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Cognitive functions in smoking and non-smoking patients with schizophrenia: A systematic review and meta-analysis of comparative studies

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ABSTRACT

The "Self-medication hypothesis" that has been developed to explain the effect of nicotine in improving aspects of cognitive impairment in schizophrenia remains controversial. This systematic review and meta-analysis compared cognitive functions between smoking and non-smoking schizophrenia patients. The PubMed, PsycINFO, EMBASE, Web of Science, and Cochrane Library databases were systematically and independently searched. Basic demographic and clinical characteristics, smoking history and cognitive performance were recorded. Seven of the 11 studies included in the study, had meta-analyzable data. Compared to non-smoking schizophrenia patients, their smoking counterparts showed significant deficits on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)-immediate memory (n = 739), the RBANS-total score (n = 739) and the Continuous Performance Test-Identical Pairs (n = 157). Two of the 4 studies without meta-analysable data did not report significant group difference in performance on the Wechsler Digit Span Task and the Beck Cognitive Insight Scale, while the other 2 studies found that non-smokers outperformed than smokers in problem solving and visual learning. In conclusion, this systematic review and meta-analysis found that smoking schizophrenia patients had worse performance in certain cognitive tasks than non-smoking patients, casting doubts on the validity of the "self-medication hypothesis" that needs to be further examined.

1. Introduction

The prevalence of tobacco smoking (smoking thereafter) in schizophrenia patients is between 58% and 90%, with an average prevalence of 62% according to a meta-analysis of 42 studies (de Leon and Diaz, 2005). This is around 5.3 folds higher than the figures in the general population (de Leon and Diaz, 2005; McClave et al., 2010) and also higher than in other psychiatric disorders, such as in bipolar disorder (44%) and in depression (43%) (Pratt and Brody, 2010; Dickerson et al., 2013). Smoking is associated with increased morbidity and mortality in schizophrenia (Winterer, 2010) with reduced life expectancy of around 20% compared with the general population (Hennekens et al., 2005), which could partly be attributed to smoking-related diseases (McClave et al., 2010; Irwin et al., 2014; Ruther et al., 2014).

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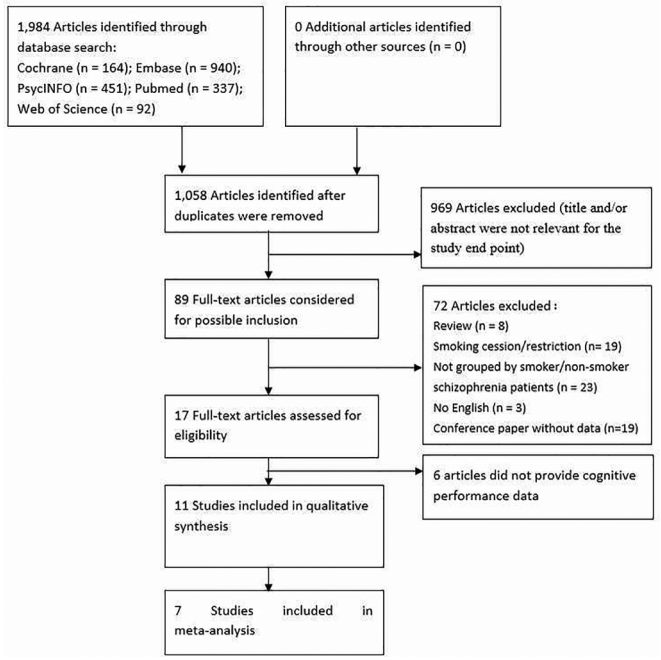

Fig. 1. Flow diagram of study selection.

The reasons for the high prevalence of smoking in schizophrenia patients are not clear. One possible explanation is the "self-medication hypothesis" (Kumari and Postma, 2005); i.e., nicotine could improve negative symptoms, extrapyramidal side effects and certain aspects of cognitive impairment through increasing dopaminergic and glutamatergic neurotransmission in the prefrontal cortex (George et al., 2002; Dervaux and Laqueille, 2008; Conway, 2009; Wing et al., 2011; Hahn et al., 2012; Ahlers et al., 2014). Smoking schizophrenia patients significantly outperform non-smokers in selective attention tasks (Hahn et al., 2012). Other studies also investigated the association between smoking and cognitive functions in schizophrenia using various measurements (George et al., 2002; Zhang et al., 2012; Iasevoli et al., 2013; Morisano et al., 2013; Reed et al., 2016), but the findings have been inconsistent. Zhang et al. (2012) found that non-smoking patients outperformed smoking patients in visuospatial memory task measured by Visuospatial/Constructional and Immediate Memory, while, in contrast, smoking patients outperformed non-smoking patients in long-term cured recall and recognition/discriminability (Morisano et al., 2013; Ahlers et al., 2014).

