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REVIEW ARTICLE

Cannabis use and transition to psychosis in individuals at ultra-high risk: review and meta-analysis

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Background. Previous research has established the relationship between cannabis use and psychotic disorders. Whether cannabis use is related to transition to psychosis in patients at ultra-high risk (UHR) for psychosis remains unclear. The present study aimed to review the existing evidence on the association between cannabis use and transition to psychosis in UHR samples.

Method. A search of PsychInfo, Embase and Medline was conducted from 1996 to August 2015. The search yielded 5559 potentially relevant articles that were selected on title and abstract. Subsequently 36 articles were screened on full text for eligibility. Two random-effects meta-analyses were performed. First, we compared transition rates to psychosis of UHR individuals with lifetime cannabis use with non-cannabis-using UHR individuals. Second, we compared transition rates of UHR individuals with a current DSM-IV cannabis abuse or dependence diagnosis with lifetime users and non-using UHR individuals.

Results. We found seven prospective studies reporting on lifetime cannabis use in UHR subjects ($n = 1171$). Of these studies, five also examined current cannabis abuse or dependence. Lifetime cannabis use was not significantly associated with transition to psychosis [odds ratio (OR) 1.14, 95% confidence interval (CI) 0.856–1.524, $p = 0.37$]. A second meta-analysis yielded an OR of 1.75 (95% CI 1.135–2.710, $p = 0.01$), indicating a significant association between current cannabis abuse or dependence and transition to psychosis.

Conclusions. Our results show that cannabis use was only predictive of transition to psychosis in those who met criteria for cannabis abuse or dependence, tentatively suggesting a dose–response relationship between current cannabis use and transition to psychosis.

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Key words: Cannabis use, psychosis, ultra-high risk.

Introduction

Cannabis is the most popular used drug worldwide, with an estimated 2.8–4.5% cannabis users in the general population and 7.1% cannabis users in western and central Europe (Degenhardt & Hall, 2012). Use of this drug has been associated with a range of adverse effects on adolescent psychosocial development and mental health (Hall & Degenhardt, 2009). In particular, the association between cannabis use and the occurrence of psychotic disorders has been well established (Arendt *et al.* 2005; Large *et al.* 2011).

Recent reviews on the association between cannabis use and psychosis risk show that cannabis use is associated with roughly a two-fold increased risk of developing psychosis (Casadio *et al.* 2011; Burns, 2013). This risk increases to almost three-fold when individuals use high-potency cannabis (skunk) (Di Forti *et al.* 2015), which is suggestive of a dose–response effect. Further evidence for a dose–response effect stems from studies of the same research group indicating that while the age of psychosis onset is 3 years younger for individuals who use cannabis than for those without such a history, the age of onset drops to 6 years earlier in those who use cannabis daily or those who use skunk (Di Forti *et al.* 2014).

Although one review on predictors of psychosis in individuals at 'ultra-high risk' (UHR) for psychosis (Yung *et al.* 2005) showed that a history of substance

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abuse was one of the risk factors associated with an increased risk of developing psychosis (Fusar-Poli *et al.* 2013), there is less evidence of a dose–response relationship in the UHR population. To date, studies investigating the association between cannabis use and transition to psychosis in UHR patients have reported inconsistent results (Korver *et al.* 2010; Dragt *et al.* 2012; Buchy *et al.* 2014; Auther *et al.* 2015). The studies that did find an association included a measurement of severity of cannabis use (i.e. lifetime history of cannabis use or cannabis abuse/dependence disorder in remission) and showed that UHR individuals who met Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria (American Psychiatric Association, 1994) for cannabis abuse or dependence showed a greater risk of transitioning to psychosis compared with UHR individuals who did not meet these criteria (lifetime users or non-users) (Kristensen & Cadenhead, 2007). This finding suggests that there might also be a dose–response relationship between cannabis use and transition to psychosis in the UHR population.

Considering the inconsistent results in former reviews (van der Meer *et al.* 2012; Addington *et al.* 2014), a more extensive synthesis of the existing data in the form of a meta-analysis is warranted in order to understand the role of cannabis use on transition to psychosis in UHR individuals. The present review and meta-analysis aimed to bring together all results on cannabis use and transition to a first episode of psychosis in UHR populations. Following evidence from previous research (Kristensen & Cadenhead, 2007; Auther *et al.* 2015) we hypothesized that (i) lifetime cannabis use is associated with transition to psychosis in UHR individuals, and that (ii) current cannabis abuse or dependence is associated with an increased risk of transition to psychosis.

