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Anxiety, depression and distress outcomes from the Health4Life intervention for adolescent mental health: a cluster-randomized controlled trial

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Mental disorders are a leading cause of disease burden worldwide. As onset typically occurs in adolescence, prevention during this period is critical. The Health4Life-school-based multiple health behavior change (MHBC) intervention targets six lifestyle risk factors: diet, sleep, physical activity, screentime, alcohol use and smoking. Health4Life has been evaluated in a cluster-randomized controlled trial in 71 Australian schools (6,639 grade seven students). This study presents intervention effects on secondary outcomes of depressive, anxiety and psychological distress symptoms. Generalized linear mixed-effect analyses of data from baseline, post-intervention (7 weeks), 12 months and 24 months showed that the Health4Life intervention was no more effective than an active control in reducing depressive, anxiety or psychological distress symptoms at a 24 or 12 month follow-up; however, there were short-term benefits for psychological distress and depressive symptoms immediately post-intervention. This study offers new evidence that multiple health behavior change interventions may improve adolescent mental health, but future research should explore methods to address anxiety and sustain effects over the longer term. A priori ANZCTR trial registration: ACTRN12619000431123.

Over the past thirty years, the global burden of disease attributed to mental disorders has grown substantially[1]. Mental disorders such as anxiety and depression now account for between 7% and 22% of overall disease burden in high-income countries. The majority of mental disorders emerge in adolescence, with a peak age of onset of 14.5 (ref. 2). Preventing mental disorders among adolescents is not only a social imperative, as mental health is a fundamental human right, but also an economic imperative because they cost the global economy between US$3.1 trillion to 6.9 trillion per year[3].

Given that 98% of young people aged 6–14 in OECD countries are enrolled in schooling[4], universal prevention interventions targeting mental disorders commonly occur in school settings. Interventions typically employ psychological and psychosocial approaches such as cognitive behavioral therapy, mindfulness, emotion regulation or a combination of these[5]. School has generally been shown to be a suitable intervention setting due to the substantial portion of waking time young people spend at school, the increasing focus on student well-being, and established referral pathways for students that need

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additional support[5]. However, school-based universal intervention effects on depressive symptoms, anxiety symptoms, and other mental health outcomes have thus far been small and transient, not typically lasting beyond first follow-up, with some even resulting in iatrogenic effects[5–7]. Where iatrogenic effects have occurred, hypothesized mechanisms include: (1) content inadvertently encouraging rumination on negative thoughts and emotions; (2) labeling of thoughts and emotions with psychological or psychiatric terminology leading to changes in self-concept and behavior (self-pathologizing); and (3) increased negative thoughts, feelings and behaviors driven by peer influence and social learning during group-based learning and discussion around mental ill health[6]. One proposed way forward for universal prevention is to use indirect approaches, targeting areas related to mental disorders but not focusing on disorders themselves[7].

The 'Big 6' lifestyle behaviors—sleep, physical activity, screen time, diet, alcohol use and smoking—are modifiable risk factors associated with mental disorders[8–10]. Mechanisms are many and varied, including: neurological (for example, impacts of sleep deprivation and nicotine on the prefrontal cortex); physiological (for example, reductions in inflammation and cortisol associated with improved diet and physical activity); and social (for example, social benefits associated with group physical activity, and social harms associated with screen time and alcohol use); and these relationships are often bidirectional[11–15]. Some studies suggest that changes in lifestyle behaviors and mental health share common predictors, such as self-efficacy, self-control and emotion regulation[16–18]. Similarly to mental disorder onset, adolescence is a time where lifestyle behaviors typically change, and then often track into adulthood[19–21]. As such, early adolescence represents an important opportunity to deliver prevention interventions targeting lifestyle behaviors and mental health.

Lifestyle behavior interventions targeting mental health have so far predominantly been employed as part of treatment protocols for adolescents with mental disorders[22,23]. Findings from such studies are promising, including a reduction of depressive symptoms in adolescents (and adults) who received non-pharmacological sleep interventions[23], and improvements in general mental health and major depressive disorder among adolescents who received physical activity interventions[22]. However, few mental health prevention interventions have targeted lifestyle modifications among adolescents, and those that do typically target a single behavior. To our knowledge, no mental health prevention interventions have employed a multiple health behavior change (MHBC) approach, in which the Big 6 behaviors are targeted simultaneously, despite the potential of MHBC interventions to efficiently promote holistic lifestyle improvements[24]. As educators are time-poor and required to address both physical and mental health in the health education curriculum, it follows that universal MHBC programs targeting lifestyle behaviors could be efficient and feasible for both chronic disease prevention and mental health. Furthermore, MHBC interventions for universal prevention in mental health may avoid the aforementioned mechanisms that are implicated in the iatrogenic effects of more traditional universal prevention interventions that directly target mental disorders[6].

The Health4Life Initiative is a school-based MHBC intervention targeting the Big 6 lifestyle behaviors[25,26]. Health4Life was developed through co-design between school students, educators and researchers. It consists of six online lessons delivered weekly in class during year 7 health education (first year of secondary school in Australia; students aged 12 to 13 years old). Students also receive access to an accompanying smartphone app for use in their own time. The app contains universal prevention content and further selective intervention content that is unlocked on the basis of lifestyle behaviors reported by students at follow-up. All content is delivered online, offering a cost-effective and scalable approach. Employing principles of social influence, social cognition, social learning and self-determination, education is delivered via online cartoon storylines featuring characters the same age as the target students. In addition to targeting knowledge and behavior change around the Big 6, lessons covered assertive communication and refusal skills, goal-setting skills, links between the Big 6 and mental health, and knowledge around physical, social and emotional benefits of health and wellbeing. Content targeted improvements in self-efficacy, coping skills, problem solving skills, social connection, perceived competence and perceived autonomy[25,26] (see Methods for further details on the intervention content). Intervention in year 7 (ages 12–13) was timed to occur before the mean age of onset for mental disorders. Health4Life has been evaluated in a cluster-randomized controlled trial (CRCT), including 71 schools across three Australian States (New South Wales, NSW; Queensland, QLD; Western Australia, WA)[25].