Given the high rates of smoking and cognitive deficits in schizophrenia, and their negative impact on health outcomes, it is important to examine the relationship between smoking and cognition. Thus, a systematic review and meta-analysis of comparative studies of cognitive functions in smoking and non-smoking schizophrenia patients was conducted. Based on the literature, it was hypothesized that smoking patients would have a significantly better cognitive performance than their non-smoking counterparts.

2. Methods

2.1. Selection criteria

According to the PICOS strategy, the following inclusion criteria were used: Participants (*P*): smoking patients with schizophrenia; the diagnosis of schizophrenia and smoking were established in the studies included in the meta-analysis. Comparison (*C*): control group was non-smoking patients with schizophrenia. Outcomes (*O*): the outcome measures were cognitive functions measured using any standardized neuropsychological instruments, such as the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and the Brief Assessment of Cognition in Schizophrenia (BACS). Study design (*S*): case-control study (smoking vs. non-smoking schizophrenia patients) or cohort study (smoking vs. non-smoking schizophrenia patients; only baseline data were extracted for analyses).

2.2. Search methods

The PubMed, PsycINFO, EMBASE, Web of Science and Cochrane Library databases were systematically and independently searched from their inception date until April 8, 2018 by two reviewers (YYW and SW). The following search terms were used: ("Schizophrenia"[Mesh] OR "schizophrenia" OR "schizophrenic disorder" OR "disorder, schizophrenic" OR "schizophrenic disorders" OR "dementia praecox") AND ("smoking"[Mesh] OR "tobacco"[Mesh] OR "nicotine"[Mesh] OR "smoking" OR "tobacco" OR "cigarette" OR "nicotine") AND ("cogniti*" OR "Neuropsycholog*" OR "Memory" OR "Executive Function*" OR "Attention"). Reference lists of relevant reviews and articles were also hand-searched to avoid missing any relevant articles. Corresponding authors of relevant articles were contacted for necessary information if needed.

2.3. Data extraction

Two reviewers (YYW and SW) systematically and independently screened the articles and extracted data. Any inconsistencies in the above procedures were resolved by a discussion with a third reviewer (YTX). The following information were extracted and tabulated: sample size, study setting, patients' demographic and clinical information, current number of cigarettes smoked, length of smoking and cognitive performance.

2.4. Quality assessment

As there were no healthy controls in the studies, three domains of the Newcastle-Ottawa Scale (NOS) were used for study quality assessment: (1) subject selection; (2) comparability of the case and control groups; and (3) the ascertainment of either the exposure or the outcome used (Deeks et al., 2003). Any disagreements were discussed and resolved with a third reviewer (YTX).

2.5. Data synthesis and statistical analyses

The RevMan software, Version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen) was used to perform the meta-analysis. Due to the discrepancy in measurements and demographic characteristics between studies, the random effects model was used in all meta-analytic outcomes as it is more conservative than the fixed-effects model (DerSimonian and Laird, 1986). Standardized mean difference (SMD) with 95% confidence intervals (CIs) was used for continuous outcomes. Study heterogeneity was measured using I^2; I^2 values greater than 50% indicated significant heterogeneity (Higgins et al., 2003). All meta-analytic outcomes were 2 tailed, with significance level set at 0.05.

3. Results

3.1. Literature search and study characteristics

Eleven case-controls studies of the 1,984 potentially relevant articles initially identified were included in the systematic review (Fig. 1). The 11 studies comprised 1437 schizophrenia patients; 916 smokers and 521 non-smokers with mean ages of 38.4 and 38.1 years, respectively (Table 1). Three studies were conducted in the United States (n = 176), two studies each in China (n = 824), Germany (n = 152) and Turkey (n = 176) and one study each in Italy (n = 59) and Canada/

Table 1
Study characteristics and main findings of the studies included in the meta-analysis.

