

Smoking behaviour characteristics of non-selected smokers with childhood Attention Deficit /Hyperactivity Disorder (AD/HD) history: a systematic review and meta-analysis.

Guillaume FOND^b,MD, Anderson Loundou^d, Sebastien GUILLAUME^b,MD PhD, Xavier QUANTIN^c MD PhD, Alexandra MACGREGOR^b,MD, Régis LOPEZ^c, MD PhD, Philippe COURTET^b MD PhD, Paquito BERNARD^c, PhD, Daniel BAILLY^e MD PhD, Mocrane Abbar M.D, Marion Leboyer^a,MD PhD, Laurent Boyer^c MD PhD

^aUniversité Paris Est-Créteil, Pôle de psychiatrie des hôpitaux universitaires H Mondor, INSERM U955, Eq Psychiatrie Génétique, Fondation FondaMentalFondation de coopération scientifique en santé mentale.

^aInserm U1061, Montpellier, Université Montpellier 1, Services universitaires de psychiatrie, université Montpellier 1, CHU Montpellier, F-34000, France

^cDépartement universitaire de pneumonologie et d'addictologie, université Montpellier 1, Epsilon EA 4556, Institut régional du Cancer de Montpellier, CHU Montpellier, France

^d Aix-Marseille Unit, EA 3279 – Public Health, chronic diseases and quality of life - Research Unit, 13005 Marseille, France.

^eUniversité Montpellier 1, INSERM 1061, Centre de référence national narcolepsie hypersomnie idiopathique, Unité des troubles du sommeil, CHU Montpellier F-34000, France

*Corresponding author

Dr Guillaume Fond

Pole de Psychiatrie, Hôpital A. Chenevier, 40 rue de Mesly, Créteil F-94010

tel (33)1 78 68 23 72 fax (33)1 78 68 23 81

guillaume.fond@gmail.com

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Abstract

Introduction. It is unclear whether adult smokers with childhood attention deficit/hyperactivity disorder history (CH) have more severe smoking behaviour than non-CH smokers, while it is clearly suggested that CH adolescents have more severe smoking behaviour than CH adolescents. The aim of the present comprehensive meta-analysis is to determine if CH smokers have more severe smoking behaviour characteristics than those without, and the effect of age on the association between CH and smoking behaviour.

Methods. We included all case-control studies and first round data collection of observational studies addressing the difference in smoking behaviour characteristics of CH smokers vs non-CH smokers, with validated scales or structured interviews; without any language or date restriction.

Results. Nine studies (including 365 smokers with CH and 1708 smokers without) were included. Compared to non-CH smokers, CH smokers smoked significantly more cigarettes (SMD = 0.15, 95% CI 0.01-0.28, $p=0.04$) and began to regularly smoke earlier (SMD = -0.28, 95% CI -0.49;-0.07, $p=0.01$) but were not significantly more nicotine dependent (SMD = 0.23, 95% CI -0.04-0.48, $p=0.08$). After removing the single adolescent study, the significant association between CH and number of daily smoked cigarettes disappeared, and subgroups analyses confirmed that the significant association between CH and number of daily smoked cigarettes disappeared as age increased.

Conclusion. Our meta-analysis illustrates a clinically important link between CH and tobacco smoking in adolescence but not later in life. Further high quality studies are needed to confirm this finding, as only two studies included participants with a mean age below 20 years.

Keywords: Attention Deficit/Hyperactivity Disorder (AD/HD), smoking, nicotine dependence, tobacco.

Introduction

Attention-Deficit/Hyperactivity Disorder (AD/HD) involves impairing core symptoms of inattention and hyperactivity/impulsivity in children (“childhood AD/HD” (CH)) [1]. The “self-medication” theory suggests that subjects treat their inattentive symptoms by nicotine consumption [13, 22]. Other authors suggest that higher novelty seeking among children and adolescents with CH leads to earlier tobacco exposure [41]. Identifying smoking characteristics of CH smokers is of major importance in order to guide further research and to consider offering specific treatments for these smokers in tobacco cessation programs.

