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Short-term effect of air pollution on attention function in adolescents (ATENC!Ó): A randomized controlled trial in high schools in Barcelona, Spain

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ABSTRACT

Background: The recent evidence of the short-term impact of air pollution on youth cognitive functions is based primarily on observational studies.

Objectives: We conducted a randomized controlled trial to assess whether purifying the air of the classrooms produced short-term changes in attention processes of adolescents.

Methods: We recruited a total of 2,123 adolescents (13–16 years old) in 33 high schools in Barcelona metropolitan area (Spain). In each school, adolescents from each class were randomly split into two equal-sized groups and assigned to two different classrooms. A set of two air cleaner devices with the same appearance (one recirculating and filtrating the air and the other only recirculating the air) was used. Each one of the devices was placed at random at one of the two classrooms. Students were masked to intervention allocation and had to complete several computerized activities for 1.5 h, including an attention test (Flanker task) to be performed at baseline and at the end of the intervention. The response speed consistency, expressed as hit reaction time standard error (HRT-SE, in ms), was measured as the primary outcome. Analyses were conducted using conditional linear regressions with classroom as strata, adjusted for variables that may differ from one class to another such as temperature, humidity and carbon dioxide concentration.

Results: Average levels of $PM_{2.5}$ and black carbon throughout the 1.5 h of experiment were 89% and 87%, respectively, lower in the classrooms with air cleaner than in the control classrooms. No differences were found in the median of HRT-SE between classrooms with cleaned air and normal air (percent change: 1.37%, 95% confidence interval: −2.81%, 5.56%). Sensitivity analyses with secondary attention outcomes resulted in similar findings.

Conclusions: Cleaning the air of a classroom to reduce exposure to air pollutants for 1.5 h did not have an impact on the attention function of adolescents. Still, in light of previous evidence suggesting an association between air pollution and attention, further experimental studies should explore other short-term timescales of exposure and age ranges.

Abbreviations: HRT-SE, standard error of the hit reaction time; ANT, Attention Network Task.

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1. Introduction

Air pollution is a major causative agent of non-communicable diseases worldwide (Cohen et al., 2017). Over the last decade, compelling evidence has accumulated on the harmful effects of inhaled pollutants on the respiratory and cardiovascular systems (Thurston et al., 2017). A growing research from animal, epidemiological and toxicology studies has recently pointed out potential adverse effects of air pollution on the central nervous system (Block et al., 2012; Grandjean and Landrigan, 2014; Guxens and Sunyer, 2012; Patten et al., 2020). In particular, traffic-related air pollutants (TRAP) including carbon monoxide (CO), nitrogen oxides (NO_x), particulate matter with a diameter less than 2.5 μm ($PM_{2.5}$), and ultrafine particles (UFP, number concentration of particles less than 0.1 μm) have been linked to an array of adverse neurodevelopmental outcomes in children (e.g. autism spectrum disorders) and neurodegenerative disorders in adults (e.g. Alzheimer's disease) (Power et al., 2016; Suades-González et al., 2015).

Though biological mechanisms linking exposure to air pollution with brain health have yet to be fully elucidated, experts consider oxidative stress and neuro-inflammation amongst the main and basic contributory features (Allen et al., 2017; Thomson, 2019). The potential neurotoxicity of TRAP has been identified by experimental and controlled animal studies observing similar brain responses after exposure to PM and UFP, air pollution components mainly originating from diesel exhaust (Calderón-Garcidueñas et al., 2008; Costa et al., 2017) and sometimes only after a short-term exposure to air pollutants (Levesque et al., 2011). Children and adolescents, whose brains have not reached full maturation, are especially sensitive to these pollutant-induced disease processes (Faustman et al., 2000; Grandjean and Landrigan, 2014; Steinberg, 2005). Findings from observational studies of various child cohorts have shown how long-term exposure to TRAP could be associated with neurodevelopmental impairments such as hyperactivity, poorer cognitive functions and psychomotor deficits (Guxens et al., 2014; Min et al., 2017; Perera et al., 2009; Suglia et al., 2008; Wang et al., 2009).

Considering the possible impact of TRAP on children neurodevelopment, schools have been characterized in the literature as an environment of particular concern since they are often nearby busy roads and are places where children spend much of their time (Forns et al., 2016; Pujol et al., 2016; Saenen et al., 2016; Sunyer et al., 2015; Wang et al., 2009). Several works have been carried out by the scientific community showing how TRAP can influence air pollution exposure levels inside schools (Blondeau et al., 2005; Che et al., 2020; Lee and Chang, 1999; Reche et al., 2014; Rim et al., 2017). There are numerous observational studies linking cognitive and academic performance in youth and air quality in schools measuring a range of pollutants including NO_2, $PM_{2.5}$, BC (Forns et al., 2016; Forns et al., 2017; Sunyer et al., 2015). One prospective cohort study linked the levels of TRAP in schools in Barcelona with the cognitive development of 2,715 children between 7 and 10 years of age (Sunyer et al., 2015). This study showed that children who attend schools with higher air pollution levels had a slower cognitive development (7% annual gain) than those who go to schools with lower levels of air pollution (12% annual gain). Analyzing the different emission sources of $PM_{2.5}$ sampled in the filters, the study concluded that traffic-related $PM_{2.5}$ was the only source of fine particles that affected cognitive development (Basagaña et al., 2016). These results suggest that TRAP have a potential negative and rapid effect on schoolchildren's cognitive development. This same cohort in Barcelona was later used to assess the association between daily variation in TRAP and attention (Sunyer et al., 2017). It was found that the results of attention tests were worse in days with higher air pollution, suggesting a potential acute effect of air pollution on attention.

