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ORIGINAL PAPER

Tobacco smoking is associated with antipsychotic medication, physical aggressiveness, and alcohol use disorder in schizophrenia: results from the FACE-SZ national cohort

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Abstract

Tobacco smoking is common in schizophrenia and is one of the main causes of premature mortality in this disorder. Little is known about clinical correlates and treatments associated with tobacco smoking in patients with schizophrenia. Still, a better characterization of these patients is necessary, in a personalized care approach. Aggressiveness and childhood trauma have been associated with tobacco smoking in general population, but this association has never been explored in schizophrenia. Our study examines the clinical and therapeutic characteristics of tobacco smoking in schizophrenia. 474 stabilized patients (mean age = 32.2; 75.7% male gender; smokers $n = 207$, 54.6%) were consecutively included in the network of the FondaMental Expert centers for Schizophrenia and assessed with valid scales. Current tobacco status was self-declared. Aggressiveness was self-reported with Buss–Perry Aggressiveness Questionnaire and Childhood Trauma with Childhood Trauma Questionnaire. Ongoing treatment was reported. In univariate analysis, tobacco smoking was associated with lower education level ($p < 0.01$), positive syndrome ($p < 0.01$), higher physical aggressiveness ($p < 0.001$), alcohol dependence ($p < 0.001$), and First Generation Antipsychotics (FGAs) use ($p = 0.018$). In a multivariate model, tobacco smoking remained associated with physical aggressiveness ($p < 0.05$), current alcohol dependence ($p < 0.01$) and FGA use ($p < 0.05$). No association was observed with childhood trauma history, mood disorder, suicidal behavior, psychotic symptom, global functioning or medication adherence. Patients with tobacco use present clinical and therapeutic specificities, questioning the neurobiological links between tobacco and schizophrenia. They could represent a specific phenotype, with specific clinical and therapeutic specificities that may involve interactions between cholinergic–nicotinic system and dopaminergic system. Further longitudinal studies are needed to confirm the potential efficacy of second generation antipsychotics (SGAs) on tobacco use in schizophrenia and to develop effective strategies for tobacco cessation in this population.

Keywords Tobacco smoking · Schizophrenia · Antipsychotics · Aggressiveness · Childhood trauma · Alcohol dependence

Introduction

Tobacco smoking is common in schizophrenia (SZ) [1]. It is one of the main causes of premature mortality in this disorder [2]. However, despite the high frequency of comorbid tobacco use in schizophrenia, little is known about clinical correlates or pharmacological treatments associated with tobacco smoking in patients.

Compared to non-SZ smokers, smokers with schizophrenia have been found to have younger age at onset of tobacco smoking, earlier onset of the illness or a higher mean pack year [3]. Studies examining the association of smoking status with positive or negative symptoms in patients with schizophrenia yielded inconsistent results [1, 4, 5]. These discrepancies may be explained by the lack of antipsychotic treatment analyses in studies examining clinical

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characteristics in SZ smokers, whereas certain treatments may have an impact on negative or positive symptoms. Second generation antipsychotic (SGAs) have been suggested to be associated with better improvement of both psychotic symptomatology and nicotine dependence [6, 7]. On the other hand, tobacco smoking may increase or decrease antipsychotic metabolism in an antipsychotic-dependent manner, which may in turn impact treatment response [8, 9]. Tobacco cessation efforts are less effective in schizophrenia patients than in general population, despite research which demonstrates that patients have the same desire to quit smoking [10]. This may result from dysexecutive syndrome, which is characterized by intact initial motivation, but decreased pursuit of goals. The self-medication hypothesis and notion of common vulnerability to addiction are also regularly evoked in discussion of the high rate of tobacco dependence in this population [11]. Finally, there is no clear recommendation concerning the treatment of comorbid tobacco smoking in schizophrenia. Efficiency of common tobacco cessation treatment have showed modest results [12]. On the other hand, the effect of depression and other psychotropic drugs (antidepressants, anxiolytics, and anticholinergics) has cursively been explored in schizophrenia while tobacco smoking has been associated with depression and higher anxiolytic consumption [1, 13]. Overall, SGA could be associated with less tobacco smoking in SZ patients.

