Temporal Association Between Childhood Depressive Symptoms and Alcohol Problem Use in Early Adolescence: Findings from a Large Longitudinal Population-based Study

Luca Saraceno

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

Dedication

To my parents, for their continuous love and support and for having taught me to believe in my dreams.

TABLE OF CONTENTS

PART III

PART V

LIST OF TABLES

LIST OF FIGURES

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DECLARATION

This work has not previously been accepted in substance for any degree and is not concurrently submitted in candidature for any degree.

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This thesis is being submitted in partial fulfilment of the requirements for the degree of PhD.

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This thesis is the result of my own independent work/investigation, except where otherwise stated. Other sources are acknowledged by explicit references.

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ETHICAL STATEMENT

Ethical approval for this doctoral research was obtained from the Avon Longitudinal Study of Parents and Children (ALSPAC) Law and Ethics committee and the Local Research Ethics committee. This doctoral research was specifically funded by a studentship awarded to Luca Saraceno by the Department of Psychological Medicine and Neurology of Cardiff University.

THESIS SUMMARY

Alcohol problems during adolescence have been linked to a variety of adverse consequences, including illicit drug use, delinquency and increased risk of morbidity and mortality. Depressive symptoms can increase the risk of development of alcohol problems in young people and a number of risk factors in common for both behaviours has been identified. However, the peer group plays an important role in the development of both depressive symptoms as well as alcohol problem use. Moreover, the relationship may also differ for boys and girls.

My thesis addresses the nature of the longitudinal relationship between depressive symptoms at age 10 years and alcohol problem use at age 14 years, investigating in particular the differences between genders in the pattern of a large number of non-genetic covariates considered as potential confounders of such relationship and the moderating effects of age 10 and age 14 peers influences. Data were obtained from 4220 participants in the Avon Longitudinal Study of Parents and Children (ALSPAC), a large population-based UK birth cohort.

Childhood depressive symptoms were associated with increased risk of alcohol problem use in early adolescence for girls (O.R. 1.14, p-value=0.016) but not boys. Covariates describing particularly the family and social environment influenced this association for girls. This association became smaller when these covariates were taken into account. Having a strong bond with alcohol-drinking peers at age 14 interacted with depressive symptoms to increase risk of alcohol problem use in 14 years old girls (O.R. 1.18, p-value=0.030). These findings corroborate the growing evidence that family-related interventions to reduce alcohol use are particularly effective for girls. Future policy will have to consider that girls who experience high levels of depressive symptoms may be at

particular risk of alcohol problem use if they affiliate with a peer group exerting strong pressure to drink.

PART I

CHAPTER 1: ALCOHOL PROBLEM USE IN YOUTH AND COMORBIDITY WITH DEPRESSIVE SYMPTOMS

1.1 Introduction

Harmful use of alcohol is a major public health issue, placing a heavy social, medical and economic burden on the world. According to the World Health Organization (WHO) in 2004 about 2 billion people worldwide consumed alcoholic beverages and over 75 million had a diagnosis of alcohol use disorders (AUDs) (WHO, 2004a). Apart from the direct effects of intoxication and dependence, alcohol is estimated to cause approximately 20% to 30% of each of the following worldwide: oesophageal cancer, liver cancer, cirrhosis of the liver, and epilepsy, and is a major contributor to fatalities associated with homicides and motor vehicle accidents (WHO, 2004b). A clear figure of the social and economical burden of heavy alcohol consumption is given by the cost of alcohol-related harm from the National Health Service (NHS) of the United Kingdom (UK), which has been estimated around £8.7–9.0 billion (Cabinet Office, 2004).

Alcohol problem use has been associated with depressive disorders (depression and anxiety) in a number of samples of adolescents (Stice et al., 1998, Turner et al., 2005) and an increasing research and clinical interest in the aetiological relationships between both behaviours exists (Clark et al., 1996). Moreover, depression is the leading cause of nonfatal disability worldwide, with the greatest impact on younger generations (Lopez et al., 2006).

Different terms are used in the literature to describe alcohol problems; some are more common and informal (e.g. excessive/ harmful alcohol use), while others have a more defined meaning within specific classifications (e.g. alcohol abuse/ alcohol dependence (AD) within

the DSM-IV classification (APA, 2000)). Still, some of the latter terms are sometimes also used more informally. This applies also to depressive symptoms, with terms like depression and depressive traits used more informally, while terms such as Major Depressive Disorder are more rigorously clinically-defined (APA, 2000).

Table 1.1 reports the clinical criteria that need to be met in order to perform a clinical diagnosis of Alcohol Dependence or Major Depressive Disorder according to the DSM-IV classification of mental disorders (APA, 2000).

Table 1.1: DSM-IV criteria for Alcohol Dependence and Major Depressive Disorder

Alcohol Dependence	A maladaptive pattern of alcohol use, leading to clinically significant impairment or distress, as manifested by three or more of the following seven criteria, occurring at any time in the same 12-month period: 1. Tolerance, as defined by either of the following: • A need for markedly increased amounts of alcohol to achieve intoxication or desired effect. • Markedly diminished effect with continued use of the same amount of alcohol. 2. Withdrawal, as defined by either of the following: • The characteristic withdrawal syndrome for alcohol (refer to DSM-IV for further details). • Alcohol is taken to relieve or avoid withdrawal symptoms. 3. Alcohol is often taken in larger amounts or over a longer period than was intended. 4. There is a persistent desire or there are unsuccessful efforts to cut down or control alcohol use. 5. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol or recover from its effects. 6. Important social, occupational, or recreational activities are given up or reduced because of alcohol use. 7. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the alcohol (e.g., continued drinking despite recognition that an ulcer was made worse by alcohol consumption).
Major Depressive Disorder	Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. 1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others). 3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. 4. Insomnia or hypersomnia nearly every day. 5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down). 6. Fatigue or loss of energy nearly every day. 7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick). 8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others) 9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

Throughout this thesis, where possible, I have used the specific terminology reported in cited references; however, the generic terms "alcohol problem use" and "depressive symptoms" were used whenever the sources I cited together differed in the definition and assessment of alcohol use and misuse or depressive symptoms and disorders. Table 1.2 reports the specific terminology used to define alcohol and depressive problems by the papers cited in Chapters 1 and 2 of this thesis. 23 different terms, ranging from "alcohol abuse" to "substance use disorders" were used to describe what I generically define as "alcohol problem use" and 11 different terms, ranging from "anxiety" to "suicidal behaviour" were used to describe what I generically define as "depressive symptoms."

Table 1.2: Terminology used by the papers cited in Chapters 1 and 2 of this thesis

	Alcohol problem use	Depressive symptoms
1	Alcohol abuse	Anxiety
2	Alcohol misuse	Anxiety disorder
3	Alcohol problems , problem drinking	Depression
4	Alcohol sensitivity	Depressive symptoms
5	Alcohol tolerance	Internalizing problems
6	Alcohol use and problem use	Major Depressive Disorder
7	Alcohol use disorders	Neuroticism
8	Alcoholism (alcohol dependence)	Other traits associated with internalizing disorders
9	Antisocial alcoholism	Post Traumatic Stress Disorder
10	Binge and harmful drinking	Psychological distress
11	Drug and alcohol use	Suicidal behaviour
12	Drug use	
13	Excessive alcohol consumption	
14	Heavy alcohol use	
15	Heavy drinking of alcohol	
16	High alcohol consumption	
17	Illicit drug use	
18	Other traits associated with alcohol problems	
19	Substance abuse (including alcohol)	
20	Substance dependence	
21	Substance use	
22	Substance Use (including alcohol use)	
23	Substance use disorder	

1.2 The burden of harmful alcohol use in youth

Alcohol is the most prevalent substance used during the developmental period of adolescence (defined by the WHO as age 10-19 years (WHO Europe, 2005)) (BMA BOSE, 2003) and alcohol involvement in young people has been associated with increased risk of tobacco and drug use, academic failure, delinquency, pregnancy and sexually transmitted disease, traffic accidents and other injuries (Donovan, 2004, Flowers, 1999, Kandel et al., 1993, Sutherland et al., 1998, U.S. Department of Justice, 2007).

Across the whole European Union (EU) >90% of 15-16 year olds have imbibed alcohol at some point in their lives, on average initiating use at 12.5 years of age and getting intoxicated for the first time at 14 years of age; 13% of 15-16 year olds have been intoxicated more than 20 times in their lives (Anderson et al., 2006b). The average amount of alcohol consumed on a single occasion by 15-16 year old European youth is over 60 grams of alcohol in northern Europe, and nearly 40 grams of alcohol in southern Europe (Anderson et al., 2006b). Quantifying this in naturalistic terms, since 8 grams of alcohol are equivalent to 1 UK alcohol unit (10 ml of pure alcohol), 60 grams of alcohol would correspond approximately to one fourth of a bottle of spirit (Alcohol by volume (ABV) 40%), or four pints of beer (ABV 3.5%) or a bottle (750 ml) of white wine (ABV 10.5%) (Drinkaware, 2010). Teenagers in the UK have one of the highest rates of substance use in Europe (SCIAOD, 2000) and are more likely to have experimented with alcohol as well as illicit drugs than their peers elsewhere in Europe (EMCDDA, 2007, SCIAOD, 2000). Furthermore, although the percentage of British adolescents aged 11-13 years who do not consume alcohol has been increasing since 2001 (from 39% in 2001 to 46% in 2006), the weekly consumption in this age range has almost doubled, indicating heavier use among those who do drink (from 5.6 units in 2001 to 10.1 units in 2006) (NHS, 2007). Statistics report that approximately 1% of 14–16 year olds in the

UK drink alcohol nearly every day (EMCDDA, 2007), and are therefore at high risk of AUDs (McArdle et al., 2007).

In the United States of America (U.S.A.) the average age of consuming the first drink is 11 years for boys and 13 years for girls. In 2004, 19% of 8th graders (13–14 years old) and 48% of 12th graders (17-18 years old) reported alcohol use in the previous month (Johnston et al., 2005). Epidemiological studies conducted in the U.S.A. reported that in 2001 the annual prevalence of AUDs was 5% in both boys and girls aged 12–17 years, with a peak prevalence of 20% in men and 10% in women between the ages of 18–23 years (Harford et al., 2005).

Since adolescents are highly vulnerable to social influences (Kandel et al., 1987), have lower alcohol tolerance levels and become dependent at lower doses than adults (Chen et al., 1997), the period of adolescence is a key developmental time frame with respect to the development of subsequent alcohol related problems in adulthood.

Moreover, the age of adolescence overlaps for a large extent with puberty, which is a period of increased vulnerability and adjustment for young people (Caspi et al., 1991). Along with the physical changes, puberty brings about major psychological and social changes that are likely to cause stress and susceptibility to psychiatric disorders (Kaltiala-Heino et al., 2011, Patton et al., 2004), as adolescents may experience not only transitional stress due to new psychological adaptations and an accumulation of stressful events (e.g., (Rudolph et al., 1999)), but also stress related to disparities between their chronological age, social age and biological maturation (Glaser et al., 2011, Petersen, 1980).

Longitudinal studies (DeWit et al., 2000, Grant et al., 1998) have indicated that initiating alcohol use before age 15 considerably increases the risk of development of alcohol abuse or dependence in adulthood. A longitudinal study of youth in the United States conducted by Grant and colleagues estimated that each year of delayed onset of alcohol consumption reduces this risk of future alcohol related problems by 7.0% (Grant et al., 2001). It has also

been estimated that, compared with early adulthood onset (Hingson et al., 2009), adolescent onset of alcohol use doubles the risk of having a diagnosis of AD or alcohol abuse in adulthood.

Alcohol use during adolescence is also associated with an increased risk of illicit drug use (Sutherland et al., 1998). In a cross-sectional study of 17–18-year-old adolescents, Kandel and Yamaguchi (Kandel et al., 1993) observed that alcohol and tobacco use tend to precede and increase the use of illicit drugs.

The list of other social and health consequences of harmful use of alcohol in youth is expansive. For example, in 2005 71% of all deaths of those aged 10–24 years in the U.S.A. resulted from four causes: motor vehicle crashes, other unintentional injuries, homicide and suicide (Eaton et al., 2006). Risk of these four causes of death is increased when adolescents consume alcohol, particularly in large amounts. Results from the U.S.A. 2005 national Youth Risk Behaviour Survey indicated that 9.9% of high school students had driven a car or other vehicle after they had been drinking alcohol, while 25.5% had $\geq$1 episode of heavy drinking during the 30 days preceding the survey (Eaton et al., 2006).

Furthermore, there is also a considerable association between harmful use of alcohol and youth criminality. In the U.S.A. in 2006, 116,280 underage persons were arrested for offences directly related to alcohol; this illustrates an 8.4% increase from 2005 (U.S. Department of Justice, 2007). Juveniles arrested for other crimes such as drug abuse violations, prostitution and disorderly conduct were also frequently under the influence of alcohol (Flowers, 1999).

Finally, there is an increasing concern about the burden of the effects that ethanol may exert on adolescents' developing brains. Since ethanol is a neuro-toxic substance, its consumption can affect several brain mechanisms at the base of human cognitive and emotional functioning. Cortical growth and structural changes of the brain (Yurgelun-Todd, 2007)

continue to take place throughout adolescence (Crews et al., 2007), occurring until at least age 21 (Lewinsohn et al., 1993). During adolescence ethanol may affect in particular the fine modelling of the frontal cortex (Sher, 2006a) and the hippocampus (De Bellis et al., 2000); brain structures fundamental for memory processes; and the function of the hypothalamic-pituitary-adrenal axis (HPA), which is crucial for the response to stress (Dai et al., 2007, Prendergast et al., 2007). The HPA axis is a very complex neuro-endocrine system, which is fundamental for emotion regulation; its activity also modulates addictive behaviour. Alteration of this system has been associated with alcohol abuse and dependence, Major Depressive Disorder and anxiety disorder (Sher, 2007).

1.3 Adolescent "alcohol problem use" and "depressive symptoms"

Depression is a common mental health problem during adolescence. In the EU 4% of 12- to 17-year-olds and 9% of 18-year-olds suffer from depression (WHO Europe, 2005). Studies indicate that in the UK 5% of those aged 11-16 are affected with clinically diagnosed Major Depressive Disorder (MDD) or anxiety disorder (Green et al., 2005), while in the U.S.A. 20% of youth may experience an episode of depression before age 18 (Lewinsohn et al., 1991). MDD co-occurs frequently with anxiety disorder, with approximately 25-50% of depressed youth having co-morbid anxiety disorders and about 10-15% of youths with anxiety disorder also suffering from depression (Axelson et al., 2001).

Many studies indicate that depression plays a fundamental role in the development of AUD (Bukstein et al., 1992, Clark et al., 1997b). However, the developmental relationship between the two traits remains unclear, with a number of studies reporting that depressive symptoms precede alcohol problem use (Bukstein et al., 1992, Buydens-Branchey et al., 1989, Hahesy et al., 2002, Kuo et al., 2006) while others report the opposite (Alati et al., 2005, Costello et al., 1999, Deykin et al., 1987, Hovens et al., 1994, White et al., 2001). It also remains unclear

which shared factors may increase the risk of co-morbidity between alcohol problem use and depressive behaviour in youth. Both behaviours have been reported to share non-genetic risk factors (Windle et al., 1999). In addition, a number of twin studies have indicated that both adolescent and adult alcohol problem use as well as depressive symptoms are influenced by genetic factors (Hopfer et al., 2003, Middeldorp et al., 2005) and that some overlap exists in the genetic influences on both behaviours (Kendler et al., 2003, Tambs et al., 1997).

The high co-morbidity between depressive symptoms and alcohol problem use might therefore be explained by the large number of common genetic and non-genetic risk factors for both phenotypes (Kendler et al., 1993). However other mechanisms may also be taken into account. Tension Reduction Theory (Greeley et al., 1999), for example, suggests that children with depression may experiment with substances in an attempt to self-medicate their depressed mood (King et al., 2004). The available evidence suggest that, because adolescence and young adulthood (Blazer et al., 1994, Disorder, 2005) are pivotal periods of physical and psychological development, juvenile onset of alcohol problem use (as reviewed in paragraph 1.2) or depressive symptoms may be particularly predictive of continued problems in adulthood (Blazer et al., 1994, Disorder, 2005). Prospective studies have estimated that adolescent onset of depressive symptoms is associated with a two-to-threefold increased risk of adulthood MDD or anxiety disorder (Pine et al., 1998).

In adulthood, one of the most extreme possible consequences of MDD, suicide, is also strongly associated with a diagnosis of AUDs. Up to 40% of persons with alcohol dependence attempt suicide at some point in their lives, while 7% end their lives by committing suicide (Sher, 2006b). Moreover the lifetime risk of suicide in alcohol dependence has been estimated at 15% (Miles, 1977), with a relative risk (RR) of suicide among "alcohol abusers" of 6.9 (Rossow et al., 1995). In Accident & Emergency (A&E) settings in particular, a strong association has been observed between suicide attempt and

alcohol use, with 10-69% of suicide completers and 10-73% of suicide attempters testing positive for alcohol in the blood (Cherpitel et al., 2004).

With regards to the co-morbidity between alcohol problems and depression, a longitudinal study by Hasin *et al.* observed that subjects suffering for both depression and alcohol dependence are at particularly high risk of committing suicide: one out of every twenty patients with alcohol dependence who are hospitalized for depression die by committing suicide within two years (Hasin et al., 1989).

Many studies conducted in young people as well as in adult samples provide evidence that depression, especially early-onset depressive symptoms (Deas et al., 2002), can precede alcohol problem use (Bukstein et al., 1992, Buydens-Branchey et al., 1989, Clark et al., 1997b, Hahesy et al., 2002, Kuo et al., 2006). A better understanding of the relationships between alcohol problem use and depressive symptoms in adolescence is important for, and contributes to, the development of optimal prevention and early intervention approaches.

CHAPTER 2: RISK AND PROTECTIVE FACTORS FOR HARMFUL ALCOHOL USE AND DEPRESSIVE SYMPTOMS IN YOUTH

2.1. Introduction

The purpose of this chapter is to describe the most relevant shared risk and protective factors associated with the development of both alcohol problem use and depressive symptoms in adolescence that have been reported in published literature.

It is well established that both genetic and non biological factors contribute to the development of psychiatric disorders (for a review see Cooper *et al.* (Cooper et al., 2001)). As a result of their frequent co-occurrence, alcohol abuse and depressive disorders are expected to share these factors to a degree.

A large number of risk and protective factors were identified through systematic bibliographic searches. These factors may be divided into non-genetic and genetic factors that may contribute to the co-morbidity between alcohol problem use and depressive symptoms in adolescence and were identified through epidemiologic and molecular studies. In the first part of this chapter I initially described the role that non-genetic factors identified in epidemiological studies may have in the development of both conditions, while in the last part of the chapter I provided a brief overview of all the genetic risk and protective factors that have been identified by molecular studies investigating the genetic underpinnings of AUDs and mood disorders. Genetic factors have been established as being important in the development of both alcohol problem use and depressive symptoms; however, in my dissertation I focused only on the role of non-genetic factors.

2.2 Criteria for the identification of relevant epidemiological and molecular studies

Systematic bibliographic searches were conducted on the databases *MEDLINE*, *EMBASE* and *PsycINFO* through the OvidSP platform (Ovid, 2010) and on the database *Web of Science* through the platform ISI Web of Knowledge (Thomson Reuters, 2010), all accessed November 3rd 2007 (see Table 2.2 for the settings of the searches). Further articles were identified trough cited references in the papers gathered trough these searches.

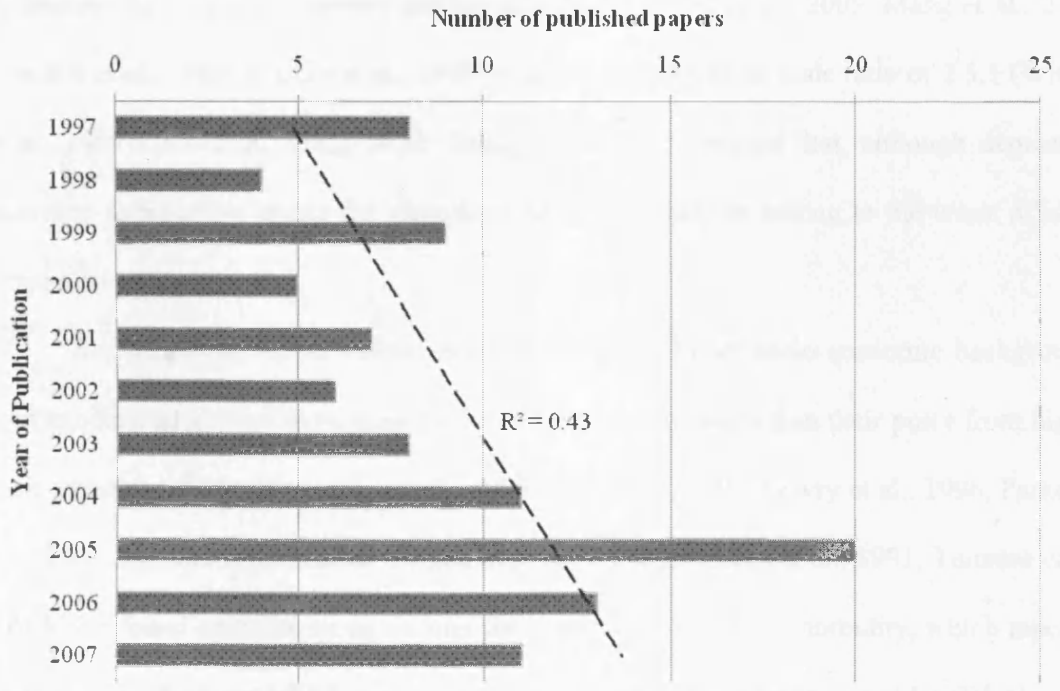
Table 2.2: Search parameters used in the identification of common risk factors for alcohol problem use and depressive symptoms

	Operator	Definition
1	Keywords*	Alcohol Abuse OR Alcohol Misuse OR Alcohol Dependence OR Alcoholism.
2	Keywords*	Depression OR Anxiety OR Mood Disorders OR depressive Disorders.
3	Boolean operator	#1 AND #2
4	Keywords*	Environmental Exposure OR Environment OR Environmental Risk Factor.
5	Keywords*	Genetic Predisposition to Disease OR Polymorphism, Genetic OR Genetic Risk Factor OR Genotype OR Polymorphism, Single Nucleotide.
6	Keywords*	Risk factors.
7	Boolean operator	#4 OR #5 OR #6
8	Boolean operator	#3 AND #7
9	Limits "Language"	English Language.
10	Limits "Field of studies"**	Bioethics OR Systematic Reviews OR Toxicology OR Therapy OR Diagnosis OR Prognosis OR Reviews OR Clinical Prediction Guides OR Qualitative Studies OR Aetiology.
11	Limits "Kind of studies"**	Case Reports OR Classical Article OR Clinical Conference OR Clinical Trial, All Phases OR Comment OR Comparative Study OR Congresses OR Consensus Development Conference OR Controlled clinical trial OR Editorial OR Evaluation Studies OR Government Publications OR Guideline OR Journal Article OR Lectures OR Letter OR Meta Analysis OR Multicenter Study OR Practice Guideline OR Randomized Controlled Trial OR Review OR Twin Study OR Validation Studies.
12	Limits "Subjects of studies"**	(Male OR Female) AND (Humans) AND (Neonatal OR Infancy OR Childhood OR Preschool Age OR School Age OR Adolescence*** OR Young Adulthood***).
13	Limits "Time span"	3 November 1997 – 3 November 2007.
14	Boolean operator	#8 AND #9 AND #10 AND #11 AND #12
15	Selection	Removal of duplicates and manual purging of articles not responding to desirable criteria.

*The search also included further related terms (e.g. alcohol abuse, alcohol misuse, alcohol abuser(s), etc.).
**Limits definitions varied somewhat in different databases.
***The official definition of adolescence has been proposed by the World Health Organization, as those between the ages of 10-19 years (WHO Europe, 2005). I included in the search limits for the database PsychINFO the age range "young adulthood" (18-29 years old) in order to be sure to include all the articles concerning adolescents. I generally excluded from the literature review the studies undertaken in samples composed by young adults and adults only, unless they were providing information of great interest and were easier to generalize to adolescents.

As a result of the bibliographic searches, 267 papers were identified, of which 102 were read in detail (see Figure 2.2 for the frequency of identified papers per year of publication). The remaining papers were not relevant to the current review, or were reports of old studies that had been replicated more recently. As shown in Figure 2.1 (graphic generated using Microsoft Office Excel 2007 for Windows (Microsoft Corporation, 2006)), an increasing trend is observable (β=0.88, t(9)=2.59, p=0.029; R^2=0.43, F(1, 9)=6.71, p=0.029) in the number of publications between 1997-2007 that focused on common risk factors for both depressive symptoms and alcohol problem use, with a maximum of 20 papers per year being published in the year 2005.

Figure 2.1: Number of papers gathered through bibliographic searches per year of publication[1]



[1]Total number of papers read in detail, N=102.

2.3 Factors identified in epidemiological studies contributing to risk of alcohol problem use and depressive symptoms in adolescence

Through bibliographic searches, I identified a number of epidemiological studies that reported risk and protective factors for both alcohol problem use and depressive symptoms, which are summarized in Table 2.3.

2.3.1 Socio-demographic factors

- *Gender:* Males have been reported to be at greater risk for early-onset of alcohol use as well as heavier use (Cooper, 1994, Ohannessian et al., 2004, Verbrugge, 1985, Waldron, 1983). However, this gender gap may be closing in the UK, where adolescent females are now reported to drink as much as their male counterparts (IAS, 2007).

Adolescent females are at greater risk for depression (Bond et al., 2005, Maag et al., 2005, Smucker et al., 1986, Windle et al., 1999) with a reported female/male ratio of 2.5:1 (Windle et al., 1999). However, Maag *et al.* (Maag et al., 2005) argued that, although depression scores on average are higher for girls, boys are more likely to belong to the worst affected depression group.

- *Socioeconomic status (SES):* Adolescents from lower socio-economic backgrounds tend to consume alcohol more frequently and in greater quantity than their peers from higher socioeconomic groups (Droomers et al., 2003, Ellis et al., 1997, Lowry et al., 1996, Parker et al., 1980), although some studies contradict these findings (Green et al., 1991, Tuinstra et al., 1998). We found only one study, among those concerned with co-morbidity, which reported an association between MDD and low SES in subjects aged 12 years and older (Wang et al., 2004a).
- *Educational level:* Studies have been ambiguous, with alcohol problem use having been associated with higher (Moore et al., 2003) (in adults only) as well as lower (Arellano et

al., 1998, Casswell et al., 2003, Droomers et al., 1999, Paschall et al., 2000) (both in adults and adolescents) educational level. In adolescents, alcohol problem use has been linked with lower parental educational level (Gogineni et al., 2006). A link has also been reported between lower educational level and development of depression (Midanik et al., 2007).

- *Ethnicity:* U.S.A.-based studies indicate Caucasian adolescents may have greater risk of developing alcohol problem use than other groups, in particular African-American adolescents (Adlaf et al., 1989, Maag et al., 2005, Singer et al., 1987), although this has not always been replicated (Guerra et al., 2000).

Findings for depressive symptoms are similarly difficult to interpret, with some studies reporting greater levels of depressive symptoms in Caucasians (Doerfler et al., 1988, Roberts et al., 1992), and some in African-Americans (Emslie et al., 1990, Schoenbach et al., 1982), while a longitudinal study found no difference between both ethnic groups (Garrison et al., 1990). Maag *et al.* (Maag et al., 2005) reported that African-Americans, while not at increased risk for depression, may be more likely to experience depression and alcohol problem use concomitantly.

2.3.2 Substance-related behaviour

- *Binge-drinking:* Binge-drinking has been defined as the consumption of ≥5 drinks in a row for men and ≥4 drinks for women in a single episode at least once in two weeks, where the duration of the drinking episode should also be taken into account (Alcoholism, 2004). A strong link has been reported between binge-drinking in adolescence and later development of AUD (Jennison, 2004, McCarty et al., 2004).

Longitudinal studies reported adolescents' binge drinking as a strong risk factor for the development of later AUD (Jennison, 2004, McCarty et al., 2004). Hill *et al.* (Hill et al., 2000) found four binge-drinking trajectories from age 13 to 18: 1) early heavy; 2) increasers;

3) late onseters; and 4) non-bingers. Early–onset, heavy binge-drinking may in particular predict future risk of AUD, with a study reporting that 84% of males and 73% of females engaging in this type of binging received an AUD diagnosis seven years later (Chassin et al., 2002). Binge-drinking may also increase risk of depressive symptoms, with a longitudinal study conducted in an adult sample suggesting that male (but not female) binge-drinkers had a threefold increased risk of developing anxiety and depression three years later compared with non-binge-drinking men (Haynes et al., 2005).

- *Other substance use:* Heavy alcohol use correlates strongly with cigarette and illicit drug use (Goddard et al., 1999, Sutherland et al., 2001). Several longitudinal studies reported that nicotine dependence and cannabis use predict adolescents' alcohol problem use (Poikolainen et al., 2001, Riala et al., 2004), and heavy use of these substances has been linked to rapid progression from the first drink of alcohol to AD (Sartor et al., 2007). The concurrent use of alcohol with marijuana and other illicit drugs has also been associated with depression (Midanik et al., 2007). Several studies reported many risk factors in common for alcohol abuse, cigarette smoking or cannabis use. Those factors might modify the development of alcohol problem use directly or influence the risk of other substance use. Common risk factors for alcohol problem use and cigarette or marijuana smoking are: male gender, low SES (Midanik et al., 2007), sleep problems (Tynjala et al., 1997, Vignau et al., 1997), novelty seeking (Nixon et al., 1990, Pomerleau et al., 1992, Tavares et al., 2005) and strict dieting (Krahn et al., 2005), which is a risk factor especially for cigarette smoking, probably used as a means to control weight (Pomerleau et al., 2001). Furthermore, low SES (Wang et al., 2004a) and sleep problems in particular (Ehlers et al., 1988, Gregory et al., 2002) have also been implicated in the development of depressive symptoms.

2.3.3 Family environment

Although family background is included in my paragraph on non-biological risk factors, it should be emphasized that family relations are influenced by the behaviours of family members, which are partially under the influence of genes that may be shared by parents and offspring (Shelton et al., 2008a).

- *Adverse rearing environment:* Family environments characterized by high conflict, parental divorce, low parental monitoring and discipline and lack of warmth and nurturing (Chassin et al., 2002, Hawkins et al., 1992, Sartor et al., 2007) and, at the extreme end, parental neglect (Guo et al., 2002) and physical and sexual abuse (Becker et al., 2006, Clark et al., 1997a) have been reported to contribute to an increased risk of development of adolescent alcohol problem use. Some evidence suggests that the impact of physical abuse on the development of later alcohol problem use may be stronger for girls than boys (Gogineni et al., 2006). Similarly, adverse family experiences, including neglect and abuse (Hussey et al., 2006) have also been related to depressive symptoms in both adults (Herman et al., 1994) and adolescents (Smart et al., 1993).

- *Family history of alcohol problems:* In a longitudinal study by Alati and colleagues, maternal heavy drinking alone was found to account for 15% (girls) and 21% (boys) of the risk of AD (Alati et al., 2005). Other studies in adults suggest that parental heavy drinking may be a more salient risk factor for females than males (Curran et al., 1999). Gender of the alcoholic parent may differentially affect offspring risk of alcohol problem use (Bidaut-Russell et al., 1994), with studies in adolescents (Cotton, 1979) and adults (Bohman et al., 1981) indicating the risk may be greater for same-sex (e.g., mother–daughter pairs) than opposite-sex family members (e.g., father–daughter pairs). Density of familial alcoholism (number of alcoholic parents or other relatives) has been found to be a strong predictor of

both adults' (Hesselbrock, 1982) and adolescents' (Lieb et al., 2002) alcohol problem use, a finding that can indicate either non-genetic or genetic risk factors, or both.

Children of alcoholics have also been reported to be at an increased risk for depressive symptoms (Chassin et al., 1999, Christensen et al., 2000, Sher, 1997) and for co-morbid alcohol problems, anxiety and depression (Chassin et al., 1999), especially, as reported in adults, the offspring of alcoholic mothers (Zuckerman et al., 1989). Part of this risk may relate to prenatal exposure to alcohol (O'Connor et al., 2006).

- *Maternal depression:* Maternal depression may contribute to adolescents' risk of heavy alcohol use (Alati et al., 2005) as well as depression (Hamilton et al., 1993, Jacob et al., 1997). One explanation may be that maternal depression contributes to disruption of prenatal and postnatal mother–child interactions (O'Connor et al., 2006).

2.3.4 Social environment

- *Peer influences:* A longitudinal study by Aseltine *et al.* (Aseltine et al., 1998), found that close relationships with friends protect against the development of depression; however, friendships with deviant peers correlated positively with adolescent alcohol problem use (Beitchman et al., 2005, Wills et al., 1989). Peer alcohol use influences the initiation as well as continuation of adolescent alcohol use (Musher-Eizenman et al., 2003, Nation et al., 2006), with perceived peers' attitudes toward alcohol and number of alcohol-using peers serving as important factors contributing to adolescents' alcohol problem use (Bray et al., 2003, Oetting et al., 1987, Sale et al., 2003, Wills et al., 2001).

Lack of social support by friends can contribute to the development of depression (Beitchman et al., 2005). Positive peer groups can serve as positive role models, and the exclusion from such social networks can drive adolescents towards deviant peer groups, thus increasing risk of substance abuse (Beitchman et al., 2005).

- *Stress:* A link has been reported between stress and alcohol problem use in adolescents (Jose et al., 2000, King et al., 2003, Wills et al., 1992) and adults (Linsky et al., 1985). The self-medication model suggests that individuals drink to regulate negative affect and to cope with negative life events (Peirce et al., 1994, Wills et al., 1992). Linsky *et al.* (Linsky et al., 1985) studied the correlation between alcohol related problems and stress in 50 U.S.A. states. On the basis of Bales' Theory, which correlates the rate of alcoholism in cultures or societies with levels of stress (tension and frustration) (Bales, 1946), the three global measures of stress examined by Linsky *et al.* explained 27% of the variation in cirrhosis death rates, 14% of the variation in alcoholism and alcoholic psychosis and 47% of the variation in alcohol consumption rates (Linsky et al., 1985). The link between stress and alcohol problem use can be explained by Conger's Tension Reduction Theory (Conger, 1956), which posits that alcohol consumption is motivated by the desire to relieve anxiety and cope with stress.

Stress also increases the risks of anxiety (Copeland et al., 2007) and depression (Garber, 2006, Turner et al., 2004). Garber (Garber, 2006) describes three models (supported by longitudinal studies) linking stress and depression: the Stress Exposure Model (stating that exposure to a stressful event will increase likelihood of depression) (Brown, 1993); the Stress-Generation Model (reported in adults, suggesting that depressed individuals contribute to negative events by their own behaviour) (Hammen, 1991); and the Reciprocal Model, that combines these two models and highlights the "vicious circle" between depression and stress (Kim et al., 2003).

- *Religion:* Kendler and colleagues identified religion as a protective factor for both alcohol problem use and depressive symptoms using a large longitudinal study in an adult sample (Kendler et al., 1997). They underlined that, although very important in human society and behaviour (Institute, 1995), religion has been relatively neglected in studies

exploring the aetiology of mental illness (Crossley, 1995) and substance abuse (Gartner et al., 1991). Kendler *et al.* (Kendler et al., 1997) distinguished three dimensions of religion: personal devotion, institutional conservatism and personal conservatism. In adults, these authors identified a lack of personal devotion to be most strongly related to current use of alcohol and a lifetime history of alcohol abuse, a finding also replicated in youngsters (Rachal et al., 1982). Religion has also been reported to be protective against psychological distress; personal devotion in particular may moderate the effects of stressful life events on depressive symptoms, both in adults (Williams et al., 1991) and adolescents (Maton, 1989).

2.3.5 Personality and psychopathologies

2.3.5.1 Personality and cognition

- *Personality:* Novelty seeking, one dimension of Cloninger's trait and character inventory (TCI) (Cloninger et al., 1993) has been associated with AD in adult samples (Nixon et al., 1990). Adult alcohol-dependent subjects have also been found to have higher scores on the TCI dimension of harm avoidance (tendency to worry, fear of uncertainty, shyness, and tendency to tire easily) (Tavares et al., 2005), suggesting a link between alcohol problem use and vulnerability to anxiety (Ball et al., 2002). Although personality factors belonging to Cloninger's TCI (Cloninger et al., 1993) may have been studied most extensively in relation to psychopathology, other dimensions of personality have also been reported to play a role in addiction and depressive disorders (Anderson et al., 2006a). As reported by Anderson and Smith (Anderson et al., 2006a), behavioural disinhibition, behavioural under-control and impulsivity might be associated with adolescents' alcohol abuse. The association between disinhibition and alcohol problem use has been confirmed by cross-sectional studies in youngsters (Anderson et al., 2005, Katz et al., 2000). In a sample of non-alcoholic women,

Grau and Ortet (Grau et al., 1999) documented an association between alcohol consumption and personal dispositions toward impulsivity and risk taking. According to Wadsworth and colleagues (Wadsworth et al., 2004), the association between heavy alcohol consumption and risk-taking is consistent with the Sensation Seeking Theory proposed by Zuckerman *et al.* (Zuckerman et al., 1964), which has been used to explain alcohol drinking in a sample of young adults (Conrod et al., 1997). A cognitive factor that has been implicated in the development of depressive symptoms is behavioural inhibition (Gray, 1991). Rothbart and Mauro have described behavioural inhibition in childhood as a construct involving expressions of inhibition (inhibited speech, gestures, motor activity, and withdrawal), negative emotional reactions and physiological responses (Rothbart et al., 1990). A longitudinal study by Caspi and colleagues confirmed that inhibition assessed in early childhood was related to depression in young adults (Caspi et al., 1996).

- *Cognition:* Positive alcohol expectancy, referring to expected rewarding effects of alcohol (Prescott et al., 2004) (i.e. facilitation of social interactions, enhancement of excitement, improved motor performance and escape from negative affect (Christiansen et al., 1989, Kassel et al., 2000, Newcomb et al., 1988)) has been reported to influence adolescents' alcohol problem use in both cross-sectional (Anderson et al., 2006a) and longitudinal studies (Anderson et al., 2006a, Christiansen et al., 1989, Smith et al., 1995).

Some (Lee et al., 1993), but not all, studies (Rohsenow, 1983) reported that negative alcohol expectancies may protect against heavy alcohol use (Leigh et al., 1993). A number of studies have attempted, with positive results (Darkes et al., 1998, Sharkansky et al., 1998, Wiers et al., 2004), to reduce rates of alcohol problems by modifying adolescents' alcohol expectancies, although other findings suggest caution against that (Dermen et al., 1998, Jones et al., 2001).

A cognitive factor that has been related to the development and maintenance of depressive symptomatology in adolescents is depressive cognitive style, referring to a negative view of oneself, the future and the world (Beck, 2002, Laurent et al., 1993, Miles et al., 2004).

2.3.5.2 Psychopathologies

Many studies have indicated that AUDs may precede the onset of other mental disorders. However, a considerable number of studies in adolescent samples with co-morbid psychiatric pathologies have also indicated that AUDs developed subsequently to the onset of the psychiatric illness (for a review see Deas *et al.* (Deas et al., 2002)).

- *Externalizing disorders:* Externalizing disorders such as conduct disorder (CD) (Sher, 1991, Stice et al., 1998, Turner et al., 2005, Zucker et al., 1994) and attention deficit hyperactivity disorder (ADHD) (Biederman et al., 1995, Biederman et al., 1998, Kim et al., 2006, White et al., 2001, Wilens, 1998, Wilens et al., 1997, Wilens et al., 2002) have been reported to be important precursors to the development of alcohol problem use in both adolescence and adulthood (Biederman et al., 1995, Biederman et al., 1998, Kim et al., 2006, White et al., 2001, Wilens, 1998, Wilens et al., 1997, Wilens et al., 2002). Sartor and colleagues (Sartor et al., 2007) found that CD was the strongest predictor of early-onset alcohol initiation (associated with 2.5 times increased risk). CD is also reported to precede depression in almost three-quarters of cases (Nock et al., 2006). It has been theorized that this link may be explained by a chain reaction of developmental failures experienced by youth with conduct problems (Capaldi, 1992, Capaldi et al., 1999).

ADHD has also been implicated in depressive symptoms (Wilens et al., 1997) as well as in early-onset alcohol problem use and the transition from substance abuse to dependence (Biederman et al., 1995, Biederman et al., 1998, Kim et al., 2006, White et al., 2001, Wilens, 1998, Wilens et al., 1997, Wilens et al., 2002).

Finally, antisocial behaviour, antisocial personality disorder (Becker et al., 2006, Hussong et al., 1998, Kuperman et al., 2001) and oppositional defiant disorder (ODD) (Gogineni et al., 2006), have also been reported to predict adolescents' alcohol problem use; additionally, ODD has been implicated in the development of depression in youth (Angold et al., 1993).

- *Bipolar disorder:* The frequent co-occurrence of bipolar disorder (BD) and AD, originally identified by Kraepelin (Kraepelin, 1976), has long been recognized (Preisig et al., 2001, Salloum et al., 2000) in adults. Some (Freed, 1969, Reich et al., 1974) (but not all (Mayfield et al., 1968)) studies have indicated that excessive drinking predominates in the manic rather than the depressive phase of BD.

BD tends to develop in late adolescence or early adulthood (Pini et al., 2005), and therefore the number of studies in young samples is limited. However, there is an increasing research interest in the relationship between BD and alcohol and substance abuse in adolescence (Jolin et al., 2007, Wilens et al., 2004, Wilens et al., 1999).

- *Eating disorders:* Both dieting and binge-eating severity in adolescence are strongly associated with the frequency and intensity of alcohol use (Krahn et al., 1992, Krahn et al., 2005, Stewart et al., 2000). Binge-eating, dieting, smoking and heavy alcohol drinking may represent a "cluster" of risky behaviours in adolescence (Jessor et al., 1991). Anorexia nervosa (AN) and bulimia nervosa (BN) are associated with alcohol abuse for distinct reasons: in women diagnosed with AN excessive concern with body weight and shape, and use of vomiting to control weight, heightens the vulnerability for development of AUD; however, in women diagnosed with BN, risk factors may be more global and related to psychosocial functioning (Franko et al., 2005). Finally, Alati *et al.* (Alati et al., 2005) have suggested that strict adherence to a diet may increase the risk of substance abuse, since the rewarding value of alternate reinforcers (i.e. substances or highly palatable "binge" foods) is enhanced (Krahn, 1991).