It has been suggested that CH adolescents have a high lifetime prevalence of tobacco smoking, smoke more cigarettes and have a younger age at smoking onset [20] (for a recent review of AD/HD and tobacco smoking in adolescents, see [29]). A 16-year follow-up study revealed that nicotine dependence increases over AD/HD subjects’ lifetime (with a rate of 27% in adulthood versus 11% during adolescence) [4]. Contrary to adolescent studies, adult studies (mean age 40 years) focus on populations of smokers in order to initiate and maintain tobacco cessation, so they do not allow to establish a clear link between AD/HD and tobacco smoking. Most of these studies reported no association between CH and number of daily smoked cigarettes, nicotine dependence or age at onset of regular smoking, which seems contradictory with adolescent data [3, 9, 17, 22, 24, 27, 32, 47].

The aim of the present study is to determine if CH smokers have more severe smoking behaviour characteristics than non-CH smokers and whether these characteristics vary according to age.

Method

Search strategy

A specific search strategy was developed for the interface PubMed (MEDLINE database), based on a combination of MeSH terms “attention deficit / hyperactivity disorder”, as well as indexed terms related to “tobacco smoking” from different computerized databases: PubMed (from 1966 to september 2013), Embase (from 1980 to september 2013), PsychINFO (from 1806 to september 2013), BIOSIS (from 1926 to september 2013), Science Direct (from 2006 to september 2013), and Cochrane CENTRAL (from 1993 to september 2013). Furthermore, we searched ProQuest Dissertations and Theses Full Text Database to identify unpublished dissertations.

Criteria for selecting articles

We considered published and unpublished controlled trials for inclusion. Studies were included without any language or date restriction if they met the following criteria: (i) All controlled trials addressing the difference in tobacco consumption in CH smokers versus non-CH smokers(ii) CH diagnoses based on validated scales or structured interviews. The manuscripts with the following criteria were excluded: (i) absence of comparison between CH smokers versus non-CH smokers; (ii) if a standardized mean difference could not be calculated.

Selection of studies and data extraction

One author (A.M.) screened titles and abstracts of database records and retrieved full texts for eligibility assessment. Two authors independently checked the full text records for eligibility (G.F. and L.B.). Disagreements were resolved by consensus discussion.

The manuscripts of the studies were then independently reviewed by two of the authors (G.F. and L.B.). Data were independently extracted into a standard electronic form: first author name, date of publication, country, sample size, AD/HD scales. Any discrepancies were resolved by consensus with a third reviewer (A.M.).

Assessing the methodological quality of included studies (table 1)

The methodological qualities of included studies were assessed independently by two of the authors (G.F. and L.B.) using a validated rating scale for detecting bias in psychiatric case-control studies [21]. We adapted this scale to the subject of this meta-analysis and we explored selection bias of cases (8 items), of controls (4 items) and information bias (1 item). Any discrepancies were resolved by consensus with a third reviewer (A.M.).

Statistical Analyses

We calculated standardized mean differences (SMD) with 95% confidence intervals (CIs) for each study, defined as the difference between the 2 groups' means (smokers with AD/HD history (CH) versus smokers without (non-CH)) divided by the pooled standard deviation of the measurements. We used fixed effects [23] and random effects models [10] which account for between-study heterogeneity by weighting studies similarly, and presented them in the

forest plots. Heterogeneity was assessed using the I² statistic, which represents the percentage of variance due to between-study factors rather than sampling error [16]. We considered values of I² > 50% as indicative of large heterogeneity [43]. We used funnel plots (i.e., which estimate the number of missing studies needed to change the results of the meta-analysis) and the Egger regression intercept (i.e., which assesses the degree of funnel plot asymmetry by the intercept from regression of standard normal deviates against precision) to estimate risk of bias [5]. Forest plots were generated to show SMD with corresponding confidence intervals (CIs) for each study and the overall fixed or random effects pooled estimate. We conducted several sensitivity or influence analyses to determine the impact of several factors on effect size estimates and also to explore potential reasons for heterogeneity or inconsistency. In order to evaluate the effect of age on number of daily smoked cigarettes and nicotine dependence, the SMD were calculated in 3 age-groups (<20 years, 20-40 years, >40 years) and a meta-regression was also performed using the mean age of participants. Analyses were performed with comprehensive meta-analysis software (version 2.0, National Institute of Health) [5].

Results

Study selection

Four hundred and fifty abstracts were initially identified through database searches. We excluded 441 articles because they did not meet the inclusion criteria. The selection process is summarized in Fig. 1. In the end, we included 9 studies conducted between 2005 and 2013 in our quantitative analysis [9, 11, 17, 19, 20, 25, 27, 28, 32].

