Chronic smoking and cognition in patients with schizophrenia: A meta-analysis

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Abstract

Background: Patients with schizophrenia display a very high rate of smoking in comparison with the general population. The aim of the present meta-analysis was to assess the association between cognitive performances and smoking status in patients with schizophrenia.

Methods: This review was registered at PROSPERO, number CRD42019126758. After a systematic search on MEDLINE, PsycINFO, and clinicaltrials.gov databases, all studies measuring neurocognitive performances in both smoking and nonsmoking patients with a diagnosis of schizophrenia were included. Original data were extracted. Standardized mean differences (SMD) were calculated with the means and standard deviations extracted using a random-effect model. Cognitive performances were compared between smoking and nonsmoking patients with schizophrenia. Meta-regressions were performed to explore the influence of sociodemographic and clinical variables on SMD.

Results: Eighteen studies were included in this meta-analysis. Chronic smoking in patients with schizophrenia, compared to nonsmoking, was associated with a significant more important impairment in attention ($p = 0.02$), working memory ($p < 0.001$), learning ($p < 0.001$), executive function (EF) reasoning/problem solving ($p < 0.001$) and speed of processing ($p < 0.001$), but not in delayed memory, EF abstraction/shifting, EF inhibition and language. The meta-regression analysis found that attention impairment could be influenced by age ($p < 0.001$) and Positive and Negative Syndrome Scale (PANSS) total score ($p = 0.006$).

Conclusions: This meta-analysis provides strong evidence that, in patients with schizophrenia, chronic smoking is related to cognitive impairment. This association emphasizes the importance of paying careful attention to both tobacco addiction and cognitive functioning in patients with schizophrenia.

Keywords: Schizophrenia; Smoking; Tobacco; Cognition; Meta-analysis

1. Introduction

The mortality rate in patients with schizophrenia is 2 to 3 times higher than in the general population (Laursen et al., 2012; McGrath et al., 2008; Saha et al., 2007), which leads to a life expectancy reduction from 10 to 25 years (Laursen et al., 2012). Before suicide and accidents, cardiovascular diseases, cancers and respiratory diseases are the leading causes of this excess mortality (Crump et al., 2013; Olfson et al., 2015), making tobacco an important public health issue in these patients. Their risk of smoking is 2 to 5 times higher compared with the general population, with a prevalence of smoking of 70% (Hartz et al., 2014). Patients with schizophrenia also exhibit higher tobacco consumption, higher nicotine dependence and lower smoking cessation rate than the general population (de Leon and Diaz, 2005).

Schizophrenia is associated with an impairment across a wide range of cognitive domains (Dickinson et al., 2007; Fatouros-Bergman et al., 2014; Heinrichs and Zakzanis, 1998; Mesholam-Gately et al., 2009; Schaefer et al., 2013). These cognitive deficits are partly responsible for the functional outcomes of schizophrenia, including impaired social functioning (Fett et al., 2011; Green, 1996; Green et al., 2004, 2000). In the general population, acute nicotine administration improves performances in cognitive domains such as attention and memory, which could contribute to tobacco dependence (Heishman et al., 2010). However, the impact of chronic smoking on cognition is still unclear. Literature highlights cognitive impairment in smokers compared to non-smokers (Conti et al., 2019), as well as an increased risk of cognitive decline and dementia in elderly subjects, current or former smokers (Anstey et al., 2007; Beydoun et al., 2014; Guo et al., 2019).

Several hypotheses have been proposed to explain the association between schizophrenia and smoking, some of them suggesting that tobacco consumption could represent a form of self-medication for patients with schizophrenia, notably through cognitive enhancement (Evans

and Drobes, 2009; Kumari and Postma, 2005). However, research results are heterogeneous. Therefore, the aim of the present meta-analysis was to assess the association between cognitive performances and smoking status in patients with schizophrenia.

2. Methods

2.1. Data sources and study selection process

The study protocol is registered at PROSPERO, number CRD42019126758 (see supplementary materials), and follows the PRISMA guidelines (Liberati et al., 2009) (Data in Brief Tables 1 and 2). We carried out a search on the MEDLINE and PsycINFO databases in January 2020, without any limits on year of publication, using the key words (smoking or tobacco or nicotine or cigarette) and (schizophrenia or schizoaffective disorder or schizophreniform disorder or psychosis) and (cognition or cognitive performance or cognitive function or cognitive functioning or attention or delayed memory or working memory or learning or executive function or abstraction or inhibition or reasoning or problem solving or language or speed of processing). In order to complete this research, we checked on clinicaltrials.gov for further studies. Studies were included if (1) they were published in English in a peer-reviewed journal, (2) they included patients with a diagnosis of schizophrenia, schizoaffective disorder or schizophreniform disorder according to the DSM 3, 4, or 5, or ICD 10, (3) they performed neurocognitive tests in both smoking and nonsmoking patients, (4) they assessed the difference of these tests between these two groups, and (5) they were cross-sectional studies or longitudinal studies with cognitive assessment at baseline. Studies that did not fulfill these five criteria were systematically excluded from the analyses. Study selection was performed by one author (N.C.) and verified by another (B.R.).

2.2. Quality of assessment

Quality assessment of the included studies was performed with the modified Newcastle-Ottawa Scale (NOS), which permits to evaluate the selection, the comparability and the exposure for each article. This assessment was performed by one author (N.C.) and verified by another (B.R.). Any disagreements were discussed with a third author (C.M.).

2.3. Data extraction

When data were not available in the articles, we contacted the corresponding authors (see Acknowledgments) of each included trial by email to improve data collection and obtain the data for both smoking statuses. For each study, we thus obtained the means and standard deviations (SDs) for all neurocognitive performances according to smoking status. Cognitive variables were classified in nine domains: 1) attention, 2) delayed memory, 3) working memory, 4) learning, 5) executive function (EF) abstraction/shifting, 6) EF inhibition, 7) EF reasoning/problem solving, 8) language and 9) speed of processing. This classification was performed with the help of a neuropsychologist (M.B-L.) and based on the classification used in a recent meta-analysis on the association of cannabis with cognitive functioning in adolescents and young adults (Scott et al., 2018).

A set of sociodemographic and clinical variables was defined for the meta-regression analysis. We extracted the means and SDs for age (age variable), the percentages of females (sex variable), the means and SDs for years of illness (duration of illness variable), for years of education (education variable), for verbal intelligence quotient (IQ) (verbal IQ variable), for schizophrenia severity scores (total, positive, negative, and general symptom scores), for tobacco consumption (cigarettes per day, years of smoking, and nicotine dependence score), and for current antipsychotic treatment (chlorpromazine equivalents). Data extraction was performed by one author (N.C.) and verified by another (B.R.).

