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What are the risk and protective factors for drug misuse?

Technical Summary

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Trawsnewid **data** a **thystiolaeth** i **ddeallusrwydd iechyd cyhoeddus**

Transforming **data** and **evidence** into **public health intelligence**

Table of Contents

1 Key findings

Risk factors

We found good quality evidence supporting the hypotheses that the following are risk factors associated with drug misuse:

- Younger age at first cannabis use
- Substance using peers
- Childhood maltreatment.

We found moderate quality evidence supporting the hypotheses the following are risk factors associated with drug misuse:

- Alcohol use
- Adolescent illicit drug use (other than cannabis)
- Cigarette smoking
- Bullying perpetration
- Male gender
- Personality traits (including novelty or sensation seeking, self-control, self-esteem, coping and inhibitory control)
- Poor school engagement
- Parental drinking
- Parental illicit drug use
- Parental mental state
- Parental cigarette smoking.

We identified moderate quality evidence indicating parental education and parental monitoring are not associated with illicit drug misuse. The evidence was inconclusive for the remaining risk factors.

Protective factors

We found moderate quality evidence supporting the hypothesis that a positive attitude to school is protective against future drug misuse. Although the findings were inconclusive for religiosity and extracurricular activity, there was some evidence supporting the hypotheses that these may be protective against drug misuse.

The tables below outline the evidence grade given to each identified risk or protective factor. This information gives us a good idea of how confident we are that they are or are not risk or protective factors for drug misuse. It is likely many of them act as a multifaceted network rather than in isolation, making them extremely complex. In addition, as far as we are aware, this

is the only systematic review to have collated the evidence of risk and protective factors for drug misuse in the general population.

1.1 Socio-environmental risk factors

Risk factor	Evidence statement
Negative life events	There is some evidence supporting the hypothesis that experiencing high stress/negative life events in childhood is a risk factor for drug misuse, but it is not conclusive. [C] (Four studies, one moderate quality, two poor quality showing an association, and one moderate quality showing no association)
Socio-economic status and income	The evidence is inconsistent and it is not possible to draw a conclusion. [D] (one good quality study and four moderate quality with inconsistent findings across the studies)
Childhood IQ score (single study)	Evidence from a moderate quality single study of a strong association between high childhood IQ score and drug misuse
Domicile (single study)	Evidence from a moderate quality single study of a strong association between those living in cities and towns and drug misuse

1.2 Substance related risk factors

Risk factor	Evidence statement
Age at first cannabis use	The hypothesis that younger age at first cannabis use is a risk factor is supported by good quality evidence [A] (ten good quality, seven moderate quality and one poor quality study found an association and one moderate quality study found no association)
Substance using peers	The hypothesis that substance using peers is a risk factor is supported by good quality evidence [A] (three good quality, one poor quality)
Alcohol use	The hypothesis that alcohol use is a risk factor is supported by moderate quality evidence [B] (Eleven studies, four good, four moderate and three poor quality, found an association and one good and one moderate quality study found no association)
Adolescent illicit drug use (other than cannabis)	The hypothesis that adolescent illicit drug use (other than cannabis) is a risk factor for future/adult use is supported by moderate quality evidence [B] (three good, three moderate and one poor quality found an association and one moderate quality study found no association)
Cigarette smoking	The hypothesis that cigarette smoking is a risk factor is supported by moderate quality evidence. Seven studies found an association and two studies found no association. [B] (Three good and four moderate quality studies found an association and two good quality studies found no association)

Risk factor	Evidence statement
Prior exposure to drugs (single study)	Evidence from a single moderate quality study of a significant association between prior exposure to drugs (prior drug offers/experience) and drug misuse

1.3 Intrapersonal risk factors

Risk factor	Evidence statement
Bullying perpetration	The hypothesis that bullying perpetration is a risk factor for illicit drug use at 18 years is supported by moderate to good quality evidence [B] (one good and one moderate quality)
Gender	The hypothesis that being male is a risk factor is supported by moderate quality evidence [B] (seven good and nine moderate quality studies found an association and three moderate and one poor quality study found no association)
Personality traits	The hypothesis that certain personality dimensions (including novelty or sensation seeking, self-control, self-esteem, coping and inhibitory control) are a risk factor is supported by moderate quality evidence [B] (three good, eight moderate and one poor quality study found an association and one poor quality study found no association)
Academic achievement	There is some evidence supporting the hypothesis that low academic achievement is a risk factor, but it is not conclusive [C] (one good, four moderate and two poor quality studies found an association and one good quality and two moderate quality studies found no association)
Delinquency or aggression	There is some evidence supporting the hypothesis that delinquency or aggression are risk factors, but it is not conclusive [C] (two good, two moderate and two poor quality studies found an association and one poor quality study found no association)
Emotional and behavioural problems	There is some evidence supporting the hypothesis that emotional and behavioural problems are a risk factor, but it is not conclusive [C] (three good, one moderate and one poor quality study found an association and two good and one moderate quality study found no association)
School related problems	There is some evidence supporting the hypothesis that school related problems are a risk factor for drug misuse, but it is not conclusive [C] (three moderate and one poor quality study)
suicidal behaviour	There is some evidence supporting the hypothesis that suicidal behaviour is a risk factor, but it is not conclusive [C] (one moderate and one poor quality)
Mental disorders	The evidence is inconsistent and it is not possible to draw a conclusion [D] (three good, five moderate and two poor quality with inconsistent results across the studies)

Pubertal timing	The evidence is inconsistent and it is not possible to draw a conclusion [D] (two moderate and one poor quality with inconsistent results across studies)
Race/ethnicity	The evidence is inconsistent and it is not possible to draw a conclusion [D] (two good, six moderate quality with inconsistent results across studies)
Bully victimisation	The evidence is inconsistent and it is not possible to draw a conclusion [D] (one good and two moderate quality with inconsistent results across studies)
Truancy (single study)	Evidence from a moderate quality single study of a strong association between exclusions in the past three years and truancy in the past 12 months and drug misuse
Independent decision making (single study)	Evidence from a poor quality single study of a strong association between independent decision making and drug misuse

1.4 Interpersonal risk factors

Risk factor	**Evidence statement**
Childhood maltreatment	The hypothesis that experiencing childhood maltreatment is a risk factor is supported by good quality evidence [A] (six good and one moderate quality)
Parental drinking	The hypothesis that parental drinking is a risk factor is supported by moderate quality evidence [B] (one good, three moderate and one poor quality)
Parental illicit drug use	The hypothesis that parental illicit drug use is a risk factor is supported by moderate quality evidence [B] (three good, two moderate and one poor quality)
Parental mental state	The hypothesis that parental mental state is a risk factor is supported by moderate quality evidence [B] (two moderate quality)
Parental cigarettes smoking	The hypothesis that parental cigarette smoking is a risk factor is supported by moderate quality evidence [B] (two good and two moderate quality)
family composition	There is some evidence supporting the hypothesis that being in a single-parent family is a risk factor, but it is not conclusive [C] (three moderate studies found an association and one poor quality found no association)
Parental marital circumstances	The evidence is inconsistent and it is not possible to draw a conclusion [D] (three good and two moderate quality with inconsistent results across studies)
Friendship/peers	The evidence is inconsistent and it is not possible to draw a conclusion [D] (two moderate and one poor quality with inconsistent results across studies)
Relationship with parents	There is inconsistent and it is not possible to draw a conclusion [D] (four moderate and five poor quality with inconsistent results across studies)

Parental education	The hypothesis that parental education is not a risk factor is supported by moderate quality evidence [G] (one good quality study found an association and three moderate quality studies found no association)
Parental monitoring	The hypothesis that parental monitoring (parental knowledge of child's whereabouts) is not a risk factor is supported by moderate quality evidence [G] (two moderate quality studies found no association and one moderate quality study found an associaton)
Late bedtime (single study)	There is evidence from a good quality single study of a strong association between late bedtime and drug misuse
Out of home placement/living in care (single study)	Evidence from a moderate quality single study of a strong association between being placed out of home as a child and drug misuse
Parental criminality (single study)	Evidence from a moderate quality single study of a strong association between a parent associated with criminality and drug misuse
Structural stigma (single study)	Evidence from a poor quality single study of a strong association between structural stigma and drug misuse
Intimate partner violence (single study)	Evidence from a moderate quality single study demonstrating no association between experiencing intimate partner violence (women aged 18 to 30 years) and drug misuse
Relationship satisfaction (single study)	Evidence from a moderate quality single study demonstrating no association between relationship satisfaction and drug misuse

1.5 Protective factors

Protective factor	**Evidence statement**
Positive attitude to school	The hypothesis that a positive attitude to school is a protective factor for drug misuse is supported by moderate quality evidence [B] (two moderate quality)
Religiosity	There is some evidence supporting the hypothesis that being religious is a protective factor, but it is not conclusive [C] (two moderate and two poor quality studies found an association and one moderate quality study found no association)
Extracurricular activity	There is some evidence supporting the hypothesis that being involved in extracurricular activities is a protective factor, but it is not conclusive [C] (one moderate and one poor quality)

2 Background

Drug misuse is recognised as an important public health problem globally. An estimated 275 million people aged 15 to 64 years worldwide, used drugs at least once during 2016 (United Nations Office on Drugs and Crime, 2018). Cannabis is the most commonly used illicit drug worldwide, followed by cocaine and 3,4-methylenedioxy-methamphetamine (MDMA), however the nonmedical use of prescription opioids is becoming a major threat around the world (United Nations Office on Drugs and Crime, 2018). It is widely recognised that individuals who begin using drugs at an early age are at increased risk of being dependent or developing a substance use disorder in later life.

In England and Wales, around one in 11 (9.4%) adults aged 16 to 59 years had taken drugs in 2018 (Home Office, 2019). In Wales, the overall number of individuals admitted to hospital for poisonings with illicit drugs increased by 4.4% from 6,488 in 2017/18 to 6,786 in 2018/19 (Public Health Wales, 2019). Opioids were responsible for the highest number of hospital admissions in 2018/19, followed by cannabinoids (Public Health Wales, 2019). Admissions were six times higher amongst those from the most deprived areas compared to least deprived (Public Health Wales, 2019). A total of 327 deaths due to drug poisoning were registered in Wales in 2018, an increase of 25.8% from the previous calendar year (Public Health Wales, 2019). Heroin and other related opiates are responsible for the highest mortality rates among illegal drug users (Office for National Statistics, 2019).

A range of individual, genetic, and environmental influences have been documented as predictors for the initiation and progression of drug use. These include gender (El Arnsari et al., 2015), mental disorders (Swendsen et al., 2010), early smoking, antisocial behaviour, truancy and exclusion from school, and poor parental discipline (Dillon et al., 2007). Interventions to prevent the use and abuse of illicit drugs are commonly targeted at reducing the influence of risk factors and enhancing the effectiveness of protective factors.

A Substance Misuse Programme Board was established within Public Health Wales to provide cross-organisational oversight and direction for the coordination and implementation of activity in relation to substance misuse. This remit includes the development of evidence-based services and systems in order to prevent, identify and reduce harms and promote engagement in relation to substance misuse including illicit drugs and alcohol.

The board requested preliminary scoping work to identify research on risk factors for drug misuse. The scoping report summarised the availability of systematic reviews examining specific risk factors for drug misuse published between 2008 and 2018. No systematic reviews covering a broad range of

risk factors in any population group were identified. Next, scoping searches for primary studies on risk (2000 to 2018) and protective (2000 to 2019) factors were undertaken, which found 10 studies conducted in the UK specific to drug misuse. Subsequently the board asked the Observatory Evidence Service to undertake a review of the evidence on risk and protective factors for drug misuse[1].

3 Methods

The protocol (available on request) describes *a priori* the methods used to conduct this systematic review of primary studies.

3.1 Review questions

This systematic review addressed the questions:

3.1.1 Question 1

What risk factors (personal, interpersonal, and structural (environmental/economic) are associated with use of illicit drugs[2] or use of prescription drugs for non-prescribed purposes?

3.1.2 Question 2

What protective factors (personal, interpersonal, and structural (environmental/economic) are associated with no use of illicit drugs[2] or no use of prescription drugs for non-prescribed purposes?

3.2 Searching

CINAHL, Criminal Justice database, Embase, MEDLINE and PsycINFO databases were searched for longitudinal studies from 2000 to May 2019, when the search was conducted. Full details of the search strategy are available on request.

Searching identified both primary studies and systematic reviews. Although systematic reviews were not included in this review, their included studies were screened for relevant papers and any previously unidentified primary studies were included.

[1] This includes illicit drugs and so called 'legal highs' which are now outlawed, but may not have been at the time of publication of relevant studies, and misuse of prescription medication.
[2] This includes so called legal highs.

3.3 Screening

All identified studies were screened at title and abstract against the inclusion criteria specified in the protocol and outlined in Box 1.

A random 20% sample of titles and abstracts were screened independently by two reviewers. Any disagreements were resolved by discussion. The remaining titles and abstracts were screened by the lead reviewer. All studies included at abstract were screened at full text independently by two reviewers. Any differences in agreement at this stage were resolved by a third reviewer. All studies excluded at full text are listed in appendix 1 along with reasons for exclusion.

BOX 1: INCLUSION/EXCLUSION CRITERIA	
Inclusion criteria	**Exclusion criteria**
Study type: • Cohort and case control studies looking at risk and protective factors	Study type: • Systematic reviews and meta-analyses • Cross sectional studies • Other types of primary study designs
Source type: • Studies published in peer reviewed journals	Source type: • Other sources of literature including grey literature, conference abstracts, presentations and posters
Population: • General population • Studies conducted in pre 1974 OECD countries[3]	Population: • Other specific subpopulations such as those at risk or people with mental illness • Studies conducted in countries not conducted in pre 1974 OECD countries • Studies conducted in indigenous populations of pre 1974 OECD countries as these will not be generalisable to Wales
Outcome: • Uptake and use of illicit drugs • Use of prescription drugs for non-prescribed purposes • No use of illicit drugs or prescription drugs for non-prescribed purposes	Outcome: • Other outcomes

[3] Limiting to the pre 1974 OECD countries will increase relevance to the Wales context. These countries are; Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Japan, Luxemburg, Netherlands, New Zealand, Norway, Portugal, Spain, Sweden, Switzerland, Turkey, Italy, UK and USA.

3.4 Data extraction

Data from included studies were extracted independently by two reviewers into a data extraction table, which is available on request. All extracted data was checked in duplicate for accuracy to ensure all relevant information had been retrieved. Authors were not contacted for missing information.

We only extracted results for exposures that had undergone adjustment or modelling. These results are more likely to identify risk and protective factors because they have accounted for a variety of potential confounders.

3.5 Quality assessment

All included studies underwent quality assessment in duplicate by two reviewers, with any differences resolved by discussion. The study design specific checklist used for this is included in the supplementary material.

3.6 Evidence grading

Evidence grading of all included studies was conducted independently by two reviewers. Each study was assessed based on three criteria; (1) the direction of effect and strength of association between exposure and outcome; (2) the presence of or consideration for potential biases; and (3) whether or not potential confounding factors were controlled for. We assessed the strength of association between exposure and outcome by examining any measure of association reported in the study. As expected for these types of studies, most reported odds ratios (OR). We interpreted the ORs as follows: OR = 1 (exposure doesn't affect odds of outcome); OR > 1 (exposure associated with higher odds of outcome); OR <1 (exposure associated with lower odds of outcome). If the study reported p-values and/or 95% confidence intervals (CI), these were used to assess the precision of the measure of association reported. An evidence grade of 'good', 'moderate' or 'poor quality was assigned to each study based on these assessments. Both evidence reviewers checked each other's decisions and then came together to resolve any disagreements.

Exposures identified from the included studies were grouped into similar risk or protective factors and then underwent evidence grading to assess the strength of the evidence supporting them. This was undertaken using the schemes outlined in appendix 1, and the quality assessment of individual studies. Where only one study was identified on a risk or protective factor, the grading for that exposure was based on the single study. Where multiple studies were identified, the grading for the exposure was based on the overall body of evidence from those studies. It is important to be aware that a single study cannot demonstrate a risk or protective factor as causal, it can only show an association. Several studies demonstrating a strong association are more likely to suggest an identified

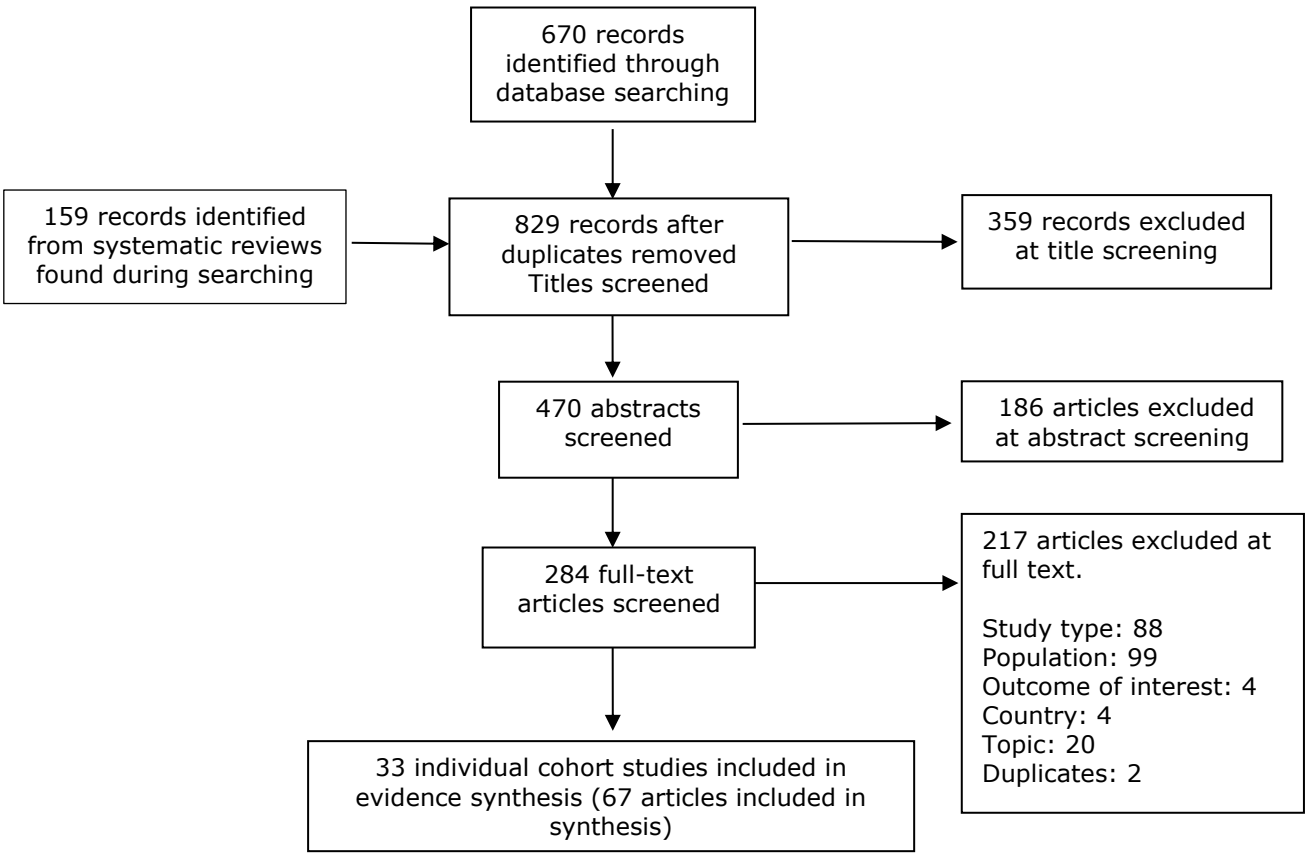
association may be a causal risk or protective factor. Finally, identified risk factors were then categorised into four domains which loosely followed a risk factor typology (Hawkins et al., 1992).

4 Results

4.1 Study selection

Details of the flow of literature through the review is summarised in figure 1 below.

Figure 1: Flow of information through the review process (The term record refers to database records, the wording changes to articles at the point in the process where the actual article is screened rather than the database record)



4.2 Cohort and included studies characteristics

The 67 included studies utilised data from 33 individual cohorts. They included a mix of prospective and retrospective cohort study designs, and one matched case control design. Cohorts were conducted in a variety of countries. Twelve were from USA; four each from Australia, United Kingdom and Finland; two each from New Zealand and The Netherlands; and one each from Sweden, Germany, Iceland, Norway and Denmark. Some of the cohorts began in the nineteen seventies (The Christchurch Health Development Study) and some continue today (The Dunedin Multidisciplinary Health and Development Study). Others were more recent and much shorter in duration (National Epidemiologic survey of Alcohol related conditions). It was not possible to establish the date or duration of eight cohorts. Included studies looked at data from a varied time-period ranging from twelve months to several years. Where multiple studies used data from the same cohort, they rarely examined data from the same time-period. Some studies also conducted different analyses on the same data, but looked at different aspects of the data, using different sub samples of the population.

Fourteen cohorts were conducted in an educational setting (mostly secondary schools, but one university), six were birth cohorts, five from community settings and eight from unknown settings. Although the majority of cohorts were specifically recruited and measures were taken via self-report, some of the data was taken from publically available national data sets. These were from countries such as Denmark where such personal information is readily available, and routinely collected.

Many of the cohorts looked at overarching topics that incorporated substance misuse, such as mental health. A small number specifically looked at substance misuse, which included alcohol and cigarette smoking as well as illicit drug use. A wide range of substances including cannabis[4], solvents, cocaine, hallucinogens, sedatives, stimulants, MDMA, heroin, amphetamines, LSD and non-prescribed prescription drugs were examined for associations. Most often cannabis use and dependence were studied in isolation, but other illicit substances were generally grouped together. Most studies measured multiple substance types or were vague in their description of the included drugs. A small number of included studies looked at alcohol, tobacco and illicit drugs under the same outcome of substance abuse, generally due to low numbers. Measures varied and included use which was described as last 30 day use, last 12 months use or ever use and substance dependence. All were self-reported, and often use a validated

[4] Authors of included studies used the terms marijuana and cannabis, but for consistency the term cannabis is used throughout.

diagnostic questionnaire such as the DSM-II-R criteria for substance dependence. Identifying substance use was usually in binary terms such as 'yes' or 'no'.

Population sizes ranged from 198 participants (3GS cohort) to 1,407,763 (no name cohort from Sweden), but generally they included between 300 and 4,000 participants. Most included mixed genders. Other participant characteristics were generally poorly reported. Table 1 below outlines characteristics of the cohorts that have been included.

Table 1. Cohort Characteristics table

Cohort name	First author/ year	Country	Setting	No. Participants	Participant Characteristics	Data collection method	Included studies
LYSPE - The Longitudinal Study of Young People in England	Department for Education/ 2011	UK	School	21,000 at wave 1	Participants in year 9 (age 13 years)	Interview	Hale and Viner (2016)
CHDS - Christchurch Child Development Study	Fergusson (2001)	New Zealand	Birth cohort	1,265 at birth	All children born during the period from 15 April to 5 August 1977. 1,265 (97%	Interview and survey (multiple informants)	Newton-Howes, (2016) Fergusson (2008) Boden (2006) Fergusson (2006) Fergusson (2003) Fergusson (2002) Woodward (2001)
EDSP - Early developmental stages of psychopathology study	Wittchen (1998)	Germany	Community	3,021 interviews completed	Sample randomly drawn from government population registers	Interview and survey (multiple informants)	Asselmann (2016) von, Sydow (2002)
GUTS - The Growing Up Today Study	Hatzenbuehler (2015)	USA	Community	16,875	Girls (n=9,033) and 58% of the boys (n=7,842). Participants predominantly white	Survey	Hatzenbuehler (2015)
ALSWH - Australia longitudinal cohort study of women's health	Brown 1998	Australia	Community	7,093	Sample of women born 1973–1978 selected from the database of the Health Insurance Commission (HIC)	database	Yorkston (2007)
3GS-OYS - Three Generational Study (3GS) an ongoing study of the children of the OYS G2 men	Unknown	USA	Offspring of fathers in existing study	?178	unknown	Survey and interview	Pears (2007)
ATP - The Australian Temperament Project	Prior (1999)	Australia	Attendees of Maternal and Child Health Centre	2,443 at enrolment	Mostly Caucasian	Survey	Stockwell (2004)

Cohort name	First author/ year	Country	Setting	No. Participants	Participant Characteristics	Data collection method	Included studies
Women 2000	Unknown	USA	Unknown (acquired through random digital sampling)	1,014	Women aged 18 to 30	Interview	Testa (2003)
WOS – West of Scotland Study	Unknown	UK	School	2,268	Unknown	National data and Survey	Markham (2012) West (2004)
ALSPAC - Avon longitudinal study of parents and children	Boyd (2013)	UK	Birth cohort	14,541 at recruitment	Unknown	Survey and interview	Dantchev (2019) Mars (2014)
BCS 1970 - 1970 British Birth Cohort	Elliot (23006)	UK	Birth cohort	16 571 eligible	Participants born in a single week in 1970 in UK	Survey, interview, school medical examination, parental report, local health authorities	White and Batty(2012)
ADD Health	Harris (2012)	USA	School	Unknown	Nationally representative sample of adolescents in grades 7-12	Survey and interview	Lanza (2002) McNeely (2004) Van den Bree (2005) Lessem (2006) Rostosky (2007) Harrell (2009) Humensky (2010) Synder (2014) Zhang (2014) Khan (2014) McGlinchey (2015)
Boy to a man	Almqvist (1999)	Finland	Birth cohort	6,017	Unknown	Survey (multiple informants)	Niemela (2008) Niemela (2011)
MUSP – The Mater-University of Queensland Study of Pregnancy	Najman (2005)	Australia	Birth cohort	7,223	Unknown	Survey	Hayatbakhsh (2006) Hayatbakhsh (2009)a Hayatbakhsh (2009)b Hayatbakhsh (2009)c Hayatbakhsh (2013) Abajobir (2017)
RAR - Reykjavik Adolescent Risk-Taking Study	unknown	Iceland	School	1,293	14 year old students (51% girls)	Survey	Adalbjarnardottir (2001)

Cohort name	First author/ year	Country	Setting	No. Participants	Participant Characteristics	Data collection method	Included studies
The 1987 Finnish Birth Cohort	Paananen (2012)	Finland	Birth cohort	60,069	Unknown	National registers and survey	Cote (2018)
NFBC 1986 - Northern Finland Birth Cohort Studies	Unknown	Finland	Birth cohort	9 479	unknown	National registers and survey	Mason (2016)
Healthy Schools and Drugs	Malmberg (2010)	The Netherlands	School	3,784	Unknown	Survey	Malmberg (2012)
No name	Steinberg (1992)	USA	School	6,357	Unknown	Survey	Darling (2005)
No name	unknown	Denmark	Birth cohort	729,560	unknown	National register	Ottosen (2016)
No name	Unknown	Norway	School	2,436	Mean age 13.45 years at wave 1	Survey	Pederson (2001)
No name	Unknown	USA	Community	939	57% male	Interview	Aseltine (2000)
No name	unknown	USA	School	1,668	mean age 12.4 (SD = 0.7)	Survey	Wills (2001) Wills (2002)
No name	unknown	Sweden	Birth cohort	1,405,763	Unknown	National registers	Gauffin (2013)
Project DARE - Drug Abuse Resistance Education	Clayton (1996)	The Netherlands	School	481	50.1% male. 79.2% Caucasian, 15.8% African American, and 5% other. Participants aged 11 and 12 at baseline	Laboratory study	Flory (2003)
NESARC - National Epidemiologic Survey of Alcohol and Related Conditions	Unknown	USA	Community	43,093	Unknown	Interview	Harrington (2011) Pacek (2013)

Cohort name	First author/ year	Country	Setting	No. Participants	Participant Characteristics	Data collection method	Included studies
Victorian adolescent study	Unknown	Australia	School	2,000	Year 9 at baseline	Interview and survey	Coffey (2003) Swift (2008) Swift (2009) Degenhardt (2010) Swift (2012)
Dunedin - The Dunedin Multidisciplinary Health and Development Study.	Poulton (2015)	New Zealand	Birth cohort	1,037	Unknown	Assessment	McGee (2000)
Monitoring the future	Johnston (2001)	USA	School	50,000	Unknown	Survey	Bryant (2003) Merline (2004)
College life	Unknown	USA	School	1,253	70.8% White, 48.6% Male and 73.5% whose mother attained bachelor's degree or more	Interview and survey	Arria (2008) Garnier-Dykstra (2012) Kaynak (2013)
Lives across time - A Longitudinal Study of Adolescent and Adult Development	Windle (2004)	USA	School	1,218	unknown	Interview and survey	Windle and Wiesner (2004)
AMHC - Adolescent Mental Health Cohort Study	Unknown	Finland	School	3,278	1609 girls and 1669 boys, with a mean age of 15.5 (SD 0.39)	Survey	Kaltiala-Heino (2011)
OYSUP - Oregon Youth Substance Use Project	Andrews (2014)	USA	School	1,075	Mean age 9.0 years (SD = 1.45). 50.3% female	National register, interview, teacher assessment	Lynne-Landsman (2010)

4.3 Quality of included studies

Individual included studies were graded as good, moderate or poor quality based on how well the study was conducted, clarity of reporting and risk of bias. Most included studies were found to be of moderate quality (n= 33), 23 were rated as good quality (n=23) and eleven as poor quality. Generally, data were collected from self-reported questionnaires or surveys, which introduces the risk of recall and reporting bias. Recruitment strategies and participant characteristics were generally very poorly reported, and one cohort paid participants in vouchers to undertake surveys. A few poor quality studies failed to explain clearly the time points the exposure and outcome were measured, so it was not possible to ascertain whether the data presented were longitudinal or cross-sectional. We decided to include poor quality studies that were reported to be longitudinal studies but excluded those that were obviously cross-sectional. As reported earlier, it was decided at data extraction to only include studies that had adjusted for confounders in their analyses. However, a number of studies reported undertaking adjustments for potential confounders in their analyses, but failed to report what the confounders were.

