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Personalized Depression Prevention: A Randomized Controlled Trial to Optimize Effects Through Risk-Informed Personalization

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Objective: To evaluate whether evidence-based depression prevention programs can be optimized by matching youths to interventions that address their psychosocial vulnerabilities.



Method: This randomized controlled trial included 204 adolescents (mean [SD] age = 14.26 [1.65] years; 56.4% female). Youths were categorized as high or low on cognitive and interpersonal risks for depression and randomly assigned to Coping With Stress (CWS), a cognitive-behavioral program, or Interpersonal Psychotherapy–Adolescent Skills Training (IPT-AST), an interpersonal program. Some participants received a match between risk and prevention (eg, high cognitive–low interpersonal risk teen in CWS, low cognitive–high interpersonal risk teen in IPT-AST), others received a mismatch (eg, low cognitive–high interpersonal risk teen in CWS). Outcomes were depression diagnoses and symptoms through 18 months postintervention (21 months total).

Results: Matched adolescents showed significantly greater decreases in depressive symptoms than mismatched adolescents from postintervention through 18-month follow-up and across the entire 21-month study period (effect size [d] = 0.44, 95% CI = 0.02, 0.86). There was no significant difference in rates of depressive disorders among matched adolescents compared with mismatched adolescents (12.0% versus 18.3%, $t_{193} = .78$, $p = .44$).

Conclusion: This study illustrates one approach to personalizing depression prevention as a form of precision mental health. Findings suggest that risk-informed personalization may enhance effects beyond a one-size-fits-all approach.

Clinical trial registration information: Bending Adolescent Depression Trajectories Through Personalized Prevention; <https://www.clinicaltrials.gov/>; NCT01948167.

Key words: depression, personalization, precision, prevention

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Depression is prevalent and the leading cause of disability worldwide.¹ Symptoms and diagnoses increase during adolescence,² and adolescent-onset depression increases risk for recurrence of depression in adulthood.³ Depression is undertreated,⁴ and existing treatments reduce only one third of the burden of depression.⁵ Preventive interventions can reach a larger number of people and may reduce the burden and prevalence of depression.^{6,7} Several youth depression prevention programs have been developed and tested. One cognitive-behavioral program with strong evidence of efficacy is Coping With Stress (CWS), which targets cognitive risks for depression. CWS decreases depressive symptoms and prevents disorder onset compared with usual care among at-risk adolescents.^{8–12} A second evidence-based prevention program is Interpersonal

Psychotherapy–Adolescent Skills Training (IPT-AST),¹³ which targets interpersonal risks. IPT-AST prevents depression diagnoses, reduces symptoms, and improves overall functioning among adolescents with elevated depressive symptoms.^{14–16} Meta-analyses indicate that both programs are efficacious, particularly in selective and indicated samples.^{17,18} However, effects for these and other depression prevention programs are small to moderate with limited evidence of sustained effects beyond 1-year follow-up in meta-analyses¹⁷ (for exceptions, see references^{8,9}).

One explanation for these relatively modest effects is that prevention programs are based on a one-size-fits-all approach in which all youths are assigned to an intervention that teaches skills to reduce a set of vulnerabilities (eg, cognitive risks) regardless of an individual youth's risk

profile. The assumption underlying this one-size-fits-all approach is that a single-modality program benefits all recipients equally. It is possible, however, that these programs are more effective for youths who exhibit risk targeted by a given intervention (ie, a match between a youth's risk profile and the prevention program), but are less effective for youths without these vulnerabilities (ie, a mismatch between a youth's risk profile and the prevention program).

Given the modest effects of one-size-fits-all prevention approaches, one possible avenue for optimizing outcomes (eg, enhancing effect sizes, lengthening effects, reducing prevalence) is a personalized, or precision mental health, approach. There has been a call to use risk markers to stratify individuals and identify who will respond better to a particular intervention.^{19,20} For depression prevention, personalization could involve assessing evidence-based vulnerabilities (eg, cognitive and interpersonal risks) and matching an individual's risk profile to a prevention program that addresses these vulnerabilities.

Preliminary evidence supports a personalized approach to depression prevention by matching youths to programs based on their risk profiles. Adolescents with high negative attributional style (cognitive risk) exhibited a 5-fold reduction in disorder onset when receiving cognitive-focused bibliotherapy compared with other interventions.²¹ Youths with high mother-child conflict (interpersonal risk) who received IPT-AST showed greater decreases in depressive symptoms than adolescents with high conflict who received school counseling.²² However, these findings are based on post hoc moderation analyses. To more rigorously test the potential benefits of personalization, a clinical trial design is needed in which youths are assessed for empirically supported risks, a priori matched or mismatched to prevention, and evaluated over time.²³

To test the benefits of personalized depression prevention (PDP), we embarked on such a randomized controlled trial. Youths in PDP were matched or mismatched to 2 evidence-based depression prevention programs (CWS and IPT-AST) that target particular depression risks. We specifically examined whether outcomes of these programs could be improved by matching youths to the prevention program that best addresses their psychosocial vulnerabilities. These findings can provide vital information on prescriptive indicators²⁴ about which particular prevention program is likely to be of most benefit to given adolescents. We used a validated risk classification system²⁵ to categorize youths as high or low on cognitive and interpersonal risks. We focused on select cognitive (negative cognitive style, dysfunctional attitudes, rumination) and interpersonal (parent-adolescent conflict, low peer support) risks because

these are empirically supported vulnerabilities for depression²⁶⁻²⁸ and are targeted in CWS or IPT-AST.

