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A cluster randomized controlled trial evaluating the effectiveness of the school-based drug prevention program #Tamojunto2.0

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ABSTRACT

Aims The study aimed to evaluate the effectiveness of the government school-based program #Tamojunto2.0, the third Brazilian version of the European drug prevention program, *Unplugged*, in preventing the use of alcohol and other drugs. **Design** A parallel, two-arm cluster randomized controlled trial was conducted in 205 classes in 73 public schools (37 intervention and 36 control) with a baseline assessment and follow-up after 9 months. **Setting** Schools in the cities of São Paulo, Fortaleza and Eusebio in Brazil. **Participants** A total of 5208 students in the 8th grade with a mean age of 13.2 years (standard deviation = 0.8 years) and an equal gender ratio. **Intervention** In 2019, the intervention group attended 12 classes of the program #Tamojunto2.0, under the supervision of a team from the Ministry of Health. The control group did not receive any intervention to prevent alcohol and drug use. **Measurements** The primary outcome measured was prevalence of binge drinking (five or more doses of alcohol in an occasion) within the past month. Secondary outcomes were prevalence of initiation and use of alcohol, tobacco, inhalants, marijuana and cocaine within the past month. **Findings** A statistically significant difference was not found in the prevalence of binge drinking within the past month between intervention and control groups [odds ratio (OR) = 0.934; 95% confidence interval (CI) = 0.761–1.146]. However, students who were exposed to the program were less likely to initiate alcohol use than those in the control group (OR = 0.782; 95% CI = 0.636–0.961). The Bayes factor for reduction in binge drinking was 0.01, providing evidence in favor of the null hypothesis for this variable. **Conclusions** The drug prevention program #Tamojunto 2.0 reduced alcohol initiation, but appeared not to reduce past-month binge drinking among 8th grade students in Brazil.

Keywords Adolescents, alcohol, drugs, prevention, randomized controlled trial, schools.

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INTRODUCTION

The global concern regarding negative consequences associated with adolescent alcohol and drug use is increasing [1]. The literature on the long-term negative consequences of adolescent-onset drug use on health and social factors [2], including alterations in the cognitive function [3–5], negative school-related outcomes [6], mental health problems [7,8] and drug and alcohol dependence [9,10], is well established. Despite this knowledge, drug consumption is still highly prevalent in this population.

A recent survey conducted in Brazil showed that, among 13–15-year-old students, 55.5% reported a life-time use of alcoholic beverages, while 9% reported illicit drug use [11]. As in most European countries, Brazil has witnessed a trend of decline in alcohol and tobacco consumption among adolescents in the past three decades [12]. However, no decline in illicit drug use was observed [13].

The prevalence rates and consequences of adolescent drug use warrant the implementation of interventions designed to delay the onset and/or decrease consumption in this age group [14,15]. Therefore, the Brazilian Ministry of Health (BMH), in partnership with

the United Nations Office on Drugs and Crime, implemented *Unplugged*, an evidence-based and school-based European drug prevention program, in Brazil.

Previous evaluations of the *Unplugged* program among European adolescents revealed its efficacy in reducing episodes of drunkenness, frequent marijuana use [16], tobacco use and drug use [17]. The program is based on the 'Comprehensive Social Influence Model' and has multiple components, including life skills, normative beliefs and drug information [18,19].

In Brazil, two versions of *Unplugged* were tested. The first version, in 2013, was a translation from the European Drug Addiction Prevention Trial (EU-Dap) version to Brazilian Portuguese. The results of a non-randomized trial suggested that the program may have played a role in a decrease in recent marijuana use and binge drinking practice [20]. In the second version, in 2014 and 2015, after a cultural adaptation was conducted by the BMH team and important content changes were made in the *Unplugged* classes, the program was renamed #Tamojunto [21]. In a large randomized controlled trial (RCT) to evaluate the effectiveness of the #Tamojunto version, an iatrogenic effect on the initiation of alcohol use was found after 9 and 21 months of follow-up [22, 23]. The adolescents in the intervention group had a 30% higher risk [95% confidence interval (CI) = 1.13–1.49] at 9 months [23] and a 13% higher risk [95% CI = 1.01–1.27] at 21 months for alcohol initiation compared to those in the control group [22]. These unexpected results are attributed to cultural adaptations of the alcohol-related components of the program. The #Tamojunto version excluded the original *Unplugged* components that reinforced non-alcohol use and replaced them with a harm reduction approach [24].

Based on the negative results found in the #Tamojunto RCT, a new adaptation of the program, now named #Tamojunto2.0, was conducted by the BMH with a focus upon reinstating the original components of the *Unplugged* program and removing the components related to harm reduction. In this context, and before attempting a national implementation of the program, we aimed to test if adolescents exposed to the school-based program #Tamojunto 2.0, the third Brazilian version of the European *Unplugged*, when compared to the non-exposed adolescents achieved the following: (1) reduced their prevalence of past-month binge drinking; (2) delayed the first use of drugs (alcohol, tobacco, inhalants, marijuana and cocaine); and (3) decreased the prevalence of past-month use of drugs (alcohol, tobacco, inhalants, marijuana and cocaine).