As the Health4Life trial tested a MHBC intervention spanning six lifestyle behaviors and mental health, it has numerous pre-registered primary and secondary outcomes (ANZCTR trial registration: ACTRN12619000431123). As such, the results of the Health4Life intervention against the pre-registered primary outcomes (six primary behavior change outcomes for the Big 6) and a number of Big-6-related secondary outcomes have been published elsewhere[27,28]. To summarize the findings, the intervention effectively increased knowledge about the Big 6, with effects sustained at 24 months post-intervention, but there was no significant between-group difference in the primary or secondary behavior change outcomes[27,28]. This work examines three further pre-registered secondary outcomes related to mental health: depressive, anxiety and psychological distress symptoms. We test the hypothesis that the Health4Life intervention is more effective than an active control group (usual health education) in improving depressive, anxiety and psychological distress symptoms at post-test (7 weeks), 12 month and 24 month follow ups[25]. We selected 24 months as the endpoint for this study to ensure consistency with the timeframe pre-registered and reported for the trial's primary outcomes[25].

Results

Participant characteristics

A total of 6,639 students from 71 schools completed the baseline survey (mean age = 12.7 years, s.d. = 0.50; 50.6% male). The Consolidated Standards of Reporting Trials (CONSORT) diagram is available in Fig. 1. Full details on the sample characteristics by time point and intervention group have been published previously[27]. Almost all students (N = 6,454; 97.2%) completed at least one follow-up survey and 5,698 (85.8%) completed two or more follow-up surveys. Retention was 76% at 24 month follow up (N = 5,014, mean age = 14.7, s.d. = 0.82). The Methods section includes a detailed description of study procedures, intervention content, measures and statistical analysis.

Attrition analysis

Results from the attrition analyses by demographic characteristics are detailed elsewhere[27]. Briefly, there was no differential attrition between intervention and control groups, but those who did not complete any follow up questionnaires (that is, they only completed the baseline) were more likely to identify as non-binary/gender fluid than male, and to report higher truancy and lower grades. There was no significant differential attrition by mean baseline anxiety symptoms, but those who did not complete any follow up questionnaires had significantly higher baseline psychological distress and depressive symptoms (Supplementary Table 1). There was weak evidence of a difference in attrition between trial groups for each outcome, with those in the intervention group less likely to have follow-up data for each of the outcomes than those in the control group (Supplementary Table 2). However, the analysis strategy accounts for missing data through maximum likelihood estimation.

Intervention fidelity and active control

Of the 3,157 students in the intervention group with available lesson completion data, 1,960 (62.1%) completed all six lessons. A total of 407

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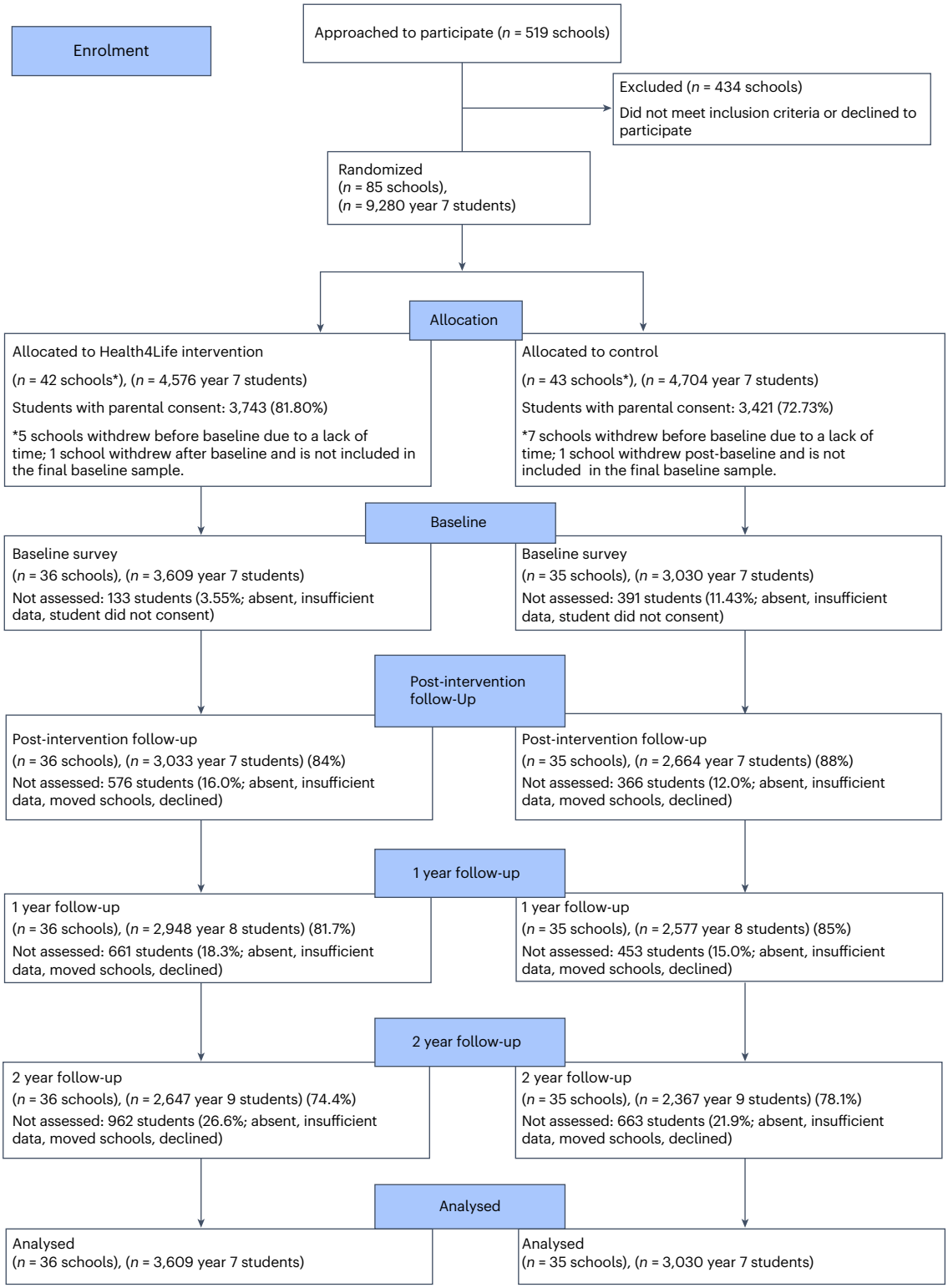

Fig. 1 | CONSORT Diagram. CONSORT diagram for the Health4Life study.

students (11.3% of all intervention students) accessed the universal Health4Life app content and five (0.1%) accessed the selective booster content. Given the very small proportion of students who engaged with the selective intervention, these five students were retained in the present analyses, but analyses do not differentiate outcomes for those who engaged with the selective intervention. Most control teachers at control schools ($N = 90$; 94%) reported delivering one or more lessons covering at least one of the Big 6; however, they were not asked to report education around mental health (see Supplementary Text 1 for further details).

