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A videogame for perceived risk of harm from opioid misuse in adolescents: a randomized controlled trial

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The opioid epidemic greatly impacts adolescents, especially those with low perceived risk of harm—an important predictor of misuse initiation. Here, to address this, we developed and evaluated PlaySmart, a videogame targeting perceived risk, in a two-arm parallel superiority unblinded randomized controlled trial with a placebo comparator. We randomized 532 participants (mean age 16.6 years; 47% female) to PlaySmart (n = 269) or control games (n = 263). Eligible students—16–19 years old, no prior opioid misuse and 'high-risk' based on substance use or mental health screens—agreed to 60-min gameplay sessions, and provided assent and parental consent if under 18 years old. Participants played during supervised after-school sessions (1 or 2 times per week for approximately 6 weeks) at 15 Connecticut high schools. Self-reported data were collected at baseline, 6 weeks and 3 months (21 October 2021 to 27 February 2024). Follow-up rates were high (231/266 (87%) PlaySmart and 234/261 (90%) control). The primary outcome was perceived risk of harm of opioid misuse at 3 months. The secondary outcomes were self-efficacy, intentions, knowledge and attitudes (positive and negative expectancies). At 3 months, 29% of PlaySmart versus 23% of control participants reported 'great risk' with no statistically significant difference between groups (95% CI, −2% to 14%; P = 0.14). Self-efficacy, intentions and positive expectancies did not differ. PlaySmart participants demonstrated knowledge gains from baseline to 3 months (2.1 (95% CI, 1.4–2.7) versus 0.1 (95% CI, −0.6–0.7); P < 0.001), and negative expectancies gains at 6 weeks (2.3 (95% CI, 1.4–3.1) versus 0.2 (95% CI, −0.7–1.1); P = 0.001). Further research is needed to enhance PlaySmart, maximizing its impact on scalable opioid misuse prevention. ClinicalTrials.gov registration: NCT04941950.

An estimated 108,000 drug overdose deaths occurred in the United States during 2023, at a rate of approximately 300 deaths per day[1]. Initiation of opioid misuse (non-medical use of prescription opioids/prescription opioid misuse and/or heroin use) often occurs in adolescence and young adulthood. Recent data indicate that although illicit drug use among youth is decreasing, fatal overdose risk among adolescents has increased[2]. In 2021, opioid toxicity accounted for over 10% of deaths in 15–19-year-olds[3]. In 2023, 12% (1.9 million) of US high-school students reported lifetime prescription opioid misuse, and 4% (624,000) reported misuse in the past 30 days, increasing the risk for overdose[4]. Given the prevalence and lethality of opioid misuse in young people, creating evidence-based scalable solutions is critical. A potential target for impacting adolescent opioid misuse is their perceived risk of harm from opioid misuse.

Adolescents' perceived risk of harm from opioid misuse is strikingly low and varies across prescription opioids and heroin. According

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to the most recent 'Monitoring the Future' (MTF) study, a nationally representative survey of American high-school students, only 28% of 10th graders perceived that trying a prescription opioid once or twice posed a great risk of harm, and only 34% of 12th graders perceived that trying any opioid other than heroin posed a great risk of harm[5,6]. Only 66% of 10th graders and 60% of 12th graders saw trying heroin as highly risky. There is an inverse relationship between perceived risk of harm from drug use and actual drug use[7]. According to a foundational paper, perceived risk of harm influences adolescent drug use by shaping attitudes and expectancies, and behavioural intentions across multiple behavioural theories, including the 'theory of planned behaviour', the 'health belief model' and 'social cognitive theory'[8].

Low perceived harmfulness being strongly associated with a high risk of misuse has been demonstrated with the non-medical use of prescription drugs[6,9–12] and heroin[13]. Individuals with low versus those with high perceived harmfulness were almost ten times more likely to use prescription opioids non-medically[10]. A similar association exists with heroin use[13]. Therefore, heightening perceived harmfulness from opioids could be a meaningful intervention to reduce the initiation of opioid misuse.

Given the magnitude of this problem among adolescents, developing and implementing effective, engaging strategies to prevent opioid misuse initiation is critical. Although there are interventions that target adolescent substance use, including opioids[14], that are used in schools[15], implementation remains challenging. School-based prevention programmes declined from 75% in 2011 to 65% in 2019[16], reflecting barriers such as limited funding, insufficient staff training, low implementation fidelity, stigma, curriculum overload and lack of leadership support[17–19]. A recent review on opioid-specific programmes noted concerns around generalizability, reach and scale[15]. Digital interventions may help address these limitations[20].

To that end, we developed an evidence-based digital intervention in the form of a videogame, PlaySmart, for adolescents aged 16–19 years, targeting perceived risk of harm from opioid misuse as a proximal outcome underlying the intervention's impact on the more distal outcome of opioid misuse initiation. Videogames as interventions meet adolescents 'where they are'. Over 85% of adolescents play videogames[21]. 'Serious games', defined as games with a primary purpose other than entertainment[22], promote health and are effective at prevention[23–28]. They facilitate opportunities for repetitive interactions to acquire new skills that can transfer to real-life situations with consistent fidelity, placing minimal demands on personnel/resources, and facilitating sustainable distribution[29–34]. Digital interventions including serious games have been developed for the prevention of adolescent alcohol, tobacco and cannabis use, but there remains a notable gap in ones focused on opioid misuse prevention[20,35–38]. To our knowledge, only formative efforts such as MedSMART[39], focused on opioid safety, and our PlaySmart videogame intervention described here specifically target adolescent opioid misuse prevention.

As part of the National Institute on Drug Abuse (NIDA) Helping to End Addiction Long-term (HEAL) prevention initiative[40], building on established theoretical constructs and extensive experience in serious videogames[23–25,41–43], and employing a user-centric approach engaging adolescents in the design/development process, we built PlaySmart, a videogame focused on opioid misuse prevention in adolescents aged 16–19 years[44]. This age group was chosen in part because the HEAL initiative specifically included it in the lower range of their target age group, and because 45% of youth with prescription opioid misuse report initiation between the ages of 16 and 18 years[45].

Through a two-arm parallel superiority randomized controlled trial, we evaluated the impact of PlaySmart, compared to a placebo comparator, on key outcomes related to opioid misuse, with the primary outcome being perceived risk of harm from opioid misuse[46]. Our hypotheses were that the PlaySmart group would demonstrate an increased perceived great risk of harm at 3 months, and for secondary outcomes, PlaySmart participants would demonstrate, in relation to opioid misuse, increased self-efficacy, decreased intentions, increased knowledge and attitudes measured both by decreased positive expectancies and increased negative expectancies.

Results

Participants

Between 21 October 2021, and 27 February 2024, 533 participants were recruited from 15 Connecticut high schools. Of the 1,062 unique individuals screened, 839 met all inclusion criteria and 533 enroled: of these, 269 were randomly assigned to the PlaySmart intervention and 264 to the control condition. One control participant was withdrawn by the principal investigator due to an incomplete parent/guardian consent form, a protocol deviation that was reported to the Institutional Review Board (IRB), resulting in a sample size of 532 (Fig. 1).

The baseline characteristics were similar across groups (Table 1). Participants (mean age 16.6 years) were 47% female and racially/ethnically diverse (45% Black, 34% White, 38% Hispanic).

Forty-five percent (238/532) of participants had mild to severe symptoms of anxiety[47], with 86% (456/532) reporting at least one anxiety symptom, and 61% (322/532) of participants had mild to severe symptoms of depression[48], with 93% (494/531) reporting at least one depression symptom. Participants reported lifetime alcohol or marijuana use (33% (175/532) and 19% (102/532)), respectively. The percentage of participants from each school ranged from 1% to 17%, with a similar number of participants in each arm at each school (Extended Data Table 1).

Primary outcome

At baseline, 16% (43/269) of the PlaySmart group and 17% (46/263) of the control group reported 'great risk of harm' from opioid misuse (Fig. 2). At the primary endpoint of 3 months, the outcome of perceived great risk of harm was not significantly different between groups. At 3 months (post randomization), 29% (66/231) of the PlaySmart group versus 23% (53/234) of the control group reported 'great risk of harm' (difference = 6%, 95% CI, −2–14%; $P = 0.14$). Among participants assessed at both baseline and 3 months ($N = 465$), 16% (36/231) of the PlaySmart group shifted from 'no great risk of harm' at baseline to 'great risk of harm' at 3 months, compared to 13% (31/234) in the control group (95% CI, −4–9%; $P = 0.47$). At 6 weeks post randomization (end of gameplay), 26% (59/230) of the PlaySmart group versus 18% (42/233) of the control group reported 'great risk of harm' from opioid misuse (95% CI, 0–15%; $P = 0.047$). Among participants assessed at both baseline and 6 weeks ($N = 463$), 14% (33/230) of the PlaySmart group shifted from 'no great risk of harm' at baseline to 'great risk of harm' at 6 weeks, compared to 7% (16/233) in the control group (95% CI, 2–13%; $P = 0.009$). Additional logistic regression mixed models using perceived 'great risk of harm' as the outcome demonstrated the following findings. The unadjusted model (model 1), models adjusted for sex and grade (model 2), and model additionally adjusted for the clustering of participants within schools (model 3) did not yield statistically significant findings (Extended Data Table 2A). The model (model 1) adjusted for sex, grade, baseline risk ('great risk of harm' versus 'no great risk of harm'), and clustering of participants within schools suggested statistically significant differences in odds of 'great risk of harm' at 6 weeks (adjusted odds ratio (aOR) 1.96; 95% CI, 1.1–3.5; $P = 0.02$) but not at 3 months (aOR 1.56; 95% CI, 0.91–2.7; $P = 0.11$) (Extended Data Table 2B).

Finally, because risk perception differs between heroin and prescription opioids, we also separately analysed the questions related to each substance[49] (Extended Data Table 3).

