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# Does tobacco use cause psychosis? Systematic review and meta-analysis



Pedro Gurillo\*, Sameer Jauhar\*, Robin M Murray, James H MacCabe

## Summary

**Background** Although the association between psychotic illness and cigarette smoking is well known, the reasons are unclear why people with psychosis are more likely to smoke than are the general population. We aimed to test several hypotheses. First, that daily tobacco use is associated with an increased risk of psychotic illness in both case-control and prospective studies. Second, that smoking is associated with an earlier age at onset of psychotic illness. Finally, that an earlier age at initiation of smoking is associated with an increased risk of psychosis. We also aimed to derive an estimate of the prevalence of smoking in patients presenting with their first episode of psychosis.

**Methods** We searched Embase, Medline, and PsycINFO and selected observational studies in which rates of smoking were reported in people with psychotic disorders, compared with controls. We calculated the weighted mean difference for age at onset of psychosis and age at initiation of smoking. For categorical outcomes, we calculated odds ratios from cross-sectional studies and risk ratios from prospective studies.

**Findings** Of 3717 citations retrieved, 61 studies comprising 72 samples met inclusion criteria. The overall sample included 14 555 tobacco users and 273 162 non-users. The prevalence of smoking in patients presenting with their first episode of psychosis was 0.57 (95% CI 0.52–0.62;  $p < 0.0001$ ). In case-control studies, the overall odds ratio for the first episode of psychosis in smokers versus non-smokers was 3.22 (95% CI 1.63–6.33), with some evidence of publication bias (Egger's test  $p = 0.018$ , Begg's test  $p = 0.007$ ). For prospective studies, we calculated an overall relative risk of new psychotic disorders in daily smokers versus non-smokers of 2.18 (95% CI 1.23–3.85). Daily smokers developed psychotic illness at an earlier age than did non-smokers (weighted mean difference  $-1.04$  years, 95% CI  $-1.82$  to  $-0.26$ ). Those with psychosis started smoking at a non-significantly earlier age than did healthy controls ( $-0.44$  years, 95% CI  $-1.21$  to  $0.34$ ).

**Interpretation** Daily tobacco use is associated with increased risk of psychosis and an earlier age at onset of psychotic illness. The possibility of a causal link between tobacco use and psychosis merits further examination.

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## Introduction

Although the association between smoking tobacco and psychosis (in particular, schizophrenia) has been acknowledged,<sup>1</sup> the reasons why people with psychosis are more likely to smoke compared with the rest of the population are still unclear. Several theories have been proposed, many focusing on the idea of self-medication—ie, smoking corrects a pharmacological abnormality (such as excessive dopamine blockade induced by antipsychotics), counteracts negative or cognitive symptoms of schizophrenia,<sup>2</sup> or relieves boredom or distress. Little attention has been directed towards the possibility that cigarette smoking might increase risk for the disorder.<sup>3</sup> This shortfall is surprising, particularly in view of the large amount of attention paid to the role of other substances of misuse (notably cannabis and stimulants) in the aetiology of psychotic illness.<sup>4–7</sup> This discrepancy is exemplified by two meta-analyses: in the first, 83 studies were included in which the onset of psychosis and cannabis use was analysed;<sup>8</sup> in the second, ten studies investigated tobacco use and onset of psychotic illness.<sup>9</sup>

In the second meta-analysis,<sup>9</sup> compared with healthy controls, an increased risk of tobacco smoking was noted in people who developed psychosis (odds ratio 6.04, 95% CI 3.03–12.02), with no difference in age at onset of psychosis between smokers and non-smokers (standardised mean difference  $-0.03$ ).<sup>10</sup> However, since that review was published in 2012, several newer studies have become available, with additional data for daily tobacco use.<sup>11–15</sup> Furthermore, standardised units were used in the 2012 meta-analysis in place of years for age at onset, which was not necessary because all studies used the same units (years).

We undertook a systematic review and meta-analysis of prospective, case-control, and cross-sectional studies to test four hypotheses. First, that an excess of tobacco use is already present in people presenting with their first episode of psychosis. Second, that daily tobacco use is associated with an increased risk of subsequent psychotic disorder. Third, that daily tobacco use is associated with an earlier age at onset of psychotic illness. Fourth, that an earlier age at initiation of smoking is associated with an increased risk

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interview with Sameer Jauhar, James MacCabe and Lancet Psychiatry Senior Editor Hannah Cagney

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of psychotic disorder. We aimed to produce a weighted mean difference in age at onset, expressed in years. Finally, we aimed to estimate the prevalence of smoking in people presenting with their first episode of psychosis.