However, Sunyer et al.'s (2017) study, like most studies investigating the effects of TRAP in schools and students' cognitive functions was observational, and consequently, subjected to potential residual confounding. Plus, with epidemiological observational studies, acute and chronic exposures could be correlated and therefore it is more difficult to disentangle acute versus chronic effects. Currently, relevant studies on air pollution and cognitive functioning in children tend to focus on chronic effects rather than on the acute effects (Clifford et al., 2016). Still, short-term effects have also been reported and they may have very relevant implications. There is substantial evidence from experimental studies of short-term effects of CO_2 levels on cognitive function (Bakó-Biró et al., 2012; Satish et al., 2012; Twardella et al., 2012), and observational studies have also reported short-term effects for other pollutants that are indicators of traffic pollution, including elemental carbon and NO_2 (Lavy et al., 2014; Mizen et al., 2020; Sunyer et al., 2017). For the latter case the evidence is still weak, and in particular the timing of exposure and potential effects is still unknown. Thus, there is a need to better pinpoint the exposure timings in the association between air pollution and cognition in youth. Conducting an experiment of short duration in schools thus becomes an opportunity to confirm the existing evidence on neurodevelopmental risks of exposure to air pollutants in students that so far is mainly observational, and to further investigate the temporality of the effects. Moreover, among the cognitive processes, attention functions are an interesting option to study the neuropsychological effects of air pollution in an experimental setting, as they can fluctuate within the same day and are susceptible to environmental factors (Ballard, 1996; Sunyer et al., 2017).

The evidence about a possible short-term effect of TRAP on students' attention function provided by an experimental study could have a major significance on public health. Such an investigation could inform school environmental health policy and support measures to improve air quality in schools. Extensive research has documented how early life interventions aiming to improve child cognitive development are foundational for socioeconomic success (Knudsen et al., 2006; Shonkoff and Phillips, 2000). Measures in reducing air pollutants in school could thus contribute alleviating important societal and economic consequences.

Therefore, to address the above-mentioned gaps in the literature and provide further knowledge helping to promote a healthier environment for adolescents to grow, we undertook a randomized controlled trial to identify if cleaning the air of a classroom had a short-term impact on the attention function of high-school students. Specifically, our aim was to test the hypothesis that air filtration could result in better performance, relative to the classroom without air filter, in attention measures among adolescents in high schools. Confirming this hypothesis would indicate in return that exposure to air pollution may worsen the attention of students.

2. Methods

2.1. Study design and population

We conducted a randomized controlled trial with 2,123 adolescent students (mean [SD] age of 14.8 [0.4] years) in a total of 33 high schools of the metropolitan area of Barcelona (Spain) (Supplementary Figure S1) between November 2018 and June 2019. Participating high schools were well distributed across the study area. For example, the participating high schools in the city of Barcelona covered the 10 districts of the city. The percentage of students attending public high schools in our sample was 76%, while the percent of students attending public schools in this age range in the study area was 57% (Generalitat de Catalunya, 2021). To recruit students, we presented the objectives and design of the study during teacher training sessions opened to all science teachers from all high schools of Barcelona metropolitan area. Teachers interested in participating signed up in an online form. Teachers from 33 high schools reached out to the research team. The participating high schools distributed informed consent forms in order to have both the students and their parents or legal guardians signed it as an agreement to participate in the study. Only students with signed informed consent and who brought it on the day of the experiment were able to participate.

There were no exclusion criteria for participation in the study. The study was approved by the Parc de Salut Mar Clinical Research Ethics Committee (approval number: 2018/7968/I). The Atencio trial was registered at the US National Institutes of Health (ClinicalTrials.gov) #NCT03762239 and reported according to the CONSORT statement.

2.2. *Study interventions and randomization*

This study was an interventional, randomized, single-blinded, 2-arm trial with equal allocation. Allocation was done completely at random. In other words, in each school, adolescents from each class were randomly split into two equal-sized groups that were randomly assigned to two different classrooms to perform simultaneously the same activity for 1.5 h (details of the randomization algorithm are provided in Supplementary Material). The latter was the maximum length of time allowed to keep the students inside the classrooms. One classroom had an internal air cleaner (recirculation and filtration) and the other had the same device but without the filter (only recirculation). The Pure Airbox device (Zonair 3D) was used to filter the air and the classroom used a sham air cleaner (same device without filters). Both of the devices have electronically commutated motors, which are known to produce very low noise levels. Assignment of cleaner to classroom was also done at random. The study was single-blind, given that adolescents were masked to intervention allocation while the study investigators and field workers were not.

Prior to starting the experiment in both classrooms, trained field workers followed a specific protocol in order to make sure that a number of conditions between the two groups were as similar as possible. Fieldworkers were randomly allocated to the two classrooms. Half an hour before the students were invited to enter in their allocated classroom, the windows were kept opened in order to ventilate the space, doors were closed, and the air cleaners were turned on. Both of the classrooms were situated on the same floor and windows facing at the same direction to the road. Student desks were placed forming a U-shape to give enough free space around the air cleaner devices. During the experiment, one window was left opened by less than two centimeters to prevent CO_2 levels to escalate and window blinds were turned down to reduce heat gain coming from sunlight.

2.3. *Procedures in the classrooms*

In both classrooms, each student was assigned to a laptop. Students were asked to complete several computerized activities for two hours using headphones to block the ambient noise. First, students had to complete an Attention Network Task-Flanker Task (ANT, adult version, Flanker task) (ANT baseline). Thereafter, students had to do an intelligence test (PMAR-R test, Primary Mental Aptitudes – Reasoning) (Thurstone, 1962). The final score of this test, defined as the total number of correct responses, represents a measure for intelligence and was used to adjust for the inductive reasoning aptitude of the student. After completing other tasks not included in the analysis (i.e. watching videos) students had to complete again the ANT (ANT post). While the overall experiment was of two hours, the period of interest in this study analysis was defined as the starting time at ANT baseline until the finish time at ANT post, which represented a period of 1.5 h.

Students were asked to remain in the classroom during all the experiment. Adherence to the intervention was defined as staying in the classroom during the total duration of the experiment, or in exceptional cases (e.g. urgent need to use the toilets, important call), leaving it for less than five minutes.