2.4. Data analyses

Data analyses were performed using RevMan, version 5.3 (Copenhagen, Denmark; the Nordic Cochrane Centre, Cochrane Collaboration). Effect sizes consisted in the standardized mean differences (SMD) between cognitive performances of smoking and nonsmoking patients. According to Cohen's method, SMDs were calculated as the differences between the means of the two groups divided by the pooled SDs. Analyses were performed in all neurocognitive domains defined above: 1) attention, 2) delayed memory, 3) working memory, 4) learning, 5)

EF abstraction/shifting, 6) EF inhibition, 7) EF reasoning/problem solving, 8) language and 9) speed of processing. All analyses were performed with a random-effect model, which considers both between-study and within-study variability (DerSimonian and Laird, 1986). An effect size was considered significant when the 95% CI excluded 0 and when the $P < .05$.

Study heterogeneity was estimated with the Q statistic, which was calculated for all analyses and considered significant when $P < .1$. When a significant level of heterogeneity was reached, the I2 index, an estimate of the total variation across the studies included due to heterogeneity rather than chance, was determined by the equation $I2=[(Q - df)/Q] * 100\%$ (Higgins et al., 2003). I2 values of 25, 50, and 75 were indicative of mild, moderate, and marked heterogeneity, respectively, between trials. In addition, to ensure that the overall results were not influenced by a single study, leave-one-out sensitivity analyses, performed by repeating the analyses with the consecutive exclusion of each study, were carried out for each analysis when more than 2 studies were included.

Funnel plots, plotting the standard error of each SMD against the SMD calculated for each study included, were drawn up when at least 5 individual studies contributed to an overall result, and their asymmetry was analyzed to assess the possible influence of publication and location biases (Higgins and Green, 2008).

Finally, we conducted meta-regression analyses based on simple linear regression models in order to assess the influence of sociodemographic characteristics, PANSS scores, smoking characteristics, and chlorpromazine equivalents on the meta-analysis effect sizes. Regression analyses were only performed when SMDs or heterogeneity were significant and when a reasonable number of data points were available, set at 5 at least.

3. Results

3.1. Article identification process

The article-selection process is described in the Figure 1 according to the PRISMA guidelines. Eighteen studies were included in this meta-analysis. Twelve studies were included in attention analysis (Dickerson et al., 2016; Hahn et al., 2012; Haig et al., 2016; Hong et al., 2011; Kem et al., 2018; Morisano et al., 2013; Reed et al., 2016; Roth et al., 2013; Stramecki et al., 2018; Vermeulen et al., 2018; Wing et al., 2011; Zhang et al., 2012); 6 studies in delayed memory analysis (Dickerson et al., 2016; Morisano et al., 2013; Núñez et al., 2015; Stramecki et al., 2018; Vermeulen et al., 2018; Zhang et al., 2012); 6 studies in working memory analysis (Haig et al., 2016; Iasevoli et al., 2013; Núñez et al., 2015; Rabin et al., 2009; Reed et al., 2016; Vermeulen et al., 2018); 8 studies in learning analysis (Dickerson et al., 2016; Haig et al., 2016; Iasevoli et al., 2013; Morisano et al., 2013; Reed et al., 2016; Stramecki et al., 2018; Vermeulen et al., 2018; Zhang et al., 2012); 6 studies in EF abstraction/shifting analysis (Ahlers et al., 2014; Bidzan, 2014; Hahn et al., 2012; Jurado-Barba et al., 2011; Morisano et al., 2013; Wing et al., 2011); 4 studies in EF inhibition analysis (Jurado-Barba et al., 2011; Morisano et al., 2013; Roth et al., 2013; Wing et al., 2011); 7 studies in EF reasoning/problem solving analysis (Dickerson et al., 2016; Haig et al., 2016; Iasevoli et al., 2013; Reed et al., 2016; Stramecki et al., 2018; Vermeulen et al., 2018; Zhang et al., 2012); 5 studies in language analysis (Dickerson et al., 2016; Iasevoli et al., 2013; Núñez et al., 2015; Stramecki et al., 2018; Zhang et al., 2012); and 8 studies in speed of processing analysis (Ahlers et al., 2014; Haig et al., 2016; Hong et al., 2011; Iasevoli et al., 2013; Morisano et al., 2013; Núñez et al., 2015; Reed et al., 2016; Vermeulen et al., 2018). Details of included studies are shown in Table 1.

3.2. Quality of assessment

The total scores of the NOS were ranged from 3 to 6. The sub-classes scores were ranged from 0 to 1 for the selectivity, from 0 to 3 for the comparability and at 2 for all studies for the exposure. For more details see Data in Brief Table 3.

3.3. Attention

Smokers showed a significant attention impairment compared to non-smokers ($p = 0.02$) (Figures 2 and S1). The leave-one-out analyses led to a loss of statistical significance when excluding Dickerson et al. (2016) ($p = 0.10$) (see Data in Brief Figure 2). For attention test, the best model for meta-regression (adjusted R-squared: 0.97; F-statistic: 89.62; $p = 0,002$) included SMD Age variable (β: -0,95; $p = 0.0009$) and SMD PANSS total score variable (β: -0,57; $p = 0.006$).

3.4. Delayed memory

Smokers showed a statistical trend to a delayed memory impairment compared to non-smokers ($p = 0.09$) (Figures 2 and Data in Brief Figure 3). The leave-one-out analyses showed a significant difference when we excluded Morisano et al. (2013) ($p = 0.02$), and Stramecki et al. (2018) ($p = 0.04$) (Data in Brief Figure 4). Meta-regression analyses did not show significant association between SMD and sociodemographic characteristics, PANSS scores, smoking characteristics, and chlorpromazine equivalents.

3.5. Working memory

Smokers showed a significant working memory impairment compared to non-smokers ($p < 0.001$) (Figures 2 and Data in Brief Figure 5). The leave-one-out analyses did not change the results.

3.6. Learning

Smokers showed a significant learning impairment compared to non-smokers ($p < 0.001$) (Figures 2 and Data in Brief Figure 6). The leave-one-out analyses did not change the results. Meta-regression analyses did not show significant association between SMD and sociodemographic characteristics, PANSS scores, smoking characteristics, and chlorpromazine equivalents.