4.4 Risk (or protective) factor evidence grading

An Observatory Evidence Service grading scheme was used to grade each risk (or protective) factor identified from the evidence (appendix 1). Using this we identified a large number of factors where the evidence appears to support the hypotheses that they may be a risk (or protective). Most were graded B (n=19) as studies generally identified a trend of association between the risk (or protective) factor and illicit drug use/misuse and were mostly of moderate quality.

4.5 Findings

A total of 41 risk factors and three protective factors were identified from the 67 included studies (Table 1). Using a socio-ecological model and a typology first described by Hawkins, Catalano and Miller in 1992, identified risk factors were grouped together into the following four domains:

- **Socio-environmental domain** four risk factors were grouped into this domain: negative life events; childhood socio-economic status; childhood IQ score; and domicile
- **Substance related domain** includes six risk factors: younger age at first cannabis use; peers' use of substances; alcohol use;

adolescent illicit drug use (other than cannabis); cigarette use; and prior exposure to drugs.

- **Intrapersonal domain** includes fourteen individual risk factors: bullying perpetration; male gender; personality traits; academic achievement; delinquency; emotional and behavioural problems; suicidal behaviour; mental disorders; pubertal timing; race and ethnicity; bullying victimisation; truancy; independent decision making; and school related problems
- **Interpersonal risk factors** was the largest domain, containing seventeen risk factors: childhood maltreatment; parental drinking; parental illicit drug use; parental mental state; parental cigarette smoking; family composition; parental marital circumstance; friendships/peers; relationship with parents; parental education; parental monitoring; late bedtime; out of home placement; parental criminality; structural stigma; intimate partner violence; and relationship satisfaction.

A characteristics and results summary table for the included studies in each risk factor is available as supplementary material.

4.6 Socio-environmental risk factors

Socio-environmental risk factors - multiple studies

4.6.1 Negative life events

Four studies (two moderate and two poor quality) examined the relationship between stressful or negative life events and illicit drug use or dependence. Three studies were conducted in USA (one moderate, two poor quality), and one in Germany (moderate quality). However, the evidence supporting this risk factor is not conclusive. Three studies (Wills et al. 2001, moderate quality; Aseltine et al. 2000, poor quality; Windle & Wiesner 2004, poor quality) reported significant associations between stressful/negative life events and cannabis use, while one study (Asselmann et al. 2016, moderate quality) did not report any association. In two studies (Aseltine et al. 2000; Windle and Wiesner 2004) that reported significant associations between stressful or negative life events and drug use, it was unclear what potential confounders were considered or whether the analysis had controlled for these.

Stressful events in these studies were drawn from multiple social stress domains including family, social, intrapersonal and interpersonal domains. It is unclear whether these various stressors are homogenous and if they individually would elicit the same effect on illicit drug use. Tools used to assess the measures varied between studies. The majority of studies

specifically assessed cannabis use, while one study focused on illicit drug abuse/dependence.

Risk factor: Negative life events There is some evidence supporting the hypothesis that experiencing negative or stressful life events in childhood is a risk factor for drug misuse, but it is not conclusive [C] (Four studies, one moderate quality, two poor quality showing an association, and one moderate quality showing no association)	
Reference	**Summary statistics**
Asselmann et al. (2016) **Cohort name:** Early developmental stages of psychopathology study (EDSP) **Study quality:** moderate	Negative life events at baseline was not significantly associated with abuse/ dependence of illicit drugs at follow-up (OR 1.01; 95% CI 0.99 to 1.04; p 0.384). Low coping efficacy was significantly associated with abuse/dependence of illicit drugs (OR 1.36; 95% CI 1.19 to 1.54; p<0.001).
Aseltine et al. (2000) **Cohort name:** No name **Study quality:** poor	Stressful life events was significantly associated with cannabis use in the past year (p<0.05).
Wills et al. (2001) **Cohort name:** No name **Study quality:** moderate	Life stress was significantly associated with substance use (adolescents and peers) p<0.01. Effects of life stress on substance use were greater for girls than for boys p<0.01.
Windle and Wiesner (2004) **Cohort name:** Lives Across Time **Study quality:** poor	Stressful life events was significantly associated with cannabis/hashish during the last 6 months (p<0.001).

4.6.2 Socioeconomic status and personal income

There is some evidence from five studies that socioeconomic status and associated measures such as disposable income and deprivation, are associated with illicit drug use. However, the evidence supporting this risk factor is inconsistent and therefore inconclusive.

Five studies (one good and four moderate quality) from five different cohorts investigated the association between socioeconomic status and substance use. The cohorts were conducted in UK (Hale and Viner, 2016; West et al., 2004, both moderate quality), USA (Humensky and Humensky, 2010; good quality and Garnier-Dykstra et al., 2012; moderate quality) and

Sweden (Gauffin et al., 2013; moderate quality). A variety of measures were used across the different studies to ascertain socioeconomic status. Three cohorts utilised validated, governmental records whilst the remaining two used recognised measures including parental occupation income, disposable income and education.

Two studies looked at deprivation (Hale and Viner, 2016; and West et al., 2004) and found no association with illicit drug use at 13, 15 or 19 years of age. West et al. (2014) also found no association with social class and illicit drug use at either 13 years or 15 years.

No association between socioeconomic status and nonmedical use of prescription stimulants was found in one study (Garnier-Dykstra et al., 2012). However, the Swedish cohort (Gauffin et al. 2013, moderate quality) identified childhood socio-economic status was associated with illicit drug abuse later in life in a stepwise manner. Although the fully adjusted model greatly attenuated the association, the effect of socio-economic status remained significant (HR 1.23, 95% CI 1.19 to 1.28) in the lowest socio-economic category.

One study from the UK (West et al., 2004) investigated participant disposable income and found it was associated with illicit drug use at both ages 13 years (OR 1.05, $p<0.001$) and 15 years (1.02, $p<0.001$). The one good quality study (Humensky and Humensky, 2010) identified higher household income was associated with higher probability of cannabis use. An additional $1,000 in annual income in adolescence was associated with an increase of 1.002 in the odds of cannabis use in early adulthood (AOR 1.002, 95% CI 1.000 to 1.003). Odds for cocaine use lost significance once controls were added to the model (AOR 1.002, 95% CI 0.999 to 1.004).

The same study (Humensky and Humensky, 2010) also looked at parental education as a measure of socio-economic status and found the odds of engaging in cocaine use in early adulthood were 1.614 times as large for an individual with a college-educated parent versus a high-school educated parent (AOR 1.614, 95% CI 1.088 to 2.395). The sensitivity analysis revealed higher household income in adolescence was associated with a higher probability of cannabis use (AOR 1.002, 95% CI 1.000 to 1.003), and cocaine use (AOR 1.002, 95% CI 1.000 to 1.004) in early adulthood when college attendance was controlled for.

Risk factor: Socioeconomic status and income

The evidence is inconsistent and it is not possible to draw a conclusion [D] (one good quality study and four moderate quality with inconsistent findings across the studies)

Reference	Summary statistics
Hale and Viner (2016) **Cohort name:** Longitudinal Study of Young People in England (LSYPE) **Study quality:** Moderate	English Index of Multiple Deprivation (IMD) was not associated with drug use.
West et al. (2004) **Cohort name:** WOS West of Scotland study **Study quality:** Moderate	Greater disposable income was associated with illicit drug use at both ages 13 years (OR 1.05 ($p<0.001$) and 15 years (1.02 ($p<0.001$). However, social class and deprivation were not associated with illicit drug use at either age.
Humensky and Humensky (2010) **Cohort name:** Add Health Study **Study quality:** Good	The odds of engaging in cocaine use in early adulthood are 1.614 times as large for an individual with a college-educated parent versus a high-school educated parent (AOR 1.614, 95% CI 1.088 to 2.395). Higher household income is associated with higher probability of cannabis use. An additional $1,000 in annual income in adolescence is associated with an increase of 1.002 in the odds of cannabis use in early adulthood (AOR 1.002, 95% CI 1.000 to 1.003). Odds for cocaine use lose significance once controls are added to the model (AOR 1.002 95% CI 0.999 to 1.004). Sensitivity analysis revealed higher household income in adolescence was associated with a higher probability of cannabis use (AOD 1.002, 95% CI 1.000 to 1.003), and cocaine use (AOD1.002, 95% CI 1.000 to 1.004) in early adulthood when college attendance is controlled for.
Gauffin et al (2013) **Cohort name:** no name **Study quality:** Moderate	In the fully adjusted model, the effect of socio-economic status on illicit drug abuse later in life was greatly attenuated to an HR of 1.23 (95% CI: 1.19 to 1.28) in the lowest socio-economic category.
Garnier-Dykstra et al. (2012) **Cohort name:** College Life **Study quality:** Moderate	No association between socio-economic status and nonmedical use of prescription stimulants was found across either of the four years.

Socio-environmental risk factors – single studies

4.6.3 Childhood IQ Scores

There is moderate quality evidence from a single UK study (White & Batty 2012) that high childhood IQ (at ages five and 10 years) is associated with an increased risk of illicit drug use in adolescence and adulthood (30 years

of age). The authors noted that this association was independent of parental and adult social class, and other risk factors for adult drug use. Data utilised in examining this association were derived from multiple waves of a large population-based birth cohort (1970 British Cohort Study).

Risk factor: Childhood IQ score Evidence from a moderate quality single study of a strong association between high childhood IQ score and drug misuse	
Reference details	**Summary statistics**
White and Batty (2012) **Cohort:** 1970 British Birth Cohort (BCS70) **Study quality:** Moderate	IQ scores at five years old were positively associated with cannabis (OR 2.25, 95% CI 1.71 to 2.97) and cocaine use (OR 2.35, 95% CI 1.41 to 3.92) in women and with amphetamines (OR 1.46, 95% CI 1.03 to 2.06), ecstasy (OR 1.65, 95% CI 1.15 to 2.36) and polydrug use (OR 1.57, 95% CI 1.09 to 2.26) in men at 30 years. IQ scores at 10 years old were positively associated with cannabis, cocaine (only at 30 years), ecstasy, amphetamine and polydrug use. Associations were stronger in women than in men and were independent from psychological distress in adolescence and life-course socioeconomic position.

4.6.4 Domicile

A single moderate quality, Swedish study (Gauffin et al. 2013) using national register data, reported an association between living in cities or towns (as opposed to rural areas) and an increased likelihood of illicit drug abuse. The exposure drug abuse referred to a participant exhibiting at least one indication of drug abuse. However, the outcome variable is primarily an indicator of the health and legal consequences of illicit drug use, rather than illicit drug abuse itself.

The primary focus of the study was on the association between childhood socioeconomic status and drug abuse. Childhood domicile was used as an indicator of socioeconomic status. Whether this was an independent risk factor, or a risk factor only where there were also other indicators of socioeconomic status, was unclear. The study authors used childhood domicile as an indicator of socioeconomic status and therefore cannot exclude the possibility of other socioeconomic status factors having an effect on illicit drug use.

Risk factor: Domicile Evidence from a moderate quality single study of a strong association between those living in cities and towns and drug misuse	
Reference details	**Summary statistics**
Gauffin, et al. (2013) **Cohort:** no name **Study quality:** Moderate	Those living in cities (HR1.66, 95% CI 0.61 to 1.71) were more likely to have at least one indication of drug abuse than those living in towns (HR1.25, 95% CI1.22 to 1.29) and rural areas (used as the reference).

4.7 Substance related risk factors

Substance related risk factors – multiple studies

4.7.1 Younger age at first cannabis use

There is good quality evidence from 19 studies of an association between younger age at first cannabis use and subsequent illicit drug misuse and dependence in adulthood.

Nineteen studies (ten good, eight moderate and one poor quality) assessed whether cannabis use at younger age was likely to be a risk factor for future illicit drug misuse. The studies used data from eight cohorts. Seven studies took place in USA (one good, five moderate, one poor quality), five in Australia (all good quality), five in New Zealand (three good quality, two moderate quality), one study took place in the UK (moderate quality) and one in Germany (good quality).

Most studies measured the exposure as use or frequency of cannabis during adolescence, sometimes defining specific age points. Those reporting age of first cannabis use measured use between the ages of 14 and 15 years (Hale and Viner, 2016; Fergusson et al., 2002), 16 to 17 years (Fergusson et al, 2008), 15 to 18 years (McGee et al., 2000) and 18 years (Merline et al., 2004). The remaining studies defined their exposure of prior cannabis use as during adolescence, previous waves or a history of cannabis use. All but one study (Bryant et al., 2003; moderate quality) identified an association between younger age at first cannabis use and future drug misuse.

Nine studies (Hale and Viner, 2016; Fergusson et al., 2003; Coffey et al., 2003; Swift et al., 2008; McGee et al., 2000; Merline et al, 2004; Kaynak et al., 2013; von Sydow et al., 2002 and Rotosky et al., 2007) examined age at first cannabis use with cannabis use as an outcome. Seven studies (Fergusson et al., 2002; Fergusson et al., 2006; Fergusson et al, 2008;

Lessem et al., 2006; Degenhardt et al., 2010; Swift et al., 2009; Swift et al., 2012) examined age at first cannabis use with other illicit drug outcomes. Finally, two studies examined the same exposure with risk of nonmedical use of prescription drugs (Harrel and Broman, 2009) or stimulants (Garnier-Dykstra et al., 2012).

One study (Fergusson et al., 2008) looked at the risk associated at two different ages, along with annual frequency of cannabis to examine any increased or decreased association with increasing age and the risk of illicit drug use. They identified much larger odds of illicit drug use amongst those with a higher annual frequency at a younger age, compared to those who did not use cannabis. Those using cannabis at least weekly at ages 16 and 17 years were over 92 times (OR 92.20, 95% CI 46.53 to 182.72) more likely than those not using cannabis to be using illicit drugs at age 25 years, and compared to those using cannabis at least monthly that age (OR 20.41, 95% CI 12.94 to 34.20), and less than monthly (OR 4.52, 95% CI 3.60 to 5.67). At ages 20 to 21 years those using cannabis at least weekly were still at considerable risk of using illicit drugs at age 25 years compared to non-cannabis users, but considerably less than those at age 16 to 17 years (OR 26.31, 95% CI 17.50 to 39.69). Those using cannabis at least monthly were still at risk (OR 8.85, 95% CI 6.74 to 11.63), as were those using cannabis less than monthly (OR 2.97, 95% CI 2.60 to 3.41), but a much reduced risk compared to their weekly using counterparts. It is important to note that the confidence intervals are very wide for the 'at least weekly' group indicating there is likely to be few participants in these groups. Similar findings were given for illicit drug abuse/dependence for both age groups. Fergusson et al. (2006) also identified a tendency for the association between cannabis use and other illicit drug involvement to decline over time.

Taking into account all the evidence, it appears those who used cannabis at a younger age are at more risk of illicit drug misuse into adulthood than those who started using cannabis later (Coffey et al., 2003; Degenhardt et al., 2010; Fergusson et al., 2002; Hale and Viner, 2016; Swift et al., 2008). However, those not reporting cannabis use until later, around age 18 years, were still at higher risk of cannabis use at age 35 years when compared to age 18 years non-cannabis users (Merline et al., 2004). It also appears those with higher cannabis use frequency are at even greater risk of future illicit drug misuse than those using cannabis occasional.

Risk factor: Younger age at first cannabis use The hypothesis that younger age at first cannabis use is a risk factor is supported by good quality evidence [A] (ten good quality, seven moderate quality and one poor quality study found an association and one moderate quality study found no association)	
Reference	**Summary statistics**
Hale and Viner (2016) **Cohort name:** Longitudinal Study of Young People in England (LSYPE) **Study quality:** moderate	Odds ratios and p-values for the association between age 19 risk behaviours and earlier risk behaviour show having tried cannabis by age 14 was strongly associated with age 19 cannabis use in the last four weeks (OR 7.81, 95% CI 6.25 to 9.75, p<0.001). Having tried cannabis by age 16 was also strongly associated with age 19 cannabis use in the last four weeks, but less so (OR 5.29, 95% CI 4.47 to 6.26, p<0.001).
Fergusson et al. (2002) **Cohort name:** The Christchurch Health Development Study (CHDS) **Study quality:** good	Estimated risk ratios for the association between cannabis use show increasing use of cannabis increases the likelihood of experimentation with other illicit drugs. However, analyses demonstrated a clear reduction in the strength of association with age. The association was particularly strong at age 14 to 15 years, with weekly users of cannabis having estimated odds of later other illicit drug use that were over 230 times those of non-users (RR 234.4, no 95% CI reported). In contrast, those using cannabis less than monthly had lower estimated odds (RR 6.2, 95% CI 12.3–117.0). This association had reduced substantially by age 20 to 21 years. Nevertheless, even at this age, there was still evidence of a strong association between cannabis and later other illicit drug use. After adjustment for confounding, weekly cannabis users had 12 times the odds of other illicit drug use compared to non-users (RR 12.0, no 95% CI reported) at age 20 to 21 years . In contrast, those reporting cannabis use less than monthly at age 20 to 21 years had lower estimated odds (RR 2.3, 95% CI 2.7 to 10.1).
Fergusson et al. (2003) **Cohort name:** The Christchurch Health Development Study (CHDS) **Study quality:** good	There were clear tendencies for rates of cannabis dependence to increase with increasing reports of positive responses to early cannabis use; those reporting five positive responses had odds of cannabis dependence that were 28.5 (95% C.I 6.3 to 133.8) times higher than those not reporting positive reactions to cannabis. The association held (odds ratio: 23.4 (95% CI: 4.0 to 135.9) after controlling for potentially confounding factors including the extent of use of cannabis prior to the age of 16 years.
Fergusson et al. (2006) **Cohort name:** The Christchurch Health Development Study (CHDS) **Study quality:** moderate	For both outcomes, the associations between frequency of cannabis use and other illicit drug involvement remained significant after adjustment for fixed and time dynamic covariate factors using the random effects and fixed-effects model. As in previous analyses, the estimates for the fixed-effects model were lower than those for the random-effects model, suggesting that the fixed-effects model was controlling for non-observed sources of confounding. For both outcomes, the fitted

	model shows significant linear age–cannabis use interactions. These interactions reflect a tendency for the association between cannabis use and other illicit drug involvement to decline over time.
Fergusson et al. (2008) **Cohort name:** The Christchurch Health Development Study (CHDS) **Study quality:** good	Cannabis use between the ages of 16 and 25 years increased the risk of illicit drug use (B 1.09, SE 0.07, p <0.0001) and abuse/dependence (B 1.11, SE 0.15, p <0.0001). Annual frequency of cannabis use made the strongest contribution to both illicit drug use and illicit drug abuse/dependence. Those using cannabis at least weekly at some point during the period 16 to 25 years had odds of illicit drug use that ranged from 92.20 (95% CI 46.53 to 182.72; age 16 to 17 years) to 7.53 (95% CI 4.48 to 12.43; age 24 to 25 years) times greater than those who did not use cannabis, and had odds of illicit drug abuse/dependence that ranged from 117.92 (95% CI 26.31 to 523.74; age 16 to 17 years) to 6.49 (95% CI 2.19 to 19.20; age 24 to 25 years) times greater than those who did not use cannabis.
Lessem et al. (2006) **Cohort name:** ADD Health Study **Study quality:** good	The logistic regression results demonstrate that adolescent cannabis users have an odds ratio of 1.83 (95% CI 1.57 to 2.13) of progressing toward young adult illicit drug use, even when controlling for other factors, compared to non-adolescent cannabis users.
Harrell and Broman (2009) **Cohort name:** ADD Health Study **Study quality:** poor	In the full sample, having a history of cannabis use predicted prescription drug misuse in young adulthood (OR 1.24, 95% CI 1.10 to 1.40, p<0.001).
Coffey et al. (2003) **Cohort name:** The Victorian Adolescent Health Cohort Study **Study quality:** good	Independent associations between young-adult cannabis dependence and adolescent exposures including regular cannabis use showed those regularly partaking in cannabis use in adolescence had odds of young adult cannabis of over four and a half times more than non-regular users (weekly: OR=4.9; daily: OR=4.6, p=0.02).
Degenhardt et al. (2010) **Cohort name:** The Victorian Adolescent Health Cohort Study **Study quality:** good	All drug use outcomes at age 24 years were more common among adolescent cannabis users than non-users, even after adjustment. Occasional adolescent cannabis users were at a risk that was intermediate between the non-users and the more frequent users. Occasional adolescent cannabis users who continued occasional use into early adulthood had higher risks of later illicit drug use. Those using cannabis at least weekly either during adolescence or at age 20 were at highest risk of drug use problems in young adulthood. This was particularly so for cannabis dependence (OR 10, 95% CI 4.7 to 22) and other substance use (OR 7.8, 95% CI 4.9 to 12).
Swift et al. (2009)	At 20 years, the occasional to abstinence (OR 1.4, 95% CI 0.68 to 2.9) and occasional persisting (OR 3.7, 95% CI 1.5 to 9.5) users both had elevated odds of weekly+ use compared to non-users, with occasional persisting

Cohort name: The Victorian Adolescent Health Cohort Study **Study quality:** good	users at highest risk. The weekly to occasional (OR 12.0, 95% CI 5.6 to 26) and weekly persisting users (OR 24.0, 95% CI 11 to 53) had markedly elevated odds of this outcome compared to non-users. Weekly to abstinence group (OR 3.9, 95% CI 0.93 to 16) were similar to the occasional persisting group.
Swift et al. (2008) **Cohort name:** The Victorian Adolescent Health Cohort Study **Study quality:** good	The risk of both frequent and dependent cannabis use at 24 years increased with increasing levels of adolescent maximum use frequency. Those who commenced use in waves 1 to 3 and those who used for more than two waves were at between two- and threefold elevated odds of frequent and dependent use outcomes at 24 years relative to later starters and those who used for one or two waves, respectively. Non-use of cannabis in adolescence was clearly protective for both wave 8 outcomes, compared even with the lowest levels of cannabis use measures.
Swift et al. (2012) **Cohort name:** The Victorian Adolescent Health Cohort Study **Study quality:** good	Cannabis use as a predictor of incident uptake and cessation from licit or illicit drug use at 24 and 28 years (waves 8 and 9) in cohort participants, adjusted for possible background confounders, showed daily users in the previous wave were most likely to take up amphetamine (HR2.9, 95% CI 1.7 to 4.8) and ecstasy (HR 2.8, 95% CI 2.0 to 4.0) use, compared to never, past, occasional and weekly users. However, weekly users were most likely to take up cocaine use (HR 2.3, 95% CI 1.5 to 3.5) than any other frequency.
McGee et al. (2000) **Cohort name:** The Dunedin Multidisciplinary Health and Development Study **Study quality:** moderate	Results from bivariate logistic regression for cannabis use and mental health from ages 15 to 18 years demonstrate prior cannabis use was associated with over three times the risk of cannabis use at ages 18 (AOR 3.07) and almost seven times the risk of cannabis use at age 21 years (AOR 6.68).
Merline et al. (2004) **Cohort name:** Monitoring the Future study **Study quality:** moderate	When compared with those who had not tried cannabis by the twelfth grade, individuals who had tried cannabis by the 12th grade had 8 times the odds of using cannabis at age 35 years (OR 8.30, $p<0.01$). History of substance use at 18 years of age, the time of the initial survey, was a strong predictor of cannabis use at age 35 years. These predictors were significant at both the bivariate and multivariate levels (multivariate ORs shown above).
Garnier-Dykstra et al. (2012) **Cohort name:** College Life **Study quality:** moderate	Cannabis use disorder was significantly associated with non-medical use of prescription stimulants and showed a stepwise increase in the first three years (year 1 AOR 2.24, 95% CI 1.48–3.41, year 2 AOR 3.05, 95% CI 1.94–4.79, and year 3 AOR 4.81, 95% CI 2.95–7.97), before dropping off slightly in year four (AOR 3.84, 95% CI 2.32–6.35).
Kaynak et al. (2013) **Cohort name:** College Life **Study quality:** moderate	Results of multivariate logistic regression analysis predicting the probability of DSM-IV cannabis dependence during the first year of college was statistically associated with high school cannabis use (OR 13.13, 95% CI 6.44 to 26.77, p value <0.001).

von, Sydow K et al. (2002) **Cohort name:** Early developmental stages of psychopathology study (EDSP) **Study quality:** good	Multiple logistic regression (controlling for age and gender) revealed that older age was associated with less incident cannabis use during the 4-year follow-up interval (OR 0.8, 95% CI 0.8 to 0.8, p<0.005). Multiple negative binomial regression confirmed a decreased risk for high cannabis consumption can be found among older participants (IRR 0.7, 95% CI 0.7 to 0.8, p <0.005). Older age at first use was associated with less cannabis dependence (OR 0.4, 95% CI 0.3 to 0.6, p<0.05) and cannabis abuse (decreasing risk with advancing age) (OR 0.8, 95% CI 0.7 to 0.8, p value <0.005).
Rostosky et al. (2007) **Cohort name:** ADD Health Study **Study quality:** moderate	Age was associated with marijuana use in the last 30 days at wave 3 in those reporting no same-sex attraction at waves one and three increasing age was just associated with a reduced risk of marijuana use (OR 0.98, 95% CO 0.96 to 0.99, p<0.01)
Bryant et al. (2003) **Cohort name:** Monitoring the future **Study quality:** moderate	There appears to be no association between age and marijuana use or rates of growth from ages 14 to 20 years.

