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Investigating causal associations of substance use with mental health and social cognitive performance in adolescence

Investigating causal associations of substance use with mental health and social cognitive performance in adolescence

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Abstract

The high association of substance use and mental health has been extensively researched, however there remains conflicting evidence in the temporal direction of this relationship. This thesis aims to investigate this association using a range of different methods to examine the direction of association between substance use and mental health problems in adolescence, and whether these are likely to be causal. I also examined the possible role of social cognition in this relationship due to its common associations with both substance use and mental health problems.

First, systematic review is used to identify any patterns in the current mental health and substance use literature. Here, I find the evidence is largely mixed and there is a general lack of bidirectional studies and null results reported. Secondly, I conducted a series of longitudinal studies in the Avon Longitudinal Study of Parents and Children (ALSPAC) comparing trends of substance use, mental health, and social cognition in both temporal directions. My results suggested two possible pathways (a) substance use impairs social cognitive performance via poor mental health or (b) substance use independently impairs both social cognitive performance and mental health. Finally, to investigate the causality of these associations I conducted a Mendelian randomisation analyses in the most robust observational results (tobacco initiation, externalising behaviour, and social communication). Here, I found some evidence of an association that genetic risk of tobacco initiation is causally associated with externalising disorders, but no evidence of a causal association of genetic risk of tobacco initiation with social cognition.

The evidence here suggests some evidence of a causal association of tobacco initiation with externalising behavior. However, the observed associations of tobacco on social cognition may be due to environmental or confounding factors. This thesis further highlights the importance of using range of difference methodological and statistical techniques each with differing underlying assumptions when investigating causal inferences.

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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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Table of Abbreviations

A	Adenine
ADHD	Attention-deficit hyperactivity disorder
ALDH2	Aldehyde dehydrogenase 2
ALSPAC	Avon longitudinal study of parents and children
ASPD	Antisocial behaviour personality disorder
AUDIT	Alcohol Use Disorders Identification Test
BAC	Blood alcohol concentration
BDNF	Brain-derived neurotrophic factor
BPD	Borderline personality disorder
BroadABC	Broad Antisocial Behaviour Consortium
CARTA	Consortium for causal analysis research in tobacco and alcohol
CB1R	Cannabinoid 1 receptor
CBD	Cannabinol
CD	Conduct disorder
CI	Confidence intervals
CIS-R	Clinical interview schedule revised
CNG	Centre National de Génotypage
CSEO	Certificate of secondary education
Δ^9-THC	Δ^9-tetrahydrocannabinol
DAG	Directed acyclical graph
DANVA	Diagnostic Analysis of Nonverbal Accuracy
DAWBA	Development and Wellbeing Assessment
DD	Dual diagnoses
DNA	Deoxyribonucleic acid
eCB	Endocannabinoid
G	Guanine
GABA	Gamma-aminobutyric acid
GWAS	Genome-wide association study
ICC	International Cannabis Consortium
IQ	Intelligence quotient
IVW	Inverse-variance weighted approach
LD	linkage disequilibrium
MR	Mendelian randomisation
NTR	Nicotine replacement therapy
nAChRs	Nicotinic acetylcholine receptors
NICE	National Institute for Health and Care Excellence
NMDA	N-methyl-Daspartate
ODD	Oppositional defiant disorder
OPCS	Office of Population Censuses and Surveys
OR	Odds ratio
PGC	Psychiatrics Genomics Consortium
PLIKSi	Psychosis-like symptoms semi-structured interview
PRIMSA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
iPSYCH	Initiative for Integrative Psychiatric Research
RCT	Randomised Controlled Trial
SCDC	Social and Communication Disorders Checklist
SDQ	Strengths and Difficulties Questionnaire
SNP	Single nucleotide polymorphism
SUD	Substance use disorders
TAG	Tobacco and Genetics Consortium
ToM	Theory of mind
WHO	World Health Organisation
WISC II	Wechsler Intelligence Scale for Children-III

1. Chapter One: Introduction

1.1. Adolescent substance use

Using recreational drugs (i.e. chemical substances ingested to induce euphoria or an altered state or of consciousness) at any point in one's lifetime may result in negative health outcomes. However, initiation and frequent use during adolescence has particularly damaging consequences, both short and long-term as adolescence is a period of developmental plasticity. Adolescence is defined as the transition period from childhood to adulthood, and the start (in mammalian species) is generally characterized by the start of sexual maturation. Additionally, this period may differ slightly across sociocultural regions, but approximately ranges from ages twelve to eighteen. This transitional period is characterized by behavioral changes including increased sensation seeking and risk-taking (Spear, 2000, 2013; Yuan, Cross, Loughlin, & Leslie, 2015), resulting from pre-pubertal increased neuroactive adrenal steroids (Forbes & Dahl, 2010; Halasz, Aspan, Bozsik, Gadoros, & Inantsy-Pap, 2013). During this time, the brain is particularly sensitive to experience-dependent plasticity within decision making and executive control areas, specifically the prefrontal cortex (Bernheim, Halfon, & Boutrel, 2013). Adolescence is a period of increased susceptibility to drug use (Agrawal et al., 2006; K. M. King & Chassin, 2007; Rhee et al., 2003), and is the time most individuals' initiate substance use (Hanna, Yi, Dufour, & Whitmore, 2001; S. H. Lai, Lai, Page, & McCoy, 2000). Adolescents typically begin to experiment with alcohol and tobacco, and progress to cannabis and other illicit drugs at later ages (Hanna et al., 2001; S. H. Lai et al., 2000). In England and Wales alone, ~18% of adolescents reported using substances within the past year and ~25% of 15 year-olds reported ever trying illicit substances (Centre, 2016b). Additionally, ~38% of school age children (11 -15) reported ever drinking alcohol (Centre, 2016a), ~35% of 15 year-olds reported ever smoking tobacco (Centre, 2016c), and ~83% of 15 year-olds reported using cannabis in the past year (Centre, 2016b).

1.1.1. Alcohol

Alcohol is a recreational drug containing ethanol (C_2H_5OH), a chemical compound produced through the fermentation of sugar by yeast. Alcoholic beverages are categorised into three classes: beer, wines, and spirits, containing between approximately 3% to 40% alcohol by volume. The effects of alcohol on the brain are dependent upon an individual's blood alcohol concentration (BAC), with low doses producing stimulating effects and high doses depressive effects (Oscar-Berman & Marinkovic, 2007). Furthermore, the pharmacokinetics of alcohol varies greatly as a function of a variety of situational factors

(Bjork & Gilman, 2014), including time since ingestion (Pohorecky & Brick, 1977), drinking rate, metabolic rate, ingestion with food, concentration of alcohol, tolerance, subjective, physiological, motor, cognitive, and additional measures such as age, sex or genetic variations (Bjork & Gilman, 2014; Reed, 1985). Ingestion of alcohol has a range of effects, with acute effects including cognitive impairment and impaired motor coordination and chronic effects including tolerance and dependence (Davies, 2003; R. A. Harris, 1999; Lobo & Harris, 2008). Ethanol is water-soluble and therefore rapidly crosses cell membranes (Marco & Kelen, 1990), being primarily absorbed in the proximal intestinal tract. Alcohol influences a variety of neurotransmitter systems (Bjork & Gilman, 2014; Eckardt et al., 1998), including gamma-aminobutyric acid (GABA), glutamate, serotonin, dopamine, and acetylcholine. At higher concentrations, alcohol binds to cell membranes subsequently altering phospholipid components of cell membranes, while at intoxication levels alcohol interacts with N-methyl D-aspartate (NMDA) and $GABA_A$ receptors to alter ion transport across cell membranes (Bjork & Gilman, 2014; Fadda & Rossetti, 1998). Low doses have stimulating effects, resulting in feelings of euphoria and disinhibition (Brust, 2010), while higher doses lead to depressive effects and stupor (Brust, 2010). A review of acute alcohol intoxication found effects to be strongest and consistent on visuomotor control, divided attention, focused attention, and subjective rating of 'high.' Impairments on response inhibition reaction time, and working memory were consistently observed in doses over 0.07% BAC (Zoethout, Delgado, Ippel, Dahan, & van Gerven, 2011).

Adolescence is a period of neural development and synaptic plasticity; it is therefore unsurprising that adolescents are more sensitive to the rewarding aspects of acute intoxication (Donovan, 2004; Kyzar, Floreani, Teppen, & Pandey, 2016). Additionally, following periods of binge drinking, adolescents experience greater neural reorganisation and degeneration compared to adults (Kyzar et al., 2016; Vetreno, Broadwater, Liu, Spear, & Crews, 2014) suggesting their cellular and molecular mechanisms have differential developmental responses to ethanol. Early onset alcohol use in adolescence is associated with high rates of binge drinking in late adolescence (i.e. high school and college age) and increased risk of later life abuse (Spear, 2015). The estimated chances of becoming addicted to alcohol following the first year of use is 2% (Lopez-Quintero et al., 2011). Alcohol dependence rates are four times higher for individuals whom begin drinking prior to the age of fourteen (Grant & Dawson, 1997). Additionally, age eighteen binge drinking behaviour is a strong predictor of dependency levels at age thirty-five (Merline, Jager, & Schulenberg, 2008). Furthermore, early alcohol use is associated with a range of problems including impaired memory, and executive and visuospatial functioning, as well as decreased grey matter associate with cognitive tasks (Jacobus & Tapert, 2013; Spear, 2014).

1.1.2. Tobacco

Tobacco is a recreational drug, whose primary constituent is nicotine ($C_{10}H_{14}N_2$), among other chemicals, heavy metals, and free radicals (Swan & Lessov-Schlaggar, 2007). Tobacco is primarily smoked in cigarettes, cigars, or pipes although can also be consumed in smokeless forms (e.g. chewing, dipping, snus). Tobacco use is highly addictive; the estimated chances of becoming dependent following the first year of onset is 2%, and (Lopez-Quintero et al., 2011). Tobacco is associated with a range of poor health outcomes, including lung cancer and cardiovascular disease (Doll & Hill, 1950). The World Health Organization, has named tobacco as the world single greatest cause of preventable death (Organisation, 2008; Organization, 2016). Acute nicotine intoxication is associated with increased cognitive performance including reaction time, selective attention, working memory and recognition memory (Swan & Lessov-Schlaggar, 2007). Nicotine enters the brain and binds to presynaptic nicotinic acetylcholine receptors (nAChRs), releasing numerous neurotransmitters involved in cognitive processes including serotonin, dopamine, and glutamate (Di Matteo, Pierucci, Di Giovanni, Benigno, & Esposito, 2007; Heishman, Kleykamp, & Singleton, 2010). Additionally, cholinergic neurons in the prefrontal cortex send projections to numerous cortical and subcortical regions, influencing cognitive functioning and motor control (Heishman et al., 2010; Woolf, 1991).

Adolescents are more susceptible to the rewarding effects of tobacco, and may report dependence at low levels of consumption (Colby, Tiffany, Shiffman, & Niaura, 2000; D. B. Kandel & Chen, 2000). Highly susceptible individuals may report problems quitting before consumption reaches two cigarettes per day (DiFranza, Savageau, Fletcher, O'Loughlin, et al., 2007). Tobacco has increased rewarding effects, and decreased negative withdrawal effects on adolescents (compared to adult smokers) (O'Dell, 2009). Rodent and pre-clinical studies have identified differences in nicotinic activity in adolescent versus adult brains. Adolescent have higher binging and expression of $\alpha 4\beta 2$ and $\alpha 7$ nAChRs compared to adults (Adriani et al., 2003; Doura, Gold, Keller, & Perry, 2008), including increased activity in the thalamus, hippocampus, and striatum (Britton, Vann, & Robinson, 2007; Kota, Martin, Robinson, & Damaj, 2007). Nicotine-enhanced neuronal activity is more robust than adults in multiple reward-related regions including the ventral tegmental area, basolateral amygdala, and nucleus accumbens shell (Dao, McQuown, Loughlin, Belluzzi, & Leslie, 2011; Shram, Funk, Li, & Le, 2007). In adolescence, dopamine neurones in the ventral tegmental area are more sensitive to nicotine-induce potentiation (Placzek, Zhang, & Dani, 2009). Acute nicotine exposure in adolescence, is associated with increased extracellular serotonin overflow in the nucleolus accumbens shell and decreased dopamine and serotonin in medial

prefrontal cortex (Shearman, Fallon, Sershen, & Lajtha, 2008). Adolescents are susceptible to increased self-administration (Adriani, Macri, Pacifici, & Laviola, 2002), intake more nicotine than adults (H. Chen, Matta, & Sharp, 2007; Levin et al., 2007; Natividad, Torres, Friedman, & O'Dell, 2013), and show less aversion to higher doses (Adriani et al., 2002; Shram, Funk, Li, & Le, 2006; Torres, Tejeda, Natividad, & O'Dell, 2008).

1.1.3. Cannabis

Cannabis (alternatively known as marijuana or weed, among a variety of other names) is a recreational drug, whose legality varies across countries. In the United Kingdom cannabis is ranked as a 'Class B' drug under the Misuse of Drugs Act (Office, 2002). However, other countries have decimalised cannabis use, and as of 2017 seventeen countries and some US states have legalised cannabis (C. Rodriguez, 2017). Cannabis is commonly inhaled in by smoking through pipes or rolled into joints. In some areas of the world, such as the United Kingdom, it is most common to roll cannabis together with tobacco to smoke. Additionally, cannabis can be made into food form and ingested. There are approximately one hundred constituents of cannabis, known as cannabinoids. The two most prominent of which are Δ^9-tetrahydrocannabinol (Δ^{9}-THC) and cannabinol (CBD) (Curran et al., 2016). Interestingly, these compounds have differing effects on the body, as Δ^{9}-THC increases anxiety and psychotic-like experiences, and impairs cognition, while CBD decreases anxiety, has anti-psychotic effects, and can aid learning (Curran et al., 2016; Englund et al., 2013; Morgan, Schafer, Freeman, & Curran, 2010). Δ^{9}-THC acts as a partial cannabinoid 1 receptor agonist (CB1R), while CBD has a range of pharmacological effects. CBD attenuates CB1R agonist effects and reduces cellular reuptake of endogenous cannabinoids (endocannabinoid and anandamide) in the brain (Alfaro et al., 2017; Curran et al., 2016; Pertwee, 2008). Current street cannabis contains much higher levels of Δ^{9}-THC comparable to CBD (ElSohly et al., 2016). Cannabis 'high' has a range of effects including feelings of euphoria, heighted senses, and increased appetite (Pertwee, 2014). The estimated chances of becoming addicted to cannabis following the first year of use is 2% (Lopez-Quintero et al., 2011).

There appears to be some age-related effects of cannabis, suggesting in some circumstances, it may be more hazardous to use in adolescence. The endocannabinoid (eCB) system regulates neurodevelopmental processes during adolescence including white-matter development and synaptic pruning. Exogenous cannabinoids may affect the functioning of the eCB system, suggesting chronic use during adolescence may disrupt these maturational processes (Lubman, Cheetham, & Yucel, 2015). Additionally, rodent studies have indicated that exposure of Δ^{9}-THC to adolescent brains results in impaired

object recognition memory (Quinn et al., 2008; Schneider & Koch, 2007), spatial, and non-spatial learning, comparative to adult brains (Cha, White, Kuhn, Wilson, & Swartzwelder, 2006). Additionally, imaging studies suggest individuals whom initiate cannabis use in adolescence display greater recruitment of neural resources, possibly reflecting compensatory activity during task-activity (Curran et al., 2016). Finally, cannabis is commonly considered a 'gateway' drug to more harmful drugs (i.e. cocaine), suggesting there is a sequential progression from 'softer' to 'harder' drugs (those with more detrimental effect on the individual and society as a whole) (D. B. Kandel, 2002). However, the evidence is mixed on this hypothesis.

1.1.4. Multi-substance use

Finally, it should be noted that substance use during adolescence often involves the use of multiple substances, as opposed to each substance individually. This may result from several reasons, one being the purely explorative and sensation seeking nature of the adolescent period (Collins, Ellickson, & Bell, 1998; Maddahian, Newcomb, & Bentler, 1985). Additionally, some substance use behaviours may increase the likelihood of other behaviours (e.g. individuals may be more prone to smoke cigarettes or cannabis after already drinking alcohol) (Martin, Arria, Mezzich, & Bukstein, 1993).

1.2. Substance use and mental health

Previous evidence suggests approximately 64% to 88% of adolescents with substance use disorders (SUDs) have at least one (often more) comorbid mental health problem (Brewer, Godley, & Hulvershorn, 2017; Chan, Dennis, & Funk, 2008; Deas & Brown, 2006; Rowe, Liddle, Greenbaum, & Henderson, 2004; Shane, Jasiukaitis, & Green, 2003; Wu, Gersing, Burchett, Woody, & Blazer, 2011). Adolescents with dual diagnoses (DD) experience exaggerated substance use behaviours, including earlier age of onset, heavier and more frequent use, and higher rates of dependency (Cadoret, Cain, & Crowe, 1983; Shane et al., 2003). Additionally, DD adolescents typically experience family, school, and legal problems (Grella, Hser, Joshi, & Rounds-Bryant, 2001; Horigian et al., 2013), and even with treatment are more likely to experience relapse (Tomlinson, Brown, & Abrantes, 2004). Comparably, adolescents with SUDs that do not have mental health problems respond better to treatment (Rowe et al., 2004).

1.2.1. Internalising disorders

Internalising disorders are grouped into two sub-categories 'distress': depression, anxiety, dysthymia, and 'fear': panic disorder, social phobia, and specific phobia (Hasin &

Kilcoyne, 2012). A recent review estimated that the prevalence of comorbid depression and SUDs in community samples of adolescence ranged from 11.1% to 32% with comorbid anxiety and SUD ranging from 7% to 40% (O'Neil, Conner, & Kendall, 2011). Rates of comorbidity in youth may additionally vary by sex, with higher rates of girls diagnosed with comorbid depression or anxiety and SUD at the age of 16 (E. J. Costello, Erkanli, Federman, & Angold, 1999).

1.2.2. Externalising disorders

Externalising disorders are characterised by aggressive, impulsive, hyperactive, and disruptive behaviours (Hinshaw, 1987). These include attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD), and antisocial behaviour personality disorder (ASPD). A literature review found higher rates of comorbid externalising and SUD diagnoses (ADHD prevalence ranging 3% to 38%; CD prevalence ranging 24% to 82%; ADHD-CD prevalence ranging 27% to 30%) compared to internalising and other mood disorders, with higher rates of diagnosis for males (Couwenbergh et al., 2006).

1.2.3. Psychosis-like disorders

Psychotic disorders are characterised by hallucinations, delusions, and disorganised thought and cognition alongside negative or manic symptoms. These include schizophrenia, schizotypal personality disorder, schizoaffective disorder, bipolar disorder, and delusional disorder (Barkus & Murray, 2010; Heckers et al., 2013). Individuals in the United States with schizophrenia use are 4.6 times more likely to use substances compared to the general population.

1.2.4. Current hypotheses

There are multiple hypotheses surrounding the relationship between mental health disorders and substance use. The ‘self-medication’ theory states that individuals already suffering from mental health disorders (or prodromal symptoms) are drawn to use substances in the belief it may alleviate their symptoms (i.e., self-medication) (Boden, Fergusson, & Horwood, 2010; Chaiton, Cohen, O'Loughlin, & Rehm, 2009; G. Taylor et al., 2014). Other theories suggest prolonged substance use results in changes in neurocircuitry over time and subsequently interferes with emotional and psychological functioning (Johnson & Kaplan, 1990; D. B. Kandel & Davies, 1986a; Markou, Kosten, & Koob, 1998). These theories are not necessarily mutually exclusive, and this association may be bidirectional; for instance, alcohol-abuse and anxiety disorders may initiate and/or trigger

one another (Kushner, Abrams, & Borchardt, 2000). Finally, there may be no causal association between mental health and substance use, and the relationships may be a product of shared risk factors (e.g., common genetic factors) (Munafo & Araya, 2010) or confounding which arises when an extraneous variable (such as sex or socioeconomic position) influences both the exposure and outcome, either directly or indirectly (S. H. Gage, Munafo, & Davey Smith, 2015).

1.3. Social cognition

Social cognition refers to the psychological processes involved in social interaction, comprising self-knowledge, perception of others, and motivational understanding (Brizio, Gabbatore, Tirassa, & Bosco, 2015; C. D. Frith, 2008). Largely, the study of social cognition is centered around childhood, specifically the diagnosis of autism, as autistic individuals are characterized by moderate to severe early onset social cognitive deficits (M. C. Lai, Lombardo, & Baron-Cohen, 2014; Thompson, 1996). However, other life periods, while less studied, are additionally relevant for the understanding of social cognitive functioning. In particular, adolescence, which is a biological and neurodevelopmental phase. Adolescence is a period that individuals begin to make sense of their own self including their feelings, desires, reactions to situations, and ways of reasoning, and need for control (Brizio et al., 2015). Furthermore, few studies examine possible decline of social cognitive ability during childhood through early adulthood (Brizio et al., 2015). Poor social cognitive ability is independently associated with both substance use and mental health problems, which may give insight into a previously unstudied variable in the association of mental health and substance use. While there exists a range of social cognitive abilities, this thesis investigates the following three: non-verbal communication, social communication, and theory of mind/ social reciprocity.

1.3.1. Non-verbal communication

Communication and social interaction does not solely occur through spoken language. Individuals may use body language to relay messages to one another, adding an additional layer of communication upon the verbal messages being delivered (Thompson, 1996). An important aspect of social communication is appropriately identifying these non-verbal signals and adequately returning them alongside verbal conversation (Thompson, 1996). These signals may include posture, gestures, or facial expressions (Gallese, Keysers, & Rizzolatti, 2004; Thompson, 1996). Here, gestures or facial expressions could be used to reinforce verbal messages (behaviour echoing conversation) or contradict them (stating ‘I’m fine’ but expressing irritation or frustration). Non-verbal communication may be

used as a substitution (nodding instead of 'yes'), or to completing speech (smiling while delivering good news). This can be used to accentuate a point (shaking head while stating 'No'), or regulating conversation (hand gestures to speed up conversation) (Thompson, 1996). Furthermore, accurately identifying facial emotions helps to identify others internal states (Elfenbein, Foo, White, Tan, & Aik, 2007). While an entire array of emotions can be expressed facially, a number appear to be universally common including happiness, contempt, sadness, surprise, disgust, fear, and anger (Cole, Jenkins, & Shott, 1989; Galati, Miceli, & Sini, 2001; Galati, Sini, Schmidt, & Tinti, 2003; Matsumoto & Willingham, 2009). Additionally, the expressive intensity of these emotions is may vary from the full emotional expression to a weaker emotionally ambiguous version or a mixture of two emotions (i.e. fear and disgust) (Adams, Penton-Voak, Harmer, Holmes, & Munafo, 2013; De Sonneville et al., 2002; Ekman, 1992). Individuals able to successfully interpret and reciprocate non-verbal cues alongside verbal communication will be more successful in social situations and understanding other's intentions.

1.3.2. Social communication

Social communication or pragmatic language is another aspect of social cognition allowing individuals to verbally transmit their thoughts and feelings to one another. These language-based verbal skills include appropriate use of structure, grammar, and vocabulary (Gibson, Adams, Lockton, & Green, 2013; Gilmour, Hill, Place, & Skuse, 2004; Leonard, 1998). Additionally, speech, tone, and connotation are all used to efficiently portray a message from one individual to another. Speech should be clear, articulate and fluid, while using producing correct sounds in the grammatically correct order (Bishop & Baird, 2001; Gilmour et al., 2004). Conversation should flow effortlessly between individuals without either being interrupted and should be coherent and intelligible (Bishop & Baird, 2001; Gilmour et al., 2004). The context of conversations generally should exist around interest to the listener, and responses should be based and appropriated adjusted on one another's' cues (i.e. reaction to sarcasm)(Bishop & Baird, 2001; Gilmour et al., 2004).This facilitates social reciprocity, or the back-and-forth flow of conversation, in which two individually can effortlessly influence the next one's behavior (Constantino & Todd, 2000). Individuals with poor social communication skills may have difficulties understanding forming strong social bonds depending on the severity of their impairments

1.3.3. Theory of mind

Theory of Mind (ToM), or mentalising, is the understanding that others' behaviors are based from their own thoughts and minds (C. Frith & Frith, 2005), and to understand this we

must project ourselves 'into their shoes.' Understanding that others, like ourselves, have their own knowledge, desires, beliefs, and at times these systems will be in conflict (with our own) (C. Frith & Frith, 2005). This enables us to understand that another's knowledge may be different from ours due to the information provided to them. For example, if John places a candy in a cupboard then leaves a room, and Jane enters the room and moves the candy to the shelf. Where would John look when he returned to the room? An individual with good ToM skills would suggest John would still look in the cupboard for his candy as he would have no knowledge that Jane had entered the room and moved the location, only an observer has this additional knowledge (C. Frith & Frith, 2005; Mahy, Moses, & Pfeifer, 2014). ToM is associated with a range of important social developmental interactions including deception, false beliefs, teaching, and capacity to empathize (C. Frith & Frith, 2005).

1.3.4. Social cognition and substance use

Substance use is associated with impaired social cognitive performance. Studies indicate that alcohol, tobacco, and cannabis may disrupt non-verbal communication. Acute intoxication from alcohol is associated with decreased reactivity to threat cues (Curtin, Patrick, Lang, Cacioppo, & Birbaume, 2001), and alcohol dependent individuals display reduced accuracy in judging sadness and disgust and require greater emotional intensity to detect fear and anger (Donadon & Osorio Fde, 2014). These impairments persist when alcohol dependent individuals are detoxified (Townshend & Duka, 2003) and can be sustained up to two months into sobriety (Kornreich et al., 2001). In daily cigarette smokers, deficits become apparent when individuals are tobacco deprived. Acute withdrawal in smokers is associated with reduced processing of happy faces relative to neutral faces (Leventhal et al., 2012) and disrupted attentional bias to facial stimuli (Adams, Attwood, & Munafo, 2014). Chronic cannabis use is associated with a reduced ability in emotion identification, specifically negative emotions (Bayrakci et al., 2015). However, the acute effects of different cannabinoids are distinct, as THC *impairs* affect recognition, but CBD *improves* affect recognition (Hindocha et al., 2015).

Experimental studies also display acute alcohol intoxication results in impaired ToM (Mitchell, Beck, Boyal, & Edwards, 2011). Alcohol dependent individual display ToM deficits, as they have difficulty identifying their own mental states and those of social partners (Bosco, Capozzi, Colle, Marostica, & Tirassa, 2014; Nandrino et al., 2014). Chronic cannabis users display no change in ToM during task performance compared to healthy

controls. However, when compared at the neuroanatomical level they show differential network activation. Heavy cannabis users display less activation in the left parahippocampal gyrus, right precuneus and cuneus, but greater activation in the left cuneus and right anterior cingulate gyrus, suggesting changes at the physiological level (Roser et al., 2012). This indicates aberrant or greater activity of ToM network, and similar changes have been observed in at-risk psychosis populations (Marjoram et al., 2006; Roser et al., 2012). Long-term cannabinoid exposure may result in changes and functionality of the endocannabinoid system, and subsequent desensitization of CB_1 receptors and may explain the compensatory elevated CB_1 receptors elsewhere in the striatum (Romero et al., 1997) observed in heavy cannabis users compared to controls (Sim-Selley, 2003).

1.3.5. Social cognition and mental health

Many of the same mental health conditions that are highly comorbid with substance use behaviours, are also characterized by poor social cognitive performance. Children or adolescents with internalising or externalising disorders show decreased recognition of facial affect and lower performance on ToM tasks compared to controls (Happe & Frith, 2014; Miers, Blote, de Rooij, Bokhorst, & Westenberg, 2013; Wagner, Muller, Helmreich, Huss, & Tadic, 2015). Psychotic disorders, which often manifest in adolescence, are characterised by multiple social cognitive deficits, and these often remain present even when the acute illness is in remission, continuing to impair social adjustment (Mercedes Perez-Rodriguez, Mahon, Russo, Ungar, & Burdick, 2015). Therefore, understanding different facets of social cognition in relation to these disorders and substance use behaviours, in order to understand whether social cognition plays a larger role in the relationship between mental health and substance use.

1.4. Causality

Ideally, to determine the effects an exposure has on an outcome we would run a randomised controlled trial (RCT). Here, individuals would be randomly assorted into an exposure or control group. Follow up over time would display any differences between groups which may be attributed to the exposure (S. H. Gage, Munafo, et al., 2015). However, particularly in substance use research, RCTs are typically impossible due to obvious ethical and practical constraints. Therefore, observational data are used, and exposure-outcome relationships examined through patterns in the general population (S. H. Gage, Munafo, et al., 2015) using analyses such as case-control, cross- sectional, longitudinal, cohort, and ecological studies. However, when the ability to randomise is lost, we lose control over the exposure of interest and the associations that arise may not be

causal. Therefore, any observed associations that arise may be due to reverse causation, residual confounding, or bias (Smith & Ebrahim, 2002). Reverse causation questions the temporality of the exposure and outcome of interest- while the two may be associated, it is possible this association exists in the opposing direction of the research question (i.e. the outcome may be influencing the exposure). For example, self-medication of one's mental health problems (exposure) may lead to subsequent substance use (outcome) problems; alternatively, prolonged substance use (exposure) resulting in neurological changes may subsequently decrease one's mental health (outcome). Confounding arises when an extraneous variable influences both the exposure and outcome either directly or indirectly (S. H. Gage, Munafo, et al., 2015) (e.g. gender is associated with both smoking behaviour and mental health problems.) Studies may address confounding by adjusting for known covariates within the analysis; however, this will always be incomplete due to any unknown/unmeasured confounders that may exist or measurement error (Fewell, Davey Smith, & Sterne, 2007; Phillips & Smith, 1992; Smith & Phillips, 1992). Selection bias arises from the nature of recruitment and measurement in observational research (Ebrahim & Smith, 2013) (e.g. drug users are less likely to be in the demographic that participate in cohort and survey data).To improve causal inference, there are a range of alternative statistical methods that attempt to address the problems inherent in observational data. These include instrument variable analysis, negative controls, cross-contextual, and family studies.

This thesis implements the use of a type of instrumental variable analysis called Mendelian randomisation (MR). MR analysis uses genetic variants robustly predicting a phenotype as an unconfounded proxy for that exposure (Burgess et al., 2015). It is based on the principle that individuals' inherit a random assortment of genes from their parents, and these genes should not be associated with potential confounders (Munafo & Araya, 2010). Therefore, in theory, a robust genetic influence to a particular exposure (e.g., smoking) would be comparable to a randomised trial in which individuals are assigned to a high or low exposure group (S. H. Gage, Smith, Zammit, Hickman, & Munafo, 2013). In addition, environmental factors cannot affect the genes that an individual is born with so analyses are not subject to reverse causality or residual confounding (Bowden, Davey Smith, & Burgess, 2015; S. H. Gage, Munafo, et al., 2015). There are some limitations to MR; this approach will be unavailable if there are no known genetic associations with a phenotype of interest. Large sample sizes are required to observe associations between genetic variants and outcomes. Finally, the genetic instrument may have pleiotropic effects (i.e. one gene effects multiple phenotypes) on the outcome and exposure, resulting in spurious findings (Bowden et al., 2015).

1.5. Aims of this thesis

The primary aim of this thesis is to determine the direction of effects, and causality of substance use behaviours and mental health outcomes in the adolescent period, and whether these effects are mediated or exacerbated by social cognitive deficits. While substance use and mental health has been studied extensively before, this attempts to address a few important issues.

First, I attempted to identify trends and/or gaps in the current substance use and mental health literature. Secondly, I attempted to use observational analyses to identify poor social cognitive performance as an additional contributing factor in either temporal direction due to its common association with both poor mental health and substance use behaviour. Finally, I attempted to use Mendelian randomisation analysis to identify any possible causal effects in previous observational analyses. Overall, this thesis examines the effects of mental health, substance use, and social cognition in adolescence as opposed to that of hardened users commonly observed in substance use literature. This thesis largely examines tobacco use, however integrates effects of alcohol and cannabis where possible to determine any patterns across the three highest globally consumed drugs. Finally, I implemented a range of methodologies allowing me to triangulate evidence across differing statistical and analytical approaches (S. H. Gage, Munafo, et al., 2015; Taylor & Munafo, 2016).

1.5.1. Systematic review (Chapter 2)

Through systematic review I sought to evaluate the current literature on the direction of tobacco use and internalising disorders (depression and anxiety). I examined longitudinal studies with tobacco use as an exposure and depression/anxiety as outcome or vice versa. My primary aims were to determine if there is a dominant temporal direction in the literature, including bidirectional. My secondary aims were to determine whether there were any gaps in the current literature.

1.5.2. Observational studies (Chapter 4 & 5)

I used a series of observational analyses conduced in the Avon Longitudinal Study of Parents and Children (ALSPAC) to investigate associations of substance use, mental health disorders, and social cognitive performance. I examined the temporal associations of mental health and substance use, and paralleled each analysis replacing the outcome with social cognition to identify any similar trends in the directionality.

1.5.3. Genetic Epidemiology (Chapters 6 & 7)

In the final two analyses, I used genetic variants associated with tobacco initiation to conduct Mendelian randomisation analyses to identify any possible causal effects of associations identified in our observational analyses.

1.6. Hypotheses

I hypothesize there will be an association of poor social cognitive performance with substance use and mental health problems, specifically mediating both temporal directions. Substance use will be associated with decreased social cognitive performance, this decreased ability to communicate and comprehend others' intentions and emotions will in turn result in decreased mental health. Additionally, poor mental health problems will be associated with poor social communicative and emotional behaviours and subsequently substance use to self-medicate or as compensatory methods.

2. Chapter Two: Systematic Review

2.1. Introduction

2.1.1. Systematic Review

Systematic reviews comprehensively appraise a specific research question and synthesises the relevant research to date to provide a conclusion of the current clinical standpoints (J. D. Harris, Quatman, Manring, Siston, & Flanigan, 2014; Moher, Liberati, Tetzlaff, Altman, & Group, 2009). They represent the gold standard for evaluating health care evidence and are commonly used to develop clinical guidelines and practice (Moher et al., 2015). By 2011, approximately 11 systematic reviews were being published daily (Bastian, Glasziou, & Chalmers, 2010). Systematic reviews are based on strict pre-defined protocols listing inclusion/exclusion criteria and methods, ensuring careful planning, transparency, and research integrity. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), is a 27-item checklist developed in 2009 to improve reporting across systematic reviews (Moher et al., 2009). PRIMSA have additionally developed a flow-diagram and analysis protocol all publicly available (http://www.prisma-statement.org/) on their website. This standardisation of systematic reviews ensures the completeness, accuracy and transparency required to synthesise clinical data.

2.1.2. Background

The high co-occurrence of smoking and mental illness is a major public health concern, and smoking accounts for much of the reduction in life expectancy associated with mental illness (Royal College of Physicians, 2013). Many studies report a positive association between smoking and mental illness, with smoking rates increasing with the severity of the disease (M. Farrell et al., 1998; Meltzer H, 1996). Individuals with mental illness also tend to start smoking at an earlier age, smoke more heavily, and are more addicted to cigarettes than the general population. For example, a recent survey suggests that 42% of all cigarettes consumed in England are consumed by those with mental illness, although this includes substance use disorders (McManus S, 2010). Additionally, while cigarette consumption in the general population has shown a sustained decrease over the past 20 years, consumption among smokers with mental illness has remained relatively unchanged (Royal College of Physicians, 2013). There is therefore a pressing need to understand the mechanisms underlying the high rate of smoking in people with mental illness. Here we focus specifically on the relationship between cigarette smoking, and depression and anxiety.

Currently, there are several hypotheses that have been proposed to explain the high rates of smoking in people with depression and anxiety. The self-medication hypothesis postulates that individuals turn to smoking to alleviate their symptoms (Boden et al., 2010; Chaiton et al., 2009; G. Taylor et al., 2014), and therefore suggests that symptoms of depression and anxiety may lead to smoking. An alternative hypothesis is that smoking may lead to depression or anxiety, through effects on an individual's neurocircuitry that increases susceptibility to environmental stressors. Animal models indicate that prolonged nicotine exposure dysregulates the hypothalamic-pituitary-adrenal system, resulting in hypersecretion of cortisol and alterations in the activity of the associated monoamine neurotransmitter system, whose function is to regulate reactions to stressors (Markou et al., 1998), an effect that appears to normalise after nicotine withdrawal (Rose, Behm, Ramsey, & Ritchie, 2001). The association between smoking and depression/anxiety may also be bidirectional, with occasional smoking initially used to alleviate symptoms, but in fact worsening them over time (Munafo & Araya, 2010). Finally, there may in fact be no causal relationship between smoking and depression/anxiety. Instead, the association may be a product of shared risk factors (e.g., common genetic influences) (Kendler et al., 1993; Munafo & Araya, 2010) or confounding. Smokers may also report that cigarettes alleviate their symptoms due to the misattribution of withdrawal relief. Given the short half-life of nicotine, which results in withdrawal symptoms (including mood symptoms) after a short period of abstinence, smokers may misattribute the relief of short-term withdrawal as reflecting a genuine anxiolytic effect of smoking (G. Taylor et al., 2014). That is, withdrawal symptoms of increased anxiety and negative affect may be misattributed as reflecting genuine mood symptoms, which would lead to the impression that smoking improves mood.