3.7. EF abstraction/shifting

Regarding EF abstraction/shifting, no difference was found between smokers and non-smokers ($p = 0.61$) (Figures 2 and Data in Brief Figure 7). The leave-one-out analyses did not change the results. Meta-regression analyses did not show significant association between SMD and sociodemographic characteristics, PANSS scores, smoking characteristics, and chlorpromazine equivalents.

3.8. EF inhibition

Regarding EF inhibition, no difference was found between smokers and non-smokers ($p = 0.28$) (Figures 2 and Data in Brief Figure 8). The leave-one-out analyses did not change the results.

3.9. EF reasoning/problem solving

Smokers showed a significant EF reasoning/problem solving impairment compared to non-smokers ($p < 0.001$) (Figures 2 and Data in Brief Figure 9). The leave-one-out analyses did not change the results. Meta-regression analyses did not show significant association between SMD and sociodemographic characteristics, PANSS scores, smoking characteristics, and chlorpromazine equivalents.

3.10. Language

Regarding language, no difference was found between smokers and non-smokers ($p = 0.1$) (Figure 2 and Data in Brief Figure 10). The leave-one-out analyses showed a significant difference when we excluded Dickerson et al. (2016) ($p = 0.02$) (Data in Brief Figure 11).

3.11. Speed of processing

Smokers showed a significant speed of processing impairment compared to non-smokers ($p < 0.001$) (Figure 2 and Data in Brief Figure 12). The leave-one-out analyses led to a loss of statistical significance when excluding Vermeulen et al. (2018) (Data in Brief Figure 13). Meta-regression analyses did not show significant association between SMD and sociodemographic characteristics, PANSS scores, smoking characteristics, and chlorpromazine equivalents.

4. Discussion

This meta-analysis showed that chronic smoking in patients with schizophrenia was associated with a significant impairment in several cognitive functions such as attention, working memory, learning, EF reasoning/problem solving, and speed of processing. No differences were found between smoking and nonsmoking patients in the domains of EF abstraction/shifting, EF inhibition, and language. Furthermore, we found that attention impairment could be influenced by age and PANSS total score.

These results are in line with a recent meta-analysis (Wang et al., 2019), which concluded that smoking patients with schizophrenia had more important deficits in attention and learning functions than non-smokers. However, we also found other smoking-related impairments in working memory, EF reasoning/problem solving and speed of processing, which were not found in the latter (Wang et al., 2019). These differences can be explained by several hypotheses. The first one rests on the number of included studies. Indeed, we included eighteen studies, whereas Wang et al. (2019) only included seven studies, which leads to a major improvement of the statistical power. For instance, regarding the analysis of attention, Wang et al. (2019) only included two studies with a total of 536 smoking patients and 203 nonsmoking patients, while we included twelve studies for a total of 2023 smoking patients and 1030 nonsmoking patients. Another hypothesis is methodological. Wang et al. (2019) chose to perform analyses by tests and not by cognitive domains. For our part, we decided to perform analyses by cognitive domains, in order to improve the statistical power, as was done in another recent meta-analysis (Scott et al., 2018).

In this meta-analysis, we found a more important impairment in chronic smoking patients with schizophrenia for attention, working memory, learning, EF reasoning/problem solving and speed of processing. These cognitive functions are principally supported by a central executive network including the prefrontal cortex (PFC) (notably for attention, working

memory, learning, EF reasoning/problem solving and speed of processing), and other brain structures like hippocampus (notably for learning and delayed memory). Few studies had investigated cerebral abnormalities in patients with schizophrenia according to their smoking status. But some of them found a decrease of grey matter in the left PFC (Yokoyama et al., 2018), dorsolateral PFC and hippocampus (Schneider et al., 2014) in smoking patients with schizophrenia compared to non-smokers. Alterations of white matter as measured by diffusion tensor imaging were also found in smoking patients with schizophrenia, with a reduction of fractional anisotropy in the frontal cortex (Cullen et al., 2012) and internal capsule (Zhang et al., 2010). These anomalies could, in part, account for our results and deeper cognitive impairments in these patients. One hypothesis that could explain such cerebral damages is an increase of oxidative stress in smoking patients (Durazzo et al., 2014; Mazzone et al., 2010; Swan and Lessov-Schlaggar, 2007). Indeed, tobacco smoke contains very high concentrations of reactive oxygen species and other oxidants which could lead to various macromolecular alterations of neuronal, glial and vascular brain tissue, as peroxidation of cellular membrane lipids, protein oxidation, DNA strand breakage, RNA oxidation or mitochondrial dysfunction and apoptosis (Durazzo et al., 2014; Mazzone et al., 2010; Valavanidis et al., 2009). Oxidative stress is also known to induce endothelial dysfunction, upregulation of inflammatory cytokines and subsequent atherosclerosis (Csordas and Bernhard, 2013). Resulting alterations of the blood–brain barrier, cerebral blood flow, and brain metabolism, could underlie the aforementioned cerebral abnormalities and cognitive impairments as well (Durazzo et al., 2017, 2015; Mazzone et al., 2010; Swan and Lessov-Schlaggar, 2007). Additionally, confounding factors related to chronic smoking could also be involved in such brain and cognitive deficits, such as alcohol consumption, environmental stress, hypertension and metabolic syndrome, lung dysfunction or depression (Bora et al., 2017; Swan and Lessov-Schlaggar, 2007).

In the general population, smokers without mental illness display cognitive impairments in different domains, such as: attention, working memory, learning, delayed memory, and processing speed, as well as executive functions (abstraction/shifting, inhibition, and reasoning/problem solving), when comparing with non-smokers (Conti et al., 2019; Durazzo et al., 2010). Language has been less explored, mainly through verbal fluency, and deficits in association with tobacco smoking have been inconsistently reported among healthy individuals (Conti et al., 2019; Durazzo et al., 2010). In patients with schizophrenia, the present meta-analysis did not find any difference between smokers and non-smokers in language, neither in EF abstraction/shifting and EF inhibition. These results are partially inconsistent with the deficit reported in healthy smokers in the recent meta-analysis by Conti et al. (2019) in the domain of cognitive flexibility. This could be due to the different construct of the cognitive categories used in our two studies. Indeed, Conti et al. (2019) gathered verbal fluency tasks with Trail Making Test B (TMT-B) and Wisconsin Card Sorting Test (WCST) in a "cognitive flexibility" category larger than the EF abstraction/shifting domain of the present meta-analysis, and highlighted a negative association with smoking that we did not find. As a consequence, verbal fluency was not independently assessed in their study and cannot be compared to our results in language function. However, and similarly to our study, Conti et al. (2019) did not find any association between smoking and cognitive inhibition ("motor impulsivity" in their study), which might be explained by the small number of studies included in both meta-analyses (n=4). In the case of the current meta-analysis, another explanation might be that deficits due to the diagnosis of schizophrenia could mask parallel associations with smoking.