At baseline we measured cognitive and interpersonal vulnerabilities to assign youths to 1 of 4 risk groups (high or low cognitive and/or interpersonal risks). Following risk classification, adolescents in each of the 4 risk groups were randomly assigned to either CWS or IPT-AST. For key risk groups, about half of participants were randomly assigned to receive a match between their risk profile and the prevention program (eg, high cognitive-low interpersonal risk randomly assigned to CWS), whereas the other half were randomly assigned to receive a mismatch (eg, high cognitive-low interpersonal randomly assigned to IPT-AST). This design enabled us to empirically test how matching and mismatching adolescents to different evidence-based programs that target particular depression risks would lead to differential depression outcomes through 18 months post-intervention. Whereas we expected no difference in outcomes between CWS and IPT-AST across the entire sample (ie, average of all 4 risk groups), we hypothesized that adolescents receiving a match between risk classification and prevention (high cognitive risk-low interpersonal risk youths receiving CWS, low cognitive risk-high interpersonal risk youths receiving IPT-AST) would show significantly lower rates of disorder and reduced symptom trajectories compared with youths receiving nonpersonalized prevention (high cognitive-low interpersonal risk youths receiving IPT-AST, low cognitive-high interpersonal risk youths receiving CWS).

METHOD

Participants

This 2-site randomized controlled trial included a sample of 204 youths recruited from the general community (94 enrolled in New Jersey and 110 enrolled in Colorado). Age of adolescents ranged from 11 to 18 years (mean [SD] = 14.26 [1.65] years); the sample was 56.4% female. Racial minorities accounted for 29% of participants; 18.1% were Hispanic/Latino. Eligibility criteria included being in grades 6-12 and adolescent and parent were English-speaking. Exclusion criteria at baseline included current major depressive disorder (MDD), dysthymia, bipolar disorder, or psychosis or active suicidal ideation or a recent suicide attempt.

Procedures

All participants completed a baseline evaluation. Measures of cognitive and interpersonal risk factors were used to assign participants to a risk classification: 26% were low cognitive-low interpersonal risk, 26% were high

cognitive–high interpersonal risk, 25% were low cognitive–high interpersonal risk, and 23% were high cognitive–low interpersonal risk. Broadly, these replicate percentages in the original risk classification work.²⁴ Within each risk classification group, we stratified on gender and used a computer-generated random numbers sequence to assign youths to CWS (n = 101) or IPT-AST (n = 103). Figure 1 illustrates the allocation to intervention condition and flow of participants. All participants were considered part of the study after randomized (intent-to-treat design).

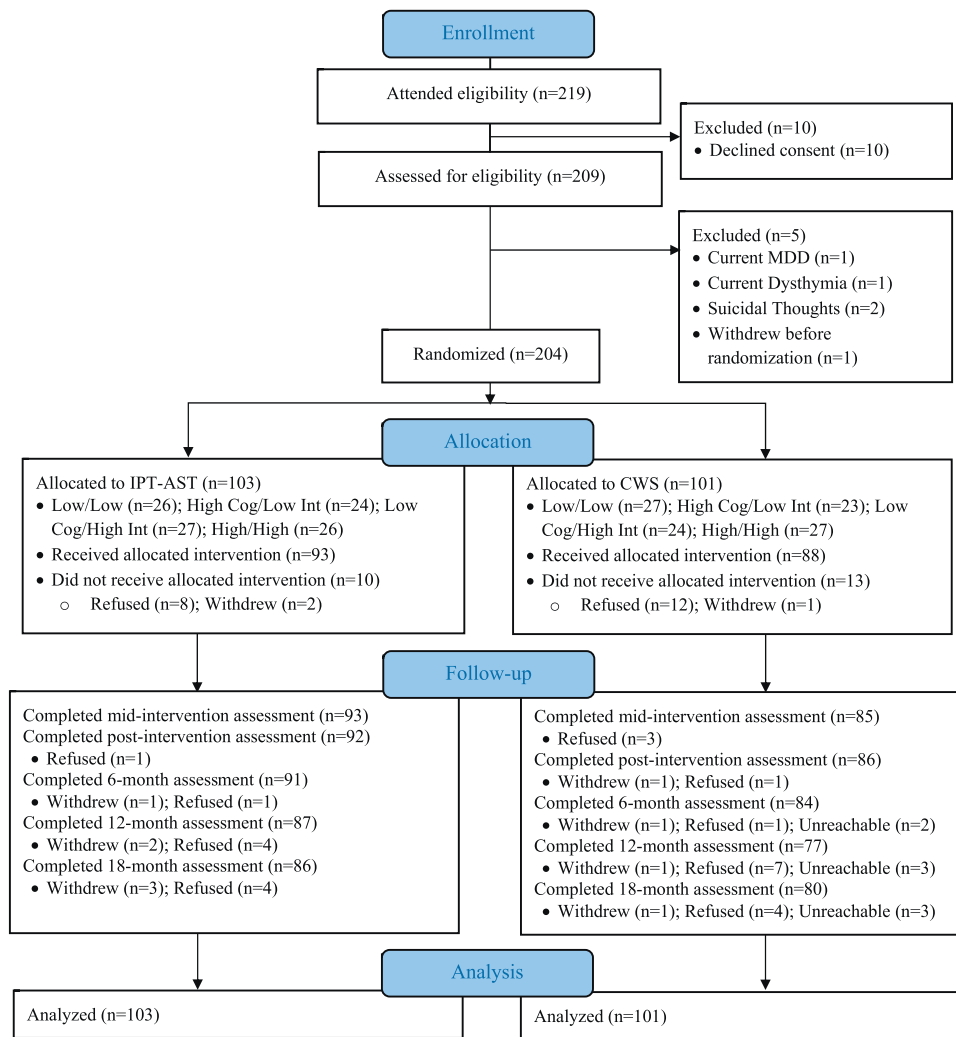
The institutional review boards of both study sites approved the study, which was registered at ClinicalTrials.gov (NCT01948167) (see Supplement 1, available online). Recruitment, outcomes, and adverse events were monitored by a data and safety monitoring board. Parents

provided written consent, and adolescents provided written assent.

