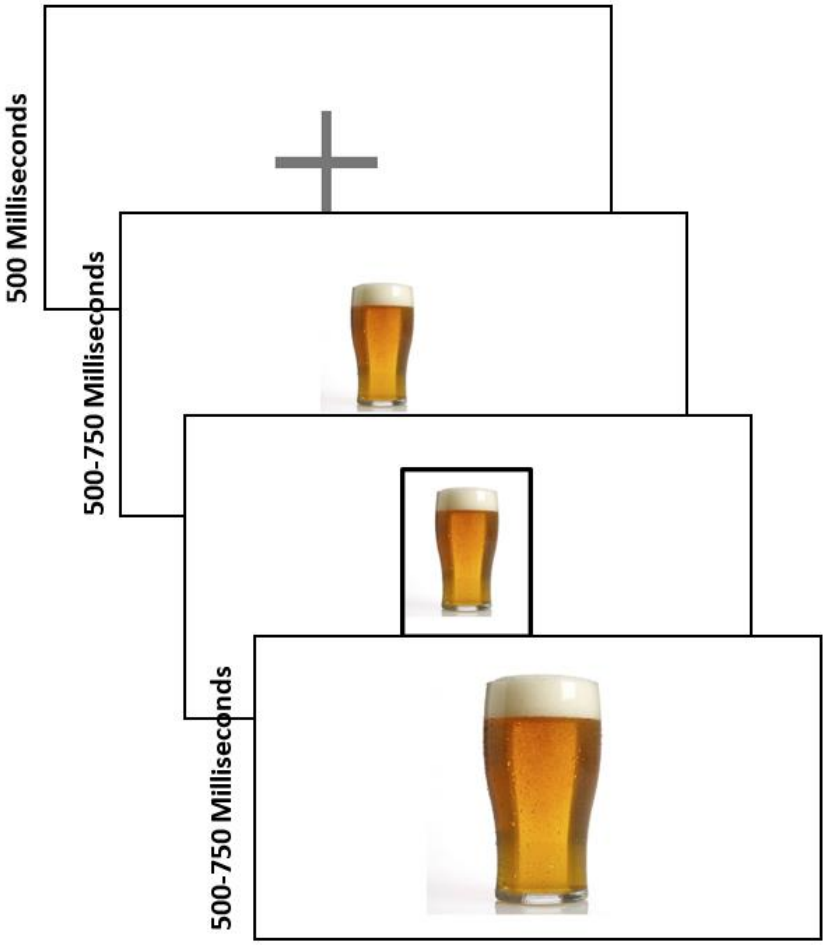


I measured alcohol approach-avoidance tendencies using the approach avoidance task (AAT) (see Figure 5.2). The AAT consisted of six practice trials (stationery equipment images), followed by two experimental blocks, each comprising 48 experimental trials (i.e., 96 experimental trials in total). Each block presented 12 alcohol images and 12 neutral images (soft drinks), and trials were split between 24 approach and 24 avoidance trials (12 per stimulus type). The presentation order of the images was randomised within the blocks and across participants. On each trial, a fixation cross appeared on screen for 500ms, before being replaced by an image (alcohol or neutral). After a short delay (500-750ms), either a solid border cue (24 trials per block: 12 alcohol, 12 neutral) or a dashed border cue (24 trials

per block: 12 alcohol, 12 neutral) appeared around the image. Participants were required to either push the image away from them (arm extension; 50% of trials) or pull the image towards them (arm flexion; 50% of trials) using a joystick, depending on the border cue (dashed versus solid, respectively). Participants were encouraged to respond as quickly and as accurately as possible. Image size changed based on joystick movement. A pull movement caused a larger version of the image to appear (creating a visual impression of the image moving closer; approach), and a push movement caused a smaller version of the image to appear (creating a visual impression of the image moving away; avoidance). RT was measured from the point at which the cue appeared to the point at which the participant made the full joystick response and the image disappeared. Shorter (faster) RTs to pull trials were indicative of an approach tendency and shorter (faster) RTs to push trials were indicative of an avoidance tendency. Each neutral (soft drink) image was matched to an alcohol image in the set based on various visual characteristics (size, brightness, resolution, and complexity). For example, to ensure images were matched for complexity, we had an equal number of alcohol and neutral images that displayed single and multiple glasses, single and multiple bottles/cartons, and static and pouring content. As shown in Figure 5.2, images were presented individually.

Two versions of the Concurrent Pictorial Choice Measure and the AAT were created in E-Prime that were identical on all the details noted above. However, one version comprised wine images and the other beer/lager images. At the start of the study, participants were asked what their drink of choice was out of the two options, and they completed the corresponding task versions. This ensured that effects were not weakened by participants seeing images of drinks they do not regularly consume, and the two versions enabled us to recruit from a wider pool of participants.

Figure 5.2. Schematic of the approach avoidance task.



5.3.3.3. Questionnaire Measures. I measured alcohol craving using the Alcohol Urge Questionnaire (AUQ) (Bohn et al., 1995). I measured subjective state anxiety (state anxiety manipulation check) and trait anxiety (participant characteristics) using the Spielberger State-Trait Anxiety Inventory state (STAI-S) and trait (STAI-T) sub-scale (Spielberger et al., 1983), positive and negative affect (state anxiety manipulation check) using the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988), and DTC motives (moderator) using the coping-anxiety subscale of the Modified Drinking Motives Questionnaire – Revised (Modified DMQ-R) (Grant et al., 2007). Participant personality characteristics were measured using the Eysenck Personality Questionnaire – Revised (EPQ-R) (Eysenck & Eysenck, 1991). I also included a novel questionnaire measure of DTC for

exploratory purposes, the Drinking Motives Checklist (DMC), designed by a collaborator – Lee Hogarth (see Appendix 5.1).

5.3.3.4. Physiological Measures. HR, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were assessed using the OMRON M6 blood pressure monitor (OMRON Healthcare, UK).

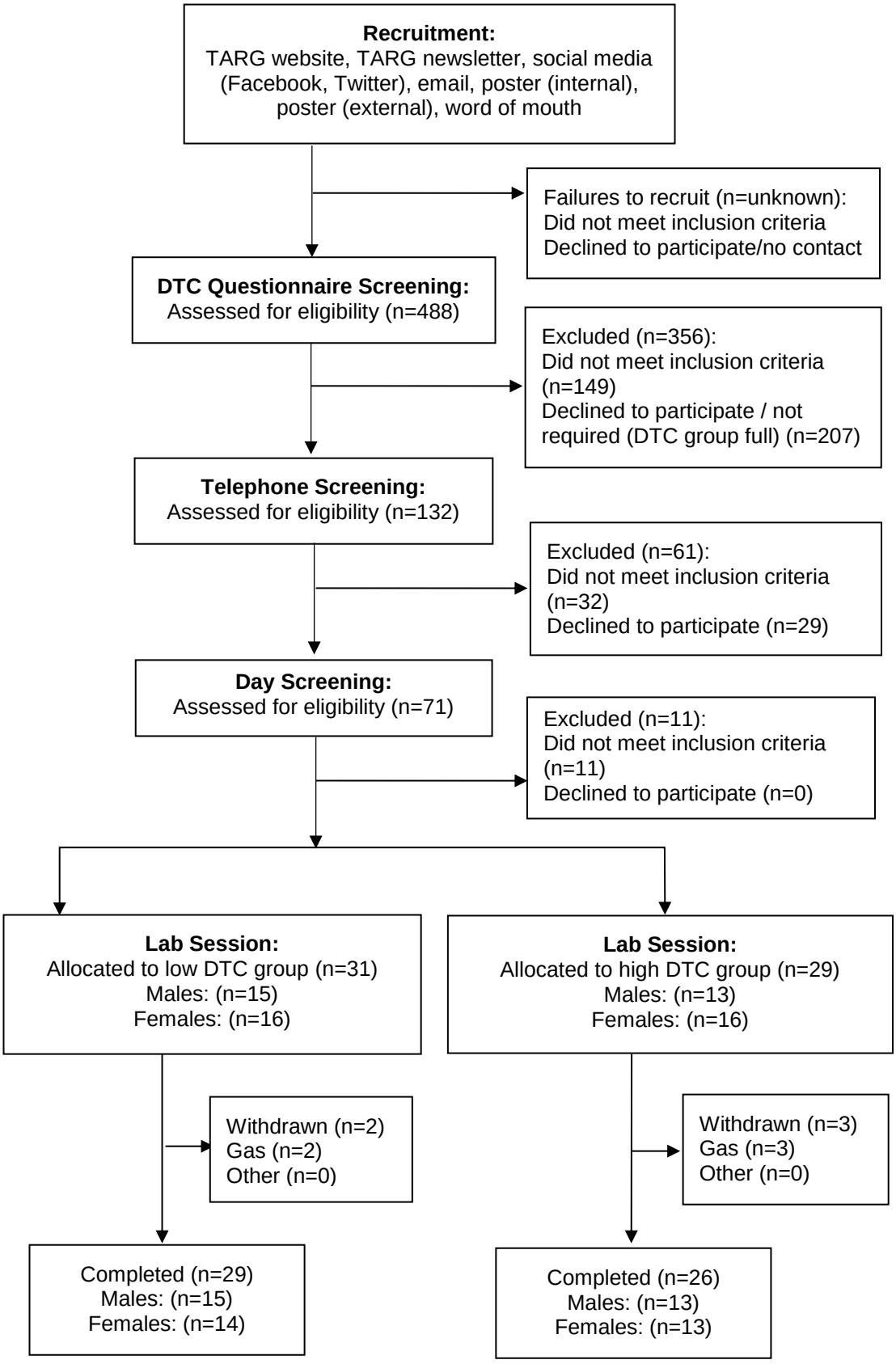
5.3.4. Procedure

There were three screening phases: online screening questionnaire, telephone screening, and day screening. First, participants read the information sheet attached to study adverts, and they were directed to an online Qualtrics questionnaire which was used to assign participants to either the low (4-8) or high (12-20) DTC group. Participants who scored 9-11 were ineligible. Second, participants who passed this screening questionnaire were contacted to complete a telephone screening to assess basic eligibility. This included questions on demographics (age, gender), caffeine consumption, alcohol consumption, smoking, and medical history. Finally, eligible participants were invited to attend a 2.5-hour laboratory session. Prior to the commencement of the experimental procedures, participants were screened further to ensure that no significant change (e.g., diagnosis of illness, use of medication) had occurred since the telephone screening, and to objectively assess eligibility. Participants provided informed consent and were reminded of their right to withdraw at any time. I objectively assessed body mass index (BMI), recent alcohol consumption (AlcoDigital 3000 breathalyser) and smoking (Pico Smokerlyser for carbon monoxide), pregnancy and recent drug use (urine screen), SBP, DBP, and HR, and psychiatric health using the MINI-International Neuropsychiatric Interview (Sheehan et al., 1998). All other criteria were assessed by self-report. All data gathered from individuals who were ineligible were destroyed using the University's confidential waste facility.

Following the day screening, participants completed baseline questionnaires (STAI-S, STAI-T, PANAS, AUQ), and baseline SBP, DBP, and HR were recorded. Participants breathed the gas (air or CO_2 first) for one minute before completing the two computer tasks (alcohol choice, AAT). Inhalations lasted a maximum of 20 minutes. Immediately after each inhalation, SBP, DBP, and HR were measured, and participants completed the STAI-S, PANAS, and AUQ, based on how they felt during the inhalation when the effects of the gas were at their peak. There was a 30-minute 'wash-out' period between inhalations. Participants remained in the laboratory for 20 minutes after the second inhalation to allow any effects of the inhalation to dissipate. During this time, they completed the EPQ-R and DMC. SBP, DBP, and HR were measured to ensure that they had returned to a normal level. Participants had the opportunity to stay longer if they felt the effects of the gas had not worn off. Each study session lasted approximately 2.5 hours, and participants were reimbursed £20. Participants were phoned 24-hours later to assess if any adverse events had occurred since the study session.

A breakdown of how the final analysis sample was determined is shown in Figure 5.3. Although 488 people completed the screening questionnaire, only 339 were eligible based in their DTC total scores (i.e., those scoring 9-11 were ineligible). Of the 132 participants who were telephone screened, 71 completed the day screening session. Eleven people failed the day screening procedures on criteria such as high blood pressure or recent drug use. Although 60 participants began the experiment, five withdrew part the way through. This left a total sample size of 55 participants (target 60) who had complete data on all three outcome measures. Due to the time constraints of the PhD, and the reduction of new sign-ups during the summer months, I stopped testing at 60 participants, despite some missing data, meaning the study had 87% (rather than 90%) power to detect the target effect size of dz = .43.

Figure 5.3. Study sample size flow diagram.



5.3.5. Data Analyses

5.3.5.1. Quality Assessment and Manipulation Check. I checked all manually inputted questionnaire data for accuracy (age, gender, drink type, task order, gas order, SBP, DBP, HR, and BMI). I performed some of the recoding of variables in Stata version 15, and all analyses and additional variable recoding were conducted using IBM SPSS Statistics version 24. I performed paired-sample t-tests to check the validity of the state anxiety manipulation, by comparing subjective (STAI-S, PANAS), and physiological (HR, SBP, DBP), responses after CO_2 versus air inhalations.

5.3.5.2. Main Analyses. For alcohol choice and alcohol craving, the primary statistical model was a 2 × 2 mixed model analysis of variance (ANOVA) with a within-subjects factor of gas (medical air, 7.5% CO_2) and a between-subjects factor of DTC status (low, high). There was an additional within-subjects factor of image type (alcohol, neutral) for the AAT data. First, I excluded all errors from the AAT data (i.e., push responses when a pull response was cued and vice versa). Second, I calculated four median RTs for each participant: approach alcohol, avoid alcohol, approach neutral, and avoid neutral. I used median RTs rather mean RTs, consistent with other research using the AAT, because medians are less sensitive to outliers and arbitrary cut-offs for extreme values are therefore not required (Wiers et al., 2010). I calculated AAT bias scores separately for alcohol and neutral stimuli, by subtracting median pull RTs from median push RTs. Negative AAT scores reflect a greater avoidance tendency (as push RTs were faster than pull RTs). Conversely, positive AAT scores reflect a greater approach tendency (as pull RTs were faster than push RTs). I then conducted a 2 x 2 x 2 mixed ANOVA to investigate the effect of state anxiety, DTC, and image type on alcohol approach-avoidance tendencies. Where there was evidence of an interaction, I conducted

post hoc simple effects analyses (paired and un-paired t-tests, depending on the variable) to explore where the differences were between the means.

5.3.5.3. Exploratory Analyses. I conducted a subgroup analysis restricted to wine drinkers and using only results from the wine stimuli for the alcohol choice task, to match the task version used and sample recruited in the previous experimental study. Secondly, I correlated subscales of the DMC with the magnitude of the difference in alcohol choice produced by CO_2, and multiple regression was used to determine if any of the subscales acted as an independent predictor. I also planned to conduct a sensitivity analysis comparing alcohol choice among individuals with high DTC and high social motives for drinking to those who drink for either or neither reason. However, there were insufficient participant numbers in some of the subgroups, so the results would not have been meaningful.

5.4. Results

5.4.1. Participant Characteristics

Participants (*n* = 60, 47% male) were aged between 18 and 34 years (*M* = 21.50, S*D* = 3.17). Trait anxiety scores ranged from 22 to 51 (*M* = 33.85, *SD* = 6.50). DTC with anxiety scores ranged from 4 to 8 (*M* = 6.45, *SD* = 1.23) for the low DTC group and 12 to 19 (*M* = 14.17, *SD* = 2.02) for the high DTC group. EPQ-R scores ranged from 17 to 30 (*M* = 23.28, *SD* = 3.41) for extraversion, 27 to 46 (*M* = 36.83, *SD* = 4.92) for neuroticism, and 6 to 26 (*M* = 18.38, *SD* = 4.09) for psychoticism.

5.4.2. Manipulation Check

Paired-sample t-tests revealed that subjective state anxiety, negative affect, HR, SBP, and DBP were higher, and positive affect was lower, following the CO_2

inhalation compared to the air inhalation (Table 5.2). This confirmed that my experimental manipulation of state anxiety was successful.

Table 5.2. Differences in state anxiety, positive and negative affect, and cardiovascular measures, following the CO_2 and air inhalations.

	Mean Difference CO_2 versus Air (SD)	Effect Size (dz)	95% CI	p-value	N
STAI-S	15.15 (10.67)	1.42	12.39 to 17.91	<.001	60
PANAS-positive	-3.03 (6.53)	0.46	-4.72 to -1.35	.001	60
PANAS-negative	6.10 (5.73)	1.06	4.62 to 7.58	<.001	60
SBP	9.34 (9.70)	0.96	6.81 to 11.87	<.001	59
DBP	3.22 (7.01)	0.46	1.39 to 5.05	.001	59
HR	11.14 (13.16)	0.85	7.71 to 14.56	<.001	59

STAI-S = Spielberger State-Trait Anxiety Inventory – state subscale; PANAS = Positive and Negative Affect Schedule; SBP = systolic blood pressure; DBP = Diastolic blood pressure; HR = heart rate.

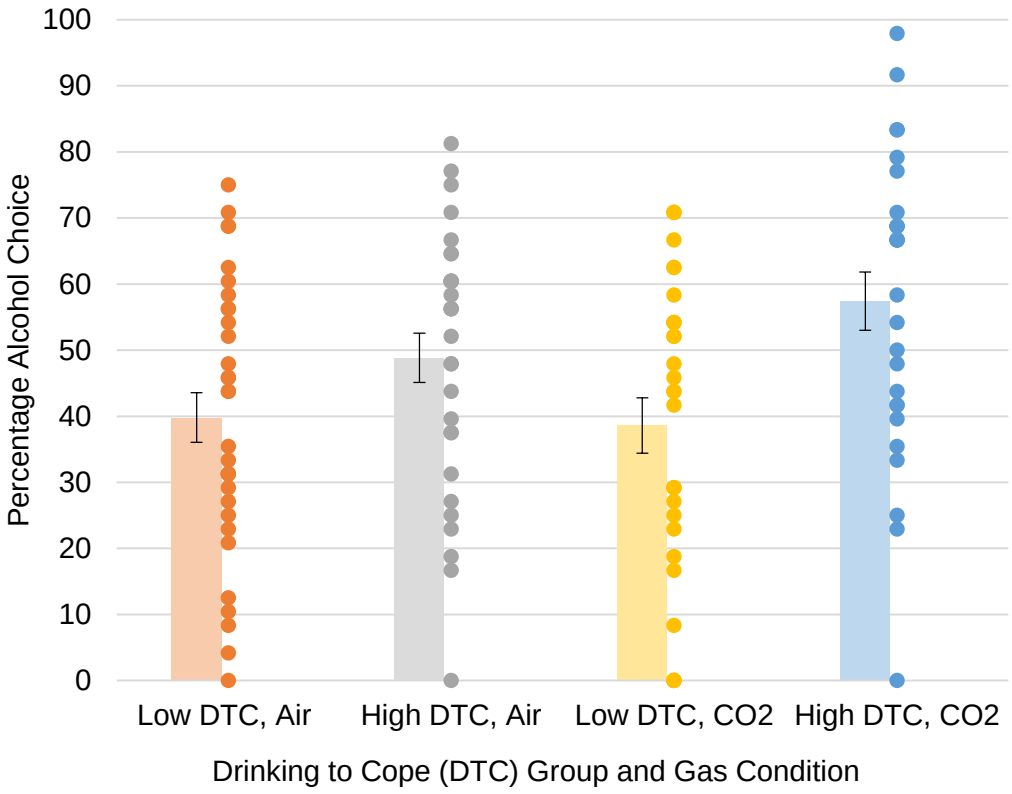
5.4.3. Main Findings

5.4.3.1. Alcohol Choice. There was weak evidence of a main effect of gas on alcohol choice ($F_{(1, 55)} = 3.27$, $p = .076$, $\eta_p^2 = .056$). Alcohol choice was higher in the CO_2 condition ($M = 48.01$, $SE = 3.05$) than the air condition ($M = 44.50$, $SE = 2.76$). There was evidence of a main effect of DTC on alcohol choice ($F_{(1, 55)} = 6.37$, $p = .015$, $\eta_p^2 = .104$). Alcohol choice was higher in the high DTC group ($M = 53.16$, $SE = 3.97$) than the low DTC group ($M = 39.34$, $SE = 3.77$).

There was also evidence of a gas x DTC interaction on alcohol choice ($F_{(1, 55)} = 6.54$, $p = .013$, $\eta_p^2 = .106$). In the air condition, there was weak evidence that alcohol choice was higher in the high DTC group than the low DTC group (48.85

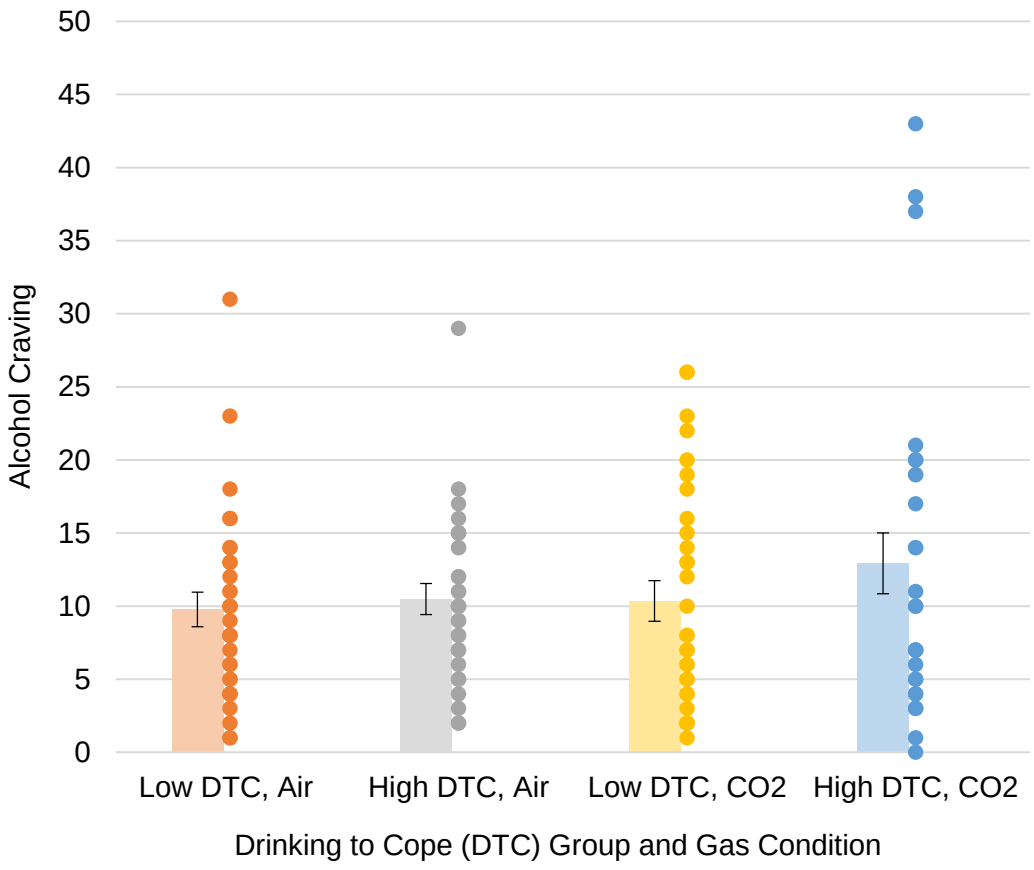
versus 39.78, p = .093). In the CO_2 condition, there was strong evidence that alcohol choice was higher in the high DTC group than the low DTC group (57.41 versus 38.61, p = .003). In the low DTC group, there was no clear evidence of a difference in alcohol choice in the air condition and the CO_2 condition (40.07 versus 38.61, p = .586). In the high DTC group, there was strong evidence of higher alcohol choice in the CO_2 condition than the air condition (57.41 versus 48.92, p = .006) (Figure 5.4). All figures display the means in each condition, error bars show the standard errors of the mean, and individual data points are also plotted to show the distribution.

Figure 5.4. Interaction between gas and drinking to cope (DTC) on alcohol choice.



5.4.3.2. Alcohol Craving. There was no clear evidence of a main effect of gas on alcohol craving ($F_{(1, 58)}$ = 2.54, p = .116, η_p^2 = .042). Alcohol craving was similar in the CO_2 condition (M = 11.64, SE = 1.24) and the air condition (M = 10.13, SE = .80). There was no clear evidence of a main effect of DTC on alcohol craving ($F_{(1, 58)}$ = 0.79, p = .379, η_p^2 = .013). Alcohol craving was similar in the high DTC group (M = 11.71, SE = 1.33) and the low DTC group (M = 10.07, SE = 1.29). There was also no clear evidence of a gas x DTC interaction on alcohol craving ($F_{(1, 58)}$ = .97, p = .330, η_p^2 = .016) (Figure 5.5).

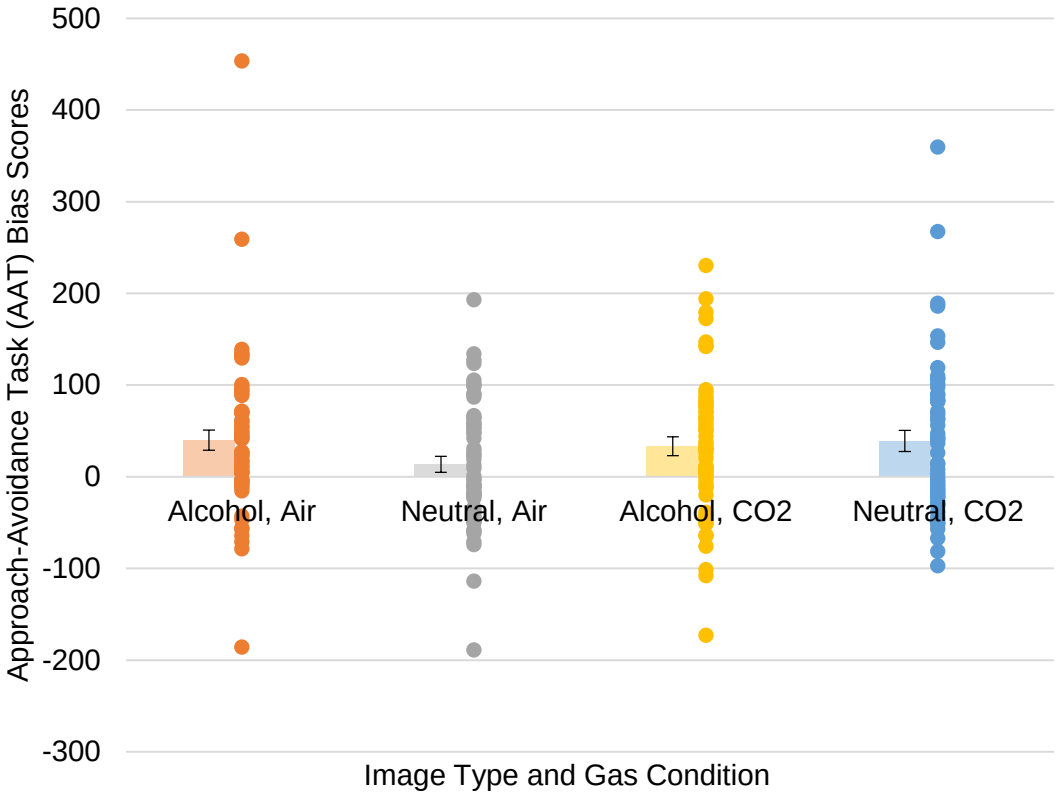
Figure 5.5. Interaction between gas and drinking to cope (DTC) on alcohol craving.



5.4.3.3. Approach-Avoidance. The was no clear evidence of a main effect of gas on AAT scores ($F_{(1, 54)}$ = .88, p = .352, η_p^2 = .016). AAT scores were similar in the CO_2 condition (M = 36.30, SE = 10.26) and the air condition (M = 27.13, SE = 8.57). There was no clear evidence of a main effect of DTC on AAT scores ($F_{(1,54)}$ = .007, p = .931, η_p^2 < .001). AAT scores did not differ in the high DTC group (M = 31.01, SE = 11.64) and the low DTC group (M = 32.41, SE = 11.24). There was weak evidence of a main effect of image type on AAT scores ($F_{(1, 54)}$ = 3.56, p = .065, η_p^2 = .062). AAT scores were higher in response to alcohol images (M = 37.71, SE = 9.03) than neutral images (M = 25.72, SE = 8.34).

There was evidence of a gas x image interaction on AAT scores ($F_{(1, 54)}$ = 4.88, p = .031, η_p^2 = .083) (Figure 5.6). In the CO_2 condition, there was no clear evidence that AAT scores differed in response to alcohol and neutral images (33.39 versus 39.01, p = .488). In the air condition, there was some evidence that AAT scores were higher in response to alcohol images than neutral images (39.95 versus 13.41, p = .027). For alcohol images, there was no clear evidence of a difference in AAT scores in the air condition and the CO_2 condition (41.94 versus 33.39, p = .517). For neutral images, there was some evidence that AAT scores were higher in the CO_2 condition than the air condition (39.01 versus 12.62, p = .037). There was no clear evidence of a gas x DTC interaction ($F_{(1, 54)}$ = .49, p = .489, η_p^2 = .009), an image x DTC interaction ($F_{(1, 54)}$ = .37, p = .543, η_p^2 = .007), or a gas x image x DTC interaction ($F_{(1,54)}$ = 2.68, p = .107, η_p^2 = .047) on AAT scores.

Figure 5.6. Interaction between gas and image type on AAT bias scores.



5.4.4. Exploratory Findings

5.4.4.1. Alcohol Choice (Wine Only). When restricting analyses to the wine drinkers (n = 25) and wine stimuli, there was no clear evidence of a main effect of gas ($F_{(1,23)}$ = 0.002, p = .964, η_p^2 = <.001), or DTC ($F_{(1, 23)}$ = 1.39, p = .251, η_p^2 = .057) on alcohol choice. There was also no clear evidence of a gas x DTC interaction ($F_{(1, 23)}$ = 2.89, p = .103, η_p^2 = .112).

5.4.4.2. Drinking Motives Checklist. The anxiety, stress, and isolation subscales of the DMC and total DMC scores positively correlated with magnitude of the difference in alcohol choice produced by the CO_2 inhalation (Table 5.3). However, linear regression revealed no clear evidence that any of the subscales independently predicted magnitude of the difference in alcohol choice, when adjusting for the other subscales (ps > .1).

Table 5.3. Bivariate correlations examining associations of subscales of the drinking motives checklist (DMC) and the magnitude of the difference in alcohol choice produced by the CO_2 inhalation.

		Depression	Anxiety	Stress	Anger	Isolation	Physical	Cognition	DMC Total	Choice Difference
Depression	r	1								
	p-value									
Anxiety	r	.49	1							
	p-value	<.001								
Stress	r	.65	.63	1						
	p-value	<.001	<.001							
Anger	r	.56	.45	.41	1					
	p-value	<.001	<.001	.001						
Isolation	r	.62	.67	.75	.46	1				
	p-value	<.001	<.001	<.001	<.001					
Physical	r	.21	.31	.18	.06	.16	1			
	p-value	.104	.017	.164	.634	.237				
Cognition	r	.23	.47	.43	.14	.51	.25	1		
	p-value	.083	<.001	.001	.281	<.001	.056			
DMC Total	r	.78	.83	.86	.59	.88	.37	.60	1	
	p-value	<.001	<.001	<.001	<.001	<.001	.004	<.001		
Choice Difference	r	.06	.30	.32	-.08	.28	.17	.19	.27	1
	p-value	.657	.025	.014	.574	.036	.220	.153	.043	

N = 60 for DMC subscale correlations. N = 57 for alcohol choice difference correlations. Pearson correlations. Choice Difference = percentage alcohol choice in the CO_2 condition minus the percentage alcohol choice in the air condition.