METHODS

Study overview and design

A two-armed, parallel, cluster RCT was conducted with 5208 students to evaluate the effectiveness of the #Tamojunto2.0 prevention program for adolescents enrolled into the 8th grade among 73 public schools in three Brazilian cities (São Paulo, Fortaleza and Eusébio). The study compared the results of the integration of #Tamojunto2.0 in the Brazilian school curricula (intervention condition) to those obtained without the integration of the program in the usual curricula (i.e. no prevention program; control condition) in 2019. The protocol of the present study was published by Sanchez *et al.* [25].

The baseline assessment was conducted before implementation of the program in February and March 2019, and the follow-up data were collected 9 months after the baseline assessment in November and December 2019, respectively. The 9-month follow-up period was defined as such because the school year period in Brazil spans from February to early December. Data were collected simultaneously in the control and intervention schools.

The trial and the pre-registered hypothesis were registered at the Registro Brasileiro de Ensaios Clínicos [Ministry of Health Brazilian Register of Clinical Trials (REBEC)] under protocol number RBR-8cnkwq (http://www.ensaiosclinicos.gov.br/rg/RBR-8cnkwq/). The implementation and cultural adaptation were responsibilities of the BMH, while the evaluation was performed by an independent team from the university. This study was approved by the Ethics in Research Committee at the Universidade Federal de São Paulo (protocol 2.806.30).

Randomization

Two random drawings were conducted by an external collaborator (H.C.M.), who has not been involved with the field. First, a list of eligible schools was retrieved from the National Institute for Educational Studies and Research 'Anísio Teixeira' (INEP), including all schools from each municipality according to the following inclusion criteria: (a) must be a public school, (b) have at least one 8th grade class, (c) had not participated in the previous RCT of the #Tamojunto and (d) belong to one of the municipalities selected by the federal government. From 388 eligible schools in the initial list, 70 schools (i.e. based on the sample size calculation) were selected as the main target schools of the study, while an extra 70 schools were put on a waiting-list, to be called in case of no immediate interest in participating in the study. Both samples were selected via an algorithm based on atmospheric noise available in http://www.random.org.

Within both sampling groups (the target group and the waiting-list group), the random assignment to the arms intervention or control group was conducted using the Efron's biased coin, allowing the maintenance of a balanced sample (1 : 1 allocation ratio per municipality) and is implemented in PASS version 22. Within the

intervention group, all 8th-grade students participated in the program #Tamojunto2.0, and the school assigned one teacher per class to receive training to incorporate the program in the school curricula. Because of the involvement of the government all schools agreed to participate, as in the previous study [23]. Three schools put on hold were invited to participate at a time when three other schools on the main target list were still deciding whether or not to participate in the study, indicating that they would potentially refuse. In the same week, all six of these schools accepted and, for ethical reasons, we decided to keep all of them in the study, thus reaching a total of 73 schools (all 70 from the original list and three from the on-hold list). Consent to participate in the study was obtained from the schools' directors before randomization, and from students and parents after randomization.

Study sample

A sample size of at least 3150 adolescents in the control group and 3150 in the intervention group was distributed among 35 clusters (schools) with at least 90 subjects in each arm. This would reach a power of 82% in identifying a difference between groups of 2.5% for the outcome of binge drinking in the past month, with an initial prevalence of 10%, a significance level of 5% and an intraclass correlation of 0.005. The PASS version 15.0 program was used in the cluster sample calculation module in RCTs for testing two proportions, based on the Donner & Klar equation [26]. The number of schools in each municipality was determined to be proportional to the capacity of the BMH team to supervise the implementation in the intervention schools.

Study intervention

The #Tamojunto2.0 program is a Brazilian Portuguese translated version of a European school-based program for substance use prevention named *Unplugged*, with a different visual identity. The *Unplugged* program was designed by the EU-Dap group [18] and consists of 12 weekly classes, which uses interactive methods and lasts for 50 minutes on average. The program includes lessons that provide information about drugs, social and interpersonal skills and personal skills. Each lesson has three to five activities addressing these topics on drug prevention [18,19]. The program is applied by trained teachers and guided by student and teacher manuals. The teacher's handbook provides information concerning each lesson's procedures, objectives, required materials, activities to be performed and tips. Both manuals are open access and are available in several languages at the website www.eudap.net.