Method

Data collection

Following the PRISMA database search guidelines (www.prisma-statement.org), relevant articles on cannabis use in UHR patients were identified using the search databases 'EMBASE', 'MEDLINE' and 'PsychINFO' from 1996 to August 2015. We combined the following sets of keywords:

(1) 'clinicalhigh risk' OR 'attenuated positive symptoms' OR 'brief limited intermittent psychotic symptoms' OR 'genetic risk and deterioration' OR 'basic symptoms' OR 'familial high risk' OR 'prodrom*' OR 'at risk mental state' OR 'ultra high risk' OR 'attenuated psychotic symptoms' OR 'high risk'

(2) 'substance abuse' OR 'substance use' OR 'substance use disorder' OR 'cannabis' OR 'marijuana' OR 'tobacco' OR 'hallucinogens' OR 'cannabis misuse'

(3) 'risk factors' OR 'psychosis' OR 'schizophrenia' OR 'schizo*' OR 'psychoti*'

The search resulted in 5559 potentially relevant articles. One study was added after manual searches in PubMed (Dragt *et al.* 2011). First, articles were screened on title. Second, abstracts were scrutinized on relevance. Third, a final screening of the full text was conducted. Eligibility was independently assessed by two researchers (K.Z. and T.K). In case of disagreement, a third researcher (M.vd.G) was consulted.

Data extraction (Fig. 1)

Articles were considered eligible if they:

(a) included data on individuals meeting UHR criteria as defined by the Comprehensive Assessment of the At-Risk Mental State (Yung *et al.* 2005), or the Structured Interview for Prodromal Syndromes (T McGlashan *et al.* unpublished observations), or the Schizophrenia Proneness Instrument, Adult Version (Schultze-Lutter *et al.* 2007), or the Schizophrenia Proneness Instrument, Child and Youth Version (Schultze-Lutter *et al.* 2012) or the Basel Screening Instrument for Psychosis (Riecher-Rössler *et al.* 2008)

(b) reported on the effect of cannabis use on transition to psychosis. Lifetime cannabis use was defined as having used cannabis at least once previously or recently but not severe enough to meet criteria for DSM-IV abuse or dependence disorder. Current cannabis abuse or dependence was defined according to DSM-IV criteria for cannabis abuse or dependence disorder (within the previous 12 months)

(c) made use of prospective designs

(d) were published in English.

Articles were excluded when cannabis use was not assessed separately from overall substance use, leaving a total of 12 publications. If publications reported findings from overlapping study samples, the study with the largest sample size was selected for the meta-analysis. For example, of the four studies from the North American Prodrome Longitudinal Study (Addington *et al.* 2007), the largest cohort (Auther *et al.* 2015) was selected instead of two previous reports (Kristensen & Cadenhead, 2007; Cannon *et al.* 2008). In addition, the cohort of Auther *et al.* (2015) was selected over Buchy *et al.* (2015) because of the more extensive statistical analysis that was used in the first study. Last, the Dutch Prediction of Psychosis Study (DUPS)