		Country	Study group (male %); Age		Diagnostic criteria	Current smoking amount (cigarettes per day)	Smoking length (years)	Cognitive domains	Cognitive measurements
			Smoker with SCZ	Non-smoker with SCZ					
1	Turan et al. (2009)	Turkey	23 (57%); 35.4 ± 10.8	20 (40%); 29.3 ± 8.4	DSM-IV criteria for SCZ	22.3 ± 9.5	14.6 ± 11.2	Attention, Working memory	WDST (Digit span forward and backward scores)
2	Wing et al. (2011)	Canada & USA	38 (63%); 41.9 ± 9.4	12 (67%); 42.5 ± 9.1	DSM-IV (SCID) criteria for SCZ or schizoaffective disorder	20.7 ± 10.5	NR	Attention, concentration, impulsivity, mental control, response inhibition and response flexibility (C-CPT,SCWT); Executive attention (WCST)	C-CPT; SCWT; WCST
3	Ekinci and Ekinci (2012)	Turkey	89 (71%); 35.9 ± 9.5	44 (57%); 37.5 ± 10.9	DSM-IV (SCID-I) criteria for SCZ	20	at least one year	Cognitive insight	Beck Cognitive Insight Scale (BCIS)
4	Hahn et al. (2012)	Germany	64 (59%); 33.6 ± 10.9	40 (45%); 37.6 ± 10.4	DSM-IV criteria for SCZ	21.5 ± 11.4	14.7 ± 6.8	Attention: Selective attention (ANT), Sustained attention (CPI-IP); Executive attention (WCST)	CPT-IP; ANT; WCST.
5	Zhang et al. (2012)	China	456(100%); 48.6 ± 9.5	124[a] (84%); 46.3 ± 11.1	DSM-IV criteria for chronic SCZ	one or more per day	more than one year	1. Immediate memory 2. Visuospatial/Constructional 3. Language 4. Attention 5. Delayed memory	RBANS[b]
6	Iasevoli et al. (2013)	Italy	31 (NR); 37.6 ± 9.9	28 (79%); 36.7 ± 11.4	DSM-IV (SCID-I) criteria for SCZ	12.5 ± 6.6	NR	1. Verbal Memory 2. Working Memory 3. Verbal Fluency 4. Processing Speed 5. Problem Solving 6. Motor Speed (not reported)	BACS[c]
7	Morisano et al. (2013)	USA	32 (81%); 41.3 ± 6.9	15 (53%); 39.9 ± 9.2	DSM-IV (SCID-IV) criteria for SCZ /schizoaffective disorder	23.7 ± 10.9	NR	Attention, working memory, processing speed, verbal learning, VSWM, Executive attention (WCST)	Wechsler intelligence and memory battery[d]; C-CPT; VSWM; WCST; TMT; California Verbal Learning Test
8	Roth et al., (2013)	USA	31 (71%); 40.2 ± 11.1	22 (64%); 41.1 ± 9.7	SCZ or schizoaffective disorder (Criteria NR)	17.0 ± 13.1	NR	Attention	C-CPT; CPT-IP; CPT-IP 3 .
9	Zhang et al., (2013)	China	88 (94%); 29.8 ± 9.3	156 (52%); 25.7 ± 9.2	DSM-IV criteria (SCID) for first-episode SCZ	NR	NR	1. Immediate memory 2. Visuospatial/Constructional 3. Language 4. Attention 5. Delayed memory	RBANS[b]
10	Ahlers et al., (2014)	Germany	24 (38%); 33.6 ± 10.6	24 (42%); 37.8 ± 10.5	DSM-IV criteria for SCZ	22.5 ± 12.3	10.7 ± 7.0	Attention, speed of processing	TAP (Digit Symbol Test, and the TMT)

(*continued on next page*)

Table 1 (*continued*)

11	Reed et al., (2016)	USA	40 (80%); 44.2 ± 13.3	36 (69%); 45.1 ± 12.7	DSM-IV-TR (SCID-I) criteria for SCZ or schizoaffective disorder	20.1 ± 11.2	22.6 ± 20.5	1. Speed of processing 2. Attention/vigilance 3. Working memory 4. Verbal learning 5. Visual learning 6. Social cognition	MCCB[e]

Note: ANT = Attention Network Test; BACS = Brief Assessment of Cognition in Schizophrenia; CPT = Continuous Performance Test; C-CPT = Conner's Continuous Performance Task; CPT-IP = Continuous Performance Test-Identical Pairs; CPT-IP 3 = Third and most difficult, block of the Continuous Performance Test-Identical Pairs; DSM-IV = Diagnostic Statistical Manual of Mental Disorders, Fourth Edition; DSM-IV-TR = Diagnostic Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; MCCB = MATRICS Consensus Cognitive Battery; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SCID-I = The Structured Clinical Interview for DSM-IV Axis I Disorders; SCWT = Stroop Color Word Test; SCZ = Schizophrenia; TAP = Testbatterie zur Aufmerksamkeitsprüfung; TMT = Trial Making Test; VSWM = Visuospatial Working Memory; WCST = Wisconsin Card Sorting Task; WDST = Wechsler Digit Span Task;
NA = Not Available; SD = standard deviation.

[a] 20 of the 124 non-smokers were former smokers.