We are therefore presented with multiple different hypotheses regarding whether there is a causal relationship between smoking and depression/anxiety, and if so what the direction of causality underlying this relationship is. While experimental studies are generally not possible, for both practical and ethical reasons, longitudinal studies may help inform our understanding of the causal relationship between smoking and depression/anxiety by clarifying the temporal association. This study aimed to systematically review the literature comprising longitudinal studies of the associations between smoking and depression/anxiety and conduct meta-analyses where possible. To the best of our knowledge this is the first systematic review of this literature.

2.1.3. Chapter aims

This chapter uses systematic review to examine longitudinal association of cigarette smoking with depression and/or anxiety in both temporal directions. Here, my main goals are to identify any major trends or gaps in the current literature.

This chapter Is largely based on a published manuscript: Fluharty, M., Taylor, A. E., Grabski, M., & Munafò, M. R. (2017). The Association of Cigarette Smoking with Depression and Anxiety: A Systematic Review. *Nicotine & Tobacco Research*, *19*(1), 3–13. http://doi.org/10.1093/ntr/ntw140

2.2. Methods

2.2.1. Identification of studies

We searched PubMed, Scopus, and Web of Science up until 1th August 2015 using the following search terms: depressi*, anxi*, smok*, tobacco, nicotine, cigarette, caus*, cohort, prospective, longitudinal. The term animal* was specified for exclusion. Two authors (MF and AT) reviewed the electronic abstracts, selecting the full-text articles to be included.

2.2.2. Selection criteria

Studies were included in the review if they met the following criteria: 1) human participants, 2) smoking as the exposure variable and depression and/or anxiety as the outcome variable or *vice versa* (depression and/or anxiety as the exposure variable and smoking as the outcome variable), 3) longitudinal study design, and 4) reported primary data not previously reported elsewhere. Studies involving cessation, withdrawal, suicide, or trauma, that recruited participants who were pregnant or diagnosed with a psychiatric illness other than depression or anxiety, or included participants with depression and anxiety comorbid with another psychiatric illness, were excluded. Studies not utilising a validated diagnostic test for depression or anxiety were excluded. Studies investigating the association of parental smoking on offspring outcomes were also excluded, as were all experimental studies (e.g., randomised controlled trials [RCTs] of smoking cessation interventions). RCTs as well as secondary analyses of RCTs were excluded.

2.2.3. Data Extraction

The following information was extracted from each of the included studies: type of depression/anxiety (major depression; generalised anxiety disorder; mixed major depression and generalised anxiety disorder), method of measuring depression/anxiety (self-report via

diagnostic test, clinical interview, or physician diagnosis) and scale used (continuous or categorical), smoking behaviour (age of smoking onset; smoking status; heaviness of smoking; tobacco dependence; smoking trajectory), sample size, mean age of participants and sex distribution of participants, population sampled (e.g., general or clinical), and length of follow up. A 100% data check was performed by the main author (MF) and a 10% data check was independently performed by second author (MG) to identify data extraction errors. Any errors identified were resolved by mutual consent.

2.2.4. Rationale for not conducting meta-analysis

A meta-analysis was not conducted as, even within the general population samples available, there was substantial heterogeneity (age, location, covariates used, time to follow-up, number of times and frequency of outcomes sampled). Additionally, the studies included were not limited to only those examining an *a priori* hypothesis of mental health and smoking; studies were included if they contained the desired outcome and exposure variables within their dataset.

2.3. Results

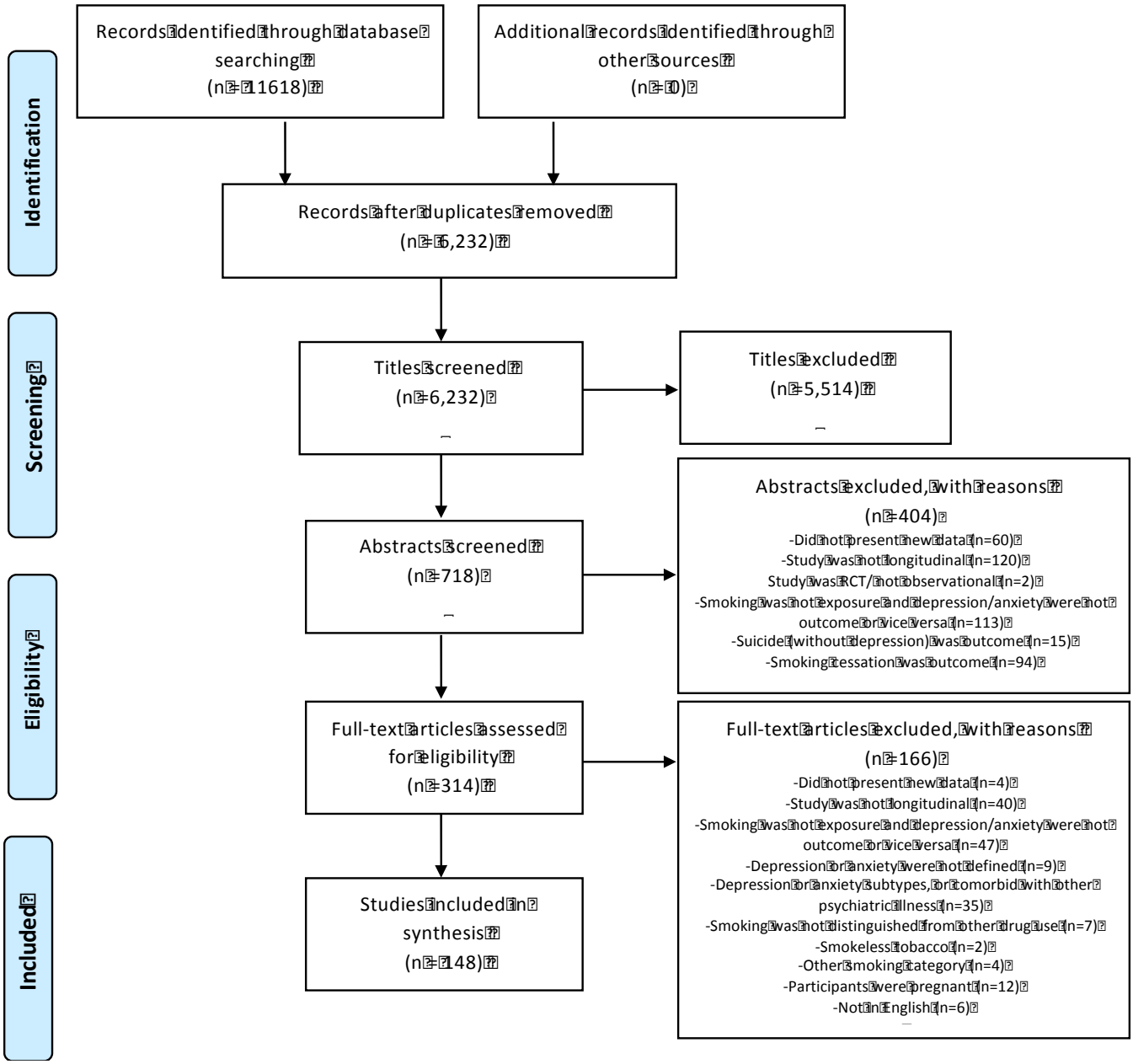
2.3.1. Characteristics of Included Studies

Of the 6,232 abstracts reviewed, 5,514 were excluded on the basis of title and 404 after reviewing the abstract. In total, 314 articles were retrieved and assessed for eligibility, and 148 met inclusion criteria (Figure 2.1). Details of included studies and excluded full text studies are provided in the appendix (see Appendix A pages 148 & 163).

Studies ranged in sample size from 59 to 90,627 participants, and in length of follow up from 2 months to 36 years. Of the 148 included studies, 99 (67%) recruited male and female participants, 16 (11%) recruited only females and 7 (5%) recruited only males, while 26 (18%) did not report the sex of the participants. In addition, 101 studies (70%) sampled participants from the general population, 15 (10%) from clinical populations and 16 (10%) from particular ethnic groups, while 16 (10%) had other selection criteria (see Appendix A page 148)

Unless otherwise stated, the associations described refer to a positive relationship between smoking and depression/anxiety (i.e., smoking is associated with increased depression/anxiety, or increased depression/anxiety is associated with increased smoking).

Figure 2.1 Identification of independent studies for inclusion in systematic review.



2.3.2. Smoking Categories

Studies were categorised based on the smoking behaviour(s) they assessed: smoking onset, smoking status, smoking heaviness, tobacco dependence, and smoking trajectory. Studies with measures of daily or weekly cigarette use were included in the smoking heaviness category. Studies that were able to establish the onset of smoking from an initially non-smoking population were included in the smoking onset category. Studies that measured tobacco dependence, for example through the DSM-IV (*Diagnostic and statistical manual of mental disorders*, 2000) or the Fagerström Test for Nicotine Dependence (Fagerstrom, Heatherton, & Kozlowski, 1990), were included in the tobacco dependence category. Studies that tracked the different paths of cigarette smoking uptake and use in a cohort were included in the smoking trajectory category, and studies that defined smokers in purely categorical terms (e.g., current, former, never) were included in the smoking status category. Table 2.1 summarises the directions of associations investigated within the studies in each smoking category.

Table 2.1: Directions of associations investigated by smoking category.

Category	Depression			Anxiety			Comorbid Depression and Anxiety		
	MH into smoking	Smoking into MH	Bidirectional	MH into smoking	Smoking into MH	Bidirectional	MH into smoking	Smoking into MH	Bidirectional
Smoking onset	13	0	1	4	0	2	5	0	1
Smoking status	29	40	8	0	4	1	1	7	0
Smoking heaviness	9	7	2	1	1	0	0	1	0
Tobacco dependence	12	2	1	6	0	0	5	1	0
Smoking trajectory	7	2	0	1	0	0	1	1	0
Any smoking category	70	51	12	12	5	3	12	10	1

The number of studies investigating each direction(s) of association for each smoking category is shown. Studies investigating multiple directions are repeated within smoking category. Please note, these only include directions investigated and differ from the overall findings within smoking groups detailed in Figure 2. MH = mental health outcome.

2.3.3. Smoking Onset

A total of 14 studies investigated the association of baseline depression with subsequent smoking onset, of which 10 (71%) found evidence to support this association (Breslau, Peterson, Schultz, Chilcoat, & Andreski, 1998; Brown, Lewinsohn, Seeley, & Wagner, 1996; Carvajal & Granillo, 2006; J. Chen et al., 2013; Fuemmeler et al., 2013;

Holahan et al., 2011; Killen et al., 1997; S. M. King, Iacono, & McGue, 2004; Naicker, Galambos, Zeng, Senthilselvan, & Colman, 2013; Weiss, Mouttapa, Cen, Johnson, & Unger, 2011) while 4 (29%) found no evidence of an association (E. Goodman & Capitman, 2000; O'Loughlin, Karp, Koulis, Paradis, & DiFranza, 2009; Senol, Donmez, Turkay, & Aktekin, 2006; Wiesner & Ittel, 2002). Five studies investigated the association of baseline anxiety on smoking onset, of which 4 (80%) found evidence to support an association with increased risk of smoking onset (Cuijpers, Smit, ten Have, & de Graaf, 2007; Marmorstein, White, Loeber, & Stouthamer-Loeber, 2010; Senol et al., 2006; Swendsen et al., 2010) and 1 (20%) found no evidence of an association (Brown et al., 1996). Six studies investigated the association of comorbid depression and anxiety with later smoking onset, of which 2 (33%) found evidence to support this association (Escobedo, Reddy, & Giovino, 1998; Patton et al., 1998), while 1 (17%) reported comorbid depression and anxiety was associated with reduced risk of smoking onset (Fischer, Najman, Williams, & Clavarino, 2012) and 3 (50%) found no evidence of an association (Hayatbakhsh, Mamun, Williams, O'Callaghan, & Najman, 2013; Leff et al., 2003; Pedersen & von Soest, 2009). One study investigated the association of smoking onset with later depression, finding evidence for this association (Breslau et al., 1998). One study investigated the association of smoking onset with later anxiety, finding no evidence for this association (Brown et al., 1996). Additionally, one study investigated the association of smoking onset with later comorbid depression and anxiety, finding no evidence for this association (Patton et al., 1998). These findings are summarised in Figure 2.2.

Figure 2.2 Main outcomes by smoking category

The main findings for each smoking category, and whether the association was found to be positive, negative or null for each direction of association investigated, is shown

2.3.4. Smoking Status

A total of 37 studies investigated the association of baseline depression with subsequent smoking status, of which 33 (89%) found evidence to support this association (Anda et al., 1990; Appleton et al., 2013; Audrain-McGovern, Lerman, Wileyto, Rodriguez, & Shields, 2004; Audrain-McGovern, Rodriguez, & Kassel, 2009; Audrain-McGovern, Rodriguez, Rodgers, & Cuevas, 2011; Black, Sussman, Johnson, & Milam, 2012; Bomba, Modrzejewska, Pilecki, & Ślosarczyk, 2004; Braithwaite et al., 2015; J. S. Brook, Balka, Ning, Whiteman, & Finch, 2006; Brown et al., 1996; Brummett et al., 2003; Byers et al., 2012; Carvajal, 2012; H. K. Clark, Ringwalt, & Shamblen, 2011; Coogan et al., 2014; Fleming, Mason, Mazza, Abbott, & Catalano, 2008; Franko et al., 2005; Gritz et al., 2003; D. B. Kandel & Davies, 1986b; Knekt et al., 1996; Leiferman, 2002; Leung, Gartner, Hall, Lucke, & Dobson, 2012; Leve, Harold, Van Ryzin, Elam, & Chamberlain, 2012; Mendel,

Berg, Windle, & Windle, 2012; Miller-Johnson, Lochman, Coie, Terry, & Hyman, 1998; Needham, 2007; Niemela et al., 2009; Park, Weaver, & Romer, 2009; Prinstein & La Greca, 2009; Repetto, Caldwell, & Zimmerman, 2005; Wickrama & Wickrama, 2010), while 4 (11%) found no evidence of an association (Audrain-McGovern et al., 2006; Kang & Lee, 2010; van Gool et al., 2007; Wang, Fitzhugh, Turner, Fu, & Westerfield, 1996). One study investigated the association of anxiety with later smoking status, finding evidence of an association (Cuijpers et al., 2007). One study investigated the association of comorbid depression and anxiety with later smoking status, finding no evidence of an association (Ferdinand, Blum, & Verhulst, 2001).

A total of 51 studies investigated the association of smoking status with later depression, of which 37 (73%) found evidence to support this association (Albers & Biener, 2002; Almeida et al., 2013; Audrain-McGovern et al., 2009; Batterham, Christensen, & Mackinnon, 2009; J. S. Brook, Schuster, & Zhang, 2004; Brown et al., 1996; Buckner & Mandell, 1990; Choi, Patten, Gillin, Kaplan, & Pierce, 1997; Clyde, Smith, Gariepy, & Schmitz, 2014; Colman et al., 2011; D. M. Costello, Swendsen, Rose, & Dierker, 2008; de Jonge et al., 2006; Dugan, Bromberger, Segawa, Avery, & Sternfeld, 2014; Duncan & Rees, 2005; Flensborg-Madsen et al., 2011; E. Goodman & Capitman, 2000; Gravely-Witte, Stewart, Suskin, & Grace, 2009; Green et al., 1992; Kang & Lee, 2010; Khaled et al., 2012; Klungsoyr, Nygard, Sorensen, & Sandanger, 2006; Kocer, Wachter, Zellweger, Piazzalonga, & Hoffmann, 2011; Korhonen et al., 2007; Leung et al., 2012; Meng & D'Arcy, 2014; Moon, Mo, & Basham, 2010; Needham, 2007; Paffenbarger, Lee, & Leung, 1994; Pasco et al., 2008; S. B. Patten et al., 2010; D. Rodriguez, Moss, & Audrain-McGovern, 2005; Schrader, Cheok, Hordacre, & Guiver, 2004; Schrader, Cheok, Hordacre, & Marker, 2006; Silberg, Rutter, D'Onofrio, & Eaves, 2003; Stein, Newcomb, & Bentler, 1996; Sweeting, West, & Der, 2007; Tanaka, Sasazawa, Suzuki, Nakazawa, & Koyama, 2011), while 14 (27%) found no evidence of this association (Aneshensel & Huba, 1983; Anstey, von Sanden, Sargent-Cox, & Luszcz, 2007; Braithwaite et al., 2015; C. Clark et al., 2007; Cuijpers et al., 2007; S. H. Gage, Hickman, et al., 2015; Julian et al., 2011; Munafo, Hitsman, Rende, Metcalfe, & Niaura, 2008; Park et al., 2009; Repetto et al., 2005; Strong, Juon, & Ensminger, 2014; Takeuchi, Nakao, & Yano, 2004; Wang et al., 1996; Weyerer et al., 2013). Four studies investigated the association of smoking status with later anxiety, of which 2 (50%) found evidence to support this association (Cuijpers et al., 2007; Moylan et al., 2013), while 2 (50%) found no evidence of an association (Brown et al., 1996; S. H. Gage, Hickman, et al., 2015). Seven studies investigated the association of smoking status with later comorbid depression and anxiety, of which 5 (71%) found evidence to support this association (Boyes, Girgis, D'Este, Zucca, & Lecathelinais, 2013; Fergusson, Boden, & Horwood, 2011; Patel, Kirkwood, Pednekar,

Weiss, & Mabey, 2006; Pedersen & von Soest, 2009; Wagena, van Amelsvoort, Kant, & Wouters, 2005), while 2 (29%) found no evidence of an association (Bjorngaard et al., 2013; D. B. Clark & Cornelius, 2004). These findings are summarised in Figure 2.2.

2.3.5. Smoking Heaviness

A total of 11 studies investigated the association of baseline depression with subsequent heaviness of smoking, of which 8 (73%) found evidence that depression was associated with heavier rates of smoking (D. W. Brook, Brook, & Zhang, 2014; Fergusson, Goodwin, & Horwood, 2003; Holahan et al., 2011; Lekka, Lee, Argyriou, Beratis, & Parks, 2007; Maslowsky, Schulenberg, & Zucker, 2014; van Gool et al., 2003; Whitbeck, Yu, McChargue, & Crawford, 2009; Windle & Windle, 2001), while 2 (18%) found that depression was associated with reduced heaviness of smoking (O'Loughlin et al., 2009; C. A. Patten et al., 2003), and 1 (09%) found no evidence of an association (Beal, Negriff, Dorn, Pabst, & Schulenberg, 2013). One study investigated the association of baseline anxiety with subsequent smoking heaviness and found no evidence of an association (Lekka et al., 2007). Eight studies investigated the association of heaviness of smoking with later depression, of which 7 (88%) found evidence to support this association (Beal et al., 2013; Clyde et al., 2014; Galambos, Leadbeater, & Barker, 2004; Kendler et al., 1993; Klungsoyr et al., 2006; Paffenbarger et al., 1994; Windle & Windle, 2001), while 1 (13%) found no evidence of an association (D. W. Brook, Brook, Zhang, Cohen, & Whiteman, 2002). One study investigated the association of heaviness of smoking with later anxiety, and found evidence to support this association (Okeke, Spitz, Forman, & Wilkinson, 2013). One study investigated the association of heaviness of smoking with later comorbid depression and anxiety, finding no evidence of an association (Bjorngaard et al., 2013). These findings are summarised in Figure 2.2.

2.3.6. Tobacco Dependence

A total of 13 studies investigated the association of baseline depression with subsequent tobacco dependence, of which 12 (92%) found evidence to support this association (Bardone et al., 1998; Breslau, Kilbey, & Andreski, 1993; J. S. Brook, Brook, & Zhang, 2008; DiFranza, Savageau, Fletcher, Pbert, et al., 2007; Fergusson et al., 2003; Hamdi & Iacono, 2014; Denise B. Kandel, Hu, Griesler, & Schaffran, 2007; Karp, O'Loughlin, Hanley, Tyndale, & Paradis, 2006; Kendler & Gardner, 2001; Kleinjan et al., 2010; Racicot, McGrath, Karp, & O'Loughlin, 2012; Swendsen et al., 2010) while 1 (8%) found no evidence of an association (Tully, Iacono, & McGue, 2010). Six studies investigated the association of

baseline anxiety with later tobacco dependence, of which 2 (33%) found evidence to support this association (Goodwin, Fergusson, & Horwood, 2004; Denise B. Kandel et al., 2007), while 4 (67%) found no evidence of an association (Bardone et al., 1998; Breslau et al., 1993; DiFranza, Savageau, Fletcher, Pbert, et al., 2007; Woodward & Fergusson, 2001). Five studies investigated baseline comorbid depression and anxiety with subsequent tobacco dependence, of which 3 (60%) found evidence to support this association (Goodwin et al., 2013; McKenzie, Olsson, Jorm, Romaniuk, & Patton, 2010; Patton, Coffey, Carlin, Sawyer, & Wakefield, 2006) while 2 (40%) found no evidence of an association (Griesler, Hu, Schaffran, & Kandel, 2008; Pedersen & von Soest, 2009). Three studies investigated the association of tobacco dependence with later depression, of which 2 (67%) found evidence to support this association (Boden et al., 2010; Breslau et al., 1993), while 1 (33%) found no evidence of an association (Hu, Griesler, Schaffran, & Kandel, 2011). Two studies investigated the association of tobacco dependence with later comorbid depression and anxiety, of which 1 (50%) found evidence to support this association (Jamal, Willem Van der Does, Cuijpers, & Penninx, 2012), while 1 (50%) found no evidence of an association (Griesler et al., 2008). These findings are summarised in Figure 2.2.

2.3.7. Smoking Trajectory

A total of 7 studies investigated the association of baseline depression with smoking trajectory, of which 1 (14%) reported that depressive symptoms were associated with accelerated cigarette use (Hooshmand, Willoughby, & Good, 2012), 3 (43%) reported that depressive symptoms were associated with early smoking onset (Audrain-McGovern, Rodriguez, et al., 2004; J. S. Brook et al., 2006; Fuemmeler et al., 2013), 1 reported that depressive symptoms were associated with late onset smoking (Saules et al., 2004) and 2 (29%) found no evidence of an association (Juon, Ensminger, & Sydnor, 2002; H. R. White, Violette, Metzger, & Stouthamer-Loeber, 2007). One study reported evidence of an association of baseline anxiety with early and late onset smoking patterns (Hu, Griesler, Schaffran, Wall, & Kandel, 2012). Another study reported evidence of an association of baseline comorbid depression and anxiety with late onset smoking as opposed to experimental smoking (J. S. Brook, Ning, & Brook, 2006). One study reported that individuals in (smoking) starter and maintaining groups were more likely to be depressed at follow-up compared to non-smoking groups (Steuber & Danner, 2006). Finally, one study reported evidence that early onset smokers developed depression and anxiety approximately five years earlier than late onset smokers (Jamal, Does, Penninx, & Cuijpers, 2011). These findings are summarised in Figure 2.2.

2.3.8. Bidirectional Studies

Sixteen (11%) of the 148 included studies investigated the association between smoking behaviour and mental health bidirectionally (i.e., both the association between baseline mental health and later smoking behaviour, and baseline smoking behaviour and later mental health). Of these, 7 (44%) reported evidence in support of a bidirectional relationship between depression and smoking (Audrain-McGovern et al., 2009; Breslau et al., 1993; Breslau et al., 1998; Brown et al., 1996; Leung et al., 2012; Needham, 2007; Windle & Windle, 2001), and 1 (9%) reported evidence in support of a bidirectional relationship between anxiety and smoking (Cuijpers et al., 2007).

2.3.9. Sex Differences

A total of 8 studies (7% of all studies including both males and females) reported that the relationship between smoking and depression/anxiety differed between males and females. Two studies reported that depression was associated with subsequent smoking behaviour only in males (Killen et al., 1997; Repetto et al., 2005), while 1 study reported depression was associated with subsequent smoking only in females (Fleming et al., 2008) and 1 study reported that anxiety was associated with later smoking behaviour only in females (Denise B. Kandel et al., 2007). Additionally, one study reported evidence that smoking status in men was associated with later depression (Korhonen et al., 2007), and 2 studies reported evidence that smoking status had a stronger association with later depression in females than males (Duncan & Rees, 2005; Steuber & Danner, 2006). Finally, one study reported a bidirectional relationship between smoking and depression that was only observed in females (Needham, 2007).

2.3.10. Clinical Studies

Five studies investigated participants with cardiovascular problems. One study reported evidence that depression was associated with subsequent smoking behaviour (Brummett et al., 2003). The other 4 reported that smoking status was associated with later depression (Gravely-Witte et al., 2009; Kocer et al., 2011; Schrader et al., 2004; Schrader et al., 2006). Other studies of clinical populations generally reported evidence of an association between smoking and the onset of depression.

2.3.11. Ethnic Differences

Five studies recruited participants of East Asian descent (China, Japan, and South Korea), with 2 studies reporting evidence that depression was associated with later smoking behaviour (Black et al., 2012; Park et al., 2009), and 1 studies reporting no evidence of an

association (Kang & Lee, 2010). Additionally, 2 studies reported evidence for an association between smoking status and later depression (Kang & Lee, 2010; Tanaka et al., 2011), while 2 studies reported no evidence that smoking status was associated with subsequent depression (Park et al., 2009; Takeuchi et al., 2004). Three studies recruited African American participants, with 2 studies reporting evidence that depression was associated with later smoking behaviour (Miller-Johnson et al., 1998; Repetto et al., 2005), 1 study reporting no evidence that depression was associated with subsequent smoking onset (H. R. White et al., 2007), and 1 study reporting no evidence that smoking was associated with the onset of depression (Repetto et al., 2005). Four studies recruited both African American and Hispanic participants, with 3 studies reporting that depression and anxiety were associated with subsequent smoking trajectories (J. S. Brook et al., 2006; J. S. Brook et al., 2008; Judith S. Brook et al., 2006), while 1 study reported that smoking heaviness was associated with the onset of anxiety (Okeke et al., 2013). Other studies of specific ethnic groups generally reported evidence of an association between smoking and later depression and anxiety.

2.3.12. Additional Analyses

No clear pattern of results was apparent when studies with different lengths of follow-up were considered separately (see Appendix A page 168). Additionally, the findings did not vary substantially between studies using different tests (interview versus self-diagnostic test) or scales (continuous versus categorical) to diagnose depression or anxiety (see Appendix A page 169).

2.4. Discussion

In general, the findings across the studies in this systematic review were inconsistent. Nearly half of the studies reported that baseline depression or anxiety was associated with some type of later smoking behaviour, whether it be the onset of smoking itself, increased smoking heaviness, or the transition from daily smoking into dependence. These findings support a self-medication model, suggesting that individuals smoke to alleviate psychiatric symptoms (Boden et al., 2010; Chaiton et al., 2009). However, over a third of the studies found evidence for a relationship in the opposite direction, whereby smoking exposure at baseline was associated with later depression or anxiety, supporting the alternative hypothesis that prolonged smoking increases susceptibility to depression and anxiety (Markou et al., 1998; Rose et al., 2001). Of course, these two putative causal pathways are not mutually exclusive, but interestingly there were relatively few studies

reporting evidence for a bidirectional model relationship between smoking and depression and anxiety. One possible reason for this is that many studies only measured or analysed the variables in the direction of their *a priori* hypothesis. For example, studies examining factors for depression in later life measured smoking as a possible factor, but typically did not analyse the association of baseline depression with later smoking. Moreover, few studies reported null results; often these were only included alongside positive results relating to another outcome. Additionally, it is possible the associations observed between smoking and mental health are a result of shared genetic and environmental factors (Boden et al., 2010).

2.4.1. Limitations

There are several limitations that should be considered when interpreting these results. First, the studies included in this review varied substantially in population sampled, with some recruiting from the general population, and others selectively recruiting by sex, ethnicity, clinical population, or some other characteristic (e.g., at-risk adolescents). This introduced substantial heterogeneity into the review, thus making meta-analysis inappropriate. The substantial heterogeneity between study populations could be responsible for the inconsistent results observed, and future reviews should consider analysing different populations individually. Second, there was also substantial variation in study designs, including in length of follow up (between 2 months and 36 years), and confounders adjusted for. Measurement of depression or anxiety was based on a wide range of different diagnostic tests, with different cut-offs for determining clinical status. Sample size also varied substantially between studies, ranging from 59 to 90,627, suggesting that some smaller studies may be inadequately powered. This may lead to an increased likelihood of false positives (Button et al., 2013) since, among statistically significant findings, as power declines the ratio of true positives to false positives decreases. This is because while 5% of null associations will be falsely declared as significant (assuming a 5% alpha level), the number of true positives correctly identified will decline as power declines (e.g., from 80% of true associations correctly declared as significant in high powered studies to, say, only 20% in low powered studies) (Button et al., 2013). However, it is also worth noting that very large samples may detect statistically significant associations which are unlikely to be of clinical or population health importance.

Third, we only included published studies, and while the inclusion of unpublished studies may increase the likelihood of including lower quality work which has not been peer-reviewed, it may also decrease publication bias, in which studies are only published if they have positive results. By expanding our search to include non-published studies, it is

possible we may have found more instances of null results. Fourth, we did not investigate whether quality of the individual studies was related to the nature of the results reported. However, this would be challenging given the diversity of study designs among the included studies. Fifth, while we were able to categorise and investigate a range of different smoking behaviours, the same level of detail was not available for depression and anxiety. Future reviews should investigate individual symptomology (e.g., negative affect, somatic features, etc.) and their relationship with smoking behaviour, as previous research has indicated that specific symptoms may be differentially associated with smoking motivations and tobacco withdrawal (Leventhal, Ameringer, Osborn, Zvolensky, & Langdon, 2013; Leventhal, Zvolensky, & Schmidt, 2011; Mickens et al., 2011b). However, this analysis was not possible with the data reviewed here. Sixth, we only focused on depression, anxiety, or comorbid depression and anxiety. However, several studies identified during screening included depression or anxiety subtypes (e.g. post-traumatic stress disorder or social anxiety). These were excluded, in order to maximise comparability among included studies. Future studies should explore whether there is a more consistent pattern of relationship between smoking behaviour and these other diagnostic categories. However, given the disparate results we observed in our more focused review, it is perhaps unlikely that clear relationships will emerge.

2.4.2. Future directions

Despite the advantages of longitudinal studies, they cannot by themselves provide strong evidence of causality. Future studies should therefore employ methods which enable stronger causal inference, such as Mendelian randomisation (S. H. Gage et al., 2013). Two studies which have used Mendelian randomisation have found no evidence to support a causal association between smoking and depression and anxiety (Bjorngaard et al., 2013; A. E. Taylor et al., 2014), while another found evidence to suggest that smoking was associated with lower odds of depression during pregnancy (S. J. Lewis et al., 2011). The results of these studies suggest that observational findings of an association of smoking status with later psychological distress may be a result of shared vulnerability, residual confounding, or reverse causality (e.g., psychological distress associated with later smoking behaviour) (A. E. Taylor et al., 2014). However, this review yielded the most findings in the direction of psychological distress associated with later smoking behaviour. This review found slightly more evidence to support a direction of psychological distress predicting later smoking behaviour, which is not inconsistent with these MR studies (S. J. Lewis et al., 2011; A. E. Taylor et al., 2014). However, while both depression and anxiety are highly heritable (Hamet & Tremblay, 2005; Norrholm & Ressler, 2009), genome-wide association studies

(GWAS) have not yet identified robust variants for anxiety, and have only recently identified variants strongly associated with depression (Power et al., 2017). An unpublished analysis conducted in the Tobacco and Alcohol Research Group found depression was highly associated with smoking initiation (Sallis, 2018). In summary, we found overall inconsistent findings regarding whether smoking leads to depression and anxiety, depression and anxiety results in smoking or increased smoking behaviour, or there is a bidirectional relationship between the two.

2.5. Chapter summary

In chapter 2 I conducted a systematic review of the current literature of longitudinal studies of mental health and cigarette smoking. The evidence was largely inconsistent regarding whether smoking leads to depression and anxiety, whether depression and anxiety results in increased smoking behaviour, or there if there is a bidirectional relationship between the two. No patterns emerged when we stratified by smoking behavior, gender, clinical status, or ethnicity. Additionally, I found studies were largely conducted in the direction of their *a priori* hypothesis, suggesting bidirectional associations will remain unmeasured subjecting findings to reverse causation. Taking this into account, my next analyses (Chapter 3-4) examine longitudinal association of substance use and mental health in both temporal directions.

3. Chapter Three: Avon Longitudinal Study of Parents and Children (ALSPAC) methods and materials

3.1. Introduction

3.1.1. Chapter aims

In this Chapter, I will describe the prospective birth cohort that is used for the series of longitudinal analyses reported in Chapters 4-5 and a Mendelian randomisation analysis reported in Chapter 6. This will include details on cohort description, sample size, and variables used. Where possible variables remained consistent across chapters.

3.2. Cohort description

The Avon Longitudinal Study of Parents and Children (ALSPAC) alternatively known as 'Children of the 90s,' is a longitudinal prospective birth cohort based in Bristol, UK and conducted by The University of Bristol. The study recruited pregnant women with delivery dates between 1 April 1991 and 31 December 1992. ALSPAC originally enrolled 14,541 pregnancies, later excluding 674 for a final number of 13,867 pregnancies and 13,761 unique women (Boyd, Golding, Macleod, Lawlor, Fraser, Henderson, Molloy, Ness, Ring, & Davey Smith, 2013). Second phases of recruitment occurring at offspring 7 and 8 years identified a further 706 pregnancies for a total of 15,247 enrolled pregnancies (Fraser et al., 2013).

The ALSPAC maternal sample was compared to the Avon population as well as the general British population using the 8-month prenatal questionnaire and the 1991 census. ALSPAC mothers were more likely than the general Avon and British populations to live in owner-occupied accommodation and overcrowded conditions, have access to a car, be married, and were of higher socioeconomic status. Additionally, cohort mothers were less likely to be non-white (Fraser et al., 2013).

ALSPAC children were compared to national averages at age 16 using the National Pupil Database. ALSPAC children had higher educational attainment, were more likely to be white, and less likely to be eligible for free school meals. Attrition rates at age 18 indicate high responders are more likely to be female, white, and less likely to be eligible for free school meals, while individuals lost to attrition were more likely male and eligible for free school meals (Boyd, Golding, Macleod, Lawlor, Fraser, Henderson, Molloy, Ness, Ring, & Davey Smith, 2013).

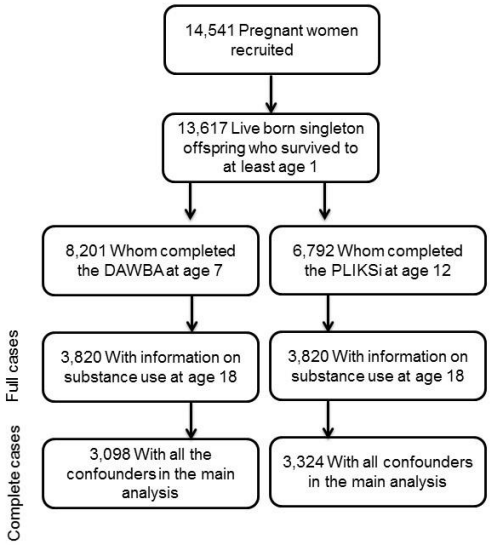
ALSPAC assessments are frequently administered totaling 68 data collection time points from birth to age 18, including 34 child-completed questionnaires, 9 clinical assessments and 25 maternal-reported questionnaires about the child. Information collection in ALSPAC is rich and diverse including phenotypic, genetic, and biological sampling across different time points (Boyd, Golding, Macleod, Lawlor, Fraser, Henderson, Molloy, Ness, Ring, & Davey Smith, 2013).