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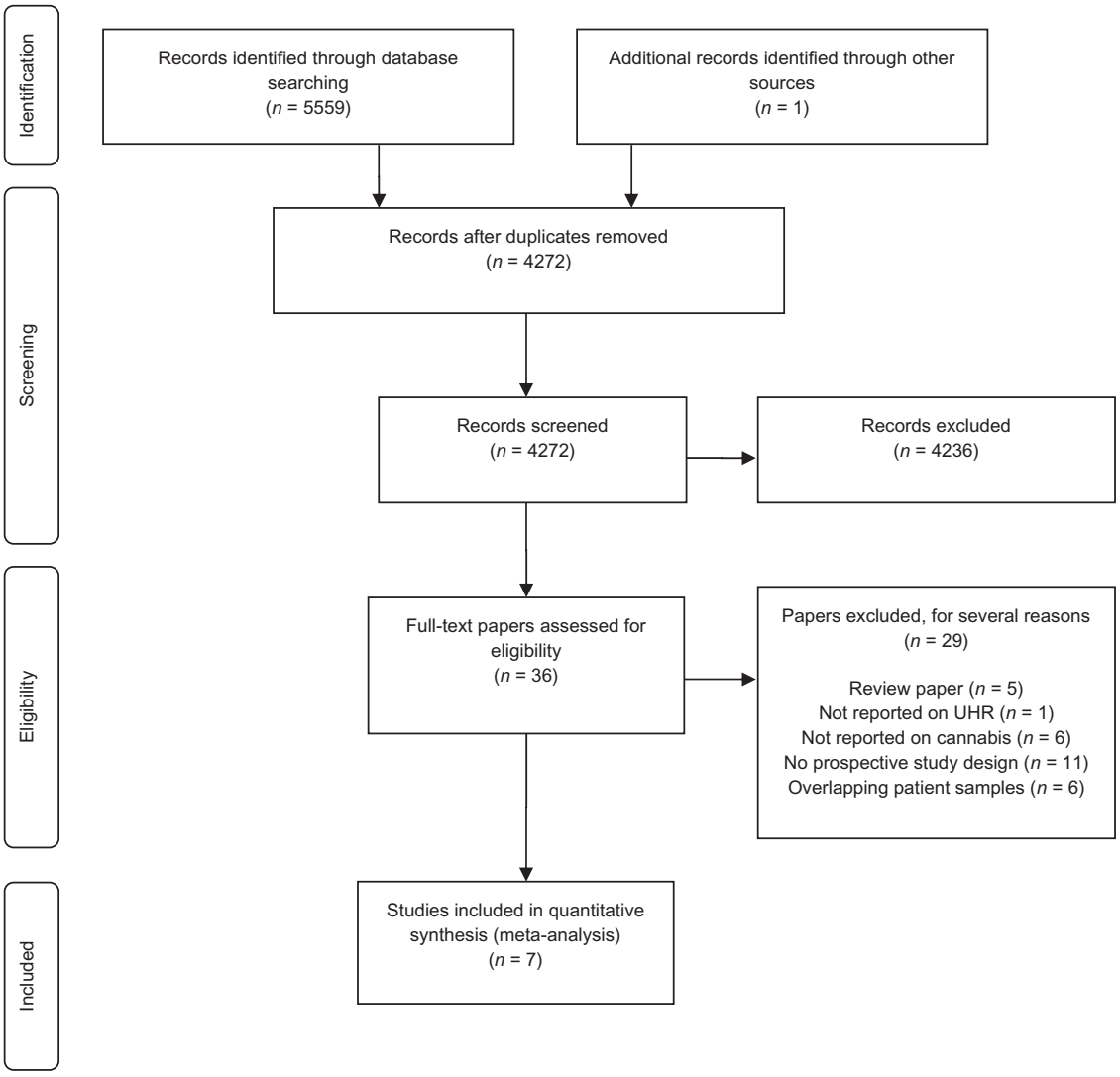

Fig. 1. Flowchart of selected studies. UHR, Ultra high risk.

was part of the larger European Prediction of Psychosis Study (EPOS) cohort, and we therefore selected the study reporting on the larger EPOS cohort (Dragt *et al.* 2012) instead of the three papers that reported on the DUPS cohort (Dragt *et al.* 2010, 2011; Korver *et al.* 2010).

After exclusion of studies with overlapping cohorts, seven publications were left including data of 1171 UHR patients, which were used for the quantitative syntheses (see Table 1 for characteristics of the studies). Additional data were requested and have been provided by Dr A. Auther and Dr L. Buchy.

Data analysis

We conducted two random-effects meta-analyses with Comprehensive Meta-Analysis (CMA; version 1.0.25; Biostat, USA). The first meta-analysis examined differences in transition rates between UHR individuals with lifetime cannabis use compared with those who had never used cannabis. The second meta-analysis compared transition rates between UHR individuals with cannabis abuse or dependence compared with lifetime cannabis users and non-users.