Secondary outcomes

For secondary outcomes (Figs. 3 and 4), there were no differences in self-efficacy to refuse opioids between groups (Fig. 3a). At 6 weeks, mean scores were as follows: PlaySmart = 9.1 (95% CI, 8.8–9.3); control = 9.1

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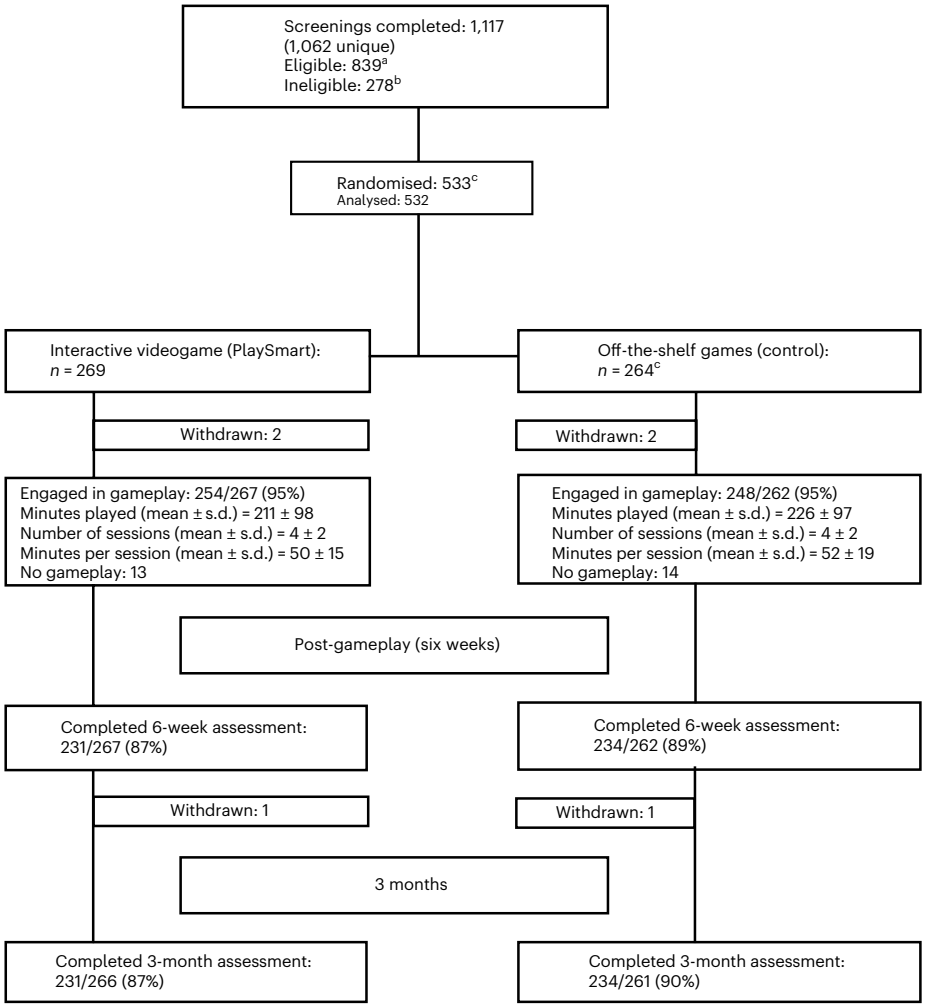

[a]Reasons that eligible individuals did not participate in the study included not returning the enrollment packet during specified enrollment window, lack of time after school, transportation issues after school, or other family, or work or school commitments after school.

[b]Reasons for ineligibility:	*N*[d]	%
Age: not 16–19	151	40
Anxiety, depression, substance use: no affirmative answers to questions on anxiety, depression, other substance use	203	53
Opioid misuse: misused opioids prior to enrolling in the study	6	2
Unwilling: Not willing to sit for 60 min per session (for up to six sessions for each) to play a videogame	15	4
Data missing: All eligibility questions missing	5	1
Total number of reasons for ineligibility	*380*	
Total number of screened individuals who were ineligible	*278*	

[d]More than one reason could be indicated

Fig. 1 | Consolidated Standards of Reporting Trials (CONSORT) diagram. Flow of participants through screening, randomization, allocation, gameplay and follow-up assessments for the PlaySmart (intervention) and control arms. [a]Reasons that eligible individuals did not participate in the study included not returning the enrolment packet during the specified enrolment window, lack of time after school, transportation issues after school, or other family, work or school commitments after school. [b]Reasons for ineligibility (*N*, %) (note that more than one reason could be indicated) were as follows. Age: not 16–19 (151, 40%). Anxiety, depression, substance use: no affirmative answers to questions on anxiety; depression, other substance use (203, 53%). Opioid misuse: misused opioids prior to enroling in the study (6, 2%). Unwilling: not willing to sit for 60 min per session (for up to six sessions for each) to play a videogame (15, 4%). Data missing: all eligibility questions missing (5, 1%). Total number of reasons for ineligibility: 380. Total number of screened individuals who were ineligible: 278. [c]One participant randomized to control was subsequently withdrawn due to a missing parental consent form. [d]More than one reason could be indicated.

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Table 1 | Baseline characteristics in the intervention and control arms

	Intervention	Control	Total
	(*N*=269)	(*N*=263)	(*N*=532)
Sex (*n*, %)[a]			
Female	127 (47%)	121 (46%)	248 (47%)
Male	142 (53%)	142 (54%)	284 (53%)
Age, years (mean±s.d.)	16.6 (0.7)	16.6 (0.7)	16.6 (0.7)
Age, group (*n*, %)			
15–16 years	146 (54%)	136 (52%)	282 (53%)
17 years	89 (33%)	94 (36%)	183 (34%)
18 years	32 (12%)	31 (12%)	63 (12%)
19 years	2 (1%)	2 (1%)	4 (1%)
Grade (*n*, %)[a]			
9th or 10th grade	44 (16%)	43 (16%)	87 (16%)
11th or 12th grade	225 (84%)	220 (84%)	445 (84%)
Race[b] (*n*, %)			
White	86 (32%)	93 (35%)	179 (34%)
American Indian/Alaskan Native	14 (5%)	8 (3%)	22 (4%)
Asian	19 (7%)	25 (10%)	44 (8%)
Native Hawaiian or Other Pacific Islander	2 (1%)	5 (2%)	7 (1%)
Black/African American	128 (48%)	113 (43%)	241 (45%)
Something else, please specify	50 (19%)	51 (19%)	101 (19%)
No response			
Ethnicity (*n*, %)			
Not Hispanic or Latinx	157 (58%)	155 (59%)	312 (59%)
Hispanic or Latinx	100 (37%)	102 (39%)	202 (38%)
Don't know	10 (4%)	5 (2%)	15 (3%)
Prefer to not say	2 (1%)	1 (0%)	3 (1%)
Familial substance misuse[b] (*n*, %)			
Father	29 (11%)	28 (11%)	57 (11%)
Mother	6 (2%)	10 (4%)	16 (3%)
Brother	3 (1%)	7 (3%)	10 (2%)
Sister	1 (0%)	4 (2%)	5 (1%)
Grandfather	13 (5%)	24 (9%)	37 (7%)
Grandmother	7 (3%)	12 (5%)	19 (4%)
Another relative	43 (16%)	36 (14%)	79 (15%)
Prefer not to say	25 (9%)	24 (9%)	49 (9%)
None	173 (64%)	164 (62%)	337 (63%)
Food worries at home (*n*, %)			
Never	185 (69%)	169 (64%)	354 (67%)
Sometimes	81 (30%)	81 (31%)	162 (30%)
A lot	3 (1%)	13 (5%)	16 (3%)
Receives free or reduced lunch at school (*n*, %)			
No	49 (18%)	55 (21%)	104 (20%)
Yes	192 (71%)	174 (66%)	366 (69%)
Don't know	28 (10%)	34 (13%)	62 (12%)
Whole school receives free or reduced lunch (*n*, %)			
No	29 (11%)	27 (10%)	56 (11%)
Yes	164 (61%)	161 (61%)	325 (61%)
Don't know	76 (28%)	75 (29%)	151 (28%)
Mental health—anxiety			
Minimal	151 (56%)	143 (54%)	294 (55%)
Mild	60 (22%)	78 (30%)	138 (26%)
Moderate	40 (15%)	34 (13%)	74 (14%)
Severe	18 (7%)	8 (3%)	26 (5%)
Mental health—depression			
No significant depressive symptoms	109 (41%)	101 (38%)	210 (39%)
Mild	80 (30%)	94 (36%)	174 (33%)
Moderate	57 (21%)	44 (17%)	101 (19%)
Moderately severe	15 (6%)	16 (6%)	31 (6%)
Severe	8 (3%)	8 (3%)	16 (3%)
Any experience with alcohol			
No	183 (68%)	174 (66%)	357 (67%)
Yes	86 (32%)	89 (34%)	175 (33%)
Any experience with marijuana			
No	213 (79%)	217 (83%)	430 (81%)
Yes	56 (21%)	46 (17%)	102 (19%)

[a]Used as stratum for randomization.
[b]More than one selection could be made.

(95% CI, 8.9–9.4; *P* value of difference = 0.95); change from baseline to 6 weeks: PlaySmart = −0.01 (95% CI, −0.3–0.2); control = −0.2 (95% CI, −0.5–0.0; *P* = 0.39). At 3 months, mean scores were as follows: PlaySmart = 9.1 (95% CI, 8.9–9.3); control = 9.3 (95% CI, 9.0–9.5; *P* = 0.33); change from baseline to 3 months: PlaySmart = 0.0 (95% CI, −0.3–0.2); control = 0.0 (95% CI, −0.3–0.2; *P* = 0.98).

There were no differences in intentions to misuse opioids between the PlaySmart and control groups (Fig. 3b). At 6 weeks, the mean scores were as follows: PlaySmart = 2.7 (95% CI, 2.5–2.8); control = 2.7 (95% CI, 2.5–2.8; *P* = 1.00); change from baseline to 6 weeks: PlaySmart = 0.0 (95% CI, −0.2–0.2); control = 0.0 (95% CI, −0.2–0.2; *P* = 0.89). At 3 months, the mean scores were as follows: PlaySmart = 2.5 (95% CI, 2.3–2.7); control = 2.5 (95% CI, 2.3–2.6; *P* = 0.73); change from baseline to 3 months: PlaySmart = −0.02 (95% CI, −0.4–0.1); control = −0.2 (95% CI, −0.4–0.0; *P* = 0.86).

For knowledge about opioids and misuse, the mean scores were similar between groups at baseline (Fig. 3c). At 6 weeks, the PlaySmart group demonstrated a significantly (*P* = 0.002) higher mean knowledge score (26.2; 95% CI, 25.6–27.5) compared to the control group (24.4; 95% CI, 23.4–25.3). The change from baseline to 6 weeks was significantly (*P* < 0.001) greater in the PlaySmart (2.2; 95% CI, 1.5–2.8) than in the control group (−0.4; 95% CI, −1.1–0.2). At 3 months, the PlaySmart group maintained a significantly higher mean knowledge score (26.5; 95% CI, 25.6–27.5) compared to the control group (24.9; 95% CI, 23.9–25.8; *P* = 0.02). The change from baseline to 3 months remained significantly greater for the PlaySmart (2.1; 95% CI: 1.4–2.7) compared to the control group (0.1; 95% CI, −0.6–0.7; *P* < 0.001).

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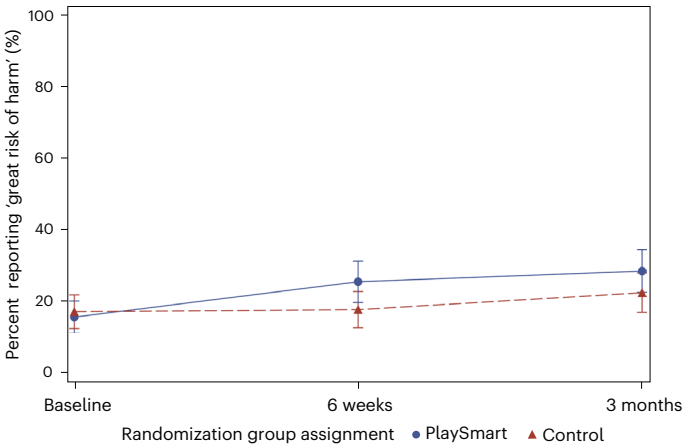

Fig. 2 | Percent reporting 'great risk of harm' at each timepoint, by treatment. Percent reporting 'great risk of harm' on an eight-item perception of risk of harm measure over time per group. Percentages and 95% CIs answering 'great risk of harm' from opioids presented for PlaySmart (blue circles and solid line) and control (red triangles and dashed line) at baseline, 6 weeks and 3 months. The numbers contributing data for PlaySmart were 269, 230 and 231 at baseline, 6 weeks and 3 months and for control were 263, 233 and 234.