It is important to note that the cross-sectional design of the studies included in the present meta-analysis does not enable to determine a causal relationship between chronic smoking

and cognitive impairment. In accordance with the self-medication hypothesis, patients with deeper cognitive deficits could tend to smoke more in order to alleviate their symptoms. On the other hand, there could be a neurobiological vulnerability to tobacco addiction in schizophrenia, due to deficits in response inhibition or to dysfunction in the dopaminergic reward system and increased impulsivity (Wing et al., 2012b, 2012a). Then, another hypothesis is that non-smokers could display better cognitive functioning than smokers because subjects with less severe cognitive impairments, notably in the domain of inhibition and other executive functions, would be more likely to avoid or quit smoking. Longitudinal studies exploring cognitive functions according to smoking status in patients with schizophrenia are scarce. A recent one (Boggs et al., 2018) did not find any significant effects of prolonged smoking abstinence or resumption on cognitive performances in patients with schizophrenia, but the follow-up did not exceed 6 weeks. Further longitudinal studies, with longer follow-ups and cognitive data preceding the initiation of smoking, are needed to precise the meaning of the association between chronic smoking and cognitive impairment in patients with schizophrenia.

However, studies that investigated first-episode psychosis did not find any significant difference in cognitive performances between smokers and non-smokers in the domains of attention, working memory, learning, delayed memory, EF inhibition, EF abstraction/shifting, EF reasoning/problem solving, language, and processing speed (Hickling et al., 2018; Sánchez-Gutiérrez et al., 2018), or showed better performances in smokers in the domains of attention and working memory (Zabala et al., 2009), all using similar tests as in the present meta-analysis. In a prospective longitudinal study (Segarra et al., 2011), higher performances in smokers in the domains of attention, working memory, and EF inhibition were lost after 6 and 12 months of tobacco abstinence. In comparison with the smoking-related deficits demonstrated in schizophrenia by the present meta-analysis, these findings could indicate that

smoking only provides an initial compensation of baseline deficits which could be deeper in smokers than in non-smokers. This also raises the fact that duration of tobacco use and lifetime tobacco exposure are possible confounding factors that should be taken into account in future research.

This meta-analysis has several limitations. The first one concerns the inclusion criteria of certain studies. Two of them did not select only patients with schizophrenia, schizoaffective or schizophreniform disorder. Stramecki et al. (2018) included patients with schizophrenia-spectrum disorders among which 92.5% were patients with a diagnosis of schizophrenia, schizoaffective or schizophreniform disorder. Another study (Vermeulen et al., 2018) also included patients with non-affective psychosis in the broad sense among which 65.5% were diagnosed as having schizophrenia. When performing the leave-one-out analyses, the exclusion of the study by Stramecki et al. (2018) did not change the results, but the exclusion of the study by Vermeulen et al. (2018) led to a loss of statistical significance regarding the impairment of speed of processing in smoking patients. Then, this result may be explained by the diagnostic heterogeneity of the patients included in this study, although the authors state that all patients were diagnosed as having non-affective psychosis. Furthermore, one study (Iasevoli et al., 2013) specifically included only treatment-resistant schizophrenia patients, while two others (Hong et al., 2011; Roth et al., 2013) did not precise their criteria for schizophrenia or schizoaffective disorder diagnoses. More generally, this meta-analysis included both patients with schizophrenia and schizoaffective disorder, but those with schizoaffective disorder may have a better cognitive functioning than those with schizophrenia (Hill et al., 2013), which may account for the heterogeneity of the study. Lastly, if most of the studies defined other substance use disorders than tobacco smoking as exclusion criterion, some of them did not precise it (Rabin 2009, Roth 2013, Bidzan 2014), or openly included patients with other substance use disorders (Jurado-Barba 2011, Vermeulen 2018),

which could also impact the results. However, the exclusion of these different studies did not change the results, except for the speed of processing analysis when Vermeulen et al. (2018) was excluded, as we mentioned before. Then, other substance use disorders than tobacco smoking may be confounding factors regarding the difference in speed of processing between smokers and non-smokers with schizophrenia. Thus, these variations in inclusion criteria could contribute to the heterogeneity of the meta-analysis.

A second limitation is the selection of only one cognitive test, sub-test or index by study to represent each cognitive domain. For this purpose, we drew upon the classification performed in a recent meta-analysis (Scott et al., 2018) to select relevant tests for each cognitive domain to assess. A last limitation concerns the antipsychotic treatment of the patients. Second-generation antipsychotics show a better improvement of cognitive deficits than first-generation ones in patients with schizophrenia (Désaméricq et al., 2014; Keefe et al., 1999; Woodward et al., 2005), but studies' findings are controversial (Keefe et al., 2007; Nielsen et al., 2015; Takeuchi et al., 2017), and high doses could on the contrary result in cognitive impairment (Elie et al., 2010; Hori et al., 2012, 2006), notably due to an excessive blockade of dopamine D2 receptors (Sakurai et al., 2013). Depending on the antipsychotic, effects on cognition could be different in certain domains (Woodward et al., 2005). For instance, clozapine has been shown to improve verbal fluency more than other second-generation antipsychotics (Woodward et al., 2005). In our case, it can be expected to have been more prescribed within the study by Iasevoli et al. (2013), which only includes treatment-resistant patients. However, the exclusion of this particular study did not change the results when performing the leave-one-out analyses. In the present meta-analysis, the six studies (Ahlers et al., 2014; Dickerson et al., 2016; Hahn et al., 2012; Iasevoli et al., 2013; Stramecki et al., 2018; Zhang et al., 2012) that controlled the antipsychotic treatment between the two groups of patients (smokers and non-smokers) did it in terms of chlorpromazine equivalents, which

does not account for possible antipsychotics' specificities on cognition. Furthermore, tobacco is known to lower serum concentrations of antipsychotics like clozapine and olanzapine (Haslemo et al. 2006; Šagud et al. 2018), so chlorpromazine equivalents may not reflect the same blood levels of antipsychotics in smokers and non-smokers. As a consequence, comparability of smoking and nonsmoking groups for antipsychotic treatment cannot be totally ensured.