Heterogeneity of study designs and protocols was tested by χ^2, reporting the I^2 statistic. I^2 could be 0%, 25%, 50% or 75%, indicating no, low, moderate or high heterogeneity (Higgins *et al.* 2003).

Publication bias is the result of selective publishing, i.e. small studies with positive outcomes are more often published than studies with negative outcomes. Publication bias of positive outcome studies was corrected using Duval and Tweedie's trim-and-fill procedure (Duval & Tweedie, 2000*a*, *b*), which generates an estimated pooled effect size after the potential influence of publication bias is adjusted for.

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Table 1. *Overview of studies on cannabis use in UHR subjects*

Author	Study and country	Participants, *n* (% male)	Mean age, years (range)	Participants who had used cannabis at baseline, *n* (%)	Follow-up, months	Cannabis use measure	UHR criteria measure	Number of transitions to psychosis	Conclusions
Phillips *et al.* (2002)	PACE, Australia	100 (49.0)	19.3 (14–28)	37 (37.0)	12	SCAN	PACE criteria	Cannabis users (in the past year) = 13, non-cannabis users (in the past year) = 19	Cannabis use is not associated with transition to psychosis in UHR patients
Corcoran *et al.* (2008)	COPE, USA	32 (81.3)	18.8 (12–25)	13 (40.6)	24	K-SADS-PL (ages 12–15 years), DIGS (16 years and over)	SIPS	No significant differences in transition rates between cannabis users and non-users	Cannabis use might be related to the exacerbation of sub-threshold psychotic symptoms, but is not associated with transition to psychosis in UHR patients
Dragt *et al.* (2012)	EPOS, Europe	245 (57.6)	22.6 (16–35)	102 (42.0)	18	CIDI	SIPS, BSABS-P	Cannabis users = 15, non-cannabis users = 22	Early-onset cannabis use is associated with earlier appearance of psychotic symptoms. Cannabis use is not related to transition to psychosis in UHR patients
Valmaggia *et al.* (2014)	OASIS, UK	182 (57.1)	22.9 (15–35)	134 (73.6)	24	CEQ	PACE criteria	Cannabis users = 17, non-cannabis users = 9	Lifetime cannabis use in UHR patients is not related to transition to psychosis. Among cannabis users, frequent use, early onset and continued use after clinical representation is related to transition to psychosis
Auther *et al.* (2015)	NAPLS, USA and Canada	341 (61.6)	18.3 (15–35)	130 (38.1)	24	SCID, K-SADS-PL	SIPS	Cannabis misusers = 29, cannabis users without impairment = 16, non-cannabis users = 56	Cannabis use is associated with transition to psychosis. However, this association is confounded by alcohol use

Auther *et al.* (2012)	RAP, USA	101 UHR 59 HC (65.3% UHR, 50.8% male)	16.1 (12–22)	42 (26.3)	36	K-SADS-E	SIPS	No significant differences in transition rates between cannabis users and non-users	Lifetime cannabis use or cannabis abuse in UHR patients is not associated with transition to psychosis
Buchy *et al.* (2014)	PREDICT, Canada and USA	170 (56.5)	19.8 (12–31)	52 (30.6)	48	AUS/DUS	SIPS	Cannabis users = 6, non-cannabis users = 23	There is no association between cannabis use and transition to psychosis in UHR patients

UHR, Ultra-high risk; PACE, Personal Assessment and Crisis Evaluation; SCAN, Schedules for Clinical Assessment in Neuropsychiatry; COPE, Center of Prevention and Evaluation; K-SADS-PL, Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present And Lifetime Version; DIGS, Diagnostic interview for genetic studies; SIPS, Structured Interview for Prodromal Syndromes; EPOS, European Prediction of Psychosis Study; CIDI, Composite International Diagnostic Interview; BSABS-P, Bonn Scale for the Assessment of Basic Symptoms – Prediction List; OASIS, Outreach and Support in South London; CEQ, Cannabis Experiences Questionnaire; NAPLS, North American Prodrome Longitudinal Study; SCID, Structured Clinical Interview for DSM; RAP, Recognition and Prevention Program; HC, healthy controls; K-SADS-E, Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiological Version; PREDICT, Enhancing the Prospective Prediction of Psychosis Study; AUS/DUS, Alcohol and Drug Use Scale.