The #Tamojunto2.0 program is the third adapted version of the *Unplugged* program in Brazil. This version, #Tamojunto2.0, was adapted in 2018 by the BMH team, who removed the changes made to alcohol use lessons included in the previous version (#Tamojunto) and reinstated the content of the original *Unplugged* version, using a different visual identity (colors and figures). The content is similar to that of *Unplugged*, except for removing the question about heroin in lesson 9 and including a question about crack cocaine. This study aimed to evaluate the #Tamojunto2.0 version as proposed by the BMH, with the same study design that was used to evaluate the #Tamojunto for an adequate comparison of the results.

The school principals asked 8th grade teachers to express their interest in delivering the program during their regular classes. Therefore, teachers of different disciplines (such as science, mathematics, arts, etc.) applied the program to their students and, in this way, they replaced 12 lessons from their regular curriculum with 12 lessons from the program. The teachers who implemented the #Tamojunto2.0 program completed 16 hours of training conducted by professionals from the BMH. To guarantee adequate implementation of the program, teachers were supervised by the coaches from the BMH who had conducted the initial training.

During program implementation, teachers had to complete a fidelity questionnaire at the end of each class to monitor the proportion of the program that was implemented. A total of 67% of the enrolled intervention classes completed the 12 lessons, varying from full implementation of all 12 lessons in Eusebio city to 50% implementation of the 12 lessons in São Paulo city. The mean number of lessons implemented per class was 8. Considering that this is an effectiveness study (real-life scenario) of a governmental program, teachers who felt overwhelmed or uncomfortable could interrupt the program implementation.

Study measures

The instrument used for data collection was the same as that used in the previous RCT of #Tamojunto in Brazil [23]. It was designed based on the EU-Dap questionnaire, which was used in the previous effectiveness evaluation of *Unplugged* [27] and translated and adapted into Brazilian Portuguese [28]. We also added a few questions from the World Health Organization questionnaire, used in the VI Brazilian Survey of Drug Use among Students [29], and from the Brazilian National Survey of School Health (PENSE) questionnaire, used by the BMH [11].

It included modules regarding the frequency of substance (i.e. alcohol, tobacco, marijuana, inhalants, cocaine and crack) use in the past month, past year and life-time. The questionnaires also gathered socio-demographic data and factors associated with drug use (normative beliefs; decision-making skills; knowledge and opinions on drugs;

refusal skills; psychiatry symptoms and school violence) to allow the analysis of moderators and mediators, besides the primary and secondary outcomes. The full description of the source of each question/scale is described by Sanchez *et al.* [25].

The data sets of the two evaluation time-points were integrated by matching self-generated code using the Levenshtein algorithm, which can identify similarities between a set of characteristics [30]. In each assessment, students provided a code on the first page of the questionnaire that involves generating letters and numbers from personal information, as previously used in other studies that evaluate drug prevention programs. This code allowed the researchers to match individual questionnaires from different evaluation time-points while providing anonymity and confidentiality of the participants, which is essential for a study of illicit behavior [31].

To avoid over-reporting drug use, questionnaires that were positive for life-time use of a fictional drug (named Holoten and Carpinol) were excluded from the analysis (35 questionnaires at baseline and 37 at follow-up).

Primary outcome

The primary outcome evaluated was the prevalence of past 30 days (past-month use = yes versus no) of binge drinking pattern of alcohol consumption. For the assessment of binge drinking, we asked the question 'in the past 30 days, have you drunk five or more doses of alcoholic beverages in a single occasion', and provided a chart and figures of the standard doses that illustrated the following: can of beer, glass of wine, bottle of 'ice' and a shot of vodka/distilled.

Secondary outcomes

The secondary outcomes analysed were the incidence of first drug use (life-time use = yes versus no) and prevalence of use in the past 30 days (past-month use = yes versus no) of the following drugs: alcohol, tobacco, marijuana, inhalants, cocaine and a binge drinking pattern of alcohol consumption. For this assessment, questions such as 'In the past month, i.e. in the last 30 days, have you drunk alcoholic beverages?' and 'Have you ever tried marijuana?' were used.

Statistical analysis

Two different paradigms were used to analyze the effects of the #Tamojunto2.0 on the use of five different drugs (last month consumed and initiation): intention-to-treat (ITT) and complier average causal effect (CACE). For ITT, multiple imputations were performed to deal with the missing data and, concomitantly, the effect is estimated among all participants without considering the extent to which they complied with the treatment requirements. The CACE involves a mixture modeling methodology [32], which robustly allows us to estimate the effect of the exposure of the #Tamojunto2.0 program among those who received the intervention (i.e. compliers) versus those who would be potential compliers, but were not exposed to the program within the control group for more information about CACE in the context of cluster RCT [33]. In other words, compliance can only be observed in those participants who are randomized to the treatment condition, and cannot be observed in participants in the control condition [34]; thus, it is necessary to use mixture modeling to estimate the potential compliers (a latent group) in the control group for comparison with the actual compliers. Adherence to the program was based on the number of attended classes wherein those students who attended all 12 classes were considered compliers, whereas the students who did not attend all 12 classes were considered non-compliers. For CACE, one should assume that there is no effect of treatment for non-compliers, given that non-compliers do not receive the treatment in either condition (i.e. intervention versus control). This assumption is often referred to as the exclusion restriction [35], which is likely to hold when treatment is truly 'all-or-nothing', in which compliers receive 100% of the intervention and non-compliers receive none. In our study, however, some students did not attend all 12 classes; thus, we could not directly use the rationale of 'all-or-nothing' and, therefore, bias in the CACE estimation could emerge [36]. Hence, we considered 12 classes (the full #Tamojunto2.0 program) as both a cut-off and definition of complier to guarantee a true estimation of the effect of the #Tamojunto2.0 program and considered any other amount of exposure as non-adherence, including participants who attended seven classes.