3.3. Sample sizes

3.3.1. Observational studies

Sample sizes varied across each analysis and temporal direction. Chapter 4 investigates the temporal associations of mental health and substance use, with mental health variables obtained from ages 7, 12, and 18 and substance use variables from ages 15 and 18. This Chapter also investigates the temporal association of social cognition and substance use, with social cognition obtained from ages 7, 8, and 18 and substance use from ages 15 and 18. Figures 3.1 to 3.4 display flow diagrams for the final sample sizes for each analysis:

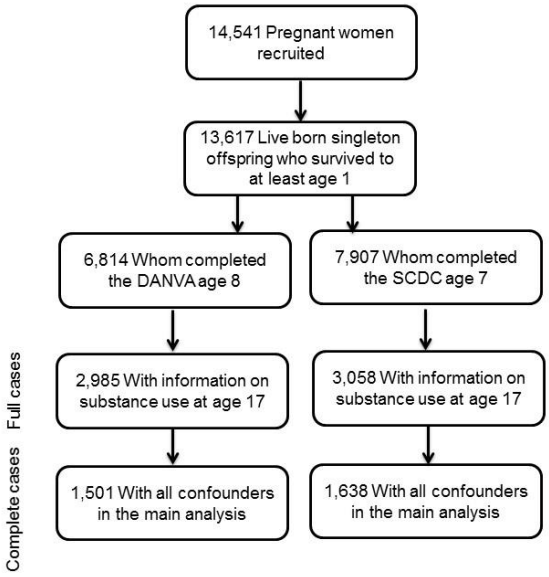
Figure 3.1 Flow diagram of the final sample size in the analysis of childhood mental health predicting substance use



Full Cases: total sample

Complete cases: sample restricted to data available at all time points

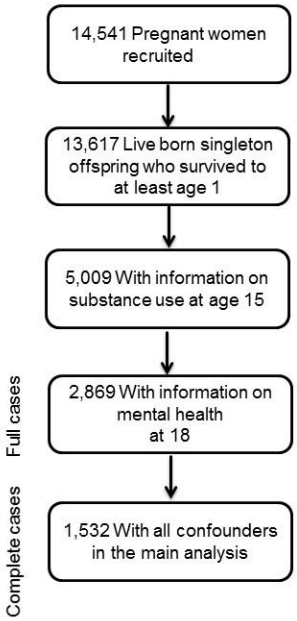
Figure 3.2 Flow diagram of the final sample size in the analysis of childhood social cognition predicting substance use



Full Cases: total sample

Complete cases: sample restricted to data available at all time points

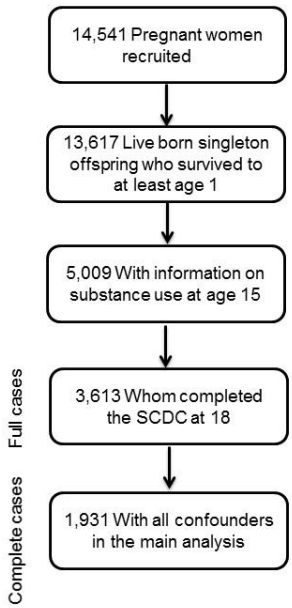
Figure 3.3 Flow diagram of the final sample size in the analysis of adolescent substance use predicting mental health



Full Cases: total sample

Complete cases: sample restricted to data available at all time points

Figure 3.4 Flow diagram of the final sample size in the analysis of adolescent substance use predicting social cognition

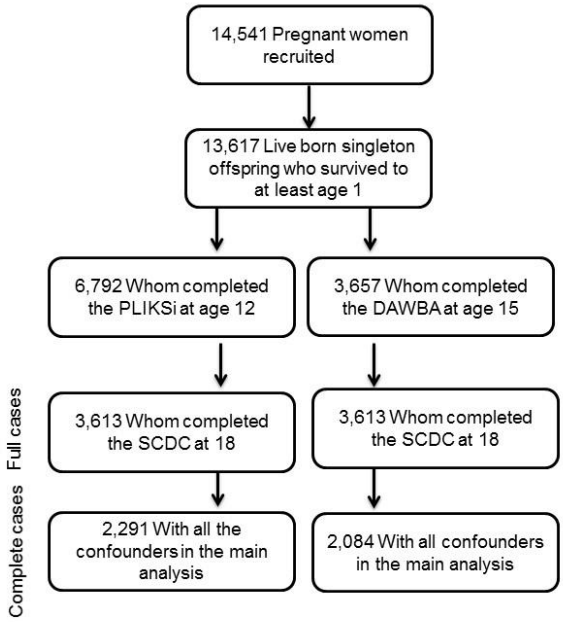


Full Cases: total sample

Complete cases: sample restricted to data available at all time points

Chapter 5 investigates the temporal association of mental health and social cognition with mental health variables obtained from ages 7, 12, and 18 and substance use from ages 15 and 18. Figures 3.5 and 3.6 display the final sample sizes for each analysis:

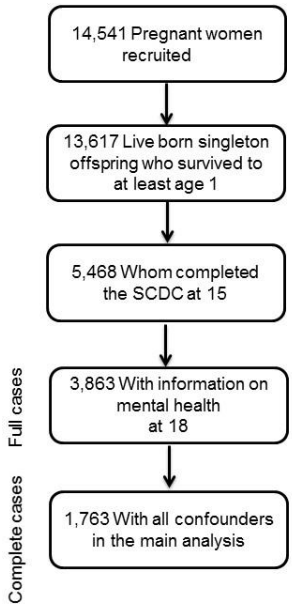
Figure 3.5 Flow diagram of the final sample size in the analysis of adolescent mental health predicting social cognition



Full Cases: total sample

Complete cases: sample restricted to data available at all time points

Figure 3.6 Flow diagram of the final sample size in the analysis of adolescent social cognition predicting mental health



Full Cases: total sample

Complete cases: sample restricted to data available at all time points

3.3.2. Genetic analyses

Chapter 6 investigates the association of smoking genotype with mental health and social cognitive variables obtained from age 18. Figures 3.7 to 3.8 display flow diagrams for the final sample sizes for each analysis:

Figure 3.7 Flow diagram of the final sample size in the analysis of adolescent substance use predicting mental health

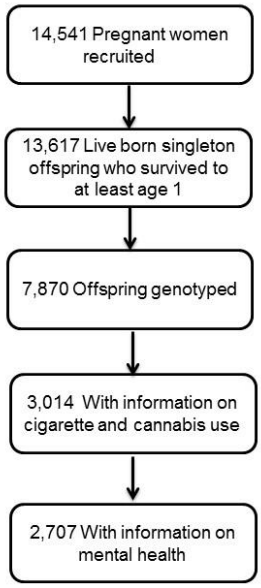
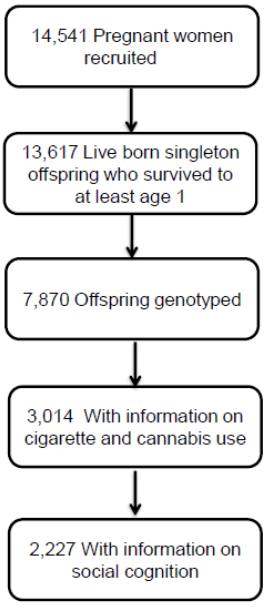


Figure 3.8 Flow diagram of the final sample size in the analysis of adolescent substance use predicting social cognition



3.4. Variables

My aim was to create variables that were consistent with previous studies using ALSPAC data, as well as comparable across earlier and later ages. However, some measures vary slightly due to differences in wording, availableness, and/or appropriate scales used for the age group.

3.4.1. Substance use

Current use (age 15): Current use of alcohol, tobacco, and cannabis at age 15 was collected via a computer session during a clinic visit. Initially, individuals were asked if they had tried each drug, and the frequency of recent use. The two questions for each drug were then merged to create a binary variable of 'current use' to capture individuals whom have not just tried a drug but have continued to use. Young persons' reporting ≥ 20 drinks in the past 6 months, smoking cigarettes in the past 30 days, and using cannabis within the past 12 months were classified as current users of each respective substance. This variable was developed to capture individuals' who were actively engaging in each substance, as opposed to those whom had only used once (ever/never use). However, it's also possible some first-time users would be captured in this variable if those individuals had initially used within the time frame (specifically past 30 days for cigarettes and cannabis).

Current use (age 18): Current use of alcohol, tobacco, and cannabis at age 18 was collected via a computer session during a clinic visit. Initially, individuals were asked if they had tried each drug, and the frequency of recent use. The two questions for each drug were then merged to create a binary variable of 'current use' to capture individuals whom have not just tried the drug but have continued to use. Young persons' reporting smoking cigarettes in the past 30 days and using cannabis within the past 12 months were classified as current users of each respective substance.

Due to widespread acceptance of alcohol use in the UK, the alcohol variable was measured slightly different from the others, as non-users may differ in regards to other societal factors comparable to social drinkers (e.g., abstainers for religious reasons (Michalak, Trocki, & Bond, 2007; Wallace, Brown, Bachman, & LaVeist, 2003), or individuals with high anxiety (Pardini, White, & Stouthamer-Loeber, 2007)). Here we initially asked if the young person had tried alcohol, then merged this score with their score on the Alcohol Use Disorders Identification Test (AUDIT), to create a binary measure of current use (see Appendix B page 170 for full questionnaire). The AUDIT is a 10-item questionnaire developed by the World Health Organisation (WHO) to assess alcohol consumption and drinking behaviour, where scoring ≥ 8 indicates hazardous drinking (Babor, 2001).

Finally, a binary variable was created by merging the three new variables together to capture a measure of 'multi-substance use.' Here, individuals indicating they were current users of all three substances were categorized as 'multi-substance users.' Individuals using 1-2 substances were categorized as non-multi-substance users.

Frequency (age 18): Measures of frequency differed for each substance and questions were as follows *(a) frequency young person has a drink containing alcohol (b) young person smokes every week (c) frequency young person smokes cannabis*. Answers for each were collapsed into a binary measure of weekly versus non-weekly use to stay systematic across substances.

Age of onset (age 18): Age of onset was a categorical measure based on self-reported *age in years at first (a) full drink (b) smoked a whole cigarette, or (c) when they first took cannabis.* Any ages below 6 were discarded on the unlikely event of substance use at such an early age.

3.4.2. Mental health

Childhood mental health (ages 7 and 15): Attention-deficit hyperactivity disorder (ADHD), depression, conduct disorder (CD), depression, and anxiety were assessed at age 7 via

parent- and teacher-report using the Development and Wellbeing Assessment (DAWBA) questionnaire (R. Goodman, Ford, Richards, Gatward, & Meltzer, 2000) (http://dawba.info/). Parent and teacher responses were combined for each child, and from each response 'bands' created, ranging from unlikely to probable. The DAWBA bands have 6 ordered categorical variables corresponding to the likelihood of a positive diagnosis (<.01%, .05%, 3%, 15%, 50%, and >70%) within the sample. The 'bands' have previously been validated in a sample of UK children (R. Goodman et al., 2000), while the DAWBA has been validated for use in both clinical and non-clinical samples.

Childhood Psychosis-like symptoms (ages 12 and 18): Psychosis-like symptoms were assessed at age 12, slightly later than the other mental health variables. Psychosis-like symptoms were assessed via self-report at age 12 via the PLIKSi semi-structured interview (see Appendix B pages 171-174 for full questionnaire) (Zammit et al., 2008). A binary variable indicating suspected or definite symptoms was used as the psychosis exposure measure.

Depression and anxiety (age 18): Measures of depression and anxiety were also assessed at age 18 using the Clinical interview schedule (CIS-R) via a self-administered computerised interview (see Appendix B pages 175-186 for full questionnaire) (G. Lewis, Pelosi, Araya, & Dunn, 1992). A binary variable indicating a primary diagnosis of major depression or a primary or secondary diagnosis of anxiety was taken as the outcome measures.

Antisocial behavior (age 18): Information on antisocial behaviour was measured at age 18 by via self-reported offenses in the past 12 months similar to the core offenses in the 2005 Offending, Crime, and Justice Survey (mugging, shop lifting, breaking and entering, selling drugs, fire setting, buying stolen goods) (Boyd, Golding, Macleod, Lawlor, Fraser, Henderson, Molloy, Ness, Ring, & Smith, 2013; Kretschmer et al., 2014). If individuals responded positively to one or more items, they were rated as demonstrating antisocial behaviour.

3.4.3. Social cognition

Non-verbal communication (age 8): Non-verbal communication at age 8 was measured via computer session during a clinic visit using the faces subset of the Diagnostic Analysis of Nonverbal Accuracy (DANVA) (Nowicki & Duke, 1994). This contains 24 photographs of children's faces displaying an either high or low intensity version of the following emotions: happy, sad, fear, or anger. Each photograph was displayed to the children for 2 seconds and they responded as to what emotion they perceived. Scoring ≥ 7 total errors on the DANVA was coded as poor performance (Nowicki & Duke, 1994).

Social communication (ages 7, 14, 18): Social communication was measured by maternal completion of The Social and Communication Disorders Checklist (SCDC) at offspring age 7 via questionnaire (see Appendix B page 187 for full questionnaire). The SCDC is a 12-item questionnaire with responses ranging from 0-2 (i.e. 'not true', 'quite or sometimes true', and 'very often true') designed to measure past 6 months' social functioning. Scores range from 0-24 with higher scores indicating more social cognitive difficulty. Scoring ≥ 8 out of a possible of 24 as poor performance (Robinson et al., 2011).

Social reciprocity (ages 7, 14, 18): Social reciprocity at age 7 was derived from 5 sub-questions on the SCDC that were specifically designed to measure social reciprocity (D. H. Skuse, Mandy, & Scourfield, 2005; D. Skuse et al., 2004). Responses of yes to ≥ 3 questions was coded as poor performance.

3.4.4. Confounders

A range of variables were considered as potential confounders for substance use, mental health, and social cognition. These were comprised of established risk factors for all three variables which we felt the assumption of a causal predictive relationship could be justified. These were divided into 3 main categories: (1) pre-birth/ demographic confounders, (2) maternal substance use, and (3) childhood confounders

3.4.4.1. Pre-birth/ demographic confounders

Sex*:* Previous evidence suggests there are sex differences in substance use behaviours [231, 232], for example males are more likely to be heavier cigarette smokers (West, 1999) In terms of mental health, internalising disorders are more prominent in females, while externalising disorders common among males (Seedat et al., 2009). Finally, there are sex differences in social cognition, as women perform better in affect recognition tasks compared to men (Hall & Matsumoto, 2004). Here, we used a binary male/female measure recorded at offspring birth.

Parity: Evidence from longitudinal studies suggest birth order is associated with increased substance use, particularly for middle and last-born children (Argys, Rees, Averett, & Witoonchart, 2006; Warren, 1966). Birth order is associated with mental health as first-born children were more susceptible to mental health problems (Risal & Tharoor, 2012). Additionally, birth order was predictive of social cognition, specifically poor communication skills in children (Tomblin, Hardy, & Hein, 1991). Here, we used a continuous measure of parity that was recorded at baseline.

Socioeconomic status: Socioeconomic status is associated with substance use and mental health and social cognition, as lower socioeconomic status in childhood is associated with higher rates of mental health and substance use (Benjet, 2010; Bradley & Corwyn, 2002; Buu et al., 2009; Coyne, Langstrom, Rickert, Lichtenstein, & D'Onofrio, 2013; Lopez-Castroman, 2014; Stone, Becker, Huber, & Catalano, 2012) and in adulthood and maladaptive social functioning (Bradley & Corwyn, 2002). The following variables were used as measures of socioeconomic status:

Maternal social class: A categorical measure of maternal social class was recorded at baseline (Benjet, 2010; Bradley & Corwyn, 2002; Buu et al., 2009; Coyne et al., 2013; Lopez-Castroman, 2014; Stone et al., 2012). Maternal and paternal social occupation was recorded at baseline, and used to allocate mother and partner to social class groups using 1991 Office of Population Censuses and Surveys (OPCS) classification (Surveys, 1991) with the following categories: *(a) I Professional (b) II Managerial and technical (c) III Skilled (non-manual) (d) III Skilled (manual) (e) IV Party-skilled (f) Unskilled.*

Maternal education status: A measure of maternal education status was recorded at baseline (Benjet, 2010; Bradley & Corwyn, 2002; Buu et al., 2009; Coyne et al., 2013; Lopez-Castroman, 2014; Stone et al., 2012), and categorized into the following categories*: (a) Certificate of secondary education (CSEO (b) Vocational and skill qualifications (c) O level (examination taken and passed at 16* years) (d) A level (examination taken and passed at 18 years) (e) University degree.

Maternal home ownership status: A measure of maternal home ownership status was collected at baseline (Benjet, 2010; Bradley & Corwyn, 2002; Buu et al., 2009; Coyne et al., 2013; Lopez-Castroman, 2014; Stone et al., 2012) and categorized into the following categories: *(a) Owned (b) subsidised rented (c) non-subsidised rented.*

3.4.4.2. Maternal substance use confounders

Parental substance use is associated with increased likelihood of offspring substance use (242-243), mental health problems (Bountress & Chassin, 2015). Additionally, parental substance use can create a disharmonious environment subsequently altering offspring's emotional and social competence (Engels, Finkenauer, Meeus, & Dekovic, 2001).

Maternal binge drinking: Measures of maternal drinking behaviours were collected at offspring age 12 via questionnaire. These included the number of units each day per week of beers, wines, spirits, sherries, ready mixed, and/or low alcohol drinks the mother regularly consumes. These measures were combined to form a binary measure of maternal binge

drinking (>21 units per week / averaging 3 units per day) (Arria, Mericle, Meyers, & Winters, 2012; Chassin, Pitts, & Prost, 2002).

Maternal smoking: Maternal cigarette smoking behaviour (Arria et al., 2012; Chassin et al., 2002) was collected at offspring age 12 via questionnaire. These measures were combined to form a binary ever/never measure of maternal smoking.

Maternal cannabis use: Maternal cannabis use (Arria et al., 2012; Chassin et al., 2002) was collected at offspring age 9 via questionnaire. This was used to form a binary ever/never measure of maternal cannabis use.

3.4.4.3. Childhood confounders

IQ: Low IQ in childhood is associated with early onset substance use (Kaplow, Curran, Dodge, & Gr, 2002) development of adult mental health problems (Koenen et al., 2009), and decreased social cognitive performance (D. H. Skuse et al., 2009). Here, we used Intelligence quotient (IQ) which was as collected at age 8 via the Wechsler Intelligence Scale for Children-III (WIS-C) (Lavin, 1996) results of which were categorized as follows: *(a) Exceptionally low (b) Low (c) Low average (d) Average (e) High average (f) High (g) Exceptionally high.*

Victimization: Children whom experience bullying are more likely to develop mental health problems (Arseneault, Bowes, & Shakoor, 2010) engage in substance use behavior (Tharp-Taylor, Haviland, & D'Amico, 2009) and have poor social skills (Crawford & Manassis, 2011). We used a binary measure of victimization (Dodge et al., 2003; Salmivalli, Lagerspetz, Bjorkqvist, Osterman, & Kaukiainen, 1996; Tharp-Taylor et al., 2009) that was collected at age 8 via a modified version of the Bullying and Friendship Interview Schedule (Wolke, Woods, Stanford, & Schulz, 2001) (see Appendix B page 188 for full questionnaire).

Borderline personality disorder (BPD): Borderline personality disorder is highly comorbid with substance use disorders (Trull, Sher, Minks-Brown, Durbin, & Burr, 2000), and is characterized by a range of symptoms that are common across internalizing (apathy and anxiety), externalizing (anger and impulsivity), and psychotic-disorders (paranoid dissociative symptoms and identity disturbance) (Lieb, Zanarini, Schmahl, Linehan, & Bohus, 2004). Additionally, individuals with BPD have reduced emotional empathy (Roepke, Vater, Preissler, Heekeren, & Dziobek, 2013). We used a binary measure of borderline personality disorder (Roepke et al., 2013; Trull et al., 2000) that was collected at age 8 via interview.

Peer problems*:* Childhood peer problems are associated with later life substance use (Fergusson, John Horwood, & Ridder, 2005; Heron, Maughan, et al., 2013; Mason, Campbell, King, & Sonenklar, 2016) increased externalizing behaviour, and poor emotion regulation and social understand (Hughes, White, Sharpen, & Dunn, 2000). We used a continuous 0-10 measure of peer problems (Murphy, Faulkner, & Farley, 2014) that was collected at age 8 via maternal-completed Strengths and Difficulties Questionnaire (SDQ) (R. Goodman, 2001) (see Appendix B page 189 for full questionnaire).

3.4.4.4. Additional confounders

In Chapter 4 one set of analyses examines the temporal direction of association of early substance use on subsequent mental health or social cognitive performance. In these analyses, we additionally adjust for childhood mental health or social cognition where appropriate.

Previous mental health: Age 7 DAWBA and age 12 PLIKS as described above

Previous social cognitive performance: Age 7 SCDC and SCDC sub-scores as described above

3.4.5. Logistic regression

Given the skew in the distribution of our data, binary variables were created and logistic regressions performed. Although dichotomising data in this way will result in some loss of information and power, logistic regression is subject to fewer assumptions than linear regression.

3.5. Chapter summary

In this chapter, we outlined details of ALSPAC, a prospective birth cohort based in Bristol. In ALSPAC mothers and their offspring are rigorously followed up through a series of questionnaires and clinic visits. This thesis is specifically interested in the temporal association of substance use, mental health, and social cognition in childhood to late adolescence. Where possible we attempted to keep variables consistent across ages, although there are some differences due to practicality and availability. ALSPAC will serve as the sample for the observational analyses in Chapters 4 and 5, and a Mendelian randomisation analysis in Chapter 6 (more genetic-specific information will be addressed in this chapter).

4. Chapter Four: Temporal associations of social cognition, mental health, and substance use

4.1. Introduction

The current study, conducted in ALSPAC, attempted to build upon previous knowledge of an association between poor mental health and substance use by investigating both temporal directions, as highlighted in Chapter 2. I investigated multiple mental health conditions including internalising, externalising, and psychosis-like symptoms with the three most commonly consumed drugs globally. Each analysis was repeated replacing mental health with social cognitive variables, allowing a direct comparison of any similar patterns of association. Initially, I analysed poor mental health (exposure) at age 7 on subsequent substance use (outcome) at age 18, and again reanalyzed replacing social cognition as the age 7 exposure. The second analysis, in the opposing direction, examines substance use initiation (exposure) age 15 on subsequent poor mental health at age 18 (outcome), and again reanalyzed with social cognition at age 18 (outcome).

4.1.1. Chapter aims

In this Chapter I investigated both temporal directions of mental health and substance use, and repeated each analysis replacing mental health with social cognition to examine common underlying patterns.

This chapter is largely based on the published manuscript: Fluharty M, Heron J, Munafo M (2017) Longitudinal associations of social cognition and substance use in childhood and adolescence: Findings from the Avon Longitudinal Study of Parents and Children. *European Child and Adolescent Psychiatry.* doi: 10.1007/s00787-017-1068-x

4.2. Temporal associations of childhood mental health and social cognition with adolescent substance use

4.2.1. Methods

Participants and variables from the Avon Longitudinal Study of Parents and Children have previously been described in detail in Chapter 3; a summary of these methods will be included below.

4.2.1.1. Participants

Participants for this analysis were drawn from the ALSPAC birth cohort, a prospective birth cohort based in Bristol, UK. The analysis of the association between childhood mental health and subsequent substance use was further restricted to parents who had completed the Development and Well-Being Assessment (DAWBA) (N = 8,201) when their offspring were age 7, offspring who had completed the psychosis-like symptoms semi-structured interview (PLIKSi) (N = 6,792) at age 12, and who had taken part in the substance use computerised assessment at age 18 (N = 8,058).

The analysis of the association between childhood social cognition and subsequent substance use was restricted to the offspring of parents who had completed the Social and Communication Disorders Checklist (SCDC) (N = 3,007), SCDC sub-scale (N = 3,058) at age 7, and/or offspring who had completed the Diagnostic Assessment of Non-Verbal Accuracy (DANVA) (N = 2,985) at age 8, and offspring who had taken part in the substance use computerised assessment at age 18 (N = 3,820). Flow diagrams (Figures 3.1 and 3.2) display the final sample size for each temporal association analysis.

4.2.1.2. Mental health exposures (age 7)

Mental health diagnoses including attention-deficit hyperactivity disorder (ADHD), depression, conduct disorder (CD), and anxiety were assessed at age 7 via parent- and teacher-report using the DAWBA questionnaire (R. Goodman et al., 2000) (based on ICD-10 and DSM-IV criteria). Parent and teacher responses were combined for each child and from each response 'bands' created, ranging from unlikely to probable. Psychosis-like symptoms were a binary variable variable indicating suspected or definite symptoms assessed via self-report at age 12 via the PLIKSi semi-structured interview (Zammit et al., 2008).

4.2.1.3. Social cognition exposures (age 7/8)

Non-verbal communication was assessed at age 8 via computer session during a clinic visit using the faces subset of the DANVA; scoring ≥ 7 total errors on the DANVA was coded as poor performance (Nowicki & Duke, 1994). Social communication was measured by maternal completion of SCDC at offspring age 7 via questionnaire; scoring ≥ 8 out of a possible of 24 was coded as poor performance (Robinson et al., 2011). Social reciprocity at age 7 was derived from 5 questions on the SCDC that were specifically designed to measure social reciprocity (D. H. Skuse et al., 2005; D. Skuse et al., 2004); responses of yes to ≥ 3 questions was coded as poor performance.

4.2.1.4. Substance use outcomes (age 18)

Measures of alcohol, tobacco and cannabis use were collected at age 18 via a computer-based assessment during a clinic visit. Individuals were classified as users of each

substance, and a user of all three substances if appropriate. Individuals scoring ≥ 8 on the Alcohol Use Disorders Identification Test (AUDIT), smoking cigarettes in the past 30 days, or using cannabis in the past 12 months were classified as users of each respective substance. Individuals using all three substances were further classified as multi-substance users. Frequency of use was categorised as either non-weekly or weekly use. Finally, age of onset was a categorical measure based on self-reported first use of each respective substance.

4.2.1.5. Confounders

Based on the literature, risk factors for poor mental health, social cognition, and substance use were considered as potential confounders, grouped into three categories: (1) pre-birth/ demographic (2) maternal substance use (3) offspring. The pre- birth/ demographic confounders adjusted for sex, parity, maternal social class, and maternal home ownership status. Maternal substance use confounders additionally adjusted for maternal binge drinking, maternal cannabis use, and maternal smoking. Offspring confounders additionally adjusted for IQ, peer problems, victimization, and borderline personality diagnosis.

4.2.1.6. Statistical analysis

First, I examined the association of mental health at age 7 with subsequent substance use behaviour at age 18. Then, I examined the association of social cognition at age 7/8 with subsequent substance use behavior at age 18. I assessed both temporal relationships before and after adjustment for covariates using logistic regression. I examined the impact of confounding by comparing unadjusted results with those adjusted for pre-birth / demographics confounders (model 1), and then additionally and cumulatively maternal substance use (model 2), childhood confounders (model 3). Finally, I ran a second set of confounder-adjusted analyses only including the complete cases from model 3. Both analyses were conducted unstratified and stratified by sex. Analyses were conducted in full (total sample) and complete cases (sample restricted to data available at both time points). Analyses were conducted in Stata version 13 (Stata Corp LP, College Station TX USA).

4.2.1.7. Secondary analysis

A secondary analysis was conducted after initial investigation of the DANVA exposure results. This followed the same statistical procedure as above but investigated response accuracy to individual emotions (happy, sad, fear anger) and level of affect intensity (low to high) of emotions as opposed to task accuracy as a whole.

4.2.2. Results

4.2.2.1. Characteristics of participants

Data were available on N= 3,820 participants for the analysis of childhood mental health with subsequent substance use, and N = 3,058 participants for the analysis of childhood social cognition with subsequent substance use. Characteristics of these participants are shown in Table 4.1. Confounder characteristics and associations with each outcome are presented in Table 4.2. The results presented below are from the fully adjusted models. Unadjusted and partially adjusted models, and a comparison of full (total number) and complete cases (number restricted to those with data in both time points), are presented in pages 190-195 of Appendix C. In general, sex-stratified analyses did not indicate any clear differences in the strength of association observed for males and females separately. The results are therefore presented unstratified, except where indicated, with sex stratified analyses presented in pages 196-201 of Appendix C.

Table 4.1 Participant demographics – childhood mental health/ social cognition on later substance use

Childhood mental health (age 7)

		Probability of disorder					
	N	~<0.1%	~0.5%	~3%	~15%	~50%	~>70%
ADHD	8,201	63% (5,182)	25% (2,021)	6% (496)	4% (338)	1% (100)	1% (64)
CD	8,109	0	60% (4,831)	38% (3,094)	2% (130)	0.4% (33)	0.3% (21)
Depression	8,201	62% (5,041)	35% (2,798)	0	2% (190)	1% (52)	0.02% (2)
Anxiety	8,197	0	49% (4,045)	48% (3,900)	3% (235)	0.2% (17)	0
PLIKS	6,791	86% (5865): none	14% (927): suspected/definite				

Childhood social cognition (age 7/8)

	N	Normal	Poor
Social communication	7,907	90% (7,138)	10% (6,814)
Social reciprocity	8,058	84% (6,757)	16% (1301)
Non-verbal communication	8,201	16% (1,301)	22% (1,524)

Late adolescent substance use (age 18)

		Current use		Frequency of use		
	N	No	Yes	*N*	≥ *Weekly*	< *Weekly*
Cannabis	3,820	70% (2,656)	30% (1,164)	1,187	85% (1,014)	15% (173)
Tobacco	3,820	71% (2,702)	29% (1,118)	1,181	61% (716)	39% (465)
Alcohol	3,820	57% (2,196)	43% (1,624)	3,887	74% (2,875)	26% (1,012)
Multi-substance	3,820	86% (3,268)	14% (552)			

Age of first substance

Age	*N*	Cannabis	Tobacco	Alcohol
Six	1,443	0% (0)	0.10% (1)	0.20% (3)
Seven	1,443	0% (0)	0.14% (2)	0.69% (10)
Eight	1,443	0.10% (1)	0.30% (4)	0.90% (13)
Nine	1,443	0.14% (2)	0.50% (7)	1% (21)
Ten	1,443	0.14% (2)	2% (21)	6% (81)
Eleven	1,443	1% (16)	5% (70)	7% (96)
Twelve	1,443	4% (51)	11% (160)	17% (250)
Thirteen	1,443	9% (133)	17% (246)	23% (335)
Fourteen	1,443	17% (246)	21% (307)	25% (354)
Fifteen	1,443	24% (345)	20% (293)	15% (212)
Sixteen	1,443	31% (447)	17% (242)	4% (60)
Seventeen	1,443	12% (447)	6% (81%)	0.50% (8)

Table 4.2 Descriptive statistics of confounders - childhood mental health/ social cognition on later substance use

	Tobacco user		**Cannabis user**		**Alcohol user**	
	N (%)	*p*	*N (%)*	*p*	*N (%)*	*p*
Demographic / pre-birth						
Sex						
Males	451 (40%)	0.006	582 (50%)	<0.001	748 (46%)	0.015
Female	666 (60%)		582 (50%)		876 (54%)	
Maternal home ownership status						
Owned	851 (83%)	0.003	903 (385)	0.302	1278 (86%)	0.524
substidised rented	91 (9%)		75 (7%)		96 (6%)	
non-substidised rented	88 (9%)		89 (8%)		112 (8%)	
Maternal social class						
I Professional occupations	62 (7%)	0.152	91 (10%)	0.093	158 (9%)	0.370
II Managerial and technical occupations	334 (37%)		377 (40%)		635 (36%)	
III Skilled non-manual occupations	348 (39%)		339 (36%)		716 (40%)	
III Skilled manual occupations	62 (7%)		54 (6%)		119 (7%)	
IV Partly-skilled occupations	77 (9%)		66 (7%)		130 (7%)	
V Unskilled occupations	13 (1%)		12 (1%)		24 (1%)	
Mothers highest qualification						
Certificate of secondary education (CSE)	145 (14%)	<0.001	110 (11%)	<0.001	160 (11%)	1.000
Vocational and skill qualifications	73 (7%)		61 (6%)		104 (7%)	
O level (examination taken and passed at 16 years)	357 (35%)		321 (32%)		501 (34%)	
A level (examinations taken and passed at 18 years)	287 (28%)		250 (25%)		421 (28%)	
University degree	170 (16%)		250 (25%)		292 (20%)	
Maternal						
Maternal smoking						
Smoker	166 (20%)	<0.001	157 (17%)	<0.001	192 (15%)	0.001
Non-smoker	683 (80%)		753 (83%)		1065 (85%)	
Maternal cannabis use						
Cannabis user	54 (6%)	<0.001	66 (7%)	<0.001	66 (5%)	0.001
Non-user	845 (94%)		901 (93%)		1,271 (95%)	
Maternal harmful drinking						
Harmful drinker	305 (33%)	<0.001	334 (37%)	<0.001	454 (37%)	<0.001
Non-harmful drinker	526 (63%)		567 (63%)		779 (63%)	
Offspring						
Borderline personality disorder (BPD)						
BPD present	68 (8%)	0.001	59 (6%)	0.188	72 (6%)	0.753
No BPD	817 (92%)		883 (94%)		1,213 (94%)	
Victimisation						
Childhood victimization	319 (35%)	0.200	339 (35%)	0.016	449 (34%)	0.091
No victimization	595 (65%)		633 (65%)		891 (66%)	
IQ						
Exceptionally low	11 (1%)	0.007	8 (1%)	<0.001	7 (1%)	0.389
Low	37 (4%)		29 (3%)		41 (3%)	
Low average	89 (10%)		76 (7%)		120 (9%)	
Average	397 (42%)		374 (34%)		561 (41%)	
High average	209 (22%)		320 (29%)		301 (22%)	
High	111 (12%)		133 (12%)		173 (13%)	
Exceptionally high	82 (9%)		149 (14%)		172 (13%)	
	M (SD)	*p*	*M (SD)*	*p*	*M (SD)*	*p*
Demographic / pre-birth						
Parity	0.82 (.90)	<0.001	0.78 (.90)	0.013	0.78 (0.87)	0.005
Peer Problems	0.98 (1.30)	0.622	0.92 (1.31)	0.237	0.91 (1.29)	0.074

P-values were calculated by chi squared or analysis of variance.

4.2.2.2. Association of childhood mental health with adolescent substance use

4.2.2.2.1. Externalising disorders (attention-deficit hyperactivity disorder and conduct disorder).

Probable diagnoses of ADHD and CD at age 7 were associated with increased odds of tobacco use at age 18 (ADHD: fully adjusted OR 1.25, 95% CI 1.09 to 1.43, P = 0.002; CD fully adjusted 1.26, 95% CI 1.26 to 1.56, P = 0.031); these results are shown in Tables 4.3-4.5. Probable diagnosis of ADHD at age 7 was associated with increased odds of more frequent tobacco use at age 18 (fully adjusted OR 1.31 95% CI 1.04 to 1.65, P = 0.021), and increased odds of trying tobacco at a younger age (fully adjusted OR 0.85 95% CI 0.73 to 0.98, P = 0.030). Additionally, probable diagnoses of ADHD and CD at age 7 were associated with increased odds of cannabis use at age 18 (ADHD: fully adjusted OR 1.16, 95% CI 1.02 to 1.33, P = 0.029 CD: fully adjusted OR 1.40 95% CI 1.14 to 1.73, P = 0.001). Probable diagnosis of ADHD at age 7 was associated with increased odds of trying cannabis at a young age (fully adjusted OR 0.82, 95% CI 0.70 to 0.97, P = 0.018), while probable diagnosis of CD at age 7 was associated with increased odds of more frequent cannabis use at age 18 (fully adjusted OR 1.62, 95% CI 1.03 to 2.45, P = 0.037). In stratified analyses, associations were slightly stronger for females with respect to cannabis outcomes (see pages 197-199 in Appendix C).

4.2.2.2.2. Internalising disorders (depression and anxiety).

Probable diagnosis of depression at age 7 was associated with increased odds of alcohol use at age 18 (fully adjusted OR 1.32, 95% CI 1.13 to 1.55, P ≤ 0.001); these results are shown in Tables 4.3-4.5. Probable diagnoses of depression and anxiety at age 7 were associated with increased odds of more frequent alcohol use at age 18 (depression: fully adjusted OR 1.24, 95% CI 1.04 to 1.47, P = 0.015; anxiety: fully adjusted OR 1.37, 95% CI 1.11 to 1.69, P = 0.003). Additionally, probable diagnoses of depression and anxiety at age 7 were associated with increased odds of all substance use at age 18 (depression: fully adjusted OR 1.36, 95% CI 1.11 to 1.67, P = 0.003; anxiety: fully adjusted OR 1.40 95% CI 1.08 to 1.82, P = 0.012).