4.7.2 Substance using peers

Four studies (three good and one poor quality) looked at whether having peers that use substances are likely to be a risk factor for later illicit drug misuse. Two studies used data from the same cohort (CDHS) in New Zealand. The remaining two studies were from Spain and USA. The studies all assessed drug use/dependence. For two studies (one good quality, one poor quality) this was use of cannabis only. The studies using data from the CDHS cohort (both good quality) looked at use and dependence of cannabis and other drug use and dependence of drugs excluding cannabis. All four studies relied on self-reported data.

Each of the four studies found that substance using peers were a significant risk factor for both illicit drug use and dependency. Three of the studies used DSM-IV criteria to define dependence, whereas one study (Van den Bree and Pickworth, 2005; poor quality) assessed the '5 stages of cannabis involvement', which were (1) initiation of experimental use, (2) initiation of regular use, (3) progression to regular use, (4) failure to discontinue experimental use, and (5) failure to discontinue regular use.

There were differences between the two studies using data from the same cohort. Boden et al. (2006) looked at peer substance use at age 15 years, and then assessed cannabis and other drug use / dependence at age 25 years. Fergusson et al. (2008) assessed the percentage extent of affiliation with substance using friends at ages 16, 18, 21 and 25 years (26-50%, 51-

75% and 76-100%) on the odds of later illicit drug use / dependence (excluding cannabis use) at ages 16 to 17 years, 20 to 21 and ages 24 to 25 years. Unusually, adjusted odds ratios were the same for each age group and each percentage extent of affiliation.

Risk factor: Substance using peers The hypothesis that substance using peers is a risk factor is supported by good quality evidence [A] (three good quality, one poor quality)	
Reference	**Summary statistics**
Boden et al. (2006) **Cohort name:** The Christchurch Health and Development Study (CHDS) **Study quality:** good	Substance-using peers at age 15 years was identified as a key risk factor for both illicit drug use (B 0.06 SE 0.01 p<0.0001) and dependence (B 0.04 SE 0.01 p<0.0001) using proportional hazard models to identify any drug use and dependence by age 15 years.
Fergusson et al. (2008) **Cohort name:** The Christchurch Health and Development Study (CHDS) **Study quality:** good	Using repeated logistic regression models this study identified affiliation with substance-using peers as a pathway to illicit drug use and abuse/dependence. Interestingly, the odds of illicit drug use and abuse/dependence remained the same in each of the three groups, regardless of age. Those with the most affiliation with substance-suing peers experienced the highest odds of later illicit drug use (26% to 50% affiliation OR 1.38, 95% CI 1.23 to 1.55; 51% to 75% affiliation OR 1.91, 95% CI 1.52 to 2.41; and 76% to 100% affiliation (OR 2.64, 95% CI 1.88 to 3.74) and abuse/dependence (26% to 50% affiliation OR 1.80, 95% CI 1.38 to 2.36, 51% to 75% affiliation OR 3.25, 95% CI 1.90 to 5.58, and 76% to 100% affiliation OR 5.87, 95% CI 2.61 to 13.20). Adjusted odds ratios were the same for each age group and each percentage extent of affiliation. The results of these analyses suggest that the time-dynamic substance use and peer factors mediated the linkages between the predictors and both illicit drug use and illicit drug abuse/dependence, indicating that the pathway to involvement with illicit drugs leads through the use of cannabis and other substances, and through social processes including affiliation with substance-using peers.
von, Sydow et al. (2002) **Cohort name:** Early developmental stages of psychopathology study (EDSP) **Study quality:** good	Peer drug intake was associated with an increased odds of first time cannabis use in former non-users (OR 1.8, 95% CI 1.3 to 2.4, p <0.05) and cannabis use frequency in former non-users (IRR 1.6, 95% CI 1.1 to 2.2, p <0.05).
Van den Bree and Pickworth (2005)	Peer involvement with substances predicted initiation of experimental cannabis use (OR 1.79 for boys and OR

Cohort name: ADD Health Study **Study quality:** poor	2.94 for girls), initiation of regular use (OR 2.72 for boys and girls combined), failure to discontinue experimental use (OR 0.65 for girls), and failure to discontinue regular cannabis use (OR 0.62 for boys and girls combined) between waves one and two.

4.7.3 Alcohol use

Thirteen studies utilised data from nine different cohorts to investigate the association between alcohol and drug use. These were conducted in New Zealand (three good and one moderate quality), USA (two moderate and two poor quality), UK (one moderate quality), Iceland (one moderate quality) and Australia (two good and one moderate quality).

Most exposures reporting age, measured alcohol consumption at age 14 years. McGee et al. (2000) measured consumption at age 15 years and two measured consumption at age 16 years (Hale and Viner, 2016; Fergusson, 2008). Substance use mostly involved cannabis use, but illicit drug use, amphetamine and prescription drug use were included. A few studies looked at dependence.

Studies generally found an association between adolescent alcohol use and later illicit drug misuse. However, there were some exceptions. Three good quality studies from New Zealand (Boden et al., 2006; Fergusson et al., 2008; Newton-Howes and Boden, 2016), using data from the same cohort, identified no association with cannabis or illicit drug dependence, but two of them found an association with illicit drug use. One good quality study from Australia (Hayatbakhsh et al. 2009a) identified an associated risk between age 14 years alcohol use and age 21 years amphetamine use disorder. A poor quality study from USA (Harrell & Broman 2009) identified an association with prescription drug misuse.

The single study reporting alcohol consumption at two age points (Hale and Viner, 2016) identified those drinking at age 16 years (OR 3.06, 95% CI 2.52 to 3.71, $p<0.001$) were more at risk of cannabis use at age 19 years than those drinking at age 14 years (OR 1.70, 95% CI 1.17 to 2.49, p 0.006). Those drinking regularly at both 14 and 16 years had almost four times the risk of any drug use in the last four weeks at age 19 years compared to those who did not drink (OR 3.96, 95% CI 2.92 to 5.35, $p <0.001$).

A single, good quality, study from New Zealand (Fergusson et al. 2008) identified a stepwise increase in risk of illicit drug use associated with increasing frequency of alcohol with those drinking almost every day at almost six times the risk than those who never drank (OR 5.70, 95% CI 3.03 to 10.70 for ages 16-17, 20-21 and 24-25). Another good quality study (Newton-Howes and Boden 2016) also from New Zealand found no

link between younger age at first drink and cannabis or illicit drug dependence.

Risk factor: Alcohol use The hypothesis that alcohol use is a risk factor is supported by moderate quality evidence [B] (Eleven studies, four good, four moderate and three poor quality, found an association and one good and one moderate quality study found no association)	
Reference	**Summary statistics**
Hale and Viner (2016) **Cohort name:** Longitudinal Study of Young People in England (LSYPE) **Study quality:** moderate	Regular alcohol use (at least once a week) at age 14 years was statistically significantly associated with any drugs in the last four weeks at age 19 years (OR 1.70, 95% CI 1.17 to 2.49, p 0.006). At age 16 years the odds of those drinking alcohol regularly being associated with any drug use in the last four weeks at age 19 years had increased to over three times compared to those who did not drink (OR 3.06, 95% CI 2.52 to 3.71, p<0.001). Those drinking regularly at both 14 and 16 years had almost four times the increased odds of any drug use in the last four weeks at age 19 compared to those who did not drink (OR 3.96, 95% CI 2.92 to 5.35, p <0.001).
Boden et al. (2006) **Cohort name:** The Christchurch Health and Development Study (CHDS) **Study quality:** good	Any illicit drug use was significantly associated with frequency of alcohol consumption at age 14 years (B 0.18, SE 0.04, p <0.0001), but not any illicit drug dependence.
Fergusson et al. (2008) **Cohort name:** The Christchurch Health and Development Study (CHDS) **Study quality:** good	Parameter estimates from multivariate regression models showed illicit drug use was significantly associated with frequency of alcohol between ages 16 and 25 years (B 0.58 SE 0.11 p< 0.01), but not illicit drug abuse/dependence. There was also a stepwise increase in risk of illicit drug use associated with increasing frequency of alcohol with those drinking almost every day at almost six times the risk than those who never drank (OR 5.70, 95% CI 3.03 to 10.70 for ages 16-17, 20-21 and 24-25).
Newton-Howes and Boden (2016) **Cohort name:** The Christchurch Health and Development Study (CHDS) **Study quality:** good	Lower age at first drink was not associated with higher rates of cannabis dependence after adjusting for statistically significant covariates (B –0.05, 95% CI –0.31 to 0.22 p >0.60). Likewise, lower age at first drink was not associated with other illicit drug dependence between 15 years and 35 years after adjusting for all statistically significant covariates (B–0.29, 95% CI –0.73 to 0.15, p >0.10).
Yorkston et al. (2007) **Cohort name:** The Australian longitudinal study on women's health	Women who continued a low-risk drinking habit and those who did not drink alcohol were less likely to initiate illicit drug use [prevalence ratio (PR) 0.36, 95% CI 0.21 to 0.62]. The likelihood of beginning to use illicit drugs was enhanced for all other patterns involving at-

Study quality: moderate	risk drinking behaviour. Illicit drug initiation was reduced for women whose first sexual experience occurred between 2000 and 2003 (PR 0.58, 95% CI 0.26 to 0.92), and for women who were not yet sexually active (PR 0.36, 95% CI 0.21 to 0.56).
Harrell and Broman (2009) **Cohort name:** ADD Health Study **Study quality:** poor	The findings of multivariate analysis in the full sample identified having a history of alcohol use predicted prescription drug misuse in young adulthood (OR 1.14, 95% CI 1.06 to 1.23, p<0.001).
Khan et al. (2014) **Cohort name:** ADD Health Study **Study quality:** moderate	Among white males, controlling for gender, poverty, delinquency, maternal education, and adolescent substance use suggested any adolescent alcohol use was associated with elevated odds of adulthood cannabis use, and white males who had been occasional or frequent heavy drinkers experienced elevated odds of adulthood cocaine use. Frequent heavy users with high risk of problems had over three times the odds of adulthood cannabis use (AOR 3.60, 95% CI 2.11 to 6.15) and cocaine use (AOR 3.12, 95% CI 1.62 to 6.01). Among white females, alcohol experimentation was not associated with adulthood cocaine use. Occasional or heavy use female users with alcohol-related problems in adolescence had elevated odds of adulthood cocaine use, with the strongest associations observed among women who had been frequent heavy users with a high risk of alcohol-related problems (AOR: 3.12, 95% CI 1.62 to 6.01).
Hayatbakhsh et al. (2009) a **Cohort name:** The Mater-University of Queensland Study of Pregnancy (MUSP) **Study quality:** good	Adolescents who drank alcohol when they were 14 years were substantially more likely to have used amphetamines or to have met the criteria for AUD at 21 years. Multivariate analysis identified alcohol consumption at 14 years predicted amphetamine use in those who drank one or less drink per day (ever use ≤1 drink per day OR 1.8, 95% CI 1.4 to 2.3 p <0.001, PAR 21.2; but not those who drank >1 drink per day (OR 2.3, 95% CI 0.8 to 6.3, PAR 1.6). However amphetamine use disorder at age 21 years was associated with both those who drank ≤1 drink per day or more (≤1 drink per day OR 1.7, 95% CI 1.0 to 2.9, p <0.05, PAR 19.0; > 1 drink per day (OR 4.1, 95% CI 1.0 to 15.8, p <0.05, PAR 3.8).
Hayatbakhsh, et al. (2009) b **Cohort name:** Mater-University of Queensland Study of Pregnancy (MUSP) **Study quality:** good	Multivariate models found an almost doubled risk associated with age 14 drinking and cannabis use without disorders (OR 1.9, 1.4 to 2.7, p 0.001) and cannabis use with disorder (OR 1.9, 1.3 to 2.8, p 0.01) at age 21 years.
Adalbjarnardottir and Rafnsson (2001)	Drinking at age 14 years was significantly associated with illicit drug use at age 17 years (B 1.31, p 0.001, SE 0.23, OR 3.70).

Cohort name: Reykjavik Adolescent Risk-Taking Study (RAR) **Study quality:** moderate	
McGee et al. (2000) **Cohort name:** The Dunedin Multidisciplinary Health and Development Study **Study quality:** moderate	Logistic regression analyses showed no association between alcohol use at age 15 years and cannabis use at age 18 years. However, a significantly increased odds of cannabis use at age 21 years was found in those who used alcohol at ages 15 (OR 1.62, 95% CI 1.23 to 2.13) and 18 years (OR 1.71, 95% CI 1.26 to 2.31).
Garnier-Dykstra et al (2012) **Cohort name:** College Life **Study quality:** moderate	Those identified with alcohol use disorders were significantly more at risk of non-medical use of prescription stimulants than those who did not have alcohol use disorders in years two (AOR 1.89, 95% CI 1.24 to 2.87, p<.05) and three (AOR 1.76, 95% CI 1.15 to 2.69, p<.05), but not year four of the study (AOR 1.24, 95% CI 0.77 to 2.02).
Windle and Wiesner (2004) **Cohort name:** Lives Across Time **Study quality:** poor	Analyses appear to indicate there is a stepwise association between alcohol use and cannabis use. Abstainers had the lowest frequency of cannabis use, and the chronic alcohol users reported the highest frequency of cannabis use.

4.7.4 Adolescent illicit drug use (other than cannabis)

Eight studies (three good, four moderate and one poor quality) using data from six different cohorts identified an association between adolescent illicit drug use and future/adult drug misuse. Six studies were from USA and one study (good quality) from Germany, UK (moderate quality) and Finland (moderate quality).

All, but one study (Kaltiala-Heino et al., 2011) found an association between prior use of illicit drugs and drug misuse. All three good quality studies (Von sydow et al., 2002; Lessem et al., 2006; Snyder and Rubenstein, 2014) found an increased risk (between OR 1.3 and OR 7.1) associated with adolescent illicit drug use (excluding cannabis) and future illicit drug use. Although wording of the exposure measured varied, they examined broadly similar substances (amphetamines, cocaine, opioids, and hallucinogens). Age at which exposure was measured did, however, vary across the good quality studies, ranging between 11 and 18 years. Interestingly, the one study (Von Sydow et al., 2002) looking at illicit drug use at a specific age (14 years), compared to a broad range of ages identified the highest risk (OR 7.1, CI 1.8 to 28.2, p <0.05). However, it is important to note the wide confidence intervals in this study. In addition, Snyder and Rubenstein (2014) identified a decreasing risk of 19% with

every one standard deviation increase in age (OR 0.81, 95% CI 0.70 to 0.93, p<0.001). However, this was only in the female heavy use group. Nevertheless, we could broadly interpret this as suggesting there may be an association between those using illicit drugs at a younger age and an increased risk of future drug misuse. This is supported by West et al. (2004), who also found a significant association between those reporting drug use at age 13 years (OR 1.05, p<0.05), but not age 15 years participants.

Risk factor: Adolescent illicit drug use (other than cannabis) The hypothesis that adolescent illicit drug use (other than cannabis) is a risk factor for future/adult use is supported by moderate quality evidence [B] (three good, three moderate and one poor quality found an association and one moderate quality study found no association)	
Reference	**Summary statistics**
von, Sydow et al. (2002) **Cohort name:** Early developmental stages of psychopathology study (EDSP) **Study quality:** good	Prior experiences with illegal drugs play a significant role in the initiation of cannabis consumption and the transition to cannabis use disorders in adolescents and young adults. Cannabis dependence was predicted primarily by baseline use of other illicit drugs (OR 7.1, 95% CI 1.8 to 28.2, p<0.05).
Lessem et al. (2006) **Cohort name:** ADD Health Study **Study quality:** good	Logistic regression results demonstrate adolescent hard drug use was associated with progressing toward young adult illicit drug use (OR 1.31, 95% CI 1.11 to 1.54), even when controlling for other factors. Only the 30-day frequency of use measures for other illicit drugs at the early time point were not significant.
Harrell and Broman (2009) **Cohort name:** ADD Health Study **Study quality:** poor	A history of adolescent inhalant use at wave one increased the likelihood of nonmedical prescription drug use in wave three (OR 1.33, 95% CI 1.04 to 1.71, p<0.05).
Snyder and Rubenstein (2014) **Cohort name:** ADD Health Study **Study quality:** good	Age was only associated with illicit drug use in the heavy versus normative female group with an OR 0.81 (95% CI 0.70 to 0.93, p<0.001). We can interpret this to mean there is a 19% decrease in use with every one standard deviation increase in age.
Merline et al. (2004) **Cohort name:** Monitoring the future **Study quality:** moderate	Those who had tried any illicit drug other than cannabis by their senior year had 5 times the odds of using cocaine (OR 5.24, p<0.01) and 3 times the odds of misusing prescription drugs (OR 3.06, p<0.01) at age 35 years, compared with those who had not. History of substance use at 18 years of age, the time of the initial survey, was a strong predictor of cocaine use, and misuse of prescription drugs at age 35 years. These

	predictors were significant at both the bivariate and multivariate levels (multivariate ORs shown above).
Arria et al. (2008) **Cohort name:** College life **Study quality:** moderate	Results of logistic regression showed prior nonmedical use of both prescription stimulants (AOR 4.6, 95% CI 2.6 to 8.4, p<0.0001) and prescription analgesics (AOR 2.6, 95% CI 1.4 to 5.0, p0.003) predicted nonmedical use of prescription drugs during the past year.
West et al. (2004) **Cohort name:** West of Scotland study (WOS) **Study quality:** moderate	Younger age was significantly associated with illicit drugs at S2 (OR 1.05, p<0.05), but not S4, when participants were older.
Kaltiala-Heino et al. (2011) **Cohort name:** Adolescent Mental Health Cohort Study (AMHC) **Study quality:** moderate	Age itself showed no statistically significant association to any illegal drug use among boys (OR 1.6, 95% CI 0.9 to 2.6) or among girls (OR 0.6, 95% CI 0.3 to 1.1).

4.7.5 Cigarette smoking

Nine studies (five good and four moderate) investigated associations between cigarette smoking and frequency and illicit drug misuse. These studies came from seven different cohorts, three of which were conducted in Australia (Yorkston et al., 2007; Hayatbakhsh et al., 2009a; Hayatbakhsh et al., 2009b), three in New Zealand (Boden et al., 2006; Fergusson et al., 2008; McGee et al., 2000), and one each in Iceland (Adalbjarnardottir and Rafnsson, 2001Coffey et al., 2003) and UK (Hale and Viner, 2016).

Measures of cigarette smoking generally referred to ages between 14 and 25 years. Some studies investigated smoking at two different ages to compare the risks associated with these. Those that did generally found a slightly smaller, but still greater risk than non-smokers in the older age group when compared to the younger age.

Eight of the nine studies identified an increased risk of substance use in those using tobacco in adolescence. Most were looking at cannabis use, but some investigated multiple different illicit substances, and one specifically looked at the risk associated with Amphetamine use. Of those reporting risk as an odds ratio (six studies) the risk of substance use among smokers varied between 1.5 times greater and up to 4.5 times greater than those who did not report cigarette smoking. Obviously, these were looking at smoking among different age groups, different substances, and the outcome was measured at different ages, so a direct comparison is not advisable. The two studies that did not identify an association were both

good quality studies, one from New Zealand (Fergusson et al. 2008) and one from Australia (Coffey et al. 2003).

Risk factor: Cigarette smoking The hypothesis that cigarette smoking is a risk factor is supported by moderate quality evidence. Seven studies found an association and two studies found no association. [B] (Three good and four moderate quality studies found an association and two good quality studies found no association)	
Reference	**Summary statistics**
Hale and Viner (2016) **Cohort name:** Longitudinal Study of Young People in England (LSYPE) **Study quality:** moderate	Regular smoking at age 16 years was associated with over four times the risk of age 19 years drug use in the last four weeks (OR 4.44, 95% CI 3.65 to 5.41). However, age 14 years smoking was not associated with age 19 years drug use.
Boden et al. (2006) **Cohort name:** The Christchurch Health and Development Study (CHDS) **Study quality:** good	Proportional hazards regressions models identified an association between frequency of cigarette smoking at age 14 years and illicit drug use by age 15 years ($p<0.0001$).
Fergusson et al. (2008) **Cohort name:** The Christchurch Health and Development Study (CHDS) **Study quality:** good	Multivariate regression models found no association between frequency of cigarette smoking between ages 16 and 25 years and illicit drug use and/or abuse/dependence.
Yorkston et al. (2007) **Cohort name:** The Australian longitudinal study on women's health **Study quality:** moderate	Women with all patterns of cigarette smoking except adopting and then giving up smoking between 2000 and 2003 were significantly more likely to initiate illicit drug use than continuing non-smokers. Initiation of illicit drug use was higher in those who newly adopted (adjusted prevalence ratio (aPR) 2.61, 95% CI 1.62 to 4.21), recommenced (aPR 2.79, 95% CI 1.99 to 3.92) or continued to smoke (aPR 2.76, 95% CI 2.29 to 3.33), compared to those who continued to be non-smokers (no figures available).
Hayatbakhsh et al. (2009) a **Cohort name:** The Mater-University of Queensland Study of Pregnancy (MUSP) **Study quality:** good	Multivariate regression analyses identified adolescent smoking was associated with both amphetamine use and use disorder. Those smoking less than ten cigarettes per day at age 14 years had a higher risk of amphetamine use disorder (OR 2.6, 95% CI 1.2 to 5.7, $p<0.05$) than amphetamine use (OR 1.7, 95% CI 1.1 to 2.7, $p<0.05$). Those smoking ten or more cigarettes a day at age 14 years had a higher risk of amphetamine use (OR 2.2, 95% CI 1.3 to 3.8, $p<0.01$), but a slightly

	smaller, risk of amphetamine use disorder (OR 2.4, 95% CI 1.0 to 5.9, p<0.05).
Hayatbakhsh et al. (2009) b **Cohort name:** The Mater-University of Queensland Study of Pregnancy (MUSP) **Study quality:** good	Analyses adjusted for all other covariates identified smoking at age 14 years was associated with two and a half times higher risk of cannabis use at age 21 years (OR 2.5, 95% CI 1.7 to 3.6, p<0.001) and cannabis use disorder (OR 2.5, 95% CI 1.6 to 3.8, p<0.001) compared to those who had never smoked.
Adalbjarnardottir and Rafnsson (2001) **Cohort name:** Reykjavik Adolescent Risk-Taking Study (RAR) **Study quality:** moderate	Those who had tried smoking at age 14 were three and a half times more likely to report illicit drug use at age 17 years (OR 3.5, B 1.27, p<0.001) than those who hadn't tried smoking.
Coffey et al (2003) **Cohort name:** The Victorian Adolescent Health Cohort Study **Study quality:** good	Analyses identified cigarette smoking frequency was not associated with cannabis dependence at age 20 years, however smoking persistence was found to be associated with cannabis dependence at age 20 years (OR 1.9, 95% CI 1.1 to 3.2, p<0.02).
McGee et al. (2000) **Cohort name:** The Dunedin Multidisciplinary Health and Development Study **Study quality:** moderate	Analyses showed participants reporting smoking at age 15 years were at greater risk of cannabis use at age 18 years (OR 1.72, 95% CI 1.15 to 2.58). Those reporting smoking at age 18 years were at slightly less risk, but still had greater risk of cannabis use at age 21 years than those who did not report smoking (OR 1.55, 95% CI 1.17 to 2.05).