Model development

Predicted scores and log effect sizes from conditional models adjusting for gender identity and school site are presented in Table 1, along with raw mean symptom scores. Supplementary Figure 1 shows plotted raw symptom scores by intervention group and time point.

Table 1 | Raw summary data for each outcome by time and intervention status, and conditional model predicted values and log effect sizes

		Baseline	Post-intervention	12 months	24 months
Depressive symptoms (patient health questionnaire for adolescents)					
Mean (s.d.)	Control	5.11 (5.13)	4.99 (5.66)	5.98 (6.08)	6.63 (6.33)
	Intervention	5.05 (5.16)	4.68 (5.74)	5.77 (6.22)	6.64 (6.65)
Predicted (95%CI)	Control	3.1 (2.92, 3.28)	2.93 (2.76, 3.11)	3.53 (3.33, 3.73)	3.9 (3.68, 4.14)
	Intervention	3.16 (3.00, 3.33)	2.71 (2.56, 2.86)	3.49 (3.31, 3.68)	3.9 (3.69, 4.12)
Expβ (95% CI), *P*	Intervention versus control	n/a	0.91 (0.85,0.97), <0.001	0.97 (0.91,1.03), 0.33	0.98 (0.92,1.04), 0.53
Anxiety symptoms (PROMIS anxiety pediatric)					
Mean (SD)	Control	23.25 (10.61)	23.30 (11.55)	24.59 (12.29)	25.27 (12.70)
	Intervention	22.90 (10.57)	22.46 (11.45)	23.70 (12.34)	24.60 (12.70)
Predicted (95%CI)	Control	19.52 (18.84, 20.22)	19.63 (18.95, 20.33)	20.36 (19.67, 21.09)	21.24 (20.48, 22.03)
	Intervention	19.38 (18.75, 20.03)	19.48 (18.86, 20.13)	20.17 (19.52, 20.84)	20.99 (20.28, 21.72)
Expβ (95% CI), *P*	Intervention versus control	n/a		1.00 (0.99,1.01), 0.69	
Psychological distress symptoms (Kessler 6)					
Mean (SD)	Control	6.93 (5.34)	6.71 (5.65)	7.91 (6.25)	8.21 (6.17)
	Intervention	6.81 (5.45)	6.35 (5.88)	7.51 (6.29)	7.93 (6.31)
Predicted (95%CI)	Control	4.99 (4.67, 5.33)	4.77 (4.46, 5.10)	5.58 (5.22, 5.96)	5.83 (5.45, 6.23)
	Intervention	4.99 (4.69, 5.31)	4.53 (4.26, 4.83)	5.46 (5.12, 5.81)	5.7 (5.35, 6.07)
Expβ (95% CI), *P*	Intervention versus control	n/a	0.95 (0.91,1.00), 0.04	0.98 (0.93,1.02), 0.35	0.98 (0.93,1.02), 0.35

Table 2 | Sensitivity analyses model-predicted values and log effect sizes

		Baseline	Post-intervention	12 months	24 months
Depressive symptoms					
Predicted (95%CI)	Control	3.91 (3.56, 4.30)	3.69 (3.36, 4.07)	4.48 (4.08, 4.93)	5.03 (4.57, 5.53)
	Intervention	3.93 (3.60, 4.28)	3.37 (3.08, 3.68)	4.4 (4.02, 4.80)	4.94 (4.52, 5.40)
Expβ (95% CI), *P*	Intervention versus control	n/a	0.91 (0.85,0.97), <0.001	0.98 (0.92,1.04), 0.47	0.98 (0.92,1.04), 0.52
Anxiety symptoms					
Predicted (95%CI)	Control	21.94 (20.95, 22.98)	22.08 (21.09, 23.13)	22.99 (21.96, 24.07)	24.09 (22.98, 25.26)
	Intervention	21.44 (20.54, 22.39)	21.57 (20.66, 22.52)	22.44 (21.50, 23.43)	23.49 (22.47, 24.55)
Expβ (95% CI), *P*	Intervention versus control	n/a		1.00 (0.99,1.01), 0.85	
Psychological distress symptoms					
Predicted (95%CI)	Control	5.99 (5.50, 6.53)	5.72 (5.25, 6.24)	6.78 (6.22, 7.39)	7.1 (6.51, 7.74)
	Intervention	5.88 (5.43, 6.37)	5.34 (4.92, 5.79)	6.5 (6.00, 7.05)	6.84 (6.31, 7.43)
Expβ (95% CI), *P*	Intervention versus control	n/a	0.95 (0.91,0.996), 0.04	0.98 (0.93,1.02), 0.31	0.98 (0.94,1.03), 0.45

Intraclass correlation coefficients for each outcome are presented in Supplementary Table 3.

Sensitivity analyses

Models were also tested with covariates of family affluence and cultural and linguistic diversity added and fit statistics substantially improved (Supplementary Table 4). As such, interpretation of intervention effects uses these models, which adjust for gender identity, school site, relative family affluence and cultural and linguistic diversity and have nested random effects of participant within school.