4.2.2.2.3. Psychosis-like symptoms.

There was no clear evidence of an association of probable diagnosis of PLIKS with current use, frequent use, or age of onset; these results are shown in Tables 4.3-4.5.

4.2.2.3. Association of childhood social cognition with adolescent substance use

4.2.2.3.1. Non-verbal communication

Poor non-verbal communication at age 8 was associated with decreased odds of alcohol (fully adjusted OR 0.72, 95% CI 0.56 to 0.94, P = 0.011), tobacco (fully adjusted OR 0.66, 95% CI 0.49 to 0.88, P = 0.005), and cannabis use at age 18 (fully adjusted OR 0.60, 95% CI 0.45 to 0.81, P = 0.001). These results are shown in Table 4.6. No clear evidence of association was observed for age of onset, or frequency of use (non-weekly/weekly) at age 18 (See pages 194-195 in Appendix C).

4.2.2.3.2. Social communication and social reciprocity

There was no clear evidence of an association of either poor social communication or social reciprocity at age 7 with alcohol, tobacco, cannabis, or all substance use at age 18. These results are shown in Table 4.6. Additionally, no clear evidence of association was observed for age of onset, or frequency of use (non-weekly/weekly) at age 18 (See pages 194-195 in Appendix C).

4.2.2.3.3. Exploratory analysis

To further investigate the association of nonverbal communication and current substance use, I investigated the DANVA by individual emotion and intensity. There was no clear pattern of association across the individual emotions (see page 202 in Appendix C). However, individuals displaying reduced ability to identify emotions in general, as demonstrated by poor identification of both ‘low’ and ‘high’ intensity emotionally expressive faces, had decreased odds of substance use onset, similar to the results seen above. Poor identification of low and high intensity faces at age 7 was associated with decreased odds of alcohol, tobacco, and cannabis use at age 18, and this was robust to adjustment (see Table 4.7 for details).

4.2.3. Summary

These results indicate that, in this cohort, poor childhood mental health at age 7 is associated with subsequent substance use at age 18. Specifically, externalising disorders (ADHD and conduct disorder) were associated with tobacco and cannabis use behaviours, while internalising disorders (depression and anxiety) were associated with later alcohol use behaviours, and a range of disorders (conduct disorder, depression, and anxiety) contributed to use of all substances. These findings replicate previous ALSPAC evidence that externalising disorders are associated with alcohol (S. B. Cho et al., 2014; Heron, Maughan, et al., 2013), tobacco (Heron, Hickman, Macleod, & Munafo, 2011), and cannabis, (Heron, Barker, et al., 2013; Kretschmer et al., 2014; McGee, Williams, Poulton, & Moffitt, 2000; Zohsel et al., 2016) while internalising disorders are associated with later alcohol use (Edwards, Joinson, et al., 2014; Saraceno, Heron, Munafo, Craddock, & van den Bree, 2012).

In contrast, poor non-verbal communication at age 8 is associated with *decreased* alcohol, tobacco, and cannabis. Adjustment for pre-birth / demographic, maternal, and childhood confounders strengthened the associations for tobacco and cannabis use but weakened the associations for alcohol. We analysed individual emotions within the DANVA to identify whether sensitivity to specific emotions were driving this association. No pattern of association was found for individual emotions, although poor identification of both low and high intensity of emotional expression was associated with alcohol, tobacco, cannabis, and all substance use. Adjustment for confounders strengthened associations for alcohol, tobacco, and cannabis, but weakened the association for all substance use. Interestingly, poor non-verbal communication appeared to be protective against later substance use; thus the deficits in non-verbal communication previously reported in substance users are more likely to be the outcome of prolonged use (Adams et al., 2014; Bayrakci et al., 2015; Donadon & Osorio Fde, 2014; Kornreich et al., 2001; Townshend & Duka, 2003), as opposed to reflecting self-medication of these deficits.

Taken together, poor childhood mental health and social cognitive performance have opposing relationship with adolescent substance use. While poor mental health is associated with increased substance use behaviours, poor social cognitive performance is associated with some decreased use behaviours.

4.3. Temporal associations of early adolescent substance use with mental health and social cognition

4.3.1. Methods

4.3.1.1. Participants

The analysis of the association between early adolescent substance use and subsequent mental health was restricted to offspring who had taken part in the substance use computerised task at age 15 (N = 5,009), offspring who had completed the CIS-R at age 18 (N = 4,563), offspring who had completed the computerized task on self-reported criminal offenses (N = 4,017), and offspring who had completed the psychosis-like symptoms semi-structured interview (PLIKSi) (N = 4,718) at age 18.

The analysis of the association between early adolescent substance and subsequent social cognition was further restricted to the offspring who had taken part in the substance use computerised task (N = 5,009) at age 15, and offspring whose parents had completed the Social and Communication Disorders Checklist (SCDC) (N = 5,506) at age 17. Flow diagrams (Figures 3.3 and 3.4) show the final sample size for each temporal association analysis.

4.3.1.1.1. Substance use exposures (age 15)

Use of alcohol, tobacco, and cannabis at age 15 was collected via computer session during a clinic visit. Individuals were first classified as either current or non-users of each substance. Next, individuals reporting ≥ 20 drinks in the past 6 months, smoking cigarettes in the past 30 days, or using cannabis in the past 12 months were classified as 'current' users of each respective substance.

4.3.1.1.2. Mental health outcomes (age 18)

Binary measures of depression and anxiety were assessed at age 18 using the CIS-R via a self-administered computerised interview (G. Lewis et al., 1992). Psychosis-like symptoms were a binary variable indicating suspected or definite symptoms assessed via self-report at age 18 via the PLIKSi semi-structured interview (Zammit et al., 2008). Information on antisocial behaviour was measured at age 18 by via self-reported offenses in the past 12 months (Boyd, Golding, Macleod, Lawlor, Fraser, Henderson, Molloy, Ness, Ring, & Smith, 2013; Kretschmer et al., 2014); individuals were classified as antisocial if they responded positively to one or more items.

4.3.1.1.3. Social cognitive outcomes (age 18)

Social communication was measured by maternal completion of SCDC at offspring age 18 via questionnaire, scoring ≥ 8 out of a possible of 24 was coded as poor performance (Robinson et al., 2011). Social reciprocity at age 18 was derived from 5 questions on the SCDC that were specifically designed to measure social reciprocity (D. H. Skuse et al., 2005; D. Skuse et al., 2004). Responses of yes to ≥ 3 questions was coded as poor performance.

4.3.1.1.4. Confounders

Based on the literature, risk factors for substance use, poor mental health, and social cognition were considered as potential confounders; grouped into three categories (1) pre-birth/ demographic (2) maternal substance use (3) offspring. Additionally, for the analysis of the association between age 15 substance use and subsequent mental health we adjusted for (4) previous incidence of mental health problems (age 7 DAWBA probable diagnosis or age 12 PLIKSi semi-structured interview). For the analysis of the association between substance use at age 15 and subsequent social cognition at age 18 we adjusted for (4) previous incidence of poor social cognition (age 7 social communication or social reciprocity).

4.3.1.2. Statistical analysis

First, I examined the association of early substance use behaviour at age 15 with subsequent mental health at age 18. Next, I examined the association of early substance behaviour use at age 15 with subsequent social cognition at age 18. I assessed both these temporal relationships before and after adjustment for covariates using logistic regression. I examined the impact of confounding by comparing unadjusted results with those adjusted for pre-birth / demographics confounders (model 1), and then additionally and cumulatively maternal substance use (model 2), childhood confounders (model 3), and (for the association of early adolescent substance use with subsequent social cognition) history of mental health or social cognition at age 7/8 (model 4). Finally, I ran a second set of confounder-adjusted analyses only including the complete cases from model 4. Both analyses were conducted unstratified and stratified by sex. Each analysis was conducted in full (total sample) and complete cases (sample restricted to data available at both time points). Analyses were conducted in Stata version 13 (Stata Corp LP, College Station TX USA).

4.3.2. Results

4.3.2.1. Characteristics of participants

Data were available on N = 5,009 participants for the analysis of early adolescent substance use at age 15 with subsequent mental health and social cognition at age 18. Characteristics of these participants are shown in Table 4.8. Confounder characteristics and associations with each outcome are presented in Table 4.9. The results presented below are from the fully adjusted models. Unadjusted and partially adjusted models and comparison of full (total number) and complete cases (number restricted to those with data in both time points) are presented are presented in pages 203-204 of Appendix C. In general, sex-stratified analyses did not indicate any clear differences in the strength of association observed for males and females separately. The results are therefore presented unstratified, except where indicated, with sex stratified analyses presented in pages 205-206 of the Appendix.

Table 4.8 Participant demographics - adolescent substance use on later mental health/ social cognition

Early adolescent substance use (age 15)			
	N	No	Yes
Cannabis	5,048	81% (4,064)	19% (984)
Tobacco	5,107	83% (4,214)	17% (893)
Alcohol	5,051	81% (4,077)	19% (974)

Adolescent mental health (age 18)			
	N	No	Yes
Antisocial behaviour	4,017	84% (3,355)	16% (662)
Depression	4,053	92% (4,203)	8% (360)
Anxiety	4,053	89% (4,041)	11% (522)
PLIKS	4,718	91% (4286): none	9% (432): suspected or definite

Adolescent social cognition (age 18)			
	N	Normal	Poor
Social communication	5,468	88% (4,833)	12% (4,300)
Social reciprocity	5,571	66% (635)	23% (1,271)

Table 4.9 Descriptive statistics of confounders - adolescent substance use on later mental health/ social cognition

	Depression		Anxiety		Antisocial behaviour		Psychotic-like symptoms		Poor social communication		Poor social reciprocity	
	N (%)	*p*	*N (%)*	*p*	*N (%)*	*p*	*N (%)*	*p*	*N (%)*	*p*	*N (%)*	*p*
Demographic / pre-birth												
Sex												
Males	90 (25%)	<0.001	139 (27%)	<0.001	395 (60%)	<0.001	154 (36%)	0.001	299 (47%)	0.497	599 (47%)	0.332
Female	270 (75%)		383 (73%)		266 (40%)		278 (64%)		366 (53%)		672 (53%)	
Maternal home ownership status												
Owned	258 (79%)	<0.001	383 (80%)	<0.001	497 (84%)	0.273	294 (75%)	<0.001	478 (82%)	0.007	973 (82%)	<0.001
substidised rented	44 (13%)		62 (13%)		53 (9%)		62 (16%)		57 (10%)		109 (9%)	
non-substidised rented	26 (8%)		31 (7%)		43 (7%)		35 (9%)		51 (9%)		99 (8%)	
Maternal social class												
I Professional occupations	17 (6%)	0.569	28 (7%)	0.556	45 (9%)	0.774	25 (8%)	0.031	35 (7%)	0.261	74 (7%)	0.827
II Managerial and technical occupations	104 (37%)		154 (38%)		203 (40%)		104 (31%)		185 (36%)		384 (37%)	
III Skilled non-manual occupations	113 (41%)		161 (40%)		190 (37%)		135 (41%)		234 (45%)		437 (42%)	
III Skilled manual occupations	18 (6%)		22 (5%)		32 (6%)		25 (8%)		24 (5%)		59 (6%)	
IV Partly-skilled occupations	20 (7%)		34 (8%)		38 (7%)		35 (11%)		35 (7%)		71 (7%)	
V Unskilled occupations	6 (2%)		8 (2%)		5 (1%)		8 (2%)		4 (1%)		13 (1%)	
Mothers highest qualification												
Cerfiicate of secondary education (CSE)	39 (12%)	0.177	64 (14%)	0.190	73 (12%)	0.582	70 (18%)	<0.001	70 (12%)	0.049	129 (11%)	0.193
Vocational and skill qualifications	22 (7%)		34 (8%)		48 (8%)		31 (8%)		58 (10%)		103 (9%)	
O level (examination taken and passed at 16 years)	126 (39%)		167 (36%)		197 (33%)		156 (40%)		201 (34%)		422 (35%)	
A level (examinations taken and passed at 18 years)	92 (28%)		134 (28%)		169 (28%)		71 (18%)		170 (29%)		328 (27%)	
University degree	47 (14%)		73 (9%)		109 (18%)		63 (16%)		97 (16%)		212 (18%)	
Maternal												
Maternal smoking												
Smoker	53 (20%)	0.001	76 (20%)	<0.001	82 (16%)	0.009	60 (20%)	<0.001	94 (18%)	0.003	173 (16%)	0.011
Non-smoker	212 (80%)		311 (80%)		429 (84%)		242 (80%)		430 (82%)		899 (84%)	
Maternal cannabis use												
Cannabis user	11 (4%)	0.851	21 (5%)	0.278	28 (5%)	0.007	17 (5%)	0.120	21 (4%)	0.724	50 (5%)	0.336
Non-user	279 (96%)		401 (95%)		506 (95%)		303 (95%)		542 (12%)		1059 (95%)	
Maternal harmful drinking												
Harmful drinker	76 (30%)	0.837	116 (31%)	0.899	177 (35%)	0.020	80 (27%)	0.118	143 (28%)	0.189	312 (30%)	0.625
Non-harmful drinker	174 (70%)		255 (69%)		327 (65%)		215 (73%)		366 (72%)		726 (70%)	
Offspring												
Borderline personality disorder (BPD)												
BPD present	28 (10%)	0.001	43 (11%)	<0.001	40 (8%)	0.020	49 (16%)	<0.001	40 (9%)	<0.001	66 (8%)	0.003
No BPD	249 (90%)		354 (89%)		493 (93%)		262 (84%)		423 (91%)		865 (93%)	
Victimisation												
Childhood victimization	106 (36%)	0.195	164 (39%)	0.005	204 (37%)	0.004	135 (43%)	<0.001	207 (41%)	<0.001	373 (38%)	<0.001
No victimization	188 (64%)		260 (61%)		350 (63%)		178 (57%)		296 (59%)		612 (62%)	
IQ												
Exceptionally low	3 (1%)	0.719	7 (2%)	0.012	3 (1%)	0.829	7 (12%)	0.015	0.389	13 (2%)	<0.001	17 (2%) 0.003
Low	10 (2%)		13 (3%)		18 (3%)		11 (3%)			33 (6%)		55 (5%)
Low average	21 (7%)		44 (10%)		51 (9%)		40 (12%)			60 (12%)		121 (12%)
Average	138 (46%)		195 (46%)		229 (41%)		144 (44%)			232 (45%)		431 (42%)
High average	65 (22%)		72 (17%)		126 (22%)		65 (20%)			98 (19%)		206 (20%)
High	33 (11%)		57 (13%)		61 (11%)		37 (11%)			43 (8%)		94 (9%)
Exceptionally high	29 (10%)		39 (9%)		76 (13%)		21 (6%)			42 (8%)		99 (10%)
									M (SD)	*p*	*M (SD)*	*p*
Demographic / pre-birth												
Parity	0.74 (0.95)	0.059	0.79 (0.91)	0.143	0.73 (0.89)	0.964	0.75 (0.93)	0.753	0.67 (0.85)	0.047	0.65 (0.83)	<0.001
Peer Problems	1.19 (1.50)	0.014	1.24 (1.49)	<0.001	1.04 (1.43)	0.462	1.40 (1.70)	<0.001	1.63 (1.72)	<0.000	1.38 (1.58)	<0.001

P-values were calculated by chi squared or analysis of variance.

4.3.2.2. Association of early adolescent substance use with mental health

4.3.2.2.1. Externalising disorders (antisocial behaviour)

Current alcohol use at age 15 was associated with increased odds of antisocial behaviour at age 18 (fully adjusted OR 2.72, 95% CI 1.96 to 3.77, P ≤ 0.001); these results are shown in Table 4.10. Current tobacco use at age 15 was associated with increased odds of antisocial behaviour at age 18 (fully adjusted OR 4.34, 95% CI 3.04 to 6.20, P ≤ 0.001). Finally, current cannabis use at age 15 was associated with increased odds of antisocial behaviour at age 18 (fully adjusted OR 4.79, 95% CI 3.48 to 6.60, P ≤ 0.001).

4.3.2.2.2. Internalising disorders (depression and anxiety)

Current alcohol use at age 15 was associated with increased odds of depression (fully adjusted OR 2.21, 95% CI 1.40 to 3.48, P = 0.001) and increased odds of anxiety at age 18 (fully adjusted OR 1.75, 95% CI 1.18 to 2.57, P = 0.005); these results are shown in Table 4.10. Current tobacco use at age 15 was associated with increased odds of depression (fully adjusted OR 1.83, 95% CI 1.15 to 2.93, P = 0.011) and anxiety at age 18 (fully adjusted OR 1.81, 95% CI 1.23 to 2.68, P = 0.003). Finally, current cannabis at age 15 use was associated with increased odds of depression (fully adjusted OR 1.89, 95% CI 1.20 to 2.98, P = 0.006) and anxiety at age 18 (fully adjusted OR 1.42, 95% CI 0.96 to 2.10, P = 0.080).

4.3.2.2.3. Psychosis-like symptoms

Current tobacco use at age 15 was associated with increased odds of PLIKS at age 18 (fully adjusted OR 2.83, 95% CI 1.87 to 4.30, P ≤ 0.001); these results are shown in Table 4.10. Current cannabis use at age 15 was associated with increased odds of PLIKS at age 18 (fully adjusted OR 2.35, 95% CI 1.57 to 3.54, P ≤ 0.001).

4.3.2.3. Associations of early adolescent substance use with social cognition

4.3.2.3.1. Social communication

Increased odds of poor social communication at age 17 was associated with earlier adolescent alcohol (fully adjusted OR 1.48, 95% CI 1.01 to 2.16, P = 0.046), and tobacco use (fully adjusted OR 1.86, 95% CI 1.27 to 2.72, P = 0.001) at age 15. These results are shown in Table 4.11. In stratified analyses, associations were slightly stronger for males, with respect to tobacco outcomes.

4.3.2.3.2. Social reciprocity

Increased odds of poor social reciprocity at age 17 was associated with earlier adolescent alcohol (fully adjusted OR 1.57, 95% CI 1.18 to 2.05, P = 0.002), tobacco (fully adjusted OR 1.84, 95% CI 1.37 to 2.48, P = 0.001), and cannabis use at age 15 (fully adjusted OR 1.57, 95% CI 1.18 to 2.08, P = 0.002). These results are shown in Table 4.11. In stratified analyses, associations were slightly stronger for males, with respect to tobacco outcomes (see page 206 in Appendix C)

4.3.3. Summary

Early cannabis and tobacco use were associated with later externalising, internalising, and psychosis-like disorders, while alcohol use was associated with later externalising and internalising disorders. These findings mirror previous findings within this cohort suggesting cannabis and tobacco use are associated with internalising disorders (Degenhardt et al., 2013; S. H. Gage, Hickman, et al., 2015), and psychosis-like symptoms (S. H. Gage et al., 2014; Zammit, Owen, Evans, Heron, & Lewis, 2011), while alcohol use is associated with internalising disorders (Edwards, Heron, et al., 2014; Pesola et al., 2015). Additionally, early alcohol, tobacco, and/or cannabis use at age 15 is associated with poor social communication and social reciprocity at 17. In all cases, adjustment for pre-birth, maternal, childhood, or previous indication of poor social cognition (age 7) did not substantially alter these associations. As both analyses adjust for previous poor mental health and social cognition prior to the onset of any substance use (age 7), this suggests that being a current user of alcohol, tobacco, and cannabis is associated with decreased mental health and social cognitive abilities.

These results suggest, in this temporal direction, there are common patterns of substance use associated with both mental health and social cognitive capacities. There appears to be some evidence of a bidirectional association with externalising disorders with tobacco and/or cannabis, however generally more symptoms (both mental health and social cognitive) appear after the onset of substance use. However, following the onset of substance use the temporal direction of association of mental health and social cognitive performance is still unknown.

4.4. Discussion

4.4.1. Mental health and substance use

This analysis suggests that externalising disorders show as association with cannabis and tobacco in both temporal directions, while internalising disorders display a similar bidirectional association with alcohol. However, the onset of cannabis and tobacco use was associated with a wider range of mental health problems in later years including internalising and psychosis-like symptoms. This suggests that while externalising disorders may work in both temporal directions, internalising and psychosis-like disorders have a different relationship to cannabis and tobacco use (either uni-directional, or as a result of shared genetic and/or environmental risk factors). One possible explanation is that individuals with externalising disorders may be drawn to tobacco and/or cannabis use through high levels of impulsivity or sensation seeking (Ortal et al., 2015). However, prolonged nicotine use may

result in the dysregulation of the hypothalamic-pituitary-adrenal systems, resulting in hypersecretions of cortisol and changes in monoamine neurotransmitter activity (Markou et al., 1998); similarly, sustained cannabis use may cause shifts in amygdala functioning resulting in hypersensitivity of perceived threat (Spechler et al., 2015). Subsequently suggesting the onset of tobacco and cannabis may aid in the development of internalising disorders such as anxiety and depression.

4.4.2. Social cognition and substance use

These analyses suggest that social cognitive deficits may result from the initiation and/or regular use of these substances. While previous literature has suggested these social cognitive deficits can arise during periods of acute intoxication (Curtin et al., 2001; Hindocha et al., 2015) or withdrawal (Adams et al., 2014), our results suggest these deficits remain present over longer periods of time among users. Alcohol dependence has been associated with impaired semantic memory (i.e., deficits general knowledge accumulated through personal experience). As semantic memory may be necessary for the maintenance of social networks (Labouvie-Vief & Blanchard-Fields, 1982), this may subsequently lead to more specific social cognitive deficits (Nandrino et al., 2014). Prolonged nicotine exposure may dysregulate the hypothalamic-pituitary-adrenal system, resulting in hypersecretions of cortisol and alterations in the activity of the associated monoamine neurotransmitter system, which contributes to stress-regulation (Markou et al., 1998). This may result in individuals being more susceptible to environmental stressors and associated difficulties with affect and emotional regulation (Joormann & Quinn, 2014; Joormann & Stanton, 2016). Finally, evidence from imaging studies indicate neuroanatomical changes in heavy cannabis uses associated with prolonged endocannabinoid exposure, and the subsequent desensitisation of CB_1 receptors in the brain, requiring compensatory CB1 receptor activity elsewhere in the striatum (Marjoram et al., 2006; Romero et al., 1997; Roser et al., 2012; Sim-Selley, 2003). Previous literature indicates strong familial bonds and open communication within families and schools may serve as a protective factor, or help to delay adolescent substance initiation (A. D. Farrell & White, 1998; Kliewer & Murrelle, 2007; McArdle et al., 2002; Spoth, Redmond, Shin, & Azevedo, 2004). However, in the other temporal direction (i.e., poor social cognition and subsequent substance use) there is currently little evidence. Our analyses help to rule out the possibility of reverse causality and strengthen our findings that substance use is associated with later impaired social cognition. Additionally, this analysis suggested that poor non-verbal communication may in fact be *protective* with respect to subsequent substance use. While this is clearly an area that warrants additional research and replication, one possible explanation for this finding is that adolescents with poor

emotion recognition skills may be less likely to have larger social groups (Barth & Bastiani, 1997; Leppanen & Hietanen, 2001) and therefore less likely to engage in substance use due to less social inclusion (McCrady, 2004; Shadur & Hussong, 2014; Urberg, Degirmencioglu, & Pilgrim, 1997).

4.4.3. Strengths

There are several strengths of these analyses. First, as previously mentioned our recent systematic review of smoking and mental health concluded relatively few studies investigate both temporal directions rather than only that of their *a priori* hypothesis (M. Fluharty, Taylor, Grabski, & Munafo, 2016). Second, this analysis was conducted in a rich data set with multiple mental health, social cognitive and substance use variables collected at several time-points throughout the adolescence and early adulthood. Third, these analyses were conducted in both temporal directions and investigated the associations of commonly consumed drugs with a range of mental health disorders and facets of social cognition in parallel. Fourth, this study investigated a range of different substance use behaviours, mental health disorders, and social cognitive behaviours within the same cohort. Fifth, variables were systematic and comparable across category and age group. Finally, a robust approach was taken to minimise confounding by integrating a range of confounders from pre-birth throughout adolescence.

4.4.4. Limitations

There are also some limitations of this study to consider. First, our substance use variables rely on self-report and have not be biochemically verified. Additionally, we drew our outcomes from age 18, which provided us with a large sample size of individuals whom had ever used substances. However, there were notably fewer individuals answering questions regarding frequency of use, which may have contributed to the low power for these analyses. Second, as smoking cannabis in joints in the common consumption method within the United Kingdom, cannabis is rolled and smoked together with tobacco (as opposed to alone in pipes as is the predominate method in the United States). Therefore, it is difficult to differentiate effects from tobacco and cannabis, as cannabis-using individuals' may underestimate their tobacco intake by not quantifying tobacco rolled with joints when answering tobacco consumption questions. This may explain why our cannabis and tobacco exposures yield many of the same outcomes, and suggests the possibility that the common outcomes for cannabis and tobacco use may be driven by effects of tobacco. Future studies should sample participants from cohorts where cannabis is primarily smoked alone to identify if results replicate. Third, some of our exposures were self-reported by the child

(DANVA) while others were parent-completed (SCDC and DAWBA). Previous studies have indicated parental rating of offspring well-being to be more positive compared to self-report by offspring (Waters, Stewart-Brown, & Fitzpatrick, 2003). Similarly, the maternal-reported measure of SCDC recorded when offspring were aged 17 may be capturing a breakdown in family communication or adolescent disobedience, as opposed to social cognition, due to the generally rebellious nature of the adolescent period. However, a genome-wide association study conducted in ALSPAC found evidence of a genome-wide association of SCDC measures at age 17, suggesting there is a genetic architecture of social communication that can be reliably captured by the maternal SCDC measure (St Pourcain et al., 2014). Fourth, SCDC scores are known to remain constant across age groups (Robinson et al., 2011), while studies have indicated DANVA scores to improve with age (Nowicki & Duke, 1994). This is a potential problem if the ranking of scores across the population is not consistent; however, previous ALSPAC studies have indicated a test-retest reliability in the DANVA of 0.84 (Barona, Kothari, Skuse, & Micali, 2015). Fifth, as maternal data are collected frequently and are more extensive than partner data within ALSPAC, we only investigated the impact of maternal confounding. Sixth, it is possible that our variable for multi-substance current use simply reflects current cannabis use, since cannabis users typically also consume alcohol and tobacco (Raphael, Wooding, Stevens, & Connor, 2005). Seventh, one temporal direction (childhood mental health/social cognition associated with later substance use) captured a longer time span, from age 7 to 18, while another (early substance use associated with mental health/social cognition) analysed data collected between the ages of 15 to 18 (i.e., a relatively short period). Therefore, despite the strong associations observed, further studies over larger age gaps may be required to fully tease apart the effects between differing temporal directions. However, these ages were chosen to capture an early measure of regular use in adolescence and the next available measure of mental health/ social cognition. Eighth, as our measures were not over a long course of time, we only measured effects of current users not withdrawal, or ex-substance users, and as previously noted – some effects only became apparent (particularly for tobacco) when the individual is in a period of acute withdrawal, additionally some deficits can linger months into sobriety for hardened users (Kornreich et al., 2001). Ninth, there was evidence of differential loss to follow-up, as some children with probable diagnoses of ADHD, conduct disorder, anxiety, and high SCDC were slightly more likely to drop out of the study before substance use at age 18 obtained, additionally individuals identifying as substance users at age 15 were more likely to drop out before obtaining information on mental health and social cognition at age 18. However, this does not necessarily imply selection bias in the association between social cognition and later substance use (Carter, Imlach-Gunasekara,

McKenzie, & Blakely, 2012), and comparisons of full and complete cases display little change in results due to sample size.

4.4.5. Conclusion

Overall, childhood mental health and social cognitive ability had differing associations with later substance use initiation. While some mental health problems were specifically associated with substance use (i.e. internalising disorders and alcohol; externalising disorders and tobacco/cannabis), there was either no association between poor social cognition and substance use or (for emotional affect recognition) decreased substance use. In the opposing temporal direction, adolescent substance use initiation was associated in an overall decline of both mental health and social cognition.

4.5. Chapter summary

In this chapter, a series of longitudinal studies were conducted to identify the temporal associations of substance use with both mental health and social cognitive performance. This was done in to understand whether social cognition followed any similar patterns as those observed in substance use and mental health. Here, we found poor childhood mental health and social cognitive performance had opposing effects on later substance use. As mental health was generally associated with increased substance use, while there was no or decreased association of early social cognition with later substance use. However, in the opposing direction, following the onset of adolescent substance use, there was a general decline in all areas of mental health and social cognition. This suggests that substance use may be driving the decline of both mental health and social cognitive performance. However, the temporal relationship of mental health and social cognition (if any) following the onset of substance use is still unknown and will be explored further in the next chapter.

5. Chapter 5 Temporal associations of mental health and social cognition following substance use initiation

5.1. Introduction

The analyses in Chapter 4 indicated a similar decline in both mental health and social cognitive performance following the onset of substance use in adolescence. While mental health and social cognition have typically not been examined together with substance use, previous evidence has suggested that they are both independently associated with a decline following substance use (Baingana, al'Absi, Becker, & Pringle, 2015; Bayrakci et al., 2015; Leventhal et al., 2012). Furthermore, prior evidence suggests mental health and social cognition may be associated with one another, as many mental health disorders are characterised by poor social cognition such as poor affect recognition and theory of mind (Happe & Frith, 2014; Miers et al., 2013; Wagner et al., 2015). However, following the onset of substance use the temporal association of mental health and social cognition with one another is still unknown.

5.1.1. Chapter aims

In this Chapter I investigate both temporal directions of association of mental health and social cognitive performance in late adolescence in the ALSPAC birth cohort.

5.2. Methods

Participants and variables from the Avon Longitudinal Study of Parents and Children have previously been described in detail in Chapter 3; a summary of these methods will be included below.

5.2.1. Participants

Participants for this analysis were drawn from the ALSPAC birth cohort. The analysis of the association between mental health with subsequent social cognitive performance following the onset of substance use was further restricted to parents who had completed the Development and Well-Being Assessment (DAWBA) (N = 3,657) when their offspring where age 15, offspring who had completed the psychosis-like symptoms semi-structured interview (PLIKSi) (N = 6,792) at age 12, and who had taken part in Social and Communication Disorders Checklist at age 18 (N = 3,613).

The analysis of the association between social cognition with subsequent poor mental health following the onset of substance use was further restricted to offspring who had taken part in Social and Communication Disorders Checklist at age 15 (N = 5,468), and offspring who had completed the CIS-R at age 18 (N = 4,563), offspring who had completed the computerized task on self-reported criminal offenses (N = 4,017), and offspring who had completed the psychosis-like symptoms semi-structured interview (PLIKSi) (N = 4,718) at age 18). Flow diagrams Figures 3.5 and 3.6 display the final sample size for each temporal association analysis.

5.2.2. Variables

5.2.2.1. Mental health

Mental health diagnoses including attention-deficit hyperactivity disorder (ADHD), depression, conduct disorder (CD), and anxiety were assessed at age 15 via parent- and teacher-report using the DAWBA questionnaire (R. Goodman et al., 2000) (based on ICD-10 and DSM-IV criteria). Parent and teacher responses were combined for each child and from each response 'bands' created, ranging from unlikely to probable. Psychosis-like symptoms were coded as a binary variable indicating suspected or definite symptoms assessed via self-report at ages 12 and 18 via the PLIKSi semi-structured interview (Zammit et al., 2008). Binary measures of depression and anxiety were assessed at age 18 using the CIS-R via a self-administered computerised interview (G. Lewis et al., 1992). Information on antisocial behaviour was measured at age 18 by via self-reported offenses in the past 12 months (Boyd, Golding, Macleod, Lawlor, Fraser, Henderson, Molloy, Ness, Ring, & Smith, 2013; Kretschmer et al., 2014); Individuals were classified as antisocial if they responded positively to one or more items.

5.2.2.2. Social cognition

Social communication was measured by maternal completion of the Social Communication Disorders Checklist (SCDC) at offspring ages 15 and 18 via questionnaire, scoring ≥ 8 out of a possible of 24 was coded as poor performance (Robinson et al., 2011). Social reciprocity at age 18 was derived from 5 questions on the SCDC that were specifically designed to measure social reciprocity (D. H. Skuse et al., 2005; D. Skuse et al., 2004). Responses of yes to ≥ 3 questions was coded as poor performance.

5.2.2.3. Confounding variables

Based on the literature, risk factors for poor mental health and social cognition were considered as potential confounders, grouped into three categories: (1) pre-birth/ demographic, (2) maternal substance use, and (3) offspring. The pre-birth/ demographic

confounders adjusted for sex, parity, maternal social class, and maternal home ownership status. Maternal substance use confounders additionally adjusted for maternal binge drinking, maternal cannabis use, and maternal smoking. Offspring confounders additionally adjusted for IQ, peer problems, victimization, and borderline personality diagnosis.

Additionally, for the analysis of the association between age 15 mental health and subsequent social cognition I adjusted for (4) previous incidence of poor social cognition (age 7 social communication or social reciprocity). Or for the analysis of the association between age 14 social cognition with the association between subsequent mental health I adjusted for (4) previous incidence of mental health problems (age 7 DAWBA probable diagnosis or age 12 PLIKSi semi-structured interview).

5.2.3. Statistical analysis

First, I examined the association of poor mental health on subsequent social cognition. Next, I examined the association of poor social cognition on subsequent mental health. I assessed both these temporal relationships before and after adjustment for covariates using logistic regression. I examined the impact of confounding by comparing unadjusted results with those adjusted for pre-birth / demographics confounders (model 1), and then additionally and cumulatively maternal substance use (model 2), childhood confounders (model 3), and previous mental health/ or social cognition (model 4). Finally, I ran a second set of confounder-adjusted analyses only including the complete cases from model 4. Each analysis was conducted in full and complete cases. Analyses were conducted in Stata version 13 (Stata Corp LP, College Station TX USA).

5.3. Results

5.3.1. Characteristics of participants

Data were available on N = 1,883 participants for the analysis of mental health with subsequent social cognition in substance users, and N=1,763 for the analysis of social cognition with subsequent mental health in substance users. Characteristics of these participants are presented in Table 5.1 Confounder characteristics and associations with each outcome are presented in Table 4.9. The results presented below are from the fully adjusted models. Unadjusted and partially adjusted models and comparison of full and complete cases are presented in pages 207-207 of Appendix C.

Table 5.1 Participant demographics - adolescent mental health and social cognition

Early adolescent mental health (age 15)

		Probability of disorder					
	N	~<0.1%	~0.5%	~3%	~15%	~50%	~>70%
ADHD	4,757	73% (3,458)	15% (729)	7% (350)	4% (176)	0.5% (23)	0.4% (21)
CD	4,742	68% (3,213)	0	28%(1,340)	3% (118)	0.7% (31)	0.8% (40)
Depression	8,083	63% (5,041)	35% (2,798)	0	2% (190)	0.6% (52)	0.02% (2)
Anxiety	8,197	0	49% (4,045)	48% (3,900)	3% (235)	0.2% (17)	0
PLIKS	6,792	86% (5,865): none	14% (927): suspected or definite				

Late adolescent mental health (age 18)

	N	No	Yes
Antisocial behaviour	4,017	84% (3,355)	16% (662)
Depression	4,053	92% (4,203)	8% (360)
Anxiety	4,053	89% (4,041)	11% (522)
PLIKS	4,718	91% (4286): none	9% (432): suspected or definite

Early adolescent social cognition (age 15)

	N	Normal	Poor
Social communication	6,293	91% (6,296)	9% (627)
Social reciprocity	6,967	81% (5,649)	19% (1,318)

Late adolescent social cognition (age 18)

	N	Normal	Poor
Social communication	5,468	88% (4,833)	12% (635)
Social reciprocity	5,571	66% (635)	23% (1,271)

5.3.2. Association of mental health with subsequent social cognitive performance in substance users

Diagnosis of depression at age 15 was associated with increased odds of poor social communication (fully adjusted OR 1.31, 95% CI 1.12 to 1.54, P = 0.001) and social reciprocity at age 18 (fully adjusted OR 1.24 95% CI 1.09 to 1.41, P = 0.001); these results are shown in Table 5.2. Diagnosis of anxiety at age 15 was associated with increased odds of poor social communication (fully adjusted OR 1.44, 95% CI 1.10 to 1.89, P = 0.008) and social reciprocity at age 18 (fully adjusted OR 1.50, 95% CI 1.23 to 1.84, P< 0.001). Diagnosis of ADHD at age 15 was associated with increased odds of increased odds of poor social communication (fully adjusted OR 2.10, 95% CI 1.75 to 2.51, P < 0.001) and social reciprocity at age 18 (fully adjusted OR 1.84, 95% CI 1.59 to 2.12, P < 0.001). Diagnosis of conduct disorder at age 15 was associated with increased odds of poor social communication (fully adjusted OR 2.23, 95% CI 1.76 to 2.83, P $\leq$ 0.001) and social reciprocity at age 18 (fully adjusted OR 2.07, 95% CI 1.70 to 2.52, P $\leq$ 0.001). There was no evidence of an association between psychosis-like symptoms and social cognition.