Substance related risk factors – single studies

4.7.6 Prior exposure to drugs

A single, UK cohort, of moderate quality found a significant association between prior exposure to drugs, defined as offers of drugs (at or before the age of 11 years) and illicit drug use at ages 13 and 15 years. The odds of illicit drug use at age 13 years associated with prior exposure was over four and a half times (OR 4.79) that of those who had no prior exposure. Although this dropped by age 15 years, those with prior exposure still had higher odds (OR 2.76) of illicit drug use than those without.

Risk factor: Prior exposure to drugs Evidence from a single moderate quality study of a significant association between prior exposure to drugs (prior drug offers/experience) and drug misuse	
Reference	**Summary statistics**
West et al. (2004) **Cohort name:** West of Scotland study **Study quality:** moderate	Analyses showed prior exposure to drugs was highly associated with illicit drug use at age 13 years (OR 4.79, p<0.001) and age 15 years (OR 2.76, p<0.001).

4.8 Intrapersonal risk factors

Intrapersonal risk factors – multiple studies

4.8.1 Bullying perpetration

There is moderate evidence from two studies that bullying perpetration in childhood is associated with an increased risk of illicit drug use at 18 years of age.

A large, good quality study from the UK (Dantchev and Wolke 2019), identified someone who bullied their siblings is at significantly increased risk of illicit drug use. However, when imputed data was used to account for various confounders, although this was still significant, the risk was much smaller (OR 1.08, 95% CI 1.03 to 1.14). A large study from Finland (Niemela et al., 2011) identified male frequent bullies at age 8 years were two and a half times at risk of illicit drug use at age 18 years than non-bullies (OR 2.5, 95% CI 1.2 to 5.4, p 0.023). The findings of this study may not be generalisable to females.

Risk factor: Bullying perpetration The hypothesis that bullying perpetration is a risk factor for illicit drug use at 18 years is supported by moderate to good quality evidence [B] (one good and one moderate quality)	
Reference	**Summary statistics**
Dantchev and Wolke (2019) **Cohort name:** Avon Longitudinal Study of Parents and Children (ALSPAC)	Examining children according to the roles they assumed in sibling bullying revealed that bullies were at increased risk of illicit drug use (OR 1.45; 95% CI 1.12 to 1.87). Children who reported perpetrating sibling bullying several times a week were furthermore at higher odds of reporting illicit drug use (OR 1.48; 95%CI, 1.17 to 1.88). A linear trend was identified between sibling

Study quality: good	bullying perpetration and illicit drug use indicating a dose-response relationship. Using the imputed dataset and accounting for various confounders slightly attenuated the associations (illicit drug use OR 1.08; 95% CI 1.03 to 1.14).
Niemela et al. (2011) **Cohort name:** Boy to a Man Study **Study quality:** moderate	Authors found in multivariate analyses that bullying others frequently at age 8 years (OR 2.5, 95% CI 1.2 to 5.4, p 0.023) predicted illicit drug use at age 18 years.

4.8.2 Male gender

Twenty studies (seven good, 12 moderate and one poor quality) examined the risk associated with gender and substance use. They used data from fourteen different cohorts which took place in UK, USA, Finland, Iceland, Australia, New Zealand and Sweden. In the majority of studies, the terms 'gender' and 'sex' were used interchangeably to refer to biological sex.

Overall, males appear to be at more risk of substance use than females. Thirteen studies identified the male gender to be associated with increased risk of substance use. Two studies identified females as being at less risk (one moderate quality and one good quality) and one study identified females to be at greater risk (moderate quality). Four studies found no association (one poor quality and three moderate quality).

Of the studies reporting odds ratios and finding a significant association between males and substance use, the risk varied between OR 1.5 (95% CI 1.1 to 1.9, p<0.01) and OR 3.4 (B 1.22 p<0.001) when compared to females. However, the risk appeared to fluctuate with age in males. The highest risk appeared to be associated with age 17 years (OR 3.4, B 1.22 p<0.001) (Adalbjarnardottir and Rafnsson, 2001), which dropped to OR 1.71 (95% CI 1.27 to 2.29) (McGee et al. 200) at age 18 years. The most commonly studied age was age 21 years, where cannabis use was associated with increased odds between OR 1.22 (95% CI 1.10 to 1.35) and OR 1.61 (95% CI 1.17 to 2.22). Cannabis dependence in males at age 21 years was almost three times the risk of dependence in girls (OR 2.9, 95% CI 2.3 to 3.6, p<0.001) (Hayatbakhsh et al., 2009b). Male participants were almost 50% more likely to report amphetamine use (OR 1.5, 95% CI 1.1 to 1.9, p<0.01) or disorder by age 21 years (OR 1.7, 95% CI 1.0 to 2.7, p<0.05) (Hayatbakhsh et al., 2009a).

Being female was generally associated with less drug use. Females, aged 19 years, were nearly half as likely to have used drugs in the last four weeks than males (OR 0.47, 95% CI 0.40 to 0.54, p<0.001) (Hale and Viner, 2016). The risk further reduced for cannabis dependence (OR 0.38, 95% CI 0.22 to 0.66, p<0.01) at age 20 years (Coffey et al., 2003),

cannabis use (OR 0.56, p<0.01) (Merline et al., 2004) and cocaine use (OR 0.49, p<0.01) at age 35 years (Merline et al., 2004).

Risk factor: Gender The hypothesis that being male is a risk factor is supported by moderate quality evidence [B] (seven good and nine moderate quality studies found an association and three moderate and one poor quality study found no association)	
Reference	**Summary statistics**
Hale and Viner (2016) **Cohort name:** Longitudinal Study of Young People in England (LSYPE) **Study quality:** moderate	Being female was associated with just under half the risk of age 19 years drug use in the last four weeks when compared to males (OR 0.47, 95% CI 0.40 to 0.54, p<0.001).
Boden et al. (2006) **Cohort name:** The Christchurch Health and Development Study (CHDS) **Study quality:** good	Proportional hazards regression models identified illicit drug use and dependence at age 25 years was higher in males (p<0.0001).
von Sydow et al. (2002) **Cohort name:** Early developmental stages of psychopathology study (EDSP) **Study quality:** good	Multiple logistic regression of cannabis use incidence among former non users showed males were almost twice as likely to use cannabis than females (OR 1.9, 95% CI 1.4 to 2.7, p <0.05). Cannabis use frequency was also associated with male gender (IRR 3.3, 95% CI 2.3 to 4.7, p< 0.05). However being male was not associated with cannabis dependence.
West et al. (2004) **Cohort name:** West of Scotland study **Study quality:** moderate	Males were over one and a half times more likely to use illicit drugs at age 13 years (OR 1.63, p<0.001), compared to females. However, there was no statistical differences between gender and risk of illicit drug use at age 15 years.
Lessem et al. (2006) **Cohort name:** ADD Health Study **Study quality:** good	Being male was associated with increased odds of young adult illicit drug use (OR 1.27, 95% OR 1.12 to 1.45, p<0.0025).
Rostosky et al. (2007) **Cohort name:** ADD Health Study **Study quality:** moderate	Analyses identified females were not significantly more likely to have used cannabis in the last 30 days at wave three than males.
Harrell and Broman (2009)	Multivariate logistic regression showed no association between gender and risk of prescription drug misuse.

Cohort name: ADD Health Study **Study quality:** poor	
Hayatbakhsh et al. (2013) **Cohort name:** The Mater-University of Queensland Study of Pregnancy (MUSP) **Study quality:** moderate	Cox proportional hazards model identified males at slightly greater risk of cannabis use at age 21 years compared to females (OR 1.22, 95% CI 1.10 to 1.35).
Hayatbakhsh et al. (2009) a **Cohort name:** The Mater-University of Queensland Study of Pregnancy (MUSP) **Study quality:** good	Results of the multivariate logistic regression showed that male participants are almost 50% more likely to report amphetamine use (OR 1.5, 95% CI 1.1 to 1.9, $p<0.01$) or disorder by early adulthood (OR 1.7, 95% CI 1.0 to 2.7, $p<0.05$).
Hayatbakhsh et al. (2009) b **Cohort name:** The Mater-University of Queensland Study of Pregnancy (MUSP) **Study quality:** good	Adjusted for all other covariates, males were almost three times more likely than females to have ever reported cannabis abuse or dependence (OR 2.9, 95% CI 2.3 to 3.6, $p<0.001$), although they were equally likely to report ever use of cannabis.
Adalbjarnardottir and Rafnsson (2001) **Cohort name:** Reykjavik Adolescent Risk-Taking Study (RAR) **Study quality:** moderate	At age 17 years, boys were more likely to have tried illicit drugs (OR 3.4, B 1.22 $p<0.001$) than girls.
Mason et al. (2016) **Cohort name:** Northern Finland Birth Cohort **Study quality:** good	Being male was correlated to lifetime illegal drug use (–0.03, $p <0.05$).
Wills et al. (2001) **Cohort name:** no name **Study quality:** moderate	No correlation between gender and substance use was identified from the analyses.
Gauffin. et al. (2013) **Cohort name:** no name **Study quality:** moderate	Cox regression models identified males were more likely to have at least one indication of illicit drug abuse than females (HR 2.39, 95% CI 2.34 to 2.45).

Coffey et al. (2003) **Cohort name:** The Victorian Adolescent Health Cohort Study **Study quality:** good	Females were significantly less likely to report cannabis dependence (OR 0.38, 95% CI 0.22 to 0.66, p<0.01) than males.
McGee et al. (2000) **Cohort name:** The Dunedin Multidisciplinary Health and Development Study **Study quality:** moderate	Bivariate analyses identified males to be nearly two times more likely to use cannabis (OR 1.71, 95% CI 1.27 to 2.29) than females at age 18 years. By 21 years, the increased risk of cannabis use had decreased very slightly (OR 1.61, 95% CI 1.17 to 2.22), but was still over one and a half times greater than females.
Bryant et al. (2003) **Cohort name:** Monitoring the Future **Study quality:** moderate	Females increased their cannabis use more than males at age 14 (0.17, p<0.05). However, the quadratic results for cannabis use indicated that females decelerated their rates of increase in cannabis use more than males during the period from age 14 to age 20 years.
Merline et al. (2004) **Cohort name:** Monitoring the Future study **Study quality:** moderate	Multivariate analyses identified women as being at less risk of cannabis use (OR 0.56, p<0.01) and cocaine use (OR 0.49, p<0.01). However, no association between gender and prescription drug use was identified.
Garnier-Dykstra et al. (2012) **Cohort name:** College Life **Study quality:** moderate	No statistically significant association was found between gender and nonmedical use of prescription stimulants.
Kaynak et al. (2013) **Cohort name:** College Life **Study quality:** moderate	Being male was significantly related to cannabis dependence during the first year of college (OR 1.97, 95% CI 1.10 to 3.52, p 0.02).

4.8.3 Personality traits

There is moderate quality evidence of an association between certain personality traits in childhood and illicit drug use and/or dependence in adolescence and young adulthood. Thirteen studies (three good, eight moderate and two poor quality) looked at various different personality dimensions and were assessed using different measurement tools/scales.

These studies came from nine different cohorts conducted in USA (six), Germany (two), New Zealand (two), and one each in UK, Iceland and

Netherlands. Exposure measures included novelty or sensation seeking (five studies), self-control (four), psychological distress (three), self-esteem (one), coping (two) and inhibitory control (one). Again, outcomes varied with some looking at cannabis use only, illicit drug use and non-prescription drugs or a mixture. Some studies also looked at use and dependence separately. A number of studies used a composite measure combing alcohol, cigarette and illicit drugs as the outcome.

Of the good and moderate quality studies, only one moderate study (Arria et al., 2008) did not find an association between non-prescription drugs and sensation seeking. The childhood personality traits that were found to predict illicit drug use included psychological distress; high novelty seeking; high sensation seeking; high behavioural inhibition; low self-esteem; poor self-control; loneliness; low coping efficacy; low perceived harmfulness of prescription drugs relative to other drugs like alcohol, cannabis and cocaine; and disengagement (anger, avoidance). Due to differences in the exposure measures, caution should be applied when attempting to group studies and interpret findings.

Risk factor: Personality traits The hypothesis that certain personality dimensions are a risk factor is supported by moderate quality evidence [B] (three good, eight moderate and one poor quality study found an association and one poor quality study found no association)	
Reference	**Summary statistics**
Hale and Viner (2016) **Cohort name:** Longitudinal Study of Young People in England (LSYPE) **Study quality:** moderate	A General Health Questionnaire score above 4, indicating psychological distress at age 15 was associated with increased age 19 years drug use (OR 1.72, 95% CI 1.43 to 2.06, p<0.001).
Boden et al. (2006) **Cohort name:** The Christchurch Health and Development Study (CHDS) **Study quality:** good	Proportional hazards regression models in which the hazards or instantaneous risks of onset of cannabis and other illicit drug use and dependence by age 25 years were modelled as log-linear functions of a range of social, childhood and related risk factors. Results indicate illicit drug use (B 0.09, SE 0.01, p<0.0001) and dependence (B 0.13, SE 0.02, p<0.0001) was predicted by novelty-seeking.
Fergusson et al. (2008) **Cohort name:** The Christchurch Health and Development Study (CHDS)	Analyses using repeated measures logistic regression models suggested that novelty-seeking predicted later illicit drug use and abuse/dependence. There was a stepwise association between novelty-seeking scores and risk of illicit drug use at ages 16 to 17 (26-50% score AOR 1.19, 95% CI 1.05 to 1.32, 51-75% score AOR 1.38, 95% CI 1.11 to 1.73, 76-100% AOR 1.62,

Study quality: good	95% CI 1.16 to 2.28) and 20 to 21 years (26-50% score AOR 1.17, 95% CI 1.05 to 1.32, 51-75% score AOR 1.38, 95% CI 1.11 to 1.73, 76-100% score AOR 1.62, 95% CI 1.16 to 2.28). Adjusted odds ratios for illicit drug use dependence are not shown, but reported to be significant.
Von Sydow et al. (2002) **Cohort name:** Early developmental stages of psychopathology study (EDSP) **Study quality:** good	Multiple logistic regression (controlling for age and gender) of cannabis dependence in baseline users without disorder (predictors of progression into cannabis abuse in former users without use disorder) showed an increased association with increasing age in self-esteem (VK score) (OR 1.9, 95% CI 1.1 to 3.2,p <0.05), measure of distress (OR 1.7, 95% CI 1.1 to 2.8, p <0.05) and self-control and coping skills (VK score) (OR 0.4, 95% CI 0.2 to 0.9, p <0.05).
Asselmann et al. (2016) **Cohort name:** Early Developmental Stages of Psychopathology Study (EDSP) **Study quality:** moderate	Low levels of coping efficacy at baseline predicted the onset of abuse/dependence of illicit drugs (adjusted OR 1.36, 95% CI 1.19 to 1.54, p < 0.001) at follow-up.
Pears et al. (2007) **Cohort name:** Three Generational Study (3GS) and Oregon Youth Study (OYS) **Study quality:** poor	Analyses in this generational study aimed to investigate the relationships between parenting and substance use, and how generational alcohol and illicit drug use may be mediated by inhibitory control. However, the analyses also investigated the association between G2 inhibitory control in adolescence and later substance use. It found G2's inhibitory control was then negatively (-0.36, p<0.01) associated with his later illicit drug use.
Adalbjarnardottir and Rafnsson (2001) **Cohort name:** Reykjavik Adolescent Risk-Taking Study (RAR) **Study quality:** moderate	Sequential logistic regression showed perceived control at age 14 was significantly associated with adolescent substance use at age 17 (χ^2 (B)-1.12, *SE* 0.33, OR 0.32, p<0.001). Those girls who showed less personal control at age 14 were more likely to have tried illicit drugs at age 17, compared with girls who showed more personal control (probabilities of 0.10, 0.06, and 0.04, for low, medium, and high personal control, respectively). For boys, perceived control at age 14 seems unrelated to their illicit substance use at age 17 (probabilities of 0.19, 0.19, and 0.18 for low, medium, and high personal control, respectively).
Malmberg et al. (2012) **Cohort name:** The Healthy School and Drugs Cohort **Study quality:** poor	Pearson, biserial, and tetrachoric correlations of personality dimensions (T1) and substance use (20 months later) revealed a significant relationship with sensation seeking (0.28, p<0.001), but not anxiety, hopelessness and impulsivity. Further modelling confirmed a non-significant relationship between impulsivity and hopelessness with lifetime cannabis use. Further analyses revealed no significant differences in substance use between the different sub-profiles for both boys and girls.

Wills et al. (2001) **Cohort name:** no name **Study quality:** moderate	The substance use indices were intercorrelated and the correlations increased with age; correlations were mostly in the range from 0.30 to 0.60. The analytic model (latent-growth analysis) was based on three indicators for peer use; the sum of scores for friends using tobacco, alcohol, and cannabis at a given time point (7th grade, 8th grade, or 9th grade). In the final model, disengagement coping was related to more initial peer use, more initial adolescent use, and greater rate of growth in adolescent use (/ = 2.74, p < 0.01). Behavioural coping was related to lower initial level of adolescent use and lower rate of growth in peer use (t = 2.57, p < 0.01).
Wills and Stoolmiller (2002) **Cohort name:** no name **Study quality:** moderate	Substance use intercept and slope coefficients, by quartiles for change in good or poor control showed there was a significantly greater rate of growth of substance use at wave 4 among participants who showed increases in poor self-control and a significantly lower rate of growth among participants who showed increases in good self-control.
Bryant et al. (2003) **Cohort name:** Monitoring the Future **Study quality:** moderate	Effect sizes from final hierarchical linear growth models of monthly cannabis use including age 14 status showed students who reported higher levels of loneliness (-0.15 p <0.05) increased their cannabis use more than their counterparts. However, quadratic results show no associated rates of increase in cannabis use.
Arria et al. (2008) **Cohort name:** College Life study **Study quality:** moderate	Results of logistic regression predicting nonmedical use of prescription drugs during the past year (Time 3), among those with opportunity to use found a non-statistical association between sensation-seeking and prescription stimulants (AOR 1.1, 95% CI 1.0 to 1.2, p 0.189) and prescription analgesics (AOR 1.1, 95% CI 0.9 to 1.3, p 0.240). Low perceived harmfulness was significantly associated with the use of both prescription stimulants (AOR 10.3; 95% CI 3.2 to 33.0; p<0.0001) and prescription analgesics (AOR 9.6; 95% CI 2.1 to 44.0; p=0.004).
Kaynak et al (2013) **Cohort name:** College Life Study **Study quality:** moderate	Results of logistic regression analysis predicting the probability of DSM-IV cannabis dependence during the first year of college demonstrate a significant association with sensation seeking (OR 1.16, 95% CI 1.01 to 1.33).

4.8.4 Academic achievement

There is some evidence from ten studies that low academic achievement in adolescence increases the likelihood of illicit drug use and dependence in adulthood. However, the evidence supporting this risk factor is not conclusive. Ten papers (two good, six moderate and two poor quality) examined this relationship. Five studies were from USA (three moderate

and two poor quality), two from Australia (both good quality), and one each from UK (moderate quality), Finland (moderate quality) and Sweden (moderate quality). Two of the US studies utilised data from the same cohort, likewise the two Australian studies. The exposures were assessed using a range of measurement scales and included various measures of academic attainment including school performance, school failure, and grade point average. Outcome measures varied and included cannabis use (four studies), nonmedical prescription stimulant use (one study), amphetamine use and amphetamine use disorder (one study), cannabis use and cannabis use disorder (one study), and illicit drug use (two studies).

Generally, the studies identified an association between academic achievement and substance use. Three studies looked at nonmedical prescription drug use (Harrell and Broman, 2009; Merline et al., 2004; Garnier-Dykstra et al., 2012). They all identified a significant association between level of education and lower nonmedical prescription drug use. In two studies the direction of the results was unclear (level of education and grade point average). We have therefore assumed they imply higher education, or higher grades, may be a protective factor.

Risk factor: Academic achievement There is some evidence supporting the hypothesis that low academic achievement is a risk factor, but it is not conclusive [C] (one good, four moderate and two poor quality studies found an association and one good quality and two moderate quality studies found no association)	
Reference	**Summary statistics**
Hale and Viner (2016) **Cohort name:** Longitudinal Study of Young People in England (LSYPE) **Study quality:** moderate	Low academic attainment at age 14 was not significantly associated with drug use at age 19 (OR 0.95, 95% CI 0.77 to 1.16, p 0.590).
Harrell and Broman (2009) **Cohort name:** ADD Health Study **Study quality:** poor	Education was significantly associated with prescription drug misuse (OR 0.95, 95% CI 0.91 to 0.99, p<0.05). However, it was not possible to ascertain from the sources if this OR related to higher or lower education. We can only presume it refers to higher education being significantly associated with less prescription drug misuse.
Niemela, et al. (2008) **Cohort name:** Boy to a man **Study quality:** moderate	Multinomial logistic regression analysis identified poor school performance at age 8 was not significantly associated with self-reported illicit drug use in early adulthood (OR 0.7, 95% CI 0.3 to 1.3).
Hayatbakhsh et al. (2009) a	Low child school performance in adolescence was not significantly associated with amphetamine use (OR 0.9,

Cohort name: Mater-University of Queensland Study of Pregnancy (MUSP) **Study quality:** good	95% CI 0.5 to 1.5) and amphetamine use disorders (OR 1.2, 95% CI 0.5 to 3.2) at 21 years.
Hayatbakhsh et al. (2009) b **Cohort name:** Mater-University of Queensland Study of Pregnancy (MUSP) **Study quality:** good	Below average school performance at 14 years was significantly associated with cannabis use (OR 1.6, 95% CI 1.1 to 2.4, p 0.05) and cannabis use disorder (OR 2.0, 95% CI 1.3 to 3.0, p 0.01) at 21 years
Gauffin et al. (2013) **Cohort name:** no name **Study quality:** moderate	School failure was significantly associated with illicit drug abuse (HR 4.22, 95% CI 4.13 to 4.31) between the ages of 20 and 35 years.
Bryant et al. (2003) **Cohort name:** Monitoring the Future study **Study quality:** moderate	Low academic achievement was significantly associated with increased cannabis use (mean quadratic growth – 0.20, p<0.05).
Merline et al. (2004) **Cohort name:** Monitoring the Future study **Study quality:** moderate	Being a college graduate was significantly associated with lower use of cannabis (OR 0.57, p<0.01), cocaine (OR 0.53, p <0.01) or misuse of prescription drugs (OR 0.4, p <0.01) at age 35 years.
Garnier-Dykstra et al. (2012) **Cohort name:** College Life Study **Study quality:** moderate	Grade point average (GPA) was significantly associated with nonmedical prescription stimulant use at year 1, 2, 3 and 4. However, it was not clear if the aOR referred to a lower or higher GPA. The source implies it refers to a higher GPA, meaning a higher GPA is protective against nonmedical prescription stimulant use in these years (year 1 aOR 0.68, 95% CI 0.50 to 0.92, p <0.05, year 2 aOR 0.65, 95% CI 0.47 to 0.89, p <0.05, year 3 aOR 0.51, 95% CI 0.35 to 0.75, p <0.05, and year 4 aOR 0.59, 95% CI 0.39 to 0.90, p <0.05).
Windle and Wiesner (2004) **Cohort name:** Lives across time **Study quality:** poor	Low grade point average (GPA) was significantly associated with cannabis use (p<0.001).

4.8.5 Delinquency or aggression

Seven papers (two good, two moderate and three poor quality) examined the relationship between delinquency or aggression and illicit drug use or dependence. Three studies were from USA (Van den Bree and Pickworth, 2005; Harrell and Broman, 2009; Windle and Wiesner, 2004; all poor quality), two from Australia (Hayatbakhsh et al., 2009a; Hayatbakhsh et al., 2009b; both good quality), and one each from Finland (Kaltiala-Heino et al., 2011; moderate quality) and the UK (Hale and Viner, 2016; moderate quality). Two of the US studies utilised data from the same cohort, likewise the two Australian studies.

The exposures assessed included delinquency (Hale and Viner, 2016; Van den Bree and Pickworth, 2005; Windle and Wiesner, 2004; Kaltiala-Heino et al., 2011), delinquency and/or aggression (Hayatbakhsh et al., 2009a; Hayatbakhsh et al., 2009b; Harrell and Broman, 2009) and violent behaviour (Harrell and Broman, 2009). Various scales were used in measuring the exposure. Outcome measures varied and included cannabis use/ involvement (three studies), prescription drug misuse (one study), amphetamine use and amphetamine use disorder (one study), cannabis use and cannabis use disorder (one study), and illegal drug use (one study).

All three studies examining the relationship between delinquency and illicit drug use/dependence reported significant associations between the exposure and outcome. The two Australian studies utilising data from the same cohort found significant associations between aggression/ delinquency and amphetamine use or disorder and cannabis use or disorder respectively. One study (Kaltiala-Heino et al., 2011) assessing both delinquency and aggression, reported significant associations between delinquency at age 15 and illegal drug use at age 17 years in both boys (OR 1.1; 95% CI 1.0 to 1.3) and girls (OR 1.2; 95% CI 1.1 to 1.4). However, aggression at age 15 years was not significantly associated with illegal drug use in either boys (OR 1.0; 95% CI 1.0 to 1.1) or girls (OR 1.0; 95% CI 1.0 to 1.0) at age 17 years. In one USA study (Harrell and Broman, 2009) violent behaviour was not significantly associated with prescription drug abuse (reported by authors, no data provided).

Risk factor: Delinquency or aggression There is some evidence supporting the hypothesis that delinquency or aggression are risk factors, but it is not conclusive [C] (two good, two moderate and two poor quality studies found an association and one poor quality study found no association)	
Reference	**Summary statistics**
Hale and Viner (2016) **Cohort name:** Longitudinal Study of	Delinquency at age 14 years (OR 2.08; 95% CI 1.69 to 2.54; p<0.001), age 16 years (OR 2.58; 95% CI 2.06 to 3.22; p<0.001), and both age 14 and 16 years (OR 5.32; 95% CI 4.34 to 6.53; p <0.001) was significantly associated with drug use at age 19 years.