Intervention effects

Table 2 and Figs. 2–4 summarize the between-group differences in depressive, anxiety and psychological distress symptoms at each time point. For anxiety symptoms, no significant differences were observed between the intervention group and the active control group over time. For depressive symptoms and psychological distress symptoms, there were no significant intervention effects at the primary endpoint of 24 month follow-up or at the 12 month follow-up; however, there was evidence of temporary effects immediately post-intervention (7 week follow up) for both depressive and psychological distress symptoms. As demonstrated in Figs. 2 and 4, the reductions (slopes) in depressive symptoms and psychological distress symptoms between baseline and post-intervention are steeper for the intervention group than the control group. Between baseline and post-test, model-predicted mean depressive symptoms dropped by 5.6% in the control group (3.91 [3.56, 4.30] to 3.69 [3.36, 4.07]) compared with 14.3% in the intervention group (3.93 [3.60, 4.28] to 3.37 [3.08, 3.68]), Expβ: 0.91 (0.85,0.97), $P < 0.001$,

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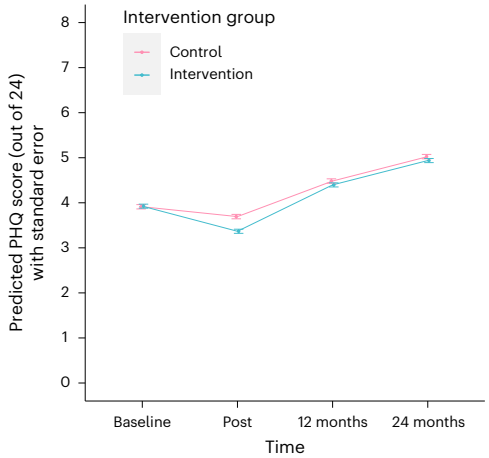

Fig. 2 | Model-predicted depressive symptoms by intervention group. Data are presented as model-predicted mean patient health questionnaire (PHQ) symptoms ± s.e. The results were estimated using type I negative binomial models with the glmmTMB package in R; $N = 6{,}005$ participants included in model.

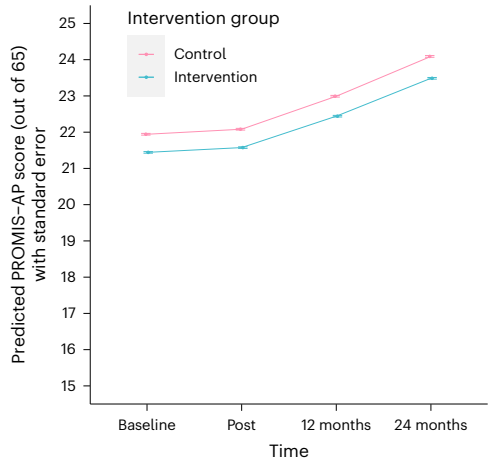

Fig. 3 | Model-predicted anxiety symptoms by intervention group. Data are presented as model-predicted mean PROMIS anxiety paediatric (PROMIS-AP) symptom score ± s.e. The results were estimated using type II negative binomial models with the glmmTMB package in R; $N = 6{,}006$ participants included in model.

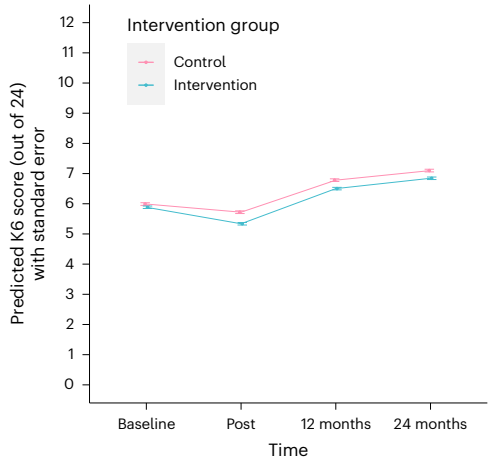

Fig. 4 | Model-predicted psychological distress scores by intervention group. Data are presented as the model-predicted mean Kessler six-item scale (K6) score ± s.e. The results were estimated using type I negative binomial models with the glmmTMB package in R; $N = 6{,}006$ participants included in model.

standardized mean difference (SMD): −0.093 (−0.147, −0.037). Model-predicted mean psychological distress symptoms dropped by 4.5% in the control group (5.99 [5.50, 6.53] to 5.72 [5.25, 6.24]) compared with 14.8% in the intervention group (5.88 [5.43, 6.37] to 5.34 [4.92, 5.79]); Expβ, 0.95 (0.91,1.00), 0.04; SMD, −0.074 (−0.138, −0.009). All effects converted to SMD are presented in Supplementary Table 5. There was no evidence of iatrogenic effects—the intervention group were not worse off than the active control group for any of the three outcomes at any time point (Table 2).

Intervention acceptability is detailed elsewhere[27]. Briefly, 74.8% of students rated the school-based component as good or very good, and 74.7% enjoyed the cartoon-based style of learning and stories presented in the cartoons. Among teachers, 84% rated the program favorably and 71% thought the cartoon stories held student attention well. Among students that downloaded the app, 80% of said they would recommend it to a friend.

Discussion

Health4Life represents the first universal prevention intervention worldwide to target mental health improvements through a MHBC framework. This study presents findings from a CRCT examining the efficacy of the Health4Life intervention on reducing pre-registered secondary outcomes of psychological distress, depressive and anxiety symptoms. Findings show no significant differences in symptoms for any of the three outcomes in the intervention group compared with the active control group (health education as usual) at the primary endpoint of a 24 or 12 month follow up. However, at post-intervention follow up (7 weeks), adolescents who received the Health4Life intervention had a significantly greater decrease in psychological distress and depressive symptoms compared with those in the active control condition. Importantly, these effects held when adjusting for key social determinants of health (gender identity, school site, family affluence, and cultural and linguistic diversity). There were no significant between-group differences for anxiety symptoms at post-intervention follow up. These findings are somewhat consistent with other school-based prevention interventions targeting mental health through more traditional psychological approaches such as cognitive behavioral therapy, with a recent meta-analysis finding that intervention effects—if any—peaked in the short-term (0–6 months) and then dissipated for depressive symptoms[5]. This is in line with Health4Life effects on depressive symptoms. However for anxiety symptoms, the review found that effects—if any—peaked in the medium term (6–12 months)[5]. Health4Life did not conduct a 6 month follow up so we cannot say whether effects occurred at six months; however, there were no effects on anxiety at 12 month follow up. There was no evidence of iatrogenic effects of the Health4Life intervention, with no worsening of symptoms for any of the three outcomes at any time point.