2.4. *Attention outcomes*

Both primary and secondary outcomes of this study were derived from the post ANT (Forns et al., 2014). This test displayed a row of five arrows appearing either above or below a fixation point. Participants had to use the arrow keys from the keyboard to indicate as quickly as possible if the central arrow was pointing to the left or to the right. They had to ignore the flanker arrows, which randomly pointed in either the same (congruent) or opposite (incongruent) direction than the middle arrow. The target can be preceded by no cue; a center cue or a double cue, which informs about the upcoming of the target but not on its location; or an orienting cue that alerts about the upcoming of the target as well as its location (spatial cue) (Forns et al., 2014). The task was divided into four experimental blocks of 32 trials each for a total of 128 trials.

The primary outcome of this study was the response speed consistency throughout the post ANT. Specifically, this is a measure related to attentiveness calculated as hit reaction time (RT, in ms) standard error for correct responses (HRT-SE). A lower HRT-SE indicates consistent reaction times and thus, a better attention performance (Suades-González et al., 2017).

In addition, we included in this study a total of five secondary outcomes from post ANT. First, impulsivity score, which corresponds to the number of incorrect responses (responses made in the opposite direction to the direction of the target arrow). Second, selective attention score, which refers to the number of omission errors (failure to respond to the stimulus). Third, alerting score, a score computed by subtracting the median reaction time (RT) for double cue from median RT for the no cue condition (calculations performed after removing the incongruent trials). Fourth, orienting score, which is a score computed by subtracting the median RT for spatial cue from the RT for central cue (calculations performed after removing the incongruent trials). Fifth, conflict score or executive attention, a score calculated as the median RT for each flanker condition (across cue conditions) and subtracting the congruent from the incongruent RTs (Suades-González et al., 2017).

2.5. *Exposure assessment*

The primary exposure of interest was the intervention arm (classrooms with air filter versus classrooms without air filter). The secondary exposures of interest were means of $PM_{2.5}$ and BC concentrations levels. The air pollution exposure assessment took place continuously during all the experiment session of two hours. For each classroom, we used a DustTrak® Aerosol Monitor 8520/8530 (TSI, USA) to measure $PM_{2.5}$ concentrations ($\mu g/m^3$), a Microaeth micro-aethalometer sensor AE51 (AethLabs, USA) to measure black carbon (BC, $\mu g/m^3$) levels, and an Extech monitor SD800 (USA) to measure levels of CO_2 (ppm) and values of temperature (^oC) and relative humidity (%). Also, it was after the onset of the study trial that we decided to measure noise. Therefore, were able to measure noise in a subgroup of 22 high schools, using a NSRT-mk2 sound level meter (Class 1, Convergence Instruments, Canada), and obtained the A-weighed equivalent sound pressure level (LAeq, in dB) for the period of the intervention. We calculated mean $PM_{2.5}$, BC and CO_2 concentrations, temperature, relative humidity and Leq from the starting time of the baseline ANT to the finishing time of the post ANT.

2.6. *Sample size calculation*

A previous study detected a mean reduction of 5 ms in HRT-SE calculated from the ANT test, associated with a 37% increase in the concentration of NO_2 (Sunyer et al., 2017). With the air cleaner it was expected to achieve an 80% reduction in the concentration of $PM_{2.5}$, which is why we expected to find a difference of 10 ms in HRT-SE between the group in the filtered classroom and the one in the regular classroom. Bearing in mind that the standard deviation (SD) of HRT-SE is 90 ms (Sunyer et al., 2017), to have a statistical power of 80% with a type I error of 5% in the comparison of the two groups in an unadjusted analysis, it was necessary to include 2,500 students. Assuming a participation of 25 of the 30 children for each participating class, the participation of 100 classes was required. By recruiting high schools with two or more class groups, it was expected to have to recruit about 35 high schools.

2.7. Statistical analysis

The statistical analyses follow a pre-specified statistical analysis plan made public before data collection (Barcelona Institute for Global Health, 2018). Baseline characteristics of adolescents in the two groups were calculated using percentages for categorical variables and medians and 1st and 3rd quartiles for continuous variables. The following baseline variables were summarized: sex, age, PMA-R results, and baseline ANT measures, including attentiveness (HRT-SE), impulsivity, selective attention, alerting score, orienting score and conflict score. P-values corresponded to a permutation test for equal medians, except in the case of sex, for which a permutation test for equal distribution was used. We conducted a permutation test because of the very low counts for category "other" in the variable sex and the skewed distribution of the numeric variables. Students not having completed both ANT tests or showing low accuracy were excluded from the main analysis. An ANT test was considered a low accuracy test when the number of correct responses was less than 70%. A post hoc power analysis was carried out to evaluate the sample size of the main analysis (analytical sample size) (described in Supplementary Material).

We performed both the same principal and sensitivity analysis for the primary and secondary outcomes. The principal analysis was conducted using conditional linear regression with class group as strata. Class group represented the group of students from the same class in the same high school that were randomly split into each arm and that undertook the experiment on the same day and time. Intervention arm (classrooms with air filter versus classrooms without air filter) was the explanatory variable of interest in our model. The primary outcome variable, HRT-SE from post ANT, and the secondary exposure variables, means of $PM_{2.5}$ and BC concentrations, were log-transformed to meet the assumptions of the linear regression model. For those outcomes that were log-transformed, results associated with arm were expressed as the relative (percent) changes in the median of the outcome when comparing the arm with filter in the classroom with the arm without filter in the classroom (control) (Barrera-Gómez and Basagaña, 2015). For untransformed secondary outcome variables, they were expressed as additive changes in the mean of the outcomes. In models using log-transformed mean $PM_{2.5}$ or mean BC, results were computed for a percent increase in the exposure equivalent to a change from the first to the third quartile of exposure. Models were adjusted for covariates selected a priori: year of birth, sex, average temperature during the experimental session, average relative humidity during the experimental session, and average CO_2 concentration during the experimental session, as these conditions could differ between the two classrooms.