Young People in England (LSYPE) **Study quality:** moderate	
Van den Bree and Pickworth (2005) **Cohort name:** ADD Health Study **Study quality:** poor	Delinquency was significantly associated with initiation of experimental cannabis use for boys (OR 1.30; 95% CI 1.17 to 1.54) and girls (OR 1.34; 95% CI 1.16 to 1.55), initiation of regular use (OR 1.36; 95% CI 1.13 to 1.64) for boys and girls combined, progression to regular use (OR 1.35; 95% CI 1.09 to 1.68) for boys, failure to discontinue experimental use (OR 0.71; 95% CI 0.61 to 0.84) for boys, and failure to discontinue regular use (OR 0.77; 95% CI 0.66 to 0.90) for boys and girls combined.
Harrell and Broman (2009) **Cohort name:** ADD Health Study **Study quality:** poor	Violent behaviour was not significantly associated with prescription drug abuse (no stats given). Non-violent delinquent behaviour was significantly associated with prescription drug abuse (OR 1.04; 95% CI 1.01 to 1.07; p<0.01).
Hayatbakhsh et al. (2009) a **Cohort name:** Mater-University of Queensland study of Pregnancy (MUSP) **Study quality:** good	High levels of aggression/delinquency in adolescence was significantly associated with amphetamine use (OR 1.6; 95% CI 1.1 to 2.5; p<0.05) and amphetamine use disorder (OR 2.9; 95% CI 1.5 to 5.8; p<0.01) at 21 years.
Hayatbakhsh et al. (2009) b **Cohort name:** Mater-University of Queensland study of Pregnancy (MUSP) **Study quality:** good	Aggression/delinquency was significantly associated with cannabis use (OR 1.5; 95% CI 1.1 to 2.3; p<0.05) and cannabis use disorder (OR 2.7; 95% CI 1.7 to 4.1; p<0.001) at 21 years.
Windle and Wiesner (2004) **Cohort name:** Lives Across Time **Study quality:** poor	Delinquent activity was significantly associated with cannabis use (p<0.001).
Kaltiala-Heino et al. (2011) **Cohort name:** Adolescent Mental Health Cohort Study (AMHC) **Study quality:** moderate	Delinquency at age 15 was significantly associated with illegal drug use in both boys (OR 1.1; 95% CI 1.0 to 1.3) and girls (OR 1.2; 95% CI 1.1 to 1.4) at age 17. However, aggression at age 15 was not significantly associated with illegal drug use in either boys (OR 1.0; 95% CI 1.0 to 1.1) or girls (OR 1.0; 95% CI 1.0 to 1.0) at age 17.

4.8.6 Emotional and behaviour problems

Eight studies (five good, two moderate and one poor quality) investigated associations between emotional and behavioural problems and illicit drug use or dependence. Of the eight studies, two were conducted in New Zealand (both good quality), two in USA (one good, one poor quality), and one each from Finland (moderate quality), Australia (good quality), Denmark (good quality), and Norway (moderate quality). The two New Zealand studies utilised data from the same cohort.

There is some evidence that emotional and behavioural problems in adolescence increase the likelihood of illicit drug use and dependence in adulthood. However, the evidence supporting this risk factor is not conclusive. Emotional and behavioural disorders are a broad group of disorders, however the studies reporting this measure in this review only covered conduct problems and ADHD. One good quality study (Ottosen et al., 2016) examining ADHD with comorbid disorders including conduct disorder, depression, bipolar disorder, and schizophrenia, found that comorbidities further increased the risk of substance use disorder in ADHD. Four studies (three good and one moderate quality) examined conduct problems alone. One moderate quality study (Niemela et al., 2008) examined the relationship between conduct problems, hyperactivity, and emotional problems on illicit drug use. One good quality study (Hayatbakhsh et al., 2009a) examined the relationship between attention problems on amphetamine use and amphetamine use disorder. One poor quality study (Flory et al., 2003) assessed both ADHD and conduct problems.

Of the studies that assessed the relationship with conduct problems, four studies (Boden et al., 2006, good quality; Lessem et al., 2006, good quality; Pederson et al., 2001, moderate quality; Flory et al., 2003, poor quality) reported a significant relationship between conduct problems and illicit drug use or dependence. The association reported in two studies (Fergusson et al., 2008, good quality; Niemela et al., 2008, moderate quality) did not reach statistical significance. Of the studies reporting ADHD (Ottosen et al., 2016) or hyperactivity (Flory et al., 2003), one poor quality study (Flory et al., 2003) reported a significant association with cannabis use/dependence and hard drug use/dependence, while the association reported in two studies (one good and one moderate quality) was not statistically significant. One good quality study (Ottosen et al., 2016) examined ADHD with comorbid disorders including conduct disorder, depression, bipolar disorder, and schizophrenia, and found that comorbidities further increased the risk of substance use disorder in ADHD. However, the confidence intervals are extremely wide. One moderate quality study (Niemela et al., 2008) reported a non-significant relationship between emotional problems and illicit drug use.

Risk factor: Emotional and behavioural problems There is some evidence supporting the hypothesis that emotional and behavioural problems are a risk factor, but it is not conclusive [C] (three good, one moderate and one poor quality study found an association and two good and one moderate quality study found no association)	
Reference	**Summary statistics**
Boden et al. (2006) **Cohort name:** The Christchurch Health and Development Study (CHDS) **Study quality:** good	Using proportional hazard regression modelling that adjusted for other known risk factors (gender, ethnicity, education), conduct problems at age 14 was shown to be significantly associated with any illicit drug dependence by age 25 ($p<0.05$).
Fergusson et al. (2008) **Cohort name:** The Christchurch Health and Development Study (CHDS) **Study quality:** good	Multivariate logistic regression modelling was conducted adjusting for time-dynamic factors (annual frequency of cannabis use ages 16 to 25 years; affiliation with substance-using peers ages 16 to 25 years; frequency of alcohol use and cigarette smoking, ages 16 to 25 years), and including fixed and time-dynamic covariates, and lagged illicit drug use. Conduct problems at ages 7 to 13 years was not significantly associated with illicit drug use ($p >0.10$) and illicit drug abuse/dependence ($p >0.30$) at ages 16 to 25 years.
Lessem et al. (2006) **Cohort name:** ADD Health Study **Study quality:** good	Conduct disorder was significantly associated with young adult illicit drugs (excluding cannabis) (OR 1.17; 95% CI 1.13 to 1.22; $p <0.0025$).
Niemela et al. (2008) **Cohort name:** Boy to a man **Study quality:** moderate	Associations between childhood and early adulthood variables and illicit drug involvement found conduct problems (OR 0.9; 95% CI 0.4 to 2.2), hyperactive problems (OR 0.5; 95% CI 0.2 to 1.3), and emotional problems (OR 0.9; 95% CI 0.5 to 1.2) at age 8 years were not significantly associated with self-reported illicit drug use.
Hayatbakhsh et al. (2009) a **Cohort name:** Mater-University of Queensland Study of Pregnancy (MUSP) **Study quality:** good	Attention problems in adolescence was not significantly associated with amphetamine use (OR 1.3; 95% CI 0.8 to 2.0) and amphetamine use disorders (OR 0.6, 95% CI 0.2 to 1.6) at 21 years.
Ottosen et al. (2016) **Cohort name:** no name **Study quality:** good	ADHD with no comorbid psychiatric disorders significantly increased the risk of cannabis (female HR 7.15; 95% CI 5.07 to 10.09); (male HR 4.20; 95% CI 3.36 to 5.24), and other illicit substances (female HR 4.79; 95% CI 3.16 to 7.26); (male HR 4.10; 95% CI 3.24 to 5.21) abuse.

	ADHD with comorbid bipolar disorder was significantly associated with an increased risk of cannabis (HR 45.71; 95% CI 14.24 to 146.73; p<0.05) and other illicit substances (HR 25.88; 95% CI 6.01 to 111.50; p<0.05) abuse in females only. Having comorbid ODD/CD or schizophrenia resulted in a higher risk of all 3 types of SUD, in both females and males (p <0.005). Comorbid depression also added significantly to the risk of cannabis abuse in females and males with ADHD, compared to ADHD alone (p <0.05).
Pederson et al. (2001) **Cohort name:** no name **Study quality:** moderate	Logistic regression was conducted to analyse the associations between risk factors at T1 and cannabis use at T2. Early conduct problems were significantly associated with subsequent cannabis initiation. The effect was significantly stronger in girls than in boys. Serious CP was found to have a moderate effect upon cannabis initiation in boys (aOR 1.70; 95% CI 1.44-2.02), whereas aggressive (aOR 1.64; 95% CI 1.24-2.17) and covert CP (aOR 1.85; 95% CI 1.43-2.40) had strong effects in girls.
Flory et al. (2003) **Cohort name:** Project DARE **Study quality:** poor	Childhood HIA was significantly associated with cannabis use (p < 0.01), cannabis dependence (p < 0.01), hard drug use (p < 0.01), and hard drug dependence (p < 0.01). Similarly, childhood conduct problems were significantly associated with cannabis use (p < 0.01), cannabis dependence (p < 0.01), hard drug use (p < 0.01), and hard drug dependence (p < 0.01).

4.8.7 School related problems

There is some evidence from four studies of an association between school related problems and later drug misuse. However, the evidence supporting this risk factor is not conclusive. The studies used data from three different cohorts. Two looked at cannabis use outcomes (both from USA) and two looked at illicit drug use outcomes (both from UK).

We have included a variety of exposures under this category, so caution should be applied when interpreting the results. Exposures included getting into trouble (Van den Bree and Pickworth, 2005), School interest, effort and level of school difficulty (Bryant et al., 2003) and lower school engagement or disengagement (West et al., 2004; Markham et al., 2012).

The two moderate quality UK studies (West et al., 2003; Markham et al., 2012) looked at school disengagement at 13 years and 15 years in UK school children. Although both studies identified an association, they disagreed on which age was associated with the most increased risk. West et al. (2004) identified lower school engagement at age 15 carried the most increased risk of illicit drug use (OR 1.14, p<0.001). In contrast, Markham et al. (2012) identified the younger age of 13 years to be associated with

the most increased risk of illicit drug use (OR 1.87, 95% CI 1.53 to 2.28, p<0.001). This is an intriguing finding as they both used the same data and analysed using multi-level and random effects logistic regression.

Risk factor: school related problems There is some evidence supporting the hypothesis that school related problems are a risk factor for drug misuse, but it is not conclusive [C] (three moderate and one poor quality study)	
Reference	**Summary statistics**
Van den Bree and Pickworth (2005) **Cohort name:** ADD Health Study **Study quality:** poor	Getting into trouble in school was significantly associated with the initiation of experimental cannabis use in boys (OR 1.17; 95% CI 1.02 to 1.35). Being unhappy in school was significantly associated with the initiation of experimental cannabis use in girls (OR 1.21; 95% CI 1.08 to 1.36). Getting into trouble in school was significantly associated with the initiation of regular cannabis use in both boys and girls (OR 1.57; 95% CI 1.31 to 1.88). Getting into trouble in school was significantly associated with the progression to regular cannabis use in girls (OR 1.60; 95% CI 1.28 to 2.01)
Bryant et al. (2003) **Cohort name:** Monitoring the Future **Study quality:** moderate	Of the three exposures (school interest, perceived school difficulty, effort and school bonding), only adolescents who reported higher levels of school difficulty in eighth grade increased their cannabis use less than those who reported lower levels of school difficulty (linear growth rate -0.17, p<0.05). School interest, effort and school bonding were not found to be associated with cannabis use.
West et al. (2004) **Cohort name:** West of Scotland Study (WOS) **Study quality:** moderate	This cohort was looking to identify school effects on the pupil behaviour, such as illicit drug use. Part of the analyses investigated pupil composition. This involved a focus on the extent to which pupils' perceptions of school life (which amongst others included school engagement) together with an aggregated ethos measure, reduced the school variance identified in earlier analyses. This identified lower school engagement was statistically significantly associated with illicit drug use at ages 13 (OR 1.08, p<0.05), but more so at age 15 years (OR 1.14, p<0.001).
Markham et al. (2012) **Cohort name:** West of Scotland Study (WOS) **Study quality:** moderate	Disengagement at age 13 years was associated with later ever use of illicit drugs (OR 1.87, 95% CI 1.53 to 2.28, p<0.001) and at age 15 years (OR 1.59, 95% CI 1.36 to 1.86, p<0.001). At school level, illicit drug use was higher in schools with high levels of teacher-pupil disengagement.

4.8.8 Suicidal behaviour

There is some evidence from two studies that suicidal behaviour increases the likelihood of illicit drug use but the evidence is not conclusive. The two studies reporting this measure focused only on self-harm and suicidal ideation respectively. In the moderate quality UK study (Mars et al., 2014), individuals who self-harmed (with or without suicidal intent) at age 16 years were found to be at increased risk of problem cannabis and illicit drug use at 18 years. In this study, the authors noted the difficulties inherent in establishing suicidal intent accompanying an episode of self-harm. Suicidal intent was determined from self-reports which may be prone to response and reporting bias. The other study (Zhang et al., 2014) examined a reciprocal association between substance use (cigarette smoking, use of alcohol, cannabis, and other illegal drugs) and suicidal ideation among adolescents and young adults. The findings showed a unidirectional association between the two measures, with suicidal ideation increasing the risk of illicit drug use. The study authors noted the use of self-reported data and a number of other methodological shortcomings, which could impact the validity of study findings. Both studies reported significant associations between the respective suicidal behaviours and illicit drug use. However, as the exposure and outcomes measured in both were very different it is difficult to draw any firm conclusions about suicidal behaviour being a risk factor for substance use.

Risk factor: suicidal behaviour There is some evidence supporting the hypothesis that suicidal behaviour is a risk factor, but it is not conclusive [C] (one moderate and one poor quality)	
Reference	**Summary statistics**
Mars et al. (2014) **Cohort name:** Avon Longitudinal Study of Parents and Children (ALSPAC) **Study quality:** moderate	Self-harm (with and without suicidal intent) at age 16 years was significantly associated with later problem cannabis use ($p < 0.001$) and illicit drug use ($p < 0.001$) at 18 years.
Zhang and Wu (2014) **Cohort name:** ADD Health Study **Study quality:** poor	Suicidal ideation in adolescence was significantly associated with cannabis use ($p < 0.001$) and other illegal drug use ($p<0.001$) in young adulthood.

4.8.9 Mental disorders

The evidence reported for mental disorder as a risk factor for illicit drug use is inconsistent and it is not possible to draw conclusions. Ten studies (three good, five moderate and two poor quality) from nine cohorts investigated the associations between mental disorders and substance misuse. Cohorts were conducted in USA (one good, one moderate and two poor quality), Finland (two moderate quality), New Zealand (two moderate quality), Australia (good quality) and Germany (good quality). Of the studies reporting this measure, depression was the most prevalent mental disorder followed by anxiety disorders.

Three studies assessed mental disorders generally, most assessed depression, major depressive disorder or depressive symptoms and the remaining assessed anxiety/ depression and mood and/or personality disorders as the exposure. A variety of measures were used including clinical, parent, teacher and self-reported scales. Two studies, one from New Zealand and one from Finland (McGee et al., 2000; Kaltiala-Heino et al., 2011) measured mental disorders and depressive symptoms respectively, but gave no information on how data was obtained.

It is not possible to draw any conclusions about the relationship between drug use and mental disorders including depression and anxiety as included studies found conflicting results. Woodward and Fergusson (2001) identified a linear association between a number of anxiety disorders and illicit drug dependence. However, Harrington et al. (2011) failed to find an association between anxiety and incident drug use. Three studies found no association between depression and prescription drug (Harrell and Broman, 2009), amphetamine use (Hayatbakhsh et al., 2009a) or substance use (Kaltiala-Heino et al., 2011). However, a good quality study (Pacek et al., 2013) and a poor quality study (Windle and Wiesner, 2004) identified an association between depression and cannabis use disorder.

Risk factor: Mental disorders The evidence is inconsistent and it is not possible to draw a conclusion [D] (three good, five moderate and two poor quality with inconsistent results across the studies)	
Reference	**Summary statistics**
Woodward and Fergusson (2001) **Cohort name:** The Christchurch Health Development Study (CHDS)	Significant linear associations were found between the number of anxiety disorders reported in adolescence and a range of adverse outcomes in early adulthood. Specifically, as the number of anxiety disorders increased there was a corresponding increase in young people's subsequent risk of illicit drug dependence ($p < .001$). After adjusting for confounders significant associations remained between the extent of anxiety disorder in adolescence and young people's later risks of

Study quality: moderate	illicit drug dependence (p <0.05). Adolescents with three or more anxiety disorders had rates of later illicit drug dependence that were almost 4 times higher than those of their non-anxious peers.
von Sydow et al. (2002) **Cohort name:** Early developmental stages of psychopathology study (EDSP) **Study quality:** good	Participants with baseline other mental disorders was associated with cannabis use incidence in former non-users (OR 1.9, 95% CI 1.2 to 3.0, p <0.05), but not cannabis use frequency. No association was found among baseline users without disorder and progression to cannabis dependence.
Harrell and Broman (2009) **Cohort name:** ADD Health Study **Study quality:** poor	Depression at wave 1 was not correlated with prescription drug misuse at wave 3.
Niemela et al. (2008) **Cohort name:** Boy to a man **Study quality:** moderate	Childhood psychopathology did not predict self-reported drug use at age 18.
Hayatbakhsh et al. (2009) a **Cohort name:** The Mater-University of Queensland Study of Pregnancy (MUSP) **Study quality:** good	No association was found between youth self-reported anxiety/depression and young adults amphetamine ever use or use disorders.
Pacek et al. (2013) **Cohort name:** National Epidemiologic Survey of Alcohol and Related Conditions (NESARC) **Study quality:** good	In the adjusted model, individuals with baseline depression were significantly more likely to develop cannabis use disorders (AOR 2.28, 95% CI 1.28 to 4.05) as well as cannabis abuse (AOR 2.96, 95% CI 1.55 to 5.65) than were individuals without baseline depression. However, no association was found between baseline depression and cannabis dependence. Furthermore, individuals with baseline depression were significantly more likely than those without depression to develop incident co-occurring alcohol and cannabis dependence (AOR 4.51, 95% CI 1.31 to 15.60).
Harrington et al. (2011) **Cohort name:** National Epidemiologic Survey of Alcohol and Related Conditions (NESARC) **Study quality:** moderate	With the notable exception of anxiety disorders, having a mood disorder at Wave 1 predicted incident drug use within 3 years among lifetime abstainers at wave 1. This relation persisted even after controlling for sociodemographic factors, childhood adversity, and a family history of drug and alcohol problems (AOR 1.31, 95% CI 1.04 to 1.64, p <0.05).
McGee et al. (2000)	Mental disorder at age 15 led to a small but significantly elevated risk of cannabis use at age 18 years (AOR 1.55 no 95% CI reported). Mental disorder at age 18 years

Cohort name: The Dunedin Multidisciplinary Health and Development Study **Study quality:** moderate	had no associated risk with cannabis use at age 21 years (AOR 1.08, no 95% CI reported, but bivariate model was not significant: OR1.11, 95% CI 0.78 to 1.58).
Windle and Wiesner (2004) **Cohort name:** Lives Across Time **Study quality:** poor	Analyses found a statistically significant association between depressive symptoms and cannabis trajectory groups.
Kaltiala-Heino et al. (2011) **Cohort name:** Adolescent Mental Health Cohort Study (AMHC) **Study quality:** moderate	No associations were found between depressive symptoms at baseline and age 17 years substance use behaviours in boys or girls.

4.8.10 Pubertal timing

The evidence reported for early pubertal timing is inconsistent and it is not possible to draw conclusions. Three studies (two moderate and one poor quality) from three different cohorts looked at early pubertal timing as a potential risk factor for illicit drug misuse. Two were from the USA (Lanza and Collins, 2002; poor quality; Lynne-Landsman et al., 2010; moderate quality) and one from Finland (Kaltiala-Heino et al., 2011; moderate quality). One study focussed on female pubertal timing only (Lanza and Collins, 2002), whilst the other two looked at pubertal timing in both females and males. Outcomes observed varied across studies and included cannabis use (Lanza and Collins, 2002), initiation (Lynne-Landsman et al., 2010) and illegal drug use (Kaltiala-Heino et al., 2011). None of the studies reporting an association with early pubertal timing and illicit drug use are directly comparable as they used methods.

One moderate quality study from USA (Lynne-Landsman et al., 2010), measured the risk of illicit drug use initiation associated with early pubertal timing according to a risk trajectory - based on the sum of eight indicators of household risk. When looking at the sample as a whole, however, it found little difference in cannabis initiation in the eighth grade between early and on-time/late maturers. In addition, cannabis initiation was measured in 9th grade which equates to age 14 to 15 years. The other study from Finland (Kaltiala-Heino et al., 2011) reporting a significant association between early pubertal timing and illicit drug use looked at ever use of illegal drugs by the age of 17 years.

As none of the studies reporting an association with early pubertal timing and illicit drug use are comparable, it was not possible to estimate an overall effect size estimate.

Risk factor: Pubertal timing The evidence is inconsistent and it is not possible to draw a conclusion [D] (two moderate and one poor quality with inconsistent results across studies)	
Reference	**Summary statistics**
Lanza and Collins (2002) **Cohort name:** Add Health Study **Study quality:** poor	Females who experience early pubertal timing (prior to 12 years of age) were 2.5 times (Risk ratio (RR) 2.5, 95% CI 1.4 to 4.3) more likely to have ever used cannabis in the 7th grade compared to on-time or late maturing females. This statistically significant increased risk continued into the 8th grade, but at a reduced rate (RR 1.7, 95% CI 1.1 to 2.6).
Kaltiala-Heino et al. (2011) **Cohort name:** Adolescent Mental Health Cohort Study (AMHC) **Study quality:** moderate	Early pubertal timing in girls and boys was not associated with significantly increased odds of any illegal drug use at age 17 (OR 1.9, 95% CI 0.9–3.8 for boys and OR 1.1, 95% CI 0.6 to 2.0) for girls). Boys experiencing a normative age at oigarche were actually twice as likely than boys aged 14 or more at oigarche to have used any illegal drug by age 17 (OR 2.0, 95% CI 1.2 to 3.7).
Lynne-Landsman et al. (2010) **Cohort name:** Oregon Youth Substance Use Project (OYSUP) **Study quality:** moderate	A significant interaction between pubertal timing and household risk trajectory group was found regarding the adolescent's own cannabis use in the past year, $F(5, 577)$ 4.79, $p<0.001$, η 0.04. Follow-up pairwise comparisons revealed early pubertal maturation was associated with higher levels of eighth-grade adolescent cannabis use only among individuals within the moderate high and very high household risk trajectory groups. The averages reported in Table 3 indicate that early maturers within the very high trajectory group reported using cannabis a couple of times in the past year, with an average of 3 to 5 times in the past month. This was in contrast to both early and on-time/late maturers from the other household risk trajectory groups, whose reports of cannabis use were near zero. Looking at the sample as a whole, the majority of early maturers (Mean 0.71. SE 0.10) in this study did not differ from on-time/late maturers (mean 0.20 SE 0.05) regarding cannabis initiation in the eighth grade.

4.8.11 Race and ethnicity

There is some evidence from eight studies that race/ethnicity is associated with illicit drug use. However, the evidence supporting this risk factor is inconsistent and therefore inconclusive. Of note, some of the papers reporting this exposure, used the terms 'race' and 'ethnicity'

interchangeably. The range of ethnic groups reported varied according to the study's country of origin. Thus, findings from some ethnic groups such as Māori and Hispanic may not be relevant to Wales.

Eight studies (two good, six moderate quality) investigated the association between race and ethnicity and illicit drug misuse. These used data from cohorts conducted in UK (one moderate quality), New Zealand (one good quality), and USA (four moderate quality and one good quality).

Of the good quality studies, one from New Zealand (Boden et al. 2006) found Māori ethnicity to be predicative of any illicit drug use by age 25 years (B 0.39, SE 0.16, p <0.05), but not any illicit drug dependence. The other good quality study from USA (Lessem et al. 2006) identified whites were over five times more likely to report the use of young adult illicit drug use (excluding cannabis) than non-whites (OR 5.16, 95% OR 4.15 to 6.41, p<0.0025).

Two moderate quality studies found no association between ethnicity or race and illicit drug misuse. One looked specifically at nonmedical use of prescription drugs (Garnier-Dykstra et al. 2012) and the other at cannabis dependence (Kaynak et al. 2013). In addition, Merline et al. (2004) failed to identify significant differences between ethnicity and cocaine use at age 35 years.

Most studies used white ethnicity as a reference to compare others. Of the remaining studies finding an association, generally white ethnicity was considered a risk factor, along with mixed ethnicity.

Risk factor: Race and ethnicity The evidence is inconsistent and it is not possible to draw a conclusion [D] (two good, six moderate quality with inconsistent results across studies)	
Reference	**Summary statistics**
Hale and Viner (2016) **Cohort name:** Longitudinal Study of Young People in England (LSYPE) **Study quality:** moderate	Analyses identified Asian (OR 0.32, 95% CI 0.24 to 0.43, p <0.001) and black (OR 0.55, 95% CI 0.35 to 0.88, p 0.012) ethnicities to be protective against cannabis use at age 19 years compared to white ethnicity. However, mixed ethnicity was associated with increased risk of cannabis use at age 19 years (OR 1.79, 95% CI 1.31 to 2.45, p <0.001).
Boden et al. (2006) **Cohort name:** The Christchurch Health and Development Study (CHDS) **Study quality:** good	Parameter estimates for proportional hazard models identified Māori ethnicity (B 0.39, SE 0.16, p <0.05) as predicative of any illicit drug use by age 25 years, but not any illicit drug dependence.

Wills et al. (2001) **Cohort name:** no name **Study quality:** moderate	Latent-growth analyses tested predictions about relationships of ethnicity to initial levels (intercept) and to growth over time (slope) in substance use. Black (-0.14) (-0.10) ethnicity were negatively correlated with adolescent substance use, but no ethnicity was correlated with adolescent growth of substance use.
Bryant et al. (2003) **Cohort name:** Monitoring the Future **Study quality:** moderate	Other minority students (not African Americans or Latinos) increased their cannabis use significantly less than White students (-0.22, p,0.05). Quadratic results indicated other minority students, compared with White, increased their use less yet accelerated their use more from age 14 to age 20 years (0.25, p<0.05).
Merline et al. (2004) **Cohort name:** Monitoring the Future **Study quality:** moderate	Multivariate analyses indicated African Americans were less at risk of using cannabis (OR 0.55, p 0.01) and prescription drug misuse (OR 0.33, p 0.01) than those reporting white and other ethnicity at 35 years. No significant differences were identified between ethnicity and cocaine use at age 35 years.
Garnier-Dykstra et al. (2012) **Cohort name:** College Life Study **Study quality:** moderate	Logistic regression models showed no association between race and nonmedical use of prescription stimulants across any of the four years the cohort was conducted.
Kaynak et al. (2013) **Cohort name:** College Life Study **Study quality:** moderate	Results of logistic regression analysis predicting the probability of DSM-IV cannabis dependence during the first year of college found no association with race/ethnicity.
Lessem et al. (2006) **Cohort name:** Add Health Study **Study quality:** good	Logistic regression identified whites were over five times more likely to report the use of young adult illicit drug use (excluding cannabis) than non-whites (OR 5.16, 95% OR 4.15 to 6.41, p<0.0025).