[b] RBANS: 1. Immediate Memory (comprised of List Learning and Story Memory tasks); 2. Visuospatial/Constructional index (comprised of Figure Copy and Line Orientation tasks); 3. Language (comprised of Picture Naming and Semantic Fluency tasks); 4. Attention (comprised of Digit Span and Coding tasks); and 5. Delayed Memory (comprised of List Recall, Story Recall, Figure Recall, and List Recognition tasks).

[c] BACS: 1. Verbal Memory by the List Learning task; 2. Working Memory by the Digit Sequencing task; 3. Verbal Fluency by the Category Instances task; 4. Processing Speed by the Symbol Coding task; 5. Problem Solving by the Tower of London task. 6. Motor Speed by the Token Motor task

[d] The authors did not report scores

[e] MCCB: 1. Speed of processing (comprised of Brief Assessment of Cognition in Schizophrenia: Symbol Coding, Category Fluency: Animal Naming, and the Trail Making Test: Part A), 2. Attention/Vigilance (comprised of the CPT-IP), 3. Working memory (comprised of the Wechsler Memory Scale Spatial Span and the Letter-Number Span), 4. Verbal learning (comprised of the Hopkins Verbal Learning Test), 5. Visual learning (comprised of the Brief Visuospatial Memory Test-Revised), 6. Reasoning and problem solving (composed of the Neuropsychological Assessment Battery: Mazes), and 7. Social cognition (comprised of the Mayer-Salovey-Caruso Emotional Intelligence Test: Managing Emotions)

United States (n = 50). Ten studies used DSM-IV (American Psychiatric Association, 1994) and DSM-IV-R (American Psychiatric Association, 2000) to diagnose schizophrenia, and one study did not mention diagnostic criteria (Table 1).

3.2. Assessment quality and quality of evidence

The total scores of the amended NOS ranged from 3 to 5 (Table 3). The scores of the selection and comparability ranged from 0 to 1, and from 1 to 2, respectively and the all outcome subscale score was 2. Ten studies reported adequate definitions of schizophrenia. Six studies matched education level and 10 studies matched age.

3.3. Cognitive functions in schizophrenia

Seven of the 11 studies that reported data on cognitive performance measured by various instruments had meta-analysable data (Table 1). Cognitive domains reported by two or more studies were synthesised: speed of processing (Trail Making A and B), RBANS: (immediate memory, visuospatial/constructional index, language, attention, delayed memory, and total score), Continuous Performance Test-Identical Pairs (CPT-IP; d', hit rate, and hit response time), Conner's Continuous Performance Task (C-CPT; d', hit rate, hit response time, commission errors, and variability), and Wisconsin Card Sorting Task (WCST; perseverative errors, categories completed, and errors) (Figs. 2a and 2b). Compared with non-smoking patients, smoking patients showed significant worse performance in RBANS-immediate memory (n = 739; SMD: −0.22, 95% CI: −0.39 to −0.05, I^2 = 0%, p = 0.01), RBANS-total score (n = 739; SMD: −0.23, 95% CI: −0.40 to −0.07, I^2 = 0%, p = 0.006) and CPT-IP-hit response time (n = 157; SMD: 0.35, 95% CI: 0.03 to 0.67, I^2 = 0%, p = 0.03).

Four studies reported non-meta-analysable data; 2 studies did not find any significant group differences in cognitive performance on the Wechsler Digit Span Task and Beck Cognitive Insight Scale, while in the other 2 studies non-smokers outperformed smokers in problem solving measured with the BACS, and in the visual learning domain of the Brief Visuospatial Memory Test-Revised task. In addition, these 2 studies did not find group differences in the BACS domains except for problem solving, and neither of the MATRICS Consensus Cognitive Battery (MCCB) domains except for the visual learning domain (Table 2).

4. Discussion

This was the first systematic review and meta-analysis of comparative studies of cognitive performance in smoking and non-smoking schizophrenia patients. Compared with non-smokers, smokers showed more deficits in aspects of cognitive performance including the RBANS-immediate memory, RBANS-total score and the CPT-IP-hit response time. No significant group differences in other cognitive domains were observed.