Furthermore, sensitivity analyses specified a priori were performed. The principal analysis model was additionally adjusted for the same outcome measured in the baseline session (Model 1), for the results of the PMA-R test (number of correct responses) as a way to control for student's inductive reasoning aptitude (Model 2) and for the mean noise level (LAeq) (Model 3). Based on the principal analysis model, models 4 and 5 replaced the arm indicator by the log-transformed average values of BC or $PM_{2.5}$ from the starting time of baseline ANT until finishing time of post ANT, as air pollution concentrations widely differed between schools. These analyses could better characterize the exposure–response function. Moreover, we conducted sex-stratified analyses using the same methodology described above, as previous studies have suggested sex-specific neurodevelopmental effects of air pollution (Costa et al., 2017; Kern et al., 2017).

We also applied two post hoc sensitivity analyses using the principal analysis model. In one analysis, we avoided adjusting for individual covariates (i.e. sex and year of birth) to prevent overadjustment. In another analysis, we included the participants with low accuracy in the ANT test, as they could reflect a vulnerable group especially affected by the air pollution intervention. All analyses were conducted using Stata 14.0 (StataCorp, College Station, TX, USA) and R 3.5 (R Foundation for Statistical Computing, Vienna, Austria). The dataset is available for download and free use through the file repository Zenodo (Gignac et al., 2020).

3. Results

Based on 33 participating high schools, 2,760 students were estimated eligible for the present study (Fig. 1). As the total number of eligible students was not retrieved at the onset of the study, this estimation was based on the maximum number of students per class ($n = 30$), and thus it was likely to be overestimated. A total of 2123 (79.9%) students were randomized to the classrooms with filter ($n = 1,068$) or the classrooms without filter (1,055) (Fig. 1). The mean number of participating individuals per class group was of 23.9. Two students, one in each arm, did not complete the 2-hours experiment because they had an appointment to the doctor. Baseline characteristics of the analytical sample ($N = 1,993$) were similar in the two study groups (Table 1). There were also no differences when including students that did not complete the ANT tests or with low accuracy (i.e. number of correct responses lower than 70%) ($N = 2,123$) (Supplementary Table S1). In addition, we asked the students to guess in which intervention arm they were allocated. The percentage of correct guesses was 50%, i.e. the same expected by chance. This shows that the masking of the intervention allocation worked.

Among 1.5 h experimental sessions, averages of mean of CO_2 concentrations, Leq, temperature, and relative humidity were similar in both study groups, except for $PM_{2.5}$ and BC mean concentrations (Table 2). Results indicated that average $PM_{2.5}$ and BC concentrations were strongly reduced (89% and 87%, respectively) in classrooms in the intervention group (classrooms with air filter) in comparison with classrooms in the control group (classrooms without air filter). These differences were already observed when participants entered the classroom, as the air cleaner had already been working for 30 min. Fig. 2 shows the distribution of median concentrations of $PM_{2.5}$ and BC between the two groups. Classrooms with air filter had in general very low median concentration levels of both air pollutants. Classrooms without air filter had a wide distribution in pollutant levels, with even some classrooms with levels comparable to those of classrooms with filtered air. This is so because some schools were in small towns and close to natural spaces.

Table 3 presents the changes in attention outcomes when comparing the filter group to the non-filter group. We found a non-significant 1.37% (95% confidence interval (-2.81%, 5.56%)) higher median of HRT-SE in the classrooms with filtered air compared to classrooms with normal air (Table 3). Differences in secondary attention outcomes were also small and non-significant. Moreover, our stratified analysis by sex did not document any appreciable difference in the median of HRT-SE and the secondary attention outcomes between both groups (Supplementary Table S2).

In our sensitivity analyses, we fitted five different models estimating the percent change in attentiveness (HRT-SE) outcome (Table 4). Model 1, 2, 3 resulted in non-significant −0.31%, −0.20 and −1.07% difference, respectively. When we repeated the analyses with $PM_{2.5}$ and BC as the explanatory variables (Model 4 and 5), effects were similar to those found using intervention as arm and were still not significant. The same models but using secondary outcomes resulted in similar findings (Supplementary Table S3). Furthermore, when not adjusting for the individual covariates of sex and year of birth or when including participants with low accuracy in ANT, effects were similar to those found in the main analysis and were still not significant (Supplementary Table S4 and S5).