Study characteristics

Overall, 365 CH smokers and 1708 non-CH smokers were included. Table 1 describes the qualities of the included studies. Overall, the included studies had a low risk of bias. Table 2 describes the key characteristics of the included studies: studied population, country, number of CH smokers and non-CH smokers, mean age, CH diagnosis criteria. Six were conducted in the USA, 2 in Germany and one in France.

Measures

CH was diagnosed with clinical interviews based on DSM-IV criteria in 8 studies. In our previous study, we used the Wender Utah Rating Scale (short version) (WURS) (25 items) which is one of the self-report adult scales that evaluates CH with the most robust psychometric statistics and content validity [2, 7, 26, 33-36, 38, 44]. The cut-off score was >46 [35]. Nicotine (NIC) dependence was assessed by Fagerstrom Test for Nicotine Dependence (FTND) [15] in all of the studies.

Results

CH and daily smoked cigarettes (figure 2): we identified 8 studies comparing daily smoked cigarettes between CH smokers and non-CH smokers. CH smokers smoked significantly more cigarettes than non-CH smokers (SMD = 0.15, 95% CI 0.01-0.28, $p=0.04$).

CH and NIC dependence (figure 3): we identified 7 studies comparing NIC dependence in CH smokers and in non-CH smokers. There was no statistical difference between the two groups (SMD = 0.23, 95% CI -0.04-0.48, $p=0.08$).

CH and age at first cigarette (figure 4): we identified 4 studies comparing age at first cigarette in CH smokers and non-CH smokers. There was no statistical difference in age at first cigarette between the two groups (SMD = -0.10, 95% CI -0.26-0.06, $p=0.20$).

CH and age at onset of regular smoking (figure 5): we identified 7 studies comparing age at onset of regular (daily) consumption between CH smokers and non-CH smokers. CH smokers began to regularly smoke earlier than non-CH smokers (SMD = -0.28, 95% CI -0.49;-0.07, $p=0.01$).

Sensitivity analysis

After removing the study on adolescents [20]; the difference in daily smoked cigarettes between CH and non-CH smokers became non significant. In line with this finding, when we considered age, we found that this difference was higher before the age of 20 (SMD = 0.39, 95% CI 0.33;0.74, $p=0.03$) and tended to decline thereafter (between 20 and 40 years old : SMD = 0.17, 95% CI -0.03;0.37, $p=0.09$; and after 40 years old: SMD = 0.02, 95% CI -

0.21;0.24, $p=0.89$) (figure 6). The meta-regression analysis confirmed graphically this trend although the p -value was superior to 0.05 (slope = -0.012, z -value = -1.61, $p = 0.10$) (see appendix).

Publication bias

On the funnel plots, the studies were reasonably symmetrical, except for 2 outliers studies on nicotine dependence [25] and age at regular smoking onset [9] (Appendix: the four funnel plots). Because the p -values of the Egger's regression intercept were 0.80 (*daily smoked cigarettes*), 0.56 (*NIC dependence*), 0.88 (*age at first cigarette*) and 0.63 (*age at onset of regular smoking*), the asymmetry was considered to be statistically non-significant.

Discussion

To our knowledge, this study is the first meta-analysis that aims to estimate smoking behavior characteristics of CH smokers compared to non-CH smokers. Following a broad search in various databases, we found 9 studies with an overall sample size of 365 CH smokers and 1708 non-CH smokers for this meta-analysis.

The first finding of our study is that CH smokers consume significantly more cigarettes than non-CH smokers do. However, this link doesn't seem to be uniform throughout life: on the one hand, we found in the sensitivity analysis that the association between number of cigarettes smoked each day and CH was no longer significant after removing the only adolescent study. On the other hand, we also found that the difference in the number of daily smoked cigarettes between CH smokers and non-CH smokers was higher before the age of 20 than after, with a decreasing gradient (figure 6). This suggests that the association between CH and tobacco smoking is stronger in adolescents than in adults. Two explanations for this result may be suggested: on one hand, the number of daily smoked cigarettes increases throughout life in non-CH smokers, thus rendering the difference between CH-smokers and non-CH smokers non-significant in samples of 40 year-old smokers [18], and in the other hand, AD/HD symptomatology (especially hyperactive symptoms) improves throughout life, which may attenuate the difference between smokers with AD/HD history and those without. Further studies are warranted to determine if smokers with persistent AD/HD in adulthood have heavier smoking behavior than smokers with AD/HD history. We tried to

answer to this question in a previous study including 373 smokers [11], and found no significant difference. Studies are too few in number to answer to this question with a meta-analytic approach and future studies should focus on this point.