The results did not support the "self-medication hypothesis" (Kumari and Postma, 2005) that patients smoke to improve cognitive impairment, and were not consistent with studies that found cognitive benefits of smoking in schizophrenia (Wing et al., 2011; Hahn et al., 2012; Ahlers et al., 2014). However, it should be noted that the number of studies and cognitive domains examined in this meta-analysis were limited: 4 of the 11 studies did not report meta-analysable data; variability existed in the 11 studies in terms of the study settings (inpatients or outpatients), sample size, age range and cognitive measurements; furthermore, schizoaffective disorder was included in some studies (Wing et al., 2011; Morisano et al., 2013; Roth et al., 2013; Reed et al., 2016), all of which could bias the findings to an uncertain extent. In addition, smoking rates tend to significantly increase with the progress of schizophrenia (Zhang et al., 2012). It is possible that smoking patients who had already severe cognitive impairment seek "self-medication" by smoking, which could partly explain poorer cognitive

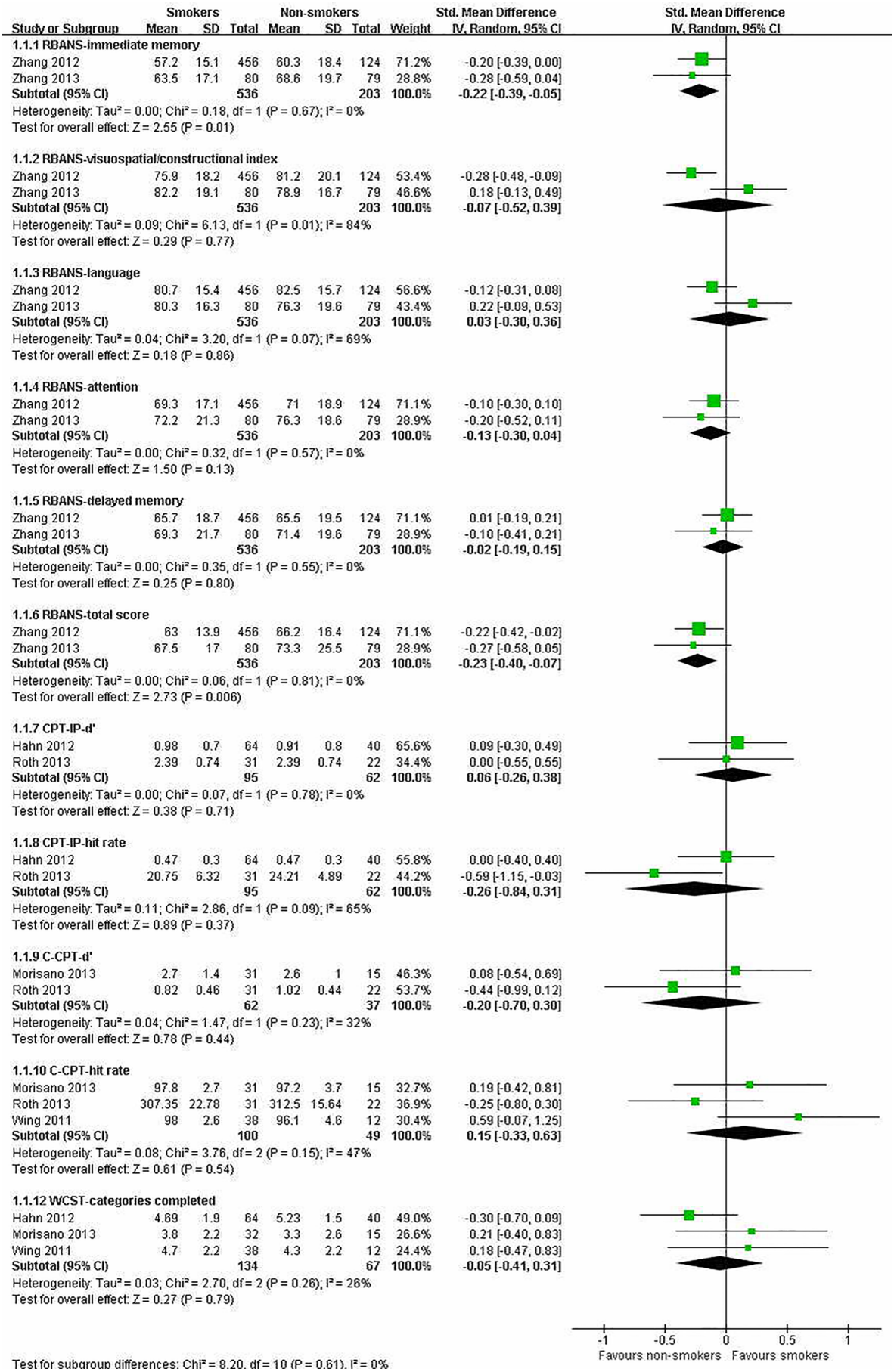

Fig. 2a. Effect of smoking on cognitive performance in schizophrenia: forest plot.