Results

Effect of lifetime cannabis use on transition to psychosis

Seven studies reported on lifetime cannabis use and were used for the first meta-analysis examining the relationship between lifetime cannabis use and transition to psychosis in UHR individuals (Phillips *et al.* 2002; Corcoran *et al.* 2008; Auther *et al.* 2012, 2015; Dragt *et al.* 2012; Buchy *et al.* 2014; Valmaggia *et al.* 2014). Overall, cannabis use was not significantly associated with an increased risk of transition to psychosis with an odds ratio (OR) of 1.14 [95% confidence interval (CI) 0.856–1.524, $p = 0.37$, see Fig. 2]. The Q test and I^2 indicated that the study design and protocol of the included studies were not heterogeneous (see Table 2). Although Egger's regression test was not significant ($p = 0.16$), there was an indication of publication bias in the funnel plot (three studies missing). A trim-and-fill procedure showed a slightly higher OR of 1.31, but this remained statistically insignificant (see Table 2).

Effect of current cannabis abuse or dependence on transition to psychosis

Of the seven studies included in the first meta-analysis, five studies determined cannabis abuse or dependence according to DSM-IV criteria. These five studies were examined separately in a second meta-analysis in which we investigated whether current cannabis abuse or dependence was associated with an increased risk of transition to psychosis in UHR individuals (Phillips *et al.* 2002; Auther *et al.* 2012, 2015; Buchy *et al.* 2014; Valmaggia *et al.* 2014). The results showed that current cannabis abuse or dependence was significantly associated with psychosis risk with an OR 1.75 (95% CI 1.135–2.710, $p = 0.01$). Our results showed no indication of heterogeneity: the Q test was not significant and $I^2 = 0$ (see Table 2). Egger's regression test was far from significant ($p = 0.58$), but the funnel plot showed that one study was missing. A trim-and-fill procedure slightly increased the OR to 1.81 (see Table 2).

Discussion

In the present study we investigated the literature on the role of lifetime cannabis use on transition to psychosis in UHR populations. More specifically, we examined whether meeting DSM-IV criteria for current cannabis abuse or dependence was associated with an increased risk of transition. Our results suggest that current cannabis abuse or dependence, but not

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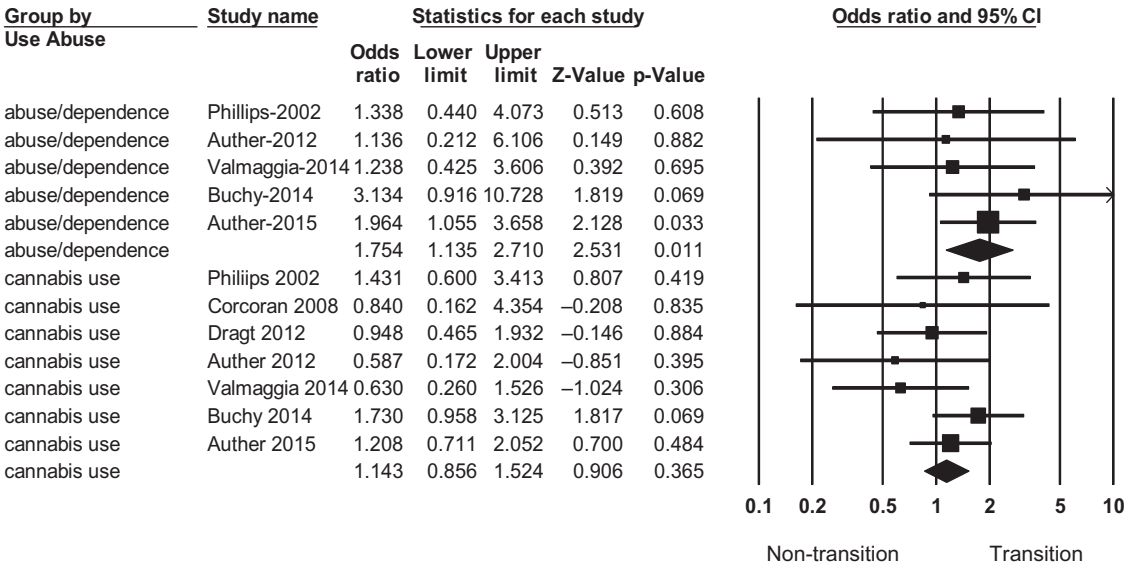

Fig. 2. Overview of studies that investigated cannabis use and transition to psychosis. CI, Confidence interval.

lifetime use, is associated with an increased risk of transitioning to a first episode of psychosis.