For the attitudes measure (Fig. 4), for the positive expectancies questions (the goal is to reduce scores), at 6 weeks, the mean scores were as follows, with PlaySmart (10.2; 95% CI, 9.3–11.0) and control (10.3; 95% CI, 9.5–11.2; $P = 0.80$) being comparable, showing similar changes from baseline to 6 weeks: PlaySmart (−0.2; 95% CI, −1.0–0.7) and control (−0.6; 95% CI, −1.4–0.2; $P = 0.49$). At 3 months, the PlaySmart group exhibited a lower mean score (9.7; 95% CI, 8.8–10.5) compared to the control group (10.6; 95% CI, 9.7–11.4; $P = 0.15$), with similar changes from baseline to 3 months: PlaySmart (−0.7; 95% CI, −1.5–0.2) and control (−0.3; 95% CI, −1.2–0.5; $P = 0.59$).

For the negative expectancies questions in the attitudes measure (the goal is to increase scores), at 6 weeks, the mean scores were comparable: PlaySmart (18.8; 95% CI, 17.8–19.7) and control (17.8; 95% CI, 16.9–18.8; $P = 0.18$). The change from baseline to 6 weeks was significantly ($P = 0.001$) greater in the PlaySmart group (2.3; 95% CI, 1.4–3.1) than in the control group (0.2; 95% CI, −0.7–1.1). At 3 months, mean scores were similar between the two groups, PlaySmart (18.7; 95% CI, 17.7–19.7) and control (18.8; 95% CI, 17.9–19.8; $P = 0.85$), with similar changes from baseline to 3 months: PlaySmart (2.2; 95% CI, 1.3–3.1) and control (1.2; 95% CI, 0.3–2.1; $P = 0.11$).

Initiation of opioids was minimal, with no difference between the groups in prescription opioid misuse (PlaySmart, 5%; control, 2%; $P = 0.12$ at 6 weeks; PlaySmart, 1%; control, 1%; $P = 0.66$ at 3 months) or heroin use (PlaySmart, 0.4%; control, 0%; $P = 0.31$ at 6 weeks; PlaySmart, 0%; control, 0.4%; $P = 0.32$ at 3 months) (Extended Data Table 4).

There were no substantial differences between per-protocol unadjusted models, models including random school cluster, or models adjusted for the randomization variables (Extended Data Table 5).

Gameplay experience

The PlaySmart group played an average of 211.1 min (50.4 min per session), and the control group played 226 min (52.4 min per session) out of the target 300 min of gameplay time, as established during pilot testing. Following gameplay, 84% (227/269) of those who played the PlaySmart game answered questions related to their gameplay experience. They answered agree/strongly agree to the following: the game helped them learn important things (93%, 210/227), they found the game easy to understand (86%, 196/227), they enjoyed the game (79%, 178/226), they were not frustrated by the game (75%, 170/227), and they felt in control of the game (73%, 165/227).

Harms

There were two mild adverse events reported, one at baseline and one at 6 weeks. Both events, described as discomfort during gameplay and discomfort from prolonged exposure to the intervention, were deemed possibly related to the study.

Data completeness

Completeness of assessments was ≥85%, with 87% (464/532; 231 PlaySmart, 233 control) of participants completing the primary outcome assessment for perceived risk of harm from opioids at 3 months. This represents a 13% loss, well below the design parameter used for sample size and power estimation, set at 16%, with an appropriate sample size inflation accounting for this loss. Notably, several strategies contributed to our strong study retention rates, including consistent research staff at each school who built trusting relationships, regular reminders to participants at each contact point, and active school support in locating students and providing flexible scheduling.

Discussion

This randomized controlled trial describes the impact of the videogame PlaySmart on participants' perceived risk of harm from opioid misuse. The PlaySmart group did not show a significant difference in perceived risk of harm at the primary outcome timepoint of 3 months. Although there was a significant increase in perceived risk of harm from opioid misuse at the 6-week assessment (immediately following gameplay), this was not sustained at 3 months. The PlaySmart participants exhibited significant improvements in knowledge and negative expectancies about opioid misuse compared to the control group, but not self-efficacy, intentions or positive expectancies. Youth who played PlaySmart also reported high levels of satisfaction with the game, underscoring its potential as an engaging prevention tool.

Although participants in neither group reported meaningful levels of initiation of opioid misuse by the 3-month timepoint, and, as such, we were not yet able to detect a between-groups difference or demonstrate the relationship between perceived risk of harm and actual use, our study's goal of examining perceived risk does align with research emphasizing the role of perceived risk of harm as a potential predictor of substance misuse in adolescents. We chose to target perceived risk of harm from opioid misuse because national data on adolescents, and our study data, reveal persistently low risk perceptions for both prescription opioids and heroin. In addition, research continues to demonstrate that lower perceived risk among adolescents is significantly associated with increased likelihood of actual misuse, underscoring the need for interventions that effectively shift these perceptions[50,51]. There are, however, few studies that examine interventions targeting perceived risk of harm[19]. A non-experimental pre–post study by Fuentes and colleagues[52] found that, immediately post-intervention, perceptions of use being 'very dangerous' (a proxy for 'great risk of harm') increased by 16% for smoking one cigarette (23.9% to 39.9%), 16.2% for alcohol (43.8% to 60%) and 9% for marijuana (57% to 66%). Although opioids were not assessed in ref. 52, the findings for marijuana are directionally consistent with the 6-week findings in the current study—26% of PlaySmart versus 18% of controls endorsing great risk of harm from opioid misuse (8% difference). This underscores the importance of new interventions targeting accurate risk perception in mitigating substance use, including opioid misuse. We anticipate being better able to demonstrate this relationship with longer-term outcomes at our 6- and 12-month timepoints.

Our study also adds to the literature about the impact of game-based learning and the value of digital interventions for reach and scale. For example, the observed increase in opioid-related knowledge and attitudes among PlaySmart participants is consistent with our previous research and that of others on the efficacy of serious games in enhancing health-related outcomes in domains such as substance use, sexual health and mental health[23–25,42,53,54]. The incorporation of

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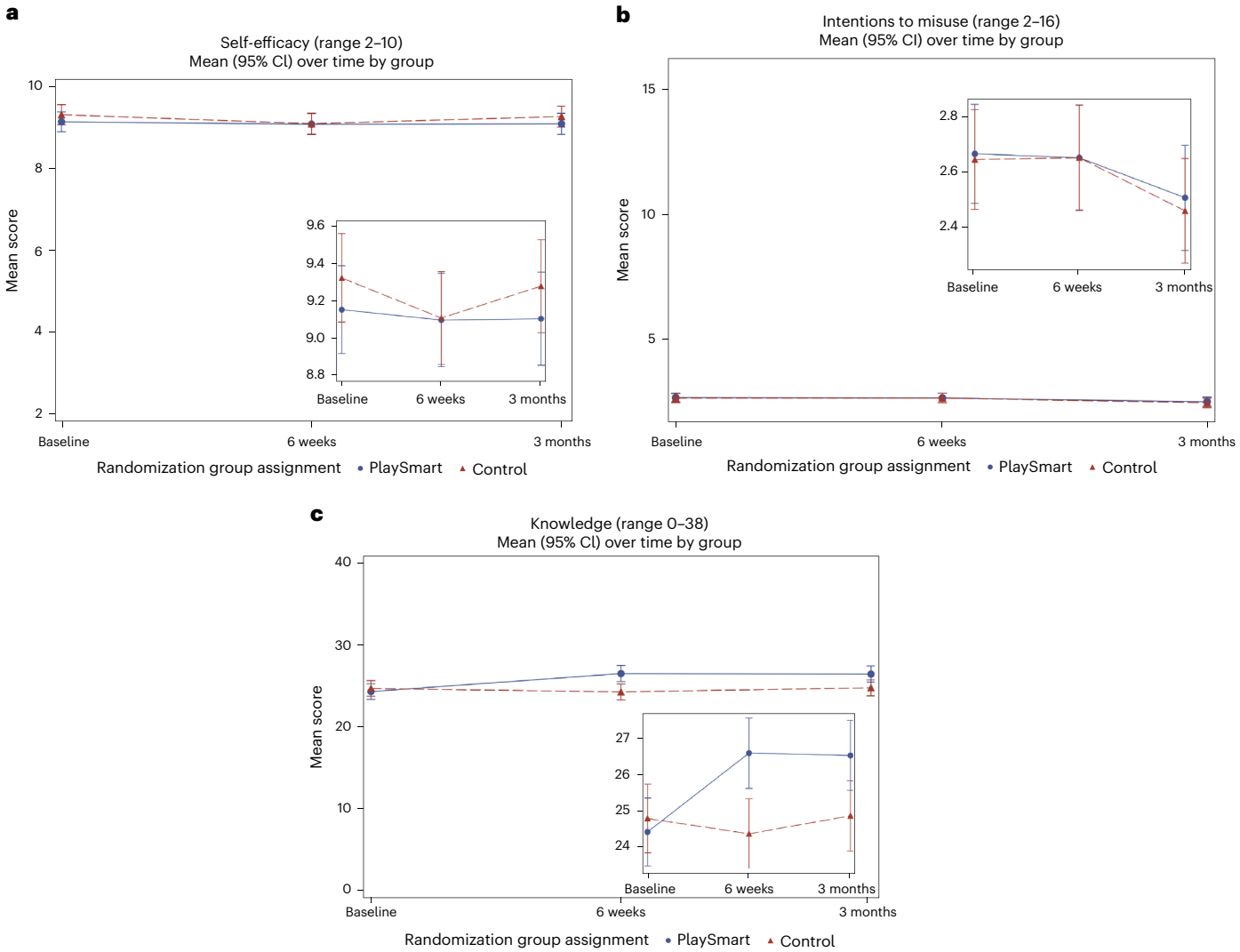

Fig. 3 | Changes in self-efficacy, intentions and knowledge. a, Mean self-efficacy scores (range 2–10) over time by group. **b**, Mean intentions to misuse opioids (range 2–16) over time by group. **c**, Mean knowledge scores (range 0–38) over time by group. Mean scores and 95% CIs presented for PlaySmart (blue circles and solid lines) and control (red triangles and dashed lines) at baseline, 6 weeks and 3 months. Scores were generated using a linear mixed model with fixed effects for randomization group, time, interaction of randomization group and time, and random participant. The range of each instrument is noted in each panel. The numbers contributing data for the self-efficacy outcome for PlaySmart were 268, 231 and 231 and for control were 263, 233 and 234 at baseline, 6 weeks and 3 months, respectively. The numbers contributing data for the intentions to misuse outcome for PlaySmart were 268, 230 and 231 and for control were 263, 233 and 234 at baseline, 6 weeks and 3 months, respectively. The numbers contributing data for the knowledge outcome for PlaySmart were 269, 231 and 231 and for control were 263, 234 and 234 at baseline, 6 weeks and 3 months, respectively.

behaviour change theories and user-centred design in PlaySmart probably contributed to its effectiveness, highlighting the importance of integrating evidence-based frameworks into videogame intervention development[44].