The results of the present meta-analysis have important implications in both research and clinical fields. They encourage further longitudinal research to clarify the meaning of the association between chronic smoking and cognitive impairments in patients with schizophrenia. Cross-sectional studies should also be continued, given the relatively small number of studies included and the level of statistical heterogeneity whitin some cognitive functions in the present meta-analysis (e.g. EF inhibition, language, and delayed memory). Future research should also take into account possible confounders as we mentioned before, such as tobacco exposure history, other substance abuses and psychotropic drugs intake, along with relevant psychological and physical conditions. In clinical practice, health professionals should carefully consider tobacco dependence and cognitive performances of patients with schizophrenia, from diagnosis to prevention and treatment.

In conclusion, this meta-analysis provides strong evidence that, in patients with schizophrenia, chronic smoking is related to impairments across several cognitive domains. Although the precise mechanisms of this association remain controversial, it highlights the importance of paying careful attention to both tobacco addiction and cognitive functioning in patients with schizophrenia.

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Figures and table

Figure 1: Article identification process

Figure 2: Forest plot for each cognitive function

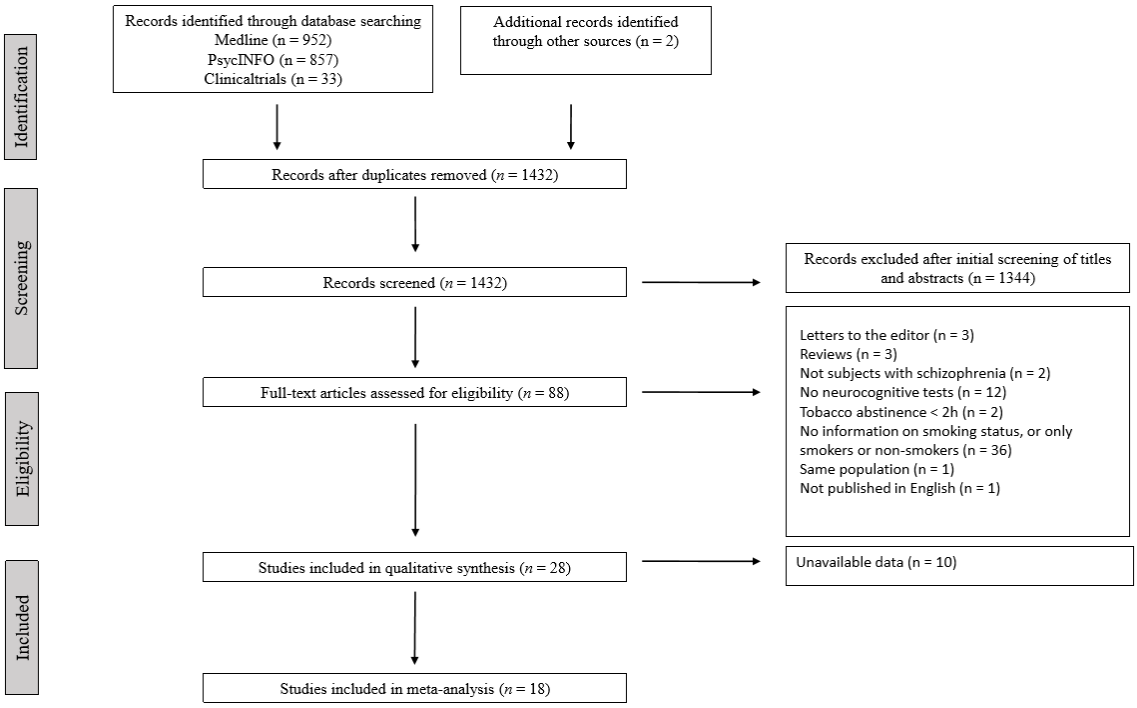
Table 1: Included studies

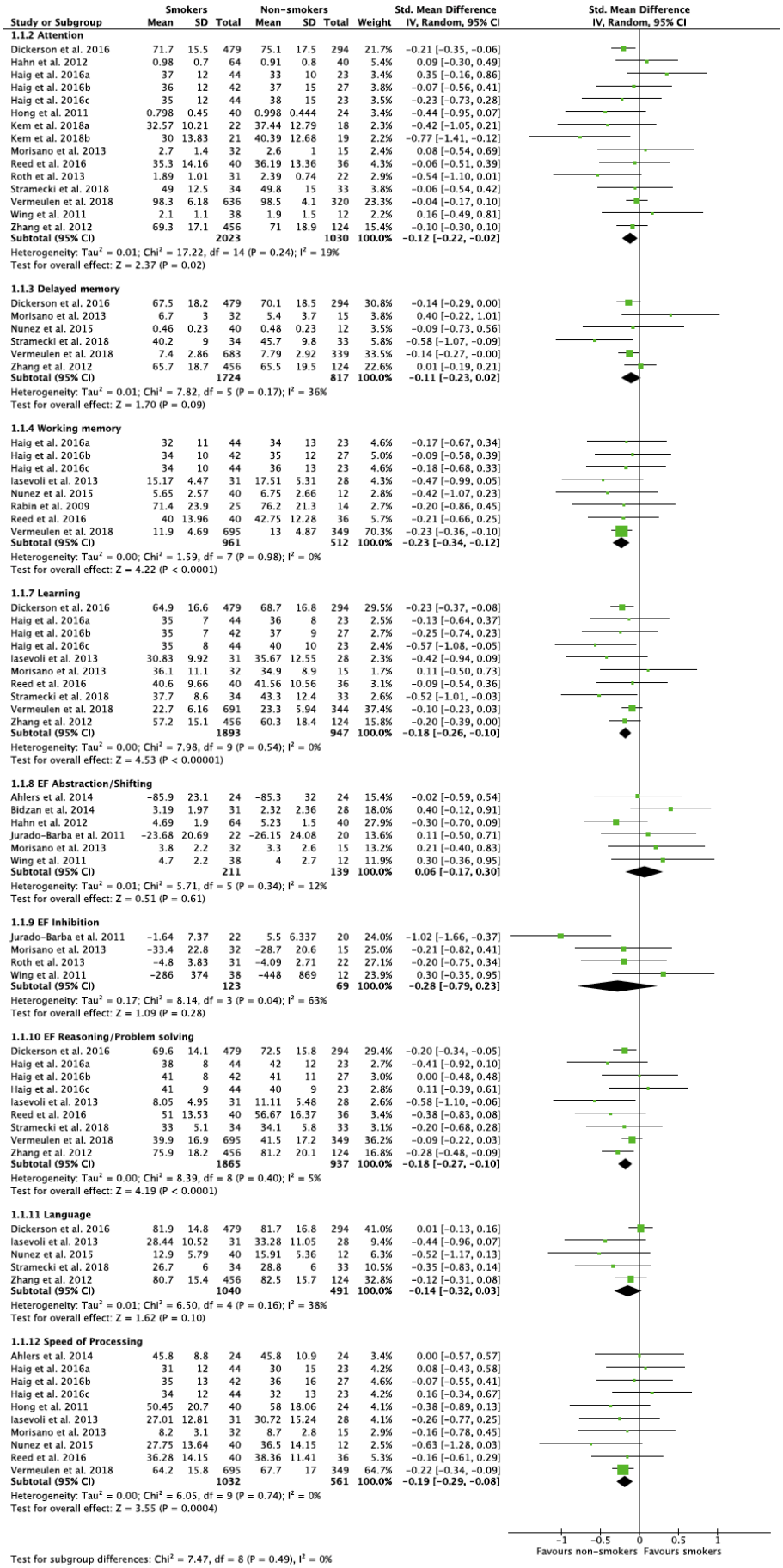
Study	Number of patients included (S/NS)	Female (%) (S/NS)	Mean age (years) (S/NS)	Diagnosis criteria (interview)	Tobacco consumption (c/d)	Cognitive domains	Cognitive tests
Rabin 2009	25/14	46.1/54.5	44.2/38.5	SCZ; SCZ aff DSM-IV (SCID)	22.4 ± 13.3	Attention; Working Memory; EF Abstraction/Shifting	CPT; VSWM task; WCST
Jurado-Barba 2011	22/20	NA / NA	NA / NA	SCZ DSM-IV (SCID)	NA	EF Abstraction/Shifting; EF Inhibition	WCST; SCWT
Hong 2011	40/24	32.5/37.5	42.2/44.0	SCZ; SCZ aff	18.15	Attention; Speed of Processing	CPT; Digit Symbol test
Wing 2011	38/12	36.8/33.3	41.9/42.5	SCZ; SCZ aff DSM-IV (SCID)	20.7 ± 10.5	Attention; EF Abstraction/Shifting; EF Inhibition	CPT; WCST; SCWT
Hahn 2012	64/40	40.6/55	33.6/ 37.5	SCZ DSM-IV	21.4 ± 11.4	Attention; EF Abstraction/Shifting	CPT-IP; ANT; WCST
Zhang 2012	456/124	NA/NA	48.6/46.3	SCZ DSM-IV	NA	Attention; Learning; Delayed Memory; Language; EF Reasoning/Problem Solving	RBANS
Iasevoli 2013	31/28	15.1/21.4	37.6/ 36.6	SCZ DSM-IV (SCID) Treatment resistance [a]	12.5 ± 6.6	Working Memory; Learning; Language; EF Reasoning/Problem Solving; Speed of Processing; Motor Speed (NR)	BACS