Intervention Conditions

Coping With Stress. We used the Prevention of Depression study manual.¹² CWS consisted of 8 weekly group sessions (90 minutes each), 2 parent group sessions (90 minutes each), and 3 booster sessions (60 minutes each) in the 6 months following group sessions. CWS teaches teenagers to identify negative thoughts, evaluate accuracy of these thoughts, and generate alternative thoughts. Adolescents also learn problem-solving skills. During booster sessions, cognitive restructuring and/or problem-solving skills were reviewed, and additional modules (more problem solving, relaxation, assertiveness, and behavioral activation) could be introduced.

FIGURE 1 CONSORT Diagram



Note: Low/Low = low cognitive–low interpersonal; High Cog/Low Int = high cognitive–low interpersonal; Low Cog/High Int = low cognitive–high interpersonal; High/High = high cognitive–high interpersonal.

There were 20 CWS groups including 2–8 participants with a mean (SD) of 4.50 (1.70) adolescents per group. Adolescents attended 80% of the group sessions and 84% of the booster sessions. The first parent session was attended by 78% of parents, and 81% attended the second session. All groups had 2 graduate student leaders. Leaders read the CWS manual, attended a 1-day workshop, and completed a mock group or listened to recordings of other CWS groups. All CWS sessions were audio recorded. An experienced CWS supervisor listened to at least 50% of group and booster sessions as part of weekly supervision and rated session fidelity (adherence to session content and quality of techniques) using a CWS checklist. Adherence (96.4%) and quality (96.6%) were high. Another CWS supervisor rated 10% of randomly selected sessions; intraclass correlation coefficients for interrater reliability were 0.88 for adherence and 0.89 for quality.

Interpersonal Psychotherapy–Adolescent Skills Training. In PDP, IPT-AST consisted of 1 pregroup session (90 minutes), which parents were invited to attend; 8 weekly group sessions (90 minutes each); an individual midgroup session, which parents were invited to attend (60 minutes); and 3 individual booster sessions (60 minutes each) in the 6 months following group sessions.¹³ During the pregroup session, adolescents' relationships are reviewed and interpersonal goals identified. In group sessions, youths discuss links between relationships and mood, learn different communication strategies, and apply these strategies to improve their relationships. In the midgroup and booster sessions, interpersonal strategies are reviewed and applied to current relationship problems.

There were 20 IPT-AST groups including 3 to 8 participants (mean [SD] 4.85 [1.57] adolescents). Adolescents attended 87% of the group sessions and 88% of the booster sessions. All adolescents attended the pregroup session, and 98% attended the midgroup session. All groups had 2 graduate student leaders. Training for IPT-AST leaders mirrored the training described above for CWS. An experienced IPT-AST supervisor listened to at least 50% of group and individual sessions as part of weekly supervision and rated session fidelity using the IPT-AST supervision checklist (unpublished measure, 2005). Adherence (99.4%) and quality (96.6%) were high. Another IPT-AST supervisor rated 10% of randomly selected sessions for reliability; intraclass correlation coefficients were 0.86 for adherence and 0.89 for quality.

Measures

Depression Diagnoses. Depression diagnoses were assessed by trained independent evaluators (IEs) who administered

the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (K-SADS-PL)²⁹ to adolescents and parents at baseline; immediately postintervention; and 6, 12, and 18 months postintervention. IEs (research assistants or graduate students) used youth and parent reports on the K-SADS-PL to determine youths' diagnostic status using best estimate diagnostic procedures.³⁰ Adolescents were deemed to have a current or past depressive episode if they met *DSM-IV* criteria for MDD-definite or MDD-probable (4 threshold symptoms with at least 2 weeks duration and significant distress/impairment).

IEs were highly reliable ($\kappa = 0.96$ for 10 practice cases; $\kappa = 0.94$ for 10% of randomly selected completed evaluations). IEs were naïve to intervention condition. When the masking was broken, adolescents were assigned a new IE. IEs guessed participants' intervention assignment after completing evaluations. The mean correct classification rate was 47.5%, or chance level, providing evidence that IEs remained naïve to intervention condition.

Depression Symptoms. Depression symptoms were assessed with the Children's Depression Inventory (CDI),³¹ which was completed at baseline, midintervention; immediately postintervention; and 6, 12, and 18 months postintervention. Cronbach's α across administrations ranged from .81 to .91.

Cognitive and Interpersonal Risks. Cognitive and interpersonal risks at baseline were assessed by 3 cognitive measures and 2 interpersonal measures.²⁵ Youths were classified as high cognitive risk if they scored above the cutoff on any of the following 3 cognitive measures: 3.4 or higher on the Adolescent Cognitive Style Questionnaire (ACSQ),³² a valid measure of negative cognitive style³³ ($\alpha = .92$); 36 or higher on the Children's Dysfunctional Attitudes Scale (CDAS),³⁴ a validated measure of dysfunctional attitudes³⁵ ($\alpha = .86$); or 29 or higher on the rumination subscale of the Children's Response Styles Questionnaire (CRSQ),^{26,36} ($\alpha = .92$).

Youths were classified as high interpersonal risk if they had high parent–adolescent conflict and/or low peer support as measured by the Network of Relationships Inventory (NRI).³⁷ A parent conflict score (both parents averaged) of 15.5 or higher ($\alpha = .93$ for mother conflict; $\alpha = .91$ for father conflict) and/or a score of 23 or below on same-sex peer support ($\alpha = .86$) indicated interpersonal risk.