5.5. Discussion

5.5.1. Summary of Findings

In support of my first hypothesis, there was some evidence that experimentally-manipulated state anxiety increases alcohol choice compared to low state anxiety, although the effects were weaker than the findings of the original experimental study. There was also evidence of an interaction between state anxiety and DTC, with higher alcohol choice among high DTC individuals than low DTC individuals, particularly in the CO_2 condition compared to the air condition. Contrary to my second hypothesis and the results of Chapter 4, there was no clear evidence of an effect of state anxiety on alcohol craving. Finally, although there was evidence of an interaction between state anxiety and image type on AAT bias scores, this was not in the direction predicted. Approach tendencies were higher in response to alcohol images than neutral images in the air condition, but not in the CO_2 condition, contrary to my hypothesis.

Exploratory analyses revealed no clear evidence of an effect of state anxiety, DTC, or an interaction between the two, on alcohol choice, when restricting analyses to the wine drinkers and wine stimuli only. However, these analyses were underpowered (n = 25), which likely explains the null findings. Three of the subscales of the novel drinking motives checklist (anxiety, stress, and isolation), and DMC total scores positively correlated with magnitude of the difference in alcohol choice produced by the CO_2 inhalation. However, none of the subscales were independent predictors.

5.5.2. Original Research Contribution

This study replicates and extends our original experimental study. It suggests that the effect of 7.5% CO_2 induced state anxiety on alcohol choice is reliable, and DTC

moderates these effects. To the best of my knowledge, this is the first study to investigate the effect of experimentally-induced state anxiety on alcohol-related outcomes, and the moderating role of DTC, using the 7.5% CO_2 model of anxiety induction. I have therefore built on other anxiety-induction experimental studies that have used other methods of manipulating anxious states such as guided imagery, social stress, and negative mood induction procedures (Fox et al., 2007; Thomas et al., 2012). There was some evidence of an effect of state anxiety on alcohol choice, and an interaction between state anxiety and DTC on alcohol choice, supporting Hardy and Hogarth (2017), and Hogarth and colleagues (2018), respectively. However, there was no clear evidence of an effect of state anxiety on alcohol craving, failing to support previous anxiety-induction experiments (Fox et al., 2007; Kwako et al., 2015).

There are several possible reasons why I did not find an experimental effect of state anxiety on alcohol craving. Most participants found the CO_2 inhalation to be unpleasant; PANAS positive scores were lower and PANAS negative scores were higher following the CO_2 inhalation compared to the air inhalation. There may be a difference between alcohol craving in response to artificially induced anxiety in a laboratory setting compared to naturally-occurring anxiety in a real-world setting (Chapter 4), which throws into question whether the experiment had ecological validity. There may be a timing effect, where the urge to drink alcohol comes later, rather than immediately after an aversive experimental procedure. The CO_2 challenge is considered to create physiological anxiety. It is not driven by a cognitive component of anxiety; the cognitive effects might occur downstream. I also had stricter exclusion criteria in the current study (low risk drinkers only) compared to Chapter 4 (any alcohol drinker), which may also explain the inconsistent alcohol craving findings. Excluding high risk and alcohol-dependent

drinkers may have excluded people who are likely to exhibit alcohol craving in the first place, as cravings are induced by repeated exposure.

The disparate findings between alcohol choice and alcohol craving could be explained by the nature of both measures: alcohol choice is indirect whereas alcohol craving is direct. As mentioned previously, direct and indirect measures have different strengths and weaknesses (Klein et al., 2011). The instructions for the alcohol choice task were implicit for simplicity – participants were asked to select an image out of the two presented, and they could interpret those instructions in their own way. The choice task may therefore reflect a more subconscious, automatic motivation for alcohol, compared to the AUQ, which explicitly asks participants how much they crave an alcoholic drink right in that moment.

The inconsistent alcohol choice and AAT findings could be due to differences in the neutral stimuli (food versus non-alcoholic drinks). Therefore, the effect of state anxiety on alcohol choice may instead be attributable to thirst, or decreased appetite for food, rather than motivation for alcohol specifically. However, there were very weak correlations between alcohol choice and thirst (r_s = .10) and hunger (r_s = -.13) in Chapter 4 where I collected that data. I was relying on tasks that already existed, and I was aiming to replicate a previous study. It was therefore not appropriate to change the task in this instance, as any differences in findings may have consequently been attributable to task variation. A future study could include three types of image (alcoholic drink, non-alcoholic drink, food), to tease apart preferences. Adding labels to the images may also improve clarity (i.e., non-alcoholic, alcoholic). For example, a glass of cola could be construed as a non-alcoholic drink or a mixer for an alcoholic drink. Better still, giving participants the

option to consume real food and drinks would also overcome the artificiality of the computer tasks.

5.5.3. Limitations and Future Directions

There are some further limitations with the measures. First, food images may not be the most suitable neutral stimuli in the Concurrent Pictorial Choice Measure, given that some individuals emotionally eat to cope with stress and anxiety (Thayer, 2001). Second, participants may have selected alcohol images if the food images did not reflect their preferences. Likewise, participants may not be responsive to all pictures of alcoholic drinks if they prefer specific brands (Field & Christiansen, 2012). Third, an important feature of the AAT seen in the literature is the zooming function (Klein et al., 2011). When participants push and pull the joystick the images should shrink and grow, creating the visual impression of the drinks moving away or towards the participant, respectively (Klein et al., 2011). I did not have this zooming function in my AAT, because E-prime did not have this capability. Instead, the medium starting image changed to a small or large version upon joystick movement. In a future study, this zooming function should be programmed in using software which has this capability, to determine whether the effect is there with a more sophisticated AAT. Fourth, joystick direction is ambiguous; some argue that pushing is conversely indicative of approach (reaching) and pulling is indicative of avoid (withdrawing). Fifth, it could also be argued that the computer tasks (AAT, choice) lack ecological validity. Joystick movement and keyboard responses to alcohol images on a computer screen may not reflect a true desire for alcohol (Klein et al., 2011). Finally, to ensure the DTC group allocation was reliable, I could have asked participants to complete the MDMQ-R again upon arrival of the study session.

This study also had sample limitations. First, experimental studies typically have less representative samples (Woods et al., 2015), and the current study was no exception. Because testing could only occur during office hours, individuals in full time employment were likely deterred from participating in a 2.5-hour study. This resulted in a potentially less representative student sample, which may bias my results since students are younger and more educated than the general public (Hanel & Vione, 2016) and binge drinking rates are higher in this age group (NHS digital, 2018). Second, because of the strict screening criteria, individuals with a personal history of psychiatric disorders were not eligible to participate. This may have consequently affected the high DTC group, given that DTC is associated with internalising disorders (Stapinski et al., 2016). The effects seen in this sample may therefore be an underestimate compared to the potential effects seen in the wider population which include clinical populations.

5.6. Chapter Conclusions

In summary, I found experimentally-induced state anxiety increased alcohol choice, and DTC moderated these effects, supporting my hypothesis. Alcohol choice was higher among high DTC individuals than low DTC individuals, particularly in the CO_2 condition compared to the air condition. I found no clear evidence of an effect of state anxiety on alcohol craving or an interaction between state anxiety and DTC on alcohol craving, failing to support my hypothesis. State anxiety also did not affect AAT bias scores in the direction predicted. These findings differ from Chapter 4, where I found evidence of an association between state anxiety and alcohol craving, but not alcohol choice. In the next chapter, I will summarise and evaluate all four PhD studies in my thesis discussion.

Chapter 6: Discussion

6.1. Chapter Overview

The principal purpose of this thesis was to investigate whether (a) there is a positive relationship between anxiety and alcohol use, and (b) drinking to cope (DTC) motives moderate the relationship between anxiety and alcohol use. It is important to identify potential risk factors for problematic alcohol use, given the health (Rehm et al., 2010), social, and economic consequences (Prime Minister's Strategy Unit, 2004) associated with problem drinking. Furthermore, establishing whether the relationship between anxiety and alcohol use differs depending on a third variable (moderation) is useful for understanding whether anxiety is only or differently related to alcohol use or alcohol problems in one subgroup (aetiology). This in turn could help to determine which subgroups may benefit most or at all from a future intervention (treatment). DTC is potentially a modifiable risk factor and target for prevention.

I conducted four studies that used different research methods: a systematic review and meta-analysis (Chapter 2), a cohort study (Chapter 3), an online cross-sectional study (Chapter 4), and an experimental study (Chapter 5). By triangulating results from observational and experimental studies that have different potential limitations and sources of bias, I aimed to strengthen the inference I can make from the evidence. Coherence between observational and experimental findings increases the likelihood that a relationship is robust and causal (Hill, 2015).

In this final chapter I will:

- Summarise the main findings from each chapter in relation to my two thesis hypotheses.

- Discuss the similarities and differences between my findings and the published literature.
- Critically evaluate the novel contributions and implications of my research.
- Describe the limitations of my studies and consider what I would do differently given what I have learnt.
- Recommend avenues for future research.

6.2. Summary of Thesis Findings

Regarding my first thesis question, there was some evidence that anxiety is positively related to more problematic alcohol use (Chapters 2 and 3). However, evidence for a relationship between anxiety and more general levels of consumption (Chapters 2 and 3), and motivation for alcohol (Chapters 4 and 5) was less clear. Regarding the second thesis question, the observational data indicated there was no clear evidence that DTC motives moderated associations between anxiety and alcohol use (Chapters 3 and 4), although there was some experimental evidence to support an interaction between state anxiety and DTC on alcohol choice (Chapter 5). The main findings from each chapter in response to the original questions posed in Chapter 1 are summarised in Table 6.1.

Table 6.1. Summary of main findings from each chapter.

Chapter	Main Research Questions	Main Research Findings
Chapter 2: Systematic Review and Meta-Analysis	(a) Is child and adolescent anxiety positively associated with later alcohol use outcomes?	(a) Some evidence for a positive relationship between anxiety and later alcohol use disorders. (a) No clear evidence of a relationship between anxiety and later drinking frequency/quantity or later binge drinking.
Chapter 3: Cohort Study	(a) Is adolescent generalised anxiety disorder (GAD) positively associated with alcohol use outcomes in late adolescence and early adulthood? (b) Do drinking to cope (DTC) motives moderate these associations?	(a) Evidence of a positive association between GAD and frequent drinking, frequent bingeing, hazardous drinking, and harmful drinking at age 18. (a) Evidence of a positive association between GAD and harmful drinking only at age 21. (b) No clear evidence that DTC motives moderate associations between GAD and any alcohol outcome.
Chapter 4: Online Cross-Sectional Study	(a) Is naturally-occurring state anxiety positively associated with alcohol use outcomes (b) Do DTC motives moderate these associations?	(a) No clear evidence that naturally-occurring state anxiety is associated with alcohol choice. (a) Very weak evidence that naturally-occurring state anxiety is positively associated with alcohol craving. (b) No clear evidence that DTC motives moderate associations between naturally-occurring state anxiety and alcohol choice and alcohol craving.
Chapter 5: Experimental Study	(a) Does experimentally-induced state anxiety affect alcohol use outcomes? (b) Do DTC motives moderate these effects?	(a) Weak evidence that experimentally-induced state anxiety increases alcohol choice. (a) No clear evidence that experimentally-induced state anxiety increases alcohol craving or approach tendencies towards alcohol stimuli. (b) Evidence that DTC motives moderate the effect of experimentally-induced state anxiety on alcohol choice only.

6.2.1. Chapter 2: Systematic Review and Meta-Analysis

In Chapter 2, I presented a systematic review of 51 prospective cohort studies from 11 countries that investigated associations between child and adolescent anxiety and later alcohol use and alcohol use disorders. I summarised the results in a narrative synthesis, as well as a meta-analysis of a subset of three studies examining the relationship between generalised anxiety disorder and alcohol use disorder. By synthesising the published literature, I attempted to bring some clarity to the inconsistent results found previously.

There was some evidence for a positive relationship between anxiety and alcohol use disorders, supporting my first thesis hypothesis. However, associations of anxiety with drinking frequency/quantity and binge drinking were unclear and inconsistent - there were a similar number of positive, negative and equivocal results. Based on the data from three studies included in the meta-analysis, there was no clear evidence of an association between generalised anxiety and alcohol use disorder. I also explored whether sources of between-study heterogeneity explained any of the inconsistencies in findings, including type of anxiety, developmental period (childhood versus adolescence), length of follow-up, confounders adjusted for, and sample size. However, there were no clear patterns based on these study characteristics that could explain differences in findings (see Chapter 2 discussion for elaboration).

6.2.2. Chapter 3: Cohort Study

In Chapter 3, I conducted secondary data analyses of an established longitudinal cohort study. I focused on one anxiety disorder, adolescent generalised anxiety disorder (GAD), for consistency with Chapter 5 (the 7.5% carbon dioxide [CO_2] challenge is considered to be an experimental model of GAD (Bailey et al., 2011a)). I addressed some of the limitations of other prospective cohort studies (seen in

Chapter 2), by statistically adjusting for a range of potential confounders that are associated with anxiety and alcohol use, and by using a large sample size to improve power. I also extended the Chapter 2 findings by investigating whether a theoretically relevant moderator, DTC, influenced associations between anxiety and alcohol use outcomes.

Consistent with the first thesis hypothesis, GAD at age 18 was cross-sectionally positively associated with frequent drinking, frequent bingeing, hazardous drinking, and harmful drinking. There was also evidence that GAD was prospectively associated with more harmful drinking at age 21. However, I found no clear evidence of a prospective relationship between GAD and frequent drinking, frequent bingeing, and hazardous drinking at age 21. There was strong evidence of an association between DTC and all alcohol outcomes, but contrary to my second thesis hypothesis, DTC did not moderate associations between GAD and the alcohol outcomes.

The Chapter 3 findings are somewhat consistent with the findings of previous prospective cohort studies summarised in Chapter 2. In my systematic review, only one out of five prospective associations between a generalised anxiety exposure and a drinking frequency or drinking quantity outcome was classed as positive, and one out of three prospective associations with a binge drinking outcome was classed as positive. These two positive associations were from the same study that measured only general anxiety using a single question rather than GAD. So overall these findings in Chapter 2 support Chapter 3, where I found no clear evidence of a prospective association between GAD and frequent drinking and frequent bingeing.

There were also some inconsistencies between Chapters 2 and 3. In my systematic review, zero out of seven associations between a generalised anxiety exposure and an alcohol use disorder outcome were positive, and my meta-analysis revealed no clear evidence of an association between generalised anxiety and alcohol use disorders. However, in Chapter 3, I found evidence of a positive prospective association between adolescent GAD and later harmful drinking. These differences may be due to differences in the outcome measures used. It could be that GAD predicts harmful drinking but not alcohol use disorders. Six of the seven associations in Chapter 2 were also based on a sample size smaller than 1,000 participants, therefore these studies may have been underpowered to detect an association if one exists (Type II error).

6.2.3. Chapter 4: Online Cross-Sectional Study

My third study was motivated by a previous experimental study in our group that found experimentally-induced state anxiety (using the 7.5% CO_2 model of anxiety induction) led to higher alcohol choice in social drinkers compared to low state anxiety (medical air inhalation). The primary aim of Chapter 4 was to examine whether this finding could be replicated in an observational study of naturally-occurring state anxiety. As shown in Chapter 2, many observational studies have focused on trait anxiety or anxiety disorders, whereas fewer have looked at state anxiety. Exploring a possible state-trait distinction was therefore another motivation for the study. I also explored whether DTC moderated associations between state anxiety and alcohol outcomes in this older sample. As suggested in my discussion of Chapter 3, DTC may be more common among adults compared to adolescents, as alcohol is more accessible for adults, and adults may have greater self-awareness of their motivations for drinking.

Contrary to my first thesis hypothesis, and the results of the previous experimental study, there was no clear evidence of an association between naturally-occurring state anxiety and alcohol choice. However, there was weak evidence that state anxiety was positively associated with alcohol craving. The most plausible explanation for why these online survey data did not replicate the original experimental effect was the low levels of state anxiety in this online sample (i.e., possible Type II error). Low levels of state anxiety would contribute to smaller effect sizes, and therefore low power to detect a true association. Consistent with my Chapter 3 results, but contrary to my second thesis hypothesis, there was no clear evidence that DTC motives moderated associations between naturally-occurring state anxiety and alcohol choice and alcohol craving.

Exploratory analyses revealed positive associations between trait anxiety and alcohol craving and harmful drinking, consistent with Chapter 3 (GAD shares underlying cognitive processes with trait anxiety (Eysenck, 1997)). But again, DTC did not moderate associations between trait anxiety and frequent drinking, frequent bingeing, hazardous drinking, and harmful drinking. The associations between DTC and frequent drinking, frequent bingeing, hazardous drinking and harmful drinking were qualitatively similar to Chapter 3, with the strongest evidence for harmful drinking. Although the magnitudes of the associations were much smaller compared to Chapter 3, which may be due to the difference in sample size.

6.2.4. Chapter 5: Experimental Study

My final study described in Chapter 5 investigated the effects of experimentally-manipulated state anxiety on alcohol choice, alcohol craving, and alcohol approach-avoidance using the 7.5% CO_2 model to induce state anxiety. This study partially replicated the original experimental study by examining whether state

anxiety increased alcohol choice. It also extended the original experimental study because I explored whether these effects differed by DTC status.

Chapter 5 differs from the previous chapters in several ways. First, in Chapter 4, I assessed naturally-occurring state anxiety using a questionnaire, whereas in Chapter 5 I experimentally-manipulated state anxiety, to reduce confounding and avoid reverse causation. Second, in Chapters 3 and 4, a continuous DTC measure was dichotomised after data collection at the upper quartile, whereas in Chapter 5, I recruited participants based on high and low DTC scores, removing the middle part of the distribution. Third, in Chapters 3 and 4 I compared anxiety levels at the between-participant level, whereas in Chapter 5, I used a within-participant design, which avoids the limitations caused by individual differences.

In support of my first thesis hypothesis there was some evidence that experimentally-manipulated state anxiety increased alcohol choice compared to low state anxiety, although the effects were weaker than the findings of the original experimental study. There was no clear evidence of an effect of state anxiety on alcohol craving, and approach tendencies to alcohol (versus neutral) images were not higher in the high state anxiety condition than the low state anxiety condition. The disparate findings between alcohol choice and alcohol craving could be due to the measures used. As an indirect measure, alcohol choice may reflect a more subconscious, automatic motivation for alcohol, compared to the direct alcohol urges questionnaire which explicitly asks participants how much they crave an alcoholic drink right in that moment. The latter may have been more greatly affected by the unnatural laboratory environment and experience of anxiety. In line with my second thesis hypothesis, there was evidence of an interaction between state anxiety and DTC on alcohol choice. Alcohol choice was higher among high DTC individuals than low DTC individuals, particularly in the CO_2 condition

compared to the air condition. There was no clear evidence that DTC moderated the effects of state anxiety on alcohol craving and alcohol approach tendencies, failing to support the second thesis hypothesis.

There were discrepancies between the observational results presented in Chapter 4 and the experimental results presented in Chapter 5. In Chapter 4, I found weak evidence for an association between state anxiety and alcohol craving, but no clear evidence of an association between state anxiety and alcohol choice. However, in Chapter 5, there was evidence for a weak effect of state anxiety on alcohol choice, but no clear evidence for an effect of state anxiety on alcohol craving. These differences may be because state anxiety levels in the online study were much lower than the experimental study, reducing the power to detect a true association. Secondly, the experimental study may have limited external validity; the effects of artificially induced state anxiety on alcohol craving and choice may lack generalisability to more real-world experiences of state anxiety, and findings based on a predominantly student sample (Chapter 5) may not be generalisable to an older, more diverse sample (Chapter 4). Finally, the absence of evidence for an effect of state anxiety on alcohol craving in Chapter 5 may have been due to the exclusion of high risk and alcohol-dependent drinkers from this sample.

6.3. Original Research Contributions and Strengths

This thesis offers distinct contributions to research on the relationship between anxiety and alcohol use. In Chapter 2, I synthesised previously unconnected findings in the largest systematic review of prospective cohort studies investigating associations of child and adolescent anxiety and later alcohol use and disorders. My systematic review was comprehensive; I included a wide range of anxiety exposure variables and alcohol outcome variables, unlike some other reviews or meta-analyses which have focused on one anxiety disorder (Bartel et al., 2018;

Schry & White, 2013). By conducting a systematic review with a meta-analytical component, my results are likely to be less biased and subjective, compared to unsystematic literature reviews (DeMartini & Carey, 2011; Morris et al., 2005). The Chapter 2 findings were generally consistent with previous systematic reviews, which suggest anxiety disorders may be associated with alcohol problems (Schry & White, 2013), but the relationship between anxiety and general levels of consumption is more unclear (Groenman et al., 2017; Hussong et al., 2017). However, a recent meta-analysis found a positive association of child and adolescent internalising disorders, but not anxiety disorders alone, with later AUD (Meque et al., 2019). Although this paper only included four studies that looked at anxiety specifically.

In Chapter 3, I examined cross-sectional and prospective associations between adolescent GAD and four alcohol use outcomes, using data from the Avon Longitudinal Study of Parents and Children (ALSPAC). Compared to some other cohort studies in the field, my sample was large, I adjusted analyses for several potential confounders, and I completed a series of sensitivity analyses to ensure the robustness of the evidence. In this cohort, GAD in adolescence was associated with harmful drinking in early adulthood, which was not consistent with some other cohort studies that found no clear evidence of a prospective relationship between adolescent GAD and later problem drinking (Abram et al., 2015; Wolitzky-Taylor et al., 2012; Zimmermann et al., 2003). My study was also novel as I examined whether DTC moderated associations between GAD and alcohol use in a late adolescent sample, using cross-sectional and prospective data. To the best of my knowledge, previous cohort studies that have examined this interaction have used adult samples (Menary et al., 2011), or cross-sectional data only (Goldstein et al., 2012).

Chapters 4 and 5 examined the relationship between state anxiety and direct (alcohol craving) and indirect (alcohol choice) alcohol related outcomes, using both observational and experimental methods, in order to triangulate the evidence with an earlier experimental study from our research group. By focusing on state anxiety, I have added to previous observational studies that have used measures of trait anxiety and anxiety disorders (Malmberg et al., 2012; Zimmermann et al., 2003). In addition, by using the 7.5% CO_2 model of anxiety induction, I have built on other anxiety-induction experimental studies that have utilised other methods of manipulating anxious states to investigate the relationship between anxiety and alcohol-related outcomes (Fox et al., 2007; Thomas et al., 2012). Chapters 4 and 5 are also novel as I investigated whether DTC motives moderated associations between state anxiety and alcohol-related outcomes, extending the original experimental study. The Chapter 5 findings are consistent with previous research that suggests negative affect increases alcohol choice (Hardy & Hogarth, 2017), particularly among individuals who drink to cope (Hogarth et al., 2018). However, there was no clear evidence of an effect of state anxiety on alcohol craving, which is not consistent with some other anxiety-induction experiments (Fox et al., 2007; Kwako et al., 2015).

6.4. Limitations

This thesis has several limitations. Here I will summarise general limitations which have impacted multiple chapters. Limitations that are chapter specific will not be repeated here.

Chapters 2, 3, and 4 suffer from limitations that are common to observational studies. Causality cannot be inferred from observational studies, due to the absence of randomisation and potential for confounding. Reverse causation (alcohol use increasing anxiety) is a possibility in the cross-sectional analyses

described in Chapters 3 and 4, although I adjusted for earlier alcohol use to reduce this. In Chapter 3, I considered excluding individuals who were hazardous and harmful drinkers at baseline to reduce the risk of reverse causation in the prospective analyses. However, I decided against this, as a substantial proportion of the sample would have been lost. I adjusted my analyses presented in Chapters 3 and 4 for several relevant confounders, although there may still be residual confounding. Although in Chapter 3 for example, fully adjusted point estimates were not too dissimilar to unadjusted point estimates in the multiply-imputed data. This suggests that reductions in sample size in adjusted models, rather than confounding, more likely explains the variations in estimates in the available data. Some of the studies included in Chapter 2 were limited as authors did not adequately consider (or report) confounding adjustment. Although I restricted my systematic review to prospective cohort studies to elucidate the temporal sequence of anxiety and alcohol use, some critics may argue a wider time gap than six months (minimum eligibility requirement) between the exposure and outcome would give more certainty of temporal direction. Although 92% of the included studies had a follow up period greater than six months.

My studies that involved new data collection (Chapters 4 and 5) were powered for the primary thesis hypothesis, which examined the relationship between state anxiety and alcohol choice. The studies were not powered to examine the secondary thesis hypothesis, which tested the moderating role of DTC on the relationship between state anxiety and alcohol outcomes. These latter analyses were therefore exploratory, and findings may need to be interpreted with care. The absence of clear evidence to support my second thesis hypothesis may therefore be because the studies were not adequately powered to detect the associations/effects. However, the ALSPAC study in Chapter 3 did have a large sample size, with adequate statistical power to detect modest associations, and I

still found no clear evidence that DTC moderates associations between anxiety and alcohol use. The DTC results from Chapters 4 and 5 may thus still be reliable.

Some of my measures have weaknesses, which may threaten the internal validity of the studies. As mentioned previously, direct and indirect measures have different strengths and limitations (Klein et al., 2011). The assessment of alcohol use and DTC using self-report methods is subject to memory and/or social desirability biases (Turner et al., 2018). There may be measurement error and under-reporting if people forget, are dishonest, or if they lack the insight to recognise that their alcohol use is related to their anxiety as a coping mechanism. There may also be measurement error when alcohol use is measured prior to the legal drinking age (Chapter 2 and 3). Future studies could utilise more objective measures of alcohol use, such as transdermal alcohol sensors. Transdermal devices can provide valid and reliable continuous measures of frequency and quantity of alcohol use in people's natural environments (Leffingwell et al., 2013). Dichotomising DTC at the upper quartile (Chapters 2 and 3) may have reduced the power. Recruiting participants based on DTC and excluding the middle part of the distribution in Chapter 5, ensured there were distinctly high and low levels of DTC in this sample. I could have asked participants to complete the drinking motives questionnaire again upon arrival, in case there were within-participant fluctuations in DTC that may have changed group allocation. The state anxiety variable in Chapter 4 did not have enough variance, so it was difficult to examine the relationship in that online sample. If I was going to measure naturally-occurring state anxiety again as an exposure, I would first include a screening questionnaire to ensure there were roughly equal numbers of participants experiencing high and low state anxiety.

There were also some limitations with the indirect alcohol measures I used in Chapters 4 and 5. Regarding the Concurrent Pictorial Choice Measure, participants may have selected the alcohol images if the food images of typical UK meals did not reflect their preferences. Likewise, participants may not have be responsive to all pictures of alcoholic drinks if they preferred specific brands (Field & Christiansen, 2012). Given that some individuals emotionally eat to cope with stress and anxiety (Constant et al., 2018; Thayer, 2001), and other individuals experience a decreased appetite when experiencing anxiety, food images may also not be considered neutral stimuli. As I was aiming to replicate a previous study, I could not change the task, as any differences in findings may have therefore been attributed to task differences. However, in a future study, the task could be adapted to include two types of neutral stimuli, non-alcoholic drinks and food, to tease apart possible effects of state anxiety on appetite, thirst, and motivation for alcohol specifically. There were also flaws with the AAT, including the lack of zooming function (Klein et al., 2011), and the ambiguity of joystick direction; some critics argue that pushing is conversely indicative of approach (reaching) and pulling is indicative of avoid (withdrawing). These factors may have contributed to the lack of clear evidence for an effect of state anxiety on alcohol approach tendencies in Chapter 5.

Finally, there are limitations related to external validity. The 7.5% CO_2 challenge may lack generalisability to real-world experiences of state anxiety. The computer tasks used in Chapters 4 and 5 may also lack ecological validity; joystick movement and computer keyboard responses may not accurately depict a true motivation for alcohol (Klein et al., 2011). Chapters 3, 4, and 5 all had UK samples. As Europe has the highest rates of alcohol consumption, my findings may therefore not be globally representative (Peacock et al., 2018; WHO, 2018).

6.5. Future Directions: Topics

6.5.1. Moderators of the Relationship between Anxiety and Alcohol Use

Overall, where there was evidence of a relationship between anxiety and alcohol use (small p-values), the magnitude of the associations or effects (point estimates) tended to be small. This suggests the relationship is more likely to be weak, less likely to be causal (Hill, 2015), or the relationship is dependent on moderating factors. Most of the evidence from this thesis indicated that DTC motives do not moderate the relationship between anxiety and alcohol use. Future research is needed to identify other individual difference and contextual factors that reliably moderate the relationship. In terms of intervention, moderating variables that are feasible to change have the greatest utility. Although fixed factors such as gender and age group, can identify subgroups to target.

First, there may be inter-individual variation (differences between individuals with anxiety). Populations are heterogeneous; not all people with anxiety consume more alcohol or develop alcohol problems. Several studies have examined individual difference variables that potentially moderate the relationship between anxiety and alcohol use, for example gender (Buckner & Turner, 2009; Swendsen et al., 2000), age (Aseltine & Gore, 2000; Colder et al., 2013), perceptions of peers' drinking behaviour (Kenney et al., 2018), neuroticism (Carney et al., 2000), and impulsivity (Adams et al., 2019). However, findings are often mixed. Second, there may be intra-individual variation (differences across time and situations for the same individuals). There is evidence that the relationship between affect and drinking behaviour is context dependent. For example, Mohr and colleagues (2001) found that solitary drinking (at home and alone) was more common on days with more negative interpersonal experiences, and drinking with other people was more common on days with more positive interpersonal experiences. A future study

could investigate whether the relationship between anxiety and alcohol use is influenced by the presence of other stressors, in line with a diathesis-stress model (Bartel et al., 2018). Stressful events could be measured as in the study by Minami and colleagues (2017), whereby participants reported if they had experienced stressful events, the type (i.e., interpersonal, work/school, financial, health, trauma and other), and the severity.

6.5.2. Preferential Choice of Alcohol to Cope with Anxiety

Another possible explanation for some of the mixed evidence and small effect sizes, is that people cope with anxiety using different strategies, such as exercise, social support, food, anxiolytic medication, psychological therapies, and illicit drugs. It has been hypothesised that people with anxiety may be more likely to use alcohol or sedatives to try to increase relaxation, whereas people with depression may be more likely to use a stimulant (Borges et al., 2018). However, this is not consistently supported (Pasche, 2012). For example, one study found that the odds of developing lifetime depressant abuse or dependence (alcohol, cannabis, sedatives) and stimulant abuse or dependence (cocaine, amphetamine), were similar for people with mood disorders and anxiety disorders (Martins & Gorelick, 2011). The preferential choice of alcohol over other substances to cope with anxiety is affected by other factors, including personality, accessibility, personal experience, cultural and subcultural drinking norms, legality, and considerations of potential impairments and harms (Sher & Grekin, 2015). Some experimental studies have indicated that individuals consume more alcohol when a negative experience is anticipated, and when alternative methods of coping with the experience (e.g., relaxation techniques to reduce arousal, preparation for a task) are limited or unavailable (Sher & Grekin, 2015). It is important to identify which individuals with anxiety are susceptible to self-medication with alcohol, rather than choosing more adaptive methods of coping with anxiety.

6.5.3. Different Anxiety Symptoms and Alcohol Outcomes

Future research should look more closely at the specific symptoms of anxiety disorders, given their complexity and heterogeneity. For example, social anxiety disorder is a multidimensional disorder characterised by affective, cognitive, and behavioural symptoms (Lemyre et al., 2019). Some research has already shown differences in the relationship with alcohol depending on anxiety symptoms. For instance, Stewart and colleagues (2006) found fear of negative evaluation was positively associated with drinking problems, whereas social avoidance and distress were negatively associated with drinking frequency. And there is evidence that physical and cognitive symptoms have differential associations with drinking behaviour (Nichter & Chassin, 2015). Identifying if specific anxiety symptoms are a risk factor for alcohol problems would help to inform intervention efforts. However, alcohol use and abuse may be too widespread to find specific effects of anxiety disorders or symptoms.