In addition, a digital intervention such as PlaySmart potentially mitigates some of the substantial implementation barriers. For example, a recent study evaluating a school-based harm reduction programme for high-school students, Safety First, reported an impact on knowledge and decision-making skills[55]. However, they also concluded that, although the curriculum showed important improvements, it required educator training and coaching to implement, potentially limiting broad-scale reach. Similarly, studies of effective adolescent substance prevention programmes such as LifeSkills Training and the Strengthening Family Program, which require consistent structural oversight, have demonstrated that classroom-level factors can significantly impact engagement and retention[56], and translation to a virtual platform can help mitigate these barriers[57]. Most studies do not specify actual hours of engagement, but our study was able to document that, on average, our participants played PlaySmart for three-and-a-half hours, providing evidence of student-level engagement. Therefore, videogames like PlaySmart may offer unique advantages beyond impact, including engagement, consistent delivery and fidelity, and scalability.

Several limitations to our study must also be discussed. The sample was drawn from one US state (Connecticut), so generalizability to other populations may be limited, though it is important to note that our sample was sociodemographically diverse and from high schools in different regions of the state. Although our questions on actual substance use do ask about experience with fentanyl, the questions we used for perceived risk of harm from opioids were drawn from the MTF Study[49], which did not include fentanyl. Future studies should include an assessment of perceived risk of harm from fentanyl specifically, given its emerged prevalence. In addition, our measures were collected by self-report. Although this may introduce social desirability bias, we optimized our methods through strategies we used in previous trials collecting sensitive data from young people, ensuring privacy and

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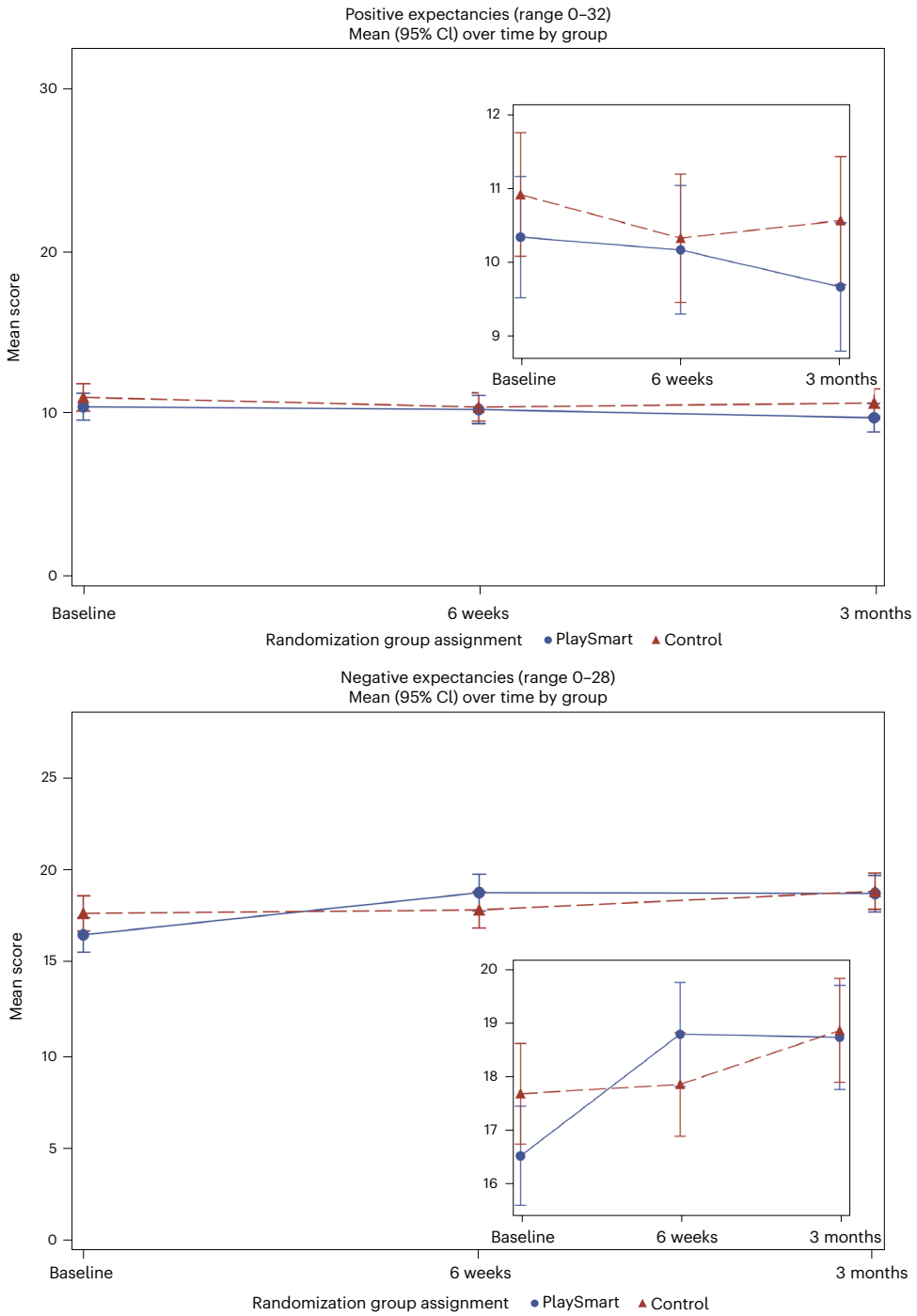

Fig. 4 | Changes in attitudes: positive and negative expectancies. Attitudes—positive expectancies (range 0–32) means (95% CIs) over time by group (top) and negative expectancies (range 0–28) means (95% CIs) over time by group (bottom). Mean scores and 95% CIs are presented for PlaySmart (blue circles and solid lines) and control (red triangles and dashed lines) at baseline, 6 weeks and 3 months. Scores were generated using a linear mixed model with fixed effects for randomization group, time, interaction of randomization group and time, and random participant. The numbers contributing data for each attitude outcome for PlaySmart were 269, 229 and 230 and for control were 259, 233 and 233 at baseline, 6 weeks and 3 months, respectively.

confidentiality, with the goal of enhancing disclosure and reducing bias[24,25]. Although data on both sex and gender were collected, we did not examine potential differences in intervention effects by gender due to small subgroup sizes and the scope of the current analyses.

Furthermore, the current study reports short-term outcomes, and 6- and 12-month data are forthcoming. National data indicate that if an adolescent has not started opioid misuse by age 16 years, the estimated average age of initiation would probably be around 18–19 years, so we may be able to capture the impact of the PlaySmart intervention at 12 months follow-up in some participants[58]. Given the strong established inverse relationship between perceived risk of harm from opioid misuse and actual misuse, this further bolsters the value of this measure as a proxy when actual misuse may be delayed.

Our current findings did not demonstrate a statistically significant increase in perceived risk of harm in the PlaySmart group at 3 months. Notably, the baseline proportion of perceived risk of harm from opioids in our cohort was lower than the one used in our power calculations (17% versus 32%). The higher estimate was based on single-item data

from the 2018 MTF survey[49], but our primary outcome required endorsement of 'great risk' across all eight opioid-related items, yielding a more conservative parameter estimate. Accordingly, the discrepancy in baseline rate probably reflects differences in how the outcome was operationalized (for example, single-item measures versus composite), potentially limiting our power to detect the hypothesized effect, and is now noted as a limitation. Importantly, a significant change was seen at 6 weeks, but was not sustained. This finding may highlight the need for a booster at a timepoint between gameplay and 3 months. Although PlaySmart did significantly improve knowledge, we know that knowledge is necessary but not sufficient for behaviour change. Behaviour change is a complex, multistep process, and although we aimed to target a number of key behavioural antecedents, such as findings in the broader substance-misuse literature, impacting all these outcomes was challenging[59].

Further work is needed to refine the design of PlaySmart to achieve stronger and more durable effects on risk perception. These efforts might include incorporating into the game adaptive features such as personalized feedback, booster sessions and storyline extensions to reinforce key prevention messages and counter the decline in impact observed at 3 months. We will also examine how expanded narratives and contextually relevant storylines influence outcomes to optimize the long-term impact of PlaySmart on opioid misuse prevention. Collectively, these potential avenues for the further enhancement and design of PlaySmart will help to identify the most promising strategies to strengthen the intervention's durability and real-world application.

Our conclusions are thus tempered to reflect the preliminary nature of the findings, and a next step is to examine the longer-term outcomes (for example, at 6 and 12 months) to more fully assess the programme's potential impact before recommending broader dissemination. There is a continued opioid crisis in the United States and an urgent need for engaging, scalable and effective interventions targeting opioid misuse prevention in adolescents[20]. We hypothesize that the combination of the increase in knowledge and negative expectancies around opioid misuse, as key behavioural antecedents, in conjunction with future efforts to bolster risk perception, holds the promise of substantially impacting opioid-misuse risk perceptions and behaviours in adolescents.

Methods

Study design, settings and participants

Through a two-arm parallel superiority randomized controlled trial using a placebo comparator, we evaluated the efficacy of the original videogame PlaySmart[44]. This study was approved by the Yale IRB (protocol #2000030553) and registered on ClinicalTrials.gov (NCT04941950). The trial protocol and statistical analysis plan can be accessed at www.clinicaltrials.gov. High schools were eligible if they were in Connecticut. Students were eligible if they (1) were aged 16–19 years (grades 9–12); (2) attended high school (preferably enroled in the school's school-based health centre); (3) reported no prior opioid misuse; (4) were considered to be 'high-risk' based on at least one of the following baseline criteria: (a) past 30-day use of cigarettes, e-cigarettes/Juul, alcohol, marijuana (including synthetics), amphetamines, cocaine, benzodiazepines, ecstasy, bath salts or other non-opioid prescription or illicit drugs OR (b) a score of ≥1 on the modified Patient Health Questionnaire-2 (PHQ-2) depression screener OR (c) a score of ≥1 on the modified Generalized Anxiety Disorder-2 (GAD-2) anxiety screener; (5) were willing to participate in 60-min gameplay sessions; and (6) provided assent and parental/guardian consent if under 18 years of age.

Participants self-reported both sex (male/female) and gender at baseline. For the present analyses, sex was included as a covariate given the study design, but gender was not included in the analysis due to small subgroup size. Additionally, race and ethnicity were self-reported to describe the sample and assess generalizability, but they were not used in primary analyses.

Participants played their assigned games (PlaySmart or control) on research-provided iPads during supervised, after-school sessions (1 or 2 times per week for approximately 6 weeks; ~60 min per session). Research assistants recorded session start and end times to monitor attendance and exposure. There was no required minimum dosage or content completion. Additional study procedures and methods have been published previously[46]. The full study protocol is available in Supplement Information 1.

Randomization

Randomization, block sizes 2 and 4, was stratified by sex and grade (9/10th and 11/12th) and was operationalized through REDCap P11. The randomization scheme was generated by the senior biostatistician (T.C.K.) and implemented by a separate research study team responsible for the online randomization platform and data entry system.

Research staff accessed the system after participants were screened, consented and completed baseline assessments to enter stratification data and receive randomization assignments.

The study team remained blinded to outcomes until after database lock and statistical reports were prepared.

