RESEARCH ARTICLE

The prevalence of secondhand smoke exposure and related factors among schoolchildren in Northeast Thailand [version 1; peer review: 1 approved, 3 approved with reservations]

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Abstract

Background: The prevalence of tobacco consumption in Thailand has gradually declined; however, the prevalence of exposure to secondhand smoke (SHS) is still high. The objective of this study is to estimate the prevalence of SHS exposure and examine the association between exposure to SHS and depressive symptoms among schoolchildren, and test for moderation by the number of smokers in household.
Methods: We conducted a cross-sectional study of 1105 schoolchildren. Socioeconomics factors, depressive symptoms and exposure to SHS variables were collected. We used the chi-square test for testing the factors associated to SHS exposure. In addition, we used the Mantel Haenszel test for testing interaction effect of depression to SHS exposure by the number of smokers in home. Multiple logistic regression was used to test the factors related to SHS exposure adjusted for confounders.
Results: The prevalence of exposure to SHS was 58.2% (95%CI: 55.2, 61.1). The schoolchildren with abnormal depression status were 1.8 times more likely to have been exposed to SHS (95%CI: 1.3, 2.5). In addition, the number of smokers in the home did not modify the association between exposure to SHS and depressive symptoms (P: 0.964).
Conclusions: An association between exposure to SHS and depressive in schoolchildren was observed, but this relationship was not affected by the number of smokers in children's homes.

Keywords
schoolchildren, adolescent, secondhand smoke exposure, depression, number of smokers

Open Peer Review

Reviewer Status ❓❓✔❓

	Invited Reviewers			
	1	**2**	**3**	**4**
version 1 21 Sep 2020	❓ report	❓ report	✔ report	❓ report

1. **Pongdech Sarakarn** [iD], Khon Kaen University, Khon Kaen, Thailand
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2. **Kyaw Ko Ko Htet** [iD], Ministry of Health and Sports, Pyin Oo Lwin, Myanmar

3. **Hendra Kurniawan**, Syiah Kuala University, Banda Aceh, Indonesia

4. **Roongnapa Khampang**, Health Intervention and Technology Assessment Program, Nonthaburi, Thailand

Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: Intarut N: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Pukdeesamai P**: Data Curation, Methodology, Visualization

Introduction

In Thailand, the prevalence of tobacco consumption among people aged 15 years old or above has decreased from 32.0% in 1991 to 19.1% in 2017; however, the prevalence of exposure to secondhand smoke (SHS) in the home remains quite high, 32.7% in 2017[1]. Exposure to SHS has been linked to several diseases including cancer and heart disease, especially in children and non-smokers[2]. Many strategies have been implemented to reduce non-smokers' exposure to SHS, including legislation to prevent smoking in public places and health promotion[3]. Laws have been passed to ban smoking on public transport, in airports, in restaurants, and in schools; however, this legislation does not cover private places such as the home.

Home is a place where family members in a range of activities, and is a common location for exposure to SHS[4–6]. Most studies to date show that exposure to SHS is linked to depression, including SHS exposure occurring in the home[7–11]. Just one study found no such connection[12]. Limited data is presently available on the association between SHS exposure and depression in schoolchildren. We therefore conducted this study to investigate whether or not there is an association between SHS exposure and depressive symptoms in this population, and whether the number of smokers in children's households affects this association.

Methods

Study design

This cross-sectional survey was conducted in nine schools located in northeast Thailand from August in 2018 to March in 2019.

Sample size calculation

We calculated the sample size for this survey as the following formula: $n = (z_{\alpha/2}^2 \times p \times q) / d^2$ in which α is 0.05; p is 0.232 that was reported from Leung L *et al.*[13], q=1-0.232=0.768; d=0.035. In addition, we multiplied the total sample size with design effect 1.5. So, in total at least 900 participants were needed.

Data collection

Schools were selected by simple random sampling from the list of schools provided by the Office of the Basic Education Commission (OBEC). We contacted nine schools to describe our study and invite them to participate in the study. In each school, students in grades 6 to 8 (13 to 15 years old), were asked to participate in the study. The rationale for using these grades was that students of this age group still mostly stay within their homes outside of school and therefore would be more likely to be exposed to SHS if a smoker was present in the household. The total number of students in grade 7 (Mattayomsuksa 1), grade 8 (Mattayomsuksa 2), and grade 9 (Mattayomsuksa 3) from the selected school was 2278. All were asked to complete the questionnaire by themselves following instructions from a research assistant. Students that were part of the same household as an existing participant or had any psychiatric disorders as identified by their teacher

were excluded. After filling in the self-report questionnaire, students were asked to deliver questionnaires to their guardians to collect information on household variables. A guardian was defined as mother, father, or relation. They were asked to return these questionnaires to a teacher within 7 days. The questionnaire for student and parents are available as extended data[14]. A total of 1103 families completed the questionnaires, equating to a response rate of 48.4% (1103/2278). We excluded 4 cases because there was not reporting of SHS exposure, so a total of 1099 participants were analyzed. Participants provided written informed consent form to participate in this study. A consent form was provided to the children who then took them home for their parents/guardians to review. This included a consent form for the parent/guardian and assent form for the child to complete. The child then returned these to school.