Although we cannot be sure of the mechanisms underlying short-term improvements in depressive and psychological symptoms, the Health4Life intervention targeted skills and knowledge that have been shown to be associated with mental health outcomes including self-efficacy, healthy coping skills, problem solving skills, social connection, perceived competence and perceived autonomy[29–32]. Furthermore, as the intervention employed a healthy lifestyle lens to target these skills and did not focus on symptoms of mental ill health, it is possible it avoided the hypothesized mechanisms for iatrogenic effects in other more traditional universal mental health interventions (including increased rumination, self-pathologizing and negative affect, inadvertently driven by intervention content and group-based delivery)[6]. Indeed, the Health4Life intervention is in line with the recommendation from P. Cuijpers[7] to use an indirect approach to addressing mental

health, focusing on areas related to mental disorders (in this case the Big 6 lifestyle behaviors and related behavior-change skills) but not the disorders themselves[7].

There is global evidence that youth mental health was disproportionately impacted by the COVID-19 pandemic[33]. The Health4Life in-class intervention and post-intervention follow-up occurred in 2019 before pandemic; however, 12 and 24 month follow ups occurred in 2020 and 2021. Throughout those two years there were prolonged lockdowns and school closures in Australia. Given the aforementioned meta-analysis found that prevention intervention effects on anxiety symptoms were greater at 6–12 months than immediately post-intervention[5], it is possible that Health4Life intervention effects on anxiety symptoms may have been dampened by the impact of the pandemic at the 12 month follow up.

The majority of students completed all six lessons of the school-based program; however, engagement with the app was poor for both the universal and selective prevention content. The app was available and intended to be used for the two years following delivery of the initial school-based program. This was intended to reinforce intervention content, primarily goal-setting skills, throughout the study period. The selective app-based content may have been particularly beneficial in addressing mental disorder symptoms, as it was targeted to students who reported at-risk levels of behavior in any of the Big 6 and included cognitive behavioral therapy and motivation enhancement techniques. Failure to engage students with the app-based components of the intervention may therefore have been a missed opportunity to bolster intervention effects on mental disorder symptoms.

Implications and future research

In universal prevention, it is common for effect sizes to be small, but these small effect sizes may offer substantial population-level health benefits when scaled[34,35]. However, the trial must have been well-designed and sufficiently powered, the intervention must be able to scale efficiently with good fidelity, and there needs to be minimal opportunity costs (time or resources that could be spent on more effective initiatives) or evidence of iatrogenic effects or harms[6,7]. The Health4Life trial includes a large sample size spanning three Australian states at opposite sides of the continent, representing one of the largest prevention trials in Australia so far. It also encompasses all three school types in Australia: government or 'public'; independent or 'private' (secular or non-secular); and catholic (non-secular). It includes schools in both major city and regional areas. The trial had high retention, with 97.2% of students completing at least one of three follow up surveys over 24 months. The trial is well-powered to detect effects, providing confidence in the findings presented. Despite the lack of effects at the primary time point of 24 months, short-term improvements in depressive and psychological distress symptoms, improvements in knowledge around the Big 6, and positive student and teacher evaluations suggest that Health4Life may offer extra benefit compared with usual health education. As the intervention is delivered online and aligned to the national- and state-based school health education curriculums, it can be readily scaled to low cost, with exact replication of intervention content. However, further intervention refinements should seek to achieve effects on the Big 6 behaviors and anxiety, and more lasting effects for psychological distress and depressive symptoms. Future research could examine intervention effects on mediating factors such as self-efficacy, coping skills, problem-solving skills, social connection, perceived competence, and perceived autonomy. This may indicate optimizations to increase mental health effects. For instance, it may be that coping skills—which are known to be important in anxiety management—were not effectively improved, thus providing one possible optimization to better target anxiety symptoms. Future research could trial different approaches to deliver the app-based components, particularly the selective intervention content. While the present study adjusted for social determinants, future research should actively investigate whether certain subgroups experienced differential intervention effects to inform future optimization and targeting and ensure no evidence of iatrogenic effects among subgroups of participants.

Limitations

Findings should be interpreted with consideration of several limitations. First, although the sample size is large, it is not population-representative, which limits generalizability of findings. However, the size of the sample and randomization stratification somewhat mitigate this limitation. Furthermore, teacher logbooks did not ask about mental health initiatives being run at schools; thus, there is a chance that intervention effects were either biased towards the null (if control schools delivered efficacious mental health initiatives) or were contaminated (if intervention schools delivered efficacious mental health initiatives). Finally, attrition differed on the basis of outcomes, with those who did not complete any follow ups having significantly higher baseline psychological distress and depressive symptoms and those in the intervention group less likely to have follow-up data for each of the outcomes than those in the control group; however, the analysis strategy accounts for missing data through maximum likelihood estimation.

Conclusion

The Health4Life intervention was no more effective than an active control in reducing depressive, anxiety or psychological distress symptoms at the primary endpoint of a 24 month follow-up, or at a 12 month follow-up; however, there were short term benefits for psychological distress and depressive symptoms immediately post-intervention. When compared with other school-based mental health prevention interventions—which generally use more traditional psychological approaches—the Health4Life intervention is unique as it targets lifestyle risk factors known to interact with mental health. This study offers new evidence that MHBC interventions may offer an indirect method to target mental health improvements among adolescents; however, further research is needed to understand how to sustain effects over the long-term.

Methods

Study procedure, recruitment and randomization

The Health4Life CRCT follows the CONSORT guidelines, and was prospectively registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12619000431123). The study protocol has been published elsewhere[25]. This work follows the CONSORT reporting checklist (Supplementary Table 6). The trial was approved by ethics boards from the University of Sydney (HREC2018/882), Curtin University (HRE2019-0083), University of Queensland (2019000037), NSW Department of Education (SERAP 2019006) and relevant Catholic Dioceses. As is standard practice for school-based CRCTs, schools were recruited through convenience and purposive sampling, with 519 schools approached across NSW, QLD and WA. An a priori power analysis was conducted for primary outcomes but not for secondary outcomes[25]. The methodology proposed by M. Heo and A. C. Leon was used[36]. The power was set to 0.80; the correlation among level-1 data (repeated measurements over time for one student) was set to 0.60; and the number of time points was set to five. A mean of 70 students per school from 72 schools was estimated, and a minimum detectable effect size of 0.158 was set on the basis of alcohol use, which was the targeted risk behavior with the lowest anticipated prevalence at baseline. The significance level was set at 0.008 based on a Bonferroni correction due to six outcomes ($\alpha = 0.05/6$). A total of 72 schools would have enabled analysis within each trial site separately (eight intervention and eight controls in each of the four trial sites); however, this sample size was not achieved due to school withdrawal.