Eating disorders in both male and female adolescents have been linked with depression, and it has been suggested that body image factors, such as body dissatisfaction (Santos et al., 2007), or peer victimization and marginalization (especially for obese adolescents) (Robinson, 2006), may moderate depression risk.

- *Sleep problems:* Sleep problems, primarily insomnia, have been reported to precede the onset of alcohol problem use among adults (Brower, 2001, Roehrs et al., 1999). Studies have reported associations between alcohol use and delayed bedtime and irregular sleep schedule in children (Tynjala et al., 1997, Vignau et al., 1997, Wong et al., 2004).

Instability in biological rhythm, of which sleep problems are one indicator, has been linked to the risk of depression (Ehlers et al., 1988). Gregory and O'Connor (Gregory et al., 2002) found that sleep problems at age four predicted depression/anxiety in mid-adolescence, and that the correlation between sleep problems and depression/anxiety is stronger in adolescence than in childhood (Gregory et al., 2002).

Table 2.3: Summary of literature search for factors identified through epidemiological studies contributing to the risk of both alcohol problem use and depressive symptoms in adolescence

Domain	Risk factor	Alcohol problem use		Depressive symptoms	
		Association	Lack of association	Association	Lack of association
Socio-demographic	Gender	[Cooper, 1994, Ohannessian et al., 2004, Verbrugge, 1985, Waldron, 1983][A]	None	[Bond et al., 2005, Maag et al., 2005, Smucker et al., 1986, Windle et al., 1999][B]	None
	Socioeconomic status	[Droomers et al., 2003, Ellis et al., 1997, Lowry et al., 1996, Parker et al., 1980, Wang et al., 2004a][C] [Green et al., 1991][D]	None	[Wang et al., 2004a][C]	None
	Educational level	[Arellano et al., 1998, Casswell et al., 2003, Droomers et al., 1999, Paschall et al., 2000][E] [Moore et al., 2003][F] [Gogineni et al., 2006][G]	None	[Midanik et al., 2007] [E]	None
	Ethnicity	[Adlaf et al., 1989, Maag et al., 2005, Singer et al., 1987][H] [Guerra et al., 2000][I]	None	[Doerfler et al., 1988, Roberts et al., 1992][H] [Emslie et al., 1990, Schoenbach et al., 1982][I]	[Garrison et al., 1990]
Substance-related	Binge-drinking	[Chassin et al., 2002, Jennison, 2004, McCarty et al., 2004]	None	[Haynes et al., 2005]	None
	Other substances use	[Poikolainen et al., 2001, Riala et al., 2004, Sartor et al., 2007]	None	[Midanik et al., 2007]	None
Family environment	Adverse rearing environment	[Becker et al., 2006, Chassin et al., 2002, Clark et al., 1997a, Gogineni et al., 2006, Guo et al., 2002, Hawkins et al., 1992, Sartor et al., 2007]	None	[Herman et al., 1994, Hussey et al., 2006, Smart et al., 1993]	None
	Family history of alcohol problems	[Bohman et al., 1981, Chassin et al., 1999, Cotton, 1979, Curran et al., 1999, Deykin et al., 1987, Hesselbrock, 1982, Lieb et al., 2002]	None	[Chassin et al., 1999, Christensen et al., 2000, O'Connor et al., 2006, Sher, 1997, Zuckerman et al., 1989]	None
	Maternal depression	[Deykin et al., 1987]	None	[Hamilton et al., 1993, Jacob et al., 1997]	None
Social environment	Peer influence	[Aseltine et al., 1998, Beitchman et al., 2005, Wills et al., 1989][J] [Bray et al., 2003, Musher-Eizenman, 2003, Nation et al., 2006, Oetting et al., 1987, Sale et al., 2003, Wills et al., 2001][K]	None	[Beitchman et al., 2005][L]	None

Table 2.3 continued...

	Table 2.3 continued...				
Social environment	Stress	[Jose et al., 2000, King et al., 2003, Linsky et al., 1985, Wills et al., 1992]	None	[Brown, 1993, Copeland et al., 2007, Garber, 2006, Hammen, 1991, Kim et al., 2003, Turner et al., 2004]	None
	Religion[M]	[Rachal et al., 1982, Williams et al., 1991]	None	[Kendler et al., 1997, Maton, 1989, Williams et al., 1991]	None
Personality and psycho-pathologies	Personality	[Anderson et al., 2006a, Anderson et al., 2005, Conrod et al., 1997, Grau et al., 1999, Katz et al., 2000, Nixon et al., 1990, Wadsworth et al., 2004, Zuckerman et al., 1964][N] [Tavares et al., 2005][O]	None	[Ball et al., 2002, Caspi et al., 1996, Gray, 1991, Rothbart et al., 1990][O]	None
	Cognition	[Anderson et al., 2006a, Christiansen et al., 1989, Kassel et al., 2000, Newcomb et al., 1988, Prescott et al., 2004, Smith et al., 1995][P] [Lee et al., 1993, Leigh et al., 1993][Q]	[Rohsenow, 1983][o]	[Beck, 2002, Laurent et al., 1993, Miles et al., 2004][R]	None
	Ex-ternalizing disorders	[Clark et al., 1996, Sartor et al., 2007, Sher, 1991, Turner et al., 2005, Zucker et al., 1994][S] [Biederman et al., 1995, Biederman et al., 1998, Kim et al., 2006, White et al., 2001, Wilens, 1998, Wilens et al., 1997, Wilens et al., 2002][T] [Becker et al., 2006, Gogineni et al., 2006, Hussong et al., 1998, Kuperman et al., 2001][U]	None	[Capaldi, 1992, Capaldi et al., 1999, Nock et al., 2006][S] [Wilens et al., 2002][T] [Angold et al., 1993][U]	None
	Bipolar disorder	[Kraepelin, 1976, Preisig et al., 2001, Salloum et al., 2000]	None	None[V]	None
	Eating disorders	[Franko et al., 2005, Krahn et al., 1992, Krahn et al., 2005, Stewart et al., 2000]	None	[Robinson, 2006, Santos et al., 2007]	None
	Sleep problems	[Brower, 2001, Roehrs et al., 1999, Tynjala et al., 1997, Vignau et al., 1997, Wong et al., 2004]	None	[Ehlers et al., 1988, Gregory et al., 2002]	None

[A] Males; [B] Females
[C] Low socioeconomic status; [D] High socioeconomic status
[E] Low educational level; [F] High educational level; [G] Parental educational level; [H] Caucasians; [I] African Americans
[J] Friendship with deviant peers; [K] Alcohol misuse by peers; [L] Exclusion from peer social network
[M] Protective factor
[N] Novelty seeking, disinhibition, risk tacking, impulsivity; [O] Harm avoidance, behavioural inhibition
[P] Positive alcohol expectancies; [Q] Negative alcohol expectancies (protective); [R] depressive cognitive style
[S] Conduct disorder; [T] Attention deficit hyperactivity disorder; [U] Oppositional defiant disorder and antisocial personality
[V] Depression is a feature of bipolar disorder, also known as manic-depressive syndrome

2.4 Interactions between factors identified through epidemiological studies

A number of papers have focused on interactions between the risk factors described above in the development of adolescent alcohol problem use. In contrast, I found only one such paper on depressive symptoms.

- Parental drinking (Jacob et al., 1991, Weinberg, 1997, Whipple et al., 1995) and parental depression (Hamilton et al., 1993, Jacob et al., 1997, Kim-Cohen et al., 2005) may interact to increase disturbances in family relationships, including parent-child relations (O'Connor et al., 2006), thus increasing the risk of adolescent alcohol problem use (Jacob et al., 1991).

Low parental control may interact with adolescents' impulsivity and disinhibition as well as their engagement with deviant peers to increase the risk of adolescent heavy alcohol use (Bates et al., 1995a).

- Peer influences may moderate relations between family environmental risk factors and alcohol and substance abuse (Chassin et al., 2002). It has been hypothesized that stress in the family environment (e.g., family conflict, lack of support, harsh discipline) results in affiliation with a negative peer network, which models and reinforces substance use (Dishion et al., 1988).

Conduct disorder may exert its influence on the onset and perpetuation of heavy alcohol use through engagement with deviant peers who reinforce heavy drinking (Fowler et al., 2007b, Jessor et al., 1977). With respect to depression, it has been reported that among children with ADHD, those with co-morbid ODD have a greater risk of depressive symptoms, compared with children with ADHD without co-morbid ODD (Biederman et al., 1995, Biederman et al., 1998, Wilens, 1998, Wilens et al., 1997, Wilens et al., 2002).

2.5 Genetic factors associated with the development of alcohol problem use and depressive symptoms

2.5.1 Heritability of AUDs and depressive disorders

A number of genes have been associated with both alcohol problem use and depressive symptoms (Clark et al., 1996). A review of adolescent twin studies by Hopfer *et al.* (Hopfer et al., 2003) reported that the magnitude of genetic influence on adolescent alcohol problem use is quite modest (compared to adults (Goldman et al., 2005)) and appears to be moderated by measures of use (Hopfer et al., 2003). Fowler *et al.* (Fowler et al., 2007a) reported that initiation of alcohol use and progression to heavier alcohol use during adolescence had separate but related underlying aetiologies. With respect to initiation of alcohol use, environmental influences that make twins more similar (common environment) tended to be greater (explaining 65% of the variation) than genetic influences (explaining 26% of the variation). However, genetic influences were found to be stronger with regards to progression to heavier use (explaining up to 64% of the variation). In a Finnish study on 5,638 twins, the heritability of drinking measures (frequency and amount of alcohol intake) ranged from 0.36 to 0.40 (Kaprio et al., 1987). Moreover, the genetic liability to alcoholism is shared with other substance dependence, especially nicotine, with 50% of candidate genes being in common (Goldman et al., 2005). Heritability of anxiety/depression has been assessed in samples of young people, ranging between 7% and 15% (Towers et al., 2000).

Several genes have been associated with both alcohol problem use and depressive symptoms, as their inherited functional variants might alter the physiological mechanisms of reward, cognition, stress coping, emotion regulation and neuronal plasticity (Oroszi et al., 2004).

However, the number of genetic informative studies done in youngsters is small compared to the research conducted in adults; this is likely due to ethical constraints that might arise from

genetic studies in young samples (Knoppers et al., 2002) and to the lower frequency of clinically diagnosed psychiatric illnesses in young people. Moreover, the literature for candidate susceptibility genes has long been inconclusive, with positive findings generally being followed by negative findings (summarized in Table 2.4), a situation which is in contrast to the epidemiological literature (see Table 2.3). Due to the paucity of molecular genetic studies in adolescents specifically, the paragraph below also includes relevant articles from the literature on adults (identified through cited references in the papers yielded by my literature search). This seems a valid approach, given the consideration that the alleles of a genetic polymorphism do not change over time (Garber, 2006). Table 2.4 lists the papers that have analyzed the associations between specific genetic polymorphism and AUDs or depressive disorder.

2.5.2 Neurotransmitter receptor genes

- *GABA Receptors:* The gamma-aminobutyric acid (GABA) system has been implicated in alcohol's sedating effects and the development of tolerance (Hiller-Sturmhofel et al., 2004) as well as anxiety- and depression-related traits (for a review see (Petty, 1995)). An association has been reported between the functional Pro/Ser genotype in the gene *GABRA6* (5q34) coding for the GABA receptor subunit alpha-6 (Pro385Ser polymorphism) and low benzodiazepine sensitivity (a marker for AD (Iwata et al., 1999)), and low response to alcohol and AD, by some (but not all (Song et al., 2003)) studies (Radel et al., 2005, Schuckit et al., 1999). The Pro/Pro genotype has also been associated with neuroticism (Sen et al., 2004b), a personality trait associated with depression/anxiety (Marques et al., 2006). However, the need for replication of these findings has been stressed (Song et al., 2003), particularly because other *GABRA6* polymorphisms have been related to an attenuated rather than heightened stress response (Uhart et al., 2004).

- *Dopamine receptor D2:* The dopaminergic system plays a key role in the reward circuitry of the brain (Noble, 2000), on which addictive substances act.

The dopamine receptor D2 (*DRD2,* 11q23) gene has been associated with AD, from a study indicating DRD2 receptor avidity is lower in alcohol-preferring individuals than in control subjects (Hietala et al., 1994). A number of studies have reported an association between the *DRD2* Taq A1 variant and alcohol problem use (Goldman, 1995, Noble, 2003, Noble et al., 1991, Reich et al., 1999); however, other studies have not replicated these findings (Bolos et al., 1990, Lu et al., 1996). A study in Han Chinese men reported a higher Taq A1/B1 haplotype frequency in alcoholics who also had co-morbid anxiety disorder or MDD (Huang et al., 2007). However, some studies have found no evidence of association between *DRD2* gene variants and susceptibility to MDD (Cusin et al., 2002).

- *Muscarinic Acetylcholine Receptors:* The Cholinergic Muscarinic Receptor 2 (*CHRM2*, 7q31-q35) belongs to muscarinic acetylcholine receptors (Nathanson, 1987), which are involved in many functions in the brain, including attention, learning, memory and cognition (Baxter et al., 1999).

Recently, some studies have reported variants within the 5'-UTR of *CHRM2* influence risk of both AD and MDD (Luo et al., 2005, Wang et al., 2004b), with the latter study suggesting SNP rs1824024, in particular, may be linked to susceptibility for both AD and affective disorders (Luo et al., 2005). The first study (Wang et al., 2004b) also reported associations with AD and/or depression for two other SNPs (termed SNP1 and SNP2); however, the effects were complex. The results showed that allele T and genotype C/T of SNP1 and/or genotype C/T of SNP2 may protect against AD and/or MDD, but that the interaction of the SNP1 T-allele and the SNP2 C-allele may increase risk for both these disorders. Further haplotype analyses (Wang et al., 2004b) suggested that the most common haplotype (rs1824024–rs2061174–rs324650, T–T–T) might be protective against risk for alcoholism,

MDD and the co-morbid phenotype. However, not all studies have found associations between *CHRM2* variants and AD (Dick et al., 2007a).

2.5.3 Neurotransmitter transporters

Serotonin (5-hydroxytryptamine, 5-HT) contributes to many physiological functions (Lesch et al., 1996), including a key role in the brain reward circuitry (Koob et al., 1997). Serotonin is released in response to alcohol (Yoshimoto et al., 1992) and low central serotoninergic activity has been correlated with an increased alcohol tolerance and vulnerability for alcohol problem use (Hallikainen et al., 1999, Koob, 2003, Turker et al., 1998).

- *Serotonin transporter:* A number of studies have focused on the relationship between the serotonin transporter (5-HTT) gene (*SLC6A4*, 17q11.1-q12) and alcohol problem use (Edenberg et al., 1998, Gelernter et al., 1997, Gorwood et al., 2000, Hallikainen et al., 1999, Hammoumi et al., 1999, Ishiguro et al., 1999, Kweon et al., 2005, Mannelli et al., 2005, Matsushita et al., 2001, Munafo et al., 2005, Olsson et al., 2005b, Preuss et al., 2001, Sander et al., 1998, Thompson et al., 2000, Turker et al., 1998, Wiesbeck et al., 2004). Impairments in 5-HTT function have considerable impact on extracellular levels of 5-HT (Lesch, 2005). A deletion/insertion polymorphism affects the transcriptional control region upstream of the *SLC6A4* transcription initiation site (Heils et al., 1996). The long and short variants of *SLC6A4* have a length, respectively, of 528 base pairs (bp) (L-allele) and 484bp (S-allele) (Heils et al., 1996). The S-allele (defined also as 5-HTTLPR) is associated with an approximately 50% reduction in transporter availability, resulting in a consequent increase in synaptic 5-HT concentration compared with L-allele (Enoch, 2006).

The S-allele has been associated with a number of alcohol-related phenotypes, including high ethanol tolerance (Turker et al., 1998); type-2 alcoholism (Hallikainen et al., 1999) (characterized by early-onset, impulsivity and antisocial personality traits (Cloninger, 1987));

binge-drinking in Japanese alcoholics (Matsushita et al., 2001); alcohol-related antisocial behaviour (Ishiguro et al., 1999); and combined alcohol-seeking with risk-taking behaviour (Sander et al., 1998).

The S-allele has also been investigated in relation to mood-related phenotypes (Gorwood et al., 2000, Hammoumi et al., 1999, Kweon et al., 2005, Mannelli et al., 2005, Munafo et al., 2005, Olsson et al., 2005b), including depression (Enoch, 2006) and neuroticism (Greenberg et al., 2000, Lesch et al., 1996, Marques et al., 2006).

Furthermore, a meta-analysis showed a significant effect of the S-allele both in relation to alcohol problem use (among individuals with alcoholism and a co-morbid psychiatric condition, or with early-onset or more severe AD) (Feinn et al., 2005) and in relation to the trait of neuroticism (the latter finding confirmed in two meta-analyses (Schinka et al., 2004, Sen et al., 2004a)).

2.5.4 Neurotransmitter metabolizing genes

- *Monoamine oxidase A (MAOA): MAOA* is involved in the metabolism of dopamine, serotonin and norepinephrine (Shih et al., 1999). A functional 30bp repeat variable-number-tandem-repeat (VNTR) polymorphism in the promoter region of the *MAOA* gene (Xp11.3) has been reported to alter its transcriptional efficiency (Huang et al., 2007). 'High-activity' alleles (3.5 or 4 copies of the repeat sequence) show a two- to ten-fold higher transcription rate of the *MAOA* gene than 'low-activity' alleles (3 or 5 copies) (Sabol et al., 1998).

The *MAOA* VNTR 3-repeat (low-activity) allele has been associated with antisocial alcoholism among German men (Samochowiec et al., 1999). Schmidt and colleagues (Schmidt et al., 2000) replicated these findings and observed a gender difference in the phenotypic effects on alcoholics, which seems plausible considering the X-chromosomal localization of the *MAOA* gene. Alcoholic men had higher scores on antisocial traits, whereas

alcoholic women showed more depression. Other studies, however, found no association between the *MAOA* VNTR and AD (Koller et al., 2003). *MAOA* low activity variants have also been associated with MDD in adulthood (Brummett et al., 2007, Yu et al., 2005). However, other studies reported an association of seasonal depression with high-activity alleles (Gutierrez et al., 2004), or no association at all (Kunugi et al., 1999).

- *Catechol-O-Methyltransferase (COMT): COMT* is involved in the metabolism of dopamine and norepinephrine (Enoch, 2006). *COMT* contains a common functional polymorphism producing a Val/Met substitution at codons 108/158 (Lachman et al., 1996). The $COMT^{108/158}$ Met variant is associated with 40% less COMT activity in the brain than the Val allele, resulting in reduced dopamine turnover and an increased vulnerability to the development of AD (Tiihonen et al., 1999). The interpretation of the findings regarding the relationship between the $COMT^{108/158}$ Met variant and AD is complex, since positive findings have been reported in different populations, but with opposite effects (Enoch, 2006). The Met158 allele has been associated with increased social drinking and late-onset alcoholism in European Caucasian men (Kauhanen et al., 2000, Tiihonen et al., 1999); however, it has been found to protect against alcoholism in Plains American Indians (Enoch et al., 2006). According to Enoch (Enoch, 2006), the opposite effects of Met158 might be explained by the differing drinking patterns: among Europeans the Met158 allele may be a vulnerability factor for a drinking pattern centred on relief of anxiety, whereas among American Indians, the anxious, cautious personality associated with the Met158 allele may protect against episodes of excessive heavy drinking (Enoch et al., 2006). However, not all studies in Caucasians have replicated the association with $COMT^{108/158}$ Met variant and risk of AD (Foroud et al., 2007). The $COMT^{108/158}$ Met variant has also been associated with anxiety (Enoch et al., 2003, Olsson et al., 2005a). In a longitudinal study of Australian adolescents, carriers of the Met/Met genotype were found to have a twofold greater risk of reporting episodes of anxiety

(Olsson et al., 2005a). The association of this variant with anxiety might be mediated by the neural response to unpleasant stimuli, which would be greater depending on the presence and the number of Met158 alleles (Smolka et al., 2005). Nevertheless, a recent systematic review of the *COMT*$^{108/158}$ Met variant polymorphism concluded that *COMT* is probably not "a gene for" any mental disorder, but might have pleiotropic effects (influencing multiple phenotypic traits) on human behaviour (Hosak et al., 2007).

2.5.5 Other genes

- *Brain derived neurotrophic factor:* Brain-derived neurotrophic factor (*BDNF*, 11p13) belongs to a neurotrophin superfamily responsible for promoting and modifying growth, development and survival of neuronal populations (Duman et al., 2006). Chronic alcohol exposure may affect *BDNF* mRNA expression and significantly reduce BDNF secretion. This may impact the role of BDNF in neuroprotection as well as regulate the behavioural response to ethanol through changes in synaptic plasticity (Crews et al., 2003, Kovalchuk et al., 2002, Luo et al., 1998, McGough et al., 2004, Sakai et al., 2005).

Uhl *et al.* (Uhl et al., 2001) reported that a dinucleotide-repeat variant (Val66Met), located close to the 5'-end of the *BDNF* gene, was associated with drug-abuse vulnerability. This allele variant, affecting intracellular trafficking and activity-dependent secretion of BDNF (Chen et al., 2004, Egan et al., 2003), has been further investigated. Matsushita *et al.* (Matsushita et al., 2004) reported a significant association between the *BDNF* Val66Met variant and AD with violent tendencies in Japanese male alcoholics. Another study, however, did not replicate that finding (Tsai et al., 2005).

Studies of human cortex have indicated carriers with the *BDNF* Val/Met or Met/Met variant have reduced amplitude of evoked potentials (Kleim et al., 2006) and reduced volume of cerebral neocortex grey matter (Pezawas et al., 2004), findings which have stimulated studies

of a possible role of BDNF in the development of major depression (Chen et al., 2001, Karege et al., 2002, Ribeiro et al., 2007, Schumacher et al., 2005). Ribeiro *et al.* reported that individuals homozygous for the Met variant of the Val66Met allele are at an increased risk of MDD (Ribeiro et al., 2007). However, another study has not replicated these findings (Tsai et al., 2003).

Table 2.4: Summary of literature search for factors identified through molecular studies contributing to risk of both alcohol problem use and depressive symptoms in adolescence[1]

Domain	Risk factor	Alcohol problem use		Depressive symptoms	
		Association	**Lack of association**	**Association**	**Lack of association**
Neurotransmitters receptors	*GABRA6* Pro385Ser	(Iwata et al., 1999, Radel et al., 2005, Schuckit et al., 1999)	(Song et al., 2003)	(Sen et al., 2004b)	(Uhart et al., 2004)
	DRD2 Taq A1	(Goldman, 1995, Huang et al., 2007, Noble, 2003, Noble et al., 1991, Reich et al., 1999)	(Bolos et al., 1990, Lu et al., 1996)	(Huang et al., 2007)	(Cusin et al., 2002)
	CHRM2 SNPs 5'-UTR	(Luo et al., 2005, Wang et al., 2004b)	(Dick et al., 2007a)	(Luo et al., 2005, Wang et al., 2004b)	None
Neurotransmitters transporters	*SLC6A4* S-allele (5-HTTLPR)	(Edenberg et al., 1998, Gelernter et al., 1997, Gorwood et al., 2000, Hallikainen et al., 1999, Hammoumi et al., 1999, Ishiguro et al., 1999, Koob, 2003, Kweon et al., 2005, Mannelli et al., 2005, Matsushita et al., 2001, Munafo et al., 2005, Olsson et al., 2005b, Preuss et al., 2001, Sander et al., 1998, Thompson et al., 2000, Turker et al., 1998, Wiesbeck et al., 2004) (Feinn et al., 2005)*	None	(Enoch, 2006, Gorwood et al., 2000, Greenberg et al., 2000, Lesch et al., 1996, Marques et al., 2006, Olsson et al., 2005b) (Schinka et al., 2004, Sen et al., 2004a)*	None
Neurotransmitters metabolizers	*MAOA* promoter VNTR	(Samochowiec et al., 1999, Schmidt et al., 2000)[A]	(Koller et al., 2003)[A]	(Schmidt et al., 2000)[AB] (Brummett et al., 2007, Yu et al., 2005)[A] (Gutierrez et al., 2004)[C]	(Kunugi et al., 1999)
	COMT Val158Met	(Kauhanen et al., 2000, Tiihonen et al., 1999) (Enoch et al., 2006)[D]	(Foroud et al., 2007)	(Enoch et al., 2003, Olsson et al., 2005a, Smolka et al., 2005)	(Hosak et al., 2007)
Other genes	*BDNF* Val66Met	(Matsushita et al., 2004)	(Tsai et al., 2005)	(Ribeiro et al., 2007)	(Tsai et al., 2003)
	GABRA6 Pro385Ser	(Iwata et al., 1999, Radel et al., 2005, Schuckit et al., 1999)	(Song et al., 2003)	(Sen et al., 2004b)	(Uhart et al., 2004)

1. Although my literature search focussed on adolescents, it did yield articles based on different age groups. To indicate which studies were not conducted specifically in adolescents, I have used the following notations:
Bold **reference**: Study (or review of studies) undertaken in adults;
Underlined reference: Study (or review of studies) undertaken in young adults (20-29 Years old);
Italic *reference*: Study (or review of studies) undertaken in populations composed of people of all ages;
* Meta-analysis.
[A] Low activity variant.
[B] In women only.
[C] High activity variant.
[D] Protective in Plain American Indians.

2.6 Epistasis

In most psychiatric disorders, multiple genes are thought to contribute to the phenotype (Goldman et al., 2005). The synergic action of several genes on a phenotype is referred to as epistasis (Schumann, 2007, Schumann et al., 2003). Schumann (Schumann, 2007) suggested that genetic liability might be explained by two parallel genetic mechanisms: heterogeneity and poly/oligogenicity. Heterogeneity (the presence of a variety of genetic defects which cause the same disease) can account for single gene variants giving rise to different aspects of phenotypes, while poly/oligogenicity refers to situations where phenotypes arise due to additive and interactive effects of functional mutations within different genes (Schumann, 2007). Although accounts of epistasis influencing addiction in humans are still rare (Van den Bree, 2005), some publications have suggested such effects play a role in the development of alcohol problem use or depressive symptoms.

- A longitudinal study in low alcohol-responsive men by Schuckit and colleagues (Schuckit et al., 1999) reported that all subjects with two *5-HTT* promoter L-alleles as well as the Pro/Ser alleles at the Pro/Ser genotype of the *GABRA6* had developed AD at 15-year follow-up. Heinz *et al.* (Heinz et al., 2001) hypothesized these two polymorphisms might increase the risk of alcohol problem use by influencing the activity of the brain reward circuitry (Di Chiara et al., 1996, Diana et al., 1993).

Of relevance to depressive symptoms, Sen and colleagues (Sen et al., 2004b) reported that the combination of the *GABRA6* Pro/Pro genotype and *5-HTT* S-allele was strongly associated with neuroticism.

- Huang and colleagues hypothesized that the low activity variant of the *MAOA* repeat promoter polymorphism increases susceptibility to AD in subjects also possessing the *DRD2* Taq A1/A1 genotype, particularly in individuals co-morbid for alcoholism and anxiety/depression (Huang et al., 2007).

2.7 Gene-environment interaction

Gene-environment interaction occurs when genes and environmental factors jointly influence the probability that psychopathology will develop. It has also been described as the situation where the effect of exposure to an environmental pathogen on health is conditional on a person's genotype (or conversely, where environmental experience moderates genes' effects on health) (Moffitt et al., 2005). Gene-environment interactions have been long suspected in psychiatry, and empirical findings of measured gene-environment interaction are now increasingly emerging (Moffitt et al., 2005), after seminal papers by Caspi *et al.* (Caspi et al., 2002, Caspi et al., 2003). For example, Dick *et al.*, using a genetically informative twin-family design, observed that parental monitoring strongly moderates the effects of addiction susceptibility genes in 12 years-old adolescents (Dick et al., 2007b).

- Caspi and colleagues reported that the low-*MAOA* activity genotype increased the risk of developing CD in the presence of adverse childhood experiences (Caspi et al., 2002). This hypothesis has been confirmed by another longitudinal study (Foley et al., 2004) and a meta-analysis (Kim-Cohen et al., 2006), suggesting that such interactions predict adolescents' CD, one of the major psychiatric condition antecedent to adolescent alcohol problem use (Alati et al., 2005, Becker et al., 2006, Chassin et al., 1999, Chassin et al., 2002, Hussong et al., 1998, Sartor et al., 2007, White et al., 2001).
- Caspi *et al.* (Caspi et al., 2003) reported that the *5-HTT* S-allele interacts with cumulative stressful life events to contribute to the severity of depressive symptoms, a finding replicated by other studies (Taylor et al., 2006, Wilhelm et al., 2006). Hariri and colleagues reported that individuals with the *5-HTT* S-allele have greater amygdala activation in response to negative stimuli (Hariri et al., 2005), and a greater coupling between the amygdala and the ventromedial prefrontal cortex (Heinz et al., 2005), a limbic brain area implicated in depression (Drevets, 2003).

- Kaufman and colleagues (Kaufman et al., 2007) have found that the risk of early-onset of alcohol use (a risk factor for development of AD) may be greater in the presence of experiences of maltreatment during childhood, particularly for children who possess the *5-HTT* S-allele (Grant et al., 1998).

PART II

CHAPTER 3: OVERALL STUDY DESIGN

3.1 Purpose of the research

The purpose of my research is to investigate the temporal association between depressive traits in childhood (at age 10) and alcohol problem use in early adolescence (at age 14). I focus particularly on the role that gender differences and peer influences play in the relationship between age 10 depressive symptoms and age 14 alcohol problem use, using data collected as part of the Avon Longitudinal Study of Parents and Children (ALSPAC) (Golding et al., 2001), one of the world's largest and most comprehensive cohort studies (Wise, 2001).

3.2 Theoretical rationales

3.2.1 Association between depressive symptoms and alcohol problem use in youth

As extensively reviewed in Chapter 2, the co-morbidity between depressive symptoms and alcohol problem use might be explained by the large number of genetic and non-genetic risk factors that both phenotypes share in common; however, two additional intriguing theoretical rationales of the association between the two behaviours in youth may be provided by Tension Reduction Theory (Greeley et al., 1999) and Family Interaction Theory (Brook et al., 1998).

While Tension Reduction Theory (Greeley et al., 1999) suggests that anxious youngsters might drink alcohol to reduce stress (Kalodner et al., 1989) and, therefore, children with depression may begin to experiment with alcohol in an attempt to self-medicate (King et al.,

2004), Family Interaction Theory argues that both adolescent personality (including depression) and dysfunction in the complex interaction processes between family and social environments may increase the risk of substance misuse in young people (Brook et al., 1998). With my thesis I aim to contribute to the knowledge base addressing the developmental pathways between depression and alcohol problem use in youngsters, for which there is still a lack of understanding (King et al., 2004), and particularly to elucidate which factors impact the relationship between these two behaviours.

3.2.2 Gender differences in the association between depressive symptoms and alcohol problem use in youth

As reported in paragraph 2.3, adolescent girls are at greater risk for depression than boys (Bond et al., 2005, Windle et al., 1999), whereas males have been reported in past surveys to be at greater risk for early-onset of alcohol use as well as heavier use (Cooper, 1994, Ohannessian et al., 2004, Verbrugge, 1985, Waldron, 1983).

However, as recently reviewed by Conley *et al.* (Conley et al., 2009), prior to adolescence rates of depression are similar for boys and girls (Hammen, 2003, Hankin et al., 2001) or slightly favor boys (Anderson et al., 1987, Hankin et al., 1998). Depression increases then sharply in adolescence, particularly for girls (Kessler et al., 2001), whereas findings for boys are mixed, with some studies reporting slight increases (Angold, 1992, Hankin et al., 1998, Weissman et al., 1987), and others reporting stable rates (Ge et al., 2001, Twenge et al., 2002, Wichstrom, 1999) or even decreases (Angold, 1996). Furthermore, some studies reported that boys are more likely to belong to the worst affected depression group than girls (Maag et al., 2005).

Inconsistent evidence regarding the precise age of onset of this emerging sex difference might be explained by findings that pubertal development, rather than chronological age,

accounts for the difference (Angold et al., 1998, Conley et al., 2009, Glaser et al., 2011, Hayward et al., 1999, Joinson et al., 2011). Compared to their on-time or late-maturing peers, in fact, early-maturing girls typically exhibit more depressive symptoms and mood problems (Benjet, 2002, Ge et al., 2001, Hayward et al., 1997, Kaltiala-Heino et al., 2003), whereas among boys, late maturation often is associated with elevated depressive symptoms compared to early and on-time maturation (Benjet, 2002, Dorn, 2003, Ge et al., 2001, Hayward et al., 1997, Kaltiala-Heino et al., 2003, Weichold, 2003); before Tanner Stage III (which is the third of five possible stages of breast development and pubic hair growth in girls, and of genital development and pubic hair growth in boys (Tanner, 1969)), in fact, boys show higher rates of depression than girls, and the prevalence of depression appears to fall in boys at an earlier pubertal stage than that at which it begins to rise in girls (Angold et al., 1998) and recent transition to Tanner Stage III or higher had a transient effect in reducing the prevalence of depression in boys (Angold et al., 1998).

Also concerning alcohol consumption, the situation is apparently reversing, with girls, both in the USA and in the UK, now drinking more alcohol and being at greater risk of developing alcohol problems than are boys (Abuse, 2003, Schinke et al., 2008). As reported by a recent review by Smith et al. of the alcohol drinking trends in the UK, the average alcohol consumption has increased in women of all ages, and in men 35 years and older, whereas consumption in men aged 16 to 24 and 25 to 34 years has either slightly decreased or shown little change (Smith, 2009). The same authors, analyzing the results of six primary epidemiological studies focusing on alcohol consumption among UK adolescents (i.e., the Smoking, Drinking and Drug Use among young people in England Survey (SDD) (Fuller, 2006, Fuller, 2008), the Health Survey for England (HSE) (Statistics, 2006), the Scottish Schools Adolescent Lifestyle and Substance Use Survey (SALSUS) (Maxwell, 2006), the Scottish Health Survey (SHS) (Bromley, 2005), and the European School Survey Project on

Alcohol and other Drugs (ESPAD) (Hibell et al., 2004)), observed that although there has been a decrease in the prevalence of weekly drinking, such decline was more evident in boys than girls, resulting in some cases in the reversing of the gender gap in drinking frequency (Smith, 2009). Furthermore, despite such reduction in the frequency of alcohol consumption, data from the European Schools Survey Project on Alcohol and other Drugs (ESPAD) for pupils 15 and 16 years old in the UK shows an increasing trend in prevalence of drunkenness and binge drinking in young British adolescents, particularly among girls (Hibell et al., 2004, Smith, 2009).

Nevertheless, the current literature is still inconclusive with respect to whether the relationship between depressive symptoms and alcohol problem use is different for males and females (Bukstein et al., 1992, Clark et al., 1997b, Karlsson et al., 2006, Schwinn et al. 2010). Evidence from large population-based longitudinal studies is lacking. One recent study by Marmorstein based on the AddHealth sample (Marmorstein, 2009) has indicated that high levels of depressive symptoms at ages 11-21 were associated with higher levels of alcohol problems at ages 11-23 and ages 18-28, and that this link was stronger among females (Marmorstein, 2009). However, with the exclusion of gender, the influence of covariates on these relationships was not examined. Moreover, because of the wide age range of the AddHealth sample (approximately ten years), it remains unclear how depressive symptoms during a specific developmental period are related to alcohol problem use at a later date.

I intended to address this issue by studying the relationship between depressive symptoms in childhood and alcohol problem use in early adolescence. My findings are particularly relevant for the development of prevention/intervention programmes aimed at the early stages of risk, since the evidence illustrates that the earlier such programmes are implemented, the greater their likelihood of having a positive impact (van Lier et al., 2009).

3.2.3 Peers' influences in the development of alcohol problem use and depressive symptoms in youth

As reported in paragraph 2.3, peer influences are one of the strongest risk factors for both depressive symptoms (Aseltine et al., 1998) and alcohol problem use in youth (Beitchman et al., 2005, Wills et al., 1989), thus having an implication in the development of both behaviours (Beitchman et al., 2005). Peer groups can play an important role in the initiation and progression of alcohol and other substance use among adolescents (Bates et al., 1995b, Curran et al., 1997, Van den Bree, 2005, van den Bree et al., 2005, van den Bree et al., 2004). Peers may influence adolescent drinking by serving as role models and influencing attitudes toward alcohol. According to a social learning approach (Bandura, 1986), friends are major role models among adolescents, and alcohol-consuming peers can provide opportunities for drinking and encourage heavy alcohol use (Akers, 1985, Bandura, 1986, Hawkins et al., 1992, Jessor et al., 1991, Kaplan et al., 1984, Oetting et al., 1986, Oetting et al., 1987). Although not yet sufficiently understood, alternative mechanisms suggest that adolescents may also selectively seek out or be sought out by deviant peers because they share common traits (e.g. similar drinking habits) (Deater-Deckard, 2001, Fergusson et al., 2002, Fowler et al., 2007b, Kandel, 1985). An alternative mechanism, partially or wholly causal, arises from processes of peer influence and socialization, which, through a variety of mechanisms, increase the susceptibility of young people who affiliate with deviant peers to substance problems (Fergusson et al., 1999a, Fergusson et al., 2002, Fergusson et al., 1999b).

In addition, it is becoming increasingly clear that peer influences, particularly influences of one's closest friends, can moderate the relationship between a risk-increasing trait such as risk taking tendency (Epstein et al., 2002) or conduct disorder (Glaser et al., 2010) and adolescent substance misuse.

Although the majority of studies focused more on peers' influences as a risk factor for alcohol problem use in adolescents (Barnes, 2009, Wood et al., 2004b), the protective role of strong bonding with peers for adolescents' mental health has also been observed for both depressive symptoms (Aseltine et al., 1998) and alcohol problem use (Verkooijen et al., 2007, Wills et al., 2004).

Peers have been commonly referred to as an important environmental risk factor for adolescent substance use and problem use. However, Fowler *et al.* found that genetic influences explained about 30% of the variation of twins' reports of their friends' alcohol use (Fowler et al., 2007b), which is compatible with a selection process, whereby genetically influenced characteristics of adolescents influence them in the selection of their peers (or vice versa, they are selected by their peers for these characteristics) (Bouchard, 1994). However, despite the documented strength of peer influences on adolescents' substance involvement and mood (with peer rejection and peer victimization being particularly associated with depression in young people) (Deater-Deckard, 2001, Fowler et al., 2007b, Kandel, 1985), there are no studies in the main scientific literature aiming to better understand the link between childhood depressive symptoms and alcohol problem use in early adolescence after taking into account the effects of peer influences as possible moderators in this relationship. One of the aims of my thesis is therefore to examine whether the relationship between childhood depressive symptoms and alcohol problem use in adolescence is influenced by peer factors.

Furthermore, peer influences would be more amenable for intervention than other risk factors (e.g. stressful events).

Interventions promoting a healthier social environment and reducing the risk represented by negative peer influences in the development of alcohol problem use among adolescents have the advantage of being more easily carried out in school settings, which represents one of the

main environments in which children and adolescents socialize, develop and maintain relationships with their peers (Waters et al., 2010), and also a privileged setting in which effective early forms of prevention and intervention targeted towards this age group may be set in place (Allott et al., 1999). As observed by Fletcher *et al.* in a recent review of school's effects on young people's substance use, there is a relationship between modifications of the school environment to increase student participation, improve peer relationships, and promote a positive school ethos and a reduction in students' drug and other substances use (Fletcher et al., 2008).

3.3 The analysis at a glance

The analysis of the association between childhood depression and alcohol problem use in early adolescence is conducted both in the complete sample of boys and girls and in boys and girls separately, and will be performed in three stages.

1) In the first stage of the analysis I investigate the direct association between the age 10 depressive symptoms and age 14 alcohol problem use in simple univariable models and the moderating effect of gender in such association (see Results in Chapter 7).

2) In a second stage of the analysis I include in such models relevant covariates chosen on the basis of the results of my bibliographic searches on non-genetic risk factors in common for both alcohol problem use and depressive symptoms in young people (see paragraphs 2.3, 2.4 and 2.5). Missing data in the covariates will be imputed (see Results in Chapter 8).

3) In the third and final stage of the analysis I will investigate the moderating effect of peers' influences at age 10 years and at age 14 years in the relationship between age 10 depressive symptoms and age 14 alcohol problem use, testing the interaction between age 10 depressive symptoms and age 10 or age 14 peers' influences in the univariable models of age

10 depressive symptom and age 14 alcohol problem use. If the analysis on the univariable models will provide evidence of an interaction between age 10 depressive symptoms and age 10 or age 14 peers' influences, this will be repeated in the multivariable model including the relevant imputed covariates (see Results in Chapter 9).

PART III

CHAPTER 4: METHODS USED TO IDENTIFY THE STUDY SAMPLE AND SELECT THE RELEVANT VARIABLES

4.1 The Avon Longitudinal Study of Parents and Children (ALSPAC)

4.1.1 History of the Avon Longitudinal Study of Parents and Children

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a large longitudinal population-based birth cohort study conducted in the Avon area in England, Great Britain. The original ALSPAC participants were 14,541 pregnant women living in one of three Bristol-based health districts in the former County of Avon with an expected delivery date between April 1991 and December 1992 (ALSPAC, 2010). These women were all invited to take part in the ALSPAC study (also called the 'Children of the '90s' study) and 85% accepted this invitation and gave informed consent to be involved in multiple evaluations per year during their pregnancies and the postnatal period. These pregnancies resulted in 14,062 live births, of which 13,971 babies were still alive at 12 months (Golding et al., 2001, Schuckit et al., 2008). These children turned 18 in the years 2009/ 2010. By the age of ~5.5 years questionnaires were also sent to children. In 2006 ALSPAC actively engaged with approximately 11,500 children and their families, of whom approximately 8,000 responded regularly to questionnaires and attended the annual "clinics" to take part in face-to-face assessments (Golding, 2006).

4.1.2 Representativeness of the ALSPAC sample

One of the major advantages that make the ALSPAC sample unique is that its socio-economic characteristics are broadly similar to those of the overall population of Great Britain, therefore enabling a better inference of the results obtained in the sample to the overall British population. The ALSPAC Study Team assessed the representativeness of the ALSPAC sample using the 1991 British census and comparing the socio-economic data of the whole British population of mothers with infants aged <1 year with the data of those residents in the Avon area. The socio-economic characteristics of the population of mothers with infants aged <1 year living in the whole area of Avon were then compared with those of the ALSPAC population of mothers completing questionnaires eight months post-delivery (ALSPAC, 2010). The results of these comparisons, which are available on the ALSPAC official website (ALSPAC, 2010), are reported in Table 4.1. When comparing the Avon area with the rest of Britain, it was observed that the mothers of infants in Avon were slightly more likely to live in owner-occupied accommodation and to have a car available to the household, and less likely to have one or more persons per room and be non-Caucasian than those in the rest of Britain; whereas comparing the ALSPAC sample with the Avon population of mothers of infants aged<1 year - similar to all studies where a representative sample has been attempted - a slight shortfall in the less affluent families and in ethnic minority mothers was observed (ALSPAC).