We also found that CH smokers were not statistically more NIC dependent than non-CH smokers ($p=0.08$). Only one of the included studies found a significant association between AD/HD and NIC dependence [25] whereas the others found none. This result is not consistent with previous results suggesting that CH smokers are significantly more likely to experience a certain number of nicotine withdrawal symptoms, including irritability and difficulty concentrating [32]. Only one of the studies that found no significant association between AD/HD and NIC dependence was conducted on subjects under the age of 20, however a single study is not sufficient enough to assert that CH adolescent smokers are not significantly more NIC dependent than non-CH adolescent smokers and further studies in adolescent smokers' samples are warranted. As NIC dependence was not assessed in the second study of smokers aged <20 , this lack of data may explain the difference in our results between daily smoked cigarettes and NIC dependence.

The third finding of our study is that CH smokers began to regularly consume tobacco earlier than non-CH smokers, while there was no significant difference for age at first cigarette. CH seems to be a risk factor for earlier regular smoking but not for younger age at first cigarette, which is not consistent with the hypothesis of novelty seeking (CH adolescents may seek more new experiences than non-CH adolescents)[31]. These findings are however consistent with the self-medication hypothesis, i.e. that CH adolescents may attempt to improve their attention abilities by nicotine auto-administration. It can be therefore reasonably suggested that public health interventions should focus on the prevention of early tobacco smoking initiation in AD/HD adolescent, and on early tobacco cessation in AD/HD adolescent smokers by specific therapies.

AD/HD treatments (such as methylphenidate) have also been suggested to play a role in earlier and enhanced tobacco consumption, however it remains unclear which of the illness or the treatment may induce more severe smoking behaviour[6, 8, 12, 14, 30, 37, 40, 42, 45, 46]. None of the included studies reported data on current or previous consumption of methylphenidate and its association with tobacco smoking, which is a clear limitation for our understanding of the link between CH and tobacco smoking behavior. Further studies should include AD/HD medication history in order to determine whether AD/HD or AD/HD

medication are associated with higher tobacco smoking.

Our review has several limitations. Associations with several outcomes and subgroup analyses could not be evaluated owing to the paucity of data. These include expired carbon monoxide levels (an objective marker of tobacco smoking), psychiatric comorbidities (alcohol and other substance dependencies, depression status) and medications. As most of the studies recruited smokers in a hospital or via various media outlets, and consecutively administered a structured interview or a questionnaire of CH, it is unlikely that controls were not comparable to cases (selection bias), and as the number of daily smoked cigarettes was reported independently of CH status, an information bias is also highly unlikely. However, no information about differences between refusers and participants was given in any of the studies: as some trials were smoking cessation trials, it can be hypothesized that refusers may be the heavier smokers and that AD/HD may be more prevalent in this population (non-response bias). Some studies included patients in a hospital, but these patients were outpatients consulting for tobacco cessation. As mentioned above, it is unclear if this population is representative of the general population of smokers, but this population is at least representative of smokers seeking to quit smoking. All these biases should be taken into account for further studies. Last but not least, studies are few in number and only three Western countries were represented (USA, Germany and France). The tests for funnel plot asymmetry should not be used with less than 10 studies due to the power lack to detect a real asymmetry[39]. In the same way, statistical power was probably too low to detect a significant result in the meta-regression. On the other hand, the low number of studies limits our understanding of the association in various settings and restricts the generalizability of our findings. Further studies in other countries and especially studies in adolescents are warranted to confirm our results.

Conclusion

From a clinical perspective, our meta-analysis clearly suggests that the link between AD/HD history and tobacco smoking is stronger in subjects under the age of 20 than in older adults. All clinicians dealing with adolescent populations, and especially AD/HD adolescents, should keep encouraging their patients to consider early smoking cessation. It is however unclear if improving the detection and the treatment of AD/HD may improve tobacco

cessation.

Conflicts of interest

None declared

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