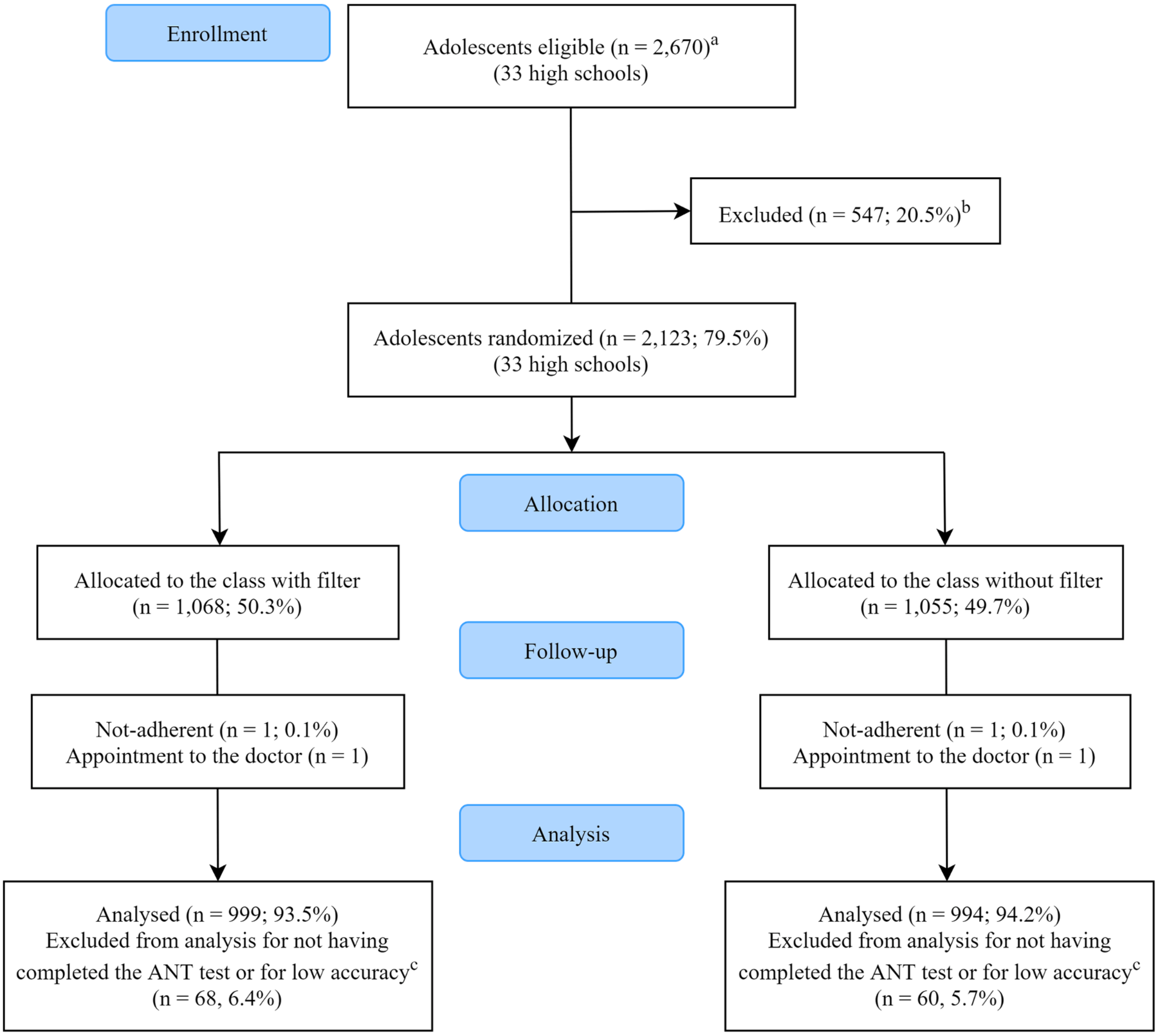

Fig. 1. Flow diagram of study subjects. Note: ANT, Attention Network Task. [a]Estimated number based on the total participating classes (89) and the maximum allowed number of students per class (30). This number likely represents an overestimation, and therefore the reported participation rates are likely underestimated. [b] Reasons for exclusion before allocation were parents or legal guardians who did not sign the consent form or students who declined to participate. [c]A test was considered low accuracy test when the number of correct responses was less than 70%.

Table 1
Baseline characteristics of the study participants (n = 1,993).

Characteristics	Median (25th, 75th percentile)		p-value
	Filter group (N = 999)	Without filter group (N = 994)	
Female sex (%)	51.5	48.6	0.47
Age (year)	14.7 (14.6, 14.8)	14.7 (14.6, 14.9)	0.89
PMA-R (number)[a]	17 (12, 20)	16 (11, 20)	0.08
HRT-SE (ms)	164.1 (114.5, 237.3)	158.6 (110.7, 238.5)	0.27
Impulsivity (number)	2 (1, 3)	2 (1, 3)	1.00
Selective attention (number)	0 (0, 1)	0 (0, 0)	1.00
Alerting score (ms)	34.5 (5, 66)	35.5 (10, 64.5)	0.65
Orienting score (ms)	14 (−12, 40)	14.8 (−9, 40.5)	0.74
Conflict score (ms)	78 (58.5, 100)	76.5 (56, 97.5)	0.39

Note: PMA-R, Primary Mental Aptitudes – Reasoning; HRT-SE, hit reaction time standard error. p-values correspond to a permutation test for equal medians, except in the case of sex, for which a permutation test for equal distribution was used. There were no significant between-group differences at baseline.

[a] Data were available for 1988 adolescents.

4. Discussion

In this randomized controlled trial analyzing 1,993 adolescents of the Barcelona metropolitan area, we did not find that cleaning the air of a classroom to reduce exposure to air pollutants had a short-term impact on adolescents' attention processes. Notwithstanding the absence of differences in attention performance between the two arms, average levels of $PM_{2.5}$ and BC for a period of 1.5 h were 89% and 87% lower in the classrooms with filtered air than in the control classrooms.

This study was conducted in 33 high schools of Barcelona metropolitan area, the latter being one of the most polluted cities in Europe with concentration levels of $PM_{2.5}$ and NO_2 above the WHO recommendations (Rico et al., 2019). In Spain, students spend an average of 30 h per week at high schools (O'Donnell et al., 2010), and thus ensuring healthy school environments is necessary. However, many schools in Barcelona are very close to traffic, and consequently, at risk of being exposed to high ambient air pollution levels. Rivas et al. (2014) observed that the mean $PM_{2.5}$ concentration measured indoor schools in Barcelona was even higher than the mean $PM_{2.5}$ level at the reference urban background station, mainly due to relevant school-related source contributions of $PM_{2.5}$. In our experiment, some classrooms without the air filter reached median concentrations of $PM_{2.5}$ up to 66.5 μg/m^3. Of

Table 2

Average $PM_{2.5}$, BC, CO_2 concentrations, temperature, relative humidity and Leq levels under the filter and non-filter group during the 1.5-hour experimental session.