Data Analysis

All models were fit using SAS 9.4.³⁸ To examine differences on depression diagnoses, we modeled diagnosis (presence

versus absence during the 21-month study window) using logistic regression. For depressive symptoms, we implemented a 2-level hierarchical linear model to examine differences on symptom change over time. The first level models individual scores over time. At the second level, individual intercepts and slopes are analyzed as outcomes within IPT-AST and CWS. We conducted a piecewise hierarchical linear model to evaluate change within 2 legs of time in addition to overall change over the 21 months: change from baseline to postintervention (3 months post-baseline) and change from postintervention through the 18-month follow-up. Degrees of freedom were estimated with the Kenward-Roger approximation.³⁹ For effect sizes, we present proportions, odds ratios (ORs), and incidence rate ratios (IRRs) for binary variables and *d* for continuous variables.

For our primary hypotheses regarding personalization, comparisons within risk classifications were evaluated through linear contrasts using the logistic regression models for diagnosis and fitted hierarchical linear models for symptoms, focusing on comparing the off-diagonal risk classification groups (high cognitive–low interpersonal risk and low cognitive–high interpersonal risk). We compared high cognitive–low interpersonal risk adolescents who received CWS (match) with high cognitive–low interpersonal risk adolescents who received IPT-AST (mismatch) and low cognitive–high interpersonal risk adolescents randomly assigned to IPT-AST (match) with low cognitive–high interpersonal risk adolescents randomly assigned to CWS (mismatch). Consistent with our design to evaluate personalization a priori via matching and mismatching, half (51%) of adolescents in these 2 groups received a match between their risk classification and prevention assignment, and half (49%) received a mismatch. To further evaluate the potential benefits of matching, we performed additional analyses comparing all adolescents who received a matched intervention across these 2 risk classifications (high cognitive–low interpersonal risk in CWS; low cognitive–high interpersonal risk in IPT-AST) with adolescents in these 2 groups who received a mismatch.

With a proposed sample of 135 in the off-diagonal groups, we had 83.3% power to detect a difference of 25% in diagnoses; with 98 adolescents in the off-diagonal groups, power was 71.2% to detect this difference. For symptoms, power was calculated for the clustered design using estimates based on prior prevention studies.^{8-12,14-18,21,22} Power was 82.9% to detect a moderate effect size with a sample of 135. With the observed sample size, we had 78.4% power to detect

moderate effects. We included covariates if a variable was imbalanced across intervention conditions within the risk classification groups. Only age ($p = .003$) and ethnicity ($p = .10$) were imbalanced across risk classifications and were included as covariates. Additionally, we included lifetime depression history, using a broad definition that included MDD, MDD-probable, or minor depressive disorder (2 or 3 threshold symptoms with at least 2 weeks' duration and significant distress/impairment), as a covariate, as it was significantly associated with outcomes. There were no differences between study sites on baseline diagnoses, symptoms, or lifetime diagnoses ($p \geq .33$).

RESULTS

Preliminary Analyses

Table 1 provides descriptive statistics. Among adolescents who received the allocated intervention, retention rates through 18-month follow-up were 92% in IPT-AST and 91% in CWS. One participant in the low cognitive–high

TABLE 1 Descriptive Statistics for Main Study Variables

	Total	IPT-AST (n = 103)	CWS (n = 101)	p
Clinical measures				
Baseline depressive symptoms (CDI)	4.38 (4.32)	4.68 (4.51)	4.08 (4.12)	.32
Baseline MDD probable (K-SADS-PL), %	1.5	1.9	1.0	.99
Lifetime depression diagnosis (K-SADS-PL) ^a , %	34.8	37.9	31.7	.35
Risk classification measures at baseline				
Negative cognitive style (ACSQ)	2.78 (0.82)	2.86 (0.75)	2.69 (0.89)	.15
Dysfunctional attitudes (CDAS)	32.25 (7.31)	33.07 (7.45)	31.42 (7.10)	.11
Rumination (CRSQ)	23.62 (8.13)	23.95 (8.45)	23.29 (7.82)	.56
Parent–adolescent conflict (NRI)	12.62 (4.75)	12.29 (4.81)	12.95 (4.69)	.33
Peer support (NRI)	25.95 (6.01)	25.80 (5.57)	26.10 (6.46)	.73

Note: Values are reported as mean (SD) except where noted. ACSQ = Adolescent Cognitive Style Questionnaire; CDAS = Children's Dysfunctional Attitudes Scale; CDI = Children's Depression Inventory; CRSQ = Children's Response Styles Questionnaire; CWS = Coping With Stress; IPT-AST = Interpersonal Psychotherapy–Adolescent Skills Training; K-SADS-PL = Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version; MDD = major depressive disorder; NRI = Network of Relationships Inventory.

^aLifetime depression diagnosis includes MDD definite, MDD probable, and minor depression.

interpersonal risk class withdrew from CWS. The 3 participants who withdrew from IPT-AST belonged to the following classifications: high cognitive–low interpersonal, low cognitive–high interpersonal, and high cognitive–high interpersonal. Pattern-mixture models⁴⁰ indicated that intervention effects were not dependent on patterns of missing data ($p > .14$ for CDI, $p > .68$ for diagnosis). CDI scores required square root transformation to guarantee multivariate normality of the residuals.