## Methods

### Systematic review

We did a systematic review in accordance with MOOSE<sup>16</sup> and PRISMA<sup>17</sup> guidelines. We searched Embase (from 1980 to 2014 [week 4]), Medline (1980 to 2014 [week 4]), and PsycINFO (from 1980 to 2014 [week 3]) with the search terms “schizophrenia” OR “schizo\*” OR “psychosis” AND “nicotine” OR “smoking” OR “cigarette smoking”, with no language restriction. We screened the abstracts of articles and retrieved the full text of relevant studies; we also checked reference lists and citation histories. Two of us (PG and SJ) selected studies.

We included studies that used ICD or DSM criteria (from DSM III and ICD-8 onwards) for psychotic disorders: schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, non-affective psychotic disorder, atypical psychosis, psychotic depression, and bipolar mania with psychotic features. To assess the prevalence of smoking in patients presenting with their first episode of psychotic illness, we included studies in which the rates of smoking were reported for people having contact with secondary mental health services for the first time. For our first hypothesis, we included studies that also contained a control group, so we could calculate odds ratios in addition to prevalence. For our second hypothesis, we included prospective studies in which rates of smoking (daily tobacco use) were reported for patients who developed or had psychotic disorders compared with controls, enabling calculation of risk ratios. For our third and fourth hypotheses, we included prospective and case-control studies, and for the onset of psychosis we also included cross-sectional studies.

We excluded studies on the basis of insufficient data or if they met our exclusion criteria. These criteria were a primary focus on people with substance-induced psychosis, organic psychosis, or learning disability.

### Data collection

We extracted data according to a specific protocol. First, we identified the proportion of smokers and non-smokers with a diagnosed first episode of psychosis. Second, we ascertained the risk of psychosis in daily smokers and non-smokers from longitudinal prospective studies. Third, we established the mean (with SD) age at onset of psychotic illness for daily smokers and non-smokers. Finally, we looked at initiation of tobacco smoking in patients diagnosed with psychotic illness versus controls, comparing smokers with non-smokers. For every study, we extracted specific data to include in the model: author, country, and year of publication; type of study (ie, prospective, cross-sectional, case-control,

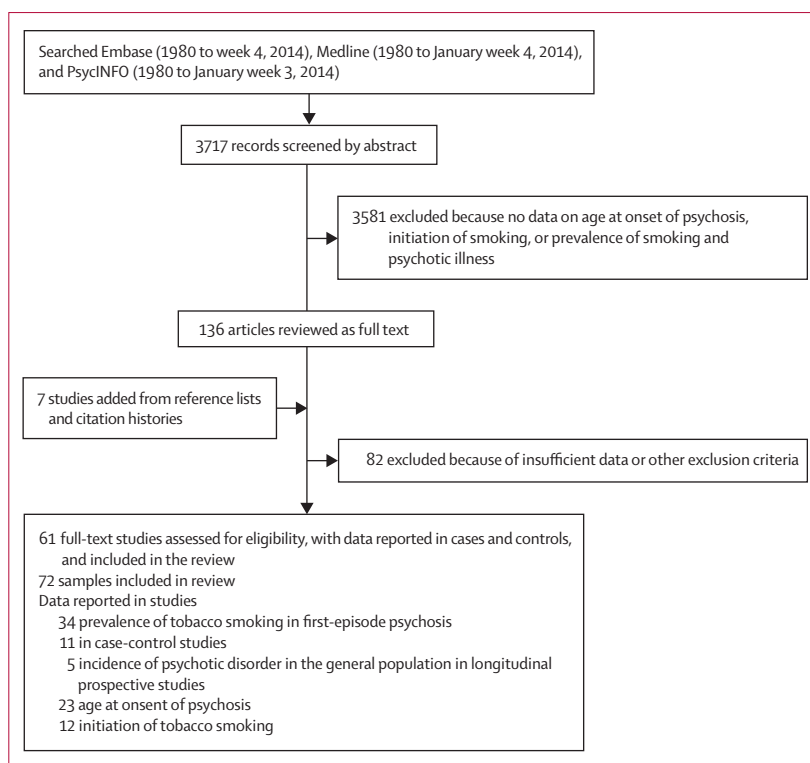


Figure 1: Search process

retrospective); demographic characteristics (eg, sex, age); clinical assessments (ie, diagnostic criteria, disease diagnosed); cannabis and other substances of misuse (ie, alcohol, caffeine, cocaine).