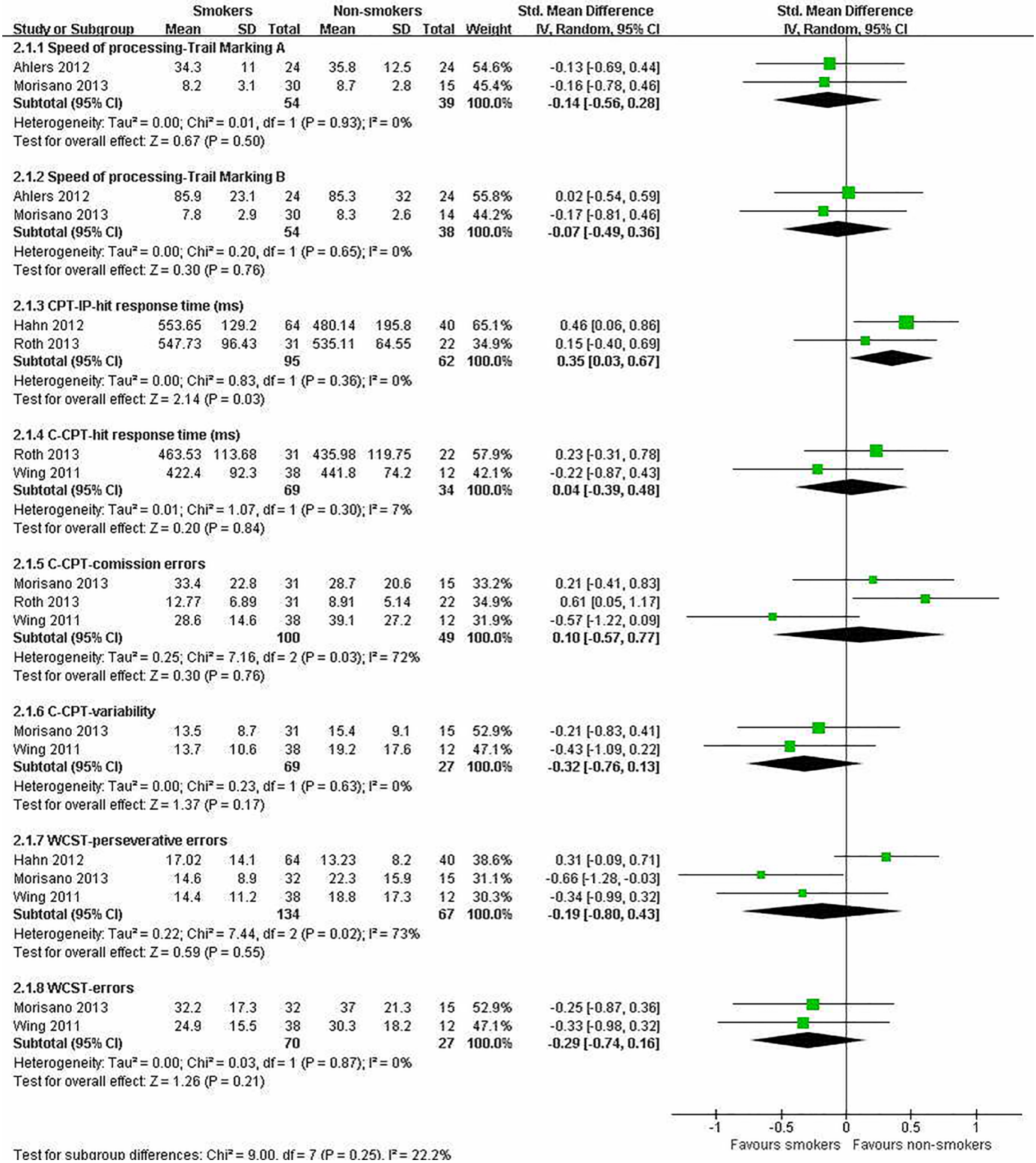

Fig. 2b. Effect of smoking on cognitive performance in schizophrenia: forest plot.

performance in certain domains in smoking patients.

There were further limitations to this study. First, several variables related to cognitive deficits in schizophrenia, such as duration of illness, age of onset, adolescent age group and use of psychotropic medications, were not analysed due to insufficient data. It is possible that cognitive function of adolescents with early onset schizophrenia could be more affected by the illness itself, thus, further studies are warranted to address this issue. Second, as shown in the NOS assessment, smoking and non-smoking patients were not well matched in several studies in terms of age and educational level that has significant impact on cognitive performance. Third, only a limited number of cognitive domains were reported in included studies and could be analyzed. Fourth, due to the lack of prospective cohort studies, only cross-sectional comparative studies were included in this systematic review thus the causality

Table 2
Main findings of the studies assessing cognitive performances (studies not included in meta-analysis are highlighted in grey).