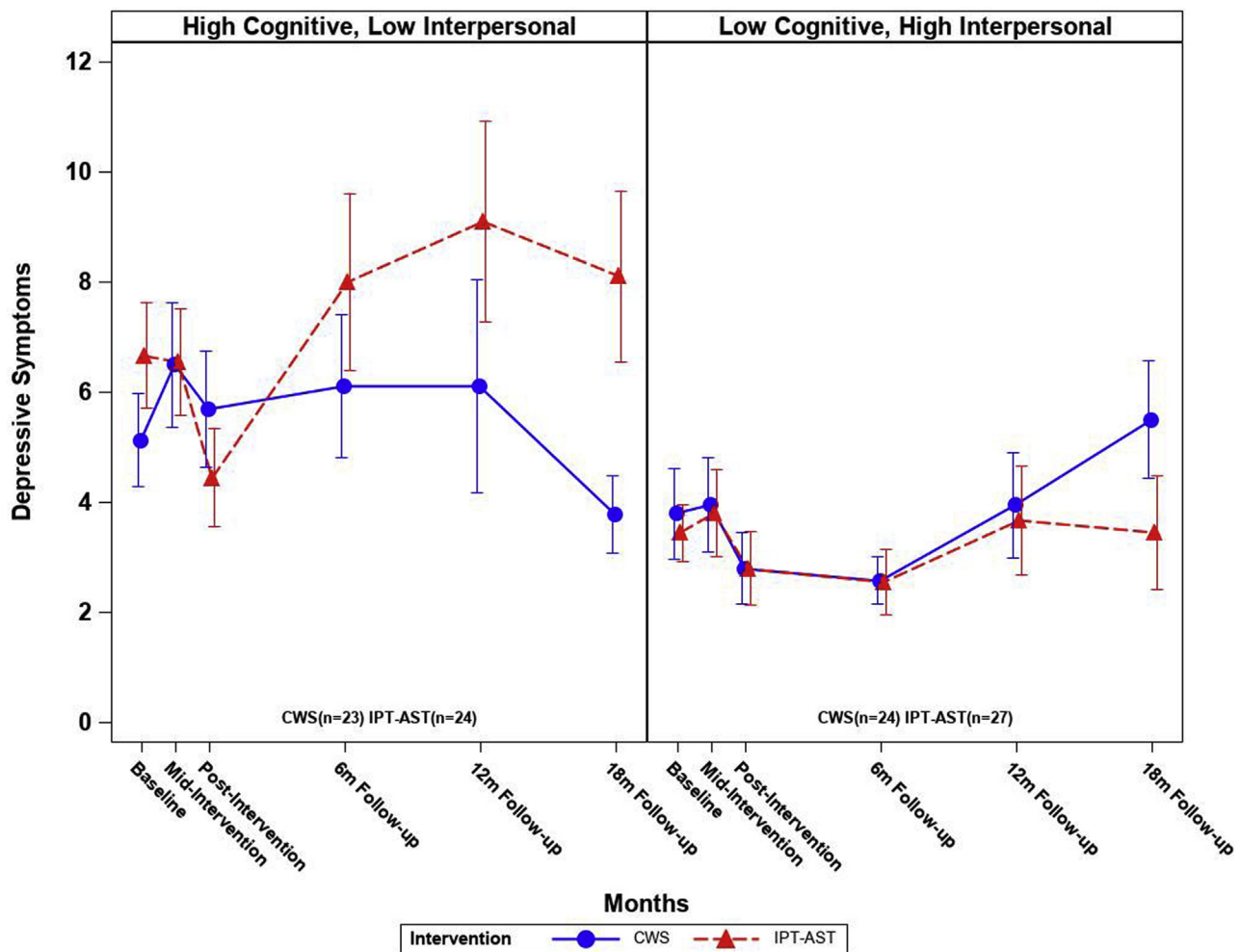
Overall Intervention Effects

Across the whole sample (ie, all 4 risk classifications), as expected, rates of depression diagnoses did not differ between the 2 interventions: 14.4% in CWS and 18.2% in IPT-AST ($t_{198} = 0.69, p = .49$). Similarly, there were no significant differences between CWS and IPT-AST in change in depressive symptoms ($p > .55$).

Personalized Prevention Effects

Although low cognitive–high interpersonal risk youths matched to IPT-AST showed lower rates of depression diagnoses compared with youths who received CWS (9.5% versus 25.2%), this difference fell short of statistical significance ($t_{193} = 1.30, p = .20, OR = 3.22 [95\% CI = 0.54, 19.11], IRR = 0.38 [95\% CI = 0.08, 1.81]$). For high cognitive–low interpersonal risk youths, rates of depression diagnoses were 19.6% in CWS and 19.9% in IPT-AST ($t_{193} = -0.02, p = .99, OR = 0.99 [95\% CI = 0.20, 4.89], IRR = 0.99 [95\% CI = 0.30, 4.18]$). See Supplement 2, available online, for rates among other groups. Across these 2 risk groups, matched adolescents had nonsignificantly lower rates of diagnoses than mismatched adolescents, 12.0% versus 18.3% ($t_{193} = 0.78, p = .44, OR = 1.65 [95\% CI = 0.46, 5.85], IRR = 0.65 [95\% CI = 0.29, 2.29]$).

FIGURE 2 Depressive Symptom Trajectories by Risk Classification Groups for the Different Intervention Modalities to Test Personalization by Matching and Mismatching



Note: CWS = Coping With Stress; IPT-AST = Interpersonal Psychotherapy–Adolescent Skills Training.

Figures 2 and 3 illustrate trajectories of depressive symptoms by intervention condition, focusing on the 2 risk classification groups of interest, using observed data at each time point to graph the trajectories. Table 2 provides the model-based estimates and contrasts for the high-low/low-high risk groups that provide the essential tests relevant to evaluate personalization and the contrasts for matched versus mismatched youths in these 2 risk groups (see Table S1, available online, for other risk groups).