5.4.1. Association of social cognition with subsequent mental health in substance users

There was no clear evidence of an association of adolescent social communication or social reciprocity with later depression, anxiety, antisocial behaviour, or psychosis-like symptoms; these results are sown in Table 5.3.

5.5. Discussion

Adolescent mental health conditions including depression, anxiety, ADHD, and conduct disorder at age 15 were associated later poor social cognitive performance at age 18, and adjustment for pre-birth, maternal, childhood, or previous social cognitive performance did not substantially alter these associations. However, there was no evidence of an association of social cognitive performance at age 15 with later mental health problems at age 18. As these analyses adjust for previous incidence of poor social cognitive performance prior to the onset of substance use and mental health problems, this suggests that mental health problems are associated with subsequent decreased social cognitive performance.

5.5.1. Strengths

There are several strengths of this analysis. First, as in Chapter 4, these analyses investigate both temporal directions. Second, they are conducted in a rich dataset over multiple time-points. Third, variables were systematic and comparable across category and age group. Finally, a robust approach was taken to minimise confounding by integrating a range of confounding from pre-birth throughout adolescence.

5.5.2. Limitations

There are also several limitations to consider. First, some of the exposures were self-reported by the child (CIS-R and PLIKS), while others were parent-completed (SCDC). Previous studies have indicated parental rating of offspring well-being to be more positive compared to self-report by offspring (Waters et al., 2003). Second, the maternal-reported measure of SCDC recorded when offspring were aged 17 may be capturing a breakdown in family communication or adolescent disobedience, as opposed to social cognition, due to the generally rebellious nature of the adolescent period. However, a genome-wide association study conducted in ALSPAC found evidence of a genome-wide association of SCDC measures at age 17, suggesting there is a genetic architecture of social communication that can be reliably captured by the maternal SCDC measure (St Pourcain et al., 2014). Third, as maternal data are collected frequently and are more extensive than partner data within ALSPAC, we only investigated the impact of maternal confounding. Fourth, there was some evidence of differential loss to follow-up, as some adolescents with ADHD and anxiety at 15 were slightly more likely to drop out of the study before social cognition was obtained at 18, likewise individuals with high SCDC at 15 were slightly more likely to drop out before obtaining information on mental health at 18. However, this does not necessarily imply selection bias in the association between social cognition and later

substance use (Carter et al., 2012), and comparisons of full and complete cases display little change in results due to sample size.

5.5.3. Conclusion

Previously, in Chapter 4, we investigated the common associations of mental health and social cognition with substance use, finding evidence that mental health and social cognition both declined following the onset of adolescent substance use. In this set of analyses, I investigated the temporal association of mental health and social cognition finding evidence that poor mental health was associated with subsequent social cognitive decline. Taken together, this suggests two possible pathways to social cognitive decline: (a) substance use is independently associated with decline in both mental health and social cognition (see figure 5.1), or (b) substance use is associated with decline in social cognition via mental poor mental health (see Figure 5.2).

Figure 5.1 Substance use has independent effects on mental health and social cognition

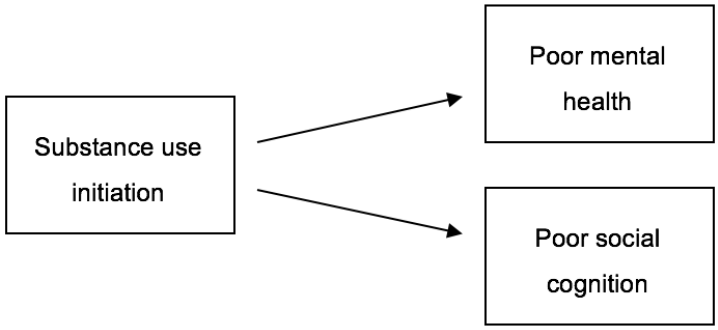
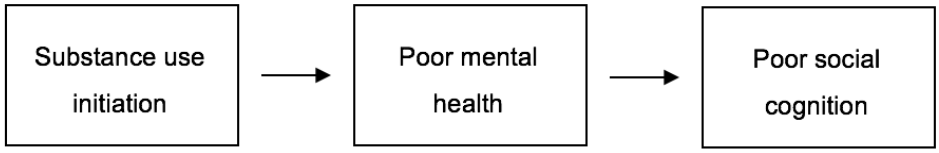


Figure 5.2 Substance use is associated with social cognition via mental health



5.6. Chapter summary

In this Chapter, I examined the temporal association of mental health and social cognition in late adolescence, finding evidence that mental health problems were associated with decreased social communication and social reciprocity. The evidence presented in Chapter 4 suggests that substance use precedes decline in both mental health and social cognitive performance, there are two possible pathways. First, either substance use is independently

associated with decline in both mental health and social cognition. Second, that substance use is associated with decreased social cognition via poor mental health. The following Chapters will use additional methods to investigate causal inferences of these associations, particularly focusing on externalising disorders which have had the strongest evidence in my results thus far.

6. Chapter 6: A Mendelian randomisation analysis of associations between substance use with externalising disorders and social cognitive outcomes

6.1. Introduction

Previous longitudinal evidence suggests substance use initiation is associated with increased risk of later mental health problems (M. Fluharty et al., 2016). These findings were particularly robust for tobacco and cannabis use with later externalising disorders (i.e. antisocial behaviour). There is also evidence that substance use initiation is associated with increased risk of later poor social cognitive functioning, and again these findings are particularly robust for tobacco and cannabis and later social cognitive outcomes.

However, as discussed in Chapter One, assessing causality solely from observational analysis is challenging due to a number of problems inherent to conventional epidemiological methods (Fewell et al., 2007; Phillips & Smith, 1992; Smith & Phillips, 1992). While researchers would ideally control for all possible confounding variables, these variables need to be both comprehensively identified and accurately measured to eliminate the possibility of residual confounding (S. H. Gage, Munafo, et al., 2015). However, researchers can never be completely positive all possible confounders of an association are known.

Ideally, researchers would conduct a randomised control trial (RCT) to investigate causal associations. RCTs are typically the gold standard for assessing causality, as they minimize the risk of confounding and selection bias through randomisation (Akobeng, 2005). In RCTs, participants are randomised into either an active or control group. The active group would receive an intervention (exposure) while the control group receives a placebo. Each group would be followed up across a period of time, and the outcome of interested measured (S. H. Gage, Munafo, et al., 2015; Smith & Ebrahim, 2002). However, the use of RCTs in substance use research is often impractical or unethical.

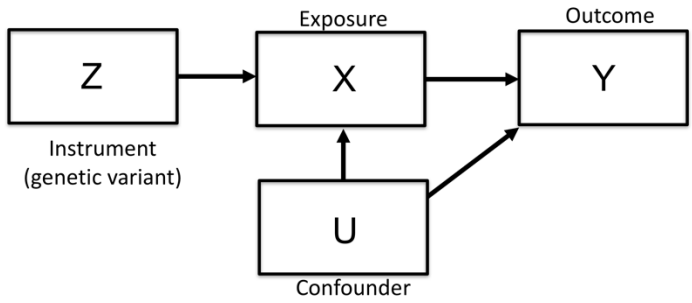
6.1.1. Mendelian randomisation

When RCTs are not possible, we can turn to alternative methods to counteract residual confounding and reverse causality. Instrumental variable analysis, originally developed in the economics literature, assigns a proxy variable to the exposure which is not associated with confounders. A specific type of instrumental variable analysis, Mendelian randomisation, uses a genetic variant as the instrumental variable or proxy measure

(Burgess et al., 2015; S. H. Gage et al., 2013). This relies on two properties of how humans inherit their genotype. First, genes are inherited independently from one another through meiosis. Second, genes are inherited independently from the environment. Mendelian randomisation takes its name from Gregor Mendel's first and second laws of inheritance. First, at gamete formation, each cell contains one allele per gene. Second, the law of independent assortment, states alleles will sort randomly and so the chances of inheriting a specific allele are independent of inheriting another (Smith & Ebrahim, 2003). Based on these assumptions, genetic instruments in Mendelian randomisation are not subject to the confounding typical of observational analyses.

To identify an appropriate genetic variant as a proxy, the variant must be known to alter the effect of a modifiable risk factor. The genetic variant must meet four assumptions to be suitably used in a Mendelian randomisation analysis. First, the genetic variant must be robustly associated with an exposure of interest. Second, the variant should not directly affect the outcome of interest, except via the exposure. Third, the variant should be independent of all possible confounders affecting the relationship of interest. Fourth, the variant should not introduce any additional confounding into the association (Katikireddi, Green, Taylor, Davey Smith, & Munafo, 2017). Figure 6.1 shows a directed acyclical graph (DAG) of Mendelian randomisation.

Figure 6.1 Model of Mendelian randomization



6.1.1.1. Mendelian Randomisation for behavioural outcomes

Mendelian randomisation may be used to understand causal influences on behavioral outcomes, and with more GWAS there are better instruments for these phenotypes with the increasing availability of large biobanks.

As discussed above, MR relies on the assumption that genes are randomly assorted at birth and inherited independently from the environment; therefore, genotypes of interest should not be associated with confounders (e.g., socioeconomic status). However, there are some situations in which the MR assumptions may still be violated.

First, a suitable genetic variant must be identified for the exposure of interest. For MR analysis to be accurate, the phenotypes used need to accurately reflect the exposure of interest. Mental health phenotypes can be particularly noisy, given the range of symptoms experienced as part of a particular trait, the overlap between traits, and the range of methods used to measure them (S. H. Gage et al., 2013).

Second, social pressures on certain behaviours may cause bias in the genotype-exposure associations. Individuals' are unlikely to be aware of their physiological phenotypes and therefore their behaviour will not be affected. However, this may be different for some behavioural phenotypes. For example, using genes associated with adverse alcohol reactions as a measure for alcohol consumption may produce skewed results, specifically in heavy drinking populations as social standards may cause these individuals to continue drinking despite possible adverse reactions (D. A. Lawlor, Harbord, Sterne, Timpson, & Smith, 2008).

Third, MR may be affected by population stratification, which may in turn result in bias as MR assumes population homogeneity with consistent allele frequencies. As populations combine there may be differences in ancestry and subsequent underlying genetic proportions; therefore, results may be distorted if there are different proportions of the proxy genotype across sub-populations (S. H. Gage et al., 2013; Lee, Wright, & Zou, 2011).To reduce population stratification the gene-exposure and gene-outcome associations should be ideally conducted in the same population (D. A. Lawlor et al., 2008).

Fourth, linkage disequilibrium (LD) may complicate interpretation. LD occurs when some genotypes are more likely to be inherited together then by chance. As the proxy gene should only affect the outcome via the exposure, if a linked gene directly affects the outcome (i.e. pleiotropy) it may be driving an observed association instead of the exposure. In this case, there may be alternative pathways (other than that of the exposure of interest) directly influencing the outcome (Angrist, Imbens, & Rubin, 1996; Sheehan & Didelez, 2005). A strength of MR is genetic heterogeneity, in which multiple genes may be associated with a single phenotype, but are not in LD. This allows us to test for pleiotropy by producing estimates using different variants (S. H. Gage et al., 2013; Smith, 2011). If both instruments are independently associated with the outcome via the same pathway, this suggests a true causal association rather one than due to pleiotropy (Smith, 2011).

Fifth, bias may be generated through assortative mating. Assortment results in an association of mother-father genetic variants generated through individual attraction based on specific heritable traits (i.e., smokers are more likely to reproduce with other smokers

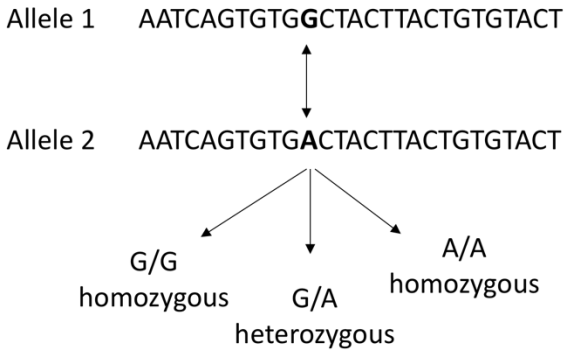
(Watson et al., 2004)). If assortative mating occurs, this may violate the assumption of assortment on the exposure of interest, creating spurious associations (D. Lawlor et al., 2017).

Finally, it's important to note that MR can be used to determine if an association is causal, but not necessarily display the underlying mechanisms. For example, while tobacco may be associated with mental health problems, this may be because it influences use of other substances via the gateway effects (S. H. Gage et al., 2013).

6.1.1.2. Genetic instruments

Through the use of twin-studies, a number of different substances, including tobacco and cannabis use, have been identified as being moderately to highly heritable (Agrawal et al., 2006; Li, Cheng, Ma, & Swan, 2003; Verweij et al., 2010). However, more recently, genome wide association studies (GWAS) have allowed us to identify specific genes responsible (Begum, Ghosh, Tseng, & Feingold, 2012; Cantor, Lange, & Sinsheimer, 2010). GWAS studies generally focus on identifying associations between single nucleotide polymorphisms and traits of interest. SNPs are variations occurring in a single nucleotide at a particular genome position. For example, in a particular stretch of deoxyribonucleic acid (DNA) a guanine (G) base may be replaced by an adenine (A) base; see Figure 6.2.

Figure 6.2 Example of a single nucleotide polymorphism



The Tobacco and Genetics Consortium (TAG) conduced a GWAS meta-analysis across 16 studies (N= 74,053). TAG harmonised smoking variables across each cohort to examine four aspects of smoking behaviour in individuals of European descent. These included smoking initiation, smoking quantity, age of onset, and smoking cessation. Eight SNPs were identified as genome-wide significant for smoking initiation located around brain-derived neurotrophic factor (*BDNF*) on chromosome 11. *BDNF* is highly expressed in the hippocampus and prefrontal cortex. These areas have been previously associated with

cognitive enhancing effects of nicotine (Levin, McClernon, & Rezvani, 2006). Genetic variations in the *BDNF* may modify the rewarding effects of nicotine through dopamine reward modulation, subsequently leading to nicotinic salience and continued use.

The International Cannabis Consortium (ICC) conducted a GWAS meta-analysis investigating lifetime cannabis use in 13 cohort studies (N= 32,330) of individuals of European descent. While no SNPs were identified as genome-wide significant, a number of SNPs were identified as approaching genome-wide significance. The most significant SNP identified was rs4984460 ($P= 4.6 \times 10^{-7}$) on chromosome 15 in an intergenic region between the *LOC400456/LOC145820* and *MIR1469* and *NR2F2* genes. However, the biological explanations behind cannabis use are still unclear. This may be due to the nature of how this phenotype was measured, as 'ever/never use' may capture both single use and prolonged heavier use (S. H. Gage et al., 2016).

6.1.2. Chapter aims

In this Chapter, I use Mendelian randomisation analysis to determine whether the previously observed associations between cigarette and cannabis use with externalising behaviours and social communication are causal. Based on the results in my previous Chapters, and the literature discussed, I hypothesis these associations will be causal.

6.2. Methods

6.2.1. Participants

Participants were drawn from the ALSPAC cohort, as described in detail in Chapter 3. This sample is further restricted to individuals with genotypic information (N=7,870), and with information on antisocial behaviour (N = 2,919) and/or who had taken part in Social and Communication Disorders Checklist at age 18 (N = 3,613); see Figures 3.7 and 3.8.

6.2.2. Phenotypic measures

6.2.2.1. Externalising disorder

Antisocial behaviour was a binary measure of self-reported offenses at age 18 based on self-reported offenses in the past 12 months (Boyd, Golding, Macleod, Lawlor, Fraser, Henderson, Molloy, Ness, Ring, & Smith, 2013; Kretschmer et al., 2014).

6.2.2.2. Social cognition

Social communication was measured by maternal completion of SCDC at offspring age 18 via questionnaire, scoring ≥ 8 out of a possible of 24 was coded as poor performance

(Robinson et al., 2011). Social reciprocity at age 18 was derived from 5 questions on the SCDC that were specifically designed to measure social reciprocity (D. H. Skuse et al., 2005; D. Skuse et al., 2004). Responses of yes to ≥ 3 questions was coded as poor performance.

6.2.2.3. Substance use

Tobacco and cannabis use were measured at age 18 via computerized-based assessment during a clinic visit. A binary variable indicating ever or never use (i.e., initiation) of each substance respectively was used as the exposure variable. These variables were chosen to mirror the variables used to determine the genetic association of tobacco and cannabis use within their respective GWAS.

6.2.2.4. Confounders

Confounding variables were grouped into three categories (1) pre-birth/ demographic (2) maternal substance use (3) offspring. The pre- birth/ demographic confounders adjusted for sex, parity, maternal social class, and maternal home ownership status. Maternal substance use confounders additionally adjusted for maternal binge drinking, maternal cannabis use, and maternal smoking. Offspring confounders additionally adjusted for IQ, peer problems, victimization, and borderline personality diagnosis.

6.2.3. Genotype

6.2.3.1. Genetic sample

ALSPAC offspring were genotyped using the Illumina HumanHap550 Quad Array Platform (by 23andMe subcontracting the Wellcome Trust Sanger Institute, Cambridge, UK and the Laboratory Corporation of America, Burlington, NC, US) and imputed to the 1000 genomes reference panel (Paternoster et al., 2011).

6.2.3.2. Genetic risk scores for tobacco initiation

A total of 8 SNPs were identified from the Tobacco and Genetics Consortium (TAG) as reaching genomewide significance ($P < 5 \times 10^{-8}$) for tobacco initiation (Tobacco & Genetics, 2010). As these SNPs were all in high linkage disequilibrium (LD) with one another, they were pruned based on values obtained in SNAP (http://www.broadinstitute.org/mgp/snap/) where $r^2 > 0.9$ SNPs were randomly selected, and the other correlated SNPs removed from the analysis leaving 4 SNPs. These 4 SNPs were highly correlated; therefore, the strongest SNP, rs6265 (accounting for ~0.03% of the variance in smoking initiation) was selected. Then, using a less stringent P-value ($P < 10^{-6}$), a further 21 SNPs were identified see Table

6.1. Polygenic risk scores were then created for tobacco initiation by summing the number of tobacco initiation increasing alleles across all 22 SNPs creating an additive genetic model.

Table 6.1 SNPs associated with tobacco initiation ($P < 10^{-6}$)

SNP	Chromosome	Reference allele	OR	SE
rs926246	1	T	0.09	0.02
rs7548367	1	C	0.06	0.01
rs11892348	2	A	-0.05	0.01
rs10937751	4	A	0.07	0.01
rs7663808	4	A	-0.06	0.01
rs10013579	4	T	0.06	0.01
rs1448438	4	T	0.06	0.01
rs13131292	4	A	-0.11	0.02
rs725695	5	A	-0.05	0.01
rs1986692	7	A	0.06	0.01
rs2449222	8	T	-0.09	0.02
rs10108954	8	T	-0.17	0.03
rs16904189	8	T	-0.15	0.03
rs6265	11	T	0.06	0.02
rs11030084	11	T	-0.07	0.01
rs1817648	12	T	-0.05	0.01
rs739484	12	T	-0.09	0.02
rs11067275	12	T	0.07	0.01
rs11246771	12	T	-0.08	0.02
rs9521281	13	T	-0.07	0.02
rs241526	14	T	-0.05	0.01
rs11570441	17	C	0.11	0.02

6.2.3.3. Genetic risk scores for cannabis initiation

A total of 153 SNPs were identified from the International Cannabis Consortium (ICC) as reaching near genomewide significance ($P < 10^{-5}$) for cannabis initiation (Stringer et al., 2016). Explaining 13-20% of the phenotypic variance of ever/never cannabis smoking across the genome. The ALSPAC cohort was included in the original GWAS, and therefore removed from the analysis. A large number of the remaining SNPs were at high linkage disequilibrium (LD), they were pruned based on values obtained in SNAP (http://www.broadinstitute.org/mgp/snap/) where $r^2 > 0.9$ SNPs were randomly selected, and the other correlated SNPs removed from the analysis. Following LD pruning, 21 SNPs remained, see Table 6.2. Finally, polygenic risk scores were created for cannabis initiation by summing the number of cannabis increasing alleles across all 21 SNPs.

Table 6.2 SNPs associated with cannabis initiation ($P < 10^{-5}$)

SNP	Chromosome	Reference allele	β	SE
rs3738226	1	T	0.09	0.02
rs73067624	1	T	-0.20	0.04
rs74944517	2	T	0.24	0.07
rs2033867	2	A	0.26	0.06
rs2326313	3	A	0.11	0.03
rs13063578	3	A	-0.10	0.03
rs7675351	4	A	-0.18	0.03
rs6840574	4	T	-0.14	0.04
rs7700636	5	A	-0.14	0.04
rs12518098	5	C	0.11	0.02
rs353253	5	A	-0.13	0.03
rs1554927	8	A	-0.08	0.02
rs12789616	11	A	-0.09	0.02
rs7107987	11	A	0.27	0.06
rs12313672	12	T	0.13	0.03
rs17237367	15	A	-0.12	0.03
rs4984458	15	A	-0.11	0.02
rs4984460	15	T	-0.14	0.02
rs8041045	15	A	0.11	0.02
rs8102250	19	C	-0.16	0.03
rs113019398	20	T	-0.17	0.04

6.2.4. Statistical analysis

I estimated the associations (odds ratios and 95% confidence intervals) between the observational tobacco and cannabis measures with antisocial behaviour and social cognitive (social communication and social reciprocity) outcomes after adjusting for potential confounders and restricting the sample to only include individuals with genetic data. Next, I estimated the associations between tobacco and cannabis polygenic risk scores with antisocial behaviour and social cognitive outcomes using two-stage least squares regression. Finally, an additional sensitivity analysis was conducted for tobacco initiation using only the strongest SNP (rs6265). Analyses were restricted to unrelated individuals and those of European descent. Analyses were conducted in Stata version 13 (Stata Corp LP, College Station TX, USA).

6.3. Results

6.3.1. Participants

Of the 7,870 children on whom genetic data were available, 1,569 (52%) had ever smoked tobacco and 1,251 (41%) had used cannabis (see Figure 3.7-3.8); full characteristics of participants are displayed in Table 6.3.

Table 6.3 Descriptive statistics

	N	*Ever use*	*Never use*
Tobacco	3,043	52% (1569)	48% (1474)
Cannabis	3,015	41% (1,251)	59% (1,764)
	N	*Positive diagnosis*	*No diagnosis*
Antisocial behaviour	2,919	16% (478)	84% (2,441)
	N	*Poor*	*Normal*
Social communication	3,930	12% (458)	88% (3,472)
Social reciprocity	4,013	23% (922)	77% (3,091)

6.3.2. Assumptions of Mendelian randomisation

The tobacco risk score was associated with tobacco ever use (OR 1.11, CI 1.03 to 1.19, P = 0.004) and the cannabis risk score was associated with cannabis ever use (OR 1.18, CI 1.09 to 1.27, P < 0.001), confirming the assumption that the polygenic risk scores were associated with expose of interest within this sample. Additionally, both tobacco and cannabis risk scores were not strongly associated with any potential confounders, as displayed in Table 6.4, confirming the assumption that the risk scores are not associated with potential confounders.

Table 6.4 Association of risk scores with potential confounders

Confounder	**Tobacco risk score**			**Cannabis risk score**		
	OR	*95% CI*	*p*	*OR*	*95% CI*	*p*
Sex	0.95	(0.92 to 0.99)	0.046	0.99	(0.95 to 1.03)	0.773
Parity	1.02	(1.00 to 1.05)	0.044	1.00	(0.98 to 1.02)	0.704
Maternal social class	0.99	(0.97 to 1.02)	0.848	0.01	(0.98 to 1.03)	0.405
Mothers highest qualification	1.01	(0.99 to 1.03)	0.137	1.00	(0.98 to 1.02)	0.511
Maternal home ownership status	0.99	(0.95 to 1.02)	0.686	1.01	(0.97 to 1.05)	0.522
Maternal smoking	1.01	(0.95 to 1.08)	0.606	1.03	(0.97 to 1.10)	0.257
Maternal cannabis use	1.02	(0.90 to 1.17)	0.665	1.10	(0.97 to 1.26)	0.115
Maternal harmful drinking	0.94	(0.87 to 1.01)	0.113	1.04	(0.97 to 1.13)	0.223
Borderline personality disorder	0.97	0.85 to 1.09)	0.628	0.95	(0.84 to 1.08)	0.474
Peer Problems	1.00	(0.98 to 1.02)	0.792	0.99	(0.97 to 1.01)	0.414
Victimisation	0.98	(0.92 to1.03)	0.404	0.98	(0.92 to 1.04)	0.550
IQ	1.00	(0.98 to 1.03)	0.622	1.00	(0.98 to 1.02)	0.839

6.3.3. Observational analysis

6.3.3.1. Antisocial behaviour

Ever use of tobacco was associated with increased odds of antisocial behaviour (OR 7.41, 95% CI 5.10 to 10.76, P < 0.001); see Table 6.5. Additionally, ever use of cannabis was associated with increased odds of antisocial behavior (OR 7.36, 95% CI 5.20 to 10.71, P < 0.001).

Table 6.5 Observational analysis of tobacco and cannabis on antisocial behaviour

	Antisocial behaviour			
	N	*OR*	*95% CI*	*p*
Tobacco	1451	7.41	5.10 to 10.76	<0.001
Cannabis	1450	7.36	5.20 to 10.41	<0.001

6.3.3.2. Social cognition

Ever use of tobacco was associated with increased odds social communication (OR 1.79, 95% CI 1.23 to 2.26, P = 0.003) and social reciprocity (OR 1.51, 95% CI 1.15 to 2.00 P = 0.003); see Table 6.6. Additionally, ever use of cannabis was associated with increased risk of social communication (OR 2.05, 95% CI 1.42 to 2.98, P < 0.001) and social reciprocity (OR 1.81, 95% CI 1.37 to 2.39, P < 0.001).

Table 6.6 Observational analysis of tobacco and cannabis on social cognition

	Social communication				Social reciprocity			
	N	*OR*	*95% CI*	*p*	*N*	*OR*	*95% CI*	*p*
Tobacco	1311	1.79	(1.23 to 2.62)	0.003	1331	1.51	(1.15 to 2.00)	0.003
Cannabis	1301	2.05	(1.42 to 2.98)	<0.001	1321	1.81	(1.37 to 2.39)	<0.001

6.3.4. Mendelian randomisation analysis

6.3.4.1. Antisocial behaviour

There was no clear evidence of an association between the tobacco risk score and antisocial behavior, these results were similar when analysed in only rs6265. Similarly, there was no clear evidence of an association between the cannabis risk score and antisocial behaviour; these results are shown in Table 6.7.

Table 6.7 Mendelian randomisation analysis of tobacco and cannabis on mental health outcomes

	Antisocial behaviour			
	N	*OR*	*95% CI*	*p*
Tobacco risk score	2695	1.43	(0.86 to 2.36)	0.172
Tobacco strongest SNP (rs6265)	2695	1.36	(0.28 to 6.56)	0.701
Cannabis risk score	2693	1.19	(0.84 to 1.67)	0.348

6.3.4.2. Social cognition

There was no clear evidence of an association between the tobacco risk score and either social communication or social reciprocity; these results are shown in Table 6.8. When only using rs6265 was used, results were similar for social communication, but the association with social reciprocity was reversed in direction. There was no clear evidence of an association between the cannabis risk score and either social communication or social reciprocity.

Table 6.8 Mendelian randomisation analysis of tobacco and cannabis on social cognitive outcomes

	Social communication				Social reciprocity			
	N	*OR*	*95% CI*	*p*	*N*	*OR*	*95% CI*	*p*
Tobacco risk score	2190	0.84	(0.50 to 1.54)	0.575	2227	1.06	(0.46 to 2.41)	0.894
Tobacco strongest SNP (rs6265)	2190	0.97	(0.52 to 1.80)	0.905	2227	0.57	(0.23 to 1.40)	0.219
Cannabis risk score	2169	1.35	(0.94 to 1.91)	0.101	2206	1.27	(0.77 to 2.09)	0.335

6.3.5. Power calculation

Power calculations were conducted using an online power calculation tool (https://sb452.shinyapps.io/power/) (Burgess, 2014).I defined the coefficient of determination as the exposure on genetic variant as R^2=0.03 (smoking); R^2=0.13 (cannabis). For antisocial behavior, based on the proportion of cases in the sample (0.16) and on the causal effect observed (OR= 1.43 smoking; OR= 1.35 cannabis), I calculated a sample of ~12,000 would be needed for the analysis of tobacco risk score and ~4000 for the analysis of cannabis risk score to achieve 80% power. However, the current analysis only provides 27% power for the tobacco analysis and 63% for the cannabis analysis. For social communication, based on the proportion of cases in the sample (0.12) and on the causal effect observed (OR= 0.84 smoking; OR= 1.35 cannabis), I calculated a sample of ~92,000 would be needed for the analysis of tobacco risk score and ~5,000 for the analysis of cannabis risk score to achieve 80% power. However, the current analysis only provides 7% power for the tobacco analysis

and 46% for the cannabis analysis. Therefore, the present analyses are likely to be considerably underpowered.

6.4. Discussion

Overall, our findings do not provide evidence for a causal effect of genetic risk for tobacco or cannabis initiation on antisocial behaviour. Additionally, there was no evidence of a causal effect of genetic risk for cannabis or tobacco initiation on social cognitive performance. This contrasts with the clear observational evidence in the previous chapters (using current use) and current analysis (using ever/never) of a strong association between tobacco and cannabis use with subsequent antisocial behaviour and poor social cognition.

There are some limitation of this study to consider. First, while this study highlights the importance of using different statistical and methodological approaches when investigating causality, it also indicates that Mendelian randomisation analyses are likely to require very large sample sizes to achieve adequate statistical power. The point estimates are of interest and generally in the direction I would expect based on the previous observational evidence. However, much larger sample sizes would be required to narrow the confidence intervals to be certain of the effect. Secondly, it should be noted that I used a more liberal P-value threshold to increase the number of SNPs used for each polygenic risk score. Increasing the number of SNPs may introduce further variance into the model and increase the risk of pleiotropy (i.e., one SNP influences multiple unrelated phenotypes). Furthermore, the results are difficult to interpret due to low statistical power. In the following Chapter, we address the issues of pleiotropy and low sample sizes using two-sample MR.

While there are no current MR studies investigating the association of tobacco and cannabis with antisocial behaviour, one study investigated the association of alcohol use on later antisocial behaviour in Asian adolescents. The aldehyde dehydrogenase 2 (*ALDH2*) gene was used to quantify alcohol ingestion, as *ALDH2* is associated with decreased drinking due to unpleasant effects of alcohol. The authors hypothesized individuals without this variant would be associated with higher substance use and antisocial behaviour via a “gateway” effect (Pingault, 2016). However, there was no association between adolescent alcohol use and later antisocial behaviour (Irons, McGue, Iacono, & Oetting, 2007).

There are also a number of studies that have investigated other mental health outcomes. A meta-analysis of MR studies investigating SNPs associated with smoking heaviness (rs16969968/rs1051730) with depression and anxiety found no causal association between smoking heaviness and increased risk of depression or anxiety, contrary to their observational analysis which found an association of smoking and risk of depression and/or

anxiety (A. E. Taylor et al., 2014). Additionally, two recent studies using two-sample MR to investigate tobacco and cannabis initiation with schizophrenia used the same initiation SNPs as the current study to generate polygenic risk scores (S. H. Gage et al., 2016; S. H. J. Gage, H.; Taylor, A.; Burgess, S.; Zammit, S.; Munafo, M. , 2016). Two-sample MR benefits from large sample sizes and can allow the analysis of associations in both causal directions (further discussion of two-sample MR in Chapter 7). There was no evidence that risk of schizophrenia was associated with smoking initiation, although there was some evidence of a causal effect of smoking initiation on risk of schizophrenia, although this effect was attenuated when the P-value was relaxed to include variants across different genes (S. H. J. Gage, H.; Taylor, A.; Burgess, S.; Zammit, S.; Munafo, M. , 2016). Additionally, there was evidence that risk of schizophrenia was associated with subsequent cannabis initiation, and conversely cannabis initiation was associated with risk of schizophrenia (S. H. Gage et al., 2016).

There are no current MR analyses investigating social cognitive outcomes of tobacco and cannabis use. Future studies with increased sample size or using two-sample MR will serve to replicate the current findings, as GWAS continue to identify genetic architecture for mental health and social cognitive outcomes.

Overall, we found no clear evidence of a causal association of tobacco or cannabis initiation antisocial behaviour or social cognitive performance. However, it is difficult to draw firm conclusions from these findings due to low statistical power. Future studies should increase the sample size or consider two-sample MR to increase power.

6.5. Chapter summary

In this Chapter, I used Mendelian randomisation analysis to investigate the possible causal effects of tobacco and cannabis initiation with antisocial behaviour and social cognitive performance. Previous observational evidence suggested an association between tobacco and cannabis initiation with an increased risk of both antisocial behaviour and poor social cognitive performance. However, there was no evidence of a causal association between tobacco or cannabis polygenic risk scores with either outcome. Although these analyses were underpowered and therefore difficult to draw strong conclusions from, suggesting future analyses should increase sample sizes or use alternative methods such as two-sample MR.

7. Chapter 7: A two-sample Mendelian randomisation analysis of the associations of tobacco initiation with ADHD and social cognitive outcomes

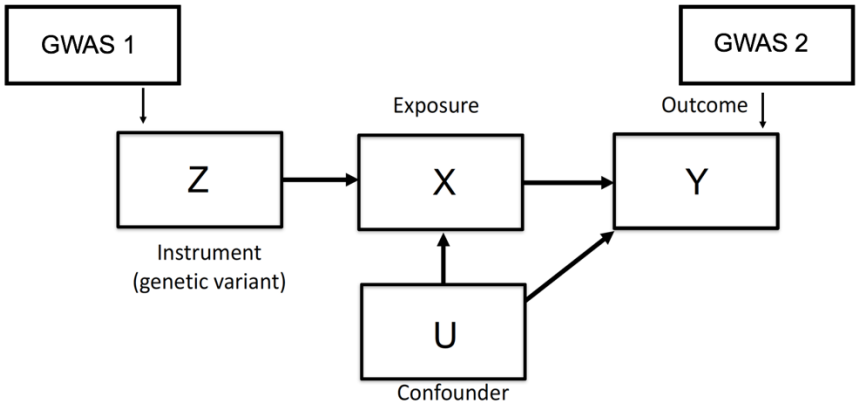
7.1. Introduction

As discussed in Chapter Six, Mendelian randomisation (MR) analysis can be used to strengthen causal inference (Burgess et al., 2015; S. H. Gage et al., 2013). However, as the genetic instruments only explain a small percentage of the variation (e.g. rs6265 explains 0.03% of the variance in tobacco initiation), MR analysis relies on large datasets (~>10,000) (Schatzkin et al., 2009). The MR analysis reported in Chapter 6, conducted in the Avon Longitudinal Study of Parents and Children (ALSPAC), was underpowered, therefore making the results difficult to interpret. Typically, to achieve the necessary power, studies recruit across multiple cohorts. For example, the Consortium for Causal Analysis Research in Tobacco and Alcohol (CARTA) examined the effects of smoking heaviness with a number of health-related outcomes across 21 cohorts in 8 countries (A. E. Taylor et al., 2014). However, as organising a consortium is beyond the scope of a PhD thesis, there are alternative methods to increase our power, including two-sample Mendelian randomisation.

7.1.1. Two-sample Mendelian randomisation

Genome wide association studies (GWAS) require large sample sizes, typically around ~100,000 with publicly-available data sets reporting on summary (SNP-level) statistics. GWAS results report the association of a specific phenotype(s) that have reached a certain p-value threshold (Burgess, Butterworth, & Thompson, 2013). Two-sample MR works on the same basic principles and assumptions as one-sample MR (i.e., genetic instruments robustly associated with a specific exposure of interest are used an unconfounded proxy measure for that exposure). However, two-sample MR uses two GWAS to identify both variant-exposure associations and variant-outcome associations using publicly-available summary data (Burgess et al., 2015). The combination of both GWAS increases the statistical power, however (similar to all meta-analyses) the quality of the overall results relies on the quality of both individual GWAS.