4.8.12 Bullying victimisation

There is some evidence from three studies that being a victim of bullying (victimisation) is associated with illicit drug use. However, the evidence supporting this risk factor is inconsistent and therefore inconclusive. Three studies (Danchev et al., 2019; good quality; Niemela et al., 2011; moderate quality; Hale and Viner, 2016; moderate quality) looked at being a victim of bullying at different ages associated with the risk of subsequent substance use between the ages of 18 and 20.

The good quality study (Danchev et al., 2019), conducted in UK, found school children aged 14 years who had been the victim of bullying were at higher odds of cannabis use at age 19 years (OR 1.34, 95% CI 1.15 to 1.55, p <0.001) compared to those who did not report being bullied.

Of the two moderate quality papers, one from Finland (Niemela et al., 2011) identified an association (OR 1.6, 95% CI 1.02 to 2.7) between males who were frequently victimised at age 8 and self-reported illicit drug use at age 18 years. As only male children were studied, the findings may not be generalisable to females.

Finally, the UK study (Hale and Viner, 2016) looked at sibling bullying at 12 years old and found no association with substance use at ages 18 and 20 years.

Risk factor: Bully victimisation The evidence is inconsistent and it is not possible to draw a conclusion [D] (one good and two moderate quality with inconsistent results across studies)	
Reference	**Summary statistics**
Hale and Viner (2016) **Cohort name:** Longitudinal Study of Young People in England (LSYPE) **Study quality:** moderate	Those who reported being a victim of bullying in the last 12 months at age 14 years were at higher odds of cannabis use at age 19 years (OR 1.34, 95% CI 1.15 to 1.55, p <.001) compared to those who did not report being bullied.
Dantchev and Wolke (2019) **Cohort name:** Avon Longitudinal Study of Parents and Children. (ALSPAC) **Study quality:** good	Cannabis and illicit drug misuse at age 18 and 20 years was not statistically significantly associated with children who were bullied or victimised by their siblings at 12 years old as the confidence intervals all cross the line of no effect. Authors also investigated associations between the frequency of victimisation and illicit drug misuse, but found no significant associations.
Niemela et al. (2011) **Cohort name:** Boy to a man **Study quality:** moderate	Authors found in multivariate analyses that being victimised sometimes was not significantly associated with illicit drug use at age 18 years. However, a small association (OR 1.6, 95% CI 1.02 to 2.7) was found between being frequently victimised at age 8 and self-reported illicit drug use at age 18 years, but this just reached significance levels.

4.8.13 Truancy

There is moderate evidence from a single UK study (Hale & Viner 2016) that truancy is associated with illicit drug use in early adulthood. The authors noted data used in establishing this association was derived from self-reports, which may be prone to response and reporting bias. However, they found a significant risk associated with both exclusion and truancy at age 14 years and age 19 years cannabis use. Although truancy was associated with the highest risk, both were associated with over twice the risk of cannabis use at the age of 19 compared to those who did not report exclusion or truancy at age 14 years.

Risk factor: Truancy Evidence from a moderate quality single study of a strong association between exclusions in the past three years and truancy in the past 12 months and drug misuse	
Reference	**Summary statistics**
Hale and Viner (2016) **Cohort name:** Longitudinal Study of Young People in England (LSYPE) **Study quality:** moderate	Exclusions and truancy at age 14 years were both associated with a significant risk of age 19 cannabis use. At age 14 truancy was associated with the highest risk (OR 2.80, 95% CI 2.34 to 3.36, p<0.001) when compared to exclusion (OR 2.08, 95% CI2.34 to 3.396, p<0.001).

4.8.14 Independent decision making

There is some evidence from a single poor-quality USA study of an association between Independent decision making (as a proxy for family functioning) and cannabis involvement in teenagers. However, the evidence supporting this risk factor is not conclusive. This study found that independent decision making was significantly associated with progression to regular cannabis use in boys (OR 1.30; 95% CI 1.05 to 1.60).

Risk factor: Independent decision making Evidence from a poor quality single study of a strong association between independent decision making and drug misuse	
Reference	**Summary statistics**
Van den Bree and Pickworth (2005) **Cohort name:** ADD Health Study **Study quality:** poor	Independent decision making was significantly associated with progression to regular cannabis use in boys (OR 1.30; 95% CI 1.05 to 1.60), but not girls. No association was found between independent decision making and any of the other four stages of cannabis involvement in boys or girls.

4.9 Interpersonal risk factors

Interpersonal risk factors - multiple studies

4.9.1 Childhood maltreatment

There is good quality evidence from seven studies (six good and one moderate quality) that childhood maltreatment is associated with an increased risk of later illicit drug use and dependence including amphetamine use and disorders or cannabis use or disorders. Two cohorts were from the USA (one moderate quality, one good quality), one from New Zealand (good quality), and one from Australia, from which four studies used data (all good quality).

Studies assessing childhood maltreatment as a risk factor for drug misuse differed in several ways which may make them less comparable. Childhood maltreatment measures included sexual abuse, physical abuse and neglect. The majority of studies (Boden et al., 2006; Hayatbakhsh et al., 2009a; Hayatbakhsh et al., 2009b; Hayatbakhsh et al., 2009c) reporting this exposure examined the association between childhood sexual abuse and illicit drug use outcomes. However, in one study (Snyder & Rubenstein 2014), incest – defined as sexual abuse by a parent or caregiver - was examined. This means that there could be added effects attributable to the relationship of the perpetrator of the abuse that could affect findings. The final three studies (Abajobir et al., 2017; good quality; Harrington et al., 2011; moderate quality) looked at the exposure of childhood maltreatment/childhood adversity. The outcome assessed also differed in some of the studies. Three studies (Hayatbakhsh et al., 2009b; Hayatbakhsh et al., 2009c; Abajobir et al., 2017) focused only on cannabis use and/or dependence, one study (Hayatbakhsh et al., 2009a) looked at

amphetamine use/disorder, and the other three studies (Boden et al., 2006; Snyder and Rubenstein, 2014; Harrington et al., 2011) looked at a variety of substance use outcomes.

Most studies found a statistically significant association between the exposures and outcomes assessed. However, Synder and Rubenstein 2014, only found a statistically significant association between incest and the likelihood of heavy-use class membership for females only. This included drinking, drugs and smoking and it was not possible to extrapolate drug use. Hayatbkhsh et al. (2009b), from a separate cohort, also found an increased risk of cannabis use among females with a history of childhood sexual abuse. Boden et al (2006) (good quality) failed to find a significant association between childhood sexual abuse (up to and including age 15 years) and any illicit drug use by age 25 years, but did find childhood sexual abuse significant for any illicit drug dependence.

One study (Abajobir et al, 2017) which looked at multiple types of childhood maltreatment, found all, except sexual abuse, were associated with cannabis dependence in the binary logistic regressions. This differed from the other papers from the same cohort, which looked specifically at childhood sexual abuse and cannabis use (Hayatbakhsh et al, 2009a; Hayatbakhsh et al., 2009b) in which statistically significant associations were found.

Risk factor: Childhood maltreatment The hypothesis that experiencing childhood maltreatment is a risk factor is supported by good quality evidence [A] (six good and one moderate quality)	
Reference	**Summary statistics**
Boden et al. (2006) **Cohort name:** The Christchurch Health and Development Study (CHDS) **Study quality:** good	Parameter estimates, standard errors and significance levels for proportional hazard models of any illicit drug use and dependence by age 25 years indicate a significant association between any illicit drug dependence and childhood sexual abuse (B 0.41 SE 0.10 p< 0.0001), but not any illicit drug use.
Snyder and Rubenstein (2014) **Cohort name:** ADD Health Study **Study quality:** good	After class membership was regressed on the individual-level, predictors in a multinomial logistic regression were used to examine the risk and protective factors (taken from wave 1). A history of incest nearly doubled the likelihood of heavy-use class membership versus the normative class for females only (females OR 1.83, 95% CI 1.14 to 2.94, males OR 1.78, 95% CI 0.90 to 3.56).
Hayatbakhsh et al. (2009) a **Cohort name:** The Mater-University of	Analyses indicated a step-wise increase in odds of amphetamine use and use disorders associated with childhood sexual abuse. Those who had experienced three or more episodes of abuse were two times more likely than those who reported no experience to have

Queensland Study of Pregnancy (MUSP) **Study quality:** good	ever used amphetamines (OR 2.00, 95% CI 1.1 to 3.5), and 2.9 times more likely to use amphetamine use disorders (OR 2.9, 95% CI 1.1 to 7.4). Those reporting childhood sexual abuse once or twice were not associated with amphetamine use (OR 1.4, 95% CI 0.9 to 2.3) or use disorders (OR0.9, 95% CI 0.3 to 2.9)
Hayatbakhsh et al. (2009) b **Cohort name:** The Mater-University of Queensland Study of Pregnancy (MUSP) **Study quality:** good	Any form of child sexual abuse was found to be statistically associated with cannabis use with (non-penetrative OR 2.3, 95% CI 1.7 to 3.1; penetrative OR 2.6, 95% CI 1.7 to 3.8) and without disorders (non-penetrative OR 1.7, 95% CI 1.3 to 2.2, penetrative OR 1.8, 95% CI 1.3 to 2.7) at age 21 years, using multivariate modelling.
Hayatbakhsh et al. (2009) c **Cohort name:** The Mater-University of Queensland Study of Pregnancy (MUSP) **Study quality:** good	Young adult men and women who reported experiencing childhood sexual abuse (CSA) had significantly higher rates of frequent use of cannabis in early adulthood, defined as use of cannabis at least ''every few days.'' In multivariate analyses, men who reported a history of CSA had an odds ratio (OR) of 2.1 (95% CI 1.1 to 3.9) for frequent use of cannabis at the age of 21 years. For women, there was an OR of 3.9 (95% CI 2.4 to 6.3). Family and individual factors measured earlier in the study did not confound these associations. The findings suggest that children experiencing CSA have a substantially greater risk of use of cannabis and, in particular, its frequent use in early adulthood.
Abajobir et al. (2017) **Cohort name:** Mater-University of Queensland study of Pregnancy (MUSP) **Study quality:** good	After hierarchically adjusting for all confounders/covariates, childhood maltreatment (AOR 2.77), emotional abuse (AOR 3.59) and neglect (AOR 3.48) were strongly associated with an early age of onset of cannabis abuse. All forms of childhood maltreatment, except sexual abuse, were associated with cannabis dependence in the binary logistic regressions. The statistical significance of any childhood maltreatment (AOR 2.47), physical abuse (AOR 2.81), emotional abuse (AOR 2.44) and neglect (AOR 2.68) remained stable after adjusting for all confounders/covariates and other forms of maltreatment in multivariable hierarchical logistic regressions. Any types of maltreatment (AOR 3.72), physical abuse (AOR 5.09) and neglect (AOR 4.92) were associated with an early age of onset of cannabis dependence, after adjusting for all covariates/confounders and overlapping forms of childhood maltreatment. Further fully adjusted analyses using weighted data to account for possible selection bias did not affect the findings of complete case analyses. For example, the AORs of cannabis abuse were 1.80 and 2.63 for any childhood maltreatment and neglect, respectively. Likewise, the association between any maltreatment, physical abuse, emotional abuse and neglect, and cannabis dependence was consistent.

	In terms of frequency, more substantiated events were associated with higher odds of cannabis use disorders. Finally, fully adjusted analyses using weighted data also revealed childhood maltreatment was also associated with age of onset of cannabis use in participants who ever smoked cannabis (i.e., n = 1,834). Additional analyses of the associations between childhood maltreatment and cannabis abuse and dependence after controlling for those participants who reported cannabis abuse (n = 17) and dependence (n = 15) outcomes before 14 years of age showed similar findings in all models (data not shown). The gender–any childhood maltreatment interaction term was significant (interaction term = 0.11, $p < 0.0001$). However, the inclusion of the interaction term in the respective fully adjusted models controlling for the main effect of gender did not change the size and direction of the association between childhood maltreatment and cannabis use disorders. In unadjusted and adjusted multinomial models, childhood maltreatment was also associated with cannabis use with and/or without any DSM-disorder. All forms of childhood maltreatment were associated with increased odds of cannabis use without any disorder in unadjusted multinomial logistic regression models. After adjusting for all confounders/covariates, childhood maltreatment (AOR 1.78) and emotional abuse (AOR 2.15) were strongly associated with cannabis use without any disorder.
Harrington et al. (2011) **Cohort name:** National Epidemiologic Survey of Alcohol and Related Conditions (NESARC) **Study quality:** moderate	Participants who reported being physically abused by a parent or guardian were almost three times more likely to report wave 2 drug use than those who did not (AOR 2.74, 95% CI 1.93 to 3.88). Those who reported being physically abused by anyone else were just over two times more likely to report wave 2 drug use (AOR 2.05, 95% CI 1.49 to 2.82). Participants reporting sexual assault were two and a half times more likely to report wave 2 drug use than those who did not (AOR 2.55, 95% CI 2.00 to 3.26). Similarly, those neglected by a parent or guardian were 2.25 times more likely to report wave 2 drug use (AOR 2.25, 95% CI 1.55 to 3.25).

4.9.2 Parental drinking

There is moderate evidence from five studies that parental alcohol consumption is associated with an increased risk of illicit drug use in later life. Three cohorts (one each of poor, moderate and good quality) were conducted in the USA and one each in UK and Australia. All five studies were from separate cohorts looking at parental drinking and participant substance use found an association. Of the three studies reporting odds ratios (West et al., 2004; Snyder and Rubenstein, 2014; Harrington et al., 2011), associations ranged from 1.42 to 2.11. However, it is difficult to

directly compare them as each used different measures to assess parental drinking. In addition, substance use outcomes varied and the age at which data was collected varied. The only good quality study from USA (Snyder and Rubenstein, 2014) found an association between parental alcohol use and substance use, however substance use included alcohol, tobacco and illicit drug use combined. In addition, alcohol consumption was assessed only in mothers in one study (Hayatbakhsh et al., 2013), while in another (Harrington et al., 2011) this variable was assessed in first-degree relatives – which would include siblings as well as parents.

Risk factor: Parental drinking The hypothesis that parental drinking is a risk factor is supported by moderate quality evidence [B] (one good, three moderate and one poor quality)	
Reference	**Summary statistics**
Pears et al. (2007) **Cohort name:** Three Generational Study (3GS) and OYS **Study quality:** poor	Analyses aimed to investigate the relationships between parenting and substance use of children and found a statistically significant correlation (0.20, p<0.01) between G1 alcohol use and G2 illicit drug use.
West et al. (2004) **Cohort name:** West of Scotland study **Study quality:** moderate	This study found respondents whose parents reported drinking at baseline were at higher risk of illicit drug use at age 15 years (OR 1.42, p<0.05).
Snyder and Rubenstein (2014) **Cohort name:** Add Health Study **Study quality:** good	Parental drinking increased the risk of substance use, but the risk associated was different for men and women. Having a parent who reported drinking was most strongly associated with heavy-use membership for females (OR 2.11, 95% CI 1.53 to 2.90, p<0.001), then moderate-use class membership in males (OR 1.84, 95% CI 1.35 to 2.50, p<0.001), and moderate-use class membership for females (OR 1.48, 95% CI 1.14 to 1.92, p < 0.001) and males (OR 1.84, 95% CI 1.35 to 2.50, p<0.001) respectively.
Hayatbakhsh et al. (2013) **Cohort name:** The Mater-University of Queensland Study of Pregnancy (MUSP) **Study quality:** moderate	Multivariable Cox proportional hazards analyses were conducted to examine the independent association between early childhood factors and age of initiation to cannabis use. Participants who reported initiation to cannabis use before the age of 15 years were more likely to have mothers who reported higher rates of alcohol consumption (>1 glass/day HR 1.69, 95% CI 1.35 to 2.11 compared to 1 glass/day HR 1.44, 95% CI 1.25 to 1.66).
Harrington et al. (2011) **Cohort name:** National Epidemiologic Survey of	Participants reporting a first-degree relative with alcohol problem were more at risk of substance/drug use (OR 1.49, 95% CI 1.27 to 1.74, p<0.001).

Alcohol and Related Conditions (NESARC) **Study quality:** moderate	

4.9.3 Parental illicit drug use

There is moderate evidence from five of the six studies (three good, two moderate and one poor quality) that parental illicit drug use is associated with an increased risk of illicit drug use and drug dependence in offspring. However, illicit drug abuse and dependency in the parent and cannabis use frequency in the offspring as a risk factor is less clear.

The six studies used data from five different cohorts originating in New Zealand (Boden et al., 2006; Fergusson et al., 2008; both good quality), Germany (von Sydow et al., 2002; good quality), USA (Harrington et al., 2011; moderate quality; Pears et al., 2007; poor quality) and Sweden (Gauffin et al., 2013; moderate quality). All measured parental illicit drug or substance use, and some combine alcohol and illicit drugs into one measure, but few identified specifically which illicit drugs were included. Harrington et al. (2011) assessed illicit drug use in first-degree relatives – which would include siblings as well as parents.

Of the good quality studies, both studies from the Christchurch Health and Development Study found a significant association with both cannabis and other illicit drug use and abuse at age 15 among those reporting parental history of illicit drug use at age 11 years (Boden et al., 2006; Fergusson et al., 2008). However, in contrast, the German cohort (von Sydow et al., 2002) identified participants reporting parental substance use problems at age 14 years, found a reduced risk of cannabis use frequency, but no association between parental illicit drug use problems and use, abuse or dependency.

Risk factor: Parental illicit drug use The hypothesis that parental illicit drug use is a risk factor is supported by moderate quality evidence [B] (three good, two moderate and one poor quality)	
Reference	**Summary statistics**
Boden et al. (2006) **Cohort name:** The Christchurch Health and Development Study (CHDS) **Study quality:** good	Proportional hazards regression models showed parental history of illicit drug use was significantly associated with cannabis and other illicit drug use (B 0.45 SE 0.13 $p<0.001$) and dependence (B 0.42, SE 0.21 $p<0.05$) by age 25 years.

Fergusson et al. (2008) **Cohort name:** The Christchurch Health and Development Study (CHDS) **Study quality:** good	Analyses using repeated measures logistic regression models suggested that parental illicit drug use was a statistically significant predictor for illicit drug use and dependence ($p < 0.001$). Multivariate regression showed a significant association remained with illicit drug use ($p < 0.05$) when the model included fixed time covariates, but was no longer significant when the model included time-dynamic covariates, and lagged illicit drug use. This means parental illicit drug use is a predictor of illicit drug use, but it is not mediated by other factors.
von, Sydow et al. (2002) **Cohort name:** Early developmental stages of psychopathology study (EDSP) **Study quality:** good	Multiple logistic regression found a reduced risk of cannabis use frequency at t1/t2 in former non-users (n= 404) among those reporting parental illicit drug use problems at baseline (IRR 0.1, 95% CI 0.00 to 0.04, $p < 0.05$). No association was found between parental illicit drug use problems and use, abuse or dependency.
Pears et al. (2007) **Cohort name:** Three Generational Study (3GS) and OYS **Study quality:** poor	Analyses aimed to investigate the relationships between parenting and substance use, and how generational alcohol and illicit drug use may be mediated by inhibitory control. In terms of direct associations between G1's behaviours and the same behaviours in G2, there was a statistically significant positive. association between G1's illicit drug use and that of G2 in late adolescence (correlation 0.35, $p < 0.01$).
Gauffin et al. (2013) **Cohort name:** no name **Study quality:** moderate	Cox regression models identified a similar association between maternal and paternal substance use and at least one indication of illicit drug abuse, with paternal substance use associated with a slightly higher risk; mother substance use (HR 1.50, 95% CI 1.45 to 1.45), father substance use (HR 1.57, 95% CI 1.53 to 1.61).
Harrington et al. (2011) **Cohort name:** National Epidemiologic Survey of Alcohol and Related Conditions (NESARC) **Study quality:** moderate	Incident drug use was associated with having a first-degree relative with a drug problem, when compared with the group of people who did not have a first-degree relative with these problems (AOR 1.40, 95% CI 1.12 to 1.76, $p < 0.01$).

4.9.4 Parental mental state

There is evidence from two moderate quality studies that having a parent with a mental disorder during the early stages of a child's development increases both the risk of initiating illicit drug use at an earlier age and developing illicit drug problems later in life. This association was found to be greater when the parent with the mental health problem is the mother (Hayatbakhsh et al., 2013; Gauffin et al., 2013).

Although each study used different exposure and outcome measures, they both used hazard ratios (95% CI) to report the risk of substance use.

Interestingly, they found a similar risk for maternal mental state of between HR 1.36 (95% CI 1.13 to 1.63; Hayatbakhsh et al., 2013) and HR 1.38 (95% CI 1.34 to 1.42; Gauffin et al., 2013) associated with parental mental state and risk of illicit drug misuse in offspring. Paternal mental state was only reported in one study (Gaufin et al., 2013), but this also reported a similar risk (HR 1.20, 95% CI 1.16 to 1.23).

The Australian study (Hayatbakhsh et al., 2013) measured exposures (maternal anxiety and depression) at age five years by using a validated questionnaire completed by the mother. In comparison, the Swedish study (Gauffin et al., 2013) utilised unspecified registers to acquire hospital information on parental (mother and father separately) mental problem admissions including self-harm. The Australian cohort looked at cannabis use and age of first use at age 21 years, but the much larger Swedish cohort looked at indications of illicit drug abuse by utilising data on hospital admissions, death and criminality associated with illicit drug abuse.

Risk factor: Parental mental state The hypothesis that parental mental state is a risk factor is supported by moderate quality evidence [B] (two moderate quality)	
Reference	**Summary statistics**
Hayatbakhsh et al. (2013) **Cohort name:** The Mater-University of Queensland Study of Pregnancy (MUSP) **Study quality:** moderate	Multivariable Cox proportional hazards analyses were conducted to examine the independent association between early childhood factors and age of initiation to cannabis use. These found five year old children whose mothers were categorised as depressed were significantly at greater risk of earlier initiation to cannabis use (HR 1.36, 95% CI 1.13 to 1.63).
Gauffin et al. (2013) **Cohort name:** no name **Study quality:** moderate	Cox regression models identified participants with a parent identified as having mental health problems was at greater risk of illicit drug use than those whose parents did not identify as having mental health problems. Those with mothers with mental health problems appeared to be at greater risk (HR 1.38, 95% CI 1.34 to 1.42) than fathers with mental health problems (HR 1.20, 95% CI 1.16 to 1.23).

4.9.5 Parental cigarette smoking

There is moderate evidence from four studies (two good and two moderate quality) of an association between parental cigarette smoking and the development of illicit drug use and drug use disorders in later life. Three studies from the same cohort were conducted in Australia and one moderate quality study was conducted in UK investigated associations between parental smoking and substance use, and most found an association.

In three of the studies, cigarette smoking was assessed only in mothers. Two papers from the same cohort (Hayatbakhsh et al., 2009b; Hayatbakhsh et al., 2013) examining cannabis use, identified a small association between maternal smoking at age 14 years and cannabis use at age 21 years. The last paper from this cohort (Hayatbakhsh et al., 2009a) looked at associations between maternal smoking and risk associated with amphetamine use at age 21 years. Although authors reported a significant risk associated with amphetamine use disorders (OR 2.2 (95% CI 1.0 to 5.0, p<0.05), the lower confidence interval lies on the line of no effect. Finally, the UK study (West et al., 2004) looked for associations between parental smoking behaviour and illicit drug use and identified parental smoking at age 13 years was significantly associated with higher risk of illicit drug use at age 15 years (OR 1.46 (p<0.001).

The UK study (West et al., 2004) relied on respondents to report information on paternal smoking behaviour, whereas the Australian cohort asked mothers directly in a separate questionnaire to those participating.

Risk factor: Parental cigarette smoking The hypothesis that parental cigarette smoking is a risk factor is supported by moderate quality evidence [B] (two good and two moderate quality)	
Reference	**Summary statistics**
West et al. (2004) **Cohort name:** WOS West of Scotland study **Study quality:** moderate	This study found respondents who reported parental smoking at age 13 years were at higher risk of illicit drug use at age 15 years (OR 1.46, p<0.001).
Hayatbakhsh et al. (2013) **Cohort name:** The Mater-University of Queensland Study of Pregnancy (MUSP) **Study quality:** moderate	Multivariable Cox proportional hazards analyses were conducted to examine the independent association between early childhood factors and age of initiation to cannabis use. These found five-year-old children whose mothers smoked were independently and significantly associated with initiation to cannabis use at an earlier age. This risk increased, the more the mother smoked (1–19 cig per day HR1.18, 95% CI 1.03 to 1.35; 20+ cig per day HR 1.26, 95% CI 1.09 to 1.45).
Hayatbakhsh et al. (2009) a **Cohort name:** The Mater-University of Queensland Study of Pregnancy (MUSP) **Study quality:** good	Multivariate analyses failed to find an association between maternal smoking at age five years and the risk of amphetamine use at age 21 years. Maternal smoking did reach significance levels for amphetamine use disorders (OR 2.2, 95% CI 1.0 to 5.0, p<0.05), but the lower confidence interval lies on the line of no effect.
Hayatbakhsh et al. (2009) b	Multivariate models identified a significant association between maternal smoking at age 14 years and lifetime cannabis use at age 21 years. Using non-smoking

Cohort name: The Mater-University of Queensland Study of Pregnancy (MUSP) **Study quality:** good	mothers as reference, participants with smoking mothers were around 50% more likely to have used cannabis with (OR 1.5, 95% CI 1.1 to 1.9, p<0.01) or without disorders (OR 1.5, 95% CI 1.2 to 1.8, p<0.001) by age 21 years.