Measurement

Depressive symptoms were measured using the Center for Epidemiological Studies-Depression Scale (CESD) questionnaire. This questionnaire comprises of 20 questions and has a Cronbach's alpha of 0.86, and was translated into the Thai language[15]. For each question, schoolchildren could respond never (0-score), rarely (1-score), often (2-score), or all the time (3-score). The scores for each question were summed, with totals ranging from 0 to 60. If the total scores of the CESD were more than 22, the schoolchildren were identified as having depressive symptoms[16].

For exposure to SHS, the schoolchildren were asked "In the past 7 days, have you inhaled any tobacco smoke?" The available answers were "inhaled on 1–3 days", "inhaled on 4–6 days", "inhaled every day", or "No". Schoolchildren who reported "no" were classified as not having been exposed to SHS, and the others were classified as having been exposed to SHS. We also collected information on variables such as the number of years of school attended, household's income per month, number of smokers in the home, school grade (grade 7, grade 8, and grade 9), perceived danger of exposure to SHS and third hand smoke, self-confidence in avoidance of SHS (scores ranged 0-20), SHS attitude (scores ranged 0-10), SHS knowledge (scores ranged 0-10), and place of exposure to SHS.

Data analysis

The association between variables and exposure to SHS were examined using Chi-square tests or Fisher's exact tests as appropriate. We also tested the effect of the number of smokers per household on the association between depressive symptom and exposure to SHS by using the Mantel-Haenszel Test. For multivariable analysis, we used multiple logistic regression for adjusting potential confounders. All data analysis was performed using R version 3.6.0[17].

Ethics

The Mahasarakham University Research Ethics Board provided ethical approval for this study (Approval number: 115/2018).

Results

A total of 1099 subjects were included in the analysis. The prevalence of exposure to SHS was 58.2% (95%CI: 55.2, 61.1). In this study, 92.9% of guardians had attended 1–6 years of school, 85.2% of participants had a household income less than 10000 Thai Baht (THB; equivalent to 218.37 USD at time of publication), and 20.8% of households had more than one person who was a smoker. Most students were in 7th grade (39.8%), and 63.4% were female. Awareness of the harm caused by SHS exposure and third hand smoke exposure was 35.1% and 57.2%, respectively. The mean scores of self-confidence in avoidance of SHS was 12.7 (SD: 5.5). The mean scores of attitude and knowledge of secondhand smoke exposure were 27.5 (SD: 3.1) and 4.5 (SD: 1.3), respectively. The characteristics of the participants are shown in Table 1 and full details for each participant available as underlying data[14].

Table 1. Characteristics and univariate analysis of participants by exposure to secondhand smoke.

	Total n=1099	No eSHS n=456	eSHS n=643	P value
Household factors				
Relation to participant				0.957
Mothe	179 (16.3)	75 (16.4)	104 (16.2)	
Father	454 (41.3)	186 (40.8)	268 (41.7)	
Relative	466 (42.4)	195 (42.8)	271 (42.1)	
The number of years attended in school				0.54
0	15 (1.4)	6 (1.3)	9 (1.4)	
1-6	1024 (93.2)	421 (92.3)	603 (93.8)	
≥ 7	60 (5.5)	29 (6.4)	31 (4.8)	
Household income per month (Thai baht)				0.342
<10,000	941 (85.6)	385 (84.4)	556 (86.5)	
≥ 10,000	158 (14.4)	71 (15.6)	87 (13.5)	
Number of smokers in house (persons)				< 0.001
None	399 (36.3)	216 (47.4)	183 (28.5)	
1	472 (42.9)	147 (32.2)	325 (50.5)	
≥2	228 (20.7)	93 (20.4)	135 (21.0)	
Schoolchildren factors				
School grade placement				0.565
Grade 7	437 (39.8)	181 (39.7)	256 (39.8)	
Grade 8	322 (29.3)	127 (27.9)	195 (30.3)	
Grade 9	340 (30.9)	148 (32.5)	192 (29.9)	
Gender				0.004
Male	403 (36.7)	190 (41.7)	213 (33.1)	
Female	696 (63.3)	266 (58.3)	430 (66.9)	
Perception about the harm of eSHS				0.778
Strong disagree	69 (6.3)	29 (6.4)	40 (6.2)	
Disagree	62 (5.7)	23 (5.1)	39 (6.1)	
Agree	385 (35.1)	166 (36.6)	219 (34.1)	
Strongly agree	581 (53)	236 (52.0)	345 (53.7)	
Perception about the harm of exposure to third hand smoke				0.046
Strong disagree	58 (5.3)	29 (6.4)	29 (4.5)	
Disagree	108 (9.8)	34 (7.5)	74 (11.5)	
Agree	628 (57.2)	255 (56)	373 (58.0)	
Strongly agree	304 (27.7)	137 (30.1)	167 (26.0)	