Furthermore, additional research is needed to explain the different associations observed for more problematic use of alcohol compared to general levels of consumption. Some researchers have suggested environmental effects may influence general consumption, whereas genetic effects may play a more important role in the development of alcohol problems. For example, using twins, Pagan and colleagues (2006) found that shared environmental factors contributed to initiation and frequency of alcohol use, whereas there was no clear evidence that shared environmental factors influenced alcohol problems in early adulthood. Instead, genetic factors played a role in alcohol problems (Pagan et al., 2006).

6.5.4. Mediators of the Relationship between Anxiety and Alcohol Use

I have not investigated the explanatory mechanisms behind the associations and effects observed in this thesis. Future studies should examine the possible biological, psychological, and social mediators of the relationship between anxiety and alcohol use. Given the mixed findings and the heterogeneity of anxiety and alcohol use, the pathways between the two are likely complex. For the purpose of this thesis, I was interested in DTC motives as a possible moderator. However, other studies have found evidence that DTC mediates the relationship between anxiety and alcohol use. For example, coping motives have been found to mediate associations between social anxiety and alcohol problems (Buckner & Shah, 2015; Stewart et al., 2006; Villarosa-Hurlocker et al., 2019). Another study showed associations between social anxiety and alcohol related negative consequences were mediated by DTC motives (Lewis et al., 2008). Mediation models require strong causal claims about the direction of effects between anxiety and alcohol use, anxiety and DTC, and DTC and alcohol use, and ideally three time-points, which I decided was beyond what was justified by the ALSPAC data.

Self-medication is one possible mechanism, but there may also be cognitive and situational mediators. Cognitive theories such as self-awareness theory (Hull, 1981) and appraisal-disruption theory (Sayette, 1993) suggest that people with anxiety may drink more alcohol because alcohol disrupts information processing - narrowing attention, and reducing self-awareness and appraisal of threats. Other plausible mechanisms have also been proposed, for example positive alcohol outcome expectancies mediated associations between social anxiety and alcohol consumption and alcohol-related problems (Papachristou et al., 2018), and solitary drinking has been found to mediate associations between negative affect and harmful drinking (Bilevicius et al., 2018).

6.6. Future Directions: Methods

For the purpose of this thesis, I used four types of research method. Other research methods could be used in future studies to examine the unanswered questions I have posed and to address the limitations identified. For example, qualitative research methods could be used to complement the quantitative research, in order to elucidate some of the mixed findings. Interviews may better capture people's views and experiences, providing richer data on when, where, why, and with whom people tend to drink alcohol to cope with anxiety. The relationship between anxiety and alcohol use could be better understood when context is provided. Qualitative methods have also been used to investigate how people perceive and interpret the Drinking Motives Questionnaire - Revised (Nehlin et al., 2018). Participants reported that some terms were equivocal, such as 'how often' and 'to get high.' Other participants highlighted that some of the situations described did not account for context. For example, responses to the item 'because it makes social gatherings more fun' may vary for work versus family social situations (Nehlin et al., 2018).

The prospective cohort studies in Chapters 2 and 3 correlate average levels of anxiety at time one with average levels of alcohol consumption at time two, using population level data. These methods are limited as they cannot capture shorter term dynamic changes in anxiety-alcohol associations and DTC, or within-participant variation, and they are affected by memory biases. DTC is considered a reactive process; it changes in response to life circumstances and emotions (Colder et al., 2019; Cooper et al., 1995). The DTC questionnaires instruct respondents to report how frequently their drinking is motivated by different reasons. The decision to drink alcohol when one feels anxious, and thus responses on DTC measures, may therefore differ between individuals (stable trait-like component) and fluctuate across time and different situations within individuals

(dynamic state-like component) (Colder et al., 2019). Ecological momentary assessment (EMA) is an event-level data collection method that could measure anxiety symptoms and drinking cognitions and behaviours, in participants' natural environments, which makes it more ecologically valid than laboratory experiments (Shiffman, 2009). With repeated real-time (or close to it) assessments of anxiety and alcohol use, EMA may be a more sensitive methodological approach to capturing the contextual complexities of the relationship between anxiety and alcohol use, and within-participant variation (Bartel et al., 2018; Shiffman, 2009). Some researchers have used EMA methods to investigate the relationship between anxiety and alcohol use (Fatseas et al., 2018; Gorka et al., 2017; Possemato et al., 2015).

EMA studies would help to determine the temporal ordering of associations. It is important to establish *when* people drink to cope with their anxiety, to inform the development of targeted interventions and prevention efforts (Slavish et al., 2019). For example, individuals with anxiety may consume alcohol in anticipation of an anxiety-provoking event (e.g., pre-drinking before a party or date if they have social anxiety disorder to boost confidence), during an anxiety-provoking event, or following an anxiety-provoking event (e.g., drinking at home after a stressful day to relax and forget worries). There is evidence that social anxiety is associated with greater solitary drinking prior to a feared social situation (Keough et al., 2016), and students drink more alcohol when in a condition involving anticipatory processing (anticipating a speech) compared to baseline (Kidorf & Lang, 1999). Other studies have shown that people report higher alcohol craving after a social situation if they are in the condition of post-event processing, which involves rumination and evaluation of one's past behaviour (Potter et al., 2016). As mentioned in Chapter 5, state anxiety may have not affected alcohol craving immediately after the CO_2 inhalation because the experimental procedure was unpleasant. Instead, the urge

to drink alcohol may have occurred later than I was able to measure. Different skills and coping strategies may be needed to help people who drink to cope with anxiety, depending on the chronology of the relationship.

Given that most of the data contributing to this thesis come from UK samples, and 50 out of the 51 studies included in my systematic review came from Western countries, it is important to conduct cross-cultural comparison studies to see if there are similarities or differences in the relationship between anxiety and alcohol use across the globe. Differences in culture, religion, social norms, wealth, and laws may affect alcohol consumption, and thus the choice to drink to cope with anxiety. Cross-cultural comparison studies could also be used to test the validity of my observational results. For example, a future study could investigate associations between GAD and harmful drinking using data from another prospective cohort study in a country with a different confounding structure. If the findings from the ALSPAC cohort can be replicated by this new study, this would increase the reliability of the evidence and would suggest that the results seen in Chapter 3 are not due to confounding. This approach for improving causal inference in observational studies was used by Brion and colleagues (2011) to investigate the effects of breastfeeding on child blood pressure, body mass index, and general cognitive ability (i.e., IQ).

To determine whether anxiety causes alcohol use or alcohol use disorders, a future study could employ causal inference methods such as Mendelian randomisation (MR). By using genetic variants associated with anxiety as a proposed instrumental variable, the technique aims to circumvent the issues of confounding and reverse causation that bias observational research, as one's genes are inherited at random during conception (Chao et al., 2017; Lawlor et al., 2008). Single nucleotide polymorphisms (SNPs) have been identified from genome wide association studies

(GWAS) that are associated with neuroticism (Okbay et al., 2016) and anxiety disorders (Otowa et al., 2016). However, these methods do not have the nuance of observational analyses. For example, the GWAS for anxiety combines individuals with a diagnosis of generalised anxiety disorder, panic disorder, and phobias. This might dilute causal effects if one hypothesises that certain types of anxiety or specific anxiety symptoms are associated with alcohol use. Furthermore, the GWAS for anxiety disorders only identified one genome-wide significant variant (Otowa et al., 2016). Therefore, there is not currently a strong enough instrument and an MR analysis is likely to be underpowered. As larger GWAS become available, it would be useful to conduct an MR analysis and triangulate the results of this with the results of this thesis to determine whether there is evidence for a causal effect.

Although I found some observational evidence of an association between anxiety and problematic alcohol use, this evidence is not conclusive, or sufficient to support strong conclusions regarding causality. Early interventions that target anxiety may have the potential to reduce problem drinking. However, given that the relationship may be affected by moderating factors, it is important to understand for whom or when interventions for anxiety may be effective for reducing drinking (Colder et al., 2017b). I agree with Colder and colleagues who advise that 'coping-oriented interventions for unselected samples may not be a wise use of resources' (Colder et al., 2017b). Secondary analyses across Studies 2-4 (Chapters 3-5) showed that DTC was consistently positively associated with alcohol-related outcomes, despite not consistently moderating the relationship between anxiety and alcohol-related outcomes. DTC may therefore be a more reliable target for intervention than anxiety.

6.7. Thesis Conclusions

Using observational and experimental methods across four studies, this thesis investigated whether: (a) there is a relationship between anxiety and alcohol-related outcomes, and (b) DTC motives moderate the relationship. Evidence from my systematic review and cohort study was suggestive of a positive prospective relationship between anxiety and problematic alcohol use, supporting my first thesis hypothesis. However, there was no clear evidence of a prospective relationship between anxiety and more general levels of alcohol consumption such as quantity and frequency of use. Furthermore, my online cross-sectional study and experimental study provided inconsistent evidence for a relationship between state anxiety and alcohol choice and alcohol craving. In support of my second thesis hypothesis, there was some experimental evidence that DTC motives moderated the effect of state anxiety on alcohol choice. However, most of the observational and experimental evidence from this thesis did not support this hypothesis.

This research has made important novel contributions to the subject of anxiety and alcohol use. First, my systematic review is the most comprehensive synthesis of previous prospective cohort studies investigating associations of child and adolescent anxiety and later alcohol use and disorders to date. Second, my cohort study has strengths compared to previous studies because of its large sample size, adjustment of several relevant confounders, sensitivity analyses examining the robustness of results, and exploration of DTC motives as a potential moderator. Third, my online cross-sectional study and experimental study aimed to replicate a previous experimental study from our research group to test whether these findings were reproducible. And finally, by using the 7.5% CO_2 challenge, I have built on previous anxiety-induction experiments that have utilised other methods of

manipulating anxious states to investigate the relationship between anxiety and alcohol-related outcomes.

Further research using different methods is needed to examine the roles of anxiety and DTC in the aetiology of alcohol use and alcohol problems. This thesis has highlighted that anxiety and alcohol use are heterogeneous, and the relationship between them is complex. It is important to identify which internal (e.g., psychological, biological) and external (e.g., situational, environmental, social) factors increase an individual's risk of developing alcohol problems, to understand which individuals with anxiety would benefit most from an intervention to reduce the risk of alcohol problems. Although there was little evidence to support DTC as a moderator of the relationship between anxiety and alcohol use, there was strong and consistent evidence that DTC is positively associated with frequent drinking, binge drinking, hazardous drinking, and harmful drinking, and it predicts alcohol choice over other rewards. DTC may therefore be a more reliable target for intervention than anxiety.

References

Abram, K. M., Zwecker, N. A., Welty, L. J., Hershfield, J. A., Dulcan, M. K., & Teplin, L. A. (2015). Comorbidity and continuity of psychiatric disorders in youth after detention: A prospective longitudinal study. *Jama Psychiatry, 72*(1), 84-93. doi:10.1001/jamapsychiatry.2014.1375

Abrams, K., Cieslowski, K., Johnson, S., Krimmel, S., Bierlein-De La Rosa, G., Barton, K., & Silverman, P. (2018). The effects of alcohol on heartbeat perception: Implications for anxiety. *Addictive Behaviors, 79*, 151-158. doi:10.1016/j.addbeh.2017.12.023

Abrams, K., Kushner, M., Medina, K. L., & Voight, A. (2001). The pharmacologic and expectancy effects of alcohol on social anxiety in individuals with social phobia. *Drug and Alcohol Dependence, 64*(2), 219-231. doi:10.1016/S0376-8716(01)00125-9

Adams, S., Ataya, A. F., Attwood, A. S., & Munafo, M. R. (2012). Effects of acute alcohol consumption on alcohol-related cognitive biases in light and heavy drinkers are task-dependent. *Journal of Psychopharmacology, 26*(2), 245-253. doi:10.1177/0269881111405355

Adams, T., Rapinda, K. K., Frohlich, J. R., O'Connor, R. M., & Keough, M. T. (2019). Impulsivity moderates the effect of social anxiety on in-lab alcohol craving. *Addictive Behaviors, 97*, 70-76. doi:10.1016/j.addbeh.2019.05.025

Adamson, J., & Templeton, L. (2012). *Silent voices: Supporting children and young people affected by parental alcohol misuse*. Retrieved from http://www.ias.org.uk/uploads/pdf/News%20stories/occ-report-silent-voices.pdf

References

Agoglia, A. E., & Herman, M. A. (2018). The center of the emotional universe: Alcohol, stress, and CRF1 amygdala circuitry. *Alcohol, 72*, 61-73. doi:10.1016/j.alcohol.2018.03.009

Agrawal, A., Dick, D. M., Bucholz, K. K., Madden, P. A. F., Cooper, M. L., Sher, K. J., & Heath, A. C. (2008). Drinking expectancies and motives: a genetic study of young adult women. *Addiction, 103*(2), 194-204. doi:10.1111/j.1360-0443.2007.02074.x

Albert, D., & Steinberg, L. (2011). Judgment and decision making in adolescence. *Journal of Research on Adolescence, 21*(1), 211-224. doi:10.1111/j.1532-7795.2010.00724.x

Allan, C. A. (1995). Alcohol problems and anxiety disorders-A critical review. *Alcohol and Alcoholism, 30*(2), 145-151. doi:https://doi.org/10.1093/oxfordjournals.alcalc.a045708

Anderson, D. J., Noyes, R., Jr., & Crowe, R. R. (1984). A comparison of panic disorder and generalized anxiety disorder. *American Journal of Psychiatry, 141*(4), 572-575. doi:10.1176/ajp.141.4.572

Angold, A., Costello, E. J., & Erkanli, A. (1999). Comorbidity. *The Journal of Child Psychology and Psychiatry, 40*(1), 57-87. doi:https://doi.org/10.1111/1469-7610.00424

Anxiety UK. (2018). Young People and Anxiety. Retrieved from https://www.anxietyuk.org.uk/get-help/anxiety-information/young-people-and-anxiety/

Arbeau, K. J., Kuiken, D., & Wild, T. C. (2011). Drinking to enhance and to cope: a daily process study of motive specificity. *Addictive Behaviors, 36*(12), 1174-1183. doi:10.1016/j.addbeh.2011.07.020

Argyropoulos, S. V., Bailey, J. E., Hood, S. D., Kendrick, A. H., Rich, A. S., Laszlo, G., . . . Nutt, D. J. (2002). Inhalation of 35% CO2 results in activation of the HPA axis in healthy volunteers.

Psychoneuroendocrinology, 27(6), 715-729. doi:10.1016/S0306-4530(01)00075-0

Armeli, S., Covault, J., & Tennen, H. (2018). Long-Term Changes in the Effects of Episode-Specific Drinking to Cope Motivation on Daily Well-Being. *Psychology of Addictive Behaviors, 32*(7), 715-726. doi:10.1037/adb0000409

Arnett, J. (1992). Reckless behavior in adolescence - a developmental perspective. *Developmental Review, 12*(4), 339-373. doi:10.1016/0273-2297(92)90013-R

Aseltine, R. H., & Gore, S. L. (2000). The variable effects of stress on alcohol use from adolescence to early adulthood. *Substance Use and Misuse, 35*(5), 643-668. doi:10.3109/10826080009148415

Asselmann, E., Pane-Farre, C., Isensee, B., Wittchen, H. U., Lieb, R., Hofler, M., & Beesdo-Baum, K. (2014a). Characteristics of initial fearful spells and their associations with DSM-IV panic attacks and panic disorder in adolescents and young adults from the community. *Journal of Affective Disorders, 165*, 95-102. doi:10.1016/j.jad.2014.04.045

Asselmann, E., Wittchen, H. U., Lieb, R., Hofler, M., & Beesdo-Baum, K. (2014b). Associations of fearful spells and panic attacks with incident anxiety, depressive, and substance use disorders: a 10-year prospective-longitudinal community study of adolescents and young adults. *Journal of Psychiatric Research, 55*, 8-14. doi:10.1016/j.jpsychires.2014.04.001

Ataya, A. F., Adams, S., Mullings, E., Cooper, R. M., Attwood, A. S., & Munafo, M. R. (2012). Internal reliability of measures of substance-related cognitive bias. *Drug and Alcohol Dependence, 121*(1-2), 148-151. doi:10.1016/j.drugalcdep.2011.08.023

References

Baer, J. S. (2002). Student factors: Understanding individual variation in college drinking. *Journal of Studies on Alcohol*, 40-53. doi:https://doi.org/10.15288/jsas.2002.s14.40

Bailey, J. E., Argyropoulos, S. V., Kendrick, A. H., & Nutt, D. J. (2005). Behavioral and cardiovascular effects of 7.5% CO2 in human volunteers. *Depression and Anxiety, 21*(1), 18-25. doi:10.1002/da.20048

Bailey, J. E., Argyropoulos, S. V., Lightman, S. L., & Nutt, D. J. (2003). Does the brain noradrenaline network mediate the effects of the CO2 challenge? Reply to reviewers' comments. *Journal of Psychopharmacology, 17*(3), 267-268. doi:10.1177/02698811030173006

Bailey, J. E., Dawson, G. R., Dourish, C. T., & Nutt, D. J. (2011a). Validating the inhalation of 7.5% CO2 in healthy volunteers as a human experimental medicine: a model of generalized anxiety disorder (GAD). *Journal of Psychopharmacology, 25*(9), 1192-1198. doi:https://doi.org/10.1177/0269881111408455

Bailey, J. E., Kendrick, A., Diaper, A., Potokar, J. P., & Nutt, D. J. (2007). A validation of the 7.5% CO2 model of GAD using paroxetine and lorazepam in healthy volunteers. *Journal of Psychopharmacology, 21*(1), 42-49. doi:10.1177/0269881106063889

Bailey, J. E., Papadopoulos, A., Diaper, A., Phillips, S., Schmidt, M., van der Ark, P., . . . Nutt, D. J. (2011b). Preliminary evidence of anxiolytic effects of the CRF(1) receptor antagonist R317573 in the 7.5% CO(2) proof-of-concept experimental model of human anxiety. *Journal of Psychopharmacology, 25*(9), 1199-1206. doi:10.1177/0269881111400650

Bailey, J. E., Papadopoulos, A., Seddon, K., & Nutt, D. J. (2009). A comparison of the effects of a subtype selective and non-selective benzodiazepine receptor agonist in two CO2 models of experimental human anxiety.

Journal of Psychopharmacology, 23(2), 117-122. doi:10.1177/0269881108089603

Baker, T. B., Piper, M. E., McCarthy, D. E., Majeskie, M. R., & Fiore, M. C. (2004). Addiction motivation reformulated: An affective processing model of negative reinforcement. *Psychological Review, 111*(1), 33-51. doi:10.1037/0033-295x.111.1.33

Bartel, S. J., Sherry, S. B., Smith, M. M., Vidovic, V. V., & Stewart, S. H. (2018). Is anxiety sensitivity a risk factor for, or complication of, alcohol misuse? A meta-analysis. *Personality and Individual Differences*, 258-263. doi:10.1016/j.paid.2018.07.031

Baxter, A. J., Scott, K. M., Vos, T., & Whiteford, H. A. (2013). Global prevalence of anxiety disorders: a systematic review and meta-regression. *Psychological Medicine, 43*(5), 897-910. doi:10.1017/S003329171200147x

Behrendt, S., Beesdo-Baum, K., Zimmermann, P., Höfler, M., Perkonigg, A., Bühringer, G., . . . Wittchen, H. U. (2011). The role of mental disorders in the risk and speed of transition to alcohol use disorders among community youth. *Psychological Medicine, 41*(5), 1073-1085. doi:10.1017/S0033291710001418

Bilevicius, E., Single, A., Rapinda, K. K., Bristow, L. A., & Keough, M. T. (2018). Frequent solitary drinking mediates the associations between negative affect and harmful drinking in emerging adults. *Addictive Behaviors, 87*, 115-121. doi:10.1016/j.addbeh.2018.06.026

Bohn, M. J., Krahn, D. D., & Staehler, B. A. (1995). Development and initial validation of a measure of drinking urges in abstinent alcoholics. *Alcoholism: Clinical and Experimental Research, 19*(3), 600-606. doi:10.1111/j.1530-0277.1995.tb01554.x 7573780

References

Borges, G., Benjet, C., Orozco, R., & Medina-Mora, M. E. (2018). A longitudinal study of reciprocal risk between mental and substance use disorders among Mexican youth. *Journal of Psychiatric Research, 105*, 45-53. doi:10.1016/j.jpsychires.2018.08.014

Boschloo, L., Vogelzangs, N., Smit, J. H., Van Den Brink, W., Veltman, D. J., Beekman, A. T. F., & Penninx, B. W. J. H. (2011). Comorbidity and risk indicators for alcohol use disorders among persons with anxiety and/or depressive disorders: Findings from the netherlands study of depression and anxiety (NESDA). *Journal of Affective Disorders, 131*(1-3), 233-242. doi:10.1016/j.jad.2010.12.014

Bouchery, E. E., Harwood, H. J., Sacks, J. J., Simon, C. J., & Brewer, R. D. (2013). Economic costs of excessive alcohol consumption in the U.S., 2006. *American Journal of Preventive Medicine, 44*(2), 198-198. doi:10.1016/j.amepre.2011.06.045

Boyd, A., Golding, J., Macleod, J., Lawlor, D. A., Fraser, A., Henderson, J., . . . Davey Smith, G. (2013). Cohort Profile: the 'children of the 90s'--the index offspring of the Avon Longitudinal Study of Parents and Children. *International Journal Epidemiology, 42*(1), 111-127. doi:10.1093/ije/dys064

Brannan, S., Liotti, M., Egan, G., Shade, R., Madden, L., Robillard, R., . . . Fox, P. T. (2001). Neuroimaging of cerebral activations and deactivations associated with hypercapnia and hunger for air. *Proceedings of the National Academy of Sciences of the United States of America, 98*(4), 2029-2034. doi:10.1073/pnas.98.4.2029

Bresin, K., Mekawi, Y., & Verona, E. (2018). The effect of laboratory manipulations of negative affect on alcohol craving and use: A meta-analysis. *Psychology of Addictive Behaviors, 32*(6), 617-627. doi:10.1037/adb0000383

References

Brion, M. J. A., Lawlor, D. A., Matijasevich, A., Horta, B., Anselmi, L., Araujo, C. L., . . . Smith, G. D. (2011). What are the causal effects of breastfeeding on IQ, obesity and blood pressure? Evidence from comparing high-income with middle-income cohorts. *International Journal of Epidemiology, 40*(3), 670-680. doi:10.1093/ije/dyr020

Bruce, S. E., Yonkers, K. A., Otto, M. W., Eisen, J. L., Weisberg, R. B., Pagano, M., . . . Keller, M. B. (2005). Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder: A 12-year prospective study. *American Journal of Psychiatry, 162*(6), 1179-1187. doi:10.1176/appi.ajp.162.6.1179

Bruckl, T. M., Wittchen, H. U., Hofler, M., Pfister, H., Schneider, S., & Lieb, R. (2007). Childhood separation anxiety and the risk of subsequent psychopathology: Results from a community study. *Psychotherapy and Psychosomatics, 76*(1), 47-56. doi:10.1159/000096364

Buckner, J. D., & Heimberg, R. G. (2010). Drinking behaviors in social situations account for alcohol-related problems among socially anxious individuals. *Psychology of Addictive Behaviors, 24*(4), 640-648. doi:10.1037/a0020968

Buckner, J. D., Schmidt, N. B., & Eggleston, A. M. (2006). Social anxiety and problematic alcohol consumption: The mediating role of drinking motives and situations. *Behavior Therapy, 37*(4), 381-391. doi:10.1016/j.beth.2006.02.007

Buckner, J. D., Schmidt, N. B., Lang, A. R., Small, J. W., Schlauch, R. C., & Lewinsohn, P. M. (2008). Specificity of social anxiety disorder as a risk factor for alcohol and cannabis dependence. *Journal of Psychiatric Research, 42*(3), 230-239. doi:10.1016/j.jpsychires.2007.01.002

Buckner, J. D., & Shah, S. M. (2015). Fitting in and feeling fine: Conformity and coping motives differentially mediate the relationship between social

anxiety and drinking problems for men and women. *Addiction Research & Theory, 23*(3), 231-237. doi:10.3109/16066359.2014.978304

Buckner, J. D., & Turner, R. (2009). Social anxiety disorder as a risk factor for alcohol use disorders: A prospective examination of parental and peer influences. *Drug and Alcohol Dependence, 100*(1-2), 128-137. doi:10.1016/j.drugalcdep.2008.09.018

Button, K. S., Ioannidis, J. P. A., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S. J., & Munafo, M. R. (2013). Power failure: why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience, 14*(5), 365-376. doi:10.1038/nrn3475

Cameron, O. G. (2001). Interoception: The inside story - A model for psychosomatic processes. *Psychosomatic Medicine, 63*(5), 697-710. doi:10.1097/00006842-200109000-00001

Cappell, H., & Herman, C. P. (1972). Alcohol and tension reduction. A review. *Quarterly Journal of Studies on Alcohol, 33*(1), 33-64.

Carney, M. A., Armeli, S., Tennen, H., Affleck, G., & O'Neil, T. P. (2000). Positive and negative daily events, perceived stress, and alcohol use: a diary study. *Journal of Consulting and Clinical Psychology, 65*(5), 788-798. doi:http://dx.doi.org/10.1037/0022-006X.68.5.788

Carrigan, M. H., & Randall, C. L. (2003). Self-medication in social phobia: A review of the alcohol literature. *Addictive Behaviors, 28*(2), 269-284. doi:10.1016/S0306-4603%2801%2900235-0 12573678

Cerda, M., Prins, S. J., Galea, S., Howe, C. J., & Pardini, D. (2016). When psychopathology matters most: identifying sensitive periods when within-person changes in conduct, affective and anxiety problems are associated with male adolescent substance use. *Addiction, 111*(5), 924-935. doi:10.1111/add.13304

References

Chambers, J. A., Power, K. G., & Durham, R. C. (2004). The relationship between trait vulnerability and anxiety and depressive diagnoses at long-term follow-up of generalized anxiety disorder. *Journal of Anxiety Disorders, 18*(5), 587-607. doi:10.1016/j.janxdis.2003.09.001

Chao, M., Li, X., & McGue, M. (2017). The causal role of alcohol use in adolescent externalizing and internalizing problems: A Mendelian randomization study. *Alcoholism: Clinical and Experimental Research, 41*(11), 1953-1960. doi:10.1111/acer.13493 28876462

Charlet, K., & Heinz, A. (2017). Harm reduction-a systematic review on effects of alcohol reduction on physical and mental symptoms. *Addiction Biology, 22*(5), 1119-1159. doi:10.1111/adb.12414

Chassin, L., Flora, D. B., & King, K. M. (2004). Trajectories of alcohol and drug use and dependence from adolescence to adulthood: The effects of familial alcoholism and personality. *Journal of Abnormal Psychology, 113*(4), 483-498. doi:10.1037/0021-843x.113.4.483

Cheng, A. T., Gau, S.-F., Chen, T. H., Chang, J.-C., & Chang, Y.-T. (2004). A 4-year longitudinal study on risk factors for alcoholism. *Archives of General Psychiatry, 61*(2), 184-191. doi:10.1001/archpsyc.61.2.184

Chow, P. I., Portnow, S., Zhang, D. H., Salemink, E., Wiers, R. W., & Teachman, B. A. (2018). Comorbid interpretation and expectancy bias in social anxiety and alcohol use. *Anxiety Stress and Coping, 31*(6), 669-685. doi:10.1080/10615806.2018.1521958

Clark, L. A., Watson, D., & Mineka, S. (1994). Temperament, personality, and the mood and anxiety disorders. *Journal of Abnormal Psychology, 103*(1), 103-116. doi:http://dx.doi.org/10.1037/0021-843X.103.1.103

Clay, J. M., & Parker, M. O. (2018). The role of stress-reactivity, stress-recovery and risky decision-making in psychosocial stress-induced alcohol

consumption in social drinkers. *Psychopharmacology, 235*(11), 3243-3257. doi:10.1007/s00213-018-5027-0

Colasanti, A., Salamon, E., Schruers, K., van Diest, R., van Duinen, M., & Griez, E. J. (2008). Carbon dioxide-induced emotion and respiratory symptoms in healthy volunteers. *Neuropsychopharmacology, 33*(13), 3103-3110. doi:10.1038/npp.2008.31

Colder, C. R., Frndak, S., Lengua, L. J., Read, J. P., Hawk, L. W., Jr., & Wieczorek, W. F. (2017a). Internalizing and externalizing problem behavior: A test of a latent variable interaction predicting a two-part growth model of adolescent substance use. *Journal of Abnormal Child Psychology*, 1-12. doi:10.1007/s10802-017-0277-6

Colder, C. R., Lee, Y. H., Frndak, S., Read, J. P., & Wieczorek, W. F. (2019). Internalizing Symptoms and Cannabis and Alcohol Use: Between- and Within-Person Risk Pathways With Coping Motives. *Journal of Consulting and Clinical Psychology, 87*(7), 629-644. doi:10.1037/ccp0000413

Colder, C. R., Scalco, M., Trucco, E. M., Read, J. P., Lengua, L. J., Wieczorek, W. F., & Hawk Jr, L. W. (2013). Prospective associations of internalizing and externalizing problems and their co-occurrence with early adolescent substance use. *Journal of Abnormal Child Psychology, 41*(4), 667-677. doi:10.1007/s10802-012-9701-0

Colder, C. R., Shyhalla, K., Frndak, S., Read, J. P., Lengua, L. J., Hawk, L. W., & Wieczorek, W. F. (2017b). The prospective association between internalizing symptoms and adolescent alcohol involvement and the moderating role of age and externalizing symptoms. *Alcoholism-Clinical and Experimental Research, 41*(12), 2185-2196. doi:10.1111/acer.13512

Collins, J. L., Thompson, K., Sherry, S. B., Glowacka, M., & Stewart, S. H. (2018). Drinking to cope with depression mediates the relationship between social avoidance and alcohol problems: A 3-wave, 18-month

longitudinal study. *Addictive Behaviors, 76*, 182-187. doi:10.1016/j.addbeh.2017.08.020

Comeau, N., Stewart, S. H., & Loba, P. (2001). The relations of trait anxiety, anxiety sensitivity, and sensation seeking to adolescents' motivations for alcohol, cigarette, and marijuana use. *Addictive Behaviors, 26*(6), 803-825. doi:10.1016/S0306-4603(01)00238-6

Conger, J. J. (1956). Alcoholism: theory, problem and challenge. II. Reinforcement theory and the dynamics of alcoholism. *Quarterly Journal of Studies on Alcohol, 17*(2), 296-305.

Constant, A., Gautier, Y., Coquery, N., Thibault, R., Moirand, R., & Val-Laillet, D. (2018). Emotional overeating is common and negatively associated with alcohol use in normal-weight female university students. *Appetite, 129*, 186-191. doi:10.1016/j.appet.2018.07.012

Cooper, M. L. (1994). Motivations for alcohol use among adolescents: Development and validation of a four-factor model. *Psychological Assessment, 6*(2), 117-128. doi:10.1037/1040-3590.6.2.117

Cooper, M. L., Frone, M. R., Russell, M., & Mudar, P. (1995). Drinking to regulate positive and negative emotions: A motivational model of alcohol use. *Journal of Personality and Social Psychology, 69*(5), 990-1005. doi:10.1037/0022-3514.69.5.990 7473043

Cooper, M. L., Krull, J. L., Agocha, V. B., Flanagan, M. E., Orcutt, H. K., Grabe, S., . . . Jackson, M. (2008). Motivational pathways to alcohol use and abuse among Black and White adolescents. *Journal of Abnormal Psychology, 117*(3), 485-501. doi:10.1037/a0012592 18729604

Cooper, M. L., Kuntsche, E., Levitt, A., Barber, L. L., & Wolf, S. (2016). Motivational models of substance use: A review of theory and research on motives for using alcohol, marijuana, and tobacco. In K. Sher (Ed.), *The*

Oxford handbook of substance use and substance use disorders (pp. 375-421). New York: Oxford University Press.