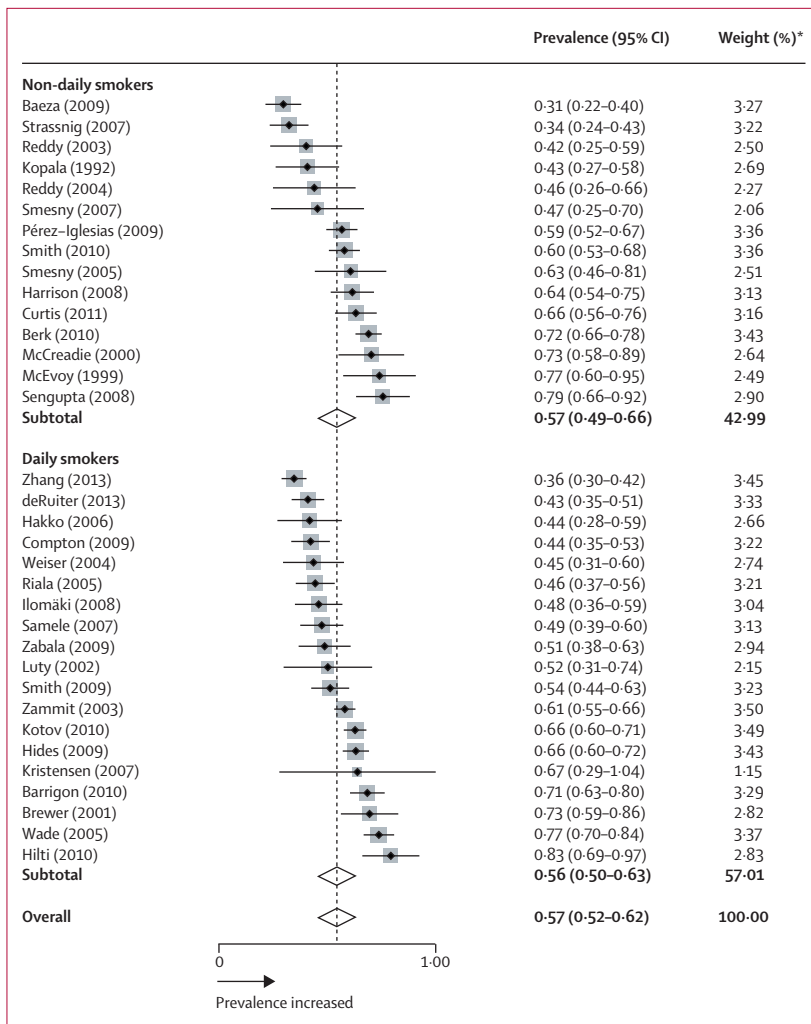
### Definitions

We identified self-reported current tobacco use in the included studies. Our preferred term was “daily tobacco use”, which we defined as either cigarettes smoked per day or by use of the term “regular smoking”, or a Fagerström Test for Nicotine Dependence score. If the study used terms such as “current smoker” or “smoker” without stipulating the number of cigarettes or packs smoked per day, we did not judge tobacco use to be daily and we did not include the study in the analysis of daily smokers.

We defined onset of psychotic illness as either first psychiatric inpatient care,<sup>18–23</sup> start of medical treatment,<sup>24</sup> the first episode of psychosis,<sup>19,20,22,23,25–39</sup> or the first diagnosis of psychotic illness.<sup>18,19,21,24,26–28,30,33,40–46</sup> Because the definitions of age at onset differed, we had to assume that the difference in age at onset between smokers and non-smokers was similar, irrespective of the definition used.<sup>3</sup> For the same reason, we used a random-effects model.

### Statistical analysis

We calculated the weighted mean difference for continuous data, which were age at onset of psychosis and age at initiation of smoking. For the categorical outcomes of rates of tobacco use in patients and controls, we



**Figure 2: Prevalence of smoking in individuals presenting with their first episode of psychosis**  
 Black diamonds represent prevalences; grey squares represent weights; horizontal lines represent 95% CIs; white diamonds represent subtotal or overall prevalence (dotted line) and 95% CIs.  
 \*From random-effects analysis.

calculated odds ratios from cross-sectional data and relative risks from prospective data.