Interventions

PlaySmart is a theory-driven, narrative Web-mobile videogame composed of up to 6 h of unique gameplay. Within the game, players navigate decisions related to peer pressure, stress and substance use, particularly opioids, while also addressing co-occurring risk factors such as mental health challenges and other substance misuse. In addition to the six main storylines, PlaySmart also features six integrated minigames that reinforce core prevention skills such as refusal skills, decision-making skills and coping strategies (Supplementary Fig. 1)[46].

Participants randomized to the experimental group accessed PlaySmart through a secure login portal (https://user.p2p-games.org/login) using a unique, randomly generated username and password created via the study's administrative site (https://admin.p2p-games.org/login). Each participant used a research-provided iPad and the same assigned iPad and login credentials across all sessions so that their progress could be saved.

Participants assigned to the control condition had access to nine videogames that contained no relevant content (for example, The Sims, Can You Escape), serving as the attention/time control.

Outcomes

Where adapted measures were used, a Cronbach's alpha[60] was generated to ensure the reliability of the questions (Extended Data Table 6). Baseline sociodemographic and clinical characteristics were collected. All measures and specific questions are described elsewhere[46], but only a subset is included in the current article. Perceived risk of harm from opioid misuse was the primary outcome and was assessed with eight questions taken from the US-based Monitoring The Future survey[49]. In the assessment, the first five of the eight questions address heroin use and the last three questions prescription opioid misuse (Supplementary Information 1). Primary and secondary outcomes were assessed at all three timepoints, as per the protocol.

Secondary outcomes included self-efficacy, intentions, knowledge and attitudes (positive and negative expectancies). Participants' self-efficacy to refuse opioids was assessed with a revised subscale from the Drug Use Resistance Self-Efficacy (DURSE) scale[61] (two items, maximum score = 10). Higher scores indicated higher self-efficacy around not misusing opioids. Intentions to misuse opioids were assessed with a modified scale from a substance-use intentions study[62] (four items, maximum score = 16). Lower scores reflected lower intentions to misuse opioids. We assessed knowledge with a 30-item scale that included 27 true/false questions and three questions allowing

participants to select all that applied. This scale was a composite of instruments from two risk behaviour studies[63,64]. Correct answers for the 27 true/false questions were given one point; any answer left blank was given a score of 0. For the three multiple-choice questions, each correct answer was given one point (combined maximum score of 27 true/false questions and three multiple-choice questions = 38). Higher knowledge scores were consistent with more accurate knowledge. Participants' attitudes were assessed using a revised scale[65] (15 items), with the first eight questions representing positive expectancies of using opioids (maximum score = 32) and the last seven representing negative expectancies of using opioids (maximum score = 28). Initiation of opioid misuse was assessed with a dichotomous (yes/no) measure of lifetime use[66–68].

Participants who played PlaySmart answered six questions about their gameplay experience.

Harms

Harms were pre-specified as any adverse events related to trial participation, including physical discomfort (for example, eyestrain, headache), emotional distress (for example, frustration, discomfort with game content) or any other negative effects reported by participants or study staff during gameplay or assessments. Adverse events were collected systematically at each gameplay session and follow-up assessment timepoint and reported to the Data Safety Monitoring Board and the IRB as appropriate. The risks associated with receiving the intervention were considered minimal.

Data collection and management

REDCap P11 was used for data collection, management and monitoring, and is further described elsewhere[46].

Statistical analyses

We followed the 'intention to treat' principle in the analyses of the outcomes. Baseline characteristics are reported using mean and standard deviation for continuous variables or *N* and percentages for binary or categorical variables. All analyses were generated using SAS software version 9.4 (SAS Institute). Statistical significance was set to 0.05, two-sided, as appropriate.

The primary hypothesis was that, at 3 months, there would be a higher proportion of PlaySmart than control participants who perceived a great risk of harm from misuse of prescription opioids and/or use of heroin. This was tested by comparing the responses to the eight questions on perceived risk of harm with those participants who reported 'great risk of harm' for all of the eight questions, being included in the 'great risk of harm' group. Otherwise, they were included in the 'no great risk of harm' group. χ^2 tests were used to compare the proportions of participants in each study arm who achieved the outcome at 3 months (post randomization) and 6 weeks (post-gameplay completion). The difference in proportion (and 95% CIs) of study participants in the two arms was also calculated at each timepoint.

Supplemental primary outcome analyses were performed with a mixed model with log link. Fixed effects for randomization group, time, interaction of treatment group by time, and random participant effect were included in all models. Unadjusted and adjusted (for grade and sex) were used to compare the two study groups using ORs and 95% CIs. Additional adjusted models with random intercepts for participant and participant clustered within school were also included to investigate if there was any effect of school on the primary outcome. A final supplemental model compared the change in odds of answering great risk of harm to all eight questions (scoring 32 on the Perception of Harm Scale) from baseline to 6 weeks or to 3 months for PlaySmart versus control. This model included fixed effects for randomization group, time, interaction of group and time, adjusted for baseline (binary risk score of 32 or less than 32), grade and sex, with random intercepts for participant and participant clustered within school.

The two study groups were also compared using χ^2 tests of the proportions who perceived a 'great risk of harm' when examining two subsets of questions from the perceived risk of harm questions: five questions addressing heroin use and three questions addressing prescription opioid misuse.

For each secondary outcome, scores were compared between the two groups using least squared means using a mixed-effects model, with random participant ID, fixed effect for time, randomization group, and interaction of time and randomization group, using all data at all timepoints. Mixed-model repeated measures analysis allows for valid inferences under the assumption that data are missing at random and makes use of all available data without the need for imputation. Scores for self-efficacy to refuse opioids were summed and ranged from 2 to 10, with higher score indicating greater self-efficacy. Scores for intentions to misuse opioids were summed and ranged from 2 to 16, with higher score indicating greater intentions. Knowledge scores were summed and ranged from 0 to 38. The knowledge score and its changes (since baseline) at 6 weeks and 3 months were compared between the two study arms. Attitudes towards misuse were categorized into positive and negative expectancies. Mixed-model repeated measures analysis for the secondary outcomes provided valid estimates under the assumption of data missing at random and used all available data without requiring imputation. Given this approach and the observed attrition pattern, additional sensitivity analyses or imputation were not conducted.

Additional models for the secondary outcomes are provided. Unadjusted models with random intercepts for participant and participant clustered within school were also included to investigate whether there was any effect of school on outcome. Additional models adjusted for the randomization stratification of grade and sex are also included.

Reported initiation of prescription opioids and/or heroin was compared between the two groups at each timepoint using χ^2 and difference in proportions (and 95% CIs).

Sample size and power

Based on estimates from drug use prevention interventions[69–71], and using data from a study examining the impact of an intervention on perceptions of harm of drug use[72], the study was powered to detect a 15% absolute difference between the PlaySmart group and the control groups in perceived risk of harm from opioid misuse at 3 months. The assumption was that, at baseline, ~32% of participants would report a 'great risk of harm' of opioid misuse[49]. Therefore, a sample size of 454 participants would be required with 90% power ($P \leq 0.05$) (Power Analysis Statistical Software (PASS); 2008), inflated to 532 participants (266 in each arm) to account for 16% loss at 3 months based on data from another randomized trial[25].

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

This study, part of the NIDA HEAL Prevention Cooperative, will deposit de-identified individual-level participant data in NIDA's National Addiction & HIV Data Archive Program (NAHDAP), maintained by NIDA. Data will become available upon publication and will remain archived indefinitely. Access is restricted to protect participant confidentiality and will be granted to qualified researchers upon approval of a research proposal that includes specific aims and an analysis plan. Approval is contingent on execution of a data use agreement, which outlines permissible uses and restrictions, including prohibitions against redistribution or re-identification of participants. Requests for access should be submitted via the NAHDAP request system. Requests are typically reviewed and responded to within 4–6 weeks.

Code availability

No custom code was developed or used in the analysis of this study. The videogame PlaySmart is publicly accessible via its distribution website, Playbl (https://playbl.com). Readers interested in access must submit a request through the website. Use of PlaySmart is governed by Playbl's standard Terms of Use and users must comply with Playbl's Acceptable Use Policy, Privacy Policy, and, where applicable, laws protecting minors. The underlying source code of the game is not being shared or made publicly available due to licensing and intellectual-property restrictions.

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Author contributions

L.E.F. and T.B. designed the trial, and L.E.F. received funding for the study. K.L., T.B. and L.E.F. designed the assessments for the study.

T.B. and L.H. conducted the study. K.M. and T.C.K. analysed the results. T.B. and L.E.F. wrote the first draft of the manuscript. T.B., L.E.F., L.H., K.L., T.C.K. and K.M. critically proofread the manuscript and provided valuable inputs for adjustment. All authors contributed to the final version of the manuscript.

Competing interests

L.E.F., a co-author on this manuscript and principal investigator on this NIH-funded study, is also a cofounder and equity holder of a spin-out company from the play2PREVENT Lab called Playbl that focuses on the marketing and distribution of our videogame interventions. This relationship is extensively managed by L.E.F. and Yale University and L.E.F. and Dartmouth College. This management, which is closely followed, includes L.E.F. (1) not being involved in any interactions with study participants including the selection, enrolment or consenting of participants, or determination of participant eligibility and (2) not participating in data collection and maintaining an independent data analysis team (Yale Center for Analytical Studies, YCAS). The other authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s44360-025-00010-z.

Correspondence and requests for materials should be addressed to Tyra Boomer.

Peer review information *Nature Health* thanks Yuhua Bao, Jennifer Hellier, Michelle Torok and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editor: Lorenzo Righetto, in collaboration with the *Nature Health* team.

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Extended Data Table 1 | Participating Schools and Enrolment in the PlaySmart Study

School (Region)	School Type/Locale	Total School Enrollment	PlaySmart Study Enrollment (N, % of Sample)
School 1-Northcentral Connecticut	Public/ Mid-size City	643	33 (6%)
School 2- Southwest Connecticut	Public/Mid-size City	2048	56 (11%)
School 3-South Central Connecticut	Public/Fringe Rural	384	48 (9%)
School 4-South Central Connecticut	Public/Large Suburb	1780	91 (17%)
School 5-Southwest Connecticut	Public Magnet/Mid- size City	642	5 (1%)
School 6- Southwest Connecticut	Public/ Large Suburb	1672	70 (13%)
School 7-Northcentral Connecticut	Public Magnet/Small City	664	36 (7%)
School 8- Southwestern Connecticut	Private/Small Suburb	757	11 (2%)
School 9-Southeastern Connecticut	Public/Fringe Rural	1005	31 (6%)
School 10-South Central Connecticut	Private/Mid-size City	714	25 (5%)
School 11- South Central Connecticut	Public/Large Suburb	1108	15 (3%)
School 12- South Central Connecticut	Public/Large Suburb	1264	43 (8%)
School 13- South Connecticut	Public/Mid-size City	1109	48 (9%)
School 14- Southwest Connecticut	Public/Mid-size City	2265	28 (5%)
School 15-Southeast Connecticut	Public/Small City	532	21 (4%)

List of the 15 schools participating in the PlaySmart randomized controlled trial, including region, school type and locale, total school enrollment, and number and percentage of students enroled in the PlaySmart study.