Missing data

For both ITT and CACE analyses, multiple imputations of the missing outcomes in the follow-up were performed, implying that all randomized subjects were analyzed, as suggested by the Consolidated Standards of Reporting Trials (CONSORT) statements [37]. Multiple imputations were performed using the Bayes estimation of an unrestricted variance–covariance model, where all variables in the data set are assumed as dependent variables. The following variables were included in the imputation step: random allocation status (control versus intervention), all five dichotomous baseline and post-intervention measures for drug use and drug initiation, age, sex, socio-economic status (SES) and the number of classes attended. Fifty imputation data sets were generated and used in the subsequent analysis using the Rubin [38] method via the maximum likelihood estimator. In Mplus, the default estimator for dichotomous outcomes or ordered-categorical outcome is weighted least-square with mean and adjusted variance

which generates prohibit estimates: not a common unity of measure used in epidemiology. In order to generate the odds ratio (OR) (a more common metric), we used maximum likelihood with robust estimator in the pooled phase of the imputation, where effects of the intervention are the pooled estimates across the 50 data sets. For each analyzed outcome, the estimates were always adjusted for sex, age and SES at baseline assessment.

Dealing with multi-level structure

All the analyses were performed in Mplus version 8.4 [39], in which the estimator used for all the analysis was the maximum likelihood with robust standard errors (MLR). The MLR accounts for the non-independence of the observation (i.e. adolescents nested in schools), and subsequently the standard error was computed, considering the multi-level structure by command in Mplus called (TYPE = Complex), as proposed by Asparouhov [40], using a sandwich estimator [41]. Given the dichotomous outcomes (drug use in the last month and initiation), logistic regressions were estimated. The level of significance was set at 5%.

For the attrition analysis, we compared students whose data from the two time-points had been matched with students who answered only the baseline questionnaire.

Bayes factor

Bayes factor was calculated using the calculator implemented by Dienes & McLatchie [42]. We used a half-normal distribution (i.e. assuming that the distribution of the p (population value | theory) is not uniform) and the input parameters coming from the previous RCT [23]. For the primary outcome (binge drinking) the mean of p (population value | theory) at zero, standard deviation of p (population value | theory) is $\sqrt{6658}*0.4525 = 11.668$.

RESULTS

Characteristics of the participants

Among the 6993 students enrolled in the 205 classes from the 73 schools randomized in the study, 5208 answered the baseline questionnaire and 3898 answered the follow-up questionnaire 9 months after baseline (resulting in a follow-up rate of 74.8%), as presented in Fig. 1.

Table 1 presents the characteristics of the students who participated in the baseline assessment of the RCT of the #Tamojunto2.0 program. The intervention and control groups were homogeneous at baseline with respect to sex, age and socio-economic classification based on the Associação Brasileira de Empresas de Pesquisa [Brazilian Association of Research Agencies (ABEP)] scale. The sample had an even gender ratio, a mean age of 13.2 years (0.8) and the subjects were from a middle SES.

Descriptive statistics for life-time and alcohol and drug use within the past month are presented in Table 2. The most prevalent drug in both the assessments and randomization groups is alcohol. Alcohol experimentation changed from 48% in both groups at baseline to 65% in the control group and 63% in the intervention group at the 9-month follow-up.

Outcomes

Table 3 depicts the effects of the #Tamojunto2.0 program based on the two analytical paradigms (ITT and CACE) regarding drug consumption. The only statistically significant outcome (also consistent across the two paradigms) was alcohol initiation (ITT's OR = 0.780, 95% CI = 0.631–0.965, $P = 0.019$), where the odds for subjects exposed to the #Tamojunto2.0 program to initiate alcohol consumption is approximately 0.780 (22% lower) for ITT and 0.707 (30% lower) for CACE, compared with the subjects in the control group. Although not statistically significant, the direction of the identified association (OR) was reversed for marijuana and inhalants; that is, while OR for all other drugs were inferior to 1, in the case of these two drugs, these values were higher than 1.