Cooper, M. L., Russell, M., Skinner, J. B., & Windle, M. (1992). Development and validation of a three-dimensional measure of drinking motives. *Psychological Assessment, 4*(2), 123-132. doi:10.1037/1040-3590.4.2.123

Costello, E. J., Copeland, W., & Angold, A. (2011). Trends in psychopathology across the adolescent years: what changes when children become adolescents, and when adolescents become adults? *Journal of Child Psychology and Psychiatry, 52*(10), 1469-1476. doi:10.1111/j.1469-7610.2011.02446.x

Crum, R. M., Mojtabai, R., Lazareck, S., Bolton, J. M., Robinson, J., Sareen, J., . . . Storr, C. L. (2013). A prospective assessment of reports of drinking to self-medicate mood symptoms with the incidence and persistence of alcohol dependence. *Jama Psychiatry, 70*(7), 718-726. doi:10.1001/jamapsychiatry.2013.1098

Curtin, J. J., Patrick, C. J., Lang, A. R., Cacioppo, J. T., & Birbaumer, N. (2001). Alcohol affects emotion through cognition. *Psychological Science, 12*(6), 527-531. doi:10.1111/1467-9280.00397

da Cruz, E. L. D., Martins, P. D. D., & Diniz, P. R. B. (2017). Factors related to the association of social anxiety disorder and alcohol use among adolescents: a systematic review. *Jornal De Pediatria, 93*(5), 442-451. doi:10.1016/j.jped.2017.05.001

Dahne, J., Banducci, A. N., Kurdziel, G., & MacPherson, L. (2014). Early adolescent symptoms of social phobia prospectively predict alcohol use. *Journal of Studies on Alcohol and Drugs, 75*(6), 929-936. doi:https://doi.org/10.15288/jsad.2014.75.929

References

de Moor, M. H., Vink, J. M., van Beek, J. H., Geels, L. M., Bartels, M., de Geus, E. J., . . . Boomsma, D. I. (2011). Heritability of problem drinking and the genetic overlap with personality in a general population sample. *Frontiers in Genetics, 2*(76). doi:10.3389/fgene.2011.00076

de Wit, H. (2000). Laboratory-based assessment of alcohol craving in social drinkers. *Addiction, 95*(8), S165-169. doi:10.1080/09652140050111735

de Wit, H., Soderpalm, A. H. V., Nikolayev, L., & Young, E. (2003). Effects of acute social stress on alcohol consumption in healthy subjects. *Alcoholism-Clinical and Experimental Research, 27*(8), 1270-1277. doi:10.1097/01.Alc.0000081617.37539.D6

Delargy, D., Shenker, D., Manning, J., & Rickard, A. (2010). *Swept under the carpet: Children affected by parental alcohol misuse* Retrieved from Alcohol Concern: London: https://www.childrenssociety.org.uk/sites/default/files/swept-under-the-carpet.pdf

DeMartini, K. S., & Carey, K. B. (2011). The role of anxiety sensitivity and drinking motives in predicting alcohol use: A critical review. *Clinical Psychology Review, 31*(1), 169-177. doi:10.1016/j.cpr.2010.10.001 21074306

Department of Health. (2003). *Comorbid Mental Disorders and Substance Use Disorders: Epidemiology, Prevention, and Treatment*. Retrieved from http://www.health.gov.au/internet/publications/publishing.nsf/Content/drug treat-pubs-comorbid-toc~drugtreat-pubs-comorbid-4~drugtreat-pubs-comorbid-4-3

Dervaux, A., & Laqueille, X. (2018). Psychiatric comorbidities of alcohol dependence. *Presse Medicale, 47*(6), 575-585. doi:10.1016/j.lpm.2018.01.005

DiChiara, G. (1997). Alcohol and dopamine. *Alcohol Health & Research World, 21*(2), 108-114.

Driessen, M., Meier, S., Hill, A., Wetterling, T., Lange, W., & Junghanns, K. (2001). The course of anxiety, depression and drinking behaviours after completed detoxification in alcoholics with and without comorbid anxiety and depressive disorders. *Alcohol and Alcoholism, 36*(3), 249-255. doi:10.1093/alcalc/36.3.249

Drummond, D. C., & Phillips, T. S. (2002). Alcohol urges in alcohol-dependent drinkers: Further validation of the Alcohol Urge Questionnaire in an untreated community clinical population. *Addiction, 97*(11), 1465-1472. doi:10.1046/j.1360-0443.2002.00252.x 12410786

DSM-5. (2019). DSM Library: Anxiety Disorders. In: American Psychiatric Association Publishing. doi:https://doi.org/10.1176/appi.books.9780890425596.dsm05

Dyer, M. L., Easey, K. E., Heron, J., Hickman, M., & Munafó, M. R. (2019a). Associations of child and adolescent anxiety with later alcohol use and disorders: A systematic review and meta-analysis of prospective cohort studies. *Addiction, 114*(6), 968-982. doi:10.1111/add.14575

Dyer, M. L., Heron, J., Hickman, M., & Munafò, M. R. (2019b). Alcohol use in late adolescence and early adulthood: The role of generalised anxiety disorder and drinking to cope motives. *Drug and Alcohol Dependence, 204*. doi:https://doi.org/10.1016/j.drugalcdep.2019.04.044

Ederer, E. M. (2004). Mental health problems in young children: Self-reports and significant others as informants. *Psychology Science, 46*, 123-140.

Edwards, A. C., Latendresse, S. J., Heron, J., Bin Cho, S., Hickman, M., Lewis, G., . . . Kendler, K. S. (2014). Childhood internalizing symptoms are negatively associated with early adolescent alcohol use. *Alcoholism-*

Clinical and Experimental Research, 38(6), 1680-1688. doi:10.1111/acer.12402

Egger, M., Davey Smith, G., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *Bmj, 315*(7109), 629-634. doi:https://doi.org/10.1136/bmj.315.7109.629

Eggleston, A. M., Woolaway-Bickel, K., & Schmidt, N. B. (2004). Social anxiety and alcohol use: Evaluation of the moderating and mediating effects of alcohol expectancies. *Journal of Anxiety Disorders, 18*(1), 33-49. doi:10.1016/j.janxdis.2003.07.005

Englund, M. M., Egeland, B., Oliva, E. M., & Collins, W. (2008). Childhood and adolescent predictors of heavy drinking and alcohol use disorders in early adulthood: A longitudinal developmental analysis. *Addiction, 103*(Suppl1), 23-35.

Englund, M. M., & Siebenbruner, J. (2012). Developmental pathways linking externalizing symptoms, internalizing symptoms, and academic competence to adolescent substance use. *Journal of Adolescence, 35*(5), 1123-1140. doi:10.1016/j.adolescence.2012.03.004

Essau, C. A., Lewinsohn, P. M., Olaya, B., & Seeley, J. R. (2014). Anxiety disorders in adolescents and psychosocial outcomes at age 30. *Journal of Affective Disorders, 163*, 125-132. doi:10.1016/j.jad.2013.12.033

Evans, D. L., Foa, E. B., Gur, R. E., Hendin, H., O'Brien, C. P., Seligman, M. E. P., & Walsh, B. T. (2012). *Treating and Preventing Adolescent Mental Health Disorders: What We Know and What We Don't Know. A Research Agenda for Improving the Mental Health of Our Youth*. New York, NY, US: Oxford University Press.

Eysenck, H. J., & Eysenck, S. B. G. (1991). *Manual of the Eysenck personality scale (adults)*. London: Hodder and Stoughton.

Eysenck, M. W. (1997). *Anxiety and cognition: A unified theory*. Hove, England: Psychology Press/Erlbaum (UK) Taylor & Francis.

Farmer, R. F., Gau, J. M., Seeley, J. R., Kosty, D. B., Sher, K. J., & Lewinsohn, P. M. (2016). Internalizing and externalizing disorders as predictors of alcohol use disorder onset during three developmental periods. *Drug and Alcohol Dependence, 164*, 38-46. doi:10.1016/j.drugalcdep.2016.04.021

Farrell, M., Howes, S., Bebbington, P., Brugha, T., Jenkins, R., Lewis, G., . . . Meltzer, H. (2003). Nicotine, alcohol and drug dependence, and psychiatric comorbidity - results of a national household survey (Reprinted from British Journal of Psychiatry, vol 179, pgs 432-437, 2001). *International Review of Psychiatry, 15*(1-2), 50-56. doi:10.1080/0954026021000045949

Fatseas, M., Serre, F., Swendsen, J., & Auriacombe, M. (2018). Effects of anxiety and mood disorders on craving and substance use among patients with substance use disorder: An ecological momentary assessment study. *Drug and Alcohol Dependence, 187*, 242-248. doi:10.1016/j.drugalcdep.2018.03.008

Feinstein, J. S., Buzza, C., Hurlemann, R., Follmer, R. L., Dahdaleh, N. S., Coryell, W. H., . . . Wemmie, J. A. (2013). Fear and panic in humans with bilateral amygdala damage. *Nature Neuroscience, 16*(3), 270-272. doi:10.1038/nn.3323

Fewell, Z., Davey Smith, G., & Sterne, J. A. (2007). The impact of residual and unmeasured confounding in epidemiologic studies: A simulation study. *American Journal of Epidemiology, 166*(6), 646-655. doi:10.1093/aje/kwm165

Field, M., & Christiansen, P. (2012). Commentary on Ataya et al. (2012), 'Internal reliability of measures of substance-related cognitive bias'. *Drug and*

Alcohol Dependence, 124(3), 189-190. doi:10.1016/j.drugalcdep.2012.02.009

Fite, P. J., Colder, C. R., & O'Connor, R. M. (2006). Childhood behavior problems and peer selection and socialization: Risk for adolescent alcohol use. *Addictive Behaviors, 31*(8), 1454-1459. doi:10.1016/j.addbeh.2005.09.015

Fitzgerald, K.-A., & Long, C. G. (2012). The influence of drinking motives and anxiety on low-, moderate- and high-risk drinkers. *Journal of Substance Use, 17*(3), 240-248. doi:10.3109/14659891.2011.565109

Foster, K. T., Hicks, B. M., & Zucker, R. A. (2018). Positive and negative effects of internalizing on alcohol use problems from childhood to young adulthood: The mediating and suppressing role of externalizing. *Journal of Abnormal Psychology, 127*(4), 394-403. doi:10.1037/abn0000337

Fox, H. C., Bergquist, K. L., Hong, K. I., & Sinha, R. (2007). Stress-induced and alcohol cue-induced craving in recently abstinent alcohol-dependent individuals. *Alcoholism-Clinical and Experimental Research, 31*(3), 395-403. doi:10.1111/j.1530-0277.2006.00320.x

Fraser, A., Macdonald-Wallis, C., Tilling, K., Boyd, A., Golding, J., Davey Smith, G., . . . Lawlor, D. A. (2013). Cohort Profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *International Journal of Epidemiology, 42*(1), 97-110. doi:10.1093/ije/dys066

Froehlich, J. C. (1997). Opioid peptides. *Alcohol Health & Research World, 21*(2), 132-136.

Fröjd, S., Ranta, K., Kaltiala-Heino, R., & Marttunen, M. (2011). Associations of social phobia and general anxiety with alcohol and drug use in a community sample of adolescents. *Alcohol and Alcoholism, 46*(2), 192-199. doi:10.1093/alcalc/agq096

Fromme, K., & D'Amico, E. J. (1999). Neurobiological bases of alcohol's psychological effects. . In K. E. Leonard & H. T. Blane (Eds.),

Psychological theories of drinking and alcoholism (pp. 422–455). New York: Guilford Press.

Gallagher, C., Radmall, Z., O'Gara, C., & Burke, T. (2017). Anxiety and depression among patients with alcohol dependence: co-morbid or substance-related problems? *Irish Journal of Psychological Medicine, 35*(2), 121-126. doi:https://doi.org/10.1017/ipm.2017.25

Garner, M. (2015). The CO2 experimental medicine model of anxiety. *European Neuropsychopharmacology, 25*, S112-S112. doi:Doi 10.1016/S0924-977x(15)30022-5

Garner, M., Attwood, A., Baldwin, D. S., & Munafo, M. R. (2012). Inhalation of 7.5% carbon dioxide increases alerting and orienting attention network function. *Psychopharmacology, 223*(1), 67-73. doi:10.1007/s00213-012-2690-4

George, D. T., Nutt, D. J., Dwyer, B. A., & Linnoila, M. (1990). Alcoholism and panic disorder - is the comorbidity more than coincidence. *Acta Psychiatrica Scandinavica, 81*(2), 97-107. doi:DOI 10.1111/j.1600-0447.1990.tb06460.x

Glautier, S., & Drummond, D. C. (1994). Alcohol dependence and cue reactivity. *Journal of Studies on Alcohol, 55*(2), 224–229. doi:https://doi.org/10.15288/jsa.1994.55.224

Gogtay, N. J., Deshpande, S. P., & Thatte, U. M. (2016). Normal Distribution, "p" Value and Confidence Intervals. *J Assoc Physicians India, 64*(8), 74-76.

Goldstein, A. L., Vilhena-Churchill, N., Stewart, S. H., & Wekerle, C. (2012). Coping motives as moderators of the relationship between emotional distress and alcohol problems in a sample of adolescents involved with child welfare. *Advances in Mental Health, 11*(1), 67-75. doi:https://doi.org/10.5172/jamh.2012.11.1.67

Goodman, A. (2010). Substance use and common child mental health problems: Examining longitudinal associations in a British sample. *Addiction, 105*(8), 1484-1496. doi:10.1111/j.1360-0443.2010.02981.x

Goodwin, R. D., Lieb, R., Hoefler, M., Pfister, H., Bittner, A., Beesdo, K., & Wittchen, H. U. (2004). Panic attack as a risk factor for severe psychopathology. *American Journal of Psychiatry, 161*(12), 2207-2214. doi:10.1176/appi.ajp.161.12.2207

Gorka, S. M., Hedeker, D., Piasecki, T. M., & Mermelstein, R. (2017). Impact of alcohol use motives and internalizing symptoms on mood changes in response to drinking: An ecological momentary assessment investigation. *Drug and Alcohol Dependence, 173*, 31-38. doi:10.1016/j.drugalcdep.2016.12.012

Gorka, S. M., Shankman, S. A., Olino, T. M., Seeley, J. R., Kosty, D. B., & Lewinsohn, P. M. (2014). Anxiety disorders and risk for alcohol use disorders: The moderating effect of parental support. *Drug and Alcohol Dependence, 140*, 191-197. doi:10.1016/j.drugalcdep.2014.04.021

Graham, J. W. (2009). Missing data analysis: Making it work in the real world. *Annual Review of Psychology, 60*, 549-576. doi:10.1146/annurev.psych.58.110405.085530

Grant, B. F., Stinson, F. S., Dawson, D. A., Chou, S. P., Dufour, M. C., Compton, W., . . . Kaplan, K. (2004). Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders - Results from the national epidemiologic survey on alcohol and related conditions. *Archives of General Psychiatry, 61*(8), 807-816. doi:10.1001/archpsyc.61.8.807

Grant, V. V., Stewart, S. H., O'Connor, R. M., Blackwell, E., & Conrod, P. J. (2007). Psychometric evaluation of the five-factor Modified Drinking

Motives Questionnaire-Revised in undergraduates. *Addictive Behaviors, 32*(11), 2611-2632. doi:10.1016/j.addbeh.2007.07.004 17716823

Groenman, A. P., Janssen, T. W. P., & Oosterlaan, J. (2017). Childhood psychiatric disorders as risk factor for subsequent substance abuse: A meta-analysis. *Journal of the American Academy of Child & Adolescent Psychiatry, 56*(7), 556-569. doi:10.1016/j.jaac.2017.05.004 28647007

Gustavsson, A., Svensson, M., Jacobi, F., Allgulander, C., Alonso, J., Beghi, E., . . . Grp, C. S. (2011). Cost of disorders of the brain in Europe 2010. *European Neuropsychopharmacology, 21*(10), 718-779. doi:10.1016/j.euroneuro.2011.08.008

Hall, W., & Farrell, M. (1997). Comorbidity of mental disorders with substance misuse. *British Journal of Psychiatry, 171*, 4-5. doi:10.1192/bjp.171.1.4

Haller, M., & Chassin, L. (2013). The influence of PTSD symptoms on alcohol and drug problems: Internalizing and externalizing pathways. *Psychological Trauma: Theory, Research, Practice, and Policy, 5*(5), 484-493. doi:10.1037/a0029335

Hammer, G. P., Prel, J. D., & Blettner, M. (2009). Avoiding bias in observational studies. *Deutsches Arzteblatt International, 106*(41), 664-668. doi:10.3238/arztebl.2009.0664

Hanel, P. H. P., & Vione, K. C. (2016). Do student samples provide an accurate estimate of the general public? *PLoS ONE, 11*(12). doi:10.1371/journal.pone.0168354

Hardy, L., & Hogarth, L. (2017). A novel concurrent pictorial choice model of mood-induced relapse in hazardous drinkers. *Experimental and Clinical Psychopharmacology, 25*(6), 448-455. doi:10.1037/pha0000155 29251973

Hardy, L., Parker, S., Hartley, L., & Hogarth, L. (2018). A concurrent pictorial drug choice task marks multiple risk factors in treatment-engaged smokers and

drinkers. *Behavioural Pharmacology, 29*(8), 716-725. doi:10.1097/Fbp.0000000000000421

Harris, R. J., Bradburn, M. J., Deeks, J. J., Harbord, R. M., Altman, D. G., & Sterne, J. A. C. (2008). Metan: fixed- and random-effects meta-analysis. *Stata Journal, 8*(1), 3-28. doi:https://doi.org/10.1177/1536867X0800800102

Hendler, R. A., Ramchandani, V. A., Gilman, J., & Hommer, D. W. (2013). Stimulant and sedative effects of alcohol. *Current Topics in Behavioral Neurosciences, 13*, 489-509. doi:10.1007/7854_2011_135

Heradstveit, O., Skogen, J. C., Boe, T., Hetland, J., Pedersen, M. U., & Hysing, M. (2018). Prospective associations between childhood externalising and internalising problems and adolescent alcohol and drug use The Bergen Child Study. *Nordic Studies on Alcohol and Drugs, 35*(5), 357-371. doi:10.1177/1455072518789852

Hibell, B., Guttormsson, U., Ahlstrom, S., Balakireva, O., Bjarnason, T., Kokkevi, A., & Kraus, L. (2012). *The 2011 ESPAD Report. Substance Use Among Students in 36 European Countries*. Retrieved from Stockholm, Sweden: http://www.espad.org/sites/espad.org/files/The_2011_ESPAD_Report_FULL_2012_10_29.pdf

Higgins, J. P. T., & Thompson, S. G. (2002). Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine, 21*(11), 1539-1558. doi:10.1002/sim.1186

Hill, A. B. (2015). The environment and disease: association or causation? (Reprinted from JRSM, vol 58, 1965). *Journal of the Royal Society of Medicine, 108*(1), 32-37. doi:10.1177/0141076814562718

Hill, K. G., Hawkins, J. D., Bailey, J. A., Catalano, R. F., Abbott, R. D., & Shapiro, V. B. (2010). Person-environment interaction in the prediction of alcohol abuse and alcohol dependence in adulthood. *Drug and Alcohol Dependence, 110*(1-2), 62-69. doi:10.1016/j.drugalcdep.2010.02.005

Hoffman, D. L., Dukes, E. M., & Wittchen, H. U. (2008). Human and economic burden of generalized anxiety disorder. *Depression and Anxiety, 25*(1), 72-90. doi:10.1002/da.20257

Hogarth, L., & Hardy, L. (2018). Depressive statements prime goal-directed alcohol-seeking in individuals who report drinking to cope with negative affect. *Psychopharmacology, 235*(1), 269-279. doi:10.1007/s00213-017-4765-8 29082424

Hogarth, L., Hardy, L., Bakou, A., Mahlberg, J., Weidemann, G., Cashel, S., & Moustafa, A. A. (2019). Negative mood induction increases choice of heroin versus food pictures in opiate-dependent individuals: correlation with self-medication coping motives and subjective reactivity. *Frontiers in Psychiatry, 10*. doi:10.3389/fpsyt.2019.00274

Hogarth, L., Hardy, L., Mathew, A. R., & Hitsman, B. (2018). Negative mood-induced alcohol-seeking is greater in young adults who report depression symptoms, drinking to cope, and subjective reactivity. *Experimental and Clinical Psychopharmacology, 26*(2), 138-146. doi:10.1037/pha0000177 29389212

Holdstock, L., & de Wit, H. (1998). Individual differences in the biphasic effects of ethanol. *Alcoholism-Clinical and Experimental Research, 22*(9), 1903-1911. doi:DOI 10.1111/j.1530-0277.1998.tb05897.x

Hull, J. G. (1981). A self-awareness model of the causes and effects of alcohol-consumption. *Journal of Abnormal Psychology, 90*(6), 586-600. doi:10.1037//0021-843x.90.6.586

Hussong, A. M., Ennett, S. T., Cox, M. J., & Haroon, M. (2017). A systematic review of the unique prospective association of negative affect symptoms and adolescent substance use controlling for externalizing symptoms. *Psychology of Addictive Behaviors, 31*(2), 137-147. doi:10.1037/adb0000247 28134539

Hussong, A. M., Galloway, C. A., & Feagans, L. A. (2005). Coping motives as a moderator of daily mood-drinking covariation. *Journal of Studies on Alcohol, 66*(3), 344-353. doi:DOI 10.15288/jsa.2005.66.344

Hussong, A. M., Hicks, R. E., Levy, S. A., & Curran, P. J. (2001). Specifying the relations between affect and heavy alcohol use among young adults. *Journal of Abnormal Psychology, 110*(3), 449-461. doi:10.1037//0021-843x.110.3.449

Hussong, A. M., Jones, D. J., Stein, G. L., Baucom, D. H., & Boeding, S. (2011). An internalizing pathway to alcohol use and disorder. *Psychology of Addictive Behaviors, 25*(3), 390-404. doi:10.1037/a0024519

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., . . . Wang, P. (2010). Research Domain Criteria (RDoC): Toward a new classification framework for research on mental disorders. *American Journal of Psychiatry, 167*(7), 748-751. doi:10.1176/appi.ajp.2010.09091379

Jane-Llopis, E., & Matytsina, I. (2006). Mental health and alcohol, drugs and tobacco: A review of the comorbidity between mental disorders and the use of alcohol, tobacco and illicit drugs. *Drug and Alcohol Review, 25*(6), 515-536. doi:10.1080/09595230600944461 17132571

Jester, J. M., Steinberg, D. B., Heitzeg, M. M., & Zucker, R. A. (2015). Coping expectancies, not enhancement expectancies, mediate trauma experience effects on problem alcohol use: A prospective study from early childhood to adolescence. *Journal of Studies on Alcohol and Drugs, 76*(5), 781-789. doi:10.15288/jsad.2015.76.781

Johnston, L. D., Miech, R. A., O'Malley, P. M., Bachman, J. G., Schulenberg, J. E., & Patrick, M. E. (2018). *Monitoring the Future national survey results on drug use: 1975-2017: Overview, key findings on adolescent drug use*. Retrieved from Ann Arbor: Institute for Social Research, The University of

Michigan http://www.monitoringthefuture.org/pubs/monographs/mtf-overview2017.pdf

Jones, T. M., Epstein, M., Hill, K. G., Bailey, J. A., & Hawkins, J. D. (2018). General and specific predictors of comorbid substance use and internalizing problems from adolescence to age 33. *Prevention Science*. doi:10.1007/s11121-018-0959-5

Jordan, C. J., & Andersen, S. L. (2017). Sensitive periods of substance abuse: Early risk for the transition to dependence. *Developmental Cognitive Neuroscience, 25*, 29-44. doi:10.1016/j.dcn.2016.10.004

Jun, H. J., Sacco, P., Bright, C. L., & Camlin, E. A. S. (2015). Relations among internalizing and externalizing symptoms and drinking frequency during adolescence. *Substance Use and Misuse, 50*(14), 1814-1825. doi:10.3109/10826084.2015.1058826

Kaye, J., Buchanan, F., Kendrick, A., Johnson, P., Lowry, C., Bailey, J., . . . Lightman, S. (2004). Acute carbon dioxide exposure in healthy adults: Evaluation of a novel means of investigating the stress response. *Journal of Neuroendocrinology, 16*(3), 256-264. doi:10.1111/j.0953-8194.2004.01158.x

Kenney, S. R., DiGuiseppi, G. T., Meisel, M. K., Balestrieri, S. G., & Barnett, N. P. (2018). Poor mental health, peer drinking norms, and alcohol risk in a social network of first-year college students. *Addictive Behaviors, 84*, 151-159. doi:10.1016/j.addbeh.2018.04.012

Keough, M. T., Battista, S. R., O'Connor, R. M., Sherry, S. B., & Stewart, S. H. (2016). Getting the party started - Alone: Solitary predrinking mediates the effect of social anxiety on alcohol-related problems. *Addictive Behaviors, 55*, 19-24. doi:10.1016/j.addbeh.2015.12.013

Kessler, R. C. (1995). The National Comorbidity Survey - preliminary results and future directions. *International Journal of Methods in Psychiatric Research, 5*(2), 139-151.

Kessler, R. C., Aguilar-Gaxiola, S., Alonso, J., Chatterji, S., Lee, S., Ormel, J., . . . Wang, P. S. (2009). The global burden of mental disorders: an update from the WHO World Mental Health (WMH) surveys. *Epidemiologia e psichiatria sociale, 18*(1), 23-33. doi:https://doi.org/10.1017/S1121189X00001421

Kessler, R. C., Nelson, C. B., McGonagle, K. A., Edlund, M. J., Frank, R. G., & Leaf, P. J. (1996). The epidemiology of co-occurring addictive and mental disorders: Implications for prevention and service utilization. *American Journal of Orthopsychiatry, 66*(1), 17-31. doi:10.1037/h0080151

Khantzian, E. J. (1990). Self-regulation and self-medication factors in alcoholism and the addictions: Similarities and differences. In M. Galanter (Ed.), *Recent developments in alcoholism* (Vol. 8, pp. 255–271). New York: Plenum Press.

Kidorf, M., & Lang, A. R. (1999). Effects of social anxiety and alcohol expectancies on stress-induced drinking. *Psychology of Addictive Behaviors, 13*(2), 134-142. doi:10.1037/0893-164x.13.2.134

King, S. M., Iacono, W. G., & McGue, M. (2004). Childhood externalizing and internalizing psychopathology in the prediction of early substance use. *Addiction, 99*(12), 1548-1559. doi:10.1111/j.1360-0443.2004.00893.x

Klein, A. M., Becker, E. S., & Rinck, M. (2011). Approach and avoidance tendencies in spider fearful children: The approach-avoidance task. *Journal of Child and Family Studies, 20*(2), 224-231. doi:10.1007/s10826-010-9402-7

Kuntsche, E., Knibbe, R., Gmel, G., & Engels, R. (2005). Why do young people drink? A review of drinking motives. *Clinical Psychology Review, 25*(7), 841-861. doi:10.1016/j.cpr.2005.06.002

Kuntsche, E., Knibbe, R., Gmel, G., & Engels, R. (2006). Replication and validation of the drinking motive questionnaire revised (DMQ-R, Cooper, 1994) among adolescents in Switzerland. *European Addiction Research, 12*(3), 161-168. doi:10.1159/000092118

Kushner, M. G., Abrams, K., & Borchardt, C. (2000a). The relationship between anxiety disorders and alcohol use disorders: A review of major perspectives and findings. *Clinical Psychology Review, 20*(2), 149-171. doi:Doi 10.1016/S0272-7358(99)00027-6

Kushner, M. G., Abrams, K., Thuras, P., & Hanson, K. L. (2000b). Individual differences predictive of drinking to manage anxiety among non-problem drinkers with panic disorder. *Alcoholism-Clinical and Experimental Research, 24*(4), 448-458. doi:10.1097/00000374-200004000-00018

Kushner, M. G., Krueger, R., Frye, B., & Peterson, J. (2008). *Epidemiological perspectives on co-occurring anxiety disorder and substance use disorder*. New York Springer.