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Extended Data Table 2 | Logistic Models for Perception of Risk of Harm Scale

Sub-table A

	Model 1		Model 2		Model 3	
	OR (95% CI)	**p**	**aOR (95% CI)**	**p**	**aOR (95% CI)**	**p**
End of Gameplay (6 weeks)	1.71 (0.97, 3.01)	0.07	1.72 (0.97, 3.04)	0.06	1.72 (0.97, 3.04)	0.06
3 months	1.41 (0.82, 2.42)	0.21	1.42 (0.82, 2.44)	0.21	1.42 (0.82, 2.44)	0.21

OR = odds ratio PlaySmart vs Control; CI = Confidence Interval

aOR = adjusted odds ratio

Model 1: fixed effects for randomization group, time, interaction of randomization group and time; random intercept for subject

Model 2: fixed effects for randomization group, time, interaction of randomization group and time, adjusted for grade and sex; random intercept for subject

Model 3: fixed effects for randomization group, time, interaction of randomization group and time, adjusted for grade and sex; random intercept for subject and subject clustered within school

Sub-table B

	Model 1	
	aOR (95% CI)	**p**
Change baseline to 6 weeks	1.96 (1.1, 3.5)	0.02
Change baseline to 3 months	1.56 (0.91, 2.66	0.11

OR = odds ratio PlaySmart vs Control; CI = Confidence Interval

aOR = adjusted odds ratio

Model: fixed effects for randomization group, time, interaction of randomization group and time, adjusted for binary perception of risk at baseline, grade and sex; random intercept for subject and subject clustered within school

Results of logistic regression models assessing intervention effects on the Perception of Risk of Harm Scale at end of gameplay (6 weeks) and at 3-month follow-up. Model 1 included fixed effects for randomization group, time, and their interaction, with a random intercept for subject. Model 2 additionally adjusted for grade and sex. Model 3 additionally accounted for clustering of subjects within schools. Odds ratios (OR), adjusted odds ratios (aOR), 95% confidence intervals (CI), and p-values are reported. Sub-table B shows changes from baseline to each follow-up adjusted for baseline binary perception of risk, grade, and sex.

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Extended Data Table 3 | Perception of Risk of Harm from Heroin (A) or Prescription Opioids (B)

A: Perceived Risk of Harm from Heroin Use; Q 1-5	PlaySmart (n, %)	Control (n, %)	Total (n, %)	Difference* (95%CI)	p-value**
Baseline	**N = 269**	**N = 263**	**N = 532**		
'No Great Perceived Risk of Harm'	207 (77%)	196 (75%)	403 (76%)	-0.02 (-0.10, 0.05)	0.51
'Great Perceived Risk of Harm'	62 (23%)	67 (25%)	129 (24%)		
End of Gameplay (6 weeks)	**N = 230**	**N = 233**	**N = 463**		
'No Great Perceived Risk of Harm'	151 (66%)	177 (76%)	328 (71%)	0.10 (0.02,0.19)	0.015
'Great Perceived Risk of Harm'	79 (34%)	56 (24%)	135 (29%)		
Baseline 'No *Great Perceived Risk of Harm' to 6-weeks 'Great Perceived Risk of Harm'*	42 (18%)	16 (7%)	58 (13%)		
3 months	**N = 231**	**N = 234**	**N = 465**		
'No Great Perceived Risk of Harm'	149 (65%)	161 (69%)	310 (67%)	0.04 (-0.04, 0.13)	0.33
'Great Perceived Risk of Harm'	82 (35%)	73 (31%)	155 (33%)		
Baseline 'No *Great Perceived Risk of Harm' to 3-months 'Great Perceived Risk of Harm'*	42 (18%)	34 (15%)	76 (16%)		

B: Perceived Risk of Harm from Prescription Opioid Misuse; Q 6-8	PlaySmart (n, %)	Control (n, %)	Total (n, %)	Difference* (95%CI)	p-value**
Baseline	**N = 269**	**N = 263**	**N = 532**		
'No Great Perceived Risk of Harm'	205 (76%)	190 (72%)	395 (74%)	-0.04 (-0.11, 0.03)	0.3
'Great Perceived Risk of Harm'	64 (24%)	73 (28%)	137 (26%)		
End of Gameplay (6 weeks)	**N = 230**	**N = 233**	**N = 463**		
'No Great Perceived Risk of Harm'	152 (66%)	170 (73%)	322 (70%)	0.0 (-0.01, 0.15)	0.108
'Great Perceived Risk of Harm'	78 (34%)	63 (27%)	141 (30%)		
Baseline 'No *Great Perceived Risk of Harm' to 6-weeks 'Great Perceived Risk of Harm'*	41 (18%)	24 (10%)	65 (14%)		
3 months	**N = 231**	**N = 234**	**N = 465**		
'No Great Perceived Risk of Harm'	152 (66%)	163 (70%)	315 (68%)	0.04 (-0.05, 0.12)	0.37
'Great Perceived Risk of Harm'	79 (34%)	71 (30%)	150 (32%)		
Baseline 'No *Great Perceived Risk of Harm' to 3-months 'Great Perceived Risk of Harm'*	38 (16%)	34 (15%)	72 (15%)		

** Risk difference for Great Perceived Risk of Harm in Intervention vs Control*

*** Chi-squared p-value*

Prevalence of adolescents reporting 'great perceived risk of harm' from heroin (panel A) and prescription opioid misuse (panel B) in PlaySmart and control groups at baseline, end of gameplay (6 weeks), and 3-month follow-up. Risk differences (intervention minus control) and associated 95% CIs and p-values from chi-squared tests are shown. For each outcome, rows show both cross-sectional distributions at each timepoint and transitions from 'no great perceived risk' at baseline to 'great perceived risk' at follow-up.

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Extended Data Table 4 | Initiation of Prescription Opioid Misuse or Heroin Use

	PLAYSMART n (%)	CONTROL n (%)	Total n (%)	Difference* (95% CI)	p-value**
Prescription opioids					
Baseline					
No	269	263	532		
End of Gameplay (6 weeks)	**N = 231**	**N = 234**	**N = 465**		0.12
Yes	11 (5)	5 (2)	16 (3)	3 (-1, 6)	
No	220 (95)	229 (98)	449 (97)		
3 months	**N = 231**	**N = 234**	**N = 465**		0.66
Yes	2 (1)	3 (1)	5 (1)	-0 (-2, 1)	
No	229 (99)	231 (99)	460 (99)		
Heroin					
Baseline					
No	269	263	532		
End of Gameplay (6 weeks)	**N = 231**	**N = 234**	**N = 465**		0.31
Yes	1	0	1	-0 (-1, 0)	
No	230 (100)	234 (100)	464 (100)		
3 months	**N = 231**	**N = 234**	**N = 465**		0.32
Yes	0	1	1	-0 (-1, 0)	
No	231 (100)	233 (100)	464 (100)		

* Risk difference for "Yes" to substance use in Intervention vs Control
** Chi-square test

Incidence of self-reported initiation of prescription opioid misuse or heroin use in the PlaySmart and control groups at end of gameplay (6 weeks) and at 3-month follow-up among participants without baseline use. Risk differences between groups (intervention minus control), 95% CIs, and p-values from chi-squared tests are reported.

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Extended Data Table 5 | Least Squared Means for Secondary Outcomes

	Unadjusted				Adjusted			
	PLAYSMART (LSmean, 95% CI)	**CONTROL (LSmean, 95% CI)**	**Total (LSmean, 95% CI)**	**p-value**	**PLAYSMART (LSmean, 95% CI)**	**CONTROL (LSmean, 95% CI)**	**Total (LSmean, 95% CI)**	**p-value**
Self-efficacy								
Baseline	9.2 (8.9, 9.5)	9.4 (9.1, 9.6)	9.3 (9.1, 9.5)	0.33	9.2 (8.9, 9.5)	9.3 (9.0, 9.6)	9.2 (9.0, 9.5)	0.32
End of Gameplay (6 weeks)	9.1 (8.9, 9.4)	9.1 (8.9, 9.4)	9.1 (8.9, 9.4)	0.98	9.1 (8.8, 9.4)	9.1 (8.8, 9.4)	9.1 (8.8, 9.4)	0.96
δ (6 weeks-Baseline)	-0.1 (-0.3, 0.2)	-0.2 (-0.5, 0.0)	-0.1 (-0.3, 0.0)	0.39	-0.1 (-0.3, 0.2)	-0.2 (-0.5, 0.0)	-0.1 (-0.3, 0.0)	0.40
3 months	9.1 (8.9, 9.4)	9.3 (9.0, 9.6)	9.2 (9.0, 9.5)	0.34	9.1 (8.8, 9.4)	9.3 (9.0, 9.6)	9.2 (8.9, 9.4)	0.33
δ (3 months-Baseline)	-0.1 (-0.3, 0.2)	-0.0 (-0.3, 0.2)	-0.0 (-0.2, 0.1)	0.98	-0.1 (-0.3, 0.2)	-0.0 (-0.3, 0.2)	-0.1 (-0.2, 0.1)	0.97
Intentions to misuse								
Baseline	2.7 (2.5, 2.8)	2.6 (2.5, 2.8)	2.7 (2.5, 2.8)	0.87	2.7 (2.5, 2.9)	2.7 (2.5, 2.9)	2.7 (2.6, 2.9)	0.86
End of Gameplay (6 weeks)	2.7 (2.5, 2.8)	2.7 (2.5, 2.8)	2.7 (2.5, 2.8)	1.00	2.7 (2.5, 2.9)	2.7 (2.5, 2.9)	2.7 (2.6, 2.9)	0.98
δ (6 weeks-Baseline)	-0.0 (-0.2, 0.2)	0.0 (-0.2, 0.2)	-0.0 (-0.2, 0.1)	0.89	-0.0 (-0.2, 0.2)	0.0 (-0.2, 0.2)	-0.0 (-0.2, 0.2)	0.90
3 months	2.5 (2.3, 2.7)	2.5 (2.3, 2.6)	2.5 (2.3, 2.6)	0.73	2.6 (2.4, 2.8)	2.5 (2.3, 2.7)	2.6 (2.4, 2.7)	0.71
δ (3 months-Baseline)	-0.2 (-0.4, 0.1)	-0.2 (-0.4, 0.0)	-0.2 (-0.3, -0.0)	0.86	-0.2 (-0.4, 0.1)	-0.2 (-0.4, 0.0)	-0.2 (-0.3, -0.0)	0.86
Knowledge								
Baseline	25.1 (23.5, 26.7)	25.4 (23.8, 26.9)	25.2 (23.8, 26.7)	0.67	25.1 (23.3, 26.8)	25.4 (23.6, 27.2)	25.2 (23.6, 26.9)	0.63
End of Gameplay (6 weeks)	27.2 (25.7, 28.8)	25.0 (23.4, 26.5)	26.1 (24.7, 27.6)	0.001	27.2 (25.5, 29.0)	25.0 (23.2, 26.8)	26.1 (24.5, 27.8)	0.001
δ (6 weeks-Baseline)	2.2 (1.5, 2.8)	-0.4 (-1.1, 0.2)	0.9 (0.4, 1.3)	<.0001	2.2 (1.5, 2.8)	-0.4 (-1.0, 0.2)	0.9 (0.4, 1.3)	<.0001
3 months	27.2 (25.6, 28.8)	25.5 (23.9, 27.0)	26.3 (24.9, 27.8)	0.010	27.2 (25.4, 28.9)	25.5 (23.7, 27.3)	26.3 (24.7, 28.0)	0.010
δ (3 months-Baseline)	2.1 (1.5, 2.8)	0.1 (-0.6, 0.7)	1.1 (0.6, 1.6)	<.0001	2.1 (1.4, 2.7)	0.1 (-0.6, 0.7)	1.1 (0.6, 1.5)	<.0001
Positive expectancy (Q 1-8):								
Baseline	10.2 (9.2, 11.2)	10.8 (9.7, 11.8)	10.5 (9.7, 11.3)	0.35	10.4 (9.4, 11.5)	11.0 (9.9, 12.1)	10.7 (9.8, 11.7)	0.36
End of Gameplay (6 weeks)	10.0 (9.0, 11.1)	10.2 (9.1, 11.2)	10.1 (9.3, 10.9)	0.81	10.3 (9.2, 11.4)	10.4 (9.3, 11.5)	10.4 (9.4, 11.3)	0.84
δ (6 weeks-Baseline)	-0.2 (-1.0, 0.7)	-0.6 (-1.4, 0.3)	-0.4 (-1.0, 0.2)	0.50	-0.2 (-1.0, 0.7)	-0.6 (-1.4, 0.3)	-0.4 (-1.0, 0.2)	0.49
3 months	9.5 (8.5, 10.6)	10.4 (9.4, 11.4)	10.0 (9.1, 10.8)	0.15	9.8 (8.7, 10.9)	10.7 (9.5, 11.8)	10.2 (9.3, 11.2)	0.16
δ (3 months-Baseline)	-0.7 (-1.5, 0.2)	-0.3 (-1.2, 0.5)	-0.5 (-1.1, 0.1)	0.59	-0.6 (-1.5, 0.2)	-0.3 (-1.2, 0.5)	-0.5 (-1.1, 0.1)	0.59
Negative expectancy (Q 9-15):								
Baseline	16.8 (15.3, 18.2)	17.8 (16.4, 19.2)	17.3 (16.0, 18.5)	0.11	16.8 (15.3, 18.4)	17.9 (16.3, 19.4)	17.4 (15.9, 18.8)	0.10
End of Gameplay (6 weeks)	19.0 (17.6, 20.5)	18.0 (16.5, 19.4)	18.5 (17.2, 19.8)	0.13	19.1 (17.5, 20.6)	18.1 (16.5, 19.6)	18.6 (17.2, 20.0)	0.14
δ (6 weeks-Baseline)	2.3 (1.4, 3.2)	0.2 (-0.7, 1.1)	1.2 (0.6, 1.9)	0.001	2.3 (1.4, 3.1)	0.2 (-0.7, 1.1)	1.2 (0.6, 1.8)	0.001
3 months	19.0 (17.5, 20.4)	19.0 (17.6, 20.4)	19.0 (17.7, 20.3)	0.98	19.0 (17.5, 20.6)	19.1 (17.5, 20.7)	19.1 (17.6, 20.5)	0.95
δ (3 months-Baseline)	2.2 (1.4, 3.1)	1.2 (0.3, 2.1)	1.7 (1.1, 2.3)	0.11	2.2 (1.3, 3.1)	1.2 (0.3, 2.1)	1.7 (1.1, 2.3)	0.11