Finally, it has been suggested that the vulnerability to schizophrenia and nicotine dependence may share common mechanisms [14], somehow outdating the previous hypothesis that patients with schizophrenia use tobacco smoking as a self-medication [5]. Considering tobacco smoking in the assessment of SZ patient, in a clinical purpose as well as in a research purpose, may open new therapeutic and physiopathological fields in the comprehension of schizophrenia, or at least improve our knowledge of this trouble. First, nicotinic acetylcholine receptors are also involved in the regulation of aggressive behaviors, and associations between tobacco smoking and aggressiveness in non-clinical samples have been largely documented [15, 16]. Despite the well-known problems of aggressive behaviors observed in SZ patients [17], this association has never been explored in schizophrenia to date. Finally, while victimization, including adverse childhood experiences, has been associated with adult current tobacco smoking in the general population [18–20], the question has not been yet addressed in schizophrenia. Still, experiencing childhood trauma affects stress responses among victims [21] and, therefore, increases their subsequent risk for substance abuse [22] and schizophrenia [23].

The objective of the present study was, therefore, to determine (i) the prevalence of tobacco smoking in a large national sample of stabilized French outpatients with schizophrenia and (ii) the clinical and treatment characteristics associated with current tobacco smoking. We hypothesized that tobacco smoking would be associated with higher aggressiveness and history of childhood trauma. In addition, it was expected that SGA administration would be negatively associated with tobacco smoking.

Methods

Study population

This study employed a cross-sectional design and relied on data collected by the FACE-SZ cohort (FondaMental Academic Centers of Expertise for Schizophrenia [24], http://www.fondation-fondamental.org). The FACE-SZ cohort is based on a French national network of ten Schizophrenia Expert Centers (Bordeaux, Clermont-Ferrand, Colombes, Créteil, Grenoble, Lyon, Marseille, Montpellier, Strasbourg, Versailles) created by the French Ministry of Research. Stable patients aged above 16 years were referred by their general practitioner or psychiatrist, who received a detailed evaluation report with suggestions for personalized interventions. Patients diagnosed with schizophrenia or schizoaffective disorder according to DSM-IV-TR [25] criteria were enrolled. All patients included were outpatients, living outside the hospital for more than 1 month at the time of evaluation; institutionalized adults were not included.

Data collected

Patients were interviewed by members of the specialized multidisciplinary team of the Expert Centers. Diagnoses interviews were carried out by two independent psychiatrists according to the structured clinical interview for mental disorders (SCID 1.0) [26]. Information on education level, duration of untreated psychosis, and illness duration (in years) was recorded. Illness duration was defined by the number of years between the first psychotic episode (reported by the patient's referring psychiatrist) and the evaluation at the Expert Center. This duration was confirmed with the use of hospitalization records and family interview. Psychotic and general psychopathology was assessed using positive and negative syndrome scale (PANSS) [27]. Current depressive symptoms were evaluated with the calgary depression scale for schizophrenia (CDRS) [28]. A score ≥ 6 indicates a current depressive episode. Manic symptoms were assessed with Young Mania rating scale [29]. Global functioning was evaluated with global assessment functioning (GAF) and adherence to medication was evaluated with brief adherence rating scale (BARS) [30, 31]. History of suicidal attempt was also self-reported and confirmed in medical files. Alcohol and tobacco consumption, as well as ongoing treatment were systematically recorded.

Current smoking was defined as current daily smoking, because non-daily smoking is rare in patients with schizophrenia [2]. Then, participants were considered as smokers if they smoked at least one cigarette daily. Participants who report no smoking or non-daily smoking were further considered as non-smokers, as were participant with nicotine substitute or using e-cigarette. Pack year was defined by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked.

Antipsychotic treatments were classified according to their ATC class. FGAs were defined by ATC class N05AA to AC (phenothiazines), NO5AD (butyrophenones), and NO5AF (thioxanthenes). SGAs were defined by ATC class N05AH (diazepines, oxazepines, thiazepines, and oxepines) and NO5AL (benzamides). All patients were on stable medication for more than 4 weeks and treated by antipsychotics (see Appendix for references of the scales). In addition to antipsychotic treatment, current add-on treatment by antidepressants, mood stabilizers, and benzodiazepines was also recorded. As benzodiazepines may be used punctually (contrary to antidepressants and mood stabilizers), only daily use of benzodiazepines for more than 4 weeks was considered as "benzodiazepine use". All patients were on stable medication for more than 4 weeks.