Figure 7.1 Model of two-sample Mendelian randomisation



Two-sample Mendelian randomisation uses GWAS summary statistics that robustly predict a phenotype of interest for both the exposure and outcome.

7.1.2. Chapter aims

This chapter examines the causal effects of tobacco initiation on attention deficit-hyperactivity disorder (ADHD) and social communication. Here, we use two-sample MR to increase power and compare findings to the both previous observational and MR analysis.

This Chapter is based largely on a manuscript currently being revised for resubmission at *Drug and Alcohol Dependence:* Fluharty M, Sallis H, & Munafo M. Investigating possible causal effects of externalising behaviours on tobacco initiation: A Mendelian randomisation analysis.

7.2. Methods

7.2.1. Exposure measures

The Tobacco and Genetics Consortium (TAG) conducted a GWAS of smoking behaviour on a sample of 74,053 individuals (Tobacco & Genetics, 2010). Smoking initiation was a binary ever/never measure with 8 single nucleotide polymorphisms (SNP)s located on the *BDNF* gene region reaching genomewide significance ($P < 5 \times 10^{-8}$) for tobacco initiation (Tobacco & Genetics, 2010). As these SNPs were all in high linkage disequilibrium (LD) with one another, they were pruned based on R^2 values obtained in SNAP (http://www.broadinstitute.org/mgp/snap/) leaving 4 SNPs. A correlation matrix was created for the remaining SNPs (Table 7.1). Two sensitivity analyses were conducted due to the high correlation of the SNPs. First, using only the strongest SNP (rs6265), and again with an

additional 21 independent SNPs that were identified using a relaxed P-value ($P < 10^{-6}$) (See table 6.1). Finally, these SNPs were extracted from ADHD and social communication GWAS for outcomes and longevity and pigmentation GWAS for positive and negative controls.

Table 7.1 Correlation matrix of BDNF SNPs associated with smoking initiation (r^2)

	rs6265	rs4923460	rs1304100	rs6484320
rs6265	1	0.817	0.652	0.603
rs4923460	0.817	1	0.798	0.775
rs1304100	0.652	0.798	1	0.598
rs6484320	0.603	0.775	0.598	1

7.2.2. Outcome measures

7.2.2.1. ADHD

For our ADHD outcome, we used summary data available from the Initiative for Integrative Psychiatric Research (iPSYCH) and Psychiatrics Genomics Consortium (PGC) GWAS of ADHD on 55,354 individuals (ages 6 to 19). ADHD was measured using binary cohort-specific diagnosis of ADHD (Demontis et al., 2017).

7.2.2.2. Social communication

For our social communication outcome, we used summary data available from a GWAS of 9,912 individuals conducted in ALSPAC (age 17) (St Pourcain et al., 2014). Social communication was measured using the Social and Communication Disorders Checklist (SCDC) (Robinson et al., 2011).

7.2.2.3. Positive and negative controls

For our positive control outcomes, we used summary data available from a GWAS of longevity (N= 75,244) (Pilling et al., 2016), and our negative control we used summary data available from a GWAS on pigmentation (N= 32,826) (Han et al., 2008).

7.2.3. Statistical analysis

SNPs associated with ADHD and social communication were identified in their respective GWAS and subsequently extracted from the tobacco GWAS (see Tables 7.2 and 7.3). SNP-exposure and SNP-outcome associations were combined using an inverse-variance weighted approach (IVW), weighted median approach, and MR-Egger regression. Here, we use multiple methods, each with differing underlying assumptions regarding instrument validity, to triangulate our results (D. A. Lawlor, Tilling, & Davey Smith, 2016). IVW weights regression of SNP-exposure and SNP-outcome coefficients restricting the intercept to zero,

and assumes all instruments are valid with no pleiotropy (Burgess et al., 2013). Weighed median provides a causal estimate if at least 50% of the instruments are valid (Mostafavi, 2016). Finally, MR-Egger uses an intercept coefficient in the weighted regression to relax the assumption that the outcome works strictly via the exposure (i.e., up to 100% of the instruments may be invalid). The intercept term displays the overall pleiotropic effect, while the slope (β) coefficient displays a causal estimate under the assumption the pleiotropic effects of the SNP on the outcome are unrelated to the associations between the SNP and exposure (Corbin et al., 2016). All analyses were conducted in R (version 3.3.2). IVW and MR-Egger analyses will be presented in text.

Additionally, to the best of our knowledge there was no overlap between samples. However, it is possible there are parents in one cohort and offspring in another.

Table 7.2 SNPs associated with tobacco initiation ($p < 10^{-8}$)

SNP	Tobacco initiation		ADHD		Social communication		Longevity		Pigmentation	
	OR	SE	OR	SE	β	SE	β	SE	OR	SE
rs6265	0.063	0.015	0.975	0.019	-0.029	0.028	-0.037	0.018	0.037	0.018
rs1304100	0.056	0.014	1.020	0.020	-0.011	0.026	0.024	0.016	0.024	0.016
rs4923460	0.060	0.014	0.969	0.032	-0.013	0.027	-0.030	0.017	0.030	0.017
rs6484320	0.060	0.014	1.029	0.029	0.003	0.027	0.025	0.017	0.025	0.017

Table 7.3 SNPs associated with tobacco initiation ($p < 10^{-6}$)

SNP	Tobacco initiation		ADHD		Social communication	
	OR	SE	OR	SE	β	SE
rs10013579	0.058	0.013	0.992	0.016	0.296	0.257
rs10937751	0.066	0.014	0.988	0.018	-0.738	0.255
rs11030084	0.067	0.015	0.973	0.019	-1.517	0.304
rs11067275	0.065	0.014	1.022	0.017	-0.075	0.277
rs11246771	0.084	0.018	0.950	0.023	0.698	0.359
rs11570441	0.110	0.024	1.049	0.030	-0.661	0.493
rs11892348	0.054	0.012	0.982	0.016	-0.381	0.261
rs13131292	0.107	0.024	1.036	0.024	-2.688	0.383
rs1448438	0.063	0.014	1.006	0.018	-1.176	0.243
rs1817648	0.052	0.012	0.980	0.015	-0.282	0.266
rs1986692	0.058	0.013	1.050	0.016	-1.463	0.242
rs241526	0.053	0.012	0.984	0.016	-0.915	0.451
rs2449222	0.091	0.020	0.966	0.027	-1.486	0.301
rs725695	0.055	0.012	0.985	0.016	1.225	0.249
rs739484	0.088	0.020	1.020	0.024	-1.831	0.398
rs7548367	0.056	0.013	1.036	0.016	0.984	0.259
rs7663808	0.059	0.013	0.995	0.016	0.775	0.262
rs926246	0.090	0.020	0.979	0.023	0.288	0.407
rs9521281	0.069	0.015	1.000	0.019	-0.076	0.316

7.3. Results

7.3.1. Association of tobacco initiation on ADHD

The 4 SNPs associated with tobacco use provided no evidence of an association with ADHD (P= 0.157), with similar results for the strongest SNP (rs6265) (P= 0.197). However, MR-Egger analysis was not possible due to the correlated SNPs. When using the 21 relaxed P-value SNPs ($P < 10^{-6}$), there was evidence of an association of tobacco use on later ADHD (OR= 1.30, 95% CI= 1.18 to 1.42, P= <0.001). MR-Egger displayed no evidence of pleiotropy (intercept: OR=1.08, 95% CI 0.98 to 1.04, P= 0.619), and little evidence of causality (slope: OR= 1.16, 95% CI 0.69 to 1.62, P= 0.554). See Table 7.4 for full results.

Table 7.4 Estimates of causal effects of the risk of tobacco initiation on ADHD

Method	**OR**	**95% CI**	***P* value**	***N SNP***
Tobacco initiation (exposure) on ADHD (outcome)				
Wald ratio	1.501	(0.885 to 2.116)	0.197	1
Likelihood based method	1.487	(0.936 to 2.038)	0.157	4
IVW	1.297	(1.175 to 1.419)	< 0.001	22
Weighted median	1.378	(1.204 to 1.552)	0.002	22
MR-Egger slope	1.155	(0.687 to 1.623)	0.554	22
MR-Egger intercept	1.008	(0.977 to 1.039)	0.619	22

7.3.2. Association of tobacco initiation on social communication

The 4 SNPs associated with tobacco use provided no evidence of an association with social communication (β= 0.217, 95% CI= -0.571 to 1.005, P = 0.589), with similar results for the strongest SNP (rs6265) (β= 0.460, 95% CI= -0.440 to 1.360, P = 0.316). As above, MR-Egger analysis was not available for these SNPs. When using the 21 relaxed P-value SNPs ($P < 10^{-6}$) there was still no evidence of an association of tobacco use on social communication (β= -0.056, 95% CI= -0.204 to 0.092, P = 0.464). See Table 7.5 for full results.

Table 7.5 Estimates of causal effects of the risk of tobacco initiation on social communication

Method	β	95% CI	*P* value	*N SNP*
Tobacco initiation (exposure) on social communication (outcome)				
Wald ratio	0.460	(-0.440 to 1.360)	0.316	1
Likelihood based method	0.217	(-0.571 to 1.005)	0.589	4
IVW	-0.056	(-0.204 to 0.092)	0.464	22
Weighted median	-0.077	(-0.312 to 0.157)	0.525	22
MR-Egger slope	-0.431	(-0.949 to 0.087)	0.119	22
MR-Egger intercept	0.027	(-0.009 to 0.064)	0.156	22

β = Standard deviation of the outcome (social communication) in the natural log odds of the exposure (smoking initiation)

7.3.3. Positive and negative controls

The 4 SNPs associated with tobacco use displayed evidence of an association with longevity (positive control) [mean difference of -0.10 in the natural log odds of longevity (95 %CI -0.17 to -0.02, P = 0.009)] and weak association with light pigmentation (negative control) (OR 1.63, 95% CI 1.11 to 2.15, P = 0.064).

7.3.4. Power calculation

I conducted a Post-hoc power calculation using an online Mendelian randomisation power calculation tool (https://sb452.shinyapps.io/power/) (Burgess, 2014). The coefficient of determination of the exposure on the genetic variant was R^2= 0.03. Based on the proportion of cases and controls (0.57 ADHD; 0.18 social communication) and the observed causal effect (OR= 1.29 ADHD; -0.06 social communication), the analysis of tobacco risk on ADHD was adequately sample sized to determine 99.9% power, and the analysis of tobacco initiation on social communication was adequately sample sized to determine 84% power.

7.4. Summary

Our results provide some evidence that tobacco initiation is causally associated with an increased risk of ADHD. However, these results are difficult to interpret because the ADHD GWAS was measured in childhood (age range 6-19) and it's likely most individuals initiated smoking ~age 15 (Centre, 2016c). Additionally, there is some evidence that genetic effects

on externalising phenotypes differ across time (i.e., different age groups) (Pappa et al., 2016). A small GWAS of adult ADHD characteristics (inattention and hyperactivity-impulsivity) (N=1,851) (Ebejer et al., 2013) showed no overlap of SNPs with the adolescent GWAS we used. However, this data was neither publicly available nor could be obtained through author correspondence.

As we cannot easily interpret these associations as adolescent tobacco use on adult ADHD (due to relatively young age of the ADHD GWAS), we may contextualize this association as intrauterine tobacco exposure via dynastic effects, in which parental genotypes affect the size and effect of an offspring's traits. For example, an effect can be exaggerated or reduced in response to adverse prenatal environments (i.e., tobacco exposure (Millard et al., 2015)). There is a range of evidence from longitudinal (D. W. Brook, Zhang, Rosenberg, & Brook, 2006), cross-contextual (Brion et al., 2010), and twin studies (Knopik, 2009) suggesting maternal smoking may be associated with offspring externalizing behaviors (Brion et al., 2010; D. W. Brook et al., 2006; Gaysina et al., 2013; Knopik, 2009). First, women with antisocial or other behavioral problems are at higher risk of smoking during pregnancy and subsequently share the risk of externalising behaviour with their offspring through genetic transmission (Knopik, 2009). Secondly, this association may be further mediated via the adverse effects of intrauterine tobacco exposure on neurodevelopment. Studies suggest nicotine inhibition of the monoamine oxidase (MAO) system is associated with offspring behavioral disorders (Baler, Volkow, Fowler, & Benveniste, 2008). However, A study of maternal smoking and offspring ADHD in biological and surrogate mothers found a stronger effect in mother-offspring pairs suggesting this association may represent an inherited risk that is further exaggerated with intrauterine tobacco exposure (Thapar et al., 2009).

While the GWAS does include individuals aged up to 19, we could examine this as tobacco exposure on the developing brain and its association with childhood ADHD. Rodent models have addressed the effects of adolescent nicotine exposure on the brain. Prolonged nicotine exposure in the developing brain produces persistent and widespread nAChR upregulation (compared to the mature brain). This results in behavioural effects, learning deficits (Fountain, Rowan, Kelley, Willey, & Nolley, 2008), and increased impulsivity (Counotte et al., 2009). Assuming the effect of tobacco initiation on the older individuals in the GWAS cohort, our findings here suggest tobacco initiation is associated with increased risk of ADHD, which largely parallels observational evidence that tobacco exposure on the developing brain is associated with risk of ADHD (Brion et al., 2010; D. W. Brook et al., 2006; Gaysina et al., 2013; Knopik, 2009), suggesting early tobacco exposure may have a causal association with

ADHD. However, as the mean age and number of individuals across age groups were unavailable, it's difficult to determine what proportion of the effect is driven by the older ages.

There was no evidence that tobacco initiation was causally associated with social communication performance. This conflicts with our earlier observational evidence (M. E. Fluharty, Heron, & Munafo, 2017), suggesting these previous findings may be a result of residual confounding. Additionally, I hypothesised that poor social cognition may arise from tobacco use via poor mental health. However, we were unable to obtain the necessary summary statistics to conduct this specific analysis (ADHD to social communication).

Additionally, there was an unexpected association: the negative effect of tobacco initiation with skin pigmentation. With hindsight, there are biological processes that could explain this. Smoking may induce oxidative stress and change inflammatory cell function by releasing proteolytic enzymes (Y. H. Cho et al., 2012). Furthermore, smoking cessation is associated with changes in skin pigmentation (Y. H. Cho et al., 2012). Overall, it is difficult to find a phenotype to use as a negative control for tobacco as there are very few biological or cognitive systems that are not influenced in some way by tobacco (Newhouse, Potter, & Singh, 2004; Yildiz, 2004).

A key strength of this analysis is the use of two-sample MR which both provides stronger causal inference than observational studies (S. H. Gage et al., 2016; S. H. Gage, Munafo, et al., 2015), and utilizes large sample sizes to provide sufficient the power required to detect small effects in complex phenotypes (Burgess et al., 2015). Additionally, by integrating other methods, such as positive and negative controls, strengths of one method will compensate and overlap with the limitations of another to provide us with true causal associations (S. H. Gage, Munafo, et al., 2015). A limitation of this study is the unavailability of a high powered GWAS for adult ADHD. Therefore, direct comparisons of tobacco initiation on subsequent ADHD could not be explored. If additional GWAS studies examine adult ADHD, replication of this study will help to strengthen these findings. Additionally, a GWAS on adult antisocial behaviour was recently published (Tielbeek et al., 2017), however I was unable to obtain the necessary summary data to run this analysis. Future studies may be able to utlise this GWAS to further investigate associations of externalising disorders on tobacco initiation.

7.5. Chapter summary

This chapter used two-sample MR to investigate the causal associations of tobacco initiation on ADHD and social communication. There was some evidence of an effect of tobacco initiation on ADHD, however due to the ages the GWAS were measured these results were

difficult to interpret. Secondly, there was no evidence of an association of tobacco initiation on social communication.

8. Chapter Eight: Discussion

8.1. Thesis aim and hypotheses

In this thesis, I aimed to investigate the direction of association between substance use and mental health problems in adolescence, and whether these are likely to be causal. I also examined the possible role of social cognition in this relationship due to its common associations with both substance use and mental health problems. I used a range of different methods to investigate these associations including a systematic review of the prior literature, observational analyses, and Mendelian randomisation (MR).

8.2. Summary of studies conducted

Initially I conducted a systematic review to identify the weight of evidence for each temporal direction and any current gaps in the literature. For this I focused specifically on tobacco use behaviours with depression and/or anxiety due to the abundance of literature available. The review examined all papers with smoking as an exposure and depression/anxiety as an outcome and vice versa. Overall, the results were mixed displaying largely conflicting evidence in the field. Furthermore, few studies investigated both temporal directions (rather than solely in direction of their *a priori* hypothesis) and even fewer published null results (often only reporting these alongside 'significant' findings).

I therefore next conducted my own observational analysis on substance use and mental health investigating this association in both temporal directions. This analysis investigated a range of mental health problems with the three most popular consumed substances globally: alcohol, tobacco, and cannabis. Additionally, analyses were repeated replacing mental health with social cognitive variables, allowing a direct comparison of patterns of association. Here, I found that poor mental health at age 7 was associated with substance use at 18, but there was no association or a decreased association with social cognition at age 7/8 with substance use at 18. In the opposite temporal direction, both mental health and social cognition at 18 declined following substance use initiation at age 15.

Next, I conducted a further observational analysis investigating the temporal direction of association of mental health with social cognition from ages 15 to 18 (likely following the onset of substance use). Here, I found evidence that poor mental health at age 15 was associated with subsequent social cognitive decline at age 18. There was no clear evidence of an association in the opposite direction (e.g. poor social cognition on later mental health problems).

With the evidence obtained from the longitudinal analyses, I hypothesised there were two possible pathways in the substance use, mental health, and social cognition relationship. First, that decline in both mental health and social cognition are independently associated with substance use initiation. Second, that substance use initiation is associated with poor social cognition via poor mental health. However, as all the evidence was from observational analyses, additional methods were required to investigate any possible causal assumptions.

I therefore next used one sample MR to examine the causal nature of these associations, specially focusing on tobacco and cannabis initiation with later externalising disorders and social communication. Tobacco initiation and cannabis initiation were chosen due to the availability of associated SNPs at the time, and mental health was narrowed to externalising disorders as the most robust observational findings were for externalising disorders. I found no evidence of an association between genetic risk for tobacco or cannabis initiation with externalising behaviour or social communication. However, these analyses were likely underpowered making them difficult to interpret.

For my final analyses, I used two-sample MR which utilises genome-wise association study (GWAS) summary statistics to achieve large sample sizes and increased power. Here, I found some evidence that tobacco initiation was casually associated with ADHD, although these results were slightly difficult to interpret due to the relatively young age range of the ADHD GWAS. I found no evidence that tobacco initiation was causally associated with social communication. Unfortunately, I was not able to investigate the association of ADHD on social communication due to unavailable data.

Overall, I found some evidence of a causal association of tobacco initiation on ADHD, which supports my earlier observational evidence. There was no evidence of a causal association of tobacco initiation on social communication, which conflicts with earlier observational evidence, suggesting this may be due to environmental or confounding factors. I was unable to investigate the causal nature of the observational association that externalising disorders are associated with decreased social cognitive performance, and it is therefore possible that poor social cognition may arise due to poor mental health following tobacco initiation.

8.3. Interpretations / Previous literature

This thesis highlights the importance of utilising multiple methods to triangulate causal inferences. My systematic review demonstrated the extent of conflicting findings in the current filed using longitudinal analyses alone, and the need to identify alternative methods that provide stronger causal inference. Reverse causation was a high risk in many studies as many analyses were only conducted in the direction of their *a priori* hypothesis.

Furthermore, many of the studies controlled for differing confounding variables which may explain the inconsistent results observed. Future reviews may want to investigate the impact of specific confounders on the direction of association observed. Additionally, study quality was not assessed, therefore possible sample and measurement bias may be contributing to the inconsistent evidence. Overall, while the literature was largely mixed, there was slightly more evidence supporting the direction of depression and/or anxiety predicting smoking behaviour. These findings support recent MR analysis, as an unpublished analysis conducted in the Tobacco and Alcohol Research Group found depression has a causal effect on smoking initiation (Sallis, 2018), while two additional MR analyses have found no evidence to support a causal association between smoking and depression and anxiety (Bjorngaard et al., 2013; A. E. Taylor et al., 2014).

The longitudinal analysis suggested a bidirectional pathway of both tobacco and cannabis with subsequent externalising disorders and vice versa. Additionally, tobacco and cannabis initiation was associated with later social cognitive decline (and all mental health problems). These findings are consistent with previous literature (Bosco et al., 2014; Donadon & Osorio Fde, 2014; Nandrino et al., 2014). However, there was no association of poor social communication/reciprocity with later substance use, and a negative association of affect recognition with substance use. These findings are important, as to my knowledge, this direction of association has not been investigated to date. Therefore, this suggests the associations of substance use with later social cognitive performance are not due to reverse causation. Furthermore, this analysis indicated an unpredicted finding of poor childhood facial affect recognition with decreased adolescent substance use. Although, it's likely this association may arise due to the overall lack in social skills and subsequent exclusion from friendship groups that may begin experimenting with drugs during adolescence. However, this is unlikely to be the sole reason behind decreased substance use, as a similar effect is not seen in social communication or social reciprocity. There was no association observed between individual emotions (happy, sad, scared etc.) with decreased substance use, only poor affect recognition overall (low and high emotional intensity). Perhaps this facet of social cognition causes more difficulties in normative socialising at younger ages compared to the other variables measured in this study. This area would be worth pursing further in future studies to determine whether it replicates across different cohorts and different measures of facial affect recognition.

The two-sample MR analyses suggest some evidence of a causal effect of tobacco initiation with ADHD, and no evidence of an association on social communication. Therefore, it's likely the observed association of substance use with subsequent poor social cognitive

performance is not causal and may arise via poor mental health or other unmeasured factors.

The association of tobacco initiation on subsequent ADHD is consistent with previous evidence from observational analyses (Brion et al., 2010; D. W. Brook et al., 2006) and twin studies (Knopik, 2009). However, this association is slightly difficult to interpret due to the young age of participants in the ADHD GWAS. Previous studies indicate the potentially harmful effect of repeated nicotine and tobacco exposure on the developing brain. Women who smoke during pregnancy expose their offspring to various compounds present in tobacco smoke during neurodevelopment; for example, tobacco exposure may alter expression of the monoamine oxidase (MAO) allele in the foetal brain, with low expression associated with violence and behavioural disorders (Baler et al., 2008). This is further observed in a surrogate study in which smoking mothers were more likely to give birth to children with ADHD (Thapar et al., 2009). Nicotinic systems may mediate the expression of ADHD as repeated nicotine administration leads to nigrostriatal and mesolimbic dopamine release, resulting in dopamine dysregulation and locomotor stimulant (Clarke, 1990; Faraone & Biederman, 1998). These findings are supported by rodent studies suggesting that nicotine administration associated with rat hyperactivity (Hagino & Lee, 1985). However, the age of the ADHD GWAS did extend from ages 8 to 19. Therefore, depending on the proportion of older age individuals, these findings may be reflecting tobacco exposure on the developing brain and its association with adolescent ADHD. These findings are consistent with previous evidence from observational and rodent studies (Brion et al., 2010; D. W. Brook et al., 2006; Gaysina et al., 2013; Knopik, 2009). Tobacco has increased rewarding effects, and decreased negative withdrawal effects on adolescents (compared to adult smokers) (O'Dell, 2009). During adolescence, dopamine neurones have heightened sensitivity to nicotine-induce potentiation in the ventral tegmental area (Placzek et al., 2009). Acute nicotine exposure in adolescence is associated with increased extracellular serotonin overflow in the nucleolus accumbens shell and decreased dopamine and serotonin in medial prefrontal cortex (Shearman et al., 2008). Adolescents are susceptible to increased self-administration (Adriani et al., 2002), consume more nicotine than adults (H. Chen et al., 2007; Levin et al., 2007; Natividad et al., 2013), and show less aversion to higher doses (Adriani et al., 2002; Shram et al., 2006; Torres et al., 2008). Furthermore, pre-clinical/rodent evidence suggests prolonged exposure of nicotine in developing brains produces more widespread nAChR upregulation and subsequent behavioral effects, learning deficits (Fountain et al., 2008), and increased impulsivity (Counotte et al., 2009).

While I only focused on externalising disorders in the final Chapters, other MR studies have examined the impact of tobacco initiation on other mental health problems. An unpublished MR analysis conducted in the Tobacco and Alcohol Research Group found no evidence of a causal association of tobacco initiation on depression (Sallis, 2018). Additionally, a MR analysis of tobacco initiation with schizophrenia risk found weak evidence of a causal association, although this effect was attenuated when the p-value was relaxed and variants from further genes were incorporated which allows from a more powerful instrument, but at a greater risk of pleiotropy (S. H. J. Gage, H.; Taylor, A.; Burgess, S.; Zammit, S.; Munafo, M. , 2016). These results highlight the importance of using additional methods, alongside traditional observational methods when investigating causal inferences. There was no causal association of tobacco use on social communication, suggesting the observed associations may be a result of residual confounding, measurement error, or bias. It is possible that tobacco use affects social communication via poor mental health; for example, poor interpersonal connections, increased stress response in social interactions, and social withdrawal in mentally ill individuals may lead to development of poor social skills (Drusch et al., 2013). However, I was unable to investigate the possible causal effects of ADHD on social communication due to the necessary GWAS summary data not being available. Additionally, out of the three measures of social cognition I used in this thesis, I only investigated the causal associations in social communication; therefore, it is possible there may be a causal effect of tobacco initiation on social reciprocity or affect recognition. Unfortunately, I could not investigate the observational association of tobacco initiation on affect recognition as affect recognition data was unavailable for older adolescents in ALSAPC. However, new data on affect recognition in older individuals in ALSPAC has been collected and will be available imminently for analysis. Additionally, a small GWAS has identified some SNPs associated with approaching genomewide significance for affect recognition (J. R. I. Coleman et al., 2017), and future studies may investigate this association.

8.4. Implications

In this thesis, I examined the possible role of social cognition in the relationship between mental health and substance use. In doing so, I explored the temporal relationship of social cognition and substance use in more depth. To my knowledge, the literature to date focuses on the acute intoxication (Adams et al., 2014; Curtin et al., 2001), withdrawal (Leventhal et al., 2012; Townshend & Duka, 2003), or prolonged and heavy use (Bayrakci et al., 2015; Romero et al., 1997) of substances on social cognition. However, I made sure to investigate both temporal directions, using relatively light substance use variables in an adolescent birth

cohort. Interestingly I found that early social cognition was not associated with later substance use, and in particular affect recognition was associated with decreased substance use. This analysis helped rule out the possibility of reverse causality and strengthened my finding that substance use is associated with later impaired social cognition. Additionally, this analysis suggested that poor non-verbal communication may in fact be protective with respect to subsequent substance use. While this is clearly an area that warrants additional research and replication, one possible explanation for this finding is that adolescents with poor emotion recognition skills may be less likely to have larger social groups (Barth & Bastiani, 1997; Leppanen & Hietanen, 2001) and therefore less likely to engage in substance use due to less social inclusion (Alfaro et al., 2017; McCrady, 2004; Shadur & Hussong, 2014; Urberg et al., 1997).

Furthermore, the evidence in this thesis suggests there is a small causal effect of smoking initiation on risk of ADHD. These findings are supported by observational evidence (Brion et al., 2010; D. W. Brook et al., 2006) twin studies (Knopik, 2009), and animal models (Hagino & Lee, 1985). One possible pathway of this association is via dynastic effects. Here, the adverse effects of intrauterine tobacco exposure on neurodevelopment may be associated with behavioural disorders (Baler et al., 2008). This information may be helpful in educating and encouraging mothers to stop smoking before pregnancy and preventing early adolescent tobacco use.

While the prevalence of smoking during pregnancy has generally declined with time (~20-35% in 1980 to ~<10% in 2010), the rates differ across socio-economic status, with the slowest rates of decline in areas of low social disadvantage (Graham, Hawkins, & Law, 2010; Lanting, van Wouwe, van den Burg, Segaar, & van der Pal-de Bruin, 2012). Additionally, smoking in pregnancy is more prevalent in some ethnic and aboriginal minorities (Johnston, Thomas, McDonnell, & Andrews, 2011; Wood, France, Hunt, Eades, & Slack-Smith, 2008). These difference in smoking rates are driven by tobacco companies increased production and marketing in low and middle-income countries, and targeted advertisement towards women (Kaufman, 2001). This suggests specific attention should be given to women in these minority groups to aid cessation attempts during pregnancy. However, the tobacco and ADHD GWAS used in this thesis were conducted in high income countries suggesting smoking during pregnancy may still be an issue in these areas. Current National Institute for Health and Care Excellence (NICE) guidelines contain advice on stopping smoking in pregnancy and childbirth. Initially, midwives should assess mothers' smoking through a carbon monoxide (CO) test, providing the mother with a physical measurement of her own smoking and its effect on others. Information should be presented

to the mother highlighting the risks smoking can have on her unborn child. Current smokers and those whom have stopped within the last 2 weeks are to be referred to local authority stop smoking services. Stop smoking advisors should then contact all referred mothers either via phone or in person and gather information on mothers' smoking heaviness and smoking behaviours of other smoking household members. Intensive support should be given to the mother throughout pregnancy and following birth, including regular monitoring of smoking status through CO tests. Finally, NRT may be prescribed following cessation (NICE, 2010).

Furthermore, Cochrane Reviews have reported on several smoking cessation interventions, both psychosocial and pharmaceutical for pregnant women. One Cochrane Review on found psychosocial interventions increased quit rates by 35% in late pregnancy with little adverse effects, proving counselling, contingency management (financial incentives), and feedback methods most successful (Chamberlain et al., 2017). A second Cochrane Review examined pharmacological interventions, finding some evidence that nicotine replacement therapy (NTR) may reduce smoking rates in late pregnancy, however this may be no more effective than placebo, with inconclusive evidence of possible adverse effects on the infant (T. Coleman, Chamberlain, Davey, Cooper, & Leonardi-Bee, 2015). My findings also suggest that early adolescent cigarette smoking may be associated with increased risk of ADHD. Therefore, there should be a focus on preventing uptake of smoking in childhood and adolescence, and further be educating individuals on the negative psychological effects as well as physiological. Children should be targeted at a young age and educated about the possible long-term effects of smoking. Current NICE guidelines indicate several possible pathways to prevention in childhood. Prevention programmes in school may be 'adult-led' or 'peer-led.' Adult-led interventions include integrating information about the harmful effects of tobacco into the curriculum. These interventions should be entertaining and interactive, specifically tailored to the age group, and help develop decision making skills and strategies to reject peer pressure (NICE, 2008). Alternatively, peer-led interventions are led by individuals nominated by the students and may be delivered in or outside the classroom. The nominated students are trained and receive support by experts to discuss society norms on smoking and benefits of not smoking (NICE, 2008). Additionally, 'organisation or school-wide' policies on smoking, such as prohibiting smoking on any area of the grounds will help minimise smoking exposure to young people. Outside schools, there should be strict prohibition of illegal tobacco sales to underage individuals. Local authorities should conduct inspections of retailers to ensure they are requesting proof of age for individuals' appearing younger than 18 (NICE, 2008).

Additionally, there is evidence that several further strategies may be effective in preventing early smoking initiation in children and adolescents. Within the family, strong parental-child bonds and open communication may help delay or prevent initiation. Media advocacy and mass media campaigns can be to change individuals' perception on tobacco use (Wallack & Dorfman, 1996). For example, the 'Truth Initiate' based in the United States runs a series of television commercials and YouTube videos exposing deceptive tobacco industry strategies (i.e. marketing to minorities or mentally ill) (Hair et al., 2017). Some government regulations may help prevent individuals from early onset smoking. Smoking bans in public places increase the perception that smoking is socially unacceptable (Wakefield et al., 2000), while restrictions on tobacco-industry advertisement (i.e. in film and television) reduce the exposure to smoking in daily life. Large adverse pictorial warning labels on cigarette packs are associated with decreased smoking rates among adolescents and non-smokers (Peebles et al., 2016; V. White, Webster, & Wakefield, 2008). Furthermore, some countries including Australia and the UK have introduced plain packaging which greatly restricts advertising on packages and increases attention drawn to pictorial warning labels, further decreasing the likelihood of adolescent smoking uptake (Germain, Wakefield, & Durkin, 2010; Maynard et al., 2014; Maynard, Munafo, & Leonards, 2013). Finally, there is evidence that increasing the price of cigarettes, known as 'price elasticity' can affect adolescent smoking consumption. While price increases may not affect adolescent experimentation, evidence suggests the price effects whether adolescents will progress to buying their own cigarettes (Nonnemaker & Farrelly, 2011; Powell, Tauras, & Ross, 2005).

Finally, many of these tobacco-prevention strategies focus on preventing sales, decreasing exposure, and providing education of long term health effects. However, education on long-term risks should consider addressing psychological and mental health outcomes alongside the well-known physiological ones (i.e. lung cancer).

8.5. Thesis strengths

Strengths of each individual study were addressed in their specific Chapter. However, there are some overarching themes across Chapters. First, this thesis utilises large rich datasets including the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort and summary data from multiple GWAS to investigate the associations of substance use, mental health, and social cognition. Secondly, due to the comprehensive data collection in ALSPAC I was able to keep variables relatively consistent across ages groups, although sometimes using a different variable was more practical for specific ages (i.e. Development and Wellbeing Assessment (DAWBA) to examine mental health in younger ages versus the Clinical Interview Schedule (CIS-R) in older ages). Third, in my observational studies I made

a robust attempt to adjust for possible confounders by examining a range of confounders in three different categories: pre-birth/ demographic, maternal substance use, childhood, and where necessary previous incident of the outcome. Fourth, I used a range of different methods each with differing underlying assumptions regarding instrument validity to triangulate the evidence across studies.

8.6. Thesis limitations

Again, individual study limitations are discussed in depth in each respective Chapter. However, there are a number of overall limitations to reiterate. First, this thesis was entirely conducted on secondary data, therefore I was limited to the variables and ages they were previously collected. While the substance use and mental health variables were robust and frequently collected in ALSPAC, there was less attention on social cognitive variables. I was limited to the DANVA and SCDC to create my social cognition variables, and unfortunately DANVA was not measured in older ages so I could not investigate both temporal directions for facial affect recognition. Secondly, I was limited by the availability of some datasets, in particular access to some GWAS. While a majority of the GWAS I used were publicly available, some required contacting authors, and even so I was not always able to obtain access for the entire dataset. For example, I was able to analyse tobacco initiation with social communication although I was unable to obtain the SNPs required to further analyse ADHD on social communication. Additionally, I was limited to the ages in which the GWAS were conducted. As ADHD was measured in childhood (age range 6-19) this made the analysis of tobacco initiation with ADHD difficult to interpret. While there were some adult GWAS of externalising disorders, these were either underpowered or the data could not be obtained. Third, I only examined positive or negative diagnosis of mental health disorders, rather than investigating individual symptomology (e.g. anhedonia, negative affect, etc.). Previous evidence suggests specific symptoms may be differentially associated with smoking behaviour (Leventhal et al., 2013; Leventhal et al., 2011; Mickens et al., 2011a). Future research may consider investigating GWAS associated with individual symptoms as they become available. For example, a GWAS on inattention and hyperactivity is available; however, it is relatively low powered (Ebejer et al., 2013). Additionally, a GWAS on delay discounting has recently been published (Sanchez-Roige et al., 2018). Fourth, I had very similar results for smoking and cannabis use in all my observational analyses, possibly resulting from the cannabis use culture in the UK, as the predominate form of smoking cannabis is rolled together with tobacco in spiffs. As nearly all the cannabis users were also tobacco users, this made teasing apart the effects of cannabis versus tobacco difficult in the observed associations. I chose to analyse the causal effects of smoking on externalising

disorders in the two-sample MR, under the assumption that tobacco was likely driving the effect. However, as I have not run an adequately powered MR on cannabis use with mental health and social cognitive outcomes I cannot be completely positive of cannabis' effect.

8.7. Future Directions

In this thesis, I used a range of methods to triangulate possible causal associations in the relationship between mental health, substance use, and social cognitive performance. My systematic review suggests future studies should look to alternative methods to replicate findings in tobacco and mental health. Additionally, observational studies should consider investigating both temporal directions to reduce the risk of reverse causation. Furthermore, the lack of null results reported suggests a possibility of publication bias. Therefore, journals should be open to accepting and publishing studies reporting null results. Some journals have been actively trying to reduce the risk of publication bias though pre-registration, in which analysis protocols are reviewed (prior to beginning the study) and the final manuscripts are re-reviewed and cannot be rejected on the basis of the study outcome. This helps reduce the risk of publication bias by the journal as well as helping to avoid poor research practices such as p-hacking (manipulating data to obtain significant effects)(Gonzales, 2015).