Table 4.1: Comparison of socio-economic characteristics of mothers of children aged<1 year either living in the whole of Great Britain or living in the Avon area or taking part in the ALSPAC study[1]

Socio-economic characteristic	Whole of Great Britain	Avon area	ALSPAC sample[#]
Owner Occupier	63.4%	68.7%	79.1%
1 + person/room	30.8%	26.0%	33.5%
Car in household	75.6%	83.7%	90.8%
Married couple	71.8%	71.7%	79.4%
Non-Caucasian mother	7.6%	4.1%	2.2%

[1]Table generated with data available on the ALSPAC website (ALSPAC, 2010).
[#] Assessment conducted when children were aged 8 months.

4.1.3 Objectives and advantages of the ALSPAC study

The ALSPAC study, one of the world's largest and most comprehensive cohort studies (Wise, 2001), aims to collect detailed data on the children as they progress from toddlerhood to adulthood with a particular focus on changes in anthropometry, attitudes and behaviour, fitness and other cardiovascular risk factors, bone mineralisation, allergic symptoms and mental health. One of the major advantages of ALSPAC is the availability of different sources of information; detailed data collection started early during pregnancy, and multi-rater information was obtained throughout the study from the mother and her partner, the child's main caregiver (usually the child's mother), the child him/herself, and other informants at certain stages, such as teachers. Information was obtained through self-administered questionnaires addressed to the children's mothers, their partners and the children themselves, data extraction from medical notes, and during annual face-to-face interviews with the children. From the time of the child's birth many different aspects of the child's environment have been monitored, and a wide range of phenotypic data collected. Moreover, the comprehensiveness of the ALSPAC approach with a total population sample unselected by disease status provides an adequate sample for performing statistical analysis and for avoiding spurious results (Ness, 2004).

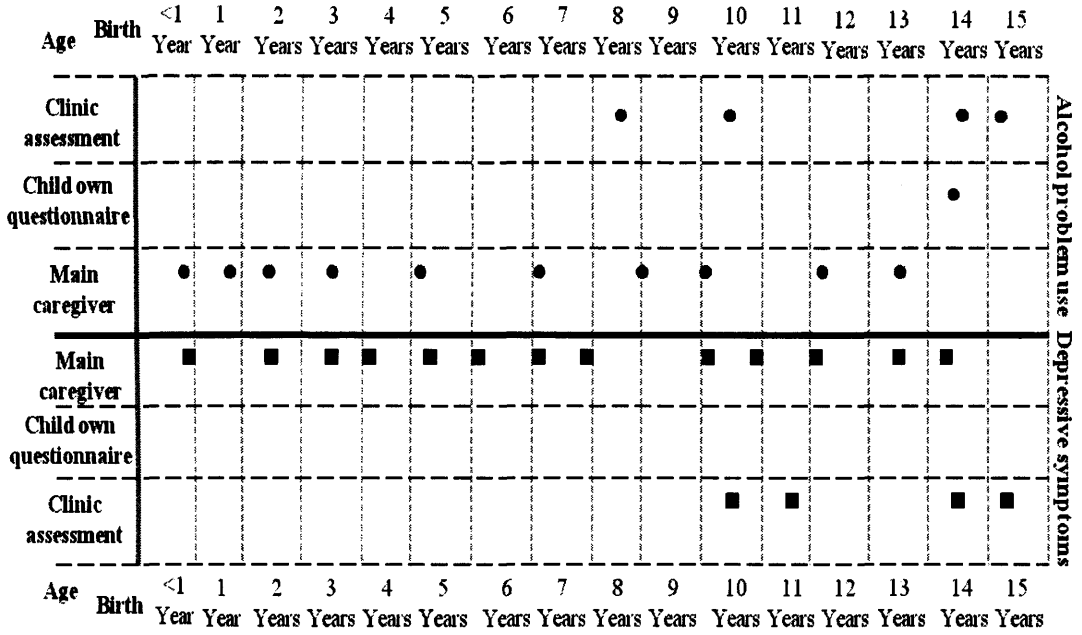
By virtue of being based in one geographic area, linkage to medical and educational records is relatively simple, and hands-on assessments of children were conducted in local facilities, reducing the time and costs necessary to access the clinics where face-to-face assessments were conducted at a minimum (Ness, 2004). From the age of 7 years onwards 7,000 and 8,000 children attended the annual "clinics" to take part in face-to-face assessments, which last for about three hours. Information obtained during clinics provide accurate data on several aspects of children's lives, such as symptoms of medical conditions, medications being taken, diet and lifestyle, attitudes and behaviour, and social and environmental features.

An additional advantage of the annual "clinics" over children-specific postal-administered questionnaires sent to their homes is the reduced risk that information is withheld or misrepresented by the children, a risk that can occur out of children's unwillingness to make their parents aware of any problems they may be facing (Golding et al., 2001).

4.1.4 Measures of alcohol problem use and depressive symptoms

Children/ adolescents' alcohol involvement and depressive symptoms have been assessed regularly (approximately yearly) during their toddlerhood, childhood and adolescence, with a first assessment on both early contact with alcoholic beverages and moodiness conducted shortly after birth. Information about alcohol use and depressive symptoms has been obtained using both child self-report as well as parental report and from age 10 also during face-to-face interviews ("clinics"). The only available DSM-IV diagnosis of MDD (DSM-IV AUDs were never diagnosed) was made when children were aged 7.5 years using the parent version of the Development and Well Being Assessment (DAWBA) (Goodman et al., 2000); 0.5% of the participant children were identified as meeting the criteria for a DSM-IV diagnosis of MDD (ALSPAC, 2010). Such prevalence is comparable with the one reported by another UK-based survey, the 1999 British Child and Adolescent Mental Health Survey, which indicated that 0.34% of 2,949 British children aged 8-10 years had a clinical diagnosis of MDD (Ford et al., 2003). Figure 4.1 displays the ages at which assessments of child /adolescent alcohol involvement or depressive symptoms were conducted and which informant provided the information.

Figure 4.1: Timeline of the measures in ALSPAC assessing children's alcohol involvement and depressive symptoms



4.1.5 Sample size

6,992 participants completed the questionnaire on depressive symptoms at age 10, while 5,038 participants completed the alcohol problem use questionnaire at age 14. 4,602 participants completed both assessments. Since I aimed to evaluate the depressive symptoms in childhood before the onset of alcohol use, it was necessary to have information about possible involvement with alcohol before the age of 10 years, which was obtained via "clinics" assessment or main caregiver report. Children were asked during the "clinics" at age 8 and age 10 whether they had ever consumed alcohol without parents' permission, and during the age 14 "clinic" it was assessed at which age they had their first whole alcoholic drink (i.e. a can of beer, a glass of wine, a bottle of "alcoholpop", a shot of spirits (vodka, gin, etc.)). The children's main caregivers were asked to describe their children's "drinking habit" before they reached the age of 10 years (when children were 103 months old), and specifically, for what concerned alcoholic beverages (wine, beer and spirits), whether their

children had alcohol more than once a week, once a week, less than once a week, or not at all and, if their children consumed alcohol, whether their children's alcohol consumption consisted of either an adult size full glass, a small size full glass, or if they simply tasted from other people's glasses. This information was used to remove all children from my sample who had consumed alcohol before or at age 10 (see results in paragraph 5.1).

4.2 Selection of variables

4.2.1 Outcome variable: Alcohol problem use

The variable to describe adolescents' alcohol use was derived from four items that had been extracted by Schuckit et al. (Schuckit et al., 2008) from the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) (Bucholz et al., 1994, Hesselbrock et al., 1999), which was administered to participants during the "Teen Focus 2" clinic (at age 14). Previous studies had found the SSAGA alcohol questions to have both higher test - retest reliabilities and validities compared to other standardized instruments such as the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) (Hesselbrock et al., 1999).

The four items used to assess adolescent alcohol involvement were: 1) frequency teenager had consumed any alcohol (such as cider, beer wine or spirits) without parents' permission in the past six months; 2) frequency teenager consumed whole alcoholic drinks (i.e. a can of beer, a glass of wine, a bottle of "alcoholpop," a shot of spirits (vodka, gin, etc.); not only sips) in the past six months; 3) largest number of whole drinks teenager had in 24-hour period in past six months; and 4) whether the adolescent had ever been intoxicated from alcohol (e.g. unable to talk or losing balance).

The interview was conducted by a trained psychologist who commenced the session with the following sentence: "Now I'm going to ask you some questions about your experiences with

alcohol in the past six months." Before asking questions 3 and 4, the psychologist explained: "The next set of questions can be with or without parents' permission, ok?"

Using the "POLYCHORICPCA" module implemented by Michael Kolenikov (Kolenikov, 2004) in STATA/IC v.10.1. for Windows (StataCorp, 2007), I created a new variable "alcohol problem use" that was based on the results of a principal component analysis (PCA) (Pearson, 1901) on a polychoric correlation matrix (Olsson, 1979, Pearson et al., 1922) of these four items (see results in paragraph 5.2.1). The PCA is a mathematical procedure that uses an orthogonal transformation to convert a set of observations of possibly correlated variables into a set of values of uncorrelated variables called principal components, and reduces the dimensionality of the data while retaining most of the variation in the data set (Jolliffe, 2002). It accomplishes this reduction by identifying directions, called principal components, along which the variation in the data is maximal. The data can be plotted in what is called a "scree plot," making it possible to assess the variation in the data set explained by each principal component and determine whether the variables can be grouped in fewer principal components (Ringner, 2008, Tabachnick, 1996). The "scree plot" reports the "eigenvalue" (which is an indicator of the amount of variation explained) of each principal component; traditionally, only principal components with "eigenvalue" ≥ 1 are considered to be worth analyzing (Gorsuch, 1983). I chose to use a polychoric correlation matrix because the items used to generate the new variable were ordinal (Wang et al., 2005). The new "alcohol problem use" variable that resulted from the PCA was subsequently divided into three levels, representing low, medium or high alcohol problem use. These were obtained by establishing cut-offs at the 55^{th} and 85^{th} percentiles for the "alcohol problem use" variable (see results in paragraph 5.2.1). Scores at or above the 85^{th} percentile were classified as high alcohol problem use, in accordance with previous studies that investigated alcohol misuse in 14-year-olds (Lintonen, 2001).

4.2.2 Predictor variable: Depressive symptoms

Depressive symptoms were measured using the Short Mood and Feelings Questionnaire (SMFQ) (Angold et al., 1995), administered to participants at age 10 during the "Focus @ 10" clinic. The final score "depressive symptoms" was divided in quartiles representing four levels of depression ("low," "medium," "high," and "very high") (see results in paragraph 5.2.2). A cut-off of 4 (corresponding to the "high depressive symptoms" level) identifies children with high risk of Depressive Disorder with sensitivity of 0.66 and specificity of 0.61 (Rhew et al., 2010), whereas a cut-off of 7 (corresponding to the "very high depressive symptoms" level) exhibits sensitivity of 76.5% and specificity of 67.7% in predicting SMFQ caseness 12 months later (McKenzie et al., 2011). The SMFQ is a short form of the Mood and Feelings Questionnaire (MFQ) (Angold et al., 1995, Angold, 1987), consisting of 13 self-report measures of childhood and adolescent depressive traits, for which criterion validity has been shown (Thapar et al., 1998). The details of the 13 items constituting the SMFQ are reported in Table 4.2. Results have revealed substantial correlations between the SMFQ, the Children's Depression Inventory (Saylor et al., 1984) and the Diagnostic Interview Schedule for Children depression scale (Costello et al., 1985, DeMaso et al., 2000). However, it is important to stress the fact that a high SMFQ score indicates the presence of a high number of depressive symptoms, but does not provide an actual diagnosis of DSM-IV MDD (APA, 2000), which is commonly assessed in children using the DAWBA test (Goodman et al., 2000).

The assessment of depressive symptoms was conducted in the following way: the children were given a series of envelopes on which were printed statements from the Short Mood and Feelings Questionnaire about how they might have been feeling or acting in the previous two weeks. These statements were first read out loud by the psychologist, after which the child

was asked to post the envelope into one of three boxes, which were marked "true," "sometimes," and "not at all." The children were told that they were going to play a posting game about how they had been feeling in the past two weeks and that there were no wrong or right answers. The child was reassured about confidentiality, and the psychologist sat behind the box reassuring the child that he/she could not see where the child was posting the envelopes.

Table 4.2: Items in the Short Mood and Feelings Questionnaire

	Question
1	I felt miserable or unhappy
2	I didn't enjoy anything at all
3	I felt so tired I just sat around and did nothing
4	I was very restless
5	I felt I was no good any more
6	I cried a lot
7	I found it hard to think properly or concentrate
8	I hated myself
9	I was a bad person
10	I felt lonely
11	I thought nobody really loved me
12	I thought I could never been as good as other kids
13	I did everything wrong

4.2.3 Covariates

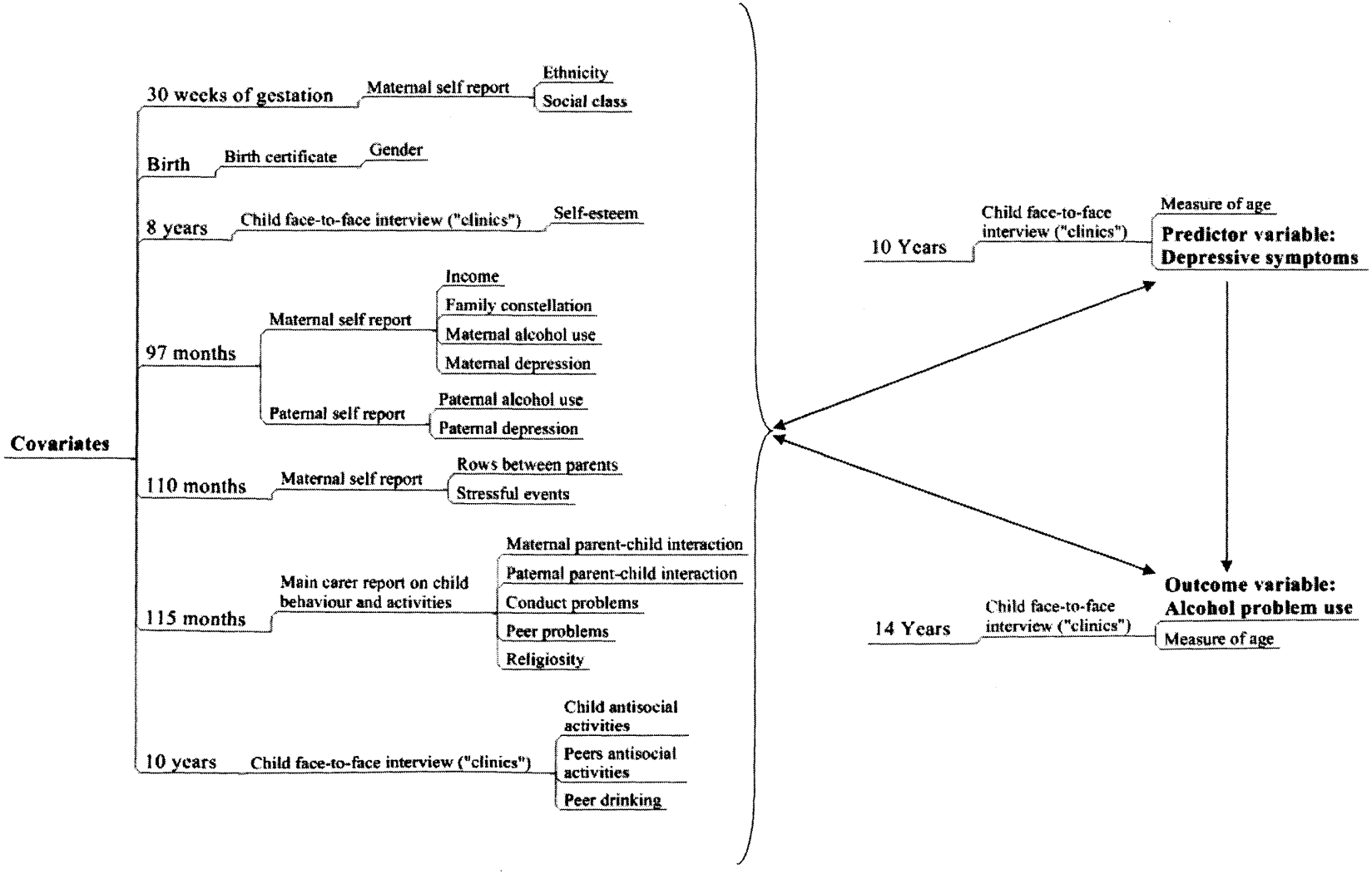
In the analyses described in the following chapters, the potentially confounding effects of a number of *a priori* selected covariates have been taken into account. These covariates were selected because of their well-established evidence for associations with depression and/or alcohol use in young people and were included in the models using theoretical framework proposed in paragraph 2.3, classifying the covariates into four major classes: "socio-demographic factors," "family environment," "social environment" and "personality and psychopathologies." Detailed information on these covariates will be provided in paragraphs

4.2.3.1, 4.2.3.2, 4.2.3.3 and 4.2.3.4, whereas their prevalence in my study sample will be described in paragraphs 5.2.3.1 and 5.2.3.2. As already reviewed in paragraph 4.1.3, two of the main advantages of the ALSPAC study are the availability of information as collected from a rich variety of sources and the regular frequency with which this information has been collected over time, which made it possible to study a range of relevant covariates that had been assessed at the same time, or close in time to my independent variable of interest (age 10 depressive symptoms). This allowed me to select the most informative source and the most proximal information for my analyses. All covariate data considered in the analyses described in the following chapters, with the exclusion of gender (which was obtained from birth certificates), came from one of four sources: 1) children/adolescents face-to-face interviews; 2) main caregiver (usually the mother) reports on offspring by postal-administered questionnaire; 3) maternal self-reports by postal-administered questionnaires; and 4) mother's partner reports on the partners themselves by postal-administered questionnaires (sent to the mothers to pass on to their partners, if they had one).

The covariates considered in my analyses provided information on the children's families (i.e., socio-demographic status and family environment) as well as children's personality and behavioral problems, social environment and stressful life events.

Most of this information was available between the ages of 8 and 10 for children, although some information was available at earlier stages. Figure 4.2 provides a graphic representation created with the program MindManager Pro 6 for Windows (Mindjet Corporation, 2007) of the exact ages of data collection for each variable.

Figure 4.2: Graphical representation of the variables included in my models, with information about the age they were collected and the source of information



4.2.3.1 Socio-demographic characteristics

- *Gender:* Information was obtained from birth certificates. Dichotomous variable coded as: "Boy"=0; "Girl"=1.

- *Age at interview:* The exact age of the child when he/she was interviewed was registered during the "Focus @ 10 clinic" (assessed at the beginning of the "clinic" by trained personnel, children aged 10 years) and during the "Teen focus 2 clinic" (assessed at the beginning of the "clinic" by trained personnel, children aged 14 years). Both variables, indicating the exact ages when the child was interviewed (named as "age 10" and "age 14" variables), were categorized in quintiles.

- *Ethnicity:* A dichotomous variable of whether the child had a Caucasian ethnic background or not (coded as: "Caucasian"=0; "Non-Caucasian"=1). This variable was derived by the ALSPAC Study Team from two questions in which the children's mother indicated her own group and the one of the biological father of the child (if known). The assessment was conducted through self-reported questionnaires administered to the mothers at 30 weeks of gestation.

- *Family social class:* This variable had been generated by the ALSPAC Study Team by coding parental occupations into six levels accordingly with the 1991 Office of Population Censuses & Surveys (OPCS) classifications (OPCS, 1991), with the 1st class being the highest. This was determined through maternal self-reports at 30 weeks of gestation.

- *Family income:* This variable provided a more specific and proximal measure of the family socioeconomic status than the "Family social class variable" described above. "Family income" variable used a measure of the average family income per week (<£100; £100 - £199; £200 - £299; £300 - £399; ≥£400) assessed by the children's mothers through the use of self-reported questionnaires when the child was aged 97 months.

- *Family constellation:* This variable was generated by me, distinguishing between two-parent families (either with both biological parents or one biological parent and one partner) and single-parent families. The variable was coded as: "Both biological parents"=0; "One biological parent and a partner"=1; "Single parent"=2. The information used was available from maternal self-report when the children were aged 97 months.

4.2.3.2 Family environment

- *Parental alcohol use:* The mothers and their partners (if present) reported on their own alcohol consumption. Alcohol consumption was self-reported by both parental figures when the children were aged 97 months. Both mother and her partner were asked to indicate the amount consumed during an average week of the following: a pub measure (1oz) of spirits; half a pint (¼litre) of beer or cider; a standard glass (125ml) of wine. These measures were selected as they correspond approximately to one British unit of alcohol (Drinkaware, 2010, Turner, 1990).

One British unit of alcohol is 10 ml of pure ethyl alcohol - the amount of alcohol the average adult can process within an hour, although the exact length of time differs depending on a person's body size (Turner, 1990). Summing the total amount of alcohol units corresponding to the indicated servings of beer (or cider), wine and spirits consumed during an average week, I obtained information on the daily alcohol units intake of the two parental figures.

- *Parent-child interaction:* The quality of mothers' and mothers' partners' parent-child interactions was measured with a questionnaire administered to the children's main caregivers, usually the mothers, when the children were aged 115 months. This questionnaire was adapted by the ALSPAC Study Team from the HOME inventory (Caldwell et al., 1984) and focused on 18 common parenting activities (see Table 4.3). The respondent (either the mother or the mother's partner) was asked about the frequency he/she was involved with each

of these activities with the child (possible answers were: "nearly every day," "2-5 times a week," "once a week," "less than once a week," "never") generating a final parenting score. The final score had been categorized by me in deciles.

Table 4.3: Parenting activities considered to assess parent-child interaction score

	Question
1	Parent baths or showers child
2	Parent makes things with child
3	Parent sings with child
4	Parent reads to or with child
5	Parent plays with toys with child
6	Parent cuddles child
7	Parent does active play with child
8	Parent takes child to park or playground
9	Parent puts child to bed
10	Parent takes child swimming, fishing or other activity
11	Parent draws or paints with child
12	Parent prepares food with child
13	Parent takes child to classes
14	Parent takes child shopping
15	Parent takes child to watch sports/football
16	Parent does homework with child
17	Parent has conversations with child
18	Parent helps child prepare things for school

- *Parental depression:* Information about parental depression (of both the child's mother and the mother's partner, if any) was assessed through self-report when children were aged 97 months. It was obtained with the self-reported Edinburgh Postnatal Depression Score (EPDS). The EPDS was developed specifically to screen for postnatal depression (Cox et al., 1987), and it is a sensitive screening instrument for the early detection of depressive symptoms as well as a sensitive diagnostic instrument for MDD (Affonso et al., 2000). The EPDS shows a strong correlation with other instruments to measure depression (Affonso et al., 2000, Beck et al., 2000), such as the Beck Depression Inventory (BDI) (Beck, 1995). The EPDS is composed of 10 items, each with possible response categories: "yes quite often," "sometimes," hardly ever" and "never". For a list of the items of the EPDS scale, see Table

4.4. Each question referred to the feelings of the mother (or her partner) in the past week. Although the measure was developed specifically for use with puerperal women, none of the ten items is specific to the post-natal experience. The principle feature of the scale that designates it as a postnatal scale is that it does not include somatic items because of the possibility of confounding somatic symptoms of depression with normal physiological symptoms at this time. This feature of the scale was a major factor in its selection for the ALSPAC study, which aimed to measure depression during pregnancy and the post-partum years. During pregnancy, there is also the possibility of confounding normal physiological symptoms with those of depression. A study of Murray and Carothers (Murray et al., 1990) found the measure to be acceptable to respondents, producing high completion rates with little evidence of response error. Assessment with this scale during pregnancy, the post-partum period and early parenthood has been validated against standardised psychiatric interviews with the results indicating the EPDS to have high sensitivity and specificity (Thorpe, 1993). The EPDS items are summed with the final score ranging between 0 and 30. I recoded the final score as a dichotomous variable (coded as: "Non-Depressed"=0; "Depressed"=1) using a cut-off of 9 of the final score. EPDS validation studies found that a cut-off score of 9 identifies probable Major Depression Disorder with a sensitivity between 78-100% and a specificity between 44-89% (Gibson et al., 2009).

Table 4.4: Items of the EPDS used to assess MDD in parents

	Question
1	I have been able to laugh and see the funny side of thing *(reversed score)*
2	I have looked forward with enjoyment to things *(reversed score)*
3	I have blamed myself unnecessarily when things went wrong
4	I have been anxious or worried for no good reason
5	I have felt scared or panicky for no very good reason
6	Things have been getting on top of me
7	I have been so unhappy that I have had difficulty sleeping
8	I have felt sad or miserable
9	I have been so unhappy that I have been crying
10	The thought of harming myself has occurred to me

- *Rows between parents:* One variable reporting the number of arguments and disagreements between parents in the previous three months, assessed through maternal self-report when children were aged 110 months, served as an estimate of the problems in the relationship between the two parents. Parental bonding, in fact, has been shown to impact the well being of the offspring (Shelton et al., 2008b, Skeer et al., 2009).

4.2.3.3 Social environment

Stressful events: Children's stressful life events were ascertained using a self-report questionnaire that was completed by the mothers when the children were aged 110 months. The mothers recorded whether they experienced any of a list of 20 upsetting events that may also have had an impact on the child. The items describing the upsetting events are reported in Table 4.5 and were adapted from a life event scale for obstetric groups (Barnett et al., 1983, Brown et al., 1978), and the use of this measure in children has been validated by other studies conducted in ALSPAC (Araya et al., 2009). Ideally, one would like to ask young children directly about such events and the impact on their lives, but this is rarely done for practical as well as ethical reasons (Araya et al., 2009).

The measure provided information on whether the event occurred when the child was 6-7 years old, when he/she was 8 years old, or in both times. Each event was therefore coded as "0" if did not happen, "1" if happened only once (when the child was either 6-7 years old or 8 years old) and "2" if the event happened in both times. A final score was generated by the ALSPAC Study Team by summing the number of occurrence of the list of the 20 upsetting events. The final score ranged from 0 to 6, with each value indicating the number of occurrences of upsetting events experienced by the child; those children who experienced ≥6 upsetting events were all grouped in the same top category ("6 or more upsetting events").

Table 4.5: Stressful events considered to assess the stressful life event score[1]

	Question
1	Husband/partner died since the study child's 6th birthday
2	One of mother's children died since the study child's 6th birthday
3	One of mother's children was ill since the study child's 6th birthday
4	Mother's husband/partner was ill since the study child's 6th birthday
5	Mother was divorced since the study child's 6th birthday
6	Mother was very ill since the study child's 6th birthday
7	Mother's husband/partner went away since the study child's 6th birthday
8	Mother and husband/partner separated since the study child's 6th birthday
9	Mother argued with husband/partner since the study child's 6th birthday
10	Mother's husband/partner was physically cruel to her since the study child's 6th birthday
11	Mother became homeless since the study child's 6th birthday
12	Mother's husband/partner was physically cruel to her children since the study child's 6th birthday
13	Mother was physically cruel to her children since the study child's 6th birthday
14	Mother attempted suicide since the study child's 6th birthday
15	Mother was convicted of an offence since the study child's 6th birthday
16	Mother's husband/partner was emotionally cruel to her children since the study child 6th birthday
17	Mother was emotionally cruel to her children since the study child's 6th birthday
18	Mother found a new partner since the study child's 6th birthday
19	A pet died since the study child's 6th birthday
20	Mother had an accident since the study child's 6th birthday

[1]Questions were repeated for the period when the child was aged 6-7 years and for the period when he/she was aged 8 years.

- *Peers' antisocial activities:* Peers' antisocial activities were assessed during the "Focus @ 10" Clinic (children aged 10 years), by means of a structured questionnaire that was adapted from a measure of self-reported antisocial behaviour for young children (Wolke et al., 1994) (see Table 4.6 for the complete list of items). The interview followed a certain order, where children were first asked if their friends had partaken in a specific activity in the past six months, after which they were asked if they themselves have taken part in this same activity in the past six months (see paragraph 4.2.3.4 for specific information on the covariate describing children's own antisocial activities). 12 activities in total were enquired about. The children were told that they were going to be asked some questions about whether their friends or they themselves had done something that could have gotten them into trouble.

Confidentiality of the children's answers was assured and they were informed that everybody was asked the same questions.

In my analyses I used the "peers' antisocial activities" variable both as covariate and as moderating variable ("age 10 peers' antisocial behaviour," see paragraph 4.2.4.1). The questionnaire included questions about peers or children themselves smoking cigarettes and cannabis, along with alcohol use without parental permission (see Table 4.6). However, when the "peers' antisocial activities" variable was considered as a covariate, the question about friends having consumed alcohol without parental permission was excluded from the final score as it was considered a separate covariate (see below), whereas when the "peers' antisocial activities" variable was used to generate the moderating variable "age 10peers' antisocial behaviour," the question about friends having consumed alcohol without parental permission was included in the final score (see paragraph 4.2.4.1).

Table 4.6: Items assessing peers' antisocial activities

	Question
1	Friends skived off school
2	Friends told off by a teacher
3	Friends destroyed something for fun
4	Friends set fire to something
5	Friends stolen something
6	Friends got into fights
7	Friends have been cruel to an animal
8	Friends smoked cigarettes
9	Friends been in trouble with the Police
10	Friends consumed alcohol without parental permission[#]
11	Friends been offered illegal drugs
12	Friends smoked cannabis

[#] Question was excluded when "peers' antisocial activities" variable was considered as a covariate and included when it was used to generate "peer pressure to engage in antisocial activities" variable (see paragraph 4.2.4.1).

- *Religiosity:* The frequency with which the child attended a place of worship (response categories: "yes, often," "yes sometimes," "not at all") was used as a measure of the religious

conservatism of the children's rearing environment. The question was asked to the main caregiver when the child was aged 115 months.

- *Peers' alcohol drinking (age 10):* A question about whether friends had ever consumed alcohol without parent permission in the past six months, extracted from the peers antisocial activities questionnaire (see above) (Wolke et al., 1994), was used to ascertain peers' drinking. Children were asked about peers' alcohol involvement during the "Focus @ 10 clinic" (children aged 10 years).

4.2.3.4 Personality and psychopathologies

- *Conduct problems and peer problems:* Child behavioural problems such as conduct problems and peer problems were ascertained using the Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1997). The child's main caregiver (usually the mother) completed the parental version of the SDQ for his/her child when the child was aged 115 months. The SDQ is a valid and reliable measure (Goodman, 2001) comprising of five subscales: "hyperactivity," "conduct problems," "emotional symptoms," "peer problems," and "prosocial behaviour." Subscales are constituted of five items each and scores for each subscale range between 0 and 10. I divided the scores of the "conduct problems" and "peer problems" subscales into tertiles, in accordance with other studies conducted in ALSPAC defining behavioural problems (with the exception of prosocial behaviour) as the highest tertile for each subscale (Wiles et al., 2006). The items constituting the SDQ conduct problem and SDQ peers problem scales are reported in Table 4.7. The main caregiver was asked whether, considering his/ her child's behaviour in the past six months, each statement was either "not true," "somewhat true" or "certainly true."

Table 4.7: Items of the SDQ used to assess conduct problems and peer problems in children

	Question (conduct problems)
1	Child has often had temper tantrums or hot tempers in past 6 months
2	Child is generally obedient, usually has done what adults request in past 6 months *(reversed score)*
3	Child often fights with other children or bullies them in past 6 months
4	Child often lies or cheats in past 6 months
5	Child steals from home school or elsewhere in past 6 months
	Question (peer problems)
1	Child is rather solitary, tends to play alone in past 6 months
2	Child has at least one good friend in past 6 months *(reversed score)*
3	Child is generally liked by other children in past 6 months *(reversed score)*
4	Child is picked on or bullied by other children in past 6 months
5	Child gets on better with adults than with other children in past 6 months

- *Child antisocial activities:* Child antisocial activities were assessed by a review of the number of antisocial activities the child had partaken in during the past six months using a short structured interview adapted from a measure of self-reported antisocial behaviour for young children (Wolke et al., 1994), which was administered to the children by trained psychologists during the "Focus @ 10 clinics" (children aged 10 years). The questions used to ascertain children's antisocial behaviour are the same as those used to assess the antisocial behaviour of their peers and are listed in Table 4.6.

Because the aim of this study is to investigate the relationship between age 10 depressive symptoms and later development of alcohol problem use, children who answered positively to the question on whether they had ever (not only in the past six months) consumed alcohol without parental permission were excluded from the study sample (see paragraph 4.1.5 for further details on the exclusion criteria used to select the study sample).

- *Self-esteem:* Self-esteem was measured when children were aged 8 years during the "Focus @ 8 clinic" using a shortened (12-item) form of Harter's Self Perception Profile for Children (Harter, 1985). The shortened measure includes the global self-worth and scholastic competence subscales. For the purpose of my analyses, only the global self-worth subscale was used. The task was conducted by a trained psychologist using post-boxes and envelopes.

Each envelope corresponded to a single item comprising two statements, one in blue writing, and one in red; for example, "Some children are often unhappy with themselves" (in blue) and "Other children are pretty pleased with themselves" (in red). All the statements of the global self-worth scale are shown in Table 4.8. There were two post-boxes (one blue, one red), and on each post-box, there were two slots: "Sort of true for me" and "Really true for me." Each statement was read aloud to the child, who had to decide whether he or she was more like the child in the blue writing or in the red (and consequently, whether to post the envelope into the blue or red post box), and then whether the relevant statement was "sort of true for him/her" or "really true for him/her" (and consequently, whether to post the envelope into the "sort of true for me" or "really true for me" slot). This allowed the child to answer sensitive questions without the member of staff being able to see what the answers were. The child was also guaranteed confidentiality. The child's responses were coded as follows: "blue, really true for me"=1; "blue, sort of true for me"=2; "red, sort of true for me"=3; "red, really true for me"=4. I categorized the final score in deciles, with a higher score corresponding to higher self-esteem.

Table 4.8: Items assessing children's global self-worth self-esteem

	Statement "blue"	Statement "red"
1	Some children are often unhappy with themselves	Other children are pretty pleased with themselves
2	Some children don't like the way they are living their life	Other children do like the way they are living their life
3	Some children are happy with themselves as a person	Other children are often not happy with themselves as a person
4	Some children like the kind of person they are	Other children often wish they were someone else
5	Some children are very happy being the way they are	Other children wish they were different

4.2.4 Moderating variables: Peers' influences

Mediation and moderation are two theories for refining and understanding a causal relationship; however the terms mediator and moderator have often been misused and

misunderstood in social and psychological research, hence a clarification is needed (Baron et al., 1986, Wu, 2008).

The classical reference paper of Baron *et al.* (Baron et al., 1986) defines a moderator variables as "a qualitative (e.g., sex, race, class) or quantitative (e.g., level of reward) variable that affects the direction and/or strength of the relation between an independent or predictor variable and a dependent or criterion variable" and a mediator variables as a "variable that accounts for the relation between the predictor and the criterion. Mediators explain how external physical events take on internal psychological significance (Baron et al., 1986)."

As reviewed in paragraph 3.2.3, one of the aims of my thesis is to examine whether the relationship between childhood depressive symptoms and alcohol problem use in adolescence is moderated by peer influences. I intend to address this issue investigating how the relationship between age 10 depressive symptoms and age 14 alcohol problem use is moderated by the combined effect of two peer influences: child's bonding with his/her peers and peer's risky behaviour.

Child's bonding with his/her peers may be considered both as a risk or a protective factor for alcohol engagement in young people, as some studies have found that peers' social support and affiliation with peers decreased substance use in adolescents (e.g. (Barnes, 2009, Wood et al., 2004b)), while other studies reported the opposite (e.g. (Verkooijen et al., 2007, Wills et al., 2004)). Both child's bonding with his/her peers and peers' risky behaviour were assessed at age 10 and at age 14 years through face-to-face interviews. Peers' risky behaviour was described either by a variable indicating peers' antisocial activities (at age 10 years) or by a variable indicating peers' alcohol drinking (at age 14 years) (see paragraphs 4.2.4.1 and 4.2.4.2 for further details). Correlations between the two variables assessing child's bonding with his/her peers and the two variables assessing peers' risky behaviour were calculated using the Pearson product-moment correlation test (for child's bonding with his/her peers

variables) (Pearson, 1901) and the Spearman's rank correlation test (for peer's risky behaviour variables) (Spearman, 1904), ran respectively by the "spearman" and the "correlate" commands in STATA/IC v. 10.1. for Windows (StataCorp, 2007) (the prevalence of the four variables in the study sample and results of the correlation tests are described in paragraph 5.2.4).

4.2.4.1 Child's bonding with his/her peers

A measure describing "child's bonding with his/her peers" was assessed on two occasions, during the face-to-face interview at age 10 years ("Focus @ 10 clinic") and during the face-to-face interview at age 14 years ("Teen Focus 2 clinic"), using six questions derived from a shortened version of the Friendships Questionnaire developed for the Cambridge Hormones and Moods Project (Goodyer et al., 1990, Goodyer et al., 1989). A trained psychologist told the children that they were going to be asked some questions about their friends (not just those at school) and their relationship with them; confidentiality was strongly emphasized. Details of the items used to ascertain bonding with peers are reported in Table 4.9.

Table 4.9: Items assessing children's bonding with their peers

	Question
1	Child is happy with the number of friends he/she has
2	Child sees close friends outside school
3	Friends understand child
4	Child can talk to friends about his/her problems
5	Child is overall happy with friends

4.2.4.2 Peers' risky behaviour

Peers' risky behaviour was described by a variable indicating peers' antisocial activities at age 10 years and by a variable indicating peers' alcohol drinking at age 14 years.

To describe peers' risky behaviour at age 10 years, I chose to use a general measure of peer's antisocial activities rather than a specific measure of peer's alcohol drinking because of the very low prevalence of alcohol consumption among children's peers at that age (see Table 5.3); moreover a number of studies conducted observed a very strong correlation between alcohol drinking and other antisocial activities in young people (Duncan et al., 2002, Young et al., 2008).

Peers' antisocial behaviour was assessed during the "Focus @ 10" Clinic (children aged 10 years), by means of a structured questionnaire that was adapted from a measure of self-reported antisocial behaviour for young children (Wolke et al., 1994) (see paragraph 4.2.3.3 for details and Table 4.6 for the complete list of items). The questionnaire included questions about peers' cigarette and cannabis smoking and alcohol use without parental permission (the difference between the "age 10 peers' antisocial behavior" variable described here and the variable defined as "peers' antisocial activities" described in paragraph 4.2.3.3 is that in this case the response to this latter question was included in the final score).

The second peers' risky behavior variable, peers' alcohol drinking, was assessed by a trained psychologist during the "Teen Focus 2 clinic" at age 14 years, when adolescents indicated how often in the past 6 months his/her friends consumed alcohol without parental permission. The specific question was: "Have any of your friends ever consumed in the past 6 months alcohol like beer cider, wine or spirits without their parents' permission?" Possible answers were: "never," "1-3 times," "≥4 times," and "once per week."

CHAPTER 5: DESCRIPTION OF THE STUDY SAMPLE AND OF THE SELECTED VARIABLES

5.1 Study sample

6,992 participants completed the questionnaire about depressive symptoms at age 10 (mean age of completion 10.64; *SD* 0.26) while 5,038 participants completed the alcohol problem use questionnaire at age 14 (mean age of completion 13.83; *SD* 0.21). 4,602 participants (32.7% of the original ALSPAC sample of 14,062 live births) completed both assessments. For 382 of these youngsters self-and/or parental report indicated they already consumed alcohol at or before age 10 years.

With regard to self-report, 445 children answered affirmatively when they were asked at the "clinics" at age 8 and age 10 whether they had ever consumed alcohol without parents' permission, and 79 children indicated at the age 14 "clinic" that they had consumed a whole alcoholic drink (meaning that they had at least a can of beer, a glass of wine, a bottle of "alcoholpop," a shot of spirits (vodka, gin, etc.)) before the age of 10 years.

Regarding parental report, parents of 382 children indicated that their child's "drinking habit" before age 10 (at 103 months of life) for what concerned alcoholic beverages (wine, beer and spirits) was to have, either more than once a week, once a week, or less than once a week, a full adult size or small size glass of alcoholic beverage. In total (because for 129 subjects more than one assessment indicated alcohol use before the age of 10 years), 777 children were identified as having consumed whole alcoholic drinks before the age of 10 years. Of these 777 participants, 382 also completed the questionnaire about depressive symptoms at age 10 and the questionnaire about alcohol problem use at age 14. Because, as explained in paragraph 4.1.5, the aim of this thesis is to examine the longitudinal relationship between childhood depression and adolescent alcohol problems, these youngsters were excluded from

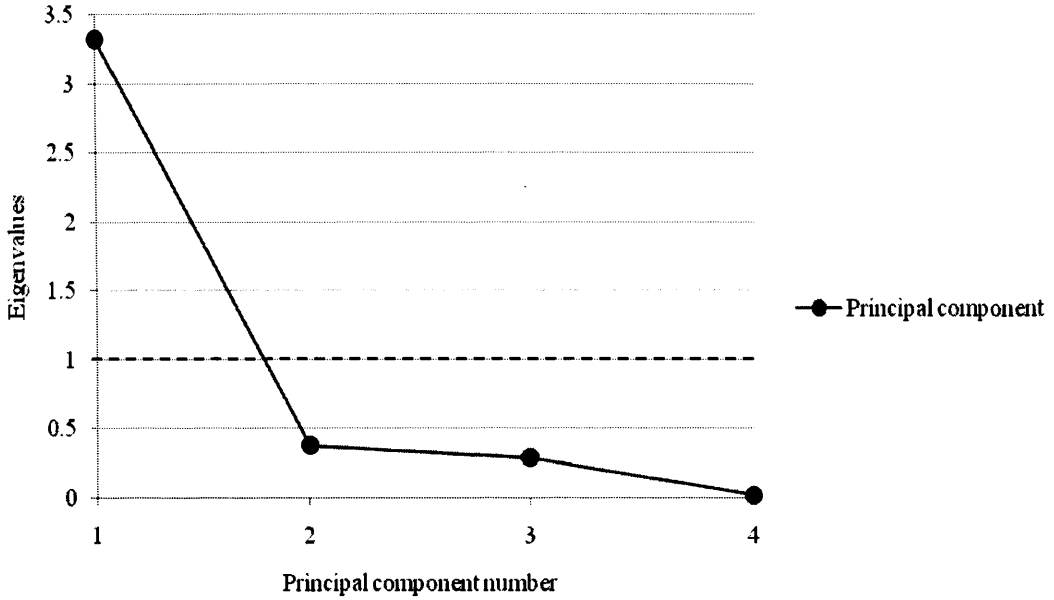
the analysis, leaving a sample size of 4,220 participants, 30% of the original ALSPAC sample of 14,062 live births.