4.9.6 Family composition

There is some evidence from four studies (three moderate and one poor quality) of an association between family composition/structure (living in a single-parent household or step-family) and illicit drug use/dependence. However, the evidence supporting this risk factor is not conclusive. Two studies were from the UK (both moderate quality), and one each from USA (poor quality) and Sweden (moderate quality). All four studies assessed family structure, specifically living in a single-parent household or step-family. Outcome measures varied and included cannabis use (one study), illicit drug use (two studies), and prescription drug misuse (one study). Three studies (Hale & Viner 2016; West et al., 2004; Gauffin et al., 2013; all moderate quality) reported significant associations between family structure and drug use, while one study (Harrell & Broman 2009; poor quality) did not find an association between being in a single-parent family or step-family and prescription drug abuse. No data was reported in the study not showing an association.

Risk factor: family composition There is some evidence supporting the hypothesis that being in a single-parent family is a risk factor, but it is not conclusive [C] (three moderate studies found an association and one poor quality found no association)	
Reference	**Summary statistics**
Hale and Viner (2016) **Cohort name:** Longitudinal Study of Young People in England (LSYPE) **Study quality:** moderate	Living in a single-parent household at age 14 was significantly associated with drug use at age 19 (OR 1.31; 95% CI 1.10 to 1.57; p 0.003).
West et al. (2004) **Cohort name:** West of Scotland study **Study quality:** moderate	An association was found between family structure and ever use of illicit drugs. Being in a step-family was significantly associated with illicit drug use at S2 (OR 1.66, p<0.01) and S4 (OR 1.55, p<0.01). Being in a lone parent family was significantly associated with illicit drug use at S4 only (OR 1.56, p<0.01).
Harrell and Broman (2009)	Being in a single-parent family or step-family at wave 1 was not significant for prescription drug abuse at wave 3 (no statistical details reported).

Cohort name: ADD Health Study **Study quality:** poor	
Gauffin et al. (2013) **Cohort name:** no name **Study quality:** moderate	Being in a single-parent household was significantly associated with illicit drug abuse (HR 1.54; 95% CI 1.50 to 1.57).

4.9.7 Parental marital circumstances

There is some evidence from five studies (three good and two moderate quality) of an association between parental marital circumstance (divorce/separation), and the subsequent use and abuse of illicit drugs. However, the evidence supporting this risk factor is inconsistent and therefore inconclusive.

Studies using data from the MUSP cohort (Hayatbakhsh et al., 2013; 2006; 2009a,b) used the Dyadic Adjustment Scale (DAS) to assess the quality of (at age 5 years) or changes in, maternal marital status (ages 7 to 14 years). The single good quality study using data from The Victorian Adolescent Health Cohort Study (Coffey et al., 2003) looked at parental divorce or separation, but no information was reported on how this was collected. Outcomes also varied from age of cannabis use onset, cannabis abuse and dependence, ever use of cannabis and amphetamine use and use disorder.

Of the two studies reporting cannabis use, one (Hayatbakhsh et al., 2013; moderate quality) found five-year-old children whose mothers were categorised as having poor adjustment in their marital relationship (HR 1.17, 95% CI 1.02 to 1.35) were independently and significantly associated with initiation to cannabis use at an earlier age. However, being un-partnered was not associated. The good quality (Hayatbakhsh et al., 2009b) study found no association between changes in marital status and cannabis use.

Of the three studies reporting cannabis dependence, those who grew up in step-parent families (Hayatbakhsh et al., 2006; moderate quality) or had changes in marital status between the ages of 5 and 14 years (Hayatbakhsh et al., 2009a; good quality) appeared to be more likely to develop cannabis use disorders. However, another good quality study (Coffey et al., 2003) did not find an association between divorce/separation and cannabis dependence.

One good quality study (Hayatbakhsh et al., 2009a) looked at changes in marital status and the risk of amphetamine use and use disorder. They found those who had experienced changes in maternal marital status between the age of 5 and 14 years were more likely to use amphetamines (OR 1.5; 95% CI: 1.1 to 1.9 for one or two changes in maternal marital status) and develop an amphetamine use disorder (OR 2.6; 95% CI: 1.1 to 6.2 for three or more changes).

Risk factor: Parental marital circumstances The evidence is inconsistent and it is not possible to draw a conclusion [D] (three good and two moderate quality with inconsistent results across studies)	
Reference	**Summary statistics**
Hayatbakhsh et al. (2013) **Cohort name:** The Mater-University of Queensland Study of Pregnancy (MUSP) **Study quality:** moderate	In the final multivariate model five-year-old children whose mothers were categorised as having poor adjustment in their marital relationship (HR 1.17, 95% CI 1.02 to 1.35) were independently and significantly associated with initiation to cannabis use at an earlier age. Being unpartnered was not associated with initiation to cannabis use.
Hayatbakhsh et al. (2009) a **Cohort name:** The Mater-University of Queensland Study of Pregnancy (MUSP) **Study quality:** good	Individuals who experienced changes in maternal marital status between the age of 5 and 14 years were more likely to use amphetamines (OR 1.5; 95% CI 1.1 to 1.9 for one or two changes in maternal marital status) or to develop an amphetamine use disorder (AUD) (OR 2.6; 95% CI 1.1 to 6.2 for three or more changes). A marginal association was observed between the mother living without a partner at 14 years and subsequent use of amphetamines but not an AUD.
Hayatbakhsh et al. (2006) **Cohort name:** The Mater-University of Queensland Study of Pregnancy (MUSP) **Study quality:** moderate	Marital circumstances of the mother when child was aged 14 years predicted risk of cannabis use disorders in their offspring. After adjustment for potential confounding factors, adolescents who grew up in step-father families were more likely to have cannabis use disorders in early adulthood and a moderate association was found for those children who experienced maternal marital disagreement (OR 1.7; 95% CI 1.0 to 2.9). However, the lower confidence interval lies at 1.0.
Hayatbakhsh et al. (2009) b **Cohort name:** The Mater-University of Queensland Study of Pregnancy (MUSP) **Study quality:** good	Children whose mothers had changed their marital status between 5 and 14 years of child's age were more likely to develop a CUD. The risk increased with increasing number of marital status changes (one or two changes OR 1.5, 95% CI 1.2 to 2.0, p<0.01; three or more changes OR 2.1, 95% CI 1.2 to 3.8, p <0.05). No association was found between changes in marital status and cannabis use (one or two changes OR 1.2, 95% CI 0.9 to 1.5; three or more changes OR 1.5, 95% CI 0.8 to 2.5).
Coffey et al. (2003)	No association was found between parental divorce/separation and cannabis dependence (OR 1.0, 95% CI 0.63 to 1.72, p 0.87).

Cohort name: The Victorian Adolescent Health Cohort Study **Study quality:** good	

4.9.8 Friendship/peers

There is some evidence from three studies (two moderate and one poor) from USA and UK of an association between relationships with friends/ peers and the subsequent use and abuse of illicit drugs. However, the evidence supporting this risk factor is inconsistent and therefore inconclusive.

The studies used a variety of different measures associated with friendships and peers, such as peer conflict (Aseltine et al., 2000), peer support for misbehaviour (Bryant et al., 2003), and having friends over often/going out with friends often (Hale and Viner, 2016), with some finding an association and some not. Therefore, it was not possible to draw a conclusion on the risks associated with friends and substance use.

The UK cohort (Hale and Viner, 2016; moderate quality) measured associations between how often participants had friends over, or went out with friends at age 14 years and cannabis use at age 19 years. They found a significant association between both measures. A poor quality cohort from USA (Aseltine et al. 2000) looked at peer conflict and past year cannabis use but found no association. Finally, a moderate quality study from USA (Bryant et al. 2003) looked at the relationship between peer support for school misbehaviour and past 30-day cannabis use. No relationship was found in those reporting peer support for school misbehaviour at age 14 years.

Risk factor: Friendship/peers The evidence is inconsistent and it is not possible to draw a conclusion [D] (two moderate and one poor quality with inconsistent results across studies)	
Reference	**Summary statistics**
Hale and Viner (2016) **Cohort name:** Longitudinal Study of Young People in England (LSYPE) **Study quality:** moderate	Logistic regression models found participants who had friends over often at age 14 years had an increased risk of drug use at age 19 years (OR 1.37, 95% CI 1.16 to 1.60, p<0.001) than those who did not. Analyses also found an increased risk of drug use at age 19 years in participants who reported being out with friends often at age 14 years (OR 1.53, 95% CI 1.33 to 1.75, p<0.001).
Aseltine et al. (2000)	Analysis using unstandardised structural coefficients to capture relationships and interactions between various

Cohort name: no name **Study quality:** poor	independent variables found no significant association, direct or indirect, between peer conflict at T2 and cannabis use at T3.
Bryant et al. (2003) **Cohort name:** Monitoring the Future **Study quality:** moderate	No significant association was found for peer support for school misbehaviour.

4.9.9 Relationship with parents

There is some evidence from nine studies (four moderate and five poor quality) of an association between a child's relationship with parents and the use of illicit drugs. However, the evidence supporting this risk factor is inconsistent and therefore inconclusive. The nine studies contributing to this risk factor analysed data from eight different cohorts. These took place in UK (two moderate and one poor quality), USA (one moderate and four poor quality) and New Zealand (one moderate quality).

Various self-reported measures were used including: parental communication/getting along with parents; parental discipline; parental care; discussing school grades and personal problems; closeness of maternal relationship; family conflict; parental attachment; parental school help; and perceived family support. There are some differences between these exposure measures even though they have been grouped together as being relevant to an individual's relationship with their parents. This needs to be considered when applying the findings. The age when exposure was measured ranged between 14 and 15 years. Substance use was described at cannabis (six studies), illicit drug use (two studies) and prescription drug use (one study).

Three sources did not find an association between relationship with parents and substance use (Pears et al., 2007; Harrell and Broman; Bryant et al., 2003). Of the remaining six sources (three moderate and three poor quality) there was a general trend that poor relationships with parents were associated with an increased risk of substance use, and good parental relationships were associated with less risk.

Risk factor: Relationship with parents There is inconsistent and it is not possible to draw a conclusion [D] (four moderate and five poor quality with inconsistent results across studies)	
Reference	**Summary statistics**
Hale and Viner (2016)	Not getting on very well with parents at age 14 years was associated with age 19 years cannabis use (OR 1.21, 95% CI 1.03 to 1.41, p 0.020). Likewise, low

Cohort name: Longitudinal Study of Young People in England (LSYPE) **Study quality:** moderate	parental communication at age 14 years was also associated with increased risk of age 19 cannabis use (OR 1.41, 95% CI 1.21 to 1.63, p<0.001).
Pears et al. (2007) **Cohort name:** Three Generational Study (3GS) and OYS **Study quality:** poor	Analyses aimed to investigate the relationships between parenting and substance use, and how generational alcohol and illicit drug use may be mediated by inhibitory control. There was a significant positive association between G1's poor discipline and G2's illicit drug use in the bivariate correlations (0.17, p <0 .05). However, this association was no longer significant in the multivariate model including G2's inhibitory control. Thus, the path between G1's parenting and G2's illicit drug use was completely mediated by G2's inhibitory control (standardised beta 0.10, p<0.05 [Z = 2.31]).
West et al. (2004) **Cohort name:** West of Scotland study **Study quality:** moderate	Results indicated good parental care (OR 0.82, p<0.001) was protective of illicit drug use at age 15 years, but not parental control (OR 1.01).
Van den Bree and Pickworth (2005) **Cohort name:** ADD Health Study **Study quality:** poor	Activities with mother was significantly associated with a failure to discontinue regular cannabis in both boys and girls (OR 1.17, 95% CI 1.02 to 1.34). Relations with mother, activities with father and family relations were all found to have no association. In addition, initiation of regular use, progression to regular use and failure to discontinue experimental use were not associated with either of the various exposures in this study.
Harrell and Broman (2009) **Cohort name:** ADD Health Study **Study quality:** poor	No significant association was found between parental relationship (measured as maternal warmth) and prescription drug misuse at wave 3.
Aseltine et al. (2000) **Cohort name:** no name **Study quality:** poor	Family conflict was significantly associated with cannabis use (B 0.6, p <0.05, *B* 0.10)
McGee et al. (2000) **Cohort name:** The Dunedin Multidisciplinary Health and Development Study **Study quality:** moderate	Low parental attachment at age 15 years was associated with an increased risk of cannabis use from ages 18 years (OR 1.64, 95% CI 1.18 to 2.28), but not age 21 years.
Bryant et al. (2003) **Cohort name:** Monitoring the Future **Study quality:** moderate	Parental school help at age 14 years was not associated with age 20 years cannabis use.

Windle and Wiesner (2004) **Cohort name:** Lives Across Time **Study quality:** poor	Participants in the chronic trajectory group had less perceived family support than those in the abstainers trajectory group. High perceived family support was significantly associated with reduced risk of cannabis use.

4.9.10 Parental education

There is moderate quality evidence from four studies (one good and three moderate quality) that parental education is not associated with the risk of illicit drug use. The single good quality paper (Humensky and Humensky, 2010) identified participants of parents with a college education experienced slightly higher odds of cannabis (AOR 1.265, 95% CI 1.038 to 1.541) and cocaine use (AOR 1.614, 95% CI 1.088 to 2.395) in early adulthood. However, the remaining studies failed to find an association.

Risk factor: parental education The hypothesis that parental education is not a risk factor is supported by moderate quality evidence [G] (one good quality study found an association and three moderate quality studies found no association)	
Reference	**Summary statistics**
Hale and Viner (2016) **Cohort name:** Longitudinal Study of Young People in England (LSYPE) **Study quality:** Moderate	Low parental education was not associated with age 19 drug use in the last four weeks (OR 0.98, 95% CI 0.81 to 1.20, p 0.862).
Humensky and Humensky (2010) **Cohort name:** ADD Health Study **Study quality:** good	Higher parental education is associated with higher rates of cannabis and cocaine use in early adulthood. For an individual with a college-educated parent, the odds of engaging in cannabis use in early adulthood are 1.265 times as large as the odds for an individual with a high school-educated parent (AOR 1.265, 95% CI 1.038 to 1.541). The odds of engaging in cocaine use in early adulthood are 1.614 times as large for an individual with a college-educated parent versus a high school-educated parent (AOR 1.614, 95% CI 1.088 to 2.395). No statistically significant effects are found for crystal methamphetamine and other drug use.
Bryant et al. (2003) **Cohort name:** Monitoring the Future **Study quality:** moderate	No association was found between parental education level and subsequent cannabis use in the last 30 days.

Kaynak et al. (2013) **Cohort name:** College Life Study **Study quality:** moderate	No association was found between mother's educational level and cannabis dependence during first year at college (OR 0.98, 95% CI 0.66 to 1.46, p 0.93).

4.9.11 Parental monitoring

Two of three studies, all moderate quality, found no association between parental monitoring (parental knowledge of child's whereabouts) and the risk of illicit drug use. The one large UK study (Hale and Viner, 2016) that did find an association asked participants about how often parents knew their whereabouts while they were out in the evening. They used a dichotomous scale of 'always' or 'not always'.

Of the two studies finding no association, one (Kaltiala-Heino et al., 2011) also asked participants about parental knowledge of participants and their friends' whereabouts, but this was a continuous scale of five possible answers. The final study looked at several different aspects including participant's perception of parental rule-setting, supervision, consequences, and monitoring during high school (Kaynak et al., 2013).

All cohorts identified participants from school settings from Finland, USA and UK.

Risk factor: Parental monitoring The hypothesis that parental monitoring (parental knowledge of child's whereabouts) is not a risk factor is supported by moderate quality evidence [G] (two moderate quality studies found no association and one moderate quality study found an associaton)	
Reference	**Summary statistics**
Hale and Viner (2016) **Cohort name:** Longitudinal Study of Young People in England (LSYPE) **Study quality:** moderate	Parents not always knowing where their child is in the evenings was found to be a significant risk factor for cannabis use (OR 1.93, 95% CI 1.68 to 2.21, p <0.001).
Kaynak et al. (2013) **Cohort name:** College Life Study **Study quality:** moderate	In bivariate analysis low parental monitoring were significantly related to cannabis dependence, but multivariate analyses indicated that higher levels of parental monitoring had no effect on reducing risk for cannabis dependence during the first year of college.
Kaltiala-Heino et al. (2011)	No statistically significant association was found between parental knowledge and subsequent illegal

Cohort name: Adolescent Mental Health Cohort Study (AMHC) **Study quality:** moderate	drug use at age 17 years (OR 0.8, 95% CI 0.6 to 1.0 in boys, and OR 0.8, 95% CI 0.6 to 0.9 in girls).

Interpersonal risk factors - single studies

4.9.12 Late bedtime

There is good quality evidence from a single USA study (McGlinchey et al., 2015) that late bedtimes in adolescence is associated with an increased risk of illicit drug use in young adulthood. The study cohort were from the USA and the study assessed the association between self-reported late bedtime (defined as 1am) and illicit drug use (defined as ever use of cannabis, cocaine, inhalants, heroin or other illegal drugs). The authors assessed the association at wave 2 of follow-up (mean age of participants 16yrs) and found that late bedtime at wave 2 predicted illegal drug use (OR 1.61, 95% CI 1.36 to 1.91, p <0.001). The authors noted that all of the data used in establishing this association were derived from self-reports, thus may be prone to response bias.

Risk factor: Late bedtime There is evidence from a good quality single study of a strong association between late bedtime and drug misuse	
Reference	**Summary statistics**
McGlinchey and Harvey (2015) **Cohort name:** ADD Health Study **Study quality:** good	Controlling for demographic factors and the matching risk behaviour/health outcome at wave 2 as covariates for the model, late bedtime at wave 2 predicted illicit drug use (OR 1.61, 95% CI 1.36 to 1.91, p <0.001). The dose effect of late bedtime at wave 2 increased the odds of engaging in illicit drug use at wave 3 (no statistics or tables showing these results).

4.9.13 Out of home placement/living in care

There is moderate evidence from a single study (Cote et al., 2018) that out-of-home placement (living in care) in early childhood is associated with an increased risk of substance-related disorders in young adulthood. The study cohort was from Finland and assessed the association between being placed outside of the home between the ages of two and six years and substance-related disorders at age 18 to 25 years. The study was a matched case-control study, matching participants placed in care with

those who were not. It found that those who had been placed as children had greater odds than never-placed controls of substance-related disorders (OR 2.10, 95% CI 1.27 to 3.48). The definition of an out-of-home placement in the study was broad, and included voluntary care agreements as well as placements in residential, foster and community or kinship care. Sub analyses were not made which looked at different types of out-of-home care. However, the substance-related disorders studied in this study, included alcohol and tobacco-use disorders which are both beyond the scope of this review.

Risk factor: Out of home placement/living in care Evidence from a moderate quality single study of a strong association between being placed out of home as a child and drug misuse	
Reference	**Summary statistics**
Cote et al. (2018) **Cohort name:** 1987 Finnish Birth Cohort **Study quality:** moderate	At ages 18 to 25 years, those who had been placed as children had greater odds than never-placed controls of substance-related disorders (odds ratio 2.10, 95% CI 1.27 to 3.48). Preschool children who were placed out-of-home were at risk of adverse outcomes as adults, even accounting for their initial circumstances. Multivariate logistic regression analysis confirmed those who had been placed as children had greater odds than never-placed controls of substance-related disorders (OR 2.19, 95% CI 1.60 to 3.01).

4.9.14 Parental criminality

A single Swedish cohort (Gauffin et al., 2013) used national registers to identify those exhibiting at least one indication of drug abuse and found participants who reported having a mother or father with a criminal conviction at age 16 years were slightly more at risk than those who did not. Those with a father who had a criminal conviction were slightly more at risk than those who had a mother with a criminal conviction. Whether this was an independent risk factor, or a risk factor only where there was also other indicators of parental psychosocial problems (substance abuse and/or mental health problems), was unclear. It should also be noted that using national registers to identify outcomes may underestimate the true risk associated with parental criminality and substance use. This is because data only included crime convictions that resulted in a sentence of probation, prison or forensic psychiatric care (as opposed to fines, community service or a suspended sentence).

Risk factor: Parental criminality Evidence from a moderate quality single study of a strong association between a parent associated with criminality and drug misuse	
Reference	**Summary statistics**
Gauffin et al. (2013) **Cohort name:** no name **Study quality:** moderate	Cox regression models identified those reporting fathers with a criminal conviction at age 16 years were slightly more at risk (HR 1.49, 95% CI 1.45 to 1.54) of at least one indication of illicit drug abuse in adulthood, compared with those reporting mothers with criminal convictions at age 16 years (HR (1.37, 95% CI 1.30 to 1.43) and those who did not report parents having a criminal conviction (reference).

4.9.15 Structural stigma

LGBTQ populations have been shown to be at greater risk for substance use and substance use disorders than heterosexuals. There is some evidence from a single, poor quality USA study of an association between state-level structural stigma against sexual minorities and illicit drug use in this group (Hatzenbuehler et al., 2015). However, the evidence supporting this risk factor is not conclusive. This study sought to determine whether sexual orientation disparities in illicit drug use are potentiated in states that are characterised by high levels of stigma surrounding sexual minorities. The results showed a significant association between structural stigma and cannabis use in both men (p 0.002) and women (p<0.001). Structural stigma was significantly associated with illicit drug use in women (p 0.004).

Risk factor: Structural stigma Evidence from a poor quality single study of a strong association between structural stigma and drug misuse	
Reference	**Summary statistics**
Hatzenbuehler et al. (2015) **Cohort name:** Growing up today study **Study quality:** poor	Structural stigma was significantly associated with cannabis use in both men (p 0.002) and women (p <0.001). Structural stigma was significantly associated with illicit drug use in women (p 0.004).

4.9.16 Intimate partner violence

There is moderate quality evidence from a single USA study (Testa et al., 2003) demonstrating no association between experiencing intimate partner

violence and the risk of illicit drug use (cannabis, cocaine, opiates, psychedelics, club drugs, barbiturates, amphetamines, inhalants, and non-prescribed prescription drugs). The sample was women aged 18 to 30 years, therefore findings may not be generalisable to older women or men.

Risk factor: Intimate partner violence Evidence from a moderate quality single study demonstrating no association between experiencing intimate partner violence (women aged 18 to 30 years) and drug misuse	
Reference	**Summary statistics**
Testa et al. (2003) **Cohort name:** Women 2000 **Study quality:** moderate	Wave 1 violence only marginally contributed to prediction of wave 2 drug use ΔR2 0.005 p 0.07. Authors examined if women who did not use drugs at wave 1 were more likely to initiate drugs at wave 2 if they experienced partner violence. No differential initiation of drug use at wave 2 was found according to whether the woman had experienced wave 1 minor or severe violence [both X2(1) <1]. Authors used frequency of drug use at wave 2, rather than drug use level as the dependent variable as they believed frequency of drug use would be more sensitive to change as a result of experiencing violence.

4.9.17 Relationship satisfaction

A single moderate quality study from USA (Testa et al., 2003), demonstrated no association between relationship satisfaction and the risk of illicit drug use. The sample was women aged 18 to 30 years, therefore findings may not be generalisable to older women or men.

Risk factor: Relationship satisfaction Evidence from a moderate quality single study demonstrating no association between relationship satisfaction and drug misuse	
Reference	**Summary statistics**
Testa et al. (2003) **Cohort name:** Women 2000 **Study quality:** moderate	Authors looked at relationship satisfaction and found a non-significant negative path from wave 1 relationship satisfaction to subsequent frequency of drug use (r -0.03) 12 months later.

4.10 Accumulating risk factors

Research shows that risk factors do not occur in isolation, but tend to cluster in the most vulnerable youth, thereby increasing their susceptibility to adverse developmental outcomes. Three sources looked at the accumulation of risk factors and substance use. Two of the three papers (both moderate quality) from UK, Australia and Finland identified increasing cumulative risks (assessed between 11 and 14 years) were associated with an increased risk of cannabis use and dependence at ages between 17 and 19 years. The indicators used to measure accumulating risk varied between studies, therefore caution should be applied when attempting to apply findings or generalise to other settings. We decided to keep them separate from the individual risk factors, without grading them.

The first (Hale and Viner, 2016), a UK based study, looked at smoking, alcohol use and delinquency at age 14 years. They constructed a 'risk score' by summing the number of risk behaviours a respondent reported being involved in. Adjusted associations between increasing risk scores at age 14 and 16 years and drug use at age 19 years found a significant stepwise association. At age 14 years, the risk of drug use at age 19 years more than doubled between risk scores of two (OR 4.15, 95% CI 3.19 to 5.38, p<.001) and four (OR 8.73, 95% CI 4.59 to 16.60, p<.001). At age 16 years the increased risk of cannabis use at age 19 years between risk scores of two (OR 5.98, 95% CI 4.84 to 7.39, p<.001) and four (OR 14.10, 95% CI 10.47 to 18.99, p<.001) almost trebled. There was also a large increased risk of age 19 cannabis use in those with a risk score of three (OR 10.70, 95% CI 8.38 to 13.66, p<.001).

Health risk behaviours at age 14 and 16 years

Hale and Viner (2016) **Cohort name:** Longitudinal Study of Young People in England (LSYPE) **Study quality:** Moderate quality	Adjusted associations between increasing risk scores at age 14 and age 16 years and drug use at age 19 years found a significant stepwise association. At age 14 years, the risk of drug use at age 19 years more than doubled between risk scores of two (OR 4.15, 95% CI 3.19 to 5.38, p<.001) and four (OR 8.73, 95% CI 4.59 to 16.60, p<.001). At age 16 years the increased risk of drug use at age 19 years between risk scores of two (OR 5.98, 95% CI 4.84 to 7.39, p<.001) and four (OR 14.10, 95% CI 10.47 to 18.99, p<.001) almost trebled. There was also a large increased risk of age 19 drug use in those with a risk score of three (OR 10.70, 95% CI 8.38 to 13.66, p<.001).