LSMean = Least squared mean, CI = confidence interval
Unadjusted = Linear mixed model; fixed effects for randomization group, time, interaction of randomization group and time; random intercept for subject and subject clustered within school
Adjusted = Linear mixed model; fixed effects for randomization group, time, interaction of randomization group and time, adjusted for grade and sex; random intercept for subject and subject clustered within school

Least-squared means (LSmean) and 95% CIs for self-efficacy, intentions to misuse, knowledge, positive expectancies, and negative expectancies at baseline, end of gameplay (6 weeks), and 3-month follow-up in the PlaySmart and control groups. Both unadjusted and adjusted linear mixed-model estimates are shown. Models included fixed effects for randomization group, time, and their interaction, with random intercept for subject clustered within school; adjusted models additionally controlled for grade and sex. Differences (δ) from baseline to each follow-up and associated p-values are provided.

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Extended Data Table 6 | Cronbach's Alphas for Secondary Outcomes

Outcome		Baseline	6-weeks	3-months
Intentions to Misuse		0.88	0.75	0.6
Self-efficacy		0.88	0.92	0.93
Attitudes	Attitudes (Q 1-15)	0.89	0.86	0.87
	Positive expectancies (Q 1-8)	0.9	0.88	0.88
	Negative expectancies (Q 9-15)	0.93	0.92	0.93
Knowledge	"Score" for each "select all that apply"	0.89	0.92	0.93
	First 27 questions only	0.92	0.94	0.95

Cronbach's alpha coefficients for intentions to misuse, self-efficacy, and attitudes (overall and by positive/negative expectancy subscales), as well as for knowledge items at baseline, end of gameplay (6 weeks), and 3-month follow-up, indicating internal consistency of each measure.

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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	REDCap P11 was used for participant data collection and randomization entry (current version is 14.5).
Data analysis	SAS software Version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses, including mixed-effects models and other inferential tests.PASS (Power Analysis Statistical Software), used in the sample-size/power calculations (PASS; 2008).

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This study, part of the NIDA HEAL Prevention Cooperative, will deposit de-identified individual-level participant data in NIDA's National Addiction & HIV Data Archive Program (NAHDAP), maintained by NIDA. Data will become available upon publication and will remain archived indefinitely. Access is restricted to protect participant confidentiality and will be granted to qualified researchers upon approval of a research proposal that includes specific aims and an analysis plan.

Approval is contingent upon execution of a data use agreement, which outlines permissible uses and restrictions, including prohibitions against redistribution or re-identification of participants. Requests for access should be submitted via the NAHDAP request system. Requests are typically reviewed and responded to within 4–6 weeks.
No custom code was developed or used in the analysis of this study. No custom code was developed or used in the analysis of this study. The videogame PlaySmart is publicly accessible via its distribution website, Playbl (https://playbl.com). Readers interested in access must submit a request through the website. Use of PlaySmart is governed by Playbl's standard Terms of Use and users must comply with Playbl's Acceptable Use Policy, Privacy Policy, and, where applicable, laws protecting minors. The underlying source code of the game is not being shared or made publicly available due to licensing and intellectual-property restrictions.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Participants self-reported both sex (male/female) and gender at baseline. For the present analyses, sex was included as a covariate given the study design, while gender was not included in the analysis dues to small subgroup size.
Reporting on race, ethnicity, or other socially relevant groupings	Race and ethnicity were self-reported by participants using predefined categories (e.g., White, Black/African American, Asian, etc.). These variables were collected to describe the sample and assess generalizability. They were not included in primary outcome analyses but may inform future subgroup or exploratory analyses. Race and ethnicity were treated as social constructs, not biological proxies.
Population characteristics	16-19 year olds were recruited from 15 geographically, racially and socio-economically diverse high schools in CT.
Recruitment	Participants were recruited from 15 Connecticut high schools between October 21, 2021 and February 27, 2024 through flyers with QR codes, school announcements, tabling during lunch periods, and classroom recruitment. Eligible students who consented (and assented, if minors) completed baseline assessments before randomization and follow-ups at 6 weeks and 3 months. Because participation was voluntary, self-selection bias is possible: students who enrolled may have been more motivated, more receptive to digital interventions, or more concerned about substance use than those who did not enroll. In addition, recruitment was limited to schools that agreed to participate, which may further limit the representativeness of the sample relative to all adolescents at risk for opioid misuse. These potential biases primarily affect the generalizability of the findings, although random assignment after enrollment helped mitigate confounding between study arms.
Ethics oversight	This randomized controlled trial was approved by the Yale University Institutional Review Board (Protocol #2000030553). The study was conducted in accordance with institutional guidelines and ICMJE recommendations for clinical research. The trial is registered at ClinicalTrials.gov: NCT04941950.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

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For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Behavioural & social sciences study design

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Study description	A quantitative wo-arm parallel superiority randomized controlled trial, to evaluate the impact of PlaySmart, compared to a placebo comparator, on key outcomes related to opioid misuse, with the primary outcome being perceived risk of harm from opioid misuse
Research sample	The research sample includes 16–19 years olds recruited from 15 Connecticut high schools who reported no prior opioid misuse, and were considered "high-risk" based on other substance use or mental health screens of depression and/or anxiety. Adolescence is a developmental period of heightened vulnerability for initiation of substance use, and national data indicate that early use of alcohol, cannabis, and the presence of mental health symptoms are associated with increased risk for later opioid misuse. Therefore, this population represents a critical target for preventive interventions. Participants (mean age 16.6) were 47% female and racially/Ethnically diverse (45% Black, 34% White, 38% Hispanic). Forty-five percent (238/532) of participants had mild to severe symptoms of anxiety, with 86% (456/532) reporting at least one anxiety symptom, and 61% (322/532) of participants had mild to severe symptoms of depression, with 93% (494/531) reporting at least one depression symptom. Participants reported lifetime alcohol or marijuana use (33% [175/532] and 19% [102/532]), respectively.
Sampling strategy	Participants were recruited from 15 Connecticut high schools that agreed to participate in the study; thus, the study sample represents a convenience sample of students at these schools. Eligible students were invited to participate, and those who consented/assented were then randomly assigned (1:1) to the PlaySmart intervention or control arm.

Sample size was determined a priori using estimates from prior drug-use prevention interventions and a study examining intervention effects on perceived risk of harm. The study was powered to detect a 15% absolute difference between PlaySmart and control in perceived risk of harm from opioid misuse at 3 months. Assuming that 32% of participants at baseline would report "great risk of harm," we calculated that 454 participants would be required to achieve 90% power at α = 0.05 (Power Analysis Statistical Software [PASS], 2008). The target was inflated to 532 participants (266 per arm) to allow for an estimated 16% attrition at 3 months, based on experience from a prior randomized trial.

As this was a quantitative randomized controlled trial, data saturation was not applicable.

Data collection

Data were collected at baseline, post-gameplay (6 weeks), and at 3-, 6-, and 12-month follow-ups using the REDCap P11 secure, web-based data capture system (only data through the 3-month follow-up are analyzed in this article). Participants completed the self-administered questionnaires either in person on research-provided iPads at school or remotely on their own device (phone, tablet, or computer) via a secure study link.

No individuals other than the participants and trained research staff were present during in-person survey sessions. For remote participation, assessments were completed independently without anyone present.

Research staff conducted eligibility screening, obtained consent/assent, and implemented randomization using the REDCap randomization module; therefore, they were not blinded to participants' study arm assignment.

Blinding of participants to study arm was not feasible because the intervention involved a distinct videogame, but all instructions and assessments were administered in a neutral manner without disclosure of the study hypotheses.

Timing

Rolling enrollment for the study occurred between October 21, 2021 and February 27, 2024. Data collection occurred between October 21, 2021 and March 1, 2025.

Data exclusions

Data of one participant was excluded from the analysis, because they were withdrawn by the Principal Investigator due to an incomplete consent form.

Non-participation

A total of seven participants withdrew or were withdrawn from the study. Two withdrew at baseline at the request of a parent/guardian, one withdrew at baseline due to a schedule conflict with college classes, one withdrew after gameplay due to work commitments, one withdrew at the 3-month follow-up due to lack of time/interest, one withdrew after gameplay citing loss of interest, and one was withdrawn by the study team due to invalid parental consent. No withdrawals were related to adverse events.