We used Stata version 10 with the metan command. We judged a p value less than 0.05 significant. We used a random-effects model in all analyses because we expected the data to be heterogeneous across studies. We calculated  $I^2$  values to test for heterogeneity between studies. We deemed  $I^2$  less than 25% to have low heterogeneity, 25–75% to have medium heterogeneity, and greater than 75% to have high heterogeneity. We also assessed publication bias and selective reporting with Egger’s and Begg’s tests<sup>47,48</sup> and by inspecting the symmetry of funnel plots, as recommended in the Cochrane handbook.

**Role of the funding source**

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the

report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

**Results**

61 studies comprising 72 samples were analysed (figure 1; appendix pp 1–2). 7475 people with psychosis were smokers (mean 33.2 per sample [SD 195.7]) and 5670 people with psychosis were non-smokers (mean 20.7 per sample [SD 148.1]). Figure 2 shows the prevalence of smoking in people presenting with their first episode of psychosis. 34 samples were analysed, from 34 studies (appendix p 3).<sup>11,15,19–23,29,31–33,35–39,46,49–65</sup> In the total sample of smokers, prevalence of smoking in people presenting with their first episode of psychosis was 0.57 (95% CI 0.52–0.62;  $p < 0.0001$ ). Between-sample heterogeneity was significant, with an  $I^2$  of 88.0%.

All definitions of smoking (including daily smoking) were included in our analysis of smoking prevalence in people presenting with their first episode of psychosis. 12 samples were obtained for the analysis, from 11 case-control studies.<sup>15,21–23,32,34–39</sup> Compared with controls, the overall prevalence of smoking in people presenting with their first episode of psychosis was three times higher (odds ratio 3.22, 95% CI 1.63–6.33;  $p = 0.001$ ; figure 3). Between-sample heterogeneity was significant, with an  $I^2$  of 82.1%. Findings of Begg’s test ( $p = 0.007$ ) and Egger’s test ( $p = 0.018$ ) suggested that publication bias might have been present. In the analysis of daily smoking status, four samples were identified, from three studies,<sup>15,21,32</sup> with an overall odds ratio of 1.01 (95% CI 0.58–1.76;  $p = 0.976$ ; figure 3). Between-sample heterogeneity was significant, with an  $I^2$  of 53.3%.

In our analysis of daily tobacco use and risk of psychotic disorder, five longitudinal prospective studies were identified of six samples from the general population (all samples measured risk of schizophrenia).<sup>18–20,46,66</sup> Compared with non-smokers, the incidence of new psychotic disorders in daily smokers was higher (overall risk ratio 2.18, 95% CI 1.23–3.85;  $p = 0.007$ ; figure 4). Between-sample heterogeneity was significant, with an  $I^2$  of 97.7%. Some evidence was recorded that publication bias contributed to the findings, supported by Egger’s test ( $p = 0.002$ ) and Begg’s test ( $p = 0.024$ ). We also identified one study comprising a cohort of prodromal individuals,<sup>33</sup> in which the risk ratio of developing new-onset psychotic illness in daily smokers versus non-smokers was 7.00 (95% CI 2.35–20.83).

In our analysis of daily tobacco use and age at onset of psychosis compared with non-smokers, 26 samples were included, from 23 studies.<sup>13,19,25–28,30,40–43,46,53,59,61,67–74</sup> Daily smokers developed psychotic illness at an earlier age, compared with non-smokers (24.25 years vs 25.63 years; weighted mean difference  $-1.04$ , 95% CI  $-1.82$  to  $-0.26$ ;  $p = 0.009$ ; figure 5). Between-sample heterogeneity was significant, with an  $I^2$  of 66.3%. No evidence was recorded that publication bias contributed to the findings,