When considering adherence to the 12 lessons of the program ($n = 1428$ participants), as described in Table 4, the OR for those students enrolled in classes that received all 12 lessons is even lower (OR = 0.707, 95% CI = 0.646–1.440, $P = 0.022$) when compared with the students who were in the control group and would behave as potential compliers if exposed to the #Tamojunto2.0 program. The potential compliers are students who were not exposed to the #Tamojunto2.0 program; therefore, compliant behavior was not directly observed in these students. Hence, students in the classes where the full program was implemented had a 30% lower chance of initiating alcohol use than those who were not exposed to any lesson in the program.

Derivation of Bayes factor for the primary outcome (binge drinking) was 1/100, reinforcing the evidence in favor of the null hypothesis

Attrition

Attrition analysis showed that drug use was more common among students not followed up than among students followed up. For example, the prevalence of life-time alcohol use at baseline was 46.8% among the followed-up students and 54.8% among the not-followed-up students ($P < 0.001$). No gender differences were noted in the attrition analysis; however, older students and an increased number of students from the

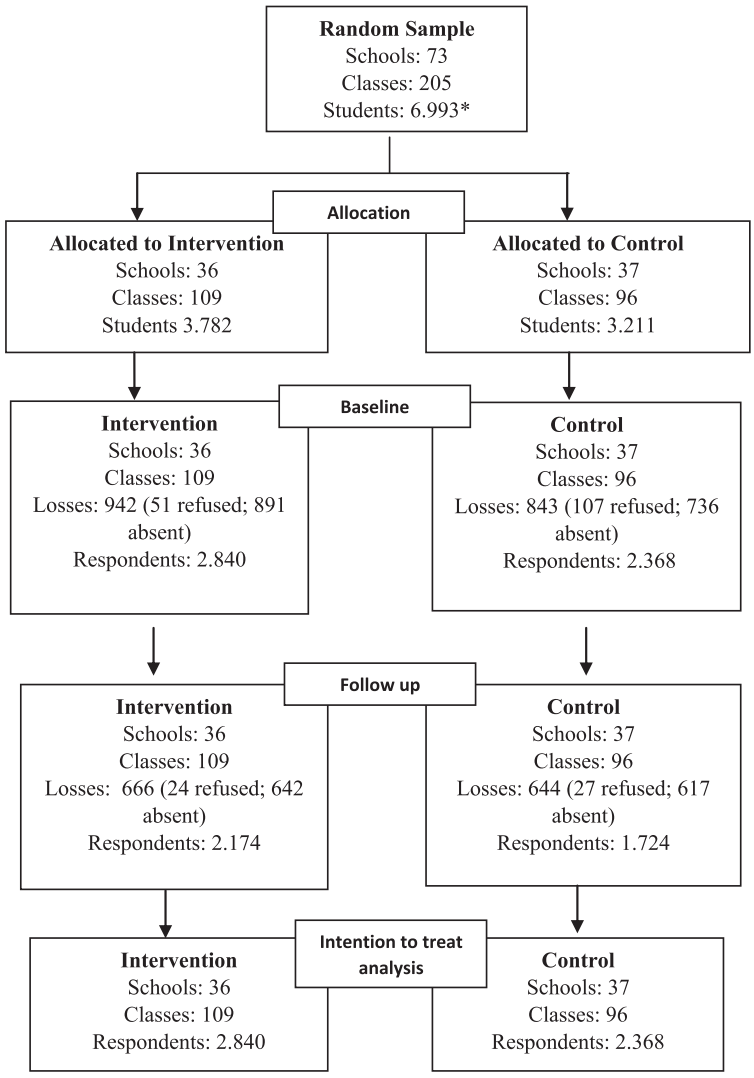

Figure 1 Flow-chart of the randomized controlled trial to assess the effect of the drug use prevention program #Tamojunto2.0.

control group were lost to follow-up. Further details of these analyses are presented in Supporting information, Table S1.

Prediction of adherence

Using the CACE analysis, one might evaluate the predictors of adherence at individual-level measures; the only statistically significant predictor of adherence was observed in past-month drug use outcome, where the baseline assessment of inhalant use reduced the OR of being adherent [OR = 0.535 (0.314; 0.914), $P = 0.022$]. Further details of these analyses are presented in Supporting information, Table S2.

DISCUSSION

In this study, we used a cluster RCT to evaluate the effectiveness of a European school-based drug prevention program that was implemented in Brazilian schools as part of a public policy that aims to reduce drug use among adolescents. The results showed that undergoing the #Tamojunto2.0 program reduces the chances of 8th grade students initiating alcohol use. This delay in alcohol use initiation in the intervention group can vary from 22 to 30%, depending on the analysis paradigm approach used (ITT or CACE, respectively), compared with the subjects of the control group. However, no effects were found on the prevention of any other drug initiation or prevalence of past-month drug use.