Randomization

Randomization, block sizes 2 and 4, was stratified by sex and grade (9/10th and 11/12th) and was operationalized through REDCap P11. The randomization scheme was generated by the senior biostatistician and implemented by a separate team responsible for the online randomization platform and data entry system, with no involvement from the study team.
Research staff accessed the system after participants were screened, consented, and completed baseline assessments to enter stratification data and receive randomization assignments. The study team remained blinded to outcomes until after database lock and statistical reports were prepared.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☐ Antibodies
☐	☐ Eukaryotic cell lines
☐	☐ Palaeontology and archaeology
☐	☐ Animals and other organisms
☐	☒ Clinical data
☐	☐ Dual use research of concern
☐	☐ Plants

Methods

n/a	Involved in the study
☐	☐ ChIP-seq
☐	☐ Flow cytometry
☐	☐ MRI-based neuroimaging

Antibodies

Antibodies used

Describe all antibodies used in the study; as applicable, provide supplier name, catalog number, clone name, and lot number.

Validation

Describe the validation of each primary antibody for the species and application, noting any validation statements on the manufacturer's website, relevant citations, antibody profiles in online databases, or data provided in the manuscript.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	*State the source of each cell line used and the sex of all primary cell lines and cells derived from human participants or vertebrate models.*
Authentication	*Describe the authentication procedures for each cell line used OR declare that none of the cell lines used were authenticated.*
Mycoplasma contamination	*Confirm that all cell lines tested negative for mycoplasma contamination OR describe the results of the testing for mycoplasma contamination OR declare that the cell lines were not tested for mycoplasma contamination.*
Commonly misidentified lines (See ICLAC register)	*Name any commonly misidentified cell lines used in the study and provide a rationale for their use.*

Palaeontology and Archaeology

Specimen provenance	*Provide provenance information for specimens and describe permits that were obtained for the work (including the name of the issuing authority, the date of issue, and any identifying information). Permits should encompass collection and, where applicable, export.*
Specimen deposition	*Indicate where the specimens have been deposited to permit free access by other researchers.*
Dating methods	*If new dates are provided, describe how they were obtained (e.g. collection, storage, sample pretreatment and measurement), where they were obtained (i.e. lab name), the calibration program and the protocol for quality assurance OR state that no new dates are provided.*

☐ Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.

Ethics oversight	*Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.*

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	*For laboratory animals, report species, strain and age OR state that the study did not involve laboratory animals.*
Wild animals	*Provide details on animals observed in or captured in the field; report species and age where possible. Describe how animals were caught and transported and what happened to captive animals after the study (if killed, explain why and describe method; if released, say where and when) OR state that the study did not involve wild animals.*
Reporting on sex	*Indicate if findings apply to only one sex; describe whether sex was considered in study design, methods used for assigning sex. Provide data disaggregated for sex where this information has been collected in the source data as appropriate; provide overall numbers in this Reporting Summary. Please state if this information has not been collected. Report sex-based analyses where performed, justify reasons for lack of sex-based analysis.*
Field-collected samples	*For laboratory work with field-collected samples, describe all relevant parameters such as housing, maintenance, temperature, photoperiod and end-of-experiment protocol OR state that the study did not involve samples collected from the field.*
Ethics oversight	*Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.*

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	Trial registration materials were submitted to ClinicalTrials.gov on June 23, 2021, and assigned the number NCT04941950.
Study protocol	The full study protocol and statistical plan can be accessed at Clinicaltrials.gov.
Data collection	Participants were recruited from 15 Connecticut high schools between October 21, 2021 and February 27, 2024 .Data was collected for the study from October 21, 2021 through March 1, 2025.

Outcomes

Perceived risk of harm from opioid misuse, was the primary outcome and was assessed with 8 questions taken from the U.S.-based Monitoring the Future. In the assessment, the first 5 of the 8 questions address heroin use and the last 3 questions prescription opioid misuse.

Secondary outcomes included self-efficacy, intentions, knowledge, and attitudes (positive and negative expectancies). Participants' Self-efficacy to refuse opioids was assessed with a revised subscale from the Drug Use Resistance Self-Efficacy (DURSE) scale (2 items, maximum score=10). Higher scores indicated higher self-efficacy around not misusing opioids. Intentions to misuse opioids were assessed with a modified scale from a substance use intentions study (4 items, maximum score=16). Lower scores reflected lower intentions to misuse opioids. Knowledge was assessed with a 30-item scale that included 27 true/false questions and 3 questions allowing participants to select all that applied. This scale was a composite of instruments from two risk behavior studies. Correct answers for the 27 true/false questions were given 1 point; any answer left blank was given a score of 0. For the 3 multiple choice questions, each correct answer was given 1 point (combined maximum score of 27 true/false questions and 3 multiple choice questions=38). Higher knowledge scores were consistent with more accurate knowledge. Participants' attitudes were assessed using a revised scale (15 items) with the first 8 questions representing positive expectancies of using opioids (maximum score=32) and the last 7 representing negative expectancies of using opioids (maximum score=28). Initiation of opioid misuse was assessed with a dichotomous (yes/no) measure of lifetime use.

Participants who played PlaySmart answered 6 questions about their gameplay experience.

Dual use research of concern

Policy information about dual use research of concern

Hazards

Could the accidental, deliberate or reckless misuse of agents or technologies generated in the work, or the application of information presented in the manuscript, pose a threat to:

No	Yes	
☐	☐	Public health
☐	☐	National security
☐	☐	Crops and/or livestock
☐	☐	Ecosystems
☐	☐	Any other significant area

Experiments of concern

Does the work involve any of these experiments of concern:

No	Yes	
☐	☐	Demonstrate how to render a vaccine ineffective
☐	☐	Confer resistance to therapeutically useful antibiotics or antiviral agents
☐	☐	Enhance the virulence of a pathogen or render a nonpathogen virulent
☐	☐	Increase transmissibility of a pathogen
☐	☐	Alter the host range of a pathogen
☐	☐	Enable evasion of diagnostic/detection modalities
☐	☐	Enable the weaponization of a biological agent or toxin
☐	☐	Any other potentially harmful combination of experiments and agents

Plants

Seed stocks

Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.

Novel plant genotypes

Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.

Authentication

Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.

ChIP-seq

Data deposition

☐ Confirm that both raw and final processed data have been deposited in a public database such as GEO.

☐ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links *May remain private before publication.*	*For "Initial submission" or "Revised version" documents, provide reviewer access links. For your "Final submission" document, provide a link to the deposited data.*
Files in database submission	*Provide a list of all files available in the database submission.*
Genome browser session (e.g. UCSC)	*Provide a link to an anonymized genome browser session for "Initial submission" and "Revised version" documents only, to enable peer review. Write "no longer applicable" for "Final submission" documents.*

Methodology

Replicates	*Describe the experimental replicates, specifying number, type and replicate agreement.*
Sequencing depth	*Describe the sequencing depth for each experiment, providing the total number of reads, uniquely mapped reads, length of reads and whether they were paired- or single-end.*
Antibodies	*Describe the antibodies used for the ChIP-seq experiments; as applicable, provide supplier name, catalog number, clone name, and lot number.*
Peak calling parameters	*Specify the command line program and parameters used for read mapping and peak calling, including the ChIP, control and index files used.*
Data quality	*Describe the methods used to ensure data quality in full detail, including how many peaks are at FDR 5% and above 5-fold enrichment.*
Software	*Describe the software used to collect and analyze the ChIP-seq data. For custom code that has been deposited into a community repository, provide accession details.*

Flow Cytometry

Plots

Confirm that:

☐ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☐ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☐ All plots are contour plots with outliers or pseudocolor plots.

☐ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	*Describe the sample preparation, detailing the biological source of the cells and any tissue processing steps used.*
Instrument	*Identify the instrument used for data collection, specifying make and model number.*
Software	*Describe the software used to collect and analyze the flow cytometry data. For custom code that has been deposited into a community repository, provide accession details.*
Cell population abundance	*Describe the abundance of the relevant cell populations within post-sort fractions, providing details on the purity of the samples and how it was determined.*
Gating strategy	*Describe the gating strategy used for all relevant experiments, specifying the preliminary FSC/SSC gates of the starting cell population, indicating where boundaries between "positive" and "negative" staining cell populations are defined.*

☐ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.

Magnetic resonance imaging

Experimental design

Design type	*Indicate task or resting state; event-related or block design.*

Design specifications

Specify the number of blocks, trials or experimental units per session and/or subject, and specify the length of each trial or block (if trials are blocked) and interval between trials.

Behavioral performance measures

State number and/or type of variables recorded (e.g. correct button press, response time) and what statistics were used to establish that the subjects were performing the task as expected (e.g. mean, range, and/or standard deviation across subjects).

Acquisition

Imaging type(s)

Specify: functional, structural, diffusion, perfusion.

Field strength

Specify in Tesla

Sequence & imaging parameters

Specify the pulse sequence type (gradient echo, spin echo, etc.), imaging type (EPI, spiral, etc.), field of view, matrix size, slice thickness, orientation and TE/TR/flip angle.

Area of acquisition

State whether a whole brain scan was used OR define the area of acquisition, describing how the region was determined.

Diffusion MRI ☐ Used ☐ Not used

Preprocessing

Preprocessing software

Provide detail on software version and revision number and on specific parameters (model/functions, brain extraction, segmentation, smoothing kernel size, etc.).

Normalization

If data were normalized/standardized, describe the approach(es): specify linear or non-linear and define image types used for transformation OR indicate that data were not normalized and explain rationale for lack of normalization.

Normalization template

Describe the template used for normalization/transformation, specifying subject space or group standardized space (e.g. original Talairach, MNI305, ICBM152) OR indicate that the data were not normalized.

Noise and artifact removal

Describe your procedure(s) for artifact and structured noise removal, specifying motion parameters, tissue signals and physiological signals (heart rate, respiration).

Volume censoring

Define your software and/or method and criteria for volume censoring, and state the extent of such censoring.

Statistical modeling & inference

Model type and settings

Specify type (mass univariate, multivariate, RSA, predictive, etc.) and describe essential details of the model at the first and second levels (e.g. fixed, random or mixed effects; drift or auto-correlation).

Effect(s) tested

Define precise effect in terms of the task or stimulus conditions instead of psychological concepts and indicate whether ANOVA or factorial designs were used.

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference

Specify voxel-wise or cluster-wise and report all relevant parameters for cluster-wise methods.

(See Eklund et al. 2016)

Correction

Describe the type of correction and how it is obtained for multiple comparisons (e.g. FWE, FDR, permutation or Monte Carlo).

Models & analysis

n/a	Involved in the study
☐	☐ Functional and/or effective connectivity
☐	☐ Graph analysis
☐	☐ Multivariate modeling or predictive analysis

Functional and/or effective connectivity

Report the measures of dependence used and the model details (e.g. Pearson correlation, partial correlation, mutual information).

Graph analysis

Report the dependent variable and connectivity measure, specifying weighted graph or binarized graph, subject- or group-level, and the global and/or node summaries used (e.g. clustering coefficient, efficiency, etc.).

Multivariate modeling and predictive analysis

Specify independent variables, features extraction and dimension reduction, model, training and evaluation metrics.