Furthermore, I found observational evidence that substance use was associated with subsequent externalising disorders and social cognitive decline. However, there was only a causal effect observed for the association of tobacco initiation with ADHD. This further highlights the need to integrate multiple methods with stronger causal inference. First, as higher-powered adult ADHD GWAS data become available it will be important to identify if these findings replicate. While I did find a causal effect, the effect was small and difficult to interpret due to the age range in the ADHD GWAS. Second, future studies should identify if the effect observed is due to prenatal nicotine exposure or early tobacco exposure in adolescents. This suggests the need to investigate the genetic architecture of ADHD in adulthood. Evidence from other externalising disorders (e.g. aggression) GWAS have displayed a difference in genetic associations across different ages (Pappa et al., 2016). Therefore, this may be a worthwhile investigation for future ADHD GWAS studies. Third, it is important to identify if this association is found in other externalising disorders such as aggression or antisocial behaviour. Currently, both an aggression (Pappa et al., 2016) and antisocial behaviour (Tielbeek et al., 2017) GWAS have identified SNPs of interest for each respective phenotype, although I was unable to obtain the necessary SNPs for this analysis. Fourth, as discussed above, the ADHD-associated SNPs were associated with presence or absence of diagnosis and not symptoms. Future GWAS may consider investigating SNPs

associated with individual symptoms rather than binary diagnosis to obtain a further understanding on the direct effect an exposure may be having on the outcome (i.e. anhedonia as opposed to purely depression). There are currently some adult GWAS available of specific symptoms including impulsivity and hyperactivity (Ebejer et al., 2013) and delay discounting (Sanchez-Roige et al., 2018) which could be used to investigate these associations. Fifth, the observational evidence suggests similar effects of tobacco and cannabis with externalising disorder and social cognitive outcomes. However, I chose to only investigate tobacco use in our higher-powered MR analysis. As the majority of cannabis users in ALSPAC were likely to be using it together with tobacco, I decided to only investigate genetic risk of smoking as I hypothesised this to be driving the effect. However, it's possible cannabis use may have been driving the effect and therefore may explain the small effect on externalising disorders and no effect on social cognition. Therefore, this association should be tested using cannabis associated SNPs from the International Cannabis Consortium. Sixth, this thesis used smoking initiation and age of onset associated SNPs to stay consistent with my earlier observational analyses in adolescence. Future studies may want to examine this association in heaviness of smoking and cessation SNPs which are also available from the TAG GWAS. Seventh, I was unable to test the hypothesis that substance use was associated with poor social cognition via mental health problems due to restricted access to the social communication GWAS. This analysis is currently being conducted by another group and the necessary data were therefore unavailable for me to use. This upcoming analysis may help identify any missing links in this association of interest.

Finally, my observational associations of childhood social cognitive performance on adolescent substance use were unexpected and worth further investigation. I found evidence that poor facial affect recognition was associated with decreased adolescent substance abuse, while there was no association of social communication or social reciprocity with later substance use. As far as I am aware, these analyses were the first to examine this temporal direction; therefore, future studies may want to examine these associations to determine if they replicate. I hypothesised that individuals with poor facial affect recognition may be less likely to be included in social groups and subsequently less likely to be exposed to substances during an experimental period. However, this does not explain why this result was only observed for one facet of social cognition. Future studies examining this association may want to examine these associations using different social cognitive variables to determine if this association is observed only in non-verbal communication deficits. While this study used the emotional faces task of the Diagnostic

Analysis of Nonverbal Accuracy (DANVA), further studies may consider using the body language tasks including postures and gestures.

8.8. Conclusions

Overall, this thesis identified several areas of interest in the association of substance use, mental health, and social cognition. First, I identified a lack of longitudinal studies investigating both temporal directions and publishing null results. Second, I found no observational evidence that poor social cognition lead to later substance use. There was evidence that substance use initiation was associated with a decline in both mental health and social cognitive performance with further evidence displaying social cognitive performance additionally declined following poor mental health. My MR analyses displayed a small causal effect of tobacco initiation on ADHD, and no causal effect of tobacco initiation on social communication. Overall, this thesis highlighted the importance in utilising multiple methods when investigating causal associations.

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10. Appendix

Appendix A **Systematic Review Tables**

Details of included studies in the Systematic review

	First author	Year	Length to follow up	Sample size	Participant population	% Female	Age at baseline	Study country	Smoking categories	Main outcome
1	Albers	2002	4 years	552	General population	50%	13.4	United States	Smoking status	Smoking at baseline impacted depressive symptoms at follow-up.
2	Almeida	2013	8 years	4,636	General population	0%	65	Australia	Smoking status	Women smokers had greater probability of becoming depressed.
3	Anda	1990	1 year	2,963	General population	57%	24 to 76	United States	Smoking status	Percentage of current smokers increased as CES-D scores increased.
4	Aneshensel	1983	1 year	742	General population	n/a	18	United States	Smoking status	There was moderate correlation between smoking and depression, but did not appear to be a causal effect.
5	Anstey	2007	8 years	1,116	Elderly in residential care	n/a	n/a	Australia	Smoking status	Current smoking was not a predictor of depression.
6	Appleton	2013	10 years	8,137	General population	0%	54.8	France and United Kingdom	Smoking status	Lifetime smoking was associated with onset of depression.
7	Audrain-McGovern	2004	4 years	968	General population	52%	9th grade	United States	Smoking trajectory	Adolescents with depression were more likely to be early adopting smokers.
8	Audrain-McGovern	2004	2 years	615	General population	54%	9th grade	United States	Smoking status	Association of depression and smoking status; the presence of

										DRD2 A1 allele nearly doubled the odds of smoking status.
9	Audrain-McGovern	2006	4 years	1,053	General population	52%	9th grade	United States	Smoking status	Depressive symptoms did not have an effect on smoking progression.
10	Audrain-McGovern	2009	4 years	1,039	General population	53%	9th grade	United States	Smoking status	Bidirectional relationship between adolescent smoking and depression.
11	Audrain-McGovern	2011	4 years	834	General population	52%	18	United States	Smoking status	Depressive symptoms had an effect on smoking trend.
12	Bardone	1998	8 years	459	General population	100 %	15	New Zealand	Tobacco addiction	Adolescent depression increased the risk of young adult tobacco dependence, there was no effect of anxiety.
13	Batterham	2009	4 years	6,715	General population	51%	20 to 24, 40 to 44, 60 to 64	Australia	Smoking status	Risk of depression was higher for smokers.
14	Beal	2013	7 years	262	General population	100 %	11	United States	Smoking heaviness	Higher levels of smoking predicted high depression scores; high depression scores did not predict smoking.
15	Bjorngaard	2013	2 years	53,601	General population	n/a	10 to 12	Norway	Smoking heaviness	Smoking had no association with later depression and anxiety.
16	Black	2012	1 year	5,287	Chinese	50%	16.2	China	Smoking status	CES-D scores were predictive of smoking status.
17	Boden	2010	25 years	1,265	General population	50%	18	New Zealand	Tobacco addiction	Increased rates of nicotine dependence were associated with depressive symptoms.
18	Bomba	2004	16 years	265	General population	65%	n/a	Poland	Smoking status	Adolescents with depression reported smoking in adulthood.

19	Boyes	2013	1 year	1,154	Diagnosed with cancer in past 6 months	42%	18 to 80	Australia	Smoking status	Current and former smokers had 2x the odds of depression and anxiety.
20	Braithwait	2015	2 years	5,609	HIV positive ageing veterans	4%	50.6	United States	Smoking status	Current smoking was associated with depression, Current depression was not associated with prior smoking.
21	Breslau	1993	1.2 years	995	General population	62%	21 to 30	United States	Tobacco addiction	Progression to nicotine addiction in smokers was linked to a prior history of depression, but not anxiety.
22	Breslau	1998	5 years	974	General population	62%	21 to 30	United States	Smoking onset	Depression at baseline was associated with the progression to daily smoking and history of daily smoking was associated with an increased risk of depression.
23	Brook	2002	13 years	736	General population	50%	14	United States	Smoking heaviness	The frequency of tobacco use was not associated with the risk of depression.
24	Brook	2004	13 years	688	General population	51%	17	United States	Smoking status	Smoking was associated with depressive symptoms at follow-up.
25	Brook	2006	13 years	451	African American and Puerto Ricans	51%	26	United States	Smoking status, smoking trajectory	Depression was a risk factor for smoking (verses non smoking) and early continuous smoking.
26	Brook	2006	10 years	662	African American and Puerto Ricans	51%	26	United States	Smoking trajectory	Individuals with depression and anxiety were more likely to be late onset smokers than experimental smokers.
27	Brook	2008	12 years	475	African Americans and Puerto Ricans	48%	14	United States	Tobacco addiction	Depression predicted a positive diagnosis of

										nicotine dependence.
28	Brook	2014	22 years	607	General population	54%	14	United States	Smoking heaviness	Individuals with chronic high depressed mood were heavy smokers.
29	Brown	1996	1 year	1,507	General population	52%	16.6	United States	Smoking onset	Smokers had elevated rates of depression and depression predicted smoking; there were no effects of anxiety.
30	Brummett	2003	15 years	1,250	Coronary artery disease patients	18%	51	United States	Smoking status	Baseline depression scores were associated with smoking patterns.
31	Buckner	1990	1 year	1,263	Previously convicted for marijuana	48%	24.5	United States	Smoking status	Baseline tobacco use resulted in 1.17 relative risk of depressed mood at follow up.
32	Byers	2012	20 years	7,240	General population	100 %	72.8	United States	Smoking status	Baseline smoking increased the severity of depression.
33	Carvajal	2006	10 months	1,137	General population	55%	11 to 14	England	Smoking onset	Depressive symptoms predictive smoking initiation.
34	Carvajal	2012	18 - 19 months	744	General population	57%	6th grade	United States	Smoking status	Depressive symptoms predicted future smoking.
35	Chen	2013	12 years	4,088	Head and neck cancer patients	51%	14.7	United States	Smoking onset	Depressed mood was associated with a smoking risk group.
36	Choi	1997	4 years	6,863	General population	n/a	12 to 18	United States	Smoking status	Smoking at baseline predicted depressive symptoms, greater effect in female.
37	Clark	2004	6 years	572	Children of parents with Substance Abuse Disorders	22%	10 to 12	United States	Smoking status	Daily smoking did not predict anxiety or depression disorders.
38	Clark	2011	30 days	7,742	General population	51%	n/a	United States	Smoking status	Baseline depressed mood predicted an

										increased in lifetime cigarette use.
39	Clark	2007	2 years	1,615	General population	n/a	11 to 14	United Kingdom	Smoking status	Smoking was not associated with an increased risk of depressive symptoms.
40	Clyde	2014	3 years	1,196	Type 2 diabetes patients	53%	n/a	Canada	Smoking status, smoking heaviness	Moderate to heavy smoking was associated with depression.
41	Colman	2011	6 years	585	General population	64%	16+	Canada	Smoking status	Daily smoking predicted repeated depressive episodes.
42	Coogan	2014	12 years	31,848	African Americans	100 %	21 to 69	United States	Smoking status	Women with higher depressive symptoms were more likely to be smokers.
43	Costello	2008	5 years	11,559	General population	52%	15.9	United States	Smoking status	Individuals with high levels of tobacco use were likely to be in early and high depressed mood groups.
44	Cuijpers	2007	3 years	4,796	General population	n/a	18 to 64	Netherlands	Smoking onset, smoking status	Smoking was associated with the development of an anxiety disorder but not a depressive disorder, and anxiety disorders were associated with smoking onset. No effect of depression.
45	de Jonge	2006	1 year	614	Ill elderly patients	66%	60 to 80	Netherlands	Smoking status	Smoking was a risk factor for depression at follow-up.
46	Di Franza	2007	4 years	1,246	General population	52%	12.2	United States	Tobacco addiction	Depressed mood was a risk factor for nicotine addiction, there was no effect of anxiety.
47	Dugan	2014	10 years	2,891	General population	100 %	46	United States	Smoking status	Smokers were at increased risk for developing depressive symptoms.

48	Duncan	2005	1 year	13,068	General population	52%	11 to 21	United States	Smoking status	Smoking increased the odds of high depressive symptoms in females, but not males.
49	Escobedo	1998	4 years	7,885	General population	n/a	18 to 80	United States	Smoking onset	Symptoms of depression and anxiety increase the likelihood of smoking initiation during adolescence.
50	Ferdinand	2001	8 years	2,600	General population	n/a	10 to 14	Netherlands	Smoking status	Depression and anxiety were not predictors of tobacco use.
51	Fergusson	2003	21 years	1,061	General population	50%	16 to 21	New Zealand	Smoking heaviness, tobacco addiction	Depression was associated with a 19% increase in cigarette intake.
52	Fergusson	2011	25 years	1,265	General population	50%	17 to 18	United States	Smoking status	Increased nicotine was associated with depressive and anxiety symptoms.
53	Fischer	2012	21 years	3,803	General population	51%	14	Australia	Smoking onset	Depression and anxiety was associated with reduced smoking rates.
54	Fleming	2008	3 years	885	High-risk behavioural problem children	47%	12.9	United States	Smoking status	Depressive symptoms were associated with smoking in females.
55	Flensborg-Madsen	2011	26 years	18,146	General population	66%	20+	Denmark	Smoking status	Smokers were at an increased risk for being hospitalised for depression.
56	Franko	2005	10 years	1,727	General population	100 %	9 to 10	United States	Smoking status	Mild and moderate depressed groups were more likely to smoke in adulthood.
57	Fuemmeler	2013	13 years	11,639	General population	53%	15	United States	Smoking onset	Having more depressive symptoms at baseline was related to a greater probability of smoking at follow up.
58	Fuemmeler	2013	19 years	14,779	General population	53%	15.6	United States	Smoking trajectory	Depressive symptoms were

										associated with smoking uptake.
59	Gage	2015	3 years	4,561	General population	73%	16 to 18	United Kingdom	Smoking status	Smoking at 16 was not associated with increased odds of depression or anxiety at 18 (after adjustment)
60	Galambos	2004	4 years	1,322	General population	51%	12 to 19	Canada	Smoking heaviness	Depressive symptoms increased as smoking levels increased.
61	Goodman	2000	1 year	15,651	General population	49%	11 to 21	United States	Smoking onset, smoking status	Depression was not associated with later smoking; smoking was associated with later depression.
62	Goodwin	2004	21 years	1,053	General population	50%	16 to 21	New Zealand	Tobacco addiction	Adolescent anxiety disorders were related to an increased risk of nicotine dependence.
63	Goodwin	2013	10 years	3,021	General population	50%	14 to 22	Germany	Tobacco addiction	Baseline depression and anxiety were likely to have increased or persistent nicotine addiction symptoms.
64	Gravely-Witte	2009	9 months	1,498	Coronary artery disease patients	33%	59	Canada	Smoking status	Current and former smokers had greater depressive symptoms.
65	Green	1992	5 years	1,070	General population	n/a	65	United Kingdom	Smoking status	A past history of smoking was predictive of depression.
66	Griesler	2008	2 years	1,039	General population	54%	14.1	United States	Tobacco addiction	There were no associations between smoking and depression and anxiety in either direction.
67	Gritz	2003	1 year	659	General population	63%	12.9	United States	Smoking status	Depression was a predictor for smoking a year later.
68	Hamdi	2014	12 years	1,252	Twins	53%	17	United States	Tobacco addiction	Depression was associated with an increased likelihood of

										nicotine dependence.
69	Hayatbakhsh	2011	21 years	3,714	General population	100 %	5	Australia	Smoking onset, smoking heaviness	Internalising problems did not increase the risk of onset of smoking.
70	Holahan	2011	8 years	90, 629	Postmenopausal women	100 %	63.6	United States	Smoking onset	Baseline depressive symptoms were related to smoking uptake and heavier smoking.
71	Hooshmand	2012	4 years	4,412	General population	49%	9th grade	Canada	Smoking trajectory	Higher depressive symptoms resulted in accelerated cigarette use.
72	Hu	2011	2 years	660	General population	54%	6th to 10th grade	United States	Tobacco addiction	Nicotine dependence did not predict depressive symptoms.
73	Hu	2012	4.5 years	877	General population	n/a	14.1	United States	Smoking trajectory	Early and late onset smokers were more likely to have been previously diagnosed with an anxiety disorder.
74	Jamal	2011	8 years	1,055	General population	66%	41.9	Netherlands	Smoking trajectory	Early onset smokers developed depression and anxiety disorders 5 years earlier than late onset smokers.
75	Jamal	2012	2 years	1,725	Depressed or anxious	n/a	18 to 65	Netherlands	Tobacco addiction	Improvement in depressive and anxiety scores were slower in nicotine dependent smokers compared to other groups.
76	Julian	2011	5 years	663	Systemic lupic erythematosus (SLE) patients	89%	20 to 60	United States	Smoking status	Smoking was not associated with the development of depression in patients with lupus.
77	Juon	2002	26 years	952	General population	52%	1st grade	United States	Smoking trajectory	Lifetime depression was not associated with any

										smoking trajectories.
78	Kandel	1986	9 years	1,004	General population	66%	24.7	United States	Smoking status	Depression in adolescence resulted in both currents and lifetime cigarette use.
79	Kandel	2007	1 year	1,039	General population	57%	14	United States	Tobacco addiction	Depressive symptoms, and anxiety symptoms in female, were associated with progression to nicotine addiction.
80	Kang	2010	1 year	13,052	Low income Koreans	n/a	20+	South Korea	Smoking status	Baseline smoking was associated with later depression, no effect of depression with later smoking.
81	Karp	2006	4.5 years	1,089	General population	66%	12 to 13	Canada	Tobacco addiction	Higher depression levels, and slower CYP2A6 activity, were associated with risk of conversion to nicotine dependence.
82	Kendler	1993	2 years	1,566	Twin pairs	100 %	30.9	United States	Smoking heaviness	As cigarette consumption increased, so did rates of lifetime depression.
83	Kendler	2001	7 years	144	Monozygotic twins	100 %	n/a	United States	Tobacco addiction	There appears to be an environmental, not genetic, link between depression and nicotine addiction.
84	Khaled	2012	12 years	3,824	General population	49%	45+	Canada	Smoking status	There was a higher risk of depression among current and former smokers than never smokers.
85	Killen	1997	4 years	1,901	General population	47%	15	United States	Smoking onset	Depression was a risk factor for smoking onset in males, not females.
86	King	2004	3 years	1,402	Twins	52%	11	United States	Smoking onset	Depression doubled the odds of first

										time tobacco use by age 14.
87	Kleinjan	2010	1 years	641	General population	n/a	14 to 17	Netherlands	Tobacco addiction	Depressed mood predicted high dependence scores.
88	Klungsøyr	2006	11 years	1,190	General population	50%	18 and over	Norway	Smoking status, smoking heaviness	Smokers had an increasing risk of depression.
89	Knekt	1996	14 years	7,219	General population	50%	30+	Finland	Smoking status	The degree of depression score modulated the risk of smoking.
90	Kocer	2011	4 years	2,199	Cardiac rehabilitation outpatients	13%	61.7	New Zealand	Smoking status	Persistent smoking after outpatient cardiac rehabilitation resulted in depressive symptoms.
91	Korhonen	2007	15 years	9,098	Twins	55%	15	Finland	Smoking status	Male smoking was associated with risk of depression.
92	Leff	2003	2 years	59	At-risk adolescents	23%	13	United States	Smoking onset	Mood and anxiety problems did not predict smoking initiation.
93	Leiferman	2002	3 years	9,953	General population	100 %	15 to 49	United States	Smoking status	Women whom were depressed were more likely to smoke.
94	Lekka	2007	1 year	353	High security inmates	0%	38.7	United Kingdom	Smoking heaviness	Depression, not anxiety, was a risk factor for number of cigarettes.
95	Leung	2012	13 years	2,191	General population	100 %	18 to 23	Australia	Smoking status	Smokers had higher odds of developing depression; depressive symptoms were associated with smoking.
96	Leve	2012	3 years	264	General population	100 %	11.6	United States	Smoking onset	Depressive symptoms at Time 1 were associated with smoking at Time 3 *(UK cohort was excluded from analysis due to being part of RCT).

97	Marmorstein	2010	14 years	503	General population	0%	6.6	United States	Smoking onset	Anxiety predicted increased risk for first tobacco use during the next year.
98	Maslowsky	2014	2 years	2,003	General population	57%	8th grade	United States	Smoking heaviness	Higher levels of depression in 8th grade predicted increased cigarette smoking.
99	McKenzie	2010	11 years		General population	n/a	14.9	Australia	Tobacco addiction	Individuals with high levels of anxiety and depressive symptoms had an increased risk of nicotine dependence.
100	Mendel	2012	10 years	1,205	General population	n/a	10th- to 11th grade	United States	Smoking status	Less of a decrease in depressive symptoms throughout adolescence to adulthood in continued smokers.
101	Meng	2014	16 years	12,227	General population	52%	12 to 24	Canada	Smoking status	Smokers were more likely to develop depression at follow-up.
102	Miller-Johnson	1998	4 years	340	African Americans	n/a	6th grade	United States	Smoking status	A distinct pathway of tobacco use was seen for comorbid depression.
103	Moon	2010	2 years	2,735	General population	51%	16	United States	Smoking status	High depressive symptoms at wave II were characteristic of baseline smoking.
104	Moylan	2013	19 years	441	General population	51%	18 months	Norway	Smoking status	Early smoking predicted anxiety.
105	Munafó	2008	1 year	12,149	General population	50%	15	United States	Smoking status	Depressed mood was not associated with the odds of regular smoking at follow up.
106	Naicker	2013	15 years	1,027	General population	89%	12	Canada	Smoking onset	Depressed adolescents were more likely to transition into adulthood smoking.

107	Needham	2007	6 years	10,828	General population	42%	18 to 26	United States	Smoking status	Adolescents with depression had greater likelihood of smoking, females who were smokers were also likely to be later depressed.
108	Niemela	2009	10 years	2,307	General population	0%	8	Finland	Smoking status	Depressive symptoms at age 8 were associated with an increase in smoking at age 18.
109	Okeke	2013	5 years	892	Mexican-origin and Hispanics	52%	11 to 13	United States	Smoking heaviness	Anxiety scores were associated with smoking levels.
110	O'Loughlin	2009	5 years	877	General population	50%	12.7	Canada	Smoking onset, smoking heaviness	Depression symptoms were not associated to smoking initiation; high depression scores were associated with lower rate of daily smoking.
111	Paffenbarger	1994	23 to 27 years	10,201	General population	0%	35 to 74	United States	Smoking status, smoking heaviness	Smoking increased the relative risk of first instance depression, and a greater risk with 1+ pack/day smokers.
112	Park	2009	1 year	4,110	South Koreans	52%	15	South Korea	Smoking status	Depression had a positive effect in experimental and daily smoking, while smoking has no effect on depression.
113	Pasco	2008	3 years	671	General population	100 %	20 to 93	Australia	Smoking status	Smoking increased the risk of first episode depression.
114	Patel	2006	1 year	8,595	Indian	100 %	18 to 45	India	Smoking status	Tobacco use was associated with depression and anxiety.
115	Patten	2010	12 years	15,252	General population	50%	n/a	Canada	Smoking status	Smoking increased the risk of persistent,

										reoccurring depression.
116	Patten	2003	11 years	813	Treated for alcoholism	44%	41.5	United States	Smoking heaviness	Current or former tobacco use was lower among individuals seeking treatment for alcohol with a prior depression diagnosis.
117	Patton	1998	3 years	2,031	General population	53%	14.5	Australia	Smoking onset	Depression and anxiety predicted smoking onset and transition to daily smoking; smoking was not associated with later depression and anxiety.
118	Patton	2006	10 years	1,943	General population	52%	14 to 15	Australia	Tobacco addiction	The presence of depression and anxiety symptoms were predictors of nicotine dependence.
119	Pedersen	2009	13 years	1,501	General population	n/a	13	Norway	Smoking onset, smoking status, tobacco addiction	Depression and anxiety were not predictors for smoking initiation.
120	Prinstein	2009	6 years	250	General population	60%	10.8	United States	Smoking status	There was an association between childhood depressive symptoms and adolescent cigarette use.
121	Racicot	2012	4 years	1,293	General population	49%	12 to 13	Canada	Tobacco addiction	Depression was associated with a higher dependence score.
122	Repetto	2005	8 years	623	African Americans	51%	14.5	United States	Smoking status	Depressive symptoms influences cigarette use, predominantly for males.
123	Rodriguez	2005	4 years	925	General population	52%	9th grade	United States	Smoking status	Baseline smoking effected depressive symptoms.
124	Saules	2004	4 years	636	General population	100 %	First year of	United States	Smoking trajectory	Late onset smoking was a risk factor for

							univer sity			the development of depression.
125	Schrader	2004	1 year	833	Cardiac patients	n/a	18 to 75	Australia	Smoking status	Baseline smokers were likely to be depressed at follow-up.
126	Schrader	2006	1 year	739	Cardiac patients	n/a	18 to 84	Australia	Smoking status	Baseline smoking was a predictor of moderate to severe depression at follow-up.
127	Senol	2006	6 years	119	Medical school students	34%	18	Turkey	Smoking onset	Higher anxious students started smoking, no effect of depression.
128	Silberg	2003	6 years	1,076	Twins	55%	12 to 16	United States	Smoking status	Smoking was associated with later depression, more so in females.
129	Stein	1996	13 years	461	General population	71%	grades 7 to 9	United States	Smoking status	Smoking predicted depression at follow-up.
130	Steuber	2006	1 year	14,634	General population	51%	14 to 15	United States	Smoking trajectory	Starters, quitters, and maintainers were more likely to be depressed at Time 2 than non-smokers.
131	Strong	2014	36 years	703	African Americans	51%	6 to 7	United States	Smoking status	There was no association between depression and regular smokers.
132	Sweeting	2007	4 years	2,005	General population	49%	15	United Kingdom	Smoking status	Depressed mood was higher among current smokers.
133	Swendson	2010	11 years	5,001	General population	n/a	15 to 54	United States	Smoking onset, tobacco addiction	Anxiety disorders were associated with smoking onset; mood disorders were associated with the development od nicotine dependence from daily use.
134	Takeuchi	2004	1 year	1,060	Japanese workers	32%	35	Japan	Smoking status	No effect that smoking could increase the risk of depression in this cohort.

135	Tanaka	2011	7 years	9,201	Japanese	n/a	40 to 69	Japan	Smoking status	Women who were smokers were at risk for developing depression.
136	Tully	2010	6 years	756	Twins	45%	15	United States	Tobacco addiction	There was no predictive relationship between depression and nicotine dependence.
137	van Gool	2007	6 years	1,169	General population	48%	48.9	Netherlands	Smoking status	There were no longitudinal associations between smoking behaviour and depressed mood.
138	van Gool	2003	6 years	1,280	Chronic somatic diseases	n/a	55 to 58	Netherlands	Smoking heaviness	Persistent depression was associated with an increase in cigarette consumption of 2 per week.
139	Wagena	2005	1 year	4,520	COPD patients	n/a	42	United States	Smoking status	The risk of depression and anxiety was highest in smokers.
140	Wang	1996	3 years	5,855	General population	n/a	12 to 18	United States	Smoking status	No association of depression into smoking, or smoking into depression.
141	Weiss	2011	3 years	1,771	General population	55%	6th grade	United States	Smoking onset	Depressive symptoms were associated with the risk of smoking initiation.
142	Weyerer	2013	3 years	2,512	Non-dementia elderly patients	65%	79.6	Germany	Smoking status	Baseline smoking was not predictive of later life depression.
143	Whitbeck	2009	8 months	743	Indigenous Native Americans	n/a	10 to 13	Canada	Smoking heaviness	Depressed females reported higher rates of smoking compared to depressed males.
144	White	2007	12 years	281	African Americans	0%	13	United States	Smoking trajectory	Depression was not a predictor of early or late onset smoking.
145	Wickrama	2010	11 years	11,500	General population	n/a	13	United States	Smoking status	Smoking prevalence was high among

										adult in depressive groups.
146	Wiesner	2002	1 year	657	General population	55%	11	Germany	Smoking onset	Depressive symptoms did not result in smoking initiation.
147	Windle	2001	2 years	1,218	General population	52%	15.5	United States	Smoking heaviness	Heavy smoking predicted later depression symptoms, and high persistent depressive scores were predictive of increased cigarette use.
148	Woodward	2001	21 years	964	General population	50%	14 to 16	New Zealand	Tobacco addiction	After adjusting for possible confounders, adolescent anxiety did not predict subsequent nicotine addiction.

Details of excluded studies in the Systematic review

	First Author	Year	Journal	Reason for exclusion
1	Brook	2008	Nicotine Tob Res	Depression and anxiety were not defined, or an unreliable diagnostic test was used
2	Grenard	2006	Nicotine Tob Res	Depression and anxiety were not defined, or an unreliable diagnostic test was used
3	Malmberg	2013	Addict Behav	Depression and anxiety were not defined, or an unreliable diagnostic test was used
4	Orlando	2001	J Consult Clin Psychol	Depression and anxiety were not defined, or an unreliable diagnostic test was used
5	Sorensen	2011	Nordic Journal of Psychiatry	Depression and anxiety were not defined, or an unreliable diagnostic test was used
6	Tjora	2014	Addiction	Depression and anxiety were not defined, or an unreliable diagnostic test was used
7	Wu	1999	Am J Public Health	Depression and anxiety were not defined, or an unreliable diagnostic test was used
8	Wu	2008	J Stud Alcohol Drugs	Depression and anxiety were not defined, or an unreliable diagnostic test was used
9	Xie	2013	Nicotine Tob Res	Depression and anxiety were not defined, or an unreliable diagnostic test was used
10	Bares	2012	Addict Behav	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
11	Berk	2010	Journal of Dial Diagnosis	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
12	Breslau	1999	Arch Gen Psychiatry	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses

13	Brook	2013	Am J Public Health	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
14	Brook	2012	Am J Addict	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
15	Conwell	2003	J Paediatr Child Health	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
16	Dierker	2001	J Am Acad Child Adolesc Psychiatry	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
17	Dodd	2010	Compr Psychiatry	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
18	Fagan	2009	Nicotine Tob Res	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
19	Georgiades	2007	J Child Psychol Psychiatry	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
20	Goodman	2010	Addiction	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
21	Goodwin	2011	Drug Alcohol Depend	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
22	Griesler	2011	Addiction	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
23	Heffner	2012	Bipolar Disord	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
24	John	2004	Drug Alcohol Depend	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
25	Johnson	2000	JAMA	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
26	Johnson	2009	Drug Alcohol Depend	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
27	Korhonen	2011	Nicotine Tob Res	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
28	Lien	2009	J Adolesc Health	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
29	Makinen	2010	Psychiatry Research	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
30	Malmberg	2012	J Youth Adolesc	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
31	Malmberg	2013	Addict Behav	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
32	Mino	2001	Prev Med	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
33	Mojtabai	2013	Am J Public Health	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
34	Nay	2013	Psychiatry Research	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
35	Schneider	2014	J Affect Disord	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
36	Smith	2014	J Addict Med	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
37	Smith	2014	Am J Public Health	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
38	Trautmann	2015	Addict Behav	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
39	Tucker	2003	J Adolesc Health	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
40	van der Velden	2008	Drug Alcohol Depend	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
41	Waldrop	2014	Am J Addict	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
42	Weinstein	2008	Addict Behav	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
43	Winefield	1992	Psychol Rep	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses

44	Zehe	2013	Addict Behav	Depression or anxiety subtypes included, or were comorbid with other psychiatric illnesses
45	Bhome	2014	Curr Opin Pulm Med	Does not present new data
46	Cavailles	2013	Eur Respir Rev	Does not present new data
47	Gage	2013	Depress Anxiety	Does not present new data
48	Park	2007	Taken Kanho Hakhoe Chi	Does not present new data
49	Audrain-McGovern	2012	Drug Alcohol Depend	Other smoking category
50	Chaiton	2010	Addict Behav	Other smoking category
51	Chung	2010	Addict Behav	Other smoking category
52	Polen	2004	Psychol Addict Behav	Other smoking category
53	Beijers	2014	Addict Behav	Pregnant cohort
54	Beijers	2014	PloS one	Pregnant cohort
55	Bogaerts	2013	Obes Facts	Pregnant cohort
56	DeWilde	2013	Nurs Res	Pregnant cohort
57	Gavin	2011	Women Health	Pregnant cohort
58	Lewis	2011	PloS one	Pregnant cohort
59	Meyer	1994	Paediatr Perinat Epidemiol	Pregnant cohort
60	Paarlberg	1999	Psychol Health	Pregnant cohort
61	Pritchard	1994	J Epidemiol Community Health	Pregnant cohort
62	Rubio	2008	Alcohol Clin Exp Res	Pregnant cohort
63	Solomon	2007	Drug Alcohol Depend	Pregnant cohort
64	Zambrana	1997	Pediatr Nurs	Pregnant cohort
65	Hermes	2012	Addiction	Smokeless tobacco
66	Sihvola	2008	Addiction	Smokeless tobacco
67	Akechi	2001	Cancer	Smoking or depression/anxiety not exposure or outcome
68	Albers	2003	Pediatrics	Smoking or depression/anxiety not exposure or outcome
69	Artaud	2013	BMJ	Smoking or depression/anxiety not exposure or outcome
70	Atkinson	2015	PloS one	Smoking or depression/anxiety not exposure or outcome
71	Bolognini	2003	Subt Use Misuse	Smoking or depression/anxiety not exposure or outcome
72	Broms	2012	Nicotine Tob Res	Smoking or depression/anxiety not exposure or outcome
73	Brook	2010	Nicotine Tob Res	Smoking or depression/anxiety not exposure or outcome
74	Brook	2004	J Genet Psychol	Smoking or depression/anxiety not exposure or outcome
75	Brook	2014	Nicotine Tob Res	Smoking or depression/anxiety not exposure or outcome
76	Brooker	2008	Subt Use Misuse	Smoking or depression/anxiety not exposure or outcome
77	Brunet	2014	BMC Psychiatry	Smoking or depression/anxiety not exposure or outcome
78	Brunet	2014	Prev Med	Smoking or depression/anxiety not exposure or outcome
79	Copeland	2014	J Am Acad Child Adolesc Psychiatry	Smoking or depression/anxiety not exposure or outcome
80	Costello	2008	Health Psychol	Smoking or depression/anxiety not exposure or outcome

81	Crane	2015	Addict Behav	Smoking or depression/anxiety not exposure or outcome
82	Damen	2013	Eur J Prev Cardiol	Smoking or depression/anxiety not exposure or outcome
83	Ernst	2006	Pediatrics	Smoking or depression/anxiety not exposure or outcome
84	Fergusson	1996	Arch Gen Psychiatry	Smoking or depression/anxiety not exposure or outcome
85	Haller	2014	Drug Alcohol Depend	Smoking or depression/anxiety not exposure or outcome
86	Hamer	2013	Brain Behav Immun	Smoking or depression/anxiety not exposure or outcome
87	Kandel	1987	J Youth Adolesc	Smoking or depression/anxiety not exposure or outcome
88	Kirisci	2004	Drug Alcohol Depend	Smoking or depression/anxiety not exposure or outcome
89	Kulsoon	2015	Neuropsychiatr Dis Treat	Smoking or depression/anxiety not exposure or outcome
90	Lemonge	2013	Am J Epidemiol	Smoking or depression/anxiety not exposure or outcome
91	Lillehoj	2004	Subst Use Misuse	Smoking or depression/anxiety not exposure or outcome
92	Lundin	2015	Epidemiol Psychiatr Sci	Smoking or depression/anxiety not exposure or outcome
93	Miller	2013	Respir Med	Smoking or depression/anxiety not exposure or outcome
94	Moller	2013	Addiction	Smoking or depression/anxiety not exposure or outcome
95	Mun	2008	Dev Psychopathol	Smoking or depression/anxiety not exposure or outcome
96	Newcomb	1986	Am J Public Health	Smoking or depression/anxiety not exposure or outcome
97	Newcomb	1986	Am J Public Health	Smoking or depression/anxiety not exposure or outcome
98	Paunesku	2008	J Cogn Behav Psychother	Smoking or depression/anxiety not exposure or outcome
99	Poutanen	2008	Nord J Psychiatry	Smoking or depression/anxiety not exposure or outcome
100	Purcell	2014	Early Interv Psychiatry	Smoking or depression/anxiety not exposure or outcome
101	Rottenberg	2013	J Am Med Dir Assoc	Smoking or depression/anxiety not exposure or outcome
102	Samuelsson	2013	BMC Public Health	Smoking or depression/anxiety not exposure or outcome
103	Scourfield	2003	J Child Psychol Psychiatry	Smoking or depression/anxiety not exposure or outcome
104	Shanahan	2011	Psychol Med	Smoking or depression/anxiety not exposure or outcome
105	Sieber	1990	Drug Alcohol Depend	Smoking or depression/anxiety not exposure or outcome
106	Smith	2013	PloS one	Smoking or depression/anxiety not exposure or outcome
107	Smokowski	2009	J Prim Prev	Smoking or depression/anxiety not exposure or outcome
108	Tait	2013	J Clin Psychol	Smoking or depression/anxiety not exposure or outcome
109	Vie	2015	Eur J Public Health	Smoking or depression/anxiety not exposure or outcome
110	Weekes	2011	J Natl Med Assoc	Smoking or depression/anxiety not exposure or outcome
111	Weinberger	2012	Addiction	Smoking or depression/anxiety not exposure or outcome