For the Cochrane handbook see <http://handbook.cochrane.org>

See Online for appendix

as shown by Egger's test ( $p=0.149$ ) and Begg's test ( $p=0.103$ ). When the analysis was divided according to the study country,<sup>75</sup> a significant difference was noted between group means (one-way ANOVA  $F=4.32$ ;  $p=0.049$ ). Our analysis was based on data showing differences in the age at initiation of smoking in countries in Europe, North America, and Australasia (eg, Australia, Finland, Spain, Sweden, and the USA) versus countries in Asia and the Middle East (eg, Egypt, Japan, and Turkey); specifically, women in Asian countries were seen to begin smoking at a later age. In Europe, North America, and Australasia, 18 samples from 16 studies were analysed,<sup>13,19,25,26,28,40-43,46,53,59,61,67,68,70</sup> with a weighted mean difference of  $-1.56$  (95% CI  $-2.52$  to  $-0.59$ ;  $p=0.002$ ; figure 5). In Asia and the Middle East, eight samples from seven studies were analysed,<sup>27,30,69,71-74</sup> with a weighted mean difference of  $0.24$  ( $-0.56$  to  $1.04$ ;  $p=0.554$ ). No between-sample heterogeneity was recorded, with an  $I^2$  of 0%.

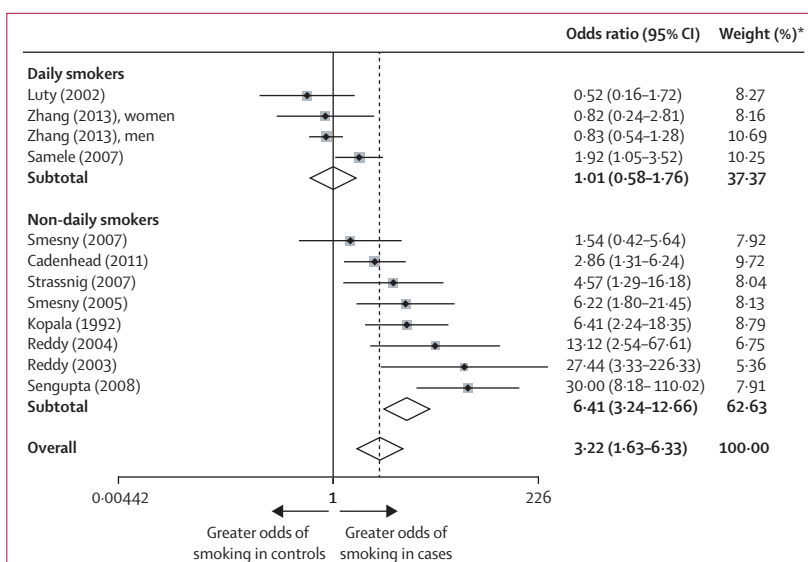
In the analysis of age at initiation of smoking in people with psychosis compared with controls, 15 samples were identified from 12 studies.<sup>12,14,19,24,26,31,32,43-45,53,76</sup> Age at initiation of smoking cigarettes did not differ between patients with psychosis and controls, with a weighted mean difference of  $-0.44$  (95% CI  $-1.21$  to  $0.34$ ;  $p=0.270$ ; figure 6). Between-sample heterogeneity was significant, with an  $I^2$  of 81.0%. No evidence was recorded that publication bias contributed to the findings, supported by Egger's test ( $p=0.957$ ) and Begg's test ( $p>0.99$ ).

## Discussion

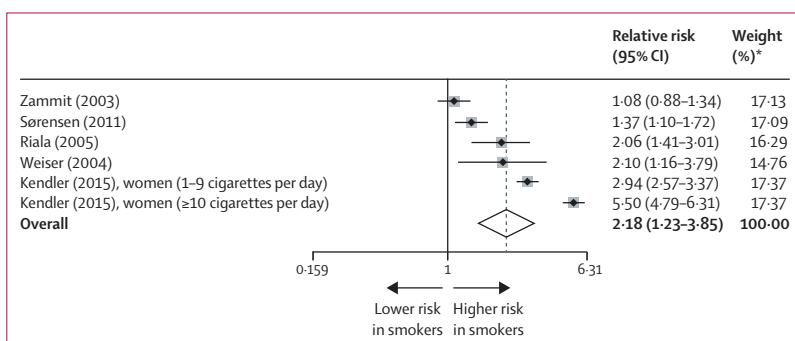
The findings of our systematic review and meta-analysis show that daily tobacco use is associated with an increased risk of psychotic disorder and an earlier age at onset of psychotic illness. However, the effect of smoking seems to be modest.