The final sample of 6,639 students from 71 schools provided sufficient power for primary outcome analysis in the overall sample but not by trial site.

Post-hoc power analysis for the present study was conducted, again using the methodology from M. Heo and A. C. Leon[36]. The power was set to 0.80, the correlation among level-1 data was set to 0.60, significance level was set to 0.05, and the number of time points was set to four. The actual mean number of students at participating schools (n = 93) was used. Effect sizes of 0.17 and 0.16 were set for depression and anxiety symptoms respectively, consistent with mean effects identified in a 2021 meta-analysis of universal school-based prevention interventions[5]. The psychological distress effect size was set to 0.13, consistent with mean effects of psychoeducation-focused universal prevention interventions in another meta-analysis[37]. Post-hoc power analysis confirmed that the present study is sufficient powered to detect these effect sizes, with ten schools (five intervention, five control) required for anxiety and depressive symptoms, and 16 schools (eight intervention, eight control) required for psychological distress.

A biostatistician with no role in school recruitment performed randomization using the Blockrand function in R. Stratification was applied during randomization based on school region (NSW major city, NSW regional, WA and QLD) and school gender composition (co-educational, predominately male [>60%] or predominately female [>60%]). As is routine for school-based interventions, researchers, students and teachers were not blind to allocation. All year 7 students were eligible, but participation required active student consent and either passive or active parental consent, depending on ethics board requirements[25]. Students completed four online questionnaires during class: baseline (2019, year 7), post-test (at an average of 7 weeks after the baseline, 2019), 12 months (2020, year 8) and 24 months (year 9). Hard copy surveys or research-assistant-administered in-person surveys were offered to facilitate feasibility and accessibility.

The Health4Life Intervention and active control

Health4Life used a staged prevention approach. First, a universal prevention program was delivered in year 7 (2019, ages 12–13), which included six cartoon-led lessons with storylines and characters based on real stories from adolescent co-designers, optional accompanying teacher-facilitated activities, a universal behavior-tracking app and tailored individual feedback. Detail on the co-design approach and intervention content is published elsewhere[26,38]. Briefly, the cartoon storylines in each lesson covered one-to-two of the Big 6, and related concepts (Supplementary Fig. 2 contains an example of the cartoon slides). The optional teacher-facilitated activities reinforced lesson content through a range of mediums including interactive online exercises, quizzes and take-home tasks (for example, Supplementary Fig. 3). The tailored feedback compared student's reported Big 6 behaviors with Australian health guidelines and employed a traffic-light system to show areas for improvement (for example, Supplementary Fig. 4). The universal app prompted students to monitor Big 6 behaviors, view their progress over time and set goals with badges as rewards.

A selective intervention—via additional booster content unlocked on the universal behavior tracking app—was available to students who, based on responses to the 12 and 24 month surveys, were 'at risk' for two or more of the Big 6. Booster content covered goal-setting and behavior-change skills informed by cognitive behavioral therapy and motivation enhancement techniques.

Schools in the control condition delivered their usual health education lessons. At the time of trial delivery, the health education syllabus varied by state but included content on some or all the Big 6 and wellbeing. Teachers reported the extent of education on the Big 6 through a logbook[25].

Measures

Mental health outcomes. *Depressive symptoms*. Depressive symptoms over the prior seven days were assessed using the validated 9-item Patient Health Questionnaire for Adolescents scale (PHQ-A)[39]. The PHQ-A has been evaluated in several adolescent samples and has demonstrated satisfactory sensitivity (75% to 89.5%), specificity (77.5% to 94%), diagnostic agreement and overall diagnostic accuracy in identifying youth who met the DSM-IV criteria for major depression compared with clinical interview[39,40]. The PHQ-A is version of the PHQ-9 (adult scale) with slight modifications to wording to make it adolescent-friendly. The ninth item of the PHQ-A (measuring suicidal ideation) was removed for the Health4Life trial at the request of the ethics board, resulting in an adolescent version of the PHQ-8 (PHQ-A-8). Past comparisons between the adult versions of the PHQ-9 and PHQ-8 have found strong correlation (0.996), and minimal decreases in sensitivity and specificity[41]. A confirmatory factor analysis of the Spanish version of the PHQ-A has been conducted in adolescents, testing both the 9-item version (PHQ-A) and an 8-item version with removal of the suicidal ideation item (PHQ-A-8). The authors report that the 8-item version of the scale had substantially better fit and conclude than the modified PHQ-A-8 (which has a total score out of 24) should be used for adolescents[42].

Psychological distress. Psychological distress over the prior four weeks was assessed using the total score (also out of 24) for the Kessler 6-item scale in which participants report how frequently they felt hopeless, nervous, restless and other feelings[43]. The Kessler 6-item scale has demonstrated good internal consistency and predictive validity among adolescents[44].

Anxiety. Anxiety symptoms over the prior 7 days were assessed with the 13-item PROMIS Anxiety Pediatric (PROMIS-AP) scale in which participants report how frequently they experienced feelings of worry, fear, dread and so on, adding to a total score ranging from 13–65 (ref. 45). The PROMIS-AP has been shown to be more reliable than other anxiety measures among adolescents[45].

Sociodemographic factors. Students reported their gender identity, with options of 'male', 'female', 'non-binary/gender fluid', 'different identity' and 'prefer not to say'. Selecting 'different identity' prompted an open-ended text box in which participants specified their identity. Two researchers (S.S. and another researcher with expertise in gender identities and health) independently reviewed 'different identity' responses and recoded phony answers (such as 'helicopter') as missing. The two recoded datasets were then compared, combined and merged into the main datafile. Following this process, participants that identified as non-binary, gender fluid or a genuine different identity were combined into one group. Although sex at birth was also captured in the questionnaire, gender identity has been used for analysis, recognizing the fact that non-binary and gender diverse young people have unique experiences that are often associated with unique social and health outcomes. Relative family affluence was measured using the Family Affluence Scale third edition (FASIII) at baseline[46], which was developed specifically for children and adolescents, who are often unaware of their household income and other standard indicators of socioeconomic status. It captures wealth signifiers such as the number of vehicles owned and the number of bathrooms at home. The total score was then ridit transformed, whereby scores across the sample are scaled to a normal distribution, to provide an indication of relative family affluence within the sample[46]. Cultural and linguistic diversity was identified through combining students who indicated they were born in a non-English speaking country and/or primarily spoke a language other than English at home at baseline.