5.2 Selection of variables

5.2.1 Outcome variable: Alcohol problem use

The four SSAGA (Bucholz et al., 1994, Hesselbrock et al., 1999) indicators assessed when children were 14 years old (mean age at assessment 13.8 years, *SD*=0.2, see Table 5.1 for their frequency of endorsement in the 4,220 participants included in my study sample) correlated between r=+0.68 to r=+0.91 and were combined into an "alcohol problem use" factor, based on the results of a principal component analysis (PCA) (Pearson, 1901) (see paragraph 4.2.1 for further details on the PCA). The derived variable "alcohol problem use" (*M*=-2.16, *SD*=0.70) was the first of four principal components generated by PCA, the only component with "eigenvalue" ≥1 ("eigenvalue"=3.32, see the "scree plot" displayed in Figure 5.1), accounted for 83% of the variation and its score ranged between -2.66 and 1.00. This variable was positively skewed (skewness=1.57); as 54.5% of the participants scored -2.66 (the lowest score). The greatest contribution to the "alcohol problem use" derived variable was given by the alcohol problem use indicators 1 ("consumed alcohol without parental permission") and 3 ("largest number of whole drinks in 24 hour-period") (covariance matrix range: -0.77 to +0.26), whereas indicators 2 ("frequency of whole alcoholic drinks") and 4 ("ever been intoxicated from alcohol") contributed less (covariance matrix range: -0.59 to +0.24). In accordance with previous studies (Lintonen, 2001), the outcome variable was categorized in "low," "medium," or "high" alcohol problem use, with cut-offs at ~55th and ~85th percentiles.

Figure 5.1: "Scree plot" of first four principal components generated by the PCA[1]



[1]Only principal components with "eigenvalue" ≥1 are retained.

5.2.2 Predictor variable: depressive symptoms

In accordance with previous studies (Rhew et al., 2010), the predictor variable, SMFQ measure of depressive symptoms (see paragraph 4.2.2; *M*=4.05, *SD*=3.53, minimum score=0, maximum score=23, skewness=1.43) (Angold et al., 1995) assessed when children were 10 years old (mean age at assessment 10.6 years, *SD*=0.2) was divided in quartiles resulting in four possible levels of depressive symptoms: "low depressive symptoms" (SMFQ score of 0 to 1); "medium depressive symptoms" (SMFQ score of 2 to 3); "high depressive symptoms" (SMFQ score of 4 to 6); and "very high depressive symptoms" (SMFQ score of ≥7). At age 10 years, 26.8% of the 4,220 participants included in my study sample experienced high depressive symptoms, and 18% of them experienced very high depressive symptoms (see Table 5.1).

Table 5.1: Prevalence of alcohol problem use and depressive symptoms in the study sample

Variable	Categories	%
Consumed alcohol without parental permission*	Never	79.2
	1-3 times	14.8
	>4 times	4.8
	once per week	1.2
Frequency of whole alcoholic drinks*	Never	58.2
	<Monthly	33.9
	<Twice a month	4.1
	<Weekly	1.9
	<Twice a week	1.5
	≥Twice a week	0.3
Largest number of whole drinks in 24 hour-period*	0 drinks	57.5
	1-2 drinks	24.2
	3-4 drink	10.3
	≥5drinks	8.1
Ever been intoxicated from alcohol*	Yes	93.8
	No	6.2
Alcohol problem use[A]	Low	54.2
	Medium	31.0
	High	14.9
Depressive symptoms[B]	Low	25.7
	Medium	29.6
	High	26.8
	Very high	18.0

* Four items used to construct the "alcohol problem use" variable (A).
[A] The outcome variable was the first of three components generated by the principal component analysis. To define alcohol problem use I categorized that variable in "low," "medium," or "high" alcohol problem use.
[B] The predictor variable was divided in quartiles obtaining four possible levels of depressive symptoms: "low," "medium," "high," and "very high."

5.2.3 Covariates

Most of the information provided by the covariates included in my analyses was collected when children were aged 8-10 years. Figure 4.3 gives a graphic representation of the exact ages of data collection for each covariate. Details concerning the assessment used and the collection procedure for each covariate are reported in paragraph 4.2.3.1 for covariates describing children's socio-demographic characteristics, in paragraph 4.2.3.2 for covariates describing children's family environment, in paragraph 4.2.3.3 for covariates describing

children's social environment and in paragraph 4.2.3.4 for covariates describing children's personality and psychopathologies.

5.2.3.1 Socio-demographic characteristics

Table 5.2 reports the prevalence of the socio-demographic information for the study sample of 4,220 children. With the exclusion of gender and of the age measures at age 10 years and at age 14 years, all the other socio-demographic covariates contained missing data. Results indicated that slightly over half of the participating children were female (52.2%). The majority of the retained sample of children (96.5%) came from a Caucasian ethnic background, 89.4% lived with both biological parents and 16.2% belonged to the highest social class. Since the socio-demographic characteristics measured in the original ALSPAC sample when children were aged 8 months (which were used to assess the representativeness of the ALSPAC sample with respect to the whole British population, see paragraph 4.1.2 and Table 4.1) are not the same socio-demographic characteristics assessed in my study sample (see Table 5.2), it was impossible to precisely assess the representativeness of my study sample with respect to the original ALSPAC sample. However, it was possible to give an estimate of the differences between my study sample and the original ALSPAC sample if three assumptions are made. These assumptions are: 1) that all the children's biological parents were cohabiting when the children were aged 8 months; 2) that the mother's ethnic background was equivalent to the ethnic background of her child; and 3) that all the families not owning a car belonged to the lowest social class.

Bearing in mind the limits imposed by these assumptions, it was possible to compare my study sample with the original ALSPAC sample when children were aged 8 months. Results of this comparison indicate that in my study sample there was a further shortfall in the representativeness of families not composed by both biological parents (20.6% in the original

ALSPAC sample versus 10.6% in my study sample) and of families belonging to the lowest social class (10.2% in the original ALSPAC sample versus 2.1% in my study sample), similar to all studies where a representative sample has been attempted (ALSPAC). However, this shortfall was not observed for non-Caucasian families, which instead appeared being more represented in the study sample (3.5%) than in the original ALSPAC sample (2.2%).

Table 5.2: Socio-demographic characteristics of the study sample

Covariate	Categories	N	%
Gender*	Females	4220	52.2
	Males		47.8
Covariate	**Measure unit**	**N**	***M* (*SD*)**
Age10[A]*	Years	4220	10.6 (0.2)
Age14[B]*	Years	4220	13.8 (0.2)
Covariate	**Categories**	**N**	**%**
Ethnicity	Caucasian	4056	96.5
	Non Caucasian		3.5
Social class	I	3995	16.2
	II		34.2
	III Non Manual		13.4
	III Manual		26.1
	IV		8.0
	V		2.1
Income per week	<£100	3294	1.4
	£100 - £199		7.1
	£200 - £299		15.1
	£300 - £399		19.9
	≥£400		56.5
Family constellation	Both biological parents	3524	89.4
	1 Biological parent & Partner		4.9
	Single Parent		5.7

* Absence of missing data.
[A] Age of assessment of depressive symptoms; variable categorized in quintiles.
[B] Age of assessment of alcohol problem use; variable categorized in quintiles.

5.2.3.2 Family environment, social environment, and personality and psychopathologies

The frequency of endorsement in the 4,220 participants included in my study sample of the covariates belonging to family environment, social environment and personality/ psychopathologies domains is reported in Table 5.3. All the covariates contained missing

data, with the highest rate of "missingness" being observed for the variables describing mother's partner's alcohol use (3,149 participants with missing information) and mother's partner's depression (2,146 participants with missing information).

Considering the family environment domain, the average parental daily alcohol consumption was 0.7 alcohol units for the mothers and 1.8 alcohol units for their partners. With respect to parental depressive symptoms, 21.2% of mothers and 11.2% of their partners were classified as being possibly depressed (EPDS score>9) (Affonso et al., 2000, Gibson et al., 2009) when children were aged 97 months and, when children were aged 110 months, 4.4% of the children's families were experiencing a very high level of conflict between partners (>13 rows occurred between the two partners in the previous three months).

Concerning the social domain, 4.2% of children in the study sample experienced>6 upsetting stressful events between the ages of 6 - 8 years and 18.9% of children were often attending a place of worship when they were aged 115 months. At age 10 years 6.2% of children in the study sample reported that in the previous six months their friends had partaken in ≥3 antisocial activities, whereas 3.0% of children reported that in the same period their friends had consumed alcohol without parental permission.

Finally, considering the personality and psychopathologies domain, 13.0% and 25.3% of children in the study sample were rated by their main caregiver at age 115 months as having respectively SDQ conduct problems and SDQ peer problems (third tertile of the SDQ subscale score) (Goodman, 1997, Wiles et al., 2006), whereas at age 10 years 0.2% of the children in the study sample self-reported having partaken in ≥3 antisocial activities.

Table 5.3: Prevalence of all the covariates belonging to the family environment, social environment and personality & psychopathologies domains

Factor Domain	Covariate	Measurement Unit	N	*M* (*SD*)
Family environment	Mother's alcohol use[A]	Daily alcohol units	1993	0.7 (0.9)
	Mother's partner's alcohol use[A]	Daily alcohol units	1071	1.8 (1.9)
	Mother-child interaction[B]	Parenting score	3454	39.3 (8.4)
	Mother's partner's-child interaction[B]	Parenting score	3573	27.2 (9.9)
	Covariate	**Categories**	**N**	**%**
	Mother's depression	No Depression	3593	78.8
		Possible Depression		21.2
	Mother's partner's depression	No Depression	2074	88.8
		Possible Depression		11.2
	Rows between parents[C]	Never	3394	16.4
		1-3 times		51.0
		4-7 times		20.8
		8-13 times		7.3
		>13 times		4.4
Social environment	Child stressful events[D]	No events	3301	26.9
		1 event		28.4
		2 events		19.5
		3 events		11.3
		4 events		6.4
		5 events		3.3
		≥6 events		4.2
	Peers' antisocial activities[E]	No activities	3795	63.4
		1 activity		22.4
		2 activities		8.0
		≥3 activities		6.2
	Religiosity (attends place of worship)[F]	Never	3627	49.4
		Sometimes		31.7
		Often		18.9
	Peers' alcohol drinking[G]	Peers do not drink	3994	97.0
		Peers drink		3.0
Personality and psycho-pathologies	Child conduct problems[H]	1st tertile	3587	40.5
		2nd tertile		46.5
		3rd tertile		13.0
	Child peer problems[H]	1st tertile	3494	49.7
		2nd tertile		25.0
		3rd tertile		25.3
	Child antisocial activities[E]	No activities	4146	88.6
		1 activity		9.4
		2 activities		1.8
		≥3 activities		0.2
	Covariate	**Measurement Unit**	**N**	***M* (*SD*)**
	Child self-esteem[B]	Self esteem score	3611	19.4 (3.3)

[A] Measure accounted for alcohol unit from beer, wine and spirits consumed during an average week.
[B] Variable categorized in deciles.
[C] Number of arguments and disagreements between parents in the previous three months was used as an estimate of the bonding of the relationship between the two parents.
[D] The measure provided information of whether each event occurred when the child was 6-7 years old, when he/she was 8 or in both occasions.
[E] The questionnaire included questions about cigarettes and cannabis smoking in previous 6 months.
[F] Used as a measure of the religious conservatism of the children's rearing environment.
[G] Question extracted from the peers' antisocial behaviour questionnaire at age 10 years.
[H] Main carers completed the parental version of the SDQ for their child.

5.2.4 Moderating variables: peers' influences

At age 10 years 6.6% of children in the study sample reported that their friends had partaken in ≥3 antisocial activities in the previous six months (note that this variable is different from the covariate "peers' antisocial activities" reported in Table 5.3, as in this case the response to the question on whether friends had ever consumed alcohol without parental permission was not considered separately but was instead included in the final "age 10 peers antisocial behaviour score"), whereas at age 14 years 7.5% of children in the study sample reported that their friends had consumed alcohol without parental permission at least once per week in the previous six months. The correlation between the two measures was Pearson's rho=0.13, $p<0.001$ (see Table 5.4).

Concerning the measures of children's bonding with their peers (minimum score 0, maximum score 8), the average bonding score at age 10 years was slightly lower than the average bonding score at age 14 years (M=6.1, SD=1.9 and M=6.6, SD=1.8 respectively) and the correlation between these two variables was Spearman's r=0.27, $p<0.001$ (see Table 5.4). My choice of using two different measures to assess peers' risky behaviour (i.e. age 10 years peer's antisocial activities and age 14 years peer's alcohol drinking) was appropriate, since many studies found a strong association between these two measures in young people (Duncan et al., 2002, Young et al., 2008); moreover my correlations results suggest that the correlation between the measure of peers' antisocial behaviour and peers' alcohol drinking is comparable to the correlation between the two measures of children's bonding with their peers at age 10 and 14 years, which were assessed using an identical questionnaire (Goodyer et al., 1989) (see paragraph 4.2.4.1). The correlation coefficients between the two pairs of variables were in fact both comprised between 0.1 and 0.3 (Westgard, 1999).

Table 5.4: Frequencies of the peers' influences variables in the study sample and correlations between the two measures of child's bonding with his/her peers and the two measures of peers' risky behaviour

Variable	Categories	N	%	Spearman's correlation†
Age 10 peers' antisocial behaviour[A B]	No activities	3738	63.4	rho=0.13 p<0.001
	1 activity		21.9	
	2 activities		8.1	
	≥3 activities		6.6	
Age 14 peers' alcohol drinking[B]	Never	3795	58.8	
	1-3 times		23.6	
	≥4 times		10.1	
	Once per week		7.5	

Variable	Measurement Unit	N	*M* (*SD*)	Pearson's correlation
Child bonding with peers at age 10 years[C]	Bonding score	4150	6.1 (1.9)	r=0.27 p<0.001
Child bonding with peers at age 14 years[C]	Bonding score	4194	6.6 (1.8)	

† Statistically significant results are shaded.
[A] Variable included information on whether friends had consumed alcohol without parental permission in the previous six months.
[B] Variables describing peers' risky behaviour.
[C] Minimum score 0, maximum score 8.

PART IV

CHAPTER 6: METHODS AND PROCEDURES FOR THE ANALYSIS OF THE TEMPORAL ASSOCIATION BETWEEN DEPRESSIVE SYMPTOMS AT AGE 10 YEARS AND ALCOHOL PROBLEM USE AT AGE 14 YEARS

6.1 Methods: statistical models

6.1.1 Regression model: Generalized Ordered Logistic model

In my study sample, the relationship between depressive symptoms at age 10 years and alcohol problem use at age 14 years was analyzed using Generalized Ordered Logistic regression models (GOLOGIT). GOLOGIT regressions were performed using the "GOLOGIT2" module (Williams, 2006) implemented in STATA/IC v.10.1. for Windows (StataCorp, 2007).

The GOLOGIT2 module is a user written program by Richard Williams (Williams, 2006), and it is inspired by Vincent Fu's GOLOGIT routine (Fu, 1998) for STATA (StataCorp, 2007).

A number of articles and books have described in great detail the statistical and mathematical principles of the GOLOGIT model, which are summarized in the papers cited here (Long et al., 2006, Norusis, 2005, Peterson et al., 1990, Williams, 2006). However, as Fu notes (Fu, 1998), researchers have given the GOLOGIT model brief attention (Clogg, 1994) but have generally passed over it in favour of more well-known models, such as the Ordered Logistic Regression model (OLOGIT) or the Multinomial Logistic Regression model (MLOGIT).

The default GOLOGIT results are similar to the ones of a binary logistic regression. When number of categories of the dependent variable is=2, the GOLOGIT model is equivalent to a

single logistic regression model. When the number of categories of the dependent variable are>2, the model becomes equivalent to a series of binary logistic regressions (the number of logistic regression equations being equivalent to the number of categories of the dependent variable -1) where the categories of the dependent variable are combined (Williams, 2006).

In the analyses I conducted, "alcohol problem use" at age 14 years was the outcome variable (AKA the dependent variable); since there were three possible levels of "alcohol problem use" ("low," "medium," and "high," see Table 5.1), running GOLOGIT2 would be comparable to running two equations of two binary logistic regression analyses. In these two equations the dependent variable was coded as follows: in the first one the category "low (L)" alcohol problem use was coded as=0 and the combined categories "medium (M)" & "high (H)" alcohol problem use were coded as=1 (this equation will be defined from now onwards as "L versus M&H equation"), whereas in the second one the combined categories "low (L)" & "medium (M)" alcohol problem use were coded as=0 and the category "high (H)" alcohol problem use were coded as=1 (this equation will be defined from now onwards as "L&M versus H equation"). However, the simultaneous estimation of all equations causes results to be different than those that would be obtained if the equations would be estimated separately, especially if parallel-lines constraints are either imposed or relaxed for different covariates in the model (see paragraph 6.1.1.1 for a more detailed description of the characteristics of the GOLOGIT2 module).

Using the results of the GOLOGIT models, I will present only the results of the "L&M versus H equation" of the GOLOGIT models analyzed and will omit those of the "L&M versus H equation. This will avoid a tedious and lengthy description of the results of the GOLOGIT models and will focus the attention on how depressive symptoms at age 10 are associated with high alcohol problem use at age 14, rather than how they are associated with the broader, more heterogeneous and less high-risk category of medium and high alcohol

problem use. From a public health policy perspective this approach may contribute to help policymakers develop specifically targeted prevention and treatment programs towards the highest risk groups (Lintonen, 2001, Viner et al., 2007), rather than those that are one-size-fits-all, which have often been demonstrated to be ineffective (Boyd, 2005, Zucker et al., 2005).

6.1.1.1 Vantages and characteristics of the GOLOGIT2 module

The major strength of GOLOGIT2 module as opposed to modules fitting other regression models (e.g. OLOGIT, MLOGIT) is that it can fit three special cases of models: the logistic regression model (in case the outcome is a dichotomous variable) and the parallel-lines/ non parallel-lines/ partially parallel-lines (often defined as partial proportional odds) models (in case the outcome is a categorical variable) (Peterson et al., 1990, Williams, 2006).

The parallel-lines model is based on a parallel-lines assumption, which requires the "β" regression coefficients to be the same for each category of the dependent variable. The "β" regression coefficients are the measures of the effect on the independent variable of a unit change in the predictor variable or in the covariates (AKA the independent variables), by using them in an equation with the corresponding values of the independent variable it is possible to compute the expected probability for an observation (Norusis, 2005). An example of a parallel-line model is represented by the OLOGIT regression model (Long et al., 2006).

In the non parallel-lines models, the parallel-lines assumption is violated (or "relaxed"), which means that the "β" regression coefficients are assumed to be different for all the categories of the dependent variable. An example of a non parallels-lines model is the MLOGIT regression model (Long et al., 2006).

A key problem with the parallel-lines models is that its assumptions are often violated; it is common for one or more β coefficients to be different across the categories. The parallel-

lines models are therefore often overly restrictive and simplistic. The option of using a non-parallel model has the opposite problem, especially when the model includes a large number of independent variables (like in the case of my thesis). By freeing all independent variables from the parallel-lines constraint, the number of different β coefficients across the categories of the dependent variable may become so large that it would be very complicated to interpret the results of the model. GOLOGIT2 overcame this limitation by fitting a partial proportional odds model (AKA a partially parallel-lines model), where the parallel-lines constraints are relaxed (i.e. non-parallel) only for selected independent variables where this is justified, maximising both the informativeness and straightforwardness of the results (Williams, 2006). Three options of the GOLOGIT2 module may be used to define more precisely the parallel lines constraints of any covariate in the final model. The "autofit" option automatically identifies partial proportional odds models that fit the data; two other options, the "pl" (parallel lines) option and the "npl" (nonparallel lines) option, can be used to have greater control over the final model specification. However, a limit in the use of these options exists: while "pl" and "npl" can be used together, "autofit" can only be used alone (Williams, 2006). When "autofit" is specified, GOLOGIT2 goes through an iterative process. First, it fits a totally unconstrained model (equivalent to a MLOGIT model in which all the independent variables are freed from the parallel-lines constraint); subsequently, a Wald test is conducted for each independent variable to verify whether the variable meets the parallel-lines assumption. The Wald test works by testing the null hypothesis that a set of parameters is equal to some value. In this case the parameters used by the Wald test are the log-likelihoods (*L*s) (which correspond to the *P* of obtaining the observed results given the β coefficient estimate; see paragraph 6.2.1 for the use of *L* in the likelihood ratio test) of each independent variable of the GOLOGIT model. In practice, the Wald test tests the null hypothesis that that all the *L*s are equal across the equations, or in other words, that the difference between the *L*s

is=0; this difference is then compared against a χ^2 distribution (Harrell, 2001, Wald, 1939). Because *L* depends by the β coefficient, an equal *L* across the equations of the GOLOGIT model would correspond to equivalent β coefficients of the independent variable (Harrell, 2001). Therefore, if the Wald test is statistically non-significant (p-value>0.05, null hypothesis accepted) for one or more variables, the independent variable with the least significant value on the Wald test is constrained to having equal effects (AKA equal βs) across equations (i.e., it meets the parallel-lines assumption).

The model is then refitted with the parallel-lines constraints imposed for that specific independent variable, and the process is repeated until there are no more variables meeting the parallel-lines assumption (Williams, 2006).

An additional feature of the GOLOGIT2 module is the "predict" post-estimation command, which gives the expected probability of the fitted model (Williams, 2006); the expected probability can then be plotted against the categories of the independent variable (in my case, age 10 depressive symptoms). Because GOLOGIT2 runs two parallel equations (L versus M&H equation and L&M versus H equation, see paragraph 6.1), it is necessary to specify for which equation the predicted probability has to be estimated. In my analyses I estimated the predicted probability of the L&M versus H equation only.

6.1.2 Data imputation model: Multiple Imputation by Chained Equation model

Missing values represent a common issue in longitudinal studies. As Vandenbroucke has argued, prospective studies provide one of the strongest methodologies for studying aetiological mechanisms (Vandenbroucke, 2008); however, such studies are vulnerable to selection biases as a result of individuals becoming lost to follow-up (Wood et al., 2004a). Particular subgroups within longitudinal studies may be more likely to drop out or otherwise lead to missing data, such as young people with higher rates of mood and behavioral

problems (Wolke et al., 2009, Wood et al., 2004a). Therefore, it can be expected that missing values can also be a problem for the current study, because of its focus on such problems (e.g., depressive symptoms, alcohol problem use and a large number of behavior-related risk factors).

Missing data are unavoidable in epidemiological and clinical research, but their potential to undermine the validity of research results has often been overlooked in medical literature (Wood et al., 2004a). The risk of bias due to missing data depends particularly on the reasons why data are missing (Little et al., 2002). Reasons for missing data are commonly classified as: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR) (Little et al., 2002). When it is plausible that data are not MCAR, analyses based on complete cases only (i.e., based only on the subset of participants with all the information available) may be biased (Sterne et al., 2009).

Major prospective cohort studies, such as the ALSPAC study, provide one of the strongest methodologies for studying aetiological mechanisms, but are also the most vulnerable to selection biases as a result of losses to follow-up (Vandenbroucke, 2008), with missing data being particularly consistent in variables ascertaining behavioural problems (Wolke et al., 2009); imputation of the missing data may therefore be a solution to reduce bias (Sterne et al., 2009).

Imputation was conducted using a Multiple Imputation by Chained Equation (MICE) approach (Carlin et al., 2008, Royston, 2004, Royston, 2005) (the acronym was apparently coined by Steff van Buuren (van Buuren et al., 1994), see paragraph below for a more detailed description of the characteristics of this powerful statistical technique), which was performed using the "ICE" module implemented by Patrick Royston (Royston, 2005) in STATA/IC v.10.1. for Windows (StataCorp, 2007).

6.1.2.1 Principles and characteristics of the Multiple Imputation by Chained Equation model

MICE (Royston, 2004) is a relatively flexible, general purpose approach to dealing with missing data and is now available in standard statistical software (van Buuren, 2005). ICE command performs MICE in STATA and imputes missing values by using switching regression, an iterative multivariable regression technique (Royston, 2005), which is based on a methodology originally developed by Donald Rubin (often defined as "Rubin's rules") (Rubin, 1976).

As summarized by Sterne *et al.*, in order to analyze cases with missing data, MICE uses a two-stage approach (Sterne et al., 2009). The first stage consists of the creation of multiple copies of the dataset, with the missing values replaced by imputed values. These are sampled from their predictive distribution based on the observed data; thus, multiple imputation is based on the Bayesian Inference Theory, which states that the likelihood that a particular hypothesis is true (i.e., the value of imputed data) is determined by some observed evidence (i.e., the values of the available data), the so-called "posterior probability" of the hypothesis (Bernardo, 2000, Sterne et al., 2009). Each variable containing missing data is imputed using a specific imputation equation that is equivalent to a regression model having the variable to be imputed as the dependent variable and all other variables in the datasets as independent variables. In other words, if the variable to be imputed is a dichotomous variable, the imputation equation will be equivalent to a logistic regression, whereas if the variable will instead be continuous, the imputation equation will be equivalent to a linear regression, and so on (Royston, 2005).

The imputation procedure must be a multiple iterative process, as it has to fully account for all uncertainty in predicting the missing values by injecting appropriate variability into the imputed values; after all, it is never possible to know the true values of the missing data. This

is because single imputation, which is obtained by performing the imputation just once for each missing value, does not reflect the uncertainty stemming from the fact that the imputed values are plausible replacements for the missing values but are not the true values themselves. As a result, analyses of singly imputed data that treat the imputed values as if they were measured values tend to produce estimated standard errors that are too small, confidence intervals that are too narrow, and significance tests that reject the null hypothesis too often when it is true (CDC, 2008, Sterne et al., 2009). Moreover, the MICE model must include not only the predictor variable and the covariates, but also the outcome variable; outcome inclusion has been advocated as being a successful strategy to deal with selective missing values, and it has been observed that imputation models not accounting for the outcome variable yielded very biased (underestimated) coefficients (Moons et al., 2006).

Multiple imputation allows the uncertainty due to imputation to be reflected in the analysis (Rubin, 1978, 1987). With multiple imputation, M>1 plausible sets of replacements are generated for the missing values, each in a different dataset, thereby generating M completed datasets. The M sets of imputations for the missing values are ideally independent draws obtained from the predictive distribution of the missing values conditional on the observed values (using a Bayesian approach, as explained earlier) (CDC, 2008, Rubin, 1978, Rubin, 1987b).

The second stage comprises of the use of standard statistical methods to fit the specified models to each of the imputed datasets. Each of the M completed datasets is analyzed separately using the method that would be applied if the data were complete, and the variation in results among the M datasets provides a measure of missing-data uncertainty in addition to the usual variation due to sampling. Estimated associations in each of the imputed datasets will differ because of the variation introduced in the imputation of the missing values, and the results are only useful when averaged together to give overall estimated

associations. Standard errors, confidence intervals and significance levels are calculated using Rubin's rules (Rubin, 1987b), which take into account the variability in results between the imputed datasets, thus reflecting the uncertainty associated with the missing values (Sterne et al., 2009).

In STATA all the imputed datasets can be stored along with the original data in a single dataset with a vertically stacked format, in which every entry is repeated for the M number of imputations. This makes the M imputed dataset easier to be stored and analyzed. The analysis of the stacked datasets is then performed setting the prefix "mim" above the fitting or estimation command of choice; "mim" enables STATA to accommodate data imputed by any method. MIM, in association with the option "category(fit)," can validly fit every regression model available in STATA (including the GOLOGIT model) and, in association with the option "category(combine)," can give parameter estimates and confidence intervals computed according to Rubin's rules for Bayesian inference for any estimation and post-estimation command (Carlin et al., 2008).

6.1.2.2 Auxiliary variables included in the MICE imputation model

The theoretical possibility of including auxiliary variables has been explored in the context of Multiple Imputation by Meng (Meng, 1994) and Rubin (Rubin, 1987a). Both of these authors argued that nontrivial improvements in efficiency and bias may accrue when auxiliary variables are added to an imputation procedure, even when the auxiliary variables are not included in subsequent analyses of the imputed data (Collins et al., 2001, Meng, 1994, Rubin, 1987a). In addition to the variables considered in my subsequent analyses, the multiple imputation procedure must therefore simultaneously consider two other kinds of variables: variables that might be associated with the dependent variable (age 14 alcohol problem use in

the case of my analyses) and variables that might be associated with information missingness (Collins et al., 2001, Taylor et al., 2002).

To maximise the efficiency of my imputation procedure I therefore included in the MICE model five auxiliary variables (for their prevalence in the study sample see Table 8.1): two variables (house crowding index and parental education) that have been reported as being associated with information missingness in longitudinal studies based on adolescent samples (Lingam et al., 2010, Patton et al., 2002) and three variables being theoretically associated with the dependent variable "age 14 alcohol problem use" (overt bullying status, age 14 years depressive symptoms and sensation seeking) (Topper et al., 2011). These variables were included in the imputation model only, with its sole purpose being to improve the performance of the missing data method; however, they were not included in any of the subsequent analyses, as doing this could have altered the meaning of the model and the coefficients being estimated (Collins et al., 2001).

I Variables associated with information missingness

1. House crowding index was based on the number of persons normally residing in the household divided by the number of rooms in regular use. Both pieces of information were provided by postal-administered questionnaires filled by the mothers when children were aged 97 months. I divided the resulting crowding index score in four categories: "low" (index $\leq$0.5); "medium" (index>0.5 and $\leq$0.75); "high" (index>0.75 and $\leq$1) and "very high" (index>1).

2. The "parental education" variable was obtained combining information on maternal and paternal educational level, which were self-reported by postal-administered questionnaires by the mothers and their partners (if present) before the birth of the study children, at 30 and 34 weeks of gestation respectively. Possible levels of education were:

"Certificate of Secondary Education (CSE)," "vocational education," "O level," "A level" and "University Degree." The "parental education" variable indicated the educational level of the parental figure with the highest education. In case of single-parent families, the "parental education" variable corresponded to the mother's educational level.

II Variables associated with the dependent variable

1. Overt (i.e., direct) bullying status was assessed using a modified version of the Bullying and Friendship Interview Schedule (BFIS) (Wolke et al., 2000). The information was collected by trained psychologists when children were aged 10 years during the "Focus @ 10" clinic.

The child was asked whether he/she had ever been involved, either as victim or perpetrator, into five bullying-related events in the past six months (see Table 6.1) and the frequency with which each event took place (possible answers: never; 1-3 times in past 6 months;>4 times in last 6 months but less than once a week; at least once a week). A child was classified as an overt victim of bullying if he/she was on the receiving end of any of the five components of overt bullying at least>4 times in the last six months. Children who responded with never or 1-3 times having been bullied for each of the four questions were categorised as not being victims. The same strategy was used to classify children as perpetrators/ non-perpetrators of bullying. Children were then grouped in four bullying statuses: "overt bullies," "overt victims," "overt bullies / overt victims" and "neutral."

Table 6.1: Bullying-related events ascertained

	Bullying victim	**Bullying perpetrator**
1	Had personal belongings taken	Taken personal belongings from others
2	Been threatened/blackmailed	Threatened/blackmailed others
3	Been hit/beaten up	Hit/beaten up others
4	Been tricked in a nasty way	Tricked others in a nasty way
5	Been called bad/nasty names	Called others bad/nasty names

2. "Age 14 years depressive symptoms" was measured using the SMFQ (Angold et al., 1995); it is therefore the same measure of depressive symptoms I used in my analyses as predictor variable (see paragraph 4.2.2) being ascertained by a trained psychologist at the same moment when alcohol problem use was assessed (during the "Teen Focus 2" clinic, children aged 14 years). Similar to the "age 10 depressive symptoms" variable (see paragraph 4.2.2), the depressive symptoms score at age 14 years was divided into quartiles of "low," "medium," "high" and "very high" depressive symptoms.

3. Sensation-seeking has been defined as "the need for varied, novel and complex sensations and experienced and the willingness to take physical and social risks for the sake of such experiences" (Zuckerman, 1979). Sensation-seeking was ascertained using a modified version of the Arnett's Inventory of Sensation Seeking (AISS) questionnaire (Arnett, 1994), which was administered during the "Focus @ 11" clinic when children were aged 11 years. The interview was performed on a computer; the child was presented with 20 possible behaviours (see Table 6.2), each appearing on the screen and being spoken to the child via headphones. The child was given four options to rate each behaviour: "not like me at all," "not much like me," "quite like me" and "very like me." I divided the final score into deciles.

Table 6.2: Items assessing sensation-seeking score

	Statement
1	When the water is very cold, I prefer not to swim even if it is a hot day *(reversed score)*
2	When I listen to music I like it to be loud
3	I stay away from movies that are said to be frightening *(reversed score)*
4	I like to ride on the roller coaster and other fast rides
5	I would never gamble with money, even if I could afford it *(reversed score)*
6	I like a movie where there are lots of explosions and car chases
7	It would be interesting to see a car accident happen
8	I like the feeling of standing next to the edge on a high place and looking down
9	I think it would be exciting to be in a battle during a war
10	I think it's fun and exciting to perform or speak before a group
11	If it were possible to visit another planet or the moon for free, I'd be among the first to sign
12	I enjoy playing exciting computer games
13	I like using the diving boards when I go swimming
14	I don't worry about coming home later than I'm supposed to
15	I don't do my homework until the very last minute
16	I am happy to go to new places or do new things on my own without friends or family
17	My parents or carers would be worried if they knew about some of the things I do
18	I always join in with what my friends are doing, even if I am not very sure about it
19	When I ride a bike I go as fast as I can whenever possible
20	I enjoy playing sports and activities which could be dangerous

6.2 Methods: statistical tests

6.2.1 Test for difference between models: Likelihood Ratio test

A very important component of statistics is the interpretation of observed data as indicative of statistical evidence. However, there is no consensus among statisticians on what constitutes statistical evidence and how to measure its strength. Confidence intervals, p-values and posterior probability distributions are commonly used to interpret and communicate statistical evidence (Zhang, 2009). Hacking suggested that the likelihood function is the optimal mathematical representation of statistical evidence and that likelihood ratios test (LR) is one of the most reliable methods to assess the strength of statistical evidence for evaluating one statistical hypothesis versus a second (Hacking, 1965).

As already reviewed in paragraph 6.1.1.1, the log-likelihood (L) of a single independent variable corresponds to the probability (P) of obtaining the observed results given the β coefficient estimate; however, the more complex the model, the greater the number of Ls for the single βs will be necessary to estimate. Hence, in the case of an entire model, the L of the model is the value that is maximized by a process (often defined as Maximum Likelihood Estimation, or "MLE" (Pratt, 1976)) that computes the maximum L value for the β coefficient of each independent variable in the model. To simplify (more details about the MLE procedure can be found in the references provided), MLE, iteratively, starting from randomly allocated values, "guesses" the values of the L of the independent variables in the model, gradually increasing them until they converge to a maximum single value (the L of the model). This L value is the one that maximises the P of obtaining the observed results (Clayton, 1993, Hacking, 1965, Kirkwood, 2003, Pratt, 1976, Royall, 1997). The L of a model is therefore an indicator of how well the model fits the data; the higher the L, the better the model fits the data (Hacking, 1965). L is a negative value; therefore, a higher value will correspond to a less negative value.

In hypothesis testing, the Likelihood Ratio (LR) test uses the values of L to compare two models where one is a restricted form of the other (this procedure is often defined as "nesting" the restricted model into the unrestricted one) (Clayton, 1993, Kirkwood, 2003). The test statistics is equivalent to [-2 * (L(restricted model) – L(unrestricted model))] (Kirkwood, 2003). Because minus becomes a plus in the calculation (L is a negative value), it follows that the L of the unrestricted model will be added to the L of the restricted model and the resulting value will be multiplied by -2. LR is therefore a positive value and it will increase its value as the L of the unrestricted model becomes less negative (increases). Therefore, the greater LR is, the greater the evidence will be in favour of the unrestricted model (as explained earlier, the higher the L, the better the model fits the data). Because LR

can be approximated to a quadratic equation, its value is compared against a χ^2 distribution with degrees of freedom (d.f.) equivalent to the number of additional parameters (for example, additional covariates) of the unrestricted model compared to the restricted one (Clayton, 1993, Kirkwood, 2003, Royall, 1997).

For the analyses I conducted, LR tests were performed using the post-estimation command "lrtest" in STATA/IC v. 10.1. for Windows (StataCorp, 2007). The command "lrtest" was used to compare GOLOGIT models in which the predictor (depressive symptoms at age 10 years) and the covariates were entered in different ways (i.e., in either a linear, quadratic or categorical fashion) and for hypothesis testing of interaction, comparing models with and without the interaction between age 10 "depressive symptoms" variable and "peers' influences" variables at either age 10 or age 14 years.

6.2.2 Tests for gender differences in the prevalence of the variables: X^2 test and Mann-Whitney-Wilcoxon test

As reviewed in paragraph 3.2.2, there is convincing evidence for gender differences in the prevalence as well as risk factors associated with depressive symptoms and alcohol problem use. I therefore divided the sample into boys and girls, conducting all the analyses on both the total sample of both boys and girls (from here onwards defined as "total sample"), and on boys and girls separately. In order to investigate differences in the prevalence of the single variables (predictor, outcome, covariates and moderating variables) between boys and girls, I used the X^2 test for the categorical/ dichotomous variables and the Mann-Whitney-Wilcoxon test for the continuous ones.

- *X^2 test:* The X^2 test (Pearson, 1900) is a nonparametric (i.e., that it does not make assumptions on the distribution of the data) statistical test for categorical variables used to determine whether a distribution of observed frequencies differs from the theoretical

expected frequencies (Daniel, 2010). To perform the X^2 test in STATA/IC v. 10.1. for Windows (StataCorp, 2007), the option "chi2" was added after the command "tabulate."

- *Mann-Whitney-Wilcoxon test:* The Mann-Whitney-Wilcoxon test (MWW test), which is often also called the "Mann-Whitney U" test, is a nonparametric statistical test for continuous variables (Mann, 1947). The MWW test can be used in the same situations in which the two independent samples Student's t-test could be used, although it is considered to be preferable to the Student's t-test when the variable's values are not normally distributed and the sample size is sufficiently large (Conover, 1980), which is the case of all the continuous variables included in my analyses. The "ranksum" command was used to perform the MWW test in STATA/IC v. 10.1. for Windows (StataCorp, 2007).

6.3 Analytical procedures

6.3.1 Analysis of univariable GOLOGIT models of age 10 years depressive symptoms and age 14 years alcohol problem use

The procedures described in the following four steps were taken while performing the analysis of the univariable models of age 10 depressive symptoms and age 14 alcohol problem use and helped me to decide: 1) whether to impose an equal (parallel lines assumption accepted) or a different (parallel lines assumption rejected) effect of age 10 depressive symptoms in the L versus M&H equation and the L&M versus H equation of the GOLOGIT model (procedure described in step 2); and 2) the most appropriate format of the depression variable I would use in the subsequent analyses (procedure described in step 3). The procedure described in step 4, finally, helped me to generate a model in which it was possible to observe the direct relationship between age 10 depressive symptoms and age 14 alcohol problem use.

The analysis was conducted in both the total sample and in boys and girls separately.

1. Gender differences in the prevalence rate of the four indicators of age 14 alcohol problem use, of the predictor variable "age 14 alcohol problem use" (see paragraph 4.2.1 for more information about the predictor variable) and on the outcome variable "age 10 depressive symptoms" (see paragraph 4.2.2 for more information on the outcome variable) were investigated with X^2 tests (see paragraph 6.2.2 for more information on the X^2 test). Results are reported in paragraph 7.1.

2. The variable "age 10 years depressive symptoms" was entered in a univariable GOLOGIT regression model (see paragraph 6.1.1 for more information on the GOLOGIT model) as single predictor of "age 14 alcohol problem use" in three possible ways: a) as a linear variable, b) as a categorical variable and c) as a quadratic variable (the generated multiplying the variable by itself). In all three cases the "autofit" option associated with the GOLOGIT2 command was specified (for more information on "autofit" see paragraph 6.1.1.1).

3. The LL of the univariable GOLOGIT models in which "age 10 depressive symptoms" were entered as either a categorical or a quadratic variable were compared with the more parsimonious model in wich age 10 depressive symptoms were entered as a linear variable were compared using a LR test, in which one model was nested within the other. The LR test provided information on the validity of a simplifying assumption for a model (in this case, whether a linear model is as good as a more complex model, such as a categorical or a quadratic one; see paragraph 6.2.1 for more information on the LR test). Results are reported in the paragraph 7.2.

4. The univariable GOLOGIT models that were identified as better fitting the data were run, and expected probability of the fitted models was predicted using the "predict" post-

estimation command (see paragraph 6.1.1.1 for more information on the "predict" command). The expected probability estimates were plotted against the four categories of the "age 10 depressive symptoms" variable ("low," "medium," "high" and "very high"). Results are shown in paragraph 7.3.

6.3.1.1 Analysis of univariable GOLOGIT model of age 10 years depressive symptoms and age 14 years alcohol problem use in the total sample: moderating effect of gender

The procedure described in the following two steps was performed in order to evaluate the possible moderating effect of gender in the univariable GOLOGIT model obtained with the procedures described in paragraph 6.3.1, step 2. However, it must be noted that the result of this analysis was not used to decide whether or not to conduct the entire analysis on the two genders separately, but only to confirm or reject the hypothesis of a direct moderating effect of gender in the univariable relationship between age 10 depressive symptoms and age 14 alcohol problem use. Hence, the entire analysis outlined in paragraph 3.3 has been conducted in both genders independently from the results of this test, as one of the scopes of my thesis is to evaluate the pattern of covariates correcting the relationship between age 10 depressive symptoms and age 14 alcohol problem use in the two genders.

1. In order to generate the interaction terms, the variable "age 10 depressive symptoms" was centred at its mean (subtracting the value of the variable's mean to every variable's value) and it was multiplied with the binary variable describing the child's gender. In this way I obtained the interaction term: "age 10 depressive symptoms **X** gender".
2. A LR test (see paragraph 6.2.1) comparing 1) a bivariable GOLOGIT model without interactions (i.e., a model having as independent variables: a) "age 10 depressive symptoms"

and b) "gender") and 2) an interaction bivariable GOLOGIT model (i.e., a model having as independent variables: a) "age 10 depressive symptoms" and b) "gender" and also including the interaction term: "age 10 depressive symptoms **X** gender" was conducted in the total sample (see results in paragraph 7.4).