Low cognitive–high interpersonal risk adolescents matched to IPT-AST showed significantly greater decreases in depressive symptoms over 21 months than adolescents in this risk group who received CWS. High cognitive–low interpersonal risk adolescents matched to CWS showed significantly greater decreases in depressive symptoms from postintervention through 18 months than adolescents in this risk group who received IPT-AST. Matched adolescents showed significantly greater decreases in depressive symptoms than mismatched adolescents from postintervention through 18-month follow-up and across the entire 21-month study period.

DISCUSSION

The PDP study examined a novel approach to personalizing depression prevention. Specifically, we investigated whether

youths who received an intervention consistent with their risk classification showed better outcomes (ie, lower rates of disorder onset and fewer depressive symptoms) compared with youths mismatched between modality and risk profile. We replicated in this independent PDP sample our previously validated risk classification system²⁵ and applied this system to categorize adolescents on depression risk based on documented cognitive and interpersonal vulnerabilities. We then randomly assigned youths within each risk classification group to IPT-AST or CWS, 2 programs with prior evidence of efficacy. CWS teaches skills to reduce cognitive risk, and IPT-AST emphasizes strategies to address interpersonal vulnerabilities. For our primary aim to examine the benefits of personalization, we focused on adolescents exhibiting low cognitive–high interpersonal risk and exhibiting high cognitive–low interpersonal risk. This enabled us to directly evaluate, a priori, the hypothesized effect of personalization of depression prevention by comparing prospective depression outcomes for adolescents who received a matched prevention program compared with adolescents who received a mismatch. We supplemented these analyses by examining whether adolescents who received a matched intervention across these 2 risk classification groups had better outcomes than adolescents who received a mismatch.

FIGURE 3 Depressive Symptom Trajectories by Matching and Mismatching

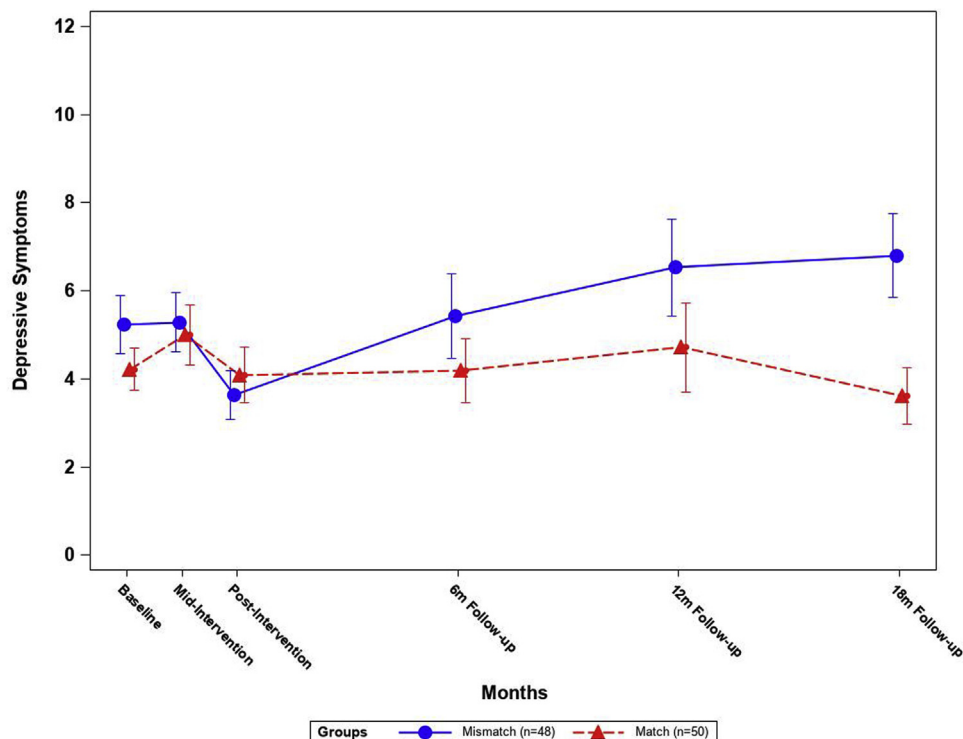


TABLE 2 Change in Depressive Symptoms Over Follow-up for Key Off-Diagonal Risk Classification Groups to Test Personalization by Intervention Matching

	Estimated change		Intervention contrast			Effect size	
	CWS (SE) n = 23	IPT-AST (SE) n = 24	t	df	p	d	(95% CI)
High cognitive risk-low interpersonal risk (n = 47)							
Leg 1 change	+1.00 (1.25)	−0.06 (1.41)	1.64	193	.10	0.38	(−0.02, 0.77)
Leg 2 change	−1.90 (1.49)	+2.82 (1.17)*	−2.68	193	.01	0.64	(0.24, 1.04)
Total change	−0.90 (1.64)	+2.76 (2.04)	−1.18	193	.24	0.30	(−0.09, 0.68)
Low cognitive risk–high interpersonal risk (n = 51)							
Leg 1 change	−2.26 (1.31) [†]	−1.52 (0.60)*	0.59	193	.56	0.13	(−0.25, 0.51)
Leg 2 change	+2.92 (1.10)**	+1.12 (1.35)	1.25	193	.21	0.28	(−0.11, 0.66)
Total change	+0.66 (1.17)	−0.40 (1.25)	1.98	193	.049	0.51	(0.12, 0.90)
	Estimated change		Contrast			Effect size	
	Match (SE) n = 50	Mismatch (SE) n = 48	t	df	p	d	(95% CI)
Match vs. mismatch (n = 98)							
Leg 1 change	−0.27 (0.26)	−1.17 (0.54)*	0.82	193	.41	0.16	(−0.26, 0.58)
Leg 2 change	−0.41 (1.45)	+2.87 (0.83)***	−2.80	193	.01	0.57	(0.16, 1.02)
Total change	−0.67 (0.47)	+1.70 (1.17)	−2.17	193	.03	0.44	(0.02, 0.86)

Note: The significance patterns under estimated change refer to within intervention change for the particular time frames (ie, leg 1, leg 2, total change). CWS = Coping With Stress; IPT-AST = Interpersonal Psychotherapy–Adolescent Skills Training.