Kushner, M. G., Mackenzie, T. B., Fiszdon, J., Valentiner, D. P., Foa, E., Anderson, N., & Wangensteen, D. (1996). The effects of alcohol consumption on laboratory-induced panic and state anxiety. *Archives of General Psychiatry, 53*(3), 264-270. doi:10.1001/archpsyc.1996.01830030086013

Kushner, M. G., Sher, K. J., & Erickson, D. J. (1999). Prospective analysis of the relation between DSM-III anxiety disorders and alcohol use disorders. *American Journal of Psychiatry, 156*(5), 723-732. doi:10.1176/ajp.156.5.723

Kushner, M. G., Sher, K. J., Wood, M. D., & Wood, P. K. (1994). Anxiety and drinking behavior - moderating effects of tension-reduction alcohol outcome expectancies. *Alcoholism-Clinical and Experimental Research, 18*(4), 852-860. doi:DOI 10.1111/j.1530-0277.1994.tb00050.x

Kwako, L. E., Schwandt, M. L., Sells, J. R., Ramchandani, V. A., Hommer, D. W., George, D. T., . . . Heilig, M. (2015). Methods for inducing alcohol craving in individuals with co-morbid alcohol dependence and posttraumatic stress disorder: behavioral and physiological outcomes. *Addiction Biology, 20*(4), 733-746. doi:10.1111/adb.12150

Kyzar, E. J., Zhang, H., & Pandey, S. C. (2019). Adolescent alcohol exposure epigenetically suppresses amygdala arc enhancer RNA expression to confer adult anxiety susceptibility. *Biological Psychiatry, 85*(11), 904-914. doi:10.1016/j.biopsych.2018.12.021

Lakens, D. (2013). Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. *Frontiers in Psychology, 4*(863). doi:10.3389/fpsyg.2013.00863

Lawlor, D. A., Harbord, R. M., Sterne, J. A. C., Timpson, N., & Smith, G. D. (2008). Mendelian randomization: Using genes as instruments for making causal inferences in epidemiology. *Statistics in Medicine, 27*(8), 1133-1163. doi:10.1002/sim.3034

Lawlor, D. A., Tilling, K., & Davey Smith, G. (2016). Triangulation in aetiological epidemiology. *International Journal Epidemiology, 45*(6), 1866-1886. doi:10.1093/ije/dyw314

Leffingwell, T. R., Cooney, N. J., Murphy, J. G., Luczak, S., Rosen, G., Dougherty, D. M., & Barnett, N. P. (2013). Continuous objective monitoring of alcohol use: Twenty-first century measurement using transdermal sensors. *Alcoholism-Clinical and Experimental Research, 37*(1), 16-22. doi:10.1111/j.1530-0277.2012.01869.x

References

Lemyre, A., Gauthier-Legare, A., & Belanger, R. E. (2019). Shyness, social anxiety, social anxiety disorder, and substance use among normative adolescent populations: A systematic review. *American Journal of Drug and Alcohol Abuse, 45*(3), 230-247. doi:10.1080/00952990.2018.1536882

Levenson, R. W., Sher, K. J., Grossman, L. M., Newman, J., & Newlin, D. B. (1980). Alcohol and stress response dampening: pharmacological effects, expectancy, and tension reduction. *Journal of Abnormal Psychology, 89*(4), 528-538. doi:http://dx.doi.org/10.1037/0021-843X.89.4.528

Lewis, G., Pelosi, A. J., Araya, R., & Dunn, G. (1992). Measuring psychiatric-disorder in the community - a standardized assessment for use by lay interviewers. *Psychological Medicine, 22*(2), 465-486. doi:https://doi.org/10.1017/S0033291700030415

Lewis, M. A., Hove, M. C., Whiteside, U., Lee, C. M., Kirkeby, B. S., Oster-Aaland, L., . . . Larimer, M. E. (2008). Fitting in and feeling fine: Conformity and coping motives as mediators of the relationship between social anxiety and problematic drinking. *Psychology of Addictive Behaviors, 22*(1), 58-67. doi:10.1037/0893-164x.22.1.58

Luczak, S. E., Glatt, S. J., & Wall, T. L. (2006). Meta-analyses of ALDH2 and ADH1B with alcohol dependence in Asians. *Psychological Bulletin, 132*(4), 607-621. doi:10.1037/0033-2909.132.4.607

Lumen. (2019). Types of Research Studies. Retrieved from https://courses.lumenlearning.com/boundless-psychology/chapter/types-of-research-studies/

Lyvers, M., Hanigan, C., & Thorberg, F. A. (2018). Social interaction anxiety, alexithymia, and drinking motives in Australian university students. *J Psychoactive Drugs, 50*(5), 402-410. doi:10.1080/02791072.2018.1517228

References

Mackie, C. J., Castellanos-Ryan, N., & Conrod, P. J. (2011a). Personality moderates the longitudinal relationship between psychological symptoms and alcohol use in adolescents. *Alcoholism: Clinical and Experimental Research, 35*(4), 703-716. doi:10.1111/j.1530-0277.2010.01388.x

Mackie, C. J., Conrod, P. J., Rijsdijk, F., & Eley, T. C. (2011b). A systematic evaluation and validation of subtypes of adolescent alcohol use motives: Genetic and environmental contributions. *Alcoholism-Clinical and Experimental Research, 35*(3), 420-430. doi:10.1111/j.1530-0277.2010.01359.x

MacKinnon, D. P. (2011). Integrating mediators and moderators in research design. *Research on Social Work Practice, 21*(6), 675-681. doi:10.1177/1049731511414148

Maggs, J. L., Patrick, M. E., & Feinstein, L. (2008). Childhood and adolescent predictors of alcohol use and problems in adolescence and adulthood in the National Child Development Study. *Addiction, 103*, 7-22. doi:10.1111/j.1360-0443.2008.02173.x

Magrys, S. A., & Olmstead, M. C. (2015). Acute Stress Increases Voluntary Consumption of Alcohol in Undergraduates. *Alcohol and Alcoholism, 50*(2), 213-218. doi:10.1093/alcalc/agu101

Malmberg, M., Kleinjan, M., Overbeek, G., Vermulst, A. A., Lammers, J., & Engels, R. (2013). Are there reciprocal relationships between substance use risk personality profiles and alcohol or tobacco use in early adolescence? *Addictive Behaviors, 38*(12), 2851-2859. doi:10.1016/addbeh.2013.08.003

Malmberg, M., Kleinjan, M., Vermulst, A. A., Overbeek, G., Monshouwer, K., Lammers, J., & Engels, R. C. (2012). Do substance use risk personality dimensions predict the onset of substance use in early adolescence? A

variable- and person-centered approach. *Journal of Youth and Adolescence, 41*(11), 1512-1525. doi:10.1007/s10964-012-9775-6

Mann, C. J. (2003). Observational research methods. Research design II: cohort, cross sectional, and case-control studies. *Emergency Medicine Journal, 20*(1), 54-60. doi:10.1136/emj.20.1.54

Marmorstein, N. R. (2015). Interactions between internalizing symptoms and urgency in the prediction of alcohol use and expectancies among low-income, minority early adolescents. *Substance Abuse: Research and Treatment, 9*(Suppl 1), 59-68. doi:10.4137/sart.s31438

Marmorstein, N. R., White, H. R., Loeber, R., & Stouthamer-Loeber, M. (2010). Anxiety as a predictor of age at first use of substances and progression to substance use problems among boys. *Journal of Abnormal Child Psychology, 38*(2), 211-224. doi:10.1007/s10802-009-9360-y

Mars, B., Collishaw, S., Smith, D., Thapar, A., Potter, R., Sellers, R., . . . Thapar, A. (2012). Offspring of parents with recurrent depression: Which features of parent depression index risk for offspring psychopathology? *Journal of Affective Disorders, 136*(1-2), 44-53. doi:10.1016/j.jad.2011.09.002

Marshall, E. J., & Farrell, M. (2004). Substance use and psychiatric comorbidity. *Psychiatry, 3*(1), 55-58. doi:https://doi.org/10.1383/psyt.3.1.55.30297

Marshall, S. W. (2007). Power for tests of interaction: Effect of raising the Type I error rate. *Epidemiologic Perspectives and Innovations, 4*, 4. doi:10.1186/1742-5573-4-4

Martins, S. S., & Gorelick, D. A. (2011). Conditional substance abuse and dependence by diagnosis of mood or anxiety disorder or schizophrenia in the U.S. population. *Drug and Alcohol Dependence, 119*(1-2), 28-36. doi:10.1016/j.drugalcdep.2011.05.010

Masserman, J. H., & Yum, K. S. (1946). An analysis of the influence of alcohol on experimental neuroses in cats. *Psychosomatic Medicine, 8*(1), 36-52. doi:10.1097/00006842-194601000-00004

McKenzie, M., Jorm, A. F., Romaniuk, H., Olsson, C. A., & Patton, G. C. (2011). Association of adolescent symptoms of depression and anxiety with alcohol use disorders in young adulthood: Findings from the Victorian Adolescent Health Cohort Study. *Medical Journal of Australia, 195*(3), S27-S30. doi:https://doi.org/10.1111/j.1360-0443.2010.03002.x

McLean, C. P., Asnaani, A., Litz, B. T., & Hofmann, S. G. (2011). Gender differences in anxiety disorders: prevalence, course of illness, comorbidity and burden of illness. *Journal of Psychiatric Research, 45*(8), 1027-1035. doi:10.1016/j.jpsychires.2011.03.006

McManus, S., Bebbington, P., Jenkins, R., & Brugha, T. (2016). *Mental health and wellbeing in England: Adult psychiatric morbidity survey 2014.* Retrieved from https://webarchive.nationalarchives.gov.uk/20180328140249/http://digital.nhs.uk/catalogue/PUB21748

McNally, R. J. (2002). Anxiety sensitivity and panic disorder. *Biological Psychiatry, 52*(10), 938-946. doi:https://doi.org/10.1016/S0006-3223(02)01475-0

Menary, K. R., Kushner, M. G., Maurer, E., & Thuras, P. (2011). The prevalence and clinical implications of self-medication among individuals with anxiety disorders. *Journal of Anxiety Disorders, 25*(3), 335-339. doi:10.1016/j.janxdis.2010.10.006

Meque, I., Dachew, B. A., Maravilla, J. C., Salom, C., & Alati, R. (2019). Externalizing and internalizing symptoms in childhood and adolescence and the risk of alcohol use disorders in young adulthood: A meta-analysis

of longitudinal studies. *Australian and New Zealand Journal of Psychiatry*. doi:https://doi.org/10.1177/0004867419844308

Merline, A., Jager, J., & Schulenberg, J. E. (2008). Adolescent risk factors for adult alcohol use and abuse: Stability and change of predictive value across early and middle adulthood. *Addiction, 103*, 84-99. doi:10.1111/j.1360-0443.2008.02178.x

Merrill, J. E., Wardell, J. D., & Read, J. P. (2014). Drinking motives in the prospective prediction of unique alcohol-related consequences in college students. *Journal of Studies on Alcohol and Drugs, 75*(1), 93-102. doi:10.15288/jsad.2014.75.93

Miettunen, J., Murray, G., Jones, P., Maki, P., Ebeling, H., Taanila, A., . . . Moilanen, I. (2014). Longitudinal associations between childhood and adulthood externalizing and internalizing psychopathology and adolescent substance use. *Psychological Medicine, 44*(8), 1727-1738. doi:10.1017/S0033291713002328

Miloyan, B., & Van Doorn, G. (2019). Longitudinal association between social anxiety disorder and incident alcohol use disorder: results from two national samples of US adults. *Social Psychiatry and Psychiatric Epidemiology, 54*(4), 469-475. doi:10.1007/s00127-018-1569-z

Minami, H., Frank, B. E., Bold, K. W., & McCarthy, D. E. (2017). Ecological momentary analysis of the relations among stressful events, affective reactivity, and smoking among smokers with high versus low depressive symptoms during a quit attempt. *Addiction*. doi:10.1111/add.13964 28779527

Moberg, C. A., & Curtin, J. J. (2009). Alcohol selectively reduces anxiety but not fear: Startle response during unpredictable versus predictable threat. *Journal of Abnormal Psychology, 118*(2), 335-347. doi:10.1037/a0015636

References

Mohlman, J., de Jesus, M., Gorenstein, E. E., Kleber, M., Gorman, J. M., & Papp, L. A. (2004). Distinguishing generalized anxiety disorder, panic disorder, and mixed anxiety states in older treatment-seeking adults. *Journal of Anxiety Disorders, 18*(3), 275-290. doi:10.1016/S0887-6185(02)00261-X

Mohr, C. D., Armeli, S., Tennen, H., Carney, M. A., Affleck, G., & Hromi, A. (2001). Daily interpersonal experiences, context, and alcohol consumption: Crying in your beer and toasting good times. *Journal of Personality and Social Psychology, 80*(3), 489-500. doi:10.1037//0022-3514.80.3.489

Monteiro, M. G., Schuckit, M. A., & Irwin, M. (1990). Subjective feelings of anxiety in young men after ethanol and diazepam infusions. *Journal of Clinical Psychiatry, 51*(1), 12-16.

Morris, E. P., Stewart, S. H., & Ham, L. S. (2005). The relationship between social anxiety disorder and alcohol use disorders: A critical review. *Clinical Psychology Review, 25*(6), 734-760. doi:10.1016/j.cpr.2005.05.004 16042994

Nehlin, C., Wennberg, M., & Oster, C. (2018). How do people with mood and anxiety disorders perceive and interpret the Drinking Motives Questionnaire? A think-aloud study in a clinical setting. *Addiction Science & Clinical Practice, 13*. doi:ARTN 7

10.1186/s13722-018-0109-1

Nelson, E. C., Grant, J. D., Bucholz, K. K., Glowinski, A., Madden, P. A. F., Reich, W., & Heath, A. C. (2000). Social phobia in a population-based female adolescent twin sample: co-morbidity and associated suicide-related symptoms. *Psychological Medicine, 30*(4), 797-804. doi:Doi 10.1017/S0033291799002275

References

NHS. (2019). Alcohol Support: Binge Drinking. Retrieved from https://www.nhs.uk/live-well/alcohol-support/binge-drinking-effects/

NHS digital. (2018). *Statistics on Alcohol*. Retrieved from https://files.digital.nhs.uk/60/B4D319/alc-eng-2018-rep.pdf

NICE. (2010). *Alcohol-use disorders: prevention*. Retrieved from https://www.nice.org.uk/guidance/ph24/chapter/2-Public-health-need-and-practice

NICE. (2011). In *Alcohol-Use Disorders: Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence*. Leicester (UK).

Nichter, B., & Chassin, L. (2015). Separate dimensions of anxiety differentially predict alcohol use among male juvenile offenders. *Addictive Behaviors, 50*, 144-148. doi:10.1016/j.addbeh.2015.06.031

NIH. (2019a). Alcohol Use Disorder. Retrieved from https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/alcohol-use-disorders

NIH. (2019b). Potential Threat ("Anxiety"). Retrieved from https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/constructs/potential-threat-anxiety.shtml

Nolen-Hoeksema, S. (2004). Gender differences in risk factors and consequences for alcohol use and problems. *Clinical Psychology Review, 24*(8), 981-1010. doi:10.1016/j.cpr.2004.08.003

O'Hara, R. E., Armeli, S., & Tennen, H. (2014). Drinking-to-cope motivation and negative mood-drinking contingencies in a daily diary study of college students. *Journal of Studies on Alcohol and Drugs, 75*(4), 606-614. doi:https://doi.org/10.15288/jsad.2014.75.606

Ohannessian, C. M. (2014). Anxiety and substance use during adolescence. *Substance Abuse, 35*(4), 418-425. doi:10.1080/08897077.2014.953663

Okbay, A., Baselmans, B. M. L., De Neve, J. E., Turley, P., Nivard, M. G., Fontana, M. A., . . . Study, L. C. (2016). Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. *Nature Genetics, 48*(12), 1591-1591. doi:10.1038/ng1216-1587b

Olgiati, P., Liappas, I., Malitas, P., Piperi, C., Politis, A., Tzavellas, E. O., . . . Serretti, A. (2007). Depression and social phobia secondary to alcohol dependence. *Neuropsychobiology, 56*(2-3), 111-118. doi:10.1159/000112952

Oliva, F., Nibbio, G., Vizzuso, P., Sodano, A. J., Ostacoli, L., Carletto, S., & Picci, R. L. (2018). Gender differences in anxiety and depression before and after alcohol detoxification: Anxiety and depression as gender-related predictors of relapse. *European Addiction Research, 24*(4), 163-172. doi:10.1159/000490046

Ollendick, T. H., & King, N. J. (1994). Diagnosis, assessment, and treatment of internalizing problems in children - the role of longitudinal data. *Journal of Consulting and Clinical Psychology, 62*(5), 918-927. doi:10.1037//0022-006x.62.5.918

Olthuis, J. V., Watt, M. C., Mackinnon, S. P., & Stewart, S. H. (2015). CBT for high anxiety sensitivity: Alcohol outcomes. *Addictive Behaviors, 46*, 19-24. doi:10.1016/j.addbeh.2015.02.018

Oscar-Berman, M., & Marinkovic, K. (2007). Alcohol: Effects on neurobehavioral functions and the brain. *Neuropsychology Review, 17*(3), 239-257. doi:10.1007/s11065-007-9038-6

Otowa, T., Hek, K., Lee, M., Byrne, E. M., Mirza, S. S., Nivard, M. G., . . . Hettema, J. M. (2016). Meta-analysis of genome-wide association studies of anxiety disorders. *Molecular Psychiatry, 21*(10), 1391-1399. doi:10.1038/mp.2015.197

Pagan, J. L., Rose, R. J., Viken, R. J., Pulkkinen, L., Kaprio, J., & Dick, D. M. (2006). Genetic and environmental influences on stages of alcohol use across adolescence and into young adulthood. *Behavior Genetics, 36*(4), 483-497. doi:10.1007/s10519-006-9062-y

Papachristou, H., Aresti, E., Theodorou, M., & Panayiotou, G. (2018). Alcohol outcome expectancies mediate the relationship between social anxiety and alcohol drinking in university students: The role of gender. *Cognitive Therapy and Research, 42*(3), 289-301. doi:10.1007/s10608-017-9879-0

Pardini, D., White, H. R., & Stouthamer-Loeber, M. (2007). Early adolescent psychopathology as a predictor of alcohol use disorders by young adulthood. *Drug and Alcohol Dependence, 88*(SUPPL.1), S38-S49. doi:10.1016/j.drugalcdep.2006.12.014

Parrish, K. H., Atherton, O. E., Quintana, A., Conger, R. D., & Robins, R. W. (2016). Reciprocal relations between internalizing symptoms and frequency of alcohol use: Findings from a longitudinal study of mexican-origin youth. *Psychology of Addictive Behaviors, 30*(2), 203-208. doi:10.1037/adb0000138

Pasche, S. (2012). Exploring the comorbidity of anxiety and substance use disorders. *Current Psychiatry Reports, 14*(3), 176-181. doi:10.1007/s11920-012-0264-0

Peacock, A., Leung, J., Larney, S., Colledge, S., Hickman, M., Rehm, J., . . . Degenhardt, L. (2018). Global statistics on alcohol, tobacco and illicit drug use: 2017 status report. *Addiction, 113*(10), 1905-1926. doi:10.1111/add.14234

Peeters, M., Monshouwer, K., van de Schoot, R., Janssen, T., Vollebergh, W. A., & Wiers, R. W. (2014). Personality and the prediction of high-risk trajectories of alcohol use during adolescence. *Journal of Studies on*

Alcohol and Drugs, 75(5), 790-798. doi:https://doi.org/10.15288/jsad.2014.75.790

Pitkanen, T., Kokko, K., Lyyra, A.-L., & Pulkkinen, L. (2008). A developmental approach to alcohol drinking behaviour in adulthood: A follow-up study from age 8 to age 42. *Addiction, 103*, 48-68. doi:10.1111/j.1360-0443.2008.02176.x

Possemato, K., Maisto, S. A., Wade, M., Barrie, K., McKenzie, S., Lantinga, L. J., & Ouimette, P. (2015). Ecological momentary assessment of PTSD symptoms and alcohol use in combat veterans. *Psychology of Addictive Behaviors, 29*(4), 894-905. doi:10.1037/adb0000129

Potter, C. M., Galbraith, T., Jensen, D., Morrison, A. S., & Heimberg, R. G. (2016). Social anxiety and vulnerability for problematic drinking in college students: the moderating role of post-event processing. *Cognitive Behaviour Therapy, 45*(5), 380-396. doi:10.1080/16506073.2016.1190982

Prescott, C. A., Cross, R. J., Kuhn, J. W., Horn, J. L., & Kendler, K. S. (2004). Is risk for alcoholism mediated by individual differences in drinking motivations? *Alcoholism-Clinical and Experimental Research, 28*(1), 29-39. doi:10.1097/01.Alc.0000106302.75766.F0

Prime Minister's Strategy Unit. (2004). *Alcohol Harm Reduction Strategy for England*. London Retrieved from http://www.ave.ee/download/Alcohol%20England.pdf

Prior, K., Mills, K., Ross, J., & Teesson, M. (2017). Substance use disorders comorbid with mood and anxiety disorders in the Australian general population. *Drug and Alcohol Review, 36*(3), 317-324. doi:10.1111/dar.12419

Public Health England. (2016). *The Public Health Burden of Alcohol and the Effectiveness and Cost-Effectiveness of Alcohol Control Policies: An evidence review*. London

Public Health England. (2019). *Health Matters: tobacco and alcohol CQUIN*. Retrieved from https://www.gov.uk/government/publications/health-matters-preventing-ill-health-from-alcohol-and-tobacco/health-matters-preventing-ill-health-from-alcohol-and-tobacco-use

Pulkkinen, L., & Pitkanen, T. (1994). A prospective study of the precursors to problem drinking in young adulthood. *Journal of Studies on Alcohol, 55*(5), 578-587. doi:https://doi.org/10.15288/jsa.1994.55.578

Ramchandani, V. A., Stangl, B. L., Blaine, S. K., Plawecki, M. H., Schwandt, M. L., Kwako, L. E., . . . Zakhari, S. (2018). Stress vulnerability and alcohol use and consequences: From human laboratory studies to clinical outcomes. *Alcohol*, 75-88. doi:10.1016/j.alcohol.2018.06.001 30322482

Raymond, J. G., Steele, J. D., & Series, P. (2017). Modeling trait anxiety: From computational processes to personality. *Frontiers in Psychiatry, 8*(1). doi:10.3389/fpsyt.2017.00001

Rehm, J. (2011). The Risks Associated With Alcohol Use and Alcoholism. *Alcohol Research & Health, 34*(2), 135-143.

Rehm, J., Baliunas, D., Borges, G. L. G., Graham, K., Irving, H., Kehoe, T., . . . Taylor, B. (2010). The relation between different dimensions of alcohol consumption and burden of disease: an overview. *Addiction, 105*(5), 817-843. doi:10.1111/j.1360-0443.2010.02899.x

Reynolds, C. R., & Kamphaus, R. W. (2013). DSM-5 Diagnostic Criteria Generalised Anxiety Disorder. Retrieved from https://images.pearsonclinical.com/images/assets/basc-3/basc3resources/DSM5_DiagnosticCriteria_GeneralizedAnxietyDisorder.pdf

Rousseau, G. S., Irons, J. G., & Correia, C. J. (2011). The reinforcing value of alcohol in a drinking to cope paradigm. *Drug and Alcohol Dependence, 118*(1), 1-4. doi:10.1016/j.drugalcdep.2011.02.010 21414732

Royston, P., & White, I. R. (2011). Multiple Imputation by Chained Equations (MICE): Implementation in Stata. *Journal of Statistical Software, 45*(4), 1-20. doi:10.18637/jss.v045.i04

Salom, C. L., Betts, K. S., Williams, G. M., Najman, J. M., Scott, J. G., & Alati, R. (2014). Do young people with comorbid mental and alcohol disorders experience worse behavioural problems? *Psychiatry Research, 219*(2), 372-379. doi:10.1016/j.psychres.2014.05.056

Savage, J. E., Kaprio, J., Korhonen, T., Pulkkinen, L., Rose, R. J., Verhulst, B., & Dick, D. M. (2016). The effects of social anxiety on alcohol and cigarette use across adolescence: Results from a longitudinal twin study in Finland. *Psychology of Addictive Behaviors, 30*(4), 462-474.

Sayette, M. A. (1993). An appraisal-disruption model of alcohol's effects on stress responses in social drinkers. *Psychol Bull, 114*(3), 459-476.

Scalco, M. D., Colder, C. R., Hawk, L. W., Read, J. P., Wieczorek, W. F., & Lengua, L. J. (2014). Internalizing and externalizing problem behavior and early adolescent substance use: A test of a latent variable interaction and conditional indirect effects. *Psychology of Addictive Behaviors, 28*(3), 828-840. doi:10.1037/a0035805

Scalzo, A. C., & Martinez, J. A. (2017). Not all anxiety is the same: How different "types" of anxiety uniquely associate with college students' drinking intentions. *Journal of College Student Development, 58*(6), 943-947. doi:10.1353/csd.2017.0073

Schmidt, N. B., Buckner, J. D., & Keough, M. E. (2007). Anxiety sensitivity as a prospective predictor of alcohol use disorders. *Behavior Modification, 31*(2), 202-219. doi:10.1177/0145445506297019

Schry, A. R., & White, S. W. (2013). Understanding the relationship between social anxiety and alcohol use in college students: A meta-analysis.

Addictive Behaviors, 38(11), 2690-2706. doi:10.1016/j.addbeh.2013.06.014

Schuckit, M. A., & Hesselbrock, V. (1994). Alcohol dependence and anxiety disorders: What is the relationship? *Am J Psychiatry, 151*(12), 1723-1734. doi:https://doi.org/10.1176/ajp.151.12.1723

Sharbanee, J. M., Hu, L., Stritzke, W. G. K., Wiers, R. W., Rinck, M., & MacLeod, C. (2014). The effect of approach/avoidance training on alcohol consumption is mediated by change in alcohol action tendency. *PLoS ONE, 9*(1). doi:10.1371/journal.pone.0085855

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., . . . Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59* 22-33.

Sher, K., & Levenson, R. (1982). Risk for alcoholism and individual differences in the stress–response-dampening effect of alcohol. *Journal of Abnormal Psychology, 91*, 350-367. doi:10.1037//0021-843x.91.5.350

Sher, K. J., & Grekin, E. R. (2015). Alcohol and Affect Regulation. In J. J. Gross (Ed.), Handbook of Emotion Regulation (Second ed.). New York: The Guilford Press.

Shiffman, S. (2009). Ecological momentary assessment (EMA) in studies of substance use. *Psychological Assessment, 21*(4), 486-497. doi:10.1037/a0017074

Sinha, R. (2001). How does stress increase risk of drug abuse and relapse? *Psychopharmacology, 158*(4), 343-359. doi:10.1007/s002130100917 11797055

Slavish, D. C., Scaglione, N. M., Hultgren, B. A., & Turrisi, R. (2019). An ecological momentary assessment of affect, mental health symptoms, and

decisions to drink among first-year college women: A pilot study. *Prevention Science, 20*(5), 753-764. doi:10.1007/s11121-018-0966-6

Smith, J. P., & Randall, C. L. (2012). Anxiety and alcohol use disorders: Comorbidity and treatment considerations. *Alcohol Research: Current Reviews, 34*(4), 414–431.

Spencer, E. A., Mahtani, K. R., & Brassey, J. (2018). Catalogue of Bias: Misclassification bias. Retrieved from https://catalogofbias.org/biases/misclassification-bias/

Spielberger, C. D., Gorsuch, R. L., Lushene, R., Vagg, P. R., & Jacobs, G. A. (1983). *Manual for the State-Trait Anxiety Inventory*. Palo Alto, California Consulting Psychologists Press.

Stanley, L. R., Miller, K. A., Beauvais, F., Walker, P. S., & Walker, R. (2014). Predicting an alcohol use disorder in urban American Indian youths. *Journal of Child & Adolescent Substance Abuse, 23*(2), 101-108. doi:https://doi.org/10.1080/1067828X.2012.748601

Stapinski, L. A., Edwards, A. C., Hickman, M., Araya, R., Teesson, M., Newton, N. C., . . . Heron, J. (2016). Drinking to cope: A latent class analysis of coping motives for alcohol use in a large cohort of adolescents. *Prevention Science, 17*(5), 584-594.

Steele, C. M., & Josephs, R. A. (1988). Drinking your troubles away. II: An attention-allocation model of alcohol's effect on psychological stress. *Journal of Abnormal Psychology, 97*(2), 196-205. doi:10.1037//0021-843x.97.2.196

Steele, R. G., Forehand, R., Armistead, L., & Brody, G. (1995). Predicting alcohol and drug use in early adulthood: The role of internalizing and externalizing behavior problems in early adolescence. *American Journal of Orthopsychiatry, 65*(3), 380-388. doi:10.1037/h0079694 7485423

Sterne, J. A., White, I. R., Carlin, J. B., Spratt, M., Royston, P., Kenward, M. G., . . . Carpenter, J. R. (2009). Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *Bmj, 338*, b2393. doi:10.1136/bmj.b2393

Stevens, S., Rist, F., & Gerlach, A. L. (2009). Influence of alcohol on the processing of emotional facial expressions in individuals with social phobia. *British Journal of Clinical Psychology, 48*, 125-140. doi:10.1348/014466508x368856

Stewart, S. H., & Devine, H. (2000). Relations between personality and drinking motives in young adults. *Personality and Individual Differences, 29*(3), 495-511. doi:10.1016/S0191-8869(99)00210-X

Stewart, S. H., & Kushner, M. G. (2001). Introduction to the Special Issue on "Anxiety Sensitivity and Addictive Behaviors". *Addictive Behaviors, 26*(6), 775-785. doi:https://doi.org/10.1016/S0306-4603(01)00236-2

Stewart, S. H., Morris, E., Mellings, T., & Komar, J. (2006). Relations of social anxiety variables to drinking motives, drinking quantity and frequency, and alcohol-related problems in undergraduates. *Journal of Mental Health, 15*(6), 671-682. doi:10.1080/09638230600998904

Stice, E., Barrera, M., Jr., & Chassin, L. (1998). Prospective differential prediction of adolescent alcohol use and problem use: Examining the mechanisms of effect. *Journal of Abnormal Psychology, 107*(4), 616-628. doi:10.1037//0021-843X.107.4.616

Strandheim, A., Bratberg, G. H., Holmen, T. L., Coombes, L., & Bentzen, N. (2011). The influence of behavioural and health problems on alcohol and drug use in late adolescence - a follow up study of 2 399 young Norwegians. *Child and Adolescent Psychiatry and Mental Health, 5*. doi:10.1186/1753-2000-5-17

Sun, L., Windle, M., & Thompson, N. J. (2015). An exploration of the four-factor structure of the drinking motives questionnaire-revised among undergraduate students in china. *Substance Use and Misuse, 50*(12), 1590-1598. doi:10.3109/10826084.2015.1027924

Sung, J., Lee, K., Song, Y.-M., & Kim, J.-H. (2011). Relationships between state and trait anxiety inventory and alcohol use disorder identification test scores among Korean twins and families: The Healthy Twin Study. *Twin Research and Human Genetics, 14*(1), 73-78. doi:10.1375/twin.14.1.73 21314258

Swendsen, J. D., Tennen, H., Carney, M. A., Affleck, G., Willard, A., & Hromi, A. (2000). Mood and alcohol consumption: An experience sampling test of the self-medication hypothesis. *Journal of Abnormal Psychology, 109*(2), 198-204. doi:10.1037//0021-843X.109.2.198

Swift, R., & Davidson, D. (1998). Alcohol hangover - Mechanisms and mediators. *Alcohol Health & Research World, 22*(1), 54-60.

Swift, W., Slade, T., Carragher, N., Coffey, C., Degenhardt, L., Hall, W., & Patton, G. (2016). 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. *Journal of Studies on Alcohol and Drugs, 77*(5), 757-765. doi:10.15288/jsad.2016.77.757

Taugher, R. J., Lu, Y., Wang, Y. M., Kreple, C. J., Ghobbeh, A., Fan, R., . . . Wemmie, J. A. (2014). The bed nucleus of the stria terminalis is critical for anxiety-related behavior evoked by CO2 and acidosis. *Journal of Neuroscience, 34*(31), 10247-10255. doi:10.1523/Jneurosci.1680-14.2014

Thayer, R. E. (2001). *Calm energy: How people regulate mood with food and exercise*. Oxford: Oxford University Press.

The Cochrane Collaboration. (2011). *Cochrane Handbook for Systematic Reviews of Interventions* In J. P. T. Higgins & S. Green (Eds.). Retrieved

from https://handbook-5-1.cochrane.org/chapter_5/5_6_defining_the_scope_of_a_review_question_broad_versus.htm

The Department of Health. (2003). *Comorbid Mental Disorders and Substance Use Disorders: Epidemiology, Prevention and Treatment*. Australia Retrieved from http://www.health.gov.au/internet/publications/publishing.nsf/Content/drugtreat-pubs-comorbid-toc~drugtreat-pubs-comorbid-4~drugtreat-pubs-comorbid-4-3

Thomas, S., Bacon, A. K., Sinha, R., Uhart, M., & Adinoff, B. (2012). Clinical laboratory stressors used to study alcohol-stress relationships. *Alcohol Research-Current Reviews, 34*(4), 459-467.