The prevalence of smoking in patients presenting with their first episode of psychosis was 57% (95% CI 52–62). From our analysis of case-control studies, the overall risk of smoking in individuals having their first episode of psychosis was three times higher than that for non-smokers, with a suggestion of possible publication bias. However, when we restricted the analysis to three studies in which daily cigarette smoking was specified, the association disappeared. Our findings differ from those of a previous meta-analysis,<sup>9</sup> in which risk of smoking in first-episode psychosis was much higher, but a different set of studies were included in that meta-analysis. Our analysis consisted of studies published up to 2014, and we included two cohorts from China,<sup>15</sup> a country with a lower prevalence of smoking than Europe and North America. To acknowledge differences between countries, we analysed cohorts from the general population around the world (appendix p 3).<sup>77</sup> Few studies reported daily smoking status.

Analysis of five longitudinal prospective studies<sup>18-20,46,66</sup> showed that the risk of psychotic disorder was increased



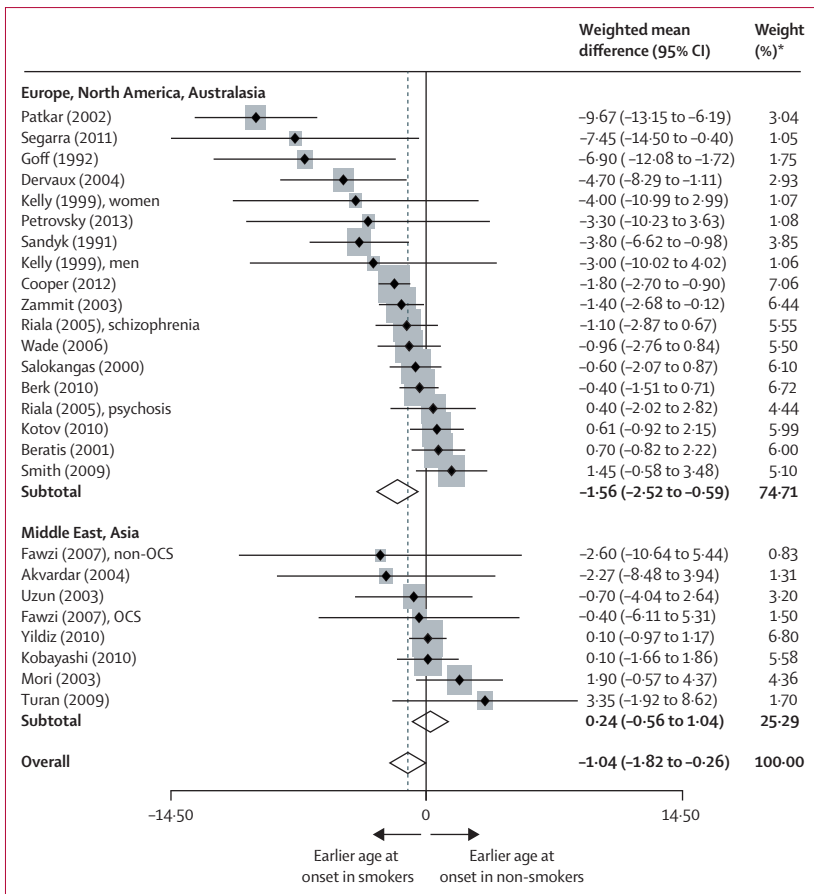
**Figure 3: Odds ratio of smoking daily and non-daily, in people with first-episode psychosis versus controls** Black diamonds represent odds ratios; grey squares represent weights; horizontal lines represent 95% CIs; white diamonds represent subtotal or overall odds ratios (dotted line) and 95% CIs. \*From random-effects analysis.



**Figure 4: Risk of psychosis in prospective studies in daily smokers versus non-smokers** Black diamonds represent relative risks; grey squares represent weights; horizontal lines represent 95% CIs; white diamond represents overall relative risk (dotted line) and 95% CI. \*From random-effects analysis.

modestly by daily smoking. In two other studies that did not meet our inclusion criteria—one of prodromal psychosis<sup>33</sup> and another looking at the risk of developing non-affective psychosis in individuals who had been smoking for at least 9 years<sup>78</sup>—the risk was much higher.