6.3.2 Missing data imputation

The following four steps were taken in order to investigate the pattern of data missingness (procedure described in steps 1 and 2) and to impute the missing data (procedure described in steps 3 and 4), obtaining a dataset in which all the variables of interest were fully available for each participant in the study sample (N=4200). It must be noted that the entire ALSPAC dataset (N= 14,062 live births) was used in the imputation procedure, obtaining therefore a complete set of information for each child enrolled in the ALSPAC study. However, the analysis using the imputed variables (described in the steps below) was conducted only on the participants included in the study sample (N=4200) and not on the entire ALSPAC dataset. I chose to do so because, for those children who did not have provided at least both information on alcohol problem use and depressive symptoms, the amount of information originally available may have been extremely limited and/ or extremely antecedent to the years of interest (as in some cases, the only information available was the gender of the participant child, which was provided for all the live births).

1. An indicator of missingness (indicating whether the information was available or not available) was generated for each variable included in the imputation model (predictor, outcome variables, covariates and moderating variables). The indicators of missingness for each variable were summed, obtaining a score describing the amount of information missing per each participant in the study sample. Gender difference in the total amount of information

missing was assessed using MWW test (see paragraph 6.2.2 for more information on the MWW test; results are reported in paragraph 8.1.2).

2. The association between two variables theoretically associated with information missingness (house crowding index and parental education, see paragraph 6.1.2.2) and the indicator of the amount of information missing per each participant in my study sample was investigated using the Spearman's rank correlation test (Spearman, 1904). Gender differences in the amount of missing data for each variable imputed were assessed using X^2 test (see paragraph 6.2.2 for more information on the X^2 test; results are reported in paragraph 8.1.2).

3. A MICE imputation model (see paragraphs 6.1.2 and 6.1.2.1 for more information on MICE) was defined on the basis of the type of variables included in it. As reviewed in paragraph 6.1.2.1, each variable in the MICE imputation model must be imputed using a specific imputation equation that is equivalent to a regression model having the variable to be imputed as dependent variable. Table 6.3 reports the type of imputation equation that was specified for each variable included in the MICE imputation model.

Because of the broad variety of variables included in the imputation model (e.g., continuous, ordered categorical, non-ordered categorical and dichotomous variables, see Tables 5.1, 5.2, 5.3 and 5.4 and Table 8.1), a different imputation equation had to be specified for each variable (either linear regression, OLOGIT regression, MLOGIT regression (used only for the non-ordered categorical variable "bullying status"), or logistic regression).

Following the guidelines suggested by Moons *et al.*, the predictor variable was also included in the MICE imputation model (Moons et al., 2006) (see paragraph 6.1.2.1); however, this was not included in the form of the derived variable "age 14 alcohol problem use," but in the form of the four SSAGA items (Bucholz et al., 1994, Hesselbrock et al., 1999) used to generate it (see paragraph 4.2.1). This was done because outcome variable "age 14 alcohol problem use" is the first of four principal components generated by a PCA procedure

(Olsson, 1979, Pearson et al., 1922) (see paragraph 4.2.1), and therefore, its distribution depends on the distribution of the four variables used to generate it (Jolliffe, 2002).

Table 6.3: Type of imputation equation that was specified for each variable included in the MICE imputation model

Variable's class	Variable	Imputation equation
Outcome variable[#]	Consumed alcohol without parental permission	OLOGIT regression
	Frequency of whole alcoholic drinks	OLOGIT regression
	Largest number of whole drinks in 24 hour-period	OLOGIT regression
	Ever been intoxicated from alcohol	Logistic regression
Predictor variable	Age 10 depressive symptoms	OLOGIT regression
Socio-demographic factor domain covariates	Gender	Logistic regression
	Age10	OLOGIT regression
	Age14	OLOGIT regression
	Ethnicity	Logistic regression
	Social Class	OLOGIT regression
	Income per week	OLOGIT regression
	Family constellation	OLOGIT regression
Family environment factor domain covariates	Mother's alcohol use	Linear regression
	Mother's partner's alcohol use	Linear regression
	Mother-child interaction	Logistic regression
	Mother's partner's-child interaction	Linear regression
	Mother's depression	Logistic regression
	Mother's partner's depression	Logistic regression
	Rows between parents	OLOGIT regression
Social environment factor domain covariates	Child stressful events	OLOGIT regression
	Peers' antisocial activities[$]	OLOGIT regression
	Religiosity (attends place of worship)	OLOGIT regression
	Peers' alcohol drinking[$]	Logistic regression
Personality and psycho-pathologies factor domain covariates	Child conduct problems	OLOGIT regression
	Child peer problems	OLOGIT regression
	Child antisocial activities	OLOGIT regression
	Self-esteem	OLOGIT regression
Peers' influences (moderating variables)[$]	Age 14 peers' alcohol drinking	OLOGIT regression
	Child bonding with peers at age 10 years	Linear regression
	Child bonding with peers at age 14 years	Linear regression
Auxiliary variables (included only in the imputation model)	House crowding index	OLOGIT regression
	Parental education	OLOGIT regression
	Bullying status	MLOGIT regression
	Sensation-seeking	Linear regression
	Age 14 depressive symptoms	OLOGIT regression

[#] SSAGA items used to generate, using PCA, the outcome variable "age 14 alcohol problem use."
[$] Age 10 years peers' antisocial activities and age 10 years peers' alcohol drinking were combined to generate the moderating variable "age 10 years peers' antisocial behaviour" (see paragraph 4.2.4.2).

4. When the MICE imputation procedure was started, the model was run iteratively for 50 cycles of imputation, generating 50 complete dataset that were stacked into a single

dataset (from here onwards defined as "the imputed dataset") for subsequently being analyzed.

6.3.3 Analysis of multivariable GOLOGIT models of age 10 years depressive symptoms and age 14 years alcohol problem use in the original (non-imputed) dataset

The following seven steps were taken while performing the analysis of the multivariable model of age 10 depressive symptoms and age 14 alcohol problem use.

Using the procedures described below I obtained a model in which the direct relationship between age 10 depressive symptoms and age 14 alcohol problem use was corrected by taking into account the effect of relevant covariates.

The analysis, with the exception of step 3, was conducted in both the total sample and in boys and girls separately.

1. The carefully *a priori* selected covariates, chosen after careful examination of the relevant literature and described in Table 5.2 and Table 5.3, were tested for gender differences using either the X^2 test (for the categorical/ dichotomous variables) or the MWW test (for the continuous variables) (see paragraph 6.2.2 for more details on these statistical tests; results are reported in paragraph 8.2.1).

2. In every bivariable and multivariable GOLOGIT model that was drawn (see paragraph 6.1.1 for more information on the GOLOGIT model), the parallel lines assumption for age 10 depressive symptoms was maintained identical to the one that was identified in the GOLOGIT univariable model using the "autofit" option (see step 2 of paragraph 6.3.1). To do so, the "pl" (parallel lines assumption imposed) or "npl" (parallel lines assumption relaxed) options were specified (for more information on "autofit," "pl" and "npl," see paragraph 6.1.1.1). I chose to do this in order to obtain bivariable and multivariable

GOLOGIT models in which the effect of depressive symptoms was comparable to the one identified in the univariable GOLOGIT model.

As reviewed in paragraph 6.1.1.1, a limit of the GOLOGIT2 module is that it is not possible to use the option "autofit" (which tests whether the parallel lines assumption should be imposed or relaxed) when either the "npl" or the "pl" options are being used (Williams, 2006). Since I was interested in having bivariable GOLOGIT models in which the effect of age 10 years depressive symptoms was comparable to the one observed in the univariable one (the effect of age 10 years depressive symptoms being kept fixed with either the "npl" or the "pl" options as described above), I also had to arbitrarily specify either the "pl" or "npl" option for any of the covariates being entered in the GOLOGIT models. I chose to use the "pl" option; for every covariate this imposed equal effect in the L versus M&H equation and the L&M versus H equation of the GOLOGIT model, and resulted in GOLOGIT models more easily interpretable than the ones I could have obtained if I would have specified the "npl" option instead.

3. For each covariate I followed the same procedure as for the depressive symptom variable (described in steps 2 and 3 of paragraph 6.3.1). Each covariate was specified in three different ways: as being linear, categorical or quadratic and it was singularly included in the univariable GOLOGIT model that was identified with the procedure described in paragraph 6.3.1. I generated in this way a bivariable GOLOGIT model accounting for one covariate only.

The two GOLOGIT models in which each covariate was entered in either a categorical or quadratic fashion were subsequently compared with the more parsimonious model in which the covariate was entered in a linear fashion using a LR test (see paragraph 6.2.1 for more information on the LR test).

This analysis was conducted on the total sample and in the non-imputed dataset only; results are reported in paragraph 8.2.2. The results obtained were then generalized to boys and girls and to the imputed variables. I chose to do so to ensure the comparability of the estimates of the covariates included in the subsequent multivariable GOLOGIT models drawn from the non-imputed and from the imputed datasets and based on the total sample and on the subsamples of boys and girls. Explaining this with a practical example, it would not have been possible to compare the estimates of a covariate that in one case is entered as linear (d.f.=1; hence 1 single coefficient to be estimated) and in the other case is entered as categorical (d.f.=number of categories – 1; hence number of categories -1 coefficients to be estimated) (Kirkwood, 2003).

4. Starting from the domain of socio-demographic factors (see Table 5.2), each covariate (entered with the "pl" option imposed as described in point 2 and in either a categorical, quadratic or linear way as identified in point 3) was independently tested for significance level in the bivariable GOLOGIT model (see results in paragraph 8.2.3).

5. In the multivariable GOLOGIT model, only the covariates that were statistically significant (p-value<0.05) when tested in the bivariable GOLOGIT models were entered. In case any of the covariates describing mother's partner's behaviour and attitudes (mother's partner's alcohol use, mother's partner's parent-child interaction and mother's partner's depression) and about the relationship between the two parental figures (rows between parents) (see Table 5.2 for the prevalence of these variables in the study sample) was statistically significant when tested in the bivariable GOLOGIT model, the sensitivity analysis described in step 6 was performed; otherwise, I skipped directly to step 7.

6. As described by the "family constellation" variable in Table 5.2, 5.7% of the children in the study sample (information on family constellation was available for 3,524 children) were living in single-parents families composed by a single female parental figure (usually

the mother), and therefore, information provided by the covariates describing mother's partner's behaviour and attitudes and about the relationship between the two parental figures (see step 5) was not relevant for them.

Hence, in case any of those mother's partner's-related covariates was still statistically significant (p-value<0.05) when included in the GOLOGIT multivariable model, two GOLOGIT multivariable models (one accounting for children with both parental figures including the mother's partner's covariate, and one accounting for children with a single maternal figure excluding such covariate) were drawn. If, on the contrary, the covariate became statistically non-significant (p-value $\geq$0.05), the covariate was excluded from the analysis and the multivariable GOLOGIT model was based on children living in both single and two-parents families (see results in paragraph 8.2.4).

7. A final GOLOGIT multivariable model, correcting the relationship between age 10 years depressive symptoms and age 14 years alcohol problem use, was run (see results in paragraph 8.2.5 for the total sample and in paragraph 8.2.6 for the boys and girls subsamples).

6.3.4 Analysis of multivariable GOLOGIT models of age 10 years depressive symptoms and age 14 years alcohol problem use in the imputed dataset

Analysis of the multivariable GOLOGIT models based on the imputed dataset was conducted following the same procedure used for the multivariable GOLOGIT models based on the non-imputed dataset and described in steps 3, 4, 5, 6 and 7 of paragraph 6.3.3. However, in the imputed dataset the procedure described in step 6 (i.e., the sensitivity analysis of the covariates describing mother's partner's behaviour and attitudes and the relationship between the two parental figures) was conducted with an additional passage. As explained in paragraph 6.3.2, the MICE procedure imputed all the missing values in the covariates,

however also including those values of the mother's partner's related covariates that were correctly missing in the non-imputed dataset (because the information could not be provided) for those children living in single-parent families. Hence, to conduct the sensitivity analysis only on the subsample of children living in two-parent families, children living in single-parent families had to be excluded on the basis of the imputed "family constellation" variable.

In the bivariable and multivariable GOLOGIT models drawn from the imputed datasets, I included the same predictor (age 10 years depressive symptoms) and outcome (age 14 alcohol problem use) variables that I included in the GOLOGIT models drawn from the non-imputed dataset. In this way the GOLOGIT models drawn from both the imputed and non-imputed datasets were based on the same study sample (4,220 participants).

Thus, the difference between the GOLOGIT models drawn from the two datasets (imputed and non-imputed) was that in the models drawn from the imputed dataset (but not in those drawn from the non-imputed one), I included the imputed covariates and the imputed moderating variables (imputed using a MICE procedure, see paragraph 6.3.2) in order to obtain GOLOGIT models that were all based on the same sample size (N=4220) and were not affected by the presence of missing values in the covariates and/ or in the moderating variables (see results in paragraphs 8.2.3, 8.2.4, 8.2.5 and 8.2.6).

Hence, the results obtained from the analysis of the imputed dataset - because of their greater informativeness - have been described more extensively than the results based on the non-imputed dataset, which have been reported solely as confirmatory results of my analyses.

6.3.5 Univariable and multivariable GOLOGIT models accounting for the moderating effects of peers' influences

The following twelve steps were taken while performing the analysis of models accounting for the moderating effects of peers' influences and based on both the univariable and the multivariable GOLOGIT models obtained with the procedures described in paragraphs 6.3.1 and 6.3.4. The procedures described here, with the exclusion of step 4, were all conducted in the imputed dataset only.

Using the procedures described below, I obtained a model in which the direct relationship between age 10 depressive symptoms and age 14 alcohol problem use was corrected by taking into account the effect of relevant covariates, and in which the moderating effects of peer's influences were taken into account. I also obtained a graphical representation of the moderating effect of peers' influences in the direct relationship between age 10 depressive symptoms and age 14 alcohol problem use.

The analysis was performed twice, once accounting for peers' influences at age 10 years and once accounting for peers' influences at age 14 years (see paragraph 4.2.4).

3. Using the univariable GOLOGIT model obtained with the procedure described in paragraph 6.3.1, a trivariable GOLOGIT model was generated, including each of the variables describing peers' influences (i.e., the variable describing the child's bonding with his/ her peers and the variable describing the peers' risky behaviour (see Table 5.4)).

As it was done for the covariates included in the GOLOGIT multivariable model (see paragraph 6.3.2, step 2), the parallel lines assumption for age 10 depressive symptoms was maintained identical to the one that was identified in the GOLOGIT univariable model (see step 2 of paragraph 6.3.1), whereas the variables describing peers' influences were entered with the parallel lines assumption imposed using the option "pl" (see paragraph 6.1.1.1). This

was done for all the trivariable, quadrivariable and multivariable GOLOGIT models described in the steps that follow.

The peers' influences variables were entered with a linear format in all the GOLOGIT interactions models I generated. I decided to do so for two reasons: 1) if the variables would have been entered in a categorical format, the interaction of the two peers influences variables would have created 36 interaction variables, whose estimation would have been problematic as some of the categories might not have had sufficient data for being correctly estimated (the variables describing peers' influences were a 4 categories variable (peers' risky behavior) and a 9 categories variable (child bonding with his/ her peers) (see Table 5.4)); and 2) if the variables would have been entered as quadratic, their interaction would have generated a quartic variable, whose correct estimation would have required the use of the "fracpoly" command for the analysis of fractional polynomials (Sauerbrei et al., 2006), which does not support the GOLOGIT regression command in STATA/IC v.10.1. for Windows (StataCorp, 2007).

4. In order to generate the interaction terms, the variables were centred at their mean (subtracting the value of the variable's mean to every variable's value), reducing the covariance and by consequence the collinearity between the variables (Aiken, 1991). In this way I obtained four interaction terms: 1) "age 10 depressive symptoms **X** child's bonding with his/ her peers," 2) "age 10 depressive symptoms **X** peers' risky behaviour," 3) "child's bonding with his/ her peers **X** peers' risky behaviour," and 4) "age 10 depressive symptoms **X** child's bonding with his/ her peers **X** peers' risky behaviour."

5. A LR test comparing 1) a trivariable GOLOGIT model without interactions (i.e., a model having as independent variables: a) "age 10 depressive symptoms," b) "peers' risky behaviour" and c) "child's bonding with his/her peers") and 2) a three-way interaction trivariable GOLOGIT model (i.e., a model having as independent variables: a) age 10

depressive symptoms," b) "peers' risky behaviour" and c) "child's bonding with his/her peers," and also including the four interaction terms: d) "age 10 depressive symptoms **X** child's bonding with his/ her peers," e) "age 10 depressive symptoms **X** peers' risky behaviour," f) "child's bonding with his/ her peers **X** peers' risky behaviour," and g) "age 10 depressive symptoms **X** child's bonding with his/ her peers **X** peers' risky behaviour") was conducted in the total sample. The analysis was conducted on both the imputed and non-imputed dataset; in case of statistically significant results, the three-way interaction trivariable GOLOGIT model was further analyzed with the procedure described in steps 7-12 (see results in paragraph 9.1).

6. Gender differences in the variables describing peers' influences (see Table 5.4) were tested using either the X^2 test (for the variables describing peers' risky behaviour) or the MWW test (for the variables describing child's bonding with his/her peers) (see paragraph 6.2.2 for more details on these statistical tests; results are reported in paragraph 9.2).

7. The variable "gender" was included in the three-way interaction trivariable GOLOGIT model described in step 5, generating a quadrivariable GOLOGIT four-way interaction model (i.e., a GOLOGIT model having all four interaction terms described in step 4, interacting with gender as well). A LR test comparing the quadrivariable GOLOGIT model without interactions (including gender) and this four-way interaction quadrivariable GOLOGIT model (including gender) was conducted. The analysis was conducted on both the imputed and non-imputed dataset; in case of statistically significant results, the three-way interaction trivariable GOLOGIT model was further analyzed with the procedure described in steps 6 (see results in paragraph 9.3).

8. LR tests were conducted on the boys and girls subsamples, following the same procedure indicated in steps 1-3 for the total sample. The analysis was conducted on both the imputed and non-imputed dataset; in case of statistically significant results, the three-way

interaction trivariable GOLOGIT model was further analyzed with the procedure described in steps 7-12 (see results in paragraph 9.4).

9. In case the results of the LR tests described in step 3 and 6 were statistically significant in the imputed dataset (p-value<0.05), the significance level of the three interaction terms, which included age 10 depressive symptoms (i.e., 1) "age 10 depressive symptoms **X** child's bonding with his/her peers," 2) "age 10 depressive symptoms **X** peers' risky behaviour," and 3) "age 10 depressive symptoms **X** child's bonding with his/ her peers **X** peers' risky behaviour") was tested in the trivariable GOLOGIT models accounting for the three-way interaction based either on the total sample (if the LR test described in step 5 was statistically significant), or on the two genders separately (if the LR test described in step 6 was statistically significant), or on both (if both the LR tests described in step 5 and 6 were statistically significant) (see results in paragraph 9.5).

10. In order to correctly interpret the three-way interaction estimate, I had to consider separately the possible combinations of child bonding with his/her peers and of peers' risky behaviour (Aiken, 1991). I divided the variable describing child's bonding with his/her peers (see Table 5.4) in "low" and "high" "child's bonding with his/her peers" (cut-off at the ~50th percentile) and recoded the variable describing peers' risky behaviour (see Table 5.4) in two categories; "low" and "high" "peers' risky behaviour". Therefore, for peers' alcohol drinking I distinguished between peers who had never consumed alcohol in previous six months (low) and peers who had consumed (with any frequency) alcohol in the previous six months (high); whereas for peers antisocial behaviour I distinguished between peers who had never partaken in any antisocial activity (low) and peers who had partaken in at least one (high)).

11. I separately ran the univariable GOLOGIT model indentified in paragraph 6.3.1 for four times in the following groups: 1) children with low bonding with peers and whose peers have low risky behaviour; 2) children with high bonding with peers and whose peers have

low risky behaviour; 3) children with low bonding with peers and whose peers have high risky behaviour; and 4) children with high bonding with peers and whose peers have high risky behavior.

12. The expected probabilities of all those four univariable GOLOGIT models were predicted using the "predict" post-estimation command (see paragraph 6.1.1.1 for more information on the "predict" command). The expected probability estimates were plotted against the four categories of the "age 10 depressive symptoms" variable ("low," "medium," "high" and "very high"). As a reference line, it was included in the graph the plot of the expected probability of the univariable GOLOGIT model not accounting for interaction (see step 4 in paragraph 6.3.1) (see results in paragraph 9.6).

13. The four interaction terms listed in step 2 were included in the multivariable GOLOGIT models that were identified with the procedures described in paragraphs 6.3.3 and 6.3.4. LR tests were conducted to compare the multivariable GOLOGIT model and the three-way interaction multivariable GOLOGIT model in both the non-imputed and the imputed dataset (see results in paragraph 9.7).

14. If the results of the LR test conducted in step 11 were statistically significant (p-value<0.05), a three-way interaction multivariable GOLOGIT model drawn from the imputed dataset was generated (see results in paragraph 9.6).

CHAPTER 7: RESULTS OF THE UNIVARIABLE GOLOGIT MODELS

7.1 Gender differences in the predictor and outcome variables

As reviewed in paragraph 3.2.2, there is convincing evidence for gender differences in the prevalence as well as risk factors associated with depression and alcohol misuse. I therefore divided the sample into boys and girls and compared the prevalence rates of predictor and outcome variables in the two genders with a X^2 test (see paragraph 6.4.1, step 1). Results are presented in Table 7.1. Results for the total sample have been presented in Table 5.1.

Boys were more likely to have experienced higher levels of depressive symptoms in childhood ($X^2(3)=11.08$, $p=0.011$) than girls, whereas girls were significantly more likely to experience alcohol problem use ($X^2(2)=9.02$, $p=0.011$).

As explained in paragraph 4.2.1, the "alcohol problem use" variable was the first of four principal components created with a PCA procedure based on four SSAGA items (Bucholz et al., 1994, Hesselbrock et al., 1999). Gender differences were observed for two of these items (see Table 7.1): the frequency the teenager has had whole alcoholic drinks (not sips) in the past six months (boys reported higher frequencies, $X^2(5)=23.89$, $p<0.001$), and the largest number of whole drinks the teenager has had in a 24-hour period (girls reported larger amounts than boys, $X^2(3)=12.09$, $p=0.007$).

Table 7.1: Prevalence of alcohol problem use and depressive symptoms for boys and girls separately

		Boys (N=2018)	Girls (N=2202)	
Variable	**Categories**	**%**	**%**	**X^2†**
Consumed alcohol without parental permission*	Never	80.1	78.4	$X^2(3)$ 7.15 p=0.067
	1-3 times	13.4	16.1	
	>4 times	5.3	4.3	
	once per week	1.2	1.1	
Frequency of whole alcoholic drinks*	Never	60.5	56.1	$X^2(5)$ 23.89 p<0.001
	<Monthly	30.9	36.7	
	<Twice a month	3.9	4.3	
	<Weekly	2.5	1.4	
	<Twice a week	1.8	1.2	
	≥Twice a week	0.4	0.3	
Largest number of whole drinks in 24 hour-period*	0 drinks	59.9	55.2	$X^2(3)$ 12.09 p=0.007
	1-2 drinks	23.2	25.0	
	3-4 drink	9.0	11.5	
	≥5drinks	7.9	8.3	
Ever been intoxicated from alcohol*	Yes	94.3	93.3	$X^2(1)$ 1.55 p=0.213
	No	5.8	6.7	
Alcohol problem use[A]	Low	56.6	52.0	$X^2(2)$ 9.02 p=0.011
	Medium	29.1	32.7	
	High	14.3	15.3	
Depressive symptoms[B]	Low	23.5	27.7	$X^2(3)$ 11.08 p=0.011
	Medium	29.5	29.6	
	High	28.3	25.5	
	Very high	18.7	17.3	

† Cross-tabulation of each variable with gender. Pearson's X^2 reported. Statistically significant (p-value<0.05) results are shaded.

* Four items used to construct the "alcohol problem use" variable (A).

[A] The outcome variable was the first of three components generated by the principal component analysis. To define alcohol problem use I categorized that variable in "low," "medium," or "high" alcohol problem use.

[B] The predictor variable was divided in quartiles obtaining four possible levels of depressive symptoms: "low," "medium," "high," and "very high."

7.2 Formats and parallel lines assumptions of the "age 10 years depressive symptoms variable" in the total sample and in the two genders separately

As explained in paragraph 6.3.1, steps 2 and 3, I conducted a number of tests to decide on the most appropriate representation of the independent variable in subsequent models.

First, LR tests were conducted, comparing three GOLOGIT univariable models: two GOLOGIT models with age "10 depressive symptoms" entered in either a categorical or a

quadratic format versus a more parsimonious GOLOGIT model with "age 10 depressive symptoms" entered in a linear format. The results in the total sample indicated that the more complex models (depressive symptoms entered in categorical or quadratic formats) did not fit the data significantly better than the more parsimonious one (depressive symptoms entered linearly), which was therefore chosen as the standard model in subsequent analyses (LR $X^2(4)=4.13$, $p=0.389$ comparing models with depressive symptoms entered as a categorical or as a linear variable and LR $X^2(1)=1.24$, $p=0.265$ comparing models with depressive symptoms entered as a quadratic or as a linear variable).

The same results were obtained when analyzing the formats of the depressive symptoms in the subsamples of boys and girls separately. For the subsample of boys they were: LR $X^2(2)=0.35$, $p=0.841$ comparing models with depressive symptoms entered in a categorical versus a linear format and LR $X^2(1)=0.33$, $p=0.564$ comparing models with depressive symptoms entered in a quadratic versus a linear format, whereas for the subsample of girls results were: LR $X^2(4)=2.70$, $p=0.609$ comparing models with depressive symptoms entered in a categorical versus a linear format and LR $X^2(1)=1.06$, $p=0.302$ comparing models with depressive symptoms entered in a quadratic versus a linear format.

Therefore, in all the subsequent analyses conducted on both the total sample, and on the subsamples of boys and girls separately, age 10 years depressive symptoms was entered as a linear variable.

As explained in paragraph 6.3.1 step 2, the option "autofit," which performs a Wald test on the independent variable in the model to verify whether the variable meets the parallel-lines assumption, was specified in each of the three univariable GOLOGIT models described above. Because the Wald test tests the null hypothesis that the effect of the independent variable is equal across the equations (i.e., that the parallel lines assumption is valid, see

paragraph 6.1.1.1), a statistically significant ($p<0.05$) Wald test indicates that the variable does not meet the parallel lines assumption.

In the models of interest (the ones in which age 10 depressive symptoms was entered as a linear variable), the results of the Wald tests indicated that: in the total sample (Wald $X^2(1)=6.96$, $p=0.008$) age 10 depressive symptoms did not meet the parallel lines assumption; in the subsample of boys (Wald $X^2(1)=1.27$, $p=0.258$) age 10 depressive symptoms did meet the parallel lines assumption; whereas in the subsample of girls (Wald $X^2(1)=6.02$, $p=0.014$), similarly to the total sample, age 10 depressive symptoms did not meet the parallel lines assumption.

7.3 Univariable GOLOGIT models of the association between age 10 depressive symptoms and age 14 alcohol problem use

Following the results described in paragraph 7.2, estimates of age 10 depressive symptoms were obtained using univariable GOLOGIT models in which age 10 depressive symptoms variable was entered in a linear format. Parallel lines assumption was relaxed in the total sample and in the subsample of girls using the option "npl," whereas it was imposed in the subsample of boys, using the option "pl."

As explained in paragraph 6.1.1, in all my analyses I present only the results of the "L&M versus H equation" of the GOLOGIT models I developed ("L&M versus H equation" is equivalent to a binary logistic regression in which the outcome variable is divided in two categories: 1) adolescents who developed high alcohol problem use, and 2) adolescents who developed either low or medium alcohol problem use).

In the total sample each increase in the level of childhood depressive symptoms was found to be associated with a statistically significant 9% increase in the risk for early adolescence high alcohol problem use (O.R. 1.09, 95% C.I. 1.01; 1.18, $p=0.029$), which resulted in a 27%

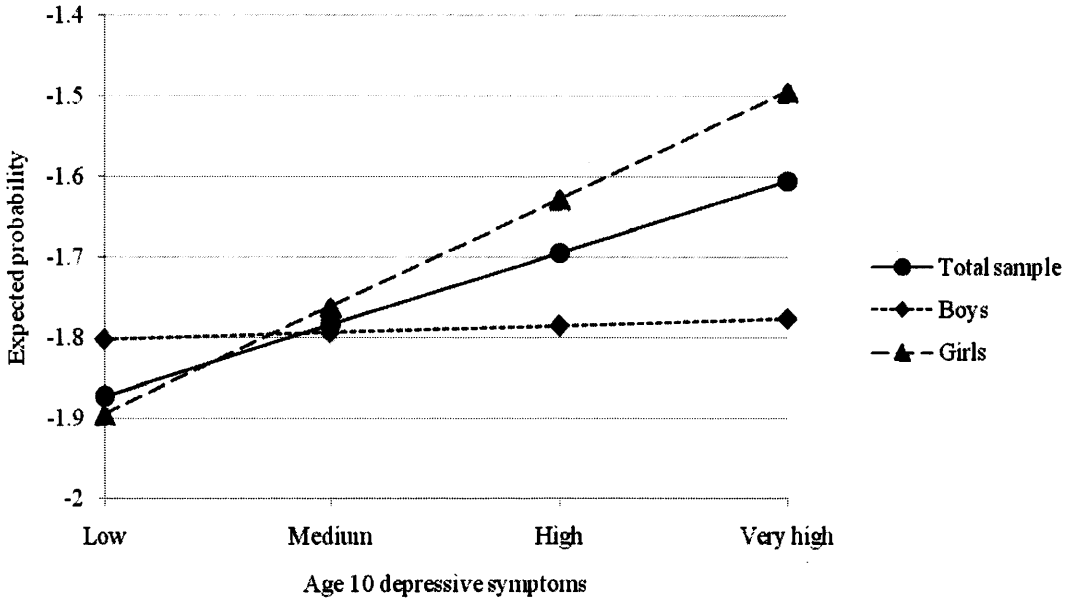
increased risk for those adolescents who experienced very high depressive symptoms in childhood versus those who experienced low depressive symptoms. Examining the genders separately, in girls, childhood depressive symptoms were more strongly associated with risk of alcohol problems in early adolescence than for boys. With progressively higher levels of depressive symptoms girls had experienced in childhood, an association with a 14% greater risk of developing high alcohol problem use in early adolescence (O.R. 1.14, 95% C.I. 1.02; 1.27, p=0.016) was found, which resulted in a 42% increased risk for those girls who experienced very high depressive symptoms in childhood compared to those who experienced depressed symptoms at low levels.

In boys, on the other hand, the association between childhood depression and alcohol problems at age 14 years was negligible, with all four categories of childhood depressive symptoms being associated with similar levels of alcohol problem use in early adolescence (O.R. 0.99, 95% C.I. 0.91; 1.07, p=0.838).

As explained in paragraph 6.3.1 step 4, I used the post-estimation command "predict" to estimate the expected probability of each of the three GOLOGIT models (corresponding to the expected probability of developing high alcohol problem use). In Figure 7.1, the expected probability estimates for the GOLOGIT model in the total sample and in the boys and girls subsamples are shown graphically, plotting them against the four categories of the "age 10 depressive symptoms" variable ("low," "medium," "high" and "very high").

This graphical representation of the expected probability of the three GOLOGIT models clearly illustrates how only the total sample and the girls subsample (but not the boys subsample) an increase in the level of depressive symptoms in childhood corresponded to an increase in the expected probability of developing high alcohol problem use in early adolescence.

Figure 7.1: Expected probability of developing high alcohol problem use in adolescence by level of severity of childhood depressive symptoms; results are shown for the total sample and for both genders separately



7.4 Results of the LR test assessing the moderating effect of gender in the univariable GOLOGIT model

As explained in paragraph 6.3.1.1, step 2, I performed a LR test to compare two models based on the total sample: 1) a bivariable GOLOGIT model without interactions (i.e., a model having as independent variables: a) "age 10 depressive symptoms" and b) "gender") and 2) an interaction bivariable GOLOGIT model (i.e., a model having as independent variables: a) "age 10 depressive symptoms" and b) "gender" and also including the interaction term: "age 10 depressive symptoms **X** gender") . The scope of this analysis was to confirm or reject the hypothesis of a direct moderating effect of gender in the univariable relationship between age 10 depressive symptoms and age 14 alcohol problem use.

Results of the LR test indicated that, concerning the bivariable GOLOGIT model accounting for gender, the more complex interaction model including the interaction term "age 10

depressive symptoms **X** gender" did not fit the data significantly better than the more parsimonious model not including the interaction term (LR $X^2(1)=0.49$, $p=0.483$).

However, although gender did not moderate the relationship between age 10 depressive symptoms and age 14 alcohol problem use, the subsequent parts of the analysis were nevertheless conducted both on the total sample and on boys and girls separately. This was done because one of the scopes of my thesis is to evaluate the pattern of covariates correcting the relationship between age 10 depressive symptoms and age 14 alcohol problem use in the two genders.

7.5 Results of the univariable GOLOGIT models: synthesis of the chapter

In summary, in this chapter I observed that in my study sample boys were more likely to have experienced higher levels of depressive symptoms in childhood than girls, whereas girls were significantly more likely to experience alcohol problem use.

In the total sample each increase in the level of childhood depressive symptoms was found to be associated with a statistically significant 9% increase in the risk for early adolescence high alcohol problem use, for girls such increased risk corresponded to 14%, whereas for boys the relationship between childhood depressive symptoms and adolescence alcohol problem use was non-significant.

Despite this gender difference in the univariable GOLOGIT model described in this chapter, results of the LR test indicated that gender does not moderate the relationship between childhood depressive symptoms and alcohol problem use in adolescence. Nevertheless, it was decided that the subsequent analyses would have been conducted on both the total sample and the two separate genders, as one of the scopes of the thesis is to evaluate the gendered pattern of covariates correcting the univariable GOLOGIT model.

CHAPTER 8: MISSING DATA IMPUTATION AND RESULTS OF THE MULTIVARIABLE GOLOGIT MODELS

8.5 Missing data imputation

8.1.1 Auxiliary variables included in the MICE imputation model

As explained in paragraph 6.1.2.2, five auxiliary variables (that were not used in any of the subsequent analyses) were included in the MICE imputation model. Two variables were included because of their theoretical association with information missingness (i.e., house crowding index and parental education) and three variables because of their theoretical association with the dependent variable "age 14 alcohol problem use" (i.e., bullying status, age 14 years depressive symptoms and sensation seeking).

Frequencies of the crowding index variable indicated that 23.7% of children in the study sample lived in houses with a crowding index ≤ 0.5 and 5.0% of them lived in houses with a crowding index>1. With regard to parental education, 15.6% of children had both parents holding only a CSE, whereas 25.3% of children in the study sample had at least one of the two parents holding a university degree certificate.

Concerning the variable "overt bullying status," the majority of the children in the study sample were identified as "neutral" (79.3%); the remaining 20.7% belonged to one of the three other alternative bullying statuses (i.e., bullying perpetrators (0.7%), bullying victims (15.8%) and bullying perpetrators-victims (4.2%)).

Finally, with regards to depressive symptoms at age 14 years, comparing these data with those on depressive symptoms available at age 10 years (see Table 5.1) there was a reduction in the prevalence of high depressive symptoms (26.8% at age 10 years versus 17.8% at age

14 years), but on the other hand there was an increase in the prevalence of very high depressive symptoms (18.0% at age 10 years versus 23.1% at age 14 years).

Table 8.1: Auxiliary variables included in the MICE model

Variable	Categories	N	%
House crowding index[A]	≤0.5	3400	23.7
	>0.5 - ≤0.75		39.9
	>0.75 - ≤1		31.4
	>1		5.0
Parental education[A]	CSE	4149	15.6
	Vocational education		7.3
	O level		24.9
	A level		27.0
	University Degree		25.3
Overt bullying status[B]	Bullying perpetrator	4099	0.7
	Bullying victim		15.8
	Bullying perpetrator-victim		4.2
	Neutral		79.3
Age 14 years depressive symptoms[B C]	Low	3966	30.1
	Medium		29.0
	High		17.8
	Very high		23.1
Variable	**Measurement Unit**	**N**	***M* (*SD*)**
Sensation-seeking[B]	Sensation-seeking score	3970	5.4 (2.8)

[A] Auxiliary variables associated with information missingness.
[B] Auxiliary variables theoretically associated with the outcome variable "age 14 alcohol problem use."
[C] The variable "age 14 years depressive symptoms" was divided in quartiles in the same way it was done for the predictor variable "age 10 years depressive symptoms" (see paragraph 4.2.2), obtaining four possible levels of depressive symptoms at age 14 years: "low," "medium," "high," and "very high."

8.1.2 Pattern of data missingness

Table 8.2 reports the frequency of missing variables for all 35 variables (see Table 6.3) that were included in the MICE imputation procedure. In my study sample (N=4220), only 5.9% of participants (N=247) had information available for all those 35 variables. At the other extreme, the maximum number of missing variables per participant was 19, with only 11 participants (0.3% of the study sample) missing such a large amount of information, whereas 9.5% of the study sample (N=400) had no information available for>10 variables (see Table 8.2).

MWW test results comparing the total number of missing variables in boys and girls (see paragraph 6.3.2, step 1) indicated that there was no statistically significant gender difference in the total amount of data missingness (*M* boys=4.6, *SD*=3.9; *M* girls=4.4, *SD*=3.9; MWW z=-1.88, p=0.060).

Results of the Spearman's rank correlation test (see paragraph 6.3.2, step 2) indicated that in my study sample "house crowding index" and "parental education" variables were significantly associated (p-value<0.05) with the number of missing variables per participant, with parental education being more strongly inversely associated with missingness (Spearman's rho=-0.21, p<0.001) than house crowding index, which was only mildly positively associated with the number of missing variables per participant (Spearman's rho=0.06, p<0.001).

Table 8.2: Frequency of missing variables in the total sample for all 35 variables included in the MICE imputation procedure

Missing variables	N participants[#]	% of the study sample	Cumulative %
0	247	5.9	5.9
1	495	11.7	17.6
2	747	17.7	35.3
3	742	17.6	52.9
4	560	13.3	66.1
5	312	7.4	73.5
6	203	4.8	78.3
7	191	4.5	82.9
8	137	3.3	86.1
9	102	2.4	88.5
10	84	2.0	90.5
11	60	1.4	91.9
12	60	1.4	93.4
13	47	1.1	94.5
14	78	1.9	96.3
15	60	1.4	97.8
16	45	1.1	98.8
17	24	0.6	99.4
18	15	0.4	99.7
19	11	0.3	100.0

[#] Total sample N=4220 participants.

Among all 35 variables included in the MICE model (see Table 6.3), only eight variables (i.e., age 10 depressive symptoms, the four SSAGA indicators of age 14 alcohol problem use, gender, age of assessment of depressive symptoms ("age 10" variable) and age of assessment of alcohol problem use ("age 14" variable)) were fully available for all the 4,220 participant children included in the study sample. All other 27 variables, including the five auxiliary variables described in paragraph 8.1.1, were differently available (some more, some less available) only for a fraction of the participant children (see Tables 5.1, 5.2 and 5.3 and Table 8.1).

Table 8.3 reports the number of missing values for each of the variables included in the MICE model, both for the total sample (N=4220) and boys (N=2018) and girls (N=2202) separately. Among the 27 variables containing missing values, the one with the smallest proportion of missing data was "age 14 child's bonding with his/her peers," with only 26 participants (17 boys and 9 girls) without this information available, whereas the variable with the greatest proportion of missing data was paternal alcohol use, with 3,149 participants (1,496 boys and 1,653 girls) missing this information.

Results of X^2 test comparing the rates of missingness for each covariate in boys and girls indicated that for most variables these rates were comparable (see Table 8.3). However, for three covariates (i.e., "social class" ($X^2(1)=5.39$, $p=0.020$), "child's antisocial activities" ($X^2(1)$ 7.69, $p=0.006$) and "peers' antisocial activities" at age 10 years (X2(1) 49.34, $p<0.001$)) and for three moderating variables (i.e., "age 14 peers' alcohol drinking" ($X^2(1)$ 34.93 $p<0.001$), child's bonding with peers at age 10 years ($X^2(1)$ 7.73 $p=0.005$) and "age 10 years peers' antisocial behaviour" ($X^2(1)$ 7.73 $p=0.005$, see footnote of Table 8.3), boys had a higher rate of missingness than girls.

Table 8.3: Number of missing values per each variable included in the MICE model and gender differences in missingness rate

Variables' class	Variable	Missing Total sample (N=4220)	Missing Boys (N=2018)	Missing Girls (N=2202)	X^2 test of gender difference in missingness†
Outcome variable#	Consumed alcohol without parental permission	0	0	0	N/A*
	Frequency of whole alcoholic drinks	0	0	0	N/A*
	Largest number of whole drinks in 24 hour-period	0	0	0	N/A*
	Ever been alcohol-intoxicated	0	0	0	N/A*
Predictor variable	Age 10 depressive symptoms	0	0	0	N/A*
Socio-demographic factor domain covariates	Gender	0	0	0	N/A*
	Age10	0	0	0	N/A*
	Age14	0	0	0	N/A*
	Ethnicity	104	25	79	$X^2(1)$ 1.09 p=0.294
	Social Class	265	145	120	$X^2(1)$ 5.39 p=0.020
	Income per week	926	447	479	$X^2(1)$ 0.10 p=0.755
	Family constellation	696	324	372	$X^2(1)$ 0.53 p=0.464
Family environment factor domain covariates	Maternal alcohol use	2227	1087	1140	$X^2(1)$ 1.85 p=0.173
	Paternal alcohol use	3149	1496	1653	$X^2(1)$ 0.48 p=0.486
	Mother-child interaction	766	365	401	$X^2(1)$ 0.01 p=0.917
	Mother's partner's-child interaction	683	309	374	$X^2(1)$ 2.17 p=0.141
	Maternal depression	627	306	321	$X^2(1)$ 0.28 p=0.593
	Mother partner's depression	2146	1005	1141	$X^2(1)$ 1.71 p=0.191
	Rows between parents	826	384	442	$X^2(1)$ 0.72 p=0.393
Social environment factor domain covariates	Child stressful events	919	428	491	$X^2(1)$ 0.73 p=0.392
	Peers' antisocial activities$	425	276	149	$X^2(1)$ 49.34 p<0.001
	Religiosity (attends place of worship)	593	264	329	$X^2(1)$ 3.01 p=0.083
	Peers' alcohol drinking$	226	122	104	$X^2(1)$ 3.63 p=0.057
Personality and psycho-pathologies factor domain covariates	Child conduct problems	633	296	337	$X^2(1)$ 0.33 p=0.563
	Child peer problems	726	348	378	$X^2(1)$ 0.01 p=0.946

Table 8.3 continued...