Morisano 2013	32/15	18.7/46.6	41.3/ 39.9	SCZ; SCZ aff DSM-IV (SCID)	23.7 ± 10.9	Attention; Working Memory; Learning; EF Abstraction/Shifting; Speed of Processing	CPT; Digit Span (NR); VSWM task; CVLT-II; WCST; TMT-B; TMT-A
Roth 2013	31/22	29.0/36.3	40.2/ 41.0	SCZ; SCZ aff	17.0 ± 13.1	Attention	CPT; CPT-IP
Ahlers 2014	24/24	62.5/58.3	33.6/ 37.8	SCZ DSM-IV	22.5 ± 12.3	Attention (NR); EF Abstraction/Shifting; Speed of Processing	TAP-Divided Attention (NR); TMT-B; Digit Symbol test; TMT-A
Bidzan 2014	31/28	38.7/64.2	38.2/ 40.3	SCZ ICD-10	NA	EF Abstraction/Shifting	WCST
Nuñez 2015	40/12	NA/NA	NA/NA	SCZ DSM-IV	NA	Working Memory; Learning; Delayed Memory; Language; Speed of Processing; Motor Speed	LNS; FDS; Recognition tests; Verbal fluency tests; Digit Symbol test; Digit Copy test
Dickerson 2016	479/294	32.6/45.2	40.7/ 37.9	SCZ; SCZ aff; schizophreniform disorder DSM-IV (SCID)	NA	Attention; Learning; Delayed Memory; Language; EF Reasoning/Problem Solving	RBANS
Haig 2016	130/73	NA/NA	NA/NA	SCZ DSM-IV (MINI)	NA	Attention; Working Memory; Learning; EF Reasoning/Problem solving; Speed of Processing	MCCB
Reed 2016	40/36	20.0/30.5	44.2/45.1	SCZ; SCZ aff DSM-IV (SCID)	20.0 ± 11.2	Attention; Working Memory; Learning; EF Reasoning/Problem Solving; Speed of Processing; Social cognition	MCCB
Kem 2018	43/37	NA/NA	NA/NA	SCZ DSM-IV (SCID)	NA	Attention	MCCB Attention/Vigilance
Vermeulen	636/320	17.2/36.9	26.8/29.2	Non-affective	17.8 ± 8.6	Attention; Working Memory; Learning; Delayed	CPT; Arithmetic task; AVLT immediate

2018				psychotic disorder DSM-IV		Memory; EF Reasoning/Problem Solving; Speed of Processing	recall; AVLT delayed recall; Block design task; Digit Symbol test
Stramecki 2018	34/33	38.2/54.6	31.6/29.0	Schizophrenia-spectrum disorder DSM-IV (OPCRIT checklist)	NA	Attention; Learning; Delayed Memory; Language; EF Reasoning/Problem Solving	RBANS

ANT: Attention Network Test; AVLT: Auditory Verbal Learning Test; BACS: Brief Assessment of Cognition in Schizophrenia; c/d: cigarettes/day; CVLT-II: California Verbal Learning Test-Second Edition; CPT: Continuous Performance Test; CPT-IP: CPT-Identical Pairs; EF: Executive Function; FDS: Forward Digit Span; LNS: Letter-Number Sequencing; MCCB: MATRICS Consensus Cognitive Battery; MINI: Mini International Neuro-psychiatric Interview; NA: not available; NS: non-smokers; NR: not reported; OPCRIT: Operational Criteria for Psychotic Illness; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; S: smokers; SCID: Structured Clinical Interview for DSM-V; SCWT: Stroop Color and Word Test; SCZ: schizophrenia; SCZ aff: schizoaffective disorder; TAP: Test of Attentional Performance; TMT(-A/-B): Trail Making Test (Part A/B); VSWM: Visuospatial Working Memory; WCST: Wisconsin Card Sorting Test.