*p < .05; **p < .01; ***p < .001; [†]p < .10.

Partially in line with study hypotheses and in support of precision mental health approaches, adolescents classified as low cognitive–high interpersonal risk for depression who received IPT-AST (a match between risk profile and prevention modality) showed better long-term depression outcomes (medium, but nonsignificant, effect for diagnoses; significant reduction in symptoms) than adolescents in this group who received CWS (a mismatch between risk and prevention). Adolescents classified as high cognitive–low interpersonal risk for depression who received the matched prevention program (CWS) improved on depressive symptom trajectories during the follow-up period, although there was no significant difference in diagnosis rates. Supplemental analyses further suggest the potential benefits of matching youths to prevention program, particularly for symptoms. Taken together, our results support the value of assessing depression vulnerabilities to determine which evidence-based prevention program (cognitive-behavioral or interpersonal) to offer adolescents.

In the overall sample, there were no significant differences in outcomes between youths who received IPT-AST or CWS. We did not expect a difference between these prevention programs for the average youth, representing the one-size-fits-all approach and analysis, because the literature documents relative equal efficacy of both

programs.^{8-12,14-16,41} Additionally, prior work found no significant difference in depressive symptoms between CWS and IPT-AST in a universal sample of adolescents.⁴² Importantly, and in line with our primary hypothesis, we found some evidence of differential effects of these programs in the matched versus mismatched risk classification groups.

We observed some indication that matching youths to prevention programs based on risk leads to differential rates of depression onset over 18-month follow-up. This was the case only for youths at low cognitive–high interpersonal risk who received IPT-AST compared with CWS. The odds of experiencing a depressive disorder were 3.2 times greater for youths who received a mismatched intervention (CWS) compared with youth in IPT-AST, although this difference was not statistically significant. Additionally, the IRR was 0.38, indicating a 62% reduction in prospective depressive disorder when high interpersonal risk youths were matched to IPT-AST. Meta-analysis of depression prevention on average, for one-size-fits-all approaches, reveals an IRR of 0.78, meaning a 22% reduction in depression diagnosis when receiving prevention without risk consideration.⁴³ This highlights a potential opportunity to augment the preventive effects of IPT-AST by providing this program to youths who are at risk for depression by virtue of high parent–child conflict and/or low peer support.

We did not see differential rates of depression onset in adolescents at high cognitive–low interpersonal risk for depression randomly assigned to CWS or IPT-AST. Although we did not find evidence that personalization enhanced the effects of CWS on depression diagnoses, our study and past trials show effects of CWS for reducing depression onset.^{8–11} Furthermore, the analyses combining the matched adolescents across these 2 risk classification groups suggest potential, albeit modest, benefits of matching youths to prevention program on rates of depression onset. Across these 2 classification groups, the odds of experiencing a depressive disorder were 1.7 times greater for youths who received a mismatched intervention compared with a matched intervention. Although the difference in rates is not significant, there was a 35% reduction in prospective depressive disorder when adolescents received a matched intervention. This compares favorably to the 22% reduction in a meta-analysis in which most studies compared an active prevention program with a no-intervention control group.⁴³

PDP also showed differential effects on depressive symptoms. Youths who received a matched preventive intervention experienced relatively stable symptoms or a modest decrease in symptoms over time, whereas youths who received a mismatch experienced a small increase in depressive symptoms. The differences in rates of change were small, and these differences were not consistent across the 2 risk groups. In the low cognitive–high interpersonal risk group, we found a significant difference across the entire 21-month study period, whereas in the high cognitive–low interpersonal risk group the significant difference was in the 18-month follow-up period when CWS youths showed a decline in depressive symptoms and IPT-AST youths showed an increase in symptoms. In the matched versus mismatched analyses across the 2 classification groups, there were significant differences across the follow-up and the entire 21-month study period.

This sample had relatively low levels of baseline depressive symptoms compared with prior indicated prevention studies, which enrolled youths with elevated symptoms. This may explain the lack of significant differences during the active phase of the intervention, as there was limited room for improvement. Additionally, neither intervention changed symptoms in the high cognitive–low interpersonal risk group in the active phase of the intervention (baseline to postintervention), whereas the low cognitive–high interpersonal group exhibited change under both interventions. This suggests that early change may be harder to achieve in the high cognitive risk group, with stable negative beliefs

conferring vulnerability, whereas the high interpersonal risk group may be more amenable to early change. Future research can evaluate the hypothesis that youths with elevated cognitive risks are more resistant to intervention effects in the short-term relative to youths with interpersonal risks.

Over time, the high cognitive–low interpersonal risk group improves over the follow-up period with the right intervention matched to their risk, whereas with a mismatched intervention these high cognitive risk youths experienced deteriorating symptom trajectories over time. Likewise, the high interpersonal risk group maintained the early gains over longer follow-up when matched to IPT-AST, whereas symptoms worsened over time when mismatched to CWS. So, in the follow-up phase, mismatched adolescents showed a statistically significant increase in depression symptoms, whereas adolescents who received a matched intervention either showed modest reductions in symptoms or exhibited more stability via lack of significant increases in symptoms. Finding these longer-term prevention effects for adolescents who received an intervention targeting their particular vulnerabilities compared with adolescents who received a mismatch to another evidence-based intervention underscores the potential of personalization.