Mean environmental characteristics (25th, 75th percentile)	Filter group[a]	Without filter group	*p*-value
$PM_{2.5}$ (μg/m^3)	2.5 (1.3, 2.9)	23.0 (15.4, 27.4)	<0.01
BC (ng/m^3)	178.3 (77.0, 214.0)	1384.7 (752.3, 1658.1)	<0.01
CO_2 (ppm)	1874.8 (1510.7, 2129.9)	1930.3 (1556.8, 2187.6)	0.78
Temperature (°C)	22.1 (20.4, 23.3)	22.1 (20.4, 23.0)	0.94
Relative humidity (%)	52.3 (46.8, 56.2)	52.3 (46.1, 57.4)	0.82
Leq (dB)	67.4 (61.2, 64.4)	83.6 (61.6, 65.5)	0.38

Note: BC, black carbon; CO_2, carbon dioxide; dB, decibel; Leq, equivalent continuous sound level; ppm, parts per million; $PM_{2.5}$, particulate matter with diameter less than 2.5. p-values correspond to Wilcoxon Signed-Rank test.

[a] Number of classrooms within the filter group and within the without filter group are 81 and 88, respectively.

note, WHO suggests that the 24-hour mean value of $PM_{2.5}$ should not exceed 25 μg/m^3. However, indoor $PM_{2.5}$ is not necessarily a key indicator of TRAP in schools since it is also generated by other sources such as clothes fibers, chalk dust and sand-filled playgrounds (Rivas et al., 2014). Considering the limitations of using indoor $PM_{2.5}$, we also measured BC in order to have a better indicator of TRAP inside schools. Plus, BC was found highly correlated with UFP (Rivas et al., 2014), the latter being small enough (less than 0.1 μm) to be able to translocate to the brain through the bloodstream from deposits in the respiratory tract (Nemmar et al., 2002). Where the urban background reference for Barcelona presents an average ambient BC concentration of 1200 ng/m^3 (Reche et al., 2011), in this study, a number of classrooms without air filter in our study showed much higher levels.

The randomized design and large sample size of our study provides a strong evidence that filtering the indoor air in schools for 1.5 h did not affect the attention in adolescents during that time interval. Our results may be due to the fact that a short-term relationship between TRAP and attention does not exist, but given the particularities of our trial the following alternative explanations will be discussed: (1) the relationship

Table 3

Changes in attention outcomes comparing the filter group to the non-filter group (n = 1,993).

Attention Outcomes at post ANT	Change	95% CI	*p*-value
Attentiveness, HRT-SE (%)[a]	1.37	(−2.81, 5.56)	0.52
Impulsivity (number)[b]	−0.13	(−0.49, 0.24)	0.50
Selective attention (number)[b]	−0.05	(−0.20, 0.10)	0.47
Alerting score (ms)[b]	−3.38	(−8.51, 1.74)	0.20
Orienting score (ms)[b]	−0.25	(−5.10, 4.60)	0.92
Conflict score (ms)[b]	−1.36	(−4.94, 2.22)	0.46

Note: ANT, Attention Network Task, CI, confidence interval; HRT-SE, hit reaction time standard error. All effects are calculated using conditional linear regression with classroom as a fixed effect. Model was adjusted for year of birth, sex, average temperature during the experimental session, average relative humidity during the experimental session, and average CO_2 concentration during the experimental session.

[a] Association reported as percent change in the median of the outcome.

[b] Association reported as additive change in the mean of outcome.