Effect of cannabis use on transition to a first episode of psychosis

Lifetime cannabis use was not predictive of transition to psychosis. This finding is in contrast to studies in the general population, in which associations between cannabis use and psychotic symptoms have been established (Van Os *et al.* 2002; Casadio *et al.* 2011). The lack of an association between lifetime cannabis use and psychosis could be explained by the fact that the association is too weak to detect (Addington *et al.* 2014). For instance, the definition of lifetime cannabis use (having used cannabis at least once) may have resulted in a group of subjects in which dose and impact of cannabis use is that minimal that its influence on transition is negligible. It might also be that lifetime cannabis use is associated with attenuated positive symptoms or UHR status, but not with transition to psychosis, although this was not investigated in the present study. In examining current cannabis abuse or dependence, the association between cannabis use and psychosis did become apparent. A possible explanation for our findings may be that because lifetime use was defined as previous or current cannabis use, the group of lifetime users might have resulted in mainly previous cannabis users. Subjects in the group of cannabis abuse or dependence were all currently using cannabis, which might explain the increased effect of current cannabis abuse or dependence on transition to psychosis.

Our results suggest that there might be a dose–response relationship between cannabis use and transition to psychosis, since our findings show that current cannabis abuse or dependence, but not lifetime cannabis use, is associated with an increased risk of psychosis. Our results are supported by findings from studies in the general population (Van Os *et al.* 2002; Smit *et al.* 2004; Moore *et al.* 2007) and psychosis samples (Zammit *et al.* 2002; Arseneault *et al.* 2004; Di Forti *et al.* 2014), in which dose–response relationships between cannabis use and psychosis have already been demonstrated. In these studies, type of cannabis (skunk or high potency) and frequency of cannabis use were in particular associated with an increased risk of psychosis (Di Forti *et al.* 2015). However, in the UHR studies that we included, the findings concerning frequency of cannabis use and the risk of transition to psychosis are inconsistent. For instance, while Phillips *et al.* (2002) reported that there was no difference in frequency of cannabis use in relation to transition to psychosis, Valmaggia *et al.* (2014) reported that frequent use and early onset of cannabis use were associated with an increased risk of transition to psychosis. Therefore, it is important to further investigate this relationship in future UHR research.

Our meta-analytical results should be interpreted cautiously because the OR of 1.75 was moderate and based on a limited number of studies. However, our results correspond with previous research. For instance, in the general population an OR of 1.4 was found for individuals who had ever used cannabis and the onset of psychosis, and an OR of 2.1 for individuals who used cannabis most frequently (Moore *et al.* 2007), which is further supportive for a dose–

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Table 2. *Random effect sizes, heterogeneity and publication bias in the main and sensitivity analyses*

Effects on transition	Random effect sizes				Heterogeneity			Publication bias	
Analysis	Number of contrasts	Risk ratio (95% CI)	*Z*	*p* value of *Z*	*Q* (df)	*p* value of *Q*	I^2	Funnel plot	Trim-and-fill-corrected risk ratio (95% CI)
Cannabis lifetime	7	1.143 (0.86–1.52)	0.906	0.365	5.459 (6)	0.486	0[a]	3 missing	1.308 (0.97–1.77)
Cannabis abuse/ dependence	5	1.754 (1.14–2.71)	2.571	0.011	1.873 (4)	0.759	0[a]	1 missing	1.809 (1.18–2.76)

CI, Confidence interval; *Q*, value for heterogeneity tested by χ^2; df, degrees of freedom; I^2, degree of heterogeneity.
[a] No heterogeneity.

response relationship. Our slightly lower OR compared with the OR for frequent cannabis use might be due to the fact that a large proportion of the UHR individuals in our meta-analysis may have received some form of therapeutic intervention for their attenuated psychotic symptoms. A therapeutic intervention aimed at the prevention of psychosis may have resulted in lower transition rates (Stafford *et al.* 2013; van der Gaag *et al.* 2013), which subsequently might have affected the possibility to detect an effect of cannabis use on psychosis.