	Studies	Cognitive domain	Cognitive measurements	Findings comparing smokers and non-smokers with SCZ
1	Turan et al. (2009)	Attention, Working memory	WDST (Digit span)	**No significantly difference**: in digit span scores (forward and backward)
2	Wing et al. (2011)	Attention, concentration, impulsivity, mental control, response inhibition and response flexibility (C-CPT,SCWT); Executive attention (WCST)	C-CPT; SCWT; WCST	**Smokers better than non-smokers**: smoker outperformed in SCWT reaction times in the Neutral ($p < 0.01$), Congruent ($p < 0.01$) and Incongruent ($p = 0.02$) conditions. The significant effects persisted after IQ scores adjustment
3	Ekinci and Ekinci (2012)	Cognitive insight	Beck Cognitive Insight Scale (BCIS)	**No significantly difference**: no significant difference was found
4	Hahn et al. (2012)	Attention: Selective attention (ANT), Sustained attention (CPI-IP); Executive attention (WCST)	CPT-IP; ANT; WCST.	**Smokers better than non-smokers**: SCZ smoker outperformed in selective attention (ANT) with $p < 0.05$. **No significantly difference**: CPT-IP and WCST did not reveal any significant difference.
5	Zhang et al. (2012)	1. Immediate memory 2. 2.Visuospatial/Constructional 3. Language 4. Attention 5. Delayed memory	RBANS[b]	**Non-smokers better than smokers**: on the RBANS total score ($p < 0.05$) and the Visuospatial/ Constructional index ($p < 0.005$), and a trend toward a significant difference on the Immediate Memory index ($p = 0.057$). After controlling for age, number of hospitalizations, PANSS total score and negative symptom subscores, as well as antipsychotic drugs and anticholinergic drugs among the patients, both the overall RBANS and the Visuospatial/Constructional index remained significant.
6	Iasevoli et al. (2013)	1. Verbal Memory 2. Working Memory 3. Verbal Fluency 4. Processing Speed 5. Problem Solving 6. Motor Speed (not reported)	BACS[c] battery	**Non-smokers better than smokers**: on the problem solving cognitive task ($p = 0.02$). **No significantly difference**: Performances on the other cognitive tasks (i.e., verbal fluency, verbal memory, working memory, processing speed) were not significant different between smoker and non-smokers.
7	Morisano et al. (2013)	Attention, working memory, speed of processing, verbal learning, VSWM, Executive attention (WCST)	Wechsler intelligence and memory battery[d]; Digit Span (Forward and Backward)[d]; C-CPT; VSWM; WCST; TMT; California Verbal Learning Test-Second Edition (CVLT-II)	**No significantly difference**: C-CPT, WCST, TMT, VSWM, Digit span **Smokers better than non-smokers**: On long-term cued recall and recognition/ discriminability in California Verbal Learning Test, with $p < 0.05$ and $p < 0.01$ respectively. A trend toward a significant difference on short-term cued recall, with $p = 0.06$. The significant remained after co-varying for group differences in age, gender, and years of education.
8	Roth et al. (2013)	Attention	C-CPT; CPT-IP; CPT-IP 3 .	**Non-smokers better than smokers**: on the majority (4 out of the 6 composite measures) of the CPT-IP-3 composite scores: d′ ($p < 0.01$), Hit Rate ($p < 0$ 01), Hit Rate Reaction Time Standard Deviation ($p < 0.01$) and Random Errors ($p < 0.05$). In Commission Errors composite (1 out of 6) of the C-CPT, with $p = 0.03$. In of Hit Rate ($p < 0.05$). Hit Response Time SD ($p < 0.01$), and Response Style/Randoms ($p < 0.01$) composites (3 out of 6) of the CPT-IP. **No significantly difference**: in other composites of CPT-IP, CPT-IP-3 and C-CPT.

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Table 2 (*continued*)

9	Zhang et al. (2013)	1. Immediate memory 2. Visuospatial/Constructional index 3. Language 4. Attention 5. Delayed memory	RBANS[b]	**No significantly difference**: no difference in the RBANS total score and individual index score. Excluding former smokers from the non-smoker group, these results remained unchanged
10	Ahlers et al. (2014)	Attention, speed of processing	TAP (Digit Symbol Test, and the TMT)	**Smokers better than non-smokers**: in valid reactions ($p < 0.01$) and errors of omission ($p < 0.01$).
11	Reed et al. (2016)	1. Speed of processing 2. Attention/vigilance 3. Working memory 4. Verbal learning 5. Visual learning 6. Reasoning and problem solving 7. Social cognition	MCCB[c]	**Non-smokers better than smokers:** on the visual learning domain (Brief Visuospatial Memory Test-Revised task), with $p = 0.003$. This finding remained statistically significant when participants who were not on antipsychotic medication ($n = 3$) were excluded, and after Bonferroni correction. **No significantly difference**: in processing speed, attention/vigilance, reasoning/problem solving, working memory, verbal learning, and social cognition