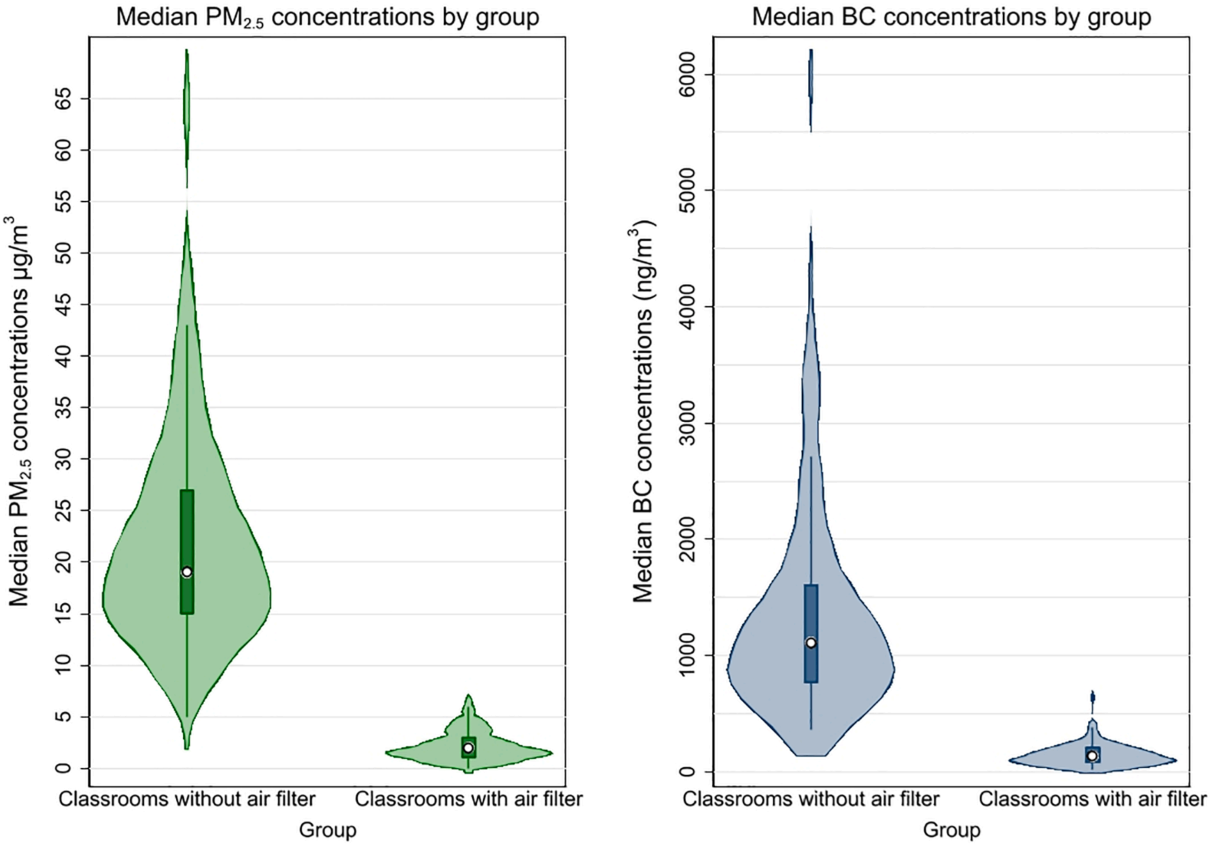

Fig. 2. Violin plots of median values of $PM_{2.5}$ and BC concentrations during the experiment by group. The white dot represents the median of median values, the darker bar in the center of the violin represents the interquartile range and the thin vertical line extended from the darker bar represents the lower and upper adjacent values.

Table 4
Percent change (95% confidence interval (CI) in attentiveness (HRT-SE)), after further adjustments (models 1 to 3) or using BC and $PM_{2.5}$ as explanatory variables (models 4 and 5).

Sensitivity models	Change (%)	95% CI	*p*-value
Model 1	−0.31	(−3.48, 2.85)	0.85
Model 2	−0.20	(−3.36, 2.96)	0.90
Model 3	−1.07	(−5.03, 2.96)	0.60
Model 4	−1.02	(−4.69, 2.65)	0.59
Model 5	−1.02	(−4.93, 2.89)	0.61

Note: CI, confidence interval. Model 1, is based on the principal analysis model and adjusted for HRT-SE at baseline ANT. Model 2, is model 1 additionally adjusted for PMA-R. Model 3, is model 2 additionally adjusted for average Leq. Model 4, is using BC as explanatory variable and Model 5, is using $PM_{2.5}$ as explanatory variable. For Model 4 and Model 5, percent changes in the median of HRT-SE are computed for a 4.2 and 1.4 fold increase in the exposure of $PM_{2.5}$ and BC, respectively, equivalent to a change from the first to the third quartile of exposure.

exists but at other short-term timescales, (2) the relationship exists but we did not observe it because of the cognitive test used, (3) the relationship does not exist in the adolescence period, and (4) the relationship exists but for higher changes of exposure levels.

The lack of significant results in our study for a short-term relationship between TRAP and attention does not correspond with prior findings from observational studies (Dorizas et al., 2015; Saenen et al., 2016; Sunyer et al., 2017). A panel study with repeated measurements in Belgian schoolchildren with a mean (SD) age of 10.2 (1.3) years found an association between recent exposure to air pollution (same day up to 2 days before) with neurobehavioral performance (Saenen et al., 2016). Selective attention, which was measured using the Stroop test, was significantly associated with recent $PM_{2.5}$ exposure monitored inside classrooms, corresponding to 42.7 ms longer mean reaction time for an IQR increment in $PM_{2.5}$ exposure. Sunyer et al. (2017) reported that daily ambient levels of NO_2 and elemental carbon had acute associations with impaired attention functions. They found that an IQR increase in daily levels was associated with a 5 ms (95% CI, 2.7, 7.3) increase in HRT-SE. It should be noted, though, that our study evaluated a much shorter exposure period. However, our results are consistent with some findings from observational studies investigating the effect of prolonged exposure to air pollution on attention in schoolchildren (van Kempen et al., 2012; Alvarez-Pedrerol et al., 2017). In particular, Alvarez-Predrerol et al. (2017) observed no significant associations between BC, NO_2 and $PM_{2.5}$ commuting home-to-school exposure and inattentiveness in children between 7 and 11 years old. Similar to our study, attention was measured by means of the hit reaction time standard error from the ANT test.

The consideration of exposure time scales needs to take into account the timing between exposure and the manifestation of biologic effects and the timing between removal of exposure and recovery from the harmful effects. In a double blind randomized crossover study in 10 adults, spontaneous changes in frontal cortex activity (related to attention processes) were detected only 30 min after starting exposure to diesel exhaust and they were detected up to one hour after the exposure ceased (Crüts et al., 2008). This suggest that while there may be an acute cortical stress response, this effect on the human brain may also last for hours. In our study, students had been breathing polluted air before entering the classroom, and thus, the 1.5 h exposure period to cleaner air might not have been enough to have a 'recovery' effect. In order to have perfect control of the air pollution levels students were breathing during the experiment, we asked them to remain in the classroom and avoid leaving it for no good reason. In accordance with the high school teachers, that maximum feasible time was set to two hours. School studies with longer duration will likely to have the students outside and thus breathing normal air for some time. Therefore, this generate other hypotheses to be tested, e.g. whether reducing the air pollution exposure during school time leads to better results. In one such study, Wargocki et al. (2008) conducted a randomized crossover trial study with 190 Danish children aged 10 to 12 exposed for a week to filtered air and for another week to non-filtered air. The study found that reducing the concentration of ultrafine particles in classrooms resulted in some improvements in the speed at which schoolwork tasks were performed. Such significant effects on performance on the speed were also found in similar intervention conducted by the same researchers (Wargocki and Wyon, 2007). Their results in contrast with ours suggest that longer time periods (in the order of days) may be needed to detect the benefits of cleaner air. Apart from that, the speed performance outcome in Wargocki et al. (2008) was defined as how quickly each student worked per unit of time in number comparison, reading and comprehension tasks, while in our study we calculated the speed consistency, an outcome that is more related to attentiveness. This could also explain the discrepancy of our findings with theirs.