In our analysis, daily use of tobacco was associated with an earlier onset of psychosis compared with non-smokers. These findings conflict with previous reports,<sup>7,10</sup> in which no relation was noted between smoking status and age at onset of psychosis. This discrepancy could be accounted for by differences in culture—eg, in countries such as the USA and the UK, both boys and girls initiate smoking at an earlier age (around 17 years old),<sup>28,32,43</sup> whereas in countries such as Egypt and Turkey, boys start to smoke earlier than do girls.<sup>79</sup> In a Chinese study,<sup>80</sup> the mean age at onset of regular smoking in a cohort with schizophrenia was 20.8 years. Possible reasons for taking up smoking early could be related to self-medication for symptoms



**Figure 5: Difference in age at onset of psychosis, in countries around the world, for daily smokers versus non-daily smokers**

Black diamonds represent weighted mean differences; grey squares represent weights; horizontal lines represent 95% CIs; white diamonds represent subtotal or overall weighted mean differences (dotted line) and 95% CIs. OCS=obsessive-compulsive symptoms. \*From random-effects analysis.

of anxiety or isolated psychosis and might be shared with other risk factors for psychosis, such as early life stressors or living in an urban setting. Therefore, for individuals at increased risk, smoking could have an additive effect.

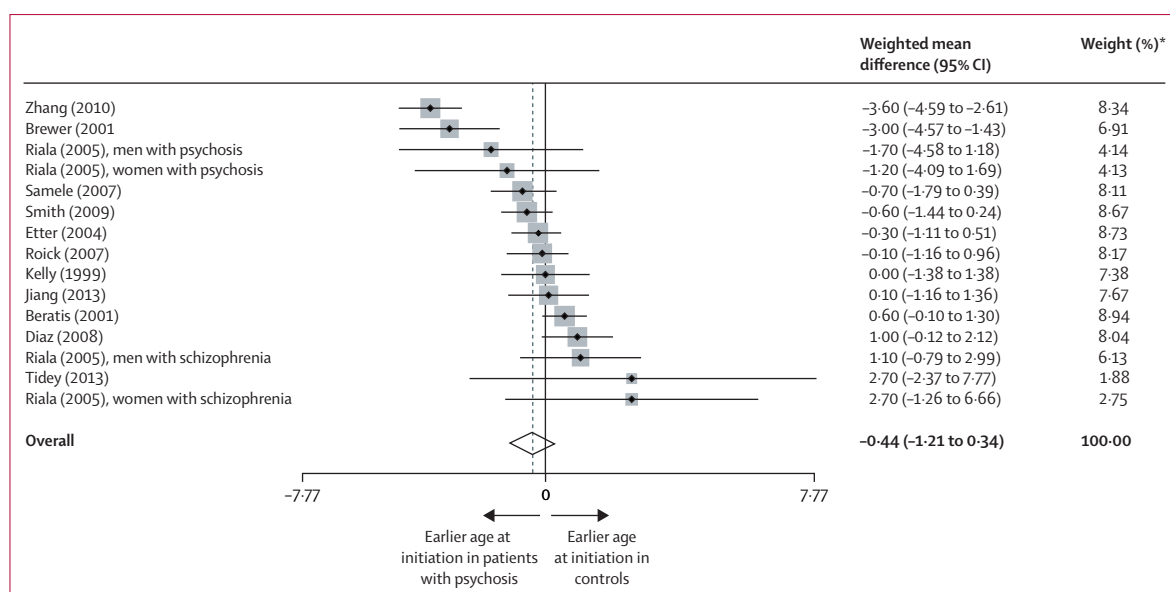
In our analysis, people with psychosis began smoking 0.44 years earlier than did controls, although this difference was not significant. Findings of another meta-analysis estimated a pooled interval of 5.8 years between age at initiation of daily tobacco use and onset of psychosis.<sup>9</sup> In another study, children who started smoking at 15 years or younger were more likely to develop non-affective psychosis than were individuals smoking at a later age.<sup>78</sup>

In view of all our findings, we think that the earlier onset of psychosis and higher risk in smokers of developing psychosis (albeit based on few studies) calls into question the self-medication hypothesis. The excess of smoking nicotine by people with psychosis has been assumed to be secondary to several factors associated with psychosis, subsumed under the umbrella term self-medication. Nicotine use has been suggested to reduce

cognitive deficits and symptoms (such as visuospatial working memory and attention deficits,<sup>81</sup> working memory, and selective attention),<sup>82</sup> P50 inhibition,<sup>83</sup> sensory gating, smooth pursuit, and antisaccadic eye movements.<sup>84</sup> Nicotine has also been postulated to reduce sedating and other effects of antipsychotic drugs<sup>28</sup> and to diminish negative symptoms of psychosis. Use of nicotine at a young age could be attributed to self-medication for anxiety in individuals at the prodromal stage of illness. However, a 2008 review stated that the tobacco industry monitored or directly funded research promoting the self-medication hypothesis, in particular, biological research.<sup>85</sup> Furthermore, direct behavioural evidence has failed to show attentional benefits with nicotine by comparison with placebo, in smokers with schizophrenia versus controls.<sup>86</sup>