	Total n=1099	No eSHS n=456	eSHS n=643	P value
Self-confidence in avoidance of eSHS score				
Mean (SD)	12.7 (5.5)	13.3 (5.7)	12.3 (5.2)	< 0.001
Median (Q1,Q3)	13 (10, 17)	14 (10, 18)	12 (9,16)	
SHS attitude				0.636
Mean (SD)	27.5 (3.1)	27.5 (3.1)	27.5 (3.1)	
Median (Q1,Q3)	28 (25, 30)	28 (25, 30)	28 (26, 30)	
SHS knowledge				0.513
Mean (SD)	4.5 (1.3)	4.5 (1.4)	4.5 (1.3)	
Median (Q1,Q3)	5 (4, 5)	5 (4, 6)	5 (4, 5)	
Place of exposure				
Home	409 (37.2)	0 (0)	409 (63.6)	
Friend's home	108 (9.8)	0 (0)	108 (16.8)	
School	103 (9.4)	0 (0)	103 (16.0)	
Temple	12 (1.1)	0 (0)	12 (1.9)	
Market	88 (8.0)	0 (0)	88 (13.7)	
Public transport	21 (1.9)	0 (0)	21 (3.3)	
Other	47 (4.3)	0 (0)	47 (7.3)	
Multiple exposure				
No exposure	456 (41.5)	456 (100)	0 (0)	
1 place	518 (47.1)	0 (0)	518 (80.6)	
≥ 2 places	125 (11.4)	0 (0)	125 (19.4)	
Center for Epidemiological Studies Depression (CESD)				
Normal	878 (79.9)	390 (85.5)	488 (75.9)	<0.001
Abnormal	221 (20.1)	66 (14.5)	155 (24.1)	

eSHS = Exposure to secondhand smoke

In Table 1, information is presented on the association between participant risk factors and SHS exposure. The results show there was a statistically significant association between SHS exposure and the number of smokers per household (P value: < 0.001), gender (P value: 0.004), awareness of the harm caused by third hand smoke exposure (P value: 0.046), and self-confidence in avoidance of SHS exposure (P value < 0.001). A statistically significant association was not detected between SHS exposure and relation of the parent/guardian to the school child (P value: 0.957), the number of years attended in school (P value: 0.540), household income per month (P value: 0.342), school grade placement (P value: 0.565), perception about the harm of eSHS (P value:0.778), SHS attitude (P value:0.636), and SHS knowledge (P value:0.513). In Table 2, we present results from the multiple logistic regression model to control for confounder factors. Our analysis shows that schoolchildren with an abnormal CESD state are 1.8 times more likely to have been exposed to SHS (95%CI: 1.3, 2.5; P value <0.001) than those with a normal CESD state, with adjustment made for the number of years of school attended, household income per month, perception about the harm caused by SHS exposure, perception about the harm caused by third hand smoke exposure, SHS attitude, SHS knowledge, and self-confidence in avoidance of SHS exposure.

We also investigated the effect of the number of smokers per household. In households with no smokers, schoolchildren who reported depressive symptoms were 1.8 times (95%CI: 1.0, 3.1) more likely to exposed to SHS than those who were not. In households with one smoker, schoolchildren who had depressive symptoms were 1.9 times (95%CI: 1.1, 3.3) more likely to exposed to SHS. Lastly, in households with two or more smokers, schoolchildren who reported depressive symptoms were 1.7 times (95%CI: 0.8, 3.6) more likely to be exposed to SHS than those who reported no depressive symptoms (Table 3). The results of the Mantel-Haenszel test show there was no statistically significant difference between the number of smokers per household and the association between SHS exposure and depression symptoms.

Discussion
This study shows there is a high prevalence of SHS exposure in schoolchildren in northeast Thailand, and a statistically significant association between SHS exposure and depressive

Table 2. Effect of the number of smokers per household on the association between exposure to secondhand smoke and depression.