Thomas, S. E., Randall, C. L., & Carrigan, M. H. (2003). Drinking to cope in socially anxious individuals: A controlled study. *Alcoholism-Clinical and Experimental Research, 27*(12), 1937-1943. doi:10.1097/01.Alc.0000100942.30743.8c

Thompson, K. D., Leadbeater, B. J., & Ames, M. E. (2015). Reciprocal effects of internalizing and oppositional defiance symptoms on heavy drinking and alcohol-related harms in young adulthood. *Substance Abuse: Research and Treatment, 9*, 21-31. doi:10.4137/SART.S33928

Todd, M., Tennen, H., Carney, M. A., Armeli, S., & Affleck, G. (2004). Do we know how we cope? Relating daily coping reports to global and time-limited retrospective assessments. *Journal of Personality and Social Psychology, 86*(2), 310-319. doi:10.1037/0022-3514.86.2.310 14769086

Torvik, F. A., Rosenstrom, T. H., Gustavson, K., Ystrom, E., Kendler, K. S., Bramness, J. G., . . . Reichborn-Kjennerud, T. (2019). Explaining the association between anxiety disorders and alcohol use disorder: A twin study. *Depression and Anxiety, 36*(6), 522-532. doi:10.1002/da.22886

References

Turner, S., Mota, N., Bolton, J., & Sareen, J. (2018). Self-medication with alcohol or drugs for mood and anxiety disorders: A narrative review of the epidemiological literature. *Depression and Anxiety, 35*(9), 851-860. doi:10.1002/da.22771

UCLA: Statistical Consulting Group. (2019). Ordered logistic regression: Stata data analysis examples. Retrieved from https://stats.idre.ucla.edu/stata/dae/ordered-logistic-regression/

Verburg, K., Pols, H., de Leeuw, M., & Griez, E. (1998). Reliability of the 35% carbon dioxide panic provocation challenge. *Psychiatry Research, 78*(3), 207-214. doi:10.1016/S0165-1781(98)00009-2

Villarosa-Hurlocker, M. C., Bravo, A. J., Pearson, M. R., & Team, P. S. S. (2019). The relationship between social anxiety and alcohol and marijuana use outcomes among concurrent users: A motivational model of substance use. *Alcoholism-Clinical and Experimental Research, 43*(4), 732-740. doi:10.1111/acer.13966

Villarosa-Hurlocker, M. C., Whitley, R. B., Capron, D. W., & Madson, M. B. (2018). Thinking while drinking: Fear of negative evaluation predicts drinking behaviors of students with social anxiety. *Addictive Behaviors, 78*, 160-165. doi:10.1016/j.addbeh.2017.10.021

Virtanen, P., Nummi, T., Lintonen, T., Westerlund, H., Hagglof, B., & Hammarstrom, A. (2015). Mental health in adolescence as determinant of alcohol consumption trajectories in the Northern Swedish Cohort. *International Journal of Public Health, 63*(3), 335-342. doi:10.1007/s00038-015-0651-5

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect - the Panas Scales. *Journal of Personality and Social Psychology, 54*(6), 1063-1070. doi:10.1037//0022-3514.54.6.1063

Weekes, J. C., Cotton, S., & McGrady, M. E. (2011). Predictors of substance use among black urban adolescents with asthma: A longitudinal assessment. *Journal of the National Medical Association, 103*(5), 392-398. doi:10.1016/s0027-9684(15)30335-7

Wells, G. A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2019). The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Retrieved from http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

White, I. R., Royston, P., & Wood, A. M. (2011). Multiple imputation using chained equations: Issues and guidance for practice. *Statistics in Medicine, 30*(4), 377-399. doi:10.1002/sim.4067

Whiteford, H. A., Degenhardt, L., Rehm, J., Baxter, A. J., Ferrari, A. J., Erskine, H. E., . . . Vos, T. (2013). Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet, 382*(9904), 1575-1586. doi:10.1016/S0140-6736(13)61611-6

Whiteford, H. A., Ferrari, A. J., Degenhardt, L., Feigin, V., & Vos, T. (2015). The global burden of mental, neurological and substance use disorders: An analysis from the Global Burden of Disease Study 2010. *PLoS ONE, 10*(2). doi:10.1371/journal.pone.0116820

WHO. (2018). *Global status report on alcohol and health 2018*. Retrieved from https://www.who.int/substance_abuse/publications/global_alcohol_report/en/

Wiers, R. W., Rinck, M., Dictus, M., & Van den Wildenberg, E. (2009). Relatively strong automatic appetitive action-tendencies in male carriers of the OPRM1 G-allele. *Genes Brain and Behavior, 8*(1), 101-106. doi:10.1111/j.1601-183X.2008.00454.x

Wiers, R. W., Rinck, M., Kordts, R., Houben, K., & Strack, F. (2010). Retraining automatic action-tendencies to approach alcohol in hazardous drinkers. *Addiction, 105*(2), 279-287. doi:10.1111/j.1360-0443.2009.02775.x

Wolitzky-Taylor, K., Bobova, L., Zinbarg, R. E., Mineka, S., & Craske, M. G. (2012). Longitudinal investigation of the impact of anxiety and mood disorders in adolescence on subsequent substance use disorder onset and vice versa. *Addictive Behaviors, 37*(8), 982-985. doi:10.1016/j.addbeh.2012.03.026

Wolitzky-Taylor, K., Drazdowski, T. K., Niles, A., Roy-Byrne, P., Ries, R., Rawson, R., & Craske, M. G. (2018). Change in anxiety sensitivity and substance use coping motives as putative mediators of treatment efficacy among substance users. *Behaviour Research and Therapy, 107*, 34-41. doi:10.1016/j.brat.2018.05.010

Wolke, D., Waylen, A., Samara, M., Steer, C., Goodman, R., Ford, T., & Lamberts, K. (2009). Selective drop-out in longitudinal studies and non-biased prediction of behaviour disorders. *British Journal of Psychiatry, 195*(3), 249-256. doi:10.1192/bjp.bp.108.053751

Woods, A. T., Velasco, C., Levitan, C. A., Wan, X., & Spence, C. (2015). Conducting perception research over the internet: a tutorial review. *PeerJ, 3*, e1058. doi:10.7717/peerj.1058

Woodward, L. J., & Fergusson, D. M. (2001). Life course outcomes of young people with anxiety disorders in adolescence. *Journal of the American Academy of Child & Adolescent Psychiatry, 40*(9), 1086-1093. doi:10.1097/00004583-200109000-00018

World Health Organisation. (2001). *The Alcohol Use Disorders Identification Test, Guidelines for Use in Primary Care*. In T. Babor, J. Higgins-Biddle, J. Saunders, & M. Monteiro (Eds.). Retrieved from https://apps.who.int/iris/handle/10665/67205

Zhou, H., Polimanti, R., Yang, B. Z., Wang, Q., Han, S. Z., Sherva, R., . . . Gelemter, J. (2017). Genetic risk variants associated with comorbid alcohol dependence and major depression. *Jama Psychiatry, 74*(12), 1234-1241. doi:10.1001/jamapsychiatry.2017.3275

Ziemann, A. E., Allen, J. E., Dahdaleh, N. S., Drebot, I. I., Coryell, M. W., Wunsch, A. M., . . . Wemmie, J. A. (2009). The amygdala is a chemosensor that detects carbon dioxide and acidosis to elicit fear behavior. *Cell, 139*(5), 1012-1021. doi:10.1016/j.cell.2009.10.029

Zimmermann, P., Wittchen, H. U., Hofler, M., Pfister, H., Kessler, R. C., & Lieb, R. (2003). Primary anxiety disorders and the development of subsequent alcohol use disorders: A 4-year community study of adolescents and young adults. *Psychological Medicine, 33*(7), 1211-1222. doi:10.1017/s0033291703008158

Appendices

Appendix 2.1. Excluded full-text articles with reasons.

First Author	Year	Title	Reason for Exclusion
Gerbino	2017	Protective and risk factors of alcohol and drug abuse in adolescence	Not English language
Hinckers	2005	Alcohol consumption in adolescence - social and individual influential factors	Not English language
Andréasson	1992	Antecedents and covariates of high alcohol consumption in young men	Cross-sectional / follow-up < 6 months
Birrell	2005	Anxiety disorders and first alcohol use in the general population. Findings from a nationally representative sample	Cross-sectional / follow-up < 6 months
Donbaek	2014	Post-traumatic stress disorder symptom clusters predicting substance abuse in adolescents	Cross-sectional / follow-up < 6 months
Goldstein	2012	Coping motives as moderators of the relationship between emotional distress and alcohol problems in a sample of adolescents involved with child welfare	Cross-sectional / follow-up < 6 months
Goodwin	2004	Association between anxiety disorders and substance use disorders among young persons: Results of a 21-year longitudinal study	Cross-sectional / follow-up < 6 months
Sartor	2007	The role of childhood risk factors in initiation of alcohol use and progression to alcohol dependence	Cross-sectional / follow-up < 6 months
Delfabbro	2016	Mid-adolescent predictors of adult drinking levels in early adulthood and gender differences: Longitudinal analyses based on the South Australian School Leavers Study	No anxiety exposure
Edwards	2016	A prospective longitudinal model predicting early adult alcohol problems: evidence for a robust externalizing pathway	No anxiety exposure
Buckner	2009	Understanding social anxiety as a risk for alcohol use disorders: Fear of scrutiny, not social interaction fears, prospectively predicts alcohol use disorders	Anxiety not in childhood/adolescence
Buckner	2009	Social anxiety disorder as a risk factor for alcohol use disorders: A prospective examination of parental and peer influences	Anxiety not in childhood/adolescence
Cheng	2013	Correlates of adult binge drinking: Evidence from a British cohort	Anxiety not in childhood/adolescence
Haller	2014	Risk pathways among traumatic stress, posttraumatic stress disorder symptoms, and alcohol and drug problems: A test of four hypotheses	Anxiety not in childhood/adolescence

Swendsen	2010	Mental disorders as risk factors for substance use, abuse and dependence: Results from the 10-year follow-up of the National Comorbidity Survey	Anxiety not in childhood/adolescence
Zatzick	2002	Posttraumatic stress, problem drinking, and functional outcomes after injury	Anxiety not in childhood/adolescence
Wu	2010	Trauma, posttraumatic stress symptoms, and alcohol-use initiation in children	PTSD exposure
Cisler	2011	PTSD symptoms, potentially traumatic event exposure, and binge drinking: A prospective study with a national sample of adolescents	PTSD exposure
Goldstein	2011	The relationship between post-traumatic stress symptoms and substance use among adolescents involved with child welfare: Implications for emerging adulthood	PTSD exposure
Alamian	2012	Individual and social determinants of multiple chronic disease behavioral risk factors among youth	No alcohol outcome
Bardone	1998	Adult physical health outcomes of adolescent girls with conduct disorder, depression, and anxiety	No alcohol outcome
Barnea	1992	Personality, cognitive, and interpersonal factors in adolescent substance use: A longitudinal test of an integrative model	No alcohol outcome
Brook	2012	Individuality and contextual Influences on drug dependence: A 15-year prospective longitudinal study of adolescents from Harlem	No alcohol outcome
Lewinsohn	2008	Separation anxiety disorder in childhood as a risk factor for future mental illness	No alcohol outcome
Lillehoj	2004	Internalizing, social competence, and substance initiation: influence of gender moderation and a preventive intervention	No alcohol outcome
Loeber	1999	Developmental aspects of delinquency and internalizing problems and their association with persistent juvenile substance use between ages 7 and 18	No alcohol outcome
Siebenbruner	2006	Developmental antecedents of late adolescence substance use patterns	No alcohol outcome
Sung	2004	Effects of age at first substance use and psychiatric comorbidity on the development of substance use disorders	No alcohol outcome
Teichman	1989	Personality and substance use among adolescents: A longitudinal study	No alcohol outcome
Zehe	2013	Social and generalized anxiety symptoms and alcohol and cigarette use in early adolescence: The moderating role of perceived peer norms	No alcohol outcome
Cerdá	2013	Cumulative and recent psychiatric symptoms as predictors of substance use onset: Does timing matter?	Alcohol initiation was only outcome
Donovan	2011	Childhood risk factors for early-onset drinking	Alcohol initiation was only outcome
Fite	2006	Childhood behavior problems and peer selection and socialization: Risk for adolescent alcohol use	Alcohol initiation was only outcome

Geels	2013	Developmental prediction model for early alcohol initiation in Dutch adolescents	Alcohol initiation was only outcome
Kaplow	2001	The prospective relation between dimensions of anxiety and the initiation of adolescent alcohol use	Alcohol initiation was only outcome
McCarty	2012	Emotional health predictors of substance use initiation during middle school	Alcohol initiation was only outcome
Farmer	2013	Aggregation of lifetime Axis I psychiatric disorders through age 30: Incidence, predictors, and associated psychosocial outcomes	No association between anxiety and alcohol use
Skeer	2009	A prospective study of familial conflict, psychological stress, and the development of substance use disorders in adolescence	No association between anxiety and alcohol use
Costello	1999	Development of psychiatric comorbidity with substance abuse in adolescents: Effects of timing and sex	Concurrent or retrospective analyses, despite prospective data
Black	2015	Course of alcohol symptoms and social anxiety disorder from adolescence to young adulthood	Concurrent or retrospective analyses, despite prospective data
Colder	2017	Internalizing and externalizing problem behavior: A test of a latent variable interaction predicting a two-part growth model of adolescent substance use	Concurrent or retrospective analyses, despite prospective data
Pape	2016	Associations between emotional distress and heavy drinking among young people: A longitudinal study	Concurrent or retrospective analyses, despite prospective data
Stice	1998	A longitudinal grouping analysis of adolescent substance use escalation and de-escalation	Concurrent or retrospective analyses, despite prospective data
Wennberg	2002	Psychosocial characteristics at age 10; differentiating between adult alcohol use pathways: A prospective longitudinal study	Concurrent or retrospective analyses, despite prospective data

Appendix 2.2. Characteristics of included studies (complete data extraction).

Study	Sample and Country	% Male	Anxiety Type (Measure) Age Respondent	Alcohol Use Type (Measure) Age Respondent	Follow-Up Time	Analysis Method and Results Summary	Confounders	Sample Size	Count Result (Y/N)	Evidence (N/WN/E/WP/P/U)
(Abram et al., 2015)	Youth at a juvenile detention centre, USA	64	Generalised anxiety disorder (GAD) (DISC-2.3) 10-19 (median 15) Self-report	Alcohol use disorder (AUD) (DISC-IV) 15-25 (median 20) Self-report	5 years	***Logistic regression:*** GAD → AUD OR [95% CI]: Males 1.0 [0.2 to 5.0], p > .05 OR [95% CI]: Females 0.7 [0.1 to 5.6], p > .05	Baseline AUD	1504 (960 M, 544 F)	Y Y	E E
(Asselmann et al., 2014b)	Early Developmental Stages of Psychopathology Study, Germany	33	Panic attacks (DSM-IV-TR M-CIDI) 14-24 (median 19) Self-report	Alcohol use disorder (DIA-X/M-CIDI) 21-34 Self-report	10 years	***Logistic regression:*** Panic attacks → AUD OR [95% CI]: 2.40 [1.12 to 5.16], p = .025	Sex, age, and agoraphobia, GAD, social phobia, major depressive disorder, dysthymia, substance use disorder at T1	122	Y	P
(Behrendt et al., 2011)	Early Developmental Stages of Psychopathology Study, Germany	51	Specific phobias (DIA-X/M-CIDI) 14-24 Self-report	Alcohol use, alcohol abuse, alcohol dependence (DIA-X/M-CIDI)	10 years	***Cox regression:*** Specific phobia → alcohol abuse HR [95% CI]: 1.07 [0.8 to 1.4], p = .574 Specific phobia → alcohol dependence HR [95% CI]: 1.62 [1.1 to 2.3], p = .007 Social phobia → alcohol abuse HR [95% CI]: 1.26 [0.8 to 1.8], p = .187	Age, gender, any mood disorder, non-alcohol substance use disorders (SUD)	2929	N Y N	P

				1.6, 3.5, and 8.2 years later Self-report		Social phobia → alcohol dependence HR [95% CI]: 1.39 [0.8 to 2.2], p = .155 Panic attacks → alcohol abuse HR [95% CI]: 1.34 [0.9 to 1.9], p = .084 Panic attacks → alcohol dependence HR [95% CI]: 1.35 [0.8 to 2.1], p = .158 Any anxiety disorder → alcohol abuse HR [95% CI]: 1.07 [0.8 to 1.3], p = .472 Any anxiety disorder → alcohol dependence HR [95% CI]: 1.59 [1.1 to 2.2], p = .003	(nicotine, cannabis, other illegal drugs), externalising disorders		Y N Y N Y	WP WP P
(Bruckl et al., 2007)	Early Developmental Stages of Psychopathology Study, Germany	49	Separation anxiety disorder (SAD): subthreshold, threshold (M-CIDI) 14-17 Self-report	Alcohol abuse, alcohol dependence (M-CIDI) 20 and 42 months later Self-report	20 months; 42 months	***Cox regression:*** Threshold SAD (vs. no) → alcohol abuse HR [95% CI]: 0.5 [0.0 to 2.8], no p value Threshold SAD (vs. no) → alcohol dependence HR [95% CI]: 4.7 [1.7 to 12.4], no p value Subthreshold SAD (vs. no) → alcohol abuse HR [95% CI]: 0.9 [0.5 to 1.6], no p value Subthreshold SAD (vs. no) → alcohol dependence HR [95% CI]: 2.1 [1.1 to 4.1], no p value ***Logistic regression:*** SAD → alcohol dependence OR [95% CI]: 3.3 [1.06 to 10.2], no p value	Age and sex	1090	N N N N Y	P
(Buckner et al., 2008)	Oregon Adolescent Depression Project, USA	41	Social anxiety, generalised anxiety, separation anxiety, panic disorder, obsessive-compulsive disorder (OCD), overanxious disorder, specific phobia (K-SADS, K-SADS-P) 16 Self-report	Alcohol abuse, alcohol dependence (LIFE, SCID-4) 30 Self-report	14 years	***Logistic regression:*** OCD → alcohol abuse OR [95% CI]: 2.44 [0.41 to 14.72], p > .05 OCD → alcohol dependence OR [95% CI]: 5.18 [0.86 to 31.26], p > .05 Over-anxious disorder → alcohol abuse OR [95% CI]: 0.28 [0.04 to 2.12], p > .05 Over-anxious disorder → alcohol dependence OR [95% CI]: 1.37 [0.43 to 4.43], p > .05 Specific phobia → alcohol abuse OR [95% CI]: 0.78 [0.22 to 2.73], p > .05 Specific phobia → alcohol dependence OR [95% CI]: 1.89 [0.69 to 5.18], p > .05 Separation anxiety disorder → alcohol abuse OR [95% CI]: 0.56 [0.23 to 1.35], p > .05 Separation anxiety disorder →alcohol dependence OR [95% CI]: 0.87 [0.41 to 1.85], p > .05 Social anxiety disorder → alcohol abuse OR [95% CI]: 0.48 [.11 to 2.11], p > .05 Social anxiety disorder → alcohol dependence	Gender	816	N Y N Y N Y N Y N	WP E WP E

						OR [95% CI]: 3.98 [1.51 to 10.47], p < .01 Panic disorder → alcohol abuse OR [95% CI]: 0.52 [0.06 to 4.23], p > .05 Panic disorder → alcohol dependence OR [95% CI]: 5.82 [1.38 to 24.57], p < .05 ***Hierarchical logistic regression:*** Social anxiety disorder → alcohol dependence OR [95% CI]: 4.47 [1.48 to 13.45], p <.01 Panic disorder → alcohol dependence OR [95% CI]: 2.36 [0.25 to 21.96], p > .05	T1 AUD, mood disorder, conduct disorder, gender		Y N Y N N	P P
(Cerda et al., 2016)	Pittsburgh Youth Study, USA	100	Anxiety problems (CBCL, TRF, YSR, YASR) 13-19 (annual or semi-annual) Caregiver-, teacher-, self-report	Alcohol frequency, alcohol quantity (Substance Use Scale from NYS) 13–19 (semi-annual) Self-report	6 years	***Quasi-Poisson models:*** Changes in anxiety → changes in frequency Rate ratio [95% CI]: 0.98 [0.95 to 1.02], no p value Changes in anxiety → changes in quantity Rate ratio [95% CI]: 0.99 [0.97 to 1.00], no p value	Frequency model: age, prior marijuana frequency and alcohol quantity. Quantity model: additionally, conduct problems, peer delinquency, and frequency (instead of quantity)	487	Y N	WN
(Cheng et al., 2004)	Taiwan Aboriginal Study Project, Taiwan	30	Anxiety disorders (Chinese CIS) 15-24 Self-report	Time to onset of alcoholism (Chinese CIS) 4 years later Self-report	4 years	***Cox proportional hazards regression:*** Anxiety disorders → alcoholism Relative risk [95% CI]: 0.65 [0.20 to 2.10], p = .47	None/no information	164	Y	E
(Colder et al., 2013)	From a longitudinal study of adolescent substance use, USA	45	Internalising problems (YSR) 11-13 Self-report	Alcohol use (NYS) 12-16 Self-report	3 years	***Structural equation model:*** Internalising symptoms → alcohol use Beta (standardised) = − 0.09, p >.10	Gender and age	367	Y	E

(Dahne et al., 2014)	From a longitudinal study of HIV-related risk behaviours, USA	56	Social phobia (SP) (RCADS) 11, 12, 13, 14, 15 Self-report	Alcohol use (modified version of YRBSS) 11, 12, 13, 14, 15 Self-report	1-4 years	***Generalized estimating equations (GEEs):*** Social phobia baseline → alcohol consumption OR [95% CI]: 1.06 [1.00 to 1.12], p = .051 Social phobia prior year → alcohol consumption OR [95% CI]: 1.06 [1.01 to 1.11], p = .03	Baseline age, gender, MDD symptoms, linear effect of time, interaction between baseline SP symptoms and time, interaction between MDD symptoms and time	277	N Y	P
(Edwards et al., 2014)	Avon Longitudinal Study of Parents and Children, UK	51	Internalising symptom trajectories (SDQ) 3, 6, 8, 9, 11 Maternal report	Whole drink, drank without parental permission, ever binge, number of whole drinks in past 6 months 13 Self-report	Trajectories (max 8 years)	***Growth mixture modelling:*** Internalising symptoms → number of drinks Standardised parameter estimates [95% CI]: Persistently high class (vs. stable low) −.92 [−1.04 to −.80], p < .01 Mid-childhood increase class (vs. stable low) −.66 [−1.01 to −.31], p < .01 High to low class (vs. stable low) −.78 [−1.07 to −.48], p < .01 Low to high class (vs. stable low) 1.04 [−.42 to 0.63], p = .70 Internalising symptoms → ever binge drinking Low to high (vs. stable low) OR [95% CI]: .75 [.58 to .99], p = .04 Mid-childhood increase (vs. stable low) OR [95% CI]: .72 [.57 to .91], p = < .01 Persistently high (vs. stable low) OR [95% CI]: .94 [.65 to 1.35], p = .72 High to low (vs. stable low) OR [95% CI]: .88 [.68 to 1.15], p = .36 Internalising → whole drink past 6 months Persistently high OR [95% CI]: .83 [.61 to 1.12], p = .22 Low to high OR [95% CI]: .83 [.67 to 1.02], p = .08 Mid childhood increase OR [95% CI]: .87 [.73 to 1.04], p = .12 High to low	Sex, maternal depression, income, and correlations among predictive variables	11157	Y N N N N N Y N N N N	N E

						OR [95% CI]: .77 [.62 to .95], p = .02 Internalising → drank without permission Persistently high OR [95% CI]: .87 [.61 to 1.24], p = .44 Low to high OR [95% CI]: .86 [.67 to 1.09], p = .21 Mid-childhood increase OR [95% CI]: 1.04 [.85 to 1.27], p = .71 High to low OR [95% CI]: .75 [.58 to .97], p = .03			N N N N N	
(Englund et al., 2008)	Minnesota Longitudinal Study of Parents and Children, USA	53	Internalising behaviour (TRF of Child Behavior Checklist) 9 Teacher-report	Abstainers, moderate drinkers, heavy drinkers, and alcohol use disorder (Adult Health Survey) 19, 23, 26, 28 Self-report	10-19 years	***Multinomial logistic regression:*** M: Internalising → abstainers vs. heavy users (19) OR [95% CI]: 1.05 [0.98 to 1.14], p > .05 M: Internalising → moderate vs. heavy users (19) OR [95% CI]: 1.05 [0.99 to 1.12], p > .05 M: Internalising → abstainers vs. heavy users (23) OR [95% CI]: 1.00 [0.87 to 1.14], p > .05 M: Internalising → moderate vs. heavy users (23) OR [95% CI]: 0.97 [0.91 to 1.03], p > .05 M: Internalising → abstainers vs. heavy users (26) OR [95% CI]: 0.99 [0.90 to 1.10], p > .05 M: Internalising → moderate vs. heavy users (28) OR [95% CI]: 1.01 [0.95 to 1.07], p > .05 F: Internalising → abstainers vs. heavy users (19) OR [95% CI]: 0.95 [0.87 to 1.04], p > .05 F: Internalising → moderate vs. heavy users (19) OR [95% CI]: 0.99 [0.93 to 1.05], p > .05 F: Internalising→ abstainers vs. heavy users (23) OR [95% CI]: 0.82 [0.67 to 1.01], p > .05 F: Internalising → moderate vs. heavy users (23) OR [95% CI]: 0.97 [0.92 to 1.04], p > .05 F: Internalising → abstainers vs. heavy users (26) OR [95% CI]: 0.99 [0.91 to 1.09], p > .05 F: Internalising → moderate vs. heavy users (28) OR [95% CI]: 1.00 [0.93 to 1.07], p > .05	No information	158-170	 N N N N Y N N N N N Y N	 E E
(Englund & Siebenbruner, 2012)	Minnesota Longitudinal Study of Parents and Children, USA	55	Internalising symptoms (TRF, YSR) 7, 9, 12, 16	Frequency and quantity of alcohol use (Adolescent Health Survey) 16	9 years max	***Path models from developmental cascade modelling:*** Internalising symptoms → alcohol use Unstandardised parameter estimates [95% CI] .01 [−.03 to .04], p > .05 Internalising symptoms → level of use [95% CI] −.01 [−.03 to .00] p > .05	Gender, socioeconomic status, mother's age at child's birth, child's minority status	191	 N Y	 E

			Teacher-report, self-report	Self-report						
(Essau et al., 2014)	Oregon Adolescent Depression Project, USA	41	Anxiety disorders (K-SADS, LIFE, SCID) Assessed 16, 17, 24, 30. Childhood (before 11), adolescent (after 11) Self-report	Alcohol use disorder (K-SADS, LIFE, SCID) 24, 30 Self-report	14-19 years	***Binomial distribution with logit link function:*** Childhood anxiety → alcohol use disorder OR [95% CI]: 0.93 [0.74 to 1.16], p > .0025 Adolescent anxiety → alcohol use disorder OR [95% CI]: 1.29 [1.15 to 1.43], p < .0025	Gender, MDD, AUD, SUD, and disruptive disorder before age 19	816	N Y	P
(Farmer et al., 2016)	Oregon Adolescent Depression Project, USA	38 (No AUD); 55 (AUD)	Anxiety disorders (AD) (K-SADS, LIFE, SCID-NP) Assessed 16, 17, 24, 30. Childhood (8-12), early-to-middle adolescence (13-17), late adolescence (18-20), early adulthood (21-30) Self-report	Alcohol use disorder (DSM III-R, DSM-IV, K-SADS, LIFE, SCID-NP) Assessed 16, 17, 24, 30. Childhood (8-12), early-to-middle adolescence (13-17), late adolescence (18-20), early adulthood (21-30) Self-report	14 years	***Cox proportional hazard modelling*** AD in childhood → early-to-middle adolescent AUD HR [95% CI]: 1.38 [0.67 to 2.87], p > .05 AD in early-to-middle adolescence → late adolescent AUD HR [95% CI]: 1.53 [0.72 to 3.22], p > .05 AD in childhood → late adolescent AUD onset HR [95% CI]: 1.58 [0.70 to 3.55], p > .05 AD in late adolescence → early adult AUD onset HR [95% CI]: 0.88 [0.43 to 1.82], p > .05 AD in early-to-middle adolescence → early adult AUD onset HR [95% CI]: 1.71 [0.93 to 3.15], p > .05 AD in childhood → early adult AUD onset HR [95% CI]: 1.15 [0.58 to 2.25], p > .05	Gender, race/ethnicity, puberty onset, repeating a grade before age 12, at T1: dual vs. single parent household, at least one parent completed college, mean age of heads of household; number of older siblings, externalising disorders	641	N N N Y N N	E
(Fröjd et al., 2011)	Adolescent Mental Health Cohort Study, Finland	44	General anxiety (1 item), social phobia (SPIN) 15-16 Self-report	Frequent alcohol use, frequent drunkenness 17-18 Self-report	2 years	***Logistic regression:*** General anxiety → frequent alcohol use IOR [95% CI]: 2.4 [1.2 to 4.8] Social phobia → frequent alcohol use IOR [95% CI]: 0.5 [0.3 to 0.8] General anxiety → frequent drunkenness IOR [95% CI]: 1.5 [0.6 to 3.9] Social phobia → frequent drunkenness IOR [95% CI]: 0.3 [0.1 to 0.8]	Sex, family structure, parental education, depression	2070	Y Y Y Y	P N WP N

(Goodman, 2010)	The British Child and Adolescent Mental Health Surveys, UK	52	Internalising symptoms (SDQ, DAWBA), internalising disorder (clinical diagnosis) 11-12, 13-14, 15-16 Clinician-, parent-, teacher-report	Frequent alcohol consumption (different item for each group) 3 years later Self-report	3 years	***Logistic regression:*** Internalising (SDQ) → frequent consumption OR [95% CI]: 0.96 [0.91 to 1.02], p > .05 Internalising (DAWBA) → frequent consumption OR [95% CI]: 0.93 [0.75 to 1.16], p > .05 Internalising disorder → frequent consumption OR [95% CI]: 1.01 [0.52 to 1.95], p > .05	Gender, age, baseline substance use, smoking, alcohol use, cannabis use and other illicit drug use, survey year, country, ethnic group, parent education, housing tenure, family type	3607	N N Y	E
(Goodwin et al., 2004)	Early Developmental Stages of Psychopathology Study, Germany	No info	Panic attacks (M-CIDI) 14-24 Self-report	Alcohol use disorder (M-CIDI) 14-25 and 34-50 months later Self-report	14-25 months; 34-50 months	***Multiple logistic regression:*** Panic attacks → alcohol use disorder OR [95% CI]: 2.4 [1.2 to 5.1], p < .05	Age, gender, and other mental disorders	2548	Y	P
(Gorka et al., 2014)	Oregon Adolescent Depression Project, USA	44 (no anxiety); 30 (anxiety)	Anxiety disorders (K-SADS) 16 Self-report	Alcohol use disorder (K-SADS, LIFE) 16, 17, 24, 30 Self-report	1-14 years	***Cox proportional hazards models:*** Anxiety disorders → time to develop an AUD HR [95% CI]: 1.07 [0.87 to 1.33], p = .51 (maternal support) HR [95% CI]: 1.13 [0.89 to 1.44], p = .30 (paternal support)	Gender, parental education, number in household, whether biological parent, birth order, lifetime MDD or externalising disorder, coping skills	817	Y N	E
(Haller & Chassin, 2013)	From a longitudinal study of familial alcoholism, USA	62	Internalising symptoms (CBCL, CDIS-III-R) 11-15 Self-report	Alcohol problems (from Sher's 1987 questionnaire) 25 Self-report	12 years	***Correlations:*** Internalising symptoms → alcohol problems -.05, p >.10 ***Path analyses:*** No direct paths between adolescent internalising symptoms and alcohol problems. No numbers reported.	None for this analysis	166	N Y	U