Aggressiveness was evaluated with the Buss–Perry aggression questionnaire (BPAQ), a self-report scale that provides a valid and reliable measure of aggression in adult population. The BPAQ has 29 items, subdivided in four factors: physical aggression (nine items), verbal aggression (five items), anger (eight items), and hostility (eight items). Only the physical aggression sub-score was considered, reflecting clearly aggressiveness behavior [32]. Moreover, the four sub-scores of the BPAQ are highly correlated ($p < 10^{-3}$) and thus collinear.

Adverse childhood experience was evaluated with the Childhood Trauma Questionnaire, a 28-item self-report inventory that provides a brief, reliable, and valid screening for childhood maltreatment [33, 34].

Ethical concerns

The study was carried out in accordance with ethical principles for medical research involving humans (WMA, declaration of Helsinki) and all participants gave their written informed consent. The assessment protocol was approved by the relevant ethical review board (CPP-Ile de France IX, January 18th, 2010). All data were collected anonymously.

Statistical analysis

The socio-demographic, clinical, and treatment characteristics were compared between the two groups according to their smoking status. Data were expressed as proportions or means and standard deviations. Chi-square test and Student's *t* test were used to compare respectively qualitative and quantitative variables, allowing univariate analyses. Multivariate analyses using multiple linear regressions (simultaneous model) were then performed to determine variables potentially associated with the smoking status. The relevant variables to the models were selected from the univariate analysis based on a threshold p value ≤ 0.20. As more traditional levels (such as 0.05) can fail to identify variables known to be important, we chose a p value cut-off point of 0.20 for the selection process of variables in a multivariate model [35]. The final model incorporated the standardized ß coefficients, which represent a change in the standard deviation of the dependent variable resulting from a change of one standard deviation in the various independent variables. The independent variables with the higher standardized beta coefficients are those with a greater relative effect. Age and sex were forced in the final model as confounding factors. The statistical significance level was set at $p < 0.05$ for a two-sided test. Data were analyzed using the SPSS 15.0 software (SPSS Inc., Chicago, IL). This study being confirmatory, no correction for multiple assessments was carried out [36].

Results

Characteristics of the sample

Overall, 474 patients with schizophrenia were included in this study (non-smokers, $n = 215$; smokers, $n = 259$). Table 1 shows clinical and socio-demographic characteristics of the sample, as well as ongoing treatments. The majority of the sample ($N = 359$; 75.7%) was men, with a sample mean age of 32.2 ± 9.5 years. Mean age at schizophrenia onset was 21.7 ± 6.2 years and mean illness duration was 10.3 ± 8.1 years; with a mean PANSS total score of 71.5 ± 18.7. The prevalence of smoking was 54.6%, with a mean age at tobacco onset of 17.2 years (SD = 3.9). The mean lifetime tobacco consumption was 7.22 pack year (SD = 11.1).

Univariate and multivariate analyses

The results of the univariate analysis are presented in Table 1. In the univariate analyses, tobacco smoking was significantly associated with lower education level (University level) ($p = 0.006$), more positive symptoms ($p = 0.006$), higher scores of physical aggression ($p < 0.001$), and current alcohol dependence ($p < 0.01$). Regarding the antipsychotic treatments, tobacco smoking was associated with FGA use ($p = 0.018$). No associations were observed between tobacco smoking and sex, age of schizophrenia onset, psychotic

Table 1 Socio-demographic, clinical characteristics, and univariate analysis of a sample of 474 patients with schizophrenia as a function of their smoking status