[a] Non-response to 2 or 3 antipsychotic agents, given at therapeutic doses and ≥ 6 weeks


Identification
Screening
Eligibility
Included
Records identified through database searching
Medline (n = 952)
PsycINFO (n = 857)
Clinicaltrials (n = 33)
Additional records identified through other sources (n = 2)
Records after duplicates removed (n = 1432)
Records screened (n = 1432)
Records excluded after initial screening of titles and abstracts (n = 1344)
Full-text articles assessed for eligibility (n = 88)
Letters to the editor (n = 3)
Reviews (n = 3)
Not subjects with schizophrenia (n = 2)
No neurocognitive tests (n = 12)
Tobacco abstinence < 2h (n = 2)
No information on smoking status, or only smokers or non-smokers (n = 36)
Same population (n = 1)
Not published in English (n = 1)
Studies included in qualitative synthesis (n = 28)
Unavailable data (n = 10)
Studies included in meta-analysis (n = 18)


Smokers
Non-smokers
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
1.1.2 Attention
Dickerson et al. 2016 71.7 15.5 479 75.1 17.5 294 21.7% −0.21 [−0.35, −0.06]
Hahn et al. 2012 0.98 0.7 64 0.91 0.8 40 5.4% 0.09 [−0.30, 0.49]
Haig et al. 2016a 37 12 44 33 10 23 3.4% 0.35 [−0.16, 0.86]
Haig et al. 2016b 36 12 42 37 15 27 3.8% −0.07 [−0.56, 0.41]
Haig et al. 2016c 35 12 44 38 15 23 3.5% −0.23 [−0.73, 0.28]
Hong et al. 2011 0.798 0.45 40 0.998 0.444 24 3.4% −0.44 [−0.95, 0.07]
Kem et al. 2018a 32.57 10.21 22 37.44 12.79 18 2.3% −0.42 [−1.05, 0.21]
Kem et al. 2018b 30 13.83 21 40.39 12.68 19 2.2% −0.77 [−1.41, −0.12]
Morisano et al. 2013 2.7 1.4 32 2.6 1 15 2.4% 0.08 [−0.54, 0.69]
Reed et al. 2016 35.3 14.16 40 36.19 13.36 36 4.3% −0.06 [−0.51, 0.39]
Roth et al. 2013 1.89 1.01 31 2.39 0.74 22 2.9% −0.54 [−1.10, 0.01]
Stramecki et al. 2018 49 12.5 34 49.8 15 33 3.8% −0.06 [−0.54, 0.42]
Vermeulen et al. 2018 98.3 6.18 636 98.5 4.1 320 23.3% −0.04 [−0.17, 0.10]
Wing et al. 2011 2.1 1.1 38 1.9 1.5 12 2.2% 0.16 [−0.49, 0.81]
Zhang et al. 2012 69.3 17.1 456 71 18.9 124 15.4% −0.10 [−0.30, 0.10]
Subtotal (95% CI) 2023 1030 100.0% −0.12 [−0.22, −0.02]
Heterogeneity: Tau² = 0.01; Chi² = 17.22, df = 14 (P = 0.24); I² = 19%
Test for overall effect: Z = 2.37 (P = 0.02)
1.1.3 Delayed memory
Dickerson et al. 2016 67.5 18.2 479 70.1 18.5 294 30.8% −0.14 [−0.29, 0.00]
Morisano et al. 2013 6.7 3 32 5.4 3.7 15 3.8% 0.40 [−0.22, 1.01]
Nunez et al. 2015 0.46 0.23 40 0.48 0.23 12 3.5% −0.09 [−0.73, 0.56]
Stramecki et al. 2018 40.2 9 34 45.7 9.8 33 5.8% −0.58 [−1.07, −0.09]
Vermeulen et al. 2018 7.4 2.86 683 7.79 2.92 339 33.5% −0.14 [−0.27, −0.00]
Zhang et al. 2012 65.7 18.7 456 65.5 19.5 124 22.6% 0.01 [−0.19, 0.21]
Subtotal (95% CI) 1724 817 100.0% −0.11 [−0.23, 0.02]
Heterogeneity: Tau² = 0.01; Chi² = 7.82, df = 5 (P = 0.17); I² = 36%
Test for overall effect: Z = 1.70 (P = 0.09)
1.1.4 Working memory
Haig et al. 2016a 32 11 44 34 13 23 4.6% −0.17 [−0.67, 0.34]
Haig et al. 2016b 34 10 42 35 12 27 5.0% −0.09 [−0.58, 0.39]
Haig et al. 2016c 34 10 44 36 13 23 4.6% −0.18 [−0.68, 0.33]
Iasevoli et al. 2013 15.17 4.47 31 17.51 5.31 28 4.3% −0.47 [−0.99, 0.05]
Nunez et al. 2015 5.65 2.57 40 6.75 2.66 12 2.8% −0.42 [−1.07, 0.23]
Rabin et al. 2009 71.4 23.9 25 76.2 21.3 14 2.7% −0.20 [−0.86, 0.45]
Reed et al. 2016 40 13.96 40 42.75 12.28 36 5.7% −0.21 [−0.66, 0.25]
Vermeulen et al. 2018 11.9 4.69 695 13 4.87 349 70.3% −0.23 [−0.36, −0.10]
Subtotal (95% CI) 961 512 100.0% −0.23 [−0.34, −0.12]
Heterogeneity: Tau² = 0.00; Chi² = 1.59, df = 7 (P = 0.98); I² = 0%
Test for overall effect: Z = 4.22 (P < 0.0001)
1.1.7 Learning
Dickerson et al. 2016 64.9 16.6 479 68.7 16.8 294 29.5% −0.23 [−0.37, −0.08]
Haig et al. 2016a 35 7 44 36 8 23 2.5% −0.13 [−0.64, 0.37]
Haig et al. 2016b 35 7 42 37 9 27 2.7% −0.25 [−0.74, 0.23]
Haig et al. 2016c 35 8 44 40 10 23 2.4% −0.57 [−1.08, −0.05]
Iasevoli et al. 2013 30.83 9.92 31 35.67 12.55 28 2.3% −0.42 [−0.94, 0.09]
Morisano et al. 2013 36.1 11.1 32 34.9 8.9 15 1.7% 0.11 [−0.50, 0.73]