Table 1 Distribution of adolescents who participated in the randomized controlled trial of the #Tamojunto2.0 program at the baseline according to socio-demographic variables, drug use, bullying and the allocation group, 2019 (n = 5208)

	Total (N = 5208)		*Control group (n = 2368)*		*Intervention group (n = 2840)*	
	N	*%*	*n*	*%*	*n*	*%*
City						
São Paulo	2373	45.57	926	39.10	1.447	50.95
Fortaleza	2051	39.38	1022	43.16	1.029	36.23
Eusébio	784	15.05	420	17.74	364	12.82
Gender						
Boys	2576	50.06	1140	48.63	1.436	50.06
Girls	2570	49.94	1024	51.37	1.366	49.94
Age (years)						
12–14	4645	91.44	2.081	90.16	2.564	208
15–17	535	8.56	227	9.84	92.50	7.5
Mean age (SD)	13.23 ± 0.85		13.28 ± 0.89		13.19 ± 0.81	
ABEP score						
A (45–100)	179	3.48	71	3.08	108	3.86
B (29–44)	1279	24.84	522	22.21	757	27.05
C (17–28)	2809	54.55	1.304	55.49	1.505	53.77
D/E (1–16)	882	17.13	453	19.28	429	15.33
Mean score (SD)	24.75 ± 9.19		24.16 ± 9.15		25.25 ± 9.19	
Life-time drug use						
Alcohol	2516	48.80	1149	48.89	1367	48.72
Binge drinking	1106	21.32	523	22.15	583	20.63
Tobacco	614	11.93	304	12.92	310	11.10
Inhalants	1026	20.03	477	20.38	549	19.73
Marijuana	424	8.27	221	9.42	203	7.29
Cocaine	36	0.71	16	0.69	20	0.72
Past-month drug use						
Alcohol	1.129	21.88	540	22.96	589	20.98
Binge drinking	786	15.19	386	16.38	400	14.19
Tobacco	155	3.01	82	3.48	73	2.62
Inhalants	210	4.09	108	4.60	102	3.66
Marijuana	167	3.26	95	4.06	72	2.58
Cocaine	12	0.24	7	0.30	5	0.18

[a]Socio-economic classification according to ABEP. SD = standard deviation; ABEP = Associação Brasileira de Empresa de Pesquisa (Brazilian Association of Research Agencies).

The positive effect regarding the initiation of alcohol use is in line with the results of other school-based programs that are based on life skills training or social influence theory [43–45], especially considering the results obtained in the study that evaluated the *Unplugged* program [27]. However, it is important to note that our results are not exactly as expected because, in the *Unplugged* trial, a reduction was observed in the prevalence of a recent drunk episode and marijuana use [16,27]. Nevertheless, it must be noted that the prevalence of use of all substances in the European population is much higher than that in the Brazilian population [46], which facilitates the identification of positive effects [47].

In particular, these findings regarding the positive effect of the #Tamojunto2.0 program on alcohol initiation are completely opposite from the iatrogenic effect previously found in the evaluation of the first version of the #Tamojunto program, and reinforces the main hypothesis on the iatrogenic nature of the previous results, which suggested inadequacy of the cultural adaptations made in the alcohol-related components [22,23]. One possible explanation for these opposing results is that the program was only able to demonstrate positive preventive results after returning to its original curriculum (student and teacher manual), especially the components related to non-use of alcohol by adolescents, that were only replaced by the prevention of alcohol intoxication [24]. Another hypothesis is related to the changes made to the teachers training program. Because of the iatrogenic results of the previous version of the program, in this new version teachers were instructed on the importance of the non-use of alcohol, and they received more information regarding the harm that alcohol can cause to adolescents' brains [48]. It is well known that there

Table 2 Distribution of drug use in the last month and initiation of drug use among adolescents who participated in the study to evaluate the effect of #Tamojunto2.0 at the baseline and at the 9-month follow-up according to the allocation group, 2019

		Past-month drug use				*Drug use initiation*			
		Control group		*Intervention group*		*Control group*		*Intervention group*	
		n/N	*%*	*n/N*	*%*	*n/N*	*%*	*n/N*	*%*
Baseline	Binge drinking	386/2356	16.4	400/2819	14.2	523/2361	22.2	583/2826	20.6
	Alcohol	540/2352	23.0	589/2808	21.0	1149/2350	48.9	1367/2806	48.7
	Tobacco	82/2355	3.5	73/2786	2.6	304/2253	12.9	310/2792	11.1
	Marijuana	95/2342	4.1	72/2788	2.6	221/2347	9.4	203/2783	7.3
	Inhalants	108/2346	4.6	102/2788	3.7	477/2340	20.4	549/2782	19.7
	Cocaine	7/2333	0.3	5/2773	0.2	16/2334	0.7	20/2769	0.7
9-month follow-up	Binge drinking	287/1711	16.8	336/2164	15.5	533/1709	31.2	647/2166	29.9
	Alcohol	310/1721	18.0	355/2169	16.4	1125/1719	65.4	1365/2168	63.0
	Tobacco	81/1717	4.7	81/2166	3.7	333/1718	19.4	383/2167	17.7
	Marijuana	84/1707	4.9	102/2155	4.7	232/1719	13.5	264/2167	12.2
	Inhalants	89/1720	5.2	114/2169	5.3	491/1688	29.1	618/2153	28.7
	Cocaine	3/1702	0.2	10/2152	0.5	6/1700	0.4	13/2144	0.6