	Table 8.3 continued...				
Personality and psycho-pathologies factor domain covariates	Child antisocial activities	74	41	33	$X^2(1)$ 7.69 p=0.006
	Self-esteem	609	291	318	$X^2(1)$ 0.00 p=0.984
Peers' influences (moderating variables)[$]	Age 14 peers' alcohol drinking	604	356	248	$X^2(1)$ 34.93 p<0.001
	Child bonding with peers at age 10 years	70	45	25	$X^2(1)$ 7.73 p=0.005
	Child bonding with peers at age 14 years	26	17	9	$X^2(1)$ 3.23 p=0.072
Auxiliary variables (included only in the imputation model)	House crowding index	820	390	430	$X^2(1)$ 0.03 p=0.869
	Parental education	71	41	30	$X^2(1)$ 2.85 p=0.091
	Bullying status	121	59	62	$X^2(1)$ 0.04 p=0.834
	Sensation-seeking	250	122	128	$X^2(1)$ 0.10 p=0.749
	Age 14 depressive symptoms	254	116	138	$X^2(1)$ 0.50 p=0.479

† Pearson's X^2 reported. Statistically significant (p-value<0.05) results are shaded.
* Pearson's X^2 test not possible when missing values in both boys and girls are equal to 0.
[#] SSAGA items used to generate, using PCA, the outcome variable "age 14 alcohol problem use."
[$] Age 10 years peers' antisocial activities and age 10 years peers' alcohol drinking were combined to generate the moderating variable "age 10 years peers' antisocial behaviour" (see paragraph 4.2.4.2). Missing data in "age 10 years peers' antisocial behaviour" variable were: total sample=567 (342 boys and 225 girls); X2 test for gender difference in missingness: $X^2(1)$ 40.99, p<0.001.

8.2 Results of the multivariable GOLOGIT models

8.2.1 Gender differences in the covariates

Table 8.4 describes the gender differences among the socio-demographic covariates used in the multivariable models, while information about the covariates belonging to the family environment, social environment and personality and psychopathology domain is given in Table 8.5 (see paragraph 6.3.3, step 1). No differences were found between boys and girls for all the covariates belonging to the socio-demographic domain. However, among the family environment domain covariates, girls reported higher levels of mother-child interaction (MWW z=-4.34, p<0.001), whereas boys reported higher levels of father-child interaction (MWW z=5.56, p<0.001). Among the covariates belonging to social environment domain,

boys reported higher levels of peers' alcohol drinking ($X^2(1)=5.39$, $p=0.020$) and peers' antisocial activities ($X^2(3)=190.62$, $p<0.001$). Among the covariates of the personality and psychopathology domain boys also reported higher scores of own antisocial activities ($X^2(3)=206.26$, $p<0.001$).

Table 8.4: Socio-demographic covariates presented for boys and girls separately

Covariate	Measure unit	N boys/ N girls	*M* (*SD*) boys	*M* (*SD*) girls	MWW†
Age10[A]*	Years	2018/2202	10.6 (0.2)	10.6 (0.2)	z=0.98 p=0.325
Age14[B]*	Years	2018/2202	13.8 (0.2)	13.8 (0.2)	z=0.98 p=0.325
Covariate	**Categories**	**N boys/ N girls**	**% boys**	**% girls**	**X2¥**
Ethnicity	Caucasian	1993/2123	96.7	96.3	$X^2(1)$ 0.50 p=0.479
	Non Caucasian		3.3	3.7	
Social class	I	1873/2082	17.1	15.5	$X^2(5)$ 4.14 p=0.530
	II		34.1	34.4	
	III Non Manual		13.5	13.3	
	III Manual		25.4	26.7	
	IV		8.2	7.8	
	V		1.8	2.4	
Income per week	<£100	1571/1723	1.2	1.5	$X^2(4)$ 1.80 p=0.773
	£100 - £199		7.0	7.2	
	£200 - £299		15.5	14.7	
	£300 - £399		20.5	19.4	
	≥£400		55.8	57.2	
Family constellation	Both biological parents	1694/1830	90.1	88.7	$X^2(2)$ 1.84 p=0.399
	1 Biological parent & Partner		4.6	5.3	
	Single Parent		5.4	6.0	

† Wilcoxon-Mann-Whitney test (z score). Statistically significant (p-value<0.05) results are shaded.
¥ Cross-tabulation of each variable with gender. Pearson's X^2 reported. Statistically significant (p-value<0.05) results are shaded.
* Absence of missing data.
[A] Age of assessment of depressive symptoms. Variable categorized in quintiles.
[B] Age of assessment of alcohol problem use. Variable categorized in quintiles.

Table 8.5: Prevalence of all the covariates belonging to the family environment, social environment and personality and psychopathologies domains for boys and girls separately

Factor Domain	Covariate	Measurement Unit	N boys/ N girls	*M* (*SD*) boys	*M* (*SD*) girls	MWW†
Family environment	Mother's alcohol use[A]	Daily alcohol units	931/1062	0.7 (0.9)	0.7 (1.0)	z=0.22 p=0.824
	Mother's partner's alcohol use[A]	Daily alcohol units	522/549	1.7 (1.6)	1.9 (2.1)	z=-0.66 p=0.507
	Mother-child interaction[B]	Parenting score	1653/1801	38.7 (8.4)	39.8 (8.3)	z=-4.34 p<0.001
	Mother's partner's-child interaction[B]	Parenting score	1709/1828	28.1 (10.0)	26.2 (9.6)	z=5.56 p<0.001
	Covariate	**Categories**	**N boys/ N girls**	**% boys**	**% girls**	**X2¥**
	Mother's depression	No Depression	1712/1881	79.6	78.0	$X^2(1)$ 1.22 p=0.268
		Possible Depression		20.4	22.0	
	Mother's partner's depression	No Depression	1013/1061	89.1	88.5	$X^2(1)$ 0.21 P=0.644
		Possible Depression		10.9	11.5	
	Rows between parents[C]	Never	1634/1760	16.5	16.4	$X^2(4)$ 1.75 p=0.781
		1-3 times		51.1	51.0	
		4-7 times		20.1	21.4	
		8-13 times		7.8	6.9	
		>13 times		4.4	4.4	
Social environment	Child stressful events[D]	No events	1590/1711	28.1	25.8	$X^2(6)$ 5.00 p=0.543
		1 event		28.1	28.7	
		2 events		18.7	20.2	
		3 events		10.9	11.7	
		4 events		6.4	6.4	
		5 events		3.8	2.9	
		≥6 events		4.1	4.3	
	Peers' antisocial activities[E]	No activities	1742/2053	51.6	73.4	$X^2(3)$ 190.62 p<0.001
		1 activity		29.0	16.8	
		2 activities		10.7	5.7	
		≥3 activities		8.8	4.3	
	Religiosity (attends place of worship)[F]	Never	1754/1873	53.3	95.6	$X^2(2)$ 0.69 p=0.710
		Sometimes		29.6	3.9	
		Often		17.1	0.6	
	Peers' alcohol drinking[G]	Peers do not drink	1896/2098	96.3	97.6	$X^2(1)$ 5.39 p=0.020
		Peers drink		3.7	2.4	
Personality and psycho-pathologies	Child conduct problems[H]	1st tertile	1722/1865	39.7	41.3	$X^2(2)$ 1.21 p=0.545
		2nd tertile		46.9	46.2	
		3rd tertile		13.4	12.6	
	Child peer problems[H]	1st tertile	1670/1824	48.4	50.8	$X^2(2)$ 2.37 p=0.306
		2nd tertile		25.2	24.8	
		3rd tertile		26.4	24.4	
	Child antisocial activities[E]	No activities	1977/2169	81.1	95.3	$X^2(3)$ 206.26 p<0.001
		1 activity		15.7	3.7	
		2 activities		2.8	0.9	
		≥3 activities		0.4	0.0	

Table 8.5 continued...

Table 8.5 continued...

Personality and psycho-pathologies	Covariate	Measurement Unit	N boys/ N girls	*M* (*SD*) boys	*M* (*SD*) girls	MWW†
	Child self-esteem[B]	Self-esteem score	1727/1884	19.3 (3.4)	19.5 (3.3)	z=1.65 p=0.098

† Wilcoxon-Mann-Whitney test (z score). Statistically significant (p-value<0.05) results are shaded.
¥ Cross-tabulation of each variable with gender. Pearson's X^2 reported. Statistically significant (p-value<0.05) results are shaded.
[A] Measure accounted for alcohol unit from beer, wine and spirits consumed during an average week.
[B] Variable categorized in deciles.
[C] Number of arguments and disagreements between parents in the previous three months was used as an estimate of the bonding of the relationship between the two parents.
[D] The measure provided information of whether each event occurred when the child was 6-7 years old, when he/she was 8 or in both occasions.
[E] The questionnaire included questions about cigarettes and cannabis smoking in previous six months.
[F] Used as a measure of the religious conservatism of the children's rearing environment.
[G] Question extracted from the peers' antisocial behaviour questionnaire at age 10 years.
[H] Main carers completed the parental version of the SDQ for their child.

8.2.2 Analysis of the covariates: formats of the covariates

As explained in paragraph 6.3.3, steps 2 and 3, I conducted a number of tests to decide the most appropriate representation of the covariates to be included in subsequent GOLOGIT models.

As explained in paragraph 6.3.3, step 2, all the covariates were entered in the bivariable GOLOGIT models with parallel lines assumption imposed; concerning the parallel lines assumption of age 10 depressive symptoms variable, this was imposed for the total sample and for the subsample of girls and relaxed for the subsample of boys (see paragraph 7.2).

To ensure the comparability of the estimates of the covariates in the final multivariable GOLOGIT models drawn from the non-imputed and from the imputed dataset, and based on both the total sample and the boys and girls subsample, this analysis was conducted on the total sample and in the non-imputed dataset only, with the obtained results then being generalized to boys and girls and to the imputed variables (see paragraph 6.3.3, step 3).

Table 8.6 reports the results of the LR tests comparing bivariable GOLOGIT models accounting for age 10 depressive symptoms (linearly entered, see paragraph 7.2), age 14 alcohol problem use and each of the covariates listed in Tables 5.2 and 5.3 (with the

exclusion of the dichotomous covariates, i.e., gender, ethnicity, paternal and maternal depression and age 10 peers' alcohol drinking) entered in three possible formats (categorical, quadratic and linear).

For each covariate, the more parsimonious model with the covariate entered as linear was compared with the less parsimonious models with the covariate entered as quadratic or as categorical. The two models with the covariate entered as quadratic or categorical were compared with each other only when both of them would have fit the data significantly better (p-value<0.05) than the model with the covariate entered as linear (see Table 8.6).

Results indicated that for most of the covariates a linear format would have fit the data better than the more complex quadratic and categorical formats (see Table 8.6).

However, in the socio-demographic factor domain, for age of assessment of depressive symptoms ("age 10" covariate) and for age assessment of alcohol problem use ("age 14" covariate), both the quadratic and the categorical representations fit the data significantly better than the more parsimonious linear format (for age 10 assessment of depressive symptoms: $X^2(1)=4.91$ P=0.026 quadratic format versus linear format and $X^2(3)=8.52$ P=0.036 categorical format versus linear format; for age 14 assessment of alcohol problem use: $X^2(1)=12.91$ P<0.001 quadratic format versus linear format and $X^2(3)=16.00$ P=0.001 categorical fashion versus linear fashion, respectively; see Table 8.6). Further comparison between the former two models, i.e., with the covariates entered in a quadratic format (1 degree of freedom) versus with the covariates entered in a categorical format (3 degrees of freedom) revealed that for both age 10 assessment of depressive symptoms as well as age 14 assessment of alcohol problem use the less parsimonious, categorical models did not fit the data significantly better than the more parsimonious, quadratic models ($X^2(3)=6.47$ P=0.091 for age 10 assessment of depressive symptoms and $X^2(3)=6.83$ P=0.078 for age 14

assessment of alcohol problem use, see Table 8.6), thus both these variables were entered as quadratic in the subsequent bivariable and multivariable GOLOGIT models.

Similar results were obtained for two covariates belonging to the family environment factor domain: for maternal and paternal alcohol use LR tests indicated that these covariates should have been entered in a quadratic format rather than a linear format ($X^2(1)=3.95$ P=0.046 and $X^2(1)=5.56$ P=0.018, respectively; see Table 8.6).

Table 8.6: Comparison of bivariable models of age 10 depressive symptoms and age 14 alcohol problem use with covariates entered in either quadratic, categorical or linear formats in the total sample

Factor Domain	Covariate	Quadratic versus Linear[$]	Categorical versus Linear[$]	Quadratic versus Categorical[$] *	Final representation decided upon†
Socio-demographic	Gender	N/A	N/A	N/A	Dichotomous[#]
	Age10	$X^2(1)=4.91$ p=0.026	$X^2(3)=8.52$ p=0.036	$X^2(3)=6.47$ p=0.091	Quadratic
	Age14	$X^2(1)=12.91$ p<0.001	$X^2(3)=16.00$ p=0.001	$X^2(3)=6.83$ p=0.078	Quadratic
	Ethnicity	N/A	N/A	N/A	Dichotomous[#]
	Social Class	$X^2(1)=0.01$ p=0.916	$X^2(4)=1.19$ p=0.879	N/A	Linear
	Income per week	$X^2(1)=0.23$ p=0.632	$X^2(3)=4.22$ p=0.239	N/A	Linear
	Family constellation	$X^2(1)=0.95$ p=0.329	$X^2(1)=0.95$ p=0.329	N/A	Linear
Family environment	Mother's alcohol use	$X^2(1)=3.95$ p=0.046	$X^2(4)=7.59$ p=0.107	N/A	Quadratic
	Mother's partner's alcohol use	$X^2(1)=5.56$ p=0.018	$X^2(5)=7.30$ p=0.199	N/A	Quadratic
	Mother-child interaction	$X^2(1)=0.31$ p=0.575	$X^2(8)=7.12$ p=0.523	N/A	Linear
	Mother's partner's-child interaction	$X^2(1)=0.42$ p=0.516	$X^2(8)=8.64$ p=0.373	N/A	Linear
	Mother's depression	N/A	N/A	N/A	Dichotomous[#]
	Mother's partner's depression	N/A	N/A	N/A	Dichotomous[#]
	Rows between parents	$X^2(1)=0.66$ p=0.415	$X^2(3)=5.5$ p=0.139	N/A	Linear
Social environment	Child stressful events	$X^2(1)=0.33$ P=0.567	$X^2(3)=3.1$ P=0.691	N/A	Linear
	Peers' antisocial activities	$X^2(1)=2.95$ p=0.086	$X^2(2)=0.11$ p=0.947	N/A	Linear
	Religiosity (attends worship)	$X^2(1)=0.87$ p=0.351	$X^2(1)=0.87$ p=0.243	N/A	Linear
	Peers' alcohol drinking	N/A	N/A	N/A	Dichotomous[#]

Table 8.6 continued...

Table 8.6 continued...

Personality and psycho-pathologies	Child conduct problems	$X^2(1)=1.62$ p=0.203	$X^2(1)=1.62$ p=0.203	N/A	Linear
	Child peer problems	$X^2(1)=0.75$ p=0.385	$X^2(1)=1.62$ p=0.203	N/A	Linear
	Child antisocial activities	$X^2(1)=0.05$ p=0.826	$X^2(2)=4.32$ p=0.115	N/A	Linear
	Self-esteem	$X^2(1)=0.05$ p=0.831	$X^2(2)=1.67$ p=0.432	N/A	Linear

$ LR test results; statistically significant (p-value<0.05) results are shaded.
* LR test comparing models with covariate entered in quadratic and categorical formats performed only in case both those models fitted the data significantly better (p-value<0.05) than the model with covariate entered using a linear format (otherwise N/A=not applicable, it is indicated).
† Indicates the most appropriate format (linear, quadratic or categorical) for each variable when this was entered in subsequent bivariable and multivariable GOLOGIT models.
# Comparison of data fittings of dichotomous variables cannot be performed (N/A=not applicable).

8.2.3 Analysis of the covariates: selection of covariates to be included in multivariable models

In order to identify those covariates to be included in the final models, the statistical significance of all the covariates was tested by entering each of them (starting with the covariates belong to the socio-demographic factor domain and ending with those belonging to the personality factor domain, as described in paragraph 6.3.3, step 4) independently in a bivariable GOLOGIT2 model in which age 14 years alcohol problem use is predicted by age 10 years depressive symptoms.

Table 8.7 reports the estimates (O.R., 95% C.I. and p-value) for each covariate when this was entered independently in a bivariable GOLOGIT model in the total sample. Estimates from the subsamples of boys and girls are reported in Table 8.8 and Table 8.9, respectively. These analyses were conducted on both the non-imputed and imputed datasets (see paragraph 6.3.4).

Due to the presence of missing values in the covariates (see Table 8.3), each bivariable GOLOGIT model drawn from the non-imputed dataset was based on a different subset of participants; on the contrary, there were no differences in the numbers of participants on which each bivariable GOLOGIT model was based upon when this was drawn from the

imputed dataset (see paragraph 6.3.4). Please note that only the results of the "L&M versus H equation" of the GOLOGIT models are reported (see paragraph 6.1.1; "L&M versus H equation" is equivalent to a binary logistic regression in which the outcome variable is divided in two categories: 1) adolescents who developed high alcohol problem use, and 2) adolescents who developed either low or medium alcohol problem use).

As explained in paragraph 6.3.3, step 5, I included in the multivariable models (for both the total sample and the subsamples of boys and girls separately) only those covariates that, when tested in a bivariable model, were statistically significant (p-value<0.05).

When considering the total sample, the following covariates reached the threshold of $p<0.05$ when tested in bivariable GOLOGIT models drawn from the non-imputed and imputed datasets (see Table 8.7 for detailed estimates).

- *Socio-demographic domain*
    - *Non-imputed dataset:* gender (p=0.007); age of assessment of depressive symptoms (age 10) (p=0.025); age of assessment of alcohol problem use (age 14) (p<0.001) and family constellation (p=0.034).
    - *Imputed dataset:* gender (p=0.007); age of assessment of depressive symptoms (age 10) (p=0.025); age of assessment of alcohol problem use (age 14) (p<0.001) and family constellation (p<0.001).
- *Family environment domain*
    - *Non-imputed dataset:* mother's and mother's partner's alcohol use (with both covariates having p<0.001); mother-child interaction (p=0.003).
    - *Imputed dataset:* mother's and mother's partner's alcohol use (with both covariates having p<0.001) and mother-child interaction (p=0.003).

- *Social environment domain*
    - *Non-imputed dataset:* all the covariates were significant: childhood stressful events (p=0.047); peers' antisocial activity (p<0.001); religiosity (p=0.001); age 10 years peers' alcohol drinking (p=0.009).
    - *Imputed dataset:* all the covariates were significant: childhood stressful events (p=0.028); peers antisocial activities (p<0.001); religiosity (p=0.001) and age 10 years peers; alcohol drinking (p=0.012).
- *Personality and psychopathologies domain*
    - *Non-imputed dataset:* child peer problems (p=0.001); child antisocial activities (p<0.001).
    - *Imputed dataset:* child conduct problems (p=0.037); child peer problems (p=0.001) and child antisocial activities (p<0.001).

The only covariate that was estimated to be significant in the bivariable GOLOGIT model drawn from the imputed dataset (p=0.037) but not in the bivariable model drawn from the non-imputed dataset (p=0.055) was child conduct problems, which was therefore included as a covariate in the multivariable GOLOGIT models based on the imputed dataset (but not in those based on the non-imputed dataset).

Table 8.7: Estimates of each covariate when tested independently in bivariable GOLOGIT models drawn from both the non-imputed and the imputed datasets and based on the total sample

		Non-imputed dataset				Imputed dataset			
Factor Domain	**Covariate**	**O.R.**	**95% C.I.**		**p[$]**	**O.R.**	**95% C.I.**		**p[$]**
Socio-demographic	Gender*^	0.85	0.76	0.96	0.007	0.85	0.76	0.96	0.007
	Age10*^	1.05	1.01	1.10	0.025	1.05	1.01	1.10	0.025
	Age14*^	1.19	1.14	1.24	<0.001	1.19	1.14	1.24	<0.001
	Ethnicity	1.31	0.94	1.83	0.107	1.30	0.94	1.81	0.114
	Social Class	1.01	0.96	1.06	0.73	1.00	0.96	1.05	0.917
	Income per week	1.04	0.98	1.11	0.19	1.04	0.97	1.11	0.253
	Family constellation*^	1.34	1.02	1.75	0.034	1.58	1.21	2.05	0.001
Family environment	Mother's alcohol use*^	1.23	1.13	1.33	<0.001	1.20	1.11	1.29	<0.001
	Mother's partner's alcohol use*^	1.15	1.08	1.24	<0.001	1.13	1.07	1.19	<0.001
	Mother-child interaction*^	0.97	0.94	0.99	0.003	0.96	0.94	0.99	0.003
	Mother's partner's-child interaction	0.98	0.96	1.00	0.054	0.98	0.95	1.00	0.063
	Mother's depression	1.01	0.86	1.18	0.931	1.01	0.86	1.19	0.879
	Mother's partner's depression	1.02	0.78	1.33	0.888	1.12	0.86	1.45	0.400
	Rows between parents	1.06	0.99	1.13	0.106	1.06	0.99	1.14	0.075
Social environment	Child stressful events*^	1.04	1.00	1.09	0.047	1.05	1.00	1.09	0.028
	Peers' antisocial activities*^	1.16	1.08	1.25	<0.001	1.16	1.09	1.25	<0.001
	Religiosity (attends a place of worship)*^	0.87	0.80	0.94	0.001	0.87	0.80	0.95	0.001
	Peers' alcohol drinking*^	1.58	1.12	2.24	0.009	1.56	1.10	2.21	0.012
Personality and psycho-pathologies	Child conduct problems^	1.10	1.00	1.21	0.055	1.11	1.01	1.22	0.037
	Child peer problems*^	0.87	0.81	0.94	0.001	0.88	0.81	0.95	0.001
	Child antisocial activities*^	1.40	1.20	1.62	<0.001	1.38	1.19	1.60	<0.001
	Self-esteem	1.03	0.97	1.09	0.336	0.98	0.96	1.01	0.209

[$] Statistically significant (p-value<0.05) estimates of the covariates when tested in the bivariable GOLOGIT models are shaded.

* Covariate entered in multivariable GOLOGIT model drawn from the non-imputed dataset.

^ Covariate entered in multivariable GOLOGIT model drawn from the imputed dataset.

Analyzing the two gender subsamples separately, the results indicated that different sets of covariates should be entered in the multivariable GOLOGIT models for boys and for girls. When accounting for the subsample of boys only, the following covariates reached the threshold of p-value<0.05 when tested in bivariable GOLOGIT models drawn from the non-imputed and imputed datasets were found (see Table 8.8 for detailed estimates).

- *Socio-demographic domain*
    - *Non-imputed dataset:* age of assessment of alcohol problem use ($p<0.001$) (age 14).
    - *Imputed dataset:* age of assessment of alcohol problem use (age 14) ($p<0.001$).
- *Family environment domain*
    - *Non-imputed dataset:* mother's and mother's partner's alcohol use (respectively, $p=0.026$ and $p=0.049$).
    - *Imputed dataset:* mother's and mother's partner's alcohol use (with both covariates having $p=0.002$).
- *Social environment domain*
    - *Non-imputed dataset:* peers' antisocial activities ($p<0.001$) and age 10 years peers' alcohol drinking ($p=0.001$).
    - *Imputed dataset:* peers' antisocial activities ($p<0.001$) and age 10 years peers' alcohol drinking ($p=0.001$).
- *Personality and psychopathologies domain*
    - *Non-imputed dataset:* child antisocial activities ($p<0.001$).
    - *Imputed dataset:* child conduct problems ($p=0.037$) and child antisocial activities ($p<0.001$).

Similar to the total sample, the only covariate in the subsample of boys that was estimated to be significant in the bivariable GOLOGIT model drawn from the imputed dataset (p=0.037), but not in the bivariable model drawn from the non-imputed dataset (p=0.055), was child conduct problems, which was therefore included as a covariate in the multivariable GOLOGIT models based on the imputed dataset (but not in those based on the non-imputed dataset).

Table 8.8: Estimates of each covariate when tested independently in bivariable GOLOGIT models drawn from both the non-imputed and the imputed datasets and based on the subsample of boys

		Non-imputed dataset				Imputed dataset			
Factor Domain	**Covariate**	**O.R.**	**95% C.I.**		**p$**	**O.R.**	**95% C.I.**		**p$**
Socio-demographic	Age10	1.09	1.00	1.19	0.061	1.09	1.00	1.19	0.062
	Age14*^	1.23	1.13	1.34	<0.001	1.23	1.13	1.34	<0.001
	Ethnicity	0.89	0.45	1.77	0.736	0.91	0.46	1.80	0.783
	Social Class	1.02	0.92	1.13	0.722	1.02	0.92	1.12	0.728
	Income per week	0.94	0.82	1.07	0.338	0.96	0.85	1.09	0.54
	Family constellation	0.89	0.47	1.70	0.73	1.36	0.79	2.35	0.267
Family environment	Mother's alcohol use*^	1.22	1.02	1.46	0.026	1.24	1.09	1.42	0.002
	Mother's partner's alcohol use*^	1.17	1.01	1.37	0.049	1.17	1.06	1.28	0.002
	Mother-child interaction	0.99	0.94	1.04	0.762	0.98	0.94	1.03	0.477
	Mother's partner's-child interaction	1.01	0.96	1.06	0.829	1.00	0.95	1.05	0.864
	Mother's depression	1.32	0.96	1.81	0.093	1.29	0.94	1.76	0.12
	Mother's partner's depression	1.34	0.77	2.34	0.295	1.32	0.84	2.07	0.223
	Rows between parents	0.99	0.85	1.14	0.863	1.02	0.89	1.18	0.763
Social environment	Child stressful events	1.03	0.95	1.12	0.493	1.05	0.96	1.14	0.274
	Peers' antisocial activities*^	1.48	1.29	1.69	<0.001	1.45	1.27	1.65	<0.001
	Religiosity (attends a place of worship)	0.85	0.71	1.02	0.077	0.83	0.69	1.00	0.053
	Peers' alcohol drinking*^	2.53	1.48	4.33	0.001	2.46	1.43	4.22	0.001
Personality and psycho-pathologies	Child conduct problems^	1.21	1.00	1.48	0.055	1.23	1.01	1.49	0.037
	Child peer problems*^	0.85	0.71	1.01	0.064	0.86	0.72	1.02	0.081
	Child antisocial activities*^	1.89	1.53	2.33	<0.001	1.86	1.51	2.29	<0.001
	Self-esteem	1.02	0.90	1.15	0.815	1.00	0.88	1.14	0.961

$ Statistically significant (p-value<0.05) estimates of the covariates when tested in the bivariable GOLOGIT models are shaded.

* Covariate entered in multivariable GOLOGIT model drawn from the non-imputed dataset.

^ Covariate entered in multivariable GOLOGIT model drawn from the imputed dataset.

When considering only the subsample of girls, compared to the boys subsample, a greater number of covariates reached the threshold of p-value<0.05 when tested in bivariable GOLOGIT models drawn from the non-imputed and imputed datasets (see Table 8.9 for detailed estimates).

- *Socio-demographic domain*
    - *Non-imputed dataset:* age of assessment of depressive symptoms (age 10) (p=0.016); age of assessment of alcohol problem use (age 14) (p<0.001) and family constellation (p=0.018).
    - *Imputed dataset:* age of assessment of depressive symptoms (age 10) (p=0.017); age of assessment of alcohol problem use (age 14) (p<0.001) and family constellation (p=0.001).
- *Family environment domain*
    - *Non-imputed dataset:* mother's and mother's partner's alcohol use (p<0.001 and p=0.016 respectively); mother-child interaction (p=0.001) and rows between parents (p=0.003)
    - *Imputed dataset:* mother's and mother's partner's alcohol use (p<0.001 and p=0.002 respectively); mother-child interaction (p=0.003) and rows between parents (p=0.007)
- *Social environment domain*
    - *Non-imputed dataset:* childhood stressful events (p=0.007); peers' antisocial activity (p=0.039) and religiosity (p=0.034).
    - *Imputed dataset:* childhood stressful events (p=0.008); peers' antisocial activity (p=0.046) and religiosity (p=0.035).

- *Personality and psychopathologies domain*
    - *Non-imputed dataset:* child conduct problems (p=0.047) and child peer problems (p=0.035).
    - *Imputed dataset:* child conduct problems (p=0.041) and child peer problems (p=0.032).

These results indicate that the same covariates that were found statistically significant (p-value<0.05) in the non-imputed dataset were also statistically significant (p-value<0.05) in the imputed dataset.

Table 8.9: Estimates of each covariate when tested independently in bivariable GOLOGIT models drawn from both the non-imputed and the imputed datasets and based on the subsample of girls

		Non-imputed dataset				Imputed dataset			
Factor Domain	**Covariate**	**O.R.**	**95% C.I.**		**p[$]**	**O.R.**	**95% C.I.**		**p[$]**
Socio-demographic	Age10*^	1.07	1.01	1.14	0.016	1.07	1.01	1.14	0.017
	Age14*^	1.21	1.14	1.28	<0.001	1.21	1.14	1.28	<0.001
	Ethnicity	1.37	0.88	2.12	0.164	1.37	0.89	2.12	0.154
	Social Class	1.02	0.95	1.08	0.639	1.01	0.95	1.08	0.705
	Income per week	1.07	0.98	1.17	0.133	1.05	0.96	1.15	0.279
	Family constellation*^	1.55	1.08	2.24	0.018	1.77	1.25	2.50	0.001
Family environment	Mother's alcohol use*^	1.25	1.13	1.40	<0.001	1.20	1.09	1.32	<0.001
	Mother's partner's alcohol use*^	1.12	1.02	1.22	0.016	1.12	1.04	1.20	0.002
	Mother-child interaction*^	0.95	0.92	0.98	0.001	0.95	0.92	0.98	0.003
	Mother's partner's-child interaction	0.98	0.95	1.01	0.21	0.98	0.95	1.01	0.206
	Mother's depression	0.91	0.74	1.13	0.391	0.93	0.75	1.15	0.509
	Mother's partner's depression	0.93	0.64	1.36	0.72	1.13	0.80	1.60	0.480
	Rows between parents	1.15	1.05	1.26	0.003	1.13	1.03	1.24	0.007
Social environment	Child stressful events*^	1.08	1.02	1.14	0.007	1.08	1.02	1.14	0.008
	Peers' antisocial activities*^	1.12	1.01	1.25	0.039	1.12	1.00	1.25	0.046
	Religiosity (attends a place of worship)*^	0.89	0.79	0.99	0.034	0.89	0.79	0.99	0.035
	Peers' alcohol drinking	1.48	0.88	2.48	0.135	1.47	0.88	2.46	0.137
Personality and psycho-pathologies	Child conduct problems*^	1.14	1.00	1.30	0.047	1.14	1.01	1.30	0.041
	Child peer problems*^	0.89	0.80	0.99	0.035	0.89	0.80	0.99	0.032
	Child antisocial activities	1.29	0.95	1.74	0.098	1.29	0.95	1.75	0.098
	Self-esteem	1.03	0.95	1.12	0.428	1.03	0.95	1.11	0.543

[$] Statistically significant (p-value<0.05) estimates of the covariates when tested in the bivariable GOLOGIT models are shaded.

* Covariate entered in multivariable GOLOGIT model drawn from the non-imputed dataset.

^ Covariate entered in multivariable GOLOGIT model drawn from the imputed dataset.

8.2.4 Sensitivity analysis for the estimation of mother's partner's / relationship between partners related covariates in single parent and two-parent families

As explained in paragraph 6.3.3, steps 5 and 6, a sensitivity analysis was conducted on both the non-imputed and imputed datasets following the statistically significant results (p-value<0.05) of four bivariable GOLOGIT models accounting for the mother's partner's / relationship between partners related covariates (i.e. mother's partner's alcohol use, mother's partner's parent-child interaction and mother's partner's depression and rows between parents).

The results of the bivariable GOLOGIT models reported in paragraph 8.2.3, in fact, indicated that the "mother's partner's alcohol use" covariate was statistically significant (p-value<0.05) in bivariable GOLOGIT models based on both the total sample (p<0.001 in the non-imputed dataset, p<0.001 in the imputed dataset) and on the subsamples of boys (p=0.049 in the non-imputed dataset, p=0.002 in the imputed dataset) and girls (p=0.016 in the non-imputed dataset, p=0.002 in the imputed dataset), whereas the "parental rows" covariate was statistically significant (p-value<0.05) in the bivariable GOLOGIT model based on the subsample of girls only (p=0.003 in the non-imputed dataset, p=0.007 in the imputed dataset) (see Tables 8.7, 8.8 and 8.9).

This sensitivity analysis was conducted because, for 5.7% of the children in the total sample (5.4% of the subsample of boys and 6.0% of the subsample of girls; see Table 5.2 and Table 8.4) who, at age 97 months were living in single parents families composed by a single female parental figure (usually the mother) (information on family constellation was missing for 696 children in total: 324 boys and 372 girls, see Table 8.3), the covariates describing mother's partner's alcohol use and rows between parents were not relevant.

Results of the sensitivity analysis indicated that, when "mother's partner's alcohol use" and "rows between parents" covariates were included in multivariable models drawn from the

imputed dataset (which were including all the covariates statistically significant (p-value<0.05) when tested in the bivariable GOLOGIT model), none of them reached the significance level threshold of p-value<0.05 (see Table 8.10). Both covariates were therefore excluded from all the final multivariable models based on the non-imputed sample.

In order to conduct the sensitivity analysis on the imputed dataset, as explained in paragraph 6.3.4, the frequencies of the imputed covariate "family constellation" (93.1% of children living in two-parent families (87.7% in families with both biological parents and 5.4% in families with the biological mother and her partner) and 6.9% of children living in single-parent families) were used to exclude those children living in single-parent families.

Results of the sensitivity analysis conducted on the imputed dataset were similar to those obtained from the sensitivity analysis conducted on the non-imputed dataset, with both "mother's partner's alcohol use" and "rows between parents" covariates not reaching the significance level of p-value<0.05 (see Table 8.10).

These results justified the exclusion of these two family environment domain covariates from the final multivariable models and allowed me to conduct the analysis without the need to conduct separate analyses in subgroups of children living with either one or two parents.

Table 8.10: Sensitivity analysis of mother's partner's / relationship between partners related covariates in the subsample of children living in two-parent families[1]

		Non-imputed dataset				Imputed dataset				
		N*	O.R.	95% C.I.	p	N[$]	O.R.	95% C.I.	p	
Mother's partner's alcohol use	Total sample	421	1.01	0.83 1.23	0.882	3906	1.08	0.99 1.18	0.052	
	Girls subsample	214	0.95	0.73 1.24	0.754	2026	1.06	0.95 1.19	0.273	
	Boys subsample	304	1.18	0.83 1.67	0.351	1880	1.11	0.98 1.27	0.086	
Rows between parents	Girls subsample	214	1.01	0.64 1.58	0.979	2026	1.10	0.96 1.27	0.180	

1. Multivariable GOLOGIT model including all the covariates statistically significant in the bivariable GOLOGIT models (see paragraph 8.2.3). Only the estimates of the covariates "mother's partner's alcohol use" and "rows between parents" are reported.

* Reduced sample size in the non-imputed dataset due to the presence of missing values in covariates.

[$] Reduced sample size in the imputed dataset due to the exclusion of the children living in single-,parent families (corresponding to 6.9% of the total sample (N total sample=4220); 7.4% of girls (N subsample of girls=2202) and 6.4% of boys (N subsample of boys=2018)). Imputed "family constellation" covariate was used to identify those children living with one parent only.

8.2.5 Final multivariable GOLOGIT models drawn from the non-imputed and imputed datasets: total sample

Results of the multivariable analysis using the non-imputed and the imputed covariates are presented for the total sample in Table 8.11.

Please note that, as explained in paragraph 6.1.1, for this analysis (and likewise for the analysis described in paragraph 8.2.6 below), I present only the results of the "L&M versus H equation" of the multivariable GOLOGIT models I developed (see paragraph 6.3.3, step 7), hence focusing on the role that age 10 years depressive symptoms and the other relevant covariates have in predicting age 14 years high alcohol problem use ("L&M versus H equation" is equivalent to a binary logistic regression in which the outcome variable is divided in two categories: 1) adolescents who developed high alcohol problem use, and 2) adolescents who developed either low or medium alcohol problem use).

These analyses were based on sample size of N=1220 and N=4220, respectively. With the inclusion of the relevant covariates, the relationship between childhood depressive symptoms and adolescent high alcohol problem use was diminished compared to the univariable model (see paragraph 7.3), both in the imputed as well as the non-imputed dataset (O.R. 1.05, 95% C.I. 0.97; 1.15, p=0.22 for the imputed dataset and O.R. 0.94, 95% C.I. 0.79; 1.13, p=0.52 for the non imputed dataset, respectively).

The analysis for both the non-imputed and in the imputed dataset showed that in the total sample, the relationship between age 10 depressive symptoms and age 14 alcohol problem use was influenced by a number of covariates belonging to all the factor domains taken into account. The following covariates were statistically significant (p-value<0.05) when included in the final multivariable GOLOGIT model drawn from the imputed dataset based on the total sample. Due to the difference in the size of the sample on which these two multivariable GOLOGIT models were based (imputed dataset N=4220 and non-imputed datasets N=1220), some differences were observed in the covariates estimation across the two multivariable GOLOGIT models (see Table 8.11).

- *Socio-demographic domain*
    - *Model drawn from the imputed dataset:* gender (O.R. 0.78, 95% C.I. 0.68; 0.89, p<0.001, gender coded as girls=0, boys=1); age of assessment of alcohol problem use (age 14) (O.R. 1.18, 95% C.I. 1.13; 1.23, p<0.001) and family constellation (O.R. 1.60, 95% C.I. 1.23; 2.09, p=0.001).
    - *Differences between the two models (imputed versus non-imputed):* family constellation was no longer statistically significant in the model drawn from the non-imputed dataset (O.R. 1.36, 95% C.I. 0.84; 2.20, p=0.210).

- *Family environment domain*
    - *Model drawn from the imputed dataset:* mother's alcohol use (O.R. 1.19, 95% C.I. 1.11; 1.28, p<0.001) and mother-child interaction (O.R. 0.96, 95% C.I. 0.94; 0.99, p=0.004).
    - *Differences between the two models (imputed versus non-imputed):* mother-child interaction was no longer statistically significant in the model drawn from the non-imputed dataset (O.R. 0.96, 95% C.I. 0.92; 1.01, 0.089).
- *Social environment domain*
    - *Model drawn from the imputed dataset:* peers antisocial activities (O.R. 1.13, 95% C.I. 1.04; 1.23, p=0.003) and religiosity (O.R. 0.89, 95% 0.82; 0.97, p=0.008).
    - *Differences between the two models:* None.
- *Personality and psychopathologies domain*
    - *Model drawn from the imputed dataset:* Child peer problems (O.R. 0.84, 95% C.I. 0.78; 0.91, p<0.001) and child antisocial activities (O.R. 1.28, 95% C.I. 1.08; 1.51, p=0.005).
    - *Differences between the two models (imputed versus non-imputed):* child antisocial activities was no longer statistically significant in the model drawn from the non-imputed dataset (O.R. 0.87, 95% C.I. 0.59; 1.28, p=0.488).

Table 8.11: Final multivariable GOLOGIT models drawn from the non-imputed and the imputed datasets predicting age 14 years high alcohol problem use for the total sample

		Non-imputed dataset (N=1220)[#]				Imputed dataset (N=4220)[#]			
		O.R.	95% C.I.		p[$]	O.R.	95% C.I.		p[$]
Age 10 depressive symptoms		0.94	0.79	1.13	0.520	1.05	0.97	1.15	0.220
Factor Domain	**Covariate**	**O.R.**	**95% C.I.**		**p[$]**	**O.R.**	**95% C.I.**		**p[$]**
Socio-demographic	Gender	0.77†	0.61	0.98	0.034	0.78†	0.69	0.89	<0.001
	Age10	1.03	0.95	1.13	0.436	1.00	0.96	1.05	0.906
	Age14	1.10	1.02	1.20	0.019	1.18	1.13	1.23	<0.001
	Ethnicity								
	Social Class								
	Income per week								
	Family constellation	1.36†	0.84	2.20	0.21	1.60†	1.23	2.09	0.001
Family environment	Mother's alcohol use	1.30†	1.17	1.44	<0.001	1.19	1.11	1.28	<0.001
	Mother's partner's alcohol use								
	Mother-child interaction	0.96	0.92	1.01	0.089	0.96	0.94	0.99	0.004
	Mother's partner's-child interaction								
	Mother's depression								
	Mother's partner's depression								
	Rows between parents								
Social environment	Child stressful events	0.99	0.92	1.07	0.822	1.04	0.99	1.08	0.092
	Peers' antisocial activities	1.29	1.10	1.50	0.001	1.13	1.04	1.23	0.003
	Religiosity (attends a place of worship)	0.86	0.74	1.00	0.047	0.89	0.82	0.97	0.008
	Peers' alcohol drinking	1.27	0.60	2.71	0.528	1.28	0.88	1.85	0.200
Personality and psycho-pathologies	Child conduct problems^					1.08	0.98	1.20	0.114
	Child peer problems	0.78†	0.67	0.90	0.001	0.84	0.78	0.91	<0.001
	Child antisocial activities	0.87	0.59	1.28	0.488	1.28	1.08	1.51	0.005
	Self-esteem								

[#] Number of participants with available information for all the covariates included in the models.

[$] Estimates of the multivariable GOLOGIT model including all the covariates that were statistically significant (p-value<0.05) in the bivariable GOLOGIT models (see paragraph 8.2.3.). Sensitivity analysis excluded mother's partner's related covariates (see paragraph 8.2.4.). Statistically significant (p-value<0.05) estimates are shaded.

†O.R. ≥1.30 or ≤0.80.

^ Included only in the multivariable GOLOGIT model drawn from the imputed dataset (see Table 8.7.).

8.2.6 Final multivariable GOLOGIT models drawn from the non-imputed and imputed datasets: gender differences

Results of the multivariable analyses on the boys and girls subsamples using the non-imputed and the imputed covariates are reported in Table 8.12 (for the analysis conducted in the imputed dataset) and in Table 8.13 (for the analysis conducted in the non-imputed dataset).