Regarding the short-term assessment of attention function used in this study (ANT), the neuropsychological performance of the adolescents might not have been able to translate the neurobiological mechanisms that could have happened concurrently with the exposure for 1.5 h. Indeed, previous studies have demonstrated that in a given timeframe biological responses in the brain can occur, but they may not yet be translated into a prompt neuropsychological response (Cserbik et al., 2020; Crüts et al., 2008). For example, in Crüts et al. (2008) study, they observed functional changes in the frontal cortex after 30 min of diesel exhaust exposure using quantitative electroencephalography (QEEG). Future experimental research with similar study design may choose to include brain activity measurement tools (e.g. QEEG) and applied them before, during and after exposure to detect possible changes in the brain activities related to attention processes in adolescents. Biomarkers associated with impaired attention such as circulating inflammatory factors or urinary t,t-muconic acid are also another way to investigate acute changes (Chen et al., 2015; Cullen et al., 2017; Kicinski et al., 2016).

The bulk of literature on neurodevelopment and air pollution has been centered on early childhood and less attention has been given to the mid and late adolescence period, the period considered in this study. Thus, it is important to note that even if our results do not support the observational effects found by previous research studies, it does not indicate that those effects may not be true during early childhood. Adolescence is a complex phase of brain development, a phase where a specific time of vulnerability in terms of attention function refinement is not yet clearly determined. For instance, attentional networks (alerting, orienting, and conflict network), as the ones used as secondary outcomes in this study, tend to develop at different rates during childhood (Rueda et al., 2004). Moreover, as it is in early childhood that the attention functions rapidly start to develop (Anderson, 2002), it is plausible that acute effects of air pollution exposure have a different impact on young children than on adolescents. The adolescent brain is characterized by different maturation and stabilization processes such as cortical thinning, which may enhance neurocognitive performance (Squeglia et al., 2013). Thus, exposure to short-term air pollution may not trigger neurobiological changes as fast as it is hypothesized in early childhood. In addition, though this study included adolescents with a very limited age range (mean [SD] age of 14.8 [0.4] years), according to a neuroscience perspective, adolescents represent a heterogeneous group in terms of brain development trajectories (Foulkes and Blakemore, 2018). Thus, it may be difficult to detect a group effect when there are such individual variabilities in brain development during adolescence.

We cannot exclude the possibility that the relationship between TRAP and attention functions in adolescents may exist at higher changes in exposure dose. In fact, brain responses to acute exposure to very high levels of air pollution was documented before (diesel exhaust, 300 $\mu g/m^3$) (Crüts et al., 2008). Such extremely high values are very difficult to reach in actual urban conditions, even for short time periods. In comparison with Crüts et al. (2008) air pollution levels, the lower concentrations measured in our study is a possible explanation as to why we found no evidence of the acute neurotoxicity of TRAP. Although Barcelona is a highly polluted city, levels are markedly lower than those of Chinese or Indian cities and investigating the relationship between attention and pollution at those exposure ranges can be of interest. Where we found a mean $PM_{2.5}$ concentration in classrooms without filter of 23.0 $\mu g/m^3$, exposure assessment studies in Indian cities, including Chennai and Delhi, reported that classrooms nearby roadways can reach means of indoor $PM_{2.5}$ between 52.0 $\mu g/m^3$ and 94.4 $\mu g/m^3$ during a school weekday (Chithra and Shiva Nagendra, 2012; Goyal and Khare, 2009).

The main analysis of this study included 1,993 students, which was relatively large for an experimental research study. Indeed, conducting an experiment with an intervention of short duration helped to recruit a lot of participants, in comparison to long-term intervention that may require more engagement from them and more chance of loss to follow-up. Moreover, a short-term study design enabled us to shade more light on the cognitive effects of air pollution on a finer timescale of exposure in adolescents. Another important feature of this study was the use of mobile air cleaners, which enabled to conduct an investigation in real life conditions. This study nonetheless had limitations. Not measuring recent air pollution exposure before the intervention might have led us to miss some potential acute effects related to cleaning the air. Also, as previously discussed, when investigating an acute effect on attention functions in less than two hours, it might have been more appropriate to include brain activity measurement tools or biomarkers in order to note changes in brain regions related to attention functions instead of evaluating the attention processes resulting from those changes.

5. Conclusions

In this interventional study, cleaning the air of a classroom to reduce exposure to air pollutants for a duration of 1.5 h did not have a short-term impact on the attention of high-school students. Even though we did not find significant results, the proximity of schools to busy road and the risk for adolescents to experience high levels of air pollution remain a public health concern. The high levels of $PM_{2.5}$ measured in some of the classrooms without air filtering still have important public health implications. Specifically, in a population-level perspective, poor air quality undermining adolescents' optimal neurodevelopmental trajectories may impact the intelligence and productivity of generations over time. Further research is needed to better understand the short-term impact of air pollution on adolescent's cognitive abilities when they are in schools. We recommend future interventional studies in schools setting to consider measuring short-term exposure to air pollution over a 24 h-period and integrating tools to assess brain activity or biomarkers in addition to cognitive tests. This can help explore if short-term air pollution exposure induces small underlying neurobiological changes that may appear before the changes in attention function across cognitive tests.

CRediT authorship contribution statement

Florence Gignac: Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Data curation, Visualization. **Jose Barrera-Gómez:** Software, Formal analysis, Writing - review & editing, Data curation. **Cecilia Persavento:** Investigation, Writing - review & editing. **Caterina Solé:** Resources, Writing - review & editing. **Èlia Tena:** Resources, Writing - review & editing. **Mónica López-Vicente:** Writing - review & editing. **Maria Foraster:** Resources, Writing - review & editing. **Fulvio Amato:** Resources, Writing - review & editing. **Andrés Alastuey:** Resources, Writing - review & editing. **Xavier Querol:** Resources, Writing - review & editing. **Humberto Llavador:** Resources, Writing - review & editing. **Jose Apesteguia:** Resources, Writing - review & editing. **Jordi Júlvez:** Writing - review & editing. **Digna Couso:** Conceptualization, Writing - review & editing, Funding acquisition. **Jordi Sunyer:** Conceptualization, Writing - review & editing, Funding acquisition. **Xavier Basagaña:** Conceptualization, Formal analysis, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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