These findings are in line with post hoc moderator analyses from previous depression prevention studies.^{21,22} Cognitive risk moderated outcomes for cognitive-behavioral prevention programs, and parent–adolescent conflict moderated outcomes for IPT-AST. Importantly, PDP is the first study to a priori match or mismatch youths to a prevention program based on cognitive and interpersonal risks. Our findings suggest that providing a personalized program may increase the magnitude and length of the effects of these evidence-based programs. These findings provide preliminary prescriptive indicators²⁴ about which program may be most helpful for a given adolescent.

Taken together, the findings from PDP provide initial evidence that personalization, focused on cognitive and interpersonal vulnerabilities for depression, may enhance the effects of evidence-based depression prevention programs. Other groups have examined different individualized metrics that help quantify the benefits a person will receive from one or another intervention.²⁰ These include the Personalized Advantage Index (PAI)⁴⁴ and the Probability of Treatment Benefit (PTB)⁴⁵; evidence supports both metrics.^{46,47} Randomized controlled trials that prospectively match individuals to their optimal intervention based on these metrics and then examine outcomes will be an important next step for PAI and PTB.²⁰ We believe these

and other personalization approaches provide promising solutions to move the field forward.

Limitations of this study should be noted. First, PDP adolescents were recruited from the general community. Although results are generalizable to the broader youth population, this approach resulted in a sample with relatively low baseline levels of depressive symptoms, particularly in comparison to indicated samples in prior CWS and IPT-AST studies. This likely limited our ability to detect changes over time in depressive symptoms, especially in the active phase of the intervention; we observed statistically significant symptom changes, but these changes may have less clinical significance. Second, more than a third of the sample had experienced a prior depressive episode using a broad definition (MDD-definite, MDD-probable, or minor depression), which may impact generalizability to other samples and past prevention findings. Our findings therefore reflect both primary and relapse prevention. Finally, although the overall study was sufficiently powered to detect effects on diagnoses and symptoms, we had modest power for these analyses. As a first examination of personalizing prevention, we had to make necessary decisions to ensure study feasibility. Future research can build on these novel findings and intentionally select youths based on these risk classification groups with larger sample sizes and a no-intervention comparison condition to more robustly evaluate personalization via matching to prevention modality.

In conclusion, results from the PDP study provide preliminary a priori evidence of the benefits of personalizing depression prevention to optimize effects in a sample of diverse youths at risk for depression by virtue of cognitive or interpersonal vulnerabilities. Although results are promising, they should be viewed cautiously given that this is the first time this approach to matching has been evaluated, risk group sample sizes are modest, and there is variation in results. Replication with larger samples is warranted. Preventive interventions may need to address multiple risk and protective factors for depression to optimize effects⁴⁸ or include other approaches to personalized interventions.²⁰ Given the increasing rates of depression during

adolescence, the significant risks and impairment associated with adolescent-onset depression, and the clear promise of prevention, it is essential to try to optimize depression prevention programs and disseminate these efforts so that they can inform clinical decision making. This will ensure that more youths can receive an evidence-based prevention program that is likely to be most beneficial for them, reducing the burden of depression for both the individual and society.

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SUPPLEMENT 1**Clinicaltrials.gov Registration**

Depressive symptoms was an a priori primary outcome measure, but was erroneously listed as a secondary outcome measure in the original study registration before the commencement of data collection. This error has been corrected in the recently updated study registration (ClinicalTrials.gov NCT01948167).

SUPPLEMENT 2**Intervention Contrasts for Rates of Depression Diagnoses in Low/Low and High/High Risk Classification Groups**

For low cognitive–low interpersonal risk youths, rates of depression diagnoses were 9.1% for adolescents who

received CWS and 24.1% for adolescents who received IPT-AST ($t_{193} = -1.27, p = .20$, odds ratio = 0.32 [95% CI = 0.05, 1.88], incidence rate ratio = 0.38 [95% CI = 0.08, 1.81]). For high cognitive–high interpersonal risk youths, rates of depression diagnoses were 11.3% for adolescents who received CWS and 25.8% for adolescents who received IPT-AST ($t_{193} = -1.30, p = .19$, odds ratio = 0.36 [95% CI = 0.08, 1.68], incidence rate ratio = 0.44 [95% CI = 0.12, 1.45]).

TABLE S1 Intervention Contrasts for Change in Depressive Symptoms in Low/Low and High/High Risk Classification Groups

	Estimated change		Intervention contrast			Effect size	
	CWS (SE) n = 27	IPT-AST (SE) n = 26	t	df	p	d	(95% CI)
Low cognitive risk–low interpersonal risk (n = 53)							
Leg 1 change	0.29 (0.48)	0.55 (0.55)	-0.34	193	.74	0.08	(-0.30, 0.46)
Leg 2 change	0.63 (0.57)	0.36 (0.64)	0.40	193	.69	0.09	(-0.31, 0.47)
Total change	0.92 (0.50) [†]	0.90 (0.55)	0.08	193	.94	0.02	(-0.37, 0.40)
High cognitive risk–high interpersonal risk (n = 53)							
Leg 1 change	-0.28 (1.06)	-0.48 (1.05)	0.14	193	.89	0.03	(-0.36, 0.41)
Leg 2 change	-0.24 (1.15)	-0.80 (0.99)	0.40	193	.69	0.09	(-0.31, 0.47)
Total change	-0.52 (1.03)	-1.27 (0.94)	0.59	193	.55	0.13	(-0.26, 0.51)

Note: CWS = Coping With Stress; IPT-AST = Interpersonal Psychotherapy–Adolescent Skills Training.

[†]p < .10.