Number of smokers in house	No depression	Depression	OR (95%CI)	P value
	N with/without eSHS	N with/without eSHS		
0	145/188	38/28	1.8 (1.0, 3.1)	0.043
1	241/124	84/23	1.9 (1.1, 3.3)	0.017
≥2	102/78	33/15	1.7 (0.8, 3.6)	0.140

Homogeneity test (Mantel-Haenszel Testing), P value = 0.964, eSHS = Exposure to secondhand smoke

Table 3. Association between exposure to secondhand smoke and depression symptoms.

	n/N	Crude OR (95%CI)	Adjusted OR (95%CI)
Depression symptoms			
Normal	55.6% (488/878)	1	1
Abnormal	70.1% (155/221)	1.9 (1.4, 2.6)	1.8 (1.3, 2.5)
Number of smokers in house			
0	45.9% (183/399)	1	1
1	68.9% (325/472)	2.5 (1.9, 3.3)	2.5 (1.9, 3.3)
≥2	59.2% (135/228)	1.8 (1.3,258)	1.7 (1.2, 2.4)

Adjusted for the number of years attended in schools, household income per month, perception about the harm of SHS exposure, perception about the harm of third hand smoke exposure, SHS attitude, SHS knowledge, and self-confidence in avoiding SHS exposure scores.

symptoms in these children. The number of smokers per household did not affect this association.

The prevalence of SHS exposure in this study was 58.2%, a higher rate than a comparable study in the US where exposure was 48%[18], and a study in lower-middle-income countries where exposure was 55.9%[19]. The prevalence of tobacco use in Thailand has declined gradually, but the prevalence of SHS exposure is still quite high[1]. This may be due to non-smokers not being aware of the harms of SHS exposure or to smokers continuing to smoke in locations near non-smokers.

When a univariate analysis was performed to test the association between different factors and SHS exposure, and SHS exposure and depressive symptoms, several statistically significant associations were identified. After adjusting for potential confounding factors, we also showed that schoolchildren exposed to SHS tend to have more depressive symptoms than unexposed children. This finding is similar to several previous studies[7,20–22], except one conducted in the Netherlands[12]. Possible reasons for the disparity include differences in sample population and depressive symptom measurement. Previous studies that detected an association between SHS exposure

and depressive symptoms used a predominantly adolescent population[7,20–22], while the study that did not used an adult population. It may be that children and adolescents who are exposed to SHS are not in a position to move away from the smoker, and depressive symptoms are stimulated. Adults, by comparison, have greater autonomy and can more readily avoid SHS exposure.

Our study also investigated whether the number of smokers in a household affects the association between SHS exposure and depression. No interactive effect was detected. The association between SHS exposure and depression might be of equal magnitude regardless of the number of household smokers. Very few studies consider the interaction between known risk factors and the association between SHS exposure and depression. Our assumption was that, if there are more smokers in a household, there would be a greater chance of SHS exposure and depression.

Strengths and limitations
This study has two major strengths. It is the first study to examine how the number of smokers per household affects the association between SHS exposure and depressive symptoms.

Also, the sample size was large, so the findings should be more accurate than smaller-sized studies. Set against these two strengths are the following three limitations. Firstly, the schoolchildren were selected from northeast Thailand, and may not be representative of schoolchildren nationally. Secondly, a cross-sectional study design was used, so we cannot conclude there is a causal relationship between SHS exposure and depressive symptoms. Finally, the survey relied on self-reports, so there may be recall bias with regard to history of exposure.

Conclusion

In this study, we observed the association between SHS exposure and depressive symptoms. However, the number of smokers per household did not affect this association.

Data availability
Underlying data
Harvard Dataverse: Secondhand smoke: https://doi.org/10.7910/DVN/I7KCVH[14]

This project contains the following underlying data:

- datashsfandcesd1000research.tab (data secondhand smoke and cesd – not that Grade 1, 2 and 3 correspond with grade 7 (Mattayomsuksa 1), grade 8 (Mattayomsuksa 2), and grade 9 (Mattayomsuksa 3))

Extended data
Harvard Dataverse: Secondhand smoke: https://doi.org/10.7910/DVN/I7KCVH[14]

This project contains the following extended data:

- parent_questionaire_eng.pdf (parent questionnaire English)

- parent_questionaire_thai.pdf (parent questionnaire Thai)

- student_questionaire_eng.pdf (student questionnaire English)

- student_questionaire_thai.pdf (student questionnaire Thai)

Data are available under the terms of the Creative Commons Zero "No rights reserved" data waiver (CC0 1.0 Public domain dedication).