Statistical analysis. We employed a staged approach to model development, and tested a range of linear and generalized mixed-effects

regression methods to ascertain the best-fitting models for the outcomes. First, quadratic, linear and categorical treatments of the time point variable were tested in unconditional (that is, no covariates) generalized linear mixed-effects models for each outcome (depression, anxiety, and psychological distress symptoms). We also tested two types of random effects: (1) participant number only, to account for longitudinal design; and (2) nested random effect of participants within schools, to account for school-level clustering due to the CRCT design. The resulting six models for each of the three outcomes (three time treatments and two random effect structures tested per outcome) were compared using Akaike information criterion (AIC) and Bayesian information criterion (BIC) to identify the optimal approach to time and random effects. Nested random effects with participant within school cluster showed superior fit for all three outcomes in unconditional models (Supplementary Table 7) and, as such, this random effect structure was applied to all main models. Optimal approach to time varied by outcome, with categorical time selected for depressive and psychological distress symptoms but linear time selected for anxiety symptoms (Supplementary Table 7).

To test the main models, the intervention effects on outcomes, linear mixed-effects regressions using the lmer function in R Studio were tested first, but the scores for depression, anxiety and psychological distress outcomes had a zero inflated distribution, and quantile–quantile plots demonstrated violation of the linearity assumption (Supplementary Fig. 5). As such, generalized linear mixed effects regressions with Poisson and negative binomial distributions were tested, using the glmer, or glmmTMB functions in R. The model fit was again compared using AIC and BIC. Type I negative binomial models using glmmTMB showed best fit for depressive symptoms and psychological distress symptoms, and type II negative binomials were superior for anxiety symptoms.

As randomization was stratified by the school sex ratio (single sex versus co-educational) and school region (NSW regional, NSW major city, WA and QLD), these were included as covariates in all models. However, gender identity was chosen over sex at birth for the aforementioned reasons. As both the Big 6 and mental health are also known to be associated with socioeconomic status and cultural and linguistic diversity[47], sensitivity analyses were conducted to determine whether model fit improved when adjusting for relative family affluence, as well as cultural and linguistic diversity. Between-group raw and predicted scores for depression, anxiety and psychological distress symptoms were plotted using ggplot2, also in R. To facilitate comparison of effects with other universal prevention interventions, final model coefficients were transformed into the SMD using the countES package in R (ref. 48). All effects at all time points were examined for any evidence of iatrogenic effects of the intervention, which would be indicated by worsening symptoms in the intervention group compared to active control.

Missing data. Missing-data analysis was conducted using *t*-tests comparing whether baseline anxiety, depressive or psychological distress symptoms were significantly different between baseline-only participants versus those with data for one or more follow-up time points. Differences in attrition between the intervention group and control group were examined using binary logistic regression.

Reporting summary

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

Data availability

De-identified participant data will be made available to researchers on reasonable request to K.E.C. (katrina.champion@sydney.edu.au) when accompanied by study protocol and analysis plan. Data will be shared after the approval of a proposal by a committee of the current research team with a signed data access agreement.

Code availability

The statistical analysis code (syntax) will be made available to researchers on reasonable request to the corresponding author.

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Author contributions

S.S. led the development of this Article. All authors were involved in conceptualization. M.T., K.E.C. and N.C.N. secured funding for this

study. K.E.C. led intervention development. S.S., S.O., L.A.G. and K.E.C. led data curation. Data were directly accessed and verified by S.S., K.E.C., S.O. and L.A.G. S.S. developed the methodology and conducted formal analysis and data visualization with support from S.O. K.E.C. and L.A.G. were responsible for ethics and governance and overall trial administration with oversight from M.T. and N.C.N. N.C.N., K.E.C., L.A.G. and M.T. provided supervision. S.S. wrote the original draft, and all authors were involved in review and editing. All authors had full access to the data in the study and all had final responsibility for the decision to submit for publication.

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Competing interests

M.T. and N.C.N. are co-Directors of Climate Schools Pty Ltd and OurFutures Institute Ltd. The other authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to S. Smout.

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Software and code

Policy information about availability of computer code

Data collection	The web developers who built the intervention website built a bespoke questionnaire platform for data collection, housed within the intervention website.
Data analysis	R Studio version 2022.12.0+353 was used for analysis. Regressions were performed using the lmer, glmer, glmmTMB packages. Plots were developed using the ggplot2 package. SMDs were calculated with the countES package.

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reason when accompanied by study protocol and analysis plan. Data will be shared after the approval of a proposal by a committee of the current research team with a signed data access agreement.

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	Students reported their gender identity, with options of "male", "female", "non-binary/gender fluid", "different identity", and "prefer not to say." Selection of different identity prompted an open-ended text box where participants specified their identity. Two researchers (SS and another researcher with expertise in gender identities and health) independently reviewed "different identity" responses and recoded phony answers (such as "helicopter") to missing. The two recoded datasets were then compared, combined and merged into the main datafile. Following this process, participants that identified as non-binary, gender fluid, or a genuine different identity were combined into one group. While sex at birth was also captured in the questionnaire, gender identity has been used for analysis, recognising the fact that non-binary and gender diverse young people have unique experiences that are often associated with unique social and health outcomes.
Population characteristics	As randomisation was stratified by school sex ratio (single sex versus co-educational) and school region (NSW regional, NSW major city, WA and QLD), these were included as covariates in all models. However, gender identity was chosen over sex at birth for the aforementioned reasons. As both the Big 6 and mental health are also known to be associated with socioeconomic status and cultural and linguistic diversity, sensitivity analyses were conducted to determine whether model fit improved when adjusting for relative family affluence and cultural and linguistic diversity.
Recruitment	As is standard practice for school-based cRCTs, schools were recruited through convenience and purposive sampling, with 519 schools approached across NSW, QLD and WA. A-priori power analysis was conducted for primary outcomes but not for secondary outcomes.25 The methodology proposed by Heo and Leon was used.36 Power was set at 0.80; the correlation among level 1 data (repeated measurements over time within one student) was set at 0.60 and the number of timepoints was set at five. A mean of 70 students per school from 72 schools was estimated and a minimum detectable effect size was set at 0.158, based on alcohol use, which was the targeted risk behaviour with the lowest anticipated prevalence at baseline. A total of 72 schools would have enabled analysis within each trial site separately (8 intervention and 8 control in each of the four trial sites); however, this sample size was not achieved due to school withdrawal. The final sample of 6639 students from 71 schools provided sufficient power for primary outcome analysis in the overall sample but not by trial site. It is possible that bias may have occurred at the school-level, however every effort was made to reduce barriers to participation that may have biased the types of schools that could participate. For example, participation was free, had no teacher training required and took minimal preparation for teachers outside of class time (the program was online and "plug and play"). Given the randomized design and adjustments during analysis for clustering, any school-level factors should not have impacted between-group differences identified. However, we are transparent in the limitations section that findings may not be generalizable as the sample was not population-representative, which is a standard challenge in school-based research.
Ethics oversight	The trial was approved by ethics boards from the University of Sydney (HREC2018/882), Curtin University (HRE2019-0083), University of Queensland (2019000037), NSW Department of Education (SERAP 2019006), and relevant Catholic Diocese.