112	Weinberger	2013	Drug Alcohol Depend	Smoking or depression/anxiety not exposure or outcome
113	White	1996	Psychol Health	Smoking or depression/anxiety not exposure or outcome
114	Angst	1996	Br J Psychiatry	Smoking was not distinguished from other substance use
115	Baggio	2013	Int J Adolescent Med Health	Smoking was not distinguished from other substance use
116	Brook	2014	Am J Public Health	Smoking was not distinguished from other substance use
117	Mason	2008	Drug Alcohol Depend	Smoking was not distinguished from other substance use
118	Salom	2015	Addiction	Smoking was not distinguished from other substance use
119	Sung	2004	Drug Alcohol Depend	Smoking was not distinguished from other substance use
120	Yamaguchi	1984	Am J Public Health	Smoking was not distinguished from other substance use
121	Alt	2013	Laryngoscope	Study is not longitudinal
122	Benjamin	2013	J Consult Clin Psychol	Study is not longitudinal
123	Berlin	2008	Prev Med	Study is not longitudinal
124	Bonevski	2014	Drug Alcohol Review	Study is not longitudinal
125	Breslau	2004	Psychol Med	Study is not longitudinal
126	Callaghan	2014	J Psychiatr Res	Study is not longitudinal
127	Capron	2014	Cogn Behav Ther	Study is not longitudinal
128	Cervilla	2004	Psychol Medicine	Study is not longitudinal
129	Cohen	1991	Prev Med	Study is not longitudinal
130	Collins	2013	J Child Fam Stud	Study is not longitudinal
131	Dierker	2007	Drug Alcohol Depend	Study is not longitudinal
132	Ditre	2013	Exp Clin Psychpharmacol	Study is not longitudinal
133	Edwards	2012	J Affect Disord	Study is not longitudinal
134	Forray	2014	Addict Behav	Study is not longitudinal
135	Hanna	1999	Alcohol Clin Exp Res	Study is not longitudinal
136	Ismail	2000	Am J of Epidemiology	Study is not longitudinal
137	Keuthen	2000	Psychother Psychosom	Study is not longitudinal
138	Korhonen	2014	PloS one	Study is not longitudinal
139	Koval	1999	Addict Behav	Study is not longitudinal
140	Larsen	2009	J Psychosom Res	Study is not longitudinal
141	Lazary	2014	PloS one	Study is not longitudinal
142	Leventhal	2012	Nicotine Tob Res	Study is not longitudinal
143	Libby	2005	Addict Behav	Study is not longitudinal
144	Maniecka	2013	Int J Occup Med Environ Health	Study is not longitudinal
145	McCaffery	2008	Health Psychol	Study is not longitudinal
146	Mistry	2014	Drug Alcohol Depend	Study is not longitudinal
147	Moselhy	2012	Epidemiol Psychiatr Sci	Study is not longitudinal
148	Munhoz	2013	J Affect Disord	Study is not longitudinal
149	Murphy	2003	Am J Psychiatry	Study is not longitudinal
150	Onge	2014	J Gerontol B Psychol Sci Soc Sci	Study is not longitudinal

151	Othieno	2014	J Affect Disord	Study is not longitudinal
152	Prochaska	2014	Health Psychol	Study is not longitudinal
153	Ritt-Olson	2005	Subt Use Misuse	Study is not longitudinal
154	Strong	2007	Nicotine Tob Res	Study is not longitudinal
155	Turan	2014	Prim Health Care res Dev	Study is not longitudinal
156	Valera	2014	Nicotine Tob Res	Study is not longitudinal
157	Weinstein	2013	Psychol Addict Behav	Study is not longitudinal
158	Wilens	2013	Drug Alcohol Depend	Study is not longitudinal
159	Woolf	1999	Prev Med	Study is not longitudinal
160	Zhang	2008	Am J Geriatric Psychiatry	Study is not longitudinal
161	Carceller-Maicas	2014	Adicciones	Study not in English
162	Dupre	2013	J Gynecol Obstet Biol Reprod	Study not in English
163	Heger	2014	Prax Kinderpsychol Kinderpsych	Study not in English
164	Park	2009	J Korean Acad Nurs	Study not in English
165	Postolache	2014	Rev Med Chir Soc Med Nat Iasi	Study not in English
166	Sanchez-Villega	2008	Med Clin	Study not in English

Studies with different length to follow-up

Direction of association	Finding	≤ 1 years	> 1 to 5 years	6 to 10 years	> 10 years
Depression/anxiety exposure into smoking outcome	**Evidence for**	16 (48%)	28 (42%)	11 (35%)	14 (29%)
	Evidence against	3 (9%)	14 (21%)	1 (3%)	11 (23%)
Smoking exposure into depression/anxiety outcome	**Evidence for**	7 (20%)	13 (20%)	14 (45%)	17 (35%)
	Evidence against	5 (14%)	8 (12%)	3 (10%)	6 (13%)
Bidirectional smoking and mental health outcome	**Evidence for**	4 (11%)	3 (46%)	2 (6%)	0 (0%)
	Evidence against	-	-	-	-

Studies with different diagnostic test or scales of depression and anxiety

Direction of association	Finding	Interview*	Diagnostic test	Continuous	Categorical
Depression/anxiety exposure into smoking outcome	**Evidence for**	20 (33%)	51 (43%)	38 (41%)	29 (32%)
	Evidence against	11 (18%)	16 (14%)	12 (13%)	17 (19%)
Smoking exposure into depression/anxiety outcome	**Evidence for**	18 (30%)	32 (27%)	25 (27%)	29 (32%)
	Evidence against	8 (13%)	13 (11%)	11 (12%)	12 (13%)
Bidirectional smoking and mental health outcome	**Evidence for**	3 (5%)	6 (5%)	6 (7%)	3 (3%)
	Evidence against	-	-	-	-

*Includes two studies that used physician diagnosis.

Appendix B **Questionnaires**

The Alcohol Use Disorders Identification Test: Self-Report Version

PATIENT: Because alcohol use can affect your health and can interfere with certain medications and treatments, it is important that we ask some questions about your use of alcohol. Your answers will remain confidential so please be honest. Place an X in one box that best describes your answer to each question.

Questions	0	1	2	3	4	
1. How often do you have a drink containing alcohol?	Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week	
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more	
3. How often do you have six or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
8. How often during the last year have you been unable to remember what happened the night before because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
9. Have you or someone else been injured because of your drinking?	No		Yes, but not in the last year		Yes, during the last year	
10. Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, during the last year	
					Total	

PLIKSi semi structured interview

D3.a) How often has this happened **since your 15th birthday?**

Once or twice 1 ☐ → **go to D3b) below**

Less than once a month 2 ☐ → **go to D3b) below**

More than once a month 3 ☐ → **go to D3b) below**

Nearly every day 4 ☐ → **go to D3b) below**

Not at all 5 ☐ → **go to D4 below**

D3. b) Were you upset by this?

No, not at all upset 1 ☐ Yes, a bit upset 2 ☐

Yes, quite upset 3 ☐ Yes, very upset 4 ☐

c) If you ever thought you were being followed or spied on, did this happen **only** within 24 hours of using or taking cannabis or other drugs?

Yes, **only** within 24 hours of using cannabis or other drugs 1 ☐

No, it happened at other times too 2 ☐

D4. Have you ever heard voices that other people couldn't hear?

Yes, definitely 1 ☐ Yes, maybe 2 ☐ No, never 3 ☐ → **If no, go to D5 on page 12**

↓ ↓

If yes, go to D4a) below

a) How often have you heard voices that other people couldn't hear **since your 15th birthday?**

Once or twice 1 ☐ → **go to D4b) below**

Less than once a month 2 ☐ → **go to D4b) below**

More than once a month 3 ☐ → **go to D4b) below**

Nearly every day 4 ☐ → **go to D4b) below**

Not at all 5 ☐ → **go to D5 on page 12**

b) Were you upset by this?

No, not at all upset 1 ☐ Yes, a bit upset 2 ☐

Yes, quite upset 3 ☐ Yes, very upset 4 ☐

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D5. b) Who did you think was controlling you?

God or another religious figure 1 ☐ Someone or something else 2 ☐

c) Were you upset by this?

No, not at all upset 1 ☐ Yes, a bit upset 2 ☐

Yes, quite upset 3 ☐ Yes, very upset 4 ☐

d) If you ever thought you were under the control of some special power, did this happen **only** within 24 hours of using or taking cannabis or other drugs?

Yes, **only** within 24 hours of using cannabis or other drugs 1 ☐

No, it happened at other times too 2 ☐

D6. Have you ever seen something or someone that other people could not see?

Yes, definitely 1 ☐ Yes, maybe 2 ☐ No, never 3 ☐ → **If no, go to D7 on page 14**

↓ ↓

If yes, go to D6a) below

a) How often have you seen something or someone that other people could not see **since your 15th birthday?**

Once or twice 1 ☐ → **go to D6b) below**

Less than once a month 2 ☐ → **go to D6b) below**

More than once a month 3 ☐ → **go to D6b) below**

Nearly every day 4 ☐ → **go to D6b) below**

Not at all 5 ☐ → **go to D7 on page 14**

b) Were you upset by this?

No, not at all upset 1 ☐ Yes, a bit upset 2 ☐

Yes, quite upset 3 ☐ Yes, very upset 4 ☐

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D6. c) If you have seen something or someone that other people could not see, did this happen:

	Yes	No
i) **Only** within 24 hours of taking cannabis or other drugs?	1 ☐	2 ☐
ii) **Only** when you had a high temperature because you were ill?	1 ☐	2 ☐
iii) **Only** when you were falling asleep or as you were waking up?	1 ☐	2 ☐

D7. Have you ever felt that:

i) Your thoughts were being taken out of your head against your will?

Yes, definitely 1 ☐ Yes, maybe 2 ☐ No, never 3 ☐

ii) Someone else's thoughts were being inserted into your head against your will?

Yes, definitely 1 ☐ Yes, maybe 2 ☐ No, never 3 ☐

iii) Your thoughts were so loud that people around you could hear what you were thinking?

Yes, definitely 1 ☐ Yes, maybe 2 ☐ No, never 3 ☐ → **If no to all three questions, go to D8 on page 15**

If yes to any of the three questions above, go to D7a) below

a) How often have any of these three experiences happened **since your 15th birthday?**

Once or twice 1 ☐ → **go to D7b) below**
Less than once a month 2 ☐ → **go to D7b) below**
More than once a month 3 ☐ → **go to D7b) below**
Nearly every day 4 ☐ → **go to D7b) below**
Not at all 5 ☐ → **go to D8 on page 15**

b) Were you upset by this?

No, not at all upset 1 ☐ Yes, a bit upset 2 ☐
Yes, quite upset 3 ☐ Yes, very upset 4 ☐

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D7. c) If you did have any of these three experiences, did this happen **only** within 24 hours of using or taking cannabis or other drugs?

Yes, **only** within 24 hours of using cannabis or other drugs 1 ☐
No, it happened at other times too 2 ☐

D8. Have you ever felt that you are somebody really very special, or that you have special powers like reading people's minds, or that you have been chosen to perform great and special tasks? (This doesn't mean that you are just clever or that you come from an important family).

Yes, definitely 1 ☐ Yes, maybe 2 ☐ No, never 3 ☐ → **If no, go to D9 on page 16**

If yes, go to D8a) below

a) How often have you thought you were really very special or had special powers **since your 15th birthday?**

Once or twice 1 ☐ → **go to D8b) below**
Less than once a month 2 ☐ → **go to D8b) below**
More than once a month 3 ☐ → **go to D8b) below**
Nearly every day 4 ☐ → **go to D8b) below**
Not at all 5 ☐ → **go to D9 on page 16**

b) Were you upset by this?

No, not at all upset 1 ☐ Yes, a bit upset 2 ☐
Yes, quite upset 3 ☐ Yes, very upset 4 ☐

c) If you ever thought you were really very special or had special powers, did this happen **only** within 24 hours of using or taking cannabis or other drugs?

Yes, **only** within 24 hours of using cannabis or other drugs 1 ☐
No, it happened at other times too 2 ☐

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Depression and anxiety questions from the Clinical Interview Schedule Revised (CIS-R) interview

This computerised questionnaire has been designed to assess your health and general well-being over the WEEK which means the
PAST SEVEN DAYS. Your answers will be kept confidentially, like any medical notes.

"To begin with, I would like to ask you about your gender and physical health"

"Are you male or female?"

Male/Female

"Have you noticed a marked LOSS in your appetite in the PAST MONTH?"

No/Yes

"Have you lost any weight in the PAST MONTH?"

No/Yes

"Were you trying to lose weight or on a diet?"

No, I was not trying to lose weight/Yes, I have been trying to lose weight

"Did you lose half a stone or more, or did you lose less than this (in the PAST MONTH)?

(NOTE: Half a stone = 7 pounds or 3 kg)"

I lost half a stone or more/I lost less than half a stone

"Have you noticed a marked INCREASE in your appetite in the PAST MONTH?"

No/Yes

"Have you gained any weight in the PAST MONTH?"

No/Yes/Yes, but I am pregnant

"Did you gain half a stone or more, or did you gain less than this (in the PAST MONTH)?

(NOTE: Half a stone = 7 pounds or 3 kg)"

I gained half a stone or more/I gained less than half a stone

"In the past SEVEN DAYS have you experienced any nausea (feeling as though you were going to vomit) or vomiting?"

No/Mild/Moderate/Severe

"In the past SEVEN DAYS have you experienced any indigestion or stomach ache?"

No/Mild/Moderate/Severe

"In the past SEVEN DAYS have you experienced any pain in your knees, elbows, wrists or other joints?"

No/Mild/Moderate/Severe

"In the past SEVEN DAYS have you experienced any aches or pains in your muscles?"

No/Mild/Moderate/Severe

"In the past SEVEN DAYS have you experienced any headaches?"

No/Mild/Moderate/Severe

"In the past SEVEN DAYS have you experienced any pain in your chest?"

No/Mild/Moderate/Severe

"In the past SEVEN DAYS have you experienced a sore throat?"

No/Mild/Moderate/Severe

"In the past SEVEN DAYS have you had painful glands (lumps) in your neck or armpits?"

No/Mild/Moderate/Severe

"In the past SEVEN DAYS have you experienced dizziness or poor balance?"

No/Mild/Moderate/Severe

"Have you noticed that you've been getting tired in the PAST MONTH?"

No/Yes

"What do you think is the main reason for feeling tired?"

Problems with sleep/Tablets or medication/Physical illness/Working too hard, including looking after children/Stress, worry or other psychological reason/Physical exercise/Other cause/Don't know

"On how many days have you felt tired during the PAST SEVEN DAYS?"

None/Between one and three days/Four days or more

"Have you felt tired for more than 3 hours in total on ANY day in the PAST SEVEN DAYS?"

No, less than 3 hours/Yes, I felt tired for more than 3 hours on at least one day

"Have you felt so tired that you've had to push yourself to get things done during the PAST SEVEN DAYS?"

No/Yes, on one or more occasion

"Have you felt tired when doing things that you enjoy during the PAST SEVEN DAYS?"

No, not tired during enjoyable activities/Yes, tired during an enjoyable activity/I haven't done anything enjoyable in the past week

"During the PAST MONTH, have you felt you've been lacking in energy?"

No/Yes

"What do you think is the main reason for lacking in energy?"

Problems with sleep/Tablets or medication/Physical illness/Working too hard, including looking after children/Stress, worry or other psychological reason/Physical exercise/Other cause/Don't know

"On how many days have you felt lacking in energy during the PAST SEVEN DAYS?"

None/Between one and three days/Four days or more

"Have you felt lacking in energy for more than 3 hours in total on ANY day in the PAST SEVEN DAYS?"

No, less than 3 hours/Yes, I felt lacking in energy for more than 3 hours on at least one day

"Have you felt so lacking in energy that you've had to push yourself to get things done during the PAST SEVEN DAYS?"

No/Yes, on one or more occasion

"Have you felt lacking in energy when doing things that you enjoy during the PAST SEVEN DAYS?"

No, not lacking in energy during enjoyable activities/Yes, lacking in energy during an enjoyable activity/I haven't done anything enjoyable in the past week

"Do you feel better after resting?"

Not a lot/Only a little/Definitely better

"Does exercise make you feel exhausted the following day?"

Not at all/Sometimes/Always

"How long have you been feeling tired or lacking in energy in the way you have just described?"

Less than 2 weeks/Between 2 weeks and 6 months/Between 6 months and 1 year/Between 1 and 2 years/Two years or more

"In the PAST MONTH, have you had any problems in concentrating on what you are doing?"

No/Yes, problems concentrating on what I am doing

"Have you noticed any problems with forgetting things in the PAST MONTH?"

No/Yes

"On how many days have you noticed problems with your concentration OR your memory during the PAST SEVEN DAYS?"

None/Between one and three days/Four days or more

"In the PAST SEVEN DAYS could you concentrate on all of the following without your mind wandering?:

a whole TV programme
a newspaper article
talking to someone?"

Yes, I could concentrate on all of them/No, I couldn't concentrate on at least one of these things

"In the PAST SEVEN DAYS, have these problems with your concentration actually STOPPED you from getting on with things you used to do or would like to do?"

No/Yes

"How long have you been having problems with your CONCENTRATION as you have described?"

Less than 2 weeks/Between 2 weeks and 6 months/Between 6 months and 1 year/Between 1 and 2 years/Two years or more

"Have you forgotten anything important in the PAST SEVEN DAYS?"

No/Yes, I have forgotten something important

"How long have you been having the problems with your MEMORY as you have described?"

Less than 2 weeks/Between 2 weeks and 6 months/Between 6 months and 1 year/Between 1 and 2 years/Two years or more

"In the PAST MONTH, have you been having problems with trying to get to sleep or with getting back to sleep if you woke up or were woken up?"

No/Yes

"On how many nights in the SEVEN NIGHTS did you have problems with your sleep?"

None/Between one and three nights/Four nights or more

"Thinking about the night you had the LEAST sleep in the PAST
SEVEN DAYS, how long did you spend trying to get to sleep?

Only include time spent lying awake in bed TRYING to return to sleep."

Less than 15 minutes/Between 15 minutes and 1 hour/Between 1 and 3 hours/Three hours or more
"In the PAST SEVEN DAYS, how many nights did you spend 3 or more hours trying to get to sleep?"

None/Between one and three nights/Four nights or more

"In the PAST SEVEN DAYS, have you woken more than two hours earlier than you needed to and found that you couldn't get back to sleep?"

No/Yes, and I couldn't get back to sleep

"What are your sleep difficulties caused by?"

Noises (babies crying, busy roads etc.)/Shift work or late nights/Pain or illness/Worries/Reason not known/Other

"Has sleeping more than usual been a problem for you in the PAST MONTH?"

No/I have slept more than usual but this is not a problem/Yes

"On how many nights in the PAST SEVEN NIGHTS did you have problems with your sleep?"

None/Between one and three days/Four days or more

"Thinking about the night you slept the longest in the PAST SEVEN DAYS, how much longer did you sleep compared with how long you normally sleep for?"

Less than 15 minutes/Between 15 minutes and 1 hour/Between 1 and 3 hours/Three hours or more

"In the PAST SEVEN DAYS, on how many nights did you sleep for more than 3 hours longer usual?"

None/Between one and three nights/Four nights or more

"How long have you had these problems with your sleep as you have described?"

Less than 2 weeks/Between 2 weeks and 6 months/Between 6 months and 1 year/Between 1 and 2 years/Two years or more

"Many people become irritable or short tempered at times, though they may not show it.

Have you felt irritable or short tempered with those around you in the PAST MONTH?"

No/Yes, I have felt irritable or short tempered recently

"During the PAST MONTH, did you get short tempered or angry over things which now seem trivial when you look back on them?"

No/Sometimes/Yes

"On how many days have you felt irritable, short tempered or angry in the PAST SEVEN DAYS?"
None/Between one and three days/Four days or more

"In total, have you felt irritable, short tempered or angry for more than one hour on any day in the PAST SEVEN DAYS?"

No/Yes, I felt this way for more than one hour on at least one day

"During the PAST SEVEN DAYS, have you felt so irritable, short tempered or angry that you have wanted to shout at someone, even if you haven't actually shouted?"

No/Yes, but I didn't actually shout at someone/Yes, and I actually shouted

"In the past SEVEN DAYS, have you had arguments, rows or quarrels or lost your temper with anyone?"

No/Yes, but this was justified/Yes

"How long have you been feeling irritable, short-tempered or angry as you have described?"

Less than 2 weeks/Between 2 weeks and 6 months/Between 6 months and 1 year/Between 1 and 2 years/Two years or more

"Almost everyone becomes low in mood or depressed at times.

Have you had a spell of feeling sad, miserable or depressed in the PAST MONTH?"

No/Yes

"In the PAST SEVEN DAYS, have you had a spell of feeling sad, miserable or depressed?"

No, not in the past seven days/Yes

"During the PAST MONTH, have you been able to enjoy or take an interest in things as much as you usually do?"

Yes/No, less enjoyment than usual/No, I don't enjoy anything

"In the PAST SEVEN DAYS, have you been able to enjoy or take an interest in things as much as usual?"

Yes/No, less enjoyment than usual/No, I don't enjoy anything

"In the PAST SEVEN DAYS, on how many days have you felt sad, miserable or depressed OR unable to enjoy or take an interest in things?"

None/Between one and three days/Four days or more

"Have you felt sad, miserable or depressed OR unable to enjoy or take an interest in things for more than 3 hours in total on any day in the PAST SEVEN DAYS?"

No, less than 3 hours/Yes, for 3 hours or more on at least one day
"What is the MAIN thing that made you feel sad, miserable or depressed OR unable to enjoy or take an interest in things in the PAST
SEVEN DAYS?"

Family members, including spouse or partner/Relationships with friends or people at school of work/Housing/Money or bills/Your own physical health, including pregnancy/Your own mental health/Work or lack of work (including studying)/Legal difficulties/Political issues or the news

"In the PAST SEVEN DAYS when you felt sad, miserable or depressed OR unable to enjoy or take an interest in things, did you ever become happier when something nice happened, or when you were in company?"

Yes, always/No, I did not cheer up on one or more occasions/No, nothing cheered me up

"How long have you been feeling sad, miserable or depressed OR unable to enjoy or take an interest in things as you have described?"

Less than 2 weeks/Between 2 weeks and 6 months/Between 6 months and 1 year/Between 1 and 2 years"/Two years or more

"I would now like to ask you about when you have been feeling sad, miserable or depressed OR unable to enjoy or take an interest in things.

In the PAST SEVEN DAYS, was this worse in the morning, in the evening, or did this make no difference?"

Worse in the morning/Worse in the evening/Sometimes worse in the morning sometimes in the evening/No difference between morning and evening

"Many people find that feeling sad, miserable or depressed, OR unable to enjoy or take an interest in things can affect their interest in sex.

Over the PAST MONTH, do you think your interest in sex has increased, decreased or stayed the same?"

Not applicable/No change/Increased/Decreased

"In the PAST SEVEN DAYS, when you have felt sad, miserable or depressed OR unable to enjoy or take an interest in things have you been so restless that you couldn't sit still?"

No/Yes

"In the PAST SEVEN DAYS, when you have felt sad, miserable or depressed OR unable to enjoy or take an interest in things have you been doing things more slowly than usual, for example walking more slowly?"

No/Yes

"In the PAST SEVEN DAYS have you on at least one occasion felt guilty or blamed yourself when things went wrong, even when it hasn't been your fault?"

Never/Only when it was my fault/Sometimes/Often
"In the PAST SEVEN DAYS have you been feeling you are not as good as other people?"

No, I've been feeling as good as anyone else/Yes, I've NOT been feeling as good as others

"Have you felt hopeless at all during the PAST SEVEN DAYS, for instance about your future?"

No/Yes, I have felt hopeless sometimes

"In the PAST SEVEN DAYS, have you felt that life isn't worth living?"

No/Sometimes/Always

"Have you ever hurt yourself on purpose in any way (e.g. by taking an overdose of pills, or by cutting yourself)?"

No/Yes

"How many times have you harmed yourself in the last year?"

Not in the past year/Once/2-5 times/6-10 times/More than 10 times

"In the PAST SEVEN DAYS, have you had thoughts of harming yourself?"

No/Yes, but I would never commit suicide/Yes, I have had thoughts about it in the past week

"Have you talked to your doctor about these thoughts of harming yourself?"

Yes/No, but I have talked to other people/No

"You have said that you have thought about harming yourself.

Since this is a serious matter we would recommend that you talk to your doctor about these thoughts."

"Thank you for answering those questions on feeling unhappy or depressed. The next section is about worrying and anxiety."

"In the PAST MONTH, did you find yourself worrying more than you needed to about things?"

No/Sometimes/Often

"Have you had any worries at all in the PAST MONTH?"

No/Yes

"On how many of the PAST SEVEN DAYS have you been worrying about things?"

None/Between one and three days/Four days or more

"In your opinion, have you been worrying too much in view of your circumstances?"

No/Yes, worrying too much

"How unpleasant has your worrying been about things in the PAST SEVEN DAYS?"

Not at all/A little unpleasant/Unpleasant/Very unpleasant

"Have you worried about something for more than three hours in total on any day in the PAST SEVEN DAYS?"

No, Less than 3 hours/Yes, 3 hours or more on at least one day this week

"How long have you been worrying about things in the way that you have described?"

Less than 2 weeks/Between 2 weeks and 6 months/Between 6 months and 1 year/Between 1 and 2 years/Two years or more

"What is the MAIN thing you have been worried about in the PAST SEVEN DAYS?"

Family members, including spouse or partner/Relationships with friends or with people at school or work/Housing/Money or bills/Your own physical health, including pregnancy/Your own mental health/Work or lack of work (including studying)/Legal difficulties/Political issues or the news

"Have you been feeling anxious or nervous in the PAST MONTH?"

No/Yes

"In the PAST MONTH, did you ever find your muscles felt tense or that you couldn't relax?"

No/Sometimes/Often

"Some people have phobias; they get nervous or uncomfortable about specific things or situations when there is no real danger. For example they may get nervous when speaking or eating in front of strangers, when they are far fom home or in crowded rooms, or they may have a fear of heights. Others get nervous at the sight of things like blood or spiders.

In the PAST MONTH, have you felt anxious, nervous or tense about any specific things or situations when there was no real danger?"

No/Yes

"In the PAST MONTH, when you have felt anxious, nervous or tense was this ALWAYS brought on by the phobia about some SPECIFIC thing or did you sometimes feel GENERALLY anxious, nervous or tense?"

These feelings were ALWAYS brought on by specific phobia/I sometimes felt generally anxious, nervous or tense

"The next questions are concerned with GENERAL anxiety, nervousness or tension ONLY. Questions about the anxiety which is brought on by the phobia(s) about specific things or situations will be asked later."

"On how many of the PAST SEVEN DAYS have you felt GENERALLY anxious, nervous or tense?"

None/Between one and three days/Four days or more

"How unpleasant has your anxiety, nervousness or tension been in the PAST SEVEN DAYS?

Not at all/A little unpleasant/Unpleasant/Very unpleasant

"In the PAST SEVEN DAYS, when you've been anxious, nervous or tense, have you had ANY of the following symptoms?

heart racing or pounding, hands sweating or shaking, feeling dizzy difficulty getting breath, butterflies in your stomach, dry mouth "

No/Yes, one or more of the symptoms

"Have you felt anxious, nervous or tense for more than 3 hours in total on any day in the PAST SEVEN DAYS?"

No/Yes, more than 3 hours on at least one day

"How long have you had these feelings of general anxiety, nervousness or tension, as you have described?"

Less than 2 weeks/Between 2 weeks and 6 months/Between 6 months and 1 year/Between 1 and 2 years/Two years or more

"Sometimes people AVOID a specific situation or thing because they have a phobia about it. For instance, some people avoid eating in public or avoid going to busy places because it would make them feel nervous or anxious.

In the PAST MONTH, have you AVOIDED a specific situation or thing because it would have made you feel nervous or anxious, even though there was no real danger?"

No/Yes

"Here is a list of specific situations or things that some people feel nervous about or might avoid.

Which one of these are you MOST afraid of?"

Travelling alone by bus or train/Being far from home/Eating or speaking in front of strangers/The sight of blood/Going into crowded shops/Insects, spiders or animals/Being watched or stared at/Enclosed spaces or heights/I am not frightened of anything on this list but I am frightened of something else

"On how many days in the PAST SEVEN DAYS have you felt nervous or anxious about the situation or thing you are most frightened of?"

None/Between one and three days/Four or more days

"In the PAST SEVEN DAYS, on those occasions when you felt anxious, nervous or tense about this, did you have ANY of the following symptoms?

heart racing or pounding, hands sweating or shaking, feeling dizzy
difficulty in getting breath, butterflies in the stomach, dry mouth"

No/Yes, at least one symptom

"In the PAST SEVEN DAYS, have you AVOIDED any situations or things because it would have made you feel anxious, nervous or tense, even though there was no real danger?"

No/Yes, on one or more occasion

"How many times have you avoided such situations or things in the
PAST SEVEN DAYS?"

None/Between one and three times/Four times or more

"How long have you been having these feelings about the situations or things as you have just described?"

Less than 2 weeks/Between 2 weeks and 6 months/Between 6 months and 1 year/Between 1 and 2 years/Two years or more

"Thinking about the PAST MONTH, did your anxiety or tension ever get so bad that you got in a panic, for instance make you feel that you might collapse or lose control unless you did something about it?"

No, my anxiety never got that bad/Yes, sometimes/Yes, often

"How often has this panic happened in the PAST SEVEN DAYS?"

Not in the past week/Once/More than once

"In the PAST SEVEN DAYS, how unpleasant have these feelings of panic been?"

A little uncomfortable/Unpleasant/Unbearable, or very unpleasant

"Do these panics start suddenly so you are at maximum anxiety within a few minutes?"

No/Yes

"In the PAST SEVEN DAYS, did the worst of these panics last for longer than 10 minutes?"

Less than 10 minutes/10 minutes or more

"In the PAST SEVEN DAYS, have you worried about having another panic?"

No/Sometimes/Often

"In the PAST SEVEN DAYS when you had the panic: Did your heart beat harder or speed up?"

No/Yes

"In the PAST SEVEN DAYS when you had the panic: Did you have sweaty or clammy hands?"

No/Yes

"In the PAST SEVEN DAYS when you had the panic: Were you trembling or shaking?"

No/Yes

"In the PAST SEVEN DAYS when you had the panic: Did you have shortness of breath or difficulty breathing?"

No/Yes

"In the PAST SEVEN DAYS when you had the panic: Did you have a choking sensation?"

No/Yes

"In the PAST SEVEN DAYS when you had the panic: Did you have pain, pressure or discomfort in your chest?"

No/Yes

"In the PAST SEVEN DAYS when you had the panic: Did you have nausea (feeling as though you were going to vomit) or stomach ache?"

No/Yes

"In the PAST SEVEN DAYS when you had the panic: Did you feel dizzy, unsteady, lightheaded or faint?

No/Yes

"In the PAST SEVEN DAYS when you had the panic: Did things around you feel strange, unreal or detached OR did you feel outside or detached from yourself?"

No/Yes

"In the PAST SEVEN DAYS when you had the panic: Did you fear that you were losing control or going crazy?"

No/Yes

"In the PAST SEVEN DAYS when you had the panic: Did you fear that you were dying?"

No/Yes

"In the PAST SEVEN DAYS when you had the panic: Did you have tingling or numbness in parts of your body?"

No/Yes

"In the PAST SEVEN DAYS when you had the panic: Did you have hot flushes or chills?"

No/Yes

"Is this panic ALWAYS brought on by specific situations or things?"

No/Yes

"How long have you been having these feelings of panic as you have described?"

Less than 2 weeks/Between 2 weeks and 6 months/Between 6 months and 1 year/Between 1 and 2 years/Two years or more

"Thank you for answering those questions on anxiety and worry."

"How have ALL of these things that you have told me about affected you overall?

In the PAST SEVEN DAYS, has the way you have been feeling actually
STOPPED you from getting on with the tasks and activities you used to do or would like to do?"

"This is the end of the interview. Thank you for taking part."

Social and Communication Disorders Checklist (SCDC)

Bullying and Friendship Interview Schedule

1. Having belongings stolen [no] [yes]
2. Having been threatened or blackmailed [no] [yes]
3. Having been beaten up or hit [no] [yes]
4. Having been called nasty names [no] [yes]
5. Having nasty tricks played on them [no] [yes]
6. Other children not wanting to play with them [no] [yes]
7. Trying to get them to do something they didn't want to do [no] [yes]
8. Spreading lies or rumors about child [no] [yes]
9. Spoiling games to upset child [no] [yes]

Strengths and Difficulties questionnaire (SDQ)

	Not True	Somewhat True	Certainly True
Considerate of other people's feelings	☐	☐	☐
Restless, overactive, cannot stay still for long	☐	☐	☐
Often complains of headaches, stomach-aches or sickness	☐	☐	☐
Shares readily with other children (treats, toys, pencils etc.)	☐	☐	☐
Often has temper tantrums or hot tempers	☐	☐	☐
Rather solitary, tends to play alone	☐	☐	☐
Generally obedient, usually does what adults request	☐	☐	☐
Many worries, often seems worried	☐	☐	☐
Helpful if someone is hurt, upset or feeling ill	☐	☐	☐
Constantly fidgeting or squirming	☐	☐	☐
Has at least one good friend	☐	☐	☐
Often fights with other children or bullies them	☐	☐	☐
Often unhappy, down-hearted or tearful	☐	☐	☐
Generally liked by other children	☐	☐	☐
Easily distracted, concentration wanders	☐	☐	☐
Nervous or clingy in new situations, easily loses confidence	☐	☐	☐
Kind to younger children	☐	☐	☐
Often lies or cheats	☐	☐	☐
Picked on or bullied by other children	☐	☐	☐
Often volunteers to help others (parents, teachers, other children)	☐	☐	☐
Thinks things out before acting	☐	☐	☐
Steals from home, school or elsewhere	☐	☐	☐
Gets on better with adults than with other children	☐	☐	☐
Many fears, easily scared	☐	☐	☐
Sees tasks through to the end, good attention span	☐	☐	☐

Appendix C **Observational Tables**

Full and complete cases in the association of childhood mental health with adolescent substance use

Full and complete cases in the association of childhood mental health with adolescent frequency of use

Full and complete cases in the adjusted association of childhood mental health with age of first substance use

Full and complete cases in the association of childhood social cognition with adolescent substance use

Full and complete cases in the association of childhood social cognition with adolescent frequency of use

Full and complete cases in the association of childhood social cognition with age of first substance use

Sex stratified association of childhood mental health with adolescent substance use

Sex stratified association of childhood mental health with adolescent frequency of use

Sex stratified association of childhood mental health with age of first substance use

Sex stratified association of childhood social cognition with adolescent substance use

Sex stratified association of childhood social cognition with adolescent frequency of use

Sex stratified association of childhood social cognition with age of first substance use

Unadjusted and fully adjusted association of adolescent substance use with individual emotion

Full and complete cases in the association of adolescent substance use with mental health

Full and complete cases in the association of adolescent substance use with social cognition

Sex stratified association of adolescent substance use with mental health

Sex stratified association of adolescent substance use with social cognition

Full and complete cases in the association of mental health with social cognition

Full and complete cases in the association of social cognition with mental health