With the Bradford Hill criteria, which consider the strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy of an association,<sup>87</sup> we propose that smoking could have a causal role in psychosis. First, with respect to strength, the association noted in prospective studies undertaken in the general population shows a modest increase in relative risk. Second, the findings seem to be consistent between different populations.<sup>7,10</sup> Third, with respect to temporality, although people with psychosis do not smoke at an earlier age compared with the general population, evidence suggests that an excess of smoking precedes the onset of psychotic illness.<sup>9</sup> Fourth, daily smoking seems to have a greater effect on positive symptoms of psychosis.<sup>88</sup> Fifth, plausible mechanisms have been proposed between nicotine and the dopamine system, which have been corroborated in epidemiological and laboratory studies. Finally, the effects of nicotine exposure on the dopamine system might have similarities to psychosis.<sup>70,89,90</sup> The specificity criterion cannot be applied to smoking, because smoking affects a substantial number of disease processes. Also, the experiment criterion is not met because models of important aspects of psychotic illness in animals such as delusions and hallucinations are impossible to achieve.

In implicating nicotine to have a causal role in psychosis (the plausibility part of the Bradford Hill criteria), we must consider whether nicotine has an effect on the dopamine system, since the hypothesis of excess striatal dopamine is the leading pathogenic theory of schizophrenia.<sup>91</sup> One of the strongest links between the environment and Parkinson's disease (a dopamine deficiency disorder, in some ways the opposite of schizophrenia) is the inverse relation between nicotine and risk of Parkinson's disease.<sup>90</sup> In vivo, nicotine might increase dopamine release directly (measured by PET in the dorsal-ventral striatum and basal ganglia) to a similar degree as other drugs of misuse.<sup>70,91</sup> Another mechanism by which nicotine could cause a change in the dopamine system could be through induction of supersensitivity of D2 receptors, which has been proposed as an explanatory



**Figure 6: Difference in age at initiation of smoking in patients with established psychosis versus controls**

Black diamonds represent weighted mean differences; grey squares represent weights; horizontal lines represent 95% CIs; white diamond represents overall weighted mean difference (dotted line) and 95% CI. \*From random-effects analysis.

mechanism for several risk factors for schizophrenia and as a common pathway for psychotic symptoms.<sup>92</sup> This idea has been corroborated by work in animal models suggesting that nicotine exposure might increase D2 high-affinity receptors.<sup>93</sup> Finally, genes coding for nicotine dependence and smoking behaviour—*CHRNA3*, *CHRNA5*, and *CHRNA4*—were identified in the biggest genome-wide association study of schizophrenia to date,<sup>94</sup> giving more biological plausibility to this argument.

The main limitation of our study is the small number of longitudinal prospective studies included in the analysis of risk of developing psychosis between smokers and non-smokers. Another substantial limitation is our difficulty in obtaining the exact consumption of substances other than tobacco (eg, cannabis), because very few studies measured or controlled for these variables objectively (appendix pp 1–2). The scant measurement of these potential confounding factors is a clear source of bias.

Future studies, particularly longitudinal and prospective studies with larger sample sizes, should investigate the relation between daily smoking, sporadic smoking, nicotine dependence, and development of psychotic disorders. Adjustment should be made for the effects of other substances of misuse, enabling stringent examination of whether nicotine has a causal role in the development of psychosis. Cigarette smoking might be a hitherto neglected modifiable risk factor for psychosis, but confounding and reverse causality are possible. Notwithstanding, in view of the clear benefits of smoking cessation programmes in this population,<sup>95</sup> every effort should be made to implement change in smoking habits in this group of patients.

#### Contributors

PG did the literature search, extracted and selected articles, did the primary analysis, and wrote the report. SJ extracted and selected articles and wrote the report. JHM and RMM formulated the research question and wrote the report.

#### Declaration of interests

We declare no competing interests.

#### Acknowledgments

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