(Hill et al., 2010)	Seattle Social Development Project, USA	50	Behavioural inhibition/trait anxiety (CBCL) 14-15 Self-report	Alcohol abuse and alcohol dependence (DISC) 27 Self-report	13 years	***Multivariate linear regression:*** Behavioural inhibition/anxiety → alcohol abuse Beta (standardised): 0.01, p = .86 Behavioural inhibition/anxiety → alcohol dependence Beta (standardised): 0.04, p = .48	Ethnicity, gender, poverty, past-month drinking at age 12	640	N Y	E
(Jester et al., 2015)	Michigan Longitudinal Study, USA	69	Distress/internalising symptoms (YSR of CBCL) 12-14 Self-report	Max number of drinks, heavy episodic drinking (Drinking and Drug History questionnaire) 18-20 Self-report	6 years	***Correlations:*** Distress/internalising → maximum number of drinks in a 24-hour period .06, p > .01 Distress/internalising → heavy episodic drinking frequency .04, p > .01	None for this analysis	1064	N Y	U
(Jun et al., 2015)	Project on Human Development in Chicago Neighbourhoods, USA	51	Internalising symptoms (YSR of CBCL) 12, 15, 18 Self-report	Alcohol Use (number of days drunk alcohol in the past month) 12, 15, 18 Self-report	3 years	***Cross-lagged structural equation models:*** Internalising symptoms age 12 and alcohol use age 15 (boys or girls) p > .05 Internalising symptoms age 15 and alcohol use age 18 (boys or girls) p > .05	Gender, race/ethnicity, salary, education of primary caregivers	724	N Y	U
(King et al., 2004)	Minnesota Twin Family Study, USA	0	Separation anxiety disorder, overanxious disorder (DICA-R) 10-12 (mean 11) Self-report, maternal report	Regular use, ever drunk, heavy drinking (DICA-R) 14 Self-report	3 years	***Generalized estimating equations (GEEs):*** Separation anxiety → regular use of alcohol 14 OR [95% CI]: 1.32 [0.71 to 2.47], p > .01 Separation anxiety → heavy drinking 14 OR [95% CI]: 1.36 [0.72 to 2.57], p > .01 Separation anxiety → getting drunk 14 OR [95% CI]: 1.57 [0.96 to 2.58], p > .01 Overanxious disorder → regular use of alcohol 14 OR [95% CI]: 0.81 [0.81 to 3.60], p > .01 Overanxious disorder → heavy drinking 14 OR [95% CI]: 1.00 [0.42 to 2.41], p > .01 Overanxious disorder → getting drunk 14 OR [95% CI]: 0.99 [0.64 to 1.54], p > .01	No information	699 twin girls	N Y Y N Y Y	 WP WP E E
(Mackie et al.,	From 24 secondary schools in London with	53 (drinker); 48	Anxiety (BSI) 13, 13.5, 14, 14.5	Alcohol use (quantity x frequency)	6-18 months	***Correlations:*** Anxiety T1 → Q x F T2: 0.07, p > .05 Anxiety T1 → Q x F T3: 0.06, p > .05	None for this analysis	393	N N	

2011a)	personality risk for substance misuse, UK	(non-drinker)	Self-report	13, 13.5, 14, 14.5 Self-report		Anxiety T1 → Q x F T4: 0.14, p < .05 Anxiety T2 → Q x F T3: 0.06, p > .05 Anxiety T2 → Q x F T4:0.04, p > .05 Anxiety T3 → Q x F T4: 0.07, p > .05 ***Parallel process latent growth model:*** No clear evidence that anxiety (13) is associated with Q x F of alcohol use. No numbers reported.			N N N N Y	 U
(Maggs et al., 2008)	National Child Development Study, UK	52	Internalising behaviours (Health and Behaviour Checklists) 7, 11 Parent-report	Weekly quantity & harmful drinking (CAGE) 16, 23, 33 Self-report	9-26 years	***Hierarchical multiple regressions:*** (unstandardised) Internalising (7) → quantity (16): M: B (SE): -0.36 (0.13), p < .01 F: B (SE): -0.15 (0.08), p > .05 Internalising (11) → quantity (16): M: B (SE): -0.64 (0.14), p < .001 F: B (SE): -0.08 (0.08), p > .05 Internalising (7) → quantity (23): M: B (SE): -3.66 (0.76), p < .001 F: B (SE): -0.59 (0.26), p < .05 Internalising (11) → quantity (23): M: B (SE): -2.54 (0.82), p < .01 F: B (SE): -0.01 (0.28), p > .05 Internalising (7) → quantity (33): M: B (SE): -3.08 (0.67), p < .001 F: B (SE): -0.83 (0.28), p < .01 Internalising (11) → quantity (33): M: B (SE): -2.77 (0.72), p < .001 F: B (SE): -0.76 (0.30), p < .01	Social class, parent education years, parents read with child, social maladjustment, academic ability, externalising behaviour (age 7 for age 7 analyses and additionally at age 11 for age 11 analyses)	4756-12772	 N N N N N N Y Y N N N N	 N U
(Malmberg et al., 2013)	Healthy Schools and Drugs prevention program, Netherlands	48	Anxiety sensitivity (SURPS) 12-13, and 8, 20, 32 months later Self-report	Alcohol use and binge drinking 12-13, and 8, 20, and 32 months later Self-report	8-32 months	***Correlations:*** Anxiety sensitivity (T0) → Alcohol use (T1, T2, T3): −.10 (p < .05), −.07, −.08 (p > .05) Anxiety sensitivity (T0) → Binge (T1, T2, T3): −.09, −.08, −.09 (p < .05) Anxiety sensitivity (T1) → Alcohol use (T2, T3): −.10 (p < .05), −.07 (p > .05) Anxiety sensitivity (T1) → Binge (T2, T3): −.07, −.06 (p < .05) Anxiety sensitivity (T2) → Alcohol use (T3): −.07 (p > .05) Anxiety sensitivity (T2) → Binge (T3): −.08 (p > .05) ***Cross-lagged models:*** (standardised beta)	Sex and education level	853-979		

						Anxiety sensitivity (T0) → Alcohol use, binge (T1): 05, −.00, p >.05 Anxiety sensitivity (T1) → Alcohol use, binge (T2): -.05, .01, p >.05 Anxiety sensitivity (T2) → Alcohol use, binge (T3): −.03, −.03, p >.05			N, N N, N Y, Y	 U, U
(Malmberg et al., 2012)	Healthy Schools and Drugs prevention program, Netherlands	48	Anxiety sensitivity (SURPS) 12-13 Self-report	Lifetime prevalence of alcohol use 20 months later Self-report	20 months	***Structural equation modelling. Cross-lagged paths:*** Anxiety → alcohol use Standardised beta: -.012, p = .567	Sex and education level	648-758	 Y	 E
(Marmorstein et al., 2010)	Pittsburgh Youth Study, USA	100	Generalised anxiety and social anxiety (CBCL, YSR, TRF) 6 Parent-, teacher- and self-report	First alcohol problem (DIS) 20 Self-report	14 years	***Survival analysis:*** GAD → time from 1st use to 1st problem OR [95% CI]: 1.03 [0.92 to 1.15] SAD → time from 1st use to 1st problem OR [95% CI]: 1.03 [0.91 to 1.17]	Delinquency, interaction of anxiety and time, interaction of anxiety and delinquency	503	 Y Y	 E E
(Marmorstein, 2015)	Camden Youth Development Study, USA	50	Social and generalised anxiety symptoms (SCARED) 11 Self-report	Frequency of drinking alcohol Every 4 months for 16 months Self-report	16 months	***Multilevel models:*** Social anxiety → alcohol use frequency 0.00 (parameter estimate), p > .05 Generalised anxiety → alcohol use frequency 0.00 (parameter estimate), p > .05	Age, gender, and race	134	 Y Y	 U U
(McKenzie et al., 2011)	From secondary schools in the state of Victoria, Australia	No info	Anxiety/depression symptoms (CIS) 14-17 (6 waves every 6 months) Self-report	Alcohol abuse or dependence (CIDI) 24 Self-report	10 years	***Logistic regression:*** Anxiety/depression → alcohol abuse or dependence 1-2 waves: OR [95% CI]: 1.3 [1.2 to 1.4], p < .001 >2 waves: OR [95% CI]: 1.9 [1.7 to 2.0], p < .001	Adolescent alcohol use, tobacco use, sex, school location, country of birth, parental education, tobacco and alcohol use, marital status,	1758	 N Y	 P

(Miettunen et al., 2014)	Northern Finland Birth Cohort 1986 Study, Finland	49	Internalising problems (Rutter Scales) 8 Parent-, teacher-, self-report	Often drunk 15-16 Self-report	7 years	***Logistic regression:*** Internalising symptoms → frequent drunkenness OR [95% CI] males 0.7 [0.5 to 1.1], p > .05 OR [95% CI] females 0.8 [0.6 to 1.1], p > .05	Place of residence, family pattern, social status, parental alcohol use, and parental psychiatric disorders	6349	 Y Y	 WN WN
(Nichter & Chassin, 2015)	The pathways to desistance project, juvenile offenders, USA	100	Worry, physiological anxiety (RCMAS) 14-19 Self-report	Typical quantity of drinking, frequency of binge drinking, dependence 6 months later Self-report	6 months	***Zero-inflated poisson regression analysis:*** Physiological anxiety → quantity of drinking B (unstandardised) = .10, SE = .04, p = .001 Physiological anxiety → frequency of binging B (unstandardised) = .04, SE = .02, p = .05 Physiological anxiety →and alcohol dependence B (unstandardised) = .20, SE = .06, p = .002 Worry → quantity B (unstandardised) = -.09, SE = .03, p = .001 Worry → frequency of bingeing B (unstandardised) = -.04; SE = .01, p = .002 Worry → alcohol dependence B (unstandardised) = - .14, SE = .05, p = .002	Race/ethnicity, Wave 1 alcohol use, self-reported offending, and PST (proportion of supervised time)	818	 Y Y Y Y Y	 P WP P N N N
(Pardini et al., 2007)	Pittsburgh Youth Study, USA	100	Anxiety/withdrawal (YSR, TRF, CBCL) 13 Parent-report, teacher-report, self-report	Alcohol abuse and dependence (DIS) 20, 25 Self-report	12 years	***Zero-inflated poisson regression:*** Anxiety/withdrawal → alcohol use disorder RRR [95% CI]: .858 [.774 to .952], p = .004 ***Multinomial Logistic Regression:*** Anxiety/withdrawal symptoms → dependence RRR [95% CI] = .674 [.512 to .890], p = .005 Anxiety/withdrawal symptoms → alcohol abuse RRR [95% CI] = .814 [.610 to 1.085], p = .161	Age, minority status, socioeconomic status, family history of alcohol/drug problems, history of alcohol use and alcohol-related problems at the time of the psychopathology variables	506	 Y N	 N
(Parrish et al., 2016)	California Families Project, USA	50	Internalising symptoms (MASQ) 14, 16	Frequency of alcohol use 14, 16	2 years	***Cross-lagged latent variable regression models:*** Standardised estimates of structural coefficients Internalising symptoms (anxiety) → frequency of alcohol us: .06, p > .05	Gender, generational status, delinquency	620	 N	

			Self-report	Self-report		Internalising symptoms (anxious arousal) → frequency of alcohol use: .05, p < .05			Y	P
(Peeters et al., 2014)	From secondary special education schools, Netherlands	88	Anxiety sensitivity (SURPS) 13 Self-report	Alcohol use (quantity x frequency) and problems (trajectories) 2 year follow up (6-8 months between waves) Self-report	6 months-2 years	***Multinomial logistic regression:*** Anxiety sensitivity → onset group OR [95% CI]: 0.83 [0.48 to 1.42], p > .01 Anxiety sensitivity → early onset persistent drinking group OR [95% CI]: 0.42 [0.35 to 0.77], p < .001 Anxiety sensitivity → persistent drinking group OR [95% CI]: 0.51 [0.30 to 0.87]), no p value	No information	378	 N Y N	 N
(Pitkanen et al., 2008)	Jyväskylä Longitudinal Study of Personality and Social Development, Finland	53	Anxiety (1 item) 8, 14 Teacher-report	Heavy use, frequency of drinking, binge drinking, problem drinking (LSQ and interview questions) 20, 27, 42 Self-report	12-34 years	***Regression:*** (standardised betas) Anxiety (age 8) → heavy drinking at 20 M: beta = 0.14, p > .05; F: beta = 0.04, p > .05 Anxiety (age 8) → problem drinking at 27 M: beta = -0.15, p > .05; F: beta = 0.09, p > .05 Anxiety (age 8) → problem drinking at 42 M: beta = 0.06, p > .05; F: beta = -0.02, p >.05 Anxiety (age 8) → drinking frequency at 27 M: beta = 0.06, p > .05; F: beta = -0.06, p > .05 Anxiety (age 8) → drinking frequency at 42 M: beta = -0.03, p > .05; F: beta = -0.08, p > .05 Anxiety (age 8) → binge drinking at 27 M: beta = 0.15, p > .05; F: beta = -0.07, p > .05 Anxiety (age 8) → binge drinking at 42 M: beta = -0.03, p > .05; F: beta = -0.06, p > .05 Anxiety (age 8) → CAGE score at 27 M: beta = 0.07, p > .05; F: beta = 0.09, p > .05 Anxiety (age 8) → CAGE score at 42 M: beta = 0.08, p > .05; F: beta = 0.00, p > .05 Anxiety (age 14) → heavy drinking (age 20) M: beta = -0.24, p < .01; F: beta = -.07, p > .05 Anxiety (age 14) → problem drinking (27) M: beta = .01, p > .05; F: beta = .00, p > .05 Anxiety (age 14) → problem drinking (42) M: beta = -.14, p > .05; F: beta = -.11, p > .05 Anxiety (age 14) → frequent drinking (age 27) M: beta = -.15, p >.05; F: beta = -0.20, p < .01 Anxiety (age 14) → frequent drinking (age 42) M: beta = -.01, p > .05; F: beta = -0.19, p < .01. Anxiety (age 14) → binge drinking (age 27) M: beta = -.16, p > .05; F: beta = -.13, p > .05	Socioeconomic status, child-centred parenting, parental drinking, smoking mother, social activity, constructiveness, compliance, aggression, low self-control, school success	290-347	 N, N N, N N, N N, N N, N N, N N, N N, N N, N Y, Y Y, Y N, N N, N N, N Y, Y	 U, U U, U U, U

						Anxiety (age 14) → binge drinking (age 42) M: beta = -.16, p > .05; F: beta = -.13, p > .05 Anxiety (age 14) → CAGE score at 27 M: beta = -.09, p > .05; F: beta = -.03, p > .05 Anxiety (age 14) → CAGE score at 42 M: beta = -.03, p > .05; F: beta = -.12, p > .05			N, N N, N N, N	
(Pulkkinen & Pitkanen, 1994)	Jyväskylä Longitudinal Study of Personality and Social Development, Finland	53	Anxiety (3 items) 8, 14 Peer nomination and teacher-report	Social drinking, problem drinking, controlled drinking (CAGE) 26 Self-report	12-18 years	***Product moment correlations:*** Social anxiety age 8 (peer)→ problem drinking M: -.15, p < .05; F: .24, p < .01 Social anxiety age 8 (peer)→ social drinking M: -.20, p < .05; F: -.13, p > .05 Social anxiety age 8 (peer)→ controlled drinking M: -.18, p < .05; F: -.02, p > .05 Social anxiety age 8 (teacher) → problem drinking M: .10, p > .05; F: .17, p < .05 Social anxiety age 8 (teacher) → social drinking M: .00, p > .05; F: -.07, p > .05 Social anxiety age8 (teacher) → controlled M: -.16, p < .05; F: -.10, p > .05 Social anxiety age 14 (peer)→ problem drinking M: -.25, p < .001; F: .15, p < .05 Social anxiety age 14 (peer)→ social drinking M: -.07, p > .05; F: -16, p < .05 Social anxiety age 14 (peer) → controlled drinking M: -16, p < .05l F: -.01, p > .05 Social anxiety age 14 (teacher)→ problem drinking M: -.05, p > .05; F: .16, p < .05 Social anxiety age 14 (teacher) → social drinking M: -.22, p < .01; F: -.06, p > .05 Social anxiety age 14 (teacher) → controlled M: -.15, p <.05; F: -.05, p > .05 ***Path analysis:*** Females: anxiety T1, problem drinking T3: Beta = .22, p < .05 Males: anxiety T2, problem drinking T3: Beta = -.21, p < .01	No information	242-311	N N N N N N N N N N N N N Y Y	P N
(Savage et al., 2016)	Finn Twin12 study, Finland	51	Social anxiety (MPNI) 12	Drinking frequency, alcohol dependence (SSAGA) 14, 17, 22	Trajectories (max 10 years)	***Latent growth curve analysis:*** Peer rated social anxiety → drinking frequency Slope: -.24, p < .05 Parent rated social anxiety → alcohol use Slope: -.06, p > .05 Teacher rated social anxiety → alcohol use	No information	1225-1906	N Y	N

			Peer-, parent- and teacher-report, self-report	Self-report		Slope: -.09, p > .05 ***Regressions***: (unstandardized betas) Social anxiety (peer) → alcohol dependence 14 -.004, p < .001 Social anxiety (peer) → alcohol dependence 22 -.01, p = .001 Social anxiety (parent) → alcohol dependence 14 -.02, p > .2 Social anxiety (parent) → alcohol dependence 22 -.02, p > .2 Social anxiety (teacher)→ alcohol dependence 14 -.02, p > .2 Social anxiety (teacher)→ alcohol dependence 22 -.07, p > .2			N N N N Y N N	E
(Scalco et al., 2014)	Community sample, USA	45	Internalising problems (YSR) 11-12 Self-report	Alcohol use (YSR of Achenbach Assessment) 12-13, 13-14 Self-report	1-2 years	***Structural equations model (SEM) with latent variable interactions:*** Estimated standardised path coefficients Internalising problems → alcohol use a year later -.21, p < .05 Internalising problems → alcohol use 2 years later -.03, p > .05	Age	387	 N Y	U
(Schmidt et al., 2007)	From a primary prevention study, USA	39	Anxiety sensitivity (ASI), trait anxiety (STPI) 16-24 Self-report	Alcohol use disorder (SCID-NP) 18-26 Self-report	2 years	***Hierarchical logistic regression:*** Total ASI score → AUD B (unstandardised) = .09, SE = .03, p = .007 Physical subscale → AUD B (unstandardised) = .15, SE = .06, p = .007 Cognitive subscale → AUD B (unstandardised) = .29, SE = .14, p = .04 Social subscale → AUD B (unstandardised) = .26, SE = .14, p = .05 Trait anxiety → AUD B (unstandardised) = .06, SE = .07, p = .36	Experimental condition, trait anxiety, gender, ASI × gender	295	 Y N N N N	P
(Stanley et al., 2014)	American Indian Research data, USA	No info	Internalising behaviours (CBCL) 11 Self-report, parent-report	Alcohol use disorder (SSAGA-II) 19-20 Self-report	9 years	***Logistic regression:*** Internalising behaviour → alcohol use disorders OR [95% CI]: 0.96 [.91 to 1.02], p > .05	Gender, income	281	 Y	WN

(Steele et al., 1995)	Community sample, USA	47	Internalising behaviour problems (RBPC) 11-15 Maternal-report, teacher report	Alcohol use (MAST, NYS) 17-22 Self-report	6 years	***Hierarchical multiple regression:*** Internalising behaviour problems → alcohol use Beta weights = -0.042, p = ns	Gender, externalising problems	185-187	Y	U
(Stice et al., 1998)	Longitudinal community sample (1/2 parental alcoholism), USA	52	Internalising symptoms (CBCL) 12-16 Self-report, maternal report	Quantity and frequency of alcohol use, problem alcohol use 13-17 Self-report	1 year	***Manifest variable structural equation models:*** (Standardised path coefficient) Internalising → alcohol use (adolescent) -.01, p > .05 Internalising → alcohol use (maternal) 0.06, p > .05	Adolescent age, parental alcoholism	216	Y N	U
(Strandheim et al., 2011)	Young-HUNT 1, and Young-HUNT 2, Norway	46	Anxiety/depression (SCL 90-R, SCL-5) 13-15 Self-report	Frequent alcohol use 17-19 Self-report	4 years	***Logistic regression:*** Anxiety/depression symptoms → alcohol use total [OR 95% CI]: 0.9 [0.7 to 1.0]	Age, attention problems, conduct problems, pain and tension problems, early alcohol intoxication	2399	Y	WN
(Swift et al., 2016)	Random sample from secondary schools, Australia	50	Anxiety/depression symptoms (CIS-R) 14/15–17 (2 waves every 6 months) Self-report	Alcohol use disorder symptom classes (CIDI) 24 Self-report	10 years max	***Latent class analysis:*** Anxiety/depression → moderate (vs. mild) AUD OR [95% CI]: 1.9 [1.2 to 3.1], p < .05 Anxiety/depression → severe (vs. mild) AUD OR [95% CI]: 2.5 [1.3 to 5.0], p < .05 Anxiety/depression → severe (vs. moderate) AUD OR [95% CI]: 0.75 [0.31 to 1.8], p > .05	Age of alcohol initiation, alcohol use and problems, smoking, cannabis use, antisocial behaviour, school location, parental drinking, smoking, separation, education	1203	N Y N	P

(Thompson et al., 2015)	Victoria Healthy Youth Survey, Canada	49	Internalising symptoms (BCFPI) 12/13, 14/15, 16/17 Self-report	Heavy episodic drinking, alcohol related harms (Harmful Effects of Alcohol Scale) 12/13, 14/15, 16/17, 18/19 Self-report	2 years	***Cross-lagged panel models:*** Internalising (12/13) → HED (14/15), p > .05 Internalising (14/15) → HED (16/17), p > .05 Internalising (16/17) → HED (18/19), p > .05 Standardised estimates: Internalising (14/15) → alcohol harms (16/17) .12, p < .001 Internalising (16/17)→ alcohol harms (18/19) .10, p < .001	Mother's education as a proxy for SES	657-662	N N Y N Y	 U P
(Virtanen et al., 2015)	The Northern Swedish Cohort Study, Sweden	52	Anxiousness (DSM-5) 16 Self-report	Drinking trajectories (frequency, consumption) 16, 18, 21, 30, 42 Self-report	Trajectories (26 years max)	***Multinomial logistic regression (also with latent class growth analysis):*** Anxiousness → ordinary drinking OR [95% CI]: 1.97 [1.08 to 3.60], p < .05 Anxiousness → early onset low OR [95% CI]: 2.43 [1.21 to 4.88], p < .05 Anxiousness → early onset moderate OR [95% CI]: 2.84 [1.56 to 5.15], p < .05 Anxiousness → early onset high OR [95% CI]: 3.59 [1.89 to 6.82], p < .05 Anxiousness → late onset low trajectory OR [95% CI]: 1.54 [0.72 to 3.32], p > .05	Gender, social class of the parents	1010	 N N N Y N	 P
(Weekes et al., 2011)	Black adolescents with asthma, USA	34	Anxiety symptoms (MASC-10) 11-19 Self-report	Alcohol use frequency (from Adolescent Risk Behavior Survey) 12-20 Self-report	1 year	***Logistic regression:*** Anxiety symptoms → alcohol use OR [95% CI]: 1.12 [1.02 to 1.23], p < .05	Alcohol use T1. Age, gender, negative coping, asthma symptoms, concern, severity were removed from final model as not significant	110	 Y	 P
(Wolitzky-Taylor et al., 2012)	Northwestern-UCLA Youth Emotion Project, USA	31	Anxiety disorders (SCID-I/NP) 16 Self-report	Alcohol use disorder (SCID-I/NP) 1-4 years later Self-report	1-4 years	***Logistic regression:*** Anxiety disorders → alcohol use disorder onset OR [95% CI]: 2.71 [1.39 to 5.29], p < .01 Social anxiety disorder → AUD OR [95% CI]:2.52 [1.10 to 5.80], p < .05 Panic disorder → AUD p > .27 OCD → AUD p > .27 GAD → AUD p > .27	Gender	420-627	 Y Y Y Y Y	 P P U U U

(Woodward & Fergusson, 2001)	Christchurch Health and Development Study, New Zealand	50	Anxiety disorders (DISC supplemented by DSM-III-R) 15-16 Self-report	Alcohol abuse/dependence (CIDI) Between 16 and 21, annually Self-report	1-6 years	***Logistic regression:*** Anxiety disorders → alcohol dependence p > .70	Childhood sexual abuse, baseline alcohol abuse, deviant peer affiliations	964	Y	U
(Zimmermann et al., 2003)	Early Developmental Stages of Psychopathology Study, Germany	No info	Anxiety disorders (DIA-X/M-CIDI) 14-24 Self-report	Regular use, hazardous use, abuse, dependence, alcohol use disorder (M-CIDI) 20 and 42 months later Self-report	4 years	***Logistic regression:*** Panic disorder → at least regular use OR [95% CI]: 0.6 [0.1 to 1.9] p > .05 Panic disorder → hazardous use OR [95% CI]: 1.1 [0.3 to 3.6] p > .05 Panic disorder → abuse OR [95% CI]: 2.4 [0.4 to 11.4] p > .05 Panic disorder → dependence OR [95% CI]: 3.7 [0.8 to 15.9] p > .05 Panic disorder → any AUD OR [95% CI]: 2.8 [0.8 to 9.1] p > .05 Panic attacks →regular use OR [95% CI]: 1.8 [0.7 to 4.4], p > .05 Panic attacks → hazardous use OR [95% CI]: 2.5 [1.1 to 5.8] p < .05 Panic attacks →alcohol abuse OR [95% CI]: 2.7 [1.1 to 6.1], p < .05 Panic attacks →dependence OR [95% CI]: 1.4 [0.2 to 8.7], p > .05 Panic attacks → any AUD OR [95% CI]: 2.0 [0.8 to 4.7], p > .05 Social phobia → regular alcohol use OR [95% CI]: 1.9 [1.0 to 3.4], p < .05 Social phobia → hazardous use OR [95% CI]: 2.1 [1.2 to 3.8], p < .05 Social phobia → alcohol abuse OR [95% CI]: 0.7 [0.3 to 1.3], p > .05 Social phobia → dependence OR [95% CI]: 0.4 [0.1 to 1.4], p > .05 Social phobia → any AUD OR [95% CI]: 0.6 [0.3 to 1.1], p > .05 GAD → regular use OR [95% CI]: 1.5 [0.6 to 3.4], p > .05 GAD → hazardous use	Age, gender, other mental disorders, substance use disorders and antisocial behaviour	2548	N N N N N N Y N Y N N Y N Y N N	P E P WN

						OR [95% CI]: 1.4 [0.5 to 3.2], p > .05 GAD →abuse			Y	E
						OR [95% CI]: 0.7 [0 .2 to 2.3], p > .05 GAD → dependence			N	
						OR [95% CI]: 0.7 [0.1 to 3.5], p > .05 GAD → Any AUD			Y	E
						0.7 [0.2 to 2.0], p > .05 Specific phobia → regular use			N	
						OR [95% CI]: 0.8 [0.5 to 1.3], p > .05 Specific phobia → hazardous use			N	
						OR [95% CI]: 0.9 [0.5 to 1.4], p > .05 Specific phobia →abuse			Y	E
						OR [95% CI]: 1.1 [0.6 to 1.8], p > .05 Specific phobia → dependence			N	
						OR [95% CI]: 1.3 [0.6 to 2.4], p > .05 Specific phobia → Any AUD			Y	E
						OR [95% CI]: 1.1 [0.7 to 1.8], p > .05			N	

Note: Count Result: Y = Yes, N = No. **Evidence:** N = Negative, WN = Weak Negative, E = Equivocal, WP = Weak Positive, P = Positive, U = Unclassifiable. Vs. = versus. M = male; F = female.

Anxiety Measures: Diagnostic Interview Schedule for Children (DISC): 3; Munich-Composite International Diagnostic Interview (M-CIDI): 5; Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS): 4; Achenbach System of Empirically Based Assessment (ASEBA), Child Behaviour Checklist (CBCL)/Youth Self-Report (YSR)/Teacher's Report Form (TRF)/Young Adult Self-Report (YASR): 13; Clinical Interview Schedule (CIS)/Clinical Interview Schedule-Revised (CIS-R): 3; Revised Child Anxiety and Depression Scale (RCADS): 1; Strengths and Difficulties Questionnaire (SDQ): 1; Longitudinal Interval Follow-up Evaluation (LIFE): 2; Structured Clinical Interview for DSM (SCID)/Structured Clinical Interview for DSM Non Patient (SCID-NP): 3; Social Phobia Inventory (SPIN): 1; Clinician rated diagnosis: 1; Diagnostic Interview Schedule III Revised (DIS-III-R): 2; Diagnostic Interview for Children and Adolescents-Revised (DICA-R): 1; Brief Symptom Inventory (BSI): 1; Health and Behaviour Checklists: 1; Substance Use Risk Profile Scale (SURPS): 3; Screen for Child Anxiety Related Disorders (SCARED): 1; Rutter Scales: 1; Revised Children's Manifest Anxiety Scale (RCMAS): 1; Mini-Mood and Anxiety Symptom Questionnaire (MASQ): 1; Multidimensional Peer Nomination Inventory (MPNI): 1; Anxiety Sensitivity Index (ASI): 1; Revised Behaviour Problem Checklist (RBPC): 1; Symptom Check List (SCL-5): 1; Brief Child and Family Phone Interview (BCFPI): 1; Anxiousness (based on the symptom clusters in DSM-5): 1; Multidimensional Anxiety Scale for Children (MASC- 10): 1; State-Trait Personality Inventory(STPI): 1; and 2 researcher constructed measures.

Alcohol Measures: Diagnostic Interview Schedule for Children (DISC): 2; Diagnostic Interview Schedule (DIS): 2; Munich-Composite International Diagnostic Interview (M-CIDI): 5; Longitudinal Interval Follow-up Evaluation (LIFE): 4; Structured Clinical Interview for DSM (SCID)/Structured Clinical Interview for DSM Non Patient (SCID-NP): 5; National Youth Survey (NYS): 3; Clinical Interview Schedule (CIS): 1; Youth Risk Behavior Surveillance System (YRBSS): 1; Adult Heath Survey: 1; Adolescent Health Survey: 1; Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS): 3; Measures adapted from Questionnaire for the Alcohol, Health, and Behavior study: 1; Drinking and Drug History Questionnaire: 1; Diagnostic Interview for Children and Adolescents-Revised (DICA-R): 1; Composite International Diagnostic Interview: 3; CAGE Questionnaire (cut-annoyed-guilty-eye): 1; Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA): 2; Youth Self-Report (YSR): 1; Michigan Alcohol Screening Test (MAST): 1; Harmful Effects of Alcohol Scale: 1; Adolescent risk behaviour survey: 1; and 19 researcher constructed measures.

Appendix 3.1. Frequencies and percentages for the main variables (cross-sectional).