An Australian study looked at 22 variables between the ages of 11 and 14 years which incorporated personal and social factors combined to create a

risk index. The risk index was categorised as low, average and high. 74.1% of the cohort were in the average risk category. Analyses found a significant association between those in the high-risk category and lifetime drug use ($p<0.005$), last 30 day drug use ($p<0.005$), frequent heavy use ($p<0.001$) and drug dependence at age 17/18 years ($p<0.005$). However, only participants with complete data on substance use were included in the analyses, and of the families no longer participating a higher proportion were from lower socio-economic backgrounds.

Combined social and personal risk factors

Stockwell et al. (2004) **Cohort name:** The Australian Temperament Project (ATP) **Study quality:** Moderate quality	Results indicated most illicit drug use occurred in the highest-risk group (top 15%). Pearson Chi Square tests found a significant association between those in the high-risk categories and lifetime drug use ($p<0.005$), last 30-day drug use ($p<0.005$), frequent heavy use ($p<0.001$) and drug dependence at age 17/18 years ($p<0.005$). Sensitivity analysis confirmed those in high risk groups were more likely to use cannabis even when groupings of risk were altered and divided broadly into thirds on the basis of their Risk Index Score.

A study from Finland (good quality) did not find an association with cumulative contextual risk and substance use after accounting for associations between the outcomes due to general problem behaviour. A prenatal/cumulative risk index composed of ten indicators was used to measure contextual risk during the prenatal/birth period (Indicators: low birth weight; teenage mother; single parent; multiple unions; drop-out mother; smoking while pregnant; drinking while pregnant; paternal alcohol use; economic exclusion; and material deprivation). Measures were collected via questionnaires completed by mothers during pregnancy. This study also used a single dichotomous lifetime illegal drug use variable after small prevalence rates meant individual outcomes on cannabis, hard drugs and intravenous drugs needed to be collapsed.

Cumulative contextual risk

Mason et al. (2016) **Cohort name:** Northern Finland Birth Cohort 1986	Cumulative contextual risk (CCR) at birth was found to be a statistically significant positive predictor of substance use. The re-estimated model failed to show CCR as a statistically significant predictor of illegal drug use. Three further separate models showed there was no evidence of specific effects in relation to either substance use or conduct problems. In conclusion, there was no specific effect of CCR

Study quality: Good quality	on substance use, after accounting for associations among the outcomes due to general problem behaviour.

4.11 Protective factors

We identified three variables as potential protective factors: religiosity, extracurricular activity and a positive school attitude. A positive school attitude has moderate quality evidence supporting the hypothesis that this is a protective factor against drug misuse. Religiosity and extracurricular activity, both graded C, had some evidence supporting the hypothesis that they may be protective factors, but it is not conclusive.

4.11.1 Positive attitude to school

There is moderate quality evidence from two studies that a child's positive attitude to school may be a protective factor against future drug misuse. The studies were from the USA and UK.

All three studies used slightly different measures for attitude to school, this contributed to our grading of the evidence as inconsistent. Hale & Viner (2016) used a composite measure based on 12 items assessing how worthwhile, interesting and enjoyable students felt school was at age 14. McNeely and Falci (2004) used six questions to measure school connectedness, three assessed school belonging and three measured perception of teachers. McNeely and Falci (2004) looked at cannabis use in the last 30 days, whereas the UK study (Hale & Viner, 2016) looked at use of any drugs in the previous four-week period.

Hale and Viner (2016) found that positive attitudes towards school at age 14 years were associated with decreased risk for any drug use (OR 0.96, 95% CI 0.95 to 0.97, p<0.001). McNeely and Falci (2004) found that teacher support and social bonding were protective against transitioning into either occasional (model 1 RRR 0.87 p<0.001) or regular use (model 1 RRR 0.88 p<0.001) from no cannabis use. However, they found social belonging was not related to initiating cannabis use once teacher support was also included in the model (model 3b none to occasional RRR 1.00).

Protective factor: Positive attitude to school The hypothesis that a positive attitude to school is a protective factor for drug misuse is supported by moderate quality evidence [B] (two moderate quality)	
Reference	**Summary statistics**
Hale and Viner (2016) **Cohort name:** Longitudinal Study of	Positive attitudes towards school at age 14 years were associated with decreased risk for any drug use (OR 0.96, 95% CI 0.95 to 0.97, p<0.001).

Young People in England (LSYPE) **Study quality:** moderate	
McNeely and Falci (2004) **Cohort name:** ADD Health Study **Study quality:** moderate	Results from the multivariate models examining the relationship between school connectedness and the transition into and out of cannabis use show teacher support and social bonding are protective against transitioning into either occasional (model 1 RRR 0.87 p<0.001) or regular use (model 1 RRR 0.88 p<0.001) from no cannabis use. However, social belonging is not related to initiating cannabis use once teacher support is included in the model (model 3b none to occasional RRR 1.00).

4.11.2 Religiosity

There is some evidence from five studies (three moderate and two poor quality) that religiosity is protective against illicit drug use/dependence. However, this evidence is not conclusive. Three different cohorts looked at religiosity as a potential protective factor against the risk of substance misuse. Four studies were from the USA (three moderate, two poor quality), with three of these using data from the same cohort, and one study from Scotland (moderate quality).

The way religiosity was defined and measured varied across the five included studies. One (Rostosky et al., 2007) used a religiosity index which was calculated based on the sum of responses to three items. The range of possible religiosity scores was 0 to 9. Others just defined the exposure as "religion" or assessed the importance of religion. Outcomes also differed. One study (West et al., 2004) looked at the variation between schools in rates of illicit drug use at ages 13 and 15. Three studies (Van den Bree and Pickworth, 2005; Rotosky et al., 2007; Kaynak et al., 2013) assessed some kind of cannabis use or dependence. The final study (Harrell and Broman, 2009) looked at prescription drug misuse.

The evidence across studies was not conclusive, although some studies did find that religiosity reduced the risk of substance use in certain groups. Van den Bree and Pickworth (2005) found that religiosity reduced the risk of initiation of experimental cannabis use for girls (OR 0.78, 95% CI 0.70 to 0.87) and initiation of regular cannabis use for boys and girls combined (OR 0.83, 95% CI 0.71 to 0.97). Harrell and Broman (2009) found that higher religious attendance was related to a decreased likelihood of prescription drug misuse among Blacks. Kaynak et al. (2013) found that those who thought religiosity was moderately or extremely important appeared to be less associated with cannabis dependence during the first year of college compared with those who felt it was slightly or not important (OR 0.14, 95% CI 0.25 to 0.82). Rostosky et al. (2007) found that among the whole

sample of participants religiosity significantly reduced the odds of cannabis use (OR 0.79, 95% CI 0.72 to 0.88), but this was not the case when just analysing sexual minority sub-groups.

Protective factor: Religiosity There is some evidence supporting the hypothesis that being religious is a protective factor, but it is not conclusive [C] (two moderate and two poor quality studies found an association and one moderate quality study found no association)	
Reference details	**Summary statistics**
West et al. (2004) **Cohort name:** West of Scotland study **Study quality:** Moderate	This study found no statistically significant association between religion, specifically Catholic (age 13 OR 1.06, age 15 OR 1.07), Other (age 13 OR 0.91, age 15 OR 0.73), none (age 13 OR 1.11, age 15 OR 1.25) and ever illicit drug use.
Van den Bree and Pickworth (2005) **Cohort name:** ADD Health Study **Study quality:** Poor	Religion reduced risk of initiation of experimental cannabis use for girls (OR 0.78, 95% CI 0.70 to 0.87) (both age cohorts), initiation of regular cannabis use for boys and girls combined (OR 0.83, 95% CI 0.71 to 0.97) but not in age-specific analyses), and continuation of experimental cannabis use in younger girls.
Rostosky et al. (2007) **Cohort name:** ADD Health Study **Study quality:** Moderate	Among the whole sample of participants religiosity significantly reduced the odds of cannabis use (OR 0.79, 95% CI 0.72 to 0.88), the interaction with sexual identity groups suggest differential effects as shown by logistic regression results.
Harrell and Broman (2009) **Cohort name:** ADD Health Study **Study quality:** Poor	Higher religious attendance was related to a decreased likelihood of prescription drug misuse among Blacks, but religious importance was not associated with prescription drug misuse.
Kaynak et al. (2013) **Cohort name:** College Life Study **Study quality:** Moderate	Those who thought religion was moderately or extremely important appear to be less associated with cannabis dependence during the first year of college than those who felt it was slightly or not important (OR 0.14, 95% CI 0.25 to 0.82).

4.11.3 Extracurricular activity

There is some evidence from two studies (one moderate quality, one poor quality) that involvement in extracurricular activities is a protective factor against the use of illicit drugs. However, the evidence supporting this risk factor is inconsistent and therefore inconclusive. Both cohorts were from the USA. One included students from high schools in California (Darling, 2005) and the other students from a college in Maryland (Garnier-Dykstra et al., 2012). The study from California (Darling, 2005) looked at the use of cannabis and other drugs, whereas the study from Maryland (Garnier-Dykstra et al., 2012) looked at the nonmedical use of prescription stimulants.

It is difficult to draw comparisons between the two studies as they both focused on different types of drug use (cannabis and other drugs in the case of Darling, 2005; nonmedical use of prescription stimulants in the case of Garnier-Dykstra et al., 2012). Both studies did find that participation in extracurricular activities was associated with less illicit drug misuse in some way.

The types of extracurricular activities explored in both studies differed. Caution should be applied when attempting to apply findings or generalise to other types of extracurricular activities. Darling (2005) asked students to name their most important school-based extra-curricular activity during years 1 and 2. In year 3 they asked students whether they had participated in a wide range of extra-curricular activities. They found that more years of participation were associated with less use of cannabis and other drugs (p 0.01), even after prior adolescent characteristics were controlled for. However, the two different methods of capturing participation resulted in higher reports of participation in Year 3 than in the previous 2 years (65% vs. 56% and 54%, respectively), increasing measurement error in the longitudinal analyses. Garnier-Dykstra et al. (2012) focused only on extracurricular volunteer work involvement and religious or church groups. They found an association between participating in volunteer work and a decreased likelihood of nonmedical prescription stimulant use in year 4 of follow-up (AOR 0.57, 95%CI 0.34 to 0.94). In both studies, data was self-reported, so there is a possibility of recall and response bias.

Protective factor: Extracurricular activity There is some evidence supporting the hypothesis that being involved in extracurricular activities is a protective factor, but it is not conclusive [C] (one moderate and one poor quality)	
Reference	**Summary statistics**
Darling (2005) **Cohort name:** no name	More years of participation in extracurricular activity was associated with less use of cannabis and other drugs, (p 0.01) even after prior adolescent characteristics were controlled for.

Study quality: poor	
Garnier-Dykstra et al. (2012) **Cohort name:** College Life Study **Study quality:** moderate	Only in Year 4 was participating in volunteer work associated with a decreased likelihood of nonmedical prescription stimulants (AOR 0.57, 95%CI 0.34 to 0.94).

5 Discussion

5.1 Summary of evidence

This systematic review examined available primary evidence to identify factors that may be considered risk or protective factors of drug misuse. Research studies on risk/protective factors are usually observational rather than experimental. Conclusions about cause-effect relationships cannot be drawn from observational studies. If however, multiple good quality studies consistently demonstrate strong statistical associations between the factor and the outcome, after appropriately taking into account possible confounding factors, this is usually considered to indicate the probability of a cause-effect relationship. The findings of single studies are considered less reliable as evidence than those of multiple studies which consider the totality of the evidence.

Bearing that in mind, we identified a total of 67 individual sources utilising data from 33 cohorts from pre 1974 OECD countries and found a total of 41 potential risk factors and three potential protective factors. Socio-environmental risk factors were the smallest domain and we found limited or conflicting evidence supporting childhood IQ, domicile, negative life events and socio-economic status as risk factors for drug misuse. The substance related risk factors domain contained good quality evidence supporting the hypotheses that younger age at first cannabis use and substance using peers are associated with drug misuse. We found moderate quality evidence for alcohol use, adolescent illicit drug use (other than cannabis) and cigarette smoking. The intrapersonal domain contained 14 risk factors in total. We identified moderate quality evidence supporting the hypotheses that bullying perpetration, male gender, personality traits and poor school engagement are associated with illicit drug misuse. It was not possible to ascertain the association with illicit drug misuse in the remaining factors identified, mostly due to inconsistent findings among the included studies. The interpersonal domain contained 17 risk factors. We identified good quality evidence in support of childhood maltreatment being a risk factor for drug misuse. Moderate quality evidence was identified indicating

parental drinking, parental illicit drug use, parental mental state and parental cigarette smoking are associated with illicit drug misuse in their offspring. We also identified moderate quality evidence indicating parental education and parental monitoring are not associated with illicit drug misuse.

The three protective factors identified were positive attitude to school, religiosity and extracurricular activity. Moderate quality evidence was identified supporting the hypothesis that a positive attitude to school is protective against future drug misuse. Although the findings were inconclusive for religiosity and extracurricular activity, there was some evidence supporting the hypotheses that these may be associated with drug misuse. Further investigation is required.

Some factors incorporated several distinct elements. One example is personality traits, which included aspects such as sensation or novelty seeking, loneliness, self-control and behavioural coping. For the purpose of this review, we selected to follow the approach used in two included studies (Malberg, 2012 and Arria, 2008), in which the several personality traits were grouped together under one risk factor category. We felt this would make our risk factor list more manageable. It would have been useful to investigate these in more detail. Some of the potential risk/protective factors not identified in our review included availability or access to drugs or genetic factors that predisposed individuals to drug misuse.

Study quality varied, although most were graded as moderate (n=33). As is common with cohorts, the majority of data was collected via self-report which introduces the risk of recall and response bias. Another common issue with the included studies was the lack of information about exactly what the variables included and a clear definition was often lacking. One example of this is Asselmann et al. (2016) who contributed evidence towards the personality traits and negative life events risk factors, and failed to describe which illicit drugs were included and how this was measured. Participant characteristics were also often poorly reported, making it difficult to determine generalisability to Wales. Despite this, many studies used population data, or participants were recruited from state schools or birth cohorts, so they will mostly be generalisable.

The type of measures used to identify the exposure of interest was often very poorly reported, or the same risk factors used different measures to establish them. This made it difficult to directly compare the multiple studies. Utilising common, validated measures help to strengthen the evidence of any identified associations and give us a better idea of which are the most important risk factors to focus on.

Individual risk factors varied in terms of the exposure, the tools or definition of the exposure and the outcome being measured. As noted, these were often poorly reported in the included studies, meaning a meta-analysis was

not feasible due to the heterogeneity of the studies. In addition, some risk factors such as personality traits included a variety of traits which ordinarily would be separated into individual risk factors. However, due to the large number of risk factors identified it was felt necessary to group these together to manage the enormity of the review. It may be useful to look at some of the identified risk or protective factors with the strongest evidence and conduct a more detailed analyses of the included studies to ascertain if there are any common elements among the different exposures and outcomes used and generally interrogate the evidence further. This would increase the certainty of the evidence findings, and provide more justification for any future interventions implemented to prevent substance misuse.

As there were a large number of potential risk factors identified by this review, the typology first described by Hawkins, Catalano and Miller in 1992 was used to categorise the risk and protective factors into four distinct domains. These loosely follow a socio-ecological model and it was felt a useful way to group the risk factors, in addition to being consistent with other published reviews and therefore helpful for future work. However, in practice it was quite challenging to decide which risk factors fitted into which category. Some risk factors could have potentially gone into two domains. A good example was personality traits which could be an interaction between intrapersonal (or individual) and socio-environmental. Authors interpreted the meaning of the categories differently, making discussions necessary to agree which category to assign to the various risk factors. Although not ideal and quite subjective, it was felt this typology was a useful way to manage and categorise such a large number of risk factors.

It is necessary to include a note of caution when interpreting the findings of this review, as we need to recognise substance misuse as a complex causal pathway that is likely to result from a combination of risk factors. The longitudinal studies included have enabled us to identify relationships between risk or protective factors and different types of substance misuse. However, they do not necessarily cause substance misuse alone, or in combination with other identified risk factors. It is highly likely that they are mediated by other influences not identified within this review.

Due to the lack of methodological rigour reported in many of the included studies, it has not been possible to establish if the identified risk factors are causal risk. To establish something as a causal risk factor both correlation and precedence must be shown and exposure/reduction to the risk factor must be shown to change the outcome. This could be demonstrated in a longitudinal study with individual level data tracks changes in both risk factor and subsequent outcome. Unfortunately, it was not possible to identify this element in most of the included studies. However, it has been noted that when structuring a prevention program for a population, causal risk factors need to be targeted. It is feasible, however, that since identified

associations are often equated with risk factors there may well be effectiveness research on preventative interventions targeting associations rather than established risk factors, making this an extremely useful systematic review to undertake.

The number of studies identifying specific risk factors varied. The risk factor with the most evidence was male gender (Grade B). This was supported by 15 out of the 20 sources that investigated this risk factor. However, the risk factor younger age at first cannabis use (grade A), was supported by 18 of the nineteen included studies. Personality disorders, alcohol and cigarette smoking (grade B), academic achievement (grade C), mental disorders (grade D) were also identified as a risk factors by between ten and 16 sources. The remaining risk factors were supported by between one and nine sources.

Findings from single studies are considered less reliable as evidence than those of multiple studies which consider the totality of the evidence. Eleven risk factors were identified by a single study. These were: late bedtime; childhood IQ; domicile; truancy or exclusion from school; out of home placement; parental criminality; prior exposure to drugs; structural stigma; independent decision making; relationship satisfaction; and intimate partner violence. According to the evidence grading system for single studies, seven were identified as having an association with substance use. Relationship satisfaction and intimate partner violence were found not to be supported by the evidence (single studies). Lastly, two elements had inconclusive evidence and it was not possible to identify if there was or was not an association between them and substance use.

5.1.1 Other systematic reviews on substance misuse risk and protective factors

A scoping review conducted prior to this review identified several systematic review that often utilised cross-sectional studies in specific populations. Some also looked at a combined spectrum of substances such as alcohol, tobacco and illicit drugs, rather than drug use in isolation. Despite their differences, it is encouraging to find that many of the systematic reviews identified corroborate our findings.

Nargiso et al. (2015) identified several risk and protective factors associated with nonmedical use of prescription drugs among USA youth. They also used a socio-ecological model to classify the identified factors, mostly from cross-sectional studies. Sensibly, they applied a strict inclusion criteria, where only factors supported by a minimum of two studies were included in their review. Our review found four studies (Harrell et al., 2009; Fergusson et al., 2002; Merline et al., 2004 and Arria et al., 2008) looking at nonmedical use of prescription drugs. Two of these (Harrell et al., 2008

and Arria et al., 2008) were also included by Nargiso (2015). The other two studies from our review were outside the search date of the Nargiso (2015) review. For nonmedical use of prescription drugs specifically, we both agree that educational attainment and parental monitoring/involvement is a potential risk factor specifically for nonmedical prescription drug use. However, it should be noted that only one study (Harrell et al. 2009) from these risk factors looked at nonmedical use of prescription drugs and this does not reflect the overall findings of these risk factors (academic attainment included ten studies, evidence grade C and parental monitoring included three studies, evidence grade G). We also agree that religiosity is a potential protective factor. Also in-line with Nargiso (2015), we identified personality traits (sensation-seeking), alcohol, cannabis and other illicit drug use and delinquency as potential risk factors. Some risk factors were identified in our review, but not in the Nargiso (2015) review including being a single parent, but this was identified by a single study (Harrell et al. 2009) in our review, so may not have been included by Nargiso (2015) for that reason.

One review sought to identify risk factors specifically associated with methamphetamine use (Russell et al., 2008). Three of our included studies also looked at amphetamine use, but male gender was the only risk factor in common with those found in Russell et al. (2008). In contrast, there was disparity between psychiatric disorders and their associated risk with amphetamine use where we did not identify an association, but Russel et al. (2008) did. We also identified childhood IQ (White and Batty, 2012), changes in maternal marital circumstances, childhood sexual abuse and delinquency (Hayatbakhsh et al., 2009a) to be associated with amphetamine use. No association, however, was found with maternal cigarette smoking, attention problems, low school performance and higher parental education (Hayatbakhsh et al., 2009a and Humensky and Humensky, 2010).

Other systematic reviews identified in the scoping corroborate other risk factors. A review conducted by Hummel et al. (2012) identified pubertal timing and poor parent–adolescent relationship quality as being related to higher levels of cannabis use, as did we. Another review Hussong et al. (2017) also found mixed evidence regarding depression and anxiety and future substance use (it should be noted this included alcohol, tobacco, cannabis, illicit drugs and composite substance use).

5.2 Limitations

Cohort and case control studies are longitudinal study designs, ideal for identifying potential associations between an exposure and a prospective outcome. These types of studies are at risk of several biases, and although effort was made to identify how these had been addressed in each cohort,

it was not always possible. This means our systematic review has potential limitations.

Firstly, many of the studies, being of a general population, meant that relatively few participants had actually used drugs during the period of the cohort. This meant that analyses undertaken on potential risk factors used very few numbers of participants. Although we have gone some way to address this by narratively grouping several studies looking at the same risk factors and identified similar or different effects are across the studies, allowing us to be more confident that there is indeed an association between the two. It is important to note that the studies are very different, which is why a meta-analysis was not undertaken.

Secondly, studies were undertaken in an array of different countries and at different times. This affects the generalisability of the studies to the Welsh population today. Limiting countries to the pre 1974 OECD means they are more likely to be generalisable, however, it is important to remember each country has different laws around drug use and availability, as well as different attitudes towards drug use. These attitudes also change over time, and much of the data used in this systematic review utilises data over a wide timeframe.

Thirdly, the included studies identified risk or protective factors associated with a large variety of different drugs types. This may affect the generalisability of the individual risk or protective factors across other drugs. Also, some of the drugs examined are more common in the UK than others, and again trends of use change over time.

5.3 Conclusions

This systematic review provides a useful overview of potential factors that could contribute to increased risk of substance use among the general population. Although cohorts alone cannot infer causation, several risk factors were identified by several of the included studies. Younger age at first cannabis use, substance using peers and childhood maltreatment were the only three factors identified that contained good evidence supporting these as risk factors for illicit drug misuse. There was moderate quality evidence supporting prior alcohol use, adolescent illicit drug use (other than cannabis), cigarette smoking, bullying perpetration, male gender, personality traits, parental drinking, parental illicit drug use, parental mental state and parental cigarette smoking as potential risk factors for drug misuse. We found moderate quality evidence to suggest that parental education and parental monitoring are not associated with drug misuse. This indicates a need for further investigation.

Most identified risk factors are extremely complex and it is likely many act as a multifaceted network rather than in isolation. However, we identified several potential risk factors that could be targeted in future prevention

programmes to help reduce the number of people using drugs. In addition, as far as we are aware, this is the only systematic review to have collated the evidence of risk and protective factors for drug misuse in the general population.

6 Supplementary material

1: excluded studies

2: critical appraisal checklist

7 References

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8 Appendix

8.1 Evidence grading scheme – risk factors

Summary grading scheme for risk/protective factors with multiple studies

A. The hypothesis that this is a risk (or protective) factor is supported by good quality evidence	Mostly good quality cohort and case control studies (very low risk of confounding, bias or chance), with majority demonstrating a strong and consistent statistical association between the factor and outcome of interest
B. The hypothesis that this is a risk (or protective) factor is supported by moderate quality evidence	Moderate to good quality cohort and case control studies (low risk of confounding, bias or chance) with majority demonstrating a strong and consistent statistical association between the factor and outcome of interest
C. There is some evidence supporting the hypothesis that this is risk (or protective) factor, but it is not conclusive	Moderate to poor quality case control or cohort studies (high risk of confounding bias, or chance) with the majority demonstrating of a strong and consistent statistical association between a risk (or protective) factor and the outcome of interest
D. The evidence is inconsistent and it is not possible to draw a conclusion	Good to moderate case control and cohort studies with inconsistent findings
E. The evidence is inconsistent and it is not possible to draw a conclusion but it tends towards supporting the hypothesis that this is not a risk (or protective) factor	Good to moderate case control and cohort studies with inconsistent findings, although most demonstrate no statistical association between the factor and outcome of interest
F. There is some evidence supporting the hypothesis that this is not a risk (or protective) factor, but it is not conclusive	Moderate to poor quality case control or cohort studies (high risk of confounding bias, or chance) with the majority demonstrating no statistical association between a risk (or protective) factor and the outcome of interest
G. The hypothesis that this is not a risk (or protective) factor is supported by moderate quality evidence	Moderate to good quality cohort and case control studies (low risk of confounding, bias or chance) with majority demonstrating no statistical association between the factor and outcome of interest
H. The hypothesis that this is not a risk (or protective) factor is supported by good quality evidence	Mostly good quality cohort and case control studies (very low risk of confounding, bias or chance consistently demonstrating no statistical association between the factor and outcome of interest

Summary grading scheme for risk/protective factors with single studies

Evidence from a good quality single study of a strong association between a risk (or protective) factor and the outcome of interest	Case–control or cohort studies with a very low risk of confounding, bias or chance demonstrating a strong statistical association between a risk (or protective) factor and the outcome of interest
Evidence from a moderate quality single study of a strong association between a risk (or protective) factor and the outcome of interest	Case–control or cohort studies with a low risk of confounding, bias or chance demonstrating a strong statistical association between a risk (or protective) factor and the outcome of interest

Evidence from a poor quality single study of a strong association between the risk (or protective) factor and outcome of interest	Case–control or cohort studies with a high risk of confounding bias, or chance demonstrating a strong statistical association between a risk (or protective) factor and the outcome of interest
Evidence from a poor quality single study demonstrating no association between the risk (or protective) factor and outcome of interest	Case–control or cohort studies with a high risk of confounding bias, or chance demonstrating no statistical association between a risk (or protective) factor and the outcome of interest
Evidence from a moderate quality single study demonstrating no association between a risk (or protective) factor and the outcome of interest	Case–control or cohort studies with a low risk of confounding, bias or chance demonstrating no statistical association between a risk (or protective) factor and the outcome of interest
Evidence from a good quality single study of no association between a risk (or protective) factor and the outcome of interest	Case–control or cohort studies with a very low risk of confounding, bias or chance demonstrating no statistical association between a risk (or protective) factor and the outcome of interest

Source: Developed using NICE guideline development methods handbook and modified GRADE criteria developed for NICE Clinical Guideline Addendum 37.1 July 2014.