Table 3 Adjusted analysis of the distribution of drug use (use in the last month and initiation of use) among students participating in the cluster randomized controlled trial of the #Tamojunto2.0 program according to ITT and CACE data analysis paradigm, 2019

		Past-month drug use				*Drug use initiation*			
		n	*Odds ratio #Tamojunto2.0*[a]	*95% CI*	*P-value*	*n*	*Odds ratio #Tamojunto2.0*[a]	*95% CI*	*P-value*
Intention-to-treat[a]	Binge drinking	5208	0.934	(0.761; 1.146)	0.514	5208	0.940	(0.751; 1.175)	0.585
	Alcohol	5208	0.877	(0.690; 1.114)	0.283	5208	**0.782**	**(0.636; 0.961)**	**0.019**
	Tobacco	5208	0.832	(0.586; 1.182)	0.306	5208	0.859	(0.671; 1.099)	0.227
	Marijuana	5208	1.033	(0.742; 1.439)	0.847	5208	0.946	(0.711; 1.259)	0.705
	Inhalants	5208	1.044	(0.795; 1.369)	0.759	5208	0.977	(0.767; 1.244)	0.848
CACE[a]	Binge drinking	5208	0.892	(0.651; 1.224)	0.480	5208	0.908	(0.644; 1.281)	0.583
	Alcohol	5208	0.815	(0.579; 1.148)	0.242	5208	**0.707**	**(0.526; 0.951)**	**0.022**
	Tobacco	5208	0.751	(0.457; 1.233)	0.258	5208	0.796	(0.551; 1.149)	0.223
	Marijuana	5208	1.067	(0.605; 1.883)	0.822	5208	0.920	(0.582; 1.455)	0.721
	Inhalants	5208	1.056	(0.693; 1.610	0.798	5208	0.965	(0.646; 1.440)	0.860

[a]Analyses adjusted for sex, age and socio-economic status. CI = confidence interval; CACE = complier average causal effect; ITT = intention-to-treat. Statistically significant result in bold.

is an improvement in the teachers' implementation of the program when they receive qualified technical support, both in their initial training and throughout the application of the program [49]. We report that the RCT for #Tamojunto2.0 was developed to answer to the BMH if returning to the original content of *Unplugged* would mitigate the iatrogenic effects of its previous, adapted version.

Although the effects observed are limited to a delay of only 9 months in the initiation of alcohol use and are

Table 4 Adherence status to 12 classes by students participating in the randomized controlled trial of the program #Tamojunto2.0, 20197

		Classes Attended	*n*	*%*	*% Cumulative*
Control group	Eusébio	Missing	420	100.0	100.0
	Fortaleza	Missing	1022	100.0	100.0
	São Paulo	Missing	926	100.0	100.0
Intervention group	Eusébio	Missing	63	17.3	17.3
		12	301	82.7	100.0
		Total	364	100.0	
	Fortaleza	Missing	285	27.7	27.7
		0	96	9.3	37.0
		4	40	3.9	40.9
		7	26	2.5	43.4
		12	582	56.6	100.0
		Total	1029	100.0	
	São Paulo	Missing	319	22.0	22.0
		0	397	27.4	49.5
		4	147	10.2	59.6
		6	21	1.5	61.1
		7	18	1.2	62.3
		12	545	37.7	100.0
		Total	1447	100zz.0	

stronger among the subjects that received the complete program, delaying the initiation of drinking is an important goal for prevention efforts [50], as the age at which a person first drinks is linked with hazardous health outcomes later in life [51]. Several studies have shown that this is associated with an increased risk of later alcohol use disorders [52], vulnerability to alcohol-related problems [53–55], alcohol-related injuries [56], binge drinking pattern among adolescents [57] and alcohol dependence [58–60].

Nevertheless, we believe that the most important contribution of this study is the unprecedented use of the prevention science cycle of adaptation, implementation, evaluation, re-adaptation, re-implementation and re-evaluation of a governmental school-based program. It is important to highlight that this sequential process, called 'Feedback Loop', followed the international standards for the implementation of prevention programs [61]. The process included the first stage of need identification, proposing preventive interventions based on evidence and rigorous evaluation, and monitoring its implementation [62]. In Brazil, the process was initiated in 2013 in an attempt by the federal government to invest in the dissemination of the *Unplugged* prevention program in Brazilian schools. A cluster RCT conducted in 2014 and 2015 showed an iatrogenic result for initiation of alcohol use after 9 [23] and 21 months of follow-up [22].