Socio-demographic characteristics	Whole sample ($N=474$)		Non-smokers ($n=215$)		Smokers ($n=259$)		p
	n	(%)	n	%	n	%	
Sex (male)	359	75.7	152	70.7	207	79.9	0.550
University level	290	61.2	146	67.9	144	55.6	0.006
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	32.2	9.5	32.3	10.2	32.0	8.8	0.719
Age at tobacco onset (years)	17.2	3.9					
Lifetime tobacco consumption (pack year)	7.2	11.1					
Illness characteristics							
Age at onset (years)	21.7	6.2	21.9	7.1	21.6	5.5	0.619
Age at first antipsychotic treatment (years)	22.8	6.3	23.0	6.9	22.5	5.7	0.435
Illness duration (years)	10.3	8.1	10.3	8.8	10.4	7.5	0.888
PANSS total score	71.5	18.7	70.8	17.4	72.1	19.8	0.450
PANSS positive score	14.8	5.5	14.0	5.1	15.4	5.8	0.006
PANSS negative score	21.2	7.2	21.8	7.2	20.8	7.2	0.162
PANSS general psychopathology	35.5	10.1	35.1	9.6	35.9	10.5	0.369
Global assessment of functioning (GAF score)	48.7	12.6	48.7	11.8	48.7	11.8	0.933
BPAQ physical aggression score	19.5	7.53	18.0	7.1	20.8	7.6	<0.001
Childhood trauma (CTQ score)	41.6	11.3	40.5	10.5	42.5	11.8	0.062
	n	%	n	%	n	%	
Current depressive episode (CDSS ≥ 6)	117	15.7	51	23.7	66	25.5	0.604
Continuous schizophrenia (versus episodic)	129	29.8	62	32.1	67	27.9	0.341
History of suicidal behavior	27	5.9	9	4.3	18	7.3	0.174
Current manic episode	21	4.8	9	4.5	12	5.1	
Comorbidities							
Current alcohol dependence[a]	35	7.4	2	0.9	33	12.7	<0.001
Treatment variables							
Second generation antipsychotics (versus first generation)	341	88.8	160	93.0	181	85.4	0.018
Antidepressant	83	21.6	45	21.2	38	22.1	0.837
Benzodiazepine use	117	30.5	50	29.1	67	31.6	0.592
Bad observance (BARS score <90)	172	38.9	74	37.8	98	39.8	0.656

Mean(SD) mean +/- standard déviation, aOR, significant results (p value <0.05) in bold; *PANSS* positive and negative symptoms scale for schizophrenia; *CTQ* childhood trauma questionnaire; *CDSS* calgary depression scale for schizophrenia; *BARS* brief adherence rating scale

[a]As defined in the structural clinical interview for mental disorders (SCID-1)

symptoms, history of suicide attempts, childhood trauma, global functioning, or treatment adherence.

In multivariate analysis (Table 2), smoking was still associated with FGA use (adjusted $p=0.042$), with higher scores of physical aggressiveness (adjusted $p=0.028$), and with current alcohol dependence (adjusted $p=0.002$).

Discussion

In a large national sample of non-selected stabilized outpatients with schizophrenia, tobacco smoking was independently associated with higher physical aggressiveness level and alcohol dependence, while SGA administration has been associated with lower tobacco smoking behavior after adjustment for confounding factors. No significant association between tobacco smoking and gender, age of illness onset or psychotic symptomatology, depression, adverse childhood experience, history of suicidal behavior, global functioning, or treatment observance was observed.

The prevalence of current tobacco smoking in the present sample (54.6%) is in line with the previous results [2] and still far higher than in general population in France (around 31% in general population mean aged 40 years, versus 32 in the present study [37]). We found no association of tobacco status with male gender contrary to the general population

Table 2 Factors associated with active tobacco use: multivariate analysis

	Adjusted *p*	OR	95% IC
Socio-demographic characteristics			
University level	0.180	0.712	0.434–01.169
Illness characteristics			
CTQ score	0.633	1.005	0.983–1.028
PANSS, positive score	0.306	1.024	0.979–1.071
BPAQ physical aggression score	0.028	1.040	1.004–0.077
Comorbidities			
Current alcohol dependence[a]	0.002	10.562	2.376–46.962
Treatment variables			
SGAs (versus FGAs)	0.042	0.449	0.207–0.972

OR odd ratio, significant results (p value < 0.05) in bold, *PANSS* positive and negative symptoms scale for schizophrenia, *CTQ* childhood trauma questionnaire, *BPAQ* Buss–Perry aggression questionnaire, *SGAs* second generation antipsychotics, *FGAs* first generation antipsychotics

[a]As defined in the structural clinical interview for mental disorders (SCID-1)

[37], which may indicate either a gender-shared biological vulnerability to tobacco consumption in schizophrenia or a common vulnerability to tobacco consumption and schizophrenia.