Results of the multivariable GOLOGIT models drawn from the imputed dataset indicated that, with the inclusion of the relevant covariates, there was no longer a relationship between childhood depressive symptoms and adolescent high alcohol problem use, neither for boys (O.R. 0.92, 95% C.I. 0.84; 1.00, p=0.063), nor girls (O.R. 1.12, 95% C.I. 1.00; 1.25, p=0.058), for whom the strength of the relationship was diminished compared to the univariable model (see paragraph 7.3).

For these analyses, in the imputed dataset (see Table 8.12), a different pattern of influences of the covariates in the relationship between age 10 depressive symptoms and age 14 alcohol problem use was found for the genders.

- *Socio-demographic domain*
    - *Subsample of boys:* age of assessment of alcohol problem use (age 14) (O.R. 1.19, 95% C.I. 1.09; 1.30, p<0.001).
    - *Subsample of girls:* age of assessment of alcohol problem use (age 14) (O.R 1.20, 95% C.I. 1.13; 1.28, p<0.001) and family constellation (O.R. 1.76, 95% C.I. 1.24; 2.49, p=0.002).
- *Family environment domain*
    - *Subsample of boys:* mother's alcohol use (O.R. 1.24, 95% C.I. 1.08; 1.43, p=0.002).

- *Subsample of girls:* mother's alcohol use (O.R. 1.20, 95% C.I. 1.09; 1.32, p<0.001) and mother-child interaction (O.R. 0.95, 95% C.I. 0.92; 0.99, p=0.004).

- *Social environment domain*
  - *Subsample of boys:* peers' antisocial activities (O.R. 1.28, 95% C.I. 1.09; 1.49, p=0.002).
  - *Subsample of girls:* stressful life events (O.R. 1.06, 95% C.I. 1.00, 1.13, p=0.045) and peers' antisocial activities (O.R. 1.14, 95% C.I. 1.02; 1.27, p=0.024).
- *Personality and psychopathologies domain*
  - *Subsample of boys:* Child antisocial activities (O.R. 1.43, 95% C.I. 1.12; 1.83, p=0.004).
  - *Subsample of girls:* Child peer problems (O.R. 0.84, 95% C.I. 0.75; 0.94, p=0.002).

Table 8.12: Final multivariable GOLOGIT models drawn from the imputed dataset predicting age 14 high alcohol problem use for the two genders separately

		Boys (N=2018)#				Girls (N=2202)#			
		O.R.	95% C.I.		p$	O.R.	95% C.I.		p$
Age 10 depressive symptoms		0.92	0.84	1.00	0.063	1.12	1.00	1.25	0.058
Factor Domain	**Covariate**	**O.R.**	**95% C.I.**		**p$**	**O.R.**	**95% C.I.**		**p$**
Socio-demographic	Age10					1.03	0.96	1.09	0.419
	Age14	1.19	1.09	1.30	<0.001	1.20	1.13	1.28	<0.001
	Ethnicity								
	Social Class								
	Income per week								
	Family constellation					1.76†	1.24	2.49	0.002
Family environment	Mother's alcohol use	1.24	1.08	1.43	0.002	1.20	1.09	1.32	<0.001
	Mother's partner's alcohol use								
	Mother-child interaction					0.95	0.92	0.99	0.004
	Mother's partner's-child interaction								
	Mother's depression								
	Mother's partner's depression								
	Rows between parents								
Social environment	Child stressful events					1.06	1.00	1.13	0.045
	Peers' antisocial activities	1.28	1.09	1.49	0.002	1.14	1.02	1.27	0.024
	Religiosity (attends a place of worship)					0.91	0.81	1.01	0.084
	Peers' alcohol drinking	1.33†	0.72	2.44	0.364				
Personality and psycho-pathologies	Child conduct problems^	1.12	0.92	1.37	0.272	1.13	0.98	1.30	0.085
	Child peer problems					0.84	0.75	0.94	0.002
	Child antisocial activities	1.43†	1.12	1.83	0.004				
	Self-esteem								

Number of participants with available information for all the covariates included in the models.

$ Estimates of the multivariable GOLOGIT model including all the covariates that were statistically significant (p-value<0.05) in the bivariable GOLOGIT models (see paragraph 8.2.3). Sensitivity analysis excluded mother's partner's related covariates (see paragraph 8.2.4). Statistically significant (p-value<0.05) estimates are shaded.

†O.R. ≥1.30 or ≤0.80.

^ In the subsample of boys, included only in the multivariable GOLOGIT model drawn from the imputed dataset (see Table 8.8).

The same analyses described above were also conducted using the non-imputed dataset; however, in this case the multivariable GOLOGIT models were based on a considerably smaller sample (N=782 for boys and N=649 for girls; see Table 8.13).

Similar to the imputed dataset, the association between age 10 depressive symptoms and age 14 alcohol problem use was no longer significant in boys (O.R. 0.92, 95% C.I. 0.80; 1.07 p=0.296) and was strongly diminished in girls (O.R. 1.07, 95% C.I. 0.84; 1.36, p=0.597), compared to the one observed in the univariable models (see paragraph 7.3).

Results indicated that most of the covariates that were statistically significant when tested in the imputed dataset (see Table 8.12) were also statistically significant in the non-imputed dataset for both boys and girls. The only covariate that was statistically significant when included in the multivariable GOLOGIT model drawn from the non-imputed dataset, but not when included in the multivariable GOLOGIT model drawn from the imputed dataset was, for the subsample of boys only, the covariate age 10 years "peers' alcohol drinking" (O.R. 3.06, 95% C.I. 1.18; 7.93, p=0.021 in the multivariable GOLOGIT model drawn from the non-imputed dataset and O.R. 1.33, 95% C.I. 0.72; 2.44, p=0.365 in the multivariable GOLOGIT model drawn from the imputed dataset).

On the contrary, the following covariates no longer influenced the relationship between age 10 depressive symptoms and age 14 alcohol problem use in the subsamples of boys and girls (see Table 8.13).

- *Subsample of boys:* peers' antisocial activities (O.R. 1.25, 95% C.I. 0.97; 1.60, p=0.082) and child antisocial activities (O.R. 1.47, 95% C.I. 0.91; 2.40, p=0.119).
- *Subsample of girls:* family constellation (O.R. 1.85, 95% C.I. 0.97; 3.54, p=0.063) and stressful life events (O.R. 0.99, 95% C.I. 0.89; 1.09, p=0.774).

Table 8.13: Final multivariable GOLOGIT models drawn from the non-imputed dataset predicting age 14 high alcohol problem use for the two genders separately

		Boys (N=782)[#]				Girls (N=649)[#]			
		O.R.	95% C.I.		p[$]	O.R.	95% C.I.		p[$]
Age 10 depressive symptoms		0.92	0.80	1.07	0.296	1.07	0.84	1.36	0.597
Factor Domain	**Covariate**	**O.R.**	**95% C.I.**		**p[$]**	**O.R.**	**95% C.I.**		**p[$]**
Socio-demographic	Age10					1.09	0.97	1.22	0.166
	Age14	1.26	1.08	1.48	0.003	1.12	1.00	1.26	0.044
	Ethnicity								
	Social Class								
	Income per week								
	Family constellation					1.85†	0.97	3.54	0.063
Family environment	Mother's alcohol use	1.28	1.06	1.55	0.01	1.37†	1.18	1.58	<0.001
	Mother's partner's alcohol use								
	Mother-child interaction					0.93	0.87	0.98	0.009
	Mother's partner's-child interaction								
	Mother's depression								
	Mother's partner's depression								
	Rows between parents								
Social environment	Child stressful events					0.99	0.89	1.09	0.774
	Peers' antisocial activities	1.25	0.97	1.60	0.082	1.39†	1.12	1.73	0.003
	Religiosity (attends a place of worship)					0.92	0.75	1.13	0.438
	Peers' alcohol drinking	3.06†	1.18	7.93	0.021				
Personality and psycho-pathologies	Child conduct problems^					1.18	0.93	1.49	0.173
	Child peer problems					0.65†	0.53	0.80	<0.001
	Child antisocial activities	1.47†	0.91	2.40	0.119				
	Self-esteem								

[#] Number of participants with available information for all the covariates included in the models.

[$] Estimates of the multivariable GOLOGIT model including all the covariates that were statistically significant (p-value<0.05) in the bivariable GOLOGIT models (see paragraph 8.2.3). Sensitivity analysis excluded mother's partner's related covariates (see paragraph 8.2.4). Statistically significant (p-value<0.05) estimates are shaded.

†O.R. ≥1.30 or ≤0.80.

^ In the subsample of boys, included only in the multivariable GOLOGIT model drawn from the imputed dataset (see Table 8.8).

7.3 Missing data imputation and results of the multivariable GOLOGIT models: synthesis of the chapter

In summary, in this chapter I described the results of the imputation procedure used to impute the missing data and of the multivariable GOLOGIT models used to investigate how the relationship between childhood depressive symptoms and alcohol problem use in adolescence is corrected by a number or relevant covariates belonging to the socio-demographic, family environment, social environment and personality and psychopathology domains.

Among all 35 variables included in the imputation model, only eight variables were fully available for all the 4,220 participant children included in the study sample, reason for which a missing data imputation was considered being necessary.

In order to identify those covariates to be included in the final models, the statistical significance of all the covariates was tested by entering each of them independently in a bivariable GOLOGIT2 model in which age 14 years alcohol problem use is predicted by age 10 years depressive symptoms.

Due to the presence of missing values in the covariates, each bivariable GOLOGIT model drawn from the non-imputed dataset was based on a different subset of participants; on the contrary, there were no differences in the numbers of participants on which each bivariable GOLOGIT model was based upon when this was drawn from the imputed dataset.

I included in the multivariable models (for both the total sample and the subsamples of boys and girls separately) only those covariates that, when tested in a bivariable model, were statistically significant (p-value<0.05).

Concerning the gender difference in the pattern of covariates, when considering only the subsample of girls, compared to the boys subsample, a greater number of covariates reached the threshold of p-value<0.05 when tested in bivariable GOLOGIT models drawn from the non-imputed and imputed datasets.

Results of the multivariable analysis using the non-imputed and the imputed covariates were conducted in the total sample on sample sizes of N=1220 and N=4220, respectively.

With the inclusion of the relevant covariates, the relationship between childhood depressive symptoms and adolescent high alcohol problem use was diminished compared to the univariable, both in the imputed dataset (O.R. 1.05, p=0.22). The analysis conducted in the imputed dataset showed that, in the total sample, the relationship between age 10 depressive symptoms and age 14 alcohol problem use was influenced by a number of covariates belonging to all the factor domains taken into account.

Results of the multivariable analyses on the boys and girls subsamples using the imputed covariates indicated that, with the inclusion of the relevant covariates, there was no longer a relationship between childhood depressive symptoms and adolescent high alcohol problem use, neither for boys (O.R. 0.92, p=0.063), nor girls (O.R. 1.12, p=0.058), for whom the strength of the relationship was diminished compared to the univariable model.

The relationship between depression and alcohol use was influenced by a number of covariates, some from the personality factor domain (childhood peer problems for girls and childhood antisocial behaviour for boys), but mostly from the family and social domains. Family domain-related covariates included: maternal alcohol use for both boys and girls, and (for girls only) also family constellation, and mother-child interactions. Furthermore, in the social domain peer antisocial behaviour (for both boys and girls) and stressful life experiences for girls also had an impact on the longitudinal relationship.

Similar to the imputed dataset, the association between age 10 depressive symptoms and age 14 alcohol problem use was no longer significant in boys and was strongly diminished in girls, compared to the one observed in the univariable models.

Results indicated that most of the covariates that were statistically significant when tested in the imputed dataset were also statistically significant in the non-imputed dataset for both boys and girls.

CHAPTER 9: RESULTS OF THE UNIVARIABLE AND MULTIVARIABLE GOLOGIT MODELS ACCOUNTING FOR PEERS' INFLUENCES AT AGE 10 AND AT AGE 14 YEARS

9.1 Results of the LR tests assessing the moderating effect of for peers' influences (at age 10 and 14 years) in the total sample

As reviewed in paragraph 3.2.3 and 4.2.4, one of the aims of my thesis is to examine whether the relationship between childhood depressive symptoms and alcohol problem use in adolescence is moderated by the combined effect of two peer influences: child bonding with his/her peers, and peer's risky behaviour (see Table 5.4). Both these peers' influences were assessed by face-to-face interviews during the "clinics" at age 10 years (the same age of assessment of depressive symptoms) and age 14 years (the same age of assessment of alcohol problem use) (see paragraph 4.2.4).

Child bonding with his/ her peers was measured in both occasions with a shortened version of the Friendships Questionnaire developed for the Cambridge Hormones and Moods Project (Goodyer et al., 1990, Goodyer et al., 1989) (see paragraph 4.2.4.1). Peers' risky behavior was measured at age 10 with a structured questionnaire that was adapted from a measure of self-reported antisocial behaviour for young children and included a question on peers' alcohol drinking (Wolke et al., 1994), and at age 14 with a single question assessing how often the child's peers' consumed alcohol in the previous six months (see paragraph 4.2.4.2).

As explained in paragraph 6.3.5, steps 1, 2 and 3, I performed a LR test to compare two models: 1) a trivariable GOLOGIT model without interactions (i.e., a model having as independent variables: a) "age 10 depressive symptoms," b) "peers' risky behaviour" and c) "child's bonding with his/her peers") and 2) a three-way interaction trivariable GOLOGIT model (i.e., a model having as independent variables: a) age 10 depressive symptoms," b)

"peers' risky behaviour" and c) "child's bonding with his/her peers," and including also the four interaction terms: d) "age 10 depressive symptoms **X** child's bonding with his/ her peers," e) "age 10 depressive symptoms **X** peers' risky behaviour," f) "child's bonding with his/ her peers **X** peers' risky behaviour," and g) "age 10 depressive symptoms **X** child's bonding with his/ her peers **X** peers' risky behaviour").

These GOLOGIT models (like all the GOLOGIT models presented in these chapters) were drawn from the imputed dataset only and were based on the total sample; the analysis was conducted twice, once including peers' influences at age 10 years and once including peers' influences at age 14 years. The results of the LR test helped me decide whether the model accounting for interaction was fitting the data significantly better than the one without interaction.

- *Peers' influences at age 10 years:* Results of the LR test indicated that, with regards to the trivariable GOLOGIT models accounting for peers' influences at age 10 years, the more complex interaction model including the interaction terms "d," "e," "f" and "g" did not fit the data significantly better than the more parsimonious model not including the interaction terms (LR $X^2(4)=2.72$, $p=0.605$). Hence, the three-way GOLOGIT interaction model based on the total sample accounting for peers' influences at age 10 years was not further analyzed (see paragraph 6.3.5, step 3).
- *Peers' influences at age 14 years:* Results of the LR test, obtained comparing the trivariable GOLOGIT models with and without the inclusion of the interaction terms with peers influences at age 14 years, were similar to those obtained analyzing peers' influences at age 10 years; the more complex interaction model did not fit the data significantly better than the more parsimonious model not including the interaction terms (LR $X^2(4)=7.46$, $p=0.113$). Hence, the three-way GOLOGIT interaction model based on the total sample accounting for peers' influences at age 14 years was not further analyzed (see paragraph 6.3.5, step 3).

9.2 Gender differences in the peers' influences variables

Table 9.1 describes the gender differences from the variables describing peers' influences (see paragraph 6.3.5, step 4, note that Table 9.1 indicates the frequencies of the non-imputed variables). At age 10 boys had peers who had more risky behaviours (they had partaken in a higher number of antisocial activities) compared to the girls' peers (LR $X^2(3)$ 191.8, $p<0.001$), whereas girls had a stronger bonding with their peers than boys did (MWW $z=2.9$, $p=0.004$). At age 14 there was no longer a statistically significant difference between boys' and girls' peers' risky behaviours (peers' alcohol drinking; LR $X^2(3)$ 7.3 $p=0.062$), although girls still had a much stronger bonding with their peers than boys did (MWW $z=9.8$, $p<0.001$).

Table 9.1: Peers' influences variables presented separately for boys and girls

Variable	Categories	N boys/ N girls	% boys	% girls	X²¥
Age 10 peers' antisocial behaviour[A B]	No activities	1676/1977	51.4	73.4	$X^2(3)$ 191.8 p<0.001
	1 activity		28.8	16.1	
	2 activities		10.4	6.2	
	≥3 activities		9.4	4.3	
Age 14 peers' alcohol drinking[B]	Never	1662/1954	61.1	56.9	$X^2(3)$ 7.3 p=0.062
	1-3 times		22.0	24.9	
	≥4 times		9.4	10.7	
	Once per week		7.5	7.5	

Variable	Measurement Unit	N boys/ N girls	*M* (*SD*) boys	*M* (*SD*) girls	MWW†
Child bonding with peers at age 10 years	Bonding score	2177/1973	5.9 (2.0)	6.1 (1.9)	z=2.9 p=0.004
Child bonding with peers at age 14 years	Bonding score	2001/2193	6.4 (1.9)	6.9 (1.6)	z=9.8 p<0.001

¥ Cross-tabulation of each variable with gender. Pearson's X^2 reported. Statistically significant (p-value<0.05) results are shaded.

[A] Variable included information on whether friends had consumed alcohol without parental permission in the previous 6 months.

[B] Variables describing peers' risky behaviour.

† Wilcoxon-Mann-Whitney test (z score). Statistically significant (p-value<0.05) results are shaded.

9.3 Results of the LR tests assessing the moderating effect of peers' influences (at age 10 and 14 years) and gender in the total sample

As explained in paragraph 6.3.5, step 5, I performed a LR test to compare two models: 1) a quadrivariable GOLOGIT model without interaction (i.e., a trivariable GOLOGIT model without interactions like the one described in paragraph 9.1 also including "gender" as the fourth variable), and 2) a four-way interaction quadrivariable GOLOGIT model (i.e., a GOLOGIT model having all four interaction terms of the three-way interactions trivariable GOLOGIT model described in paragraph 9.1 interacting with gender as well).

This scope of this analysis was to determine whether the analysis investigating the effects of peers' influences should be conducted only in the total sample or also separately in the two subsamples of boys and girls.

These models were therefore based on the total sample, and the analysis was conducted twice, once including peers' influences at age 10 years and once including peers' influences at age 14 years.

- *Peers' influences at age 10 years:* Results of the LR test indicated that, concerning the quadrivariable GOLOGIT models accounting for peers' influences at age 10 years plus gender, the more complex interaction model including the interaction terms "d," "e," "f" and "g" (see paragraph 9.1) interacting with gender did not fit the data significantly better than the more parsimonious model not including any of the interaction terms (LR $X^2(10)=12.72$, $p=0.240$). Hence, the effects of age 10 peers' influences in the relationship between age 10 years depressive symptoms and age 14 years alcohol problem use was not further studied separately in the two subsamples of boys and girls (see paragraph 6.3.5, step 6).
- *Peers' influences at age 14 years:* In contrast to the results of the analysis conducted accounting for age 10 peers' influences, the results of the LR test indicated that the quadrivariable GOLOGIT models accounting for the interaction terms with peers' influences

at age 14 years plus gender did fit the data significantly better than the more parsimonious model not including any of the interaction terms (LR $X^2(10)=19.99$, $p=0.029$). These results warranted further LR tests to be conducted on the two three-way GOLOGIT interaction models based on the boys and girls subsamples and accounting for peers' influences at age 14 years (see paragraph 6.3.5, step 6).

9.4 Results of the LR tests assessing the moderating effect of for peers' influences at age 14 years in the subsamples of boys and girls

Following the results reported in paragraph 9.3, I performed a LR test comparing, in both the boys and girls subsamples, the more complex model accounting for interaction between age 10 depressive symptoms and age 14 peers' influences (i.e., child's bonding with his/ her peers at age 14 years and age 14 years peers' alcohol drinking) and the more parsimonious model not including the interaction terms (see paragraph 6.3.5, step 6).

Results of the LR test in the subsample of boys indicated that the more complex model did not fit the data better than the more parsimonious one (LR $X^2(4)=7.69$, $p=0.104$); however, the LR test conducted in the subsample of girls provided opposite results (i.e., that the model including the interaction terms did fit the data better than the models not accounting for interaction; LR $X^2(4)=9.55$, $p=0.048$). In order to better understand the role of peers' influences at age 14 years in the subsample of girls, the three-way GOLOGIT interaction model accounting for peers' influences at age 14 years was further analyzed, testing the significance levels of the three interaction terms including age 10 depressive symptoms (i.e., 1) "age 10 depressive symptoms **X** child's bonding with his/ her peers," 2) "age 10 depressive symptoms **X** peers' alcohol drinking," and 3) "age 10 depressive symptoms **X** child's bonding with his/her peers **X** peers' alcohol drinking") (see paragraph 6.3.5, step 7). Results are reported, for the imputed dataset only, in Table 9.2.

9.5 Results of the trivariable GOLOGIT interaction models accounting for peers' influences at age 14 years in the girls' subsample

Results of the analysis of the trivariable GOLOGIT interaction model in the subsample of girls indicated that the interaction term "age 10 depressive symptoms **X** child's bonding with his/ her peers **X** peers' alcohol drinking" was statistically significant (O.R 0.95, 95% C.I. 0.89; 1.00, p=0.048) and, therefore, the hypothesis of a three-way interaction between age 10 depressive symptoms, child bonding with peers at 14 years and age 14 years peers' alcohol drinking was valid (see Table 9.2).

Accounting for the moderating effect of age 14 peers' influences (i.e., child's bonding with his/ her peers and age 14 years and age 14 years peers' alcohol drinking) in the relationship between age 10 depressive symptoms and age 14 alcohol problem use, with progressively higher levels of depressive symptoms girls had experienced in childhood, there was an association with a 17% greater risk of developing high alcohol problem use in early adolescence (O.R. 1.17, 95% C.I. 1.02; 1.34, p=0.029, see Table 9.2), which resulted in a 51% increased risk for those girls who experienced very high depressive symptoms in childhood compared to those who experienced them at lower levels.

Therefore, when included in the girls' subsamples GOLOGIT univariable model described in paragraph 7.3, the combined effect of child's bonding with his/ her peers and peers' alcohol drinking further increased the risk of developing age 14 high alcohol problem use in girls who experienced very high depressive symptoms at age 10 by 9% (see Table 9.2).

Both age 14 peers' influences were statistically significant when considered individually (child's bonding with his/ her peers at age 14 years; O.R. 1.29; 95% C.I. 1.21; 1.36, p<0.001 and age 14 years peers' alcohol drinking; O.R. 2.96, 95% C.I. 2.64; 3.32, p<0.001). These results also excluded the possibility that the moderation of the relationship between age 10 depressive symptoms and age 14 alcohol problem use may be the result of the effect of only

one of the two peers' influences at 14 years taken into account; in fact, neither of the two-way interactions between "age 10 depressive symptoms **X** child's bonding with his/ her peers" and "age 10 depressive symptoms **X** peers' alcohol drinking" were statistically significant (p-value<0.005), whereas the combined effect of child's bonding with his/ her peers **X** peers' alcohol drinking had O.R. 1.09, 95% C.I. 1.02; 1.16, p=0.007 (see Table 9.2).

Table 9.2: Trivariable GOLOGIT interaction models accounting for peers' influences at age 14 years in the girls' subsample (imputed dataset)

Girls' subsample (N=2202)	**O.R.**	**95% C.I.**		**p[¥]**
Age 10 depressive symptoms NOT accounting for peers' influences[A]	1.14	1.02	1.27	0.016
Age 10 depressive symptoms accounting for peers' influences[B]	1.17	1.02	1.34	0.029
Peers' influences	**O.R.**	**95% C.I.**		**p[$]**
Child bonding with peers at age 14 years	1.29	1.21	1.36	<0.001
Age 14 years peers alcohol drinking	2.96†	2.64	3.32	<0.001
Interaction terms	**O.R.**	**95% C.I.**		**p[$]**
child's bonding with his/ her peers **X** peers' alcohol drinking[C]	1.09	1.02	1.16	0.007
age 10 depressive symptoms **X** child's bonding with his/her peers[D]	1.00	0.95	1.06	0.958
age 10 depressive symptoms **X** peers' alcohol drinking[D]	1.07	0.97	1.20	0.189
age 10 depressive symptoms **X** child's bonding with his/her peers **X** peers' alcohol drinking[E]	0.95	0.89	1.00	0.048

[¥] Univariable GOLOGIT model. Statistically significant (p-value<0.05) estimates are shaded.
[$] Trivariable GOLOGIT interaction model. Statistically significant (p-value<0.05) estimates are shaded.
†O.R. ≥1.30 or ≤0.80.
[A] Univariable model not accounting for peers' influences, reported here for reference purposes only (see paragraph 7.3 for more details).
[B] Univariable model accounting for peers' influences.
[C] Interaction between the two peers' influences variables.
[D] Two-way interaction with age 10 depressive symptoms.
[E] Three-way interaction with age 10 depressive symptoms.

9.6 Graphical representation of the univariable GOLOGIT model in the subsample of girls according to the level of bonding with peers and peers' alcohol drinking status

In order to interpret the estimate of the three-way interaction term "age 10 depressive symptoms **X** child's bonding with his/ her peers **X** peers' alcohol drinking" (O.R 0.94, 95% C.I. 0.89; 1.00, p=0.042, see Table 9.2), it was necessary to analyze how age 10 years depressive symptoms predict age 14 years alcohol problem use when children experienced different combinations of bonding with their peers at age 14 years and of age 14 years peers' alcohol drinking (Aiken, 1991).

To do so, as explained in paragraph 6.3.5, step 8, by using a cut-off at the ~50th percentile I divided the variable "child's bonding with his/ her peers at age 14 years" (see Table 5.4) in two categories: "low bonding" (frequencies in the imputed dataset: 41.3% of the total sample, 34.9% of the subsample of girls) and "high bonding" (frequencies in the imputed dataset: 58.7% of the total sample, 65.1% of the subsample of girls) and divided the variable "age 14 peers' alcohol drinking" (see Table 5.4) in "non-drinking peers" (never consumed alcohol in the previous six months, frequencies in the imputed dataset: 59.6% of the total sample, 57.7% of the subsample of girls) and "drinking peers" (consumed alcohol at least 1-3 times in the previous six months, frequencies in the imputed dataset: 40.4% of the total sample, 42.3% of the subsample of girls).

I have subsequently run the univariable GOLOGIT model in the girls subsample (see paragraph 7.3) for each of the four possible combinations of "child's bonding with peers" and peers' alcohol drinking" (see paragraph 6.3.5, step 9); i.e.: 1) "low bonding with peers" and "non drinking peers," 2) "high bonding with peers" and "non drinking peers," 3) "low bonding with peers" and "drinking peers," and 4) "high bonding with peers" and "drinking peers."

Using the post-estimation command "predict" (see paragraph 6.3.5, step 10), I estimated the expected probability of each of the univariable GOLOGIT models (corresponding to the expected probability of developing high alcohol problem use) for each of the four possible

combinations of peers' influences described above. Figure 9.1 graphically represents the expected probability estimates for the four GOLOGIT models in the subsample of girls, plotting them against the four categories of the "age 10 depressive symptoms" variable ("low," "medium," "high" and "very high").

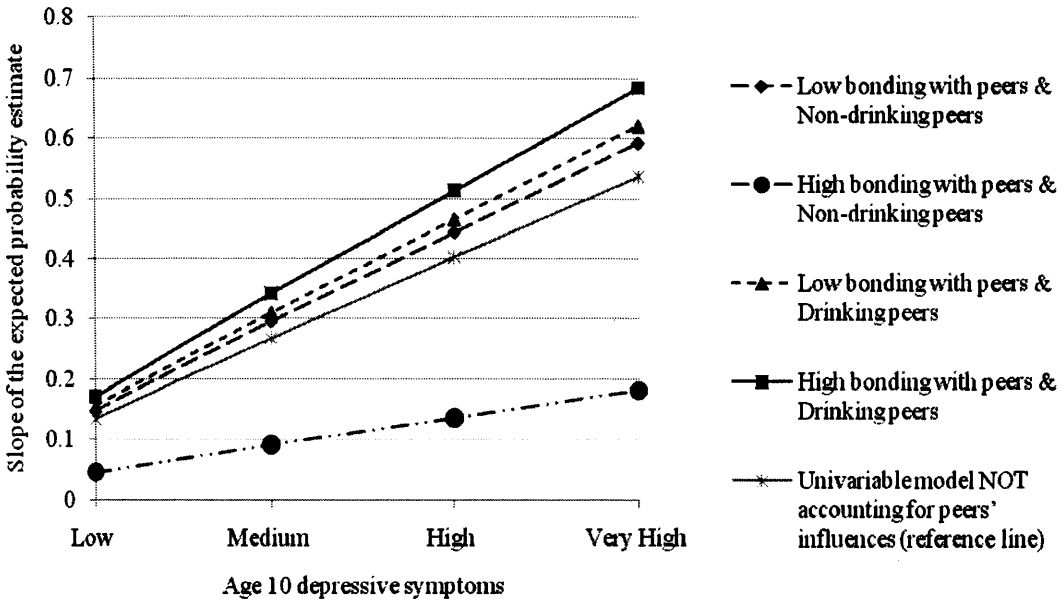
Please note that in the graph displayed in Figure 9.1 I have set constant=0 for the expected probability estimate equation of every model to allow an easier comparison to be made between the slopes of the plotted predicted probability estimates. As the reference line (coloured in light gray), I included in both graphs the expected probability estimate of the univariable GOLOGIT without accounting for peers' influences (see figure 7.1).

It was observable that, while the effect of peers' alcohol drinking was constantly increasing the risk (overall increase of the slope of the expected probability estimate (see figure 9.1) of developing age 14 high alcohol problem use, compared to the reference line) of developing high alcohol problem use at age 14 years for girls who experienced very high depressive symptoms at age 10 years compared to those who experienced low depressive symptoms at age 10 years, the effect of bonding with peers was highly dependent on the drinking status of the peers' themselves.

In fact, if girls' peers did consume alcohol in the previous six months, having a strong bond with peers increased the effect of age 10 depressive symptoms as a predictor of age 14 alcohol problem use (overall increase of the slope of the expected probability estimate (see figure 9.1) of developing age 14 high alcohol problem use, compared to the reference line). However, for girls who had a strong bond with their peers and who reported that their peers did not consume alcohol, the risk of developing high alcohol problem use at age 14 years for girls who experienced very high depressive symptoms at age 10 years, compared to those who experienced low depressive symptoms at age 10, was reduced compared to the univariable GOLOGIT model not accounting for peers' influences (overall decrease of the

slope of the expected probability estimate (see figure 9.1) of developing age 14 high alcohol problem use, compared to the reference line).

Figure 9.1: Slopes of the expected probability estimates of the univariable GOLOGIT model in the subsample of girls according to the level of bonding with peers and peers' alcohol drinking status[1]



[1]In light gray it is indicated, as the reference line, the expected probability estimate of the girls' subsamples' univariable GOLOGIT model not accounting for peers' influences (see paragraph 7.3 for details).

9.7 Results of the multivariable GOLOGIT interaction models accounting for peers' influences at age 14 years in the girls' subsample

The trivariable three-way interaction GOLOGIT model described in paragraph 9.5 was included in the multivariable GOLOGIT model (drawn from the imputed dataset) based on the subsample of girls, which has been described in detail in paragraph 8.2.6.

LR test comparing the multivariable GOLOGIT model with and without the presence of the four interaction terms, i.e.: a) "age 10 depressive symptoms **X** child's bonding with his/ her peers," b) "age 10 depressive symptoms **X** peers' risky behaviour," c) "child's bonding with

his/ her peers **X** peers' risky behaviour," and d) "age 10 depressive symptoms **X** child's bonding with his/ her peers **X** peers' risky behaviour," indicated that the more complex model (including the interaction terms) did fit the data significantly better than the more parsimonious model not including any of the interaction terms (LR $X^2(4)=10.62$, p=0.031).

Results of the three-way interaction multivariable GOLOGIT model indicated that the tree-way interaction term "age 10 depressive symptoms **X** child's bonding with his/her peers **X** peers' alcohol drinking" was statistically significant, indicating that the hypothesis of a three-way interaction between age 10 depressive symptoms, child bonding with peers at 14 years and age 14 years peers' alcohol drinking was valid also when accounting for the correcting effect of covariates (O.R. 0.94, 95% C.I. 0.89; 1.00, p=0.042, see Table 9.3).

When accounting for the moderating effects of the combination of bonding with peers at age 14 years and age 14 years peers' alcohol drinking, age 10 depressive symptoms had a stronger effect as predictor of age 14 alcohol problem use (O.R. 1.18, 95% C.I. 1.02; 1.37, p=0.030, see Table 9.3), compared to both the multivariable GOLOGIT model not accounting for peers' influences (O.R. 1.12, 95% C.I. 1.00; 1.25, p=0.058; see Table 8.12) and to the trivariable three-way interaction GOLOGIT model not accounting for the effects of the covariates (O.R. 1.17, 95% C.I. 1.02; 1.34, p=0.029, see Table 9.2).

Hence, accounting for the moderating effect of age 14 peers' influences (i.e., child's bonding with his/ her peers at age 14 years and age 14 years peers' alcohol drinking) in the relationship between age 10 depressive symptoms and age 14 alcohol problem use, and including all the relevant covariates, each increasing level of depressive symptoms girls had experienced in childhood was therefore associated with an 18% greater risk of developing high alcohol problem use in early adolescence, which resulted in a 54% increased risk for those girls who experienced very high depressive symptoms in childhood compared to those who experienced low levels of them.

Therefore, when included in the girls' subsample's GOLOGIT multivariable model described in paragraph 8.2.6, the combined effect of child's bonding with his/ her peers and peers' alcohol drinking further increased by 18% the risk of developing age 14 high alcohol problem use in girls who experienced very high depressive symptoms at age 10 (see Table 9.3).

No other significant differences were found between the three-way interaction multivariable GOLOGIT model reported in Table 9.3 and the three-way interaction trivariable GOLOGIT model reported in Table 9.2. However, some differences in the estimates of the covariates were found when comparing the three-way interaction multivariable GOLOGIT model reported in Table 9.3 with the multivariable GOLOGIT model not accounting for peers' influences reported in Table 8.12.

- *Socio-demographic domain:* no differences; both age of assessment of alcohol problem use (age 14) (O.R 1.15, 95% C.I. 1.07; 1.23, $p<0.001$) and family constellation (O.R. 1.54, 95% C.I. 1.03; 2.29, $p=0.034$) still statistically significant.
- *Family environment domain:* no differences; both mothers' alcohol use (O.R. 1.14, 95% C.I. 1.03; 1.28, $p<0.016$) and mother-child interaction (O.R. 0.96, 95% C.I. 0.93; 1.00, $p=0.048$) still statistically significant.
- *Social environment domain:* differences between the two models; both stressful life events and peers' antisocial activities no longer statistically significant in the model accounting for peers' influences (p-value ≥ 0.05).
- *Personality and psychopathologies domain:* differences between the two models; child peer problems no longer statistically significant in the model accounting for peers' influences (p-value ≥ 0.05).

Table 9.3: Multivariable GOLOGIT interaction models accounting for peers' influences at age 14 years in the girls' subsample (imputed dataset)

Girls' subsample (N=2202)		O.R.	95% C.I.		p[$]
Age 10 depressive symptoms NOT accounting for peers' influences and corrected for covariates effects[A]		1.12	1.00	1.25	0.058
Age 10 depressive symptoms accounting for peers' influences[B]		**1.18**	**1.02**	**1.37**	**0.030**
Peers' influences		**O.R.**	**95% C.I.**		**p[$]**
Child bonding with peers at age 14 years		1.28	1.20	1.36	<0.001
Age 14 years peers alcohol drinking		2.85†	2.57	3.25	<0.001
Interaction terms		**O.R.**	**95% C.I.**		**p[$]**
child's bonding with his/ her peers **X** peers' alcohol drinking[C]		1.10	1.03	1.17	0.004
age 10 depressive symptoms **X** child's bonding with his/her peers[D]		1.00	0.95	1.06	0.995
age 10 depressive symptoms **X** peers' alcohol drinking[D]		1.07	0.96	1.19	0.228
age 10 depressive symptoms **X** child's bonding with his/her peers **X** peers' alcohol drinking[E]		0.94	0.89	1.00	0.042
Factor Domain	**Covariate**	**O.R.**	**95% C.I.**		**p$**
Socio-demographic	Age10	0.98	0.92	1.05	0.637
	Age14	1.15	1.07	1.23	<0.001
	Ethnicity				
	Social Class				
	Income per week				
	Family constellation	1.54†	1.03	2.29	0.034
Family environment	Mother's alcohol use	1.14	1.03	1.28	0.016
	Mother's partner's alcohol use				
	Mother-child interaction	0.96	0.93	1.00	0.048
	Mother's partner's-child interaction				
	Mother's depression				
	Mother's partner's depression				
	Rows between parents				
Social environment	Child stressful events	1.05	0.99	1.12	0.121
	Peers' antisocial activities	0.97	0.85	1.11	0.696
	Religiosity (attends a place of worship)	0.91	0.81	1.03	0.147
	Peers' alcohol drinking				
Personality and psycho-pathologies	Child conduct problems	1.05	0.91	1.23	0.494
	Child peer problems	0.93	0.82	1.06	0.266
	Child antisocial activities				
	Self-esteem				

[$] Multivariable GOLOGIT model estimates. Statistically significant (p-value<0.05) estimates are shaded.
[A] Multivariable model not accounting for peers' influences, reported here for reference purposes only (see paragraph 7.3 for more details).
[B] Multivariable model accounting for peers' influences.
[C] Interaction between the two peers' influences variables.
[D] Two-way interaction with age 10 depressive symptoms.
[E] Three-way interaction with age 10 depressive symptoms.
†O.R. ≥1.30 or ≤0.80.

9.8 Results of the univariable and multivariable GOLOGIT models accounting for peers' influences at age 10 and at age 14 years: synthesis of the chapter

In summary, in this chapter I tested peers' influences (i.e., child's bonding with his/ her peers and peers' alcohol drinking) at both age 10 and 14 years as possible moderators of the relationship between age 10 years depressive symptoms and age 14 years alcohol problem use in both the univariable and multivariable GOLOGIT models.

In contrast to the results of the analysis conducted accounting for age 10 peers' influences, the results of the LR test indicated that the GOLOGIT models accounting for the interaction terms with peers' influences at age 14 years did fit the data significantly better than the more parsimonious model not including any of the interaction terms.

I performed therefore a LR test comparing, in both the boys and girls subsamples, the more complex model accounting for interaction between age 10 depressive symptoms and age 14 peers' influences and the more parsimonious model not including the interaction terms.

In the subsample of boys indicated that the more complex model did not fit the data better than the more parsimonious one (LR $X^2(4)=7.69$, $p=0.104$); however, the LR test conducted in the subsample of girls provided opposite results (i.e., that the model including the interaction terms did fit the data better than the models not accounting for interaction; LR $X^2(4)=9.55$, $p=0.048$).

Results indicated the combined effect of child's bonding with his/ her peers and peers' alcohol drinking further increased the risk of developing age 14 high alcohol problem use in girls who experienced very high depressive symptoms at age 10 by 9%, hence progressively higher levels of depressive symptoms girls had experienced in childhood were associated with a 16% greater risk of developing high alcohol problem use in early adolescence, which resulted in a 51% increased risk for those girls who experienced very high depressive symptoms in childhood compared to those who experienced them at lower levels.

When the peers' influences (i.e., child's bonding with his/ her peers and peers' alcohol drinking) were considered separately, it was observable that, while the effect of peers' alcohol drinking was constantly increasing the risk of developing high alcohol problem use at age 14 years for girls who experienced very high depressive symptoms at age 10 years compared to those who experienced low depressive symptoms at age 10 years, the effect of bonding with peers was highly dependent on the drinking status of the peers' themselves.

Finally, results of the three-way interaction multivariable GOLOGIT model indicated that the hypothesis of a three-way interaction between age 10 depressive symptoms, child bonding with peers at 14 years and age 14 years peers' alcohol drinking was valid also when accounting for the correcting effect of covariates (O.R. 0.94, p=0.041).

PART V

CHAPTER 10: DISCUSSION

10.1 Common risk and protective factors for harmful alcohol use and depressive symptoms in youth identified in the literature

10.1.1 Main findings

There is a strong association between alcohol problem use and depressive symptomatology in adolescence, which has been reported by many (but not all (Becker et al., 2006)) studies (Bukstein et al., 1992, Clark et al., 1997b). The link between these disorders could be direct: for example, AD may trigger depression (Kuo et al., 2006), or it could be due to the depressogenic effect of ethanol (Abraham et al., 1999). However, it is also likely that depressive symptomatology and alcohol problem use share risk factors: a number of non-genetic and genetic risk factors have been associated with the development of both disorders in adolescents. Thus, shared risk factors might contribute to the co-morbidity between both traits.

Results of a systematic review I conducted, reviewing all the epidemiological and genetic studies that focused on common factors for alcohol problem use and depressive symptoms published between the years 1997-2007, indicated that factors such as externalizing disorders (in particular conduct disorder), family alcohol problems and stress, as well as gene variants such as the 5-HTT S-allele, the MAOA low activity variant and the DDR2 Taq A1 allele have received relatively more research support for a role in the development of the co-morbidity of both disorders. Some of these factors (e.g., 5-HTT S-allele) have also been supported to play a role in the development of both behaviours by meta-analyses (Feinn et al.,

2005, Schinka et al., 2004, Sen et al., 2004a). Other factors have been less frequently studied, the support provided is weaker, or there are contradicting findings (e.g. ethnicity and the BDNF Val66Met variant). My systematic search identified only one shared protective factor (religion).

In interpreting the findings of the literature review, it is important to distinguish between risk factors and causal risk mechanisms (Beardslee et al., 1997). As Garber (Garber, 2006) suggested, risk factors are antecedents that increase the probability of an outcome over the population base rate; however, taken singularly, they do not explain the processes involved in the development of a pathological condition (Garber, 2006). The study of co-morbidity is further complicated because among risk factors, some (such as sleep problems) can be considered both potential causes as well as symptoms of alcohol problem use and internalizing symptomatology. They could therefore contribute to a vicious circle by increasing the risk of development of each disorder.

10.1.2 Reasons why genetic risk and protective factors were not included in the analyses

After the completion of the literature review, I decided to avoid analyzing the impact of genetic risk and protective factors in the relationship between childhood depressive symptoms and alcohol problem use in early adolescence.