		Frequent Drinking (18)				Frequent Bingeing (18)				Hazardous Drinking (18)				Harmful Drinking (18)			
		AD	**Imp#1**	**Imp#2**	**Imp#3**	**AD**	**Imp#1**	**Imp#2**	**Imp#3**	**AD**	**Imp#1**	**Imp#2**	**Imp#3**	**AD**	**Imp#1**	**Imp#2**	**Imp#3**
Whole sample		939 25.9%	25.9% (0.7%)	25.9% (0.7%)	25.4% (0.7%)	516 14.2%	14.2% (0.6%)	14.6% (0.6%)	14.9% (0.6%)	1551 42.8%	42.8% (0.8%)	42.8% (0.8%)	43.0% (0.8%)	209 5.8%	5.8% (0.4%)	5.9% (0.4%)	6.2% (0.4%)
GAD	**No**	826 25.3%	25.5% (0.7%)	25.6% (0.7%)	25.0% (0.7%)	460 14.1%	14.0% (0.6%)	14.4% (0.6%)	14.7% (0.6%)	1382 42.3%	42.3% (0.8%)	42.4% (0.8%)	42.4% (0.8%)	180 5.5%	5.5% (0.4%)	5.7% (0.4%)	5.9% (0.4%)
	Yes	62 32.1%	32.6% (3.4%)	31.6% (3.3%)	31.6% (3.2%)	36 18.7%	18.5% (2.8%)	17.9% (2.6%)	18.9% (2.7%)	99 51.3%	51.4% (3.6%)	50.3% (3.5%)	51.0% (3.6%)	20 10.4%	10.4% (2.2%)	10.1% (2.1%)	10.6% (2.1%)
DTC	**Low**	565 20.4%	20.4% (0.8%)	20.3% (0.7%)	19.6% (0.7%)	272 9.8%	9.8% (0.6%)	10.1% (0.6%)	10.2% (0.6%)	934 33.7%	33.6% (0.9%)	33.9% (0.9%)	34.0% (0.9%)	63 2.3%	2.3% (0.3%)	2.4% (0.3%)	2.6% (0.3%)
	High	373 44.3%	44.2% (1.7%)	44.1% (1.7%)	43.4% (1.6%)	241 28.6%	28.7% (1.6%)	29.2% (1.5%)	29.7% (1.5%)	614 72.8%	72.8% (1.5%)	71.9% (1.6%)	71.1% (1.5%)	146 17.3%	17.3% (1.3%)	17.2% (1.3%)	17.2% (1.3%)
GAD (Low DTC stratum)	**No**	520 20.3%	20.5% (0.8%)	20.5% (0.8%)	19.7% (0.8%)	257 10.0%	9.9% (0.6%)	10.3% (0.6%)	10.3% (0.6%)	866 33.8%	33.7% (0.9%)	33.9% (0.9%)	34.0% (0.9%)	59 2.3%	2.2% (0.3%)	2.4% (0.3%)	2.6% (0.3%)
	Yes	16 15.8%	16.4% (3.7%)	15.1% (3.5%)	16.5% (3.6%)	7 6.93%	6.9% (2.5%)	6.7% (2.4%)	6.9% (2.5%)	33 32.7%	32.8% (4.7%)	32.5% (4.6%)	33.8% (4.6%)	<5 <5%	2.9% (1.7%)	3.2% (1.8%)	3.8% (2.0%)
GAD (High DTC stratum)	**No**	305 43.5%	43.3% (1.8%)	43.3% (1.8%)	42.9% (1.8%)	201 28.7%	28.4% (1.7%)	29.0% (1.7%)	29.6% (1.7%)	514 73.3%	73.0% (1.6%)	72.1% (1.6%)	71.1% (1.7%)	121 17.3%	17.1% (1.4%)	16.9% (1.4%)	17.0% (1.4%)
	Yes	46 50.6%	50.6% (5.2%)	49.5% (5.0%)	49.1% (5.3%)	28 30.8%	31.3% (4.8%)	31.0% (4.8%)	32.2% (4.7%)	65 71.4%	71.4% (4.7%)	69.5% (4.9%)	68.9% (4.7%)	17 18.7%	18.8% (4.1%)	18.2% (3.9%)	18.7% (4.0%)

Numbers in the brackets indicate the precision around the estimated percentage for the imputed data. AD = available data; Imp#1: n = 3625; 100 imputations; Imp#2: n = 4600; 100 imputations; Imp#3: n = 9278; 200 imputations. GAD = generalised anxiety disorder; DTC = drinking to cope.

Appendix 3.2. Frequencies and percentages for the main variables (longitudinal).

		Frequent Drinking (21)				Frequent Bingeing (21)				Hazardous Drinking (21)				Harmful Drinking (21)			
		AD	**Imp#1**	**Imp#2**	**Imp#3**	**AD**	**Imp#1**	**Imp#2**	**Imp#3**	**AD**	**Imp#1**	**Imp#2**	**Imp#3**	**AD**	**Imp#1**	**Imp#2**	**Imp#3**
Whole sample		845 40.9%	40.5% (1.0%)	39.3% (1.0%)	36.6% (0.8%)	706 32.6%	32.7% (1.0%)	31.8% (0.9%)	29.6% (0.8%)	1246 57.6%	58.4% (1.1%)	57.7% (0.9%)	55.6% (0.8%)	280 12.9%	13.7% (0.7%)	13.7% (0.7%)	13.2% (0.6%)
GAD	**No**	786 40.3%	40.2% (1.0%)	38.9% (1.0%)	36.2% (0.8%)	635 32.6%	32.6% (1.0%)	31.9% (0.9%)	29.6% (0.9%)	1118 57.3%	58.1% (1.1%)	57.5% (1.0%)	55.3% (0.9%)	247 12.7%	13.3% (0.7%)	13.2% (0.7%)	12.7% (0.6%)
	Yes	58 46.4%	45.9% (4.3%)	45.2% (4.0%)	42.9% (3.8%)	41 32.8%	32.9% (4.1%)	31.0% (3.6%)	29.1% (3.5%)	79 63.2%	63.1% (4.3%)	60.2% (3.9%)	59.2% (4.1%)	25 20.0%	20.5% (3.2%)	20.7% (3.2%)	20.7% (3.1%)
DTC	**Low**	658 39.0%	38.5% (1.1%)	37.2% (1.1%)	34.8% (0.9%)	516 30.6%	30.5% (1.1%)	29.7% (1.0%)	27.5% (0.9%)	907 53.8%	54.2% (1.2%)	53.5% (1.1%)	51.0% (1.0%)	172 10.2%	10.5% (0.7%)	10.4% (0.7%)	10.1% (0.7%)
	High	223 47.9%	47.2% (2.1%)	45.9% (2.1%)	42.2% (2.0%)	185 39.7%	39.8% (2.0%)	38.7% (2.1%)	36.0% (2.0%)	333 71.5%	72.2% (2.1%)	71.3% (1.9%)	69.9% (1.9%)	105 22.5%	24.3% (1.9%)	24.2% (1.9%)	22.8% (1.5%)
GAD (Low DTC stratum)	**No**	598 38.5%	38.5% (1.2%)	37.2% (1.1%)	34.7% (1.0%)	470 30.3%	30.6% (1.1%)	29.9% (1.0%)	27.8% (1.0%)	830 53.4%	54.2% (1.2%)	53.5% (1.1%)	51.1% (1.1%)	156 10.1%	10.4% (0.7%)	10.2% (0.7%)	9.9% (0.6%)
	Yes	29 42.7%	42.1% (5.9%)	41.1% (5.4%)	38.2% (5.1%)	19 27.9%	28.2% (5.3%)	27.0% (4.8%)	25.4% (4.7%)	38 55.9%	54.4% (5.6%)	51.5% (5.5%)	50.1% (5.6%)	10 14.7%	15.5% (4.5%)	15.8% (4.1%)	16.3% (4.3%)
GAD (High DTC stratum)	**No**	184 47.4%	46.6% (2.3%)	45.0% (2.3%)	41.6% (2.2%)	161 41.5%	40.0% (2.3%)	38.9% (2.3%)	35.9% (2.1%)	283 72.9%	72.2% (2.1%)	71.4% (2.1%)	70.1% (2.1%)	89 22.9%	24.1% (2.1%)	24.0% (1.9%)	22.8% (1.8%)
	Yes	29 51.8%	50.4% (6.4%)	50.1% (6.2%)	48.0% (6.0%)	21 37.5%	37.7% (6.3%)	36.0% (5.7%)	33.8% (5.8%)	40 71.4%	71.4% (5.6%)	69.0% (6.0%)	68.2% (5.6%)	14 25.0%	25.7% (5.3%)	25.7% (5.1%)	24.6% (5.1%)

Numbers in the brackets indicate the precision around the estimated percentage for the imputed data. AD = available data; Imp#1: n = 3625; 100 imputations; Imp#2: n = 4600; 100 imputations; Imp#3: n = 9278; 200 imputations. GAD = generalised anxiety disorder; DTC = drinking to cope.

Appendix 3.3. Logistic regressions examining the associations of generalised anxiety disorder at age 18 with alcohol use at age 18 and 21.

			Available data		Imp#1		Imp#2		Imp#3	
	Model	**N**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**
Age 18										
Frequent Drinking	Model 1	3462	1.40 [1.02, 1.91]	.036	1.41 [1.03, 1.93]	.030	1.34 [0.98, 1.84]	.068	1.38 [1.02, 1.85]	.037
	Model 2	2603	1.71 [1.19, 2.45]	.004	1.61 [1.17, 2.21]	.003	1.45 [1.06, 2.00]	.021	1.43 [1.05, 1.93]	.021
	Model 3	1832	1.76 [1.13, 2.76]	.013	1.57 [1.13, 2.16]	.007	1.42 [1.03, 1.96]	.034	1.38 [1.01, 1.88]	.041
	Model 4	1535	1.67 [0.99, 2.82]	.055	1.50 [1.07, 2.09]	.017	1.38 [0.99, 1.92]	.059	1.33 [0.97, 1.83]	.072
Frequent Bingeing	Model 1	3462	1.40 [0.96, 2.04]	.079	1.39 [0.96, 2.02]	.083	1.29 [0.90, 1.85]	.165	1.29 [0.90, 1.86]	.165
	Model 2	2603	1.66 [1.08, 2.57]	.021	1.54 [1.06, 2.26]	.025	1.37 [0.95, 1.98]	.092	1.33 [0.92, 1.92]	.129
	Model 3	1832	1.81 [1.06, 3.09]	.031	1.51 [1.03, 2.22]	.034	1.34 [0.93, 1.95]	.118	1.29 [0.89, 1.86]	.173
	Model 4	1535	1.67 [0.88, 3.18]	.120	1.45 [0.97, 2.15]	.068	1.30 [0.89, 1.92]	.179	1.26 [0.86, 1.84]	.244
Hazardous Drinking	Model 1	3462	1.44 [1.08, 1.92]	.014	1.44 [1.08, 1.93]	.014	1.37 [1.04, 1.82]	.026	1.41 [1.06, 1.88]	.020
	Model 2	2603	1.64 [1.17, 2.30]	.004	1.52 [1.13, 2.03]	.005	1.42 [1.07, 1.89]	.015	1.44 [1.08, 1.92]	.013
	Model 3	1832	2.10 [1.37, 3.22]	.001	1.47 [1.09, 1.98]	.011	1.37 [1.03, 1.82]	.030	1.37 [1.02, 1.84]	.034
	Model 4	1535	1.98 [1.21, 3.25]	.007	1.41 [1.03, 1.92]	.030	1.33 [0.99, 1.78]	.062	1.33 [0.98, 1.81]	.065
Harmful Drinking	Model 1	3462	1.98 [1.22, 3.23]	.006	1.99 [1.22, 3.23]	.006	1.87 [1.15, 3.04]	.012	1.87 [1.16, 3.02]	.010
	Model 2	2603	2.48 [1.42, 4.33]	.001	2.05 [1.25, 3.34]	.004	1.89 [1.16, 3.09]	.011	1.89 [1.17, 3.06]	.009
	Model 3	1832	3.55 [1.90, 6.63]	<.001	1.97 [1.20, 3.25]	.008	1.81 [1.10, 3.00]	.020	1.81 [1.12, 2.93]	.015
	Model 4	1535	4.10 [1.88, 8.93]	<.001	1.87 [1.12, 3.12]	.017	1.74 [1.03, 2.92]	.037	1.73 [1.05, 2.84]	.032

Model 1 = unadjusted; model 2 = adjusted for sociodemographic confounders: gender, maternal education, family income, housing tenure, and social class; model 3 = additionally adjusted for parental confounders: parental depression, anxiety, alcohol use, and tobacco use; model 4 = additionally adjusted for adolescent confounders: tobacco use, cannabis use, drinking frequency, binge drinking, conduct problems, and emotional symptoms. AD = available data; Imp#1: n = 3625; 100 imputations; Imp#2: n = 4600; 100 imputations; Imp#3: n = 9278; 200 imputations.

Appendix 3.3. (continued)

			Available data		Imp#1		Imp#2		Imp#3	
	Model	**N**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**
Age 21										
Frequent Drinking	Model 1	2076	1.28 [0.89, 1.84]	.178	1.26 [0.88, 1.80]	.204	1.30 [0.93, 1.80]	.120	1.32 [0.93, 1.87]	.116
	Model 2	1611	1.34 [0.88, 2.06]	.176	1.38 [0.95, 2.00]	.091	1.40 [1.00, 1.97]	.052	1.41 [0.98, 2.02]	.063
	Model 3	1213	1.77 [1.05, 3.00]	.033	1.38 [0.94, 2.03]	.097	1.41 [1.00, 2.00]	.051	1.41 [0.98, 2.04]	.066
	Model 4	1043	1.44 [0.79, 2.63]	.232	1.34 [0.91, 1.99]	.138	1.40 [0.99, 2.00]	.060	1.40 [0.96, 2.04]	.079
Frequent Bingeing	Model 1	2076	1.01 [0.69, 1.49]	.953	1.01 [0.69, 1.47]	.968	0.96 [0.68, 1.35]	.817	0.98 [0.68, 1.42]	.929
	Model 2	1611	0.94 [0.60, 1.49]	.799	1.10 [0.75, 1.62]	.618	1.03 [0.72, 1.46]	.880	1.03 [0.71, 1.50]	.871
	Model 3	1213	1.03 [0.60, 1.78]	.913	1.07 [0.72, 1.60]	.724	1.02 [0.71, 1.46]	.915	1.01 [0.69, 1.48]	.939
	Model 4	1043	0.75 [0.40, 1.43]	.390	1.06 [0.71, 1.58]	.789	1.01 [0.70, 1.46]	.941	1.02 [0.69, 1.50]	.919
Hazardous Drinking	Model 1	2076	1.28 [0.88, 1.86]	.197	1.23 [0.85, 1.79]	.279	1.12 [0.80, 1.57]	.501	1.19 [0.84, 1.67]	.327
	Model 2	1611	1.31 [0.85, 2.01]	.226	1.30 [0.89, 1.90]	.174	1.17 [0.83, 1.64]	.364	1.23 [0.87, 1.75]	.232
	Model 3	1213	2.16 [1.21, 3.84]	.009	1.29 [0.88, 1.89]	.200	1.15 [0.82, 1.62]	.411	1.20 [0.84, 1.71]	.307
	Model 4	1043	1.86 [0.99, 3.49]	.054	1.26 [0.85, 1.87]	.256	1.14 [0.80, 1.62]	.462	1.20 [0.84, 1.72]	.325
Harmful Drinking	Model 1	2076	1.72 [1.09, 2.73]	.020	1.67 [1.11, 2.51]	.014	1.70 [1.14, 2.54]	.010	1.70 [1.12, 2.58]	.013
	Model 2	1611	1.51 [0.86, 2.67]	.152	1.79 [1.18, 2.71]	.006	1.79 [1.19, 2.70]	.005	1.76 [1.16, 2.68]	.008
	Model 3	1213	1.47 [0.75, 2.88]	.258	1.77 [1.16, 2.70]	.008	1.77 [1.16, 2.69]	.008	1.72 [1.12, 2.65]	.013
	Model 4	1043	1.29 [0.57, 2.91]	.536	1.68 [1.09, 2.60]	.020	1.72 [1.11, 2.65]	.015	1.69 [1.08, 2.64]	.022

Model 1 = unadjusted; model 2 = adjusted for sociodemographic confounders: gender, maternal education, family income, housing tenure, and social class; model 3 = additionally adjusted for parental confounders: parental depression, anxiety, alcohol use, and tobacco use; model 4 = additionally adjusted for adolescent confounders: tobacco use, cannabis use, drinking frequency, binge drinking, conduct problems, and emotional symptoms. AD = available data; Imp#1: n = 3625; 100 imputations; Imp#2: n = 4600; 100 imputations; Imp#3: n = 9278; 200 imputations.

Appendix 3.4. Logistic regressions examining the associations of generalised anxiety disorder at age 18 with drinking to cope motives at age 18.

		Available data		Imp#1		Imp#2		Imp#3	
Model	**N**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**
Model 1	3477	3.23 [2.41, 4.34]	<.001	3.30 [2.46, 4.44]	<.001	3.18 [2.36, 4.28]	<.001	3.15 [2.35, 4.22]	<.001
Model 2	2610	3.21 [2.28, 4.52]	<.001	3.16 [2.34, 4.25]	<.001	3.08 [2.28, 4.16]	<.001	3.05 [2.28, 4.09]	<.001
Model 3	1833	3.48 [2.28, 5.32]	<.001	3.09 [2.28, 4.18]	<.001	2.98 [2.19, 4.05]	<.001	2.92 [2.17, 3.93]	<.001
Model 4	1536	3.07 [1.88, 5.01]	<.001	3.01 [2.21, 4.09]	<.001	2.93 [2.14, 3.99]	<.001	2.86 [2.10, 3.88]	<.001

Model 1 = unadjusted; model 2 = adjusted for sociodemographic confounders: gender, maternal education, family income, housing tenure, and social class; model 3 = additionally adjusted for parental confounders: parental depression, anxiety, alcohol use, and tobacco use; model 4 = additionally adjusted for adolescent confounders: tobacco use, cannabis use, drinking frequency, binge drinking, conduct problems, and emotional symptoms. AD = available data; Imp#1: n = 3625; 100 imputations; Imp#2: n = 4600; 100 imputations; Imp#3: n = 9278; 200 imputations.

Appendix 3.5. Logistic regressions examining the associations of drinking to cope motives at age 18 with alcohol use at age 18 and 21.

			Available data		Imp#1		Imp#2		Imp#3	
	Model	**N**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**
Age 18										
Frequent Drinking	Model 1	3617	3.10 [2.63, 3.65]	<.001	3.10 [2.63, 3.65]	<.001	3.10 [2.63, 3.65]	<.001	3.15 [2.70, 3.67]	<.001
	Model 2	2730	3.15 [2.59, 3.82]	<.001	3.33 [2.82, 3.94]	<.001	3.27 [2.77, 3.87]	<.001	3.28 [2.80, 3.84]	<.001
	Model 3	1915	2.84 [2.25, 3.59]	<.001	3.26 [2.75, 3.87]	<.001	3.21 [2.71, 3.80]	<.001	3.21 [2.73, 3.77]	<.001
	Model 4	1607	2.46 [1.88, 3.21]	<.001	3.00 [2.52, 3.57]	<.001	2.95 [2.48, 3.51]	<.001	2.97 [2.51, 3.51]	<.001
Frequent Bingeing	Model 1	3617	3.68 [3.03, 4.47]	<.001	3.69 [3.03, 4.48]	<.001	3.66 [3.01, 4.44]	<.001	3.74 [3.08, 4.53]	<.001
	Model 2	2730	3.65 [2.91, 4.60]	<.001	3.85 [3.16, 4.69]	<.001	3.75 [3.08, 4.56]	<.001	3.78 [3.11, 4.60]	<.001
	Model 3	1915	3.34 [2.52, 4.43]	<.001	3.74 [3.06, 4.56]	<.001	3.65 [2.99, 4.45]	<.001	3.68 [3.02, 4.50]	<.001
	Model 4	1607	3.14 [2.27, 4.36]	<.001	3.44 [2.80, 4.23]	<.001	3.34 [2.72, 4.09]	<.001	3.38 [2.75, 4.16]	<.001
Hazardous Drinking	Model 1	3617	5.28 [4.45, 6.27]	<.001	5.29 [4.46, 6.27]	<.001	4.97 [4.20, 5.89]	<.001	4.80 [4.06, 5.67]	<.001
	Model 2	2730	4.81 [3.95, 5.86]	<.001	5.44 [4.58, 6.47]	<.001	5.08 [4.28, 6.02]	<.001	4.89 [4.13, 5.79]	<.001
	Model 3	1915	4.81 [3.79, 6.10]	<.001	5.32 [4.47, 6.33]	<.001	4.96 [4.17, 5.90]	<.001	4.76 [4.00, 5.65]	<.001
	Model 4	1607	4.34 [3.32, 5.68]	<.001	5.01 [4.19, 5.99]	<.001	4.66 [3.90, 5.56]	<.001	4.44 [3.72, 5.30]	<.001
Harmful Drinking	Model 1	3617	9.01 [6.63, 12.25]	<.001	9.00 [6.62, 12.24]	<.001	8.40 [6.18, 11.42]	<.001	7.67 [5.62, 10.45]	<.001
	Model 2	2730	8.62 [5.99, 12.41]	<.001	9.14 [6.71, 12.44]	<.001	8.45 [6.21, 11.51]	<.001	7.70 [5.65, 10.50]	<.001
	Model 3	1915	8.02 [5.18, 12.42]	<.001	8.82 [6.45, 12.04]	<.001	8.15 [5.97, 11.13]	<.001	7.49 [5.48, 10.23]	<.001
	Model 4	1607	7.06 [4.17, 11.96]	<.001	7.97 [5.81, 10.95]	<.001	7.33 [5.33, 10.07]	<.001	6.70 [4.88, 9.21]	<.001

Model 1 = unadjusted; model 2 = adjusted for sociodemographic confounders: gender, maternal education, family income, housing tenure, and social class; model 3 = additionally adjusted for parental confounders: parental depression, anxiety, alcohol use, and tobacco use; model 4 = additionally adjusted for adolescent confounders: tobacco use, cannabis use, drinking frequency, binge drinking, conduct problems, and emotional symptoms. AD = available data; Imp#1: n = 3625; 100 imputations; Imp#2: n = 4600; 100 imputations; Imp#3: n = 9278; 200 imputations.

Appendix 3.5. (continued)

			Available data		Imp#1		Imp#2		Imp#3	
	Model	**N**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**
Age 21										
Frequent Drinking	Model 1	2152	1.43 [1.17, 1.76]	.001	1.43 [1.18, 1.74]	<.001	1.43 [1.18, 1.73]	<.001	1.37 [1.13, 1.65]	.001
	Model 2	1678	1.59 [1.24, 2.02]	<.001	1.50 [1.23, 1.84]	<.001	1.51 [1.24, 1.84]	<.001	1.45 [1.19, 1.77]	<.001
	Model 3	1258	1.63 [1.22, 2.16]	.001	1.45 [1.18, 1.79]	<.001	1.47 [1.20, 1.80]	<.001	1.41 [1.15, 1.72]	.001
	Model 4	1084	1.50 [1.10, 2.06]	.012	1.37 [1.10, 1.69]	.005	1.38 [1.12, 1.70]	.002	1.33 [1.08, 1.64]	.008
Frequent Bingeing	Model 1	2152	1.49 [1.21, 1.85]	<.001	1.51 [1.24, 1.84]	<.001	1.50 [1.22, 1.84]	<.001	1.48 [1.21, 1.81]	<.001
	Model 2	1678	1.61 [1.26, 2.06]	<.001	1.58 [1.29, 1.93]	<.001	1.56 [1.27, 1.93]	<.001	1.56 [1.27, 1.92]	<.001
	Model 3	1258	1.61 [1.21, 2.14]	.001	1.52 [1.23, 1.87]	<.001	1.52 [1.23, 1.88]	<.001	1.52 [1.23, 1.88]	<.001
	Model 4	1084	1.48 [1.08, 2.03]	.015	1.45 [1.17, 1.80]	.001	1.44 [1.16, 1.80]	.001	1.46 [1.16, 1.82]	.001
Hazardous Drinking	Model 1	2152	2.15 [1.72, 2.69]	<.001	2.19 [1.75, 2.74]	<.001	2.16 [1.76, 2.65]	<.001	2.23 [1.83, 2.72]	<.001
	Model 2	1678	2.24 [1.73, 2.90]	<.001	2.28 [1.81, 2.86]	<.001	2.23 [1.81, 2.75]	<.001	2.34 [1.92, 2.86]	<.001
	Model 3	1258	2.14 [1.58, 2.90]	<.001	2.21 [1.75, 2.79]	<.001	2.18 [1.76, 2.70]	<.001	2.27 [1.85, 2.79]	<.001
	Model 4	1084	2.12 [1.52, 2.96]	<.001	2.12 [1.67, 2.69]	<.001	2.07 [1.66, 2.57]	<.001	2.15 [1.75, 2.66]	<.001
Harmful Drinking	Model 1	2152	2.56 [1.96, 3.35]	<.001	2.73 [2.13, 3.51]	<.001	2.74 [2.14, 3.51]	<.001	2.63 [2.06, 3.35]	<.001
	Model 2	1678	2.75 [2.02, 3.73]	<.001	2.83 [2.19, 3.65]	<.001	2.82 [2.19, 3.62]	<.001	2.71 [2.12, 3.47]	<.001
	Model 3	1258	2.52 [1.76, 3.59]	<.001	2.70 [2.09, 3.50]	<.001	2.70 [2.09, 3.49]	<.001	2.62 [2.04, 3.36]	<.001
	Model 4	1084	2.33 [1.56, 3.48]	<.001	2.46 [1.88, 3.22]	<.001	2.46 [1.88, 3.22]	<.001	2.40 [1.86, 3.11]	<.001

Model 1 = unadjusted; model 2 = adjusted for sociodemographic confounders: gender, maternal education, family income, housing tenure, and social class; model 3 = additionally adjusted for parental confounders: parental depression, anxiety, alcohol use, and tobacco use; model 4 = additionally adjusted for adolescent confounders: tobacco use, cannabis use, drinking frequency, binge drinking, conduct problems, and emotional symptoms. AD = available data; Imp#1: n = 3625; 100 imputations; Imp#2: n = 4600; 100 imputations; Imp#3: n = 9278; 200 imputations.

Appendix 3.6. Logistic regressions examining the interactions between generalised anxiety disorder and drinking to cope motives at age 18 on alcohol use at age 18 and 21.

			Available data		Imp 1 (n = 3625)		Imp 2 (n = 4600)		Imp 3 (n = 9278)	
	Model	**N**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**
Age 18										
Frequent Drinking	*Stratum specific*									
	Low DTC	2660	0.74 [0.43, 1.27]	.270	0.76 [0.44, 1.30]	.315	0.69 [0.40, 1.19]	.179	0.80 [0.47, 1.35]	.399
	High DTC	792	1.33 [0.86, 2.06]	.204	1.34 [0.87, 2.06]	.188	1.28 [0.84, 1.96]	.258	1.28 [0.82, 2.00]	.270
	Interaction	3452	1.80 [0.90, 3.62]	.098	1.77 [0.88, 3.54]	.108	1.86 [0.93, 3.75]	.081	1.61 [0.83, 3.15]	.161
Frequent Bingeing	*Stratum specific*									
	Low DTC	2660	0.67 [0.31, 1.45]	.309	0.67 [0.31, 1.47]	.319	0.62 [0.29, 1.33]	.222	0.62 [0.29, 1.35]	.231
	High DTC	792	1.11 [0.69, 1.78]	.678	1.15 [0.72, 1.84]	.557	1.10 [0.69, 1.77]	.691	1.13 [0.71, 1.79]	.614
	Interaction	3452	1.66 [0.67, 4.12]	.278	1.71 [0.69, 4.25]	.248	1.77 [0.71, 4.40]	.218	1.81 [0.74, 4.44]	.197
Hazardous Drinking	*Stratum specific*									
	Low DTC	2660	0.95 [0.62, 1.45]	.810	0.96 [0.63, 1.47]	.850	0.94 [0.61, 1.42]	.756	0.99 [0.65, 1.50]	.959
	High DTC	792	0.91 [0.56, 1.48]	.701	0.92 [0.57, 1.49]	.737	0.89 [0.55, 1.42]	.616	0.90 [0.57, 1.43]	.664
	Interaction	3452	0.96 [0.50, 1.82]	.896	0.96 [0.50, 1.82]	.899	0.95 [0.49, 1.82]	.869	0.91 [0.49, 1.72]	.780
Harmful Drinking	*Stratum specific*									
	Low DTC	2660	1.30 [0.40, 4.21]	.664	1.30 [0.40, 4.23]	.659	1.30 [0.41, 4.17]	.658	1.34 [0.43, 4.11]	.613
	High DTC	792	1.10 [0.63, 1.93]	.737	1.12 [0.64, 1.96]	.693	1.09 [0.62, 1.91]	.766	1.11 [0.64, 1.95]	.708
	Interaction	3452	0.85 [0.23, 3.13]	.805	0.86 [0.23, 3.17]	.820	0.84 [0.23, 3.07]	.788	0.83 [0.23, 3.02]	.780

Unadjusted model. Stratified analysis: associations of generalised anxiety disorder at age 18 with alcohol use outcomes at age 18 and 21 in each stratum of drinking to cope motives. Interaction term: interaction of GAD x DTC at age 18 on alcohol use outcomes at age 18 and 21. AD = available data; Imp#1: n = 3625; 100 imputations; Imp#2: n = 4600; 100 imputations; Imp#3: n = 9278; 200 imputations.

Appendix 3.6. (continued)

			Available data		Imp#1		Imp#2		Imp#3	
	Model	**N**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**
Age 21										
Frequent Drinking	*Stratum specific*									
	Low DTC	1621	1.19 [0.73, 1.94]	.493	1.16 [0.71, 1.89]	.550	1.17 [0.75, 1.84]	.488	1.16 [0.75, 1.78]	.502
	High DTC	444	1.19 [0.68, 2.09]	.542	1.17 [0.68, 2.00]	.578	1.23 [0.73, 2.06]	.432	1.30 [0.78, 2.17]	.318
	Interaction	2065	1.00 [0.48, 2.11]	.994	1.00 [0.49, 2.04]	.991	1.05 [0.53, 2.08]	.895	1.12 [0.56, 2.23]	.745
Frequent Bingeing	*Stratum specific*									
	Low DTC	1621	0.89 [0.52, 1.53]	.683	0.89 [0.52, 1.50]	.651	0.86 [0.53, 1.41]	.551	0.88 [0.53, 1.45]	.609
	High DTC	444	0.85 [0.47, 1.51]	.570	0.91 [0.51, 1.61]	.736	0.88 [0.52, 1.49]	.636	0.90 [0.52, 1.57]	.714
	Interaction	2065	0.95 [0.43, 2.09]	.892	1.02 [0.46, 2.27]	.955	1.02 [0.50, 2.09]	.952	1.03 [0.51, 2.09]	.936
Hazardous Drinking	*Stratum specific*									
	Low DTC	1621	1.10 [0.68, 1.80]	.693	1.01 [0.64, 1.59]	.966	0.92 [0.59, 1.45]	.728	0.96 [0.61, 1.51]	.869
	High DTC	444	0.93 [0.50, 1.73]	.813	0.96 [0.53, 1.75]	.905	0.90 [0.50, 1.62]	.719	0.92 [0.53, 1.60]	.766
	Interaction	2065	0.84 [0.38, 1.85]	.667	0.95 [0.45, 2.01]	.903	0.97 [0.46, 2.04]	.942	0.96 [0.44, 2.07]	.907
Harmful Drinking	*Stratum specific*									
	Low DTC	1621	1.54 [0.77, 3.08]	.218	1.56 [0.78, 3.11]	.208	1.63 [0.87, 3.07]	.126	1.73 [0.90, 3.32]	.099
	High DTC	444	1.12 [0.58, 2.14]	.733	1.08 [0.59, 2.00]	.798	1.09 [0.62, 1.92]	.775	1.09 [0.59, 2.02]	.772
	Interaction	2065	0.73 [0.28, 1.87]	.507	0.69 [0.28, 1.71]	.428	0.66 [0.28, 1.59]	.357	0.63 [0.26, 1.56]	.321

Unadjusted model. Stratified analysis: associations of generalised anxiety disorder (GAD) at age 18 with alcohol use outcomes at age 18 and 21 in each stratum of drinking to cope (DTC) motives. Interaction term: interaction of GAD x DTC at age 18 on alcohol use outcomes at age 18 and 21. AD = available data; Imp#1: n = 3625; 100 imputations; Imp#2: n = 4600; 100 imputations; Imp#3: n = 9278; 200 imputations.

Appendix 5.1. Drinking motives checklist (DMC).

INSTRUCTIONS: Below is a list of negative experiences that commonly trigger alcohol drinking. Please read each negative experience and tick YES or NO to indicate if you think it is an important reason for your drinking.

I am more likely to drink when I…	**YES**	**NO**
feel depressed		
feel guilty		
feel empty inside or am bored		
am fed up with life or hopeless		
let myself down		
feel worried, afraid or nervous		
feel tense or jittery		
feel or panicky		
feel wound up or agitated		
am fearful about the future		
feel stressed		
have financial problems or debt		
have difficulties at work		
have problems with housing		
have problems with friends or family		
feel angry or irritable		
am full of resentment		
have been aggressive		
lose my temper		
get into trouble		
feel lonely or isolated		
feel that people don’t like me		
feel someone has let me down		
have been criticised by someone		
argue with friends or family		
feel in pain or discomfort		
feel ill		
have a headache		
feel exhausted		
feel unusual		
can’t control my thoughts		
have trouble thinking clearly		
keep making mistakes		
have difficulty remembering things		
have difficulty getting my words out		