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

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Behavioural & social sciences study design

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Study description	Quantitative experimental design - cluster randomised controlled trial.
Research sample	Participants are Australian secondary school students from 71 schools in three Australian states (New South Wales, Queensland, and Western Australia). A total of 6,639 students completed the baseline survey (Mean age=12.7 years, SD=0.50; 50.6% male). Almost all students (N=6,454; 97.2%) completed at least one follow-up survey and 5,698 (85.8%) completed two or more follow-up surveys. Retention was 76% at 24-month follow up (N=5,014, Mean age=14.7, SD=0.82). All Year 7 students at participating schools at baseline were eligible, but participation required active student consent and either passive or active parental consent, depending on ethics board requirements.
Sampling strategy	As is standard practice for school-based cRCTs, schools were recruited through convenience and purposive sampling, with 519 schools approached across NSW, QLD and WA. A-priori power analysis was conducted for primary outcomes but not for secondary

	outcomes.25 The methodology proposed by Heo and Leon was used.36 Power was set at 0.80; the correlation among level 1 data (repeated measurements over time within one student) was set at 0.60 and the number of timepoints was set at five. A mean of 70 students per school from 72 schools was estimated and a minimum detectable effect size was set at 0.158, based on alcohol use, which was the targeted risk behaviour with the lowest anticipated prevalence at baseline. A total of 72 schools would have enabled analysis within each trial site separately (8 intervention and 8 control in each of the four trial sites); however, this sample size was not achieved due to school withdrawal. The final sample of 6639 students from 71 schools provided sufficient power for primary outcome analysis in the overall sample but not by trial site. Post-hoc power analysis for the present study was conducted, again using the methodology from Heo and Leon.36 Power was set at 0.80, the correlation among level 1 data set at 0.6, alpha at 0.05, and the number of timepoints set to four. The actual mean number of students at participating schools (n=93) was used. Effect sizes of 0.17 and 0.16 were set for depression and anxiety symptoms respectively, consistent with mean effects identified in a 2021 meta-analysis of universal school-based prevention interventions.5 The psychological distress effect size was set at 0.13, consistent with mean effects of psychoeducation-focussed universal prevention interventions in another meta-analysis.37 Post-hoc power analysis confirmed that the present study is sufficient powered to detect these effect sizes, with 10 schools (5 intervention, 5 control) required for anxiety and depressive symptoms and 16 schools (8 intervention, 8 control) required for psychological distress.
Data collection	Students completed online questionnaires during class on the intervention website. Hard copy surveys or research-assistant-administered in-person surveys were offered to facilitate feasibility and accessibility. Where students were absent from class for follow-up occasions, they were able to complete the online or hard copy survey at home.
Timing	Baseline data was collected in the mid-late 2019, post-intervention follow up was collected 6-8 weeks after baseline, also in 2019. 12 month follow up was collected in mid-late 2020. 24-month follow up was collected in mid-late 2021.
Data exclusions	The only data excluded from analyses were phony responses to gender identity. Responses were double screened by two researchers to determine valid versus phony responses and phony responses were recoded to missing.
Non-participation	A detailed CONSORT diagram is provided in the manuscript. Briefly, total of 6,639 students completed the baseline survey. Almost all students (N=6,454; 97.2%) completed at least one follow-up survey and 5,698 (85.8%) completed two or more follow-up surveys. Retention was 76% at 24-month follow up (N=5,014).
Randomization	A biostatistician with no role in school recruitment performed randomisation using the Blockrand function in R. Stratification was applied during randomisation based on school region (NSW major city, NSW regional, WA, and QLD), and school gender composition (coeducational, predominately male [>60%], or predominately female [>60%]). As is routine for school-based interventions, researchers, students and teachers were not blind to allocation.

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

Methods

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

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	ACTRN12619000431123
Study protocol	Teesson M, Champion KE, Newton NC, Kay-Lambkin F, Chapman C, Thornton L, et al. Study protocol of the Health4Life initiative: a cluster randomised controlled trial of an eHealth school-based program targeting multiple lifestyle risk behaviours among young Australians. BMJ Open. 2020;10(7):e035662.
Data collection	Data was collected in secondary schools in three Australian States: New South Wales, Queensland and Western Australia. Recruitment commenced in early 2019, baseline data was collected in the mid-late 2019, post-intervention follow up was collected 6-8 weeks after baseline, also in 2019. 12 month follow up was collected in mid-late 2020. 24-month follow up was collected in mid-late 2021.
Outcomes	As the Health4Life trial tested a MHBC intervention spanning six lifestyle behaviours and mental health, it has numerous pre-

Outcomes

registered primary and secondary outcomes (ANZCTR trial registration: ACTRN12619000431123). As such, the results of the Health4Life intervention against the pre-registered primary outcomes (six primary behaviour change outcomes for the Big 6 behaviours) and a number of Big-6-related secondary outcomes have been published elsewhere.
The present study examines three further pre-registered secondary outcomes related to mental health; depressive symptoms (Patient Health Questionnaire), anxiety symptoms (PROMIS-A) and psychological distress (Kessler 6) symptoms.