While the dose–response relationship hypothesis is supported by general population and psychosis studies (Van Os *et al.* 2002; Arseneault *et al.* 2004; Smit *et al.* 2004; Moore *et al.* 2007), our results may also suggest that there might be an underlying vulnerability for developing general psychopathology, that could result in both psychosis and cannabis abuse or dependence disorder. For instance, there are several factors that are linked to both an increased risk of psychotic disorder and cannabis abuse disorder, such as low socioeconomic status (von Sydow *et al.* 2002; Kirkbride *et al.* 2008) or traumatic life experiences (Sinha, 2008; Addington *et al.* 2013; Thompson *et al.* 2014). Thus, it remains unclear whether cannabis use directly affects the development of psychosis, or whether cannabis use and psychosis are both expressions of other underlying (adverse) environmental factors.

Another explanation for the association between cannabis and psychosis is the 'self-medication hypothesis'. This theory states that UHR individuals use cannabis in an attempt to cope with their (attenuated) psychotic symptoms (Hall & Degenhardt, 2000), although more recent studies have contradicted this theory (Smit *et al.* 2004; Valmaggia *et al.* 2014). For instance, one study reported that the main reason for termination of cannabis use was the adverse effects of cannabis use on attenuated psychotic symptoms (Valmaggia *et al.* 2014), making it unlikely that UHR subjects use cannabis in order to cope with their symptoms.

Overall, our results indicate that it is important to examine dose, frequency and amount of cannabis use and to distinguish between lifetime cannabis use and cannabis abuse or dependence in UHR subjects. In UHR studies to date, subjects who use cannabis on a frequent basis are sometimes excluded (Auther *et al.* 2015), while our results indicate that the most frequent cannabis-using population might be the group with highest psychosis risk. Although future studies should aim to further elucidate the (direction of the) association between cannabis use and psychosis, our results emphasize the need for targeted treatment interventions aiming to minimize or reduce cannabis use in this vulnerable population.

Limitations and strengths

Our meta-analytic findings must be interpreted in the light of several limitations. The first methodological issue is that the present study did not control for potentially confounding factors, known to be associated with both cannabis use and transition to psychosis. For instance, potential factors such as alcohol use, other drug use, tobacco or age of onset of cannabis use were not taken into account in our meta-analyses because these data had only limited availability (Valmaggia *et al.* 2014; Auther *et al.* 2015). Of the studies that examined confounding factors, the study of Corcoran *et al.* (2008) found that the association between cannabis use and psychosis was not affected by alcohol use, other drug use and medication (Corcoran *et al.* 2008). However, Auther *et al.* (2015) found that the relationship between cannabis use and transition to psychosis was weakened by alcohol use. Therefore, it is important to take these potentially confounding factors into account in future research. A second methodological issue is that no information on dose and type of cannabis was available. This is a limitation, because the risk of conversion to psychosis may vary with the level of tetrahydrocannabinol in

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cannabis (Di Forti *et al.* 2015) and information on dose and type of cannabis may contribute to establishing dose–response relationships between cannabis use and psychosis. A third limitation of the present study is that most studies included in the meta-analysis did not assess continued use of cannabis during the follow-up period, which could influence the risk of conversion to psychosis (Valmaggia *et al.* 2014). A fourth limitation was that our meta-analysis yielded some indication of publication bias.

Despite these limitations, the current study assembled all studies on the relationship between cannabis use and transition to psychosis and conducted the most extensive quantitative synthesis of the existing literature to date. Examining the exact dose of cannabis use is warranted for future research.

In conclusion, our results show that current cannabis abuse or dependence is associated with an increased risk of psychosis. Our results suggest that there is a dose–response relationship between cannabis use and transition to psychosis. However, our results may also indicate that cannabis use and psychosis are both expressions of other underlying (adverse) environmental factors such as low socio-economic status or traumatic life experiences. Future studies should incorporate these factors to elucidate the direction of the effect. Overall, our results indicate the need to focus on cannabis abuse or dependence in the treatment of UHR individuals.

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Declaration of Interest

None.

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