This decision was taken in concert with my supervisors; four reasons made us agree that, at the time I started the epidemiological and statistical analyses of the ALSPAC dataset (May 2008), this was a sensible choice to make:

1. In general, there was greater agreement on positive findings for factors identified through epidemiological studies than for those identified through molecular studies, for both alcohol problem use and depressive symptomatology in adolescents. For epidemiological

factors, conflicting results were found for only three risk factors (ethnicity, SES and educational level). On closer scrutiny, contradictory findings can sometimes make sense; for example, one reason for the discrepancies found with respect to SES may be that heavy alcohol consumption is more likely in those with high income but low educational qualifications (Casswell et al., 2003). In contrast, for almost all the factors identified through molecular genetic studies contradictory findings were found. Heterogeneity in the methodologies among molecular studies is likely to have contributed to the discrepancies. For example, among the studies we reviewed were: population and pedigree studies (Bolos et al., 1990), longitudinal genetically informative studies (Olsson et al., 2005a), Positron Emission Tomography (PET) studies (Hietala et al., 1994) and post-mortem receptor-binding studies (Noble et al., 1991). In addition, heterogeneity in study samples is also likely to have contributed to discrepancies in my findings. For example, among molecular studies examining the BDNF Val66Met variant, studies included male Japanese alcoholics and non-alcoholics (Matsushita et al., 2004), Chinese alcoholics, Northern-Taiwanese prisoners and controls (Tsai et al., 2005), depressed Mexican-American patients (Ribeiro et al., 2007) and untreated depressed Chinese patients (Tsai et al., 2003).

2. Moreover, due to variation in research interest for different gene variants, some variants, such as the 5-HTT S-allele, have been the focus of considerably more research attention than others, such as the CHRM2 SNPs, for which there is a paucity of studies.

3. While most epidemiological studies that were identified for my literature review were based on adolescents, the majority of molecular studies were based on adult samples. This is likely to be due to the lower frequency of clinically diagnosed alcohol dependence abuse and/or and major depressive disorder in young subjects. This would represent no problem where the study of genetic polymorphisms is concerned; however, before attempting to analyze the combined effects of genetic and non-genetic risk factors in adolescent samples, it

may be necessary to compare studies of gene expression for adult and adolescent samples, particularly because some studies of alcohol and internalizing psychopathology indicate adolescent-onset disorder may represent a more severe phenotype with worse lifetime prognosis (DeWit et al., 2000, Grant et al., 2001, Pine et al., 1999, Pine et al., 1998). Moreover, genetic influences may also affect the environment individuals experience, changing the way individuals shape, select and process their experiences, so-called active gene-environment correlation (Rutter et al., 1997).

4. Furthermore, even if gene-environment interactions are increasingly detected and replicated in psychiatry (Uher, 2008), their study is complicated by the large number of potential interactions (Owen et al., 2000); the relations between risk factors and alcohol problem use and depressive symptomatology in adolescence can be either direct or indirect, mediated or moderated by other risk factors (for a definition and examples of mediation and moderation see (Munafo, 2006)). This situation becomes even more complicated if hypothetical interactions between different genetic factors and between different non-genetic factors are also considered (see, for example, Figure 2.1 in Chapter 2, graphically representing the potential mechanisms by which genetic and non-genetic factors and their interactions may influence alcohol problem use and depressive symptomatology in adolescence).

With regard to the study of gene-environment interaction, a cautious research strategy has been suggested by Moffit et al. (Moffitt et al., 2005), which should include: the identification of possible environmental risk factors, the identification of putative susceptibility genes and the elaboration of a gene-environment interaction hypothesis that should extend beyond the initially hypothesized triad of gene, environmental factor and disorder. Owen and Cardno (Owen et al., 1999) have furthermore argued that the establishment of the role of a genetic or environmental factor in the development of a psychiatric disorder will necessarily have to be

based on a considerable number of studies, where positive findings are replicated in large new samples, with meta-analysis providing important additional support for the confirmation of a hypothesis.

5. Finally, noticeably, among the studies gathered in my systematic review, with the exception of the gene x environment interaction studies reviewed in paragraph 2.7, there was no overlap between those studies focusing on non-genetic factors and those focusing on genetic factors. This further highlights the need of addressing both genetic and environmental factors in future studies aimed to investigate the underpinnings of alcohol problem and depressive symptoms in youth, rather than considering genetic and environmental effects separately.

Given all these considerations, it was decided that at the time I planned my analyses in ALSPAC, the field of the genetics of alcohol dependence had not progressed sufficiently for me to test a finite number of *a priori* well-specified mechanisms of gene-environment interplay.

10.1.3 Update of the literature analysis for the period November 2007 – May 2011

In order to update the systematic review that I conducted at the beginning of my research (the 3rd November 2007), a new literature search was conducted in order to include into the thesis more recent articles that focused only on non-genetic risk factors in common for depression and alcohol problems in youth. This literature search was conducted semi-systematically, using the same search terms listed in Table 2.2 with the exclusion of the terms "Genetic Predisposition to Disease OR Polymorphism, Genetic OR Genetic Risk Factor OR Genotype OR Polymorphism, Single Nucleotide" (this was done because in the analysis I did not include variables describing relevant genetic variants of the participants, as I explained in the paragraph above); the date limits imposed were from the day after the initial literature search

was conducted (4th November 2007) and the 30 March 2010, date of submission of the Thesis.

18 papers were found through this search and, excluding duplicates and papers not relevant for my search (for example because they were mostly focusing on genetic risk factors for depression and alcohol problems in youth), a total of 12 papers were retained and analyzed.

A number of risk factors belonging to the domains of socio-demographic factors, family environment and personality and psychopathologies (but not social environment) were reported by these studies as being associated with the development of alcohol problem use and/or internalizing problems in youth.

- *Socio-demographic factors domain:* Residing in urban versus rural areas may contribute to differences in terms of increased risk to engage with the consumption of either alcohol or marijuana (Martino et al., 2008). Martino et al. reported that youth may engage in heavy alcohol consumption at faster rates when residing in micropolitan (as opposed to metropolitan) areas, marijuana use increases at a faster rate in youth living in urban (versus rural) areas in general. However, while the locality of an individual is important to take into consideration, factors that are associated with one's residence play greater roles; differences in the rate of change of substance use can be in fact attributed to factors such as racial/ethnic composition, residential instability, and availability of marijuana (Martino et al., 2008). Neighborhood quality was assessed also in a sample of 220 males, initially recruited as 3- to 5-year-old children of families composed by at least one alcoholic parent and neighbouring families. Longitudinal changes over two decades in neighborhood environments (i.e., high frequency of family mobility) from early childhood to adolescence had significant effects in increasing the risk of developing alcohol-use disorder, marijuana-use disorder, and major depressive disorder symptoms in late adolescence (Buu et al., 2009).

Neighbourhood characteristics were also associated also with the development of depressive symptoms. Shaefer-McDaniel reported on a sample of 126 young adolescents in three disadvantaged New York City neighbourhood that children's evaluations of neighbourhood quality were positively related to their assessments of depression and there was an positive association between the neighbourhood drug/alcohol stressor and child depression (Schaefer-McDaniel, 2009). Furthermore, among young adults, unemployment and living alone were reported as being associated with a higher risk of having suicidal ideation (Legleye et al., 2010).

- *Family environment domain:* Hill *et al.* observed that children and adolescents exposed to poor family management had an increased the risk of developing alcohol problems in young adulthood (Hill et al., 2010). A study by Mackie et al., moreover, identified four drinking motives classes (family-oriented, social, enhancement/social, and coping/social). According to the authors, heritable influences may predispose individuals to drink to cope with negative affect, for social reasons, and to a lesser extent for enhancement (Mackie et al., 2010), whereas familial environmental influences shaped family-oriented motives for drinking in adolescents (Mackie et al., 2010).

Concerning internalizing problems, bad relationship between the parents was found predictive of suicidal ideation among both young men and women (age 18-30 years) in France (Legleye et al., 2010), whereas a perceived negative family environment increased both adolescents' and their parents' depressive symptoms among shelter-recruited adolescents (Slesnick et al., 2009). Particularly in children of alcoholics, parent alcohol dependence has a unique effect on child internalizing symptoms, above and beyond those of both parent depression and antisocial personality disorder (Hussong et al., 2008). Among Children of Alcoholics Family density of alcoholism was found significantly related to the development of mental disorders (particularly depression, phobias and generalized anxiety

disorder) also in a multisite epidemiological study conducted in 8 Spanish cities, on 371 Children of Alcoholics and 147 controls aged 6-17 years (Diaz et al., 2008).

Finally parental rearing styles of rejection and lack of emotional warmth were associated with offspring social phobia. (Knappe et al., 2009). Knappe et al also observed that the analyses of interaction of parental psychopathology and parental rearing styles indicated combined effects on the risk for offspring's social phobia (Knappe et al., 2009).

- *Personality and psychopathologies domain:* Hill *et al.* using data from a community sample of 808 men and women interviewed from ages 10 to 27 in the Seattle Social Development Project found that behavioural disinhibition (but not behavioural inhibition) increased likelihood of both alcohol abuse and alcohol dependence at age 27 (Hill et al., 2010). Beck et al, moreover, observed that among college students, cognitive reasons such as drinking for social facilitation was associated with drinking and driving and housing violations (Beck et al., 2008).

Finally, a recent study by Schulte et al focusing on gender difference in the pattern of risk factors for alcohol problems in adolescence, observed that personality characteristics such as positive drinking expectancies and deviance proneness factors appeared to impact boys and girls similarly, whereas in contrast, physiological and social changes particular to adolescence appear to differentially affect boys and girls as they transition into adulthood (Schulte et al., 2009).

Overall, this new literature search showed that between November 2007 and May 2011, epidemiological studies on non genetic risk factor for alcohol and internalizing problems in youth focused mainly in the role of neighborhood quality for what concerns the socio-demographic factors domain, on the role of parental alcohol problem for what concerns the

family environment factors domain and on the role of cognitive factors such as drinking expectancies for what concerns the personality and psychopathologies factors domain.

Only 12 studies were included in this update of the bibliographic search. This is somewhat an unexpected little number if compared with the expected trend in papers publication in the years 1997 - 2007 showed by figure 2.1. According to such figure it would have been foreseeable >30 papers responding to the search criteria and being published in the past three years. However it must be underlined that such figure included both epidemiological studies focusing on non-genetic risk factors and molecular studies focusing on genetic risk factors. Therefore the numbers of epidemiological studies I would have expected to include in the thesis bibliography with this updated search would have been approximately 15. The fact that instead only 12 studies were fully analyzed indicates probably a steady increase in the number of published studies focusing on genetic risk factors for both alcohol problem use and internalizing problems in youth, with increasingly less studies focusing on non-genetic risk factors only Hopefully this research effort in the field of psychiatric genetics will shed more light on the role of genes in the development of both alcohol problems and depression in young people, providing to future researchers sufficient evidence about the role of specific genetic variants in the development of both behaviours so that a finite number of *a priori* well-specified mechanisms of gene-environment interplay may be tested.

10.2 Gender differences in the factors impacting on the relationship between childhood depressive symptoms and adolescence alcohol problem use

10.2.1 Main findings

There is a lack of understanding of the developmental relationship between depression and alcohol problem use in youngsters (King et al., 2004). It remains to be elucidated which

factors impact upon this relationship and whether the developmental pathways differ for boys and girls. My thesis aimed to contribute to this knowledge base. The study I conducted is the largest to analyze a coetaneous sample of boys and girls; I examined childhood depressive symptoms (at age 10) and alcohol problem use in early adolescence (at age 14) in a large population-based sample of narrow age range. The narrow age range means that my findings have been relatively unconfounded by differences in developmental stages between the adolescents, compared to previous studies in samples of wider age ranges (Marmorstein, 2009).

10.2.2 Link between depressive symptoms and alcohol problem use in the young

Alcohol problem use and depressive symptomatology have been increasing in frequency in adolescents in the UK and in the U.S.A. (EMCDDA, 2007, Anderson et al., 2006b, Green et al., 2005, Harford et al., 2005, Hibell et al., 2004, Lewinsohn et al., 1991, Lopez et al., 2006). These problems may be particularly common amongst British adolescents (EMCDDA, 2007, Anderson et al., 2006b, Green et al., 2005, Hibell et al., 2004), with concerns having been expressed about their declining psychological well-being (Collishaw et al., 2004). A number of studies have reported a strong association between early-onset depression and subsequent development of alcohol problem use in adolescence (Bukstein et al., 1992, Clark et al., 1997b).

My results of the univariable GOLOGIT models indicated that children who experienced very high levels of depressive symptoms in childhood had a 27% increased risk of developing alcohol problem use in early adolescence compared to those who had low levels of depressive symptoms.

10.2.3 Gender differences in the relationship between depressive symptoms and alcohol problem use and in the impact of covariates

Consistent with the most recent findings in UK-based studies (Hibell et al., 2004, Smith, 2009, IAS, 2007), I found that girls at age 14 years had higher levels of alcohol problems than boys did. Boys showed higher levels of depressive symptoms in childhood than girls, a finding in accordance with a review by Nolen-Hoeksema and Girgus, which indicated that pre-adolescent boys may either have similar or higher levels of depression to those in girls (Nolen-Hoeksema et al., 1994).

Although the LR test for the interaction between gender and age 10 depressive symptoms in the relationship between age 10 depressive symptoms and age 14 alcohol problem use was statistically non significant, the entire analysis was nevertheless carried on both the whole sample and the boys and girls separately. In fact, as reviewed in paragraph 3.2.2, large amounts of evidence suggest that underlying risk factors may be at the basis of the gender difference observed in the prevalence of alcohol problems and depressive symptoms in adolescents. Moreover, since this is the first study investigating the effects of a large number of covariates in the relationship between age 10 depressive symptoms and age 14 alcohol problem use, a deeper investigation of the role and of the pattern of the covariates in the two separate genders was warranted. Hence, although there was no evidence of a moderating effect of gender in the relationship between age 10 depressive symptoms and age 14 alcohol problem use, the analysis has been conducted in any case on both separate genders as this was decided *a priori* during the outlining of the analysis plan.

Analyzing the two genders separately in the univariable GOLOGIT models, the effect of childhood depression as a predictor of alcohol problem use in adolescence was found to be limited to female adolescents. My findings are consistent with a longitudinal study of

children of alcoholics, which reported evidence of depression and anxiety being particularly related to substance use in female adolescents (Chassin et al., 1999).

I also found evidence for gender differences in the influences of covariates on this relationship. Taking these influences into account, the positive relationship between childhood depression and alcohol problem use was slightly reduced in girls (from O.R. 1.14 to O.R. 1.12). In boys, the O.R. was also somewhat reduced (from O.R. 0.99 to O.R. 0.92), and there continued to be no evidence of a relationship.

10.2.3.1 Possible explanation for gender difference in the prevalence of depressive symptoms and alcohol problems: role of transition into puberty

As discussed in paragraph 10.2.3., in my study sample I observed that boys at age 10 had a higher prevalence of depressive symptoms than girls, whereas reversely girls had a higher prevalence of alcohol problems than boys. A possible explanation for this gender difference (particularly with regard to the excess of depressive symptoms in boys), may be found when taking into account the particular phase that children traverse between age 10 and 14; puberty. In adolescence, children enter in the multifaceted process of puberty, which involves physical and biological changes, as well as psychological and social experiences and implications (Graber et al., 1997). Pubertal development, and particularly precocious development, has been associated with heightened risk of depression and other psychiatric conditions, particularly in girls (Glaser et al., 2011, Kaltiala-Heino et al., 2011, Petersen, 1980).

According to Conley et al., pubertal transition might heighten risk for depression for various reasons (Conley et al., 2009). In particular, pubertal changes bring about negative psychological (e.g., body image) and social effects (e.g., exclusion, victimization), which in turn heighten risk for depression (Conley et al., 2009) . Puberty also brings hormonal changes

linked to negative affect and depression (Angold et al., 1999). Just as pubertal hormones differ for boys and girls, the psychological and social effects of puberty differ greatly, and these sex differences might play a central role in the emerging sex difference in adolescent depression (Conley et al., 2009).

Prior to adolescence, at the contrary, rates of depression are similar for boys and girls (for reviews, see (Hammen, 2003, Hankin et al., 2001) or slightly favour boys (Anderson et al., 1987, Hankin et al., 1998, Jorm, 1987), as in the case of my study sample. However, it should be noted that, as argued by Jorm *et al.*, any excess in young boys' rate of depression might reflect a real difference or be an artefact of reporting or observation (Jorm, 1987). The reason of such observed discrepancy might be, as suggested by Parker *et al.*, associated to the fact that, when young girls become depressed they tend to go quiet and keep to themselves, while boys are more likely to act out with anger and irritability, with such 'externalizing' behaviours in boys resulting in their 'depression' being more likely to be observed by others and so artificially inflating the rate of 'observed depression' in boys (Parker et al., 2011).

Also concerning alcohol problem use, it has been suggested that pubertal changes may play a specific role in the development of alcohol problems in adolescence, particularly among girls (Patton et al., 2004). Pubertal timing among girls has been shown to predict patterns of substance use, with early maturers reporting higher use of tobacco and alcohol in adolescence (Dick et al., 2000, Wilson et al., 1994).

Ge *et al.* suggested three hypotheses linking pubertal timing with the development of psychiatric conditions, including depression and substance abuse problems (Ge et al., 2003). The early timing (stage termination) hypothesis suggests that girls entering puberty earlier than their peers experience the biological changes too early, without having had time to gain the necessary cognitive and social skills to cope with the changes. The off-time hypothesis assumes that entering puberty at a different rate from the majority of peers, and thus without

the support of peers facing the same challenges, is stressful and causes vulnerability. Finally, according to the stressful change hypothesis, the stress and susceptibility to disorders emerge from being in a phase of change, regardless of when it occurs, and the impact of timing is an artefact that vanishes in the long run when the whole cohort has gone through puberty (Ge et al., 2003). However, as summarized by Kaltiala-Heino et al, while previous research suggests that early pubertal timing in girls is associated with both internalising and externalising psychiatric symptoms and disorders, among boys, less research on pubertal timing has been carried out, and the findings have been less consistent (Kaltiala-Heino et al., 2011). A possible explanation for such gender discrepancy in the findings' consistency of the studies investigating the effects of puberty in the development of psychiatric conditions is offered by Ge *et al.* (Ge et al., 2001). The authors hypothesize that the unique and sudden or acute nature of menarche, which is experienced only by girls, may explain why early maturers girls appear consistently more susceptible than boys to the development of psychiatric conditions, particularly depression (Ge et al., 2001). As argued by Ge *et al.*, "in a day a girl becomes a different person, and this stressful event is even more dramatic if she is one of the first among her peers to have such experience. Other indicators of pubertal change common for both genders, such as the growth of body hair development or the development of other secondary sexual characteristics, in fact, occur relatively slowly compared with the overnight transition marked by the beginning of menstruation (Ge et al., 2001)."

10.2.4 Role of family and social environments in the relationship between childhood depressive symptoms and adolescent alcohol use

The relationship between depression and alcohol use was influenced by a number of covariates, some from the personality factor domain (childhood peer problems for girls and childhood antisocial behaviour for boys), but mostly from the family and social domains.

Family domain-related covariates included: maternal alcohol use for both boys and girls, and (for girls only) also family constellation, and mother-child interactions. Furthermore, in the social domain peer antisocial behaviour (for both boys and girls) and stressful life experiences for girls also had an impact on the longitudinal relationship. Together, the patterns suggest that, for girls in particular, dysfunctional family and social processes may combine with depressive symptoms to increase the risk of alcohol misuse.

My results, suggesting that the influences of family environmental factors on the relationship between depressive symptoms and alcohol problem use are stronger for girls than boys, are consistent with some (Shelton et al., 2010, van den Bree et al., 2004) but not all earlier observations of substance use/ misuse in adolescents (Schinke et al., 2008, van den Bree et al., 2005).

Previous research has observed that low parental attachment and monitoring and an unstructured home environment are more strongly correlated with drinking amongst girls (Johnson et al., 1988). Finally, the observation that higher alcohol problem use in boys may be more strongly influenced by their own and their peers' antisocial behaviour (albeit for the latter the difference with girls is less evident) is in accordance with a recent review by Schulte *et al.* (Schulte et al., 2009), which analyzed gender differences in factors influencing alcohol use among adolescents. They observed that, since cultural norms dictate a double standard for the monitoring and punishment of deviance for girls and boys, this discrepancy between genders may allow boys to have more freedom to interact with deviant peers teaching and reinforcing alcohol use (Schulte et al., 2009).

10.2.5 Theoretical frameworks brought to explain the relationship between depressive symptoms and alcohol problem use in the young

Two theoretical models, the Tension Reduction Theory (Greeley et al., 1999) and the Family Interactional theoretical framework (Brook et al., 1998)) may be brought to explain the relationship between depression and alcohol problem use in youngsters. Tension Reduction Theory suggests that children with depression may engage in heavy alcohol use in an effort to self-medicate their mental health problems (Greeley et al., 1999, King et al., 2004). Under this theory, one would expect less of an influence of social factors (such as the family environment) on the relationship between depression and alcohol problem use than one would under the Family Interactional theoretical framework. My finding of a 42% increased risk of high alcohol problem use for girls with high depressive symptoms versus girls with low depressive symptoms in the univariable GOLOGIT model provides support for Tension Reduction Theory. However, when correcting such a univariable model with covariates describing the family and social environment domains, there was a minor reduction in the O.R. associated with the depressive symptoms variable, which was no longer statistically significant. There is, therefore, weaker evidence supporting a tension reduction theoretical model, and my findings suggest that the more complex Family Interactional theoretical framework may be brought forward to interpret the results I obtained.

These findings are of particular interest, as only few studies to date have investigated the precursors of early substance use in females (King et al., 2004). King *et al.* argued that this is perhaps due to the higher prevalence in women of later-developing substance use disorders (King et al., 2004), a situation that is now apparently reversing in the UK (Corbin et al., 2008, Schinke et al., 2008, Studies, 2007, Wallace et al., 2003, Zatzick et al., 2006).

10.3 Moderating effects of peers' influences on the relationship between age 10 depressive symptoms and age 14 alcohol problem use

10.3.1 Main findings

Peer influences are central in many theories of adolescent problem behaviour (e.g., (Akers, 1985, Bandura, 1986, Jessor et al., 1991, Oetting et al., 1987)). In general, these theories posit that youth are more likely to engage in deviant or risky behaviours if they have friends who do so.

Peers' influences at both age 10 and 14 years were tested as possible moderators of the relationship between age 10 years depressive symptoms and age 14 years alcohol problem use in both the univariable and multivariable GOLOGIT models. To my knowledge, this is the first large scale longitudinal study considering the role of peers' influences in the moderation of the link between childhood depression and alcohol problem use in adolescence. A further strength of my study is that it investigated the combined effect of two peers' influences (i.e., child's bonding with his/ her peers and peers' risky behaviour) of which one (child bonding with peers) has been reported to be both a risk (Barnes, 2009, Wood et al., 2004b) as well as a protective factor for alcohol problem use in adolescence (Verkooijen et al., 2007, Wills et al., 2004). Thus, my findings contribute to the elucidation of this discrepancy.

My results indicated that when considering both peers' influences at age 10 and 14 years, only peers' influences at age 14 years (i.e., child bonding with peers at age 14 years and age 14 peers' alcohol drinking) moderated the relationship between age 10 depressive symptoms and age 14 alcohol problem use. The reason why peers' influences at age 10 years did not have the same moderating effects of peers' influence at age 14 years is very likely due to the very low prevalence of alcohol drinking among children's peers at age 10 and to the fact that,

although mildly correlated, the risky behaviours that were assessed at the two time points were somewhat different. While at age 14 years the measure used was a specific measure of the frequency of peers' alcohol consumption, at age 10 years a wider array of peers' risky activities, not always associated with alcohol or other substances use, and including "milder" antisocial activities such as being told off by a teacher, were included in the peers' risky behaviour variable.

10.3.2 Moderating effects of peers' influences at age 14 years

Results of the interaction analysis showed five characteristics of the moderating effects of age 14 years peers' influences: 1) the moderating effect of peers' influences in the relationship between depressive symptoms and alcohol problem use was statistically significant only when gender was taken into account; 2) when the analysis was conducted separately in the two genders, peers' influences were a statistically significant moderators only in girls; 3) only the combined effects of both "child bonding with peers" and "peers' alcohol drinking" moderated the relationship between age 10 years depressive symptoms and age 14 years alcohol problem use; whereas when "child bonding with peers" and "peers' alcohol drinking" were considered separately they did not moderate such relationship; 4) girls having a strong bond with peers and having peers who did consume alcohol had an increased probability of developing high alcohol problem use at age 14 years, compared to a model not accounting for the moderating effects of peers' influences; and 5) in contrast, girls having a strong bond with peers and whose peers did not consume alcohol had a reduced probability of developing high alcohol problem use at age 14 years, compared to a model not accounting for the moderating effects of peers' influences.

Hence, when the combined effects of "child bonding with peers" and "peers' alcohol drinking" was taken into account, girls who experienced high depressive symptoms at age 10

had a 51% increased risk of developing high alcohol problem use at age 14 compared to girls who experienced low levels of depressive symptoms; furthermore, the relationship between the two behaviours was strengthened when the gender-specific covariates for girls were included in the multivariable GOLOGIT model. These results illustrating a moderating effect of peers' influences that was specific to girls are in accordance with some previous studies showing that females attribute greater importance to peer group membership than do males (Crockett, 1984, Kiuru et al., 2010).

Results of the three-way interaction GOLOGIT multivariable model indicated that girls who experienced high levels of depressive symptoms at age 10 had a 54% increased risk of developing high alcohol problem use at age 14 compared to girls who experienced low levels of depressive symptoms.

10.3.3 Possible explanations for the complex moderating effects of peers' influences: peers' alcohol drinking

The observation that a model including peers' alcohol consumption (regardless of the level of bonding with peers) increases the probability that an adolescent develops high alcohol problem use compared to a model not accounting for the moderating effects of peers influences, may be explained by Bandura's Social Learning Theory (Bandura, 1986), which suggests that individuals make assumptions about their environment based in part on their perceptions of others' behaviour and attitudes (Maisto et al., 1999). This explains why adolescents' evaluation of their peers' alcohol use is strongly associated with their own escalation to alcohol problem use (D'Amico et al., 2001). This social process, which has been often defined as peer pressure to drink (Kiuru et al., 2010), has been solidly linked to adolescents' alcohol misuse (Epstein et al., 2002, Kiuru et al., 2010). Peer pressure to drink (Kiuru et al., 2010) can be direct, including offers of alcohol, other verbal encouragement,

and teasing (Oetting et al., 1986), or may operate in a more subtle way, such as via internal self-pressure to drink and conform to group norms in order to gain social approval and facilitate social interactions (Petraitis et al., 1995). Within this theoretical framework, my findings that girls who experienced high levels of childhood depressive symptoms are more prone to be influenced by peer's alcohol use would suggest that low mood may increase sensitivity to peers' norms and behaviours. This interpretation may be supported by the observation, reported by previous studies, that a strong protective factor towards peer pressure to drink is represented by social competence, which may be defined as the ability to overcome negative circumstances (Belcher et al., 1998) and, in the context of adolescents' alcohol misuse, as the ability to assertively refuse to engage in alcohol consumption (Epstein et al., 2007, Epstein et al., 2002, Glaser et al., 2010). Such protection offered by higher social competence may be lacking in children exhibiting signs of depression (Cole et al., 1996, McCauley et al., 1993), who by consequence may have lower refusal assertiveness ability and be more vulnerable to negative peer effects than other children (Epstein et al., 2007).

10.3.4 Possible explanations of the complex moderating effects of peers' influences: bonding with peers

The effect of peer bonding as moderator between depressive symptoms at age 10 and alcohol problem use at age 14 is more complex than the one observed for peers' alcohol drinking. Such complexity is reflected by the conflicting findings reported in literature. While peers' alcohol drinking has been unanimously reported as a risk factor for adolescents' alcohol consumption, for peer affiliation/ bonding with peers (Epstein et al., 2002), the literature does not allow a firm conclusion on whether this represents either a risk or a protective factor for alcohol engagement in young people. Although the majority of studies have reported peer affiliation to be a risk factor for alcohol engagement in adolescents (Barnes, 2009, Wood et

al., 2004b), some studies have reported that strong bonding with peers may protect against high alcohol use (Verkooijen et al., 2007, Wills et al., 2004). My results indicate that both interpretations are correct; in fact, strong affiliations with peers may either increase or decrease the probability of developing high alcohol problem use in adolescence, depending, at least in girls, on the alcohol use of the peers.

Two reasons for which bonding with deviant peers may increase substance use have been extensively reported in literature. One hypothesis is based on processes of peers' selection in which young people who are prone to substance problems tend to affiliate with like-minded people (Deater-Deckard, 2001, Fergusson et al., 2002, Fowler et al., 2007b, Kandel, 1985). This hypothesis would imply that, once the common traits of antisociality of both the adolescents and their peers have been controlled for, the association between bonding with deviant peers and alcohol problem use would disappear. A second hypothesis is that the association between engagement with deviant peers and alcohol problems among adolescents arises because of the selective processes by which deviant peer affiliations are formed. In particular, it has been well documented that involvement in deviant peer groups is a selective process in which children from disadvantaged, dysfunctional, or disturbed backgrounds, which can include children at high risk of depression, are more likely to affiliate with delinquent peers (Fergusson et al., 1999a, Fergusson et al., 2002, Fergusson et al., 1999b). Results of the multivariable GOLOGIT model including peers' influence provide support for this second explanation, as the moderating effect of peers' influences in the relationship between childhood depressive symptom and adolescence alcohol problem use was mildly strengthened, rather than reduced, when covariates describing socio-demographic family, social and personality domains were taken into account.

The reasons that may explain why close bonding with lower-risk peers, such as non-alcohol drinking peers, may reduce the risk of developing high alcohol problem use, may appear

intuitive; however, this nevertheless represents an under-studied area of research (Barnes, 2009). Verkooijen *et al.* (Verkooijen et al., 2007), for example, examined the relationship between substance use and involvement in different types of youth crowds including sporty, pop, skate/hip-hop, quiet, techno, computer nerd, religious, and hippie groups. Results of their analyses, replicated by Barnes *et al.* (Barnes, 2009), showed that identification with sporty, quiet, computer nerd, and religious subgroups was associated with lower risk, while association with pop, skate/hip-hop, techno, and hippie subgroups was associated with higher substance use.

A possible explanation of this double moderating role of strong bonding with peers has been suggested by Kiuru et al., who argued that the mechanisms of "risk moderating" peer influences (i.e., close bonding with peers and peers' alcohol use) and "protection moderating" peers influences (i.e., close bonding with peers and peers' abstinence from alcohol) are in fact the same. In other words, experience with alcohol and attitudes favouring drinking may be related to popularity and high status in the peer group only when peer group norms encourage drinking. Non-drinking peer groups, in turn, may exert considerable pressure on their members to reduce drinking or to not drink at all. Consequently, depending on the peer context, a higher level of alcohol consumption or abstinence from drinking may provide a means of attaining social status, social support, and behavioural confirmation (Kiuru et al., 2010).

10.4 Limitations

The analyses I conducted on the ALSPAC dataset as part of my thesis have several limitations. First, children were asked whether they had been intoxicated from alcohol only if they had consumed ≥2 whole alcoholic drinks in 24 hours, which may exclude those who might get intoxicated on lower amounts of alcohol. However, following the most recent

guidelines on variable construction (Tannenbaum et al., 2009) I combined four items to create the alcohol problem use variable; moreover, further data inspection indicated that information about alcohol intoxication was a relatively minor contributor to this factor. Secondly, the main carer only (not the youngsters themselves) reported on their children's stressful life events. Ideally, one would like to ask young children directly about such events; however, this was not done in ALSPAC for practical as well as ethical reasons.

Regarding information related to peers, two limitations should be noted. First, children reported on both their own and their close friends' alcohol use. Although youngsters' own account of their substance use may be more reliable than those of other informants (Fisher et al., 2006), their accounts of their friends' alcohol use may be coloured by their own use (Cleveland et al., 2005). Second, children did not specify whether the peers who they were reporting the level of bonding with were the same peers that they considered when they were describing their peers' risky behaviour; i.e., the ALSPAC study team did not request to nominate (or even simply think about) specific peers before answering the questions related to peers' influences. However, this approach used to ascertain peers' influences may have had the advantage of allowing the child to describe the behaviour and attitudes of their general or their entire peer group, rather than only of a few selected members, thus overcoming the limitation of the non-representativeness of the peer network associated with studies using the "nominated peers" approach (Hill et al., 2008).

10.5 Remarks on the measure of depressive symptoms used

The SMFQ cut-off scores used to identify high and very high depressive symptoms in my study sample has been validated by a number of studies (McKenzie et al., 2011, Rhew et al., 2010); moreover the prevalence of adolescents who reported having experienced very high depressive symptoms in childhood (18.7% of boys and 17.3% of girls) was comparable with

the prevalence of depressive cases reported by other studies conducted in the UK, the USA and Australia in samples of similar age range (McKenzie et al., 2011, Stansfeld et al., 2004). For example, in an epidemiological survey assessing psychological distress in British adolescence aged 11-14 years Stansfeld and colleagues, using data from 2790 adolescents participating to the Research with East London Adolescents: Community Health Survey (RE-LACHS) and using a cut-off of 8 in the SMFQ scale, identified 18.9% boys and 29.8% girls as cases experiencing more severe depressive symptoms (Stansfeld et al., 2004).

10.6 Methodological remarks on data imputation

A common issue with longitudinal studies is the loss of information and reduction of sample size as a result of missing values, which increase the risk of selection bias as a result of loss to follow-up (Wood et al., 2004a). Missing values may particularly affect the retention in longitudinal studies of sample subgroups with higher rates of behavioral and mood problems (Wolke et al., 2009).

I imputed missing data in the covariates and in the moderating variables using a MICE approach (Royston, 2004).

As described in paragraph 6.3.2, I imputed the missing information for the entire ALSPAC dataset; however I only analyzed the imputed variables of the 4220 participants included in the study sample. This was done because including all the ALSPAC participants in the analyses based on the imputed variables of interest might have given biased results. In fact, for those children whose imputation was not based on at least the predictor and the outcome variable, the imputed variables might have been less accurate, because the estimates would have been derived from progressively fewer variables of limited informativeness (e.g. in some cases gender of the participant only) (CDC, 2008, Sterne et al., 2009). In addition, the limited amount of information on which the imputation would have been based, would have

also decreased the variability between the participants' estimates, narrowing therefore the confidence interval of the final models' results (Rubin, 1978, 1987). For those children who might have dropped out of the study at an earlier stage, moreover, many variables would have been not MAR (because the reason beyond the missingness would have not been a random attrition, but the fact of being no longer participating to the study) increasing therefore the likelihood of obtaining a biased imputed estimate (Sterne et al., 2009). It was therefore decided that, for being included in the analysis using imputed data, participants should have provided at least information about gender and age 10 depressive symptoms and age 14 alcohol problem use (participants included in the analysis N= 4220, corresponding to the study sample).

Furthermore, performing sensitivity analyses on the non-imputed dataset, I observed that the estimates of the relationship between depression and alcohol problem use obtained using the imputed covariates were much more consistent with the crude estimates than those obtained using the non-imputed covariates. This confirmed the validity of choosing this imputation approach, which had the major advantages of minimizing the selection bias due to missing data and increasing the representativeness of the sample.

10.7 Implications

Most current alcohol prevention programmes for adolescents are based on a one-size-fits-all approach, regardless of risk (Boyd, 2005), and prevention efforts have been predominantly directed towards non-drinking youths, with little evidence of their effect in youngsters who have already initiated drinking (Zucker et al., 2005). Moreover, despite trends of increasingly high alcohol use rates for girls in some societies, only very few gender-specific prevention programs have been developed (Kumpfer et al., 2008). Future policy should also take into

consideration the evidence that, for depressed girls in particular, the risk of alcohol problem use may be strongly influenced by peer and family factors. This may be particularly relevant given recent reports that girls may be at a greater risk of becoming dependent on alcohol and other substances than boys (NCASA, 2003, Schinke et al., 2008).

Such risk, combined with the increased prevalence of heavy drinking in girls in some societies, can lead to serious public health consequences in the future. As argued in an extensive review by Nolen-Hoeksema (2004) on women's and men's alcohol consumption and alcohol-related problems, in adulthood, consequences of heavy alcohol use appear to be more negative for women than men. The author concluded that women may suffer alcohol-related physical illnesses at lower levels of exposure to alcohol than men and may suffer more cognitive, physical (including reproductive) and motor impairment due to alcohol than men. Moreover, women may be more likely than men to suffer physical harm and sexual assault when they are using alcohol (Nolen-Hoeksema, 2004). Thus, my findings may prove useful in planning future alcohol prevention and intervention programmes.

In accordance with Bandura's Self-Efficacy Theory (Bandura, 1977), which posits that individuals who have less confidence in their ability to change behaviourally (such as depressed youngsters) (Gilbert et al., 1996) are less likely to actually engage in behaviour change (DeVellis et al., 2001, Miller et al., 2002), my results highlight the need for specific help programs for girls exhibiting early signs of depression, particularly where such girls are experiencing family-related and other social adversity. Furthermore, the findings suggest a different approach for boys, where the link between depressive symptoms and later alcohol problems is weaker and appears to be influenced by their own and their peers' antisocial behaviour. These findings contribute to a growing theoretical basis suggesting that family-related interventions to reduce alcohol use may be particularly effective for girls (Mason et al., 2009, Schinke et al., 2009).

My findings from the multivariable GOLOGIT interaction model indicated that the only covariate impacting the relationship between age 10 depressive symptoms and age 14 alcohol problem use once the moderating effects of peers influences had been taken into account was the family environment. This provides further insight to the ongoing debate amongst researchers on the importance of social support from family and friends on the prevention/ intervention efforts to reduce adolescent substance misuse (Park et al., 2009).

Youth who experience greater parental support tend to participate in fewer negative antisocial behaviours (Hawkins et al., 1992). This protective relationship can be explained by Social Control theory (Tornberry, 1987), which states that close relationships can have a positive influence on adolescent drinking through social support and, therefore, that parental support can have a mitigating effect on negative peer influences (Park et al., 2009).

Furthermore, my study seems to confirm that, as suggested by King et al., low mood may increase girls' vulnerability to deviant peer influences (King et al., 2004). This may be due to low mood and low self-esteem associated with depression, as girls exhibiting very high depressive symptoms may be influenced more easily by deviant peers to try substances in an effort to gain or maintain acceptance in peer networks (King et al., 2004); however, for the same reason (i.e., attaining social status, social support, and behavioural confirmation (Kiuru et al.)), they may be easily influenced by positive peers to maintain alcohol abstinence. This may have particularly important implications in policy and practice. Preventive efforts towards alcohol problem use in adolescence have increasingly focused on adolescents' social environment, particularly enhancing competency skills such as refusal assertiveness, which play an important role in school-based efforts to reduce the use of alcohol and illicit drugs (e.g., Dusenbury and Botvin, 1992; Pentz, 1985).

However, even though promoting the ability of individual adolescents to resist peer pressure to drink, for example through social skills and stress management (Byrne, 2005) may be

important, my results suggest, as has also been agued by Kiuru *et al.* (Kiuru et al., 2010), that it may be even more effective to target intervention efforts to the whole peer network in a specific setting (for example, a school) to change predominant group norms (Salmivalli et al., 2005) or to utilize identified peer group leaders as agents of social change (Miller-Johnson, 2004).

It is however important to note that my results, although very intriguing, as this was the first study attempting to investigate the role of peers influences in the relationship between childhood depressive symptoms and adolescence alcohol problem use, do not provide an evidence sufficiently strong (i.e., the effect may be still considered quite modest, particularly considering the large sample size) for influencing an immediate change in the policy and practice of prevention and intervention efforts towards alcohol problems in adolescents. Nevertheless, although more research is certainly warranted in order to replicate my results, empirical evidence may support my findings. In fact, a recent review of school-based programs by Fletcher et al, reported that those studies aimed to modify the school environment, to increase student participation, improve peer relationships, and promote a positive school ethos resulted in a reduction in students' substance use (Fletcher et al., 2008). Moreover, among the randomized control trials reviewed by Fletcher and colleagues (Fletcher et al., 2008), the ones having the greatest substantial effect in terms of reduction of adolescents' substance use were those targeting younger pupils, such as the Aban Aya Youth Project (age at baseline 10-11 years, follow up of four years) (Flay et al., 2004) and the D.A.R.E. Plus project (age at baseline 11-12 years, follow up of two years) (Perry et al., 2003). These studies indicate that early intervention programmes targeting children's social and peer environments may be most effective in reducing substance use in adolescence.

10.8 Future directions

Adolescence is a key developmental time frame for the future risk of both alcohol problem use and depressive symptoms, and further research in such samples is warranted (DeWit et al., 2000, Grant et al., 2001, Pine et al., 1999, Pine et al., 1998). Large-scale longitudinal studies of youth in which detailed epidemiological information as well as genetic data has been collected are increasingly becoming available, such as the AddHEALTH study in the U.S.A. (Bearman et al., 1997) and the ALSPAC study in the UK (Golding et al., 2001).

Moreover, my literature analysis of the molecular studies focusing on depressive symptoms and alcohol problem use indicated that further research in the field of psychiatric genetics is needed. For most of the hypothesized susceptibility genes, the presence of both positive as well as negative findings makes it difficult to draw firm conclusions on the biological underpinnings of co-morbid alcohol and internalizing disorders. One reason can be that genetically vulnerable individuals will only meet psychiatric criteria for substance dependence or mood disorder if they have experienced specific environmental stressors (gene-environment interplay). Elucidating the complex mechanisms behind the development of the traits this dissertation has focused on will require combined efforts from different research disciplines, including epidemiology, neuroscience and molecular psychiatry (Van den Bree, 2005), with the ultimate potential to integrate knowledge rather than to build separate camps of supporters (Uher, 2008).

The results of my research, although modest and requiring further replication in other samples of adolescents, both in the UK and in other countries, may have future implications in policy and practice; my findings suggest in fact that planning gender-specific help programmes and facilitating girls in seeking help when experiencing family and other social problems may not only prove effective in reducing the risk of depression but also reducing alcohol problems. The moderating effects of peers' influences in the relationship between

childhood depressive symptoms and adolescence alcohol problem use will need to be taken into account in any programme aiming to reduce the risk of developing high alcohol problem use in girls exhibiting early signs of depression, particularly in consideration of the protective role that positive peer groups may have in reducing the probability of developing high alcohol problem use.

In summary, this study found a gender difference in the relationship between childhood depression and adolescence alcohol problem use, with depressed girls at age 10 appearing markedly more at risk of developing alcohol problem use at age 14 than boys. These findings point to the need for gender-specific prevention and intervention programmes. Future policy should particularly take into consideration the evidence that, in depressed girls, the higher risk of developing alcohol problem use is strongly influenced by peer and family factors.

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PUBLICATIONS ARISEN FROM THIS DOCTORAL THESIS

- SARACENO, L., MUNAFO, M., HERON, J., CRADDOCK, N. & VAN DEN BREE, M. B. (2009) Genetic and non-genetic influences on the development of co-occurring alcohol problem use and internalizing symptomatology in adolescence: a review. *Addiction,* 104, 1100-21.

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