Reed et al. 2016 40.6 9.66 40 41.56 10.56 36 3.1% −0.09 [−0.54, 0.36]
Stramecki et al. 2018 37.7 8.6 34 43.3 12.4 33 2.6% −0.52 [−1.01, −0.03]
Vermeulen et al. 2018 22.7 6.16 691 23.3 5.94 344 37.4% −0.10 [−0.23, 0.03]
Zhang et al. 2012 57.2 15.1 456 60.3 18.4 124 15.8% −0.20 [−0.39, 0.00]
Subtotal (95% CI) 1893 947 100.0% −0.18 [−0.26, −0.10]
Heterogeneity: Tau² = 0.00; Chi² = 7.98, df = 9 (P = 0.54); I² = 0%
Test for overall effect: Z = 4.53 (P < 0.00001)
1.1.8 EF Abstraction/Shifting
Ahlers et al. 2014 −85.9 23.1 24 −85.3 32 24 15.4% −0.02 [−0.59, 0.54]
Bidzan et al. 2014 3.19 1.97 31 2.32 2.36 28 18.0% 0.40 [−0.12, 0.91]
Hahn et al. 2012 4.69 1.9 64 5.23 1.5 40 27.9% −0.30 [−0.70, 0.09]
Jurado-Barba et al. 2011 −23.68 20.69 22 −26.15 24.08 20 13.6% 0.11 [−0.50, 0.71]
Morisano et al. 2013 3.8 2.2 32 3.3 2.6 15 13.2% 0.21 [−0.40, 0.83]
Wing et al. 2011 4.7 2.2 38 4 2.7 12 11.9% 0.30 [−0.36, 0.95]
Subtotal (95% CI) 211 139 100.0% 0.06 [−0.17, 0.30]
Heterogeneity: Tau² = 0.01; Chi² = 5.71, df = 5 (P = 0.34); I² = 12%
Test for overall effect: Z = 0.51 (P = 0.61)
1.1.9 EF Inhibition
Jurado-Barba et al. 2011 −1.64 7.37 22 5.5 6.337 20 24.0% −1.02 [−1.66, −0.37]
Morisano et al. 2013 −33.4 22.8 32 −28.7 20.6 15 25.0% −0.21 [−0.82, 0.41]
Roth et al. 2013 −4.8 3.83 31 −4.09 2.71 22 27.1% −0.20 [−0.75, 0.34]
Wing et al. 2011 −286 374 38 −448 869 12 23.9% 0.30 [−0.35, 0.95]
Subtotal (95% CI) 123 69 100.0% −0.28 [−0.79, 0.23]
Heterogeneity: Tau² = 0.17; Chi² = 8.14, df = 3 (P = 0.04); I² = 63%
Test for overall effect: Z = 1.09 (P = 0.28)
1.1.10 EF Reasoning/Problem solving
Dickerson et al. 2016 69.6 14.1 479 72.5 15.8 294 29.4% −0.20 [−0.34, −0.05]
Haig et al. 2016a 38 8 44 42 12 23 2.7% −0.41 [−0.92, 0.10]
Haig et al. 2016b 41 8 42 41 11 27 3.0% 0.00 [−0.48, 0.48]
Haig et al. 2016c 41 9 44 40 9 23 2.8% 0.11 [−0.39, 0.61]
Iasevoli et al. 2013 8.05 4.95 31 11.11 5.48 28 2.6% −0.58 [−1.10, −0.06]
Reed et al. 2016 51 13.53 40 56.67 16.37 36 3.4% −0.38 [−0.83, 0.08]
Stramecki et al. 2018 33 5.1 34 34.1 5.8 33 3.1% −0.20 [−0.68, 0.28]
Vermeulen et al. 2018 39.9 16.9 695 41.5 17.2 349 36.2% −0.09 [−0.22, 0.03]
Zhang et al. 2012 75.9 18.2 456 81.2 20.1 124 16.8% −0.28 [−0.48, −0.09]
Subtotal (95% CI) 1865 937 100.0% −0.18 [−0.27, −0.10]
Heterogeneity: Tau² = 0.00; Chi² = 8.39, df = 8 (P = 0.40); I² = 5%
Test for overall effect: Z = 4.19 (P < 0.0001)
1.1.11 Language
Dickerson et al. 2016 81.9 14.8 479 81.7 16.8 294 41.0% 0.01 [−0.13, 0.16]
Iasevoli et al. 2013 28.44 10.52 31 33.28 11.05 28 9.4% −0.44 [−0.96, 0.07]
Nunez et al. 2015 12.9 5.79 40 15.91 5.36 12 6.3% −0.52 [−1.17, 0.13]
Stramecki et al. 2018 26.7 6 34 28.8 6 33 10.5% −0.35 [−0.83, 0.14]
Zhang et al. 2012 80.7 15.4 456 82.5 15.7 124 32.8% −0.12 [−0.31, 0.08]
Subtotal (95% CI) 1040 491 100.0% −0.14 [−0.32, 0.03]
Heterogeneity: Tau² = 0.01; Chi² = 6.50, df = 4 (P = 0.16); I² = 38%
Test for overall effect: Z = 1.62 (P = 0.10)
1.1.12 Speed of Processing
Ahlers et al. 2014 45.8 8.8 24 45.8 10.9 24 3.4% 0.00 [−0.57, 0.57]
Haig et al. 2016a 31 12 44 30 15 23 4.2% 0.08 [−0.43, 0.58]
Haig et al. 2016b 35 13 42 36 16 27 4.6% −0.07 [−0.55, 0.41]
Haig et al. 2016c 34 12 44 32 13 23 4.2% 0.16 [−0.34, 0.67]
Hong et al. 2011 50.45 20.7 40 58 18.06 24 4.1% −0.38 [−0.89, 0.13]
Iasevoli et al. 2013 27.01 12.81 31 30.72 15.24 28 4.1% −0.26 [−0.77, 0.25]
Morisano et al. 2013 8.2 3.1 32 8.7 2.8 15 2.9% −0.16 [−0.78, 0.45]
Nunez et al. 2015 27.75 13.64 40 36.5 14.15 12 2.5% −0.63 [−1.28, 0.03]
Reed et al. 2016 36.28 14.15 40 38.36 11.41 36 5.3% −0.16 [−0.61, 0.29]
Vermeulen et al. 2018 64.2 15.8 695 67.7 17 349 64.7% −0.22 [−0.34, −0.09]
Subtotal (95% CI) 1032 561 100.0% −0.19 [−0.29, −0.08]
Heterogeneity: Tau² = 0.00; Chi² = 6.05, df = 9 (P = 0.74); I² = 0%
Test for overall effect: Z = 3.55 (P = 0.0004)
Test for subgroup differences: Chi² = 7.47, df = 8 (P = 0.49), I² = 0%
−1 −0.5 0 0.5 1
Favours non-smokers Favours smokers