The *Unplugged* program was selected by the BMH as part of the Ministry of Health's response to the federal Plan to Combat Crack and Other Drugs (Decree 7637, 8 December 2011) focused on reducing established drug consumption and preventing future drug use initiation among Brazilians [23]. At that time, the National Drug Policy in force in Brazil (Decree 4345, 26 August 2002), in its article 6, foresaw an emphasis on harm reduction as a preventive action in the country. In this context, the content of *Unplugged* was reviewed to exclude potential 'war on drugs' components and reinforce harm reduction strategies. The cultural adaptation process of *Unplugged*, based on the Theory of Diffusion of Innovations, was described by Pedroso & Hamman [21], but does not mention the changes and/or exclusion of contents.

In 2017, the BMH hired external consultants to identify possible failures in the program's cultural adaptation process. They identified important concerns about the adaptation made in all alcohol-related content in the student's manual, especially in lesson number 3, named 'Choices—Alcohol, Risk and Protection', and incorporated harm reduction discussions in the activities [24]. In 2018, the program material was modified, returning to the original *Unplugged* content, created by the EU-Dap team, and this trial was designed to test its effectiveness.

Our study has several limitations that are worthy of mention. The main limitation is the excessive number of absent students. Indeed, we found that many students were absent from the classroom during the baseline collection, based on the number of students listed by the INEP. However, this pattern of missing data (i.e. since baseline) was expected, as it occurred in similar studies in Brazilian public schools [22,23]. Moreover, another study found that

approximately 20% of registered students are, in fact, regularly absent from public schools [63]. It is worth noting that loss of data due to follow-up (25%) is a common limitation in longitudinal studies [23,64,65], and the three missing data techniques that were used converge in terms of the point estimate and its significance. Additionally, another limitation was the difference in implementation between the three cities. Most issues associated with the full program implementation in the intervention classrooms were from São Paulo, a large urban location. This reveals the difficulties of universal implementation of programs as public policy for all Brazilian public schools, considering that there may be local barriers, such as lack of technical support throughout the application of the program and support from school management for the integration of the program into the school curriculum [66,67]. These issues related to program implementation faced in the present study reflect the general difficulties already experienced in previous studies [68]. However, as this is an effectiveness study this type of occurrence, although troublesome, has even more relevance as the final results of the program presented herein realistically simulate its actual population effect (i.e. what could be expected in the process of public policy implementation). We have conducted a process evaluation alongside the present RCT; although data are not published at this stage, they will be used in the near future to allow clearer understanding of the issues raised. Another limitation is that the present study does not allow us to state whether it was really the change in content or in the training of teachers that led to the change in the program's results. For that, an experimental design of multiple arms, which included the comparison of the effect of the two curricula in the same trial, should have been used.

After reincorporating the original components related to the non-use of alcohol by adolescents, our results suggest that the drug prevention program #Tamojunto2.0 showed positive results in the prevention of alcohol use, and demonstrated potential for expansion to the national level as public policy. It is noteworthy that the effect was even greater among the classes that received the complete program, which suggests the need for monitoring the implementation of the program to guarantee the intended results. The results suggest an important role of messages of alcohol avoidance in prevention efforts in middle adolescence. New studies should propose to compare different preventive strategies in multi-arm trials to test the hypotheses raised here. Additionally, this study presents a unique case in Brazil, in which two large RCTs were conducted to verify the effect of a program with two different versions, in a continuous and systematic process, whose main purpose was to provide subsidies for the dissemination of an evidence-based public prevention policy.

Clinical trial registration

The trial and the pre-registered hypothesis was registered at the Registro Brasileiro de Ensaios Clínicos [Ministry of Health Brazilian Register of Clinical Trials (REBEC)] under protocol number RBR-8cnkwq (http://www.ensaiosclinicos.gov.br/rg/RBR-8cnkwq/).

Declaration of interests

None.

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Author contributions

Zila M. Sanchez: Conceptualization; funding acquisition; methodology; validation; writing-review & editing. **Juliana Y. Valente:** Investigation; methodology; writing-original draft. **Patrícia P. Galvão:** Data curation; investigation; project administration; writing-original draft. **Fabiane A Gubert:** Data curation; investigation; project administration; writing-review & editing. **Márcia H. S. Melo:** Investigation; methodology; writing-review & editing. **Sheila C. Caetano:** Investigation; methodology; writing-review & editing. **Jair J. Mari:** Funding acquisition; writing-review & editing. **Hugo Cogo-Moreira:** Formal analysis; methodology; writing-review & editing.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Distribution of sociodemographic variables and drug consumption patterns among students linked and included in the longitudinal analysis (hyperlinked) and those lost to follow-up (not hyperlinked). Attrition analysis for covariates ($N = 5208$).

Table S2 Prediction of the covariates on the latent categorical variable *adherence* on odds ratio.