The association between smoking and aggressiveness in our sample might be at least in part explained by the role of nicotine use on behavioral regulation. Nicotine may induce signaling alterations through nicotinic acetylcholine receptors (nAChRs) and may impact both mood dysregulations and hostility (for review, see [16]). The role of nAChRs in the modulation of aggressiveness, agitation or hostility has been largely studied in both pre-clinical and clinical models. Animal models suggest that nicotine can reduce aggressive behavior, potentially by influencing serotonergic transmission. In humans a double-blind, placebo controlled trial of transdermal nicotine in adult smokers with schizophrenia has shown a reduction in agitation in the active arm [38], in favor of self-medication. Studies are contradictory on the effect of nicotine on core symptoms of schizophrenia in human model of psychosis [39] or on social cognition in schizophrenia patients [40]. Overall, these discrepant results may be interpreted as a specific neural action of nicotine against agitation and aggression, independently of the underlying mental disease [16]. In non-clinical participants, nicotine reduced the frequency of anger reports in smokers and non-smokers only in high-hostile individuals, independently of smoking status or gender [41]. Combined with the previous results, the present findings suggest that SZ smokers have a higher "basal" physical aggressiveness levels compared to non-smokers, which is in favor of the self-medication hypothesis in these patients, at least to counter this aggressiveness. The hypothesis of nicotine withdrawal (that may increase self-reported aggressiveness) is unlikely because patients were allowed to smoke during the 1-day long evaluation.

The prevalence of current alcohol dependence in our sample was evaluated at 7.4%, lower than that observed in the previous findings (12% in a recent meta-analysis [42]), probably because our patients are all well- stabilized outpatients. The significant association between current alcohol dependence and tobacco consumption in schizophrenia is well known. There is neither comprehensive review of the link between alcohol and tobacco consumption in schizophrenia, nor studies examining the prevalence of both disorders in a large sample [43]. This association has been established in general population and published prevalences of smoking in patients with alcohol use disorder typically are around 80% in clinical populations [44]. This high level of comorbidity is explained at least by cross reinforcement, alcohol, and nicotine potentiating each other's rewarding effects. Future studies detailing the reciprocal impact of tobacco and alcohol in schizophrenia would be of interest.

This study is the first to assess self-reported trauma history in schizophrenia patients as a function of their smoking status. We found no association between adverse childhood experience assessed with CTQ and current smoking in schizophrenia, whereas this association has been found in general population [18–20]. We recently reported an association between severe nicotine dependence in schizophrenia patients and self-reported history of childhood trauma [45], independently of depression. However, this association was very mild (OR = 1.03), although significant, in comparison with what is reported in non-SZ smokers [19]. From a biological point of view, experiencing childhood adversity might lead to several long-lasting rearrangements of brain structure, immune system, and to epigenetic modifications. Nicotinic system could be impacted as well.

Other clinical characteristics are also usually associated to tobacco smoking in general population, such as mood disorder and suicidal behavior [15]. Indeed, the previous studies have shown that smokers have significant lower of concentrations of serotonin and its metabolite in several cerebral key structures, raising the question of a significant impact of nicotine on serotonin function and/or a dysfunction of serotonin system that would predispose patients to both smoking and to suicidal acts [15]. However, neither between depressive disorder nor suicide attempts were associated with the current tobacco use in our sample of SZ patients. We could have expected such results, as aggressive and impulsive behaviors are often linked to suicidal behavior. The contrasted findings between SZ patients and non-SZ smokers could be consistent with the hypothesis that the link between tobacco and schizophrenia is somehow driven

by a specific biological shared vulnerability [43, 46]. Further pre-clinical studies are needed to better understand the specificity of the link between nicotine and schizophrenia etiopathogenesis.