Note: ANT = Attention Network Test; BACS = Brief Assessment of Cognition in Schizophrenia; CPT = Continuous Performance Test; C-CPT = Conner's Continuous Performance Task; CPT-IP = Continuous Performance Test-Identical Pairs; CPT-IP 3 = Third and most difficult, block of the Continuous Performance Test-Identical Pairs; MCCB = MATRICS Consensus Cognitive Battery; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SCWT = Stroop Color Word Test; SCZ = schizophrenia; TAP = Testbatterie zur Aufmerksamkeitsprüfung; TMT = Trial Making Test; VSWM = Visuospatial Working Memory; WCST = Wisconsin Card Sorting Task; WDST = Wechsler Digit Span Task;
NA = Not Available; SD = standard deviation.

[a] Within the 124 non-smokers, 20 of them were former smokers.

[b] RBANS: 1. Immediate Memory (comprised of List Learning and Story Memory tasks); 2. Visuospatial/Constructional index (comprised of Figure Copy and Line Orientation tasks); 3. Language (comprised of Picture Naming and Semantic Fluency tasks); 4. Attention (comprised of Digit Span and Coding tasks); and 5. Delayed Memory (comprised of List Recall, Story Recall, Figure Recall, and List Recognition tasks).

[c] BACS: 1. Verbal Memory by the List Learning task; 2. Working Memory by the Digit Sequencing task; 3. Verbal Fluency by the Category Instances task; 4. Processing Speed by the Symbol Coding task; 5. Problem Solving by the Tower of London task. 6. Motor Speed by the Token Motor task.

[d] The authors did not report scores.

[e] MCCB: 1. Speed of processing (comprised of Brief Assessment of Cognition in Schizophrenia: Symbol Coding, Category Fluency: Animal Naming, and the Trail Making Test: Part A), 2. Attention/Vigilance (comprised of the CPT-IP), 3. Working memory (comprised of the Wechsler Memory Scale Spatial Span and the Letter-Number Span), 4. Verbal learning (comprised of the Hopkins Verbal Learning Test), 5. Visual learning (comprised of the Brief Visuospatial Memory Test-Revised), 6. Reasoning and problem solving (composed of the Neuropsychological Assessment Battery: Mazes), and 7. Social cognition (comprised of the Mayer-Salovey-Caruso Emotional Intelligence Test: Managing Emotions).

Table 3
Methodological assessment of studies included in the meta-analysis by the modified Newcastle-Ottawa Scale.

Studies	Selection The case definition is adequate with independent validation	Representative-ness of cases	Comparability Cases and controls with comparable education (Or IQ)	Cases and controls with comparable age	Outcome Same method of ascertainment for cases and controls	Similar non-response rate for both groups	Total quality score
Turan et al. (2009)	1	0	0	1	1	1	4
Wing et al. (2011)	1	0	1	1	1	1	5
Ekinci and Ekinci (2012)	1	0	1	1	1	1	5
Hahn et al. (2012)	1	0	0	1	1	1	4
Zhang et al. (2012)	1	0	1	1	1	1	5
Iasevoli et al. (2013)	1	0	1	1	1	1	5
Morisano et al. (2013)	1	0	0	1	1	1	4
Roth et al. (2013)	0	0	0	1	1	1	3
Zhang et al. (2013)	1	0	1	0	1	1	4
Ahlers et al. (2014)	1	0	1	1	1	1	5
Reed et al. (2016)	1	0	0	1	1	1	4

1 represents 'yes' and 0 represents 'no'.

between smoking and cognition could not be examined. Fifth, only English-language databases were searched. Finally, different cognitive measures were used across studies, which hinders more sophisticated analyses, such as subgroup and meta-regression analyses. Moreover, publication bias could not be assessed because only a few studies used the same cognitive measures.

In conclusion, this systematic review and meta-analysis found that smoking schizophrenia patients had worse performance in certain cognitive tasks than non-smoking patients. These findings cast doubts on the veracity of the "self-medication hypothesis" in schizophrenia. The "self-medication" hypothesis needs to be further examined with large-scale prospective cohort studies employing comprehensive cognitive measures to clarify the impact of smoking on cognitive performance in schizophrenia.

Conflict of interest

The authors declare no conflict of interest in conducting this study.

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