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Open Peer Review

Current Peer Review Status: ❓ ❓ ✔️ ❓

Version 1

Reviewer Report 26 October 2020

https://doi.org/10.5256/f1000research.28736.r71751

❓ **Roongnapa Khampang**

Health Intervention and Technology Assessment Program, Nonthaburi, Thailand

Introduction:

○ Could you please elaborate more on the rationale of the study and the significance of the study to public health? Why did you choose to study the association between SHS and depression instead of other diseases? Is there a lack of evidence in Thailand? Could you also provide a bit more detail on the psychological or biological mechanisms of SHS and depression so that the readers understand why depression is important here and how could SHS associate with depressive symptoms?

○ In the method, you stated that you selected nine schools from northeast Thailand, please also provide detail in the introduction why you are interested in this area and how your findings would benefit the responsible organizations?

Methods:

○ You stated that 9 schools were randomly selected from a list of schools but did not show the distribution of the schools among provinces in northeast Thailand. Were there any schools located in the same province? What were the sizes of the school included in the study? How many schools were located in urban areas and how many were in rural areas? This detail may help readers to understand and justify the representativeness of the study samples and the generalizability of the findings especially the prevalence of SHS.

○ There is no detail on how the students (unit of analysis) were selected. Were all eligible students recruited?

Results:

○ There are some typos in the manuscript such as in Table 1, mother, strongly disagree.

○ There is no information on current smoking status of the students who were interviewed. Many studies found a positive association between smoking and depression and anxiety. Would this missing information influence the main findings?

Discussion:

- You may compare the characteristics of your study samples (both schools and students) with the figures of northeast Thailand to clarify about similarity of your samples and the population of northeast Thailand.

- How would the smoking status of the students influence your findings?

- It would be nice if you could develop policy recommendations drawing from your findings.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology, health policy or program evaluation

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 08 October 2020

https://doi.org/10.5256/f1000research.28736.r71747

✔ **Hendra Kurniawan**

Public Health and Community Medicine Department, Syiah Kuala University, Banda Aceh, Indonesia

- In the background: please clarify clearly which province in Thailand that covers the northeast Thailand area?

- If you used the CESD questionnaire, did you translate it to Thai language and validate it before or did you already have the valid Thai version?

- The category of income; household income less than 10000 Thai Baht, is mean enough or which category? Please state in your discussion part.

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PubMed Abstract | Publisher Full Text

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: public health, pulmonology, health social study

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 06 October 2020

https://doi.org/10.5256/f1000research.28736.r71749

?

Kyaw Ko Ko Htet iD

Department of Medical Research (Pyin Oo Lwin Branch), Ministry of Health and Sports, Pyin Oo Lwin, Myanmar

I have some comments:

1) Introduction:
  - Why do the investigators want to investigate the association between the secondhand smoke exposure and depression among the children? It would be better to explain the magnitude of depression among children in the introduction part.

2) Methods:
  - What is the meaning of p is 0.232?

  - How can response rate 48.4% affect the study result? Is it a study limitation?

3) Measurement:
  - For information about number of smokers in household, who completed this information? It is not clear which information was completed by children and household members.

  - In some countries, grade 8 & 9 students have experience on smoking, no information was found in this study. Can it affect the study result?

4) Results:
  - Table 2: It may need to explain how schoolchildren were exposed to secondhand smoke although there was no smoker in the house.

  - The authors may need to explain the definition of second-hand smoke and third-hand smoke. In the result on perception about the harm of exposure to thirdhand smoke, is it third- or second-hand smoke?

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Public health, NCD, TB

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 06 October 2020

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I have some comments and issues for adding and revising as follows;
1. In introduction, I don't find the literature regarding depression in schoolchildren, could you please add for completion?

2. In data collection, "in grades 6 to 8 " or "in grade 7 to 9", please clarify for this words.

3. Please clarify regarding the number of smokers in house (persons) and place of exposure in home (Table 1). I think both of these variables should be related (e.g. the number of place of exposure is 409, but the number of smokers in house (persons) (including 1,>=2) is 460).

4. In the results (page 5), please check the position of table; may mistake between "table2" and "table3".

5. In practice, I think not only the number of smokers in house (persons) can affect the exposure of smoking, but also the quantity of smoking (per persons) can relate as well. Therefore, this point should be added in the discussion or limitation parts of this study.

6. Finally, this study uses depression of schoolchildren for analyzing with the prevalence of

secondhand smoke exposure, in my opinion "the depression of schoolchildren" should be added in the title name, if possible.

These preliminary results can be important for explanation of the effects of smoking. I think this paper can be useful, especially the schoolchildren group.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Biostatistics.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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