From a therapeutic point of view, SGA use was associated with a lower rate of tobacco smoking. The cross-sectional design of our study precludes any inference of causality of this association. Inconsistent results were found on the influence of FGA versus SGA on tobacco consumption in patients with schizophrenia in the literature. On one hand, SGA showed their efficiency in reducing tobacco smoking in several studies (for review, see [7]). More specifically, clozapine has been suggested as an efficient treatment of comorbid tobacco addiction [1, 47]. SGAs share a common mechanism of a weaker dopamine D2 blockade and/or a broader base of pharmacological action than typical antipsychotics [8, 9]. On the contrary, FGAs including Haloperidol, would increase tobacco smoking [48], mostly by sharing a mechanism of potent antagonism of dopamine D2 receptor [8]. SZ smokers have been suggested to have different genetic variations in the dopamine D2 receptor and a specific profile of occupancy of dopamine D2 receptors by antipsychotic drugs [49, 50]. Overall, we confirm the previous findings suggesting that the use of SGA may be associated with lower tobacco consumption in individuals with schizophrenia. Given the potent side effects of FGAs (especially cognitive impairment and neurological side effects) and the results of the present study, their prescription should not be recommended in patients with schizophrenia and tobacco use disorder.

Our results should be interpreted in light of some limitations. First, due to the cross-sectional nature of the study, it is impossible to input any causality. Therefore, prospective studies are needed to replicate these findings in larger samples. Second, our outpatients' sample is not representative of all patients with schizophrenia, particularly because institutionalized, hospitalized, or highly disabled patients (making assessment difficult) were not referred to the Expert Centers. Third, we noticed missing data concerning cannabis use and all cannabis users were also smokers; it has, therefore, not been possible to include cannabis in the final multivariate model. Further studies should study the association between cannabis use and aggressiveness as well as medication. Fourth, it should also be determined if heavy smokers may have different characteristics compared to other SZ smokers. The daily numbered of smoked cigarette has not been reported and should be evaluated in future studies. As the purpose of this study was to compare smokers and non-smokers, the Fagerstrom questionnaire (only used to evaluate nicotine dependence in smokers) has not been included in the present study. Future studies should include Fagerstrom questionnaire to improve personalized care in SZ smokers. While our study considers participants smoking non-daily or e-cigarette users as non-smokers, they are also exposed to nicotine. The design of the FACE-schizophrenia cohort does not allow taking into account this characteristic. Further study should examine the clinical characteristics associated with this pattern of nicotine exposure in schizophrenia. Finally, the interrater reliabilities of the four PANSS scales are in the 0.80's [51]. However, no inter-reliability has been specifically calculated for the present study. As the Buss and Perry Questionnaire is a self-reported questionnaire, no inter-reliability coefficient should be calculated.

However, this study also endorses clear strengths. The multicentric network of Expert Centers covers the whole French territory and leads to homogenous groups of patients in terms of clinical severity and exposure to tobacco. One of the strengths of this study is also the use of extensive standardized diagnostic protocols across the centers, including the use of hospital records, interviews with SZ patients, their family and psychiatrists. We can also mention the relatively young age of our sample (mean age 32.3 ± 9.5 years) and the inclusion of a large number of potential confounding factors in multivariate analysis.

In conclusion, tobacco smoking is associated with more self-declared physical aggressiveness and alcohol dependence in SZ smokers after adjustment for confounding factors, while SGA administration is significantly associated with a lower rate of tobacco use. Given the recent findings about the impact of tobacco smoking on the risk of psychosis [46] and the results of the present study, tobacco consumption should be thoroughly assessed and treated in patients with schizophrenia and tobacco consumption. SZ smokers could represent a specific phenotype, with specific clinical and therapeutic specificities that may involve interactions between cholinergic–nicotinic system and dopaminergic system. Further longitudinal studies are needed to determine the potential efficacy of SGA on tobacco use in schizophrenia and to develop effective strategies for tobacco cessation in this population.

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Author contribution statement The authors had full access to all of the data in the study and take the responsibility for the integrity of the data and the accuracy of the data analysis. Dr Jasmina Mallet drafted the article and made the literature review. Dr Guillaume Fond and Dr Jasmina Mallet performed the statistical analysis. Pr Franck Schürhoff, Pr Dubertret, Pr le Strat and Guillaume Fond contributed to the interpretation of data and critically revised the article. All the authors were involved in the collection and analysis of the data. All authors contributed to and have approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study has been approved by the appropriate ethics committee and has, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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